REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Nanocarriers as pulmonary drug delivery systems

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Abstract

The lung is an attractive target for drug delivery due to noninvasive administration via inhalation aerosols, avoidance of first-pass metabolism, direct delivery to the site of action for the treatment of respiratory diseases, and the availability of a huge surface area for local drug action and systemic absorption of drug. Nanocarrier systems in pulmonary drug delivery offer many advantages such as the potential to achieve relatively uniform distribution of drug dose among the alveoli, achievement of improved solubility of the drug from its own aqueous solubility, a sustained drug release which consequently reduces dosing frequency, improves patient compliance, decreases incidence of side effects, and the potential of drug internalization by cells. This review focuses on the different types of the nanocarrier systems used in pulmonary drug delivery with special attention to their pharmaceutical aspects.

Keywords: Liposome; Nanocarrier systems; Polymeric nanoparticle; Pulmonary delivery; Solid lipid nanoparticle; Nanoemulsion.

1. Pulmonary drug delivery

Pulmonary drug delivery systems have gained increased attention for the treatment of several diseases including asthma and chronic obstructive pulmonary disease (COPD). Drug delivery to lungs through inhalation provides several advantages compared to the traditional routes such as direct access to the drug target as well as lower drug dose than required by systemic drug delivery. Accordingly, optimum drug therapy with reduced adverse reactions could be achieved (Mishra and Singh 2020; Lee et al. 2015). Furthermore, it is possible to use the pulmonary pathway to achieve either systemic or local drug effects.

Lungs are an ideal portal for the systemic drug delivery of small molecules as well as biopharmaceuticals due to their large surface area (100 m^2) available for absorption, lower metabolic activity compared to the liver and gastrointestinal tract, and abundance of capillaries. For example, peptides (e.g., insulin), small interfering Ribose Nucleic Acid (siRNA), and vaccines are good candidates for the pulmonary drug delivery (Malamatari et al. 2020).

Local pulmonary drug delivery allows the drug to come into direct contact with the pulmonary epithelium. Consequently, a fast onset of the therapeutic effect could be attained. The advantages of local delivery to lungs include the introduction of higher drug doses directly at the site of action combined with the reduction of the systemic side effects. Additionally, drug metabolism in the lung is lower compared to the normal oral pathway due to low intra- and

extracellular enzymatic activity in the lung (Rauf et al. 2017b; Lee et al. 2015; Elsayed and AbouGhaly 2016) that help the drug bypassing the first-pass liver metabolism (Rauf et al. 2017a). Furthermore, pulmonary medication delivery can provide a similar or superior therapeutic impact than systemic drug delivery at a lower cost. For example, 2-4 mg of oral Salbutamol is therapeutically analogous to 100-200 µg metered dose inhalers (MDIs) (Labiris and Dolovich 2003).

1.1. Lung deposition

The extent of particle deposition in the respiratory tract is dependent on both the physiological conditions of the patient, including breathing patterns and the general health of the lungs, and physicochemical conditions of the inhaled particles, such as shape, size, bulk density, hygroscopicity, and moisture content (Chaurasiya and Zhao 2020). After inhalation of particles, major mechanisms for deposition include impaction due to inertial forces, deposition due to gravity, and Brownian diffusion as shown in **Figure 1**.

1.1.1. Inertial impaction

Inertial impaction involves inertial deposition of particles onto the airway surfaces and occurs close to bifurcations of the large conducting airways. Most large particles (>6 µm) are deposited in the oropharyngeal and large airways because they are unable to follow the directional changes of the inspired airstream particularly in the oropharynx and at airway bifurcations. Thus, loss of drug due to inertial impaction in the oropharynx is the major hurdle to achieve lung deposition using a passive dry powder device.

1.1.2. Gravitational sedimentation

Gravitational sedimentation usually involves small particles in the size range 2–6 µm and occurs in the small conducting airways where the airflow velocity is slow.

1.1.3. Diffusion

Diffusion involves small particles (<2 µm), for which Brownian motion is important and occurs in the small airways and alveoli, where the airflow is negligible.

2. Nanocarrier systems in pulmonary drug delivery

In pulmonary drug delivery, nanocarrier systems have several advantages including relatively uniform dose distribution among the alveoli, drug protection against degradation (Khan, Saeed, and Khan 2019), better drug solubility (Singh et al. 2018), better cell penetration, as well as sustained drug release, which may reduce dosing frequency, improve patient compliance and reduce side effects

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2.1. Liposomes in pulmonary drug delivery

Liposomes are one of the most extensively investigated systems for controlled delivery of drug to the lung. Liposomes seem particularly appropriate for therapeutic agent delivery to lung, since these vesicles can be prepared from compounds endogenous to the lungs, such as the components of lung surfactant, and these properties make liposomes attractive candidates as drug delivery vehicles (Mansour, Rhee, and Wu 2009). Liposomes are defined as spherical unilamellar or multilamellar lipid vesicles. These vesicles are composed of one or more phospholipid bilayers with an aqueous center and thus have the unique ability to enclose amphiphilic, lipophilic as well as hydrophilic drug molecules inside the phospholipid bilayer or at their center (Singh, Joshi, and Verma 2016; Adel et al. 2021). Liposomal-based treatments are available in two forms: liquid and dry powder (El-Sherbiny, El-Baz, and Yacoub 2015). Adel, I.M., et al. developed Spray-Dried Proliposomes for the pulmonary delivery of curcumin for treatment of lung cancer (Adel et al. 2021). Vyas SP, Kannan ME, et al. developed a liposomal aerosol for improved delivery of rifampicin to alveolar macrophages for treatment of tuberculosis infection (Vyas et al. 2004). Stern, Ulrich et al advanced the potential of liposomes as gene carriers. These authors demonstrated that the pretreatment with cationic lipid-mediated transfer of the Na+ K+ -ATPase pump in a mouse model in vivo augmented resolution of high permeability pulmonary oedema. This demonstration of a significant reduction in pulmonary edema following in vivo gene transfer allowed raising the

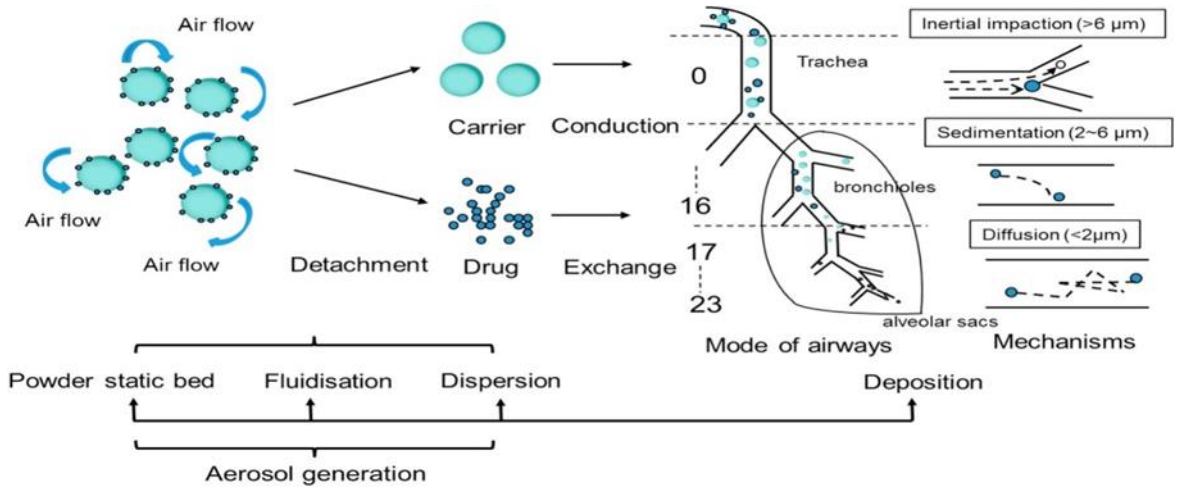

Figure 1. Mechanism of deposition of the inhaled microparticles (Chaurasiya and Zhao 2021)

possibility of gene therapy as a novel localized approach for pulmonary edema in clinical settings such as acute respiratory distress syndrome (ARDS) and lung transplantation (Stern et al. 2000). C. Loira-Pastoriza et al. developed a liquid liposome composed of Dipalmitoyl phosphatidyl choline (DPPC) to deliver Polyinosinic:polycytidylic acid (Poly I:C), an immunostimulant, for the treatment of lung cancer (LC). They used the B16F10 mouse model of metastatic LC to assess tumour growth. The results indicated that inhaling Poly I:C was more effective than injecting it intraperitoneally in delaying the formation of lung metastases with enhanced antitumor activities (Loira-Pastoriza et al. 2021) (Das et al. 2021).

2.2. Solid lipid nanoparticles (SLNs)

In the 1980s, Speiser and coworkers began to develop the use of solid lipids instead of liquid oils to achieve controlled drug release by encapsulation within a solid lipid core of an emulsion (Khanna and Speiser 1969) (Das et al. 2021). SLNs are commonly spherical in shape with a diameter in the range of 50 to 1000 nm. The key ingredients of SLN formulations include lipids, which are in the solid state at room temperature, emulsifiers and sometimes a mixture of both, active pharmaceutical ingredients (APIs) and an adequate solvent system (Duan et al. 2020). Several solid lipids such as stearic acid, triglycerides, carnauba wax, beeswax, cetyl alcohol, emulsifying wax, cholesterol butyrate, and cholesterol may be suitable for SLN preparation. SLN are advantageous because they are generally well-tolerated due to their biocompatibility and provide controlled release of drug molecules and also because of their feasibility for delivery of both lipophilic and hydrophilic drugs. Moreover, SLN do not require the use of organic solvents during formulation and are more stable than emulsions and liposomal formulations, less toxic, and offer easy cost-effective large-scale production using high-pressure homogenization (Das et al. 2021) .SLNs were tested for pulmonary administration in many experiments employing a human alveolar epithelial cell line (A549) and precision-cut lung slices from mice (Rane et al. 2018).The study found that SLNs do not promote pulmonary inflammation, indicating that they are suitable as medication carriers for pulmonary administration. Pandey and Khuller studied the chemotherapeutic potential of SLNs incorporating rifampicin, isoniazid and pyrazinamide against experimental tuberculosis, and observed the slow and sustained-release of drugs from the SLNs in vitro and in vivo (Pandey and Khuller 2005).

2.3. Nanostructured Lipid Carriers (NLCs)

The nanostructured lipid carriers (NLCs) represent an advanced type of the SLNs. These carriers can overcome the SLNs-related disadvantages, such as the drug loading capacity and formulation stability challenges by creating a less structured solid lipid matrix via mixing fluid lipid with solid lipid resulting in less drug expulsion during storage. NLCs are the products of o/w emulsion process, hence the available surfactants typically have a high HLB range, and ideally dissolved in the external aqueous phase of the emulsion. Kaur, P., et al. performed a comparison in lung deposition in vivo using Wistar rats between pulmonary delivered paclitaxel loaded-NLCs (as a dry powder

delivered using insufflators (Penny Century, PA, USA)) and orally administered methanolic PBS suspension of the drug. The results showed that the Lungs' uptake of the drug from the powdered NLCs was higher than the plain drug suspension. This could be attributed to the less clearance of the drug from the lungs due to the slow release of the drug from the NLCs and the retention of the drug in lipid nanoparticles. This indicates the superiority of local delivery via the pulmonary route (Kaur et al. 2016).

2.4. Polymeric nanoparticles

Polymeric nanoparticles (NPs) are particles within the size range from 1 to 1000 nm and can be loaded with active compounds entrapped within or surface-adsorbed onto the polymeric core (Zielińska et al. 2020). Polymeric nanoparticles play three major roles in drug delivery systems: carrying drug molecules, protecting pharmaceuticals from degradation, and controlling drug release (Mansour, Rhee, and Wu 2009; Lee et al. 2015). Polymer-based drug nanoparticle surfaces are modifiable, which improves the drug release pattern in a more controlled fashion; thus the desired therapeutic effects can be achieved for a long time (Rahman Sabuj and Islam 2021). Biodegradable or biocompatible materials, such as poly (-caprolactone) (PCL), poly (lactic acid) (PLA), poly (lactic-co-glycolic acid) (PLGA), alginic acid, gelatin, and chitosan, are utilized to make therapeutic polymeric nanoparticles (Mansour, Rhee, and Wu 2009; Lee et al. 2015). Due to their biocompatibility, surface modification capability, and sustained-release properties, polymeric nanoparticles are intensively studied using various important pulmonary drugs. These pulmonary drugs include antiasthmatic drugs, antituberculosis drugs, pulmonary hypertension drugs, and anticancer drugs. However, to avoid accumulation of polymer carriers following repeated dosing, the biodegradability and toxicity of polymers over the long term should be closely examined in the formulation of polymeric nanoparticles for pulmonary delivery (Mansour, Rhee, and Wu 2009). K. Tomoda, et al developed PLGA nanoparticles loaded with 5% of TAS-103, a dual inhibitor of DNA topoisomerase I/II, for treatment of lung cancer (Lee et al. 2015). Also, S. Azarmi, Tao X., Chen H., et al. incorporated Doxorubicin into poly (butylcyanoacrylate) nanoparticles using emulsion techniques and coated with both polysorbate 80 and dextran. These purified doxorubicin-loaded nanoparticles with mean particle size of 173 nm were then co-spray freeze-dried with lactose at low temperature to avoid decomposition and loss of drug activity (Azarmi et al. 2006).

2.5. Nanoemulsions

To date, NE are not yet fully studied for pulmonary drug delivery, and only few works and research in this area have been published. The formulation of inhalable NE is challenging due to the adverse negative interactions of lipids and surfactants on the function of lung alveoli. A summary of the previously developed inhalable NE is shown in Error! Reference source not found..

The main interest of fabricating O/W NE is due to the fact that they can dissolve large amount of hydrophobic drug within their lipophilic core (Asmawi et al. 2019; Nesamony et al. 2013; Ngan and Asmawi 2018; Wahgiman et al. 2019), and can increase the drug stability by increasing the drug resistance towards enzymatic degradation and hydrolysis (Asmawi et al. 2019; Wahgiman et al. 2019; Ngan and Asmawi 2018). The frequency and drug dosage can also be reduced because NE may sustain pulmonary drug retention for longer periods (Asmawi et al. 2019; Wahgiman et al. 2019; Ngan and Asmawi 2018). Also, they are easily prepared (Amani et al. 2010; Wahgiman et al. 2019) and have the ability of incorporation of drugs of different hydrophilicities in a single formulation (Amani et al. 2010).

On the other hand, drug microsuspensions have several drawbacks including considerable heterodispersity in concentration of the drug in the aerosolized droplets, short drug residence time in the lungs because of ciliary movement, and non-optimized drug deposition pattern (Amani et al. 2010). As a result, NE are being investigated as an alternate method for improving these drawbacks.

2.6. Micelles

Micelles have attracted attention for the delivery of poorly water-soluble drugs. Micelles are formed by self-assembly of amphiphilic molecules. The structures contain hydrophilic/polar region (head) and hydrophobic/nonpolar region (tail). Micelles are formed in aqueous solution whereby the polar region faces the outside surface of the micelle and the nonpolar region forms the core. Micelles can deliver both hydrophilic and hydrophobic agents (Joseph, Trinh, and Mitra 2017). The structure of polymeric micelles can also be chemically altered to design ideal delivery carriers. This can be tailored to improve drug stability, control drug release, and provide targeted drug delivery (El-Sherbiny, El-Baz, and Yacoub 2015). Xiao Hu, Fei-Fei Yang , et al. encapsulated curcumin

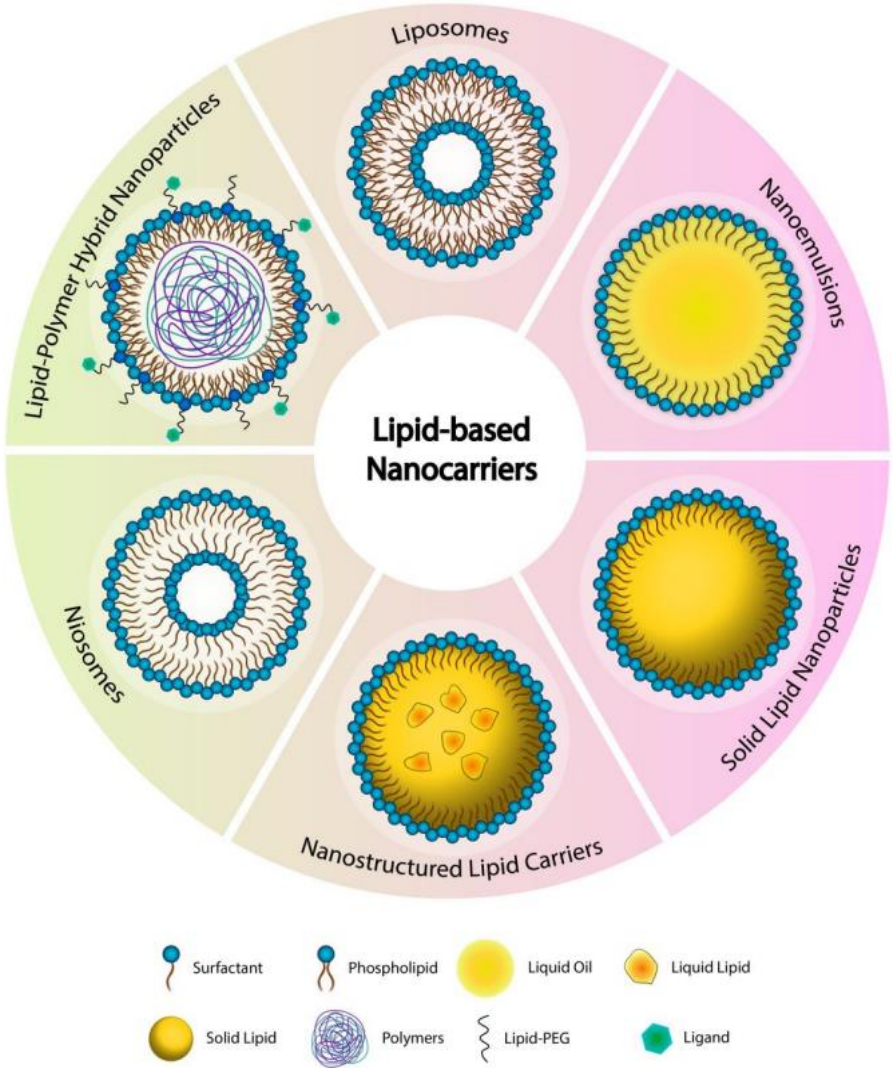

Figure 2. The various types of the lipid-based nanocarriers

acetate (CA) into PEG–PLGA micelles by a solvent evaporation method. The micellar formulation increased the stability of CA in water and physiologically relevant fluids and led to a sustained drug release in vitro. Following intratracheal (IT) administration to rats, CA loaded micelles achieved not only prolonged pulmonary retention with AUC values almost 400-fold higher than by IV route, but also local sustained release up to 24 hours (Hu et al. 2014).

Conclusion

Inhalable nanocarrier systems offer numerous advantages. The decrease in particle size leads to an increase in surface area leading to enhanced dissolution rate, as well as relatively uniform distribution of drug dose among the alveoli. In addition, by suspending the drugs in nanoparticles, one can achieve a dose that is higher than that offered by a pure aqueous solution. Nanocarrier systems can provide the advantage of sustained-release in the lung tissue, resulting in reduced dosing frequency and improved patient compliance. Local delivery of inhalable nanocarriers may be a promising alternative to oral or intravenous administration, thus decreasing the incidence of side effects associated with a high drug serum concentration.

References

Adel, I. M., M. F. ElMeligy, M. E. A. Abdelrahim, A. Maged, A. A. Abdelkhalek, A. M. M. Abdelmoteleb, and N. A. Elkasabgy. 2021. 'Design and Characterization of Spray-Dried Proliposomes for the Pulmonary Delivery of Curcumin', Int J Nanomedicine, 16: 2667-87.

Amani, A., P. York, H. Chrystyn, and B. J. Clark. 2010. 'Evaluation of a nanoemulsion-based formulation for respiratory delivery of budesonide by nebulizers', AAPS PharmSciTech, 11: 1147-51.

Asmawi, A. A., N. Salim, C. L. Ngan, H. Ahmad, E. Abdulmalek, M. J. Masarudin, and M. B. Abdul Rahman. 2019. 'Excipient selection and aerodynamic characterization of nebulized lipid-based nanoemulsion loaded with docetaxel for lung cancer treatment', Drug Deliv Transl Res, 9: 543-54.

Azarmi, Shirzad, Xia Tao, Hua Chen, Zhaolin Wang, Warren H. Finlay, Raimar Löbenberg, and Wilson H. Roa. 2006. 'Formulation and cytotoxicity of doxorubicin nanoparticles carried by dry powder aerosol particles', Int J Pharm, 319: 155-61.

Chaurasiya, Birendra, and You-Yang Zhao. 2020. 'Dry Powder for Pulmonary Delivery: A Comprehensive Review', Pharmaceutics, 13: 31.

Das, S. C., P. Khadka, R. Shah, S. McGill, and H. D. C. Smyth. 2021. 'Chapter 14 - Nanomedicine in pulmonary delivery.' in Prashant Kesharwani, Sebastien Taurin and Khaled Greish (eds.), Theory and Applications of Nonparenteral Nanomedicines (Academic Press).

Duan, Yongtao, Abhishek Dhar, Chetan Patel, Mehul Khimani, Swarnali Neogi, Prolay Sharma, Nadavala Siva Kumar, and Rohit Vekariya. 2020. 'A brief review on solid lipid nanoparticles: part and parcel of contemporary drug delivery systems', RSC Advances, 10: 26777-91.

El-Sherbiny, Ibrahim M., Nancy M. El-Baz, and Magdi H. Yacoub. 2015. 'Inhaled nano- and microparticles for drug delivery', Global cardiology science & practice, 2015: 2-2.

Elsayed, Ibrahim, and Mohamed Hassan Hany AbouGhaly. 2016. 'Inhalable nanocomposite microparticles: preparation, characterization and factors affecting formulation', Expert Opinion on Drug Delivery, 13: 207-22.

Hu, X., F. F. Yang, L. H. Quan, C. Y. Liu, X. M. Liu, C. Ehrhardt, and Y. H. Liao. 2014. 'Pulmonary delivered polymeric micelles--pharmacokinetic evaluation and biodistribution studies', Eur J Pharm Biopharm, 88: 1064-75.

Joseph, Mary, Hoang M. Trinh, and Ashim K. Mitra. 2017. 'Chapter 7 - Peptide and Protein-Based Therapeutic Agents⁎.' in Ashim K. Mitra, Kishore Cholkar and Abhirup Mandal (eds.), Emerging Nanotechnologies for Diagnostics, Drug Delivery and Medical Devices (Elsevier: Boston).

Kaur, Prabhjot, Tarun Garg, Goutam Rath, R. S. Rayasa Murthy, and Amit K. Goyal. 2016. 'Development, optimization and evaluation of surfactant-based pulmonary nanolipid carrier system of paclitaxel for the management of drug resistance lung cancer using Box-Behnken design', Drug Deliv, 23: 1912-25.

Khan, Ibrahim, Khalid Saeed, and Idrees Khan. 2019. 'Nanoparticles: Properties, applications and toxicities', Arabian Journal of Chemistry, 12: 908-31.

Khanna, S. C., and P. Speiser. 1969. 'Epoxy resin beads as a pharmaceutical dosage form I: Method of preparation', Journal of pharmaceutical sciences, 58: 1114-17.

Labiris, N. R., and M. B. Dolovich. 2003. 'Pulmonary drug delivery. Part I: physiological factors affecting therapeutic effectiveness of aerosolized medications', Br J Clin Pharmacol, 56: 588-99.

Lee, Wing-Hin, Ching-Yee Loo, Daniela Traini, and Paul M. Young. 2015. 'Inhalation of nanoparticle-based drug for lung cancer treatment: Advantages and challenges', Asian Journal of Pharmaceutical Sciences, 10: 481-89.

Loira-Pastoriza, Cristina, Kevin Vanvarenberg, Bernard Ucakar, Maria Machado Franco, Aurélie Staub, Muriel Lemaire, Jean-Christophe Renauld, and Rita Vanbever. 2021. 'Encapsulation of a CpG oligonucleotide in cationic liposomes enhances its local antitumor activity following pulmonary delivery in a murine model of metastatic lung cancer', Int J Pharm, 600: 120504.

Malamatari, Maria, Anastasia Charisi, Stavros Malamataris, Kyriakos Kachrimanis, and Ioannis Nikolakakis. 2020. 'Spray Drying for the Preparation of Nanoparticle-Based Drug Formulations as Dry Powders for Inhalation', Processes, 8: 788.

Mansour, H. M., Y. S. Rhee, and X. Wu. 2009.

'Nanomedicine in pulmonary delivery', Int J Nanomedicine, 4: 299-319.

Mishra, Brahmeshwar, and Juhi Singh. 2020. 'Novel drug delivery systems and significance in respiratory diseases', Targeting Chronic Inflammatory Lung Diseases Using Advanced Drug Delivery Systems: 57-95.

Nesamony, Jerry, Ashish Kalra, Mohamed S. Majrad, Sai Hanuman Sagar Boddu, Rose Jung, Frederick E. Williams, Alaina M. Schnapp, Surya M. Nauli, and Andrea L. Kalinoski. 2013. 'Development and Characterization of Nanostructured Mists with Potential for Actively Targeting Poorly Water-Soluble Compounds into the Lungs', Pharm Res, 30: 2625-39.

Ngan, C. L., and A. A. Asmawi. 2018. 'Lipid-based pulmonary delivery system: a review and future considerations of formulation strategies and limitations', Drug Deliv Transl Res, 8: 1527-44.

Pandey, R., and G. K. Khuller. 2005. 'Solid lipid particle-based inhalable sustained drug delivery system against experimental tuberculosis', Tuberculosis (Edinb), 85: 227-34.

Rahman Sabuj, Mohammad Zaidur, and Nazrul Islam. 2021. 'Inhaled antibiotic-loaded polymeric nanoparticles for the management of lower respiratory tract infections', Nanoscale Advances, 3: 4005-18.

Rane, Ajay Vasudeo, Krishnan Kanny, V. K. Abitha, and Sabu Thomas. 2018. 'Chapter 5 - Methods for Synthesis of Nanoparticles and Fabrication of Nanocomposites.' in Sneha Mohan Bhagyaraj, Oluwatobi Samuel Oluwafemi, Nandakumar Kalarikkal and Sabu Thomas (eds.), Synthesis of Inorganic Nanomaterials (Woodhead Publishing).

Rauf, Abdul, Aseem Bhatnagar, S. S. Sisodia, Roop K. Khar, and Farhan J. Ahmad. 2017a. 'Lungs deposition and pharmacokinetic study of submicron budesonide particles in Wistar rats intended for immediate effect in asthma', EXCLI journal, 16: 236-44.

Rauf, Abdul, Aseem Bhatnagar, Siddhraj Sisodia, Roop Khar, and Farhan Ahmad. 2017b. 'Lungs deposition and pharmacokinetic study of submicron budesonide particles in Wistar rats intended for immediate effect in asthma', EXCLI Journal, 16: 236-44.

Singh, Jagpreet, Tanushree Dutta, Ki-Hyun Kim, Mohit Rawat, Pallabi Samddar, and Pawan Kumar. 2018. ''Green' synthesis of metals and their oxide nanoparticles: applications for environmental remediation', Journal of Nanobiotechnology, 16: 84.

Singh, Narinder, Anjali Joshi, and Gaurav Verma. 2016. 'Chapter 10 - Engineered nanomaterials for biomedicine: Advancements and hazards.' in Alexandru Mihai Grumezescu (ed.), Engineering of Nanobiomaterials (William Andrew Publishing).

Stern, M, K Ulrich, C Robinson, J Copeland, U Griesenbach, C Masse, S Cheng, F Munkonge, D Geddes, and Y Berthiaume. 2000. 'Pretreatment with cationic lipid-mediated transfer of the Na+ K+-ATPase pump in a mouse model in vivo augments resolution of high permeability pulmonary oedema', Gene therapy, 7: 960-66.

Vyas, S. P., M. E. Kannan, S. Jain, V. Mishra, and P. Singh. 2004. 'Design of liposomal aerosols for improved delivery of rifampicin to alveolar macrophages', Int J Pharm, 269: 37-49.

Wahgiman, N. A., N. Salim, M. B. Abdul Rahman, and S. E. Ashari. 2019. 'Optimization of nanoemulsion containing gemcitabine and evaluation of its cytotoxicity towards human fetal lung fibroblast (MRC5) and human lung carcinoma (A549) cells', Int J Nanomedicine, 14: 7323-38.

Zielińska, A., F. Carreiró, A. M. Oliveira, A. Neves, B. Pires, D. N. Venkatesh, A. Durazzo, M. Lucarini, P. Eder, A. M. Silva, A. Santini, and E. B. Souto. 2020. 'Polymeric Nanoparticles: Production, Characterization, Toxicology and Ecotoxicology', Molecules, 25.