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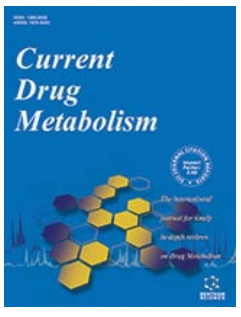

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ISSN (Print): 1389-2002
ISSN (Online): 1875-5453

Volume 24 , Issues 12, 2023

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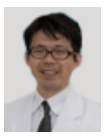

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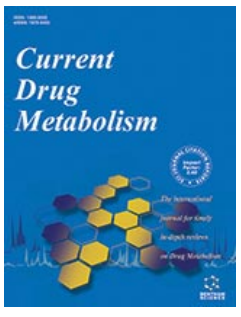

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10.2174/1389200223666220609141459

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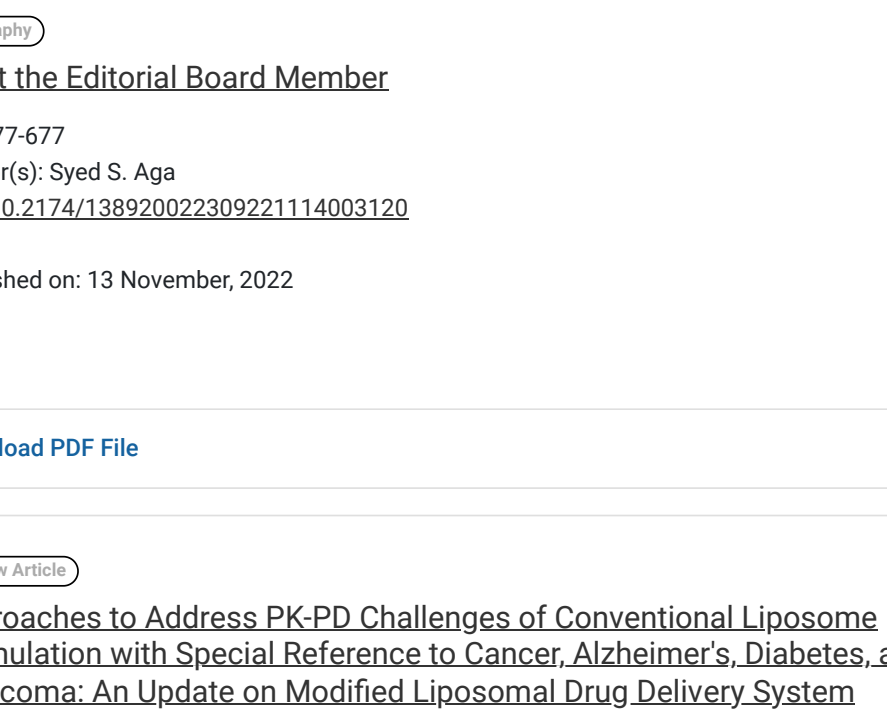

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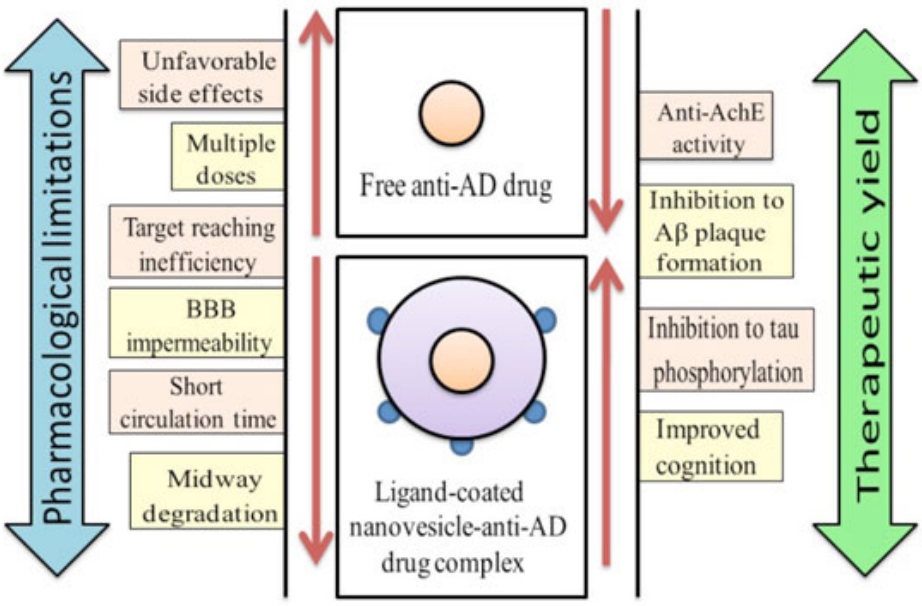
10.2174/1389200223666220526094802

Published on: 30 June, 2022



Nanovesicle-aided drug delivery approach overcomes the pharmacological drawbacks of free drug administration and enhances the therapeutic outcome of anti-AD drugs.

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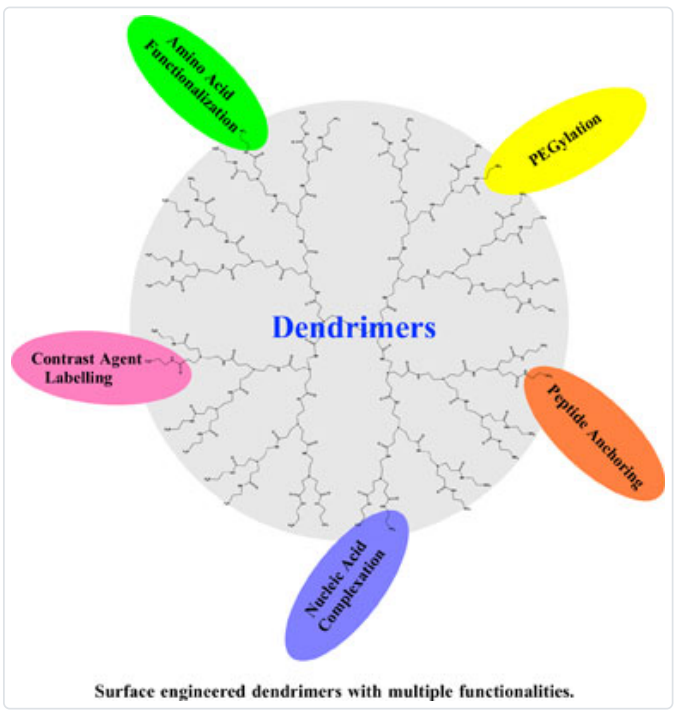
Author(s): Rakesh Kumar Sahoo, Tanisha Gupta, Sanya Batheja, Amit Kumar Goyal and Umesh Gupta*
DOI:
10.2174/1389200223666220616125524

Published on: 15 August, 2022



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Author(s): Archana Premnath, Sonu Benny, Aneesh Thankappan Presanna* and Sabitha Mangalathillam*
DOI:
10.2174/1389200223666220627103213

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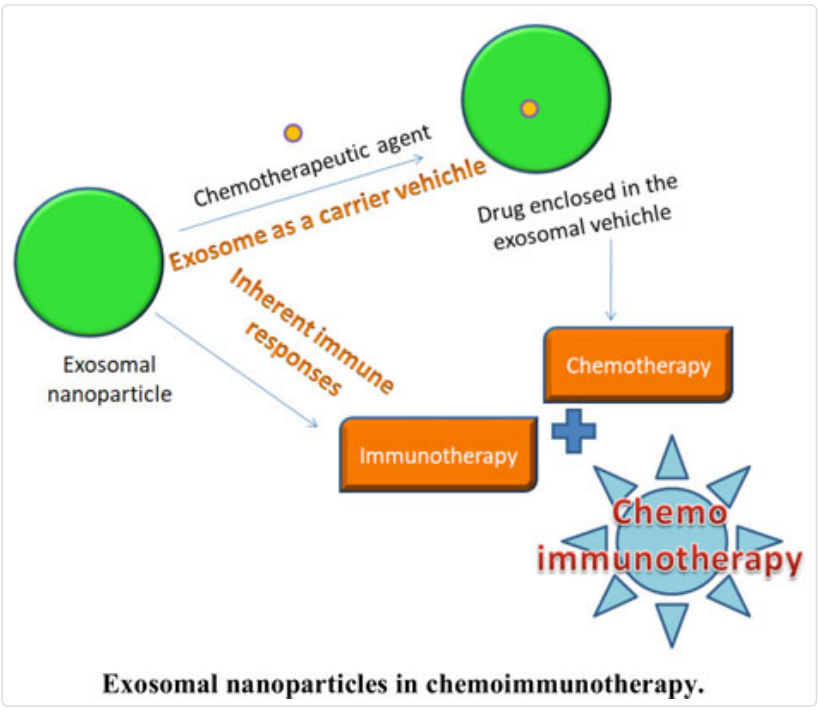

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Dysfunction of ABC Transporters at the Surface of BBB: Potential Implications in Intractable Epilepsy and Applications of Nanotechnology Enabled Drug Delivery

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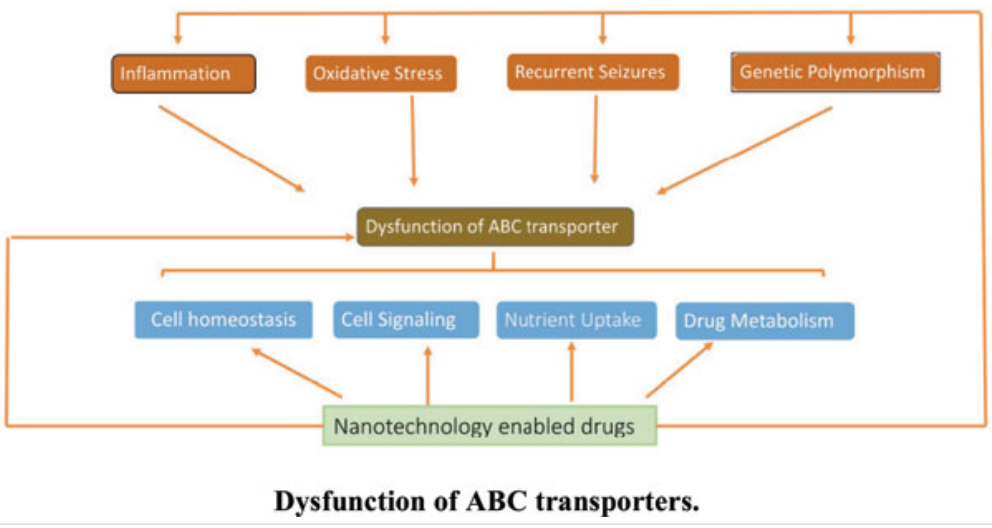
Author(s): Roohi Mohi-ud-Din*, Reyaz Hassan Mir, Prince Ahad Mir, Nazia Banday, Abdul Jalil Shah, Gifty Sawhney, Mudasir Maqbool Bhat, Gaber E. Batiha and Faheem Hyder Pottoo*

DOI:
10.2174/1389200223666220817115003

Published on: 09 September, 2022



Dysfunction of ABC transporters.

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Advances in Hybrid Vesicular-based Drug Delivery Systems: Improved Biocompatibility, Targeting, Therapeutic Efficacy and Pharmacokinetics of Anticancer Drugs

Pp: 757-780

Author(s): Aseem Setia, Ram Kumar Sahu*, Supratim Ray, Retno Widyowati, Wiwied Ekasari and Swarnlata Saraf

DOI:
10.2174/1389200223666220627110049

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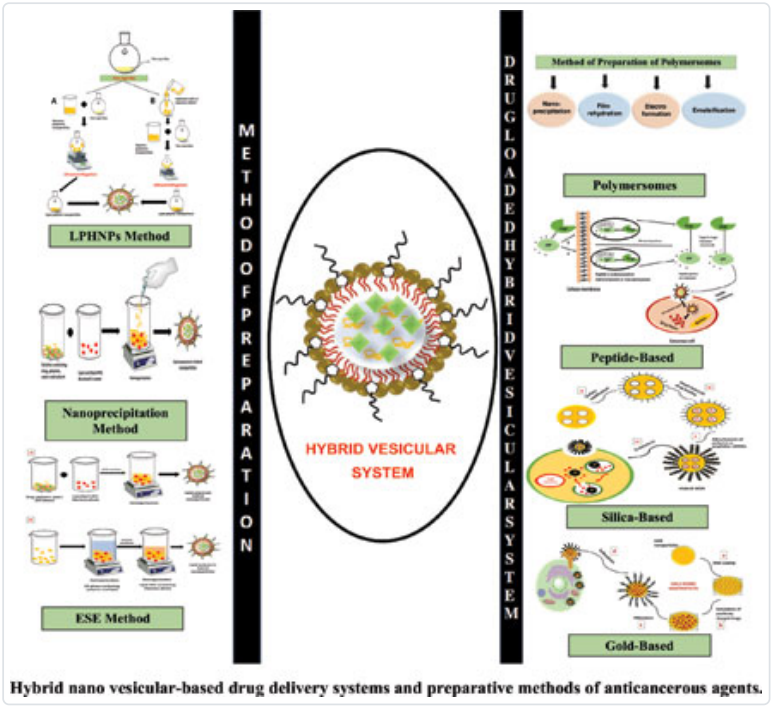

Hybrid nano vesicular-based drug delivery systems and preparative methods of anticancerous agents.

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REVIEW ARTICLE

Advances in Hybrid Vesicular-based Drug Delivery Systems: Improved Biocompatibility, Targeting, Therapeutic Efficacy and Pharmacokinetics of Anticancer Drugs

Aseem Setia[1], Ram Kumar Sahu[2,*], Supratim Ray[2], Retno Widyowati[3], Wiwied Ekasari[3] and Swarnlata Saraf[4]

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ARTICLE HISTORY

Received: March 10, 2022
Revised: April 11, 2022
Accepted: May 24, 2022

DOI:
10.2174/1389200223666220627110049

Abstract: Anticancer drugs and diagnostics can be transported in nanoscale vesicles that provide a flexible platform. A hybrid nanoparticle, a nano assembly made up of many types of nanostructures, has the greatest potential to perform these two activities simultaneously. Nanomedicine has shown the promise of vesicular carriers based on lipo-polymersomes, lipid peptides, and metallic hybrid nano-vesicle systems. However, there are significant limitations that hinder the clinical implementation of these systems at the commercial scale, such as low productivity, high energy consumption, expensive setup, long process durations, and the current cancer therapies described in this article. Combinatorial hybrid systems can be used to reduce the above limitations. A greater therapeutic index and improved clinical results are possible with hybrid nanovesicular systems, which integrate the benefits of many carriers into a single structure. Due to their unique properties, cell-based drug delivery systems have shown tremendous benefits in the treatment of cancer. Nanoparticles (NPs) can benefit significantly from the properties of erythrocytes and platelets, which are part of the circulatory cells and circulate for a long time. Due to their unique physicochemical properties, nanomaterials play an essential role in cell-based drug delivery. Combining the advantages of different nanomaterials and cell types gives the resulting delivery systems a wide range of desirable properties. NPs are next-generation core-shell nanostructures that combine a lipid shell with a polymer core. The fabrication of lipid-polymer hybrid nanoparticles has recently undergone a fundamental shift, moving from a two-step to a one-step technique based on joint self-assembly of polymers and lipids. Oncologists are particularly interested in this method as a combinatorial drug delivery platform because of its two-in-one structure. This article addresses various preparative methods for the preparation of hybrid nano-vesicular systems. It also discusses the cellular mechanism of hybrid nano-vesicular systems and describes the thorough knowledge of various hybrid vesicular systems.

Keywords: Anticancer hybrid vesicular, preparative method, cellular mechanism, biocompatibility, specific targeting.

1. INTRODUCTION

A large number of novel drug carriers have indeed been produced in the previous decade, which have enhanced the solubility and stability of free drugs while reducing their adverse effects [1]. According to studies, more than 250 nanomedicines have been approved or are nearing clinical trials at various stages of development [2]. Vesicular systems have received the most attention among the many carrier-based drug delivery technologies. For example, the core-shell structure of vesicular systems enables the encapsulation of both water-soluble and water-insoluble substances. Liposomes and polymersomes, two well-known vesicular drug delivery systems, are formed primarily by self-assembly under aquatic conditions. When the drug is administered in its free form or in conventional dosage forms, such as tablets or injections, there are numerous disadvantages, including inactivation of the drug, interactions with other drugs, rapid excretion, toxicological effects, multiple administrations, reduced plasma half-life, and lack of concentration at the target site [3]. By loading the drug into natural carriers, such as erythrocytes and lymphocytes, these and other drawbacks are eliminated or minimised. Natural properties, such as biodegradability, specificity, biocompatibility, extended lifespan, and the ability to retain large volumes, make these cells an ideal carrier for drug delivery [4]. All procedures must be performed under sterile conditions because this technology is so sensitive. The cells are extracted, processed, and loaded with drugs before they are administered. When this cellular drug delivery technology is used therapeutically, it achieves remarkable and significant effects [5].

Small molecules, genes, RNAs, peptides, and diagnostic imaging agents are just a few of the drugs that could benefit from nanotechnology's ability to improve the therapeutic index and pharmacokinetics of many drugs in a systemic context [6]. A variety of parameters, such as matrix formulation, microenvironment pH, and ambient temperature, are used to monitor the release of the payload after it is covalently grafted onto the surface of the nanocarriers. There are several key properties that affect the ability of nanoparticles (NPs) to deliver therapeutic payloads, including average nanometric size, homogeneity, and surface potential [7]. The reticuloendothelial system can be completely bypassed by surface-coated, immuno-inert NPs, thereby increasing the bioavailability of encapsulated drugs. Nanocarriers may offer the following advantages: the ability to overcome many inherent biological obstacles; enhancement of the comprehensive pharmacokinetic and therapeutic characteristics of a drug without altering its chemical architecture; enhancement of effective cellular, tissue, and molecular targeting; ability to bypass numerous innate biological obstacles; enhancement of the therapeutic index of a drug through targeted and untar-

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geted drug delivery; and simultaneous delivery of multiple drugs. Although many common cancers have seen significant improvements in survival rates over the past decade, the development of new and revolutionary cancer treatments has remained mostly unchanged [8].

Since it has been observed that the enhanced permeability and retention (EPR) effect improves pharmacokinetics and tumour deposition of payloads, nanoparticle drug delivery could be a breakthrough tool to increase treatment efficacy and reduce adverse effects [9]. Nanomedicines have been shown to enhance tumour selectivity and drug deposition in cancer cells in animal models by binding active targeting ligands to particle surfaces. On the other hand, nanomedicines have not usually improved the efficacy of chemotherapeutic therapies in the clinic. There are a number of explanations for the discrepancy between clinical outcomes in animals and humans. Because the EPR effect is less visible in human cancer, human malignancies are more diverse and human tumours are more likely to be treatment-resistant than most other cancers [10]. The development of nanoparticles with improved pharmacokinetics and multistep delivery systems, as well as the use of high-intensity focused ultrasound (HIFU) and X-rays to enhance EPR effects, may help overcome the challenges of delivering nanoparticles into human tumours. Drug resistance and tumour heterogeneity can be addressed with combination treatments that use multiple therapeutic/modal mechanisms of action to achieve multiple targets and prevent cross-resistance [11]. Clinical trials combining radiation and small molecule drugs with chemotherapy nanomedicines are now being evaluated for therapeutic efficacy after a series of failures with monotherapy [12]. This study focuses on the introduction of new hybrid nanovesicles for the encapsulation of anticancer chemotherapeutic agents. It also includes a list of different types of hybrid vesicles (Table **1**). These nanovesicles are also being studied in terms of their manufacturing processes. In the field of cancer treatment, the construction of such vesicles offers new opportunities for exploration.

Table 1. H ybrid polymeric vesicular-based drug delivery system.

Drug	Hybrid System	Preparation Technique	Type of Hybrid Vesicles	Study Outcomes	Refs.
Pemetrexed disodium	(PEG-P(TMC-DTC)-PEI)	Co-self assembly	Lipo-polymersomes	• PEM-CC9-RCPs loaded with trimethylene carbonate-co-dithiolane-trimethylene carbonate. The CC9-functionalized PEG-P(TMC-DTC)-PEI was crosslinked with the PEG-P(TMC-DTC)-PEI throughout the existence of PEM(TMC-DTC). Overall, an optimal CC9 density of 9.0% was achieved in the PEM-CC9 RCPs when used as target cells for H460 cells. • In addition, a PEM loading concentration of 14.2 wt%, a hydrodynamic size of approximately 60 nm, and glutathione-triggered PEM release were achieved. According to the results of MTT assays, the PEM-CC9 RCPs were 2.6 and 10-fold more effective against H460 cells than non-targeted PEM RCPs and free PEM controls, respectively. Compared to the therapeutic formulation of alimta, PEM-CC9-RCPs had a 22-fold longer turn around time and a 9.1-fold higher concentration in the H460 tumour. • CC9-RCPs, on the other hand, showed much better tumour penetration than RCPs. In contrast to PEM-RCPs and alimta controls, PEM-CC9-RCPs at a dose of 12.5 mg PEM-equivalent/kg effectively reduced H460 xenograft growth and significantly prolonged mouse lifespan. A novel pemetrexed nanoformulation for targeted lung cancer therapy showed a significant cure for lung cancer. These lung cancer-specific and reduction-responsive chimeric polymersomes offer a new approach to the treatment of lung cancer.	[13]
Doxorubicin	Hyaluronan-polycaprolactone polymersomes	Nanoprecipitation method	Lipo-polymersomes	• Nanoprecipitation was used to encapsulate doxorubicin in an aqueous compartment of hyaluronan polycaprolactone polymersomes. A metastatic breast cancer model was used to test the therapeutic index of the prepared formulation. The resulting polymersomes were 146.2 ± 9.6 nm in size and had an encapsulation efficiency of 54.9 ± 4.0 percent and a loading ratio of 3.6 ± 0.4 percent. The findings showed that the HA-PCL polymersomes controlled DOX release over time. • To test this, flow cytometry and MTT assays were used to detect CD44 receptor-mediated endocytosis through the formulation hyaluronan envelope. This formulation was found to have much better anticancer activity *in vivo*, greater tumour tissue necrosis, and better biodistribution compared to PEG-PCL-DOX nanoparticles.	[14]

(Table 1) contd….

Drug	Hybrid System	Preparation Technique	Type of Hybrid Vesicles	Study Outcomes	Refs.
Granzyme B-	CPP33-PEG-P(TMC-DTC)	Self-assembly process	Lipo-polymersomes	• According to the results of the study, granzyme B (GrB) is delivered with high efficiency into an orthotopic human lung tumour *in vivo via* cell-selective penetrating and reduction-responsive polymersomes (CPRPs). Cytochrome C-labelled FITC (FITC-CC) proved to be an efficient and highly proteinaceous model for CPRPs. • Lower protein release, enhanced internalisation, and cytoplasmic protein release were observed in A549 lung cancer cells with CPRPs loaded with FITC-CC compared to the non-targeted FITC-CC-loaded control. It was observed that GrB-loaded CPRPs were extremely potent against A549 lung cancer cells, having an IC_{50} value of 20.7 nM. Free GrB was virtually nontoxic when tested in the same environment. • An important finding was that the insertion of the cell-selective entering peptide could not modify the circulation time, although it may lead to a rise in the deposition of RPs in tumours. When GrB-loaded CPRPs were administered at a dose of 2.88 nmol equiv/kg to orthotopic A549- lung tumour-bearing nude mice, no weight loss and complete inhibition of tumour growth was observed during the treatment, resulting in significantly improved survival compared to non-targeted and untreated controls. These cell-selective polymersomes were used to develop a targeted protein therapy for cancer.	[15]
Doxorubicin	Using Poly(L-methionine-block-L-lysine)-PLGLAG-PEG (MLMP)	Dialysis method	Peptide-based hybrid vesicles	• The authors designed peptides with a ROS-responsive methionine, a cell-permeable lysine, and a linker cleavable by a matrix metalloproteinase. A micelle containing doxorubicin (DOX) was prepared using poly(L-methionine-block-L-lysine)- PLGLAG-PEG (MLMP). Both cleavage of MLMP by MMPS and release of DOX by ROS were observed in this cell type. • In addition, DOX transport into cancer cells was shown to be effective and apoptosis was induced *in vitro*. IR-780 dye-encapsulated MLMP showed improved targeting in the tumour and longer residence time in a biodistribution study. It was also shown that DOX (dual stimuli, MLMP) is promising as a platform for anticancer drug delivery due to its remarkable tumour inhibitory properties and nontoxicity compared to free DOX.	[16]
Paliperidone	MCF-PLA/PLGA:(75/25)	Double emulsification method	Silica hybrid nanoparticles	• Increase the solubility of paliperidone while creating long-acting, poorly soluble microspheres. For this purpose, paliperidone was first loaded on MCF silica and then encapsulated in PLA and PLGA microspheres in PLA and PLGA copolymer 75/25 w/w. • When MCF was added to paliperidone, it was found that the amorphous shape of the drug changed.	[17]
Doxorubicin	ROSP@MSN	Covalent grafting	Silica hybrid nanoparticles	• According to the findings of the research, the molecular weight must not be lower than 10 k. Using PEG10k-MSN and PEG20k-MSN, it was discovered that the ideal chain density was 0.75 weight percent and 0.075 weight percent, respectively. The minimum HSA adsorption on PEGxk-MSNs was much lower (2.5%) than that of MSNs (18.7%) without PEGylation. • To achieve optimal HSA adsorption, macrophage-derived human THP-1 monocytic leukaemia cells (THP-1 macrophages) and human red blood cells (HRBCs) adsorption was studied using MSNs and PEGylated MSNs. PEG10k MSNs were found to have low hemolysis percentages (0.9%) and low THP-1 phagocytosis (0.1%) compared to MSNs, which had hemolysis rates of 8.6 and 14.2%.	[18]

(Table 1) contd….

Drug	Hybrid System	Preparation Technique	Type of Hybrid Vesicles	Study Outcomes	Refs.
Sulfo rhodamine B	MSN- PEG-acrylate	Modified sol–gel method	Silica hybrid nanoparticles	• As a result of their huge surface area and volume, mesoporous silica nanoparticles (MSNs) are ideal nanocarriers with a high charge capacity. The particle and pore sizes can be precisely controlled, and both the inner and outer surfaces can be functionalized. A temperature-sensitive, biocompatible copolymer was used to modify the outer surface of hybrid MSNs with a diameter of about 140 nm to regulate cargo release. • It is possible to prepare nanoparticles with a polymer brush or a gel-like reactive shell grafted onto PEGacrylate macromonomers by RAFT polymerization. Optical characteristics for accountability and imaging are provided by nanoparticles containing fluorescent compounds contained in an inorganic network, which has outstanding optical properties. • When the polymer shell is hydrophilic and expands at low temperature (about 20 °C), it acts as a "pump" mechanism, preventing molecules from being released from the mesopores; when the polymer network is hydrophobic and collapses onto the silica surface, it releases the charge by "squeezing" the molecules into the silica. Gel-coated nanoparticles have improved release kinetics, which depends on the type of polymer shell used. The results of the study show that the release rate can be increased by adjusting the temperature.	[19]
No agent	GO-AuNPs	Microwave reduction	Gold hybrid nanoparticles	• Graphene oxide (GO) covalently implants a high density of accessible and bindable oxyfunctional groups and a micrometre-sized area, as found in a study. A microwave reduction method is used to stabilise and support *in situ*-generated bare surface gold nanoparticles (BSGNs). The uncovered surface of the GO-supported NPs (a) opened by 258% compared to the BSGNs, which had a comparable surfactant-covered gold surface NP. • The addition of more active sites (b) increases the catalytic reduction of p- NA by 10-100 times. For this reason, it is possible to achieve an electron density of 1.328 x 1012 cm2 by implanting BSGN on GO, which amplifies the Raman signal of the bare GO by three injections, thus converting it into an n-type semiconductor.	[20]
Tannic Acid	GO-AuNPs	Green synthesis method	Gold hybrid nanoparticles	• The authors use tannic acid (TA) as a reducing and immobilising agent to synthesise Au nanostructures on TA-functionalized graphene oxide (GO), which is reasonably green and environmentally friendly. • To regulate the morphology of Au nanostructures, one can change the amount of HAuCl4. The additive action of GO fully supports increasing the catalytic properties of Au nanostructures/GO nanocomposites in the degradation of 4-nitrophenol (4-NP).	[21]
Hydrazine hydrate	Graphene-AuNPs	Chemical reduction	Gold hybrid nanoparticles	• A composite of nanosized gold nanoparticlesand graphene was prepared in a straightforward two-step procedure on a GNPs-GR-SDS modified electrode. Blood haemoglobin (Hb) was fixed on BPG electrodes by simply dropping it on the electrodes. The haemoglobin-modified electrode was studied for direct electrochemistry and electrocatalysis. The direct electrotransfer between haemoglobin and the electrode was significantly promoted by the composites prepared in this way. • Using a phosphate buffer solution, it is possible to recognize some Hb CV peaks that are well and quasi-reversible. 81-mV spacing between the analytical peak potentials indicates the rapidity of electron transport. Another result of the study confirmed the hypothesis that immobilised Hb still has biological activity in catalysing NO. It was shown that the biosensors responded very well to the addition of NO at a pH of 7.0 and a potential of -0.82 V. The biosensors were also found to be highly responsive to the addition of Hb. The correlation coefficient was 0.9991, the linear response range of NO was 0.72-7.92 M, and the time to reach a constant current was less than three seconds.	[22]

2. CONSIDERATIONS OF BIOCOMPATIBILITY AND SPECIFIC TARGETING OF TUMOURS

An important aspect in the development of nanoparticles for *in vivo* applications is their biocompatibility [23]. The term "biocompatibility" can refer to a wide range of different issues. The biocompatibility of substances is often attributed to the fact that they are water-soluble [24]. When nanoparticles are used, an effective dose must be less lethal to the organism than the theoretical maximum toxicity of the nanoparticles [25]. The nanoparticles must not interfere with the organism's natural processes and must circulate long enough to serve their intended purpose. Regarding how long a nano-vesicle system can remain in circulation, size, shape, and charge all play a role [26]. For intravenously administered nanotherapeutics to reach the tumour, the circulation must be able to circulate for at least two hours before being flushed away by the liver or kidneys [27]. Compared with healthy blood capillaries, the arteries supplying the tumour are particularly "leaky." Various nanoparticles can enter the bloodstream through these clogged arteries and end up in tumours [28]. This effect is called enhanced permeability retention (EPR). This is not the only method by which nanoparticles can enter tumours, but it appears to be a general approach that works for a wide range of nanoparticles. It is possible to target a tumor more precisely by adding substances to the surface of nanoparticles that may have an affinity for tumour tissue or accelerate transport into malignant cells. Many tumour cells possess the folate receptor, making folic acid one of the most commonly used small molecules [29].

3. STRATEGIES FOR PROLONGED MEDICATION-BLOOD CIRCULATION

There are significant off-target effects that lead to critical adverse effects with conventional chemotherapy. It is possible to prevent the spread of drugs to healthy tissues by packaging them in carriers [30]. To increase the accumulation of the drug in the tumour, also known as the EPR effect, carriers that can remain in the bloodstream longer are needed [31]. To maximise extravasation and avoid an immune reaction, it is important to keep carriers under control to increase the likelihood that they will reach their target site, thereby promoting the EPR effect. Rapid deterioration of drug delivery systems (DDS) is mainly due to recognition by the immune system and subsequent removal of drugs from the bloodstream [32]. Therefore, despite the low immunogenicity of lipid-based drug delivery systems (LBDDS), we should continue to search for more effective strategies to avoid immune response and circulating half-lives [33].

3.1. Examining the Physicochemical Properties

3.1.1. Particle Size

Physical and chemical properties of LBDDS, including their shape, size, hydrophobicity or hydrophilicity, and surface charge, trigger an immune cell mechanism known as the mononuclear phagocyte system (MPS), which is critical for the uptake and removal of some drug carriers [34]. Immune responses are most strongly influenced by particle size. Drug carriers with a hydrodynamic size of < 20 nm or less can be easily removed from the body by the kidneys because they circulate better and stimulate the immune system [35]. Therefore, to maximise the EPR effect, most LBDDS for cancer therapy should have a size between 20 and 200 nm. Nanocarriers, especially LBDDS (size range of 100–200 nm), have been extensively explored for their ability to carry anticancer medicines to malignant tissue. Since these nanocarriers are known to aggregate in the tumour location because of the EPR effect, "passive targeting" is used in this technique for anti-cancer therapy". Because capillaries in the area of the tumour are more permeable, this effect shows how normal and cancerous tissue are different [36]. The effects of particle size on cellular absorption and biological distribution of polymeric nanoparticles (NPs) were explored by He *et al*., Rhodamine B-labelled chitosan hydrochloride-grafted NPs (CHNPs) or CMCNPs (carboxymethylchitin) were prepared to simulate polymeric NPs. The particle sizes of these NPs (ranging from 150 and 500 nm) were determined in great detail. RhB-CMCNP loaded with FITC-labelled protamine sulphate and RhB-CHNP loaded with camptothecin (CPT) were prepared with high encapsulation efficiency. Nanoparticles with a low negative charge and particle size less than 150 nm were shown to be more likely to accumulate in tumours in *in vivo* biodistribution assays. These observations suggest that drug nanocarriers with increased therapeutic efficacy and expected *in vivo* properties can be produced by changing the particle size [37]. Ekkapongpisit *et al*. demonstrated that the 50-nm silica nanoparticles were permanently accommodated in these organelles, while the 10-nm silica nanoparticles were rapidly transferred into the cytoplasm of the cell by caveolae-mediated endocytosynthesis. Carboxyl-modified 50-nm mesoporous silica nanoparticles had the lowest uptake rates, whereas the bare 10-nm mesoporous silica nanoparticles had the highest uptake rates. Serum had a detrimental effect on the uptake of polystyrene nanoparticles, which also occurred in a caveolae-independent manner. Nanoparticles with 30 nm carboxyl modification did not accumulate in lysosomes and were therefore not harmful, whereas those with 50 nm carboxyl modification of polystyrene accumulated in lysosomes and eventually led to cell lysis. Endocytosis of nanoparticles was more likely in ovarian cancer cells expressing caveolin-1 than in nonexpressing cells [38].

3.1.2. Particle Shape

For nanoparticles, cellular absorption and biodistribution, as well as *in vivo* performance, are strongly influenced by the shape of the particle, which has recently been discovered as a novel physical parameter [39]. Non-spherical particles are used to improve the therapeutic efficacy of anticancer drugs. The immune response of nanoparticles has also been affected by the antigen loading of non-spherical nanoparticles [40]. The new drug delivery research was inspired by the obvious influence of particle shape. Research suggests that microscopic particles do not necessarily elicit a stronger immune response than nanoparticles [41]. In fact, the half-life of the drug is strongly influenced by the shape of the particles. There are a number of different particle morphologies that can promote adherence to vessel walls or circulating immune cells, such as needle-like and cubic. Despite the fact that most LBDDS are spherical in nature, no one knows why their shapes affect blood flow [42]. To advance multidisciplinary research into different hybrid DDSs, it is important to keep in mind how different shapes and sizes affect blood flow.

3.1.3. Hydrophobicity

Innate and adaptive immunity can be triggered when drug carriers enter the bloodstream, but macrophages do not immediately recognise drug carriers. Drug delivery systems that use standard, non-stealth nanoparticles are immediately recognised and removed by the macrophages due to the presence of opsonin proteins in the serum. It is important to note that drug carrier surfaces are characterised by opsonization [43]. This is a process by which certain serum components bind to foreign substances. Particle surface hydrophobicity that might lead to serum protein adsorption is an important factor in this process [44]. Hydrophobic properties can be hidden by extending the hydrophilic lipid heads of amphiphilic phospholipids, which are the main components of LBDDS. This LBDD property facilitates the use of hydrophobic drug formulations *in vivo* [45]. Batrakova *et al*. explored the dose-dependent efficacy of Pluronic Block Copolymers on the cytotoxicity properties of doxorubicin (Dox) and P-glycoprotein probe rhodamine 123 (R123) accumulation in MDR cancer cells in a dose-dependent manner. Polyethylene oxide (EO) and propylene oxide (PO) seg-

ments of different lengths were used to enhance Pluronic Unimers activity in MDR cells. A study of R123 aggregation and dox cytotoxicity of pluronic copolymers found that intermediate PO chains and short EO segments were more effective in MDR cells [46].

3.1.4. Surface Charge

The surface charge is a critical mediator in the removal of LBDDSs from circulation. Thus, liposomal carriers can avoid early opsonization by having a neutral or negative surface charge [47]. When negatively charged cells or membranes come into contact with neutral or negative particles, the resulting repulsion disrupts internalisation. Cellular internalisation is enhanced by cationic liposomes, but also facilitates nontargeted binding of serum proteins. In order to estimate the surface charge, the balance of negatively and positively charged nanoparticles must be maintained on the surface. Living cells have a membrane potential, which is a different electric potential than the cell's inside. Nano-drug transmission is impeded by tissue barriers before the medicine can reach the tumour location. Tissue obstacles to the efficient transportation of nano-drugs to tumour sites include tumour stroma (*e.g.*, biological barriers) and tumour endothelium barriers (*e.g.*, functional barriers). Biological barriers are physical constructions or cell development that hinder the flow of nanoparticles. Functional obstacles can affect the transport of intact nanoparticles or nanomedicine into the tumour mass: high interstitial fluid pressure and an acidic environment. It is vital to design nanoparticles and techniques to overcome these limitations to improve cancer treatment efficacy [48]. Since the circulating positively charged lipids should be hidden, it is better to expose them in the endosomal environment after charge reversal activated by pH. Osaka *et al*. found that this is due to surface charge differences between magnetite nanoparticles. Human breast cancer cells internalised positively charged nanoparticles more than negatively charged ones, although both types of nanoparticles did so to an almost equal extent in human umbilical vein endothelial cells (HUVEC) [49].

4. STRUCTURE ELUCIDATION AND MECHANISM OF HYBRID FORMATION

Lipid-polymer hybrid nanoparticles (LPHNPs), as their name suggests, combine the advantages of polymer nanoparticles with those of liposomes [50]. The three components of the polymeric matrix are shown in Fig. (**1**). The drugs encapsulated in polymers are contained in a polymer core, which is then surrounded by a lipid monolayer [51]. Finally, the outer lipid layer PEG serves as a steric stabiliser that allows long-lasting circulation of the LPHNP while preventing destruction by the immune system. It acts as a molecular wall to keep the LPHNP core from degrading and to minimise the loss of encapsulated drugs over time by preventing water from entering the core [52]. The molecular mechanics of lipid-polymer fusion are currently under investigation. Clearly, the different techniques for producing LPHNP have different formation processes [53]. For example, one-step approaches use a lipid-rich aqueous environment to precipitate the polymer from the organic solvent, which then self-assembles into a monolayer around the core of the sample. The lipid component adheres to the polymer core, and the chain PEG expands outward into the aqueous environment during this process, which is called self-assembly. During the two-step technique, an initial bilayer structure is formed that adheres to the core. The hydrophobic contact between the polymer and lipid chains during this process subsequently causes the bilayer to dissolve. Van der Waal and electrostatic interactions are beneficial in hybrid formation [54].

4.1. Mammalian Cellular-Based Drug Delivery System

Mammalian cell-based delivery methods are gaining popularity because they can mimic many of the natural properties of their parent cells. By combining synthetic NVs with various types of cells, namely, red blood cells, platelets, and leukocytes, a series of cell membrane-enveloped nanosystems with different properties and functionalities could be generated. In short, living cells are not only promising for innovative drug delivery, but they also help us to better understand natural materials in drug delivery [55]. Cell-based DDSs are attracting increasing attention due to their low immunogenicity, long circulation time, intrinsic mutation, lack of neurotoxicity or tumorigenicity, receptor integration, and innate targeting ability [56].

Nanocarriers from eukaryotes or prokaryotes are desirable because they can be used for drug delivery. This has laid the foundation for current cell-based drug delivery systems (CBDDS) in mod-

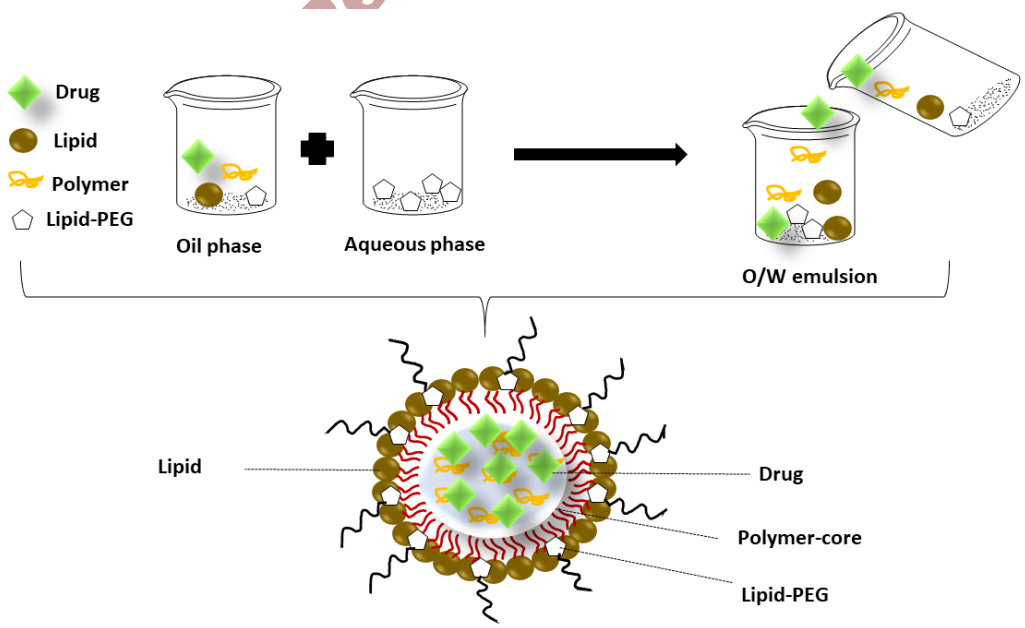

Fig. (1). There are three layers on these LPHNPs: an inner polymer core, an outer polymer lipid shell, and the final PEG layer. RGD or antibodies can be used in conjunction with a lipid–PEG layer to guarantee that the drug is delivered precisely where it is needed. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ern treatments. Organelles and even certain stem cells can be suitable payloads for this system. These include erythrocytes, lymphocytes, platelets, and even some viruses and bacteria. With CBDDS, various natural and synthetic drug carriers can be bypassed through the immune system, allowing for tailored drug delivery [57]. The goal of this system is to reduce drug-associated toxicity, bypass the immune system, and accurately hit the target. In cell-based drug delivery systems, the evasion of the immune system, the transition of the drug to the dense blood stream, the accumulation of the drug at the target site, localization in cellular compartments, and exocytosis are the distinguishing characteristics [58]. For example, loaded/modulated platelets, leukocytes, and erythrocytes are used in tumor and infection therapies. To increase the bioavailability of protein drugs in the brain, macrophages (also called leukocytes) have been forced to cross the blood-brain barrier. When loaded with antitumor antigens, natural antigen-presenting cells, like dendritic cells, can be activated and become cancer-specific. Antitumor immunity is generated by T cells. Adoptive T-cell treatment can benefit from continuous pseudoautocrine stimulation by an expanded T-cell load in most cancer immunotherapies. In most cases, intracellular encapsulation or conjugated/non-conjugated cell surface modification can deliver the cell-based payload. Electroporation in hyperosmotic loading buffers that induce water influx can be used for intracellular encapsulation, camouflage, or vectorization [59].

Extrusion can also be used to coat nanoparticles with cell-based drugs or antibodies. After electroporation, the cell membranes reveal. This method can also be used by some infections, such as Mycoplasma haemofelis, to invade mammals and attach to the surface of erythrocytes. One of the most challenging aspects of developing cell-based surface-coupled drug carriers is avoiding self-internalisation by precisely controlling size, shape, and mechanical properties [60]. Cellular cargo modified by the payload can also cause malfunction and cell disruption. Several attempts have been made in the scientific community to replace physiological processes in the disease with positive treatment outcomes. There are no physiological limitations for these cellular payloads, allowing them to achieve their therapeutic goals [61]. The main problems of these cellular cargoes include drug release and excretion, inadequate blood flow transmission, and limited intracellular trafficking ability. The most important requirements for these carriers are adequate circulation time and movement along vascular systems [62]. Increasing the circulation time of the carriers was the main focus of early research. The size of the carrier influenced the amount of drug release and drug loading. Because of these difficulties in implementation, research on cell-based delivery methods has increased.

As a result of this research, researchers have developed new strategies to deliver drugs and their carriers into circulation. Biological cells, such as erythrocytes and lymphocytes, can be used as drug carriers in cell-based drug delivery systems (Fig. **2**). In addition to acting as carriers, erythrocytes can also be used as bioreactors, encapsulating enzymes that perform the necessary reactions while remaining inaccessible to the immune system and plasma proteases; or they can be used for targeted drug delivery to specific cells in the reticuloendothelial, liver, and spleen systems, where they are most likely to be effective. A variety of medications have been tested on erythrocytes, such as enzymes, anti-inflammatory, anti-cancer, and antiviral treatments. Due to their inherent properties, such as biocompatibility and biodegradability, as well as their ability to show large amounts of drugs and deliver them efficiently, they have become one of the most amazing drug carriers. For this reason, the term "cellular drug delivery systems" was coined. While erythrocytes (especially cytotoxic T cells) are the most widely used drug transporters today, lymphocytes (especially cytotoxic T lymphocytes) are still in development [63].

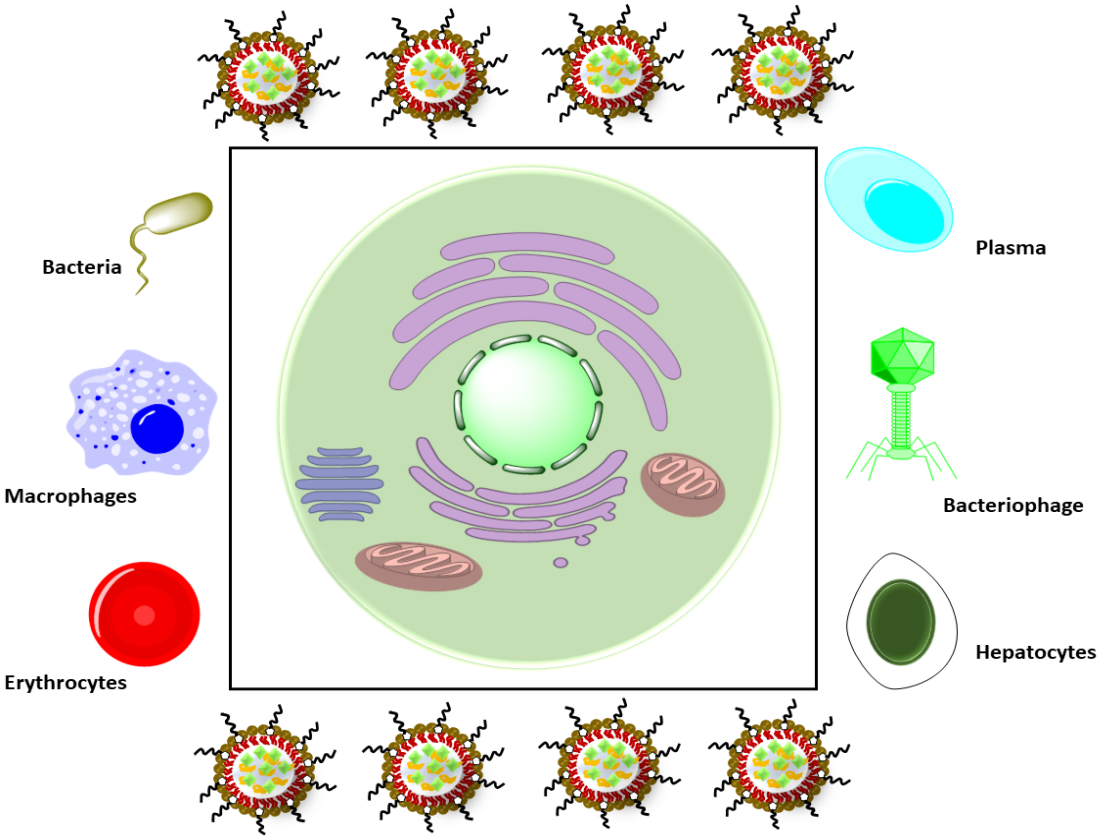

Fig. (2). Drug nanocarriers that can be modified by moving cells. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

4.2. WBCs

There are various types of white blood cells (WBCs) in the immune system, and they play a critical role in preventing inflammation, infection, and a variety of diseases [64]. There are several advantages to using white blood cells for drug delivery. These include a shorter circulation time (up to 20 days) and special properties such as strong cell contact and considerable ability to penetrate tissues, especially beyond physiological limits [65]. As a result, white blood cells are ideally suited for the delivery of novel cancer therapies because they tend to move, migrate, and adhere to endothelial tissue walls with tumour cells. The microscopic size and fragility of cell-based carriers significantly limit their ability to diffuse beyond blood vessels and contact tumour cells directly [66]. Active targeting cannot be achieved with unmodified erythrocytes. For cancer therapy, the applications of ligands directed to the surface are limited. There are many types of recognition receptors on the cell membrane of white blood cells, so they could be used to identify them. As a component of blood, they show that blood circulation has been expanded [67].

WBC-based BDDSs can thereby limit MPS breakdown, bypass the blood vascular barrier, and achieve a high degree of tissue orientation for effective drug delivery. The researchers have also used numerous immunological properties of WBCs to generate DDSs. Macrophages and monocytes offer a number of advantages, including inherent tumour-tropic, sticky, and transendothelial migration properties that can be used to deliver drugs to cancer cells or injured endothelial tissue [68]. There are a number of surface proteins on WBCs, including LFA-1, CD45, and CD3z, which play various roles in tumour adhesion and transmigration through interactions with inflammatory endothelial cells. The purification and functionalization techniques for erythrocytes and leukocytes were somewhat modified compared to those described for nanoparticles functionalized with an RBC membrane [69].

4.3. Lymphocytes

Among white blood cells, there are several subtypes of lymphocytes. T lymphocytes, B lymphocytes, and Natural killer (NK) cells make up the three basic types of lymphocytes in the body. Only during the innate immune response can NK cells become active. Foreign antigens belong to MHC class 1 molecules on the surface of host cells and are targeted by these microorganisms, which attack the host cells [70]. Cytotoxic (cell killing) granules are released from infected cells when they are recognized as NK cells. The cytotoxic action of NK cells does not require activation prior to their use. While the bone marrow produces lymphocytes that mature in the thymus, it is thought that T lymphocytes originate in the bone marrow from the same lymphoid progenitor that produces B lymphocytes, but only those progeny that will eventually give rise to T cells remain in the bone marrow and travel to the thymus for maturation. T lymphocytes, or T cells, are named as such because of their dependence on the thymus. T and B lymphocytes are said to be produced in the bone marrow and to mature in the bone marrow, respectively [71]. Immunity in humans is provided mainly by lymphocytes, which are specifically designed to attach to antigens that enter the body. Because of this unique property of lymphocytes, immune cells have been repurposed for drug delivery, indicating their important role. [72].

5. PHARMACOKINETICSS OF HYBRID VESICULAR BASED DRUG DELIVERY SYSTEM (HVBDDS)

5.1. Pharmacokinetics

With the development of innovative drug delivery methods, nanotechnology could be used strategically to increase the drug market. The implementation of such a strategy is necessary for drugs that are deemed safe and effective but fail to reach clinical outcomes because of poor biopharmacological properties, such as low solubility or poor permeability of the intestinal epithelium, which result in low bioavailability and unfavourable pharmacokinetic properties [73]. As a result, pharmaceutical companies can reformulate currently marketed drugs to extend their shelf life and improve their performance by increasing efficacy, safety, and patient compliance. This will also reduce healthcare costs in the long run. Drug molecules must be delivered to specific sites in the body for therapeutic purposes using EV pharmacokinetics. Systemic administration results in rapid accumulation of nanovesicles (NVs) in various organs, including the spleen, lungs, liver, and kidneys (RES). Avoiding deposition of MPS can improve the pharmacokinetics of EV [74].

5.2. Biodistribution of EVs Upon Administration

Almost all EVs are suddenly collected by MPSS when EVs are administered systemically. In MPS, there are macrophages that rapidly clear EVs from the bloodstream. EVs are not unique in this regard, as NVs are generally more likely to be taken up by MPSS [75]. Uptake of EVs by macrophages is facilitated by the negative charge of the EV surface, which derives from the negatively charged phospholipid phosphatidylserine (PS) recognized by macrophage PS-binding receptor molecules. The pharmacokinetics of EVs is also influenced by the source of EVs. For this reason, EVs have varied compositions. The distribution of EVs derived from different cell types varies widely. The pharmacokinetics of EVs is significantly influenced by the route of administration. As mentioned earlier, intravenous injection of EVs results in rapid elimination from the bloodstream and accumulation in organs associated with multiple sclerosis. The only way to deliver drugs to the brain is by intranasal administration. An interesting strategy for drug delivery is the oral administration of food-derived EVs. However, it is not yet clear whether or not EVs can be transported into the bloodstream *via* intestinal absorption and maintain their integrity [76].

5.3. Improvement of Pharmacokinetics

Most NVs are absorbed by MPS when administered systemically. Using this tactic, evasion of uptake by MPSS may increase EV drug delivery and allow tailored distribution to specific cells or tissues [77]. Nanoparticles containing folate (FA) functionalization were produced by Li *et al*. for targeted medication delivery and dual-controlled drug release. Hydrophilic core PLA and hydrophilic shell PEG are positioned between an amphiphilic lipid interface (PE), and the interface of the hydrophobic core is coated with the target ligand (FA). The resulting FA-PEG-PE-PLA nanoparticles have nearly 95% drug encapsulation efficiency. The new drug delivery methods allow the regulated release of drugs in the early and late phases, which is a major advantage of these new systems. According to the *in vitro* cytotoxicity and hemolysis tests, they were cytocompatible and hemocompatible. It was shown that, compared to unbound MMC, pharmacokinetic tests in rats revealed that the blood circulation time of FA-PEG-PE-PLA NPs -MMC was considerably extended. A greater level of tumor growth and therapeutic effectiveness was observed *in vivo*, but the systemic toxicities of NPs -MMC-SPC were much reduced. In the nucleus, the site of MMC activity, the FA-PEG-PE-PLA NPsMMC-SPC were perfectly suited for MMC distribution. Phospholipid-based drugs that can be dispersed and released over time may be improved by this research [78].

6. PREPARATIVE METHOD OF HVBDDS

Hybrid vesicles can be prepared in two steps or in one step. In a two-step process, the lipid/peptide and polymer components are prepared separately and then combined, whereas in a one-step process, both components are mixed [79]. A one-step strategy is be-

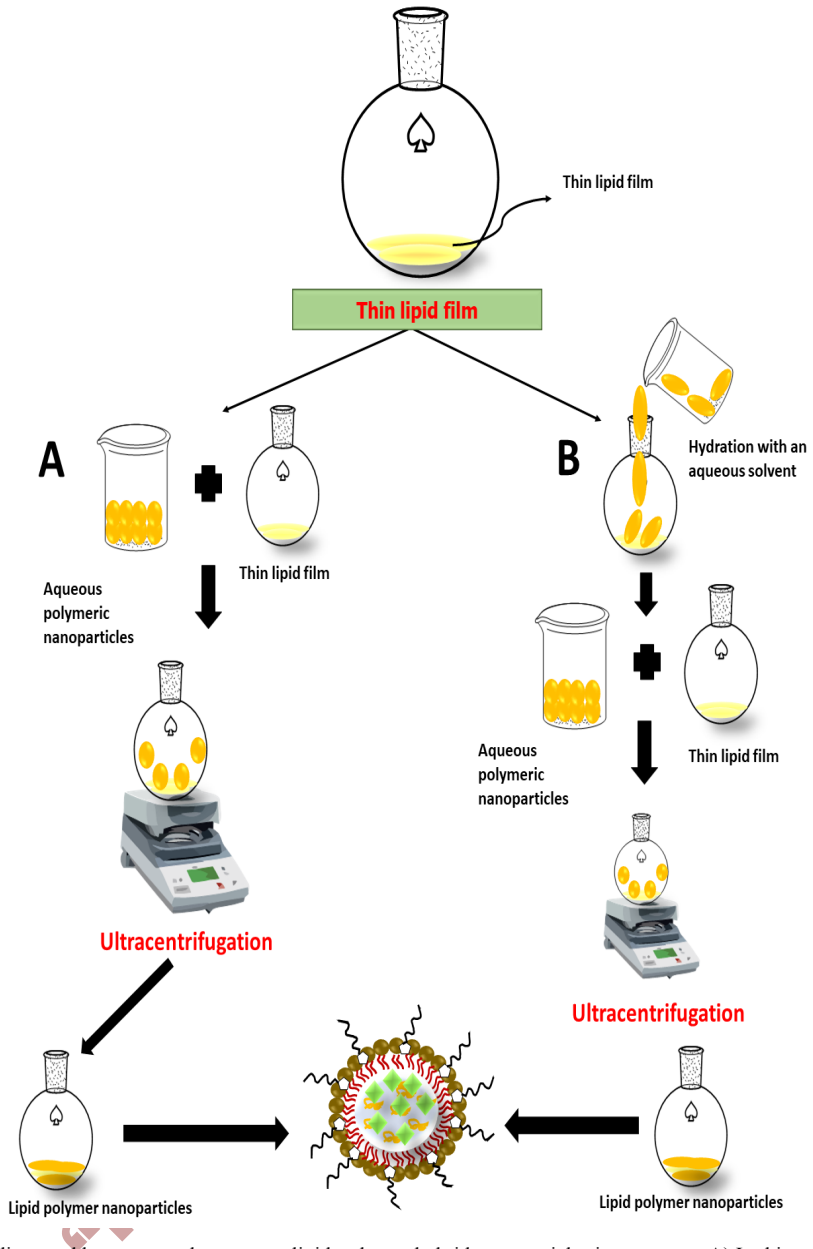

Fig. (3). The two approaches discussed here are used to prepare lipid-polymer hybrid nanoparticles in two steps. **A**) In this method, the suspension of polymeric NPs is applied to a dried lipid film. **B**) To promote the formation of vesicles, a thin lipid layer is first moistened with an aqueous solvent. Then, an aqueous preformed NPs suspension is added to the hydrated vesicles. At a temperature higher than the phase transition temperature of the lipids, the mixture is vortexed or ultrasonicated to produce hybrids using one of the methods described above. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

coming more popular due to improved product quality and performance.

6.1. Two-step Method

6.1.1. Conventional Method

LPHNPs were first synthesized by a traditional two-step method combining formulated polymeric NPs with lipid vesicles and electrostatically assimilating the latter into the former. High-pressure homogenization or nanoprecipitation are the most common methods to prepare polymeric NPs. The two-step approach can be segregated into two groups, as shown in Fig. (**3**); there are two possibilities: either the preformed polymeric NPs are added directly into the dry lipid film or they are used in preformed liposomes generated by prior hydration of the thin lipid layer. To achieve this, the suspension should be vortexed and/or sonicated, as well as heated to a temperature higher than the phase transition temperature of the lipids. LPHNPs and lipids are separated by differential centrifugation at this stage of the purification process. A technique using PLGA and cationic lipids (FA-OQLCS /PEG-OQLCS/Chol) at 30°C yields stable LPHNPs with an average diameter of 200-400 nm and an average surface potential of (+) 20-30 mV [54]. It was discovered that a hybrid nanoparticle composed of polystyrene, eiphosphatidylcholine (PC), cholesterol, and DSPE-mPEG or maleimide-DSPE-mPEG may bind to tumour necrosis factor (TNF). Porous membrane extrusion reduced the size of the NPs. Hu *et al*. used this technology to produce NPs coated on the membrane of a red blood cell (120 nm), and Sengupta *et al*. used it to produce chemotherapeutic LPHNPs (200 nm) [80, 81].

6.1.2. Non-conventional Method

In addition to the methods listed above, several other methods different from the convention were used to prepare LPHNPs [82]. Spray drying was used to disperse 400-500 nm polymeric NPs (*e.g.*, polyglutamic acid, polylysine) in DCM lipids (tripalmitin, tristearin, cetyl alcohol). LPHNPs in size range of 0.9-1.2 m were prepared by spray drying this solution using a spray dryer that was not suitable for the preparation of NPs. Smaller hybrid NPs can be prepared using the recently introduced nanometric spray dryer. Replication of particles in non-wetting templates (PRINT) is a recently investigated soft lithography approach for shaping particles to produce LPHNPs for delivery of genetic material [83].

6.2. One-step Method

Polymeric NPs and fat vesicles must be prepared independently, so the two-step approach is inefficient. A one-step technique is the most popular and efficient alternative. The one-step technique does not require preformed lipid vesicles or polymeric NPs. Lipid and polymer solutions are simply mixed, and the resulting LPHNPs self-assemble. Nanoprecipitation or electrostatic precipitation (ESE) are commonly used to make nonhybrid polymeric NPs. Lipids or PEG-lipids are used to stabilize the hybrid, whereas ionic or nonionic surfactants (poloxamer, DMAB, PVA) are used to stabilize normal nonhybrid polymeric NPS [84].

6.3. Nanoprecipitation

For classical nanoprecipitation, in which the drug and polymer must also be dissolved in water, an organic solvent (such as acetone or EtOH) that is miscible with water is required. To produce a homogeneously distributed liquid crystalline phase, the lipid/lipid PEG solution must be heated above the gel-to-liquid transition point. In the next step, the polymer is added dropwise to the aqueous lipid dispersion with constant stirring. In this way, the polymer is forced to curl up into NPs, and the lipids around it self-assemble due to hydrophobic interactions. The tails of the lipids face the polymer, while their head groups face outward toward the water. This hybrid is sterically stabilized by its PEG chains breaking away from the aqueous environment and fusing with the hydrophobic lipid tails in the inner liposome. Centrifuges are used to separate the LPHNPs from the organic medium (Fig. **4**). In a recent study, it was found that nanoprecipitated PEGylated lipid vesicles can be used to deliver mRNA-based vaccines in a noninvasive manner [85].

In terms of surface charge, particle size, and polydispersity, the molar proportions of the ingredients, the volume ratio of organic solvents to water, and the viscosity of the amphiphiles are important factors. Polymersomes and LPNs have been widely produced using this technology. To ensure that the encapsulated drug is maintained during the self-assembly process, the lipid serves as a molecular barrier. The drug's release is slowed as a result of this. To make cationic hybrid core-shell vesicles, Yang *et al*. employed nanoprecipitation. Amphiphilic polymer (mPEG-PLA) and a cationic lipid BHEM-Chol were used to prepare the siRNA transport particles. Acetonitrile and 10% ethanol were used to dissolve the cationic lipids BHEM-Chol and mPEG-PLA, respectively. Centrifugation was used to remove the organic solvent from the polymer solution following the dropwise addition of the polymer mixture to the lipid solution [86].

6.4. Emulsification–solvent Evaporation (ESE)

Figs. (**5A** and **5B**) show the single emulsified and double emulsified versions of this technique. For compounds soluble in hydrophobic solvents (oil phase), a simple ESE technique (Fig. **5A**) is used. In this approach, polymer and drug emulsions can be prepared by combining an oil-in-water (O/W) emulsion with an aqueous phase of lipids under ultrasonic or continuous stirring. To create a polymer core, the organic medium is evaporated, and lipids are simultaneously created around the polymer core. The polymer and lipid can be dissolved in the same oil phase as an apparent substitute. To test water-soluble drugs, a dual ESE approach is used (Fig. **5B**) [87]. A water-in-oil combination is prepared by first emulsifying the drug in an organic solvent (oil phase) containing both polymers and lipids. To prepare the LPHNPs, the mixture must be re-emulsified in an aqueous phase using lipid-PEG and the oil phase evaporated. Hybrids prepared using the double ESE approach, as shown in Fig. (**5B**), have certain structural defects. First, an aqueous core is enclosed by a lipid layer, followed by an intermediate

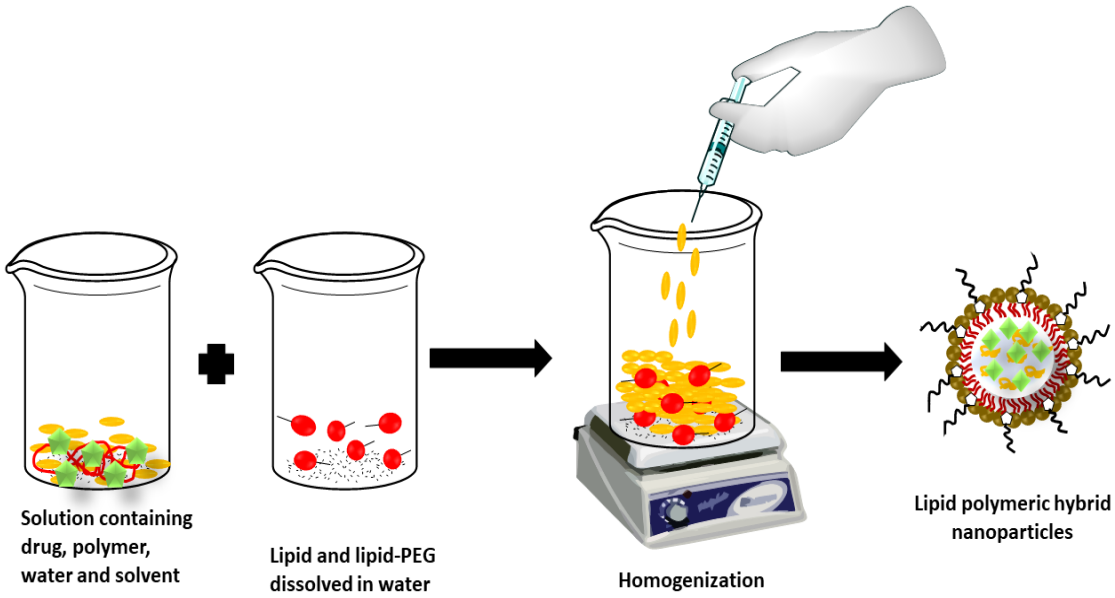

Fig. (4). Nanoprecipitation technology for the synthesis of LPHNPs using a one-step process. Description: Polymers and drug are combined in a water-soluble solvent like acetone or ethanol. Gels are formed when water is heated above the temperature at which the gel-to-liquid transition occurs for both lipids and PEGs. Drop-by-drop addition of the polymer/drug solution causes hydrophobic interactions to clump around the NP core, which results in an increase in the lipids/lipid–PEGs aggregated around the NP core. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

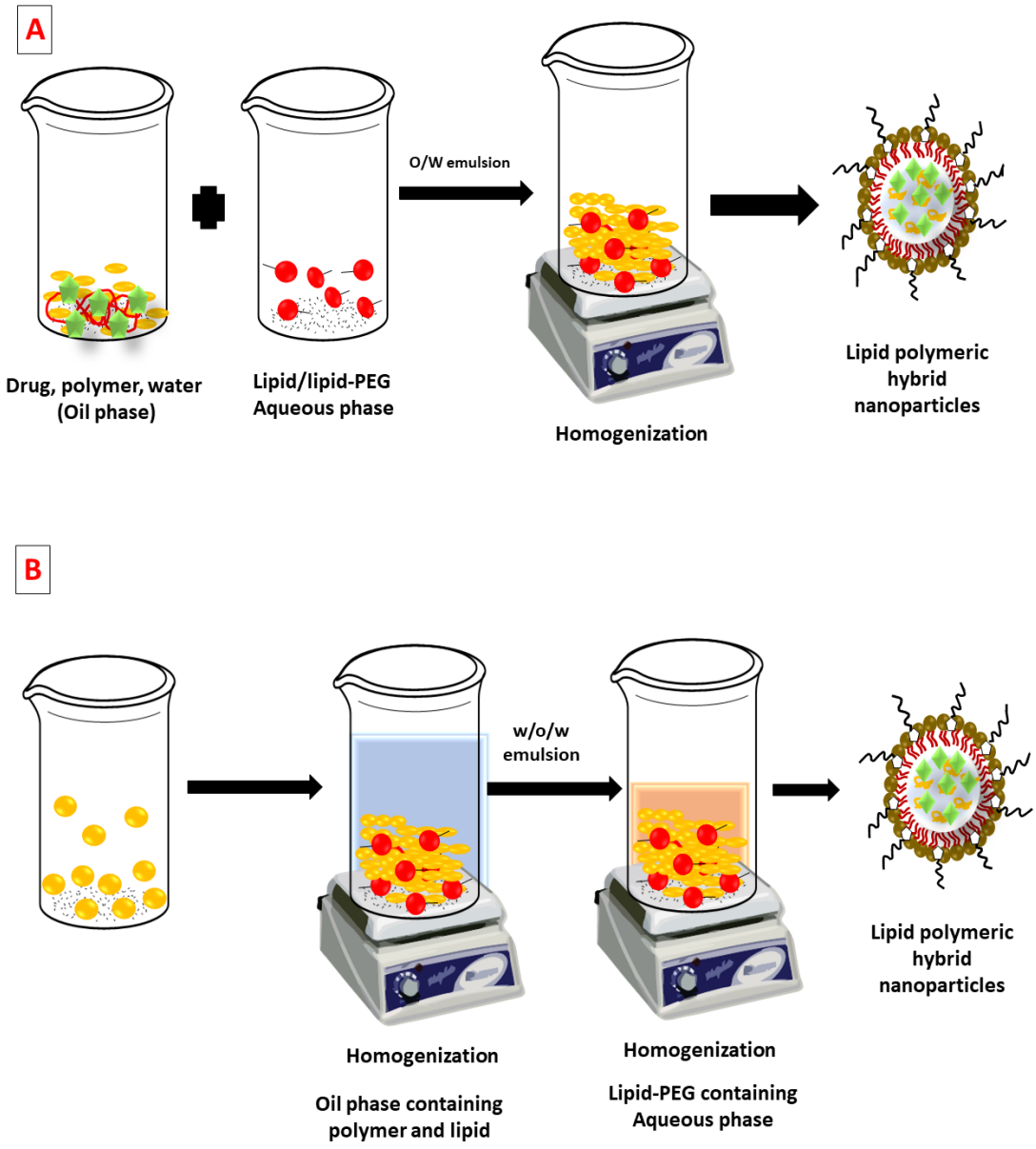

Fig. (5). The emulsion-solvent evaporation (ESE) process is used to create LPHNPs. A) Hydrophobic drugs are typically synthesized using a single ESE technique (soluble in oil phase). Drugs and polymers are dissolved in a water-immiscible solvent. An oil/water emulsion is formed by adding the resultant solution to a lipid/lipid–PEG containing aqueous phase under agitation. The oil phase evaporates, and a polymer core and lipid shell develop at the same time. B) Hydrophilic (water-soluble) medicines are prepared using the double ESE approach. Under steady stirring, an organic solvent comprising polymers and lipids emulsifies an aqueous drug solution. A w/o/w emulsion is created by re-emulsifying the lipid–PEG emulsion with an aqueous solvent. LPHNPs are formed when the oil phase evaporates. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

polymer layer, and finally, an outer lipid PEG shell. The ESE approach often produces larger LPHNPs than standard nanoprecipitation [88].

Bershteyn *et al*. used this method to prepare nanoparticles consisting of a mixture of biotin- PEG-DSPC and DMPC. Dichloromethane was used to dissolve the polymer and lipid in a 25:1 weight ratio (5 mL). An ultra-homogenizer was then used to completely emulsify the organic phase into an equal volume of water (40 mL). After 12 hours of stirring at room temperature, the dichloromethane was removed. The following are the main drawbacks of this approach: aggregation with a high polydispersity index and instability with respect to Ostwald ripening or coalescence. The encapsulation efficiency of hydrophilic drugs can be improved by reducing the PDI and optimising numerous parameters, including solvent type, amphiphile concentration, amphiphile viscosity and shear stress [89].

7. DRUG-LOADED HYBRID VESICULAR SYSTEM FOR THE TREATMENT OF CANCER

7.1. Polymeric–lipid Hybrid Nanovesicles (Lipo-polymersomes)

To address the shortcomings of polymersomes and liposomes, the development of mixed vesicles of lipids and copolymers is a potential technique that has recently been developed. This approach is useful for tailoring membrane properties. Compared to pure liposomes, hybrid vesicles based on polymer lipids exhibit higher viscoelastic properties [90]. Liposomes have a limited ability to withstand high osmotic pressure and high shear rates, which is one of

their current limitations. Drug release can be better controlled by polymer-lipid hybrid vesicles in the blood because of the higher permeability and loading efficiency provided by the lipid component. These amphiphiles must have the appropriate chemical composition and molar ratio to form a stable hybrid vesicle. In addition to the molar content, charge, and size of the individual components, the vesicles' form and stability are affected by the lipid melting point, temperature, and the copolymer membrane thickness [91]. Classifications of composition are possible for hybrid lipid-polymer vesicles, the first two involving a lipid core and the third involving a polymer core and a mixture of the two. Attempts have been made to overcome the disadvantages of liposomes and polymersomes by combining the two into a single hybrid lipopolymersome (HLP). By combining both polymers and lipids, these newly discovered nanostructured (polymersome) formulations retain the biocompatibility and biofunctionality of liposomes without losing their excellent robustness and tunable structural properties. In a recent study, the use of HLPs instead of polymersomes was found to target cancer cell receptors more effectively than polymersomes. It is possible to prepare polymersomes using a variety of techniques, including solvent exchange, film rehydration, and electroforming. Electroformed polymersomes have been prepared. Polymersomes with adequate size, monodispersity, and homogeneity in a bilayer membrane can be prepared by the double emulsion method (developed using capillary microfluidics). This technique is commonly used because of its reproducibility, simplicity, and control over nanoparticle size, which contribute to its popularity. Filter extrusion is a time-consuming and difficult way to reduce the polydispersity index of liposomes, even when the temperature is high [92].

Passive diffusion, driven primarily by concentration gradients, is the most common method for releasing drugs from polymersomes. Recently, a series of stimulus-dependent polymersomes have been developed that can release their payload in response to external or internal stimuli once they arrive at the target site. They can reduce therapeutic efficacy and adverse effects by activating drug release at the target site. Chemical (mainly through redox molecular chain composition and pH) and physical triggers are two ways stimulatory polymersomes can be created to release the therapeutic drug at the target site. These clever nanostructures are able to receive, transmit, and respond to stimuli with great efficiency. Fig. (**6**) shows polymersomes in the diseased cell releasing intracellular drugs in response to stimuli. To release the encapsulated drugs, the backbone of polymersomes dissolves intracellularly in response to

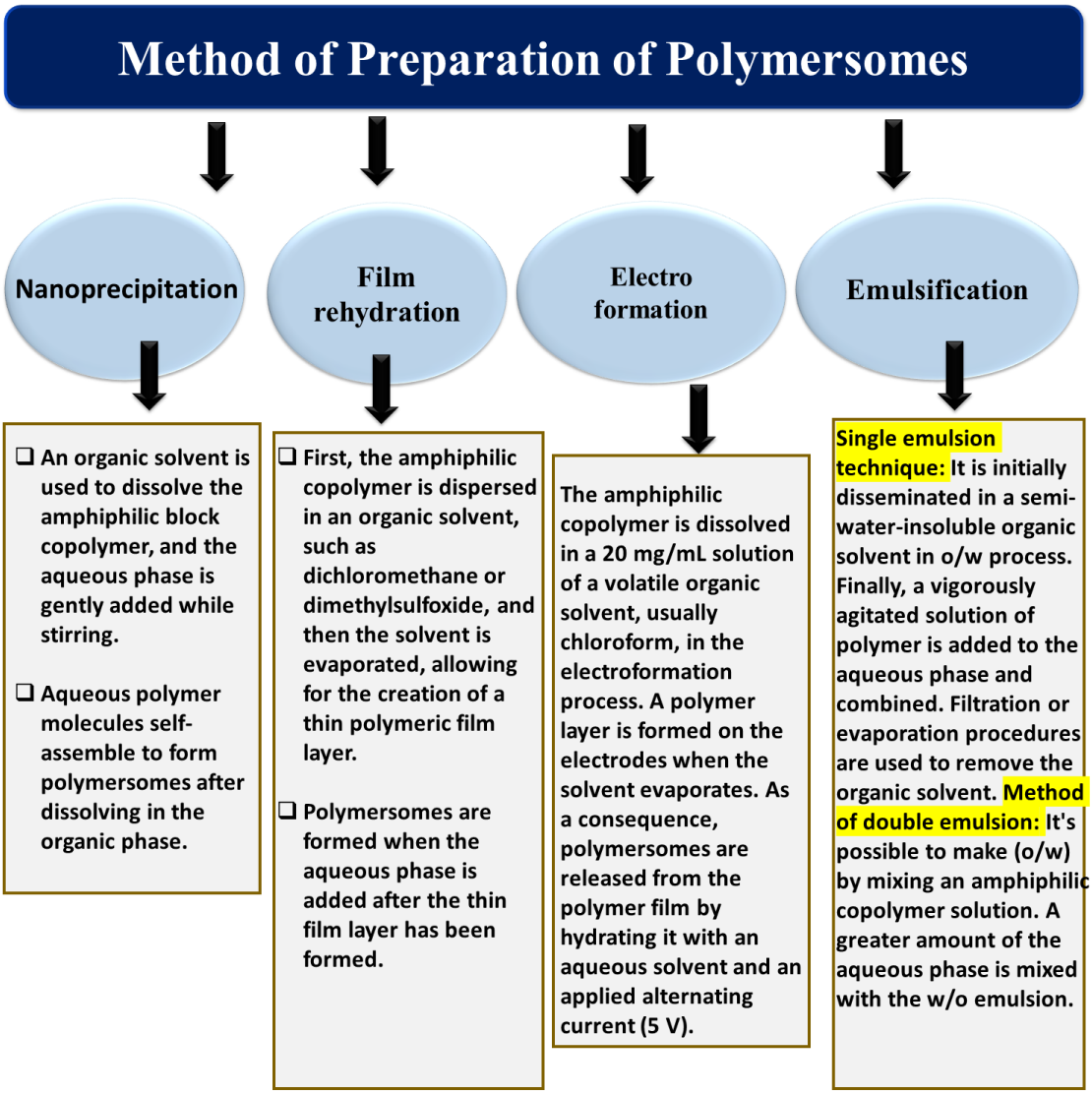

Fig. (6). Different methods of preparation of polymersomes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

abnormal stimuli such as pH, abnormal temperature, abnormal glucose levels, and oxidative stress. Over the years, polymersomes have been developed to respond to various stimuli such as enzymes, pH, photo, glucose, voltage, and magnetic fields [93].

Increasing research on biocompatible polymersomes has sparked renewed interest in their potential as delivery methods for anticancer drugs in the coming years. PEG, PLA, and polycaprolactone are all FDA-approved monomers in the United States. The development of drug resistance during therapy and the difficulty of penetrating thick tumor tissue make successful cancer therapy problematic, despite the widespread use of biocompatible polymersomes for cancer drug delivery. Therefore, polymersome-based cancer treatments, such as gene therapy, protein therapy, and chemotherapy, should be used in conjunction with polymersome-based therapies [94].

Systemic administration of an anticancer cocktail can be accomplished *via* biodegradable polymersomes, as described by Ahmed *et al*. Hydrophobic and hydrophilic drugs, paclitaxel and doxorubicin, are successfully transported through these polymer-based envelopes, which have a thick hydrophobic membrane and an aqueous lumen. Although polymersomes circulate in the body for a long period of time, the drugs they contain are degraded and released after only one day, by which time the tumours being treated have almost doubled in size. Polymersomes shrink tumours by half after five days, compared to the free drug cocktail, and have a higher maximum tolerated dose. Tumours shrink by half after five days with polymersomes. Researchers have shown that polymersomes can kill twice as many tumour cells as free drugs while increasing the maximum tolerated dose and drug accumulation in tumours. This suggests that they may be a promising method for delivering many drugs simultaneously [95]. Redox-sensitive polymersomes decorated with the peptide cNGQGEQc were prepared and loaded with DOX by Zou *et al*. It was shown that Lipo-DOX circulated longer and accumulated more in the tumour than Lipo-DOX alone in mice treated with the prepared formulation. The tolerated dose of Lipo-DOX was six times higher in mice than in the manufactured formulation [96]. Flutamide-loaded polymersomes were found to be superior to liposomal formulations in terms of *in vivo* efficacy after oral administration, as shown by Youssef S. F *et al*., who found that flutamide-loaded polymersomes had plasma concentrations 3.9 and 4.7 times higher than liposomes and drug suspensions, respectively [97]. Peptide-modified polymers containing DOX were developed by Zou Y *et al*. for the treatment of SKOV3 ovarian cancer resistant to standard chemotherapy. Biodistribution studies have shown that polymersome formulations accumulate more in tumours than lipo-DOX *in vivo* and *in vitro* tests compared to the manufactured formulation (IC50 = 8.7 DOX equiv./ml) [98].

7.2. Peptide-based Hybrid Vesicles

Extensive research on the medicinal potential of peptides has shown them to be useful in a wide variety of diseases. Peptide therapeutics, one of nature's most adaptable tools, are now gaining a deeper and more comprehensive understanding with respect to their potential use in cancer therapy and detection [99]. Peptides have multiple applications in the fight against cancer. Some possibilities include targeting cancer cells with therapies, simulating natural proteins to amplify or inhibit signaling, or mediating the transport of treatments through the barrier [100]. In recent years, there has been a surge of interest in cancer therapy using therapeutic peptides. Tumors can be driven to cell death by a variety of means, including blocking the production of angiogenesis and PPI inhibitors, enzymes, or other mechanisms that regulate gene expression or signal transduction [101]. Therapeutic peptides are preferred over those certain biologics and limited particles because they are easy to synthesize, penetrate the cell membrane, have higher activity, have limited interaction with other drugs, and are least likely to accumulate in certain body organs, such as the kidney or hepatic, have adverse effects, are comparatively less immunogenic, and have chemical and biological diversity. There are a number of serious drawbacks, including limited *in vivo* stability, almost no resistance to the action of proteolytic enzymes in serum, and a very short half-life [102]. The development of therapeutic peptides also encounters difficulties in manufacturing. The anti-tumour effects of natural peptides have been discovered in many different forms. Cyclopeptide, *Ganoderma lucidum*, a polysaccharide peptide (an antiangiogenic drug), RA -V (deoxybouvardin) obtained from *Rubia yunnanensis* (used in the treatment of human breast cancer), soybean-derived peptide, and lunasin are just a few examples of plants [103]. For the treatment of malignancies of the pancreas, prostate, and breast, animal-derived peptides have been found to be useful. These include the heart tissue-derived atrial natriuretic peptide, vascular dilator, long-acting natriuretic peptide, and kaliuretic peptide. The Angiotensin-(1-7) growth inhibitory peptides from alpha-fetoprotein, porcine spleen-derived alpha-fetoprotein, and other peptides were digested from animal proteins. The anticancer properties of tyrosereleutide and tyroservaltide are also well documented. Antitumor peptides obtained from marine sources, such as somocystinamide, A. aplidine, jaspamide, dolastatin 10, vitilevuamide, neovastate (AE -941), and mycothiazole have been shown to be effective in the treatment of cancer. The anticancer effects of peptides derived from microorganisms, such as muramyl dipeptide (MDP) from Mycobacterium, FK565, and bestatin extracted from the Streptomyces bacteria, have also been demonstrated. Preventing the degradation of blood proteases by blocking the C- and N-termini, creating cyclic peptides, substituting the D-counterpart of AA with its D-counterpart, or using synthetic AA, which are incompatible with endogenous proteases, can prolong the half-life of the peptide [104].

According to Penchala *et al*., the half-life of peptides can be prolonged without affecting their efficacy. Current information is insufficient to develop tiny compounds that can bind reversibly to other serum proteins and be used to extend the half-life of other serum proteins. Using this approach, researchers were able to increase the half-life of the agonist for gonadotropin-releasing hormone (GnRH) while maintaining binding affinity, resulting in increased efficacy in animals [105]. In this technique, peptides are readily attached to AG10, a small molecule, using short linkers. This enables it to bind precisely and reversibly to the plasma protein transthyretin (TTR) (56 kDa protein) for further distribution in the biological system. To avoid degradation by serum proteases, the peptides attracted most of the TTR to themselves and were thus preserved from degradation by the kidney. For the four peptides used in the study, the tripeptide (Arg-GlyLys-MCA), neurotensin, D-6-Lys-GnRH, and native GnRH, a 13-fold improvement in the half-life of GnRH had to be observed, especially compared to its non-native agonist. In addition, the PEGylation approach, in which PEG is conjugated with peptides, leading to polypeptide expansion that slows renal filtration and clearance, could potentially increase the half-life. With properties similar to those of the recombinant polypeptide, XTEN is a relatively stable and soluble protein with less hypersensitivity, which also resulted in an increase in peptide half-life. The half-life of teduglutide, a glucagon-like peptide-2 (GLP2), was prolonged when it was conjugated with XTEN [106].

In addition, the carboxyl groups present in the sialic acids found on the cell surface of mucopolysaccharides (such as N-glycolylneuraminic acid, N-acetylneuraminic acid, and many more) contain negative phosphate and positive ammonium charges in the cell membranes, which are believed to be the primary cause of the negative surface charges of the cells. The negative charge of tumor cell membranes is associated with their ability to invade [107]. Malignant cells and trophoblasts have strong negative surface charges, which may explain why the immune system does not reject them. Neutralizing the negative charge of tumor cells could allow

lymphocytes to approach and kill them. Due to a polarization effect, polycations attach to the negatively charged surfaces of mammalian cells, leading to charge neutralization and other cell-related effects, such as cell agglutination and cell deformation. HIV-1 Tat can penetrate cell membranes, as published in 1988 by two different laboratories working on the virus. Peptides coupled to Tat have been shown to enter cells within seconds. The motor driving this CPP has residues 48-57 GRKKRRQRRR carrying an 8-volt charge. Following this initial discovery, others have been discovered. Antp is a homeodomain of the fly consisting of residues 43-58 RQIKIWFQNRRMKWKK of the Antennapedia, which has a +7e charge. The tegument protein VP22 of herpes simplex virus type 1 (HSV-1) has a charge of +15e. It is a chimeric peptide consisting of 12 galanin residues at the N-terminus and 14 mastoparan residues plus a linking lysine of the GWTLNSAGYLLG-K-INLKALAALAKKIL-amide transporter [108]. Due to the amide group at its end, it has a charge of +15e. Peptides with a positive charge, such as this one, can penetrate the plasma membranes of living cells and transport payloads much larger than the 500 da limit. Depending on the size of the payload, the Tat peptide transports it across cell membranes with remarkable efficiency *via* two functionally distinct methods. Caveolae endocytosis and macropinocytosis allow large payloads, such as proteins or quantum dots, to enter the cytoplasmic vesicles in which they are enclosed. There are two ways to enter cells, endocytosis and transduction, both of which use membrane potential to enter the cytoplasm [109].

The results of a series of cell-penetrating peptide (CPP) conjugated therapies (CTTs) currently being tested in clinical trials are eagerly awaited. Proliferation, survival, and migration are three of the primary targets of CTTs in cancer progression. Furthermore, several of these CTTs improve the level of sensitivity of conventional cancer therapies, such as radiation and other DNA-damaging chemotherapies, allowing for a reduction in the lethal dose essential for effective therapy of the tumour. These CTTs prevent the peptide or protein bound to the CPP from interacting with tumor-specific protein-protein interactions [110]. Acidic plasma membrane motifs, such as proteoglycans and glycolipids, are targeted by CPP for peptide internalization regardless of cell type. There is still much work to be done to understand exactly how this process works, but it depends on a number of factors, including the type of CPP and the size and cargo charge. Numerous processes have been discovered to be involved in the internalisation of antp and Tat CPPs. These include caveolin-dependent endocytosis, clathrin-dependent endocytosis, direct intracellular translocation, and macropinocytosis, among other possibilities [111]. CTT avoids lysosomal destruction after endosomal internalization by an unknown method. Delivery of therapeutic doses of CTTs into the cytosol is complicated by endosomal escape, which has been well studied. Once the CTT enters the cytosol, it can immediately bind to its target (Fig. **7**). Several studies have shown that breast, lung, pancreatic, ovarian, and colon cancers benefit from CTTs. Anticancer drugs have used CTTs to decrease the nuclear translocation of oncoproteins, alter oncoprotein signaling, and disrupt cell-ECM interactions [112].

CPPs are a novel and unique approach to addressing the problem of drug bioavailability, which has led to the development of a number of new technologies. CPPs have been shown to be effective *in vivo*, making them extremely promising tools for the future. For drugs to be absorbed by the body, they must first be chemically bound to their carriers. A second technique focuses on the sustainable development of complexes with drugs that differ in chemical composition depending on the active ingredient. [113]. These two CPP techniques have been reported previously. In the presence of proteins or nucleic acids from the pep and MPG families, these relatively short amphipathic peptides can aggregate into stable NPs. Using Pep and MPG-based NPs that infiltrate cells *via* the endocytic route, it is possible to approach a broad range of cell lines and animal models. Three domains in MPG and Pep-1 are primary amphipathic peptides: a variable N-terminal hydrophobic motif; a hydrophilic lysine-rich domain derived from the NLS (Nuclear Localization Sequence) of the large T antigen of SV40 (Simian Virus 40), necessary for important linkages with nucleic acids and intracellular charge transport. The hydrophobic domain is the fundamental difference between the two peptide families. For each cargo molecule, two or more MPG or pep peptide molecules are packaged into nanoparticles, greatly increasing the stability of the cargo and its resistance to degradation within the cell [114]. Using MPG and pep peptides, it was found that their ability to bind to the lipid moiety of the membrane is critical for their cellular absorption. Based on studies of the ability of MPG to transfect reporter genes or siRNA in the existence of various endocytic blockers, the uptake of the MPG-DNA complex is, irrespective of the endosomal system, controlled by membrane permeability and depends on particle size [115]. Electrostatic interactions with DNA and the NLS motif of MPG are necessary for the transport of nucleic acids to the target nucleus. After crossing the cell membrane, the NLS domain speeds up plasmid entry into the nucleus, allowing MPG-DNA particles to make contact with nuclear import mechanisms. Because the Pep-1 cargo complex cannot be absorbed by the endosomal pathway like MPGs, it has a direct correlation to particle size and cargo type in the biological response it elicits. These properties include the capacity to degrade in a biodegradable or biodegradable manner; biocompatibility; no antigenicity; no buildup in the body; functional groups that may be used to fix chemicals; and the ability to keep the original selectivity for the target [116].

As lactic acid builds up in the body and the rate of oxidative phosphorylation decreases, most cancerous tissues are acidic. As a result, medications in delivery systems that are vulnerable to pH variations may be released prematurely. A peptide's protonation and deprotonation may be switched on or off in pH-sensitive peptide systems, allowing reaction pathways linked to protonation and deprotonation to be activated [117]. Controlling the secondary structure of peptides by conformational reversal is commonly achieved *via* the pH stimulus, which results in regulated, switchable configurations of often convoluted structures. Wei *et al*. investigated branched copolymers as drug delivery methods based on their dendritic architecture. Branched polyHPMA copolymers and DOX conjugates with an estimated molecular weight (MW) of about 165 kDa were designed and synthesized using one-pot synthesis and drug conjugation. As an intelligent nanoscale drug delivery system (NDDS), this conjugation is also further investigated. Negatively charged nanoparticles could be formed with the branched conjugate. According to dynamic light scattering (DLS) and scanning electron microscopy, the self-assembled nanoparticles had diameters of 102 and 95 nm, respectively. The decomposition of nanoparticles into low molecular weight compounds (23-25 kDa) in the presence of cathepsin B or papain was studied by DLS and size exclusion chromatography. Since the DOX was linked to the branched copolymer by a hydrazone bond formed on the nanoparticles, the drug was released as a function of pH. The conjugate-based nanoparticles accumulated more than free DOX in breast cancer cells, resulting in improved indices of cancer treatment. In addition, immunohistochemical assays demonstrated the broad distribution of the drug in breast cancer cells. Consequently, no evidence of systemic side effects was found in normal mice in *in vivo* studies. The combined branched HPMA copolymer-DOX system can be used as a safe and effective NDDS for cancer treatment that is pH and enzyme responsive [118].

Tang *et al*. have developed reversibly activated cell-penetrating peptides (RACPP) that can be activated and deactivated in response to changes in pH. RACPP is composed of oligoarginine that has been connected to a pH-sensitive masking sequence by means of a polyglycine linker. To improve the specificity and targeting of encapsulated paclitaxel delivery, the sequence HE-CPP was linked to polyethylene glycol polylactic acid polymer micelles (PMs- HE-

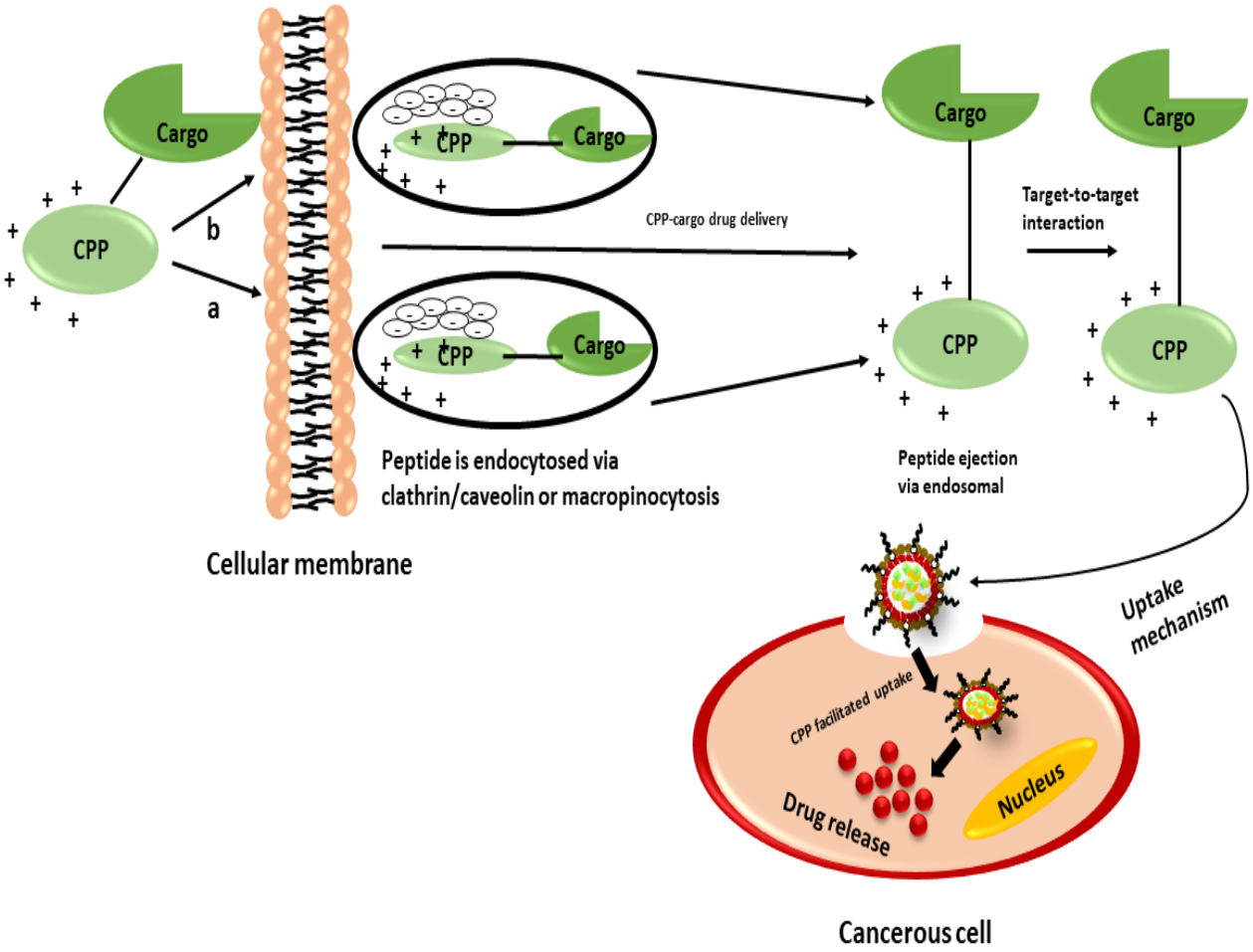

Fig. (7). CPP internalisation mechanism includes clathrin-based endocytosis, caveolin-based endocytosis, macropinocytosis, or direct intracellular translocation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

CPP) (PTX). The results of the proposed study showed that the encapsulation efficiency, charge capacity, size distribution, and reversible charge conversion in response to pH were good. It was observed that PM-HE-CPP exhibited an extremely negative zeta potential at pH 7, an almost positively charged potential at pH 6, and an extremely charged potential at lower pH. Endocytosis in the slightly acidic tumour microenvironment was enhanced by coumarin 6-loaded PMs- HE-CPP (C6/PMs- HE-CPP) *via* energy-dependent endocytosis. Furthermore, PTX/PM- HE-CPP was much more hazardous to mouse breast cancer cells (4T1) at pH 6.5 than at pH 7.4. The tumour-targeted properties of PM- HE-CPP were verified in *in vivo* imaging studies using 4T1-BALB/c tumour xenograft models. In this tumour model, PTX/PMs- HE-CPP showed better anti-tumour activity than Taxol® and unmodified polymeric micelles. Therefore, RACPPs have the potential to improve the selectivity and reversible net charge conversion properties of CPPs and enhance the ability of nanoparticles to target specific cells [119].

It is common for cancer patients to receive chemotherapy as part of their treatment. Drug delivery methods based on NPs have performed a significant role in this research since these may prevent drug side effects and enhance therapeutic potential. Penetration into tumour-associated leaky vessels, enhanced intracellular accumulation of drugs, and ultimate removal from the body without harming normal tissues are largely due to the EPR effect and self-assembled peptide-based NPs. As a result, peptide-based nanocarriers for chemotherapeutic drugs have received much attention. Hybrid hydrogels containing peptides are widely used for drug delivery [120]. Huang *et al*. used the peptides Fmoc-diphenylalanine (Fmoc- FF) and Konjac glucomannan (KGM) to prepare a unique hybrid hydrogel that exhibits amazing performance, indicating its special performance as a carrier for hydrophobic drugs. It has been demonstrated that modifying the KGM concentration, maturation time, molecular weight, or b-mannanase concentration can lead to delayed and regulated delivery of docetaxel. In this study, a novel method was developed to prepare fmoc- FF-KGM hybrid hydrogels as delayed release drug carriers [121]. Shirazi *et al*. produced four PA analogues, including one that PA4 [K(C16)-R-K(C16), which was demonstrated to increase the cellular permeability of the anti-HIV medication 2',3'-dideoxy-3'-thiacythidine and phosphopeptide (PEpYLGLD) in human leukaemia or ovarian cells after 2 hours of exposure to the compound [122]. Similarly, an epidermal growth factor (EGFR)-binding PA was used by Liang *et al*. to produce ultrastable self-assembling peptide nanovesicles (SPVs). In conjunction with therapeutic payloads, SPVs targeting EGFR have the potential to deliver additional drugs or plasmid DNA to cancer sites. The anticancer drug delivery system based on this peptide, amphiphile, has the potential to be a useful weapon in the fight against cancer. Peptide hydrogels for drug delivery can also be prepared from the PA [123].

7.3. Silica-based Hybrid Nanoparticles

Nanoparticles of silica show promising properties for use as versatile nano systems for drug delivery. They are advantageous because of their distinctive properties, which include biocompatibil-

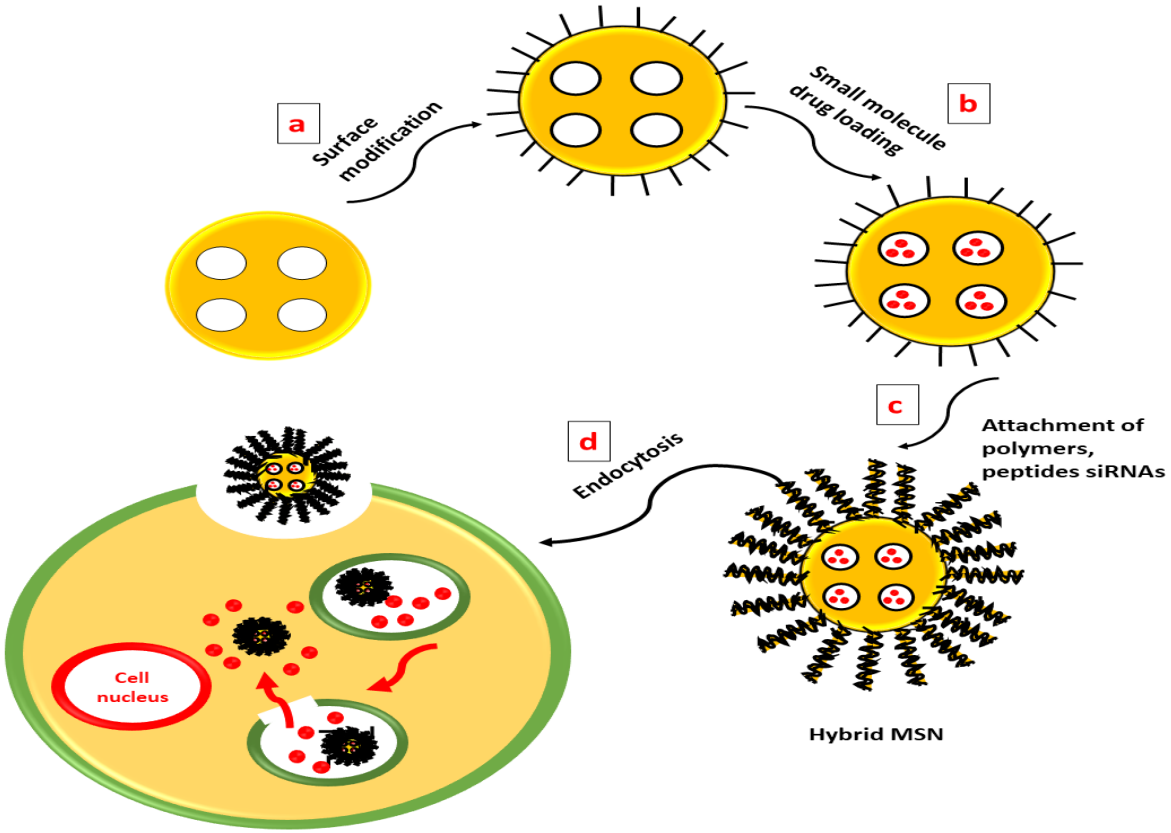

Fig. (8). The surface is initially changed with MSN, then tiny molecules are loaded, and polymers, peptides, and siRNA are functionalized. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ity, biodegradability, large surface area and pore size, low toxicity, and homogeneous dissemination of target molecules over the porous area [124]. Silanol groups on the surface of the porous silica nanoparticles interact with the RBC membrane and trigger hemolysis. The surface modification of silica nanoparticles provides a completely safe and versatile framework for nanomedicine production. Due to the presence of silanol on their surface, silica nanoparticles have a unique ability to be functionalized. Surface functionalization is required for toxicity reduction and encapsulation of medical agents with various properties [125]. To create hybrid, multifunctional, smart silica nanoparticles, surface functionalization offers the possibility of combining silica nanoparticles with many additional materials *via* ionic, van der Waals, covalent, or ionocovalent compounds. Because of the simple surface chemistry of silica, it is possible to combine it with other materials to create a hybrid structure with advanced properties that can be used in a variety of fields, including medicine. The functionalization of silica surface is usually based on the use of silane groups. There are several factors that affect the formation of smart silica-based hybrid structures, including the chemistry of the particle surface [126]. Mesoporous silica nanoparticles can be functionalized in three different topological domains: the silica framework, the pores, and the outer surface of the silica particle, all individually (Fig. **8**). An inorganic silica material can be functionalized with organic components to create fascinating hybrid materials with a variety of properties [127]. Due to the structural order of the silica framework, it is extremely thermally and mechanically stable, while additional constituents such as fluorophores and conducting polymers impart favourable optical, electrochemical, and magnetic (contrast agents for magnetic resonance imaging) properties. Functionalized silica NPs can be prepared by post-synthetic silanization, co-condensation, or surface polymerization [128]. These methods allow the flexible fabrication of silica-based hybrid structures. Hundreds of empty channels can be found in mesoporous silica nanoparticles, which include the 2D hexagonal MCM-41 and 3D cubic SBA-15 nanoparticles. Bioactive substances can be encapsulated or absorbed *via* these mesopores. Their great chemical and thermal stability, as well as their tunable pore size in the range of 2-50 nm, make them ideal for drug administration and biological applications [129]. To prepare MSN, tetraethoxysilane is hydrolyzed using a base catalyst and then condensed using a CTAB template. At the end, the MSN particles are coated with a (trialkoxy) silane containing functional groups that could be used to link peptide targeting ligands, polymers or siRNA [130]. For example, the thiol-functionalized MSN-SH was first treated with (3-mercaptopropyl)-trimethoxysilane. To obtain the desired MSN-TPP, the antibiotic peptide (KLAKLAK)2 was conjugated to TPP and then added to the resulting MSN-SH particles. Topotecan was loaded into MSN channels by swirling a topotecan hydrochloride solution and MSN-TPep in PBS overnight at room temperature. It was then electrostatically attached to the positively charged MSN-TPep nanoparticles by PEG-PLL (DMA) to generate a negatively charged MSN-TPep/ PEG-PLL (DMA) nanoparticle comprising a pH-sensitive anionic polyethylene glycol-blocked-2,3, dimethylmaleic anhydride-modified poly(L-lysine) [131].

It is possible to use nanoparticles to facilitate drug delivery in a passive manner. The shape, size, stiffness, and charge of materials can be altered to enhance nanoparticle and drug tissue accumulation, adhesion, and uptake into cells [132]. The unbound drugs can be recognised and eliminated by the RES, so polymeric drug carrier particles have an advantage over free drug delivery in terms of longer circulation time in the body. Although DOX and camptothecin are highly potent chemotherapeutic agents, their use in humans is prohibited due to the poor water solubility of the drug. Therefore, it is crucial to find a treatment for hydrophobic drug molecules.

DOX-loaded chitosan nanoparticles with a silicone oxide coating were compared with stearic acid-G-chitosan polymer micelles. The micelles had a slower release rate *in vitro*, but the nanoparticles had a higher specific surface area due to their mesoporous structure [133]. This allowed the nanoparticles to penetrate the cells more easily due to their larger specific surface area. Nanofibers of mesoporous silica composite loaded with Dox were used in another study to reduce the risk of the possibility of disease progression of breast-conserving treatment by releasing the antitumor agent in two steps (such as burst and sustained release). Before the polymer fibers can deliver the drug to the external medium, it must always be released from the solution formed in the MSNs. Indeed, RES-induced delays could lead to a delay in the identification of polymer particles. Generation II MSNs have mostly been developed in a variety of forms that could be effectively used for targeted drug delivery systems by modifying their surfaces with functional polymers such as polyethylene glycol (PEG). For example, PEG has excellent protein repellent properties and can significantly prolong circulation time. The surface of the nanoparticles was decorated with polyethylenimine poly-eth-yle-ne glycol (PEI-PEG), which was found to reduce the uptake of RES and preserve roughly 8% of the nanoparticle dose delivered at the tumour site. Another polymer used to functionalize nanocarriers is polyvinylpyrrolidone (PVP). To protect silica microspheres, PVP was adsorbed on their surface and NaOH was used as an etchant in one study. According to the preventive character of PVP and in homogenous ablation, mesopores were etched into the silica microspheres. Polymers such as PEG, PEI, PVP, chitosan, and poly-L-lactic acid (PLLA) are widely used to modify the surface of advanced organic-inorganic silica hybrids for targeting drugs to cancer cells [134]. Co-administration of Dox and siRNA targeting P-glycoprotein (Pgp), a drug exporter, was used by Meng *et al*., and they succeeded in overcoming Dox resistance in an MDR breast cancer xenograft. High-throughput screening of MCF -7/MDR breast cancer cells led to the selection of pgp siRNA from a list of drug resistance targets. It was demonstrated that a PEI-PEG functionalized with a 50 nm MSNP stably attached Dox and delivered pgp siRNA to the tumour site in a protected way in an MCF -7/MDR nude xenograft model. This 8% increase in permeability and retention at the tumour site was enabled by the reduced reticuloendothelial uptake of the nanocarrier design. Because of synergistic inhibition of tumour growth *in vivo*, the dual delivery system outperformed free Dox and the carrier loaded with either drug or siRNA alone. Several xenograft biopsies analysed showed significant knockdown of Pgp at heterogeneous tumour sites corresponding to regions where Dox was released intracellularly and induced apoptosis. However, it is not the heterogeneous PGP expression of MDR cells themselves, but the tumour microenvironment that is the source of variability. Overall, these results demonstrate that it is possible to overcome xenograft resistance to Dox with a combination of drug and siRNA nanocarriers. Furthermore, this study is the first to examine the effect of tumour microenvironment heterogeneity on the therapeutic efficacy of siRNA through *in vivo* delivery [135].

7.4. Gold-based Hybrid Nano Vesicular System

In addition to biocompatibility, plasmonic absorbance, and thiol functionalization, gold nanoparticles (AuNPs or GNPs) have unique features. Biosensing, imaging, and photothermal cancer therapy have all been investigated extensively using AuNPs. The capacity of AuNPs to pegylate cancers enables them to be concentrated in tumours [136]. The capacity to function as nanocarriers for the delivery of chemo- and biologic treatments to cancer cells is another benefit, allowing for a more comprehensive therapeutic approach. $HAuCl_4$ reduction with citrate as a reducing agent is the most commonly used method for the preparation of AuNPs. To achieve colloidal stability and functionalization, AuNPs may be simply decorated with PEG or DNA *via* thiol-Au interactions [137]. Hydrophobic interactions or chemical connections between DNA base pairs and the AuNP surface may also be used to adsorb non-thiolated DNA on AuNP surfaces. It is also feasible to load positive-charged medicines, such as Dox, onto AuNPs without the need for covalent bonds. AuNPs were integrated into DNA prior to the addition of a positively charged medication, as can be seen in Fig. (**9**). The PEG-coated AuNPs were further protected by thiol-Au interactions [138].

Once the organic or inorganic delivery system has entered the bloodstream, it is imperative that *in vivo* models be developed to deliver the drug to its target as quickly as possible. There are two ways to do this: passive targeting and active targeting. To summarise, passive targeting depends on ligands on the surface of the nanocarrier having a selective character, but likely specific identification by the cell surface receptors, whereas active targeting depends on the unique features of certain sick tissues or hypervascularized cells [139]. Proteins, peptidic sequences, or particular substrates can all be used as ligands. Additionally, a carrier optimized for *in vivo* delivery may benefit from the use of both targeting methods. Macrophage nonspecific absorption and degradation restrict nanocarriers' potency (immune response). Physical parameters such as average size and monodispersity of inorganic components like morphology and shape anisotropy must also be addressed to maximize therapeutic effectiveness [140]. It has recently been shown that the size and shape of Au nanoparticles affect their absorption into mammalian cells. It was shown that nanoparticle exocytosis corresponds linearly with particle size, which is a departure from their earlier study on cellular uptake. In addition, a paradigm for predicting the relationship between size and exocytosis has been developed for various cancer cell lines, which is of great importance for the evaluation of nanotoxicity [141]. Bhumkar *et al*. recently published a paper describing the use of functionalized gold nanoparticles as insulin carriers. Consequently, they conclude this section by demonstrating that gold nanoparticles may also transport bigger biomolecules (such as proteins) than previously thought. A biocompatible polymer, chitosan, is loaded onto gold nanoparticles as part of their technique. Chitosan, as predicted, enhanced the surface characteristics of biomolecules by increasing their binding affinity. Depending on the amount of chitosan charged, the zeta potential increased from +4.23 to +62.7 mV. Finally, the insulin-loaded samples were administered orally and nasally to increase the pharmacodynamic effect [142].

Small, biocompatible and easily modifiable gold nanoparticles (AuNPs) are a type of noble metal nanoparticles. Due to these advantages, AuNPs are widely used and studied in biochemistry and biomedical engineering. Due to their unique physical and chemical properties, AuNPs are suitable for use in cancer treatment [143]. The photoelectric absorption of AuNPs in radio sensitization can be increased while the range of the electron beam is decreased. The use of AuNPs as a radiosensitizer for cancer therapy with X-rays prolongs the lifespan of mice in *in vivo* studies. Radiosensitization is also observed in cancer cells resistant to chemotherapy [144]. Irradiation with AuNPs causes cancer cells to produce more ROS, which significantly impairs the cell's ability to divide. The radiosensitizer AuNPs had a size-dependent lethal effect. AuNPs with a size of around 13 nm have the potential to be the most toxic. When the irradiation dose is increased from 4 Gy to 8 Gy, size-dependent effects are observed. AuNPs exhibited the highest fatal effect on tumour growth in the negative control group when administered at a dose of 6 Gy. Treatments with radiosensitization only kill tumour cells and do not cause visible damage to healthy tissue. When AuNPs are greater than 30 nm, their cytotoxicity is comparable to that of 13 nm, but it is much more pronounced. PEG-coated AuNPs with a size of about 13 nm are used to increase CT imaging and radiation sensitivity [145]. Drugs and gene therapy can benefit from AuNPs coated with a variety of ligands. Not only AuNPs are widely used in radiation safety, but also a variety of other metal nano-

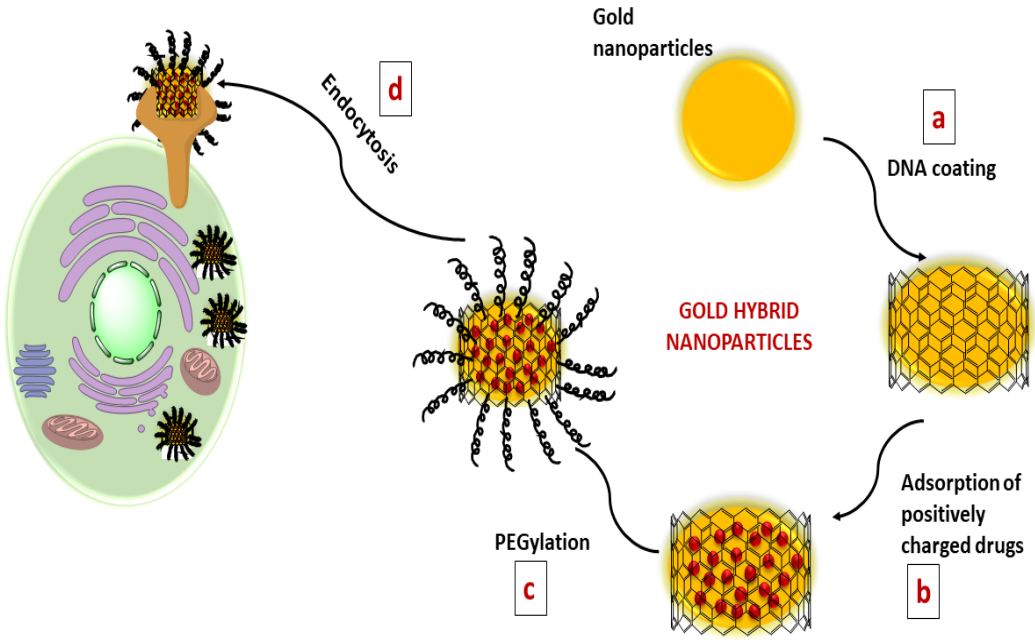

Fig. (9). For AuNPs, the particles are coated with DNA, then loaded with positively charged medicine, and finally PEGylated. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

particles. Apoptosis, oxidative stress, and membrane fluidity have all been mediated by silver nanoparticles (AgNPs). PEG and perfluorocarbon-coated tantalum-based nanoparticles, such as TaOx, are effective oxygen transporters that increase oxygen levels in cancer cells. This is because TaOx-loaded particles, such as TaOx, not only promote radiosensitization, although they often reduce hypoxia-induced radioresistance. To enhance cell growth inhibition, amorphous PEG -selenium nanoparticles act synergistically with X-rays to activate caspase-3, which is involved in cell death [146].

Using *in situ* reduction of the gold precursor HAuCl4 by HEPES diffusion and reduction, the production of Auns-based liposomes was documented by Mathiyazhakan *et al*. Laser irradiation of AuNS liposomes with near-infrared (NIR) pulses can lead to liposome disintegration and release of encapsulated drugs. DOX-AuNS liposomes showed a synergistic effect of microbubble cavitation, heating, and release of DOX compared to AuNS liposomes [147]. By using plasmonic gold nanoparticles loaded with photosensitizers, Lin *et al*. explored the methodology for theranostic applications. Polyethylene oxide-b-polystyrene was used to prepare the amphiphilic block copolymers. For synergistic photothermal/photodynamic cancer therapy, Ce6 was encapsulated in the built platform. The biocompatibility and solubility of the nanovehicle in an aqueous solution were both acceptable and practical. On the other hand, gold nanoparticles' plasmonic coupling effect showed NIR absorption in the range of 680-800 nm for gold vesicles. When the GVs and Ce6 were excited at 671nm, intense heat and singlet oxygen were produced, which killed cancer cells [148]. To fabricate photo- and thermoresponsive hybrid polymersomes, Amstad *et al*. used capillary microfluidic devices. These polymersomes were also able to accomplish temperature and photosensitivity by adding PNIPAM-b block copolymers (5 percent) into the membranes and the existence of AuNP in the hydrophobic shell. When the thermoresponsive amphiphiles' LCST (lower critical solution temperature) was exceeded by the intended temperature rise of the system, the encapsulated cargo was released. During blood circulation, drug leakage is a major problem for hydrophilic chemotherapeutic agents [149]. According to Fu *et al*., amphiphilic polyphosphazenes (PNPs) composed of amino-terminal poly(ethylene glycol) as hydrophilic chains and diethylaminoethyl-4-aminobenzoate (DEAB) as hydrophobic side groups improved the packing density of polymersomes. The DEAB units contained gold nanoparticles that served as inorganic crosslinks to build the polymer chains. Apart from an increase in tumour tissue aggregation, pH-responsive particles also had a rapid intracellular effect, while drug leakage in animals with a pH of 7.4 reduced drastically throughout the course of the investigation [150].

CONCLUSION AND FUTURE PERSPECTIVE

An essential platform for the creation of new and creative nanomedicines has been established by nanocomposites. Because of their synthetic tunability, a wide variety of nanoparticles containing several therapeutic compounds or delivery modes have been created. It is possible to include numerous therapies and/or modalities into a single nanoparticle, and to control the release of these nanoparticles to maximise the effectiveness of each therapy or modality. Drug delivery systems based on lipid nanoparticles are more advantageous than those based on colloidal or polymeric nanocarriers because of their unique properties. Lipid carriers' biocompatibility, biodegradability, scalability, and regulated and changeable release patterns are among their most significant features. Hydrophilic and lipophilic medicines can be transported *via* lipid nanoparticles. Topical, oral, parenteral, ophthalmic, pulmonary, and even brain medication administration are all options. Each mode of administration has its own advantages and drawbacks to consider while using these nanoparticles. In the near future, lipid nanoparticles could be used to deliver a wide range of pharmaceutically important active components, from tiny molecules to proteins and genes, *via* lipid nanoparticles. In the following phase, we need to focus on increasing hybrid nanoparticles' *in vivo* performance. The surface qualities of hybrid nanoparticles need to be enhanced so that they may remain in the blood for a longer period of time and target cancer cells more effectively. This can make it more difficult to find the right dosage and potentially raise the risk of experiencing negative side effects. Consequently, the composition of nanoparticles must be fine-tuned to establish the best therapeutic combinations and dosage regimens. A single delivery vehicle can offer several advantages, including cheaper production costs and higher patient compliance, as well as easier monitoring of drug release, pharmacokinetics, and

biodistribution of many medications. New therapeutic and drug delivery applications from the laboratory to the patient's bedside have been proven by LPHNPs, with a major and ongoing effect in the field of cancer. Indeed, LPHNPs have previously shown advantages over liposomes and polymeric NPs in some instances. A large-scale industrial production of NPs has already been developed that is both efficient and easy to scale up. Future clinical studies are expected to broaden the use of LPHNPs beyond the active targeting of anticancer medicines in oncology and into more general medical treatment and neurotherapeutics applications. To fully comprehend hybrid nanoparticles' *in vivo* toxicity profiles, it is imperative that their absorption, distribution, metabolism, and excretion (ADME) behaviour be well assessed. Hybrid nanoparticles, if designed properly in terms of formulation, surface characteristics, and ADME behaviour, might help close the gap between preclinical results in animal and human clinical outcomes in the treatment of cancer. A bright future for hybrid nanoparticles in nanomedicine is expected.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

Declared none.

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Current Drug Metabolism

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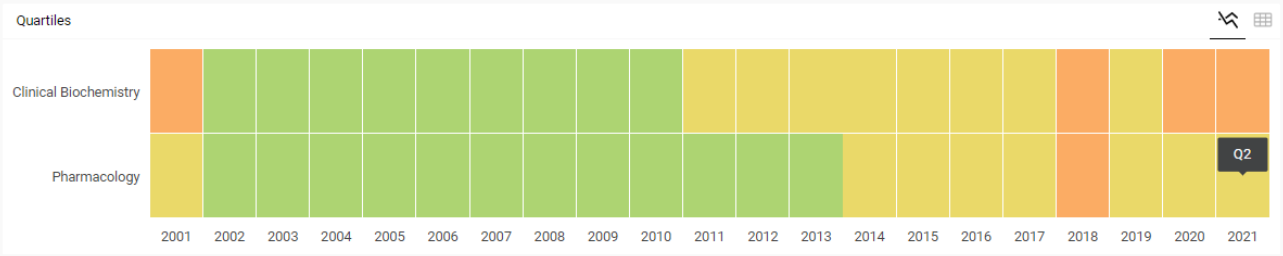

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2018	0.544
2019	0.650
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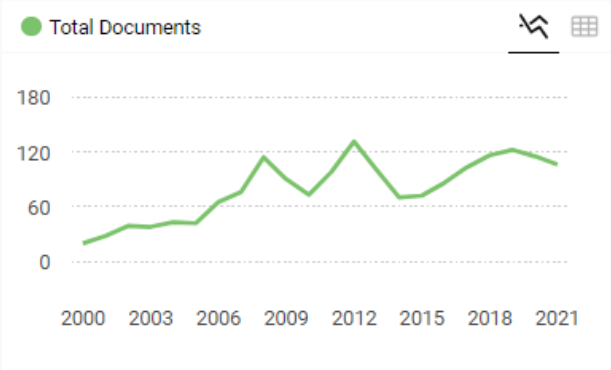

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