Review Article

Pulmonary drug delivery strategies: A concise, systematic review

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ABSTRACT

Because of limitations associated with the conventional treatment of various chronic diseases a growing attention has been given to the development of targeted drug delivery systems. Pulmonary route of drug delivery gaining much importance in the present day research field as it enables to target the drug delivery directly to lung both for local and systemic treatment. Over the last 2 decades, the systemic absorption of a broad range of therapeutics after pulmonary application has been demonstrated in animals as well as in humans. This review was prepared with an aim to discuss the technical, physiological, and efficacy aspects of the novel pulmonary route of drug targeting. The review also focuses on the mechanisms of pulmonary drug administration along with compatibility of the excipients employed, devices used, and techniques of particulate dosage production. This review was prepared based on the method of extensive literature survey on the topics covering all the aspects discussed in the present subject. Hence, the better understanding of complexes and challenges facing the development of pulmonary drug delivery system offer an opportunity to the pharmaceutical scientist in minimizing the clinical and technical gaps.

KEY WORDS: Dry powder inhaler, lung deposition, pulmonary route, targeted drug delivery

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INTRODUCTION

The efficacy of a treatment mostly depends on the techniques by which the drug is delivered and optimum concentration of the drug, above or below this range can be toxic or produce no therapeutic benefit at all. The slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutic agents to targets in tissues. The efficacy of the drug and its treatment can be achieved from the new ideas on controlling the pharmacokinetics, pharmacodynamics, immunoginecity, and biorecognition. These new strategies based on interdisciplinary approaches such as polymer science, pharmaceutical technology, bioconjugate chemistry, and molecular biology, are often called novel/advanced drug delivery systems. Different drug delivery/drug targeting systems already exist and currently under development can be efficiently used to minimize the drug degradation and loss, to prevent harmful side effects and to increase drug bioavailability. For over 20 years, the potential benefit of nanotechnology is appreciated by most of the researchers and it is providing vast improvements in drug delivery and drug targeting. New advancements in the drug delivery strategies are minimizing the unwanted toxicities and improving the efficacy of the treatments.

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Pulmonary delivery of drug has become an attractive target and of tremendous scientific and biomedical interest in the health care research area as the lung is capable of absorbing pharmaceuticals either for local deposition or for systemic delivery. The respiratory epithelial cells have a prominent role in the regulation of airway tone and the production of airway lining fluid. In this respect, growing attention has been given to the potential of a pulmonary route as a non-invasive administration for systemic and local delivery of therapeutic agents, because the high permeability and

large absorptive surface area of lungs, (approximately 70-140 m^2 in adult humans having extremely thin absorptive mucosal membrane) and good blood supply.[1-3] The alveolar epithelium of the distal lung has been shown to be an absorption site for most of the therapeutics and various macromolecules.[4-7] Further advantages over peroral applications are the comparatively low enzymatic activity, rapid absorption of drug and the capacity for overcoming first-pass metabolism. It has been already reported that, the local respiratory disorders and some systemic diseases can be well treated by delivering the drugs through pulmonary route. This includes the topical treatment of asthma, local infectious diseases, pulmonary hypertension, the systemic use of insulin, human growth hormones, and oxytocin[8-14] Presently this is true for many biotherapeutics currently injected intravenously, such as growth hormones, glucagons, or insulin, each of which could possibly be delivered to humans by inhation were the efficiency of inhalation therapy is greater.

Understanding the transport and deposition of inhaled aerosols is of fundamental importance to inhalation therapy. Herein we address issues that related to the technical, physiological, and efficacy aspects of pulmonary drug delivery system. This review also focused on transepithelial transport and mechanisms of pulmonary administration. In addition, polymer selections in dosage and types of delivery devices have also been compiled.

TRANSEPITHELIAL TRANSPORT OF DRUGS

The development of drug delivery systems for pulmonary application requires a detailed knowledge of the lung in its healthy, as well as various diseased states. The lung is composed of more than 40 different cells.[15] The human respiratory system is a complex organ system having a close structure-function relationships. This system mainly comprise of two vital regions: the conducting airways and the respiratory region. The airway is further divided into nasal cavity, and associated sinuses, and the nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles. The respiratory region consists of respiratory bronchioles, alveolar ducts, and alveolar sacs. The transepithelial transport of drugs along the respiratory epithelium from these two regions is characterized by large quantitative differences. The drug transport in upper airways is limited due to smaller surface area and lower regional blood flow. Furthermore, this region possesses a high filtering capacity and removes up to 90% of delivered drug particles. Further inhaled substances deposit on the mucus layer, which coats the walls of the conducting airways. Mucus is secreted by goblet and submucosal gland cells and forms a gel-like film consisting of mucin as the major component. Ciliated cells are also present in this region they cause propulsion of mucus upward and out of the lung, thus the lung will be cleared of foreign substances.[16] In contrast, the smaller airway and alveolar space accounts for more than 95% of the lung's surface area and is directly connected to the systemic circulation via the pulmonary circulation. Apart from this, morphology of the major alveolar epithelial cells, the pulmonary blood-gas barrier system, and size of pores and tight junction depth of alveolar and endothelial cells are most likely reasons that govern the transepithelial drug transport.[17]

MECHANISMS AND WAYS OF PULMONARY DRUG ADMINISTRATION

Over the last decade, the systemic absorption of a broad range of therapeutic agents after pulmonary application has been demonstrated in animals as well as humans. Through pulmonary route, the drug can be administered by two primary modes: first, intranasal administration, which has anatomical limitation, such as narrower airway lumen, second, oral inhalative administration. By oral inhalative administration far better results can be expected as it allows to administer very small particles with a concentration loss of only 20% in comparison with 85% by nasal route. Oral inhalative administration can again be classified as intratracheal instillation and intratracheal inhalation. The most common method used in laboratory is the intratracheal instillation. In the intratracheal instillation, a small amount of drug solution or dispersion is delivered into the lungs by a special syringe. This provides a fast and quantifiable method of drug delivery to the lungs. The localized drug deposition is achieved with a comparatively small absorptive area. So, the instillation process is much simple, non-expensive, and has non-uniform drug distribution. In preclinical animal studies, intratracheal instillation has frequently been used to assess the pulmonary absorption and systemic bioavailability, especially with regard to the precise dosing and effectiveness associated with this method.[18] However, intratracheal instillation is not a physiological route for application, and results obtained from these studies may not be transferable to aerosol applications in humans. On the contrary, inhalation method uses aerosol technique by which we can get more uniform distribution with great penetration. However, this method is more costly and difficult to measure the exact dose in lungs. The deposition of drug by aerosol administration in the pulmonary airway mainly takes place by three mechanisms:-gravitational sedimentation, inertial impaction, and diffusion. If the drug particle size is comparatively bigger, then, deposition takes place by first two mechanisms where, either sedimentation occurs due to gravitational force or inertial impaction occurs due to hyperventilation. When the particle size is smaller they deposit mainly by diffusion mechanism, which in turn is based on the Brownian motion. Apart from the pulmonary morphological aspects and ventilatory parameters size of the particles or droplets and the geometry is quite important. The size of particle or droplet in terms of diameter along with the surface electrical charges, shape of the particulate matter if it is a fiber and hygroscopy also having profound influence on drug deposition through pulmonary route.[19] The term

mass median aerodynamic diameter is used and it depends on size, shape, and density of the particulate system.

DEVICES FOR DELIVERY

The delivery device in pulmonary administration plays an important role in the success of this system. In the recent years great strides have been made in the development of advanced devices. However, devices are much less explored than powder formulations.[20] There is a wide range of passive breath driven and active power driven single/-multiple dose dry powder inhalers (DPI) available in the market. The selection of device for delivery of drugs to the lungs is an important factor in the formulation design. If the drug is planned to a specific part of lungs, then the selected device must be capable enough to generate and deliver the particles/droplets of specific aerodynamic diameter. The devices most commonly used for respiratory delivery includes nebulizers, metered-dose inhalers, and dry powder inhalers. Dry powder inhalers are of the most popular devices used to deliver drugs, especially proteins to the lungs. Some of the commercially available dry powder inhalers include Spinhaler (Fisons Pharmaceuticals, Rochester, NY) and Rotahaler (GSK, RTP, NC). Several types of nebulizers are available, namely jet nebulizers, ultrasonic nebulizers, vibrating mesh nebulizers. jet nebulizers are driven by compressed air. Ultrasonic nebulizers use a piezoelectric transducer in order to create droplets from an open liquid reservoir. Vibrating mesh nebulizers use perforated membranes actuated by an annular piezoelement to vibrate in resonant bending mode. The holes in the membrane have a large cross-section size on the liquid supply side and a narrow cross-section size on the side from where the droplets emerge. Depending on the therapeutic application, the hole sizes and number of holes can be adjusted. Selection of a suitable device depends on parameters, such as nature of the drug and its formulation, the site of action, and pathophysiology of the lung. Aqueous suspensions and solutions are nebulized effectively. Aerosols based on mechanically generated vibration mesh technologies also have been used successfully to deliver proteins to lungs[21-23] and are currently being used in the clinical trials of protein and peptide-based pharmaceuticals. Even with active research on development of DPI devices, the concept of powder interaction with device is not well understood. The relative effect of air turbulence and mechanical impaction for controlling powder dispersion in the device is still unclear. However, recent applications of computational fluid dynamics have been helpful in design and development of DPI devices and understand the effect of airflow changes and deagglomeration in the inhaler device.[24,25]

LUNG COMPATIBILITY OF FORMULATION EXCIPIENTS/POLYMERS

The important attention to be given in the development of pulmonary drug delivery system is the compatibility of polymers used in the design of particulate carriers. The safety of these polymers must be first determined and their compatibility with lung fluid is of great concern. The polymers used to prolong the release rate for chronic use may accumulate in the lung, especially in the lung periphery, which is not served by mucociliary clearance. Chronic inhalation of carrier particles has been shown to induce depletion of surfactant with subsequent recruitment of phagocytic cells.[26] The chances of presence of residual solvent in the final product leads to pulmonary toxicity. Therefore, processing techniques and formulation components must be thoroughly screened in order to avoid the toxic consequences. Carriers used in the design of dry powder inhalation formulations, such as sugars, and cyclodextrins can cause bronchoconstriction in many of the hypersensitive individuals.[27] Chronic use of proteins and other carriers, such as absorption enhancers and enzyme inhibitors, can produce immunogenicity, local irritation, and toxicity. Increased permeability may also allow transport of other toxins and antigens across the epithelial barrier.[28] These are some vital issues, which can be properly rectified through suitable models.

TECHNIQUES OF MAKING PARTICULATE MATTER FOR LUNG DELIVERY

Many conventional techniques have been reported to produce DPI formulations. However, these methods have number of limitations, such as particle size, size distribution, shape and poor control over powder crystallinity. These problems can be rectified by specialized milling techniques. Jet-milling of drug under nitrogen gas with new nanojet milling instrument is the most suitable method for creating nanoparticles meant for pulmonary drug delivery. Here, some of the important techniques are discussed in brief.

Spray drying technique

Spray drying is an advanced pharmaceutical manufacturing process used to efficiently produce respirable colloidal particles in the solid state.[29,30] Spray drying was explored in the 1980s as an alternative means of producing fine particles for pulmonary delivery. In this process, the feed solution is supplied at room temperature and pumped to the nozzle where it is atomized by the nozzle gas. The atomized solution is then dried by preheated drying gas in a special chamber to remove water moisture from the system, thus forming dry particles. This method is more promising in producing the particles of above 2-μm size. This method is reported to have better control on particle formation and hence can be easily translated to large scale production. This process is also suitable for thermolabile materials, such as proteins and peptides, because mechanical high- energy input is avoided in this process. More importantly, spray-drying can result in uniform particle morphology.[31,32]

Spray freeze drying method

This method was explored for pharmaceutical application in

early 1990s. It is an advanced particle engineering method, which combines spray-drying and freeze-drying processing steps. It involves spraying the drug solution into liquid nitrogen as a freezing medium followed by lyophilization.[33] This method produces light and porous particles and high fine particle fraction with improved aerosol performance and almost 100% yield at subambient temperatures.[34] Thermolabile protein and peptide substances, such as insulin[35] and plasmid DNA,[36] can also be formulated into dry powder inhalation products. However, this is an expensive process restricted for only expensive drug.

Supercritical fluid technology

The basic feature of this process is the controlled crystallization of drugs from dispersion in supercritical fluids, carbon dioxide. This method has been used in the pharmaceutical field for production of microparticles, nanoparticles, liposomes, and inclusion complexes. This method is used for the production of particulate pulmonary drug delivery systems containing proteins and peptides, and also used to improve the formulation properties of certain drug candidates.[37,38]

Solvent precipitation method

This method involves sono-crystallization and micro-precipitation by opposing liquid jets. Crystalline drug particles with narrow size distribution could be prepared by direct controlled crystallization.[39] Inhalable particles can be produced by rapid precipitation from aqueous solutions using antisolvents. Recently, ultrasonic radiation has been applied to control the precipitation. Various antiasthmatic drugs were prepared using the sono-crystallization technique.

Double emulsion/solvent evaporation technique

This method involves preparation of oil/water emulsion with subsequent removal of the oil phase through evaporation. The organic solvent diffuses out of the polymer phase and into the aqueous phase, and is then evaporated, forming drug- loaded polymeric nanoparticles. By this method, biodegradable polymers have been intensively investigated as carriers for respiratory solid drug nanoparticles.

Particle replication in nonwetting templates

Particle replication in non wetting templates (PRINT) is top-down particle fabrication technique developed by Dr. Joseph DeSimone and his group. This technique is able to produce uniform-sized organic micro- and nanoparticles with complete control of size, shape, and surface functionality, and helps in loading of small organic therapeutics, proteins, peptides, oligonucleotides, siRNA contrast agents, radiotracers, and flurophores.[40-42]

TREATMENT OF CHRONIC DISEASES THROUGH PULMONARY ROUTE

Many reports suggest that some chronic pulmonary diseases can be sufficiently treated through pulmonary route of drug administration; some of them are discussed below. The failure of antitubercular chemotherapy is mainly due to multidrug administration for longer period, which causes patient non-compliances in addition to high cost of treatment and systemic toxicity.[43] These reasons along with many other drawbacks associated with conventional methods of tuberculosis treatment demands the development of novel lung-targeted drug delivery approaches. Anti-tubercular drugs have been successfully entrapped and delivered in biodegradable and biocompatible polymers. Zahoor *et al*.[44] have developed inhalable alginate nano-particles as antitubercular drug carriers against experimental tuberculosis. The relative bioavailability of all drugs from the formulation have found significantly higher compared with oral free drugs when tested in guinea pigs. In another study, Justo *et al*.[45] prepared the kanamycin-loaded lipid vesicles by ethanol injection method for administration by inhalation route. The selected drug was indicated for multiresistant tuberculosis, and administration through inhalation allows both local delivery of the drug to the lungs and systemic therapy. In a study by Garcia-Contreras *et al*.[46] reported systemic delivery of insulin administered by the pulmonary route. The insulin formulations were administered by intratracheal instillation, spray instillation, and subcutaneous route. The plasma concentration of insulin and glucose were determined and pharmacokinetic analysis suggested that the drug had longer mean residence time when administered to the lungs of Sprague-Dawley rats. Glucocortcoids such as budesonide, triamcinolone acetonide, and fluticasone, have a high degree of hepatic first-pass inactivation of the swallowed fraction of the inhaled dose, whereas there is no evidence of first-pass metabolism of these drugs in lung[47,48] and when administered by inhalation are effective and widely used as anti-inflammatory agents of patient with asthma allergic rhinitis and advanced chronic obstructive pulmonary disease. In another study, Neal *et al*,[49] reported the administration of three glucocorticoids, namely budesonide, triamcinolone acetonide, and fluticasone into a cascade impactor for the treatment of asthma and advanced chronic obstructive pulmonary disease. The results revealed that this novel technique appears to be a useful method of evaluating the respiratory products administered via aerosols.

SUMMARY

The better understanding of molecular and biochemical composition of lung can be achieved through the best use of knowledge of advancement in post-genomic era, molecular biology, morphology, and physiology. This idea also helped us to understand the matters, such as molecular basis of diseases and the barriers to drug delivery. The knowledge related to effects of variety of factors, such as the basic nature of therapeutic agents, cellular aspects, properties of delivery system, aerosol

administration mechanisms, lung deposition pattern and type of drug delivery devices help the pharmaceutical scientist in successful development of pulmonary drug delivery system. Hence, better understanding of these parameters and their interrelationship will help us to maximize the efficiency and benefits of pulmonary drug delivery system. Lung as an important organ, major contribution of research in this area may help to achieve safer pulmonary drug delivery in the treatment of chronic diseases. The complexes and challenges facing the development of pulmonary drug delivery system offer lot of excitement to the pharmaceutical scientist, which in turn helps him in minimizing the clinical and technical gaps. There is a wide scope for the researchers to investigate and demonstrate good agreement between *in-vitro*, *ex-vivo*, and *in-vivo* tests used to predict drug absorption from the intact animal and, which may therefore present a solid basis for future advancement in nanomedicine strategies for pulmonary drug delivery.

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