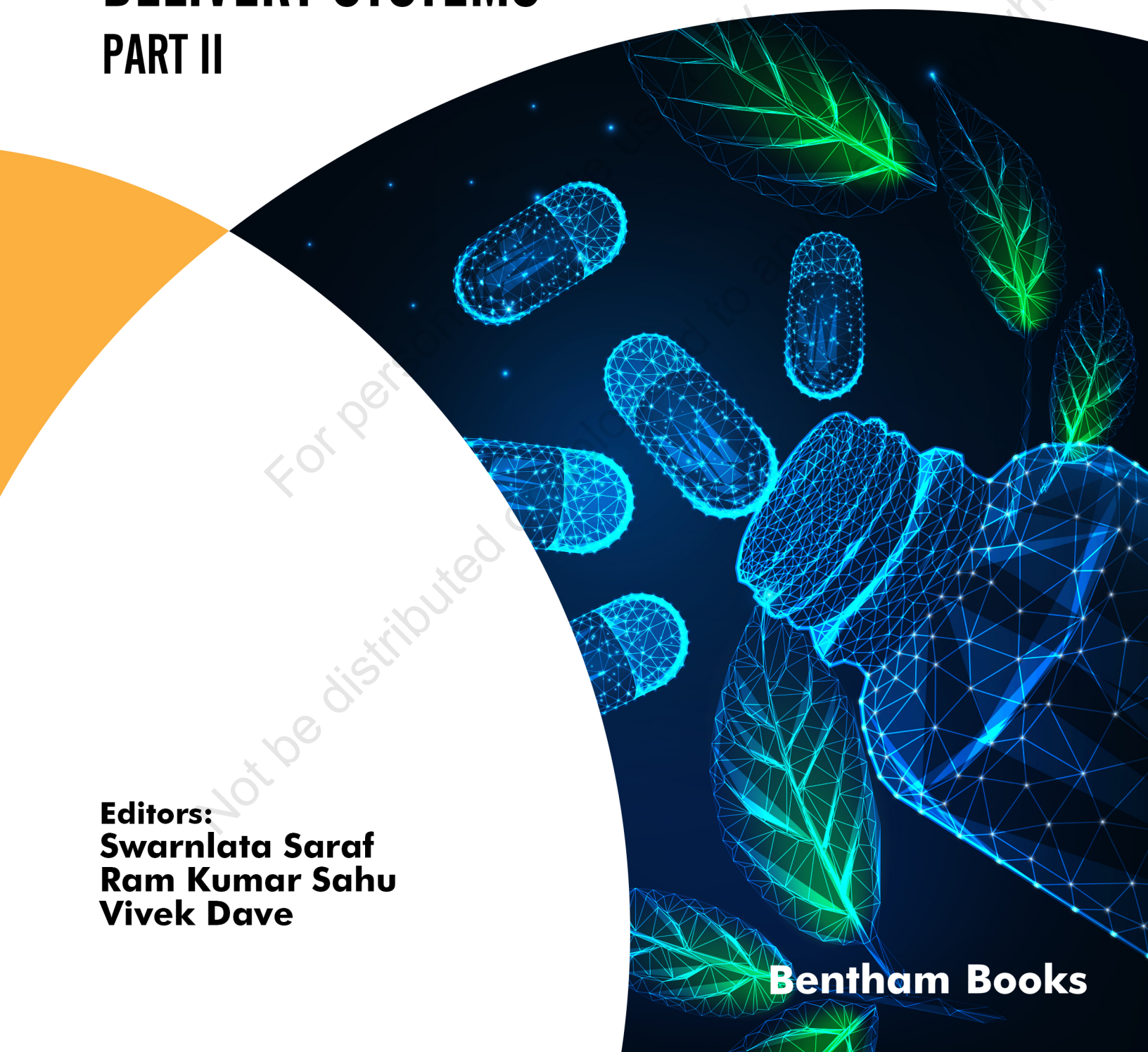
ADVANCED PHARMACEUTICAL AND HERBAL NANOSCIENCE FOR TARGETED DRUG DELIVERY SYSTEMS

PART II



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Advanced Pharmaceutical Herbal Nanoscience: Targeted Drug Delivery System

Part II

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Advanced Pharmaceutical Herbal Nanoscience: Targeted Drug Delivery System (Part II)

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FOREWORD

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Currently, various drug delivery systems are being developed to minimize drug degradation, prevent toxic effects, improve drug bioavailability, and increase drug accumulation at the disease target site. Nano based drug delivery offers significant advantages in terms of targeted drug delivery, transport, and release to achieve better therapeutic efficacy. This system is rapidly becoming one of the most important tools in the field of nanomedicine.

In the book titled "**Advance Pharmaceutical Herbal Nanoscience**: **Targeted Drug Delivery System Part II**," the author aims to provide a comprehensive overview of herbal nanoscience, including its production, evaluation, regulatory perspective and application.Herbal drugs are widely used worldwide, and their therapeutic efficacy depends on the nature of active constituents. The higher molecular weight and aqueous solubility of active ingredients, which cannot penetrate the lipid membranes of cells, lead to a decrease inbioavailability and efficacy. The combination of herbal medicine and nanotechnology has been widely recommended as nanostructured systems have the potential to overcome the above limitations. The nano-based delivery system improves the bioavailability of herbal medicines by delivering a sufficient amount of the drug to the target site of the disease.

In this book, an overview of recent advances in plant-based nanomedicine is presented. Each chapter attempts to describe the introduction, concept, progress, current status, and future prospects of plant-based nanomedicine. In addition, the book includes an overview of research in the field of plant-based nanoscience and some of the most fascinating findings from this study. The book also examined the difficulties and regulatory implications of plant-based nanoscience.

The authors of this book have succeeded in addressing the development that has been attempted in the area of novel plant-based drug delivery. This is a useful book and resourcefor undergraduate students, graduate students, researchers, and academicians who are exploring concepts for a nano-based drug delivery system and its performance.

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PREFACE

The objective of the book entitled "**Advanced Pharmaceutical Herbal Nanoscience: Targeted Drug Delivery System"** is to offer an understanding of various herbal novel drug delivery systems, their preparations, characterization and exciting range of applications. Herbal nanoscience targeted drug delivery system demands a broad range of awareness in novel drug delivery systems. It is very important to have detailed knowledge and awareness of new technology or new process about the various herbal nanoscience products and their composition. The awareness of knowledge about the properties of various herbal constituents of a nanoformulation is also very important because it decides the determination of the formulation of the delivery systems and broadly ensures its properties. This book covers a broad spectrum of herbal nanoscience topics required to appropriately give formulation procedure, evaluation and applications of herbal drug delivery systems and correlate it with treating many diseases.

It expresses huge awareness and knowledge regarding advanced pharmaceutical, herbal nanoscience targeted drug delivery systems in the aspect of the application in drug delivery and herbal nanomedicine. In addition to this, the book covers all major topics like drug development issues, adaptation to clinical use, market prospects and industrial commercialization too, which come under advanced pharmaceutical nanoscience and nanotechnology application. Apart from the application section, it discusses in detail the safety, herbal nanotechnology, regulatory, targeting aspects and social scenario of pharmaceutical nanoscience. The book not only focuses on theoretical knowledge but also considers practical aspects. The book is quite beneficial for students and researchers acrossthe globe who are indulged in the reading and investigation of advanced pharmaceutical, herbal nanoscience and related nanotechnology, thereby spreading awareness all over the globe and promoting anticipated trends in the field of nanoscience and nanotechnology. The major objective of this initiative is to bring all the fundamental concepts, target delivery, herbal bioactive, and nanomedicine, all in a common platform that will provide knowledge about all the possible advanced pharmaceutical, herbal nanoscience drug delivery systems. Some major chapters to be published in the book include nucleic acid-based therapeutic, electrosomes, aquasomes, phytosomes, guggulosome, niosomes, self nano/micro emulsified drug delivery system, the concept of targeted drug delivery system, application of herbal Bioactive and many more. This valuable resource will make the readers more aware of novel drug delivery systems as well as their promising applications in drug targeting and nanotheronostics, thereby improving the pharmaceutical world's situation.

The book's aim is to provide a single volume covering a detailed description of various herbal drug delivery systems, their principles and how these are put in use for the treatment of vivid diseases. The book has been divided into four sections. The first section deals with the fundamentals of advanced pharmaceutical nanoscience, whereas the second section deals with a detailed overview of the novel and efficient advanced pharmaceutical nanoscience delivery systems in the field of pharmaceutical science in which some major topics will be published in the book, which includes nucleic acid-based therapeutic, electrosomes, aquasomes, phytosomes, guggulosome, niosomes, self nano/micro emulsified drug, *etc*. This section is quite unique as it elaborately describes the major main beliefs and techniques of the preparations of the herbal drug delivery systems. This furnishes a quite unique and updated coverage of the essential areas that guide the underlying science behind these therapeutic delivery systems. The distinguished authors have emphasized on providing a complete insight into the advanced pharmaceutical nanoscience drug delivery systems with their convenient applications in the field of herbal nanoscience technology. The third section mainly involves diseases specific to advanced pharmaceutical nanoscience targeted drug delivery systems like cancer, infectious

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diseases, brain diseases, *etc.* Finally, the fourth and the last section of the book provides the application of herbal bioactive in pharmaceutical, herbal nanosciencetargeted drug delivery systems.

This advanced book has been designed keeping in mind the young and new researchers and scientists who are working dedicatedly in the field of health/medicine and the pharmaceutical sector. This book promises a detailed, informative description of advanced herbal and absolutely modern pharmaceutical dosage forms and drug delivery systems. The information furnished in the book is sure to serve society.

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CHAPTER 1

Pharmaceutical Nanosciences and their Application in the Delivery of Various Phytoconstituents

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Abstract: Nanoscience provides numerous opportunities for pharmaceutical scientists. Due to the continuing progress of nanoparticle-based medicines, the opportunity to treat and combat difficult diseases, especially with herbal remedies, can be achieved. The use of herbs is effective when their active constituents reach the intended target. However, the flavonoids, tannins, and terpenoids present in herbs are hydrophilic and unable to pass through cell lipid membranes. Therefore, their absorption is poor,resulting in reduced availability and biological efficacy, increased dosage, andfrequency of use. Nanoengineering has verified that nanoparticles have significantpotential as drug carriers. Size reduction methods and technologies produce a widevariety of nanostructures, which are indicative of specific physicochemical and biological properties. This delivery system plays an essential role in increasing thesolubility, bioavailability, pharmacological effect, stability, effectiveness, selectivity, and drug specificity of its bioactive constituents. Nanoscale models such as phytosomes, liposomes, nanoemulsions, nanoparticles, solid lipid nanoparticles, andethosomes are used to deliver various bioactive constituents at adequate doses to thetarget during the entire treatment period. Phospholipid complex techniques have recently been introduced to overcome these barriers either by enhancing theirdissolving capacity or their potential ability to traverse biological membranes andprotect the active herbal constituents against degradation. Therefore, this chapterdiscusses the application of nanoscience for delivering various phytoconstituents inorder to achieve therapeutic targets.

Keywords: Herbal medicine, Nanotechnology, Phytoconstituents.

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INTRODUCTION

Nanotechnology is a science that changes the dimensions of matter at the nanoscale level. Recently, this branch of science has been indispensable to the pharmaceutical and drug industries because of its potential to play a crucial role inimproving human life. These scientific applications are related to the medicalfield and include the therapeutic applications of drug delivery, enhancing drug efficacy, reducing side effects, and improving circulation and stability [1]. The majority of phytoconstituents are declared active if they are proven to have a confirmed impact on the treatment of specific diseases or pain relief and are classified as organic constituents. The active organic constituents demonstrate lowbioavailability while being predominantly non-water soluble, unstable, and the most toxic.

Nanoparticles are frequently used as therapeutic and diagnostic agents because of their advanced and essential drug delivery systems. For example, materials incorporating protein or nucleic acids require a carrier system that potentially enhances their effectiveness and shields them from undesired decreation [2]. The potency of the drug nanoparticle delivery system is directly associated with its small particles and huge surface area, thus indicating increased solubility and the capacity to pass through the blood-brain barrier (BBB), enter the respiratorysystem, and be captivated across the close connections of skin epithelial tissue cells [3].

Formulations based on herbal medicines or their active phytoconstituents remain subjected to numerous limitations [4]. Nevertheless, they are considered a major source because of their less severe side effects compared to those of synthetic drugs and the deep-seated public belief in their ability to cure or prevent various diseases. Several methods are employed to overcome these limitations, including dissolving in non-polar solvents, making injection preparations, and increasing their solubility by changing the active phytoconstituents into their salt form.These methods have several drawbacks, such as high solvent toxicity, their uncertain activity when in salt form, the presence of bioactive drug forms, and the lack of bioavailability. Consequently, special technology, namely nanotechnology, needs to be employed as a solution. With the application of nanotechnology, herbal medicines can deliver their active phytoconstituents to specific targets. These nanoparticle techniques are designed and delivered with various sizes, forms, compositions, functions, and physical/chemical modifications to suit the distinctiveness of the targeted organs and the specific drug used. The dosage forms of nanoparticles include fullerenes, emulsions, microemulsions, liposomes, liquid crystals, dendrimers, quantum dots, nanoparticles, gels, solid lipid nanoparticles, among others. This chapter will,

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therefore, briefly focus on herbal medicine nanoparticles to overcome several formulation deficiencies associated with phytoconstituents in herbs.

PHYTOCONSTITUENTS IN HERBAL MEDICINE

Phytoconstituents found in herbs are commonly referred to as secondary metabolites, namely phenolics, terpenoids, alkaloids, and anthraquinones. These compounds have high curative value, but their bioavailability and solubility are low, while their toxicity and instability may hinder their medicinal use [5].

Phenolic

Almost all plants contain phenolic compounds which are aromatic in character and contain more than one hydroxyl substituent. The main compounds are phenols, many of which are found in polyphenols, and among which more than 8,000 compounds have been identified. Based on their primary chemical structures, polyphenols are divided into stilbenes, phenolic acids, flavonoids, and lignans. Flavonoids are one of the naturally occurring polyphenols, with morethan 6,000 compounds being identified. They include flavones, flavonols, flavans,flavanones, dihydroflavanols, isoflavons, and biflavones [6]. Compounds within this class execute a protective function against free radicals, cardiovascular disease, cancer, inflammation, microbial contamination, viruses, allergies, and ulcers, among other diseases [7]. Other phenolic compounds include quinones, xanthones, coumarins, polymer lignins, and tannins. Phenylpropanoid dimers or lignans containing two C6-C3 bound by C-8 carbon centres have antiviral, anticancer, anti-inflammatory, antimicrobial, antioxidant, immunosuppressive, and hepatoprotective properties and are used in osteoporosis prevention [8].

Polyphenols have properties that are challenging to address due to the presence of several phenyl rings in the compound, the number of hydroxyl groups in the aromatic cycle, and the bioavailability of polyphenols in food that depends on pre- and post-harvest conditions and interactions with other compounds. Since these class compounds demonstrate extremely limited absorption ability, poor solubility in water, and rapid metabolism, they need to be made into several types of pharmaceutical formulations with the potential to increase bioavailability. Certain polyphenols have low stability and, therefore, selecting the liposome form for polyphenol encapsulation is considered appropriate. However, it is also important to note the characteristics of each polyphenol, which have various molecular structures within which the ring and hydroxyl numbers affect their solubility [7]. One example is that of a podophyllotoxin employed as an anti-mitotic whose high toxicity limits its use [9]. To overcome this problem, modification of the podophyllotoxin structure is undertaken in the hope that its toxicity will be reduced.

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Resveratrol is a polyphenol compound contained in *Vitis vinifera*, labrusca, and muscadine [10], which possesses anti-oxidant, anti-cancer, anti-inflammatory, and cardioprotective properties [11]. Due to being moderately water-soluble, resveratrol demonstrates full bioavailability, photosensitivity [12], and rapid metabolism [13]. Multiple nanoencapsulation of resveratrol, polymer nanoparticles, Zein-based nanoparticles, nanoemulsions, liposomes, cyclodextrins, and resveratrol have been reported to enhance bioavailability and pharmacokinetics [14 - 19]. The polyphenol will improve solubility and chemical stability if formulated with dipalmytoyl-phosphatidylcholine or distearoyl-phosphatidylethanolamine-polyethylene glycol 2000. It also prolongs efficacy andimproves protection from UV B when combined with P90G or dicetyl phosphate [7].

Curcumin (diferuloyl-methane) is moderately soluble in water, has low bioavailability and is produced in the formulation of liposomes, phospholipid vesicles, and polymer-based nano formulations [20, 21]. Oral bioavailability is nine times higher when curcumin is combined with piperine, which functions asan absorption enhancer [22]. In addition, curcumin colloid nanoparticles(theracurmin) are 27 times more effective and can inhibit alcohol poisoning [23]. Curcumin formulated in liposomes using soybean phosphatidylcholine, film hydration, and extruction (MLV) will prolong the antioxidant protective effect.On the other hand, when formulated using dimyristoyl phosphatidylglycerol and lyophilisate, it enhances the bioavailability while reducing the incidence of protease cancer and exerting an antiangiogenic effect [7].

Quercetin, a natural flavonoid in various vegetables and fruits, is 100 times more water-soluble after being formulated as a polymer nanoparticle suspension dosage form [24]. Ampelopsin, produced from *Ampelopsis grossedentata*, has anti-oxidant, anti-inflammatory, anti-hypertensive, anti-microbial, hepatoprotective, anti-carcinogenic properties, and cough-relieving effects. This compound is moderately water-soluble with very low permeability and is consequently packaged in microemulsions to increase bioavailability, solubility, and penetration [25]. Quercetin is formed in liposomes using dipalmytoyl-phosphatidylcholineand lecithin that increases solubility, bioavailability, and anti-tumor and antioxidant properties [7]. *Origanum dictamnus* extract contains anti-oxidant and anti-microbial substances due to large amounts of coumarin and flavones, which are formed into liposomes to increase their activity [26].

Encapsulation, which protects phytoconstituents, can be used to reduce the instability of the active ingredient, retard its degradation, and increase activity. For example, quercetin formed in liposomes with PEG in plasma has a life span exceeding five hours [27], whereas quercetin formulated in polymer nanoparticles

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form demonstrates increased anti-oxidant activity, while quercetin encapsulated in Eudragite nanoparticles (polymer nanoparticles) is very stable [28].

Certain other polyphenols, such as catechin, fisetin, dehydro-silymarin, and silymarin, increase bioavailability, solubility, chemical stability, while several activities in liposome form use epikuron/Tween, dioleoyl phophatidylchoo-line/PEG 2000, soybean phosphatidylcholine, lecithin, and mannitol [7].

The application of a lipid bilayer in liposomes increases catechin permeability. It occurs because of the geometric relationship between lipids in liposomes and insoluble encapsulation drugs (catechins) [7]. To date, no system has generalized the composition and encapsulation of lipids. A significant body of research has concentrated on the modification of liposome surfaces and their composition in enhancing the incorporation of insoluble drugs and well-defined target locations.

Terpenoid

Terpenoids represent the most widespread group of natural compounds, with morethan 40,000 having been identified so far. In general, the structure of terpenes is formed from isoprene units with its constituent groups in the form of cyclic unsaturated hydrocarbons at varying degrees of oxygen. Terpenoids are grouped on the basis of the number of isoprene units; monoterpenes (one isoprene), sesquiterpenes, diterpenes (two isoprenes), sesquiterpenes, triterpenes (three isoprenes), and tetraterpenes (four isoprenes). A variety of terpenoids have been found to have anti-cancer, anti-alzheimer [29], anti-microbial, anti-fungal, anti-parasitic, anti-allergic, anti-spasmodic, anti-hyperglycemic, anti- inflammatory, and immunomodulatory properties [30].

Monoterpenes constitute the main class of terpenoids that contain one isoprene unit found in floral aromas, plants containing essential oils, and aromatic plant resins [31], which act as anti-tumor agents. Thymoquinone is an active anti-oxidant, anti-inflammatory, and anti-cancer constituent of *Nigella sativa* [32, 33]. However, the compounds have limitations, such as poor solubility, extreme lipophilicity, and light and heat-instability that hinder pharmaceutical applications. Triterpenoids have more than 90 carbon skeletons with oxidative modification and skeleton glycosidation resulting in greater diversity [34]. Ursolicacid (UA) and oleanolic acid (OA) are natural triterpenoids obtained from no less than 120 plants. OA has hepatoprotective, anti-inflammatory, anti-hyperlipidemic,anti-tumor, and anti-viral qualities, whereas UA has anti-inflammatory, anti- hyperlipidemic, anti-hyperglycemic, hepatoprotective, anti-carcinogenic,neuroprotective, and anti-ulcer properties [35]. Their bioavailability is severely restricted by an extremely limited solubility in water.

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Cucurbitacins are bitter, toxic, oxidized tetracyclic triterpenoids. These compounds can be obtained from the Rubiaceae, Cucurbitaceae, Desfontainiaceae, Scrophulariaceae, Begoniaceae, Elaeocarpaceae, Polemoniaceae, Thymelaeaceae, Primulaceae, Brassicaceae, Sterculiaceae, Datiscaceae, and Rosaceae families. These compounds function as heterologous chemical secretions that protect plants from external biological threats [36], and their anti-pyretic, anti-inflammatory, anti-tumor, anti-microbial, and analgesic characteristics are useful [37].

Triptolide is an epoxide diterpenoid isolated from *Tripterygium wilfordii* and useful in treating polycystic kidney diseases, pancreatic carcinoma, autoimmune, rheumatism, leukemia, and psoriasis even though this compound demonstrates poor solubility and high toxicity. Triptolide is prepared in a microemulsion system as poly [DL-lactic acid] [38] nanoparticles, which are biocompatible and biodegradable for transdermal preparations. Since one side effect of Triptolide is irritation of the gastric system, it is encapsulated in SLN to minimize this effect [39].

Cryptotanshinone is a member of the quinoid diterpene class contained in the root of *Salvia miotiorrhiza* Bunge and has applications as an anti-inflammatory, anti-bacterial, cytotoxic, anti-oxidative, anti-angiogenic and anti-parasitic, but has poor bioavailability due to water solubility. The bioavailability of cryptotanshinone administered orally will increase when prepared in solid nano lipid formulation [40].

Thymoquinone is a monoterpene extracted from *Nigella sativa* seeds that have anticancer properties [41], poor solubility, and strong hydrophobicity. The preparation of an encapsulating thymoquinone formula with polymers [42], liposomes [43], and cyclo-dextrin [44] can overcome this problem.

Alkaloid

The structural framework for alkaloids containing nitrogen atoms as part of the heterocyclic ring structure supports significant biological activity, for example, ephedrine for asthma, morphine for analgesics, and vinblastine as an anticancer treatment. The alkaloids, vinblastine, vincristine, and vinorelbine disrupt the microtubule network, causing metaphase capture in dividing cells [45], allowing for the preparation of a controlled release formulation that would endure for a long time. However, these compounds have side effects that include hema tological toxicity, wheezing, dyspnea, vomiting, nausea, constipation, fever, chest pain, and tumors. Investigators have recently reported that the application of liposome nanocarrier preparations of vinca alkaloids alleviates these side effects [45, 46].

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Tetrandrine is a bis-benzylisoquinoline alkaloid that induces anti-tumor activity and constitutes a non-selective calcium channel blocker. Since this compound has poor water solubility, its incorporation into the SLN system [47] can improve the formula. Paclitaxel in the gelatin nanoparticle formula is an extremely effective treatment for bladder cancer because the release rate of the active ingredient and its solubility in aqueous media becomes easier [38]. This active ingredient has been certified by the FDA as an effective and non-toxic cancer treatment marketed under the tradename Abraxane.

Anabasine is a piperidine alkaloid derived from the highly toxic *Nicotiana glauca* tree but whose toxicity decreases after formulation with supramolecular nano-encapsulation [48]. Trigonelin is introduced into the chitosan nanoparticles through the formation of an ion complex between the trigonelin's anionic carboxylic acid group and the chitosan cationic amine group to form particles less than 500 nm in size, which inhibit tumor cell invasion [49].

The Epiisopiloturine in *Jaborandi epiisopiloturine* leaves affects adult and young *Schistosoma mansoni* in addition to their eggs and is difficult to dissolve. Therefore, the structure of the liposomes is induced to increase solubility through the addition of dipalmitoylphosphatidylcholine (DPPC)/cholesterol.

Anthraquinone

Anthraquinone constitutes a group of secondary metabolite compounds that occur in abundance in natural materials. Anthraquinones are quinone derivatives of anthracents with a basic structure of 9,10-anthraquinone dicetone. The presence of methoxyl, methyl, hydroxyl, and carboxyl groups attached to the core structure of 9,10-anthracenedione produces anthraquinone derivatives, which have a wide spectrum of medicinal properties [50].

This group contains the largest number of natural pigments, including 700 compounds, 200 of which are isolated from plants (roots, rhizomes, fruits, and flowers), while the rest are derived from mosses and fungi [51]. They are widely employed due to their anti-tumor, anti-inflammatory, diuretic, antiarthritic, antifungal, antibacterial, antimalarial, antioxidant, and laxative properties [52].

Hypericin, a naphthodianthrone (anthraquinone) compound that is a natural photosensitizer, demonstrates high hydrophobicity but limited solubility. The formulation of hypericin solid lipid nanoparticle (Hy-SLN) and the hypericin polymeric nanoparticle suspension is evolved to acquire preferable photodynamic and photoprotection [53].

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Photodynamic therapy has many drawbacks, including poor water solubility and photosensitizer drug toxicity; thus anthraquinone derivatives derived from biotechnology and prepared classic nanocapsule formulations containing polycoating (PLGA) are capable of increasing photosensitizer cell uptake while also being non-toxic [54].

Radix rhei contains less efficient rhein, chrysophanol, physcione, emodin, and aloeemodin. These compounds are formulated in the form of liposomes by ethanol injection method with the result that the entrapment efficiency of the liposomal encapsulation is high [55].

NANOTECH FOR THE DELIVERY OF DIFFERENT PHYTOCONSTITUENTS

The problems faced with regard to herbal formulations are those of moderate solubility in water, poor bioavailability, instability, and toxicity. Nanotechnology is effective in overcoming a number of the difficulties arising from the use of both synthetic and natural drug molecules. This technology has produced acceptable formulas, such as embedded active phytochemicals. Various nanoparticle systems such as encapsulation in the nanocarrier system and the deliverance of active compounds have been applied to support formulations. The different kinds of nanoparticles are dendrimers, solid lipid nanoparticles, liposomes, inorganic nanoparticles, microemulsions, polymer nanoparticles, and nanoflora, among others. This combination of technologies is able to achieve the last stage of active compound examination, thus enhancing the healthcare system.

Nano/submicro medicines ranging in size from 1 to 1000 nm, including liposomes, microspheres, solid lipid nanoparticles, nanoemulsions, andmicroemulsions (Fig. **1**), are frequently employed as herbal medicines, both topically and systemically [56]. This system features controlled hydrophobic and hydrophilic drug delivery, high drug-carrying capacity, superior stability [56, 57], higher surface area proportional to volume [57, 58], and has a small size that supports high skin interactions, increases skin penetration and extends the turnover number of molecules to the targeted sites through active targeting [57,59,60]. Numerous nanoparticle systems composed of biodegradable andbiocompatible materials can be applied to encase toxic drugs and transport themto specific sites around the body.

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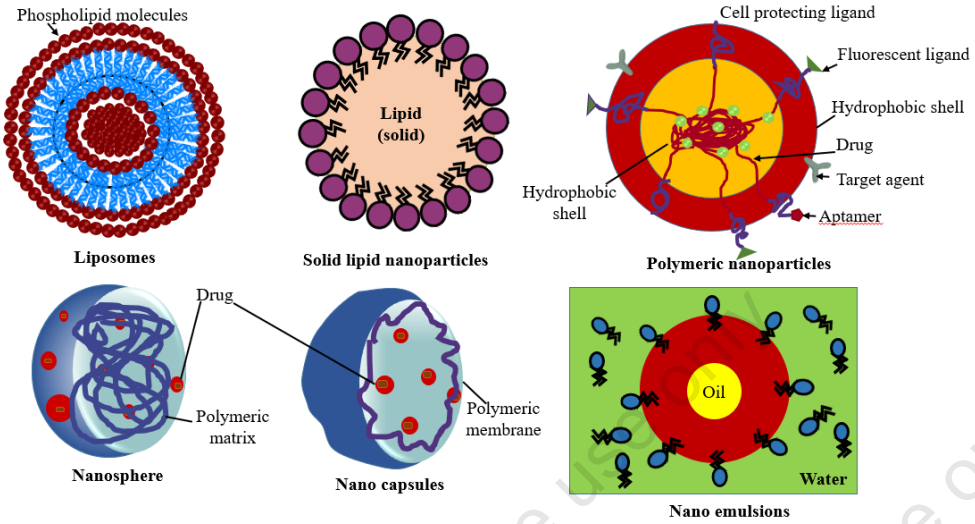

Fig. (1). Overview of nano/sub-microcarriers in herbal medicine [59].

Liposome

Liposomes are tiny vesicles consisting of one or more concentric lipid bilayers (phospholipids) between which an aqueous medium is present. The name ‘liposome’ is derived from the Greek terms, ‘lipo’, which means ‘fat’ and ‘soma,’ which translates as ‘body.’ Therefore, liposomes are described as round objects which are predominantly composed of lipids. Liposomes are categorized as cationic, neutral, or anionic because of their type of surface charge. Variations in shape, size and amount of lamellae contained in liposomes lead to their respective classification as unilamellar liposomes (ULs), small unilamellar vesicles (SUV, 25–100 nm), multilamellar vesicles (MLV), large unilamellar vesicles (LUV, 100 nm to 1 m), multivesicular vesicles (MVV). Liposomes are easily produced by disrupting the lipid membrane in an aqueous medium through a sequence of extrusion (sonication) processes combined with a freezing-thaw process.

Liposomes demonstrate strong biocompatibility and can improve physicochemical characteristics in pursuance of their lipid contexture and value. Vesicles are obtained from natural phospholipids that surround the water core. Liposomes are capable of trapping both hydrophilic and lipophilic medications in the aqueous phase and lipidic bilayer with the result that lipophilic drugs will be highlyefficient given the integrity of the membrane bilayer [33]. Plants and phytoconstituents that have been formulated using a liposome system can be seen in Table **1**.

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Table 1. Liposome in several plants [4].

Plants	Carrier system	Methods	Effects
Cratylia mollis lectin	Soybean-phosphatidylcholine, cholesterol, and stearylamine	Positively charged surfaces	Degraded toxicity and escalated antitumor activity
Quercetin	Egg phosphatidylcholine & cholesterol	Negatively charged surfaces	Efficiency is between 60%–80%
Silymarin	Lecithin and cholesterol	Reverse evaporation	Improved bioavailability and absorption
Breviscapine	Phosphatidylcholine, cholesterol, phosphatidylglycerol and triolein/ tricaprylin	Double emulsification	Prolonged sustained delivery
Camptothecin	3.5-bis (dodecyloxy) benzoic (PO)-polyethylene glycol	Coating the surface	More efficient
A. arborescens essential oil	Hydrogenated and non-hydrogenated soy phosphatidylcholine	Positively charged MLVs and SUVs	A great ability to entice EO (60%-74%)

Liposomes play an important role as a drug carrier system because they can encapsulate polar and non-polar compounds, are stable, have a lengthy shelf life, are manageable, and their biocompatibility and degradability can be regulated. Specific disadvantages of liposomes are their short half-lives and their vesicle integrity being unsuitable for non-polar drugs. Phytosomes are phospholipids of nanoparticles covalently attached to phytochemicals [61].

Liposomes are flexible because they have a lipid structure that can be adjusted to drugs and a surface that can be converted for a specific target and time. The composition is adjusted to increase drug solubility within the encapsulation system [7].

Microemulsion

Microemulsion (ME) constitutes a fluid system consisting of a simple, transparent emulsion with alcohol or medium chains (hexanol, pentanol) dissolved in an aqueous medium and including surfactants produced by the titration method. The presence of surfactants makes the system conditions thermodynamically stable with internal phase droplets at the nanoscale (10-100 nm). The active ingredients in the ME system will become distinct from the dispersion medium *via* the membrane or interface and transferred to an environment that can improve solubility, modular stability, and bioavailability profile. The increased solubility and stability of ME are capable of delivering active constituents with different levels of lipophilic/ hydrophilicity in the same formulation [62].

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An example of the use of microemulsions is that of the triptolide compound contained in the vine *Tripterygium wilfordii* Hook. F (Celastraceae). This plant has anti-inflammatory, anti-neoplastic, anti-fertility, and immunosuppressive properties, but its water solubility is very poor, and it is toxic. It is formulated in isopropyl myristate TP as oil phase, aqueous water phase, and Tween 80: 1,2-propylene glycol as surfactant: co-surfactant in order to increase the permeation profile and anti-inflammatory test [63]. In addition, *Syagrus romanzoffiana* (Cham.) Glassman (Arecaceae) pulp extract is formulated in an o/w nanoemulsion system with squalane as an oil phase and a couple of ethoxylated surfactants with oleic alcohol as non-ionic surfactant, which can increase its antioxidant activity.

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles (SLN) are colloid vehicle systems (50–1,000 nm) containing pure triglycerides and are combined with other colloid systems (emulsions, liposomes, and polymer nanoparticles) to eliminate shortages of active ingredients [64]. SLN has high physicochemical stability and provides protection against the degradation caused by labile drugs [65]. The resulting structures of this system are solid lipids or mixtures, which are stabilized by surfactants [66].

The nanostructured lipid carrier (NLC) is a colloid system that comprises a lipid and solid-phase mixture to form an irregular liquid lipid matrix, increase the encapsulation efficiency, and minimize the active particle excretion during encapsulation [67]. The solid lipid phases of the NLC system feature glyceryl dilauric, stearic acid, hydrine, cetyl alcohol, and glyceryl monostearate, while the liquid phases involve caprylic/capric acid, oleic acid, and glyceryl monodicaprylic. Generally, the manufacture of NLC systems requires 5% of the active ingredient to form part of the initial precursor mixture in order to produce adrug efficiency of approximately 3%-4% orally and 70% topically [68].

The methods of SLN and NLC formulation include high-pressure homogenization (HPH), emulsification-sonification, microemulsions, and solvent evaporation-emulsification techniques.

- HPH method involves melting the lipids so that the medicine is homogeneously dispersed in the liquid lipid. It is subsequently added to the hot surfactantsolution and homogeneously dispersed (pre-emulsified) by means of a sharp mixer. The nanoemulsion is then cooled at room temperature to form crystals. The cold HPH method is the same as its hot counterpart, but the crystallization process uses liquid nitrogen, rendering this technique safe for hydrophilic or thermolabile drugs.

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- The emulsification-sonification method involves dissolving the active ingredient in a thawed solid lipid, adding a warm water surfactant solution, and, finally, dispersing it homogeneously using a high shear mixer. The oil emulsion formed is separated using a sonicator probe according to the nanoemulsion size and then cooled.
- The microemulsion method dissolves the active ingredient in solid lipid and aqueous surfactant/cosurfactant solution that is added during light agitation to produce a clear microemulsion. It is then dissolved in cold water (2-10^{o}C)through light agitation and immediately crystallized to form SLN.
- The solvent-evaporation-emulsifying method works by dissolving lipids in an organic solvent, such as chloroform/cyclohexane, and emulsifying them with aqueous surfactants under continuous stirring.

The results of the utilization of nanostructured lipid carriers and solid lipid nanoparticles in several plants are mentioned in Table **2**.

Table 2. Nanostructured Lipid Carriers and Solid Lipid Nanoparticles in several plants [4].

Constituents	SLN/NLC formulation	Methods	Effects
Quercetin	SLNs (glyceryl monostearate, & soy lecithin)	Emulsification-sonification	Controlled release, increases bioavailability fivefold and enhances absorption within the intestines
	SLNs (glyceryl dibehenate & oleic acid)	Microemulsification	Increases efficiency (92.33%), stability and oral bioavailability
	NLCs (glyceryl monostearate, stearic acid, & soy lecithin)	Emulsion evaporation-sonification	Promotes permeation, increases the number of substances that resist in both epidermis and dermis, and enhances anti-inflammatory and anti-oxidant activities
	NLCs	Probe ultrasonication	Excellent stability
Triptolide (*Tripterygium wilfordii*)	SLNs (tristearin glyceride & stearic acid)	Microemulsification	Improves solubility and absorption into the skin.
Camptothecin	SLNs (cetyl palmitate & polysorbate 80)	Microemulsification	Increases bioavailability
Curcuminoid	SLNs (stearic acid and glyceryl monostearate)	Microemulsification	Improves stability

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Inorganic Nanoparticles

Inorganic nanoparticles are present in inorganic compounds such as ceramics, silver, carbon, and gold. These systems are classified as follows:

- Transition metal nanoparticles (Au, Ti, Pt)
  Transition metals serve as medications in cases where excitation by a radiance occurs, which damages DNA and/or modifies proteins, increases lipid peroxidation, and destroys the cell microenvironment causing death. This method can be utilized for the treatment of cancer, carriers of site-specific toxic drugs [69], and potent catalysts.
- Ceramic nanoparticles (oxides, nitrides, and carbides with silica)
  The system can be used as a hollow or core-shell coated with a biodegradable and biocompatible polymer that enhances targeted delivery properties.
- Carbon nanoparticles.

Liquid Crystalline Systems

Liquid crystal (LC) is a distinct phase between crystalline solid and isotropic liquid (mesophase) in the condensed structure. Mesophases, being cubic or hexagonal, are classified into lyotropic liquid crystals (LLCs) and thermotropic liquid crystals (TLC) [70]. TLC is a mesophase molecule that requires a specific temperature to be converted into an isotropic liquid. On the other hand, LLC is an amphiphilic molecule micelle with a tiny polar oxtail (hydrophilic) and a large apolar oxtail (hydrophobic). Mesophase can be identified using low-angle X-ray scattering (SAXS), low-angle neutron scattering (SANS), cryofracture electron microscopy, neutron diffraction, and reflected light microscopy [71].

LC application of herbal medicine is highly advantageous because it is stable, and interacts easily and optimally with specific targets to create a reliable, effective, and safe drug delivery system, whose distribution is even with the selected administration route and has minor side effects [72]. Vegetable oil is the most useful plant component for the development of this LC system because of its low molecular weight and poor viscosity. Vegetable oils produce low occlusion leading to their easy penetration in the skin and increased loading of therapeutic agents [73].

Santos and Rocha-Filho proved the effect of carbon bond length and the number of ethylene oxide groups on the stability of the nonionic emulsion in vegetable oils and recommended the use of such oils derived from apricot (*Prunus armeniaca*), pequi (*Caryocar brasiliense*), avocado (*Persea americana*), cupuassu(*Theobroma grandiflorum*), Brazil nuts (*Bertholletia excelsa*), mari-gold (*C. officinalis),*

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andiroba (*Carapa guyanensis*), passion fruit (*Passiflora edulis*), and Buriti (*Mauritia flexuosa*). For the LC lamellar crystal stage, polyoxyethylene stearyl ether (Steareth-2; HLB: 4.7) and polyoxyethylene cetyl stearyl ether (Ceteareth-5; HLB: 9.2) acted as surfactants and distilled water as the waterphase. Liquid crystal systems can be used to overcome formulation limitations in plants and phytoconstituents (Table **3**).

Table 3. Liquid crystalline systems in several plants [4].

Plants	Carrier System	Methods	Effects
Andiroba (*Carapa guyanensis* Aubl.)	• Oily phase: dicetyl phosphate, cetearyl alcohol, ceteth-10 phosphate • Aqueous phase: distilled water & PEG-12 Dimethicone	Silicone (surfactant)	Formulation viscosity, or rheological stability
Peach essential oil (*Prunus persica*)	LCs	Oil in water emulsions (o/w)	Improve physical stability
Annatto oil (*Bixa orellana*)	• Aqueous phase: Distilled water • Surfactant: oleth-20	Hydrophilic/lipophilic balance (HLB)	Constructs LC
Marigold oil (*Calendula officinalis*)	• Aqueous phase: Distilled water • Surfactant: nonionic	HLB	Stable formulation
Marigold oil (*C. officinalis*)	• Aqueous phase: Distilled water • Surfactant:polyoxyethylene alkyl/stearyl ethers	Lamellar LC phases	Stability

POLYMER NANOPARTICLES

Polymer nanoparticles are polymer-based formulations whose biodegradability and biocompatibility render them suitable as drug delivery systems because they are easy to control and target [74]. The colloid system of nanoparticles acts as a vector to manage the drug delivery and target it on a specific location. This system can escalate constituent solubility, reduce the therapeutic dose, and improve the absorption of its active components. This system can be applied tothe blood because it involves non-activate neutrophils, is steady, non- immunogenic, non-toxic, non-thrombogenic, non-inflammatory, and avoids the reticuloendothelial route. Natural ingredients are produced in this system because of their ability to provide several active compounds with a similar carrier, , supply a continuous delivery system, and reduce side effects.

Polymer nanoparticles fall within a diameter scale of 10–1,000 nm to facilitate the release of active substances to the target, increase bioavailability, and mitigate side effects [75]. The shape of the nanoparticles is differentiated according to their composition and structural organization in the form of nanocapsules (NCs) and

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nanospheres (NSs). NCs have an oil core and are encased in a polymeric membrane which soaks up the active constituents before they are dispersed throughout the oil base. NSs have a polymer structure that retains or absorbs the active ingredients. The types of polymers widely applied are copolymers with glycolic acid (PLGA) and poly-L-lactic acid (PLA) [76].

The polymer nanoparticle method is categorized as a dispersed monomer method using alkyl cyanoacrylate, *in situ* polymerization method, and polymer deposition methods using polylactic acid-co-glycolic/PLGA, acrylic/methacrylate esters, poly-caprolactone/PCL, polylactic acid/PLA, and methacrylic acid copolymers (Table **4**). The product obtained through the application of these three methods is the aqueous colloid suspension, which has the disadvantage of experiencing precipitation and being physicochemically unstable. This can be overcome by sublimation (freeze-drying) which dehydrates the substance and prevents particle aggregation [74]. Physicochemical characterizations such as morphological assessment, particle size, molecular weight allocation, zeta potential, pH establishment, drug dose in nanostructures, drug delivery kinetics, and long-term stability should be carried out after nanoparticles have been formulated.

Table 4. Polymer Nanoparticles in several plants [4].

Plant/Constituents	Parts	Carrier System	Effects
Phytolacca decandra	Root	PLGA-encapsulated forms (NPD)	Bioavailability is increased, and optimum chemopreventive treatment of lung cancer initiated
Ocimum sanctum	Leaves	Sodium alginate chitosan nanoparticles (OSN)	More effective and durable antimicrobial activity
Curcuma longa (curcumin)	Rhizome	poly(ethylene glycol) mono-acrylate, N-vinyl-2-pyrrolidone, and N-isopropylacrylamide	A significant measured distribution of 50 nm is easily dispersed in aqueous media.
		Encapsulated in PLGA nanospheres	The encapsulation effectiveness is 90.88%, the average particle size is 45 nm and is dissolved in an aqueous without surfactant.
Magnolia officinalis (honokiol)	Bark, leaves	HN-loaded polymeric nanoparticles	Low hydrophobicity and free HN
Gelsemium sempervirens J. St.-Hil (coumarin)	Leaves	Polymeric nanocapsules	Enhanced bioavailability to that of the free active constituent

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(Table 4) cont.....

Plant/Constituents	Parts	Carrier System	Effects
Harungana madagascariensis Lam. Ex Poir	Leaves	Poly (D,L-lactide-co-glycolide) (PLG) nanoparticles	Bacterial growth is reduced
Cuscuta chinensis Lam.	Seed	Nanosuspension	Antioxidant activity is increased
Ginkgo biloba (quercetin)	Leaves	• Polyvinyl alcohol (PVA) • Eudragit® E (EE) of Nanoprecipitation	Improved yield and the efficiency of encapsulation exceeds 99%.
Camptotheca acuminata Decne (camptothecin)	Bark	Hydrophobically modified glycol chitosan (HGC)	Loading efficiency exceeds 80%
Polygala senega	Rhizome	Encapsulated by PLGA.	Bioavailability is increased

Dendrimers

Dendrimers are branched macromolecules with a highly symmetrical/regular nano-size and a structure both homogeneous and monodispersed. Dendrimers are also described as nano-sized globular molecules possessing unique 3D shapes Fig.(**2**), characterized by low dispersity and multivalence with compositions that can be modified according to the desired purpose. Their structure is divided into core, branched repetitive unit layers, and corona. This drug delivery system is preferred due to its flexibility, shape, functional group, size, and a number of generations. Moreover, it is highly attractive [77].

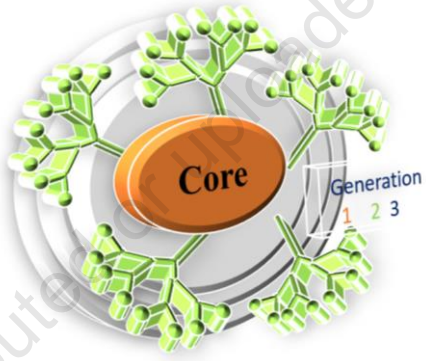

Fig. (2). 3D dendrimer shapes [78].

The mechanism of dendrimer release in drug administration involves the following sequence: (1) drug molecules are trapped in the dendrimer cavity precipitating an increase in hydrophobic molecule solubility, (2) drug molecules are conjugated with functional groups on the outer shell and their delivery rate is controlled. This system has advantages such as the ability to increase the diameter linearly and to

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achieve a rounder shape [76]. In addition, dendrimers can prevent Aβ peptide fibrillation by blocking aggregation. This is evidenced by Wasiak *et al*. by modifying the aggregation of Aβ peptide and MAP-Tau protein in cationic phosphorus dendrimers [78]. Both peptides are the main conducive agents for DA. The presence of a desiccant in the dendrimers system may also reduce the toxicity of aggregated Aβ peptides. The formulation of nanoparticles of phytoconstituents can be seen in Table **5**.

Table 5. Nanoparticle formulation on phytoconstituents [79].

Phytoconstituents	Nano/Submicrocarriers	Effects
Curcumin	SLNs	Oral bioavailability is more effective
Curcuminoids	SLNs	The release of curcuminoids as anticancer and antioxidants is prolonged.
Quercetin	Solid lipid nanoparticles SLNs	Five times greater QU-SLN bioavailability
	NLCs	NLCs have a prolonged-release, and high potency for the dermal release system.
	Liposomes	Antioxidant activity is increased, and the drug release is 74 times higher.
Glycyrrhizin acid	Nanoparticles	The bioavailability of anti-inflammatory and antihypertensive activity is improved.
Taxel	Nanoparticles	Continuous blood circulation and huge accumulation in tumors.
Camptothecin	Nanoparticles	Anticancer activity is improved.
Berberine	Nanoparticles	Sustained drug release and anticancer activity (Fukuda).
Silymarin	Liposome	More effective than silymarin suspension
Artemisinin	Nanocapsule	Anticancer activity

THERAPEUTICAL APPLICATION

Nanoparticle drug formulation development has proved beneficial in the treatment of several diseases such as cancer, AIDS and HIV, in addition, to advances in nutraceutical delivery and diagnostic testing. Nanoparticle size varies from 100 to 500 nm. Nanoparticles can be improved to become intelligent systems, excellent therapeutic and imaging packaging agents, and assuming stealth properties by manipulating the size, surface characteristics, and materials used. This system can conduct drugs to the target tissues and provide controlled-release therapy according to a continuous target in order to reduce the degree of drug toxicity and improve patient compliance [80].

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Cancer

Cancer is a complex disease that is difficult to cure due to the ability of malignant cells to divide and multiply rapidly and uncontrollably. The types of cancertherapy commonly administered to patients, both through drugs and chemotherapy, produce side effects that destroy normal cells such as those in the intestinal epithelium and hair follicles [81]. Nanoparticle development offers the prospect of a breakthrough in chemotherapy through medication delivery to the site of a tumor or a specific cell group to prevent toxic impact on another healthy organ and other tissues [82]. Micelles represent the optimum means of dissolving an insoluble drug because the nucleus is hydrophobic while the shell is hydrophilic. The PEGylated micelle surface enhances the ability of thenanocarrier to pass through tumor blood vessels and inflamed tissue by passive transport, thereby delivering a higher dose of tumor therapy. Examples of polymermicelles, including anti-cancer medications are NC-6004, NK105, NK012, NK911, SP1049C [83], and Genexol-PM [84].

Dendrimer system-based nanoparticle therapy can increase the cytotoxic drug therapeutic index through the use of biocomponents and the reduction in PEGylation, glycosylation, acetylation, and various amino acids [85, 86]. Nanoparticles, namely carbon nanotubes (CNTs), contain allotropic forms of carbon with a cylindrical frame and a number of sheets in concentric**,** which can be categorized as carbon nanotubes with associated walls (SWCNTs) and multiwalled carbon nanotubes (MWCNTs) [87, 88]. Carbon nanotubes have a highly hydrophobic hollow interior through which water-insoluble medications can easily pass.

Rheumatoid

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease of the joints due to persistent polycarticular inflammation in synovial tissues, which causes progressive deterioration of the articular cartilage and bone [89]. RA occurs due to both genetic and environmental factors [90] and an abnormal immune response leading to synovial inflammation and joint damage.

Currently available pharmaceutical drugs are administered *via* conventional dosage forms and provide therapeutic advantages to only a suboptimal level, thus posing challenges and barriers to the treatment of RA. This requires a new drug delivery strategy design for the development of a useful, targeted and safe drug delivery system with enhanced therapeutic performance [89, 91]. Nanomedicines can act as the carriers of drug delivery for effective RA management because they have unique drug delivery characteristics and are considered a very promising alternative to conventional drug therapy [92]. Among the several available RA

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drug delivery routes, topical nanomedicines are more advantageous because of their greater skin retention ability, targeted specific actions, reduced drug doses, lower side effects, increased acceptance, and higher patient adherence [91].

Oral administration of pomegranate extract is an effective treatment for cartilage damage because the extract contains ellagitannins, quercetin, ellagic acid, gallic acid, and polyphenols [93], which support downregulatory activities against JNK-MAPK and NF-jB. Thymoquinone (TQ) from *Nigella sativa* seeds has been shown to produce beneficial effects on inflammatory disorders including IBD,RA, and osteoarthritis [94] through the inhibition of serum IL-1β and TNF-αlevels in RA [95]. Resveratrol is a natural polyphenol compound obtained from grape skin (*Vitis vinifera*) and Polygonum cuspidatum root. Intra-articular resveratrol injection has been demonstrated to have potent effects against arthritis by slowing IL-1-induced apoptosis, ROS, tumor protein (p53), LTB-4, PGE2, andMPPs in animal models [96]. Hesperidin is a citrus flavonoid reported to have therapeutic benefits *vis-a-vis* arthritis through the inhibition of secondary leg swelling and downregulation of TNF-a production, IL-1, and IL-6 [97]. Curcumin is a tetraterpenoid obtained from Curcuma longa, which has anti-inflammatory, antioxidant, and anticancer properties [98]. Green Tea Extract (GTE) produces antiarthritic effects due to the presence of nontoxic epigallocatechin-3 gallate (EGCG) through the inhibition of IL-1-induced delivery of glycosaminoglycans and nitric oxide synthase stimulated by IL-1 (iNOS), nitric oxide, and JNK action [99]. Celastrol is a pentacyclic triterpene of *Trypterygium wilfordii* and has antitumour and anti-inflammatory effects through the downregulation of caspase-1 and inhibition of NF-jb activation [100]. Gambogic acid (GA) is a polyprenylated xanthone containing resin derived from Garcinia hanburyi and Garcinia Morella as an antiarthritic molecule by inhibiting the secretion of IL-1b and TNF. Synomenine is an alkaloid obtained from *Sinomenium acutum*. It is effective for RA therapy by suppressing IL-6, MMP-2, and MMP-9 in an animal model of rheumatism [101]. Centella asiatica contains asiaticoside, madecassoside, centelloside, and asiatic acid (triterpenoids), which are active as anti-inflammatory [102].

The consolidation of phytoconstituents like resveratrol, gambogic acid, thymoquinone, selastrol, hesperidin, curcumin, and polyphenols in a dose-dependent manner has great potential in RA pharmacotherapy through inflammatory mediators such as cytokines, NF-kb, nitric oxide (NO), chemokines, arachidonic acid (AA), adhesion molecules, and lipoxygenase (LOXs). Phytoconstituents have several limitations, such as non-uniform dosage, poor bioavailability, higher metabolism, and greater distribution characteristics. Limited data is available on the concentration of polyphenols in human tissue [103], *i.e.*, 2-20%. The majority of polyphenols are metabolized directly by methylation,

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glucuronidation, sulfation, and elimination by the liver, resulting in low bioavailability [103]. Oral administration of cumin causes low plasma levels as opposed to intravenous administration [22]. Resveratrol is metabolized by the small intestines, with its rapid metabolism [104] being detected in serum and plasma at a concentration of 491 90 ng/ml. Quercetin is detectable in plasma in glucuronides and sulfates unconjugated forms [105]. Herbs for RA have limited solubility and permeability, which have a higher metabolism, and have bothunsuitable doses and poor bioavailability [104, 105]. This bioactive incorporation has low water solubility and high metabolism. These drawbacks can be overcome by using nano/submicrocarrier-based drug delivery technology, which maximizes increased bioavailability, greater stability, and greater efficacy without systemic side effects [91].

To overcome the limitations of curcumin, solid lipid nanoparticles are used to effectively lower leg volume through the regulation of the oxide-inflammatory cascade and immunomodulators [106]. The development of proniosomes containing curcumin (curcumin incorporated into a nanoemulsion gel) by the transdermal route can increase skin permeation fourfold [107]. Poly (lactide-c--glycolide) (PLGA) polymer-assisted nanoparticles on thymoquinone increase the entrapment efficiency to 97.5 [108]. Microemulsion-based hydrogel on synomenine is able to suppress leg swelling through the inhibition of TNF-α, IL- 1, and PGE_2 [109]. Total paeony glucoside (TGP) incorporated into the microemulsion can increase poor oral bioavailability (3-4%) [110], leading to stability in GIT [111]. The development of nanosphere-based hydrogels and solid lipid nanoparticles in Tetrandrine has been proven to increase effectiveness [112]. In addition, the ethosome of this compound has a skin permeation of 2.1 times higher than its liposome form [113]. *Tripterygium wilfordii* Hook F (TWHF) containing triptolide (TP) is incorporated into a microemulsion based hydrogel to increase its narrow therapeutic index [114]. The medical nano/submicrons loaded in the phytoconstituent to reduce limitations in RA therapy are mentioned inTable **6**.

Table 6. Nano/submicron loading to reduced limitations on RA therapy [91].

Phytoconstituents	Nano/submicrocarriers	Remarkable Effects
Curcumin	Solid lipid nanoparticles	Extremely effective for the treatment of arthritis in rats by significantly reducing paw volume through the down-regulation of oxide-inflammatory and immune-modulatory cascade
	Nanoemulsion gel	Fourfold higher skin permeation and skin retention compared to curcumin solution in oil
	Proniosomes	Higher permeation through rat skin detected.

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(Table 6) cont.....

Phytoconstituents	Nano/submicrocarriers	Remarkable Effects
Thymoquinone	Polymeric nanoparticles	97.5% entrapment efficiency (EE) is achieved. Furthermore, higher potency as compared to thymoquinone alone is obtained.
Sinomenine	Microemulsion-based hydrogel	Greater beneficial effects are produced by suppressing paw swelling through the inhibition of TNF-á, IL-1, and PGE_2
Total glucosides of paeony (TGP)	Microemulsion	Bioavailability and stability-related problems are overcome by micro-emulsion, which also enhances drug stability in GIT and absorption
Tetrandrine	Nanospheres-based hydrogel	Absorption enhanced
	Solid lipid nanoparticles	Absorption enhanced
	Ethosomes	2-to-1 higher skin permeation in comparison to liposomes
Triptolide (TP)	Microemulsion-based hydrogel	High efficacy against RA is achieved. Furthermore, no significant toxicity was discovered during the study.
	SLNs	Rat paw volume is significantly reduced, and a protective effect against hepatotoxicity is achieved

Nutraceutical Delivery

Nutraceuticals are standardized components derived from food and consumed as a complement to allopathic therapies, which provide additional health benefits and reduce the risk of chronic disease [115]. The bioavailability and efficacy of nutraceuticals administered orally are influenced by the interaction of the matrix with food, their solubility in water, epithelial permeability, and degradation/metabolism [116]. They are lipophilic molecules that are soluble in fat (A, D, E, and K), and polyunsaturated lipids. Nanoparticle formulations in nutraceuticals [116, 117] can reduce their limitations, enabling their use as anti-inflammatories, antioxidants, antiapoptotic, and antiangiogenics.

The nanotechnology applications of nutraceutical preparations relate to nutrient delivery, food contact materials, nutrient bioavailability, security devices, sensor diagnostics, vitamin and mineral fortification, and nanoencapsulation of flavor and aromas [118], while a summary of the potential formulations of nutraceuticals as nanomaterials can be seen in Table **7**.

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Table 7. Nutraceutical formulations [118].

Phytoconstituents	Nano/submicrocarriers	Remarkable Effects
Hydrophobins (Hyd)- Vitamin D_3	Nanoencapsulation	• A potential nano-transport of hydrophobic nutraceuticals to food beverage enrichment has been discovered using Hyd. • Hyd provides significant vitamin D3 care.
Folic acid with whey protein and commercial resistant starch	Nanoencapsulation	Greater encapsulation efficiency increases folic acid stability. Bioactive stabilization is enhanced.
DL-á-tocopheryl acetate and â-carotene	Pluronic-127 and poly---caprolacotne envelop nanocapsule through emulsification- diffusion method (EDM)	EDM is a promising method for the preparation of nanoparticles for use in food materials
Vitamin D_3 entrapped with whey protein NPs of different calcium concentrations	Nanoencapsulation	Vitamin D3 with significant stability can be used in the clear beverage instead of as an enrichment agent.
Calcium and folic acid	Duel nutraceutical nanomaterial	To provide a good supply of nutrients important to human health
â-carotene, folic acid, curcumin and ergocalciferol	Protein-polysaccharide soluble nanocomplex	To intensify antioxidant activity
Carotenoids	Lipid nanocarriers	The high potency of clinical applications of novel delivery systems for lipophilic plant extracts
CoQ10	Lipid-free nanoformulation	Effective transportation to increase the oral bioavailability of CoQ10
Long-chain fatty acids and CoQ10	Nanoemulsion	Nanoemulsion delivery systems increase the oral bioavailability of lipophilic nutraceuticals
Omega-3-fatty acids and oil-soluble vitamins	Biopolymeric nanogels	• Encapsulation and shield bioactive applied only to food-grade substance • The fabricated system remedies issues surrounding food and beverage quality
Curcumin	Organogel-based nanoemulsion	Digestion of nanoemulsion is rapid and complete The oral bioavailability of curcumin improves Applied to dietary supplements, functional foods, and pharmaceutical industries
á-tocopherol	Supercritical assisted nanosuspension	Improves dissolution rate, bioavailability and stability

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(Table 7) cont.....

Phytoconstituents	Nano/submicrocarriers	Remarkable effects
(-)-epigalocatechin-3-gallate	Protein-polyphenol coassemblies: Lactoferrin based NPs	• LF-EGCG-nanoparticles and submicrometer have a purpose as EGCG protective transport to supervise other bioactive materials release. • LF-EGCG has the potency to develop food formulation based on LF as a carrier of bioactive constituents
Eugenol and clove oil	COM and EM oil titration–precipitation	The formulation in microemulsion provides an oral delivery system for clove oil in homogenous, water-based, and thermodynamically stable doses
Dextran and isoflavone genistein	Enzymatic-assisted inclusion complexation method	• DMSO-water inclusion protocol is more suitable for delivering genistein into enzymatically hydrolysed dextran • Increase the delivery of nutraceuticals by 11- to 141-fold due to the creation of novel H-bonds and the interaction of Van der Waals forces

The impact of nanotechnology on modern life is both profound and powerful. The technological speed of nanomedicine use is achieved by utilizing several kinds of nanoparticles in the prevention, diagnosis, and treatment of a wide range ofcomplex illnesses.Herbal medicines that had been previously struggled with formulation and delivery of their active ingredients are now starting to use the benefits of nanotechnology.Cosmetochem's Herbasec® has been launched as a liposomal standardized extract for use in cosmetics due to its antioxidant effect in preventing aging. Several other plants are also employed in the production of nanomedicines, such as white hibiscus, green tea, aloe vera, white tea, guarana, and liquorice root. There are also several naturally-produced phytochemicals usedas ingredients of nanomedicines such as triterpenes in *Centella asiatica*, visnadin in *Ammi visnaga*, silymarin and Silybin in milk thistle, vhamitenosides in Hawthorn blossoms, escin ß-sitosterol in horse chestnut, sericoside in *Terminalia sericea*, ginsenosides in *Panax ginseng*, polyphenols in grape seeds and green tea,ginkgo flavon glucosides, ginkgolides, and bilobalide in *Ginkgo biloba* [74]. This proves that phytoconstituents represent the future of nanotechnology related to drug delivery, and a new era of re-exploring and investigating the full potency of traditional herbs has begun. The advantages of nanoscience in analyzing herbal medicines include:

- increased solubility and bioavailability of active ingredients
- reducing the side effects and toxicity of active ingredients
- enhancing the stability of active ingredients with regard to targets

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- improving the biocompatibility and reducing the toxicity of the formulations
- increasing nanoparticle safety, and the therapeutic index of the drug

CONCLUSION

Poor absorption of certain phytoconstituents because they are hydrophilic and unable to pass through cell lipid membranes can be overcome by applying nanoengineering such as phytosomes, liposomes, nanoemulsions, nanoparticles, solid lipid nanoparticles, and ethosomes in increasing solubility, bioavailability, pharmacological effect, stability, effectiveness, selectivity, and drug specificity of the bioactive constituents.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 2

Design of Cosmeceutical Drug Delivery System: Role of Nanotechnology in Cosmeceuticals

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Abstract: Cosmeceutical treatments are one of the fastest-growing segments in personal care for conditions, including ageing, wrinkles, hair damage, and hyperpigmentation. Different local and international brands are implementing this nanotechnology to improve the quality and efficiency of their cosmetic products to make them more innovative. It opens new ideas for the cosmeceutical industries. Changes are being adopted in many sectors to make them more attractive at the molecular and atomic levels. Nanotechnology plays a vital role in the cosmeceutical industry as it has many merits, like it improves the bioavailability of drugs and, at the same time, increases the effects of cosmetics. It has many advantages like controlling, penetrating, and sustaining the release of drugs in the skin, achieving a specific target, better efficiency, and stability. The micellar nanoparticle is the upcoming field, whichis added in cosmetic products and is spread worldwide for commercial purposes. It allows the skin to percolate its bioactive component with the most significant surface area. Nano toxicological researchers are worried about the increasing use of nanoparticles in cosmetics as they can cause a health hazard and penetrate through the skin. This chapter uses nanotechnologies in cosmeceutical products, showing different types of novel carriers used to deliver cosmeceutical products that have merits, demerits, and toxicity in products.

Keywords: Biomedical, Cosmeceuticals, Herbal medicines, Liposomes, Nanocarriers, Nanomaterials, Nanotechnology.

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INTRODUCTION

The most impending technology that took place in the 21st Century is nanotechnology. In the cosmetic industry, it is considered to be most important. It is derived from two Greek words; nanos means very small, and techno means technology. Hence nanotechnology is a science and technology that deals with the structure and the techniques that modify and change the particle ranging from 1 to 100 nm [1, 2]. In 4,000 BC, nanotechnology was used for hair dye by Greek, Egyptians, and Romans. In 1959, nanotechnology was widespread in variousfields such as biology, chemistry, and physics [3]. Raymond Reed, Founder of theUS society, had devised the term ‘cosmetics’ in 1961.

Cosmetic can be explained as a product that improves the skin's quality by making it perfect and improves the skin's beauty [4]. Women in western countries were using these cosmetic products as household products in 19-century, and then in the 20th Century, they were used for the protection of the skin. In the 21st Century, cosmetic products are used by applying new ideas and the latest technologies. The Food and Drug Administration re-evaluated the term cosmetic. They explained it as the particle to be applied to the body to beautify, clean, increase the appearance of the skin, and attract the skin. In layman language, cosmetic is referred to as that item that can help to improve the appearance of the skin and its beauty and intensify the skin's cleansing [5, 6]. Shampoo, deodorant, face, hair conditioning and colouring, and a variety of other goods that aid with appearance are all included in the category of cosmetics. In the world of cosmetics, cosmetic products that are filled with biologically active or bioactive ingredients possessing therapeutic benefits on personal human appearance are known as cosmeceuticals [7]. These are specialities among drugs and beautifiers where the items are improved with quantifiable curative efficiency of bioactive parts. The definitions of the cosmeceuticals are expanded from the skin to the body up to hair to utilize them for various medicines, for example, the treatment of skin maturing, hair loss, skin dryness, dim spots on the skin, pigmentation issues, *etc.* Cosmeceuticals are not put in a specific class by the Food and Drug Administration. This term is fundamentally utilized by the skin researcher, doctors, and skincare experts to fulfil the buyers' need to keep purchasing the corrective items, particularly against maturing and sunscreen products [8]. There are now an array of cosmaceutical medicines that treat conditions, such as wrinkles, photo-ageing, hyperpigmentation, hyperproliferation, and hair damage, which have been incorporated into the curative plan [9, 10].

Cosmaceuticals is the fastest-growing segment in the personal care industry [11]. Methods are being developed to enhance and highlight the growth of cosmetic products. Following a thorough investigation, it was discovered that it has

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increased at a rate of 77% annually [12]. In the year 2018, its global market was valued at $49.5 billion. Asian countries like China, India, and Japan are making efforts to spread cosmeceuticals worldwide [13, 14]. Japan makes the most effort, and the segment is improving at a faster rate than the rest of the world. Personal care products and the industries are expanding at the fastest rate in the global marketplace [15]. Nanotechnology has many advantages in cosmeceuticals and long-term benefits for the environment and organisms. However, it has been brought to our attention that the hazards and the toxic nature of the substance are of concern [16, 17]. Many classes related to nanocarriers are nanoemulsion, stablelipid nanoparticles, liposomes, nanostructured lipid carriers, and many more, which are used to deliver nano cosmeceuticals, and they have benefits related to health and skin [18].

Merits of Nanocosmeceuticals

Nanocosmeceuticals have many merits. Different factors like physical and chemical interaction with the composition of the drug, components, additive ratio, ingredients, polymer, and preparation method enables the release of the active substance. They help in the nourishment of hair. Some of the treatments related to hair fall and the processes that help to prevent the hair from getting dull are Identik mask floral repair, Origem hair recycling shampoo, and novel hair loss control shampoo. Products, *e.g.*, Allure Eau perfume, improve the odour and last for a more extended period. The specified cosmeceuticals prevent UV rays and make the skin effective, *e.g.*, sunscreen lotion [19]. The particles from nano-formulations can quickly spread evenly on the skin as the nano-size increases their surface area. With the help of blockage, the skin gets more hydrated and can spread more rapidly. Cosmeceuticals have sensorial properties, and if compared with conventional sources, are comparatively more natural and adequate. Few nano preparations fit for both hydrophilic as well as lipophilic drug delivery. These are also used as antiwrinkle creams, whitening cream, hair loss repairing shampoo, and for many more uses [20].

Demerits of Nano Cosmeceuticals

Nano cosmeceuticals have many demerits. These are:

1. Nano cosmeceuticals cause damage to proteins, membranes, and DNA by using more and more oxygen species.

2. Some of the ultrafine nanomaterials can be harmful to the tissues of humans. They are TiO_2, carbon-based fullerenes, silver and copper nanoparticles.

3. The sunscreen used to protect from UV rays can cause harm to RNA, DNA,

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and fat present inside the cell as this sunscreen contains titanium dioxide.

4. It can cause damage to the environment.

5. Nano cosmeceutical has not been subjected to clinical trials, hence they can be harmful or toxic after use [21, 22].

NOVEL NANOCARRIERS IN COSMECEUTICALS

For the delivery of the Nanocosmeceuticals, a carrier technology provides the best approach by using active ingredients [23, 24]. The nano-preparations used as cosmeceuticals are as follows:

Niosomes

Cholesterol and non-ionic surfactants and other components related to these preparations can improve chemical stability, reduce production cost, and enhance penetration. The diameter of niosomes is 10-100 nm if studied under morphology. It is a microstructure with the centre forming layers of non-ionic surfactant in the lamellar phase [25]. It helps to deliver the compounds of both hydrophilic and hydrophobic nature. In this technique, the components are delivered to the desired place where the therapeutic effect is required. Niosomes act as carriers for delivering active ingredients in the stratum corneum and epidermis [26]. These are also used as devices to improve the content of absorbable drugs in case of novel drug delivery systems. It is also used in cosmetic products and skin applications as it has the property to remove the obstacle of the desired layer and enable it to go through the skin's living tissues. There is a need to increase the availability of ingredients already absorbed by the skin.

The factors that help in improving the formation of these preparations are the nature of encapsulated drug, temperature of hydration, shape, size, and the composition of the membrane. A niosome is a non-ionic type of surfactant vesicle that is hydrated before dispersion, also known as a proniosome. Proniosomes are used where there is a need to add drug delivery with the conventional approach [27]. Loreal developed niosomes through the research and development of synthetic liposomes in 1970 and got the trade name ‘Lancome’. Several products related to this category are sold worldwide, *e.g*., hair repairing shampoo, antiwrinkle cream, conditioner, moisturizing cream, and skin whitening [28].Various marketed formulations of niosomes and their uses are given in Table **1**.

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Table 1. Various Marketed formulations and uses of niosomes [25]

Product name	Marketed by	Uses
NIO-OXY	Naturalis	Skin lightening, Neck, and décolleté treatments
NIO-GLUCAN	Naturalis	Antiwrinkle, suncare
NIO-HYDRAN	Naturalis	Moisturizing day and night care
NIO-LIPACTIVE	Naturalis	Anti-Cellulite products, antioxidant
NIO-OLIGO HA	Naturalis	Anti-wrinkle, moisturizing, structuring and firming, regenerating and repairing.
Identik Shampoo Floral Repair	Identity	Hair repair shampoo
NIO- SEBACTIVE	Naturalis	Anti-sebum, oily skin, anti-acne

Liposomes

These are lipid bodies with two layers in the closed compartment of an aqueous solution [29]. The lipids used in liposome preparation are glycolipids, phospholipids, sterols, and sphingolipids. The size of these preparations ranges from 25 to 5000 nm. They can be used and prepared through the biological membrane by disrupting it [30]. These are biocompatible, flexible, visible, non-toxic, and biodegradable and are used in many cosmetics preparations. These are excellent for delivering both hydrophilic and hydrophobic compounds as they have quality to prevent encapsulated drugs from outside environment [31]. They fulfil one more objective of regenerating the epidermis. Phosphatidylcholine is used in products related to the skin and is also the main component for liposomes. Some ingredients used in liposomes, such as vitamin E, A and K, lycopene, *etc.*, help to improve physical, chemical and storage stability when mixed with water [32, 33]. Ceramides and cholesterol have been used in skin creams from several years as they help in making the skin look smoother, younger, and shiner. Thefirst liposomal anti-ageing cream was discovered in 1986 by the scientist Dior [34]. The name of this anti-ageing cream was ‘Capture’. Liposomes are formed to deliver pleasant smell formulations like deodorant, body spray, lipstick, antiperspirants, *etc.* These are used in various creams like sunscreen, hair cream, beauty cream, and many more. Different marketed formulations of liposomes and their uses are described in Table **2** [35, 36].

Table 2. Various Marketed formulations of liposomes and their uses [25].

Product name	Marketed by	Uses
Christian Dior Capture Totale Multi-Perfection Creme	Dior	Removes puffiness and dark circles, smooths wrinkles

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(Table 2) cont.....

Product name	Marketed by	Uses
CAPTURE TOTALEserum	Dior	Younger, stronger, and glowing skin
Decorte Moisture Liposome Face Cream	Decorte	Skin Moisturiser, anti-ageing
Decorte Moisture Liposome Eye Cream	Decorte	Dark circles
Moisture Liposome	COSME DECORTÉ	Changing skin destiny, skin toner
C-VIT Eye Contour Cream	Sesderma	Tightens the skin around eyes, bright skin
Liposome Treatment Liquid	COSME DECORTÉ	Skin moisturizer
C-VIT Revitalizing Gel Cream	Sesderma	Antioxidant increases skin luminosity and vitality, helping dull skin come back to life.
Luminescence Rejuvenating Eye Creme	Aubrey Organics	Dry skin, reduces the appearance of dark circles
Russell Organics Vitamin C Serum	Russell Organics	Reduces hyperpigmentation
Clinicians Complex Liposome Moisture Mask	Clinicians Complex	Hydrates with hyaluronic acid, energises a dull complexion, delivers essential vitamins and nutrients
Kerstin Florian Rehydrating Liposome Day Crème	Kerstin Florian	Antioxidants and anti-inflammatory botanicals for the delicate eye area, Moisturizer

Nanocapsule

L'Oréal discovered the first nano capsule-based cosmetic product in 1995 that improved and increased the quality. This preparation comprises the polymeric membrane in a liquid core at the level of 10 nm to 1000 nm [37]. It is used in the vesicular system and in cosmetic-related products because it removes unwanted odours, reduces unwanted components, and protects the skin's sensitivity. An example of a nano capsule-based product is an antiwrinkle lotion with vitamin A [38]. Applying nanocapsules containing octyl methoxycinnamate on the skin reduces UV penetration and increases skin quality [38 - 40]. A nanocapsule is used as a carrier for a sunscreen containing octyl salicylate, benzophenone-3, and octyl methoxycinnamate [41]. It provides a protective layer on the skin's surface and remains active in the sunscreen auto viable layer. Polymer polycaprolactone (PCL) is used in preparing the nanocapsule of octyl methoxycinnamate (OMC) that provides a protective cover for Ultraviolet-B (UVB) radiation. Studies show that nanocapsules containing oxybenzone reduce UV rays' penetration through the porcine ear, hair, or skin [42].

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Lipid Nanoparticles And Lipid Nano-Carriers (SLN And NLC)

In recent years, solid lipid nanoparticles have been increasing in popularity worldwide. The two necessary types of lipid base are NLC and SLN. SLN has been proved to remove or reduce the side-effects of different collateral vehicles, *e.g.*, polymeric nanoparticles, emulsion, and liposomes. SLN helps to the delivery of the drug by physical reliability [43]. To improve the effectiveness of conventional lipoidal carriers, *e.g.*, liposome and emulsion, an unconventional carrier system, SLN(solid lipid nanoparticles), was discovered in 1990 with the size ranging from 50 nm to 1000 nm. SLN comprises a unit layer of the shell with an oily core innature. In this matrix, drugs consist of solid lipids dissolved in the layer of the solid core matrix [44]. The fat matrix consists of hydrophobic chains of phospholipids. These are made from the compounds like waxes, purified triglycerides, and mixtures of glycerides. The mixture of liquid-lipid is converted into solid-lipid that is solidified at room temperature. The high-pressure homogenization and precipitation methods are the two main methods that help in the preparation of SLNs. Controlled release and sustained release SLN that are also formed by using these techniques significantly increase drug release for a longer time [45, 46]. They are UV rays blockers and help to sunscreen lotion by reducingits harmful effect. In an *in vivo* study, it has been proven that skin hydration level is increased after four weeks by adding 4% of SLNs to a conventional cream. It is used as a vehicle in the perfume to provide a prolonged fragrance effect [47].

NLCs can be used in the coming generation as an SLNs because they improve the stability and increase the potential in the loading of the drugs. It has morequalities like increasing the skin's water content and preventing the active composition against chemical degradation. It has been seen that LNPs as vehicles are being used in the products like anti-ageing, anti-acne and sunscreen [48]. These also possess skin hydrating and UV blocking properties. One more advantage of using these preparations is that they have no harmful effects and are non-toxic in nature. Lipid nanoparticles are nanoparticles composed of lipids and are novel pharmaceutical drug delivery system for pharmaceutical formulation. Solid lipid nanoparticles comprise of a solid lipid core matrix that can solubilize lipophilic molecules and emulsifiers [49]. Various marketed formulations of NLCs are given in Table **3** [25].

Table 3. List of various Marketed products of NLCs.

Product Name	Marketed by
Regeneration cream	Scholl
Intensive serum Nanorepair Q10	Dr. Rimpler
Iope super vital extra Moist eye cream	Amore pacific

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(Table 3) cont.....

Product name	Marketed by
Surmer Masque Crème Nano-Hydratant	Isabelle Lancray
Olivenöl Augenpflegebalsam	Medipharma cosmetics
Olivenol Anti-FaltenPflege	Medipharma Cosmetics
Regenerations Cream Intensive Ampoules	Scholl
Swiss Cellular White Illuminating Eye Essence	La prairie
Surmer Crème Legère Nano-Protection	Isabelle Lancray

Dr. Rimphel GmbH's Nanorepair cream and Nanorepair serum were the first two products containing solid lipid nanoparticles utilised by cosmetic businesses in October 2005, providing skin penetration. There are currently more than 30 differentNLCs containing cosmetic products in the market [50].

Nanogold and Nanosilver

"Gold and silver nanoparticles have potential as antifungal and anti-bacterial, and these are considered as an essential material in cosmeceutical products." They are used in products like face packs, deodorants, anti-ageing creams, *etc.* [51]. An ointment having silver nanoparticles can be used for skin wound disinfection and skin inflammation due to its anti-bacterial properties. Gold particles and gold nanoparticles have different properties as gold particles are yellow in colour and bigger in size, whereas gold nanoparticles have antioxidant nature with wine red colour. Gold nanoparticles are of different sizes varying from 1 nm to 8 nm and are present in different forms like spherical, multiple twined, irregular shape, nano-triangles, nanoprisms, hexagonal platelets, octahedral, *etc.* Gold nanoparticles (GNPs) have high stability, are non-cytotoxic, inert, and biocompatible [52 - 54]. Nanogold is present in both conjugated as well as unconjugated forms and is stable in dried form. They can be easily moved from one target cell to others because they have specific properties like shape, small size, shiny appearance, and large surface area. The nanogold particles are used in many cosmetic products such as deodorants, face packs, anti-ageing creams, lotions, *etc.* Some cosmetic companies use gold nanoparticles to increase the quality of their products. The utilization of GNPs has made skin immunizationand transdermal delivery more effective [55]. GNP's main characteristics are anti- septic, skin elasticity, vitalizing skin metabolism, smoothness, and delaying ageing. After the research, it has been proved that gold nanoparticles can also be used for human hair treatment [56, 57]. GNPs have an excellent soaking property in white hair in the solution containing compounds of gold. The colour of hair turns into pale yellow and then into a deep brown. These particles are formed in the central core cortex of the hair, as studied by electron microscopy, and the colour remains for a more extended period [58].

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Nanoemulsions

A nanoemulsion is a mixture of two non-miscible liquids that form droplets of nanometric size in an aqueous solution. Nanoemulsion has a better loading capacity than microemulsion [59]. The pharmaceutical industries get more benefits from an anisotropic dispersed system. Nanoemulsion is referred to as thermodynamically stable dispersion when combined in water and oily phases. Nanoemulsion moulds the product aesthetically and gives a better product having good stability. Its size ranges from 50 nm to 200 nm [60]. The advantages of nanoemulsions over macroemulsions are that they exhibit no flocculation, sedimentation, or intrinsic creaming. Nanoemulsions play a significant role as these are used in cosmetic products like skin lotion, sunscreen, and body lotion. They have high solubilization capacity, kinetic stability, low viscosity, and interfacial area. In cosmetic products, these help in hydration of the skin. These are also used in wet wipes and the nanogel system. They are being used in baby care products and makeup cleansers [61 - 63]. A list of different marketed formulations of nanoemulsion and uses are given in Table **4** [25].

Table 4. Different marketed formulations of nanoemulsion and uses.

Product Name	Marketed by	Uses
Hair Sun Protection	Korres	Prevent hair colour from fading away
Nanocream®	Sinerga	Formulation aid
Vital Nanoemulsion a-VC	Marie Louise Cosmetics	Hyperpigmentation
Bepanthol Lotion Ultra Protect	Bayer HealthCare	It soothes itchy skin and provide ingredients such as lipids and vitamins.
CHANEL Coco Mademoiselle Fresh Moisture Mist	Chanel	Moisturises the skin
Coni Beauty Hyaluronic Acid Ultra Hydration	Coni Beauty	Relieves dryness
Rhonda Allison Phyto Endorphin Hand Cream	Rhonda Allison	Tissue degradation, lessening discolouration and aging spots
NanoVital VITANICS Anti-Wrinkle Eye Cream	Vitacost Cosmetics	Anti-wrinkle, moisturizing, and elastic effects

Nano Sphere

These are spherical-shaped particles that have the structure of a core shell. Its diameter ranges from 10nm to 200nm. It is amorphous in nature. The drug is prevented from degradation by chemical and enzymatic modes and trapped in a capsule of the polymer matrix [64]. This drug is being disposed of in the polymer

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through a matrix system. Biodegradable and non-biodegradable nanospheres are the two categories of these preparations. Some of the examples of biodegradable nanosphere are modified starch nanosphere, albumin nanosphere, and gelatin nanosphere [65] and polylactic acid nanospheres are non-biodegradable. These are used in skin-related products as these help in penetrating the skin layers and provides an excellent effect on the required area. These also protect actinicageing. These are used in anti-acne, antiwrinkle, moisturizing creams, *etc.* [66].

Dendrimers

The dendrimers' terminals have a rich supply of surface functionality for nanoparticles [67]. Their lengths, with diameters in the range of 2 to 10 nm, are extremely thin. Dendrimers are an innovative new class of macromolecular architecture and are essential in the field of nanotechnology-based cosmeceuticals [68]. These are organic chemical bodies having a semi polymeric tree-like formation. Carbonsiloxane dendrimers are considered a 'luxury' they provide hair and skin with water- and sebum-proof smoothness, as well as act as adhesive substances [69]. Nowadays, a novel dendrimer that consists of hydroxyl functional groupshas its use in cosmetic products as it helps to form a thin, soft layer, increases the texture of the skin, and cleans the dirt from the skin. Dendritic macromolecules are mixed with polyhydric polyester alcohol and have been patented to be used in gel, giving style to the hair [70]. In conjunction with film-forming polymers, "dendritic macromolecules with terminal hydroxyl functional group polyester haveproduced a superior cosmetic substance with right consistency and ease of use. The formula has been patented for use on the scalp, keratin fibres, hairs, ormucous membranes by L'Oreal [71]. The compound is non-penetrating to the skindue to the resultant molecule's high molecular weight, "which minimizes thechance of inflammation or sensitization reactions when exposed to the skin. The chemical compound amine-terminated cationic dendrimers are used as amildening agent in personal care cleaning materials. They display odour-absorbing properties and are known as active agents of deodorant. Formulations containing amine-terminated dendrimers and a tanning agent may improve the strength and consistency of developed skin colouration and provide a shade similar to a natural tan. The use of cationic dendrimers in cosmetic formulations containing harsh anionic surfactants can minimize skin irritation [72]. They preserve the dispersion in the salt solution and interfere with the composition of anionic surfactants to avoid "the reduction of skin lathering, skin conditioning or washing caused by the precipitation of anionic surfactant mildness agents (linear cationic polymers). In prescription delivery systems, surface-modified dendrimershave also been used. As carriers for optimizing anti-acne agents' delivery, dendrimers containing free amino groups have also been used [73, 74].

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Nanofibres

These are the small substances that are made up of solid nanomaterials, with the size ranging from 5 nm to 500 nm. These have a porous structure consisting of a large surface area per unit mass. Their wide area of surface provides sufficient active sites for reactions. Improved properties are given by structural alteration of nanofibers, such as improved mechanical strength and greater flexibility than any other substance type. The technique of electrospinning has been used to manufacture multiple fibre assemblies. This technique will be able to manufacture an extensive range of polymers, such as chitosan, polyvinyl alcohol, collagen, gelatin, and carboxymethylcellulose [75]. Nanofibers have shown promise in different biomedical fields, such as medication and gene distribution, artificial blood vessels, and artificial organs. As cosmetic skincare masks for skin regeneration and skin cleaning; the functionalized and the non-functionalized nanofibers prepared with electrospun polymer have been used. They are also used for dressing the wounded area. They help in increasing the penetration of active ingredients into the skin and improve the efficiency of the drug as they have a high surface area [76].

Polymersomes

Polymersomes are artificial vesicles enclosed in a central aqueous cavity consisting of self-assembled block copolymer amphiphiles. The lipophilic bilayer and the hydrophilic inner core are used in both hydrophilic and lipophilic drugs. It is in an affable protein state being created by the hydrophobic core. They should have a radius ranging from 50 nm to 5 μm or more. Most of the identified polymersomes contain an aqueous solution in their center and are very useful for encapsulating and defending sensitive molecules, such as drugs, enzymes, other proteins and peptides, and fragments of DNA and RNA [77]. Their flexible nature makes it possible to control the release of the drug. Polymersomes are much better than liposomes as they contain rigid bilayers. They are mainly used in cosmetic products that are manufactured in the cosmetic industry [78].

Cubosomes

Cubosomes are specialized nanostructured particles with isolated surfactants that are submicron, and self-assembled liquid crystalline particles with a proper water ratio that offers distinctive properties [79]. Cubosomes are a bi-continuous cubic liquid phase that contains two distinct water regions separated by bilayers controlled by surfactants and wrapped into a three-dimensional, periodic, and minimal surface, forming a densely packed structure. Its size ranges from 10 nm to 500 nm. They consist of a (cavernous) honeycombed structure and appear as dots that are slightly spherical in structure. Laboratory studies try to use cubosome

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fragments as oil-in-water emulsion stabilizers and pollutant absorbents in cosmeceuticals in partnership with cosmetic companies such as L'Oreal and Nivea. Cubosomes are used in numerous areas, including food science, differential geometry, biological membranes, and digestive processes. Cubosomes are vulnerable to drug delivery because they can integrate, distribute and secure medications or cosmetic elements with different polar characteristics [80]. Their applications are in great demand in the Pharmaceutical industries [81].

MAJOR NANOCOSMECEUTICAL CLASS

Cosmeceuticals are considered the fastest growing market in the field of personal care. Nanotechnology is a field that deals with the development of materials and technologies on the scale of atoms and molecules, as well as the research and development of new ideas. Nanoparticle or ultra-fine particle is usually defined as a particle of matter between 1 nm to 100 nm [82]. Nanoemulsion is an emulsion of nano-sized emulsion that is produced to improve the delivery that deals with pharmaceutical ingredients. They are thermodynamically stable isotopic systems related to any two immiscible liquids combined to form a single-phase utilized by an emulsifying agent [83].

Skincare

Cosmetic products are also used to improve the skin's texture and help in developing collagen by removing harmful agents from the skin. The keratin treatment for the skin helps in making it shiny and healthy [84, 85]. Titanium dioxide nanoparticles and zinc oxide are being added to the sunscreen product to protect the skin from the UV effect and make the product transparent with less or no smell. Many novel components are added to the moisturizing cream so that the moisture remains in the skin for a more extended period and forms the thin layer of humectant on the skin surface, *e.g*., liposome, nanoemulsions, niosomes, SLNs, *etc.* Some products are being sold in the market for anti-ageing in the form of nano-cosmeceutical products that provide specific merits to the skin like smoothening, reducing swelling, and restoring skin collagen [86 - 88].

Haircare

Nanotechnology has also shown remarkable progress in the hair care industry. Nanotechnology is applied to hair care products in order to make hair healthier, silkier, shinier, and stronger. The hair straightening products destroy the outer layer of the hair and make them soft. Nanoemulsion is added to cosmetic productsto make the hair healthy [89, 90]. Conditioning the hair helps in improving and making them look soft, shiner, glossy, and makes the hair roots stronger. Novel carriers based on

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nanotechnology have the properties that help in repairing the damaged hair and improve its texture, shine and strength. These novel carriers are nanosphere, microemulsions, liposomes, niosomes and nanoemulsions [91].

Lip Care

The customers use various lip products like lip balm, lip gloss, lipstick, *etc*. These products are being manufactured by nano cosmeceutical industries [92]. The products and compounds that are added to the lip products help in protecting the pigment from getting removed from the lips and maintain the lip's colour for a maximum number of days. Lip volumizer helps in increasing the volume of the lip, outline the lip's portion, adds or fills wrinkles in the lip control, and hydrates the lips. Nanocosmeceutical lip volumizer contains liposomes and helps in making lip soft through trans-epidermal water loss [93 - 95].

Nail Care

Nanotechnological-based nail cosmeceuticals are much better than conventional products. It has been shown that these consist of nano-sized particles that help in improving the nails' toughness [96]. Nano Laboratories Corporation'scontributions to nanotechnological research and development have been appreciated, and the patent has been granted as ‘nano nail polish’. It has the advantage of drying at the end of the process, preventing cracking/chipping,resisting shock, and minimising scratching [97]. It also helps in applying the nail paint quickly without breaking. Quantum dots (QD) are minute, approximately 10nm or even less, and have many novel advantages [98, 99]. They can be transported and transferred to the different drug systems by controlling them and using the electromagnetic tool. QD technology is used in the treatment of nail- related disorders [100 - 103]. It has been shown that nail oil is being made, which can be used to change the colour and pattern of the nails [104].

NANOTECHNOLOGY IN HERBAL DRUGS- NANOPHYTOMEDICINE

The main components of nanophyotomedicines are standardized extract or phytocomponents. It also reduces the toxicity and harmful effects of the given drugs. As a result, the drug's productivity and demand are much more.

Nanocurcumin

It is a fat-soluble molecule that has weak stability in water. It also reduces its availability by metabolizing at a faster rate. Because of this reason, scientists have found a new method that helps in providing more advantage through a usable form and increases its utility, like in super curcumin. The small curcumin particle encapsulated by the membrane present in the oil cavity is used to correct it. It is

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helpful as it is considered as the best absorber, and its release is reduced in the bloodstream by increasing its availability. The studies in animals and *in vitro* have demonstrated that curcumin has anti-inflammatory, antioxidant, anti-arthritic, and antitumor properties. *In vivo*, pharmacokinetic studies have proven that if we compare curcumin entrapped nanoparticles with piperine, it has a minimum of nine-fold that help in increasing the oral bioavailability and works as an absorption enhancer [105].

Green Nanotechnology (Cumin- Mediated Gold Nanoparticle)

The toxic chemicals are used in these days in the process of nanoparticles production either as a stabilizing agent that prevents NP from agglomeration or in the form of a reducing agent that decreases the different metal salt for their nanoparticle. For example, sodium borohydride and hydrazine are used as reducing agents that reduce the gold reaction to produce gold and different metallic nanophytomedicine. Both hydrazine and sodium borohydride are harmfulto the environment as well as living organisms. It synthesizes its utility in plant- based phytochemicals. Nanotechnology is often referred to as green technology because of its relationship to plant indicators that provide the green approach. Carboxyl, alpha and beta-pinene, cumin alcohol, amino, thiol, *etc.*, add the properties of different phytochemicals present in a functional group inside cumin that helps in the reduction of power for reducing the gold salt to the corresponding gold nanophytomedicine. Scientists have verified through their experiment that noother individual constituent in reducing and stabilizing gold nanophytomedicine. At the same time, the chemical that is responsible for synthesizing the gold nanophytomedicine in an aqueous medium is the cocktail of the complete chemical with gum Arabic [106].

Ayurvedic Bhasma

The oldest form of nanotechnology that Ayurveda uses to treat different types of disease is a nano preparation Bhasma. This technology has been used for centuries. It is used in modern nanomedicine prepared from the metal used in different scientific processes that convert raw material into the therapeutically active form. This procedure is carried out on a regular basis by mixing theincineration of various herbal juices with the specified drugs. Its properties keep changing because of too small size. It is because of optical, electrical, biological, chemical, and organic changes. The therapeutic form of the gold metal that is made of nanoscience particles is Swarna Bhasma [107].

Aloe Vera Extract in Nanoparticles

The extract of aloe vera added to the cream and gel is used for taking care of the

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skin and curing dryness, scaling, dermatitis, anti-ageing, eczema, and flaking. Scientists in Japan have recently found that the extract of aloe vera is not able to cross the stratum corneum. The use of such hydrophilic chemicals in the skin supresses the imperishable barrier of stratum corneum, which is made up of an intercellular lipid domain and a protein that are rich in non-viable cells. The solution for this problem is to increase the dose for the skin, but it can result in inflammation. They also studied that the aloe vera liposomal form can enhance penetration and has a diameter of less than 200nm as verified by the *in vitro* testof human skin fibroblast and epidermal keratinocytes. Collagenase synthesis has been increased with 23% of liposomal extract when compared to 4% of the non- encapsulated extract [108].

EMERGING CHALLENGES AND POTENTIAL SOLUTIONS

The use of nano-sized herbal medicine improves the quality of biological activity and solves the issue related to pure herbal drugs. The problems related to the development of nanotechnology-based drug delivery system comprises of the productivity of the scale-up process. It brings new ideas for therapeutic techniques at the market rate and increases the chances of providing a multifunctional system to solve the basic biological and therapeutic requirements. However, it can lead to toxicological effects. Nanotoxicology refers to the branch of toxicology related to the unpredictable effects of nanoparticles. Even in the oldest techniques, new ideas have been applied to improve the quality of life for patients as well as to increase their efficiency. Using nanotherapeutic products is a more complicated and expensive method when compared with conventional alternatives, which results in an increase in the overall healthcare cost.However, the cost of healthcarecan be reduced by increasing productivity, preventing diseases that require expensive treatment, reducing personal healthcare costs, and reducing the length of inpatient stay. Many more new challenges are being faced, like fulfiling or meeting the international standard for biocompatibility and the aim for nanoparticle efficiency [109].

Cellular Toxicity of Zinc Oxide and Titanium Dioxide Nanoparticles

Minghong Wu and coworkers at Shangai University discovered that zinc oxide nanoparticles added to sunscreen can damage or kill the stem cells present in the brains of mice [110]. Wu *et al.* investigated the neurotoxicity of zinc oxide nanoparticles in cultures of mouse neural stem cells treated with nanoparticles starting from a range of 10 to 200 nm [109]. It has been found that zinc oxide nanoparticle forms dose-dependent but does not have size-dependent harmful effects on neural stem cells NSCs after investigating it completely for 1 day. The NSCs have reflected clear signs of apoptosis through flow cytometry, confocal

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microscopy,and transmission electron microscopy analysis. Arnaud Magrez of the NN Research Group discovered that titanium dioxide-based nanofilaments have cytotoxic effects, which is enhanced by the presence of defects on the nanofilament surface caused by chemical treatment. Internalization of nanofilaments and alterations in cell morphology have been observed [111].

Occupational Risks of Nanoparticles

Workers can be exposed to nanoparticles or nanomaterial products at the time of their manufacturing through their use, recycling, or disposal. Production, handling facilities, maintaining research, and cleaning can also lead to their exposure. Kaewamatawong calculated the power of nanomaterial compared to the micro-sized particles. Currently, there is no complete information on the total number of workers exposed to the nanomaterial particles in working area, which affects their mental health. The European agency emphasises workplace safety and health. Because nanomaterials are being incorporated into consumer products for their purpose, there are greater chances of exposure to consumers [112].

Environmental Risks of Nanoparticles

The environment is at a greater risk as these particles at the time of production, use, or disposing get mixed with air, soil, and water. If the nanomaterials are anti-bacterial in nature and are present in large amount, they can affect the bacteria in sewage and water treatment plants that contaminate water for its reuse. For example, it has been found that the toxicity of TiO_2 nanoparticles causes harm to the main body system of rainbow trout [113]. In less than an hour of exposure, nano titanium dioxide used in personal care products reduces the role of bacteria, as discovered by the University of Toledo. It is also found that it reduces a microbe that plays a significant role in the treatment of wastewater and the ecosystem. After examining carbon fullerenes, It has been shown that they can harm the brain in largemouth bass, which has been used as a model for describing the ecotoxicological effect by regulatory agencies.Fullerenes have been found to remove water fleas as well as bactericidal properties. The tendency of nanoparticles that holds the contaminating substances present in the environment like petrochemical and cadmium is being focused on byRice University - Center for Biological and Environmental Nanotechnology. It will improve the impact of this study for a long time and check the transport of pollutants in groundwater [114].

Potential Solutions

The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIC) discusses the risk management methodologies applicable for the assessment of potential adverse health and environmental impacts of nano-

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technology products, as well as the nanomaterials [115]. New test techniques includes the basic characteristics of nanomaterials to determine the pathways of possible damage that they may inflict. The following are the key criteria that are tested for the protection of nanomaterials:

Physical-Chemical Properties

Properties such as height, shape, basic surface area, agglomeration status, size distribution, surface morphology, density, solubility, and chemical properties such as structural formula/molecular structure, nanomaterial composition, phase identification, surface chemistry, hydrophilicity/lipophilicity must be analyzed [116].

Mathematical Modelling

These prediction models differ from standard analytical algorithms in that they add complication to mathematical equations by requiring the calculation of an experimentally inaccessible parameter. However, because no data on macromolecular compounds or particle composition are used in either of these models, it cannot be used with certainty to determine what might happen when those entities come into contact with the skin [117].

Microscopic Techniques

The microscopic analysis of the skin following treatment from *in vitro* experiments can gain more valuable knowledge. Although measuring the tissue to which an active agent is added may be impractical, the visualization may provide useful insight [118].

In Vitro Methods

While a range of alternative approaches and technology are available to research the molecular processes involved in the biological action of compounds, only validated methods for cosmetic products are allowed. These proven approaches can be used to evaluate cosmetic ingredients where testing is needed [119].

FUTURE PROSPECT OF NANOTECHNOLOGY IN NANO COSMECEUTICALS

Nanotechnology is becoming increasingly popular in modern cosmetics. Increasingly creative use of nanotechnology-derived materials is being acknowledged. This section discusses a number of the sophisticated applications that will help in revolutionizing the cosmetics industry. Sustained and controlled sunscreen release may likely be created, with increased moisturizing and anti-

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ageing properties. Several upcoming distribution technologies are being considered for a variety of functional purposes. Although others will not make their way out of the laboratory, some cosmetic products may bring tremendous improvement. Carbon nanobuds with combined carbon nanotubes and fullerenes have been described as rare nanomaterials. Carbon nanotubes and fullerenes, two of the most natural carbons, are made through allotropization. Carbon nanotubes are bound to fullerene as "springs/buds." They can be seen in lipsticks and mascaras in a particular proportion. In addition to the most known titanium dioxide and zinc oxide, new nano-sized metal pigments should be investigatedand proposed for coloured cosmetics.

Moreover, nanocosmetics can open new perspectives in treating complex skin problems and disorders if adequately explored. Specially shaped nanoparticles to fill uneven surfaces may open new horizons, especially after plastic surgery. The release of nanomaterials to the skin facilitated by the skin pH gradient could be activated in another promising area. Due to their exceptional water binding ability in the horny layers of the skin, enzymes conjugated with protein nanocarriers are also gaining interest. The number of patent applications received over the past five years shows that there will be an uptick in activity in the field of protein conjugation in the coming years. Despite the plethora of advantages that nanocosmetics offer, specific nanomaterials' possible dangers cannot be denied. In addition, the risk assessment of nanomaterials should be carried out based on item-by-item, using appropriate knowledge [120].

CONCLUSION

In recent years, cosmetics have become increasingly popular because more people use them, and there is a strong demand for them. The products are being manufactured by big companies, small companies, and local companiesthroughout the world. Nanotechnology helps in providing the best work in the fieldof research and business in the 21st century. The spread of cosmetic products and their commercial use have given rise to an increase in the economic and technicallevel as well as a decrement in the risk to consumers' health and skin. Therefore, the products should be manufactured in such a way that fulfils the needs and demands of the customers while not causing harm. Nanoemulsions, gold nanoparticles, SLNs, liposomes, niosomes, and nucleosomes serve as novel nanocarriers in these products. Additionally, they possess properties such as prolonged action, improved stability, improved drug loading capacity, and site-specificity. There has been a broad debate about the safety and toxicity ofcosmetic products. Customers' safety and health hazards should be prioritised in the development of the products. Combining nanotechnology with conventional herbal medicine can be useful for designing future herbal medicine with a better

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bioavailability profile and less toxicity. Investing resources for handling nanotechnology safely and ethically must be given high priority.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 3

Transfersome: A Novel Vesicular Transdermal Delivery System

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Abstract: Delivery of novel drugs *via* the transdermal route provides many benefits over traditional delivery. Drug delivery with the help of nanocarriers, such as transfersomes, is considered a promising tool in pharmaceutical research because it is safe and convenient. It provides a long duration of the activity, minimizes the adverse effect, and avoids first-pass metabolism. Furthermore, it enhances pharmacological and physiological response, and the use of penetration enhancers and non-ionic surfactant vesicles have been applied to increase the efficiency of material transfer across the intact skin. However, the inability to penetrate the barrier properties of the stratum corneum and deliver large molecules are some of its limitations. Therefore, drugs are loaded in transfersomes to resolve these problems. Transfersome is a type of vesiclethat is ultra-deformable or elastic. It is commonly used to provide efficient transdermal delivery of bioactives as a novel carrier. It offers better penetration of intact vesicles, owing to its higher deformability. Transfersomes have a hydrophobic and hydrophilic framework; thus, they are able to accommodate drug molecules with a wide degree of solubility. Transfersomes are made from natural phospholipids and possess high entrapment ability, which makes them biocompatible and biodegradable. In this chapter, we have focused on transfersomes as novel drug delivery systems for targeted delivery of therapeutics, as well as important issues related to and challenges for future clinical applications.

Keywords: Bioactive, Nanocarrier, Penetration, Stratum corneum, Transfersomes.

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INTRODUCTION

Transfersomes are recently discovered drug carriers with large molecules, and they are known for their capability to penetrate the intact skin of mammals. They are found to be highly disfigured vesicles. Generally, it can be said that transfersomes are utilised to transfer the drugs from the application to the site where the action takes place by passing them naturally through the skin.

The utilisation of lipid vesicles has been gaining attention in the therapy ofdifferent skin diseases, but the effectiveness has remained debatable. It is because of factors like liposome transport processes and localization effects, as well as the fact that they sometimes rely on certain formulations, as revealed by some reports [1].

To solve this issue, a novel drug carrier called transfersome has been used, which can pass through intact skin when administered without being covered. It is important to create a transdermal osmotic gradient that would act as an impellent for elastic transport into the skin; thus, non-occlusive conditions are essential [2].

Due to the difference in the concentration of water, the osmotic gradient occurs between the surface of the skin and the skin's inner part. This property helps penetrate the intracellular lipid pathway of the subcutaneous tissue easily, as transfersomes are strongly disfigured. A few exploratory studies have reported the existence of misdeeds in the packaging of murine subcutaneous tissue of intercellular lipids, which act as the virtual medium in which transfers could pierce. Transfersome is defined as a specially designed lipid vesicle that encloses at least one inner aqueous compartment. In Fig. (**1**), a schematic diagram of the transfersome structure is shown [1]. Ceve and Blume have introduced the second-generation vesicular carrier called Ultra deformable liposome or transfersome, which possesses a slightly small vesicular size (typically < 300nm) along with higher elasticity (usually 5-8 times higher compared to regular or conventional liposomes [3].

ADVANTAGES AND DISADVANTAGES

Transfersomes can penetrate the skin barrier by opening the pathway extracellularly between the organ cells and distorting the passages to accommodate the organ cells. Transfersomes undergo a variety of stress- dependent changes of the local carrier symphony during the process to decrease the struggle related to displacement across the confining channels. This procedure permits the conveyance of the drugs through transfersomes by easily crossing the skin diagonally. It occurs at a rate that is higher

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than other predictable formulations and is able to control the distribution of drugs in the skin extremely well.

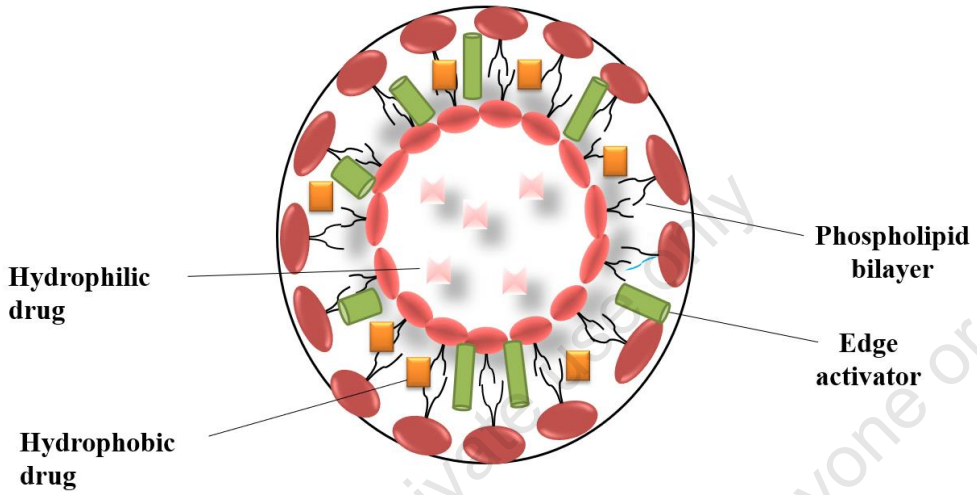

Fig. (1). Structure of Transfersomes.

The use of transfersome as a carrier for different therapeutic agents includes protein, insulin, peptides, anaesthetics, albumin, DNA, nutraceuticals, corticosteroids, gap junction protein, antigens, analgesics as well as sexhormones, and it has been confirmed that there is a significant increase in the amount of drug that is penetrated through the skin. A few researchers have illustrated the topical usage of transfersome that is trapped in the anticancer drugs.Assessment of 5-flurouracil(5-FU) methotrexate and bleomycin for skin delivery has been done by many research groups. Due to edge activators which are often single-chain surfactants, transfersomes are exceptionally versatile, destabilizing the vesicle's lipid bilayer. The function of sodium deoxycholate, spans, and tweens on the penetration of skin accumulation have been illustrated by different researchers. The use of transfersome does not require any complicated technique and can be administered by a non-occluded method. It can cross the stratum corneum's multilayered lipid matrix due to the hydration or osmotic force within the skin. However, one of the major disadvantages associated with these vesiclesis the difficulty of filling drugs into them without disrupting their deformability and elastic properties. Transfersomes are highly elastic in comparison to thestandard liposome, and they are more responsive for transportation of the therapeutic agents across the human skin [1].

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COMPOSITION AND ITS MECHANISM

A transfersome can adapt itself and improve mixed lipid aggregates. The cause of extreme distorted character on transfersomes is due to the surfactant molecules, which act as "edge activators," enabling them to compress themselves through stratum corneum's channels whose diameter is less than one-tenth of the transfersome's diameter. According to the inventors of transfersomes, liposomes that are smaller than 50 nm in size are too large to cross the channel, but transfersomes with up to 500 nm in size are able to penetrate the stratum corneum barrier by spontaneous squeezing. They propose that the transdermal gradient between the comparatively dehydrated skin surface (about 20% water) and the aqueous viable epidermal surface is due to the difference in water content, *i.e*., close to 100% [4].

Transfersome's deformability is achieved by using the proper ratio of the surface-active agent. However, one must be careful during the formulation processes as the concentration of the surface-active agents plays a pivotal role. The vesicle membrane possesses flexibility property at sublytic concentration, and demolition of vesicle will occur at higher concentration.

The possibility of complete vesicle breakdown in the skin is minimized due to the stability of the transferosomal membrane, which helps the ultra-deformable transfersome to change the membrane composition locally and reversibly after being attracted or squeezed against a small pore. This will decrease the energy value of the membrane's deformation and allow the extremely versatile particle to join initially and cross the pores easily and effectively afterwards.

The composition of carrier aggregate consists of a minimum of one amphiphat (such as phosphotidylcholine) [16], in which the aqueous solvent itself resembles a lipid bilayer that seals simple lipid vesicle. There is a tremendous increase in lipid bilayers' flexibility and permeation by the inclusion of at least one bilayer softening component (such as a biocompatible surfactant or an amphiphilic drug). Thus, the transfersome vesicle can adjust to its ambient shape easily and rapidly by optimizing the resulting flexibility and permeability. Thus, each bilayer component's local concentration can also be adjusted according to the local stress felt by the bilayer. This vesicle's main structure is quite similar to liposomes. But the transferosome varies from that of a conventional vesicle, particularly in its softness, deformability, and its ability to adjust the artificial membrane.

The enhanced transfersomes' ability to bind and retain water has proven to be another beneficial consequence of strong bilayer deformability [4, 5].

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TRANSFERSOMES PENETRATION MECHANISM

When transfersomes are given under suitable conditions, they can transfer roughly 0.1 mg of lipid every hour and a square centimetre of skin. This value is slightly higher than the gradient that is usually driven by transdermal concentration. The cause of this strong lipid movement is due to the transdermal osmotic gradient, which means that there is another important gradient available across the skin. Because of the skin penetration barrier, the osmotic gradient is developed in which water loss is prevented through the skin and maintains a difference in the activity of water in the viable part of the epidermis (75% of water content). Since ambient air is a perfect sink for the water molecule, the stabilization of this gradient is possible despite water loss from the transdermal remaining unpredictably high. Owing to the association between the hydrophilic layer residues and their proximal water molecules, all polar lipids will attract a certain amount of water, which is energetically advantageous. Thus, induced dehydration is resisted by most of the lipid bilayers. Therefore, the movement of all the lipid vesicles from polar lipids vesicle takes place at sufficiently high-water concentrations rather than the dry location. Consequently, a skin surface that is partly dehydrated by the evaporation of water loss and when lipid suspension is placed on it, the "osmotic gradient" is felt by the lipid vesicle, and they will move along the gradient to escape complete drying. This can be achieved only when they are adequately deformed enough to cross through narrow pores as transfersomes with surfactants have acceptable rheological and hydration properties which will cause greater deformability; standard liposomes are less deformable and are restricted to the surface of the skin in which complete dehydration and fusion take place due to transfersomes having more permeation capacity than liposomes. Therefore, the optimization of transfersomes will occur, and the maximum flexibility is attained so that full advantage of transdermal osmotic gradient (*i.e*., water concentration gradient) can be achieved. The barrier of skin penetration is conquered by transfersomes as they squeeze themselves along the intracellular sealing lipids of the stratum corneum [6].

Currently, the mechanism to enhance active substance delivery in and across the skin is not well understood by many. However, there are two mechanisms that have been proposed.

- When transfersomes enter the skin, they act as drug vectors that stay intact.
- Transfersomes disrupt the highly organized intercellular lipids of the stratum corneum by acting as a penetration enhancer, which facilitates the penetration in and across the stratum corneum for the drug molecule.

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Cevc and his coworkers have introduced the first mechanism in which they have suggested that the penetration of deformable liposomes into the stratum corneum is possible due to the presence of a transdermal hydration gradient in the skin through which the epidermis crosses, and the systemic circulation entry will take place afterward (Fig. **2**) [7]. Current experiments have confirmed that it is possible to enter the vesicle through the skin due to the combination of the above two mechanisms of penetration and permeation. One of the two mechanisms is possible due to the nature of the active substance (lipophilic or hydrophilic) and transfersome composition.

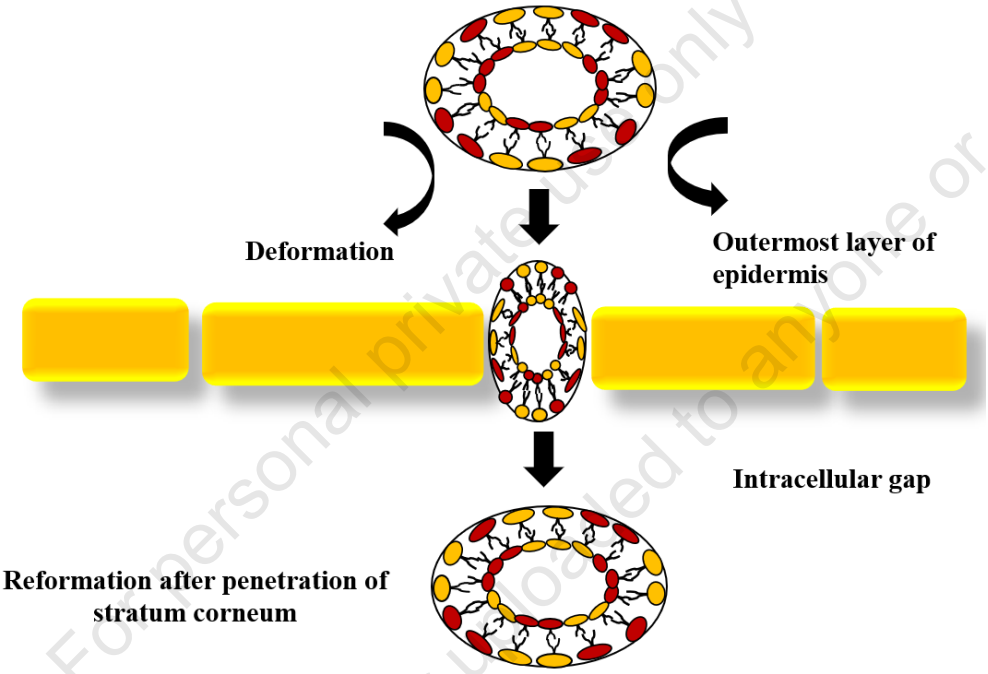

Fig. (2). Mechanism of transfersomes penetration to the skin.

APPLICATION OF TRANSFERSOMES AS THE TRANSDERMAL DELIVERY SYSTEM

Transfersome have been used for transdermal drug administration over the last decades after numerous thorough studies have been carried out [8]. Some of its applications are mentioned below:

Delivery of Antioxidant

Nanotransfersome containing epigallocatechin-3-gallate (EGCG) and hyaluronic acid was developed in 2017 by Avadhani *et al.* by utilizing a modified thin-film hydration method, followed by a high-pressure homogenization technique to

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increase their effectiveness as a UV radiation protector, antioxidant and antiaging substance [9]. In 2019, Wu *et al.* had employed a high-pressure homogenization technique in which the transfersome amalgamated with resveratrol could improve the stability, bioavailability, solubility, and safety of resveratrol [10].

Delivery of Anticancer Drug

In 2018, Jiang *et al.* had researched topical chemotherapy of melanoma in which transfersomes which were embedded by oligopeptide containing paclitaxel were developed through thin-film dispersion method. It was also shown in the experiments that transfersomes could enter the tumour cells effectively, which were composed of phosphatidylcholine, tween 80, and sodium deoxycholate [11].

Delivery of Corticosteroids

Ceve and Blume had examined the biological activity of halogenated corticosteroids armed with triamcinolone-acetonide in 2003 and 2004 by using traditional thin-film hydration techniques. It was revealed that the biological efficiency and its effect were prolonged by transfersomes with the least therapeutic dosage [12, 13].

Delivery of Anti-inflammatory Drugs

Transfersomes loaded with drugs mefenamic acid, curcumin, diclofenac sodium, and celecoxib were developed for topical administration by many researchers. The study findings had shown that transfersomes had improved the safety and effectiveness of anti-inflammatory drugs [14, 15].

Delivery of Insulin

The administration of insulin is done subcutaneously. Transfersomes containing insulin have shown its hyperglycemic effect in 90 to 180 min of administration, depending on the barrier's composition. Experiments have been conducted with another anti-diabetic drug-like repaglinide, with improved skin permeation [16, 17].

The study of the delivery of insulin *via* transfersomal gel was done by Malakar Jadupati *et al.* It was observed that the flux of insulin permeation was changed by several factors, such as the ratio of lipids and surfactants. It was also found that the optimized gel *in vitro* permeation flux was 13.50 +- 0.22 ug/cm^2/hr, which was done on the porcine ear skin with a minute error of 6.80% [18].

Cevc *et al.* have reported that in comparison to conventional vesicles, the transdermal drug penetration is 10 times greater. It has been reported that insulin's

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efficacy delivered transcutaneously has remained unaffected by any previous therapy. The normal concentration of sugar has remained for a minimum of 16 hr by non-invasive administration of insulin [13].

Delivery of Protein and Peptide

The administration of proteins, which are large biological molecules, into the body has posed some difficulties as they are completely broken down when they are given orally. The bioavailability of proteins is the same as given by the transfersome that is administered through suspension. A strong immune response is observed when transfersome preparation is applied epicutaneously, repeatedly. For example, despite several dermal challenges, serum albumin is immunologically active when transfersome is used as a carrier, along with its proteo-transfersome preparation [16, 19].

Delivery of Interferon

Interferon, or INF-α, is a leukocytic-derived natural protein and consists of antiviral and anti-proliferative effects, and transfersomes could act as a carrier for it.

It can improve the stability of such substances as it is capable of controlled release. Studies performed by Hafer *et al.* had revealed that the delivery of INF-α and IL-2 used transfersome at a concentration that was sufficient for immunotherapy [20].

Delivery of Anesthetics

Topical anaesthesia is induced in less than 10 minutes when it is applied under certain suitable conditions with the help of transfersome. The effect of anaesthesia that is administered by subcutaneous bolus injection at a comparable dose is less than the effect given by transfersomal anaesthesia. An experiment was conducted by Planas *et al.* to observe the duration and permeability of local analgesicsthrough transdermal transfersome in rats and humans. The results obtained after the experiment of transfersome analgesics with the liposomes containing lidocainewere compared. It was observed that the analgesics effect at first lasted for 6-7min and the withdrawal time was around 30s when a subcutaneous solution of 2% lidocaine solution was injected in rats, whereas the reaction to a heat stimulus was >70 seconds, or 130 percent longer in transfersomes administered liposomes than in controls where standard aqueous lidocaine solution was administered. Thus, it was concluded that the effectiveness of transfersome applied dermally was similar to that injected subcutaneously [21].

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Delivery of NSAIDs

NSAIDs are typically involved in GI irritation. This irritation could be controlled by transdermal delivery of transfersome. Swiss agency had approved ketoprofen formulation to be administered with transfersome as a carrier [22].

DELIVERY OF HERBAL DRUG

The prepared capsaicin transfersome administered topically had a marked rise in absorption due to the presence of surface-active agents, which helped penetrate the stratum corneum and supplied the nutrients locally.

The administration of curcumin, an anti-inflammatory herbal drug, by using transfersome is done to penetrate the skin. Indinavir sulphate that is administered by using transfersome shows an improved influx of indinavir in the treatment of deadly acquired deficiency syndrome. Ketoprofen transfersome causes improved penetration of the drug through the skin due to the presence of the surfactants and helps in producing anti-inflammatory activity at the site of action. Insulin that is administered by using transfersome is quite effective for hypoglycemic activity.

The deformation property of transfersome is greatly exploited, and it is used in the administration of the drug, which finds it difficult to penetrate through the skin, *e.g*., capsaicin and colchine. Transfersome also increases the efficacy of entrapment of constituents like vincristine. Several drugs like interferon-α have a short half-life due to which administration by other route is not feasible andshould be administered by transfersome as a medium to provide a therapeutic effect, along with good stability and control release.

The drugs, like norgestrol and tamoxifen, are administered with the help of transfersome to enhance effectiveness. Drugs like lignocaine and tetracycline are used in pain treatment by applying topically, *i.e*., without any non-invasive manner [23]. Hydrocortisone that is administered by using transfersome produces its effect at a lower dose in comparison to the concentration that is given currently. It has been observed that when it is applied to human serum albumin, an antibody titer is produced, which is akin in some cases and sometimes higher than the one produced by subcutaneous injection. It has also been found that the delivery of stavudine is improved by using transfersome as the carrier. Transfersomes arealso found to be used in transdermal immunization of tetanus toxoid [16, 23, 24].

REGULATORY ASPECTS

The advancement in science and technology led to the development of a new range of excipients such as lipids, surfactants, and solvents. However, there is always

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an objection among the experts and the scientific community regarding the excipient's dullness and unwanted effects. The criteria for the selection of an excipient is performing different experiments, which are restricted to the safety and toxicity involved with these excipients in transfersome-based formulation.

Consequently, a limited amount of excipients exists for the formulation of any sophisticated drug deliverance system. Once the transfersome-based formulations are evolved and cast off as vesicle forming agents, surfactant, EAs, and solvent, the inert excipients would be measured. Keeping in mind the safety concerns, we have obtained a limited number of excipients to design any drug delivery system which is highly porous such as transfersome. National Regulatory agents like WHO, US Food and Drug Administration, and International Pharmaceutical Excipient Council have created a confidential list of excipients that are generally regarded as safe (GRAS) and have been categorized clinically as nontoxic [1, 25].

A record known as 'inactive ingredient guide,' which is maintained by FDA, contains records of permitted excipients. The documentation gives us information about the excipients, particularly the value of their maximum dosage stage by a fastidious route of direction or dosage form [25]. In transfersome-based drug delivery system, the phospholipid is the most important element in the formulation. It is not always true that the fluid-chain bilayer, which is more elastic and helps transport drugs across skin obstructions, is preferred to the more rigid liposomes. Almost all the regular phosphatidylcholines (PCs) are unsaturated PC (*i.e*., soyabean phosphatidylcholine or SPC; egg phosphatidylcholine or EPC), and it is used to organize stretchy liposome as one of the GRAS-listed phospholipids, *e.g*., SPC, which obey the specification of the Food Chemical Codes. A type of surfactant that is known as an edge activator causes destabilization of the elastic liposomes, and the elasticity of the bilayer will increase concurrently. Some commonly used edge activators are sodium deoxycholate, span-8-0, sodium cholate, and tween-80. The regularly used surfactant could be replaced by chemical penetration enhancer like oleic acid, as recommended by Biju *et al.* [26].This is due to the higher inflexibility and smaller size of the mixed micelles,which will lead to a lower drug trap.

The skin permeation behaviour of elastic liposomes is regulated by the edge activator. The difference among edge activators helps decide the ideal edge activator for optimal formulation. A water-soluble ionic surfactant is sodium deoxycholate. An investigation was done on the elastic liposomes loaded with valsartan and sodium deoxylate as an edge activator.

Likewise, with sodium cholate, an edge activator is accounted as risky due to its irritation on skin and eye as well as respiratory sensitization. The safe limit of

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surfactant concentration is 10-35%, and when it is used above the concentration allowed, it can cause severe gastrointestinal discomfort. One of the efficient skin-penetration enhancers is ethanol, and it can cause a decrease in the melting point of the stratum corneum lipids when there is an interaction with the polar head group region of the lipid molecule. This can cause an increase in the fluidity and permeability of the cell membrane [1, 27].

LIMITATION OF TRANSFERSOMES

Some of the limitations of transfersomes are:

- Transfersome is susceptible to oxidative degradation in which they are chemically unstable.
- The absence of purity of natural phospholipid transfersomes as drug delivery vehicles comes in the way of the adoption of these vehicles.
- The formulation of transfersome is expensive [6].

FUTURE PERSPECTIVE

- Transfersome paves the way for vast potential therapeutic use as it is highly tolerable and efficient.
- These agents offer efficient penetration into the stratum corneum *via* passive diffusion for local and systemic as well as new upcoming therapies.

Ketoprofen (NSAID) was allowed to be marketed by a Swiss regulatory agent (Swiss Medic), which was expected to be marketed under the trademark of diractin. According to IDEA AG, there are a number of therapeutic productsbased on transfersome technology, which is currently under clinical development [4].

CONCLUSION

Although the transdermal drug delivery system has many advantages over the oral route, it is still not highly explored and requires a new technological addition to the existing methods and practices in the design of the transdermal deliverysystem. To overcome these limitations, a vesicular system is designed, such as transfersomes. This carrier mechanism is not based on the concentration gradient and operates largely on the elasto-mechanics and hydrotaxis theory. Transfersomes are extremely deformable particles that can be used to deliver drugs across the skin, which are known as biological permeability barriers. Transfersomes hold considerable promise in the delivery of a wide variety of pharmaceutical products, including large molecules such as antibiotics, hormones, and peptides, as well as medications with low penetration, owing to the

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unfavourable physicochemical characteristics. All of the above-mentioned properties of this technology could determine a good future in the delivery of transdermal drugs.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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CHAPTER 4

Self-Nano/Micro Emulsified Drug Delivery System

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Abstract: A self-emulsifying drug delivery system is defined as a mixture of isotropic substances such as oil and surfactant solvents/co-solvents, which is used for the improvement of the oral drug delivery system. The oral drug delivery system consists of soft and hard gelatin capsules. They are stable O/W emulsion preparations. There are several types of parameters used in this process. The utilisation of herbal medicine has been gaining popularity of late. Herbal drugs are also used in self-emulsion drug delivery systems due to their isotropic thermodynamic property. The lipophilic nature of this formulation could solve the problem of poor solubility of drugs. The bioavailability of poorly soluble drugs is determined by the drug dissolution process. Prodrug process is used to improve bioavailability.

Keywords: Bioavailability, Herbal drugs, Oral dosage form, SEDDS and SMEDDS.

INTRODUCTION

Isotropic substances (oil and surfactant mixture) are used for the preparation of self emulsifying drug delivery system (SEDDS). It includes several types of co-solvents and solvents. The system has diluted aqueous media, which contains oil in water emulsions and microemulsions. It can spread in the GI tract and digest in the stomach and intestine [1, 2]. The size of this emulsification is between 100 to 300 nm, but the size of the microemulsion may range about 50 nm. Self-emulsificationdrug delivery systems (SEDDS) and self-micro emulsification drug delivery systems (SMEDDS) are more stable and easy to manufacture. SMEDDS is utilised for sustained-release drug dosage as it contains a polymeric matrix. These matrixes are not ionized by pH, and when they go through the GI tract, they form gel micro polymers, and these are produced continuously with sustained matter through diffusion [3, 4]. It consists of a chain of non-ionic triglyceride oils and surfactants when ingested orally. Drugs like cyclosporine and digoxin are lipo-

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philic; therefore, they are used in SMEDDS. These drugs are used for the oral route of administration. The choice of excipient would confirm whether these drugs are in a liquid or semi-solid form. These drugs can also be given in the formof hard and soft gelatin of capsules. Bioavailability plays the main role in drug absorption. If the bioavailability of a drug is good, it will be absorbed better, but if the bioavailability of a drug is poor, it will not be absorbed into the body cavity[5, 6]. The bioavailability of a lipophilic drug is higher than usual if it is takenwith a meal that is rich in fats. This type of formulation would also enhance the drug solubility in the GI tract. Lipid base and therapeutic index-based drugswould normalise the absorption of the drug. There are various types of mechanisms that are used to enhance drug absorption:

1. P-glycoprotein-mediated inhibitions of drug and gut membrane-bound for pre-absorptive metabolism

2. Lymphatic transport promotion

3. GI membrane permeability increased

The dissolution rate will improve if some small modifications are made in the physicochemical properties, with a focus on lipid-based formulations [7, 8].

HERBAL MEDICINE IS A NOVEL DRUG DELIVERY SYSTEM

Of late, the herbal formulation is utilised more often than synthetic formulation. Several herbal formulations are currently utilised and available in the market, while others are still under development. Mucoadhesive, transdermal dosageforms, microcapsules, and nanoparticles are examples of herbal formulations. Prolonged-release dosage form could be included in the conventional dosage form. However, it would not be able to satisfy the drug holding components and the period of treatment as it is unable to respond to therapeutic dosage [9, 10]. The nano-sized dosage could be utilised in phyto-formulation, and it has advantages in herbal drugs. It enhances bioavailability, stability as well as solubility, provides toxicity protection, increases pharmacological activity, helps in macrophage distribution, and protects from degradation. The nano-sized herbal drugs are capable of removing the problems associated with plant medicines. For the purpose of encapsulation, hydrophilic and hydrophobic molecules can be encapsulated by liposomes as they are biodegradable and possess non-toxic vehicles [11, 12].

HERBAL NANOMEDICINES OF SNEDDS AND SMEDDS

Herbal medicine, which is also known as traditional medicine, has been gaining

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quite popularity of late as they are low in cost. Nowadays, every researcher has focused on medicinal plants due to their chemical composition, which can be utilised in poorly water-soluble drugs. The drugs have low absorption and bioavailability in the GI tract. Dissolution rates are used to enhance the bioavailability of solid and liquid dosage forms. The surface area is expanded in a solid dosage form, which increases the dissolution rate [13, 14]. Polymers are used to stabilise the compounds. Lipid-based excipients are used for the preparation of these formulations. SEDDS has used oil solution, emulsions, and a micellar system. On the other hand, LBDDS can avoid the dissolution of excipient digestion and colloid phases. Lamellar and hexagonal phases are obtained in the formulation of drugs. The extraction process for the herb is conducted through boiling and percolating techniques. There are different types of solvents used in this process. The plant extract is heated and dried to obtain the powder materials and pastes [15, 16]. They contain organic chemicals such as sterols, alkaloids, and tannins. The active constitute of herbal drugs is poorly soluble as it is hydrophobic and has poor distribution properties. Furthermore, it has low bioavailability, and the efficacy of treatment has been decreased as it requires regular and repeated doses. In recent times, liposomes, solid lipid nanoparticles, and nano-emulsion processes have been utilised to overcome toxicity, enhance the bioavailability and solubility as well as pharmacological activity. They are also used to improve macrophage tissues distribution. These factors would enhance stability and provide protection from physical and chemical degradation. By using the nano-sized drug delivery system, it would enhance and overcome the problems of herbal drugs. SEDDS increases the bioavailability of poorly soluble drugs; therefore, it could be a potential carrier system [17, 18].

SMEDDS and SNEDDS are used for the drug load of herbal medicine. Due to the presence of lipophilic natures, these would help to overcome issues, such as poor solubility, bioavailability, low oral absorption, and instability [19, 20]. These techniques are very easy to use and have their own advantages, such as direct production and higher loading dose as compared to any other formulation when delivering herbal medicine. SEDDS contains oil, surfactant, co-surfactant, thermodynamically stable, and isotropic. In the lymphatic pathway, drugs are easily absorbed. Globule size is used in micro-emulsion. Drugs in these sizes would be able to pass the first-pass effect. The size of the SEDDS is 5100 nm. Lipophilic capacity would aid their filling into the soft and hard gelatin capsules [21, 22]. The solubility of herbal drugs is increased by this process. SEDDS isalso used to increase the *in vivo* bioavailability of herbal drugs. SEDDS has great advantages in pharmaceuticals due to their lipophilic property. Extract chemical complexity is the most important factor in formulation success. In thisformulation, the active medicament is released. There are several vehicles used in this formulation. These vehicles would help improve the solubility, minimize the degradation process, and

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and reduce the toxicity of the drugs. These vehicles are also used to control the biological and active response in absorption [23].

SLNs, PSLCs, and LC techniques are also utilised in the manufacture of herbal formulations. These techniques would help change the behaviour property ofherbal drugs as they reintroduce the other components and also increase theeffectiveness of the active components. These are commonly used in cosmetic industries. This process would help combine the different types of active substances of hydrophilic and lipophilic molecules [24, 25].

Poor water solubility in a drug indicates low absorption, in which the rate of drug dissolution in the gastrointestinal tract often controls bioavailability. Two principles that are commonly used to increase the compound bioavailability enhance the dissolution rate of solid dosage forms and dissolve the compound in solution to obtain liquid dosage forms. In solid dosage forms, the dissolution rate is improved by expanding the surface area (such as in nanoparticles) or by stabilizing the compound's amorphous or molecular structure in polymers (for solid dispersions and complexes with cyclodextrin) [4 - 6]. Several reports have proven that solid dispersion and cyclodextrin complexes could enhance the dissolution of itraconazole, disulfiram, and glimepiride [7 - 9]. For liquid dosage forms, lipid-based excipients are used to prepare the mutations, with the compound being dissolved in solution [6]. Lipid-based drug delivery systems (LBDDS) include a range of various methods such as oil solutions, micellarsystems, emulsions, and self-emulsifying drug delivery systems (SEDDS). LBDDS avoid dissolution in the gastrointestinal tract, but they involve complex processes such as digestion of the excipients, the formation of different colloid phases, and transfer of the drug among these phases. The drug in the solution obtained from the formulation is partitioned into lamellar or hexagonal phases, which are developed during the digestion process and then into mixed micelles [6, 10]. Besides, the self-nano emulsifying drug delivery system (SNEDDS) has beenenhanced recently to obtain better dissolution and solubility. Poor water-solubilityin a drug indicates low absorption, while the rate of drug dissolution in thegastrointestinal tract often controls bioavailability. Several reports have proven that solid dispersion and cyclodextrin complexes could enhance the dissolution of itraconazole, disulfiram and glimepiride [7 - 9]. For liquid dosage forms, lipid- based excipients are used to prepare formulations in which the compound is dissolved in solution [6]. Lipid-based drug delivery systems (LBDDS) include a range of various methods such as oil solutions, micellar systems, emulsions, and self-emulsifying drug delivery systems (SEDDS). LBDDS avoid dissolution inthe gastrointestinal tract, but they involve complex processes such as digestion of the excipients, the formation of different colloid phases, and transfer of the drug among these phases. The drug in the solution obtained from the formulation is partitioned into lamellar

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or hexagonal phases, which are developed during the digestion process and then mixed into micelles [6, 10].

SELF EMULSIFICATION PROCESS

There are two types of self-emulsifying process which are:

Self-Nano Emulsifying Drug Delivery System (SNEDDS)

Self-nano emulsion is used to manufacture SNEDDS. These are of two types: oil in water and water in oil. They are heterogeneous dispersions. The mean droplet size is between 20 – 200 nm. This process helps increase the drug solubility.

Self-Micro Emulsifying Drug Delivery System (SMEDDS)

Self-nanoemulsion is used to manufacture microemulsion. These emulsion systems have the lowest chemical equilibrium. The size of the particle is the main reason for micro-emulsion and normal emulsions. The size of a normal emulsionis 0.2 to 10 μm, while the size of the microemulsions is 2 to 100 nm. A large surface area is utilised for absorption and dispersions, which will easily penetrate the GI tract and be absorbed easily. This is the reason it has higher bioavailability [26, 27].

INGREDIENTS REQUIRED FOR THE FORMATION OF SELF-EMULSIFICATION DRUG DELIVERY SYSTEM

Excipients

Excipients are selected based on the toxicity issues of the components and some restrictions are applied. Factors such as temperature and oil/surfactant ratio are considered for the self-micro emulsification process. A combination of excipients is used for an efficient self-micro emulsifying system.

In SMEDDS, the most important excipient is oil. Self-emulsification and lipophilic drugs are solubilized due to the transport fraction of lipophilic drugs in the intestinal system, which will increase the triglyceride molecular nature. To design the self-emulsification nanoformulations, long-chain triglyceride and medium-chain triglyceride are utilised. Edible oil and lipids are excluded in the development of SMEDDS as they have poor ability of drug absorption and are unable to dissolve the lipophilic drugs. Some drugs contain vegetable oils that have been modified, hydrolysed, and approved for oral use. They exhibit good solubility properties. This product has the physiological advantages of degradation in the intestine. In SMEDDS, the regular chain of triglyceride is replaced by novel semisynthetic medium-chain derivatives [28-30].

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Surfactants

There are several types of surfactants used to design the self-emulsified system. HLB (hydrophilic-lipophilic balance) is the most commonly used non-ionic surfactant, while polyoxyethylene oleate and polyglycolyzed glycerides are the most common emulsifiers. Safety plays the most important role in choosing a surfactant. Natural origin surfactant is more commonly used rather than synthetic surfactant, but the former has limitations in regards to the capacity of self-emulsifications. Furthermore, an ionic surfactant is more toxic than a non-ionic surfactant. It shows some changes in the intestinal lumen. For the formation of SMEDDS, a higher amount of surfactant and cosurfactant ratios are required. There is a relation between the surfactant concentration and droplet sizes. If the concentration of droplets is increased, there would be a decrease in droplet size. In some cases, if the concentration of the surfactant increases, the droplet size also increases. Interfacial disruption may enhance the water penetration power. Water could enter into the oil, and the increased concentration of surfactant would help oil droplets to be removed from this aqueous phase. Surfactants are used in the formulation to improve bioavailability. There are various mechanisms in which the surfactant could enter into the body cavity, such as the dissolution of the drug as well as an increase in the permeability of intestinal epithelial. The GI tract, however, may get irritated by certain surfactants. Surfactants are chosen according to the nature of hydrophilic groups [31 - 33]. There are four main types of surfactants:

a. Anionic surfactants
b. Cationic surfactants
c. Ampholytic surfactants
d. Non-ionic surfactants

Co-Surfactant

In this particular HLB, the value that ranges from 10-14 is used. Co-surfactant may contain an alcohol chain; therefore, the oil and water interfaces are reduced by the alcohols. These are used to manufacture microemulsion formulations.Surfactant is used for the manufacturing of SEDDS. The concentration of SEDDSis controlled by the surfactants. Interfacial tension is low due to the use of a co- surfactant. The finely dispersed droplets are formed by the value of the interface [34, 35]. It will absorb more surfactant and co-surfactant up to the depletion of bulk conditions to make the interfacial tension positive. The spontaneous emulsion is formed from the microemulsion. Non-ionic surfactants do not require a co-surfactant. The co-surfactant is used for the formation and solubilization of drugs in SEDDS. Oral administration of drugs would be suitable when the amount of hydrophilic

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surfactant is dissolved in self-emulsifying. When it is incorporated into the capsule dosage form, the formulations exhibit many advantages. Some migrated formulations can contain a soft and hard gelatin shell capsule [36, 37].

IMPORTANT OF SEDDS

1. Formulation of the capsule consists of poorly water-soluble compounds, which would be pre-dissolved in a solvent.

2. These pre-dissolving compounds may overcome the GI rate-limiting steps.

3. In hydrophilic solvent, when a formulation is dispersed in the GI tract, it creates problems.

4. In lipid vehicles, the drug could be less dissolved and less diluted in the GI tract.

5. Poor soluble drugs could be formulated in a solid solution with different types of water-soluble polymers.

6. Drugs require more thermodynamically stable potentials, and they contain crystallized polymers matrix.

7. There are several techniques used in SEDDS, such as calorimetry and X-ray crystallography [38 - 40].

MECHANISM OF SEDDS

The formation of microemulsion has been done by no single theory. A complex is formed at the oil and water interface. Thermodynamics theory explains the formation of micro-emulsion. The dispersion is changed due to the entropy. The energy required is greater than the surface area of dispersion, and the free energy is negative [41, 42]. These free energies would form the new surface between the phases, as shown by the equations: -

$$\Delta G = \Sigma N_л r2 \sigma$$

Where ΔG = free energy

N = number of droplets

r = radius

σ = interfacial energy

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These two layers would be separated when the interfacial area and system are reduced. Conventional emulsified agents would help in the formation of an emulsion. A monolayer is formed to surround the emulsion droplets, providing a barrier to prevent coalescence [43, 44].

DOSAGE FORMS FROM SEDDS

The liquid dosage form is usually used in SEDDS due to an excipient utilised, which it is not solid at room temperature.

Dry Emulsions

This formulation is prepared by oil in water (O/W). Spray drying, freeze-drying, and rotary evaporation are used in the emulsion, which contains a solid carrier in the aqueous phase. It emulsion will disperse *in vivo* and in an aqueous solution. This is also used in tablet and capsule preparation. Moreover, oral protein and peptone are also delivered [45, 46].

Sustained and Controlled-release Tablets

SEDDS transformation is used in solid dosage forms to reduce solidifying excipients requirements. Sustained-release tablets have a higher chance of preventing an adverse effect. Through the GI tract, self-emulsification could increase the penetration effect, thus reducing the GI tract bleeding. Self-emulsifying osmotic pump tablets are the latest, well-improved self-emulsifying tablets in which the pump carries the elementary system.

Self-emulsifying Suppositories

SEDDS can increase the GI tract absorption as well as rectal and vaginal adsorption. To obtain better results or therapeutic effects, these should be taken orally [47,48].

Implants of Self-emulsifying

The implants of self-emulsification would improve the utility and application. They are used in chemotherapeutic agents. These implants, however, have a short half-life. Nevertheless, they are capable of enhancing the stability and permeability of the self-emulsifying system. Through the compression method, itshould be wafered into a flat and smooth surface. It extends the half-life *in vitro* from 45 minutes to 130 minutes and prolongs it for 7 days [49, 50].

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DRUG PROPERTIES AND CHARACTERIZATION OF SEDDS

1. The drug concentration should not be too high.

2. These drugs must be oil soluble.

3. High melting point.

4. High value of log P.

For the Characterisation of SEDDS

1. Equilibrium Phase: In this process, non-equilibrium interfacial phenomena are used for the detection of self-emulsification behaviour.

2. Measurement of Turbidity: This process helps detect whether the dispersion has reached the target in a rapid and reproducible time. It was done by the Hach turbidity meter or the Orbeco-helle turbidity meter.

3. Size of Droplet: As the main factor, it helps determine the drug rate and extended release. It can also help determine the emulsion. For the detection of emulsion droplet size, coulter nanosizer and photon correlation spectroscopy are used. Freeze-fracture electron microscopy is used to study the dispersed phase system.

4. Measurement of Zeta Potential: This process is used for the detection of charge in the droplet. In SEDDS, the charges are negative.

5. Emulsification Time: Light microscopy is used for this process. The surface of large droplets has erosion of fine clouds due to the mechanism of emulsification. It has a reduction in droplet size.

6. Liquefaction of Time: This process is done to estimate the time required to melt the drug into the GI.

7. Small-angle Neutron Scattering: This provides information on the size and shape of droplets.

8. Small-angle X-ray Scattering: This process provides information on the size of the macromolecule, which is between 5 to 25 nm, and it should be distanced up to 150 nm. The microscale and nanoscale systems are determined with parameters such as size, shape, and distribution [51 - 53].

BIOAVAILABILITY ENHANCEMENT OF DRUGS BY SEDDS

Solubility and permeability are the main chemical stable drugs used in drug bioavailability. Poor drug absorption is caused by a combination of factors,

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including low permeability, drug extent, and rate of absorption. Due to this, it should be divided into classes I to IV. Poor bioavailability of class II drugs should depend on solubility and dissolution rate. They exhibit the bioavailability of drugs *in vivo* correlated with *in vitro* dissolution. Micronization, co-solvents, solid dispersions, and complexation are techniques used for better solubility of class II [54, 55].

SNEDDS AND SMEDDS IMPROVED DISSOLUTION RATE AND BIOAVAILABILITY OF POORLY SOLUBLE DRUG

From SNEDDS and SMEDDS, the compound of drugs will take place in the intestinal fluid due to the droplet that is transported and disintegrated in the GI tract. The particle size and polarity are used for the determination of drug release in SNEDDS and SMEDDS. In polarity, the oil droplets would reach the drug capillaries. In an animal study, this oral bioavailability has shown better absorption. It, however, has limited uses due to poor stability and large volumes. Despite this, the system has high stability and the ability to soften gelatin capsules. Nowadays, SEDDS formulations are used for HIV diagnosis [56, 57].

Surfactants' Effect

Surfactants are used to enhance the permeability interference by the single layer of lipid. Drugs are absorbed through a passive transcellular route. Surfactants will help in the partition of the cell membrane. It also enhances the permeation of lipid bilayer. It increases the dissolution rate by enhancing absorption. The large droplets are less neutralized due to the mucin and formation of the smaller micron. Coenzymes are also utilised in this. They are lipid-soluble compounds with antioxidant activity. They are also used in cardiovascular treatment. Drugs that have high molecular weight and display water insolubility are absorbed into the GI tract [58, 59].

Lipids' Effect

Lipid has shown some advantages for the oral drug delivery system. It exerts effects on the biopharmaceutical properties of the drug. The dissolution rate is increased in this process. Solubility is also increased while at the same time it degrades the chemical in the oil droplets. It also helps in the formation of lipoproteins and the transport of lymphatic promoting drugs. The acid chain of triglyceride has affected the blood and lymph absorption profile of drug components. The lipid core is associated with the intestinal lymph and is transported to the circulation system. It helps the formation of lipoprotein. Chylomicrons are formed in the systemic circulation. In intestinal cells, re- esterified fatty acids are re-esterified to form a long chain. It is secreted by exocytosis and flows through lymph vessels. This

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process increases the drug absorption into the blood [60, 61].

P-glycoprotein Inhibition

The bioavailability of hydrophobic and lipophilic drugs is increased by SEDDS in the GIT tract. The drug which is manufactured by SEDDS and SMEDDS inhibits the metabolism while the cytoplasm of the drug is increased [62, 63].

SNEDDS AND SMEDDS DRUG DELIVERY SYSTEM FOR IMPROVING THE BIOAVAILABILITY/LYMPHATIC UPTAKE/LIVER UPTAKE/ PEPTIDE

SNEDDS and SMEDDS have O/W or W/O type systems in which some additives are used as therapeutic agents. These microstructures differ from solution droplets and bi-continuous microstructures. They are thermodynamically stable. These drugs are soluble in various peptides and proteins. SMEDDS AND SNEDDS improve the absorption of drugs peptides. Surfactant, oil, and concentration of drugs are used in the formulation of this system [64, 65]. These would disperse the droplets of the microemulsion. The controlled release of drugs contains a water-in-oil type system. The parameters can be adjusted by protein and protein drugs. These contain hydrophilic molecules [66, 67]. Lymph is present in the lymphatic system and forms an intricate network. Body water maintains the lymphatic system in an intestinal fluid to return the immune cells to the lymph nodes. The SMEDDS and SNEDDS drugs are well absorbed in the lymph system. It avoids disease spreading in the lymphatic system by passing through first-pass metabolism.It can also protect from the cancerous cells that have spread throughout the body. Drugs can be delivered into the intestinal lymphatic vessels through a certain process. These vessels have endothelial cells in a single layer [68, 69]. The lymphatic vasculature contains porous walls and could be overlapped and highly gapped. By using an absorption enhancer, the macro molecule conjugated in the open paracellular pathway might be increased. The entry point of the drug is Peyer's patches. Moreover, the transcellular patches are used to absorb the drugs. These lymphatic systems' ability is increased by polymer-based lipid nanoparticles, and they are also used as therapeutic agents. The endothelial wall provides high molecular weight drugs. Lipid-based formulations are used to improve the bioavailability of poorly soluble drugs [70, 71]. If the surface area is large, the area of drug absorption is higher. Bile fluids could solubilize the emulsion globules. Surfactants would enhance the absorption of permeation changes. The value of HLB in SEDDS is smaller than 12, and in SMEDDS, the HLB value is greater than 12. These emulsions will help the drug flow into the bloodstream [72, 73].

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ADVANTAGES OF SELF-EMULSIFYING DRUG DELIVERY

1. In gastrointestinal fluids, these self-emulsions are rapidly absorbed. It takes the form of an o/w emulsion due to peristaltic agitation.

2. Hydrophobic and hydrophilic drugs are effective within the oil mixture.

3. These are used in solid dosage form and liquid dosage form.

4. In conventional dosage forms, these drugs are in a lower dose.

5. SMEDDS help distribute the drugs in the stomach and throughout the GI tract. Therefore, the irritation could be minimized, and the bulk of drug substances would come into contact with the gut wall.

6. SMEDDS formulations are fully stable, and normal emulsions are sensitive and dispersed.

7. When compared with oil solutions, it gives a large surface area of drug in between water and oil.

8. It enhances the bioavailability of the oral drug delivery system.

9. The ease of scaling up and manufacturing [74,75].

DISADVANTAGES OF SELF-EMULSIFYING DRUG DELIVERY SYSTEMS

1. In SMEDDS, *in-vitro* has a lack of predicative goods.

2. In SMEDDS, the formulation contains the soft and hard gelatin capsules, which will form the precipitate in lipophilic drugs.

3. Many challenges are expected to validate the formulation.

4. The production cost is high.

5. Incompatibility of the drug is extremely low.

6. Possible leakage of drugs would lead to less drug loading [76, 77].

EMERGING CHALLENGES AND POTENTIAL SOLUTIONS OF SNEDDS AND SMEDDS

In recent times, various types of drugs have had the same problems, which are poor solubility and poor bioavailability. The oral dosage form of tablets has poor

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water solubility as well as poor bioavailability. It should be classified as a BCS (biopharmaceutical classification system). It should be put into either class II or class IV [78, 79]. Class II and IV consist of poorly soluble drugs, while class I has highly soluble drugs. According to BCS, class III drugs have permeability issues. To minimize these problems, several processes are being developed, such as complexation, size reduction of particles, formation of salt, dispersions of solid, surfactant uses as well as nanoparticles. A lipid-based system would improve the bioavailability of poorly soluble drugs [80, 81]. The lipid-based vehicles are used in the lipophilic drug. Lipophilic drugs had their bioavailability issues addressed. SNEDDS would help improve poorly water-soluble drugs. There are different types of methods for these biopharmaceuticals. The body may easily uptake this lipid-based formulation system. The coarse powder contains fat globules. SNEDDS has contributed to the degradation of products [82, 83].

MARKETED PRODUCTS OF SEDDS

1. Sandimmune (cyclosporine) is the marketed formulation. It is used to prevent organ rejection such as kidney, liver, and heart transparent. It can be placed into BCS class IV. It contains a soft gelatin capsule. Corn oil and sorbitol are used as its ingredients.

2. Norvir (Ritronavir) is the marketed formulation that is used in HIV treatment. It should be placed into BCS class II. It is also a soft gelatin capsule. Ethanol and oleic acid are the ingredients used in this formulation [84, 85].

3. Fortovase (saquinavir) is formulated for the market. It inhibits HIV proteases. It is used as a soft gelatin capsule. Diglycerides, povidone, and medium-chain mono are used as ingredients.

4. Modafinil is used for market formulation. It is an aqueous composition of particles. It is used in the treatment of various diseases [86, 87].

5. Naproxen is the marketed preparation. It is used for the oral administration of a suitable composition. It is used in the form of an emulsion. It contains one or more surfactants. Oil and semi-solid fat are used in this preparation. It forms an oil-in-water emulsion in the GI tract.

6. Pyranone protease inhibitors are formulated for marketed preparation. These contain microemulsion compounds. They are free from alcohol and propylene glycol combined with pyranone protease inhibitors. One or more pharmaceutical surfactant is used in this formulation [88, 89].

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FUTURE PROSPECTS

SMEDDS are utilised to solve the problem of drugs solubility. They have less solubility in the GIT tract. Different types of methodology (dispersion and digestion) are used for the understanding of lipid-based formulation [90, 91]. The emulsion prefix has high stability; therefore, it can be used in the *in-situ* emulsion formulation. In the coming years, SMEDDS and SNEDDS will be used for the removal of drugs with poor solubility. But these systems have some limitations. They exhibited some problems in *in-vitro* bioavailability and development and *in-vivo* (IVIVC). Furthermore, SEOPT requires more exploitation. SMEDDS and SNEDDS are used to enhance the biological activity of herbal drugs. They also help solve the problems related to them. Clinical implementation has a challenge in viable therapies. The current challenge is to use these nanomaterial interaction technologies in therapies [92 - 94]. Scale-up processes and therapeutic approach feasibility are also included. It is also used in the fulfilment of therapeutics and biological requirements. The effectiveness of nanoparticles must be increased while also meeting toxicological and biocompatibility requirements [95 - 97].

CONCLUSION

SNEDDS and SMEDDS are used to overcome the properties of poor solubility of drugs. They are also useful for the manufacturing of hydrophobic drugs. They can improve the oral bioavailability of drugs in which the dose is reduced [98-101]. In thefuture, SMEDDS and SNEDDS would enable the application of drug deliverysystems and solve the problem of poorly soluble drugs. Herbal drugs arehydrophobic and poorly soluble. They can decrease the efficacy of the treatment and increase the dose. SNEDDS and SMEDDS are used to enhance the activity ofherbal drugs. They have porous particle sizes. They can be manufactured bygranules, tablets, capsules, and pellets. Herbal drugs, which are formulated bySNEDDS and SMEDDS, are shown to have less irritation and to avoid controlled and sustained release drugs. These techniques are effective and have high advantages like good formulation in *in-vitro* models and exhibit less allergic reaction in higher concentrations. The toxicity is reduced, activity is increased, and clinical application should be satisfied due to the development *in-vitro* and *in-vivo*. SNEDDS and SMEDDS are mainly concentrated on natural active ingredients.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 5

Phytosomes

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Abstract: The phytoconstituents, especially polyphenolic and flavonoids, have various pharmacological activities such as anticancer, antidiabetic, hepatoprotective, anti-inflammatory, antiobesity as well as cardioprotective. The polar nature and high molecular weight of these phytoconstituents would limit the rate of permeation through biological membrane and solubility, therefore, leading to a decrease in their bioavailability and therapeutic efficacy. The bioavailability of polyphenolic compounds can be improved by integrating them into the phospholipid-based self-assembled delivery systems, which are referred to as phytosomes or herbosomes. Phytosomes are vesicles in which the phospholipids bond with the hydrogen in the polyphenolic components to deliver the drugs to the targeted site without their metabolism. The present chapters discuss the preparation, properties, characterization, application, various dosage forms, and marketed formulations of the phytosomes.

Keywords: Characterization, Phytosomes, Polyphenol, Preparation.

INTRODUCTION

In recent years, the management of diseases and disorders through natural products and botanicals has gained wide popularity due to their easy availability and safety profile. However, the use of these natural/herbal-based substances as a pharmaceutical dosage form/product is limited due to the poor oral bioavailability of these bioactive phytoconstituents. Poor bioavailability of these therapeutically active constituents is mainly attributed to the poor aqueous/lipid solubility, high molecular weight, and size, as well as lower plasma membrane permeability, thus restricting their use for the effective treatment of various disorders and diseases. In the development of pharmaceutical dosage and drug products, improvement in solubility, membrane permeability, and bioavailability are some of the major constraints for these natural/phytocomponents [1]. When it comes to the improve-

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nt of the bioavailability of drugs, drug phospholipid complexes appear more promising than several other approaches explored prior. The term herbosomes, which are also termed phytosomes, refer to the active principles obtained from herbs that are rendered from the plant. Most of the phytoconstituents *viz*. flavonoids, tannins, glycosides, xanthans, carbohydrates, and derived products are aqueous soluble, which limit their bioavailability due to their complex chemical nature, such as high molecular weight and solubility. This is due to the lipophilic membrane environment, which can be a hindrance in such a cellular environment. Through the utilisation of herbosomes, the bioavailability of these extract/phytoingredients can be improved as it incorporates phospholipid molecules that contain phosphatidylcholine in its structure to form a complex with a standardized or specific pharmaceutical active ingredient of the plant, which enhances their solubility, partition coefficient, and plasma membrane permeability [2].

Phytosome/Herbosome/Pharmacosome/Liposome

PHYTOSOME^{R} is the patented name of the plant active, and the phospholipid complexation technique was first introduced by Indena, an Italian company, in 1989.

Phytosome or Herbosome

When a plant extract or phytoconstituents are complexed in an equimolar ratio with phospholipids, phosphatidylcholine, and phosphatidylserine phosphatidyl ethanolamine, the resulting complex is called a phytosome or herbosome.

Pharmacosomes

The phospholipid is complexed with a conventional drug or components of a dosage form with enhanced solubility, permeability, retention time, and bioavailability, making them a potent vehicle for the delivery of various drugs molecules [3].

Liposomes

These are colloidal or microparticles carriers that are spontaneously formed when certain lipids are hydrated in aqueous media. Liposomes consist of an aqueous volume of bioactive materials that are entrapped by one or more bilayers of natural or synthetic phospholipids [4].

PHYTOSOME *VS.* LIPOSOME

The unique difference between phytosomes and liposomes is that the bioactive

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material for the latter is dissolved in the medium that consists of a cavity or a layer of the vesicular membrane. As for the former, the bioactive material or product is an integral part of the vesicular membrane, which is stabilized through chemical bonds with the polar heads of the phospholipids [5].

PREREQUISITES FOR PHYTOSOME/HERBOSOME/LIPOSOME FORMATION

1. Active phytoconstituents or standardized extract
2. Phospholipids
3. Solvents

Selection of Active Phytoconstituents or Standardized Extract

1. Natural products may undergo some alterations or lose specific biological activity following isolation or purification techniques; therefore, a whole-plant extract is selected for complexation. The phytosomal preparations are generally conducted according to the weight basis of standardized extract and the molar basis for active phytoconstituents.
2. These plant extracts are selected based on their phytochemical and pharmacokinetic properties. Due to high molecular masses and multiple ring structures, these phytoconstituents have poor solubility, permeability, and bioavailability, hence making them suitable agents for complexation with phospholipids, which would help overcome these drawbacks.
3. Phytoconstituents consist of active hydrogens such as –OH, -NH, -COOH, - NH2, *etc.*, and they are suitable to form hydrogen bonding with N-(CH3) of phospholipid molecules. Active natural constituents with π electrons can be complexed with phospholipid molecules.
4. For the improvement of bioavailability, both hydrophilic and lipophilic phyto actives can be complexed with phospholipids [3, 6].

Phospholipids

Phospholipids are phosphorous, which consist of lipids with polar and non-polar portions.

Structure of Phospholipids

Based on the presence of alcohol on phospholipids, they can be classified into glycerophospholipids and sphingomyelins.

Glycerophospholipids

Glycerophospholipids are the backbone of the phospholipids found in the

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eukaryotic cells, possessing α-structure and L-configuration. These may be of different types due to varying head groups, such as phosphatidylcholine, phosphatidylserine, phosphatidyl ethanolamine, phosphatidylserine, phosphatedylglycerol. Furthermore, the length of the non-polar moiety also leads to different glycerophospholipids, such as dipalmitoyl, dimyristoyl, and distearoyl phospholipids. The type of bonding (Ether or Ester) between the aliphatic chain and glycerol determines different glycerophospholipids, such as plasmalogens [7].

Sphingomyelins

N-acyl-sphing-4-enine-1-phosphocholine consists of a wide range of compounds, depending upon the length and unsaturation of acyl residue and the length of sphingoid bases. Sphingomyelins are the second most abundant phospholipids. These are used in the formulation of phytosomes, liposomes, and pharmacosomes. Some of the common sources of sphingomyelins include egg yolk, soybeans, different dairy products, such as milk and cheese [8].

PHYTO-PHOSPHOLIPID COMPLEX: PHYTOSOME TECHNOLOGY

Bombardelli, in 1989, had reported the chemical bonding between phospholipids and flavonoid molecules. It was revealed that the phospholipid-active ingredient interaction was due to the formation of hydrogen bonds between the polar head and polar functionalities of the active ingredients. ^{1}HNMR and ^{13}CNMR Confirmed that the signals of fatty chains in both free and complex phospholipids have not changed, suggesting that the aliphatic chains are wrapped around the active principle, providing lipophilic envelop [9].

First-generation phyto-phospholipid complex: Phytosomes were prepared by combining a selected polyphenolic extract with phospholipids in a non-polar solvent. However, recent generations of phytosomes have been developed byusing a hydroethanolic solvent to comply with accurate food specifications. Phosphatidylcholine, a popular phospholipid, is a bifunctional compound that possesses lipophilic phosphatidyl moiety and hydrophilic choline moiety. Choline, the head of the phospholipid molecule, would bind with the phytoconstituents and phospholipid moiety containing lipid-soluble body and tail to develop the choline-bound material. Hence, phytoconstituents that produce a lipid that forms a molecular complex with phospholipid are also known as phytosomes, herbosomes, or phyto-phospholipid complexes. The term ‘phyto’ refers to a plant, while ‘some’ means that the result of this complexation technology produces a little cell, protecting them from gastric secretion and gut bacteria because of the gastroprotective property of phosphatidylcholine. In general, phytosomes are produced by a 1:1 or 2:1 molar ratio of phospholipidsand phytoconstituents through chemical bonding, having an advantage over liposome technology

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due to significant improvement in absorption, solubility, and bioavailability. Furthermore, a phytosome is deemed superior to a liposome in topical and skincare products [10].

PROPERTIES OF HERBOSOMES (PHYTOPHOSPHOLIPID COMPLEX)

Herbosomes are categorised according to their physicochemical property,biological as well, as chemical properties, and they are summarised below:

Physical Properties

Herbosomes, which are also referred to as planterosomes and phytosomes, are the result of the stoichiometric interactions between standardized phyto extract and a natural phospholipid, such as soya phosphatidylcholine or semisynthetic or synthetic phospholipid *viz* dipalmitoylphosphatidylcholine (DPPC) and dipalmitoylphosphatidylserine (DPPS) with an appropriate solvent, such as dichloromethane, chloroform. Based on different spectroscopic studies, the formation of the herbosomes is done either by the hydrogen bonding between the polar head of the phospholipid and polar parts of the phytoconstituents or covalent bonding between phytoactives and phospholipids.

When these phytophospholipid complexes are brought in contact with water, they form a shape like a micelle. In herbosomes, the plant active constituents are attached with the polar heads of phospholipids, an integral part of the micellar membrane. Catechin-distearoyl phosphatidylcholine complex is an example of theformation of herbosomes by hydrogen bonding between the phosphate ion of phosphatidylcholine and the hydroxyl group of the phenolic moiety. This interaction can be inferred by comparing the proton NMR and C^{13} NMR of the complex.

Chemical Properties

Phytosome is a complexation result between an isolated active principle or a standardized plant extract, and a phospholipid formed through hydrogen bonding or covalent bonding. They are liposomal-like structures in which the polar moiety of the phospholipids have interacted with the polar part of the phytoconstituents. This interaction leads to the changes in the chemical properties of the phytoactive that is incorporated into a phospholipid, showing solubility in non-polar solvents and moderate solubility in fats and a clear melting point. These changes in the chemical behaviour can be inferred by the application of various spectroscopic techniques, such as NMR, SEM, TEM, *etc.*

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Biological Properties

Various studies performed in animal models and human subjects have demonstrated an increase in the bioavailability of the herbosomes over conventional phytoextracts. Plant extracts and botanicals in the crude form are less biologically active than the constituents with phospholipids. These studiesalso indicate an increase in the membrane permeability and solubility, which improve its bioavailability. The lipophilic environment of the cell membrane is rapidly enhanced by complexing the plant active principles with phospholipids, leading to a transition from hydrophilic to the lipophilic environment of the cell membrane before entering into the cell. Other experiments conducted on various animal models and human subjects have also depicted improved hepatoprotective action and percutaneous absorption of herbosomes [11].

MERITS OF PHYTOPHOSPHOLIPID COMPLEXES (HERBOSOMES)

Herbosomes have shown various merits over conventional phytoextracts and botanicals. Some of the merits of herbosomes are described below:

1. Improved bioavailability targeted delivery and enhanced systemic absorption: The lipophilic portion in the structure of herbosomes makes them liable for transporting into a lipophilic environment of the cell membrane, cell, and finally into the bloodstream. When herbal extracts and the formulations are administered in the form of herbosomes, intestinal lumen absorption is enhanced, and the permeation for the topical and transdermal route of drug delivery is improved. As the bioavailability of herbosomes is improved, the quantity of the phytoactive constituents gets reduced for desired therapeutic response. Herbosomes also increase the duration of action. In the gastric environment,herbosomes have shown better stability, and are more resistant to intestinal microflora.

2. Safeguards: Herbosomes are approved for cosmetic and pharmaceutical applications due to their non-toxicity and non-mutagenicity properties. The phytophospholipid complexation system is non-invasive and passive hence it is more applicable over conventional use of phytoconstituents. Of late, hydrophilic solvent like leithanol has replaced the conventional uses of harmful organic solvents, such as dichloromethane and chloroforms, for the preparation of herbosomes, which make it safer for further clinical uses [12].

3. Other benefits: The methods of herbosome preparation do not require a complicated technical setup or huge capital investment. The toxicological profile of different components of the phytosome is well documented in the scientific literature; therefore, the high risk of drug development is at a minimum level.

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Phospholipid, which is an essential part of the herbosomes possesses significant medicinal values in humans, apart from the toxicological, physiological, and pharmacokinetic profile. Different phospholipids also provide nutritional values. Phosphatidylserine, for example, is nutritive to the brain cells.Phosphatidylcholine and choline that are rendered from phospholipids wouldexert liquefying action on the deposited fat of the liver, which may be protected inliver cirrhosis or fatty liver.

Soya phospholipids have been reported to be hepatoprotective, especially toward damages that are caused by alcohol, drugs, and toxins. Thus, it is clear that phospholipids provide a synergistic effect to the phytoconstituents for hepatoprotection. Herbosomes have shown additive properties for more clearance to cholesterol and increased distribution of high-density lipoprotein (HDL) levels in plasma. Due to the unique compatibility of phosphatidylcholine with biological membrane, the phospholipid present in the herbosomes provides the maintenance and nourishing effect to the skin. Stable emulsions and creams can be formulated from herbosomes due to their low aqueous solubility. In various recent bioavailability studies of herbosomes on animal models and human subjects, tremendous absorption of these formulations have been recorded, such as the 29-fold absorption of curcuminoids when compared to the non-herbosomal preparation of this compound [13].

PREPARATION OF HERBOSOMES

The prerequisite and basic ingredients of a typical herbosomes preparation are as follows:

Phospholipids

Phospholipids are essential parts of the herbosomes, and different types of phospholipids may be obtained from a variety of sources. A description of phospholipids has been discussed earlier.

Solvents

The selection of a solvent is a key factor for the formulation of herbosomes, and it depends on the solubility of the phytoactive constituents or standardized extract and the phospholipid. Scientists have employed a variety of solvents with different formulations for the preparation of herbosomes. Conventionally, aprotic solvents, such as ethers, aromatic alkanes, methylene chloride, and ethyl acetate, had been used, but recent scenarios show that they have been replaced with protic solvents such as ethanol and methanol for successful preparation of phytophospholipid complex. Herbosomes of silybin have been successfully prepared by using

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ethanol as a reaction medium by subsequently removing the solvent under vacuum.

In the study of solvents as a reaction medium for high percentage yield, ethanol is very useful as it leaves minimal solvent residue and has done very little damage to the phytoactive principles. Some buffer solutions and water as a solvent have also been employed. Many researchers have successfully applied the use of supercritical fluid-like carbon dioxide, having a clear advantage over aprotic and protic solvents concerning uniformity in size, shape, and size distribution of the vesicular structures. The combination of supercritical fluid (SCF) with supercritical antisolvent (SAS) is one of the promising modern techniques for the formulation of herbosomes.

Phytoconstituents

Most researchers have identified various phytoconstituents by screening them *in vitro* rather than on animal and human subjects for their pharmacological responses. In this matter, researchers have selected polyphenols for theformulations of herbosomes. The phytoconstituent, like hesperidin, is soluble inan aqueous phase, which acts as a barrier to pass through membranes. Some other phytoconstituents, such as rutin and curcumin, show lipophilicity, which makes them difficult to solubilize in gastrointestinal fluids. By complexing these lipophilic and hydrophilic active constituents with phospholipids, the solubility of these lipophilic polyphenol compounds in the aqueous phase will be improved and the membrane permeability of the hydrophilic polyphenol compounds will be enhanced. Through herbosomes formulation, which is also a phytophospholipid complex, it can protect these polyphenol constituents by destroying them from hydrolysis, oxidation, and photolysis.

Apart from polyphenols, other phytoconstituents such as siramesine andevodiamine are also suitable for phospholipid complexation. Thus, it can besuggested that polyphenols are not the only suitable phytoconstituents for herbosome preparation, as proven by other researchers. Recently, several new phytoconstituents have been successfully complexed with phospholipids to form stable and more biologically active herbosomes [14].

METHODS OF PREPARATION OF HERBOSOMES

Since the beginning of herbosomes development, different researchers have successfully developed various methods for herbosomes formulation. With the advancement of technology for the development of herbosomes, several novel methods have been successfully developed and optimised, and these methods are summarised below:

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Anti-solvent Precipitation

In this method, a specific quantity of standardized phytoextracts or phytoconstituents and phospholipids are generally placed in a reflux condenser, and the specific experimental conditions are generally maintained at below 60 °C and refluxed for 2-3 hours. The reaction mixture after it is being refluxed is generally concentrated up to 5-10 ml volume. Following that, low polarity solventlike n-hexane is added to the mixture with continuous stirring to obtain theprecipitates from it. Through this method, the herbosomes are prepared in theform of a precipitate. After filtration, the precipitate is stored in a desiccator. Aftercomplete drying, it is subjected to pulverization and powdering before it is stored in dark amber coloured glass bottles at room temperature.

Solvent Evaporation Method

In this method, an equimolar mixture of phytoextractives and phospholipids are kept in the same flask, which contains an organic solvent like chloroform. The mixture is kept at an optimum temperature between 40 to 50 °C, and it is refluxed for a specific period which is generally one hour, to attain the maximum entrapment of phytoconstituents in phospholipids to form herbosomes. The solvent used in the reaction mixture can be removed by subjecting the reaction mixture to a rota evaporator. The herbosomes are obtained in the form of a thin film. The herbosomes are dried overnight in a desiccator after being sieved *via* 100# sieve. Finally, the obtained herbosomes are stored in light-resistant, nitrogenfluxed amber-coloured glass bottles at room temperature [15].

Ether Injection Method

The selected phospholipid is dissolved in an organic solvent like diethyl ether, and the phytoextract is dissolved in an aqueous medium. Then, the dissolved phospholipid is injected into the aqueous phase containing the phytoextract that is to be entrapped into the phospholipid. The injection of the phospholipid into the aqueous media would result in the formation of cellular vesicles after the removal of the solvent at a reduced pressure, which would lead to the formation of phytophospholipid complex. (herbosomes) At low concentrations, the produced vesicles are small and uniform in size. However, different sizes of vesicles with different shapes like round, cylindrical, cube, or disc are obtained at higher concentrations. Therefore, it can be concluded that the uniformity, shape, and size of prepared herbosomes depend on the concentrations of phospholipids and phytoconstituents. Due to the non-uniformity in size and shape of the herbosomes produced, this method is not utilised often by researchers apart from some, although it is a simple and cost-effective method.

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Rotary Evaporation Method

This method is performed by mixing the phytoconstituents and a specific amount of phospholipids which is generally in the equimolar ratio, and it is dissolved in a round bottom flask with a water-miscible solvent, which is acetone. Then, the mixture is stirred for two hours, preferably at a temperature of 50 degrees Celsius in a rota evaporator. After two hours of stirring, an anti-solvent, n-hexane, is added to the obtained thin film. The precipitates obtained after filtration are generally stored in the amber-coloured glass bottles under controlled temperature and humidity.

NOVEL METHODS FOR HERBOSOMES PREPARATION

Of late, supercritical fluid has been employed for the preparation of certain larger size particles of 5-200 nanometre range. Different supercritical fluid methods have been applied by various scientists to improve the solubility of these possible drugs, which are poorly absorbed due to their low solubility properties. Some of the supercritical fluid techniques used for the production of phytophospholipid complexation are compressed anti-solvent process (PCA), gas anti-solvent technique (GAS), and solution enhanced dispersion by supercritical fluid (SEDS). Pururarin phospholipid complex has been successfully used with the application of supercritical fluid technique. In this technique, a supercritical fluid-like carbon dioxide at very high pressure and low temperature is added to the precipitation unit that has passed through a very small size nozzle into the reaction mixture of pururarin phospholipid complex. Through this technique, the uniformity, desired size, shape, and stability of the particles are achieved [16].

DOSAGE FORMS OF HERBOSOMES

The applications of herbosomes from the topical and oral routes are kept into consideration during the manufacturing process. The most suitable method is selected to manufacture the dosage forms of herbosomes to improve the bioavailability of phytoextract and provide ease of management. Different dosage forms that are successfully prepared are described as follows:

Capsules

Both hard gelatin and soft gelatin capsules of herbosomes are available in the market.

Hard Gelatin Capsule

Herbosomes can be filled in hard gelatin capsules through the direct volumetric filling method. However, there are times when the dry granulation method can be

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utilised for filling when the nature of the powder is bulky.

Soft Gelatin Capsule

Soft gelatin capsules are filled by dispersing the ingredients in the dispersion form; therefore, they are the most suited material for herbosome dosage forms. Natural or semisynthetic oil vehicles are used to fill the soft gelatin. As herbosomes are smaller than 200 micrometers in size, they provide excellent flowing properties to fill the soft gelatin capsules.

Tablets

Herbosomes are not suitable to be manufactured in tablet form due to their limited technological properties, such as flowability, stickiness bulk, and apparent density. For direct compression of herbosomes, they must be diluted with 60-70 percent excipients to improve their powder characteristics. Direct compressioncan be used to prepare the herbosomes when the powder dose is higher. Keeping the stability of herbosomes in consideration, wet granulation must be avoided because the water used during granulation could badly affect the entrapment ofthe phytoconstituents and can disrupt the vesicle. The heat that is used during the drying of granules can melt the phospholipid and consequently cause damage toit, therefore, wet granulation is not a suitable process for herbosomes manufacture.

Topical Preparations

The herbosomes are extremely suitable for topical preparations like emulsions and creams. For the formulation of a topical preparation of herbosomes, they are firstly dispersed in a small amount of oil phase and mixed with previously formulated emulsion, preferably at below 40-degree Celsius temperature. When the outer layer of the phytophospholipid complex is aqueous, they should beadded to an aqueous medium. Lastly, they are added to the already prepared emulsion, preferably under 40 degrees Celsius temperature. As herbosome is a lipid-based carrier system, if it is formulated for topical purpose in the form of aemulsion or cream, it provides a synergistic effect for absorption, membranepermeability, and bioavailability [17].

OPTIMIZATION OF HERBOSOMES

Herbosomes are optimized by taking various parameters into consideration. The prime factor for herbosomes optimization is the molar ratio of selected phospholipids and phytoextracts. Apart from that is the selection of solvent for dissolving the reaction mixture as well as the temperature at which reaction has to

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be carried out. The rotational speed for solvent evaporation technique and the method of drying with the above-mentioned parameters should be optimized for the formulation of herbosomes. All these parameters can be optimized statisticallyby designing the process through quality control (QBD) [18].

CHARACTERIZATION OF HERBOSOMES

Prepared herbosomes are characterised by various methods and instrumental techniques. Following is the description of various methods of herbosomes characterization.

Partition Coefficient and Solubility

To determine the solubility of formulated herbosomes in aqueous and aromatic solvents or n-octanol/water, the partition coefficient would characterize the active constituent, phytophospholipid complex, and unreacted mixture in physical form. The resultant phytophospholipid complex would always show better hydrophilicity and lipophilicity than active constituents individually. Herbosomes would also always show enhanced lipophilicity. When the phospholipid complex of embelin was analysed by Rahila, it was confirmed that the phospholipidcomplex of embelin had greater solubility in n-octanol than its physical mixtureand individual embelin.

Particle Size and Zeta Potential

Generally, the average particle size of herbosomes ranges from 50 nm to a few hundred microns; therefore, the determination of the zeta potential and particle size are important factors for the reproducibility and stability of the formed phytophospholipid complex. For this particular purpose, Zetasizer is utilised.

Yield

The term yield is related to the complexation rate at which the phytoconstituents phospholipid reactions occur. The weight difference between the initial weight of phytoextracts and the unreacted compound is the number of active constituents present in the complex. The amount can be determined by using the following formula [19]:

% Yield = [(A-B)/A] X100

A = Initial weight of selected phtoconstituent.

B = Weight of free active constituent.

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(A-B) = Weight of phospholipid complex.

Entrapment Efficiency

A certain amount of the complex is weighed, which is equivalent to the quantity of the active phytoextracts that have been encapsulated to determine the entrapment efficiency. The weighed amount is dissolved in a buffer solution and centrifuged for a specific period of time, usually one hour. The supernatant liquid is decanted off and centrifuged for 15 minutes at 5000 RPM speed. The supernatant liquid is filtered through a specific number of Whatman filter paper, and the clear liquid is analysed by UV or HPLC to determine the absorbance. To determine the entrapment efficiency, the following formula is used:

$$\%Entrapment\ Efficiency = \frac{Actual\ amount\ determined}{Theoretical\ amount\ present} \times 100$$

Crystallinity and Polymorphism

This is usually determined by employing differential scanning calorimetry and X-ray diffraction techniques. When the phospholipid complex is scanned through DSC, typical interaction is observed in the form of elimination of endothermic peaks, change in peaks and its onset, melting points, peak temperature, enthalpy, and related peak area. In the X-ray diffraction of a phospholipid, the reduction in the intensity of large diffraction peaks or its complete absence or disappearance is observed.

Stability of Vesicles

Determination of polydispersity index (PDI) particle size and Zeta potential is related to the stability of phospholipid vesicles. For this purpose, Zetasizer is utilised. The values for desirable particle size, Zeta potential, and PDI for a stable vesicle are 50 nm to a few µm, greater than 0.5 and greater than ±30 Mv, respectively [20].

Transition Temperature

DSC is used to determine the lipid vesicular system's transition temperature.

Measurement of Surface Tension Activity

The surface tension activity can be measured by using the Du Nouy ring tensiometer when the phospholipid complex is analysed in an aqueous media.

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Drug Release

The amount of drug content that can be released from the phytophospholipid complex is generally carried out by analysing the herbosomes through HPLC or any other suitable method of spectroscopy [20, 21].

Spectroscopic Confirmation of Herbosomes

Confirming the formation of phytophospholipid complex is the most crucial step in herbosomes technology. The success rate of the prepared herbosomes depends on the drug content and the phospholipid interaction. The formation of the herbosomal complex can be determined by the employment of the following spectroscopic techniques:

Fourier Transform IR Spectroscopy

This particular technique is able to confirm the phytophospholipid complex formation. The comparison between the spectra of herbosomes complex, individual phytoconstituents, and physical mixture of the components can confirm the formation of the phytophospholipid complexation. The spectra of herbosomes complex, physical mixture, and individual components differ from each other.FT-IR can be used as a quality control tool for the complex's stability, with micro-dispersion of a basic cosmetic gel being used for this purpose. The spectra of herbosomes in microdispersion in water or cosmetic gel are also being compared at different times [22].

Proton NMR (^{1}H NMR)

When the stoichiometric complex of catechin and other phytoextracts are subjected to proton NMR in an aqueous solvent, a marked change in PMR signalis observed, which is due to the involvement of the atoms from phospholipid complex that is different from the spectra of individual components. The signals from flavonoid protons are unable to be relieved in the complex due to thebroadening of proton spectra. All the signals from the complex have broadened while the singlet would correspond to the choline molecule with an uplift shift. Upon heating the complex at 60°C, the flavonoid moiety causes resonance, leading to the appearance of new broadband signals.

^{13}C NMR

Through C13 NMR analysis that is carried out in deuterated benzene on catechin and other similar phytoconstituents and their equimolar phospholipid complex, it is suggested that all flavonoid carbons present in the complex are visible. These signals are due to several factors, including the presence of glycerol, broadening

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of the choline portion of the phospholipid, shifting the position of some signals, retention of the sharp line of the fatty acid chains, as well as the original resonance spectra.

SEM/TEM

Scanning electron microscopy is an important tool to study the surface morphology and the solid-state properties of the formed herbosomes. Transmission electron spectroscopy produces clear information on the particle size of crystals in the nano range and the dispersion of these nanocrystals. SEM imaging has shown the presence of active phytoconstituents in a highly crystalline state, which would disappear upon complexation. Upon dilution with distilled water with slight stirring, TEM produces the vesicular structure of phytophospholipid complex.

X-Ray Diffraction

This technique is a highly effective tool to examine the compound in the microstructure form of crystalline and some amorphous substances. XRD is performed either for individual phytoconstituents or their complex and physical mixtures. When a compound is examined through XRD, intense crystalline peaks will correspond to the presence of active constituents and physical mixture. In the X-ray diffraction technique, the absence of a non-crystalline intense peak would suggest that the compound in the phytophospholipid complex is either in the molecular or amorphous form [23, 24].

MARKETED HERBOSOMES

Various manufacturers have formulated a variety of herbosomes with improved efficacy as compared to their extract or phytoconstituents. A summary of these marketed herbosomes with their application is tabulated in Table **1** [14, 25].

Table 1. Marketed formulation of Herbosomes available in the market.

Vernacular Name	Source/Origin	Active Constituents	Therapeutic Activity	Marketed Formulation
East Himalayan horse chestnut/Raman bih	*Aesculus assamica*Syn. *Aesculus punduana*Fam. *Sapindaceae*	Proanthocyanidin A_2	Improved Anti-aging effect (anti-wrinkle) protection from UV	PA2 Phytosome
Buckeye/Horse Chestnut	*Aesculus hippocastanum* Syn.*Aesculus assamica*Fam. Spindaceae	Triterpenoidal Saponins	Enhanced Anti-oedema and vasoactive properties	Escin β sitosterol Phytosome

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(Table 1) cont.....

Vernacular Name	Source/Origin	Active Constituents	Therapeutic Activity	Marketed Formulation
Himalayan ash/Flowering ash/Manna ash	*Fraxinus ornus*Syn. *Fraxinusf floribunda* Fam. Oleaceae	Esculoside (Esculin), a class of natural glycosides	Vasoactive, anticellulite	Esculoside Phytosome
Bishop's weed/Khella/Toothpick plant	*Ammi majus*Syn. *Ammi visnaga*Fam. Apiaceae	Visnadine is a potent and toxic compound	Improve microcirculation	Visnadex
Mandukparni/Brahmi	*Centella asiatica*Syn. *Hydrocotyl asiatica*Fam. *Apiaceae*	Asiatic acid, madecassic acid triterpenoids	Skin disorders, antiulcer, wound healing action	Centella triterpenoid Phytosome
Thron apple/Hawthron/May-tree	*Crategus oxyacanthoides*	Hyperin, quercitin	Nutraceutical, cardioprotective and antihypertensive	Hawthorn Phytosome
Kurkaru/Pumpkin/Field pumpkin	*Cucurbita pepo* Syn.*Curcumis pepo*Fam. *Cucurbitaceae*	Tocopherols, steroids, Carotenoids, natural pigments	Anti-inflammatory, Benign prostatic hyperplasia	Cucurbita Phytosome
Japanese knotweed	*Polygonum Cuspidatum* Fam. Polygonaceae	Ressveratrol	Free radical scavenging action	Rexatrol
Wild olive/Olive tree/Zaytoon	*Olea europaea* Fam. *Oleaceae*	Verbascoside, tyrosol, Hydroxytyrosol,	Antioxidant, antihyperlipidemic, anticancer and anti-inflammatory	Oleaselect Phytosome
Indian prickly ash/Tumburu/Chinese pepper	*Zanthoxylum bungeanum Syn. Zanthoxylum simulans* Fam. Rutaceae	Hydroxy-a-sanshool	Soothing and Anti-reddening	Zanthalene Phytosome
Bal kumari/Maiden hair Tree/Fossil tree	*Gingko biloba*	Gingko flavonoids, Gingoic acids, ginkgo flavone glucosides, ginkgolides, bilobalide, coloring pigments.	Antiamnestic, antidepressant, Cardioprotective, dermatitis, Anti-Inflammatory, Cognition enhancer, Raynaud's disease, Antiageing, anti-asthmatic	Gingkoselect Phytosome Gingko bilobaterpene Phytosome Gingko Bilobadimeric flavonoids

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(Table 1) cont.....

Vernacular Name	Source/Origin	Active Constituents	Therapeutic Activity	Marketed Formulation
Soya/Soya bean/Safed bhat	*Glycine max*Syn. *Dolichos sofa*Fam. Fabaceae	Genistein and daidzein	Antiangiogenic, anticancer, cardioprotective, immunostimulatory, and hypocholesterolemic	Soyselect Phytosome
Sweet wood/Mulethi/Yastimadhu	*Glycyrrhiza glabra* Fam. Lauraceae	Triterpenoidal saponin Glycyrrhetinic acid	Anti-inflammatory, used in dermatitis	Glycyrrhetinic acid Phytosome
Yellow sweet clover/Sparkka/Sweet lucerne	*Melilotus officinalis* Fam. Fabaceae	Melilotoside, flavanoids and terpenoids	Anti-inflammatory, in oedema, thrombophlebitis	Lymphaselect
Black Samson Echinacea/Cone flower	*Echniacea angustifolia* Fam. Asteraceae	Echinacosides and inulin	Nutraceutical, immunomodulatory	Echinacea Phytosome
Bitter orange/Mausami/ Nagaranga	*Citrus aurantium*Syn. *Citrus sinensis*Fam. *Rutaceae*	Naringenin, a flavonoidal compound	Antioxidant and anti-aging efficacy	Naringenin Phytosome,
Asiatic Ginseng/Ginseng/Renshen/Ninjin	*Panax ginseng* Fam. Araliaceae	Ginsenosides, a natural steroidal compound	Nutraceutical, immunomodulatory	Ginseng Phytosome
Millet/Broom millet/Broomcorn millet	*Panicum miliaceum* Fam. Poaceae	Mineral salts, vitamins unsaturated fatty acids, amino acids	Antistress, beauty food for skin, nails, and hairs	Millet Phytosome
Haridra/Turmeric/Yellow saffron	*Curcuma longa* Syn.*Curcuma domestica* Fam. Zingeberaceae	Curcumin, a yellow coloured natural pigment	Osteoarthritis, anticancer, Anti-inflammatory,	Curcumin Phytosome, Curcuvet (Meriva)
Tea/Shyamaparni/Black leaf tree	*Camellia sinensis* Fam. Theaceae	Epigallocatechin, epicatechin-3-O-gallate,epigallo catechin---O- gallate, catechin	Nutraceutical, anticancer, Antioxidant, atherosclerosis, hepatoprotective, antidiabetic, anti-inflammatory	Green tea Phytosome
Pine/Mritime pine/Cluster pine	*Pinus maritime*	Procyanidins, a class of natural tannins	Antiwrinkle, Anti-inflammatory, Antiallergic	Pycnogenol Phytosome
Yege/Kudzu root/Gegen	*Radix puerariae*Syn. *Pinus pinaster* Fam. Pinaceae	Puerarin, a compound of natural terpenes	cardiovascular diseases, Anti-inflammatory	Puerarin and phospholipid complex

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(Table 1) cont.....

Vernacular Name	Source/Origin	Active Constituents	Therapeutic Activity	Marketed Formulation
Knee Holly/Butcher's broom/Cladodes	*Ruscusa culeatus* Fam. Asparagaceae	Ruscogenin, neoruscogenin	Inflammation reducing, anti-ageing, Sunscreen agent	Ruscogenin Phytosome
Sandal wood/Chandana/Bhadrasara	*Santalum album* Syn.*Santalum ovatum*Fam. Santalaceae	Ximenynic acid, ethyl ximenynate	Improve microcirculation	Ximilene and Ximenoil Phytosome
Sabal/Saw palmetto	*Serenoa repens* Fam. *Arecaceae*	Phytosterols	Noncancerous prostate Enlargement	Phytosterols
Saint Mry's Thistle/Milk Thistle/Scotch Thistle	*Silybium marianum* Syn.*Cardus marianusFam.* Asteraceae	Silybin, silycristin,	Hepatoprotective, hepatitis, cirrhosis, and inflammation	Silybin Phytosome (Siliphos)
Black plum/Jamun/Jambu	*Syzygium cumini*Fam. Myrtaceae	Anthocyanins, a distinct group of natural Tannins	Hypoglycemic, anti-inflammatory, and antioxidant action	Madeglucyl Phytosome
Scotch Thistle/ Saint Mry's Thistle	*Silibium marianum Fam.* Asteraceae	Silybin	Liver protecting and anti-oxidant	Silyphos milk thistle
Silver cluster leaf/Vaalboom/Mususu	*Terminalia sericea* Fam. Combretaceae	Sericoside, glycosides	Anti-aging, skin restructuring	Sericoside
Blue berry/Lowbush blueberry	*Vaccinium angustifolium* Fam. Arecaceae	Anthocyanosides tocotrieno complex	Anti-oxidant, improves vision, brain tonic	Vita Blue Phytosome
Europian blueberry/Bilberry/Whortleberry	*Vaccinum myrtillus* Syn.*Myrtillus sylvaticus* Fam. Ericaceae	Anthocyanosides	Antioxidants, anti-inflammatory	Mirtoselect Phytosome
Grapes/Grape wine/Raisin	*Cissus vinifera*Syn. *Vitis vinifera* Fam.*Vitaceae*	Resveratrol, catechin, quercetin, epicatechin	Heart strengthening action and systemic antioxidant, nutraceutical	Biovin and leucoselect Masquiliers Phytosome
Yellow Himalayan Swertia/Swertia	*Swertia alternifolia* Fam. Gentianaceae	Xanthones 26	Hypoglycemic action	Swertia Phytosome

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LIMITATIONS OF HERBOSOMES

Herbosomes are not as prevalent in the market, despite having numerous advantages as a drug carrier. Due to various formulation limitations and difficulties, herbosomes are not the first or a popular choice for drug delivery systems. Yamila B Gnadola *et al.*, in 2014, have mentioned in their study that lecithin can induce the proliferation on MCF-7 breast cancer cell line. Several main disadvantages and limitations of phytosomes are mentioned below:

- Non-uniformity in vesicle size
- Stability of vesicles
- Phytoconstituents leaching off
- Poor yield
- High manufacturing cost
- Dosage form design
- Overdosing on vesicle rupture [26]

FUTURE PERSPECTIVES OF HERBOSOMES

Phytosomes have emerged as a novel preparation for the phytoconstituents and extracts with poor solubility profiles. By complexing these phytoactives with phospholipids, it does not only improve their solubility but also enhances the bioavailability and therapeutic efficacy. A variety of phytophospholipid complexes have been developed by various researchers for their novelty as a drug career for systemic actions. Despite having apparent advantages, the preparation, however, has its limitations, which cannot be ignored when developing new phytophospholipid complexes in the future. A prerequisite to overcome various issues of phytosomes, such as the selection of preparation technique, stability, entrapment, and actual clinical supremacy of phytosomal drug delivery systems, is that an intense research and development have to be explored effectively and selectively. For a wide range of clinical use of phytosome, non-toxic hydrophilic solvents like ethanol must be utilised rather than using toxic organic solvents for the preparation of phytosomes. The yield of phytophospholipid complex varies significantly from 25% to more than 90%, which is a result of the variation in different formulation factors, such as temperature, a drug to phospholipid ratio, and duration of the reaction.

These formulation factors must be kept in serious consideration for the future when developing the phytosomes. Each factor and parameter must be optimizedby a research-oriented approach for the best quality herbosome manufacture.Modern statistical tools, such as spherical symmetrical designing, factorial design,and other parameters must be used to optimize the phytoconstituents and phospholipid

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molar ratio, temperature, and other variables in obtaining the maximum entrapment efficiency and drug release profile [27].

CONCLUSION

Because of the lipophilic environment of the cellular membrane, flavonoids and phenolic compounds have shown poor solubility, thus resulting in poor membrane permeability and deprived bioavailability. Herbosomes are the complexation products of selected phytoconstituents with certain phospholipids such as phosphatidylcholine or phosphatidylserine. Herbosomes are amphibious microstructures with both hydrophilic and lipophilic cores, which would result in enhanced membrane permeability and as a result, increased bioavailability of phenolic and related chemicals with medicinal potential. Of late, with advancements in technology and instrumental methods of analysis, phospholipid complexes have become more popular among phototherapies. In the last few decades, herbosomes have been manufactured from conventional methods such as anti-solvent precipitation and mechanical shaking. In recent times, however, a novel method like the application of the supercritical fluid process for the manufacture of herbosomes is in demand, which is a revolutionary upshift in herbosome technology. The yield, stability, and other physicochemical properties of the phospholipid complexes have been improved tremendously. With applications of modern instrumental analytical techniques for the confirmation and characterization of herbosomes, SEM/TEM, XRD NMR, FT-IR play important roles in the quality control of these complex. These advanced instrumentations help in selection, optimization, and GMP/GLP practices for the herbosomal technology of herbosomes with their components. Herbosomes possess many applications, which include the hepatoprotective potential of hesperidin, antioxidant efficacy of tea, and Catechin herbosomes. Similarly, several herbosomes are in the market for their remarkable anticancer, hypoglycemic, and hypolipidemic actions. Finally, it can be concluded that herbosome technology is simple, reliable, and popular to improve the bioavailability of phytoextracts with poor solubility and absorption profile.

CONSENT OF PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 6

Role of Nanomedicines in Ocular Targeting Drug Delivery Systems

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Abstract: Ocular diseases have become a socioeconomic burden throughout the years. Blindness and visual impairment are the two most common ocular diseases worldwide. Not only do they affect the patient, but also the people surrounding them and the community that they are in. There are a lot of medications available for the treatment of ocular diseases, however, these have poor bioavailability because of the structure of the eyes and the barriers that they have. Nanotechnology has been providing significant contributions in the treatment of ocular diseases. Several studies and research are currently being focused on the development of nanomedicines that can achieve more than what the conventional routes of medications of ocular drugs can. Nanotechnology can also provide sustained and targeted delivery systems for ocular drugs. This chapter discusses the mechanisms that would enable nanoparticles to penetrate the ocularbarriers and eventually increase the bioavailability of drugs intended to treat ocular diseases.

Keywords: Exosomes, Glaucoma, Nanomedicine, Ocular.

INTRODUCTION

Ocular illnesses, whether they cause vision impairment or not, cause personal and financial difficulties [1]. Ocular diseases not only affect the vision but also have significant impacts on the patient's quality of life [2]. There are a lot of drug delivery systems available for the treatment of ocular diseases, but because of the anatomical structure of the eye and its physiological barriers, the efficacy of these drug delivery systems has limitations [1, 2]. Nanotechnology has been emerging in the treatment of ocular diseases as nanotechnology-based solutions for improv-

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improving ocular drug delivery systems [1]. Formulating techniques that will be effective for the therapeutics for ocular diseases is achievable through nanotechnology [1]. Numerous studies and research for nanotechnology-based techniques for the treatment and management of ocular diseases are being developed [2]. With the fast-advancing technology, the approaches based on nanotechnology will increase in numbers [1].

THE HUMAN EYE

The most dominant sense of human beings is the vision, which is crucial in everyday lives. Up to 80% of the information that a human acquires from the surroundings is perceived by vision, making it the most significant among the five human senses. Structure-wise, the human eye is a round-shaped organ and has a size of approximately 24 millimetres. The eye comprises two main parts. The first segment is the anterior segment, and the second segment is the posterior segment (Fig. **1**). Both the anterior and posterior segments of the eye have a variety of barriers that protect the eye against foreign bodies. The lens, the iris, the corneal, and the aqueous humour make up the anterior segment, while the vitreous body, retina, choroid, and back of the sclera are in the posterior region [2]. The eye also consists of three fluid chambers, which are a. anterior chamber, which is bounded by the cornea and the iris; b. posterior chamber, bounded by the iris and the lens; c. the vitreous chamber, which is bounded by the lens and the retina. The anterior chamber and posterior chamber are loaded with aqueous humor responsible for supplying oxygen and nutrients to the lens and the cornea. The vitreous humor, on the other hand, is the one filling up the vitreous chamber [1].

The cornea is transparent, and it has five layers which are the epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. The most important part of the corneal barrier is the corneal epithelium because it has many layers of corneal epithelial cells connected by tight junctions. The penetration of drugs into the ocular cavity, especially those with hydrophilic molecules, is extremely prohibited because of the tight junctions. The passing of hydrophobic molecules, on the other hand, is hindered by the corneal stroma, which is mainly consisting of hydrophilic collagen [2]. In totality, almost 90% of the barriers to medications that are hydrophilic and 10% to those that are lipophilic are made up by the corneal epithelium [1]. On the epithelial cells, there are efflux transporters that demonstrate great significance in the avoidance of the permeation of anti- glaucoma and anti-viral drugs [2].

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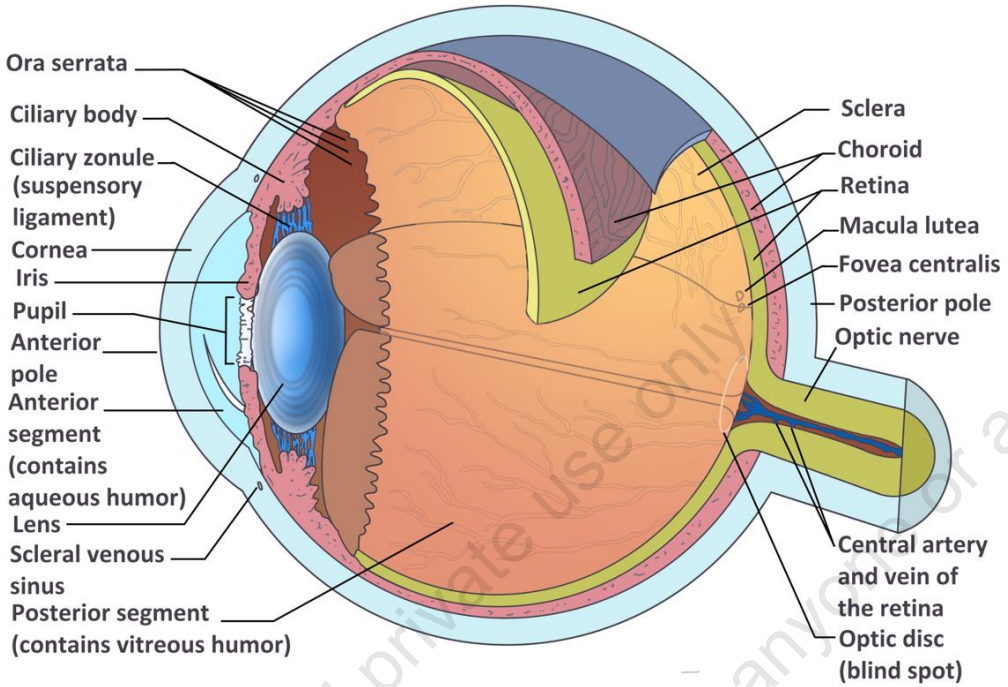

Fig. (1). The anatomy of the human eye [3].

Drug delivery into the retina is hampered by numerous barriers of the eye, including the blood-retinal barrier [4]. The domain inside the eye has two major barriers, which are the blood-aqueous barrier and the blood-retina barrier. The blood-aqueous barrier consists of the ciliary body, which has the non-pigmented epithelium. The schlemm's canal endothelium, the iris epithelium, and the iris vessel endothelium that has a tight junction are the composition of the non-pigmented epithelium of the ciliary body. The paracellular transport and the active transport are controlled by tight junctions. The blood-retinal barrier, on the other hand, is parted into the inner blood-retinal barrier and the outer blood-retinal barrier [2]. The blood-retinal barrier assists in the regulation of the homeostasis in the retina through the control of fluid and molecule exchange between the retina and the blood. The blood-retinal barrier also prohibits the penetration of macromolecules [5]. These two portions of the blood-retinal barrier prohibit the molecules from penetrating the intraocular chamber, which results in the inefficiency of the therapeutics on the intraocular tissues [2].

The administration of ocular drugs *via* the topical route to the anterior segment of the human eye is also limited because the corneal surface has clearance mechanisms [2]. Approximately 5% of lipophilic molecules and 0.5% of hydrophilic

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molecules can enter into the anterior segment of the eyes [1]. Additional reasons are the precorneal factors that include blinking of the eyes, tearturnover, tear film, drainage of the solution, and lacrimation. The human tear film has a very rapid restoration time of only 2 to 3 minutes. Due to this, most topical drugs, after administration, are, within only a few seconds already washed off.The limit of capacity in the vessel is 30 microliters, and when the volume of the therapeutic solution which is to be administered topically is more than this, most of the drug is wasted through nasolacrimal drainage. Due to these factors and the other ocular barriers (Fig. **2**), the administered drugs' efficacy is less than 5% which would suggest poor bioavailability of the ocular drugs [2].

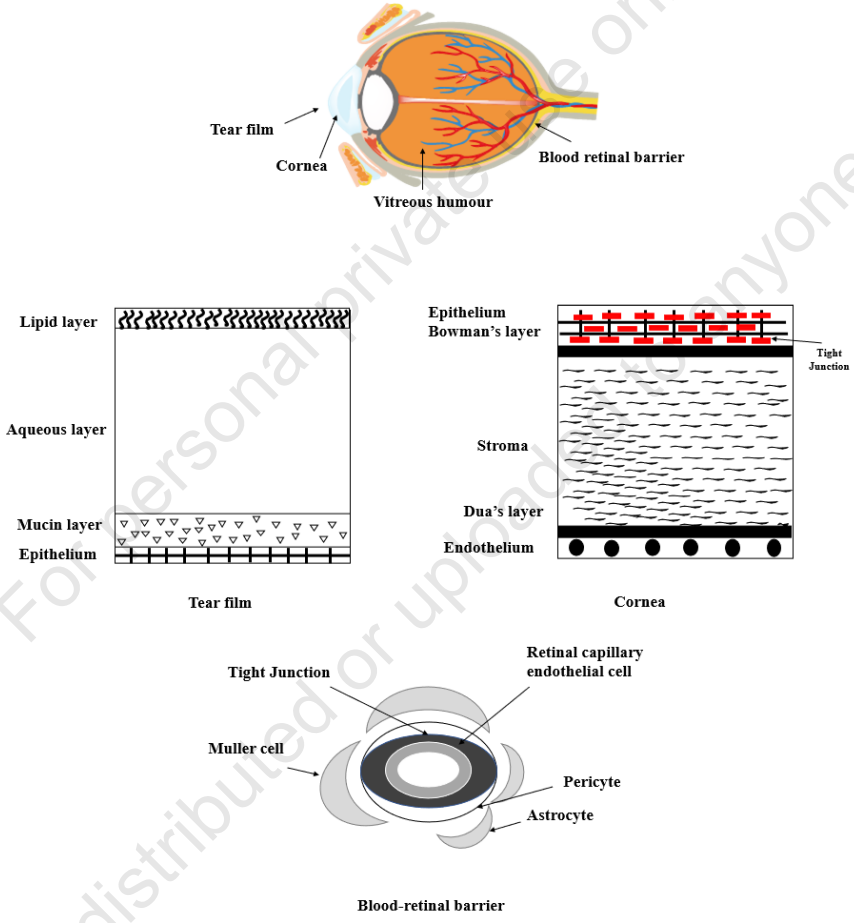

Fig. (2). Ocular barriers in drug delivery. **(A)** The human eye and its major ocular barrier. **(B)** The tear film: tear flow, protein binding, enzymatic degradation, and nasolacrimal drainage, which reduce the bioavailability of topically applied drugs. **(C)** The cornea: The tight junctions in the corneal epithelial cells and alternating polarity nature of the cornea limit drug permeation through the cornea. **(D)** Scheme of the**(D1)** retina and **(D2)** inner BRB. Red labels indicate the location of tight junctions between retinal capillary endothelial cells (inner BRB) and between retinal pigment epithelial cells (outer BRB) [1].

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DISEASES OF THE HUMAN EYE

Human vision is not the only thing that is affected by ocular diseases, as these diseases also affect the quality of life. A survey from 39 countries showed that there are approximately 285 million people suffering from impairments of vision. Among these people, 65% are more than 50 years of age [2]. In industrialized countries, the leading cause of visual impairment and blindness is disease-related retinal damage. This weighs down the economy of these countries and the quality of life of the patients [4]. It is approximated that above 1 billion people sufferfrom impairment of vision that could have been prevented by prompt treatment. These figures will rise extremely in the future decades due to lifestyle choices, such as screen time and aging [1]. Currently, 180 million people are affected by blindness. It is approximated, by 2020, that the commonness of people who suffer from blindness would increase to about 200 million globally. Not only does blindness tragically affect the patients' lives and the lives of those around them, but it also brings about extensive healthcare costs. In reality, the total health care expenditures globally were prognosticated to rise to 2.8 trillion dollars by 2020 [5]. The most common posterior segment diseases of the eyes are age-related. Thenumber of patients who suffer from posterior segment eye diseases increases with the global population's aging. Glaucomatous retinal degeneration, diabetic retinopathy (DR), and age-related macular degeneration (AMD) are some of the retinal diseases that need new treatments as the treatments of these diseases are challenging. Drug delivery to the retina is obstructed by many ocular barriers, making retinal diseases untreatable by topical, systemic, or periocular administration routes because not enough drug concentrations are delivered to the retina [4].

Currently, the available therapeutic remedies are typically aimed at restoring eyesight or detecting severe ocular diseases at an early stage. Thus, developing and improving both the diagnostics and therapeutics for ocular diseases are gaining more and more attention [2]. Several pathologies of blindness originate in the retina. It is due to this that many academic and industrial types of research are devoted to drug deliveries to the posterior portion of the eyes [5]. Important accomplishments are being put together in discovering the mechanisms of ocular pathology and ocular disease management. However, because of the physiologicalbarriers of the eyes and their anatomical structure, diagnosing and treating these diseases could be of low efficiency and low specificity [2]. Intravitreal implants and nanoparticles are two of the enhanced drug delivery systems that are continually being studied and developed. *In vitro* and *ex vivo* studies allow the investigation of the ocular barriers that affect drug delivery. *Ex vivo* explant cultures allow for experiments on larger and more relevant ocular tissues species, such as non-human primates, pigs, and even human eyes, which would provide more relevant information without

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costing too much or requiring extensive *in vivo* research. Therefore, the appropriate utilization of *in vitro* and *ex vivo* models can be a major move in designing and optimizing the therapeutics and ocular drug delivery systems [5].

The eye is one of the human body's most fragile organs. The leading cause of blindness is glaucoma. In patients with glaucoma, the progression and advancement of the disease cannot be contained by decreasing the intraocular pressure. It is due to this that there will be a future rise in the research for novel drug delivery systems and targeted therapeutics [6]. Glaucoma is distinguished by neurodegeneration. This disease has significant effects on the retinal nerve fibre layers and also on the head of the optic nerve. Glaucoma is also considered one ofthe leading causes of visual impairment globally [1].

OCULAR DRUG ADMINISTRATIONS

The barriers of the eye, both anatomical and physiological, limit the permeation of therapeutic agents and restrict efficient drug delivery to intraocular tissues [1]. For systemic routes, oral dosing and intravenous injections are the prevalent administrations for drug delivery to the eyes (Fig. **2**). The eyes' choroid has a vascular structure of the choroid plexus and has blood vessels through which the drugs can easily enter. The outer blood-retinal barrier of the RPE cells, however, is the one responsible for facilitating the entry of drugs from the choroid to the retina. Only 1 to 2% of the drugs administered could have access to the retina and vitreous body because the tight junctions of the RPE cells prevent the entrance of most drugs. It is, therefore, still a challenge for drugs to be delivered systemically to the deeper side of the eyes [2].

Topical administration is easy to use in treating ocular diseases, especially those that have effects on the eye's anterior segment (Fig. **3**) [1]. For the topical route, eye drops are the major form of administration. This is because of good compliance from the patients and also due to economic considerations. The dissolution of the drugs in the eyes is usually through two absorption routes whichare the corneal route and the conjunctiva route. The corneal route involves the cornea, the aqueous humor, and the intraocular tissue. The conjunctiva route, on the other hand, involves the conjunctiva, sclera, choroid, retina, and vitreousbody. Only less than 5% of the total drug administered reaches the aqueous humorbecause of the corneal barriers and pre-corneal factors. It is for this reason thateye drops have to be administered more frequently for them to maintain their therapeutic drug concentrations. Corneal diseases, iris diseases, and glaucoma are proven to be more

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efficiently treated by eye drops. In the treatment of posterior eyes diseases, such as intraocular cancers and retina diseases, however, eyes dropsare still less efficient even when frequent dosing regimens are used [2].

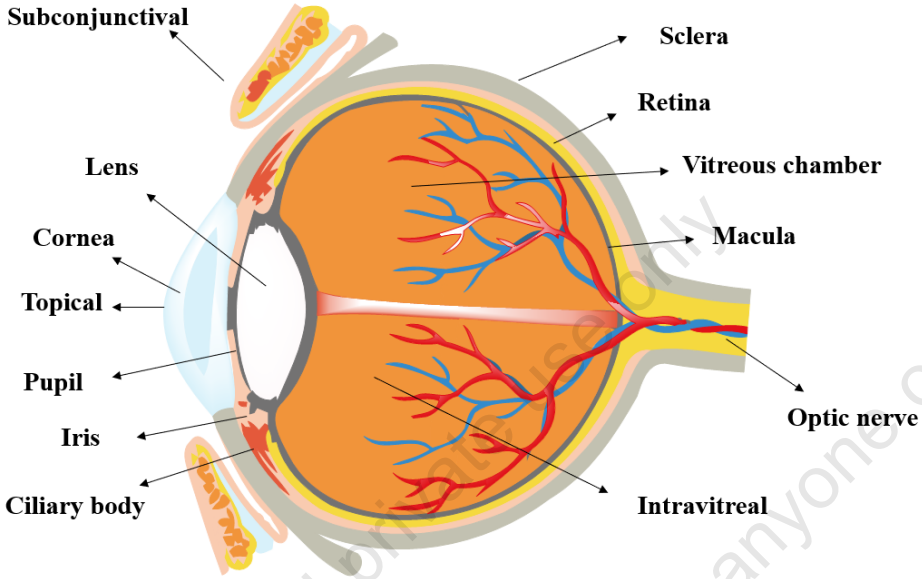

Fig. (3). Anatomy of the human eye and the routes of administration of traditional and nanosystems, with black arrows being the parts of the eye and the red arrows representing the routes [2].

Intravitreal (IVT) injections and topical injections are among the drugs that can be administered *via* injection (Fig. **3**). These drugs can either be solution or suspension and are to be administered *via* injection into the vitreous cavity, usually by a 27-gauge needle or a 30-gauge needle. The volume of solution that can be injected directly into the vitreous cavity without causing any discomfort is usually 20-100 microliters (μL). Compared to other routes of drugs for the human eyes, intravitreal injections are the ones that can provide high concentrations ofthe drug in the vitreous body and retina, and because of this, it can be considered as an efficient route in the treatment of posterior eye diseases. Because of the gel- like consistency, however, patterns of the distribution of the drugs in the vitreous cavity are heterogeneous. The molecular weight and the pathological conditionsof the vitreous cavity, and the molecular weight of the drug are relevant factors that affect the molecular distribution. Small molecules can quickly be distributed in the vitreous cavity, while linear molecules having more than 40 kDa or round molecules which are larger than 70 kDa retain longer in the vitreous cavity. Hyaluronan, a significant part of the vitreous body, interacts with cationic nanoparticles as well as liposomal gene complexes. This reaction occurs due to electrostatic interaction and results in the accumulation of nanoparticles, reducing

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the efficacy of gene delivery [2]. In retinal drug delivery systems, intraocular drug administration like intravitreal, subretinal, and suprachoroidal injections are utilized. Among these intraocular drug administrations, intravitreal injections are the only ones used clinically worldwide. IVT injections are frequently used in anti-vascular endothelial growth factor (anti-VEGF) for treating AMD. IVT injections make up 80.6% of the therapeutic market for retinal diseases. The IV injections that are accepted in the clinical setting have various advantages, and these include the following: retina delivery is ensured as the drug is directly injected into the vitreous humour, the injections bypass the different ocular barriers, and these injections have less systemic side effects. However, the problem arises for the patients and the healthcare system with the required frequent IVT dosing of these injections. The required interval of injection isdependent on the status of the disease. . For serious diseases such as wet AMD, more frequent drug administrations are accepted compared to slow-progressing early-stage diseases like dry AMD. For anti-VEGF antibodies like bevacizumab, the intervals are 1 to two months, and this results in the reduction of the compliance of the patient, which subsequently leads to suboptimal therapeutic outcomes. For molecule drugs that are small in size, the dosing intervals of the injections are too short, usually a few days, since the IVT half-lives of these molecules are normally less than 10 hours. The necessity of developing drug delivery systems for the retina that have prolonged injection intervals remains unmet [4]. Being an invasive procedure, the intravitreal injection can cause the following complications as it has to penetrate all the layers of the eye: cataract, retinal detachment, iritis, uveitis, endophthalmitis, and even intraocular haemorrhage. Repetition of injections will, of course, give rise to the occurrence of such complications. There is a route that is less invasive than the intravitreal injection, and it is the periocular injection. The periocular injection has a sequence of injections administered topically, which are needed to control the downsides of systemic administrations and increase the concentration of the drugs in the tissues of the eye. Periocular delivery includes retrobulbar, peribulbar, sub-tenon, and subconjunctival injections, and these reach the posterior segment of the eye by penetrating the scleral or the corneal choroid (Fig. **3**). These routes, however, are also not that efficient in drug retention prolongation of the drugs [2].

BARRIERS OF THE EYES

Barriers in Intravitreal Injections

The vitreous body: Structure-wise, the vitreous body is gel-like and has a volume of 4 millilitres, which amounts to 80% of the human eye. Regulating the size of the eye throughout eye development is the most considered function of the vitreous body. The vitreous body's density is estimated to be that of water as it is made up

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of extremely high water content, which is about 98-99% [5]. The vitreous humor is a gel that is clear in appearance and consists of 99% water. It also consists of glycosaminoglycans and collagen fibres. The vitreous humor also has low contents of proteins, which include proteases, protease inhibitors, growth factors, cytokines, and signalling, binding, and visual perception proteins [1]. The gel structure of the vitreous body consists of a 3-dimensional network of type II, IX, and V/XI collagen fibers. The most abundant collagen fiber type is type II, amounting to 60-75%. The strength against mechanical tensions and the flexibility of the vitreous body is accounted for by these collagen fibres. The spaces betweenthe fibrils are referred to as glycosaminoglycans (GAGs). Hyaluronic acid is a negatively charged CAG, and it represents the bulk [5].

The Inner Limiting Membrane: The inner limiting membrane (ILM) is made up of intertwined networks that are composed mainly of type IV collagen fiber, laminin, and fibronectin. The ILM makes up the boundary that separates the vitreous and the retina. It is strongly backed up by evidence that the lens and ciliary body are where ILM proteins are primarily produced during embryogenesis. The ILM is a necessity in the early stages of eye development. The absence of ILM can be connected to abnormalities of the retina. However, in a fully-matured eye, theILM is not that necessary since the peeling of ILM is not related to adverse visual effects of severe intensity [7]. The composition of the ILM, like that of thevitreous, varies throughout the regions.The thickness of the ILM varies by area, but it becomes more consistent towards the posterior pole [5].

Barriers in Subretinal Injections

The subretinal injection is injected below the neural retina and between the layers of the RPE photoreceptors. There will be a fleeting detachment between the two layers if a typical volume of 150 microliters is injected [5]. It is due to the retinal detachment that the subretinal injection is considered to have more severe complications as compared to the intravitreal injection. Retinal detachments can result in the death of the photoreceptor and even the loss of vision. Also, with the subretinal injection, there is a need for full anaesthesia and a vitrectomy after observing that this is a quite invasive route of administration [8].

The neural retina: In the back of the eye, there is a tissue that receives light and transmits this light to the brain, where signals are eventually refined and processed into images, and this tissue is called the retina. The retina allows interactions between the photoreceptors, neurons, and glial cells through its organized multilayered structure. The retina has a dense structure, and this is where the role of the retina as a barrier originates from. This dense structure hinders the free diffusion of large therapeutic molecules [5].

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Barriers in Intravenous Administration

Aside from oral dosing, intravenous injections are also among the prevalent administrations for drug delivery to the eyes [1].

The blood-retinal barrier: The blood-retinal barrier assists in controlling the homeostasis of the retina through the tight regulation of fluid and molecule exchange between the blood and the retina [5]. The blood-retinal barrier is parted into the inner and outer blood-retinal barriers. The inner blood-retinal barrier consists of the retinal vascular endothelium with tight junctions, while the outer blood-retinal barrier is composed of a monolayer retinal pigment epithelium (RPE) that also has tight junctions [1]. The tight junctions in the inner blood- retinal barrier are also known as zonula occludens, which are interlaced with adherens and gap junctions. Paracellular transport is controlled strictly by the sophisticated junction structures of the inner blood-retinal barrier [5].

Barriers in Suprachoroidal Administration

In retinal drug delivery systems, intraocular drug administration like intravitreal, subretinal, and suprachoroidal injections are utilized [4]. The suprachoroidal space is the virtual space in between the sclera and the choroid. Thesuprachoroidal administration involves the injection of therapeutics into this suprachoroidal space. This suprachoroidal space is usually nonexistent, but under the influence of the pressure that is applied by the injection and fluid volumes of up to 200 microliters, this border can open up [5].

Choroid: In between the sclera and the RPE layer is a highly vascularized layer which is the choroid. The main function of the choroid is the delivery of oxygen and nutrients to the outer retina. Thermoregulation of the retina and assistance in eye focusing are other functions of the choroid. The estimated thickness of the choroidal tissue at birth is 200 micrometres, which thins down with aging [5]. The choroid has a vascular choroid plexus structure. The blood vessels of the choroid enable the drugs to enter easily. However, the transport of drugs from the choroid to the retina is controlled by the outer blood-retinal barrier of the RPE cells, and since these RPE cells have tight junctions, the entry of most drugs is prohibited [2].

Barriers Encountered After Transscleral Administration

The transscleral drug delivery system is also known as periocular drug delivery. This delivery system is a collective term for the various routes of administration, including subconjunctival, sub-tenon, peribulbar, and retrobulbar routes [2, 5].

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The periocular injection can increase the concentration of the drugs in the intraocular tissues [2].

Sclera: The white part of the eye is called the sclera. The sclera is the outer opaque layer of the ocular sphere, and it combines with the cornea of the front of the eye. The purpose of the opacity of the sclera is to prevent light scattering internally to ensure an ideal retinal image. There is no consistent thickness of the human sclera, but on average, it is about 0.5 millimetres at the limbus to 1millimetre at the optic nerve. The following are the other mechanical functions of the sclera: providing general support to the eye, maintenance of the eye when it is moving, and protection of the eye against increased internal ocular pressure and external injuries [5].

NANOTECHNOLOGY

Biopharmaceutics is gaining more applications from the emerging fields of nanotechnology and nanoscience. Nanoscience is an interdisciplinary field that combines material science, physics, chemistry, and biology, making it a very interdisciplinary field. Nanotechnology, on the other hand, includes the design and creation of different materials at a nanometer scale in at least one dimension [2]. In other words, nanotechnology is the nanoscale engineering technology performed on nanometer scales. The recognized father of nanotechnology is Richard Feynman, and in 1959, he proposed the utilization of nanoscale machines in modifying atoms and molecules. Between 2000-2019, it is estimated that a global investment of US$150.5 billion had been made for the progressive researchand development of nanotechnology. Publications regarding nanotechnology havealso increased from 1999 to 2019, and most are focused on using nanotechnology in drug delivery systems [6].

Particles that have the size of less than 100 nm in one of the dimensions are called nanoparticles. These nanoparticles have different chemical compositions, including polymers, metal, and silica. Natural and synthetic polymers can be found in polymeric nanoparticles, whereas metal oxides and noble metals are examples of metal nanoparticles. Silicon dioxide nanoparticles (SiO_2) are a type of silica nanoparticle. Nanoparticles can also differ in size and form, for example nanorods, nanostars, and nanocages. These particles enable the combination of hydrophilic or hydrophobic therapeutic compounds [6].

Nanoparticles provide adjustable systems which eventually provide particles with specific characteristics. These particles also consist of specific performances,which are then appropriate for various applications. In the fields of biology and therapeutics, nanoparticles have been utilized in experiments for the treatment of cancer, gene therapy, and enhancing drug delivery systems [9]. In their use in

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drug delivery systems, nanoparticles improve and enhance the solubility, absorption, and eventually, the bioavailability of especially the water-insoluble compounds and large molecules. Drug delivery to specific cells, tissues, andorgans can be achieved using nanoparticles. This is of great advantage as it leads to the reduction of drug dosage, which will ultimately reduce the side effects and keep toxicological reactions at a minimum [1].

NANOTECHNOLOGY IN OCULAR DISEASES

Various applications of nanotechnology have been used in investigative studies as a new perspective in treating ocular diseases [1, 6]. It is for this reason that nanoparticles can overcome the anatomical barriers of the eye, which include the conjunctiva, the cornea, and of course, the BRB, and that nanoparticle-based drug delivery systems are now receiving attention [1].

Numerous nanotechnology-based solutions for the treatment and management of ocular diseases are being developed [1]. Some of these nanotechnology-based strategies are as follows: sustained release, enhancement and improvement of bioadhesives, stealth function, stimuli-responsive release, and specifically targeted delivery. Consequently, several attempts have been made to focus on fabricating multi-faceted nanosystems for the therapy of ocular diseases through the improvement of the delivery of drugs and therapeutics to not only the anterior segment but also to the posterior segment of the eye [2].

Several novel ocular drug delivery systems based on nanosystems are being developed. These nanosystems are as follows: nanoparticles, nano micelles, dendrimers, and cyclodextrins (Fig. **4**) [1]. These nanosystems are majorly from either natural or synthetic polymeric materials. Several of these materials are colloidal systems, including the following liposomes, niosomes, micelles, dendrimers, *in situ* hydrogels, and cyclodextrins [2]. With these nanosystems, several drugs used in the clinical practice for treating ocular diseases are being experimented and studied on; the purpose of this is to provide administrations *via* the topical, intravitreal, systemic routes. In pharmacokinetic studies, free drugs are being compared to drugs that are delivered using nanoparticle-based approaches. For this, the efficacy of nanosystems is being highlighted for ocular drug delivery systems [1].

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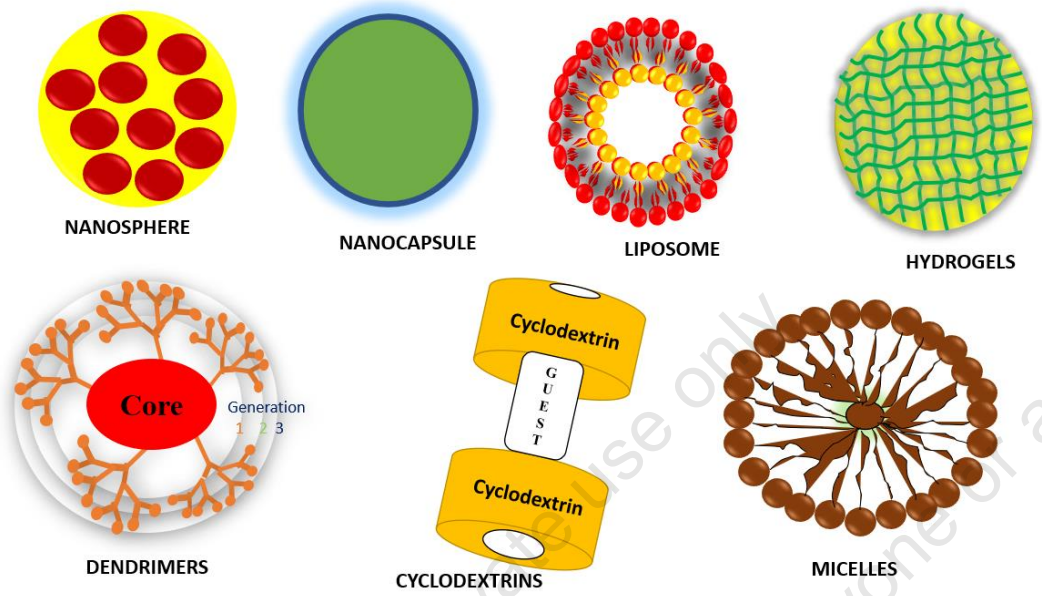

Fig. (4). Nanotechnology-based systems used in ocular diseases [2].

NANOTECHNOLOGY IN THE DIAGNOSIS OF OCULAR DISEASE

In the diagnosis of clinical ocular diseases, numerous approaches are utilized. Some of these are positron emission tomography (PET), magnetic resonance imaging (MRI), optical coherence tomography (OCT), fundus photography, ultrasonography, fluorescein angiography, and confocal microscopy. These are significant approaches for the monitoring of ocular diseases. The MRI, for example, provides imaging of neovascularizations *in vivo* to monitor the progression of ocular diseases, such as ocular tumor angiogenesis, diabetic retinopathy, and AMD. There are, however, only limited advantages for these approaches because they have poor imaging sensitivity or poor imaging resolutions. PET has high sensitivity, but its spatial resolution is limited. MRI, on the other hand, has good spatial resolution but has low sensitivity.

Nanotechnology offers several options to overcome these disadvantages [2]. Some approaches for other diseases like tumor-targeted multimodal imaging canalso be used to diagnose and even treat diseases of the eyes [10].

Anderson *et al.* used a rabbit corneal model and developed a system that exhibited site-directed contrast enhancement in angiogenic vessels. This system has an emulsion of Gd-perfluorocarbon nanoparticulate, which is associated with a biotinylated anti-αvβ3 monoclonal integrin antibody DM101. The average signal intensity of the MRI was enhanced to 25% *in vivo* 90 minutes after the administration of the targeted agent. For OCT, a particularly attractive contrast

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agent that can be used is gold nanoparticles. Because of the sizes and shapes of gold nanoparticles, the optical resonance wavelengths can be accurately tunedover broad ranges. OCT imaging of samples uses gold nanocages of about 35 nm edge length. Gold nanocages exhibited broad-spectrum absorption ofapproximately five units of magnitude, which is higher than the traditional and conventional indocyanine green in the near-infrared spectra region. For tumor imaging, quantum dots are good options as they have a wide excitation spectrum and narrow emission wavelength [2].

NANOSYSTEMS FOR THE TREATMENT OF ANTERIOR OCULAR DISEASE

Ocular anterior diseases include corneal injury, dry-eye, keratitis, conjunctivitis, and cataract. For these diseases, eye drops are the most commonly used for treatment as they are the most accessible. This route has poor bioavailability because of the corneal barriers and other pre-corneal factors. Corneal surface impairment, tear film instability, cornea inflammation, and conjunctive inflammation are some of the disorders that can result from using eye drops on a frequent and long-term basis. [2]. Eye drops can also cause blurred vision on administration as it does not quickly mix with tears after it is instilled [11]. Nanosystems are being used in the prolongation of the retention of drugs on the ocular surface as well as in the improvement of drug penetration [2].

Within the past decades, nanosystems have been developed for the diagnosis and the favorable treatment of ocular anterior disease [12]. An example of this is the flurbiprofen-loaded PLGA nanoparticles sized approximately 200 nanometers.This flurbiprofen-loaded PLGA nanoparticle exhibited burst and ensuing release profiles *in vitro*. With this therapeutical approach, anti-inflammatory responses are improved when compared to commercial eyes drops of flurbiprofen. This approach was experimented on a rabbit ocular inflammation model. To add, the nanoparticles, which are uniform in size of around 100 nanometers and which are loaded with flurbiprofen, exhibited equal inhibition on the miotic response. This is even possible at a dosage that is lower than commercial eye drops. This is associated with the elevated release of drugs from the nanoparticles and also with the ability to penetrate the aqueous humor. The only problem with this is the plausible rapid elimination of these therapeutic formulations from the surface of the eyes [2].

Gel system *in situ* is being highlighted in research, and this system includes stimuli-responsive hydrogels like thermo-, pH-, and ion-sensitive hydrogels. Upon installation of the hydrogel in the surface of the eye, the nanoparticles and the drugs can move out of the hydrogel upon blinking of the eyes, and they will be

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released sustainably. Ion-activated hydrogels, such as Timoptic-XEs, and pH-sensitive hydrogels, such as Virgans are commercially available. A micellar supramolecular hydrogel with ethylene glycol, block polymer, methoxy poly, and alpha-cyclodextrin has been invented recently [2]. Hydrogels are thixotropic,which makes them suitable for drug delivery to the eyes. *In vitro* studies exhibit that the penetration of hydrogels is better than that of the micelle formulations [13].

Contact lens users are at an advantage because of the long retention of drugs on the corneal surface. A nanowafer, which consists of a lineup of drugs, can withstand the blinking of the eyes and remain on the surface of the cornea for many hours. This therapeutic formulation can sustain a controlled release of drug for hours to days, and eventually, it provides improved and enhanced therapeutic efficacy in the treatment of corneal neovascularization [2]. The nanowafer that contains Axitinib had *in vivo* efficacy against corneal neovascularization [14].

NANOSYSTEMS FOR THE TREATMENT OF POSTERIOR OCULAR DISEASE

Posterior ocular diseases most commonly occur in the retina and the choroid. ADM, posterior uveitis, glaucoma, choroidal neovascularization (CNV), and retinoblastoma (Rb) are some of the examples of posterior ocular diseases. In general, eye drops manifest lower drug bioavailability in the tissues in the posterior segment than in the tissues of the anterior segment. The reason for this isthe lengthy diffusion distance from the surface of the cornea to the retina or the choroid. Repeated intraocular injections, however, can cause unwanted side effects and even poor patient compliance [2].

Within the past decades, a lot of effort has been put into the improvement of drug delivery systems that would be utilized for the therapy of ocular posterior disease. The focus is greatly on the improvement of controlled long-term delivery systems, and this is for the reduction of the recurrence of injections, which include nanoparticles, hydrogel, nanoimplants, and nanosized vesicles [2].

A light-activated solution created from polycaprolactone dimethacrylate (PCM) and hydroxyethyl methacrylate (HEMA) has been effectively invented and injected for use in the therapy for CNV. After the cross-linking, which is activatedby light, there would be a formation of hydrogel *in situ* for a sustained-release of Bevacizumab drug delivery system. This system's main limitation is the toxicity to the eyes of the photoinitiator [2].

The main target for numerous drugs and other gene-based therapies is the CD44 which is overexpressed in the RPE's surface [15]. A non-viral polymeric gene

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complex that is coated with hyaluronic acid was exhibited to be effectively taken up by RPE cells through the endocytosis, which is moderated by the CD44receptor. This results in a high delivery of genes and high expression of green fluorescent protein in the eye [2].

In the treatment of intraocular cancer, including uveal melanoma and retinoblastoma (Rb), the approaches needed are more complex because the biological barriers in the posterior segment of the eye are not the only thing to be considered, but also the specific microenvironment of the intraocular cancers. The folate receptor has been the subject of research. The folate receptors are overexpressed in the Rb cells, and with this, folate-linked chitosan and PLGA particles have been suggested for sustained, controlled, and targeted deliverysystem for the drug doxorubicin (DOX) in the Rb cells [2].

Nanosystem-based favorable ocular drug delivery systems have also been given focus and are under development to be used for diagnosing, treating, *etc*. [1]. Mitra *et al*. made polyethyleneimine (PEI) capped gold nanoparticles (AuNPs) combined with a novel epithelial cell adhesion molecule (EpCAM) antibody and siRNA molecules [2].

Photodynamic therapy (PDT) is a therapeutic strategy that is increasingly being used to treat a variety of diseases. PDT is made up of an activation-inducing energy laser beam, a light-activated photosensitizer, and a domain enclosed by oxygen that releases a toxic chemical. Visudyne, a commercial drug that is used inthe treatment of AMD, is a PDT product [2].

NANOSYSTEMS FOR THE TREATMENT OF GLAUCOMA

In treating glaucoma, IOP-lowering agents are the most commonly used, and they are usually administered as eye drops. For this kind of therapy, patient compliance is low because the administration of these medications needs to be done several times. This form of administration is also limited by the factors such as tear turnover, cornea permeability, short drug action duration, and the bioavailability of the medication. A more efficient drug delivery system must be at work so that these limitations can be controlled. It is with this regard that delivery systems based on nanotechnology can be of great use for new drugs that will have sustained release, enhanced bioavailabilities, precise dosing regimens, less tissue- irritant, longer shelf-life, targeted delivery, and better solubility [6].

Nanoemulsions have more drug solubility and membrane penetration. Nanodiamonds have an accessible surface area and modifiable surface chemistry. Hydrogels and nanocrystals are ideal for poorly water-soluble drugs. Dendrimers and liposomes can carry hydrophobic and hydrophilic drugs. Contact lenses have

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the capabilities for enzyme-triggered release [6]. Lastly, cyclodextrins are capable of forming inclusion complexes that enclose lipophilic drugs without changing their molecular structure (Fig. **5**) [6, 16].

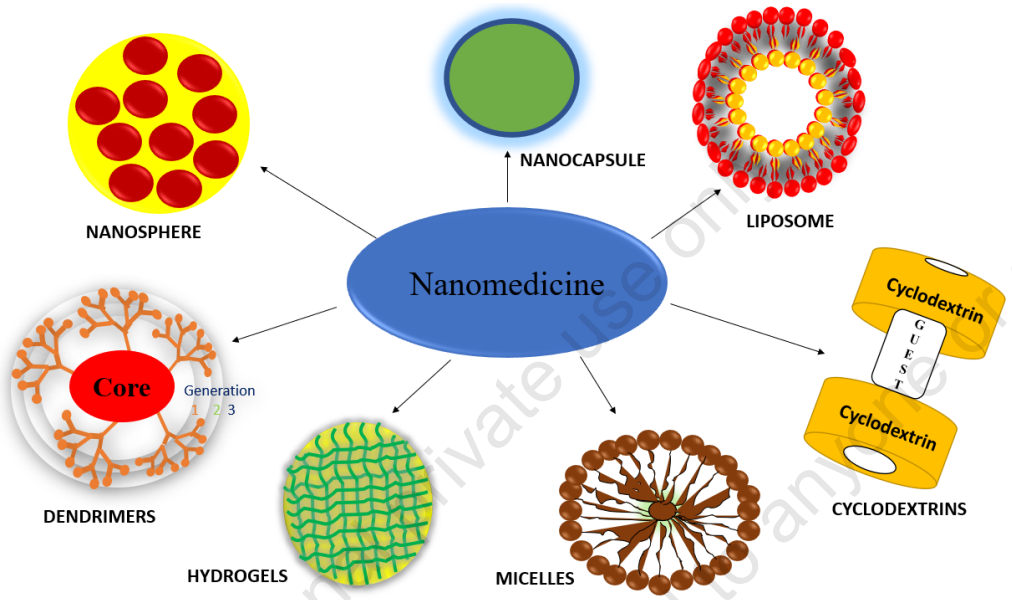

Fig. (5). A diagram of the nano-formulations utilized in the treatment of glaucoma [6].

Natarajan *et al.* innovated a nano unilamellar vesicle that is drug-loaded which is capable of reducing intraocular pressure. This can also provide sustainable drug release for over 120 days through a single subconjunctival injection. Similar systems had been expedited because of the promising results of this drug-loaded nano unilamellar vesicle [2].

EXOSOMES IN THE TREATMENT OF OCULAR DISEASES

Exosomes are nanoscale vesicles, and their diameters are about 30 to 150 nm. Exosomes consist of a lipid layer, a protein, and a genetic material. Exosomes are secreted by almost all cell types in the human body. Their functions are cell-t--cell communication, immune regulation, inflammatory response, and neovascularization. Several pieces of evidence exhibited that exosomes have a significant part in diseases like cardiovascular diseases, brain diseases, and cancer. The role that exosomes fulfil in the treatment of ocular diseases has not yet been explicitly studied and highlighted [17].

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Exosomes' functions and roles in intercellular signalling and cellular waste control are becoming increasingly clear. Exosomes released from other cells in other organs, as well as other extracellular vesicles (EVs), can be compared to exosomes released from cells in the eyes since they are believed to act in similar pathways [17].

In the eyes of patients with neovascular AMD, the released exosomes can serve as biomarkers. These exosomal biomarkers can assess the severity of AMD in patients and, therefore, be able to stratify them. OCT and fluorescein angiography can predict the disease progression, but these exosomal biomarkers can be more predictive. Exosomal biomarkers could also give off novel insights into the disease's pathophysiology [18].

Exosomes and EVs can be ideal in developing targets in the search for new biomarkers, and this is possible due to numerous unique features that they have, including the DNA, RNA, and the proteins inside the exosome, which can be protected by the lipid bilayer from the nucleases and proteases in the extracellular milieu; exosomes have tissue-, cell-, and even disease-specific nucleic acids and proteins; numerous methods for the isolation and the enrichment of exosomes from various body fluids are possible due to the hardiness of exosomes [18].

For ocular diseases that involve dysregulated angiogenesis, the approaches that are being developed and used in oncology, which use exosomes as carriers for either pro or anti-angiogenic factors, can be adjusted as they can be used in targeted drug delivery systems for the eyes [17].

Exosomes can serve as natural vehicles for the transport of proteins and small RNAs. The cells have mechanisms that can take up exosomes and extract the mRNAs to be utilized. Because of this, exosomes can be considered ideal vehicles for the delivery of gene therapy, which involves microRNAs and small interfering RNAs (siRNA) [18].

EMERGING STRATEGIES IN OCULAR DRUG DELIVERY BASED ON NANOMEDICINE

Contact Lens

The drug delivery of ocular drugs depends on overcoming the physiological and anatomical ocular barriers. It is most important to enhance the diffusion of drugs through the structure of the eye, majorly the cornea, and prolong the retention of drugs in the precorneal region. Leonardo da Vinci started the concept of contact lenses in 1508. He suggested vision improvement by immersing the eyes in a globular glass bowl that is filled with water. The contact lens that we now know was innovated by Adolf Fick in 1888. However, the innovation in contact lenses

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is still continuously going on. Although the primary use of contact lenses is to correct refractive errors, they have been utilized as means for a drug delivery system for ocular drugs [1].

Hydrogels

Hydrogels are made up of water, and structure-wise, they are polymeric and have cross-linked constructions [19]. Hydrogels are ideal for poorly water-soluble drugs because they have functional groups that are hydrophilic [6, 19]. Hydrogels are usually used for engineering functions in the management of ocular diseases because they are flexible, elastic, and hydrophilic [19, 20]. The hydrophilic character of hydrogels promotes the rapid liberation of ocular drugs [20]. Ion-activated hydrogels such as Timoptic-XEs and pH-sensitive hydrogels such as Virgans are available commercially [2].

Liu and colleagues formulated a microsphere for the delivery of the drug aflibercept. The hydrogel poly(ethylene glycol)-co-(l-lactic acid) diacrylate/N-isopropyl acrylamide (PEG-PLLA-DA/NIPAA) was used to suspend the drug [19]. The hydrogel was responsive to temperature [21]. Fig. (**6**) exhibits the drug profile of aflibercept with regards to its *in vitro* liberation from the hydrogel formulation [21].

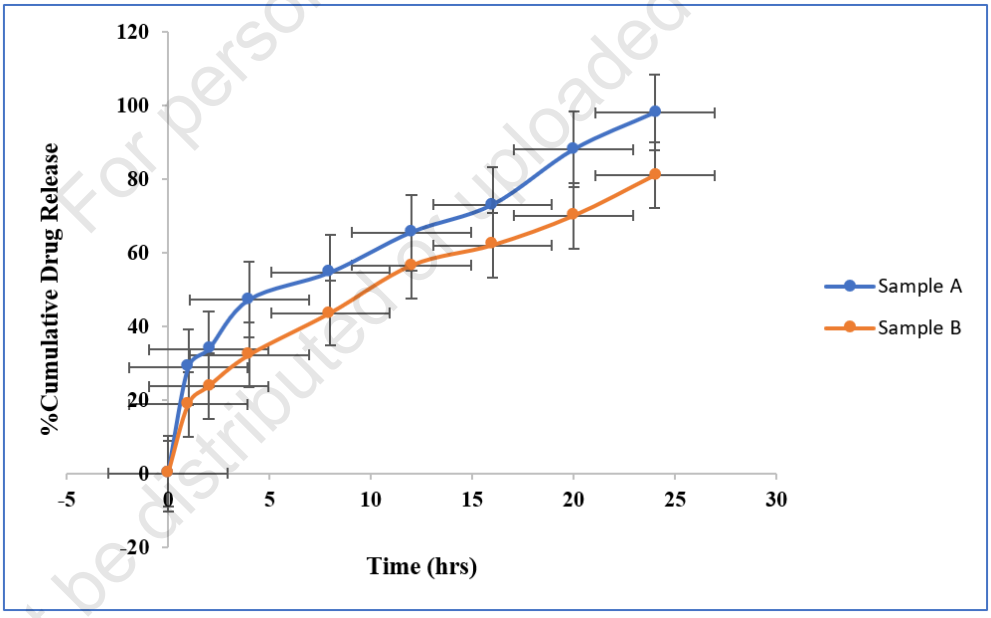

Fig. (6). Drug profile of aflibercept drug release over time [21].

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Silva and colleagues, on the other hand, designed and formulated imprinted and non-imprinted hydrogels, which are silicon-based [19]. With this formulation, the drug moxifloxacin hydrochloride was encapsulated, made into soft contact lenses (SLCs), and released at a sufficient rate that could treat eye infections [19, 22].

Liposomes

Liposomes are made up of phospholipid layers [19]. Huang Y formulated a liposomal preparation of the drugs, betaxolol hydrochloride (BH) and montmorillonite (Mt), as ophthalmic drug delivery systems for glaucoma therapy [23]. This formulation formed the Mt-BH-LP, which resolved the problem with poor bioavailability [19]. Fig. (**7**) exhibits the process of preparing the Mt-BH-LP [23].

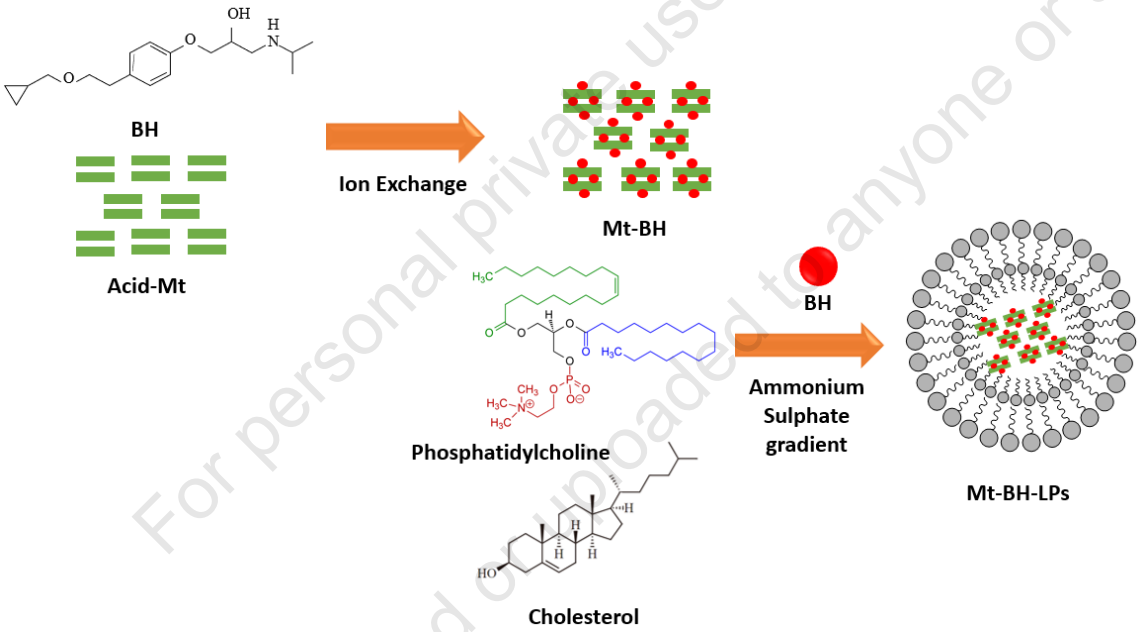

Fig. (7). Mt-BH-LP preparation process [23].

Niosomes

Niosomes are bilayered vesicles that are made up of non-ionic surfactants, which are approximately 10 nanometers to 01 micrometers in size [19]. Allam and colleagues improved the therapeutic action of vancomycin by loading it into a polymeric solution that turns it into a vancomycin niosomal gel. This formulation increases the retention time of the drug [19]. Vancomycin niosomal gel has higher antibacterial efficacy, both *in-vitro* and *in-vivo* [24].

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Solid Lipid Nanoparticle (SLN)

SLN is a nanoparticle that is colloidal, which is 10 nanometers to 01 micrometer in size [19]. Eid and colleagues utilized SLNs with chitosan and polyethylene glycol to coat ofloxacin to improve the retention time and the bioavailability ofthe drug in the therapy for eye infections [25].

Nanostructured Lipid Carrier (NLC)

NLC is a combination of drugs, lipids, and surfactants [19]. Almedia and colleagues formulated temperature-responsive ibuprofen eye drops that are made by the incorporation of lipid nanoparticles and a polymer with mucomimetic properties, Pluronic F-127. This formulation exhibited improved bioavailability and sustained release of the drug [19, 26].

Inorganic Nanoparticles

Inorganic nanoparticles have very interesting features like being highly stable, having a large surface area, and having good catalysis [19]. Li and colleagues formulated a topical therapy for treating dry eye disease (DED) using gold nanoparticles that are capped with poly catechin, which carries the nonsteroidal antiinflammatory drug amfenac [27]. The formulation was administered as a drop to the cornea to liberate the drug without having much toxicity [19].

Polymeric Micelles

Polymeric micelles have shell-like structures sized 10 nanometers to 100 nanometers. Polymeric micelles are great in solubilizing drugs, which are poorly soluble and allow alteration in the surface [19]. Li and colleagues proved that Rb1-micelles loaded with diclofenac (Rb1-Diclofenac micelles) can deliver high concentrations of the drug into the cornea, which provides therapy for inflammatory-moderated diseases of the cornea [28].

Nanosuspension

Nanosuspension is sized between 10 nanometers to 1000 nanometers. Therefore, it can pass through the ocular barriers. Güven and colleagues formulated a nanosuspension made up of polymeric Kollidon® SR loaded with olopatadine hydrochloride, which is utilized as therapy for allergic eye diseases [19].

Nanoemulsions

Nanoemulsions are in demand for the delivery of ocular drugs because these enable drugs to have high penetration to the ocular tissues by sustained-release

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mechanism. Mahboobian and colleagues formulated a nanoemulsion that is loaded with Brinzolamide (BZ) as glaucoma therapy. This formulation exhibited high penetration into the cornea. This formulation had two- or three-fold higher penetration when compared to marketed suspensions like Azopt [19].

Light-Responsive Nanoparticles

Light-Responsive nanoparticles are being utilized in the intracellular delivery of compounds and proteins, including haemoglobin, siRNA, and green fluorescent protein (GFP). For the treatment of ocular diseases, light-responsive nanoparticles are still at the early stages of discovery [1].

Mesoporous Silica Nanoparticles

In 2017, the first study of mesoporous silica nanoparticles (MSN) was conducted for the treatment of retinoblastoma. The surface of the MSNs was modified with the antibody EpCAM to increase the uptake by cells and was then utilized in the delivery of carboplatin [1].

FUTURE DIRECTIONS

Within the last 20 years, ocular nanosystems have appeared to be of great significance in treating ocular diseases. Several approaches, including the mechanisms of mucus penetration, mucoadhesion, delayed-release using nanoemulsions, controlled release of drugs, polymer-based coating to promote selectivity in permeation, and biphasic patterns of drug release, have been used in ocular nanosystems. These nanotechnology-based techniques exhibited effectiveness in providing sufficient concentration of the therapeutic agents at the action site [29].

Nanomicelle is one of the most favorable drug delivery systems used in nanomedicine. Nanomicelle formulation was used for enhanced solubility of the drug dexamethasone. This enabled the provision of therapeutic levels of dexamethasone into the back of the eye through the topical route ofadministration. This formulation can be used to treat uveitis. This, however, canstill be improved, and that would include the study of the transport of nanomicelleacross the sclera of rabbits for the delivery of the drugs to the intermediate andposterior segments of the eyes [30].

Although the ocular nanosystems have proven their importance in enhancing the delivery of drugs to the eyes, they also have certain limitations. Liposomes are very effective but have poor stability. Nanoemulsions can cause irritation and intolerance. Niosomes may have incompatibilities with ocular sites. Surface-

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modified nanoparticles can be hazardous in the long run. Ocular inserts may cause discomfort to the eyes. Nanotoxicology provides these limitations, and there is no in-depth analysis on this yet. This is the aspect of nanotechnology-based where improvements can be focused on for the enhancement of ocular treatment [29].

CONCLUSION

Although there are a lot of medications for the treatment of ocular diseases, blindness, visual impairments, and other diseases of the eyes still burden patients worldwide. Some of these diseases can be detected in their early stages so that their progress can be hampered. These diseases can also be treated with medications that can penetrate the barriers of the eyes, have sustained release mechanisms, and are present in targeted delivery systems. With nanotechnology, numerous approaches are being developed to enable the early detection of ocular diseases and provide sustained release and targeted delivery systems for their treatment. Several studies are still ongoing to improve the role of nanomedicine inthe treatment of ocular diseases, and these will continue to grow throughout the years as nanotechnology continues to advance and broaden.

CONSENT OF PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 7

Colloidosome as an Efficient Novel Drug Delivery System: An Update

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Abstract: Colloidosomes have been recognized as drug delivery systems with significant flexibilities. Colloidosomes are microcapsules having shells of fused coagulated particles, which are processed by the alignment of colloidal particles at the oil-water interface. They have adequate mechanical solidity, compatibility and are capable of encapsulating biologically sensitive materials such as hydrophilicmedicines, insecticides, protein, and aroma and delivering them to the desired location.It displays a huge potential in controlled and sustained drug delivery of activeconstituents. The permeability and dimensions of colloidal particles need to be examined prudently. Colloidsomes can be diversely applied in several fields like protein delivery, gene delivery, targeting the brain and tumour. Many scientists havebeen delighted by the responsive colloidosomes' ability to successfully deliver drugs to the targeted site without causing any side effects, particularly anticancer drugs.Encapsulation of herbal drugs like curcumin, neem oil, quinine, *etc*., can also beachieved by colloidsomes. This chapter will cover the various techniques used for thedevelopment of colloidosomes and their classification like patchy colloidosomes, aqueous core colloidosomes, responsive colloidosomes, and coated colloidosomes,along with their application in drug delivery.

Keywords: Colloidosomes, Core materials, Emulsion droplets, Responsive colloidosomes, Permeability, Microcapsules.

INTRODUCTION

The vital challenge in drug delivery is the effective encapsulation of hydrophilic drugs and delivery at the targeted site. The congregation of particles at the inter-

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face of emulsion droplets has resulted in colloidsomes, which can be further utilized for the encapsulation of materials. Colloidosomes can be defined as hollow-porous hexagonal closed packed microcapsules with elastic shells created by the self-assembly of colloidal particles at the interface of emulsion droplets.For effective drug delivery, permeability and elasticity of the colloidosomes need to be controlled due to the presence of void, which allows the penetration of drugsfor encapsulation [1, 2]. It can also be elucidated as a microcapsule having an external shell of colloidal particles. The colloidosomes were first developed by Velev *et al.* and further modified by Dinsmore *et al.* in a mild condition. Colloidsomes have evolved with time and transformed into magnetic, temperature, and pH-responsive colloidosomes [3]. The size of colloidosomes ranges from 1 nm to 1µm. Properties like shape, electrical charge, mass, and surface properties should be monitored for the formulation of stable colloidsomes [4]. Permeability, mechanical strength, and biocompatibility depend on the optimum choice of colloidal particles and environmental conditions [5]. Manufacturing of colloidsomes with metal-organic framework ensures high encapsulation percentage, complex microreactor preparation, and high molecular separation [6]. Colloidosomes are frequently utilized for the encapsulation ofbiological molecules, such as hydrophilic drugs, pesticides, proteins [7]. They canbe easily fabricated by mixing colloidosomes into the continuous phasecontaining water-in-oil emulsion assembled at the interface of both the liquids. The centrifugation and repeated washing help the assembly of the colloidosomesat the interface [8].

Diversified advantages have fascinated scientists to explore the application of colloidosomes in various applications, such as controlled drug delivery, drug of biomolecules, targeted drug delivery, *etc*. Selective release of encapsulated particles can be controlled by their permeability. The mechanical strength rendered by colloidosomes is substantially higher as compared to the self-assembled shell of liposomes. Permeability of colloidsome depends on pore size, which further depends on the size of colloidsome. Huge interstitial voids present in macromolecules and nanoscale molecules result in their high permeability. This property assists the colloidosomes in showing potential in various fields such as pharmaceutics, food industries, and cosmetic industries. The release of encapsulated particles from colloidosomes depends upon external aspects like change in temperature, pressure, pH, light, ultrasound, mechanical forces, *etc.*, which breaks the shell and releases the encapsulated particles inside [9]. Colloidosomes can bear the mechanical load due to their high mechanical strength and defined shear rates.

Along with several advantages, there are a few disadvantages of colloidosomes, as there is a coalescence of colloidosomes due to insufficient locking of shell [10].

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Due to the amphiphilic nature of resulting colloids, they can easily spread at the interface of oil/water, forming an enclosed continuous particle membrane. Organic, inorganic, and hybrid polymers can be used for the preparation of colloidosomes. The organic colloids show stimulus-responsive properties, such as light, temperature, catalyst, due to the chemical moieties and functional groups attached to the colloidosomes' surface [11].

Colloidosomes are an emerging field for the delivery of drugs owing to their small size, high entrapment efficiency, stability, and active drug loading. Targeted drug delivery without leakage and toxicity can be accomplished. The bioavailability of BCS Class II and IV drugs can be improved. Several classes of drugs, like anti-inflammatory agents, beta-blockers, anti-cancers, proteins, *etc.*, can be efficiently transported using colloidosomes [12]. Several herbal drugs can also be encapsulated efficiently in colloidosomes, and the most common among them is curcumin with various properties, such as anticancer, antioxidant, antibacterial, anti-inflammatory, and antiproliferative. These properties allure scientists to use curcumin in various fields. The formulation of curcumin poses several challenges due to its low solubility and high instability [13, 14].

This chapter elucidates the delivery of hydrophilic drugs using colloidosomes, several methods for developing colloidosomes, different types of colloidosomes, and their applications in diversified fields.

NATURAL POLYMERS FOR THE MANUFACTURING OF COLLOIDOSOMES

Chitosan

Chitosan is a polysaccharide obtained from crustacean shells chemically known as a (1-4)2-amino 2-deoxy b-D glucan (a deacetylated form of chitin). It is a highly biodegradable and biocompatible polymer consisting of amino acid groups. It is a positively charged hydro-soluble compound that tends to encapsulate a large number of substances using its interactive forces. The entrapment of material can be processed through a number of processes such as ionic crosslinking, desolvation, or ionic complexation. It can open the tight junction present between the cells facilitating the transport of substances across the cell. One example of efficient delivery is the transportation of peptides across the nasal membrane [15]. Nan F *et al.* fabricated uniformly-sized colloidosomes using chitosan-coated alginate particles for oral delivery of insulin. The formulation showed high drug encapsulation up to 96.7%, along with pH-sensitive drug release [16]. Niaz T formulated colloidosomes using alginate and chitosan around liposomes, which resulted in controlled drug release. The multi-component colloidosomes are useful in encapsulating an antimicrobial agent, which helps produce stable and

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pathogen-free food material [17].

Alginate

Alginate is an anionic polymer with high biocompatibility, low toxicity, low cost, and gelation property, which is obtained naturally from brown seaweed [18]. Alginates assist in restraining membrane porosity resulting in controlled release of the encapsulated material. It also contains a static aqueous phase which reduces the use of organic solvent. Alginate facilities a non-toxic and biodegradablemethod of sealing to encapsulate substances in colloidsomes. Fernandez-SerranoM *et al.* formulated colloidosomes made up of poly (methyl methacrylate-butylacrylate) latex shell sealed using calcium alginate. This improved the encapsulating efficiency by 60-80% and provided an economical and extendedshielding of an enzyme. These properties of alginate have expanded itsapplication in the field of medicines, and pharmaceuticals [19]. Alginate materialexhibits a huge potential for the bioencapsulation of foods, chemicals, andsynthetic protocell formation. Qu F *et al.* fabricated calcium alginate colloidosomes which showed a high encapsulating capacity of up to 85% [20].

Cellulose

Cellulose is a long chain of anhydrous-D-glucopyranose units joined covalently at C1 and C2 positions (β 1,4-glycosidic bonds). The cellulose nanocrystals can be used as a colloidal stabilizer. This furnishes colloidosomes with high tensile strength, adequate biocompatibility, high mechanical strength, elastic modulus, and renewable property. Zhang Z *et al.* used the pickering method to prepare colloidosomes that were stabilised with cinnamate modified cellulosenanocrystals. This system ensured an extended encapsulation of rhodamine B or biological molecules, such as fluorescent deoxyribonucleic acid (DNA), with the good mechanical property. Kadam SL *et al.* prepared colloidosomes using a cellulose nanofiber as the pickering emulsifier, resulting in a stable emulsion and high encapsulation of N, N-diethyl-3-methylbenzamide (DEET), an insect repellent, of about 98% [21]. The cellulose nanocrystals also possess the property to respond against several stimuli such as temperature, pH, and light. Ren G *et al.* formulated a temperature and CO_2-responsive pickering emulsion using cellulose nanocrystals, which showed its application in food, cosmetics, and drug delivery [22].

Dextran

Dextran is a homopolymer polysaccharide which is made up of α-(1 → 6) linked d-glucose as the main chain with different linkage and branches attached to it [23]. Dextran has vast applications in the formation of stable and effective

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colloidosomes. Cayre OJ *et al.* formulated pH-dependent controlled release colloidosomes microcapsule. The fluorescent labelled dextran molecule assists the uptake of the molecules at its core [24]. Douliez JP *et al.* fabricated stable colloidosomes through the pickering emulsion method. Fluorescent amine-modified polystyrene latex beads were added to dextran enriched droplets, which were dispersed in the PEG phase. The crosslinking occurs between dextran-produced droplets and polyacrylic acid, resulting in reversible swelling and selective molecular uptake and exclusion [25].

Gelatin

Gelatin is a biopolymer widely used in the food industry, confectionery, pharmaceutical/medical, and cosmetics. Gelatin is obtained from collagen by the process of hydrolysis of polypeptides. Gelatin is utilised to make colloidosomes because it has various beneficial properties, such as acting as an emulsion stabiliser [26]. Tan H formulated monodispersed gelatin particles by the two-step desolvation method. These gelatin particles were then emulsified in an oil-i-water emulsion through the homogenization method. The gelatin particle inhibited the coalescence of emulsion droplets by adhering at the oil-water interface and imparting stability to emulsion [27]. Tang R *et al.* formulated a colloidosome microsphere made up of gelatin hydrogel core and porous nanoparticle shell. The formulation helped in the identification of human mesenchymal stem cells (hMSC) in 3D cultures that function as an ECM and morphogen carrier. Colloidosomes assisted in the transport of aqueous solution without any leakage and clumping. The gelatin helped in the generation of new tissues by enhancing chondrogenesis in hMSCs [28].

SYNTHESIS OF COLLOIDOSOMES

Emulsion Based Approach

The conventional technique for the synthesis of colloidsomes is a two-step process (Fig. **1**) with certain limitations, including damage to the original structure, broader distribution of colloidosomes declining the encapsulation efficiency, uncontrolled drug delivery, inability to deliver an accurate dose of a drug, *etc.* [5]. An emulsion-based approach is a single-step process involving aqueous solution and oils to form water-in-oil / oil-in-water emulsions. The colloidal particles are adsorbed on the surface of the droplet at the interfacebetween oil and water by reducing the surface energy; this is referred to aspickering emulsions. The colloidal particles are locked at the interface, which involves sintering above the glass transition temperature (T_g) using salt or adding polycation, producing Vander Waals forces. The colloidosomes are transferred to emulsion by two approaches: centrifugation

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and filtration. The colloidal particles can be manufactured using biodegradable as well as non-degradable polymer. Thebiodegradable polymers include poly(lactic acid), poly(amino acid), and polylactone, and non-degradable polymers include poly(methyl methacrylate),polystyrene and polyvinyl chloride; cellulosic polymers such as poly (methylcellulose), poly(hexyl cellulose), and poly(cellulose acetate) and polysaccharides such as alginate, starch and chitosan [7]. The thickness of colloidosomes is determined by adjusting the flow rate of the fluids used in the preparation of emulsion that helps to maintain the mechanical strength and permeability of drugs through colloidosomes. Selective permeability can also be rendered based on different sizes of molecules. The thickness of the colloidosomes can be detected with the help of freeze-fracture cryogenic SEM [29]. The double emulsion results in a stable colloidosomes formation due to the adsorption of colloidal nanoparticles on the oil/water interface. Double emulsion resulting from microcapillary devices are monodispersed, leading to the formation of close hexagonal packing of the drops, increasing the encapsulation efficiencyup to 100%, with molecules effectively distributed into the inner aqueous liquid [30].

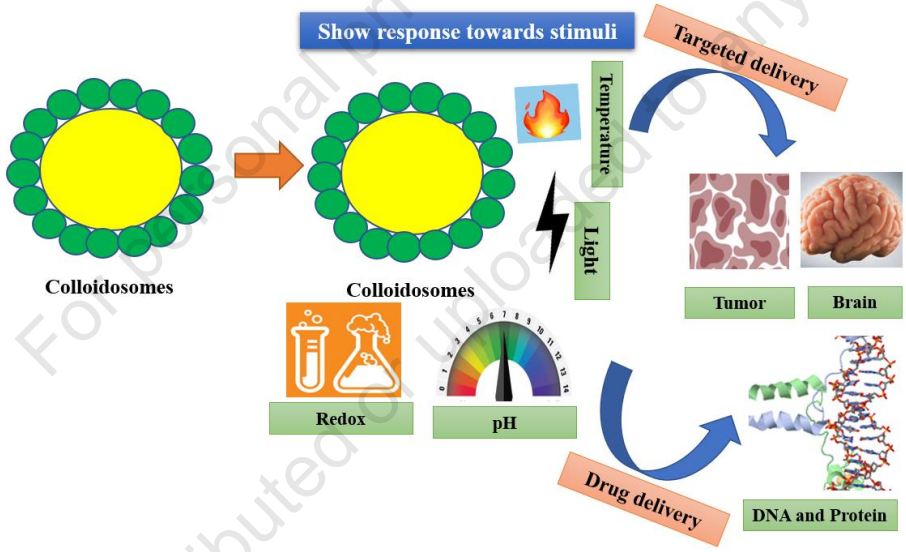

Fig. (1). Preparation methods of Colloidosomes.

Colloidosomes are used for embedding a variety of biomolecules. Encapsulation of biomolecules in a solid template is a cumbersome and time-consuming process and may destabilize the active biomolecule. The biomolecule encapsulation in colloidosomes using one step emulsion technique is a suitable and effective approach that maintains stability. Zhu G *et al.* formulated colloidosomes

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encapsulating a synthesized ZIF-8 enzyme (Zeolitic imidazolate frameworks (ZIFs)) using a one-step emulsion-based technique. The ZIF-8 is embedded in the colloidosomes at the water/butanol interface. The pickering emulsion method was utilized for the encapsulation of positively charged enzymes [31]. The use of an emulsion-based approach to manufacture metal-organic framework colloidosomes resulted in high porosity, surface area, and temperature stability. Emulsified droplet is considered to be a soft template produced by mixing immiscible solution or by making a change in the flow of immiscible fluids. Singh N *et al.* fabricated *in situ* assembled ZIF colloidosomes by using an emulsion-based soft templating approach. The colloidosomes resulted in a high percentage of encapsulation (99%) regardless of size, shape, and charge on colloidosomes [6]. The pickering emulsion technique is also used for the encapsulation of *Bacillus thuringiensis*. The technique has enhanced the activity and stability under UV-A radiation. The protective efficacy of the formulation was measured for Bt subsp. kurstaki against deactivation by UV-A irradiation and found to be effective at a concentration of 0.045% [32].

Solvent Evaporation Method

The solvent evaporation method is a widely accepted technique for the preparation of colloidosomes. It involves fewer unit operations where the chosen polymer is dissolved in an appropriate solvent (immiscible). The resulting dispersion/solution is further emulsified with water forming a distinct droplet. Theorganic solvent is evaporated after its diffusion with water from the water-air interface. As the solvent evaporates, the colloidosomes' surface hardens and maintains its stability. Separation is done using filtration and drying. The commonpolymers used in this method is PLA and PLGA. This technique is used toenhance the solubility of poorly soluble drugs [33]. Recent advances indicate the application of solvent evaporation technique to entrap highly water-soluble drugs, amine-based drugs, peptides, proteins, and vaccines [34]. Two techniques of solvent evaporation process are spray-drying and solidification of emulsion. Instruments used in the preparation of colloidsomes include homogenizers, colloid mills, and impellers. The choice of equipment depends upon the required size of colloidosomes, and the viscosity of solvent used [35, 36].

The solvent evaporation technique is used at the commercial level for the manufacturing of colloidsomes. Ismail A S *et al.* developed colloidosomes with a substantial increase in yield along with a high encapsulation efficiency using polyhydroxy butyrate as a polymer with a solvent evaporation technique [37]. The spray drying technique was used for the manufacturing of polymer shells. The concentration of latex particles used to make colloidosomes resulted in controlled shell release. Several factors, such as the concentration of latex particles, the flow

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rate of compressed gas, the temperature at the inlet, and feed rate, affected the rate of evaporation of the solvent, in turn, affecting the morphology of colloidosomes [38].

Cross-linked Colloidosomes

The cross-linked colloidosomes are formed by the covalent crosslinking of a chemical moiety at the interface of oil/water without the heating process. Numerous colloidosomes with stable encapsulated products have been constructed by the cross-linking method. Hu Y *et al.* manufactured dual functionalized poly(N-isopropylaacrylamide) microgel and N-acryloxysuccinate polymers mixed with catalyst-free BZ reaction substrate, resulting in colloidosomes with osmolality differences. It also exhibited light-induced size reduction and chemo-mechanical oscillations caused by the BZ reaction.These colloidosomes paved the way for biomimetic materials design, resulting in aphoto-regulated memory device that allows for photo-triggered protein release [11]. The sterically stabilized polystyrene latexes are produced by aqueousemulsion or alcoholic dispersion polymerization reaction between poly (glycerol monomethacrylate) based macromonomers. The cross-linking was done between hydroxyl-functional stabilizer chains within the oil droplet using polymeric diisocyanate. The permeability of colloidosomes can be steered with the deposition of polypyrrole into the exterior of colloidosomes [39]. A study by You JO *et al.* demonstrated the coordinated network with the colloidosomes consisting of heterogeneous subunits, resulting in a designed programmable material with non-uniform stresses. These colloidosomes were prepared by cross-linking diamine compounds with varying carbon chain lengths [40]. Wang *et al.* demonstrated a simple and versatile method used for cross-linking covalent inter-linking of vinyl-functionalised microgel particles adsorbed to oil droplets to form shells of doubly cross-linked microgels (DX MGs) [41]. Tan J *et al.* reported a highly monodispersed poly(glycidyl methacrylate) (PGMA) microsphere preparation at room temperature by photoinitiated RAFT dispersion polymerization. The cross-linking was done by primary amino groups on the particle surface using tolylene 2,4-diisocyanate-terminated poly(propylene glycol) (PPG-TDI) as a cross-linker. The cross-linking helped stabilize the oil-in-water pickering emulsion [42]. The pickering emulsion was also stabilized by polydopamine (PDA) nanoparticles through cetyltrimethylammonium bromide (CTAB). The cross-linking occurred at the oil-in-water interface,s allowing the assembly of PDA nanoparticles on the surface due to the reaction at the toluene phase [43].

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Layer-by Layer

Layer by layer methods of preparation of colloidosomes results in the sealing of the core until required to be released. Simple colloidosomes (uncoated) prepared by other methods do not provide have restricted application. Different materials can be used for coating the layers of colloidosomes. Impermeable secondarysilver shell colloidosomes were formed by reacting L-ascorbic acid with silver nitrate ($AgNO_3$) at the surface of the capsules. The colloidosomes encapsulate doxorubicin hydrochloride and dye solution for more than 500 h [7]. Sun Q *et al.* manufactured colloidosomes by reacting an L-ascorbic acid with $HAuC_{l4}$, resulting in an impermeable gold shell. A similar study was performed by Keen PH, where sodium carbonate was made to react with calcium chloride resulting in calcium carbonate shell formation, sealing the core containing amylase enzymefor 3 months [44]. The thickness of the shell determines the permeability and mechanical properties of colloidosomes. The thickness of the layer depends on thedeposition of polymers. The electrostatic polymeric layer produces a shell with oppositely charged polymers built by the assembly of polymeric material showing electrostatic interaction [45]. Rossier-Miranda FJ *et al.* produced a microcapsule with the help of a protein/pectin shell using an electrostatic layer-by-layer deposition method, with adsorption of larger colloidal particles on a shell. This deposition imparts strong protection for the encapsulated particles. These colloidosomes are utilized in encapsulating food products, protecting their contents from the stomach's acidity and dissolving later at the small intestine [46].The loading of the drug into the layered colloidosomes can be achieved either by using a template in the form of a droplet that is pre-loaded with the drug or performing diffusion through the polymeric layer. This technique avoids the necessity of wettability and sealing of layer, which is required for the release and to avert leakage, respectively. Gu YS *et al.* developed colloidosomes in which colloidal particles were adsorbed at the oil-water surface resulting in the encapsulation of the drug [47]. Colloidosomes with additional wettability and less permeability were developed without involving adsorption steps. The scaffold capsule is produced where the drug is loaded into the shell after its assembly. The pores generated after the assembly of colloidosomes can be filled with the additional layer. This technique is useful for the encapsulation of smaller molecules such as albumin or dextran [47].

Thermal Annealing

The thermal annealing method involves the heating step for the preparation of colloidosomes. Colloidosomes are formed by self-assembly of micrometre-sized carboxylated polystyrene latex particles at the surface of the oil-in-water/water- in-oil emulsion droplet. The droplets are sintered with latex to form the colloidal shell, which involves high temperature. The material utilized for sintering isthermal

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responsive. Additional mixing of 50% glycerol is required to raise the boiling point of aqueous media. The sintering latex required high temperature along with the addition of co-solvent to prevent evaporation, resulting in stable colloidosomes. Yuan Q *et al.* developed colloidosomes consisting of a core-shell made up of polystyrene and a shell composed of poly[2-(dimethylamino)ethyl methacrylate]-*b*-poly[methyl methacrylate] (PDMA-*b*-PMMA) formed on the surface, providing a steric stabilization. The PDMA shows thermal responsive behaviour enhancing the porosity and mechanical strength of colloidosomes [48]. One of the technical problems observed with the thermal annealing method is the inter-fusion of neighbouring colloidsomes. This problem was subdued by theaddition of poly(styrene-block-ethylene-copropylene) (PS-EP) di-block copolymer micelles, which acted as a steric stabilizer heated at 50°C. This resulted in decreased aggregation of particles [49].

Gel Trapping Technique

Another approach of developing colloidosomes in stable form is through the entrapment of aqueous gel as the internal phase. The aqueous gel is gelled in the form of a solid core. This increases the stability and structural integrity of colloidosomes [49]. Jiang H *et al.* developed sub-micron colloidosomes by inverse water-in-oil emulsion mixed with hydrophobic silica nanoparticles. Thelocking of particles takes place at the oil-water interface through a sol-gel reactionof silica. The resulting colloidosomes exhibited a long-term entrapment of themolecule. Such colloidosomes demonstrated several applications in the field ofmedicines, agrochemicals, and cosmetics [50]. Duan H *et al.* developed magneticcomposed colloidosomes entrapped with an aqueous phase in a gelled form. Thegel is formed by agarose beads. This system allows the encapsulation of hydrophilic substances [51].

TYPES OF COLLOIDOSOMES

Patchy Colloidosomes

The patchy colloidosomes are composed of heterogeneous shells containing different patches of material reflecting their individual property that differs in the whole shell [52]. The patches interact with each other, resulting in a self- assembled complex structure releasing its cargo species in a specific direction. One of the patches in the colloidosome is well defined, which allows the interaction with other particles on the surface to experience a strong anisotropic effect. The specific interaction between the patches provides a medium for the self-assembly of the targeted structure [53]. The release of encapsulated material inside the patchy colloidosome is controlled by the pH of the surrounding area. Patches tend to swell at lower pH values, releasing the encapsulated material [54]. There are many

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methods for fabricating patchy colloidosomes, which include a membrane or microfluidic emulsification, emulsification by mechanical stirring, layer by layer assembly, pan coating, spray drying, phase separation, *etc.* The surface of the patchy colloidosomes can be modified using two approaches: (i) liquid phase deposition (LPD) (ii) Vapour Phase Deposition (VPD).

The LPD includes chemical, electrochemical, electroless, and layer-by-layer techniques, while VPD includes chemical vapour deposition and molecular beam epitaxy. The LPD results in a symmetric coating of the surface. The patches can be selectively modified in the case of VPD [53]. The patchy colloidosomes are utilized for fabricating photonic crystals, targeted drug delivery, sensors, microrheological probes, self-healing material, and electronics [53]. Edlund E *et al.* adopted a design pathway for the self-assembly of a target on patchy colloidosomes assembled at a uniformed pattern. Several stripes and spots were used to develop a highly specific and functional pattern. The minimalistic model consists of alkanethiol on gold for controlling the interaction between the surface particles. This also assists the self-assembly of complex geometric structures,such as strings, membranes, cubic aggregates, colloidosomes, as well as various crystalline patterns [55].

Aqueous Core Colloidosomes

Aqueous core colloidosomes are thin shell microspheres that help encapsulate the hydrophilic material. It protects the encapsulated material from any leakage or breakage and controls the release. PLGA is the most suitable material for producing aqueous core colloidosomes. A study reports the PLGA aqueous core colloidosomes in which acetone water in mineral oil emulsion was separated in the inner core. A combination of alginate and PLGA was also prepared with a hydrophilic material in the form of a gel core using a double emulsion-based solvent evaporation method involving dichloromethane as a solvent. In another study, PLGA was dissolved in vegetable oil used as a solvent. The encapsulant chosen was Rhodamine B which also acted as a dye for detecting the water phase. The temperature of the oil/water mixture was set above a glass transition temperature. It was observed that when the volume of water was above thesolubility limit, colloidosomes were formed with PLGA nanoparticles at theinterface [56]. Keen *et al.* formulated an enzyme amylase encapsulating colloidosomes sealed with calcium carbonate shell. This system assists inencapsulating the material for several months [44]. Aqueous colloidosomes arealso reported with a shell formulated using gold, making it impermeable. Thegold-coated colloidosomes are also added with HAuCl4, surfactant, and L-ascorbic acid to form a second shell. Ultrasound triggers the release of thissystem, which results in reduced toxicity. Doxorubicin, an anticancer drug, was encapsulated inside with gold

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dithiodibutyric acid is crosslinked with proteins (rabbit Immunoglobulin G (IgG)) [57]. Cayre *et al.* fabricated an aqueous gel core surrounded by a polymeric colloidal shell forming a colloidosome microcapsule. The emulsion was prepared by templating water in oil and adding polystyrene (PS) latex particles to stabilise it. This was followed by gelling of the aqueous core. The aqueous core colloidosomes resulted in high structural integrity and mechanical strength. Theoil used in the formulation helped control membrane core size, permeability, and release of the formulation [58].

Responsive Colloidosomes

In this approach, the colloidal particles ranging from nanometer to micrometre respond to different stimuli and help in the release of the encapsulated material. Kim JW *et al.* formulated a water-based emulsion system, where an electrostatic interaction was made between charged colloidal particles and scaffolds of microgel. The electrostatic interaction varies with the fluctuation in thetemperature, which forms a uniform shell of nanoparticles with varyingpermeability [9]. The latex particles, which are considered to be the building block for the colloidosomes, are generally stabilized through responsive polymers. These particles show pH responses for the release of the encapsulated water- soluble species based on size exclusion. The oil-in-water emulsion is prepared with the help of latex particles. Oil is removed to stabilize the emulsion resulting in the collapse of the microcapsule. This can be subdued by using a pH-dependentpolymer with expandible properties. Polymer re-swells the oil droplet into its initial shape. The main aim of using a responsive material in colloidosomes is to control the release of the encapsulated material. The property of the colloidosome particle has been designed in such a way that it swells in response to temperature. Fluorescently labelled dextran molecules can be encapsulated to the core at low pH, where the capsular membrane can be expanded to maximise the pore size. Higher pH results in the contraction of the membrane and closing of the pore. Thus, dextran can be released depending upon the pH change [59]. The application of responsive release of particles in the case of colloidosomes includes a vehicle for drug delivery, microfluidic devices, bioadhesion mediators, artificial muscle, and immobilization of enzymes and cells. Thus, the responsivecolloidosomes release their content when required [60]. López-de-Luzuriaga *et al.* formulated a single-step gold nanoparticle incorporated into plasmonic colloidosomes. The nanodroplets are formed by using oleic acid and water. The spherical gold nanoparticles are incorporated at the interface of oleic acid nanodroplets to form colloidosomes [61].

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Coated Colloidosomes

Due to excessive permeability of the shell, the colloidosomes show leakage of the encapsulated material. Hence, a new approach of coating colloidosomes with material, such as silver, gold, has been proposed with the application in the food industry, as a bioreactor, and medicine field. Different polymers can also be used for such purposes [57]. A silver shell having impermeable nature was fabricated by reacting with L-ascorbic acid with $AgNO_3$ at the surface of the capsule. The silver-coated colloidosomes encapsulate doxorubicin hydrochloride and dyes for more than 500 h [57].

Hybrid Colloidosomes

Hybrid colloidosomes are the combination of various approaches which help upgrade the mechanical strength and stability of colloidosomes. Grzegorzewski F *et al.* fabricated hybrid colloidosomes consisting of multi-walled carbon nanotubes and silica hybrid microcapsules generated by pickering emulsion templating biphasic oil-in-water system. The interfacial tension at the surface wasreduced and stabilized by using (3-aminopropyl) triethoxysilane (APTES) and dodecyltriethoxysilane (DTES). The system showed encouraging results in the field of electro-optics, encapsulation, and chemical sensing [62]. Liu *et al.* fabricated hybrid colloidosomes by combining hybrid alginate hydrogel beads with porous $CaCO_3$ microparticles forming a shell. The colloidosomes were formed by the self-assembly of microparticles at the interface of a water-in-oilemulsion. The water droplet present in the emulsion contains alginate, whichreacts with Ca release from $CaCO_3$ at low pH conditions. The colloidosomes wereformed by hybrid beads of alginate and $CaCO_3$ microparticles shell. From delivering drugs, cosmetics, food supplements, and living cells, the systemdemonstrated a significant finding as a drug delivery vehicle [63].

STABILITY OF COLLOIDOSOMES

Colloidosomes are thermodynamically unstable systems. The droplets in the emulsion tend to aggregate and form a larger droplet (coalescence of liquid droplets). The aggregation of droplets takes place when the attractive force between the droplets exceeds the repulsive force, resulting in the creaming of emulsion. Moreover, the colloidal particles adsorb at the interface of oil-water causing drop-drop coalescence. The creaming can be reduced by reducing the steric hindrance at the interface. This can be achieved by using oppositely chargedparticles, which maintain stability at the interface [2].

The loading of the drug to colloidosomes also plays an important role in determining stability. If the drug is loaded by diffusion after the formation of

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colloidosomes, it may lead to difficulty in producing a stable system, and it is also time-consuming. Therefore to maintain stability, the drug should be loaded first, followed by the fabrication of colloidosomes [4].

Table 1. Plants constituent used in colloidosomes.

S.No	Herbal Drug	Biological Name	Plant Part and Active Constituent	Colloidosomes	Application	Reference
1.	Turmeric	*Curcuma longa L.*	Rhizome, Curcumin	Silica nanoparticles forming aggregates	Enhances the stability of curcumin	[64]
				Curcumin-loaded zein nanoparticles plus digestible lipid nanoparticles; Formed into colloidosomes	Increase the bioaccessibility	[65]
2.	Neem oil	Azadirachta Indica	Seed kernels of neem tree, azadirachtin	Biodegradable polymer-based encapsulation of neem oil nanoemulsion for the controlled release of AZA-A	Increased encapsulation and controlled release of Azadirachtin	[66]
3.	Cinchona	Cinchona Officinalis L.	Cinchona bark, Quinine	One-step ligand exchange reaction as an efficient way for the functionalization of magnetic nanoparticles	High colloidal stability and super-magnetic behaviour	[67]

1. Zhao Y *et al.* formulated colloidosomes using silica nanoparticles, which help stabilize the interface of oil and water. The curcumin was encapsulated within the colloidosomes, showing high stability and increased thickness [64].
2. Zou L *et al.* prepared curcumin-loaded zein nanoparticles plus digestible lipid nanoparticles formed into colloidosomes. The colloidosomes help increase the solubilization capacity of the curcumin [65].
3. Jerobin J *et al.* formulated colloidosomes by incorporating azadirachtin using odium alginate (Na-Alg) crossed linked with glutaraldehyde coated with starch and polyethylene glycol. SEM studies revealed a spherical shape of the colloidosomes. Swelling of the polymer resulted in the controlled release of the drug substance [66].
4. Mrówczyński R *et al.* formulated a colloidal nanoparticle having magnetic property due to Fe_3O_4, which helps encapsulate functionalized fatty acids, such as quinine. This formulation showed the high stability of magnetic colloidal particles [67].

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APPLICATION

For secure and effective delivery of drugs to the targeted site, drug delivery systems and drug carriers must be studied. Microcapsules are commonly used delivery carriers for the treatment of many diseases. Emulsion-based carrier is most commonly used for drug delivery, which includes nanoemulsion, solid lipid particles, liposomes, noisome, nanostructured lipid carrier, and colloidosomes [2]. Colloidosomes are considered to be a competent system for the encapsulation of drugs owing to their superior mechanical property, tunable porosity, and better mass transport [7]. The colloidosomes showed a potential application in the field of targeted drug delivery to the brain, tumour, and efficient delivery of protein and gene (Fig. **2**) [68].

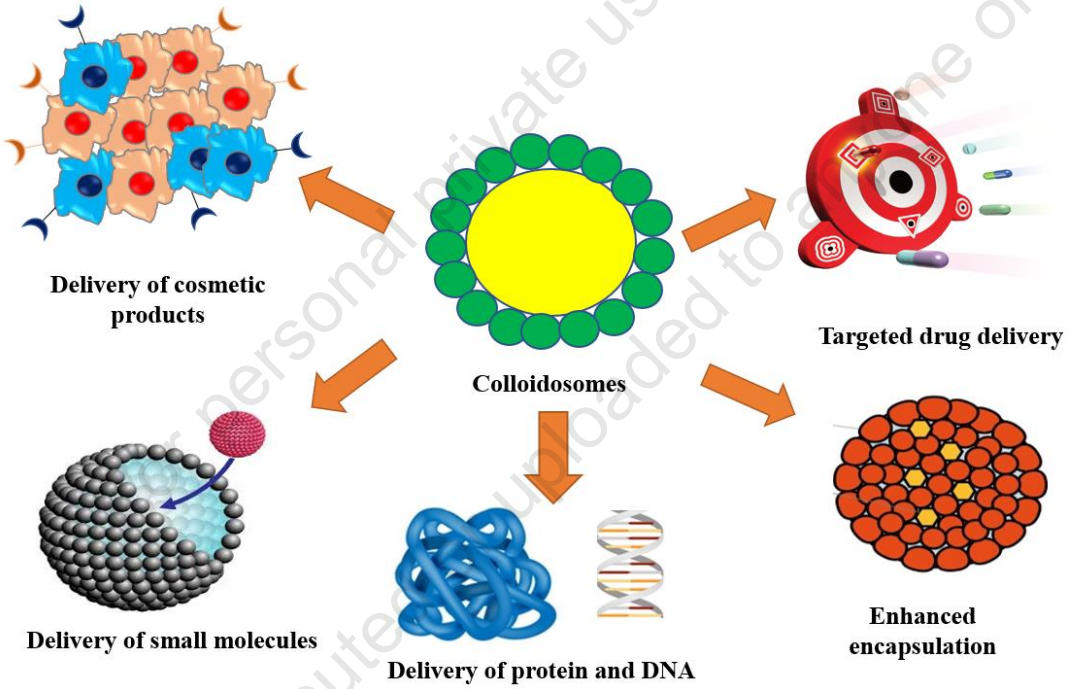

Fig. (2). Applications of Colloidosomes as drug delivery systems.

Colloidosomes for Target Drug Delivery

Drug targeting is essential as colloisomes may undergo a rapid clearance, biodistribution, show toxicity, nonspecific targeting, and low intracellular absorption before reaching its targeted site [69]. The surface modification of impermeable inorganic shells helps in targeting a specific site. Different biological materials, such as proteins, peptides, antigens, antibodies, can be attached to the

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surface, directing them to the target site. The colloidosomes, after reaching the target site, release the drug by the triggered method, mechanical breakage, dissolution of shell, diffusion through the shell, and irradiation of specific light [7]. The transport of the carrier to the targeted site depends upon submicron particle size, retention effect, pore diameter, surface area, and pore volume. Specific permeability is triggered by external factors [70]. Colloidosomesact as carriers and advanced tools for the delivery of protein, gene, brain targeting, and tumour targeting. It has a huge potential to encapsulate large amounts ofdrugs with controlled permeability [68].

Tumour Targeting

Silver-coated colloidosomes were prepared using L-Ascorbic acid embedded at the core of the microcapsule. Silver shell was further modified with 4,4'-dithiodibutyric acid and crosslinked with an antigen (rabbit Immunoglobulin G (IgG)). Targeted drug release was triggered using ultrasound [69]. Gold-coated colloidosomes also exhibit a good targeting approach for a tumour cell. They act as non-permeable materials with adequate ultrasound sensitivity and immunoassay targeting approach [57]. Gold nanosphere-based 3D plasmonic colloidosomes were formulated by the emulsion templating approach. The formulation showed good mechanical stability and potential for drug delivery [71]. Targeting towards the tumour cell is also made responsive by the use of biosensors. The molecular sensor possesses the property to respond to physical or biological stimuli. The physical stimuli, such as pH, temperature, light, ultrasound, redox potential, magnetic field, helps trigger the release of drugs from the colloidal system. The biological system includes various enzymes, which help trigger the release. Thus, nanoparticles incorporated in colloidosomes have a greatpotential in targeting the tumour cells [72].

Brain Targeting

Blood-brain barrier is considered to be a major obstacle for the treatment of many severe diseases as it acts as a rate-limiting factor for the permeability of numerous drugs. Colloidosome is considered to be one approach to deliver the drug across the brain. A different system, such as liposomes, nanoparticles, nanogels, dendrimers, microchips, *etc.*, acts as acolloidal particle to be incorporated in the form of colloidosomes for effective navigation across blood-brain barrier [73]. A Janus nanoparticle consists of a multifunctional amphiphilic particle prepared by superparamagnetic iron oxide nanoparticles. The Janus particles are fabricated with a folic acid targeting agent and doxorubicin (DOX). These particles are madepH-sensitive by incorporating imine bond. The formulation showed the potential to cross the blood-brain barrier and treat brain cancer [74].

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Colloidosomes as a Carrier of a Drug

Delivery of Small Molecules

Earlier encapsulation of small molecules in a polymer shell resulted in leakage and diffusion. Colloidosomes coated with a metal, such as gold and silver, enhanced the sealing ability and stability of a microcapsule. The coating also blocked the porous strength of the polymer shell. Sun Q *et al.* fabricated a microcapsule with gold and silver metals. *Escherichia Coli* bacterial was incorporated with colloidosomes along with the antibiotic, kanamycin. The ultrasound trigger was used to release the drug at the targeted site. It was observed that gold-coated colloidosomes encapsulated a larger amount of kanamycin compared to silver-coated colloidosomes [57]. The traditional system expressedits failure to deliver small molecular size drugs for a longer duration of time dueto porosity and less permeability of the polymer shell. Sun Q *et al.* fabricated silver-coated colloidosomes encapsulating anticancer drugs with small molecular weight. The capsule resulted in an impermeable shell activated through an ultrasound. It was effective in the delivery of a toxic drug to the targeted site for a longer duration of time [69].

Biological Molecules

Colloidosomes have great potential to deliver various biological molecules. Additionally, it can support chondrogenic differentiation of hMSCs cells. Tang R *et al.* formulated microsphere colloidosomes using a gelatin hydrogel core and porous nanoparticle shells surrounding them. The colloidosome microsphere acts as an extracellular matrix and carries the morphogen, which induces the formation of the cartilage of human mesenchymal stem cells (hMSC) in 3D cultures. The microsphere colloidosome performs a dual function as ECM and growth factor carrier effectively. This system effectively constructs the high-density 3D tissue culture [28].

Colloidosomes for Controlled and Sustained Release

Colloidosomes impart a controlled drug release mechanism for the management of many diseases. Parkinson's disease requires accurate release of drugs at a regular time interval. Delayed release of the drug may lead to the degeneration of dopaminergic neurons in substantia nigra and reduce the amount of neurotraumatic dopamine. A modified double emulsion technique is used to prepare colloidosomes fabricated with PMMA (polymethyl methacrylate) andpoly(caprolactone)(PCL) loaded with drugs levodopa (LD), carbidopa (CD), and entacapone (ENT), at a ratio of 4:1:8, showing a controlled release and helpful in the management of PD [75]. A controlled diffusion of the drug was also studied by Uhl B *et al.*, where a colloid-

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osome microcapsule was formed by the self- assembly of solid lipid nanoparticles over liquid lipid nanoparticles. The dispersion was adjusted to a pH of 3.5 to form colloidosomes. The formulation showed a potential to deliver food, cosmetics, and drugs with a controlled release rate [76]. Yang Y formulated a silica-based colloidosome using sericinmicrocapsule as the matrix. The formulation becomes stimuli-responsive towards pH, protease, and ionic strength. Thickness can be modified using a silica shell to control the targeted release of the formulation [77, 78].

Colloidosomes for Cosmetic and Dermatology

The optimal delivery system for cosmetic formulation should enhance deeper penetration of drugs into the tissues, increase the time of contact, greater stability, and avoid undesirable side effects. Liposomes are the best choice to formulate cosmetics [79 - 81]. The prime focus is on lipid-based drug delivery to improve the solubility and bioavailability of poorly water-soluble drugs. Liposomes provide controlled release of the drug, reduce toxicity, increase stability andbioavailability of several drugs. Various biopolymers can be used for fabricating liposomes. The liposomes can be incorporated into the colloidosomes for efficientdelivery of drugs through the skin [82, 83].

Table 2. Patents Available for Colloidosomes.

S.no.	Title	Patent number	Year	Clinical Use	Reference
1.	System, method, and apparatus related to colloidosomes	US20200290004A1	2020	Helps form ultra film and ultra-low density material colloidosomes	[84]
2.	Method for producing colloidosome microcapsules	US10773231B2	2020	Introduces a method for producing colloidosomes where the particle at the interface are adsorbed; polyelectrolytes, cross-linking, heat treatment, or fatty coating	[85]
3.	Polymersomes, colloidosomes, liposomes, and other species associated with fluidic droplets	US20200215193A1	2020	Colloidosome act as a vehicle for the delivery of fluorescent molecules, microparticles, pharmaceutical agents	[86]
4.	Nano-architecture colloidosomes for a controlled and triggered release	US20190290762A1	2019	Effective transport of active substances to the target site with a controlled release	[87]

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(Table 2) cont.....

S.no.	Title	Patent Number	Year	Clinical Use	Reference
5.	Methods and compositions for encapsulating active agents	US20100213628A1	2010	Colloidosomes encapsulate an active ingredient with biocompatible, substantially spherical particles in a shell.	[88]
6.	Colloidosomes having tunable properties and methods for making colloidosomes having tunable properties	US20090191276A1	2009	Stimuli help control the colloidosome's shell quality, shell permeability, and release characteristics	[89]
7.	Compositions, use, and methods for tunable tenacity of active(s) encapsulated in colloidosome architectures	WO2019241138A1	2006	Can provide improved uptake and efficient transport or delivery of active agents to intended targets	[90]

CONCLUSION AND FUTURE PROSPECTIVE

Colloidosomes have been established as effective drug delivery systems without biotoxicity. Their commercialization is feasible without major stability issues with good feasibility and low cost. The major challenge observed during the development of stable colloidosomes is the particle size (less than 100 nm). Another challenge is to control the permeability of colloidosomes for effective drug encapsulation. Colloidosomes with responsive nature can be triggered by ultrasound, temperature, pH, light and show effective delivery at the target site. Permeability can be controlled using a double-shell of polymer over the encapsulated particles. Bispecific targeting with stimulus triggering requires additional attention for improving efficacy and reducing toxicity. Surface modification with desirable properties will assist in further improving targeted delivery.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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CHAPTER 8

Herbal Nanoscience: Challenges and Regulatory Perspective

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Abstract: For many centuries, herbal medications have been widely explored and utilized in almost all regions of the world. The progression in plant-based chemical and pharmacological sciences has provided a detailed explanation of many plant-based medications. Nanomedicine and other similar nano delivery systems are a comparatively novel but rapidly developing science, where materials in the range of nanoscale are utilized to serve as means of diagnostic tools or to deliver medicinal agents to pre-determined targeted sites in a guided manner. Site-directed and tissue- targeted delivery of specific medications is among the different advantages offered by nanotechnology for treating numerous human ailments.

Recently, scientists have developed numerous outstanding uses of nanomedicine, involving immunotherapeutic agents, chemotherapeutic agents, and other biological agents for the treatment of different ailments. World Health Organization (WHO) has categorized herbal drugs into the following three types: crude plant materials, prepared plant materials, and therapeutic herbal items. In India, herbal prescriptions are managed by the Service of Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH). Regulatory provisions associated with Ayurveda, Unani, Siddha medications are mentioned in the Drugs and Cosmetics Act and Rules 1945. Herbal drug items differ from country to country, including food sources, dietary supplements,and conventional prescriptions. To recognize lately introduced revisions in regulations, a comprehensive literature review for regulations of herbal-based drug products inIndia and Europe was carried out. Different advisory groups, including the Committee on Herbal Medicinal Products (HMPC) and the board of trustees of the European Medicines Agency (EMA), have created rules for evaluating quality and pre-clinicaland clinical efficacy and safety of drugs. Drug and cosmetic acts and rules have been altered as of late to manage the safety, quality, and efficacy of herbal drug items in India. In this chapter, we have summed up all the central issues and progress made by scientists in

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the field of herbal nanomedicine , including quality control of nano-particles, herbal drug regulations and restrictions, and difficulties observed in theformation of herbal medication.

Keywords: AYUSH, Drug delivery, Drug targeting, Nanomaterials, Nanomedicine, Nanotechnology, Natural products, Quality control, Regulation.

INTRODUCTION

Since a few decades, there has been a lot of focus on improving the drug delivery framework for drugs based on herbs. In this cutting-edge world, herbal drugs are in huge demand for their utilization in fixing multiple infections with minimum harmful effects and better remedial impacts [1]. Novel herbal-based drug transporters treat the specific ailment by targeting precisely the diseased part inside the body of the patient and transferring the herbal drug to the diseased tissue. Herbal nanoscience is also known as phytotherapy. It includes the application of various plant parts (roots, leaves, stems, seeds, and flowers) for different therapeutic uses [2]. Nanotherapy is one of the flourishing areas in the development and innovation of novel medicines. Drugs must be marketed as safe and therapeutically active preparation whose performance is persistent and précised. Nowadays, new and better medicinal agents are being produced at a hastened rate. In addition, novel drug delivery technology has made possible control over drug circulation inside the body that is accomplished by integrating the drug in the transporter system or bringing variation in drug structure at the sub-atomic level. Furthermore, integrating herbal drugs in the transporter framework enhances its dissolution properties, provides better safety, efficacy, and delivery, and improves pharmacological action. For instance, phytosomal transporters have been employed for transporting herbal concentrates of ginkgo biloba (ginseng) that showed better retention qualities in contrast with normal herbal concentrates. Likewise, other nano-formulations like nanoemulsions and polymeric nanoparticles have proved to be effective in transporting herbal drugs [3 - 5].

Since previous decades, many findings have shown improvement in drug transporting structure for herbal-based drugs. These herbal-based drugs are getting more attention in the present times for their uses to treat various diseases with minimum adverse effects and better therapeutic actions [1]. Novel herbal drug-based carriers treat ailments by transporting the drug to the target area, acting precisely on the influenced or diseased part of the body of the patient. A novel drug delivery system is priceless in delivering herbal-based drug at a pre- determined rate at the specific site of action, inhibiting the noxious contact of drugs with other agents that enhances the bioavailability of drugs. Nano therapy is one of the thriving areas in the advancement of novel medications. The incorporation of

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herbal-based drugs in the transportation system enhances solubility, maintains consistency, provides safety from harmful effects, improves biological activity, ameliorates macrophage scattering in tissues, and provides protection from physical degradation.

Advantages of Herbal Drugs

1. Found to be safe: In general, it is observed that herbal drugs are shown to be more patient-friendly, have low adverse outcomes than the conventional medication, and might prove to be more effective to utilize.

2. Better efficacy: Herbal-based drugs are much more effective for cases that do not respond well to ordinary prescriptions. Vioxx, introduced in the market as a safer alternative to NSAIDs for the treatment of joint pain, was subsequently found to increase the risk of cardiovascular disease. While herbal medications for joint pain have shown much fewer complications.

3. Lower cost: Conventional drugs available in the market are found to be more costly than herbal-based drugs. Moreover, examination, testing, and advertising of conventional drugs add extensively to the expenses of physician-endorsed conventional medicines.

4. Far and wide accessibility: Herbal medications, such as spices, are commonly used as food, preventing any need of taking medication separately. Commonly employed spices, for example, peppermint and chamomile, can also be developed at home [6, 7].

Drug Delivery Systems Based On Nanomedicines

To transport natural product-derived bioactive compounds or therapeutic agents to their target location for the treatment of diseases, lately, there have been vast developments made in the field of drug delivery systems. Although in the present scenario, various drug delivery systems are in use, there are still certain challenges associated with the efficient transport of drugs to the required site, which are needed to be addressed. Thus, in current times, extensive studies on drug delivery systems that are based on nanomedicines are going on, which can promote the advanced system of drug delivery [8, 9].

Requirement for Nano based Delivery System for Herbal Remedies

Selection of nano-based herbal drug delivery system was made to get control over the drawbacks of conventionally available herbal-based drug delivery systems, which are as follows:

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- Nanoparticle-based pharmaceuticals with improved target drug delivery, safety, and effectiveness have been found that target herbal medicine to human organs, reducing the dose and increasing patient compliance.
- Nanoparticles can be employed to enhance the solubility of herbal drugs that further help target the drug to a particular site, thereby resulting in better usefulness.
- Nano-sized drugs are capable of distributing large amounts of medicines to specific target sites due to their high loading capacities and exclusive size [10].

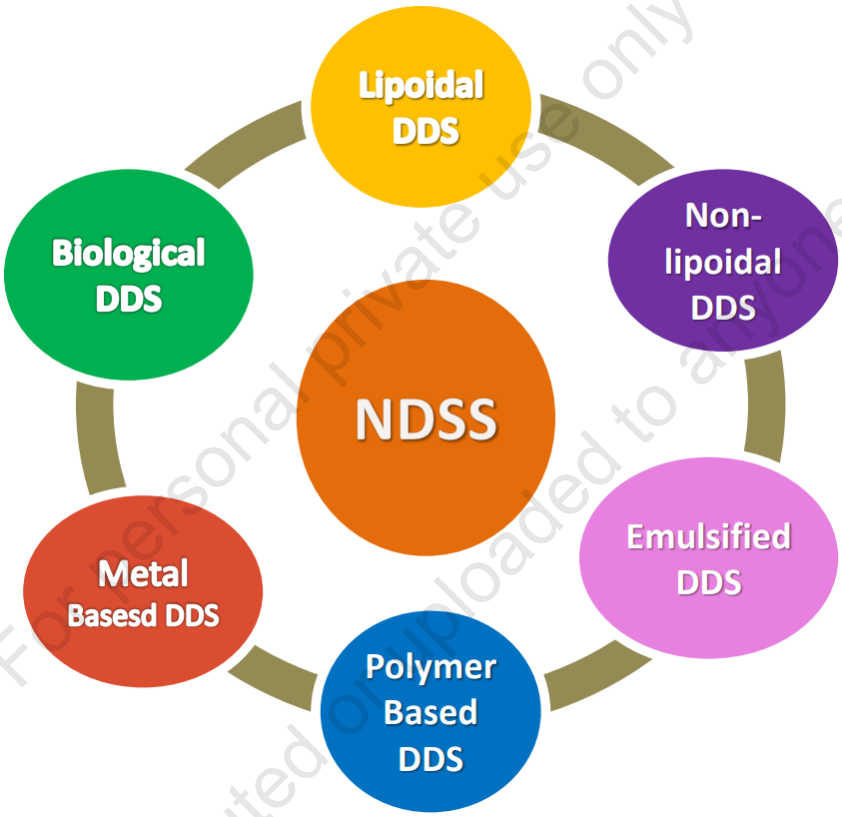

Fig. (1). Salient features of Novel Drug Delivery System.

Currently, numerous drug targeting and delivery systems are under the stages of development so that drugs having minimum degradation and side-effects can be developed; the bioavailability of drugs gets enhanced with an increase in required target-based drug accumulation [11].

Advantages of Novel Drug Delivery System

a. Amelioration of solubility
b. Improvement in bioavailability
c. Reduced toxicity

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d. Enhanced biological activity
e. Improved stability
f. Sustained delivery
g. Reduced chemical and physical degradation [12, 13]

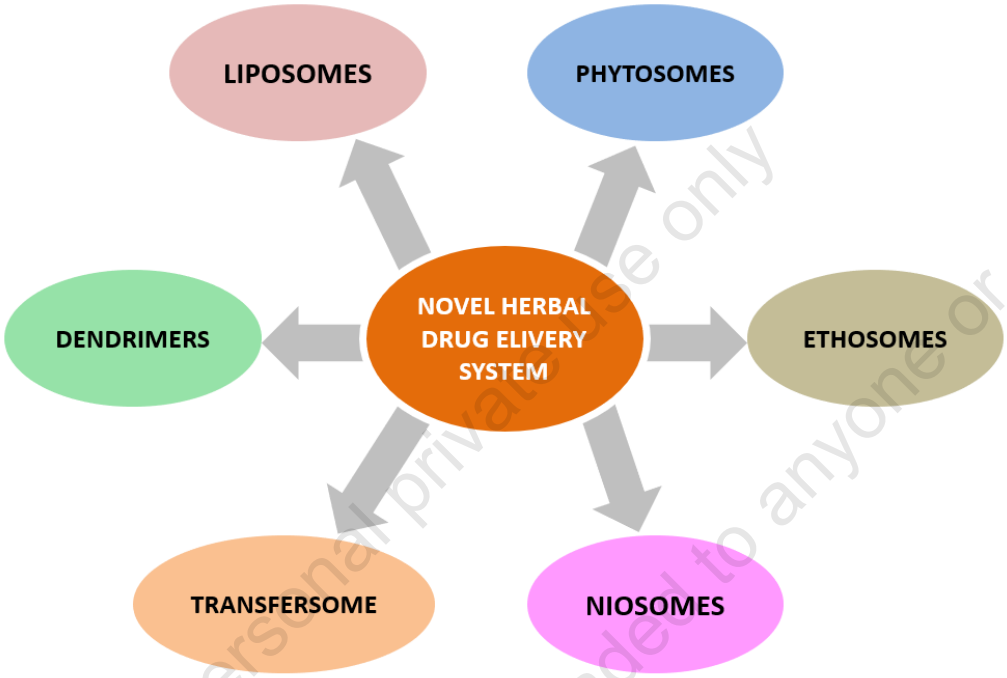

Fig. (2). Types of Novel Herbal Drug Delivery Systems.

Regulatory Guidelines for Herbal Nanomedicines

Herbal-based medicines are also entitled botanical medicines or phytomedicines. An investigation done by WHO (World Health Organization) states that eighty percent of the population of the world is currently using plant-based medicine [14].

Indian Regulations and Strategy

The national policy on conventional medicine was first made in 1940. The introduction of national laws and regulations was done in 1940, followed by amendments made in 1964, 1970, and 1982. Moreover, various specialcommittees were made that represent different forms of traditional medicine, and the first one was established in 1962. Various general research institutes were alsoestablished; the earliest one was the Central Council of Indian Medicine which was formed in 1970. In 1940, the national regulation for herbal medicine was established with

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the publication of the Drugs and Cosmetics Act, and it was foundthat the laws and regulations for herbal-based medicines were around fifty percentthe same as those for other common pharmaceutical products [15, 16]. This act states that herbal medicines can be taken in the form of dietary supplements, prescriptions, and OTC (over-the-counter medicines). Medical, health, and nutrient content claims can be made for selling these herbal-based medicines.Two national pharmacopeias of India, known as Ayurvedic and Unani pharmacopeia of India, have mentioned these herbal drugs as an important source of treatment against various ailments [17].

Quality Control Associated with Herbal Medicinal Products

All herbal-based medicines must fulfill all the conditions required for maintaining safety, quality, and efficacy, as per the Herbal Medicines categories [18]. In addition, imported herbal medicinal products should also fulfill all the conditions required for establishing their efficacy, safety, and quality control.

The national drug regulatory authority is responsible for issuing a license to wholesalers, importers, manufacturers, and assemblers of herbal-based medicines [19]. Dealers must apply for one or more licences, such as wholesalers, assemblers, manufacturers, and importers, depending on the type of drug-based business they are involved in. Local companies must apply for an import license that will further get approved by the licensing authority so that the import of herbal-based medicinal products, along with their sales and distribution, can take place in importing countries [20, 21].

For applying the requirement of an import license, the following information associated with importing company is needed

- Particulars of the company;
- Certificate of business/company registration;
- Particulars of the individual applying for the application on behalf of the company;
- Store layout plan;
- Quality control related guidelines.

The main principle of quality control is to confirm the product quality only when they meet quality specifications and standards. Various monographs, handbooks, and official pharmacopeias are available that provide information regarding appropriate standards and specifications. For selecting analytical techniques, robustness, validity, and availability of the methods must be reviewed *viz* titration of active substance, microscopic identification, and thin-layer chromatography

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(TLC) [22]. If required, a comprehensive investigation utilizing more sophisticated methods such as high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), and gas chromatography (GC) should be done.

According to the Drugs and Cosmetics Act 1940, "Ayurvedic, Siddha or Unani drugs" are inclusive of all drugs made for external or internal utilization in the diagnosis, prevention, or treatment of disease or disorder in animals or human beings, and produced entirely according to the formulae, which are provided in the traditional books like Siddha, Ayurvedic and Unani (Tibb) systems of medicine [23, 24].

European Regulations and Guidelines

Regulation of herbal-based medicines in India is made according to the "Drug and Cosmetic Act (D and C) 1940 and Rules 1945". All the regulatory provisions related to Unani, Siddha, and ayurvedic medicine are clearly mentioned in "Drug and Cosmetic Act (D and C) 1940 and Rules 1945". In India, all the approval associated with the marketing of herbal drugs and manufacturing license forherbal drugs is granted by AYUSH (a regulatory authority under the Ministry of Ayurveda, Yoga, and Naturopathy, Unani, Siddha, and Homoeopathy) [25 - 27].

Following fundamental parameters are considered essential for standardization and quality control assessment of herbal formulations:

1. Quality control assessment of crude drugs substance, plant-based formulations, and finished products.

2. Estimation of stability and shelf life.

3. Assessment of safety; documentation of safety reports based on toxicological studies or experience.

4. Efficacy assessment through ethnomedical and traditional information and investigations of biological activity [28].

Various guidelines and policies are periodically developed and reviewed by WHO, such as agricultural and collection practices (GACP, 2003), good manufacturing practices (GMP), and various research methodologies for proper utilization of herbal medicine having minimum adverse effects, confirming the safety, quality, and efficacy of the herbal-based medicine. To promote global healthcare, WHO has released the "WHO Traditional Medicine Strategy 2014–2023" that integrates complementary and traditional medicines. Such initiatives taken by WHO will help

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address the variations in regulations related to the utilization of herbal-based medicine. The establishment of the national office of the Department of Medicine and Homeopathy was done in 1995 under the Ministry of Health and Family Welfare.

There are numerous expert committees for analyzing various types of local or traditional medicine, and the first one was made in 1962 [29 - 32]. Likewise, various national research institutes working on traditional medicines have been developed in India, and the first institute was established in 1970 named the Central Council of Indian Medicine. The establishment of national regulation for herbal medicine took place in 1940 with the simultaneous publication of the Drugs and Cosmetics Act. Herbal-based medicines have to comply partly with thesame laws and regulations as given for other conventional pharmaceutical products. Herbal-based medicines are marketed in the form of OTC, prescribed medicines, and dietary supplements. Health, medical, and nutrient content claims can be made for selling herbal medicines [33].

Following alternative claims can be made for selling herbal medicines: OTC (over-the-counter medicines), self-medication and authorized medicines, herbal-based medicines as a discrete regulatory category, dietary supplements, functional foods, and others [34]. Their descriptions are mentioned below:

1. Authorized medicines: Any medicine that can only be purchased with the help of a prescription (under the order of a physician).

2. Self-medication only: Medicines that are authorized for self-medication.

3. Over-the-counter (OTC) medicines: Any medicine that can be purchased without any prescription.

4. Dietary companions: Substances which consist of a mineral, an amino acid, a vitamin, a herb, or other botanical. To enhance the total daily consumption of a concentrate, constituent, metabolite, extract, or union of this ingredient, a dietary supplement can be used.

5. Health food: These are products that are associated with particular health claims and thus are regulated differently from other foods.

6. Functional foods: They may be foods that offer health benefits more than their nutritional value and thus are managed differently from other foods.

7. Other products: They are categorized distinctively from the above-mentioned categories [35].

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Regulatory Challenges for Herbal Nanomedicines

The nation faces significant difficult situations in the turn of events and usage of the regulation of conventional and herbal drugs. These difficulties are related to the regulatory status, quality control, safety monitoring, assessment of safety and efficacy, and lack of information concerned with TM/CAM under national drug regulatory authorities [36].

Challenges Associated with the Regulatory Status of Herbal-based Medicines

Before conventional drugs came into common use, herbal medications were employed for maintaining the wellbeing of an individual. A solitary therapeutic plant might be characterized as a useful food item, a dietary supplement, or a herbal medication in various nations, depending upon the regulations controlling food sources and drugs in every country [37].

Challenges Associated with the Evaluation of Safety and Efficacy

Methods and requirements for the evaluation and assessment of efficacy and safety of herbal-based medicines are more complex as compared to common conventional pharmaceutical products. Since a single medicinal plant contains hundreds of phytoconstituents, a mixture of two or more herbal medicinal products will become rich with almost thousands of such constituents. In case if each active ingredient of the plant needs to be isolated and characterized, the time and resources required will be huge. Therefore, such investigation is very difficultin practice, specifically in the case of mixed herbal medicines [38].

Challenges Associated with Quality Control of Herbal-based Medicines

The safety and efficacy of herbal medications are firmly related to the nature of the source materials utilized in their formation. The nature of source materials further depends upon the characteristic elements (hereditary) and extraneous components (ecological conditions, development and gathering, field assortment, and post reap/assortment transport and capacity). In this manner, it is hard to perform quality controls on the crude materials of herbal prescriptions [39]. Moreover, it has been observed that there is a lack of knowledge related to herbal-based medicines within national drug authorities. Factors that are responsible for delays in information or updating of national laws, policies, and regulations for contemporary/alternative medicines, traditional medicines, and herbal-based medicines are lack of appropriate evaluation methods and poor knowledge about herbal medicines by national drug authorities [40].

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Challenges Associated with the Safety Evaluation of Herbal Medicines

Factors associated with adverse effects arising due to the consumption of herbal medicines include adulteration of herbal products, utilization of other similar species of plant by mistake, undeclared medicines, overdosage, contamination with toxic or dangerous substances, utilization of herbal medicines simultaneouslywith other medicines, and misuse of herbal medicines by either health care professionals or patients.

Thus, evaluation of adverse events associated with the use of herbal medicines is far more complicated than that of conventional pharmaceuticals [41].

Regulations

Public guidelines and enlistment of natural drugs vary from nation to nation. Natural medications are commonly used as non-physician prescribed drugs in some nations. Likewise, natural items can also be used as non-medical items. Additionally, the administrative status of a specific home-grown item may differ in various nations [42, 43].

In many countries, a huge extent of natural items enters directly into the non-professionally prescribed drugs class [44].

Changes in Regulations of Herbal Medicines Worldwide

There have been various regulatory changes all around the globe that have set up some laws and regulations for the use of medicinal plants by local people. Such regulations rely altogether upon the locale; however, it becomes a struggle to control its quality, efficacy, and safety [45].

The differences in herbal medicine regulations may be seen in Australia and New Zealand. In Australia, these medicines are regulated by the Australian National Medicines Policy. Following this arrangement, herbal medicines can be divided into three classifications: listed, registered, or exempt. In the previous two classifications, plant-based medicines should be evaluated by the Therapeutic Goods Administration of Australia and fabricated under acceptable assembling practice codes [46]. The last classification is confined to crude and raw materials [47].

However, New Zealand presently needs little oversight for the production and circulation of herbal medicines. In New Zealand, such drugs are controlled under the Medicines Act of 1981 [57]. As of late, proposed regulatory changes in the regulation of herbal medicines in New Zealand are going through the administrative cycle. In particular, the Natural Health and Supplementary Products Bill,

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whenever affirmed, would give a more grounded system to confirm wellbeing and wellbeing claims. Both in Japan and China, herbal drugs have been in use for a very long time, and they altogether coordinate with westernmedication. The Chinese Food and Drug Administration manages herbal-based medicines under the Provisions for registration of drugs (October 2007) [48].

In China, all home-grown items, including medications, normal items, and plant-based drugs, should adhere to traditional Chinese medicine (TCM) rules of enrollment, and in Japan, herbal medicines are controlled by Health and Medical Foods (HMF) under the "Food with Health Claims" regulations. These regulations are consistently reviewed, with new non-pharmacopoeial releases. The current execution of the "Food with Health Claims enactment" was established in 1991, with the latest revision done in 2015 [49].

In Russia, natural product-based pharmacopeia grade drugs are directed by the laws given in a federation known as "Flow of Medicines in the Russian Federation," which was established in September 2010 and corrected in 2014 (N-429-F3, 11/22/2014). These regulations characterize rules concerning permitting the use, transportation, import, export, and quality control of drugs [50].

In Canada, regulations associated with herbal medicines and other natural products are controlled by the Natural and Non-solution Health Products Directorate (NNHPD). In 2004, Canadian regulations were made for NaturalHealth products. These regulations necessitate that natural health products sold in Canada be authorized and assigned with a one-of-a-kind 8-digit Natural Product Number.

In the United States, herbal medicines are managed by Food and Drug Administration, with the main authoritative act coming into existence in 1994 along with the establishment of the "Dietary Supplement Health and Education Act (DSHEA)" [Public Law 103-417; October 25, 1994]. This changed TheUnited States Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U. S. C. Part 9], in this way building up a way towards the better analysis of efficacy and safety of natural items [51].

Prerequisites and strategies for quality control of completed natural items, especially for homegrown items, are more perplexing than for different drugs. The nature of such items is affected by the nature of the crude material utilized [52].

Likewise, with an increase in the availability of different medicines for human use, the use of natural medicines should be controlled by a medication regulatory structure that can guarantee the quality, safety, and efficacy of herbal drugs [53].

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Herbal Nanomedicines already Approved for Clinical Use

For the target delivery of biologically active agents or natural source-based active compounds in treating numerous ailments, researchers have recently made a huge amount of developments in the field of drug delivery.

According to WHO, herbal-based medicines can be divided into four divisions based on their source of origin, types of current usage, and evolution. Since not each category always seems equally special, they have sufficient distinctive properties for a comprehensive assessment of how efficacy, safety, and quality can be recognized and ameliorated [54].

Category 1: Indigenous Herbal Medicines

These herbal medicines are used traditionally by local communities in different regions, and because these drugs have been in use by the local population for a very long time, local people are also aware of the composition, application, and dosage of such herbal medicines. Comprehensive information on these indigenous traditionally employed herbal medicines may or may not be available. In general, these medicines are used freely by the local population or population belonging to a particular location. However, for introducing these herbal medicines in themarket or to increasing their utilization beyond the local population, certain safetyand efficacy requirements mentioned in the national regulations required for herbal medicines must be fulfilled.

Category 2: Herbal Medicines in Medicine Systems

Herbal medicines that are mentioned under this category have been in use for a long time and are accepted in countries with their uses and dosage forms availablein traditional literature of those countries. Like, Unani, Ayurveda, and Siddha belong to the class of Indian traditional system of medicines.

Category 3: Modified Herbal Medicines

Herbal-based medicines get modified in some way or the other, such as either in shape or form, including dosage form, dose, ingredients of herbal medicines, preparation methods, mode of administration, and medical indications. After getting modified, these herbal drugs must fulfill all the national regulatory needs of safety and efficacy.

Category 4: Imported Products with Herbal Medicine Base

This division of herbal medicines covers all herbal drugs that are imported, including crude materials and items. Herbal prescriptions that are imported should

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be enrolled and advertised in the nations. The efficacy and safety information must be provided to the importing country's official authorities. Herbal nanomedicine is affected by the mixtures of types of nanomaterials and herbal concentrates [55].

Emerging Challenges and Potential Solutions

It is possible that some kind of interaction can take place between nanomaterials and herbal drug particles while making herbal nanoparticles. Recently, scientists have moved their concentration towards making a drug transportation system for herbal prescriptions utilizing an improved methodology. Cuscuta Chinensis is a generally utilized conventional Chinese medication to support liver and kidney function. Because of the poor water solubility of its significant constituents, for example, flavonoids and lignans, the formulation of the drug cannot be made in oral form. Thus, in this case, nano-formulation of the drug can be made. Even though nano-pharmaceuticals may guarantee unlimited freedom in the field of drug transportation, their safety must be evaluated before employing them against any disease [56].

Toxicological effects can be observed in engineered nano-sized materials. A reduction in the size of such materials causes enhanced material interactions and changes in physicochemical and structural properties. Presently, there is still a lack of toxicological investigations reported on nanomaterials and nanomedicines, thus there is only little data available on the safety and toxicity of nanomaterials. Different varieties of literature have confirmed the potential of phytomedicine against numerous diseases. But the poor water solubility, larger molecular size, high degradation in gastric medium, and extensive metabolism are some of the disadvantages. Because of these hurdles, sometimes, these phytomedicines cannot be considered as a potential therapeutic candidate. Another important issue is the adulteration of botanical preparations. Many medicinal plants have nowadays become endangered or rare species because of the overexploitation of certain plants, fragmentation of the forest, and habitat loss. In addition, other factors such as the cost of raw materials lead to reduced availability of genuine drugs, further encouraging the substitution of plants with artificially manufactured substances, inferior commercial varieties, drugs, or cheaper plants or another vegetative part [57, 58].

Future Prospects

Nowadays, herbal healthcare products have a fast-growing market and are in increasing demand in many developing and developed countries of the world. Exhaustive research has been going on all over the globe on herbal remedies and natural products. Many institutes are performing basic and clinical trial-level

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research on drug delivery of herbal medicines [59]. With the present increasing demand for herbal nano-medicines, some potential scientific groups in the future could get attracted towards the concept of specific site-based delivery of herbal nanoparticles in various types of cancers and can potentially obtain attention-grabbing results.

With the development of nanoparticles that could deliver the precise amount of drugs to only diseased cells such as cancer or tumor cells without affecting normal cells in anyways, the utilization of nano-drug delivery systems or nanomedicine can certainly become a vast and effective area of research and development for decades to come. Nanotechnology will categorically influence herbal medicinal research, predominantly related to the bio-distribution of novel phytomedicine, and enhance the manufacturing processes employed in the preparation of theherbal nanomedicine shortly. The herbal nanomedicine development is based on the origin of the interaction between herbal products and nanomaterials. In new plant-based research and development, the formulation required for a nano dosagecomprising different nanoparticles (polymeric nanoparticles [nanospheres and nanocapsules], liposomes, pro liposomes, solid lipid nanoparticles, and nanoemulsion) is a tedious task [60]. Currently, metals-based nanoparticles that can be utilized for diagnostic purposes have also made significant progress. Thus, another area of potential research could be the utilization of metals like gold and silver in the diagnosis and treatment of various diseases providing broad utilization of nanomedicines in the near future. In this particular direction, ascientist has made a great achievement by formulating gold-nanoparticles that were found to be completely absorbed in soft tumor tissues that make the tumor susceptible to radiation-based heat therapy for selective elimination [61, 62].Despite the above-mentioned understanding of the future prospects of nano-based drug delivery systems, the real impact of these nano-based herbal medicines, especially in cancer therapy/diagnosis, remains very limited. This could be due to the novelty of this area in scientific research with the availability of only a few decades of research and thus lack of associated fundamental knowledge. One of the essential future areas related to this research could be finding the fundamental markers of diseased tissues without affecting the normal cellular process, such as key markers that allow absolute targeting.

Various biomaterials and formulation-centered nanomedicine studies appear to be in the early phase of the biomedicine applications [63].

A significant number of investigations (like animal studies and multidisciplinary research), resources, and time are required to gather data and information associated with nanomedicine-based therapeutic and diagnostic research. Furthermore, an increase in global demand for more précised medicines and diagnostic techn

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have been observed, and thus, future related to potent and effective nano-drug delivery technology and nanomedicine looks bright [64, 65].

CONCLUSION

An exponential increase in the global recognition and use of herbal medicines and related products has been observed in the current scenario. Free circulation of these herbal medicines is difficult since the utilization of herbal-based drug products differs remarkably in different countries. Among all the worldwide regulations for herbal medicinal products, European regulations were found to be the most comprehensive.

A clearly explained registration procedure for traditional or local herb-based medicinal products in the EU Member States was introduced by the Committee on Herbal Medicinal Products (HMPC), which was found according to Regulation (EC) No 726/2004 and Directive 2004/24/EC. In comparison to the US andEurope, Indian regulations are still at a preliminary stage. Efficient trade regulation and the formation of uniform standards for herbal medicinal products could be achieved by harmonizing regulations in the same way as EuropeanCountries are regulating.

India has developed guidelines for conducting a clinical trial on herbal medicines, but the registration process is not regulated properly. Thus, regulatory policies on herbal medicines require to be harmonized and strengthened on a large global scale. Now the responsibility of regulatory bodies is to analyze the controlled and quality flow of herbal products and help such products to be developed for clinicaluse.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 9

Dendrimers: A Versatile Nanoplatform for Advanced Targeting and Bioactive(s) Delivery

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Abstract: Dendrimers are radially symmetric, hyperbranched, well-organized, monodispersed, homogenous organic moieties with a three-dimensional structure. They possess terminal functional groups on the surface that improve their functionality and make them a versatile and biocompatible drug delivery module. Due to relatively low bioavailability, poor cell membrane penetration, and water solubility, about 40% of newly discovered bioactive(s) are rejected by the pharmaceutical industry. Nanomedicines based novel drug delivery technologies may be able to assist in conquering this difficulty. Nanoarchitectures with well-defined structure is gaining huge interest in biomedical applications due to their potential to cross the cell membrane and decrease the risk of premature clearance from the body. In this regard, dendrimers have been considered potential delivery modules for the bioactive(s), owingto their nanometric size, branching density, globular shape, highly reactive nature, solubility in water, and comfortable and robust synthesis methods. They could be employed as a carrier for the delivery of various therapeutic(s). They possess the abilityto decrease drug toxicity while increasing efficacy. This chapter provides a general outline of the basic introduction of dendrimers and their types, with major emphasis on their applications in advanced targeting and bioactive(s) delivery.

Keywords: Bioactive(s) delivery, Dendrimers, Drugs solubility, Nanoarchitectures, PAMAM.

INTRODUCTION

The polymers of natural or synthetic origin have always attracted research scientists in every arena of modern-day research. Among these polymers, the biodegradable polymers have further improved the bioactive delivery applicationsof the nano-drug delivery modules. The array of pharmaceutical and biomedical applications is further improved by using these nanobiopolymers in bioactive(s) delivery modules [1, 2].

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Various bioactive(s) or therapeutic moieties have some limitations, including biocompatibility issues, poor aqueous solubility, lack of specificity, and short half-life. To conquer these challenges and to improve the release pattern of these therapeutic moieties, a bioactive delivery module is needed that can deliver the bioactive(s) efficiently at the target site or site of action [3]. To some extent, conventional bioactive delivery devices are promising in conquering these hurdles. However, they are associated with certain limitations, including non- specificity, burst release, toxicity, *etc.*These challenges reduce the therapeuticefficiency of several bioactives. In this scenario, multiple efforts have been made to conquer the challenges associated with the traditional bioactive delivery modules [4]. In view of this, nanotechnology-based bioactive delivery modules offer an innovative platform to alter the characteristics of these therapeutic moieties such as solubility, biocompatibility issues, release patterns, bioavailability, and half-life. Researchers are interested in combining the deliveryof bioactive(s) or therapeutic moieties, as well as diagnostic agents, in a single device, which leads to the use of nanotechnology-based bioactive delivery modules as multifunctional platforms. Concerning this, a class of novel polymers, *i.e*., dendrimers, have emerged as the promising polymer-based advanced nanocarrier system for the delivery of several bioactive(s) or therapeutic moieties [5, 6].

Dendrimers are synthetically designed polymer-based architectures that are well known for their well-organized framework. They are in the nanometer range in size (1-10 nm). These architectures are three-dimensional and highly branched in structure. The three main components that are present in the dendritic structure are the central core, branches, and functional groups (present on the outer surface). The linked/conjugated functional or end groups that exist on the outer surface of the dendritic architectures influence the chelation ability and solubility. Moreover,they also enable the linking or attachment of the therapeutic moieties (ligands)and other biorecognizable motifs that further improve the therapeutic efficacy, whereas the central component *i.e.*, core imparts absorption capacity, capturerelease features, and provides peculiar characteristics to the cavity size [7, 8]. The last component of these polymer-based architectures is the chemical branches thatare extended in the outward direction to enable the attachment of the bioactive(s) payload. The void space present in between these chemical branches could be exploited to encapsulate the bioactive(s). These special characteristics make dendrimers a versatile nanoplatform for the delivery of bioactive(s) and diagnostic agents [9 - 11].

Apart from this, dendrimers possess several other attractive or unique features that are needed for the formulation of nanomedicines, including well-defined structure, low polydispersity index, a high degree of molecular uniformity,

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etc. These are promising scaffolds for bioactive(s) and gene delivery owing to their molecular architecture. Through electrostatic or hydrophobic interactions on their surface, they can entrap therapeutic moieties, proteins, peptides, diagnostic agents, antibodies, oligonucleotides, and nucleic acids inside interior cavities [12]. Therapeutic moieties could be linked/attached *via* a covalent bond at their terminal end (Fig. **1**). Several other applications of dendrimers reported in the recent literature include energy harvesting, gene transfection, and catalysis [13 - 15]. This chapter highlights various potential applications of dendrimers in advanced targeting and bioactive(s) delivery.

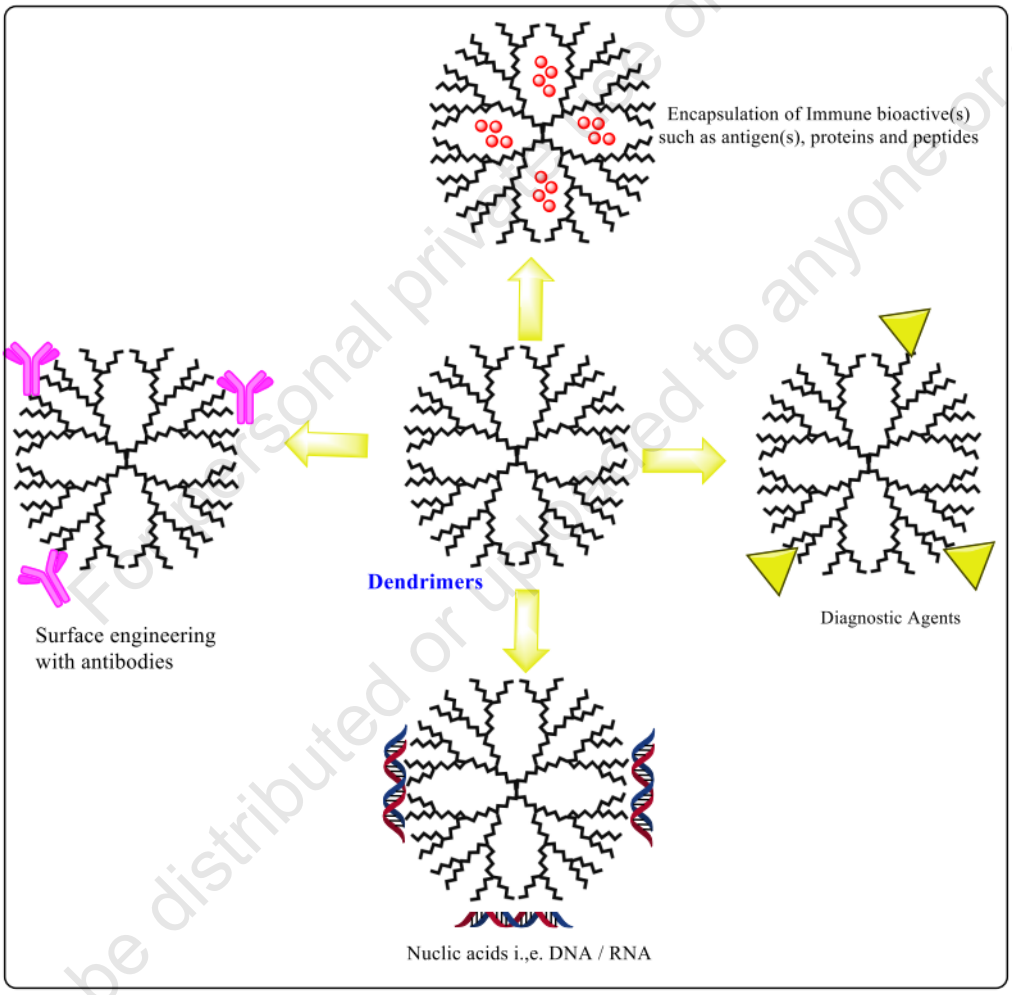

Fig. (1). Schematic representation of dendrimer and its interactions with multiple agents, *i.e*., antigen(s), proteins, peptides, diagnostic agents, antibodies, oligonucleotides, and nucleic acids (DNA and RNA).

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POTENTIAL APPLICATIONS OF DENDRIMERS

Dendrimers in Targeted Delivery of Bioactive(s)

A successful and effective targeted bioactive(s) delivery module is the need of the present juncture. The fabrication of the targeted bioactive delivery module is aimed at concentrating/accumulating the bioactive in the target site anddecreasing its concentration in the non-target site. Consequently, the localization of the bioactive could be achieved at the site of action (target site). The targeted delivery of the bioactive(s) is pivotal to decrease the side effects that are generallyassociated with conventional treatment. The aim of the targeted delivery of the bioactive(s) *via* dendrimers could be fulfilled by the surface modification oralteration of these nanocarrier systems [16 - 18]. The surface of the dendrimers could be altered by employing different targeting moieties or ligands, for example, mannose, galactose, peptides, folic acids, monoclonal antibodies, *etc.*

The targeted delivery of the bioactive(s) through dendrimers could be attained *via* two approaches, *i.e*., passive targeting and active targeting. Passive targeting, also referred to as non-specific targeting, is typically achieved by the pegylation mechanism. For instance, in the case of tumor targeting, the increase in the dendrimer's hydrodynamic radius by using pegylation results in greater accumulation/concentration of the dendrimers in the cancerous tissue *via* enhanced permeability and retention effect (EPR) effect. The EPR phenomenon is a consequence of angiogenesis that is induced by the tumors. It results inabnormal, leaky, or defective neovasculature with disorganized endothelial cells [19, 20]. Previous literature has reported multiple targeting strategies based onpassive targeting mediated *via* dendrimers delivery modules [21 - 23]. Jiang *et al.* worked on pegylated PAMAM dendrimers. PEG_{5000} was employed for the surface functionalization of the PAMAM dendrimers. Then, the bioactive, *i.e*., methotrexate, was covalently linked to the pegylated PAMAM. The blood residence time and anticancer activity were recorded to be higher in the case of methotrexate-loaded pegylated PAMAM dendrimers as compared to freebioactive. Thus, the developed carrier system could be used for the targeteddelivery of the bioactive(s) [24]. Fox *et al.* synthesized polymer conjugate ofcamptothecin (CPT) with the help of pegylated poly(L-lysine) (PLL) dendrimer. The developed formulation exhibited a prolonged blood circulation half-life (30.9 ± 8.8 h). Moreover, the uptake by the tumor was measured to be higher in the case of pegylated PLL dendrimers as compared to the free bioactive. The findings revealed that the developed formulation was avidly taken up by the solid tumors *via* passive drug targeting [25].

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Another pivotal approach that is now being used to effectively target the infected cells and to achieve enhanced specificity by using bioactive(s) loaded nanoplatforms is referred to as active targeting. In one of the studies, Kaur *et al.* developed surface-functionalized polypropylene imine dendrimers for the targeted delivery of the methotrexate. The *in vitro* release study indicates a pH-responsive release pattern of the bioactive. Cell line studies were carried out on MCF-7 breast cancer cells. The cytotoxicity and cellular uptake were found to be increased in the case of surface-functionalized polypropylene imine dendrimers compared to free bioactive. Animal studies demonstrated that the concentration of the methotrexate was increased up to 37.79 folds in the liver in 24 h in the case of nanoconjugate compared to free bioactive. These findings indicate that the developed system could be used for the targeted delivery of the bioactive(s) in the case of cancer therapy [26]. Jain *et al.* worked on amphotericin B-loaded muramyl dipeptide functionalized poly(propylene imine) dendrimers for macrophage targeting. Cell line studies were carried out on J774A.1 macrophage cells. Hemolytic toxicity study exhibited a significant reduction in toxicity in the case of the dendrimeric formulation. Animal studies were performed on infected Balb/C mice. The results showed higher antiparasitic activity in the case of developed bioactive loaded functionalized dendrimers as compared to free bioactive. The carrier seems promising and could be used for the targeted delivery of the bioactive(s) [27].

Dendrimers in Oral Delivery of Bioactive(s)

It is undeniable that the oral route is the safest and most convenient route for the administration of the bioactive(s) owing to high patient compliance. This could circumvent the pitfalls associated with the different modes of bioactive(s) delivery. However, the issues such as poor aqueous solubility and permeability of the bioactive(s) across the cell membrane limit the efficacy and advantages of the oral route [28, 29].

Dendrimers-based bioactive delivery modules have been studied previously for the oral delivery of the bioactive(s). They showed promising and remarkable results. They loosen the tight junctions of the epithelial layer; therefore, they increase the absorption and transepithelial permeability of the low molecularweight bioactive(s) [30 - 32]. In one of the studies, Goldberg *et al.* worked on third-generation PAMAM dendrimers for the oral delivery of the bioactive(s). Theauthor conjugated SN38 (bioactive) to PAMAM dendrimers to increase oral absorption and reduce the gastrointestinal toxicity of SN38. *In vitro* drug release study indicates the pH-dependent release of the SN38. An *ex vivo* study was performed on HT-29 colon cancer cells. The developed system showed IC_{50} values of 0.60 and 3.59 μM when it was kept for 48 h of incubation with HT-29 colon cancer

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cells, suggesting the efficacy of the SN38 conjugated PAMAM dendrimers. Moreover, the conjugated system also enhanced the transepithelial transport of SN38 as compared to free bioactive [33]. Najlah *et al.* designed and developed the dendrimer prodrug for the oral delivery of the bioactive. The authorconjugated Naproxen to G0 polyamidoamine (PAMAM) dendrimers. To increase the permeability of the Naproxen, one lauroyl chain was also anchored to the surface group of G0 PAMAM dendrimers. Cell line experiments were performed on Caco-2 cells. The cytotoxicity assay demonstrated that the developed conjugated system was non-toxic when it was kept with Caco-2 cells for 3 h incubation. The permeability study showed that the transepithelial permeability ofthe Naproxen was enhanced in the case of the conjugated system compared to freebioactive [34]. The above results suggest that dendrimer-based bioactive delivery modules hold the potential for the oral delivery of the therapeutics.

Dendrimers in Ocular Delivery of Bioactive(s)

The ocular formulations, such as ointments, suspensions, and solutions, are generally applied topically; however, these formulations are also associated with several challenges. The intraocular bioactive delivery suffers poor availability due to rapid elimination of the bioactive from the corneal region, nasolacrimal duct-mediated drainage of fluid, and the failure to deliver the bioactive in a sustained and controlled manner. The major obstacle in ocular bioactive delivery is to enhance the bioavailability of the bioactive(s) and protract their residence time at the corneal site. Thus, there is a need to develop such a formulation that can conquer these challenges. For this purpose, the dendrimers have been exploitedfor the delivery of bioactive(s) *via* the ocular route [35, 36]. Vandamme *et al.* developed PAMAM dendrimers for the delivery of pilocarpine nitrate and tropicamide *via* the ocular route. The PAMAM dendrimer was solubilized in the phosphate buffer solutions containing 2‰ (w/v) of fluorescein to evaluate the residence time. Animal studies were performed on albino rabbits for the quantitative and qualitative assessment of the retention time and ocular tolerance. 25 µl of dendrimer solution was applied to the eye. The residence time was measured to be prolonged for the solutions containing dendrimers [37]. Marano *et al.* worked on lipophilic amino acid dendrimer for the effective delivery of anti- VEGF oligonucleotide *via* ocular route. The fluorescein angiograms of laser photocoagulated eyes analysis demonstrated that the developed system significantly arrested the growth of choroidal neovascularization. The retinal absorption and penetration in all retinal layers were also enhanced on administering intravitreally injection of dendrimer formulations. The ophthalmological studies demonstrated no observable increase in antigen associated with inflammation [38]. The above findings suggest that the

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dendrimer-based formulations seem promising and could be used for the ocular delivery of therapeutics.

Dendrimers in Microvascular Extravasation

Dendrimers possess extravasation propensity due to nanoscale size dimensions and low molecular weight. The phenomenon (extravasation propensity) involves the movement of particles from the blood circulatory system across the endothelial lining of the walls of the capillary into the neighbouring interstitial tissues. The extravasation phenomenon is pivotal to effectively deliver the bioactive(s) at the target site or the site of action [39]. Kitchens *et al.* reported the extravasation of polyamidoamine dendrimers of different generations *via* microvascular endothelium. This phenomenon is specifically essential for tumor cell localization of anticancer bioactive(s) *via* passive targeting as well as in the diagnosis of cancer *via* magnetic resonance imaging (MRI) agents [40, 41].

Dendrimers in Intracellular Delivery of Bioactive(s)

The potential to deliver the bioactive(s) or the molecular cargo intracellularly is one of the key advantages of dendrimers. Dendrimer based formulations have been widely exploited by research scientists to achieve intracellular level bioactive targeting. Previous literature has reported that the mannosylated dendrimers hold the potential to effectively deliver the antiviral bioactive(s) to the macrophages *via* receptor-mediated endocytosis. Many scientists have reported that the uptake of anticancer bioactive loaded dendrimers was enhanced along with the consistent release of the bioactive(s) in the tumor cells. The factors such as minimum extracellular leakage and impeding the non-specific interaction of the dendrimers with systemic circulation facilitate the intracellular delivery of the bioactive(s) *via* dendrimers [42 - 44].

In one of the studies, Khandare *et al.* worked on PAMAM dendrimers. The author conjugated PAMAM dendrimers to methylprednisolone (drug) by using glutaric acid as a spacer. A549 cells (human epithelial lung carcinoma cells) were used in *ex vivo* assessment. FACS analysis (flow cytometry) demonstrated that the developed conjugated system was avidly uptaken by the macrophages. The confocal microscopy study revealed that the cellular localization was higher in the case of the dendrimer-drug conjugated system as compared to free bioactive. The above results seem promising, and the developed dendrimer-drug conjugated system could further be conjugated with targeting moiety or ligand to achieve the intracellular and targeted delivery of the bioactive(s) *in vivo* [45].

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Dendrimers in Tuberculosis Therapy

Tuberculosis (TB) is a transmissible infection that habitually affects the lungs primarily, and other organs secondarily, including the spine and brain. The causative agent of tuberculosis is *Mycobacterium tuberculosis*, which has revealed its development over time. The standard mode of transmission of the disease is through an aerosol-based system. Moreover, the development of active TB varies with different factors such as age, gender, immunity level, the period ofinfection, and geographical locations. Isoniazid and rifampicin (RIF) are the most important first-line antitubercular bioactive(s) for TB. Levofloxacin, linezolid, and Kanamycin belong to the second-line antitubercular bioactive(s). These bioactive(s) are mainly used to treat resistant TB. The drugs used for DOTS treatment show certain difficulties, such as poor bioavailability due to low solubility and thus low efficacy. Many nanocarriers like solid lipid nanoparticles, liposomes, liquid-crystalline systems microemulsions, nanoparticles, and dendrimers have been used for the delivery of antitubercular drugs. These approaches are helpful to reduce drug limitations and improve the treatment of diseases. In one of the studies, the surface of the dendrimers was modified with sugar-based molecules, such as mannose. This modification enhanced the drug targeting towards macrophages because of the presence of lectin receptors on the membrane that possesses high affinities towards mannose. Kumar *et al.*, worked on mannosylated dendrimers. The author entrapped RIF successfully with 37.34% loading efficiency into mannosylated 5th generation (5G) polypropylenimine (PPI) dendrimer. The interactions between dendrimer and drug were found to be non-covalent. Owing to the steric hindrance and deprotonation of mannosylated dendrimers surface, the mannose tethered formulations resulted in a 10-fold reduction of RIF's solubility. RIF-loaded mannosylated dendrimer had shown a significantly low cytotoxic effect on kidney cells. Mannosylated dendrimer promoted accumulation of RIF in alveolar macrophage compared to free solubilized RIF molecules. RIF was found for about ~120 h in the inner voids of mannosylated dendrimers at physiological pH of 7.4, which is an appreciably longer time. Moreover, drug entrapment capability and control release potential (36 h) also increased when PEG chains were grafted on 4G and 5G PPI dendrimers surface [46].

The association of RIF with 4th generation (G4)-PAMAM dendrimers and its molecular dynamics simulations were studied by Bellini and co-workers [47]. The simulation technique is an effective way to determine different types of association systems.According to the study, each G4-PAMAM dendrimer could hold up to 20 RIF molecules. It was agreeable with the earlier work of Kumar *et al.*, in which the author reported several RIF molecules per 5th generation (G5)- PPI dendrimer (mannosylated) was maximum ~37. The molecular dynamic simulations study

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revealed that the stability of the complex was reasonably goodat neutral pH. Thus, the dendrimers could be exploited to deliver drugs in alveolarmacrophages where the environment is acidic. Kumar and co-workers designed and developed RIF containing PEGylated 5G EDA-PAMAM dendrimers [48] andwere authorized by Fourier Transform Infrared Spectrophotometry technique and 1H-NMR spectra. The % drug entrapment of RIF was recorded to be ~99% in PEGylated dendrimer. The release of the RIF was 81% in 5 days for PEGylated dendrimers and 98% in 3 days for non-PEGylated dendrimers. The PEGylated dendrimer demonstrated lesser blood-toxicity (less than 2.5%). This is attributed to the obstructed interaction of RBCs with the surface quaternary ammonium groups of the dendrimers.

Dendrimers in CNS Delivery of Bioactive(s)

Brain diseases are continually accelerated problems because of the prominence of the blood-brain barrier (BBB) that obstructs the pervasion and admission of many bioactive to the central nervous system (CNS). Nanodevices, owing to their advantages, have been developed and designed to transport drugs into the brain. Dendrimers have attained massive consideration from researchers because of their size, effortless multi-functionalization, and inner cavities that can easily hold the drugs. The branched tertiary structure of dendrimers could be explored to carry various therapeutic moieties, including small molecules, genes, peptides, andother bioactive agents, weakening their toxicity and enhancing their effectiveness.

Administration of drugs through nasal passage is an important pathway for brain drug delivery; dendrimers may hold the prodigious potential to carry drugs *via* the nasal route to the brain, bypassing BBB. Some challenges that have to be overcome for brain delivery through the nasal pathway include obstruction by barrier imposed by nasal epithelial, speedy removal from the nasal cavity, lesser diffusion of bioactive from entry points of nerves [49], and indiscretions during a disease.

Kim *et al.* used a biodegradable PAMAM dendrimer to be complexed with siRNA as a vector for gene delivery. The beneficial effect of delivering siRNA intranasally was determined in the postischemic rat brain. The author reported thatsiRNA, which was fluorescent-labelled, accumulated in neurons and glial cells in many regions of the brain after 1 h. More pointedly, this was beneficial to reduce the volume of cerebral infarct in rats, and it was found that the rats showed improved neurological and behavioural problems. This shows the ability of dendrimers to deliver the gene into the brain [50]. Sharma *et al.* exploited click chemistry to conjugate mannose to the corona of adaptable D4-OH to discover thepotential of mannose for higher brain uptake. Mannose modification suggestively enhanced the

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internalization of dendrimers, as indicated by *in-vitro* experiments *via* carrier-mediated mannose endocytosis [51]. BBB generally expresses many transporters that encompass drug delivery to the brain, including glucose transporter [52], choline transporter, large neutral and cationic amino acid transporter [53, 54], nucleobase transporter and monocarboxylic acid transporter 1[55, 56], *etc.*

Ligand-anchored dendrimers were designed to explore their drug delivery potential exploiting the various receptors present on BBB. This study also compared the brain targeting efficiency of different ligands. An antitumor agent, paclitaxel (PTX), was delivered to the brain by conjugating various ligands like concanavalin A, sialic acid, and glucosamine to PPI dendrimer. The potential of targeting these targeting moieties (ligands) was found in the following orderconcanavalin: A < glucosamine < sialic acid. The highest potential of sialic acid made it a promising candidate to be appended to PPI to augment anticancerdelivery of the drug to the brain, thus attaining the greatest pharmacological and therapeutic effects [57]. Since transferrin was found abundantly on the BBB and its Fe^{3+} carrying capacity *via* transferrin receptor-mediated transcytosis was very effective, transferrin (Tf)-anchored third-generation (PPI) dendrimer was formulated for gene delivery into the brain [58]. Lactoferrin (a cationic glycoprotein) has been utilized to generate a lactoferrin-bearing G3 PPI dendrimerthat augmented pDNA internalization by 2.1-fold in murine brain capillary endothelial cells [59]. Since dendrimers have been found suitable for targeting the brain with multi functionalities, targeting, biodistribution, and cell interactionscan be modulated and altered. Moreover, the potential/ability for dendrimer application in nano-theranostics for brain diseases continues to increase. Sarin *et al.* reported theranostics pH-sensitive PAMAM dendrimer conjugated with doxorubicin (DOX) for brain tumors. The nanosized (7 to 10 nm) Gd-D5-DOX was found to be effective in delivering therapeutic concentrations of the drug into individual brain tumor cells across the BBB. The study proved that a single dose of the developed formulation was more effective than a free drug with an equivalent dose in confining the growth of RG-2 glioma [60]. Zhao *et al.* designedand developed PAMAM dendrimers-based formulations. The author conjugated/linked PAMAM dendrimers with CREKA (fibrin-binding peptide).The developed formulation aimed to target the extracellular fibrin in brain tumors to increase intracellular accumulation. Higher accumulation and deeper penetration were achieved with CREKA-modified PAMAM in comparison to unmodified PAMAM in glioblastoma multiform (GBM) tissue [61], demonstrating a successful approach for the treatment of tumors of the brain. Tumor capillaries express a high number of receptors, which can be exploited and provide a favourable environment for ligand-anchored dendrimeric systems to enhance drug delivery to tumour tissues [62]. Covalent attachment of specific ligands to

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dendrimer is important as it is to be recognized by receptors, antigens,or other molecules that are overexpressed on the tumor sites. Dendriticarchitectures possess specific configuration, unique physicochemical properties, and tunable surface properties and groups, which are beneficial for activetargeting; thus dendrimers are effective nano-constructs for brain diseases therapy. Polyether-copolyester (PEPE) dendrimers are reportedly less toxic and highlypermeable across the BBB, as well as possess an extended half-life [63]. Clathrin and caveolin-mediated endocytosis are the most important pathways utilized forthe effective internalization into brain vascular endothelial cells, among severalother pathways. A fascinating study that includes the utilization of RGD as atargeting ligand is reported previously. RGD-modified PEGylated PAMAMdendrimer was synthesized *via* acid-sensitive cis-aconityl linkage. This strategycould strengthen tumor targeting by interacting with the integrin receptors overexpressed on tumor cells. Apart from this, controlled release of DOX inacidulous lysosomes was attained [64]. RGD conjugation resulted in a higheraccumulation/concentration of DOX in the brain tumor as compared to the normalbrain tissue in a glioma model. The presence of BBB is the major hurdle in drugdelivery to the brain. To conquer this hurdle, dual-targeting dendrimernanoparticles have been designed that have fascinated interest because thesenanoconstructs conferred with adaptable functions that could not only transportacross the BBB but also reach tumor cells to improve the efficacy of therapeutics [65]. In a study, transferrin (Tf) and tamoxifen (TAM) were the choices oftargeting moieties for reinforcing dual targeting, *i.e*., transporting capabilityacross the BBB and for assembling DOX into glioma cells. Such dual-targeteddendrimers effectively constrain the growth of C6 glioma cells and also reducethe cytotoxicity of DOX to normal cells [65]. This approach can be simplified byusing the common receptors which are expressed on both BBB and the tumors,like transferrin receptor [66] and LRP1 [67], *etc*.Dendrimers have also beeninvestigated for the delivery of the bioactive(s) to other cerebral diseases such asAlzheimer's disease [68], stroke, and cerebral palsy [69]. It is reported thatphysicochemical properties of the dendrimer and pathophysiology of diseaseregulate BBB uptake, diffusion, and cellular uptake of dendrimers. Studies haveshown that PAMAM dendrimers of size less than 11 nm are optimum innavigating the damaged BBB in an ischemic stroke model [70]. Hydroxyl-modified 4th generation (G4) PAMAM dendrimers can cross the impaired BBBand accumulate in the diseased site of perinatal hypoxic-ischemic encephalopathy,neonatal and ischemic stroke, cerebral palsy, and hypothermic circulatory arrestinduced brain injury [71]. The accumulation of the dendrimers based formulationsat the diseased site relies on the level of BBB damage, glial activation, andseverity of brain disease. The breakdown of tight junction proteins (ZO, occludin,and claudin-5) in the BBB due to disease/brain injury could contribute to the transport of dendrimers into the brain parenchyma [72].

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Dendrimers in Transdermal/topical Delivery of Bioactive(s)

Dendrimers demonstrate improved drug properties and enhanced permeation across the skin because they are fabricated to be extremely water-soluble and biocompatible, thus delivering drugs proficiently when delivered transdermally. Dendrimer properties affect their skin penetration and the penetration of accompanied molecules. Surface charge, hydrodynamic size, molecular weight, charge density, and the nature of the interaction between the dendrimer and the active molecule influence the penetration of molecules through the skin in the presence of dendrimers [73, 74].

CONCLUSION

Appropriate selection/choice of the bioactive delivery modules is a critical factor in the domain of drug delivery. Apart from this, nanotechnology seemingly shall play an important role in future nanomedicines. It serves as a useful tool that mustbe explored and exploited further to identify and analyze the solutions for the challenges associated with the current drug delivery. The use of nanomaterials might add new dimensions to it. They may increase the specificity and sensibility to the next generation of diagnostics and treatment modalities. In the 21st century, dendrimers have emerged as a potential bioactive delivery module in the arena of nanotechnology pharmaceutical, biopharmaceutical, and biomedical applications. Dendritic nanoplatforms have demonstrated significant potential as a versatile delivery module for bioactives, proteins, peptides, DNA oligonucleotides, genes, diagnostic agents, *etc*.There are still plenty of vistas to be unfolded. Research scientists are continuously investigating and exploring the different dimensions of dendrimers as bioactive delivery modules. An interdisciplinary vision towards dendrimer hybrids with other nanoplatforms could be a potential approach. However, the toxicity concerns associated with the hybrid nanoplatforms should be investigated unless it is ruled out.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 10

Targeted Drug Delivery System to Cell and Cell Organelles

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Abstract: Today, massive investigations have been undertaken to boost the target-oriented distribution of drugs to maximize their therapeutic index. Cell targeting drug delivery is a good candidate in exhibiting therapeutic effect to severe diseases such as cancer; The extent to which the drug can achieve its intended goal is of the utmost importance. This system is designed to aid a drug's ability to pass an obstacle that it might not otherwise be able to pass through regular means; therefore, their impact is pharmacokinetic. The drug's pharmacological effects should remain untouched, like its pharmacodynamic structure. In some cases, the pharmaceutical delivery mechanism has an effect on how the drug appears to work. Drugs must overcome numeroushurdles that are on the way to the target tissue from the administration site. In certain cases, a physically defensive barrier around the drug cargo is created to help the drug navigate over certain barriers. The need for selective medication distribution has,therefore, been well acknowledged in current drug therapy. Thus, in this chapter, we discuss the different organelle targeting drug delivery systems and studies involved in it.

Keywords: Cell organelles, Targeted drug delivery, Vesicle based drug delivery.

INTRODUCTION

The regulated localization of maximum therapeutic concentrations to the cellular/subcellular site of operation in pathologically damaged tissues is one of the long-standing issues of target drug delivery. Drug molecules face several obstacles before reaching their intended place of action, and chemical degradation

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in the intracellular and systemic compartments of the human body is a possibility. Many biological boundaries can be breached as a result of this breakdown [1].

Nanoparticle agents lose the flexibility of tissues and organs, suffer from rapid *in vivo* body release, and are mostly accompanied by several other side effects, especially chemotherapeutic agents, which are usually extremely corrosive. As one of the most promising approaches to tackle this issue, drug delivery systems (DDS) have already been implemented in recent decades. Using a carrier system ensures that it is possible to improve the effectiveness and safety of medical, diagnostic, or prophylactic agents and thereby enhance their potency. These carriers' major roles involve prolonging medication half-life, efficiently hitting therapeutic drug target areas, thus minimizing the effects on non-target tissues. However, conventional DDS does not deliver truly tailored interventions and customized medical care and does not satisfy modern medicine's growing needs; thus, a daunting undertaking for clinical medicine is the development of a modern type of DDS with a truly unique emphasis (Fig. **1**) [2 - 4].

CROSSING CELLULAR BARRIERS

For drug delivery systems, a vast array of pharmacokinetic problems is being established. These also include a drug that passes one or more physiological obstacles that impede the exchange of matter in the body, tissues and/or skin materials. The skin, the fibrous tissue around a nerve, and/or the various sheaths around it are examples of recognizable or less well-defined physical entities. Barriers will not initially be identified as contributing factors by drug distribution systems. Barriers can be relatively free of living cells, such as the skin's covering, or they can be made up of organelles with associations that make them difficult to cross, such as the blood-brain barrier [5].

These mechanisms are designed to help a medication pass an obstacle that it cannot otherwise cross at safe doses through sufficient means; thus, their effect is pharmacokinetic. The pharmacological effects of the medication, like its pharmacodynamic composition, should be unchanged. There are occasions where the usage of a medication delivery system can change what the medicine appears to be doing [5].

In certain cases, the ability to move a membrane, such as skin, can mimic the impact of the drug. Any other potential virtues may be of clinical value in such cases; the drug is removed from the gastrointestinal (GI) tract and transported to the liver through portal blood flow. The ease of access to the target site affects thenature of the drug distribution process. It is easy to put the drug delivery device on the skin and keep it occlusive [5].

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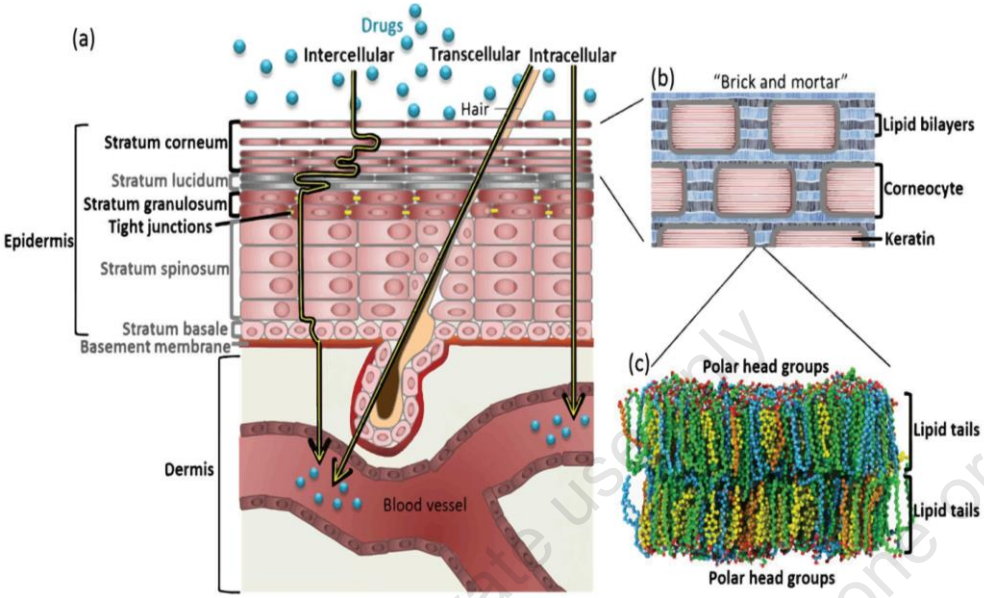

Fig. (1). Transport of drugs through the skin. **(a)** The *Stratum corneum* (SC) is the outermost layer of the skin and the major transport membrane. Molecules can penetrate *via* intercellular, transcellular, and intracellular pathways. **b)** SC permeation is mainly restricted by lipids (mortar) that fill the spaces between corneocytes (bricks). **(c)** Lipids occupying the gaps between corneocytes are organized in a bilayer form, withhydrophobic tails on the inside and polar head groups on the outside. Lipids are mostly cholesterol (yellow), free fatty acids (blue), and ceramides (green) [4].

Lipid-Based Drug Delivery System

To improve appropriate effects, and tissue targeting has been performed on lipid-based drug delivery mechanisms. Most of them have proven to be safe and stable *in vitro*. In certain tissues, massive nanoparticles are impervious to the system, including in the glomerular capillaries of the kidneys. It has also been shown that enclosing the product into enzyme groups, such as lipids, extensively changes the delivery of the drug [6].

The biological identity of a nanoparticle is complex. Unique biomolecular corona proteins are replaced over time by other proteins, which establish the cellular identity of the nanoparticle as it circulates through the system. Several studies being carried out and applied to polar nanoparticles are currently fueling the scenario. However, drug segmenting in the non-polar vehicle was ignored as contrasted to cells that might illustrate separation from the carrier to the membranes. The other players participate in an experimental situation using the physiological media; the more visible the result, the harder it would be to graspthe effect [6].

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Drugs must overcome numerous hurdles that are on the way to the target tissue from the administration site. In certain cases, a physically defensive barrier around the drug cargo is created to help the drug navigate over certain barriers. The next version of the lipid-based carrier mechanism is expected to focus more on the interactions between the carrier and the cells with the "protein-protein." A vessel that often measures its nature when it flows across the entire system would be more adaptive to the state of the target tissues. It would, therefore, be importantto study the thermodynamics of the various interactions of cell carriers between nanocarrier systems with optimum energy for drug delivery to target cells [6].

Low-density lipoproteins (LDL) cause cholesterol to spread virtually to all peripheral tissues. The LDL particle includes all the fat molecules of dominant cholesterol, phospholipids, triglycerides, and Apo B. To this day, a major obstacle will have been the effective drug carrier device for hydrophobic medicines [7]. With the assistance of ABCA1 (ATP binding cassette transporter), Apo A-1, and cholesterol esterification, cholesterol is extracted from tissues. Energy is used to setback cholesterol movement from the tissues to the site of the liver. A smart carrier system may be a nanocarrier platform to carry the drug to the cell [7].

CANCER RESEARCH AND CELLULAR DRUG DELIVERY SYSTEM

Cancer is characterized by cell groups exhibiting unregulated proliferation, invasion, and sometimes metastasis properties. Nanoparticles are used to transmit medicines to the brain by subverting the blood-brain barrier (BBB). For the treatment of Alzheimer's and other trace metal imbalance-related neurological diseases, iron chelators have been utilized. According to the American Cancer Society, nearly 7.6 million deaths were caused by cancer worldwide in 2008. Chemotherapy, radiation, and surgery are limited to the most popular cancer treatments. Many aspects decide the potency of a prescription drug. It is ofgreatest interest how far a drug can meet its targeted site of action. The need for selective medication distribution has, therefore, been well acknowledged in current drug therapy. Nanoparticles are effective carriers of drugs for the transmission of active prion disease therapeutic molecules. Several intestinal diseases have been treated through direct drug delivery, such as Crohn's disease. Intracellular drug transport, *i.e.*, multidrug resistance, which has become a big barrier in cancer chemotherapy, should surmount more significant weakness of drug activities [8].

It is important to classify drug targeting strategies into two categories: passive targeting and aggressive targeting. Passive targeting refers to a prescription or drug-carrier device's concentration at a given location. Complex modification of the nanosystem of a drug/drug carrier with the active agent requires active

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targeting. The application of a drug to specific cells was examined utilizing the existence of various receptors on the cell membrane using lipid components. The molecules implicated in some different endocytic processes that the receptor mediates have been described. This shows that drug-loaded nanoparticles, *via* the receptor-mediated endocytic pathway, result in increased absorption. For attacking different types of cells, multiple receptors, including asialoglycoprotein, epidermal growth factor, folate, chemokine, and transferrin, function as binding sites of high affinity [7].

These new systems' clinical advantages include:

- Improved vaccine effectiveness
- Site-specific delivery
- Reduced toxicity/side effects
- Improved relaxation
- Viable therapies for illnesses that were historically incurable
- Potential for prophylactic applications
- Better enforcement with patients [15].

The drug delivery nanocarrier device should propose the creation of thermodynamically improved cell-specific interaction of smart protein or epitope grafted nanocarriers. The availability of steroid hormones such as cholesterol and estrogen in the cell can boost the carriers' and drugs absorption. In lipid-based carrier systems, the membrane lipids' position will become subordinate to the function of the proteins for the drug transition from a carrier to a target cell. It was confirmed that the cancer cells were all highly drawn to their accelerated growth and development. To satisfy their growth requirements, cancer cells overexpress the relevant receptors. The higher the interaction between the cell proteins and the carrier, the stronger the vital cancer cell-carrier interaction's thermodynamic production. The job is hard and long to undertake, including the creation and high-screening processes, miniaturized experiments, and the accomplishment of quantitative methods. A detailed collection of data on contact nanocarriers could be provided by high-screening techniques that could put a whole series of different cell types on a multi-well plate [7].

The determination of these interactions will be valuable evidence in studies because it is dependent on the epitope-receptor interaction free energy state of Gibbs and the number of receptors on the cell surface. The binding of proteins in the natural environment is dynamic and vulnerable to interfering proteins that could affect the receptor-ligand interaction. The above reactions can be studied utilizing a hypothesized cell-embedded substrate in the chromatographic process, where the device can measure the threshold and absorption of the product rather than just

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the drug itself. This is not considered passive because it is the standard method for administering hydrophobic medications with an elevated saturation dose to cover for extensive metabolism and poor delivery to the chosen site of action. In specific, lipophilic hormones will have to be transferred to their target cells in a multi-step transition from tightly-connected SHBG to loosely-connected albumin and eventually to their respective G-protein coupled receptors in their target cells [7].

Protein is hormone-bound, potentially triggering a shift in the receptor's conformation and a rearrangement of the lipid around the receptor of the plasma cell, touching the receptor. Almost all of these cell membrane interactions will be aborted as the transition-facilitating receptor proteins were unusual. Only 1-2 percent of all receptor proteins would be successfully guided, allowing the hormone to reach the cell membrane. This could contribute to a rise in theduration of drug release inside the system. It was used to design some hydrophobic drugs for enhanced-specific drug distribution, where the drug-to-cell membrane transformation is thermodynamically undesirable due to the close protein-drug carrier interaction [7].

Counteracting chemical forces can be used to assess the magnitude of the drug transfer caused by the carrier-membrane. They can be guided together by the hydrophobic interior of the cell membrane and the lipid transporter. According to the researchers, reducing the drug/lipid ratio and increasing the molar fraction of PEG-lipids to solve these problems could create a nanoparticle with reduced drug inter-particle transfer and reduced drug-to-cell transformation. To induce instability of the liposomal membrane, the approach can be further characterized through liposomes to the cell membranes. Not as many examples of active, selective delivery of strongly hydrophobic drugs are available for nanoparticles containing hydrophilic drugs. If the drug is embedded in the inherent aqueous medium of liposomes, a large drug distribution concentration may be obtained. The medication must move to the cell membrane after a lipid carrier has crossed the cell membrane to enter a hypothetical steady-state. The sequence in which the protein-protein interactions occur, as well as the types of proteins, determinewhen the drug may be transferred. A lipid-based protein-integrated drug carrier needs to be thermodynamically stable in the bloodstream and have exceptionally low serum clearance kinetics. The required protein interaction between the target tissues and the carrier, on the other hand, would eventually catalyze the target- oriented distribution of the drug [7].

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GOAL OF THE DRUG DELIVERY SYSTEM

Drug delivery technology is used to modify a drug's pharmacokinetics and blood circulation. To produce a successful clinical result in the body, different variables should be considered. Chemotherapeutic medications that affect a wide variety of body tissues and cells, for example, are well-carried by large tumors. Liposomes are not an excellent option for the delivery of medicinal products that are not strong, broad, and hydrophobic because they cannot tolerate the therapeutic dosage in the small areas of the membrane of the liposome. As they pass acrossthe bloodstream to enter the tumor's microbiome, they still have a hard time protecting themselves against encounters with various blood cells and tissues. A slightly lower dose of the medication is expected to enter cancer cells in order to achieve a clinical advantage [7].

Instead, lipid emulsions or liposomes carrying drug blocking agents may be a more feasible choice for distributing these medications. Liposomes can remain stable in the blood for days and can accumulate in the tumor for one or three days after injection. The lack of a lymphatic pathway prevents the draining of the tumor, contributing to tumor tissue drug accumulation. In addition to the explanations mentioned above, the “triggered distribution of the drug” now takes part in various tissue and cellular properties. The disparity in pH, enzyme activity,and cell receptor activity between abnormal and regular tissue is an indication of this. It is strongly recommended to investigate their toxicity for hyperactivities by repeated doses. However, crucial challenges to their exploitation must be taken into consideration. Due to *in vitro* PEG-lipid hydrolysis at acidic pH, pH-sensitive PEGylated liposomes will lose their PEG chains. In a tumor, the acidic area is outside the scope of packed cell tumor vessels. In a cell population that overexpresses several receptors, lipid-based drug delivery may improve the carrier and drug cellular absorption. For example, lipid components that may be transformed to emulsifier-like species by target tissue enzymatic action could cause lipid assembly disintegration [7].

EXTRACELLULAR VESICLE-BASED DRUG DELIVERY SYSTEM

Extracellular vesicles (EVs) are molecular membrane vesicles produced by a wide range of cell types. They are key causes of intercellular interaction and thus play a role in both physiological and pathological processes. They can act as a 'molecule carrier,' with a wide range of clinical and medical purposes, such as anti-tumor, immune-modulatory, and drug delivery. According to their natural nature, they are born with strong biostability, improved longevity, and limited bioactivity [10].

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IMPORTANCE OF EV-BASED DRUG DELIVERY SYSTEM

Limited Immunogenicity and Cytotoxicity: The FDA licensed the first formulationof liposomal anticancer drug, DoxilVR in 1995. Their findings showed that IV- administered siRNA-charged exosomes were more responsive to pancreatic cancer in mice than lipid nanoparticles without some important immune response. Since EVs form in the liver and other vital organs, including the pancreas, their appearance sheds new light on new DDS. Other transport mechanisms, such as adenoviruses, lentiviruses, and retroviruses, are believed to have higher immunogenicity and cytotoxicity than EV-based DDS [10].

Stability in Circulation: EVs have a 2-20 min small half-life. PEGylation has been reported to dramatically extend the circulation period of EVs to more than 60 minutes. IgM antibodies produced against PEG decoration at repeated dosing will speed up the clearance of PEG-covered nanoparticles. Regulatory proteins such as CD55 and CD59, membrane-bound backup receptors, can be identified in APC-derived EVs to actively contribute *in vitro*. EVs, even if subjected to excessive inflammatory conditions, will continue for a very significant duration of circulation in the system [10]. The 'don't eat me' warning was communicated by a CD47-mediated EV defence from mononuclear phagocytic systems. Due to their small size and enhanced EPR effect, exosomes achieve a targeting effect fortumor tissue [10].

Cell Targeting Properties: Certain tissues can be the home of EVs extracted from cells. To better serve the possible uses of EVs as a manageable DDS, researchers have tried to modify them with ligands that can directly attach to targeted cells. To date, three methods have been attempted to alter EVs; binding of receptor-ligands, binding of antibody-antigens, and binding of cell-specific molecules. Collectively, an intrinsic targetability of EVs may be obtained by selecting unique EV donors. Hyaluronidase-engineered exosomes that dissolve the extracellular tumor aim to increase the absorption of tumor cells by utilizing a network, and drugs are also a way to provide targetability for EVs [10].

The role of lipids, proteins, nucleic acids, and other molecules in EVs has been discovered through biochemical and genetic studies constituents. EVs have been identified with 9769 proteins, 3408 mRNAs, 2838 microRNAs (miRNAs), and 1116 lipids. We successfully indicated that a hypoxic lipid membrane causes tumor cells to produce miR-21-rich exosomes, which are then delivered to non-comparable cells to support metastatic spread. In intercellular contact, the form and content of EVs vary from one another and play a key role. EVs are normal membrane vesicles engaged in intercellular contact. They can transfer their material to recipient cells *via* endogenous uptake mechanisms. This allows them suitable

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drug delivery candidates for use. The need for modular methods of EV separation and more robust approaches to drug loading are present challenges tobe tackled in major clinical trials before the introduction of EVs [10].

Low immunogenicity, intrinsic cell targeting properties, and improved flow control are all advantages that render them increasingly appealing in targeted drugtherapy. Large capacity has been explored in the treatment of numerous disorders,including malignancies and neurology. There is a great deal of preclinical evidence that the systematic use of EVs as DDS in specific scenarios may have a targeted therapeutic effect. There are major obstacles and difficulties inintegrating EV-based drug delivery, but the biomedical vesicle is highly promising in the biomedical field [9].

EXOSOMES AS NOVEL SHUTTLE DELIVERY

The exosomes are less immunogenic and more immunogenic, being normal in origin. In different body fluids like blood, urine, amniotic fluids, breast milk, and ascites, they can be found. Exosomes may deliver their cargo through the plasma membrane to a particular intracellular position in a target-specific manner. They have been used widely for the targeted distribution of these molecules as vectors. The exosomes' target specificity depends on their cellular source and can be changed to target-specific delivery of therapeutic cargo. On the extracellular membrane, the RVG peptide was overexpressed and hence localized in the brain by entering the blood-brain barrier (Fig. **2**) [11].

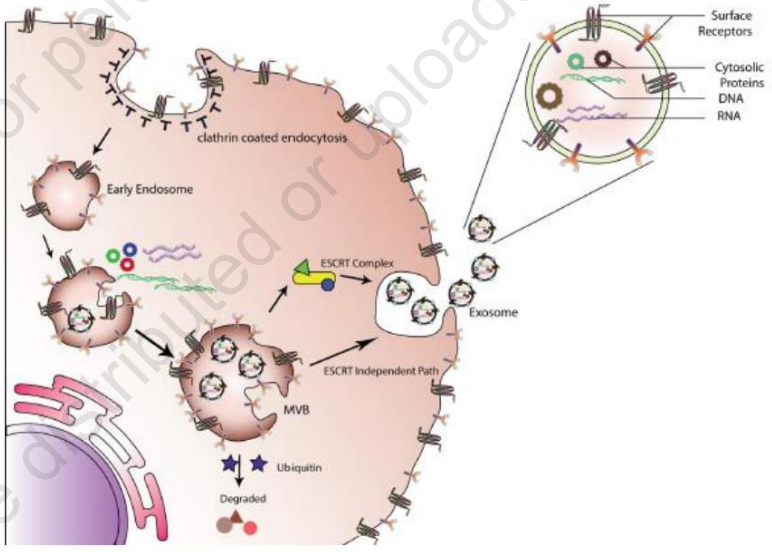

Fig. (2). Diagrammatic representation of exosome biogenesis, cargo internalization, and release [11].

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Exosome biogenesis begins through the internalization of the plasma membrane with the formation of endosomal vesicles. Exosomes consist of various protein cargos, such as cytosolic proteins and surface ligands, nucleic acids, such as DNA and RNA. A method known as exosome fusion is the release of exosomes after synthesis with the plasma membranes. Some of the preserved evolutionary sequences, such as N-ethylmaleimide-sensitive factor (SNARE), coat complex subunit, Rab, and Sec 1 proteins, are involved in the biogenesis mechanism. Biosynthesis and secretion pathways are inextricably linked since secretion is the product of biogenesis [11].

Exosomes are capable of passing biochemical material to recipient cells from donor cells. They are attractive candidates for medication distribution applications. Size, surface chemistry, inculcation, and intracellular exosomal trafficking are all poorly defined interactions. Understanding the efficacy of high- resolution subcellular exosomes, as well as the global, systematic *in vitro* geography of cell trafficking, endosomal escape, lysosomal degradation, and drug distribution, are among the activities that have yet to be accomplished. Newmethods give insight into exosomal cell mode of action and exosomal intercellular trade to explain the functions of exosomes at the cellular stage [13].

Ultimately, the endosomal-sorting complex monoubiquitinated membrane proteins are required for transport (ESCRT) dissociation and recycling and are subsequently recruited by TSG101 from the ESCRT-I complex. The hepatocyte growth factor (HRS) and the tyrosine kinase substrate are essential for biogenesis.The biogenesis of exosomes separates them from microparticles and caspase- mediated cells. The exosome in the form of a multivesicular body is then released into the microenvironment (MVBs). In a process known as biogenesis, the MVBs typically contain intraluminal vesicles (ILVs) and may bind to the plasma membrane, allowing it to be released. It is a mechanism that starts with thedevelopment of the late endosomal limiting membranes. The cells go through alternating biological processes and a process by which cells take in substances from outside of the cell by engulfing them in a vesicle in a cycle during pathogenic infection. It also raises the number of exosomes produced by infected cells [11]. About the current condition, there is a 100-fold rise in nanoparticle concentration. Exosomes preserve the increased material, lipid composition, and stability of plasmalogen during nematode infection that compensates for cholesterol and sphingomyelin levels. The viral load also triggers the developmentof exosomes. Because of their biogenic nature, exosomes are less dangerous than other natural drug delivery vehicles. The immunogenicity and toxicity of exosomes used for medicinal purposes were largely determined by the cell source and structure of exosomes used. Exosomes have also been related to the spread of contagious prions triggered

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by pathogen protein misfolding. Drug delivery by exosome is generally regarded as a safe method [11].

MITOCHONDRIA-TARGETED DRUG DELIVERY

Most mitochondria-targeted medicines have been active in clinical research in the fields of cancer and other diseases or have even been clinically implemented. The key purpose of mitochondria in human cells is to provide oxidative phosphorylation (OXPHOS) with adenosine triphosphate (ATP), but mitochondria have several other functions, including the control of apoptotic cell death [12]. The mitochondrial respiratory chain is the key cause of ROS-induced extremely reactive oxygen species (ROS), including mitochondrial DNA mutations, lipid peroxidation, protein oxidation, and alters the function of many mitochondrial matrix metabolic enzymes. Drug distribution methods focused on mitochondrial membrane capacity and the protein import machinery of the organelle will be addressed in depth below (Fig. **3**) [12].

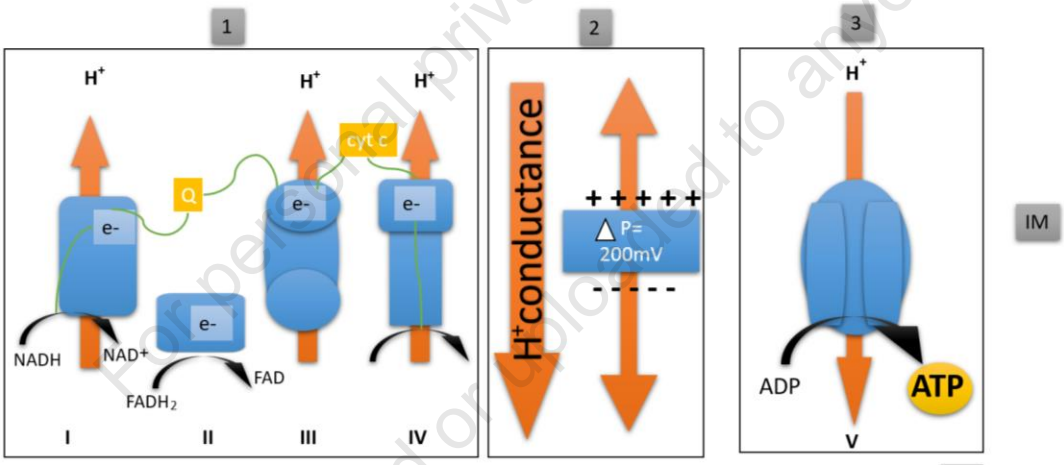

Fig. (3). Mitochondrial electron transfer system [12].

Mitochondria allow ATP to be produced by transporting electrons from food oxidation down the respiratory chain to react with oxygen. Redox energy is found by the mitochondrial inner membrane to translocate protons. This sets up a gradient in proton electrochemical potential. With electrostatic interactions, lipophilic cations may be drawn by mitochondria and accumulate in the mitochondrial matrix [12].

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MACROPHAGE DRUG DELIVERY

Macrophages are specialized cells involved in the detection, phagocytosis, and destruction of bacteria and other harmful organisms. The term macrophage comes from the Greek words *makros*, which means large, and *phagein*, which means to feed. These are advanced phagocytic cells that, by degradation and absorption, target foreign compounds, contagious bacteria, and cancer cells. In vertebrates, macrophages play a role in both unspecific protection (innate immunity) and specialised defence mechanisms (adaptive immunity) [13].

As shown in Fig. (**4**), each type of macrophage has a specific name. Macrophages are gaining significance for therapeutics dependent on carbohydrates. They express carbohydrate-binding receptors, which, through receptor-mediated endocytosis, internalize the delivery mechanism. The macrophage mannose receptor, an endocytic protein that is strongly expressed in macrophages, is one such carbohydrate-binding receptor. The binding of sulfated carbohydrates is the product of contact with splenocytes. Sulfate moiety on 4-SO_4 GalNAc has also been documented to make powerful hydrogen bonds on mannose receptors with the cysteine group (Fig. **4**) [13].

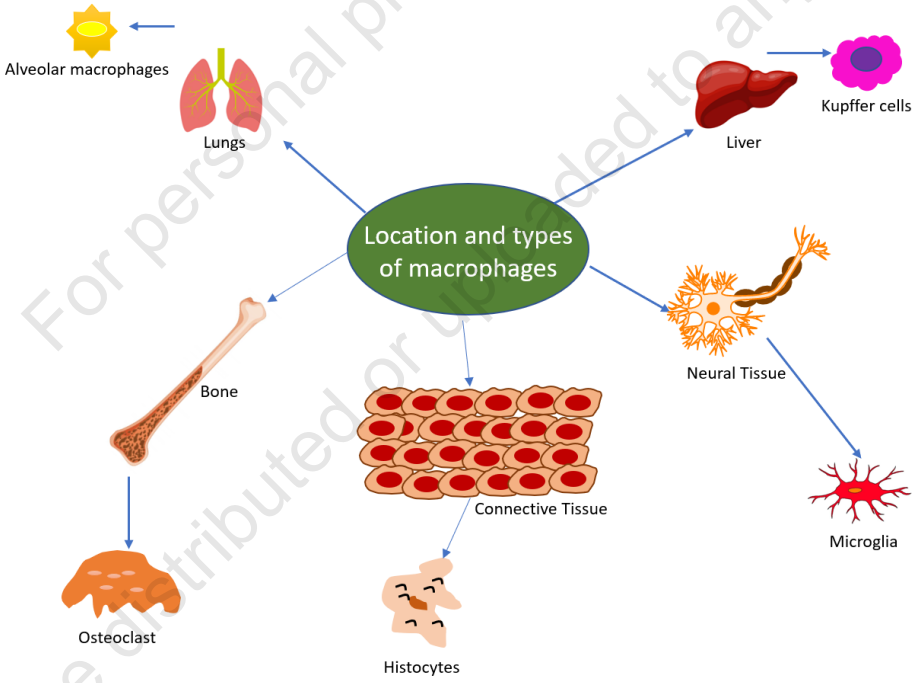

Fig. (4). Different types of macrophages and their locations [13].

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A wide variety of disorders, including chronic ulcers, allergic reactions, and pulmonary inflammatory diseases, are linked to dysregulated macrophageactivity. It has been documented that infected macrophages overexpress those receptors that can be effectively targeted by suitable drug delivery systems. The particulate existence of these vehicles can facilitate the macrophage passive homing of the trapped drug molecules. To minimize the risk of allergic reactions, nanoparticles can also include a drug to be administered to an environment with high levels of particulate nanoparticles. Nanoparticles are drug distribution devices that disperse medicine and improve drug therapeutic efficacy in the immediate vicinity of the target location (Fig. **5**) [13].

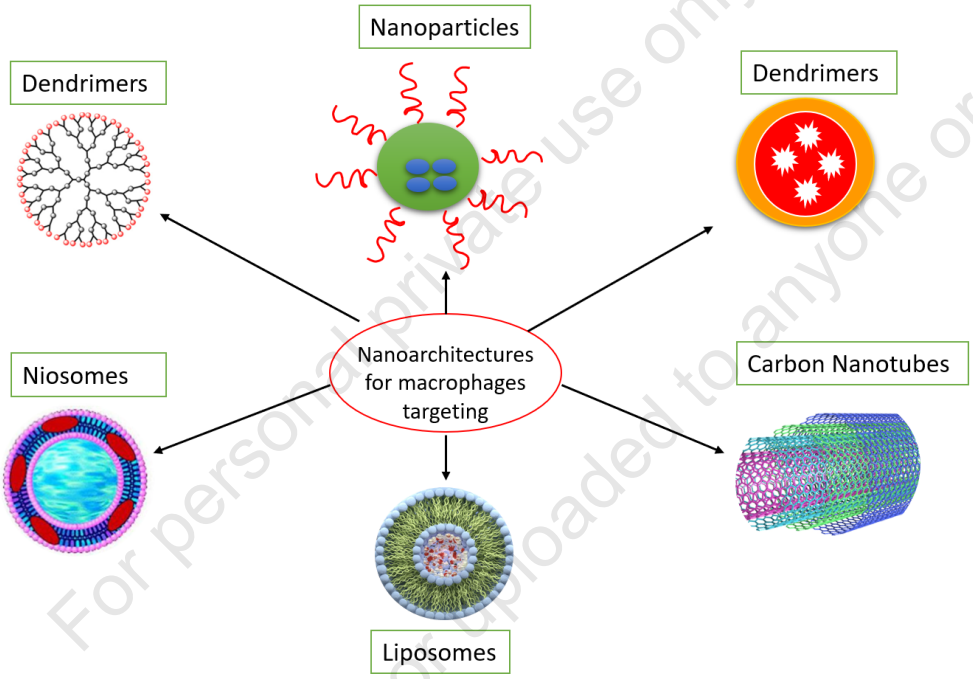

Fig. (5). Nanocarriers are used in macrophages targeting [13].

Researchers used chitosan microparticles as doxorubicin carriers to treat acute leishmaniasis using a macrophage-mediated drug targeting approach. The amount of superoxide generated by macrophages influenced the absorption of microspheres. The absorption efficiency of alveolar macrophages is alsoinfluenced by changes in the surface properties of PLGA microspheres. Theresults showed that the leishmanial parasite load of doxorubicin-encapsulated chito-mimed microparticles was very significantly reduced [13].

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CARRIER-BASED DRUG DELIVERY SYSTEM

Micelles were formed in an aqueous solution by self-assembly of amphiphilic block copolymers (ABCs). In the centre of block copolymer micelles, drugs canbe mechanically trapped and transferred at amounts that can surpass their inherent water solubility. With the aqueous surroundings, the hydrophilic blocks can form hydrogen bonds and form a close shell around the micellar heart. The body's contents are effectively preserved from aerobic respiration and enzymatic degradation. In the first instance, the corona can prevent the reticuloendothelial mechanism from recognizing and removing the micelle from the bloodstream. Block copolymers possessing unique ligands are a feasible path to a broader range of much more selective action sites [15].

Closed colloidal structures consisting of lipid bilayers are self-assembling **liposomes**. This showed that mannosylated liposomes indicated superior alveolar macrophage uptake. Macrophage specific liposomal delivery system can be used in the management of leishmaniasis using indigenous or synthetic antileishmanial compounds. Challenges of liposomal therapy are due to the larger size, stability, and storage issues, of liposomes. Niosomes, non-ionic surfactant vesicles, have higher retention capacity due to the absence of lipid molecules and their smaller size. Niosomes, being cheaper, less toxic, biodegradable, and non-immunogenic, are good alternatives as drug carriers [13, 16, 17].

Niosomes are non-ionic vesicles dependent on surfactants used for drug delivery as a carrier device. A lipid film hydration method was used to produce an antimetastatic agent, pentoxifylline (PTX)-encapsulated niosome. In the experimental metastatic B16F10 model, intravenous injection of niosomal PTX (6 and 10 mg/kg) resulted in a substantial decrease in lung nodules; PTX builds up in the liver, which is a distant target organ. To achieve the successful treatment of tuberculosis, researchers developed a niosome formulation for isoniazid delivery [13].

Hyperbranched, monodispersed, and three-dimensional macromolecules are called dendrimers, which resemble the structure of a tree. They are by far the newest nanocarrier systems used to have improved opportunities for drug distribution. A mannosylated dendritic architecture filled with rifampicin was synthesized for selective transmission of rifampicin to alveolar macrophages. It has been concluded that TuPPI has the potential to provide controlled and targeted antiretroviral bioactive delivery as a carrier device. They discovered that macrophages infected with HIV displayed greater TuPPi cellular uptake thanMo/Mac uninfected. This increased uptake was likely due to the activated state of these HIV-infected cells and may cause a drug-loaded carrier to have preferential phagocytosis, resulting in

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targeted delivery to these cells. Anti-HIV agents' protection and effectiveness may be improved by reducing the dose and side effects associated with them; the carrier mechanism may be further studied [13, 16].

Carbon nanotubes (CNTs) with a wide surface region, high aspect ratio, quasi- one-dimensional nano-needle shape, and greater biomolecule loading capacity have emerged as one of the most sophisticated nanocarriers for the distribution of different bioactive. Carbon nanotubes may be adjusted to allow for easier circulation inside the body. When they are modified to be soluble in aqueous body form fluids, there is no major toxicity. Improved anti-leishmanial efficacy of amphotericin B (AmB) using J774A.1 macrophage cells with no major cytotoxic effects has been recorded. The research investigated the potentially enhanced absorption by the macrophage J774 cell line of rhodamine B-loaded AmBmannosylated MWCNTs (AmBitubes). As mannosylation of MWCNTs significantly decreased hemolysis of erythrocytes due to inhibition, AmBitubes demonstrated the least (9.66±0.39 percent) hemolytic toxicity. The drug localization index clearly showed that, in macrophage-rich organs like the liver and spleen, the cumulative AmB-loaded CNT formulations remained significantly higher. It was found that receptor-mediated endocytosis and anionic scavenger-mediated endocytosis were involved in the absorption of CNTs [13, 16].

Polymersomes are polymeric vesicles that self-assemble from block copolymers in aqueous solutions. Researchers prepared asymmetric poly(ethylene glycol--
-poly) biodegradable chimeric polymersomes. Protein loading efficiencies of bovine serum albumin (BSA), cytochrome C (CC), lysozyme (Lys), ovalbumin (OVA), and immunoglobulin G (IgG) were all exceptionally large. Thedistribution of polymersome size and zeta potentials were not greatly altered by protein encapsulation. This method can be used to characterize intracellular and intercellular systems, which can be done by observing cell and cytoplasm systems, as well as the cytosol of cells. The optofluidic method is 100 times fasterthan similar carrier-mediated delivery methods (*e.g.*, liposomes or nanoparticles) and could be used in the development of bioactive delivery and endosomal escapestrategies, which are currently a high-priority research area [13].

Cell membrane-coated nanoparticles: This is a new nanotechnology that embeds nanoparticles in the cell membrane layer to improve surface functionality.Increased nanoparticle performance in a complex biological environment is one ofthe benefits of cell membrane coating, which benefits applications such as immunotherapies, detoxification, medication administration, phototherapies, imaging, and others [14].

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For systemic drug distribution, nanoparticles with a longer circulation lifespan offer improved tissue targeting by both passive and active pathways. To prevent nanoparticles from being picked up very quickly by the reticuloendothelial system, appropriate surface coatings are needed. Using polyethylene glycol (PEG), which improves circulation time, is the current gold standard of stealth coating. The design and development of many human-made drug delivery systemshave been inspired by red blood cells (RBCs). The difficulty of functionalizing nanoparticles presents a major challenge. According to biomedical researchers,the complex surface chemistry of the biological cell, given the abundance and complexity of proteins associated with RBC membranes [14, 15].

The cell membrane-coating technique will overcome the above problem by explicitly transferring the protein makeup on RBC surfaces that are responsible for long circulation onto synthetic nanoparticles. Polymeric nanoparticles made of poly(lactic-co-glycolic acid) can be fully wrapped on the surface of RBC membranes (PLGA). In comparison with PEG-coated counterpart nanoparticles, these nanoparticles showed a longer elimination half-life, showing superior *in vitro* clearance suppression. A variety of nanoparticle delivery platforms have been rapidly extended to the RBC membrane-coating technique, providing them cell mimicking properties and improved circulation stability. Gold nanocages and gelatin nanoparticles specifically designed to evade macrophage cells to treat antibiotic-disease-causing cells have also been used. The RBC-NPs contributed to the higher tumor accumulation and markedly increased photothermal therapy efficacy when injected into mice. The membrane coating also protected the particles from conjugated compounds that were provided to them [14 - 16].

When synthetic nanoparticles were functionalized with natural RBC membranes, they were endowed with immune evasion and long-circulation properties that are essential for drug targeting. In the case of bacterial contamination, the covered membranes may be able to contain bacterial exotoxin, resulting in improved effectiveness. A biomimetic antibiotic delivery system was shown in this study, which could potentially improve the bio-distribution and bioavailability of antibiotics [14 - 16].

CONCLUSION

Some medications have an ideal concentration range from which optimum benefit is extracted, and doses above or below this range may be harmful or generate little clinical benefit whatsoever. Various drug delivery and drug targeting technologies are currently under development to reduce drug degradation and depletion, avoid adverse side effects, and improve drug bioavailability. These modern techniques are focused on interdisciplinary methods that incorporate polymer science,

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bioconjugate chemistry, pharmaceuticals, and molecular biology. The researchers conclude that controlled and innovative distribution of medicines, which was just a fantasy or a possibility at best, is now a reality. The desire to distribute drugs to patients safely and with fewer side effects has motivated pharmaceutical companies to engage in the production of a new drug delivery system. Celltargeting carriers, which have a natural biogenesis mechanism, high biocompatibility, improved stability, and limited immunogenicity, offer several advantages as drug delivery systems (DDSs). When administered at higher doses, most of the medications that exhibit strong pharmacological activity against a specific pathogen are harmful to humans. It is also of prime importance when a drug is administered within the target cell directly to its site of action. It would be possible to develop drug delivery mechanisms that can accurately target not only tissue and cells of interest, but the cell organelle, to recognize the microenvironment of the diseased site. A wise selection of materials and goods is important, depending on the advantages and challenges of different distribution mechanisms.

FUTURE DIRECTIONS

In order to improve the number and quality of intracellular therapeutic vectors, a greater understanding of the molecular fundamentals of different diseases is required. In the future, researchers will continue to be motivated by cell-targeting drug delivery to create novel nanotherapeutics for successful disease action. They are likely to benefit from a new way of thinking about architecture and nanomedicine applications.

CONSENT OF PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 11

Nanotoxicology: Current Issues and Future Directions

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Abstract: Nanotechnology is a flourishing science that produces and designs materials at the nanoscale, which ranges from 1 to 100 nanometers. They are commonly known as nanomaterials or nanoparticles. Physical properties that characterize nanoparticles include shape, crystal structure, and solubility properties. These properties affect the behavior, fate, and transport, and ultimately the toxicity of nanomaterials or nanoparticles. They are examined and assessed whether and to what degree they are a threat to the environment or society.

Keywords: Cancer, Immune system, Nanomedicine, Nanotoxicology.

INTRODUCTION

The use of nanotechnology has increased dramatically over the years, with nanoparticles being employed in some applications, including scientific research and industrial applications [1]. These nanomaterials include nanoparticles and nanomedicines, together with nano-surfaces of composite materials [2].

Nanotoxicology is the study of the toxic or biological effects of nanomaterials (NMs). The progress of this new discipline depends heavily on developing methods to characterize and quantify NMs in biological samples, either *in vitro* or *in vivo*. There is a need to establish them for a better understanding of their medical applications apart from knowing the biochemical pathways and biomolecules. Nanomaterials need to be evolved to provide appropriate and powerful means to characterize their toxicity and or biological behaviors through various analytical techniques.

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The focus of interest in this book is to discuss the interaction between nanomaterials and the immune system on its current trends and directions.

Immune System

Our immune system protects us from harmful chemicals and other microbes. They can identify various disease-causing microorganisms and are able to distinguish them from healthy ones. Pathogens can also change our immune system's normal function. Therefore, immunotoxicity selection is an important step in research related to toxicity [3].

Despite nanoparticles being valued in the field of medicine, the safety concern of these novel materials has become popular because of the relationship between nanoparticles and the immune system. It is, therefore, beneficial if it does not react with the immune system itself.

PHYSICOCHEMICAL IDENTIFICATION OF NANOMATERIALS

One of the most common types of immunotoxicity is the interaction between the structure-activity of nanoparticles and their outcomes on the immune system.

To demonstrate, if nanoparticles with cationic surfaces interact with the biological membranes, it causes a buildup of charge on the surface of objects due to contact with other surfaces. This, in return, will result in leukocyte procoagulant activity (PCA) installation and blood coagulation. It also causes platelet activation, aggregation, and other damage to the cell [4]. The immunotoxicity of a nanoparticle influences the therapeutic payload it carries [5]. These toxicities may not be settled if procoagulant action and blood clotting are not considered during the formulation design of drugs, especially for doxorubicin, daunorubicin, and vincristine and all agents that kill cancer cells by damaging their DNA and stopping them from dividing.

ROLE OF NANOPARTICLES IN CANCER DIAGNOSIS AND TREATMENT

Drugs used in the diagnosis and treatment of cancer differ both in their formation and action. Saad Ali, in his paper [6], observed that patients treated with ipilimumab (anti-CTLA4) can demonstrate leptomeningeal enhancement on brain MR imaging mimicking metastatic disease. Another study by Fiering *et al.* has shown that using ferrous oxide nanoparticles with an amplitude that repeatedly interchange results in abnormally high body temperature. As a result, there is a buildup of mediators of adaptive immunity, which includes cytotoxic T cells, which are responsible for killing infected cells [7]. This illustrates that by using a nano delivery approach,

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the ability of the drug action to sustain is very effective.

KNOWING THE IMMUNE SYSTEM'S PART IN NANOPARTICLE DECOMPOSITION

Marketed nanomedicines at present are illustrated by environment-friendly materials. Using biodegradable materials provides little safety concern compared to those of durable nanomaterials. Progress in nanomedicine is predicted to offer solutions to difficult problems of current medicine, as shown in Fig. (**1**) [8].

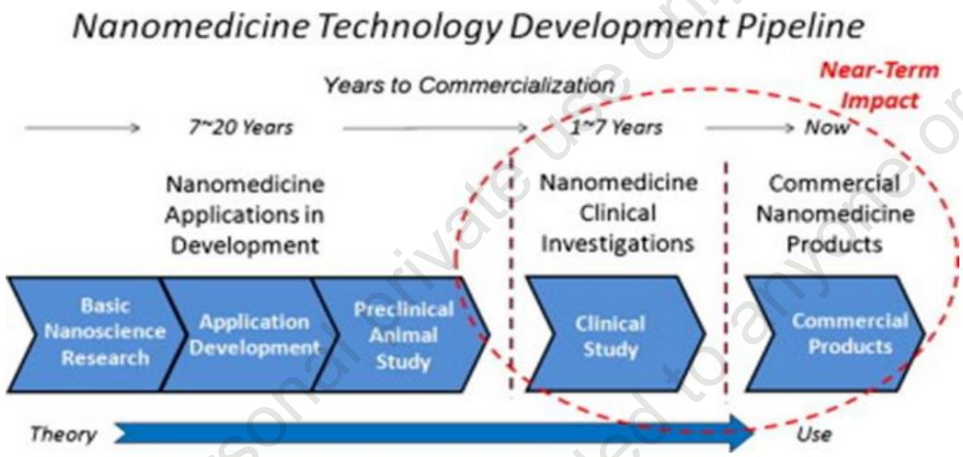

Fig. (1). Progress of nanomedicine technology [8].

UTILIZING NANOPARTICLES IN DIMINISHING TOXICITIES OF CONVENTIONAL MEDICINES

Engineered nanoparticles are another application of nanotechnology used in the redesign of conventional pharmaceuticals. It does not only reduce side effects but improves its solubility and pharmacokinetics. Other examples also show how nanotechnology results in reduced immunotoxicity if used in the reformulation of traditional drugs. Surface-active compounds of drugs are inspected based on their capacity to induce adverse reactions in vulnerable patients. Drug Paclitaxel depends on a polyethylene glycol castor oil like Cremophor-EL®, which is well known to induce allergic reaction as their old formulation include flushing, chest pain, urticarial, dyspnea, hypotension, angioedema, *etc*. The cremophor's allergic reaction mechanism has not been fully understood, but symptoms like type 1 hypersensitivity reaction suggested IgE-mediated reactions in cremophor hypersensitivity [9, 10]. As a result of this unwanted effect, the Cremophor-EL formulation of paclitaxel (Taxol®) needs to be given to the patient by IV push and administered in more or less 5 minutes. As compared to Taxol, the nano albumin

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formulation of paclitaxel (Abraxane®) is also given through IV push; however, it does not need the administration of medicine [11].

Antisense oligonucleotides encapsulated to arrest the toxicity of the complement system [12, 13] together with the redesigning of the 5-fluorouracil drug, using chitosan nanoparticles [14] are another successful result showingnanotechnology-based carriers in the reformulation, thus reducing immunotoxicity.

Nanomaterials are widely used in the medical field because of their benefits in medical therapy. Their interaction with the tissues and cells reveals detrimental effects [15]. Due to this, there were doubts that it may cause diseases; for example, the use of carcinogenic products in tobacco. However, other contributing factors in evaluating the harmful effects of nanomaterials are thedose, duration of exposure, and concentration [16, 17].

TOXICITY TESTING

Dosing in *in-vitro* experiments as compared to *in vivo* is more important in the determination of poisoning. ISSD or otherwise known as *in vitro* sedimentation, diffusion, and dosimetry, is one of the models used in the toxicity test. Release time of the drug provides an assessment of the amount of drug administered in agiven time [18]. This shows that the drug is effective therapeutically. Otheranalytical methods used to discover cell viability and proliferation are gene sequencing and identification of DNA toxicity. Furthermore, the physicochemical properties of the cell are evaluated using different forms of microscopic and spectroscopic techniques. Nanotoxicity is detected easily using a combination of all these tests [19].

Zhang et al. assess the toxic effects of nanomaterials by using a 3D chip that mimics human responses. This study exhibits the importance of toxicity for a specific organ on a real model [20]. Another study showed that nanoparticles passing across the mouse placenta shows a toxic effect. Yin et al. described that chip and titanium dioxide (TiO2) nanoparticles using the same 3D human placenta model might possess the same toxic effects [21]. Moreover, toxic effects of nanomaterials were also determined through the combination of a cell-on-a-chip and a microfluidic system [22].

CONCLUSION

The use of nanotoxicology has increased dramatically as a flourishing technology that raises concerns on the safety of nanotechnology. Safety protocols need to be addressed in developing nanoparticles, especially nanomaterials that can interact

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with the immune system. Contributing factors such as dose, duration of exposure, and concentration may need to be considered in nanotechnology development. Toxicity testing of nanoparticle drugs can be a gateway to assure the safety, quality, and effective future novel drug products.

FUTURE DIRECTIONS OF NANOTOXICOLOGY

Research on nanotechnology has significantly received advancements in the industry in the last twenty years. It adds up to various advantages and disadvantages. The effectiveness of nanomaterials is a priority for medical professionals considering their biocompatibility and biodegradability, whereas industry professionals prioritize making a new nanomaterial device at the lowest costs. Nonetheless, this raises questions on nanomaterials' possible noxious effects. Nobody knows what kind of change this technology will bring to humankind. Some governments have already installed institutional projects to regulate the use of drugs and devices, which are nanomaterial-based. United States government's principal agency for cancer research points out that "most engineered nanoparticles are far less toxic than household cleaning products, insecticides used on family pets, and personal care products". The biomaterial riskmanagement project aims to develop a risk management framework for the safeoperation of nano-biomaterials [23].

Along with the developing technology is the emerging health effects of nanomaterials on humans. *In vivo*-like methods on 3D human organs are starting to substitute traditional *in vitro* analytical methods [23, 24]. Identification of the physicochemical structures of nanomaterials is a challenging step required for *in vitro* testing [25]. Other approaches, such as Omic, and bioinformatics, provide comprehensive toxicity information on the cells processes [26 - 28]. The toxicity of nanomaterials and gene mutations should also be carefully studied. Thereshould be strict enforcement of the different regulations on the use ofnanomaterials.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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CHAPTER 12

Liposomes for Herbal Drug Delivery

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Abstract: This chapter evaluates liposomes used as delivery carriers for herbal products, which, due to poor permeability and solubility of extract components, has become a major issue in phytotherapy for treating illnesses and human health problems. Liposomes are vesicular formations with phospholipid bilayers that possess the capability to entrap both water-soluble and hydrophobic substances. However, there are several factors that should be considered with regard to herbal drugs, especially that the preparation technique should be appropriate to the solvent solubility of the plantextracts. In this regard, the ratio of phospholipids to extracts, pH stability, other liposomal components, and the ligand required to render liposome stability, circulation in the bloodstream for protracted periods, and targeted at specific organs should be investigated. The enhancement of phytochemical constituent stability within a context of environmental, physical, and chemical degradation, together with sustained or controlled drug release, can be achieved by incorporating extracts into liposomes. Moreover, the improved oral absorption of plant extracts by encapsulating them into liposomes indicates increased permeability and bioavailability *via* gastrointestinaltracts, thus enhancing pharmacological effects at low dose concentration as well as decreasing toxicity. However, thousands of constituents contained in plant extracts demonstrate various physicochemical characteristics that constitute significant challenges for liposomal delivery. Consequently, a comprehensive analysis of formulating and manufacturing aspects is required.

Keywords: Bioavailability, Human health, Illness, Liposomes, Phospholipids, Plant extracts, Solubility.

INTRODUCTION

Health problems involving chronic diseases such as cancer, diabetes, hypertension, stroke, cardiovascular disease, among others, are known to have a high prevalence [1]. They greatly affect people's quality of life, thus still constituting a major challenge that needs to be successfully addressed [2]. More-over, these diseases

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are generally slow in progression, of considerable duration, and require medical therapy [3]. Therefore, identifying appropriate treatment strategies becomes the main concern in successfully addressing them by means of both medical and non-medical therapies involving either causative or symptomatic treatments.

Medical treatment includes the use of various pharmaceutical products. Therefore, a rapid expansion in the drug product list, in addition to designing effective delivery systems to target the disease sites, is required. However, the curative effect of drugs is not the only major concern since significant attention is also devoted to avoiding severe unintended side effects on normal tissues. Minimizing the side effects of medical therapy has encouraged numerous researchers to explore various ideas and strategies for drug delivery systems [4]. In addition, pharmacological therapy-related drug development is not limited to modern synthesized pharmaceuticals but is also strongly associated with natural and biological products offering great potential within the process of new drug discovery and development [5, 6].

Natural products are compounds produced by living organisms that usually produce various pharmacological effects. Plant extract usually contains many newchemical compounds with multiple structures that may have different biological roles [7]. Between 300,000 and 400,000 plant species are known to be used as primary raw materials in the development of new compounds as active pharmaceutical ingredients, which are proven to be effective as antioxidant, antimitotic, anti-infectious, anti-inflammatory, anti-angiogenic, and anti-cancerdrugs [8, 9].

On the other hand, not all compounds extracted or isolated from natural plants or other biological sources can be synthesized into medicine. The existence of extremely complex chemical structures which are exorbitantly expensive to synthesize on an industrial scale limits their development [7]. In addition, certain problems related to poor solubility and chemical instability also constitute major limitations on their clinical uses. Complex chemical structures and high molecular weight may also affect drug absorption, thereby requiring specific drugformulation strategies [10]. The main challenge for the formulation lies in poor bioavailability [11]. For example, the use of curcumin in the treatment of various diseases, such as cancer, has limited effectiveness due to its low water solubility, limited bioavailability, expeditious systemic metabolism, and rapid elimination [12]. It has long been accepted that solubility represents a determinant factor inthe absorption of a drug and that permeability can be an important parameter for the penetration of the biological membrane by drug molecules and their entry into the blood circulation system or their diffusion into the target cells. Therefore, a modify-

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cation is required to improve their physicochemical properties, increase their stability, enhance their pharmacokinetic profiles, and minimize the sideeffects of natural drug compounds.

Over the years, nanotechnology has been widely developed in various scientific fields for medical purposes [13]. Nanomedicine, which involves the use of nanoparticles, has been extensively used to diagnose, monitor, control, prevent, and cure diseases [14]. Lipid-based nanoparticles are commonly used to protect drugs from *in vivo* degradation, control drug release, modify biodistribution, target drug delivery to disease sites, and improve solubility and bioavailability [15]. Of all nanoparticles, liposomes constitute some of the most widely studied, with certain FDA-accepted formulations being used in chronic disease therapy, such as oncology, having the greatest impact on this field. Nano-sized vesicles, compatibility and degradability in a biological environment, ability to encapsulate water-soluble and lipid-soluble substances, low toxicity, and the immunogenicity of liposomes represent significant advantages for disease therapy [16].

The word 'Liposome' is derived from the two Greek words '*Lipos'* meaning 'fat' and *'Soma'* which translates as 'body' [17]. Liposomes have a spherical vesicle-shaped formation composed of phospholipids that resemble biological membranes and act as drug carriers. Liposomes have two compartments, lipophilic and aqueous phases, and can be formed when phospholipids interact with water with the result that liposomes are able to reduce unwanted drug side effects and can be used for targeted delivery systems by altering drug distribution within the body [18].

The structure of liposomes, which consists of a bilayer membrane, means that hydrophobic drugs demonstrating low water solubility can be trapped in the membrane bilayer. Meanwhile, high levels of hydrophilic compounds can also be loaded in the aqueous intraliposomal phase [19]. By encapsulating drugs inside liposomes, drug degradation related to the physiological environment and severe side effects in healthy tissues can be significantly minimized [20]. It is possible to make a drug carrier featuring the vesicular structures of liposomes with the ability to load hydrophilic and lipophilic drugs, protecting the encapsulated drugs from environmental degradation [21]. Liposomes can also possess non-toxic biomimetic characteristics capable of increasing cell penetration, thereby enhancing their therapeutic effect. Biomimetic liposomes are extremely stable, demonstrating superiority *vis-a-vis in vitro* targeting capabilities, and achieve 2.25times deeper penetration of the 3D tumor spheroid than that of their conventional counterparts [22].

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As drug delivery carriers, liposomes have numerous advantages, which include increasing the efficacy and index of drug therapy, enhancing stability through encapsulation and biodistribution, and completing biodegradation in the body. Moreover, they are generally non-immunogenic in both systemic and non- systemic uses and significantly reduce the toxicity of encapsulated drugs, *e.g.*, amphotericin B and paclitaxel, by reducing drug exposure. Liposomes demonstrate flexibility in relation to specific ligand modification with the result that they can be targeted at specific tissues within the diseased site [23]. Inaddition, they can increase therapeutic efficacy and reduce toxic effects on normal cells through enhanced permeability and retention (EPR). This constitutes a passive and selective accumulation within tumor tissue because of increased permeability of tumor neovasculature and defective lymphatic drainage, thus increasing drug exposure to cancerous cells [24]. On the other hand, liposomes imbue hydrophobic drugs with hydrophilic properties that can reduce the frequency of dose administration [25]. Therefore, they offer numerous benefits in relation to increasing the bioavailability and the half-life of most drugs and delivering them to specific disease-target sites [21].

In liposomal preparation, phospholipid selection greatly influences the physicochemical and biological properties of liposomes. Phospholipids determine, to a large extent, the loading capabilities, drug-lipid molecular arrangement, membrane integrity, surface charge, steric resistance, and permeability of the lipid bilayer [26]. Moreover, they can also affect the interaction of liposomes with blood and tissue components during systemic administration [27]. Liposomes can undergo degradation or physical changes during manufacture or storage, through which the use of unsaturated lipids can cause possible oxidation. The partial substitution of phospholipids with cholesterol can decrease membrane fluidity and reduce the surface charge of the liposomes [28]. Liposomes are conventionally composed of phosphatidylcholine and cholesterol. However, after administration, these liposomes are predominantly recognized by the reticuloendothelial system (RES), which leads to rapid drug clearance and, ultimately, impairs drug-targeting efficiency. PEGylation involving the use of polyethylene glycol (PEG) can increase the hydrophilic properties of liposomes and provide a steric barrier to prevent serum opsonization, thus causing them to circulate for a protracted period in the body and improve drug accumulation in target tissues [27].

The ultimate goal of delivering drugs by means of liposomes is to achieve high drug levels at the target sites of, for example, tumor and inflammatory tissues. Selective drug accumulation can be accomplished by both active and passive targeting. High drug availability at target sites becomes an important factor in achieving a therapeutic effect. Therefore, a high drug concentration at the target site is imperative. Delivery systems with high drug loading, minimal leakage during

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administration, and systemic blood circulation, which only involve complete release in the target cells, need to be produced. In this regard, liposomes differ from other controlled release systems in which drug release occurs both in plasma and at the site of administration [29]. To achieve this, a combination of lipids and cholesterol can be used [30].

From the outset of their development, liposomes undergo rapid development. Conventional liposomes, which are merely composed of phospholipids, are known to have low stability and high recognition by RES, causing faster drug excretion [27]. There are currently several types of liposomes that enhance drug delivery. Based on their composition and mechanism, they can be classified into five types, namely conventional liposome, pH-sensitive liposome, cationic liposome, long-circulating liposome (LCL), and immuno-liposome. The pH- sensitive liposome type is composed of dioleoyl-phosphatidyl-ethanolamine (DOPE), which has been designed for specific drug release by means of a rapid destabilization mechanism in response to an acidic pH environment, such asendosome [31]. The cationic liposome type is composed of cationic lipids and neutral-charged lipids (co-lipids), in which cationic lipid exhibits a positive charge triggering interaction with negatively charged nucleic acid, thus increasing nucleic acid stability during systemic blood circulation and improving cellular uptake [32, 33]. To inhibit the uptake of liposomes by RES causing rapid liposome elimination, the long-circulating liposomes can be generated by theaddition of hydrophilic layers such as PEGylation on the liposomal surface, thus inhibiting protein adsorption [34]. The recent development of an immune- liposome, which recognizes tumor cells by means of antibodies, significantly enhances specific target cell internalization and intracellular drug release [35].

Several techniques have been developed to achieve liposome surface modification with different lipids or antibodies to overcome the problems associated with conventional liposome delivery. The use of PEG-lipid conjugates, target ligands, and multifunctional antibodies can be applied to liposome surface modification [36]. All of these correlate strongly with the physicochemical properties of lipids used in liposomes to determine the liposome-protein interaction in the body during administration [37].

In this chapter, the authors present an overview of the terminology used with liposomes, formulation, and multidimensional approaches to liposome production. There is also a summary of a number of liposome applications for herbal drug delivery.

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Liposomes as Drug Carriers

Liposomes were the first drug carriers created in England in the 1960s by Bangham, who conducted research predominantly focused on phospholipids and blood clotting [38]. As seen from Figure 1, liposomes are vesicle-shaped drug carriers composed of phospholipids and cholesterol [39], which are able to encapsulate both water-soluble and lipid-soluble compounds [40]. Liposomes are of various sizes, ranging from nanometers to micrometers, which are generally between 25 nm and 2.5 µm [4]. When exposed to water, lipids will tend to self- assemble, thereby forming vesicles. The hydrophilic interaction between the two polar groups and the Van der Waals interaction between the hydrocarbon tails and with water (hydrophilic interaction and hydrophobic effect) leads to the formationof a lipid-based vesicular structure [40].

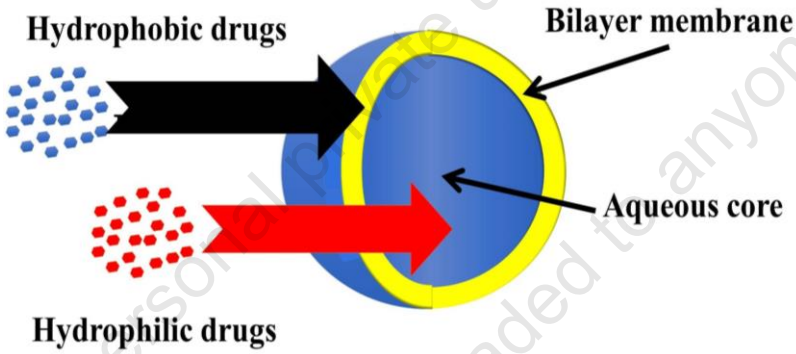

Fig. (1). The liposomal structure that enables penetration by both hydrophobic and/or hydrophilic drugs [38].

There have been numerous variations in the terminology relating to liposomes, such as ethosomes, transfersomes, and hexosomes. An ethosome, a lipid vesicle consisting of phospholipids, water, and a high concentration of ethanol, enables more efficient skin drug delivery in terms of both quantity and depth of penetration than a conventional liposome [41]. A transfersome is a highly elastic liposome composed of edge activators, *i.e.*, surfactants, enabling an improved penetration of transdermal drug delivery [42, 43]. On the other hand, a hexosome is a liposome with an internal hexagonal phase, providing superiority in formulation design, water solubility, and controlled-drug release of numeroussubstances [44].

Preparation of Liposomes

Liposomes are composed of phospholipid components, while other components such as cholesterol or PEG can be added. The characteristics of liposomes are highly dependent on the physicochemical properties of their constituent components.

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1. Phospholipids are constituent components of the hydrophobic bilayer membrane.

Liposomes can be prepared with natural and/or synthetic phospholipids. Phospholipids are the main components of the cell membrane, which possess excellent amphiphilic and biocompatible properties [45]. This amphiphilic property invests phospholipids with self-assembly properties and enables them to act as emulsifying and wetting agents. When introduced into water, phospholipids can spontaneously produce different supermolecular structures depending on their specific properties and conditions; for example, they demonstrate a tendency to form liposomes [45].

Natural phospholipids are widely derived from plant sources, such as soybean, canola, sunflower, wheat germ, and from animal sources, for instance, egg yolk and milk [45, 47]. In contrast, various types of synthetic phospholipids can be obtained from natural lipids by modifying the hydrophobic and hydrophilic regions of phospholipid molecules [40]. Synthetic and natural phospholipids have respective advantages and disadvantages. While synthetic phospholipids demonstrate comparatively high stability and purity, they are relatively expensive compared to their natural counterparts. However, obtaining consistent purity is challenging and synthetic phospholipids are relatively unstable, resulting in their metabolization into lysophospholipids during the preparation process and storage [45].

Phospholipids are amphipathic molecules composed of hydrophilic and lipophilic groups on the head and tail, respectively. The structure of phospholipids (Fig. **2**) generally consists of diglycerides, phosphate groups, *e.g.*, phosphoric acid molecules, and organic molecules such as choline. Diglycerides are glycerides consisting of two chains of fatty acids covalently bonded to a single glycerol molecule. The glycerol undergoes esterification at positions 1 and 2 with fatty and phosphoric acids at 3-position [46]. Glycerol ($C_2H_8O_3$) contains three hydroxyl groups (-OH), contributing to the solubility of phospholipid molecules in water, while fatty acid chains, whether saturated or unsaturated, possess hydrophobic properties. Thus, a phospholipid molecule has a hydrophobic tail consisting of two fatty acid chains and a hydrophilic head composed of glycerol and phosphate. A bilayer structure of liposome membrane will be spontaneously formed when the fatty acid chains of a phospholipid molecule encounter the fatty acid tail ofanother molecule with the polar head facing the water [47].

The physicochemical properties of each phospholipid are also related to the chain length of fatty acids, in which each phospholipid type has contrasting carbon atom numbers and saturation degrees, for example, hydrogenated soy phosphatidy-

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lcholine (HSPC), distearoyl phosphatidylcholine (DSPC), dipalmitoyl phosphatidylcholine (DPPC), and dimyristoyl phosphatidylcholine (DMPC) [40]. For a stable liposome formulation, saturated phospholipids can be used, whereas this is rarely the case with unsaturated phospholipids. However, this selection is highly dependent on the physicochemical characteristics of the drug [48].

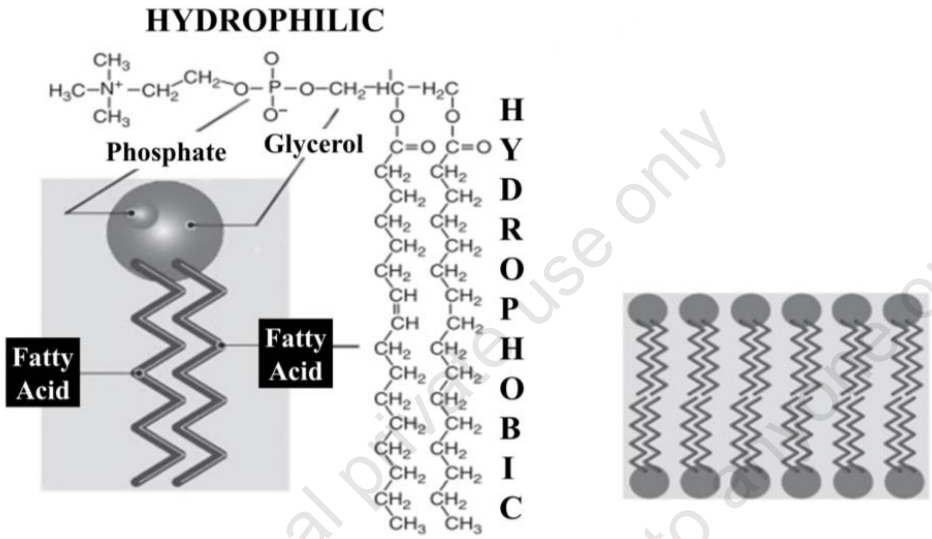

Fig. (2). The structure of phospholipids and their schematic representation in the formation of bilayer membranes of liposomes [47].

Based on the polar head group, phospholipids can be categorized as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), phosphatidylglycerol (PG), and phosphatidic acid (PA), while PC and PE have been generally used in the production of liposomes [40].

Liposomes are classified into three types according to their charge potential; cationic, anionic, and neutral, in which these surface charges largely determine the systemic circulation time, distribution, cellular uptake, and elimination of liposomes within the body [49].

A cationic liposome is generally prepared with lipids that can induce a positive charge on the liposome surface, as indicated in Table **1**. For the most part,negatively charged therapeutic agents can be incorporated into this liposome,forming stable complexes [49]. The general characteristics of cationic liposome include high water solubility and high cationic charge at physiological pH, thus promoting strong interaction with negatively charged cell membranes and improving cellular binding and uptakes [38], which strongly supports targeteddrug delivery. In contrast, anionic liposome, composed of phospholipids with an anionic head group, can affect cell signaling, protein-lipid interactions, and membrane trafficking

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[50, 51]. The charged lipids are initially used in RNAdelivery as an application supporting successful gene delivery. On the other hand, cationic liposomes frequently have problems with systemic toxicity. The use of neutrally-charged phospholipids is generally applied to overcome toxicityproblems with high drug delivery efficiency [49].

Table 1. Phospholipid types based on the types of liposomes [49].

No	Liposome Types	Phospholipids Used as the Lipid Component
1	Cationic Liposome	1, 2-dioleoyl-3-trimethylammoniumpropane (DOTAP)
		N- [1- (2,3-dioleoyloxy) propyl] -N, N, N-trimethyl-ammonium methyl sulfate
		Dioleoylphosphatidyl ethanolamine (DOPE)
		Oleic acid (OA)
		Dimethyldioctadecylammonium bromide
2	Anionic Liposome	Phosphatidylglycerol (PG)
		Phosphatidylinositol (PI)
		Phosphatidic acid (PA)
		Phosphatidylserine (PS)
3	Neutral Liposome	1,2-dioleoyl-sn-glycero-3-phosphatidylcholine (DOPC)

The most commonly employed phospholipid for preparing neutral liposome is phosphatidylcholine which consists of a hydrophilic group, *i.e.*, phosphocholine, together with a glycerol bridge and a hydrophobic region incorporating double acyl hydrocarbon chains [52]. Hydrogenated soy phosphatidylcholine (HSPC) is anon-ionic synthetic phospholipid obtained from hydrogenated natural phospholipid, which is produced from egg yolk or soy by hydrogenation. HSPC has a molecular weight of 837.44 and a number of saturated chains of 16-18 witha transition temperature (T_c) of 52°C [40, 47]. Its several advantages comprise being odorless and unaffected by oxidation [40, 53]. Moreover, it is easier to hydrogenate soybean PC in producing HSPC than synthesize DSPC as synthetic lipids. In addition, rather than DPPC or DSPC, HSPC is most often used to ensurethe stability of liposomes during systemic blood circulation.

In addition, the liposome bilayer membrane may contain other constituents such as cholesterol, hydrophilic lipids that are conjugated with lipids, and the water phase [38].

2. The hydrophilic aqueous core inside liposomes

The inner core of the liposome, surrounded by the polar head groups of the phospholipids, becomes the loading site for hydrophilic molecules. Therefore,

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most hydrophilic drugs will tend to become entrapped in this aqueous core [55]. On the other hand, the lipophilic molecules will be enmeshed in the hydrophobic portion of the phospholipid bilayer [54].

Hydrophilic drug encapsulation can be passively induced by the hydration of a buffer or solution containing hydrophilic drugs [43]. Through this method, the drug can enter the liposomal aqueous core, although a limited amount of it will remain outside the liposome section. In addition, dehydration and rehydration methods can also be applied for DNA and protein encapsulation [56]. Drugs with good permeability coefficients that are reflected in their partition coefficient (Log P) can be efficiently loaded using an active method with the presence of pH or ammonia gradient. This loading method generally produces high encapsulation efficiency, which is, in most cases, at a level of >95% [48, 57].

3. Cholesterol as an additional component of the bilayer membrane

Cholesterol is generally used to enhance the physical stability of the membrane bilayer of liposomes, which reduces the water permeability of soluble molecules across the membrane bilayer [40], thus increasing liposome rigidity and stability [47]. Cholesterol plays a major role in the regulation, dynamics, and function of liposomal bilayer membranes by decreasing the free rotational force of the phospholipid hydrocarbon chain, thereby helping to reduce the loss of hydrophilic parts and stabilize the lipid bilayer [30]. In addition, without the addition of cholesterol, liposomes can interact rapidly with plasma proteins such as albumin, transferrin, and macroglobulin, causing physical instability of the liposomes and rapid elimination from the body. Cholesterol will occupy the gap produced by the phospholipids and render the structure more rigid, thus reducing the interaction between phospholipids and plasma proteins [58]. The use of cholesterol has also been reported to affect vesicle diameter in addition to efficient drug encapsulation [30].

4. PEG-conjugated lipids form a hydrophilic layer outside the liposomes

Targeted drug delivery systems represent a promising strategy for increasing selective drug delivery to unhealthy tissue or disease sites, thereby improving therapeutic efficacy and lowering toxicity. The use of hydrophilic polymer such as polyethylene glycol (PEG) is often associated with targeting specific cells, tissue, and even intracellular localization in organelles so as to prolong circulationtime, increase drug bioavailability, and reduce unwanted side effects [59].

Liposomes are known to be very rapidly metabolized by the mononuclear phagocyte system (MPS). PEG has been used to improve drug stability and solubility, decrease toxicity, increase half-life, and reduce clearance and

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immunogenicity of liposomes [60]. PEG can be attached to the liposomal membrane surface using numerous methods, the most frequent of which is to conjugate the polymer into the membrane *via* a PEG-conjugated lipid, such as 1,2-sn-distearoyl-glycero phosphoethanolamine methoxy-polyethylene glycol 2000 (DSPE-mPEG2000) (Fig. **3**) [60].

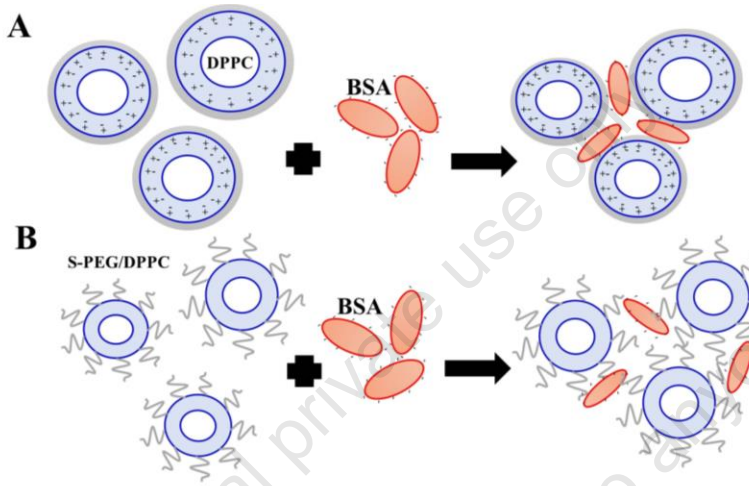

Fig. (3). Modification of DPPC vesicles by S-PEG addition on the liposome surface induces high stability in the presence of Bovine Serum Albumin [61].

The effect of PEGylation on liposomes in increasing circulation time largely depends on the length of the PEG chain and the relative density of the total lipid constitution. In general, PEG featuring longer chains represents superior steric obstacles [62]. The lipid-PEG modification sterically inhibits the interaction between liposomes and MPS, which causes rapid clearance of liposomes from the blood. Santos *et al.*'s research shows that DSPE-mPEG2000 at a concentration of ≤5 mol% levels combined with the DSPC liposome results, with the effect of extending circulation time. However, at a level between 1 and 5 mol%, it will have a different effect. The addition of DSPE-mPEG2000 also prevents liposome aggregation, thus extending circulation time [63].

Manufacturing of Liposomes

The main objectives of ideal liposome manufacture are to achieve efficient drug encapsulation, small particle size, and high stability during long-term storage. In general, liposome manufacture includes the processes of lipid hydration, particle size reduction, and separation from free drugs. Approximately ten methods are usually adopted for the preparation of liposomes, including the thin-film hydration method, micro-emulsification, sonication, membrane extrusion, the freeze-thawed

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method, the ether injection method, the ethanol injection method, the reverse- phase evaporation method, dehydration-rehydration, and the calcium-induced fusion method [64]. Method selection largely determines the unilamellarity, vesicle size, and stability of liposomes. In addition to the manufacturing method, there are two main drug loading methods into liposomes; passive loading and active loading.

Of all these manufacturing methods, thin-film hydration, reverse phase evaporation, and ethanol injection have become the most commonly used in the preparation of liposomes. The following are brief overviews of the various manufacturing methods for liposome manufacture:

1. Thin Film Hydration

The thin film hydration method is the most common and simplest liposome production technique, which involves dissolving phospholipids in organicsolvents, such as dichloromethane, chloroform, ethanol, and chloroform-methanol [64] (Fig. **4**). This is the simplest original method devised by Bangham, which, if compared to those of reverse-phase evaporation and ethanol injection, canproduce liposomes with the optimum properties and stability [40].

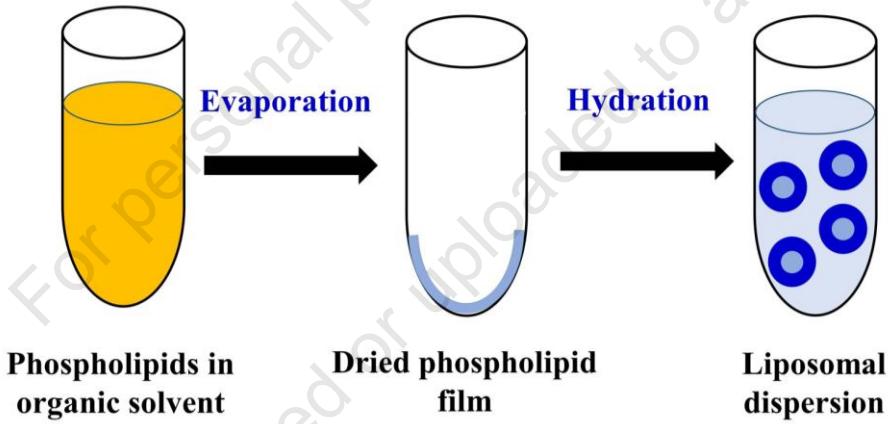

Fig. (4). The schematic representation of liposome production using the thin film hydration method [65].

At the first stage, the organic solvents with volatile properties, especially chloroform, ether, or methanol, are used to dissolve lipids. The lipid will become a thin film layer on the bottom tube wall when the solvent is evaporated using a rotary vacuum evaporator [40]. Usually, an evaporation process completed in a vacuum at a temperature of 45-60ºC will result in a homogeneous thin film layer. Nitrogen can also be used to remove the remaining solvent [64]. Furthermore, the dry, thin-film layer is hydrated under agitation with a hydration solution, such as

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distilled water, phosphate buffer, phosphate buffered saline (PBS) at pH 7.4, or normal saline at a temperature above the transition temperature of the lipid used [38]. The hydration process usually varies from 1-2 hours in duration [64].

This thin layer method will produce a heterogeneous multilamellar vesicles (MLV) liposome that requires a further process to reduce its size. For example, sonication will produce small unilamellar vesicle (SUV) liposomes and/or extrusion with a polycarbonate membrane to produce homogenous size distribution among unilamellar liposomes [38].

2. Reverse Phase Evaporation

In the reverse-phase evaporation method, phospholipids are dissolved in diethyl ether/isopropyl ether or a mixture of diethyl ether and chloroform at a volume ratio of 1:1 or a mixture of chloroform-methanol at a ratio of 2:1 v/v. Phosphate buffer or citrate-disodium hydrogen phosphate buffer is subsequently added at the aqueous phase in order to increase the drug encapsulation efficiency of the liposomes. The organic phase must remain distinct from the water phase to ensure that an oil/water emulsion is formed. Liposome formation will occur during continuous rotational evaporation of organic solvents in a vacuum, as seen in Fig. (**5**). This method produces very high drug encapsulation. However, thepossibility of remaining solvents and the difficulty of large-scale manufacturing constitute the main limitations of this method [64].

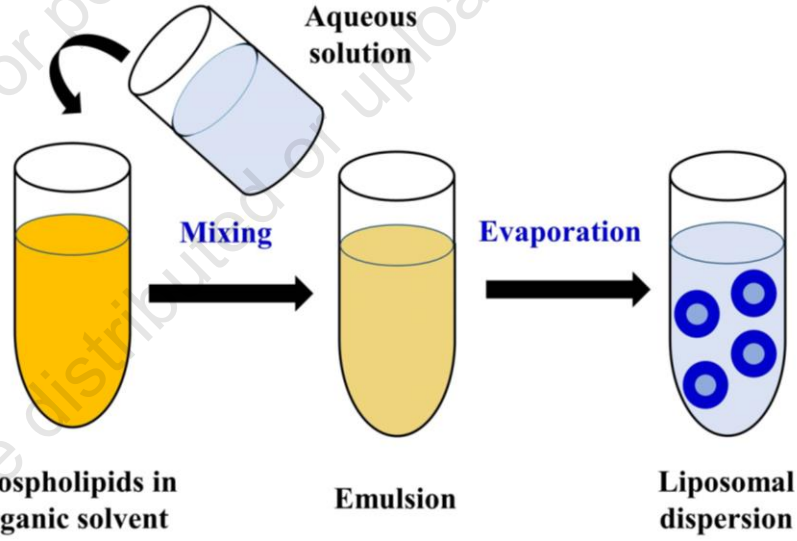

Fig. (5). A schematic representation of liposome preparation procedures involving the reverse phase evaporation method [65].

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3. Ethanol Injection

In the ethanol injection method, lipids are first dissolved in ethanol, with the resulting solution being rapidly introduced into large quantities of preheated water or in a buffer to form SUV liposomes. The incorporation of drugs in liposome vesicles depends on their hydrophilic and/or hydrophobic properties. This method uses ethanol as a relatively harmless solvent, which can also be easily scaled up. In addition, no physical or chemical treatment exists that can cause lipid damage. However, the concentration of the vesicles obtained is extremely low, and there may be an azeotropic mixture with water rendering the removal of ethanol from the final product difficult [40, 64].

The use of Liposomes for Herbal Product Delivery

Liposomes have been used for many purposes, including drug delivery systems and cosmetics, among others. In this section, the use of liposomes is focused on a herbal drug delivery system since liposomes effectively enhance the drug solubility, bioavailability, and pharmacological activity of certain compounds.

1. Liposomes Increase Herbal Drugs Solubility

Liposomes can dissolve water-insoluble drugs by trapping them in the liposomal lipid membrane. Apart from increasing their solubility and biocompatibility, the liposome structure, which is similar to that of a biological membrane, can encourage its use in delivering drugs with poor permeability [65].

The use of liposomes has been applied to *Orthosiphon stamineus* (OS) extract formulation. *Orthosiphon stamineus* Benth. is a medicinal plant commonly used as an ingredient of various traditional drugs in the treatment of angiogenesis- related diseases, such as rheumatoid arthritis, tumor edema, obesity, diabeticretinopathy, and psoriasis [66]. The ethanol extract of OS contains many flavones,including sinensetin (SIN), eupatorine (EUP), and 3′-hydroxy-5, 6, 7, 4′- tetramethoxyflavone (TMF) as markers of pharmacological activity. However, these flavones exhibit low water solubility, which limits their clinical use [67]. Increasing the solubility of lipophilic flavones produced from OS extract can increase their bioavailability and pharmacological activity.

Liposomes have been prepared to increase the solubility and permeability of OS ethanolic extract, thereby enhancing their bioavailability. Aisha *et al.* reported the use of liposomes in preparing OS extract (OS-L) by the thin film hydrationmethod, which involves dissolving phospholipids in chloroform.

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The optimum ratio of phospholipids to extract is selected according to the increase in the solubility of the OS extract in water. The liposomes are prepared using crude soybean phospholipids prepared in ethanol (PH-Et) at various weight-to-weight ratios of the OS extract. The crude soybean lecithin contains 62 ± 0.2% acetone insoluble phosphatides, while PH-Et has a phosphatidylcholine (PC) fraction of 13.4%, as determined by column chromatography. The solubility ofthe non-formulated OS extract (OS-E), as measured by UV-vis spectrophotometry, is 956±34 μg/ml. The results show a significant increase inthe water solubility of the formulation prepared on phospholipids at extract ratios of 50:50, 150:50, and 100:50, as shown in Table **2**. The formulation prepared at a weight ratio of 100:50 shows the greatest solubility improvement, albeit stilllimited. Consequently, the methanol is used to dissolve extract resulting in a significant increase in the water solubility of OS extract from 1,402 ± 66 μg/mLin ethanol to 3,979 ± 139 μg/mL in methanol (P = 0.000). The methanol used to dissolve extract has a similar boiling point to chloroform (65.0°C) as phospholipidsolvent (61.2°C), resulting in a homogenous phospholipid-extract thin film. Onthe other hand, the higher boiling point of ethanol (78.4°C) compared to chloroform tends to produce phase separation and the precipitation of phospholipid from extract mixtures [67].

Table 2. The water solubility of OS extracts prepared at various phospholipid-extract ratios in liposomes [67].

Formula	Crude soybean phospholipids prepared in ethanol/PH-Et (mg)	OS Extract/ OS-E (mg)	Solubility in water (μg/mL)
F1	150.0	50.0	1,296.5 ± 18
F2	100.0	50.0	1,401.7 ± 66
F3	50.0	50.0	1,188.8 ± 169
F4	25.0	50.0	1,018.8 ± 15
F5	25.0	75.0	1,072.6 ± 6

The interaction of the extracts with phospholipids results in changes in the infrared absorption spectrum. The most noticeable spectral change can be observed in the phospholipid polar group and may indicate the presence of hydrogen bonds between the polar phospholipid groups and the hydroxyl groups from the OS extract. Hydrogen bonds can also occur between the keto groups of flavonoids and the phospholipid oxygen groups. In addition, hydrophobic interactions occur between the flavone's methoxy group and the carbon chain in the tail portion of phospholipids [67].

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The stability study shows that the OS extract liposomes are stable at pH 5.5 and 7.4, while at a lower pH of 1.6 (gastric pH), OS liposomes experience agglomeration and precipitation. Moreover, although the OS liposomes will clump, they will re-dissolve at pH 5.5 and 7.4, which represent the pH of the intestines. No precipitation occurs at pH 1.6 by using soybean phospholipids and the OS extract as a single compound [67].

The OS extract released from the liposome is evaluated by a dialysis bag that has a molecular weight cut-off (MWCO) of 8,200 using phosphate buffer pH 6.8 media at a stirring rate of 100 rpm and temperature of 37°C. The results show that a cumulative percentage release of OS extract loaded in liposomes is 62% after 24 hours. On the other hand, the cumulative release percentage of free OS extracts is 94%. These results indicate that OS extract is stably encapsulated in liposomes, probably due to OS extract and phospholipid interaction. Consequently, results related to the slow release of flavones contained in OS extracts include rosmarinic acid (RA), sinensetin (SIN), eupatorin (EUP), and 3′-hydroxy-5,6,7,4′-tetramethoxyflavone (TMF) [67].

A further evaluation carried out on the antioxidant effect on DPPH of the extract release indicated that the OS extract loaded in liposome demonstrates stronger antioxidant activity against DPPH with an IC_{50} value of 23.5 ± 1.1 μg/ml than that of non-formulated extracts, which have an IC_{50} value of 32.4 ± 0.5 μg/ml [67]. This is because OS extract is stably encapsulated in liposomes with a slow-releaserate that enables it to maintain or increase the antioxidant activity.

A higher intestinal permeability of liposomal extracts compared to non- formulated extracts is obtained due to loading into liposomes, higher solubility, and the nano-sized vesicles that produce an increase in negative charge andenhance colloid stability. Previous studies have reported that anionic liposomes demonstrate superior colloid stability and absorption and an even higher cellular uptake rate than those of neutral and cationic liposomes. Based on the evaluation results related to the liposome formulation of the OS extract, it is clear that an increase in solubility, absorption, and antioxidant effects can intensify the pharmacological effects of the OS ethanol extract [67].

Liposome formulation to increase drug solubility has also been applied to silymarin extract. Silymarin has been known as the main flavonoid obtained from the extraction from the dried fruit of *S. marianum* and has been widely employed in the treatment of liver disease. Silybin constitutes the main and major active component of silymarin and plays a role in its pharmacological activity. Silymarinis known to be widely used in the treatment of liver disorders to reduce glutathione oxidation as a means of increasing glutathione levels in the liver, enhancing the stabilizing

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effect of liver cell membranes, and the enhancement of hepatocyte protein synthesis [68]. However, the low solubility of silymarin in water produces low oral bioavailability of approximately 20-50%. Some degradations have also been reported due to the presence of gastric juice, which limits the use of silymarin [69, 70].

Based on Wang *et al.*'s research, it has been reported that silymarin prepared as pro-liposome improves encapsulation efficiency when the drug to phospholipids mass ratio or pH is increased [65]. Pro-liposomes form a dry and readily flowing powder that will convert to liposomes after hydration. Pro-liposomes offer several advantages over conventional liposomes, such as increased stability due to the dry-solid state forms during storage [65].

The pro-liposomal silymarin is prepared with soy lecithin, cholesterol, and sodium oleate dissolved in propylene glycol to produce a silymarin proliposome solution with a transparent light yellow color. The liposome is obtained by mixing proliposomes with water resulting in vesicles with multilayer membranestructures, as seen in Figure 6, with silymarin loading at a high entrapmentefficiency [71]. The hydrated pro-liposomes produce liposomal vesicles with small particle sizes, approximately 70 nm, and are homogeneous in terms of the distribution of their size. The use of sodium deoxycholate or sodium oleate in proliposomes can facilitate the formation of liposomes without any changes in their morphological structures and stable silymarin loading even after proliposome hydration [71].

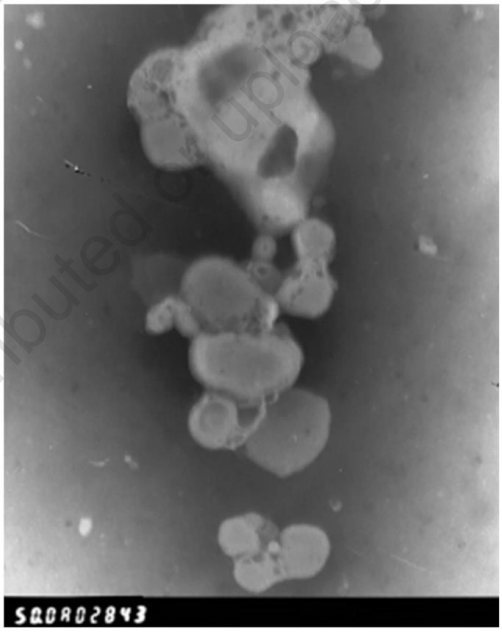

Fig. (6). Transmission electron photomicroscopy of silymarin liposome (magnification 5x1000 times) [71].

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It has also been reported that liposome is successfully used to load curcumin (CUR). Liposomes that are composed of lecithin, cholesterol, and CUR at a molarratio of 60:15:1, respectively, and prepared by reverse-phase evaporation method generate a stable, homogeneous, and semitransparent liposome with an efficient encapsulation of 89.3% [12]. The liposomes successfully increase the stability of CUR at high temperatures and/or in acidic conditions.

Liposomes Improve the Bioavailability and Pharmacological Effects of Herbal Drugs

The main challenge to the development of an oral dosage form lies in managing poor drug bioavailability, which is known to be affected by several factors, including water solubility, permeability, dissolution rate, first-pass metabolism, and pre-systemic metabolism. However, poor water solubility and limited permeability are often associated with low oral bioavailability [11]. Liposomesare potentially effective drug carriers that can promote an improvement in the solubility of drugs in water, provide protection against degradation in the gastrointestinal environment, and ensure permeability through the epithelial cell membrane, thereby increasing the bioavailability of the drug [65]. In addition, liposomal drugs are known to be of low toxicity and offer improved pharmacological effects [72].

The use of liposomes has been successfully applied to increase the bioavailability of curcumin (CUR). CUR occurs as a yellow polyphenol compound derived from the turmeric plant and has been widely used in the treatment of various cancers affecting the lungs, cervix, prostate gland, breasts, bones, and liver, in addition to inflammatory diseases [12, 68, 72]. However, CUR has poor bioavailability resulting in its low blood level [74]. Therefore, a well-designed CUR formulation is necessary to improve its efficacy.

Several studies have reported that the encapsulation of CUR into liposomes improves its stability, bioavailability, targeting properties, and anticancer effectiveness. Several methods for the preparation of CUR liposomes have been reported, including thin-film, freeze-thawing, freeze-dried, solvent injection, and reversed-phase evaporation method [12].

Liposome preparation by the thin layer dispersion method increases the stability of CUR. According to the research conducted by Chen *et al.*, the use of N- trimethyl chitosan chloride (TMC) in the CUR liposomes composed ofphosphatidylcholine, cholesterol, and D-α-tocopheryl polyethylene glycol 1000 succinate, increases the bioavailability of CUR. Another study by Gu *et al.* highlights that the preparation of liposomes coated with Carbopol is also reported to produce an increase in bio-

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availability 2.22 times higher than that of CUR liposomes without coating.

Positively hybrid charged liposomes (PHL) prepared by thin layer hydration method, as reported in the study of Pamunuwa, Karunaratne, & Karunaratne(2016), significantly reduces the release of CUR from the liposomes compared to that of negatively hybrid charged liposomes (NHL). The use of stearylamine (SA)as an additional component of the lipid bilayer successfully produces a slow CUR release from liposomes. In another study, it is reported that the use of hydroxypropyl-β- or hydroxypropyl-γ-cyclodextrin (HPβCD or HPγCD) complexes in liposomes by the thin layer hydration method results in an encapsulation efficiency 2.02 times higher than those without cyclodextrins. The use of HPβCD shows higher stability than HPγCD. The formulation of CUR liposomes in cyclodextrin can significantly increase the solubility and stability of CUR [77].

CUR liposome formulation is also carried out using a lipid composition containing different characteristics of phospholipids, including neutrally charged phospholipids of varying rigidity, *i.e.*, soy phosphatidylcholine (SPC, a non-saturated phospholipid), dipalmitoylphosphatidylcholine (DPPC, a saturated phospholipid), negatively charged phospholipids, *i.e.*, dipalmitoyl phosphatidyl-glycerol (DPPG), and a mixture of these, *i.e.*, DPPC + DPPG (7:3 $^{w}/_{w}$), with 30% mole addition of cholesterol. The results show that the charges of lipid polar head and hydrophobicity related to saturated carbon chains of phospholipid tail greatly affect the particle size and the loading efficiency of liposomal CUR. The surface charges induced by environmental pH determine protonation of the phosphate portion of phospholipid molecules, thus affecting the hydrogen bonding between molecules leading to changes in particle size, the phospholipid liquid-crystalline stating transition temperature, and the instability of the liposomes. In acidic pH, SPC-based liposomes have the smallest vesicle size and most stable liposomes, whereas, in neutral and alkaline pH, DPPG demonstrates the highest degree of physical stability. However, the deprotonation of CUR hydroxyl groups occurring at alkaline pH causes lower entrapment efficiency for all phospholipids, specifically for DPPG, which produces repulsive interaction with CUR. The high hydrophobicity of neutral CUR form renders it highly loaded with acidic pH. The more rigid the phospholipids, *i.e.*, DPPC, with saturated hydrocarbon chains in their hydrophobic tail, the higher the entrapment efficiency and the lower the release of CUR from the liposome. The use of liposomes successfully induces a sustained and prolonged release of CUR [78].

Liposome formulation is further carried out using the freeze-thawing method, in which it has been reported that the use of 10% sucrose as a cryoprotectant can

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protect liposomes from vesicle fusion and damage due to ice crystallization during the freezing process. Freeze-dried preparation itself is used to improve long-term liposome stability. The addition of sucrose demonstrates excellent maintenance of particle size as well as encapsulation efficiency, with almost 99% of CUR potentially being entrapped after rehydration [79].

Moreover, it has been reported that Hyaluronan and Eudagrite S100, both anionic polymers, can be employed as stable and effective coating substances for liposomes composed of SPC with rapid dissolution in the upper gastrointestinal tract [80]. The results show coating liposomes with these polymers producesvesicles of 220-287 nm, spherical in shape, and without any changes in dimension, even when exposed to a gastric bowel stimulated medium with high ionic strength. In addition, it produces an efficient encapsulation of CUR in the range of 78%-82%. Good water dispersion and homogeneous suspension without the presence of aggregates and precipitates being formed can be achieved. The combination of these two polymers can protect CUR from metabolism in the gastric environment. Biodistribution studies indicate that CUR levels in the liver and kidneys are low. On the other hand, there is a greater accumulation of CUR in the lower gastrointestinal tract, specifically the intestines and colon, while very low levels of CUR suspension are observed. The results show that these delivery carriers can be used to protect polyphenol compounds from the acidic gastric environment.

The solvent injection method can be performed using ethanol or ether. Through this method, phospholipids and hydrophobic drugs are dissolved together in an organic solvent as the oil phase, with the solution being rapidly injected into the water-soluble drug or aqueous phase while being stirred. Liposomes will be spontaneously formed when the organic solvent is removed. However, ether is used less frequently than ethanol because of its toxicity. CUR liposome composedof 1.0 mg of CUR with cholesterol: lecithin at a ratio of 1:3 and prepared usingthe ethanol injection method demonstrates high CUR encapsulation efficiency of up to 72% with a vesicle size of 830 nm [12]. Other research shows the use of propylene glycol liposome (PGL) as a CUR carrier prepared by the solvent injection method using ethanol produces a high CUR encapsulation efficiency of 92.74% without any aggregation or fusion, whereas conventional liposomes experience a degree of aggregation over time. It is also reported that CUR-PGL shows a gradual release up to a maximum of 46%. A 3-month stability evaluation shows that CUR-PGL has non-significant changes in the particle size, polydispersity index, and encapsulation efficiency, in contrast to the CUR liposome that experiences decreases in drug encapsulation. Therefore, the CUR- PGL formulation with the injection method is effective in increasing the efficiency of encapsulation and reducing the dosage and, inevitably, the side effects of CUR [81]. Another study by Li *et al.* on silica-

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coated ethosome shows ahigh CUR encapsulation efficiency of 80.77%. The silica-coated CUR-ethosomes are stable and gradually release CUR. Moreover, these ethosomes produce 11.86 times higher CUR bioavailability than that of the CUR suspension [82]. An *in vivo* study of mice shows that the transporting of silymarin liposomes across the intestinal biological membrane is more efficient than that of silymarin solution [71]. These results highlight the successful use of liposomes to increase thebioavailability of natural products, thereby promoting their potential applicationin clinical contexts.

The Use of Nanoliposomes for Enhanced Drug Delivery

Nanoliposomes have many advantages, including controlled drug release, tumor targeting, low toxicity, high stability, extensive bioavailability, and reduced therapeutic dosages. Drug encapsulation in the nanoliposome system can be employed to improve the physicochemical stability of CUR. The use of chitosan in the formulation of CUR nanoparticles composed of CUR: Chitosan: Tripolyphosphate at a ratio of 3:24:8 w/w, respectively, produces high CUR nanoliposome stability when stored at 4°C, with no changes observed even up to ten months later. In addition, it results in greater *in vivo* bioavailability than the CUR suspension. This is because the use of chitosan can provide a positive charge, thereby extending the contact time of the drug with the absorption surface [83]. Shin *et al.* reported that the CUR nanoliposomes prepared using an ethanol injection method with chitosan coating have spherical morphology, as presented in Figure 7 and demonstrate improved physical stability with good mucoadhesive properties, thus enhancing bioavailability [84].

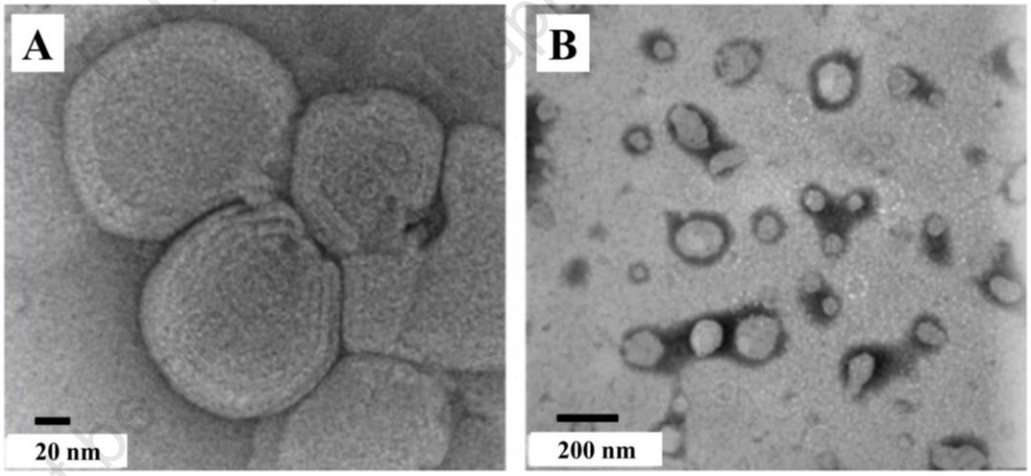

Fig. (7). Transmission electron microscopy (TEM) images of chitosan-coated CUR nanoliposomes with scales of (A) 20 nm and (B) 200 nm [84].

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On the other hand, the use of nanoliposomes is unable to prevent CUR from hydrolysis at an alkaline pH of 12.0, during which it causes degradation of nanoliposomes as well as decomposition of CUR. When nanoliposome enters the circulation system, it can be rapidly phagocytized by monocyte-macrophages [85]. In addition, it can be easily and extensively accumulated in tissues with extensive vascularization in the liver, spleen, and kidneys. Consequently, thetarget specificity cannot be maximally achieved, thus reducing the effective dose delivered to the target sites. A modified liposome with PEG or ligand binding can prove as an effective strategy in solving this problem [12, 86, 87].

Long Circulating Liposomes

The conjugation of hydrophilic polymers, such as PEG, has been extensively used to obtain long-circulating liposomes through the formation of aqueous layers on the surface of liposomes. This polymer prevents plasma protein binding to liposomes through a steric protective layer, thereby reducing the excretion of liposomes by RES and prolonging systemic blood circulation. Long circulating liposomes are known to provide a homogeneous distribution without any aggregation. Therefore, the use of long-circulating PEGgylated liposomes in the CUR liposomes results in greater stability [12].

Lin *et al.* reported that TEM analysis of liposome-PEG-polyethyleneimine (PEI) encapsulated CUR shows a coarse round shape in the presence of a hair-like surface, as shown in Fig. (**8**).

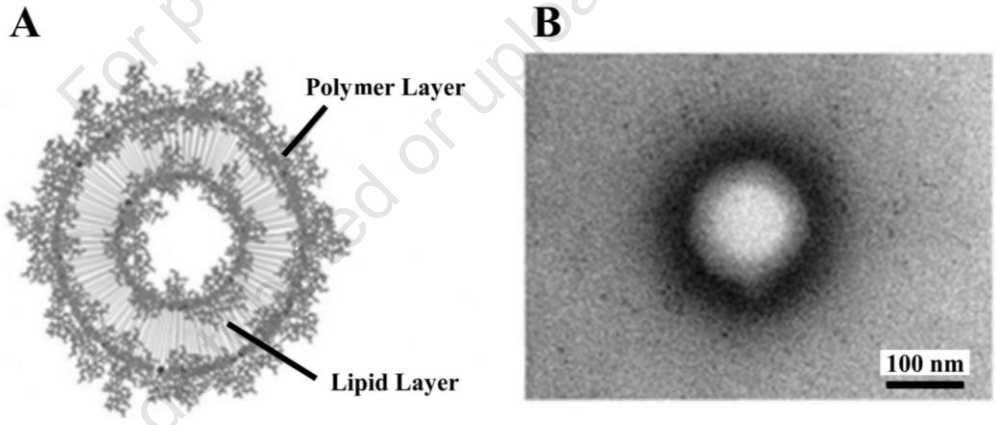

Fig. (8). Microstructures of the cationic liposome-PEG-PEI complex. **(A)** Schematic illustration of the structure of the cationic liposome-PEG-PEI complex. **(B)** TEM image showing the structure of the cationic liposome-PEG-PEI complex, consisting of the light circular area and dark corona on the surface [88].

Ligand Targeting Liposomes

Ligands can direct liposomes to bind specifically to receptors in the target cells. Therefore, the liposomes binding with ligands are generally used to enhance the therapeutic effect, produce synergies, reduce side effects, lower the dosage,

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shorten the treatment period, and produce a specific targeting effect on the body with highly selective drug delivery. Encapsulation of CUR in liposomes with folic acid modification results in solubility and increased activity in tumors [12, 88].

In addition to the use of liposomes to increase the bioavailability and pharmacological effects of CUR, liposomes are also employed to enhance the pharmacological effects of *Cistanche tubulosa*. *Cistanche tubulosa* is a parasitic plant of the Orobanchaceae family that produces various pharmacological effects, including increasing immunity and endurance, nourishing the kidneys, treating impotence, and improving intelligence. Moreover, it also possesses anti-oxidant and anti-aging properties [90]. This plant contains phenylethanoid glycosides (CPhGs) as the main component that stimulates immunity. Despite their strong pharmacological effect, CPhGs have poor oral absorption [91] that severely limits their use for clinical and therapeutic applications.

Zhang *et al.* reported that liposomes composed of lecithin, DPPC, and cholesterol at a respective weight ratio of 1:2:2 are successfully prepared for encapsulating CPhGs. The liposomes have spherical shapes, uniform surface thickness, a homogenous particle size of 216.7 nm with a zeta potential of -55.6 mV, and efficient encapsulation of 38.46%. The release profile shows a release that is close to 100% after 24 hours. Moreover, CPhG liposomes greatly inhibit HSC viability and proliferation and increase the activity of concentration-dependent apoptotic cells with an IC_{50} value of 42.5 μg/mL

Based on the evaluation results, 24 hours after exposure of CPhG liposomes to hepatic stellate cells (HSCs), and lactate dehydrogenase (LDH), an enzyme present in the cell cytosol, was released, thus indicating cell membrane damage. Moreover, the study also reported that CPhG liposomes induce apoptosis of hepatocytes, which intensifies with increasing doses of CPhGs liposomes. Inaddition, CPhG liposomes induce G1 phase cell cycle arrest. These results indicate that CPhG liposomes have a high potential for preventing and treating liver fibrosis by regulating cell proliferation, apoptosis, and cell cycle arrest [91].

The results also indicate that CPhG liposomes have a significant inhibitory effect on cell proliferation in HSCs. In addition, it has been found that p-PI3K and p-Akt levels consistently decrease in HSCs after 24 hours of CPhG liposome administration, indicating that the anti-proliferative effect of CPhG liposomes on HSCs is related to the deactivation of the PI3K/Akt pathway. CPhG liposomes at a concentration of 29.45 μg/mL can reduce the expression level of phosphorylated PI3K protein and phosphorylated Akt ($p < 0.01$) [91].

The foregoing results indicate that the use of liposomes in CPhG liposome formulation significantly improves the inhibition activity of CPhGs for HSC

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activation and reduces the progression of liver fibrosis by increasing apoptosis and regulating the cell cycle in HSC. This suggests that the liposome formulation in this study can be developed as an antifibrogenic agent for the treatment of liver fibrosis.

Factors Affecting the Encapsulation of Herbal Extract in Liposomes

In order to prepare liposomes with high encapsulation efficiency to improve solubility as well as bioavailability and pharmacological effects, there are certain critical parameters that should be identified.

1. The selection of phospholipids:

In the entrapping of hydrophobic substances, which will be located within the lipid bilayer membrane, the types of phospholipids will determine the entrapment efficiency. This is because the ordered structure of saturated phospholipid will limit the number of hydrophobic molecules located inside. In general, the less the crystalline structure of the lipid bilayer, the higher the loading capacity of the bilayer membrane since there is more space for hydrophobic molecules trapped inside. However, it will affect the molecular diffusion within the water, thus increasing drug release from liposomes [48, 92 - 94].

2. Extract to phospholipid ratio:

The drug and lipid ratio is a critical parameter that shows the capability of the liposomes to accommodate drug encapsulation, thus playing a critical role in the optimization process [95]. Most hydrophilic drugs will be trapped in the intraliposomal phase. Therefore, entrapment efficiency is significantly determined by the vesicular lipid volume capacity. In this case, the selection of phospholipids will also play a role in quantifying the capacity for entrapping drugs. Each phospholipid has a different surface area which determines the vesicle numbers in the dispersion media, thus affecting the volume of water available for loading drugs.

The ratio of extract to phospholipids affects the encapsulation for liposomalherbal preparation. The extract to phospholipid ratio in the OS liposome formulation greatly affects the extract solubility in the liposomes. The use of phospholipid:extract at a ratio of 100:50 w/w has the highest solubility, *i.e.*,1,401.7 ± 66 μg/ml [67].

In silymarin liposome formulation, the mass ratio of silymarin to phospholipids also significantly influences drug encapsulation and loading efficiency. A significant increase in encapsulation efficiency from 31% to 42% is observed when the

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drug-phospholipid ratio is increased from 1:5 to 1:10 ($P<0.01$). However, no changes are obtained after increasing the ratio to 1:20 ($P>0.05$)while the drug loading efficiency decreases.

3. pH of liposomes:

The encapsulation efficiency also changes with variations in pH. The silymarin liposomes are composed of 1 g of silymarin, 10 g of phospholipids, 5 g of cholesterol, and 0.5 g of sodium oleate and prepared with a silymarin- phospholipid at a ratio of 1:10. Adjusting the pH of liposomes to 5.0, 6.0, 7.0, and 9.0 increases their encapsulation efficiency, indicating that the larger the amount of silymarin, the more easily it is trapped when the liposomes are present in a more alkaline environment. This may be related to a chemical reaction between silymarin and phospholipids. Moreover, the improved transport of silymarin liposomes increases bioavailability up to a 1-fold increase in AUC ($P<0.01$) [71].

4. Incubation temperature

In a drug loading process involving active loading, the fluidity of the bilayer membrane determines the ability of water-soluble solutes to permeate across the membrane and enter the intraliposomal phase. The presence of pH or ammonia gradient will drive the permeation or loading process to produce high levels of the drug inside the inner water phase, which sometimes results in high dense aggregates due to oversaturated internal drug concentration. Both the incubation period and temperature affect the gel to liquid crystalline state of phospholipids asthe main component of the bilayer membrane and determine the solute transfer process from the exterior of the liposomes to their interior. This constitutes amajor factor to be considered with regard to the loading of the active substances.

CONCLUSION

The compounds contained in plant extracts exhibit various physicochemical characteristics, which constitute a significant challenge for the liposome drug delivery system. The use of liposomes to develop natural products has several benefits, such as enhancing drug solubility and increasing the bioavailability and pharmacological effects of active substances. Based on the findings of research into the use of liposomes in herbal products, there is an increase in phytochemical stability in terms of physical and chemical degradation, with sustained or controlled drug release. Moreover, an increase in the oral absorption of plant extracts in the form of liposomes indicates increased bioavailability in the gastrointestinal tract, thereby increasing the pharmacological effect at low dose concentration and reducing toxicity.

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FUTURE PROSPECTIVE

A comprehensive analysis from the formulation and manufacturing aspects to the composition of the liposome formula for the natural product drug delivery system and the appropriate manufacturing method is required. The various components contained in the plant extract, in addition to largely water-insoluble compounds, remain as challenges to the optimizing of liposomes preparation intended to improve solubility and permeability, thereby enhancing oral bioavailability. Liposomes could be beneficial, acting as potential drug delivery carriers, which enhance the biological activity of most hydrophilic and hydrophobic substances of herbal drugs due to their vesicular structures mimicking biological membranes.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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CHAPTER 13

AI in Pharmacy, Herbal Medicine and Drug Delivery: A Sci-fi or a Reality

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Abstract: Artificial Intelligence (AI) has been one of the most debated topics ofpresent times as it is transforming nature in almost every aspect. The challenge is to decide whether it will make the planet a better place to live or it will push the human race towards disaster. The seed of AI was sown during the 1950s and continues to hold great future potential. Different policies had been laid down by the government for the ethical use of robots. The chapter gives a glimpse of AI policies in India. The chapter also enumerates the correlation between natural intelligence and software throughvarious software languages like natural language processing, *etc.* It explains how this interaction between robots and natural intelligence has brought about widespread application. Robots can be used as scientists, nannies, pets, assist doctors in surgery,for cleaning, to provide security, to be used in pharmacies for automated dispensing systems, act as a virtual human body to predict how it will react to new therapeutic drugs, make drug development and drug delivery faster, *etc.* The policies regarding these robots are made so that they are not misused as their application is increasing day by day. This chapter also enumerates a lot about future aspects of artificial intelligence in traditional medicine.

Keywords: Artificial intelligence, Automated dispensing system, Ethical issue, Natural language processing, Robot scientist, Robotics, Traditional Medicine.

INTRODUCTION

Computers and software have advanced and come a long way in the past few decades. It has evolved a lot to improve our lives and make our work easier and more comfortable. Over the years, many sci-fi movies and novels have discussed advancements in science and technology. Artificial intelligence is now not only a

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subject for sci-fi but a reality. Artificial intelligence is an example of advancement in science and technology.

Artificial intelligence (AI) can be defined as the science and engineering ofmaking intelligent machines, especially intelligent computer programs. This definition was given by John McCarthy, the father of artificial intelligence. So, in brief, artificial intelligence is an amalgamation of computer science and life sciences that involves making software or a program that thinks intelligently likea human brain. It has brought about automation in many different fields. It is the most discussed topic across all industries throughout the world. As per a study performed in 2013 by Oxford University, 43% of jobs were at risk in the USA dueto automation and robotics [1].

Artificial intelligence has been a topic of debate for many years. Few people say that evolution in artificial intelligence will make work easier, more accurate, and even make the planet a better place to live in, whereas other people defend by saying advancement in artificial intelligence will decrease employment and privacy and could even cause unethical issues and long-term use of artificial intelligence would cause devastations.Artificial intelligence has the ability to multitask and may be able to mimic human characters or behaviours [2]. This is why, if artificial intelligence is not governed by a legal framework, it may lead to the extinction of humanity as a whole. Industry 4.0 is an example that explains how artificial intelligence can decrease employment and result in a high numberof unemployed people. Industry 4.0, which is also called a smart factory, employs a large number of robots in place of human staff to increase the efficacy and reproducibility of the work. The smart factory improves the product quality and also results in developing innovative products but, on the other hand, decreasesthe employment rate. So, the bigger question is whether the emergence of super- intelligent robots poses a threat to humanity or if it will lead to a new advanced beginning [3].

Currently, artificial intelligence is the most researched topic, and much advancement is already seen in this field. For example‘ Deep Mind technologies’ is a British-based Artificial Intelligence Company. This company has formed an artificial neural network that could imitate the human brain and play video games similar to humans. Deep Mind made headlines when its computer-based software Alpha Go beat a human professional player in 2015. In 2016, it launched a huge health project in collaboration with Royal Free London NHS Foundation Trust. This health project assisted acute kidney injuries [4].

Similarly, it has revolutionized the field of medicine also, for example, robotic surgery. Robotic surgery is an amalgamation of advanced computer technology

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and the experience of a skilled surgeon. It is widely used in cardiology, orthopaedics, urology, gastroenterology, gynaecology, paediatrics, *etc.* An example of a surgical robot is the da Vinci surgical robot.

Apart from this, artificial intelligence is used in various fields like economics, medicine, engineering, and the military, as well as being built into many common home computer software applications, traditional strategy games, *etc.* The biggest advantage of AI is that, unlike humans, it is more accurate, resistant to irrational thinking, and immune to sleep deprivation, distraction, information overload,short-term memory loss, *etc.* So, in a nutshell, apart from all the drawbacks, the advantages outweigh the potential disadvantage of artificial intelligence, and it is expected that artificial intelligence will solve many of our problems shortly and make our life much easier. A lot of knowledge in this field is still to be explored to enable artificial intelligence to function correctly and revolutionize the life of the human race [5]. The revolution of the human race is shown in Fig. (**1**).

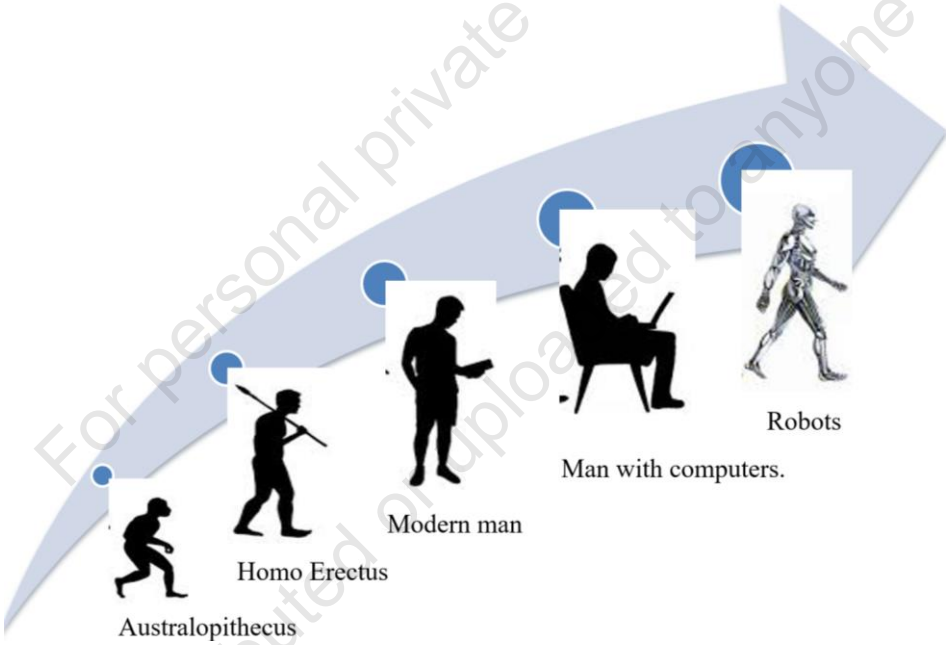

Fig. (1). Evolution of Robotics.

HISTORY OF AI

John McCarthy is known as the father of artificial intelligence. According to him, artificial intelligence is "The science and engineering of making intelligent machines, especially intelligent computer programs." John McCarthy has made

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huge contributions in the field of reasoning and computer language [6]. The roots and the intellectual concept of artificial intelligence originated from Greek mythology. In ancient times, at the time of the Second world war, Alan Turing, a British scientist who had vivid knowledge about computers, worked on decoding Enigma. Enigma was a code used by the German army to send information and messages secretly [7].

After that, the first concept of artificial intelligence started, and that concept of artificial intelligence was described at the Dartmouth Conference, where Herbret Simon and Allen Newell stated that Artificial Intelligence could transform the world. After this, artificial intelligence evolved in the following way, as shown in Fig. (**2**).

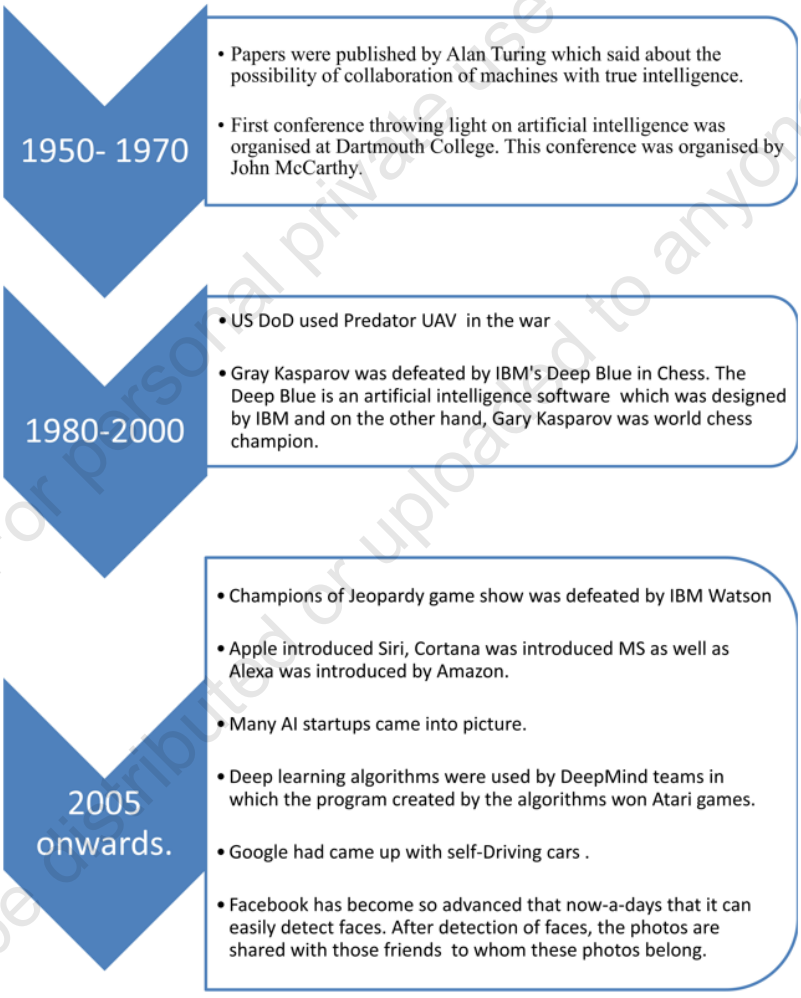

Fig. (2). Evolution of Artificial Intelligence.

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During the era of the mid-1970s and mid-1990s, computers were not properly developed, so various corporations, along with the government agencies, were losing hope in artificial intelligence. This period of acute shortage of funding for carrying out AI research was known as 'AI Winters.'

Again, American corporations gained interest in AI during the late 1990s. This was the time when the Japanese government designed a plan to developfifth-generation computers. These pieces of research further proved that innovative computers can communicate, translate languages, analyse pictures, diagnose diseases, and can also suggest treatments for different diseases. Thegrowth of artificial intelligence is given in Table **1**.

Table 1. Growth of Artificial Intelligence [9].

Years	**Innovations**
Ancient History	Greek mythology had the concept of artificial intelligence from the ancient past. There was an idea of intelligent robots.
5th century B.C.	The first formal reasoning system was deductive and was first invented by Aristotle. The formal reasoning system worked on different backgrounds like logic, physical works, psychological works, natural history, *etc.*
13th century	Invented machines for revealing non-mathematical realities.
15th and 16th century	Clocks were invented, and mechanical creatures were created as a result of that invention.
17th century	Many researchers elaborated the Cartesian mechanism in the 17th century. The mechanical digital calculating machine was created by Pascal for the first time.
18th century	Introduction of first mechanical toys.
19th century	In the 19th century, the renowned scientist George Boole designed a binary algebra that depicted the laws of thoughts.
20th century	
1923	For the first time, the word robot was used in Karel Čapek's play.
1945	The term Robotics was coined by Isaac Asimov.
1950	Alan Turing developed a test for the evaluation of intelligence, which was known as the Turing Test. This test was published as Computing Machinery and Intelligence.
1956	The term Artificial Intelligence was coined by John McCarthy.
1958	LISP programming language was first designed and developed by John McCarthy. This programming language was used for artificial intelligence for the first time.
1964	Danny Bobrow is a computer scientist who proved in his dissertation that computers can understand natural language with the help of which it can solve simple algebra.
1969	Shakey, a robot, was developed at Stanford Research Institute, which was capable of perception, locomotion, and problem solving.
1973	Edinburgh University developed a robot named Freddy, which was a famous Scottish robot.

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(Table 1) cont.....

Years	Innovations
1979	The first computer-controlled vehicle that was autonomous by nature was developed.
1985	Aaron, a drawing program, was first developed by Harold Cohen. Aaron could create original artistic images.
1990	Major advancements in the field of AI took place in machine learning, the natural language of understanding and translation, data mining, *etc.*
1997	The world chess champion, Garry Kasparov, was defeated by Deep Blue Chess, which was a computer program.
2000	Commercialized robotic pets were designed, which can interact with people. MIT presented a robot named Kismet, which can show its emotions through various facial expressions.
2011	Technology has entered our daily life; powerful processors and graphics in smartphones, as well as computers, provide users with the essence of artificial intelligence. Apple's Siri came into the market in the year 2011. Watson is a computer program that competed in a U.S. television quiz show. It appeared as an on-screen symbol and could defeat human players.
2015	Amazon Echo was presented by Amazon, which came with a voice service named 'Alexa'
2016	'DeepMind technologies' launched a huge health project in collaboration with Royal Free London NHS Foundation Trust. This health project assisted acute kidney injuries
2017	Drone-aided Healthcare service
2018+	More structured data into intelligent narratives, more smart phone automation, and much more have been observed in 2018 and will be observed in the future.

IMPORTANCE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence (AI) is a field of smart and advanced science that works and deals with the design as well as algorithms of various analysis. Artificial intelligence generally involves characteristics of borrowing from human intelligence and then implementing them as computer-friendly algorithms. It is a combination and collection of multiple advanced technologies that mimic the cognitive functions of humans [10]. In more specific terms, artificial intelligence deals with computer science, which works with symbolic programming, which is used to solve problems. The use of computers, by any means, is not new, but the collaboration of the human mind and technology has brought about significant changes in the pharmaceutical and medical industry. The most important benefit of artificial intelligence is that it includes not only medical care but also data analysis. Because these computer systems' ability to analyse data is far superior to that of humans, it is also used to automate administrative tasks. Computers can analyze a huge amount of data. Such a huge amount of data normally does not fit in conventional computers as these artificially intelligent computers are used mainly for research purposes. The computer systems can go through tons of data and can extract the essential information out of them.

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Artificial intelligence is that branch of science that has evolved into a game-changer for the medical and pharmaceutical industries. It deals with machines that help in finding solutions to complex problems in a more human-like fashion. Computers are fundamentally well suited to performing mechanical computations using fixed programmed rules. This allows the artificial machines to perform simple monotonous tasks efficiently and reliably, which humans are ill-suited to [8].

As per statistical data, the healthcare market led by artificial intelligence is likely to face a compound growth rate of 40% by 2021 annually. According to the statistical analysis, artificial intelligence holds the potential to improve healthcare outcomes by 30-40%. Moreover, a lot of research is also going on in the present times where computer programs are developed as virtual human bodies that could help analyse how people will react to new therapeutic herbal drugs. This program helps in enabling more chemical combinations so that it can be tested with fewer human trials. It adds an extra layer to the field of health care, allowing for the reduction of errors as well as the development of drugs in a faster, cheaper, and safer manner. The main importance of artificial intelligence is that it promotes as well as facilitates interpretation of outcomes with a high degree of accuracy. There is a lot of advancement of artificial intelligence in the field of pharmaceutical science, which gives a better understanding of technology and newer ways of providing treatment to patients. In the last few decades, the application of artificial intelligence for analyzing generic or biological information has gained a lot of importance. This has accelerated the process of drug discovery as well as drug delivery. The application of automated databases for swift analysis of the huge amount of data as well as Artificial Neural Networks (ANNs) for the development of novel treatment strategies has enhancedthe detection of disease progression, which in turn is predicted to have significant treatment outcomes. In short, artificial intelligence is machine learning that can save lives by detecting chronic diseases, such as Alzheimer's, diabetes, and cancers, such as breast cancer and colon cancer, early. It uses multiple automated tools like natural language processing (NLP), brain-computer interface (BCIs), Biomarkers, *etc.* [11]. Computer-assisted diagnosis, as well as the implementation of expert systems that can assist doctors and physicians, have also brought about a new edge to the healthcare system.

Advantages

Artificial intelligence is a complicated and revolutionized system that uses the complex nature of mathematics and computer science to produce and replicate cognitive human abilities. Artificial intelligence plays a great role in minimizing errors and enhances the chances of accuracy with a high degree of precision.

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Robotics is a part of artificial intelligence that is sure to bring about a revolution in the human race. Robots are nothing but artificial thinkers who can act and behave like humans, but their logical reasoning is not affected by emotions. In other words, we can say that robots are humans, with the brain but without heart. The complete absence of emotions enables the robots to think rationally, unlike humans, whose judgments are clouded by moods most of the time. This is the reason robotic judgments can rule out human efficiency [12].

In the field of medicine and pharmacy, artificial intelligence has improved communication between doctors and patients. It has been used for the assistance of healthcare providers. Medical professionals are trained and assisted by artificial simulators, which can assist doctors and physicians in surgical purposes.Computers and robots can function efficiently in the detection of neurologicaldisorders and also monitor them. They can detect various diseases beforehand likeAlzheimer's disease, cancer like colon cancer, *etc.* Artificial intelligence helps inimproving mental health and also helps in performing radiosurgery with the help of robots. In recent years, researchers at the Bio-Synergy Research Centre inSouth Korea developed CODA (Context-Oriented Directed Associations), which is a software that draws a lot of attention towards biotechnology and artificialintelligence. The main motive of the researchers was to find a therapeuticallypotential compound found in traditional medicine. The combination of extracts was explored to treat blood disorders such as anaemia.

The term fatigue is absent in the dictionary of robots. They can work for long hours without losing their efficacy and without getting distracted or bored. AI allows machine to environment interaction as well as machine to machine interactions. It shows larger valuable insights to huge datasets, which are likely to develop structured data trends in the near future. AI has taken healthcare treatments to a different level where it has helped people in understanding sign language and made it easier for people to roam around in a wheelchair [13].

The advantages of AI are all summarized in the flow diagram given in Fig. (**3**).

In the year 1956, the Dartmouth Summer Research project based on artificial intelligence was one of the most eminent and important events in the field of artificial intelligence. Various systems based on biomedical artificial intelligence became famous during the 1970s. The systems that were developed were CASNET, MYCIN, *etc.*

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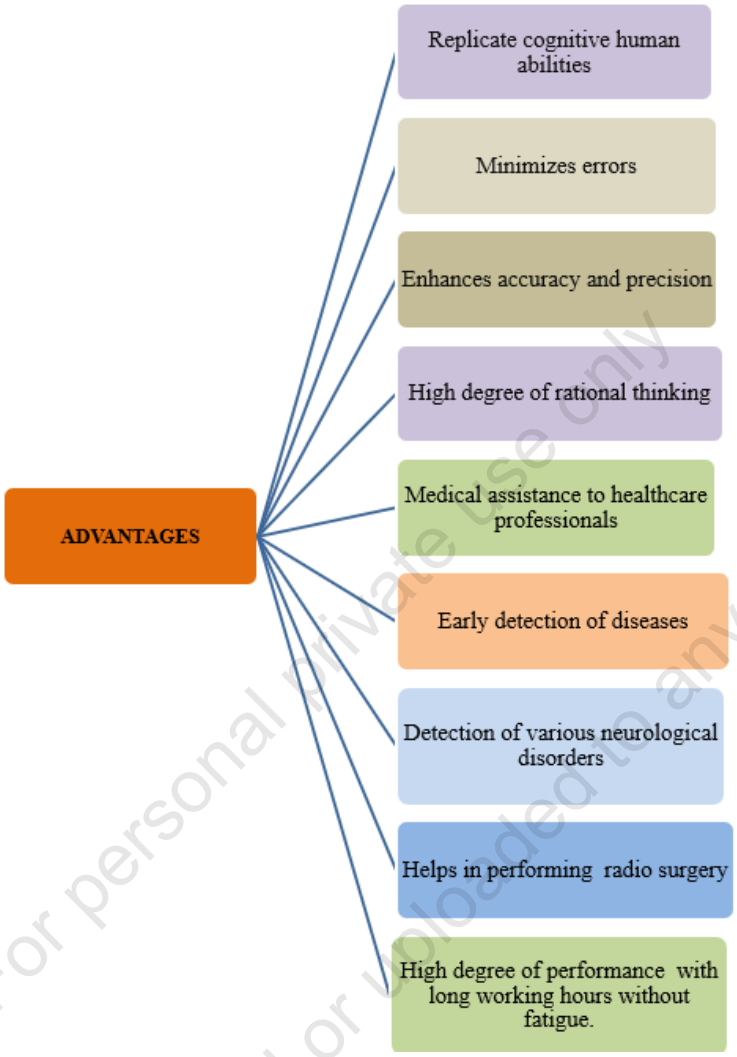

Fig. (3). Advantages of Artificial Intelligence.

RISK AND DISADVANTAGE OF AI

Artificial intelligence is one of the most debatable topics and has always been a topic of controversy. Many scientists believe that artificial intelligence would be the reason behind the destruction of mankind, and people are digging their own graves by developing artificial intelligent robots. Many even assure that artificially intelligent robots would impact the human race shortly if this issue is not taken seriously. The clearly visible disadvantage of AI is unemployment. The employ-

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ment rate has drastically decreased due to the introduction of artificially intelligent machines. The machine would replace humans in the majority of their jobs resulting in mass unemployment. A fully robotic staffed hotel in Japan, Industry 4.0, is one of the few examples that show how AI can result in mass unemployment [14]. According to a report by World Bank, the unemploymentrate of the world was 5.485% in 2017. The unemployment rate in China had increased to 4.7% in 2017 and 3.5% in India. The figures are continuously increasing, and unemployment and crimes go hand in hand [15]. When people are unemployed, they find other unfair means to earn money, and these other means can be a crime, robbery, *etc.* Unemployment would also result in poverty, hunger, and malnourishment and thereby result in an unhealthy society Unemployment can also lead to the emergence of depression and other mental disorders in people.AI would not only lead to unemployment, but according to ford, it would decrease the number of customers also as people will not have money to buy things [16].

Many sci-fi movies have already predicted the future and its disastrous outcome when robots would overcome and empower humans. If robots ever gain control over weapons and learn how to control them, they will be used in wartime and will cause massive destruction to mankind. Imagine terrorists using such kinds of robots to destroy mankind. Such conditions where technology is in the hands of the wrong people would be catastrophic.

Apart from this, we can see the drastic effect in our day-to-day life also. Artificial intelligent assistant like Siri [16] and Alexa is making people less creative, more dependent, and obese. People are so dependent on these machines that they have stopped thinking logically and creatively as they get all the information on their fingers tip. Getting dependent more on robots makes people lazy, and this becomes the root cause of many diseases like obesity, diabetes, *etc.* Moreover, robots and other AI technology lack the human touch, sentiments and are more mechanical. Because of their insensitivity, they may make dumb decisions sometimes, and their decision is sometimes difficult to understand.

Automatic self-driven cars are no more fiction but a reality. These self-driven cars do not need any driver. These cars would stripe off jobs of many trucks and taxi drivers, and a mild malfunction in the software would result in devastating results, which could have otherwise been avoided by manual drivers. In today's world of hackers, they can even hack this software and control the vehicle; therefore, these driverless cars pose a major security issue. The working of such cars in the absence of network, rain, and snow is also a challenging task. These cars can also be dangerous if they are under the control of any terrorist. The terrorist wouldload the explosive, and the car would act as a moving bomb.

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If robots become more superior to humans, it would be destructive for mankind. Humans can be enslaved by more powerful robots, who may regard humans as a waste of space and destroy them. Sophia, the robot, in an interview said that she would destroy humans. By this statement of Sophia, we can sense the future of AI [17].

However, AI would be a boon in many fields if used correctly, but if the policies and rules are not set for the development of artificially intelligent robots, it will result in massive destruction to mankind. AI has posed long-term security and safety risk and hence shouldn't be underestimated. The risk of privacy, accidents, and misuse is associated with it. Many scientists like Stephen Hawking have also warned about the devastating effect of AI [18]. Even Elon Musk, who is considered to be one of the smartest people working on AI in present times, has stated that AI would be the biggest threat to human civilization. All the disadvantages of AI are summarized below in Fig. (**4**).

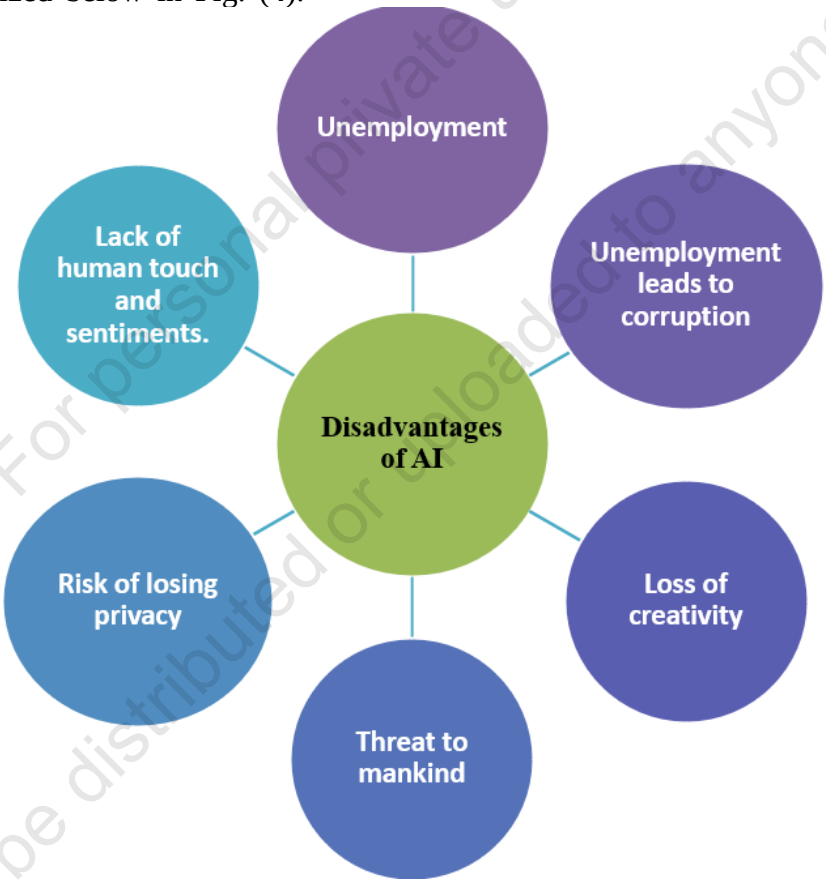

Fig. (4). Disadvantages of AI.

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ROBOTS AND ARTIFICIAL INTELLIGENCE

Defining the term 'Robot' is very difficult. The ultimate creation and collaboration of artificial intelligence and robotics can be established when thereis the recreation of the human thought process through robots. The real challenge of collaborating artificial intelligence with robotics is to decode how naturalintelligence works. Modern society uses robots for a lot of purposes in different fields. For example, the Sophia robot is a humanoid robot; The medical field also uses robots to perform surgery. Robots are used for dispensing medications in pharmacies as well as for security purposes. The usages of various robots are described in Table **2** and Fig. (**5**).

Table 2. Robots used in daily life for various purposes.

Name of robots	Created by	Purpose	Special information (if any)	Disadvantages	type	Reference
Sophia	Hanson robotics	Can talk and predict future investment initiatives. It can solve complex series of predictive algorithms based on computational statistics, rapidly processes information that she receives. Sophia bears a broad ability to recognize faces and voices.	First humanoid robot recognised with citizenship of Saudi Arabia Can give full facial expressions. Appeared in Jimmy Fellon show.	Privacy risks Threat to the human race.	Humanoid robot	[19]
Kuri	Mayfield robotics (Bosch Start-Up Platform)	Kuri is an adorable home robot that can roam around in the house, interact with the members in the house and record special moments. Designed to add spark in a human household	The best feature of Kuri is its vision, as it can capture videos of 5 seconds to keep a record of memorable moments. Can work as childcare nannies.	Mainly for entertainment purposes and childcare. People are losing the essence of the human touch.	Household Robots	[20]

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(Table 2) cont.....

Name of robots	Created by	Purpose	Special information (if any)	Disadvantages	type	Reference
Robotic Dog Aibo	Sony	The main purpose of this robot is to provide security to the house by patrolling around and also recording in its camera if something suspicious is observed.	It also forms an emotional bond with the family members. It can express its emotions. Can be used for security purposes to some extent.	Not so effective for security purposes.	Household robots	[21]
daVinci	Intuitive surgical	daVinci is an operating robot that has a telemanipulation system. This robotic system can assist surgeons in surgery.	It contains three parts which include a surgical arm cart, a conventional monitor cart, and a master cart. It can perform operations with tiny incisions that too with high precision, quicker healing, and diminished risk of infection. Mainly used for prostate, bladder and gynaecological surgeries.	High cost The lack of its touch sensation can only be partly compensated by the 3D view. It is a rigid system.	Medical robot	[22]
Versius robot	CMR surgical	Mainly used to perform surgery	Independent modular arm that can be used by the surgeon to perform surgery. Comparatively smaller in size than daVinci	Highly expensive Lacks touch sensation	Medical robot	[23]

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(Table 2) cont.....

Name of robots	Created by	Purpose	Special information (if any)	Disadvantages	type	Reference
Actuated and sensory prosthesis	MIT Biomechatronics lab	It is a robotic limb that is gyroscopically designed for the replacement of a limb.	It can manage its position in the 3D space automatically. It can adjust joints 750 times per second. It has bionic skins that can interact with the nervous system somewhat in a similar fashion as that of a normal limb.	There can be chances of failure.	Medical robot	[24]
UV-Disinfection Robot IPT 3200	Infection Prevention Technologies (iPT) is a top industry that leads the market for the manufacture of microbial desensitizing agents.	Designed to reduce healthcare-related infections. It determines the optimum level of UV rays that can provide the maximum and best disinfection so that everything in its proximity can be disinfected. It is comparatively less harmful to humans.	A study report shows that there is a 34% decrease in healthcare-related infections within 6 months.	Cannot sanitize the areas behind it.	Sanitation and disinfection robot	[25]
Robo-pigeon	Developed at Northwestern Polytechnical University	It is mainly a spy-bird programme that adds an extra feather to the surveillance network of China.	It contains GPS systems and a high-definition camera that can capture videos. It also has a flight control system. Indistinguishable from real birds.	It can reach up to a speed of 25 miles per hour, but only for 30 minutes.	Robots are used for security purposes.	[26]
Automated systems for dispensing	UCSF medical centre	Mainly prepared for dispensing of medications.	Also used for inventory management.	Increases unemployment	Robots in pharmacy	[27]

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(Table 2) cont.....

Name of robots	Created by	Purpose	Special information (if any)	Disadvantages	type	Reference
Rescue robots	SRSOES, Funded by Italian MIUR	Mainly used for predicting large-scale disasters.	The main design of the robots is to identify victims of disaster-prone unknown environments. The robots autonomously explore the environment, design a map and locate the victim on the map.	Very expensive.	Rescue robots	[28]
Drone-aided Healthcare service for patients	An associate professor, Murray Cote from the Department of Health Policy and Management at the Texas A&M School of Public Health	To provide drone-aided healthcare services to all the retired persons and to all those living in a rural area who cannot access healthcare services whenever they want.	It ensures that the people from the rural area do not remain devoid of medication due to a lack of transportation. It provides and delivers medicines to people above the age of 50 to their houses.	Rural residents often hesitate to invest in this type of project.	Healthcare providing robots in the form of a drone.	[29]
Mona, a prototype of 12 charging cells and a mobile robot.	UoM Robotic Lab.	Low cost flying wireless charging system, which was designed to study a perpetual robotic swarm.	Used for educational purposes. Significantly large battery capacity.	Co-ordination between the two robots for long term-interaction is difficult.	Electronic Swarm robot.	[30]

POLICY OF AI

AI policies are defined as public policies that maximize the benefits of AI while minimizing its potential costs and risks.

Government has two main objectives towards AI policy; the first is to invest more in AI to reap more benefits for the society and improve the country's economy and thereby GDP. Government can invest in fundamental and applied research, digital infrastructure, latest technology, and programs to motivate the private and public sector to move towards AI development; secondly, the government has to pay attention to economic and societal challenges which may arise due to the advancement in AI.

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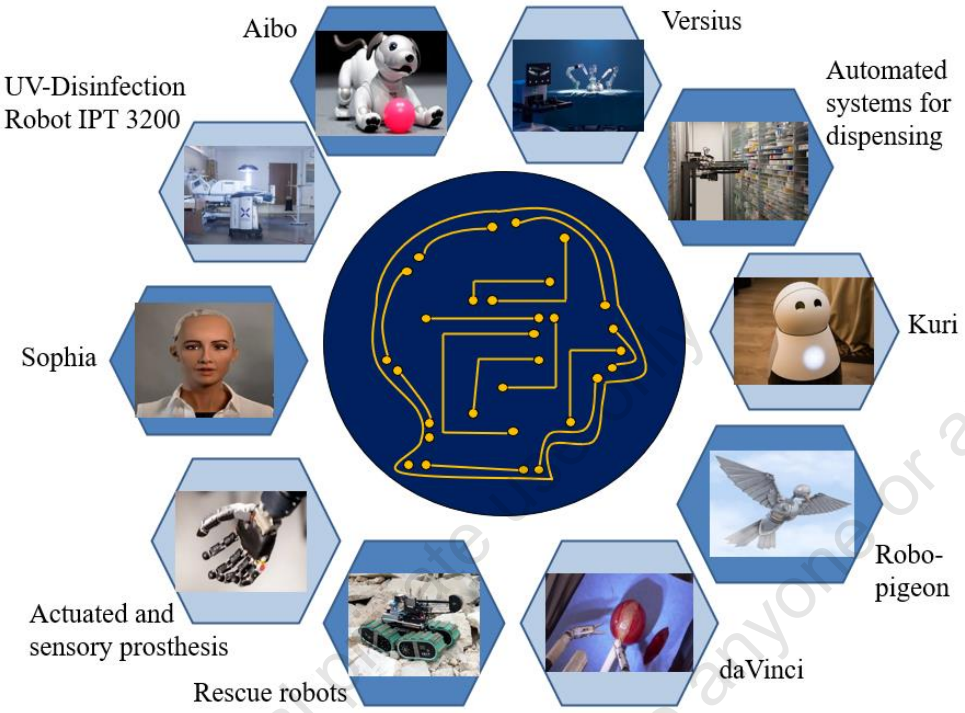

Fig. (5). Robots in daily life.

Recently national strategies have been released to promote the use and development of AI in a few countries like Denmark, France, the UK, the EU,South Korea, and India. Few countries like Canada, Japan, Singapore, China, theUAE, and Finland had also released similar strategies in the year 2017. Thesudden interest in developing the policies for AI is because of the immense useand high possibility of its potential misuse in various fields. Therefore, to get mostof the AI technologies with minimum misuse, AI policies were laid.

AI is a highly growing field, and many scientists are working on intelligent robots that can perform similar to humans. A large amount of money has been invested in these AI start-ups. Government should also encourage people to use AI. There are only 22000 Ph.D.-educated AI researchers in the world, out of which 40% are concentrated in the US. Therefore, the government should encourage more training in the industry by providing short-term training, projects, online courses, and scholarships. Almost all the national strategies include such combinations and promote AI.

In April 2018, the British government announced many initiatives that would help the UK to establish itself as a leader in AI revolutions. The measures taken by the

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British government involved new R&D tax credit, a national retraining scheme, additional funding for STEM education, a national centre for data ethics, and improvements to public digital infrastructure. Apart from the UK, many other countries like France have taken initiatives to promote AI. France's government-funded many AI start-ups and industrial projects to promote AI. The Chinese government also recently announced a $2 billion AI research park to house up to 400 companies. Apart from this, the government is also working on how to overcome the drawbacks of AI. AI has grown so tremendously, and hence in the past 18-24 months, AI strategies have been laid by many countries. France published the AI strategy in January 2017, followed by a detailed policy document in March 2018; Japan released a document in March 2017; Chinapublished the AI strategy in July 2017, and the U.K. released its industrial strategy in November 2017.

AI policy depends on a country's national strengths and weaknesses; therefore, different countries have different AI policies. Despite the different objectives of the country based on AI, AI policies can be split into 10 basic categories. These categories include basic and applied research (this include funding for basic and research by the government to promote more projects under AI), talent attraction, development and retainment (training and promoting the skilled AI talents), future work and skills (to overcome the disadvantage of AI such as unemployment, workers should be made more skilful to compete with digital economy; government should also make investments in STEM education, lifelong learning, national retraining program); industrialization of AI technology (developing AI ecosystems and clusters), AI in the government (encourage uptake of AI in the government), data and digital infrastructure (data is the most important part in AI, therefore governments are developing many platforms for safe and easy exchange of data), ethics (government is developing code of ethics and standards to avoid misuse of AI), regulations (regulations laid for AI, *e.g.*, regulations for autonomous cars and autonomous weapons), inclusion (national strategy to use AIwisely and not to destroy mankind), foreign policy (to develop global standard) [31].

AI Policy of India

In the budget speech for 2018-19, the honourable finance minister mandated NITI Aayog to establish a national program on AI with the main objective to guide the R&D in new and advanced technologies. NITI Aayog has mainly adopted three approaches, which include undertaking exploratory proof-of-concept AI projects in various areas, crafting a national strategy for building a vibrant AI ecosystem in India, and collaborating with various experts and stakeholders. NITI Aayog has also partnered with several expert AI technology players to execute AI, especially in the

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field of agriculture and health. The brand name for their project is #AIforAll. AI for all mainly focuses on empowering and improving human capabilities to address the challenges like affordability, shortage, inconsistency of skilled expertise, and other global challenges. It also focuses on partnership,collaborations, and aspiring young budding scientists towards AI. The government of India has a huge role to play to lay the roadmap for AI. NITIAayog focuses mainly on healthcare (increased access to affordable medicines), agriculture (increase productivity and reduced waste), education (access to quality education), smart cities and infrastructure, smart mobility, and transport (improved and safe mode of transport). The Centre of Research Excellence, abbreviated as CORE, and the International Centres of Transformational AI,abbreviated as ICTAI, are two tired structures that address India's AI research aspiration. CORE focuses on improving knowledge of core research and encouraging innovation and creativity, whereas ICTAI focuses on deploying application-based research and private-sector cooperation. NITI Aayog has its main focus in the healthcare field, and hence it is working along with Microsoft and Forus Health to bring out technology in patient treatment, *e.g.*, for the early detection of diabetic retinopathy as the main project. Under this project, Forus Health came up with a portable device named 3Nethra, which could scan common eye problems. AI capabilities were integrated into this device using Microsoft's retinal imaging APIs, which allowed the operator of 3Nethra to get AI-powered insights even in the cases when eye check-up camps were in remote areas with nil or intermittent connectivity to the cloud. The resultant technology solution had also solved the quality issues of the captured image and evaluated the usability of the captured image.

Therefore as a gist, India is a budding country with high potential. India isfocusing on the IT sector and has accepted the high potential of AI and has hence laid down national strategies for AI. The government is supporting and funding many start-ups and playing a critical role as a catalyst in supporting partnerships, providing access to infrastructure, *etc.*, and also the government has focused onthe ethics and safe use of AI [32].

Fairness, Ethics, and Human Rights

The field of AI is growing exponentially, and with the exponential growth of AI, there is increased concern on ethics, fairness, and algorithm biases. These challenges are mainly related to access and inclusion.

There are many principles that are laid down for the ethical use of AI. These principles include the following points:

Core public agencies like the one responsible for criminal justice, education,

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healthcare, and welfare should no longer use "black box" Ai and algorithm systems. This system includes the use of robots without validation or review. The use of such robots which aren't validated raises concerns. Therefore, these robots should undergo auditing, testing, reviewing, and be subjected to accountability standards before releasing it for public use.

The standards should be periodically reviewed and should be transparent. Moreover, the role of the robot should be clear, and its responsibility should be shared between the organization deploying the robot and the organization manufacturing the robot. There should be transparency, the company should be accountable for their product, and the product should in no way harm the human race.

Encouraging AI Research

This is mainly achieved by collaboration between the government and large companies, which promote accessibility and encourage innovation due to increased investment in R&D. For example, the Government of Karnataka had collaborated with NASSCOM to set up a Centre of Excellence for Data Science and Artificial Intelligence (CoE-DS&AI) based on a public-private partnership model. This collaboration aims to accelerate the ecosystem in Karnataka by providing the impetus for the development of data science and artificial intelligence across the country.

Other Laws which Directly or Indirectly Influence AI

Data Protection Act

India is a data-rich country, and the lack of a robust privacy regime means both the public and commercial sectors have easier access to large data than in other countries with stringent privacy regulations. India also lacks the formal regulatory regimen for anonymization. India needs to enact strong privacy legislation to address the emerging AI challenges. This privacy legislation should also address questions like the use of publicly available data for training algorithms, how privacy legislation can be applied to autonomous decision making, and howtraditional data categories need to be revisited in light of AI.

A data protection bill for India was written by the Srikrishna committee in August 2018. This bill, though, does not state the key responsibility of the data controller. These bills need a lot of amendments for addressing the data protection for AI; moreover, the dilemma between AI and the need for access to larger quantities of data for multiple purposes and privacy should be emphasized.

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Consumer Protection Law

The consumer protection law was passed in 2015, and this law elaborately describes unfair trade practices. This law prevents the disclosure of other people's personal information unless it is required by law. The consumer's personal information should be safeguarded. Moreover, no technologies would be supported that harm the human race and cause destruction. The same applies to AIalso [33].

TOOLS OF ARTIFICIAL INTELLIGENCE

Artificial intelligence uses a large number of tools that have gained huge popularity in the field of pharmacy. The tools of artificial intelligence use high- impact software and technologies that can meet the current needs of the pharmaceutical industry. Some tools shown in Fig. (**6**) below have become famous in the pharmaceutical sector [34].

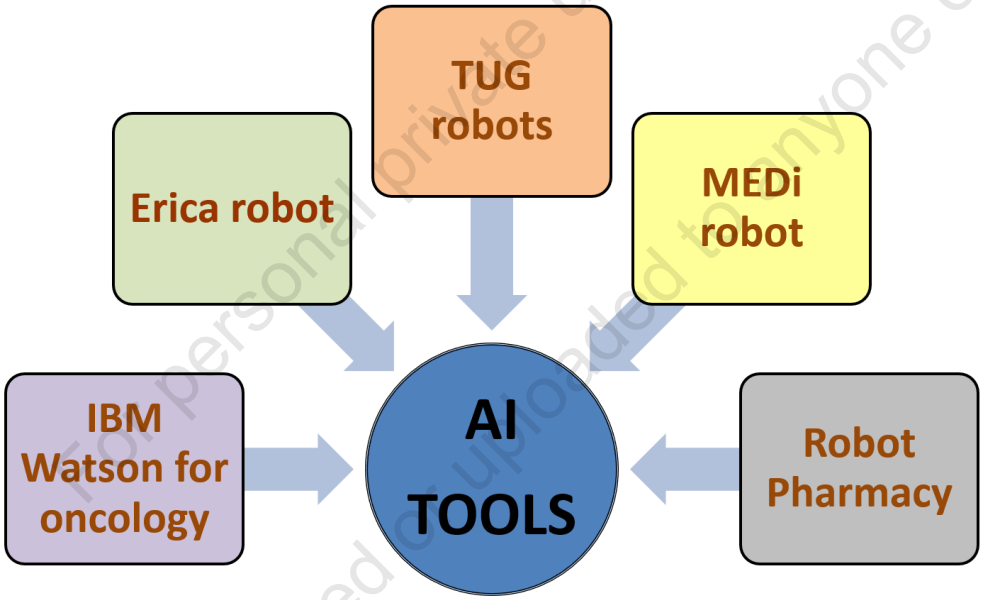

Fig. (6). Tools of Artificial Intelligence.

IBM Watson for Oncology

Watson is a supercomputer that was designed by IBM. This supercomputer was designed in collaboration with sophisticated analytical tools as well as various software of artificial intelligence, which is capable enough to assist oncologists. Watson helps oncologists to make better decisions regarding the treatment of cancer. It screens and analyses the medical data of the patients from a wide

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network. The data analysed includes a past history of the patients, clinical reports, *etc*. From all these data, Watson enlists all the critical information about the patients in simple English language, which assists as well as enables the oncologists to make a perfect decision regarding those patients who are suffering from cancer [42].

In a recent case study, it was found that a 37 years old lady was suffering from breast cancer which was spreading in both her breasts rapidly. The condition was so worse that there was a need to remove both breasts. Every detail about the patient was fed in Watson by Dr. Somashekhar, and it gave viable options for treatment within just 60 seconds.

Erica Robot

Erica is considered to be the most beautiful and intelligent android, which has been developed by a Japanese scientist as well as a professor from Osaka University named Hiroshi Ishiguro. Erica, being a robot, can speak Japanese and also bears attractive human-like facial expressions with an ability to answer questions. Erica is a unique robot that was designed with Asian facial features, and it also has the desire to chat with a partner.

TUG Robots

TUG robots were mainly designed for the carrying and delivery of loads. These robots autonomously travel in hospitals to carry, load, and unload medications, meals, specimens, *etc*. The TUG robots have two types of configuration. One is a fixed cart, and another is an exchange base platform. The fixed cart is used for the transport of various medications, sensitive items, specimens used in the laboratory, *etc*. On the other hand, the exchange base platform is mainly used for loading and unloading materials in several types of racks, carts, *etc*. The touch screen for the users in the robots is very simple, and they can be easily operated for inputting data and orders so that the TUG robots can work accordingly for the delivery and pickup of the materials.

Robot Pharmacy

UCSF Medical Centre has designed robotic technology to prepare, deliver as well as track the medications. As per their report, the data has been quite satisfactory, which says that about 350,000 medication doses were accurately prepared. The robotic technology can prepare oral and injectable medicines. Computers first get orders of medications from the pharmacists and the physicians by an automated system. After that, the accurate doses of the pills are selected, packed, and dispensed. This is followed by machines that assemble the doses onto a bar-coded

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plastic ring. In that bar-coded plastic ring, all the medicines are incorporated that have to be taken within 12 hours. The machines can also prepare sterile preparations for chemotherapy. The automated system has the facility of controlling inventory management as well.

MEDi Robot

MEDi means a Medicine and Engineering Designing Intelligence. It is a pain management robot that was developed by a professor at the University of Calgary, Alberta. Professor Tanya Beran made this robot so that it can decide the medical procedure which will be done on the children so that they do not scream. The robot was developed for pain management, but with time, its uses increased. In present times, this robot is used to establish comport in the patient during the procedures.

Magnetoelectric Nanorobots

Magnetoelectric nanorobots are efficient nanodevices for successful drug delivery. The movement of these nanorobots is controlled by a magnetic field, and the release of their cargos is controlled and target-specific. In case of increased drug loading, pretreatment of nanowires with polydopamine is done to adsorb the drug on the surface of the nanorobot. Magnetic resonance imaging (MRI)-baseddrug delivery systems with MRI propulsion and tracking modules, controller, anddrug-loaded nanocapsules increase the efficiency and decrease the side effects ofthe drug. Nanorobots combined with MRI enables real-time monitoring of nanocapsules with the help of an active targeting mechanism. It uses goldnanoparticles, metallic nanoshells, quantum dots as its carrier modules. Application of the appropriate algorithms to control these nanocarriers against theenvironmental perturbations and providing a 3D navigation path for enhancedtargeting accuracy are required [35 - 37].

DNA Nanorobots

DNA nanorobots show their use in drug delivery, biosensing, triggering apoptosis, *etc.* These are activated by external nucleic acids, which interact with the complementary counterparts on nanorobots. ANNs help in optimizing the performance of nanorobots conjugated with biosensors and transducers, with the ability to detect tumor cells with targeted drug delivery. This is very much significant in cancer therapy and reduces adverse drug reactions. Thesenanorobots are also able to detect β-catenin and E-cadherin, which help in target identification and localized therapeutic delivery [38 - 40].

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DRUG DISCOVERY AND DRUG DESIGN

In science fiction stories from the 1950s, machines that could reason and think like humans were common. Moreover, machines which could discover and develop drugs were almost unimaginable. However, in 2019, we can concludethat artificial intelligence has brought about a massive transformation in the pharmacy at a time when many pharmaceutical sectors are experiencing a decline in production. The production and the productivity rate of the pharmaceutical industry are on the verge of decline. There is almost a 90% failure rate after modelorganisms are used for testing therapies in clinical trials. On the other hand, drug discovery and drug development have always been very complicated as well as challenging processes. Also, for the development of new drugs, the cost exceeds almost 2.6 billion dollars. But still, despite all these inconveniences, there has always been a need to explore new drugs and address their success in the treatment of various diseases at a cheaper and faster rate. All these problems are somewhat reversed by the recent advancements in the field of artificial intelligence. In the year 2017, many pharmaceutical companies came in partnership with artificial intelligence start-ups. The pharmaceutical companies have started their internal R&D programs as well.

A recent example of the collaboration of artificial intelligence with drug discovery has been taken up by a renowned company named GSK. A new and completely fresh drug discovery unit was set up by GSK in the year 2017 to check whether machine learning in collaboration with artificial intelligence can hasten as well as facilitate drug discovery or not. GSK aims to check whether the integration of artificial intelligence and machine learning with the biological hypothesis is as effective as human pharmacological analysis or not [41].

QSAR Studies

One of the key primary steps of drug discovery is assay. It is the initial step of drug discovery where the computational or biological experiment is performed to determine a small compound that is capable enough to treat the diseases. After carrying out the assay, the very next step of drug discovery is drug screening. In the drug screening process, a large number of compounds are tested against the assay to find the best-fitted compound. Then finally, mathematical equations are used for the final screening. However, the chances of declaring a chemical compound as a successful drug are very low. Therefore, designing and performing experiments according to traditional methods are very costly, and this is thereason that many new methods have been formulated. Quantitative structure- activity relationship (QSAR) studies are mathematical models that attempt toderive structure-related features of a compound that can elaborate both biological as well as physico-

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chemical properties of the chemical entity. The predictors used in QSAR studies give a brief idea about the relationship between the biological activities and chemical structures of the moiety. Therefore, in totality, QSAR studies help predict new molecules by mathematical expressions, which, when validated carefully, can predict the response of chemical structures. These studies can be disease-specific as well, such as for anti-cancer activity [42].

Eve- the Scientist Robot

The drug development process came about with revolution when the robot scientist Eve was artificially designed. Eve was efficient enough to increase the economy and shorten the development time of the drug development process. Eve, which was developed specifically for the drug development process, was highly intelligent and efficient in the cheaper and faster mode of drug discovery. The robot starts its drug discovery process by screening the randomly chosen subset of compounds that are preferred to be used for the experiments. It performsvarious statistical as well as mathematical models to investigate QSAR studies fornew compounds. The hardware of the robotic system is so powerful that it can screen about 10000 compounds or even more per day. Eve's robotic system is a comprehensive and advanced system that can carry out screening of drug library, hit confirmation as well as cycles of QSAR hypothesis testing with selected compounds. As per Cambridge University, the robot scientist is capable of screening potential drugs almost independently. The university also claims that Eve has reduced the time of drug discovery and development to a large extent. This had been proved to be a very successful approach in the path of discovering as well as developing anti-cancer drugs, which also have anti-malarial activity [43].

In Silico Medicines

Insilico medicine first launched its AI project in which the company claims to use solutions of neural networks. The company in this project claims to generate deep neural networks and then sell those with its solutions to different biotechnological and pharmaceutical companies. The main aim of this company is to apply a generative adversarial network (GAN) and reinforce learning new algorithms to generate new molecular structures that can identify the biological root or the actual origin of a particular disease. GAN is a branch of AI that deals with two sub-branches, *i.e.*,a generator and a discriminator. The generator produces real- looking images, and on the other hand, the discriminator attempts to recognize which one is real and which one is not. This reasoning between the generator and the discriminator improves the accuracy of the system. They also deal with the idea of developing new ideas of drug design and discovery, biomarkers, computer simul-

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ations, *etc.* The company has also collaborated with GSK to improve the drug discovery process [44].

Artificial Intelligence Related Start-ups

Benevolent Bio is a London-based AI start-up. The main function of this start-up is that it incorporates data from various sources like patients records, reports of clinical trials, research papers as well as patents. From all these data and records, the start-up works on forming relationships between biological entities like genes, proteins, diseases, and the drug candidate. This relation summarized from all the collected data was used to plot knowledge graphs for analyzing the correlation between various parameters, like a medical condition and the genes affecting it, a physiological response in the body, and the protein responsible for it [45].

APPLICATION OF AI IN HEALTHCARE AND PHARMACY

AI has been a highly discussed topic in the past few years. It has varied use and applications in different fields. At present, no field appears to be completely devoid of artificial intelligence, and health care and medicine are no exception. AIcan streamline the workflow give a more specific result with the least errors, making this technology highly useful in the field of healthcare.

Customised Treatment

With the emergence of AI, healthcare providers are now able to prescribe customised medicine to patients based on their genetic makeup. There are different AI software that is used for customised treatment. GNS healthcare work on reverse engineering and forward simulation (REFS) and help in prescribing personalised medicine to the patients. Reverse engineering and forward simulation (REFS) uncover the elements and find the combination of such elements which would affect the drug's response in a particular patient. Anothersoftware, SkinVision, allows users to assess the fatal disease online. This app is clinically proven and is also CE certified, and can detect more than 1000 skin lesions [46].

CLINICAL TRIAL RESEARCH

Testing a new drug has always been a cumbersome process, and the process has been slow and expensive. Automation in certain stages of clinical trials has solved such problems. Clinical trials are the most expensive affair, and there is a high amount of risk involved, and failure in clinical trials can result in the loss of a large amount of capital. AI has a high potential to change every stage of clinical trials ranging from finding a trial to adherence to medication.

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AI software can be used to recruit patients for clinical trials. This software can match the health records of patients and determine whether they can participate in the clinical trial studies or not. AI software helps in matching the correct patient for the correct clinical trials. This software extract information of the patient from his/her medical records and compare it with the ongoing trials, and suggests matching studies. An example of software that recruits patients for studies is Antidote's Connect Network, Deep6AI.

Secondly, AI can also be utilised in collecting data at a patient's comfort. Software like Research Kit makes it easy for a patient to sign up and participate inthe clinical trial using iPhone. The patients no longer have to go to hospitals to fillout the questionnaire. Instead, he/she can perform activities using the advanced sensor in iPhone and generate accurate data, and the data can be sent directly tothe company performing clinical trials.

Thirdly, AI can also be used in managing the clinical trial workflow and optimizing the clinical trials. AI is a cloud-based study optimiser platform and helps researchers manage the clinical trial workflow. In this AI-based software,the user uploads their research protocol in pdf or word format, and the software identifies the risk factor and potential barriers. The software also helps in storing large amounts of data in one place. Moreover, AI can also be used to increase adherence to the medication by the patients.

In the near future, AI would be used extensively for smarter decision-making in clinical trials. AI could detect patterns observed in patients, manage a largeamount of data and thereby accelerate the drug discovery process. AI can be used to tackle and evaluate large amounts of data and images and devise hypotheses beyond human ability. Therefore, these tools can be used to determine in which condition the drug would be more likely to succeed [42].

DATA MANAGEMENT

Artificial intelligence has also been used in tackling the enormous amount of data and organising the data properly for quick and easy referral. It also increases the transparency of the workers. CloudMedX is used to combine evidence-based algorithms and manage big data of clinical studies. So, in a nutshell, AI can help in collecting, organizing, and better analyzing the data from a different database. AI helps in storing data digitally and increases the ease of transferability. The use of ML handwriting recognition technology can help speed up the transferring of data onto systems.

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Cancer Diagnosis

Approximately 12 million Americans are misdiagnosed annually. AI helps in solving this problem. AI-powered diagnostic systems are built with an algorithm that can feed in a large number of patients' data, recognise patterns, and spot relationships to ultimately arrive at a clinical decision. AI offers the advantage of obtaining data that is unbiased, more accurate, efficient, and accurate. Even nowadays, technology like IBM's Watson is learning to recognise patterns in imaging and text in electronic records to predict diseases like cancer, *etc.*, more accurately. IBM Watson Health and IBM Watson genomics partnered in October 2016 and came up with integrated cognitive computing and genomic tumour sequencing and precision medicines. This thereby helps in decreasing the number of mistreatments, thereby making patient treatment more accurate and streamlined [34].

Epidemic Outbreak Prediction

Predicting the outbreak of an epidemic is very important for good health maintenance. AI can be used to predict such epidemic outbreaks by collecting data from various sources like satellites and other parameters, which affect the outbreak of the disease. For example- to predict the outbreak of malaria, artificial neural networks can be used to predict the outbreak of malaria and consider parameters like rainfall, temperature, positive case number, history, *etc.* ProMed-mail is one such software that helps in monitoring the epidemic outbreak of diseases.

Accessible Healthcare

The latest advancement in AI in healthcare is home health using AI. A recent start-up named Your.MD has used AI to bring physicians to patients' homes. This program has also had an advanced medical data model, which links the probability between a patient's symptom and his condition. This software uses machine-learning algorithms and NLP (Natural Language Processing) to directly communicate with the patient and give them accurate health advice based on the disease encountered. There is a also software that uses AI to track the sleep, motion, heartbeat, pulse rate, *etc.*, of the user, and this software has been linked with smartphones/smart watches, making it more accessible and feasible to the user [42].

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The Future Aspect of AI

Robotic Scientists

AI has shown immense scope in the science field. After the Eve robot discovered that an ingredient commonly found in toothpaste can cure malaria, it became a hot topic of discussion. In the future, we could expect more robots to do research and come up with new inventions. Robots would soon invade the drug discovery process completely and make work more efficient [43].

Automated Transport

Self-driving cars are definitely the future of artificial intelligence in transportation. However, the first self-driving automobiles have already been observed. This concept came when RCA labs in 1953 had built a miniature carthat could only show automated locomotion on the laboratory floors. Although the technology needs some improvement, driverless cars will soon hit the market in the next few years. Google had already started to work on self-driven cars in 2012 and it is currently one level down from full automation [44].

Taking over Dangerous Jobs

In the coming few years, robots will be overtaking dangerous jobs and avoiding disasters. These hazardous jobs may include bomb defusing, chemical industry, *etc.* This will help save the lives of many humans and avoid mishaps. Many jobs, such as welding and moving heavy objects, will be taken over by robots in thenear future.

Robotic Friend

Robotic friends who can speak and understand the emotions of a person are no more sci-fi, and in the future, many such robots will be marketed. Till now, the majority of the robots are emotionless, but sooner robots with emotions will be developed. One such example in such direction is a robot named “Pepper” made by a Japanese company. This robot has been programmed to understand human emotion and has its own set of expressions, allowing it to act as a human friend and alleviate stress and loneliness [45].

Robots as Caretakers

Robots could even replace the jobs of caretakers in the near future. Robots could act as a nanny or caretakers for elders. Many scientists are working on such robots where AI can be utilised to help seniors with everyday work and make senior citizens less dependent on other humans. Robots can also take care of children.

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Robots as a Pet

These robots are already in the market, and sooner with a few advancements, the product will conquer the market. The robotic pet is an artificial intelligent- oriented pet. These robots act in the same way as a pet will. These dogs will also replicate a patient's love and absence of loneliness [21].

Robot-assisted Surgery

We already have robots that assist in surgeries, such as the Da Vinci robot, but this robot's disadvantage is that it lacks touch sensation. Therefore, future robots will have tactile sensations, be flexible, and cost-effective. In a nutshell, the future of robot-assisted surgery is wide and exciting, with enormous possibilities for enhancing health care, increasing efficiency, and so on. Google and Johnson & Johnson have partnered together to develop a next-generation robotic surgeon that would be available in 2020 [45].

Artificial Intelligence on Herbal Medicine

Though artificial intelligence is still not being applied hugely in the field of herbal medicine, certain studies are performed which show the successful impact of artificial intelligence on herbal drug delivery. The importance of Traditional Chinese Medicine (TCM) is growing day by day throughout the world due to its effective clinical treatment. But, the problem of depending on empirical values while selecting cluster centres with the help of traditional clustering algorithms persists in this method. This problem is overcome by proposing an artificial bee colony algorithm by which cluster centres can be selected automatically and applied to aggregate Chinese Herbal Medicines. This includes a new neighbour nectar finding technique and then using this algorithm to optimise the different parameters. The study results showed that this algorithm was far more effective than the other approaches in showing good clustering quality with accuracy on UCI and TCM datasets [46].

Artificial neural network modelling was utilized for the optimization of multicomponent herbal medicines. The conventional method for the identification of toxic chemicals in multicomponent herbal medicines was based on single-component separation, which was time-consuming and inefficient in detecting the interaction between the components. Thus, it led to the search for an alternative routine, *i.e.*, artificial neural network modelling, which could detect the components more appropriately. The most popularly used artificial neuralnetwork is the BP neural network, which consists of the input layer, hidden layer, and output layer. Its applications are mainly functional approximation, patternrecognition, and data compression. In the above study, this method was first ever applied to detect

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and optimize the components of sodium fascinate injection(SAI). The neural network toolbox of MATLAB 2016 software was utilized inthis case. The study results obtained were seen to be consistent with those in the literature, which provided a preliminary judgment for product optimization. A prediction model was constructed with the help of the BP neural network, and the expected proportion of each component was set based on "gray correlation"analysis (GCA). The best proportion of each SAI component was found to be A: B: C: D: E: F=0.7526: 0.5005: 5.4565: 1.4149: 0.8113: 1.0642. In conclusion, the study provided a reliable, scientific, and efficient approach for the optimization of the components of multicomponent drugs, which might have a good prospect of popularization and application in the development of herbal medicines [47].

An ontology-based model for AI-assisted medicine side-effect (SE) prediction was developed. Three major components, the drug model, the treatment model, and the AI-assisted prediction model, of the proposed model, were presented. For validating the proposed model, an ANN structure was established, which was trained by 242 TCM prescriptions. These data were gathered from ancient TCM book and SE reports, in which two ontology-based attributions, hot and cold, were introduced to evaluate if the prescription will cause SE or not. The results revealed the relationship between the ontology-based attributions and the corresponding predicted indicator, which was learned by AI for predicting SE, which proved that the proposed model had potential in AI-assisted SE prediction. However, due to its dependence on sufficient clinic data, much deeper exploration is required for enhancing the accuracy of the prediction [48].

Drug repositioning, which is also called drug repurposing, is being used as an alternative to drug development. In recent times, large volumes of information related to drugs and diseases have led to the development of various computational approaches for drug repositioning. Though herbal medicines have agreat impact on current drug discovery, still a large number of herbal compounds are present with no definite indications. Here, the authors fabricated acomputational model to detect the unknown pharmacological effects of herbal compounds with the help of machine learning techniques. Depending on theassumption that similar diseases can be treated by similar drugs, they made use of four categories of drug-drug similarities, such as gene ontology, chemical structure, side-effects, and targets) and three categories of disease-disease similarities, such as gene ontology, phenotypes, and human phenotype ontology. Then, the associations between drugs and disease were predicted with the use of employed similarity features. The prediction models were constructed using classification algorithms, such as logistic regression, random forest, and support vector machine algorithms. By

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cross-validation, the random forest approach showed the best performance (AUC = 0.948), which also had the best performance in an external validation assessment using an unseen independent dataset (AUC = 0.828). Then, the constructed model was applied to depict the potential indications for existing drugs and herbal compounds. Therefore, new indications for 20 existing drugs and 31 herbal compounds were depicted and validated using clinical trial data. In conclusion, herbal compounds were considered to be drug candidates for related diseases, which was important to be further developed [49].

Table 2. Artificial Intelligence in Herbal Medicine.

Technology	Objective	Conclusion	Reference
Artificial bee colony algorithm	Proposing an artificial bee colony algorithm by which cluster centres can be selected automatically and applied to aggregate Chinese Herbal Medicines.	This algorithm was far more effective than the other approaches in showing good clustering quality with accuracy on UCI and TCM datasets as well.	[46]
Artificial neural network modelling	This modelling was utilized for the optimization of multicomponent herbal medicines.	The study provided a reliable, scientific, and efficient approach for the optimization of the components of multicomponent drugs, which might have a good prospect of popularization and application in the development of herbal medicines.	[47]
An ontology-based model for AI-assisted medicine side-effect (SE) prediction	An ontology-based model for AI-assisted medicine side-effect (SE) prediction was developed.	The relationship between the ontology-based attributions and the corresponding predicted indicator, which was learned by AI for predicting SE, proving that the proposed model had potential in AI-assisted SE prediction.	[48]
A computational model for drug repositioning	The authors fabricated a computational model to detect the unknown pharmacological effects of herbal compounds with the help of machine learning techniques.	Herbal compounds were considered to be drug candidates for related diseases, which is important to be further developed.	[49]

Artificial intelligence is a highly debatable topic; few scientists have an optimistic approach, whereas others have a pessimistic approach towards AI. Technology is moving at a breakneck speed, and it has affected our lives in many ways. In another few years, AI would be a reality. The future of AI is hazy, but surely it is going to impact every aspect of our life.

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CONCLUSION

The chapter highlights the substantial growth of automation and the incorporation of artificial intelligence in our day-to-day life. The growing health care sector is showing a futuristic perspective of introducing robots in day-to-day operations. Robotics and artificial intelligence are rapidly replacing the jobs of human professionals. Not only the health care sector, but the government sectors have also started collaborating with different industries to incorporate AI into theirdaily activities. The main motivation of this book chapter is to provide vivid information about how artificial intelligence is overpowering manually operated activities in every important sector of our lives, including clinical research, data management, drug diagnostics, pathology, herbal medicine, *etc.* Though the economy is uplifted by this new concept of artificial intelligence and robotics, stilla lot of research is yet to be done. We cannot be so sure of all the possible benefitsbecause the negative aspects are yet to be studied and mitigated properly.

CONSENT OF PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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Declared none.

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SUBJECT INDEX

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Swarnlata Saraf

Dr. Swarnlata Saraf graduated from the Indian Institute of Technology, BHU, Varanasi and received her Ph.D. from Dr. H. S. Gour University Sagar, India. She guided 40 Master's Degrees and 19 Ph.D. students. She wrote 6 books and numerous chapters in edited books, filed patents and contributed to more than 200 scientific publications. She served as an editorial board member, reviewer of research journals and books. She served as an expert of national and international research projects and its screening committee. According to Google Scholar, she bears 9200 citations, H-index 47 and i-10 index 170 and has received national awards from various professional bodies. She handled research projects funded by national public agencies (India). As per a recently released database by Stanford University, she is among the top 2% of World Scientists. Her areas of interest are pharmaceutics, nanotechnology, herbal drug delivery, and cosmetic technology. She has widely travelled abroad like USA, UK, Switzerland, Singapore, UAE and many more for official, professional and academic activities.

Ram Kumar Sahu

Dr Ram Sahu is a result oriented, high energy, hands-on proficient with a successful record of achievements. He has completed his Ph.D. from Banasthali University, Jaipur (Rajasthan), India and M Pharm from Dr. M. G. R. Medical University, Chennai, India. Currently, he is an assistant professor at the Department of Pharmaceutical Sciences, Assam University (A Central Government University), Silchar (AS), India. He also holds the position of associate professor at Pharmacy Department, Pt. Deendayal Upadhyay Memorial Health Sciences and Ayush University of Chhattisgarh, Raipur (CG) and Columbia Institute of Pharmacy, Raipur. He had more than 15 years of teaching experience along with research experience. He delivered guest lectures at various Universities of Malaysia, Thailand, Philippines and Indonesia. Dr. Sahu's research work highlights novel drug delivery system, isolation and characterization of active constituents, formulation and standardization of herbal drugs, screening and evaluation of various pharmacological activities of samples. He has made innovative, outstanding and original contributions both in education and research in the area of natural products. Under his supervision, 03 Ph.D. scholars and 26 PG students have been awarded. Dr. Sahu was appointed as co-supervisor for M Pharm students in the MSU University Malaysia. He has received many awards from international and Indian conferences. He is an editorial board member and reviewer of various national and international peer-reviewed journals. Dr. Sahu has been an invited speaker and panellist at various international and Indian conferences.

Vivek Dave

Vivek Dave, presently working in the capacity of Associate Professor at Central University South Bihar, Gaya, Bihar has commendable experience and skills coupled with sound theoretical knowledge. Besides his past experiences with many pharmacy colleges, he also worked for more than 8 years at the Banasthali University, Rajasthan soon after pursuing his Ph.D. from Banasthali University itself. During his Ph.D., he worked on the design and evaluation of aceclofenac and esmolol HCl containing ocular drug delivery system. He did his Masters in Pharmaceutics on Aceclofenac ethosomes for enhanced transdermal drug delivery system. His expertise in working with the formulation and development of novel drug delivery systems like PEGylated liposome, ethosomes, nanoparticle, quantum dots has shaped the leading scientific high impact research and book publications of international repute. Currently, he is working on nano-formulation for therapeutic managements of various diseases like Alzheimer's, inflammation, and cancer, etc. He has been the recipient of several awards in various conferences, seminars and conventions, including a prestigious award, "Best Sustainability Award" on Smart Shoe sole in the 2019's International Conference on Future Healthcare and Economic Development from Medical Device Innovation Center (MDIC), National Cheng Kung University, Taiwan. Dr. Dave is also acting as a regular reviewer of journals of national and international repute of different publishing houses, namely Wiley, Springer, Elsevier, BMC, etc.

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