International Journal of Medical

Reviews and Case Reports.

E-ISSN 2534-9821

International Journal of Medical Reviews and Case Reports.

2022, Vol: 6, Issue: 13

Required files to be uploaded

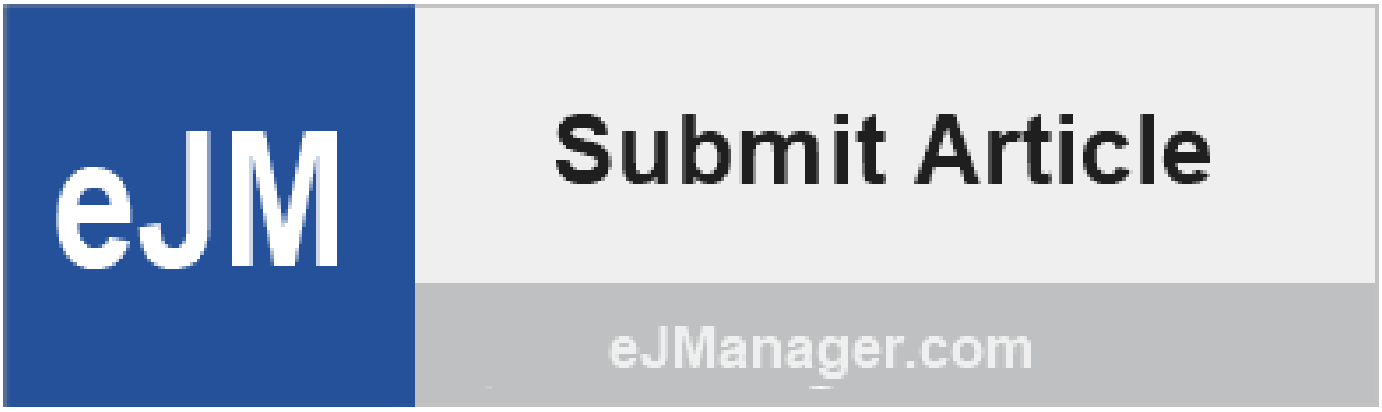
Copyright Transfer Form (https://www.ejmanager.com/mnstemps/172/stdfls/Copyright Transfer Form.doc)


(https://orcid.org/register)

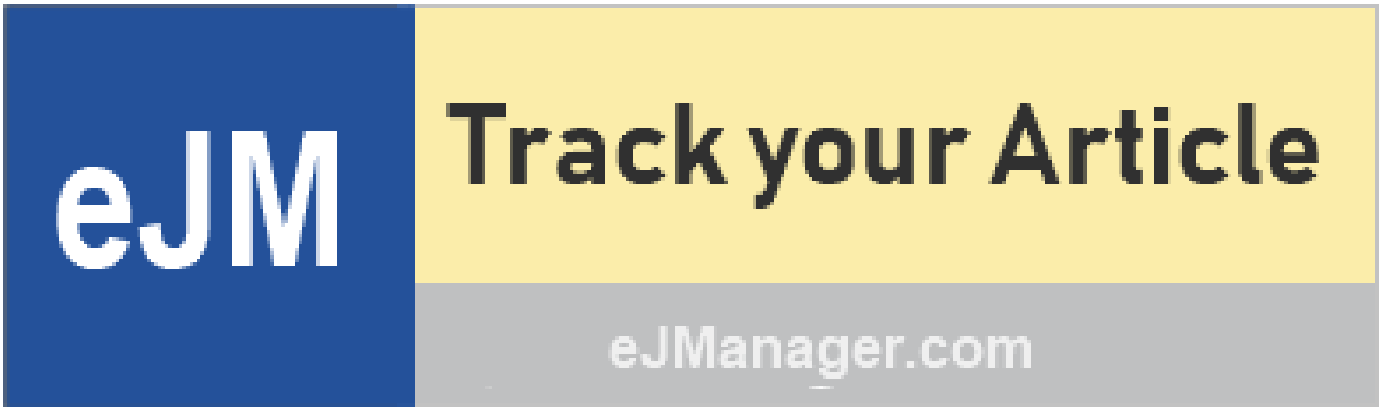
(https://www.crossref.org/)



(https://creativecommons.org/)



(http://www.ejmanager.com/my/ijmrcr/)



(http://www.ejmanager.com/my/ijmrcr/submit.php?isl=track)

Protection of Research Participants (Statement On Human And Animal Rights) (http://www.mdpub.net/?sec=policyhar)

Privacy Policy (http://www.mdpub.net/?sec=policyprivacy)

Publication Ethics and Publication Malpractice Statement (http://www.mdpub.net/?sec=policypubethics)

Corrections, Retractions & Expressions of Concern (http://www.mdpub.net/?sec=correctionretractionconcern)

Self-Archiving Policies (http://www.mdpub.net/?sec=selfarchivingpolicy)

Statement of Informed Consent (http://www.mdpub.net/?sec=informedconsent)

Advertising Policy (http://www.mdpub.net/?sec=policyadvertising)

Terms of Use (http://www.mdpub.net/?sec=policytermofuse)

License Information (http://www.mdpub.net/?sec=licenseinfo)

Copyright Information (http://www.mdpub.net/?sec=copyrightinfo)

Contact Information

Any correspondence, queries or additional requests for information on the manuscript submission process should be sent to the International Journal of Medical Reviews and Case Reports editorial office as follows:

Bulgarian Association of Young Surgeons (BAYS);

National Center of Public Health and Analyses (NCPHA), floor 2, office № 31, Sofia 1431, Bulgaria.

inkov@journalmedica.com (mailto:inkov@journalmedica.com)

Financial department is managed by International Sci Ink Press.

It is a company registered in Bulgaria with registered no. 205414288 and registered address at 57 Antim I str., Vazrazhdane, Sofia, 1303, Bulgaria.

Tel: +359883427500

E-ISSN 2534-9821

2022, Vol: 6, Issue: 13

Current Issue (http://www.mdpub.net/?sec=cissue) 6/13
Online First (http://www.mdpub.net/?sec=aip)
Archive (http://www.mdpub.net/?sec=archive)
Aims and Scope (http://www.mdpub.net/?sec=aimsscope)
Abstracting & Indexing (http://www.mdpub.net/?sec=jindex)
Most Accessed Articles (http://www.mdpub.net/?sec=mosta)
Most Downloaded Articles (http://www.mdpub.net/?sec=mostd)
Most Cited Articles (http://www.mdpub.net/?sec=mostc)

Required files to be uploaded

Copyright Transfer Form (https://www.ejmanager.com/mnstemps/172/stdfls/Copyright Transfer Form.doc)

« Previous Issue (index.php?iid=2022-6-1.000&jid=172)

Next Issue » (index.php?iid=2022-6-3.000&jid=172)

Int J Med Rev Case Rep. Year: 2022, Volume: 6, Issue: 2

» Abstract (?mno=81713) » PDF (index.php?fulltxt=81713&fulltxtj=172&fulltxtp=172-1621176131.pdf) » doi: 10.5455/IJMRCR.CHARACTERISTICOFMETABOLICSTATUSINBLINDPEOPLE (http://dx.doi.org/10.5455/IJMRCR.CHARACTERISTICOFMETABOLICSTATUSINBLINDPEOPLE)

Case Report

8. **Hyperactive Delirium Management Due to Electrolyte Imbalance in Geriatric Patients**
   Putu Juni Wulandari, R.A. Tuty Kuswardhani
   Int J Med Rev Case Rep. 2022; 6(2): 35-40
   » Abstract (?mno=123506) » PDF (index.php?fulltxt=123506&fulltxtj=172&fulltxtp=172-1631413455.pdf) » doi: 10.5455/IJMRCR.HyperactiveDeliriumManagementDuetoElectrolyteImbalanceinGeriatricPatients (http://dx.doi.org/10.5455/IJMRCR.HyperactiveDeliriumManagementDuetoElectrolyteImbalanceinGeriatricPatients)

Original Research

9. **Hospital based prospective, non-randomized descriptive study to find out the incidence of intraoperative awareness during general anaesthesia and evaluation of the risk factors causing awareness.**
   Saagari Gupta, Swaraj Jyoti Sonowal, Vandana Singh Delwal, Archana Khokar
   Int J Med Rev Case Rep. 2022; 6(2): 41-45
   » Abstract (?mno=122467) » PDF (index.php?fulltxt=122467&fulltxtj=172&fulltxtp=172-1631217507.pdf) » doi: 10.5455/IJMRCR.Hospitalbasedprospectivenon-randomizeddescriptivestudytofindouttheincidenceofintraop (http://dx.doi.org/10.5455/IJMRCR.Hospitalbasedprospectivenon-randomizeddescriptivestudytofindouttheincidenceofintraop)

Case Report

10. **Recurrence of Primary Spontaneuous Pneumothorax of Female with Presented of Left Inferior Lobe Lung Bullae : A Case Report and Review**
    Yessicha Kurniawati, Kadek Surya Atmaja, Wayan Wahyu Semara Putra, Ni Made Dwita Yaniswari,
    Int J Med Rev Case Rep. 2022; 6(2): 46-49
    » Abstract (?mno=59394) » PDF (index.php?fulltxt=59394&fulltxtj=172&fulltxtp=172-1614343358.pdf) » doi: 10.5455/IJMRCR.Primary-spontaneuous-pneumothorax-recurrence (http://dx.doi.org/10.5455/IJMRCR.Primary-spontaneuous-pneumothorax-recurrence)

11. **MYT1L duplication in a Portuguese patient with intellectual disability and obesity**
    Lorena Stella, Joana Tenente, Rita Quental, Helena Santos, Miguel Leo
    Int J Med Rev Case Rep. 2022; 6(2): 50-52
    » Abstract (?mno=140417) » PDF (index.php?fulltxt=140417&fulltxtj=172&fulltxtp=172-1641254165.pdf) » doi: 10.5455/IJMRCR.MYT1LduplicationinaPortuguesepatientwithintellectualdisabilityandobesity (http://dx.doi.org/10.5455/IJMRCR.MYT1LduplicationinaPortuguesepatientwithintellectualdisabilityandobesity)

12. **A Cervical Carcinoma Patient with Therapy-related Myeloid Neoplasm after Chemotherapy and Radiotherapy**
    Komang Agus Wira Nugraha, Ni Made Renny Anggreni Rena, Herman Saputra
    Int J Med Rev Case Rep. 2022; 6(2): 53-59
    » Abstract (?mno=5375) » PDF (index.php?fulltxt=5375&fulltxtj=172&fulltxtp=172-1642394171.pdf) » doi: 10.5455/IJMRCR.CervicalCarcinomaPatientwithTherapy-relatedMyeloidNeoplasm (http://dx.doi.org/10.5455/IJMRCR.CervicalCarcinomaPatientwithTherapy-relatedMyeloidNeoplasm)

13. **A Rare Case of Myeloproliferative Neoplasm with Eosinophilia Presenting with Simultanoeus Ocular, Neurological, and Cutaneous Manifestations**
    Fadlila Fitriani, Ilsya Asti Naraswari, Raden Mas Agit Sena Adisetiadi, Hanggoro Tri Rinonce, He Yeon Asva Nafaisa, Yohanes Widodo Wirohadidjojo, Mardiah Suci Hardianti
    Int J Med Rev Case Rep. 2022; 6(2): 60-65
    » Abstract (?mno=82404) » PDF (index.php?fulltxt=82404&fulltxtj=172&fulltxtp=172-1639924562.pdf) » doi: 10.5455/IJMRCR.ARareCaseofMyeloproliferativeNeoplasmwithEosinophiliaPresenting (http://dx.doi.org/10.5455/IJMRCR.ARareCaseofMyeloproliferativeNeoplasmwithEosinophiliaPresenting)

Review Article

14. **Coagulopathie et coagulation intravasculaire disséminée associées au COVID-19**
    Hamza Choukrallah, Anas El Mokri, Hanane Choukrani, Merouane Selmaoui, Ismail Benhar, Ghali Benouna, Rachida Habbal
    Int J Med Rev Case Rep. 2022; 6(2): 66-75
    » Abstract (?mno=134163) » PDF (index.php?fulltxt=134163&fulltxtj=172&fulltxtp=172-1634639741.pdf) » doi: 10.5455/IJMRCR.Coagulopathieetcoagulationintravasculaire (http://dx.doi.org/10.5455/IJMRCR.Coagulopathieetcoagulationintravasculaire)

Case Report

15. **Spondylodiscitis revealing aerococcus viridans infective endocarditis: Rare case report**
    Hamza Choukrallah, Hanane Choukrani, Karim Mounaouir, Anas El Mokri, Ismail Benhar, Abdenasser Drighil, Keltoum Boumlik, Salwa Hafoud, Soufiane El

Rhanbaz
Int J Med Rev Case Rep. 2022; 6(2): 76-79
» Abstract (?mno=18940) » PDF (index.php?fulltxt=18940&fulltxtj=172&fulltxtp=172-1637611847.pdf) » doi: 10.5455/IJMRCR.SPONDYLODISCITISREVEALINGAEROCOCCUSVIRIDANS (http://dx.doi.org/10.5455/IJMRCR.SPONDYLODISCITISREVEALINGAEROCOCCUSVIRIDANS)

Review Article

16. **La maladie coronarienne: Facteurs de risque et traitement**
Hamza Choukrallah, Hanane Choukrani, Anas El Mokri, Ismail Benhar, Ghali Benouna
Int J Med Rev Case Rep. 2022; 6(2): 80-85
» Abstract (?mno=134157) » PDF (index.php?fulltxt=134157&fulltxtj=172&fulltxtp=172-1634637803.pdf) » doi: 10.5455/IJMRCR.LAMALADIECORONARIENNE (http://dx.doi.org/10.5455/IJMRCR.LAMALADIECORONARIENNE)

Case Report

17. **Anaesthetic management for patient with severe mitral stenosis to isthmolobectomy operations: Case report**
Jorza Sepmiko, Dewa Ayu Mas Shintya Dewi, Rindha Dwi Sihanto
Int J Med Rev Case Rep. 2022; 6(2): 86-90
» Abstract (?mno=80768) » PDF (index.php?fulltxt=80768&fulltxtj=172&fulltxtp=172-1620779972.pdf) » doi: 10.5455/IJMRCR.ANESTHETICMANAGEMENTFORPATIENTWITHSEVEREMITRALSTENOSISTOISTHMOLOBECTOMYOPERATIONS (http://dx.doi.org/10.5455/IJMRCR.ANESTHETICMANAGEMENTFORPATIENTWITHSEVEREMITRALSTENOSISTOISTHMOLOBECTOMYOPERATIONS)

Original Research

18. **Correlation between homocysteine and osteoprotegerin (OPG) serum with bone mineral density in women with systemic lupus erythematosus**
Pande Ketut Kurniari, I Putu Bayu Triguna, Gede Kambayana, Tjokorda Raka Putra
Int J Med Rev Case Rep. 2022; 6(2): 91-95
» Abstract (?mno=74350) » PDF (index.php?fulltxt=74350&fulltxtj=172&fulltxtp=172-1618761158.pdf) » doi: 10.5455/IJMRCR.CorrelationbetweenhomocysteineandosteoprotegerinOPGserum (http://dx.doi.org/10.5455/IJMRCR.CorrelationbetweenhomocysteineandosteoprotegerinOPGserum)

Case Report

19. **Cardiac resynchronization therapy with physiological left bundle branch pacing as a treatment for arrhythmogenic cardiomyopathy with left ventricle involvement: a new therapeutic approach?**
Albina Aldomà-Balasch, Isabel Hernández-Martín
Int J Med Rev Case Rep. 2022; 6(2): 96-100
» Abstract (?mno=130120) » PDF (index.php?fulltxt=130120&fulltxtj=172&fulltxtp=172-1633353406.pdf) » doi: 10.5455/IJMRCR.Cardiacresynchronizationtherapywithphysiologicalleftbundlebranchpacing (http://dx.doi.org/10.5455/IJMRCR.Cardiacresynchronizationtherapywithphysiologicalleftbundlebranchpacing)

20. **Early Pathological Diagnosis for Earlier treatment: A case of Lupus Nephritis.**
Jayashankar Chinnappa Anjanappa, Prakash Bhanu, Shalini A S, Ramya S S, Hari Bhargavi Battula, Sania Saba, Ishaq Mohammed, Amey Joshi
Int J Med Rev Case Rep. 2022; 6(2): 101-104
» Abstract (?mno=76451) » PDF (index.php?fulltxt=76451&fulltxtj=172&fulltxtp=172-1639819288.pdf) » doi: 10.5455/IJMRCR.EarlyPathologicalDiagnosisforEarliertreatment (http://dx.doi.org/10.5455/IJMRCR.EarlyPathologicalDiagnosisforEarliertreatment)

Contact Information

Any correspondence, queries or additional requests for information on the manuscript submission process should be sent to the International Journal of Medical Reviews and Case Reports editorial office as follows:

Bulgarian Association of Young Surgeons (BAYS);

National Center of Public Health and Analyses (NCPHA), floor 2, office № 31, Sofia 1431, Bulgaria.

inkov@journalmedica.com (mailto:inkov@journalmedica.com)

Financial department is managed by International Sci Ink Press.

It is a company registered in Bulgaria with registered no. 205414288 and registered address at 57 Antim I str., Vazrazhdane, Sofia, 1303, Bulgaria.

Tel: +359883427500

MICROSPHERES FOR INHALATION DELIVERY (CHARACTERISTICS AND IN VITRO RELEASE)

Noorma Rosita *, **Tekla Kalalo** *, **Andang Miatmoko** *, **Yashwant Pathak** ** and **Dewi Melani Hariyadi** *,[1]
* Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia , ** College of Pharmacy, University of South Florida, United States

ABSTRACT Background: Microspheres are one of the potential lung delivery systems for lungs and respiratory diseases because of their ability to encapsulate various types of drugs, biocompatibility, high bioavailability, protect drugs from environmental effects such as humidity, heat, oxidation, and can release drugs in a sustained or prolonged release. The suitability of microspheres to be delivered by inhalation is determined by the characteristics and release of the drugs from the microspheres. The characterization and release study of microspheres is influenced by several factors such as the type of polymer used, polymer concentration, polymer ratio, type of crosslinker, the concentration of crosslinker, and method of encapsulation. **Methods of review:** This scoping review consists of 32 publications from the periods between 2007 and 2021. Publications were extracted from a search engine using various keywords. Data of publications that met the criteria were extracted manually. **Conclusions:** This review focuses on the characteristics and release of microspheres for inhalation using polymers and various encapsulation methods.

KEYWORDS Microspheres, inhalation, characteristics, in vitro release, respiratory diseases

Introduction

Drug delivery system through the lungs in the form of inhalation is the best choice for diseases of the lungs. The inhalation route provides many advantages over the oral route, such as a high surface area with a fast absorption due to high vascularity, avoiding the first-pass effect, reducing the dose, reducing systemic absorption, and reducing side effects[1]. Despite the advantages of lung conduction, to achieve effective lung deposition, the particles must have an aerodynamic diameter in the range of 0.5–5 μm. Particles with a diameter bigger than 5 μm will be suspended in the upper respiratory tract, while particles <0.5 μm are more likely to be cleared during expiration[2].

To overcome this problem, microspheres are chosen as the carrier system because of the use of smaller doses, having a small size, and can be used for a prolonged therapeutic effect[3].

Microspheres are particles of 1-1000 μm consisting of a biodegradable polymer matrix in which the drugs can be naturally degraded in the body, low biocompatibility, immunogenicity, and toxicity, as well as high bioavailability and sustained release capability for a long time[4]. The development of microspheres delivery system for inhalation involves three requirements, which are biocompatibility and relatively fast biodegradability of the forming polymer to avoid the accumulation of toxic substances in the lungs, especially in the case of long-term treatment such as tuberculosis chemotherapy, high drug loading to minimize the administration of inert substances, and the aerodynamic diameter of the particles ranges from 1-5 μm[5]. This review will examine the microspheres system focusing on physical characteristics and in vitro release of inhaled microspheres with several polymers and encapsulation methods.

Microspheres

Microspheres play an important role in increasing the bioavailability of conventional drugs and minimizing side effects. Microspheres are used to protect drugs from environmental effects such as humidity, heat, oxidation and to mask unpleasant tastes and odours. Microspheres are classified into two types, namely

DOI: 10.5455/IJMRCR.MicrospheresforInhalationDelivery
First Received: December 4, 2021
Accepted: January 3, 2022
Associate Editor: Ivan Inkov (BG);
[1]Corresponding author: Prof. Dewi Melani Hariyadi, PhD, Apt. Faculty of Pharmacy Universitas Airlangga, Surabaya Indonesia 60115, +62 31 5933150; Fax +62 31 5935249, email: dewi-m-h@ff.unair.ac.id

microcapsule and micromatrix. The microcapsule is a reservoir device in which a polymeric material coats the drug core. In contrast, the micromatrix contains the drug, which is uniformly dispersed in a polymeric matrix. In addition, the choice of polymer used for the manufacture of microspheres plays an important role in the drug delivery process [6].

Inhalation microspheres

As an inhalation delivery, the size of the microsphere particles plays a role in determining the deposition mechanism and the deposition site in the lungs. Particle deposition in the lungs depends on physiological factors such as respiratory rate and frequency, breath-holding, and airway humidity. In order for inhaled particles to reach the lower respiratory tract, they must have a diameter between 0.5 μm and 5 μm. Particles larger than 5 μm are usually deposited in the upper respiratory tract, where they are easy to clean, while particles smaller than 0.5 μm cannot be deposited and will be exhaled again[2]. Microspheres are one of the systems that can be used for delivery to the lungs. The small size and spherical shape formed from certain polymers can provide a controlled release pattern, making them suitable for pulmonary delivery systems. Uses of polymers in microspheres include synthetic polymers, including non-biodegradable polymers such as silicon, ethyl vinyl acetate (EVA), and biodegradable synthetic polymers such as polylactic acid (PLA), polycaprolactone (PCL), polyglycolic acid (PGA) and polylactic-co-glycolic acid (PLGA). On the other hand, natural polymers include proteins (e.g. gelatin, collagen, and lectin) and polysaccharides (e.g. alginate, pectin, and chitosan)[6].

Characterization and study of the release of a microsphere are influenced by several factors, such as the type of polymer used, polymer concentration, polymer ratio, type of crosslinker, the concentration of crosslinker, and the method of manufacture. Research by Athamneh et al. finds that the morphology of sodium alginate-hyaluronic acid microspheres is spherical, and the size distribution of different microspheres is found depending on the composition of the polymer solution, its dynamic viscosity, and the stirring rate during the ionic gelation process[2]. Hariyadi et al. produce microspheres ranging in size from 1.23 μm - 1.43 μm through the manufacture of ciprofloxacin microspheres with alginate polymer for inhalation delivery with several polymer concentrations and aerosolization techniques. The higher the alginate concentration, the particle size also increases. The increase in alginate content is followed by an increase in the diameter of the microspheres, which result in an increase in the viscosity of the alginate solution used so that large alginate droplets are formed when adding alginate solution to the crosslinking solution and causing the resulting microspheres to be larger[4]. In addition to particle size, Alipour et al. find the effect of the drug to polymer mass ratio for drug loading and entrapment efficiency of sodium alginate-paclitaxel microspheres for inhalation. Drug loading and encapsulation efficiency of microparticles depend on the manufacturing conditions. Among all the formulations made, maximum drug loading and encapsulation efficiency up to 61% are obtained with the highest mass ratio of paclitaxel to alginate and the highest external oil phase volume. These results are in accordance with the results of other researchers who study the effect of the mass ratio of the drugs to the polymer, the volume of the external oil phase and $CaCl_2$ to mass ratio of alginate in the production of microparticles using alginate [1].

In addition to physical characteristics, there are also several studies related to the study of the release of inhaled microspheres. Rifampicin release study by Diab et al. in phosphate buffer pH 7.4 shows the release of rifampicin from microspheres occurs in a sustained release; 71% of rifampicin is released over a week. No burst release is observed, as about 10% of rifampicin is released during the first 3 hours[5].

Inhalation delivery devices

1. Dry Powder Inhaler (DPI)

DPI is a respiratory propulsion device that contains a micro-sized (approximately under 5 μm) drug powder formulation and delivers the drugs into the respiratory tract during oral inhalation. DPI is commonly used to treat respiratory diseases, such as asthma, bronchitis, emphysema, and chronic obstructive pulmonary disease. Some of the advantages of using DPI include that DPI can provide various dosage variations from less than 10 mg to more than 20 mg through one short inhalation. When the drug is deposited in the lungs, DPI has fewer side effects because the rest of the body is not exposed to the drug and has less potential to be extracted from the components of the device[7].

DPI has been frequently used in recent years to treat several local and systemic diseases and has been shown to be superior to other formulations. The features of this device are attributed to the solid form of the active substance, which increases stability, is easy to use, and can be administered in large doses. In addition, other risks, such as fragmentation, decomposition, and microbiological contamination at doses, are smaller than the risks in liquid formulations. The active ingredients used for the formulation of DPI can be small molecules or macromolecules, hydrophilic or hydrophobic, amorphous or crystalline, and have local or systemic sites of action[8].

2. Nebulizer

There are two types of nebulizers, which are jet and ultrasonic, and what distinguishes them is the force used to generate an aerosol of the respective liquid. Depending on the make and model, the nebulizer produces 1–5 μm droplets. It does not require patient coordination between inhalation and activation, making it useful for pediatric, elderly, ventilated, and unconscious patients or those unable to take pMDI or DPI. Nebulizer can deliver larger doses than other aerosol devices, although this requires a longer administration time[9].

The jet nebulizer is based on the Venturi principle, which states that the pressure of a fluid decreases as it passes through a narrow cross-sectional area. In this nebulizer, a stream of air moves through a small capillary tube at high speed, creating a low pressure that pushes the liquid for aerosol up the capillary tube. The high-velocity blast of air carrying the droplets will hit the bulkheads, which are placed in different numbers and positions depending on the jet nebulizer design. The main problems with jet nebulizers are the requirement for a compressor which is sometimes impractical to generate aerosols, the noise some of them produce, and the drop in temperature of the liquid in the nebulizer chamber due to evaporation of the liquid in the nebulized droplets[9].

3. Pressurized Metered Dose Inhaler (pMDI)

pMDI is a device in which the drugs are mixed into a tube with a propellant, and the carried mixture is dispensed in precisely measured quantity on the device driver. The main components

of a typical MDI are the housing, gauge valve, and actuator. There are several advantages of pMDI, including easy to control, compact and convenient, high reliability, accurate measurement performance, and relatively inexpensive. Meanwhile, the disadvantage of pMDI is that it contains propellants such as Chlorofluorocarbons (CFCs) which damage the ozone layer[7].

Polymeric microspheres

1. Sodium Alginate

Sodium Alginate is a copolymer consisting of β-1,4 D-mannuronic acid and α-L-Guluronic acid monomer, forming a homogeneous or heterogeneous block pattern[1]. The advantages of using alginate polymers are that it is non-toxic, biodegradable, biocompatible, and relatively inexpensive[4]. Alginates can be crosslinked in an aqueous solution with divalent cations (e.g. Ca^2+, Ba^2+, and Sr^2+) for the formation of microspheres[10].

2. Carrageenan

Carrageenan is the generic name for a family of high molecular weight sulfated polysaccharides obtained by the extraction of certain species from red seaweed. It consists of galactose and anhydrogalactose units linked by glycosidic[24]. Carrageenan polymer is a natural polymer that is biodegradable, economical, and widely used for encapsulation. To form a gel of carrageenan microspheres, monovalent crosslinkers, such as K^+, Na^+, and Li^+3 are needed.

3. Chitosan

Chitosan is a high molecular weight polysaccharide linked by β-1,4 glycosides. This polymer consists of N-acetyl-glucosamine and glucosamine. Chitosan is a cationic polyelectrolyte that is non-toxic, biocompatible, biodegradable and has been shown to be enzymatically degraded by the body, including in organs such as the lungs[9]. This polymer is also hydrophilic and soluble in acidic solvents, making it easy to encapsulate hydrophilic drugs[11].

4. Xyloglucan

Xyloglucan is a naturally occurring polysaccharide isolated from `Tamarindus indica` seed core. Polymers have properties such as having high viscosity, wide pH tolerance, and adhesion. In addition, other advantages of xyloglucan are non-carcinogenicity, mucoadhesiveness, biocompatibility, high drug storage capacity, and high thermal stability. These advantages lead to its application as an excipient in hydrophilic drug delivery systems[12].

5. PLGA (poly(lactic-co-glycolic acid))

PLGA is one of the polymers used as a carrier for drug delivery to alveolar macrophages. This polymer has biocompatible and biodegradable properties, which is hydrolytically degraded into non-toxic oligomers or monomers of lactic acid and glycolic acid and has been widely used as a drug carrier[13].

Physical characteristics of inhalation microspheres

1. Morphology

Morphological testing aims to evaluate the shape and surface structure of the formed microspheres. This test usually uses Scanning Electron Microscopy (SEM). The formed microspheres are usually spherical in shape and the surface is smooth or rough[4].

2. Particle Size

Particle size analysis of microparticles above 3 μm in diameter is usually carried out using the laser light diffraction (LD) method or using a Coulter Counter. In the laser light diffraction (LD) method, the distribution shows the span-value, d0.1, d0.5, and d0.9, which is a parameter that can be used to compare results. The polydispersity index (PDI) determined by dynamic laser light scattering shows the size distribution at the lower part of the microparticle size[14]. Another method used to measure particle size is by using an optical microscope[4].

3. Drug Loading and Encapsulation Efficiency

The amount of drug absorbed in the microspheres system is determined directly by calculating the total concentration in the microspheres against the theoretical concentration of the drug added to the formula.

Drug loading and encapsulation efficiency can be determined by the formula below[1]:

$$\texttt{Drug loading}(\%) = \frac{\texttt{drug weight in the microsphere}}{\texttt{microsphere weight}} \times 100\%$$

$$\texttt{Encapsulation efficiency}(\%) = \frac{\%\texttt{drug loading}}{\%\texttt{theoretical content}} \times 100\%$$

4. Swelling Index

The swelling index aims to observe the state of dry particles under various conditions. Swelling index (S%) can be calculated using swollen particle diameter (d_s) and the initial particle diameter before reconstitution (d_i), with the following formula[14]:

$$S(\%) = \frac{d_s - d_i}{d_i} \times 100\%$$

5. Mucoadhesion in the respiratory tract

Mucoadhesion is the interaction of molecules with the mucosal layer (biological tissue) in order to stick together. Mucoadhesion techniques can increase the mean residence time of therapeutic agents and enforce a high concentration gradient of drug molecules across the epithelium. Mucoadhesion occurs through several mechanisms such as chain interlocking, diffusion, and chemical reactions (hydrogen bonds). Mucoadhesive agents are usually high molecular weight polymers that can interact with the mucin layer of the respiratory epithelium due to hydrogen bonding and electrostatic, hydrophobic, or van der Waals interaction. Mucoadhesive polymers are needed to prolong the residence time of the drug, thereby increasing the absorption of the drug through the mucosa at a controlled rate and enhancing the therapeutic effect[15].

Mucoadhesion testing can be done using the falling liquid film technique[16]. The formula for calculating mucoadhesion is as follows:

$$\%\texttt{Mucoadhesion} = \frac{\texttt{A} - \texttt{B}}{\texttt{A}} \times 100\%$$

Where A is the actual amount of drugs in the microspheres and B is the number of drugs in the washing liquid[10].

6. Mass Mean Aerodynamic Diameter (MMAD)

MMAD is a parameter that affects the deposition of inhaled particles. In theory, MMAD can be calculated using the following formula: $\texttt{MMAD} = d(\rho/\rho_0 X)^{1/2}$

Where d is the geometric diameter resulting from the particle size measurement, p is the tapped density, ρ_0 reference density

Table 1 Physical Characteristics of Inhaled Microspheres of Various Polymers

Polymers	Drugs	Microspheres Compositions	Methods	Inhalation Delivery Devices	Physical Characteristics	References
Sodium Alginate and Hyaluronic Acid	-	Sodium Alginate, Hyaluronic acid, $CaCl_2$, $CaCO_3$, Water, Span 80	Emulsion gelation, with CO_2 supercritical drying	DPI	• Morphology of microspheres is spherical. Different size distribution of microspheres depends on the composition of the polymer solution, dynamic viscosity, and agitation rate during the emulsion gelation process. • The microspheres show low density and high porosity as well as good in vitro aerodynamic properties with d_A value of about 5 μm.	[10]
Sodium Alginate	Ciprofloxacin	Ciprofloxacin, sodium alginate, $CaCl_2$, Maltodextrin	Ionotropic gelation by aerosolization method. Drying with freeze dry	DPI	• Microsphere morphology is spherical. • Particle size ranges from 1.23 - 1.43 μm. The higher the alginate concentration, the larger the particle size. • Yield ranges from 70.63% - 82.94%. • Drug loading and encapsulation efficiency are 2.82% - 4.13% and 27.39% - 80.74%.	[4]
Sodium Alginate	Paclitaxel	Paclitaxel, sodium alginate, $CaCl_2$, HPMC, Tween 85	Emulsification/gelation method	DPI	• Morphology is spherical with particle diameter of <5 μm. • Average volume diameter of microparticles is 2 to 10 μm. • Drug loading and encapsulation efficiencies are 7.8 to 19.5% and 35 to 61% depends on the manufacturing conditions. • The maximum encapsulation efficiency is obtained with the highest mass ratio of paclitaxel to alginate and the highest external oil phase volume.	[1]
Sodium Alginate	Rifampicin	Rifampicin, β-cyclodextri, sodium alginate, isopropyl alcohol (IPA)	Spray drying	DPI	• The yield is 60%. • Drug loading is 62.1%-71.2%. • The particle size for alginate microspheres is 6.634 μm, while the drug-loaded spray-dried alginate microspheres with cyclodextrin are 6.234 μm. Particle size is affected by the viscosity of the solution on the droplet size during the atomization process. • SEM shows pure Rifampicin in crystalline form with a characteristic shape, whereas drug-free alginate microspheres are spherical and free-flowing with a smooth surface. The presence of the drug and cyclodextrin affects the morphological characteristics of the microspheres obtained by the spray drying method. • MMAD shows that nearly 75% of alginate microspheres is within the inhaled size range, with an MMAD of 5.424 m.	[19]
Kappa Carrageenan	Ciprofloxacin	Ciprofloxacin, kappa carrageenan, maltodextrin, KCl	Ionotropic gelation by aerosolization method. Drying with freeze dry	DPI	• Morphology is spherical with a smooth surface. • Yield is 36.42% - 89.33% • Particle size is less than 4 μm with an average of about 1.4 to 1.6 μm • Adsorption efficiency is 10.54% - 28.69%. • Drug loading is 13% to 18%. The higher the concentration of polymer and crosslinker, the efficiency of entrapment and drug loading also increases.	[3]
Chitosan	Ofloxacin	Ofloxacin, chitosan, acetic acid, dichloromethane, liquid paraffin, span 80, lecithin, glutaraldehyde	Emulsification W/O	DPI	• Morphology is spherical and ranging from 1 to 6 m. • Ofloxacin content is 27% (w/w).	[11]
Chitosan	Levofloxacin	Levofloxacin, chitosan, glutaraldehyde, acetic acid, genipin, DL-glyceraldehyde, glutamic acid	Spray drying	DPI	• Morphology is spherical with smooth surface. • EE is about 110% and 120%. • All formulations exhibit high dispersibility with an ED value of around 90%, indicating that the microsphere powder is efficiently emitted from the DPI. • For microspheres crosslinked with genipine and glutamic acid, the MMAD value is around 5 μm, a value suitable for delivery to the conductive zones of the lungs (trachea, bronchi, and terminal bronchioles) where P. aeruginosa infection is present.	[20]
Chitosan	Quercetin and Paclitaxel	Paclitaxel, quercetin, chitosan, oleic acid, hydroxypropyl-β-cyclodextrin, lactose, mannitol	Spray drying	DPI	• PTX and QUE are efficiently encapsulated in polymeric microspheres. • Drug loadings of PTX and QUE are 15.36% and 14.79%, and EE is 92.6% and 90.3%, respectively. • Yield is about 70%	[21]
Chitosan	Rifampicin and Rifabutin	Rifampicin, rifambutin, chitosan, Tripolyphosphate	Ionic gelation and drying by spray drying	DPI	• Yield is 9%-30% for Rifampicin microparticles and decreases with an increasing amount of tripolyphosphate. • The particle size is below 5 μm. Particle size increases with increasing concentration of tripolyphosphate, both for rifampicin and rifambutin microparticles. • Drug loading is 45%-60% for rifampicin microparticles and 70%-89% for rifambutin microparticles. Amount of drugs loaded into the microparticles decreases with an increase in the concentration of added tripolyphosphate.	[12]
Xyloglucan	Montelucast	Montelucast, xyloglucan, lactose monohydrate	Spray drying	DPI	• Morphology is spherical with smooth surface. • Particle size is 6 μm • MMAD is 2.53 μm, suitable for inhalation delivery in the lower lungs. • Encapsulation efficiency ranges from 79.16% - 85.39%.	[16]
PLLA (poly(L-lactic acid))	Gefitinib	Gefitinib, PLLA, ethanol, dichloromethane	Supercritical anti-solvent (SAS)	DPI	• Morphology of pure gefitinib is in the form of large and irregular yellow crystals, PLLA particles are flocculated and irregular, and PLLA-gefitinib microspheres are smaller and almost spherical. • Particle size ranges from 1.5 μm - 4.5 μm. • Drug loading is 15.82% • EE is 94.91%	[22]

PLLA (poly(L-lactic acid))	Insulin	Insulin, PLLA, dichloromethane, AB	Emulsion-combined precipitation of compressed CO_2 antisolvent (PCA) process	DPI	• Morphology is rough and porous. • Drug loading ranges of 4.85%-6.90% and encapsulation efficiency is 68.97%-97.02%. • Geometric mean diameter (Dg) is 15.62 μm and aerodynamic diameter (Da) is 4.31 μm.	[23]
Polyvinyl alcohol (PVA)	Nifedipine	Nifedipine, PVA, ethanol	Spray drying	DPI	• Morphology is spherical with a rough surface. • Size of the microspheres is 7.8 to 13.9 μm (7.8 μm for 50% PVA, 13.1 μm for 70% PVA, and 13.9 μm for 90% PVA), while the particle size of the raw material is 78.5 μm. As the concentration of PVA increases with drug concentration, the particle size of the microspheres also increases. • Drug loading ranges of 8%-59.05% and encapsulation efficiency is about 82.18%-118.11%. • MMAD cannot be determined accurately and is estimated to be more than 13 μm.	[24]
PLGA (poly(lactic-co-glycolic acid))	Levofloxacin	Levofloxacin, PLGA, hydrochloric acid, dichloromethane, PBS, lauric acid	Double emulsion solvent evaporation	DPI	• Morphology is spherical and the particle size is 4.6 μm and 4.3 μm. • Encapsulation efficiency is 3.30% and 0.30% and drug loading is 9.91% and 0.90%. • MMAD is 7.1 μm.	[25]
PLGA (poly(lactic-co-glycolic acid))	Rifampicin	Rifampicin, PLGA, leucine, dichloromethane	O/W emulsion	DPI	• Morphology for rifampin microspheres is spherical with a smooth surface, while the microparticles prepared with various concentrations of leucine (0.1%, 0.2%, 0.3%, 0.4%, and 0.5%) are not spherical. • Particle size of the rifampicin microspheres is 5.9 μm and microparticles added with leucine is 5-6 μm. • Encapsulation efficiency of rifampicin microspheres is 96.17% and Encapsulation efficiency the addition of leucine is 70.47%-96.17% at different concentrations.	[26]
PLGA (poly(lactic-co-glycolic acid))	Rifampicin	Rifampicin, PLGA, PVA, dichloromethane	Emulsion-solvent evaporation	DPI	• Morphology is spherical. • Narrow size distribution with an average diameter of 2.84 m. • Loading efficiency is 40%.	[13]
PLGA (poly(lactic-co-glycolic acid))	Rifampicin	Rifampicin, PLGA, dichloromethane, chloroform, sucrose palmitate	O/W emulsion solvent evaporation	DPI	• Morphology is spherical with smooth surface. • Drug loading ranges from 7.0%-42.4% and encapsulation efficiency ranges from 21.1%-63.5%. • Particle size is 1.5 μm-7 μm. • MMAD is 4.5μm.	[5]
PLGA (poly(lactic-co-glycolic acid))	Rifampicin	Rifampicin, PLGA, ethyl acetate, PVA, hydrochloric acid, HP (2-hydroxypropyl--cyclodextrin, borate buffer	Solvent evaporation	DPI	• Particle size ranges from 2.06 μm-5.51 μm. • EE is 31.5%-73.4%. • MMAD is 3.36 μm-5.26 μm (the higher the concentration of PLGA physical characteristics, the higher MMAD). • Morphology is spherical.	[27]
PLGA (poly(lactic-co-glycolic acid))	Etoposide	Etoposide, PLGA, chloroform, PVA, mannitol	Emulsion solvent evaporation	DPI	• Morphology is spherical with smooth surface. • Particle size is 11.8 μm. • Drug loading is 7.7%. • Encapsulation efficiency is 84.2%. • MMAD is 2.83μm.	[28]
PLGA (poly(lactic-co-glycolic acid))	Moxifloxacin	Moxifloxacin, PLGA, dichloromethane, methanol, PVA	Solvent evaporation	DPI	• Particle size is 3.16 μm. • Morphology is spherical with smooth surface. • DL is 21.98% and EE is 78.0%. • MMAD is 2.85μm.	[18]
PLGA (poly(lactic-co-glycolic acid))	Doxorubicin and Paclitaxel	Doxorubicin, paclitaxel, PLGA, dichloromethane, ammonium bicarbonate, PVA	W/O/W double emulsification and solvent evaporation	DPI	• DL efficiency of DOX microspheres is 60% and PTX microspheres is 80%. • Geometric diameter is 11.47 μm. • MMAD is 3.52 μm.	[29]
PLGA (poly(lactic-co-glycolic acid))	Oridonin	Oridonin, PLGA, dichloromethylene, Span 80, NH_4HCO_3	Electro spraying	DPI	• Oridonin-EPM morphology is roughly spherical with many nanopores on the surface. • Average geometric size is 5.23 μm. • Tapped density is very small. • MMAD 2.1 μm.	[30]
Sodium Alginate	Ciprofloxacin	Ciprofloxacin, sodium alginate, $CaCl_2$, maltodextrin	Ionotropic gelation by aerosolization method.	DPI	• Surface morphology of the Ciprofloxacin HCl-alginate microspheres is small, smooth, and round. The higher the concentration of alginate and crosslinkers, the resulting particles are more round and fine. • Particle size of Ciprofloxacin HCl-alginate microspheres is less than 3 μm, which is suitable for inhalation delivery. The higher the concentration of alginate and $CaCl_2$, resulting in a smaller particle size. • Drug loading increases significantly from 15% to 79% by increasing the alginate concentration. • Encapsulation efficiency is 14% - 95% by increasing alginate as much as 2% to 3.5%. • Yield is above 71%.	[31]

Table 2 In Vitro Release Inhalation Microspheres

Polymers	Drugs	Microspheres Compositions	In Vitro Release Methods	Release Profiles	Release Kinetics	References
Sodium Alginate	Ciprofloxacin	Ciprofloxacin, sodium alginate, $CaCl_2$, Maltodextrin	Dissolution	• Release of ciprofloxacin using PBS medium is for 24 hours. • Release of ciprofloxacin for 24 hours reaches 80-100%. • Release of the drug from the alginate is pH dependent. The release is continuous either by diffusion or slow erosion of the polymer matrix.	• The selected kinetic model is zero order. • The rate of drug release is constant over time without being affected by the concentration of the drug in the dosage form.	[4]
Chitosan	Paclitaxel and Quercetin	Paclitaxel, quercetin, chitosan, oleic acid, hydroxypropyl-β-cyclodextrin, lactose, mannitol	dialysis bag and receptor chamber	• At pH 7.4, pure paclitaxel and quercetin are almost completely released within 8 hours, while the release of paclitaxel and quercetin from polymer microspheres shows two stages (burst release and sustainable release). • In the initial 2 hours, the microspheres show a release of 21.87% in paclitaxel and 27.83% in quercetin. • Sustained release of paclitaxel and quercetin occurs over the remaining time resulting in the release of 41.40% paclitaxel and 52.88% quercetin from the microspheres. • Burst release of paclitaxel and quercetin from microspheres is observed for 2 hours, with 17.98% and 34.08% respectively. • Burst release is followed by sustained release for up to 48 hours.	• The release of paclitaxel and quercetin from the microspheres at pH 7.4 and pH 4.5 follows the Korsmeyer–Peppas model. • The mechanism of release of paclitaxel and quercetin from microspheres is Fickian diffusion.	[21]
PLGA	Rifampicin	Rifampicin, PLGA, dichloromethane, chloroform, sucrose palmitate	Dialysis bag	• Release of Rifampicin using PBS medium is for 160 hours. • Release of rifampicin from microspheres occurred in a sustained release, 71% of rifampicin is released over a week. No burst release is observed, as about 10% of rifampicin is released during the first 3 hours.	• The data match with the Higuchi model showing a good correlation indicating that the release of rifampicin is influenced by Fickian diffusion from the polymer matrix.	[5]

is 1 g/cm^3, and X is the form factor, which is 1 if the resulting particle is spherical[17].

The determination of MMAD for inhalation microspheres is determined using the Anderson cascade impactor. The impactor cascade determines the aerodynamic properties of aerosol particles by separating the particles on the impactor plate according to their size. Briefly, the steps carried out are 50 mg of prepared microspheres filled into 7 capsules and inserted into the inhaler device. The inhaler device is then connected to the impactor cascade. The microspheres are then inserted into the cascade impactor at a flow rate of 28.3 L/min for 10 seconds. MMAD is determined using the online MMAD calculator[18].

7. Porosity

Microparticles porosity plays an important role in the swelling test, reconstitution, and release mechanism. This parameter can be measured directly using a mercury porosimeter[14]. The formula for the porosity of microspheres can be determined by the formula below[10]:

$$\varepsilon(\%) = \left(1 - \frac{\rho_{bulk}}{\rho_{sket}}\right) \cdot 100$$

Where `bulk` is the bulk density, and `sket` is the skeletal density measured by helium pycnometry[10].

The physical characteristics of various inhalation microspheres of different polymers can be seen in table 1.

In vitro release study

The release of the active substance from the polymer matrix is a complex release system because the release from this matrix can exhibit simultaneous drug and profound modification of the polymer matrix structure. There are several factors that influence drug release from the polymer matrix, including polymer swelling, polymer erosion, drug diffusion, distribution of drug dispersion in the matrix, the ratio between polymer and drug, and the geometry of the matrix itself. In vitro release mechanisms vary, including diffusion, erosion, osmotic release, or a combination of the former and can be interpreted based on the Fick, Higuchi, Korsmeyer-Peppas, Weibull, and Kopcha models[1]4.

The sustained release mechanism shows slow release for a long period of time. Sustained-release prolongs drug therapy for a longer period of time, whereas burst release is a higher initial drug delivery in a short time[3]2.

There are several methods for the dissolution of multiparticulate systems according to USP 42-NF 37. Equipment and volume are selected based on the yield of the dosage form in the medium and volume. Compendial rotating basket (USP Apparatus 1) and reciprocating cylinder (USP Apparatus 3) can be used for non-disintegrating coated beads and flow-through cells (USP Apparatus 4) can be used for several beaded products. In addition, non-compendial apparatus, such as mini-paddle equipped small-volume apparatus, dialysis tubes, or rotating bottles, can also be used14.

For inhalation microparticles, USP 2 (rotating paddle apparatus) can be used with certain modifications. In addition to USP 2, the dialysis bag method is one of the methods used to test the release of inhaled particles. The drug is arranged in a semipermeable dialysis bag, which is immersed in the dissolution medium. Drug diffusion occurs between the two liquid phases, and although static and sinks conditions are maintained, and this method does not simulate an air-liquid transition14.

Some descriptions of the release methods, kinetics and profile of the inhalation microspheres of several polymers can be seen in Table 2.

Conclusion

Inhalation delivery systems in the form of microspheres provide many advantages compared to conventional dosage forms, such as increasing efficacy, reducing toxicity, and increasing patient compliance. In addition, this system can protect drugs from the harsh environment. The characteristics of microspheres formed from various polymers and in vitro release study of microspheres are the determining factors for the feasibility of

microspheres to be delivered by inhalation before a series of stability and activity tests.

Conflict of Interest

The authors declared no conflict of interest.

Author's Contribution

This paper was compiled by a research team which consisted of a team of 5 people, namely Noorma Rosita, Tekla Kalalo, Andang Miatmoko, Yashwant Pathak, Dewi Melani Hariyadi contributed in :

1. Conception and design, data acquisition, or data analysis and interpretation;
2. Drafting the article or critically revising for important intellectual content;
3. Final approval of the version to be published; and
4. Agreement to be accountable for all aspects of the work.

Acknowledgements

Authors thank to Faculty of Pharmacy Universitas Airlangga for the facilities and research supports.

References

1. Alipour S, Montaseri H, Tafaghodi M. Preparation and characterization of biodegradable paclitaxel loaded alginate microparticles for pulmonary delivery. Colloids and Surfaces B: Biointerfaces. 2010;81(2):521-529. doi:10.1016/j.colsurfb.2010.07.050
2. Athamneh T, Amin A, Benke E, et al. Alginate and hybrid alginate-hyaluronic acid aerogel microspheres as potential carrier for pulmonary drug delivery. Journal of Supercritical Fluids. 2019;150:49-55. doi:10.1016/j.supflu.2019.04.013
3. Hariyadi DM, Hendradi E, Sharon N. Development of carrageenan polymer for encapsulation of ciprofloxacin hcl: In vitro characterization. International Journal of Drug Delivery Technology. 2019;9(1):89-93. doi:10.25258/ijddt.9.1.14
4. Hariyadi DM, Hendradi E, Kurniawan TD. Alginate Microspheres Encapsulating Ciprofloxacin HCl: Characteristics, Release and Antibacterial Activity. International Journal of Pharma Research and Health Sciences. 2019;7(4):3020-3027. doi:10.21276/ijprhs.2019.04.02
5. Diab R, Brillault J, Bardy A, Gontijo AVL, Olivier JC. Formulation and in vitro characterization of inhalable polyvinyl alcohol-free rifampicin-loaded PLGA microspheres prepared with sucrose palmitate as stabilizer: Efficiency for ex vivo alveolar macrophage targeting. International Journal of Pharmaceutics. 2012;436(1-2):833-839. doi:10.1016/j.ijpharm.2012.07.036
6. Uyen NTT, Hamid ZAA, Tram NXT, Ahmad N. Fabrication of alginate microspheres for drug delivery: A review. International Journal of Biological Macromolecules. 2020;153:1035-1046. doi:10.1016/j.ijbiomac.2019.10.233
7. Kendre P, Kadu P, Gursal K. Dry Powder Inhaler: A Review Enhancement of drug solubility View project Journal of Advanced Drug Delivery (JADD) Dry Powder Inhaler: A Review. Published online 2018. https://www.researchgate.net/publication/305706145
8. Akdağ Y. Development of dry powder inhaler formulations for drug delivery systems. Journal of Research in Pharmacy. 2019;23(6):973-987. doi:10.35333/jrp.2019.62
9. Ibrahim M, Verma R, Garcia-Contreras L. Inhalation drug delivery devices: Technology update. Medical Devices: Evidence and Research. 2015;8:131-139. doi:10.2147/MDER.S48888
10. Athamneh T, Amin A, Benke E, et al. Alginate and hybrid alginate-hyaluronic acid aerogel microspheres as potential carrier for pulmonary drug delivery. Journal of Supercritical Fluids. 2019;150:49-55. doi:10.1016/j.supflu.2019.04.013
11. Park JH, Jin HE, Kim DD, Chung SJ, Shim WS, Shim CK. Chitosan microspheres as an alveolar macrophage delivery system of ofloxacin via pulmonary inhalation. International Journal of Pharmaceutics. 2013;441(1-2):562-569. doi:10.1016/j.ijpharm.2012.10.044
12. Pai R v., Jain RR, Bannalikar AS, Menon MD. Development and Evaluation of Chitosan Microparticles Based Dry Powder Inhalation Formulations of Rifampicin and Rifabutin. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2016;29(2):179-195. doi:10.1089/jamp.2014.1187
13. Tomoda K, Makino K. Effects of lung surfactants on rifampicin release rate from monodisperse rifampicin-loaded PLGA microspheres. Colloids and Surfaces B: Biointerfaces. 2007;55(1):115-124. doi:10.1016/j.colsurfb.2006.11.030
14. Lengyel M, Kállai-Szabó N, Antal V, Laki AJ, Antal I. Microparticles, microspheres, and microcapsules for advanced drug delivery. Scientia Pharmaceutica. 2019;87(3). doi:10.3390/scipharm87030020
15. Mehta P. Dry Powder Inhalers: A Focus on Advancements in Novel Drug Delivery Systems. Journal of Drug Delivery. 2016;2016:1-17. doi:10.1155/2016/8290963
16. Mahajan HS, Gundare SA. Preparation, characterization and pulmonary pharmacokinetics of xyloglucan microspheres as dry powder inhalation. Carbohydrate Polymers. 2014;102(1):529-536. doi:10.1016/j.carbpol.2013.11.036
17. Microspheres as pulmonary delivery systems - A review. Journal of Chinese Pharmaceutical Sciences. 2021;30(7):545-555. doi:10.5246/jcps.2021.07.043
18. Vishwa B, Moin A, Gowda D v., et al. Pulmonary targeting of inhalable moxifloxacin microspheres for effective management of tuberculosis. Pharmaceutics. 2021;13(1):1-17. doi:10.3390/pharmaceutics13010079
19. S JP, Devi K, Devi K, Suresh S. Formulation and Evaluation of Novel Spray-dried Alginate Microspheres as Pulmonary Delivery Systems of Rifampicin in Rats. Indian Journal of Pharmaceutical Education and Research. 2015;49(4):320-328. doi:10.5530/ijper.49.4.9

20. Gaspar MC, Sousa JJS, Pais AACC, et al. Optimization of levofloxacin-loaded crosslinked chitosan microspheres for inhaled aerosol therapy. European Journal of Pharmaceutics and Biopharmaceutics. 2015;96:65-75. doi:10.1016/j.ejpb.2015.07.010

21. Liu K, Chen W, Yang T, et al. Paclitaxel and quercetin nanoparticles co-loaded in microspheres to prolong retention time for pulmonary drug delivery. International Journal of Nanomedicine. 2017;12:8239-8255. doi:10.2147/IJN.S147028

22. Lin Q, Liu G, Zhao Z, Wei D, Pang J, Jiang Y. Design of gefitinib-loaded poly (L-lactic acid) microspheres via a supercritical anti-solvent process for dry powder inhalation. International Journal of Pharmaceutics. 2017;532(1):573-580. doi:10.1016/j.ijpharm.2017.09.051

23. Chen AZ, Tang N, Wang S bin, Kang YQ, Song HF. Insulin-loaded poly-l-lactide porous microspheres prepared in supercritical CO2 for pulmonary drug delivery. Journal of Supercritical Fluids. 2015;101:117-123. doi:10.1016/j.supflu.2015.03.010

24. Saigal A, Ng WK, Tan RBH, Chan SY. Development of controlled release inhalable polymeric microspheres for treatment of pulmonary hypertension. International Journal of Pharmaceutics. 2013;450(1-2):114-122. doi:10.1016/j.ijpharm.2013.04.011

25. Gaspar MC, Pais AACC, Sousa JJS, Brillaut J, Olivier JC. Development of levofloxacin-loaded PLGA microspheres of suitable properties for sustained pulmonary release. International Journal of Pharmaceutics. 2019;556:117-124. doi:10.1016/j.ijpharm.2018.12.005

26. Takeuchi I, Taniguchi Y, Tamura Y, Ochiai K, Makino K. Effects of L-leucine on PLGA microparticles for pulmonary administration prepared using spray drying: Fine particle fraction and phagocytotic ratio of alveolar macrophages. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2018;537:411-417. doi:10.1016/j.colsurfa.2017.10.047

27. Doan TVP, Couet W, Olivier JC. Formulation and in vitro characterization of inhalable rifampicin-loaded PLGA microspheres for sustained lung delivery. International Journal of Pharmaceutics. 2011;414(1-2):112-117. doi:10.1016/j.ijpharm.2011.05.007

28. Feng R, Zhang Z, Li Z, Huang G. Preparation and in vitro evaluation of etoposide-loaded PLGA microspheres for pulmonary drug delivery. Drug Delivery. 2014;21(3):185-192. doi:10.3109/10717544.2013.840813

29. Feng T, Tian H, Xu C, et al. Synergistic co-delivery of doxorubicin and paclitaxel by porous PLGA microspheres for pulmonary inhalation treatment. European Journal of Pharmaceutics and Biopharmaceutics. 2014;88(3):1086-1093. doi:10.1016/j.ejpb.2014.09.012

30. Zhu L, Li M, Liu X, Jin Y. Drug-Loaded PLGA Electrospraying Porous Microspheres for the Local Therapy of Primary Lung Cancer via Pulmonary Delivery. ACS Omega. 2017;2(5):2273-2279. doi:10.1021/acsomega.7b00456

31. Hariyadi DM, Hendradi E. Optimization performance and physical stability of ciprofloxacin HCLCA alginate microspheres: Effect of different concentration of alginate and CACL2. International Journal of Drug Delivery Technology. 2020;10(1):89-94. doi:10.25258/ijddt.10.1.15

32. Huang X, Brazel CS. On the Importance and Mechanisms of Burst Release in Matrix-Controlled Drug Delivery Systems. Vol 73.; 2001. www.elsevier.com/locate/jconrel