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A COMPREHENSIVE REVIEW ON RECENT ADVANCES IN PULMONARY DRUG DELIVERY SYSTEM.

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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.

Pulmonary drug delivery represents an attractive, non-invasive administration option. In addition to locally acting drugs,molecules that are intended to produce systemic effects can be delivered via the pulmonary route. Several factors need to be considered in the context of delivering drugs to or via the lungs—in addition to the drug itself, its formulation into an appropriate inhalable dosage form of sufficient stability is critical. It is also essential that this formulation is paired with a suitable inhaler device, which generates an aerosol of a particle/droplet size that ensures deposition in the desired region of the respiratory tract. Lastly, the patient's pathophysiology and inhalation manoeuvre are of importance. This Special Issue brings together recent advances in the areas of inhalation device testing, aerosol formulation development, use of in vitro and in silico models in pulmonary drug deposition and drug disposition studies, and pulmonary delivery of complex drugs, such as vaccines, antibiotics and peptides, to or via the lungs.

Keywords

Dry powder inhaler, lung deposition, pulmonary route, targeted drug delivery, ,aerosols, lungs,

Inhalation biopharmaceutics, lung disease

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, immunogenicity, 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.

Pulmonary route have been used to treat various respiratory diseases for centuries. Ancient inhalation therapies included the use of leaves from plants, vapors from aromatic plants, balsams, and myrrh. In the 1920 s adrenaline was introduced as a nebulizer solution, in 1925 nebulizer porcine insulin was used in experimental studies in diabetes, and in 1945 pulmonary delivery of the recently discovered penicillin was investigated 2, 3. Steroids had been introduced in the mid 1950s for the treatment of asthma and nebulizers were enjoying widespread use. In 1956 the pressured metered dose inhaler (pMDI) was introduced, over the past 5 decades, helped by the advances in molecule design and drug discovery the pMDI has risen to become the main stay of asthma treatment. Over the decade certain drugs have been sold in compositions suitable for forming drug dispersion for pulmonary delivery to treat various conditions in humans. Such pulmonary drug delivery compositions are designed to be delivered by inhalation by the patient of drug dispersion so that the active drug within the dispersion can reach the lung. It has been found that certain drugs given by pulmonary route are readily absorbed through the alveolar region directly into blood circulation. Pulmonary route possesses many advantages over other routes of administration for the treatment of specific disease states, particularly lung associated large protein molecules which degrade in the gastrointestinal conditions and are eliminated by the first pass metabolism in the liver can be delivered via the pulmonary route if deposited in the respiratory zone of the lungs. By facilitating the systemic delivery of large and small molecule drugs through inhalation deep into the lung, this advanced pulmonary technology provides a unique and innovative delivery alternative for therapies that must currently be administered by injection (i.v., i.m., s.c.) or by oral delivery that causes adverse effects or is poorly absorbed. New dispersible formulations and drug aerosol delivery devices for inhalable peptides, proteins and various small molecules have, in the past decade, become of increasing interest for the treatment of systemic and respiratory diseases 1, 3.These include, but also extend well beyond, the traditional and long available (although still underutilized) therapies for asthma and chronic obstructive pulmonary disease (COPD). Advances in the use of the lungs as portals for delivery of medication to the blood stream have greatly expanded the potential applications of pulmonary delivery. This advanced technology was initially applied to the systemic delivery of large molecules, such as insulin, interferon-b, or a1 proteinase inhibitor 4

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. 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. 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.

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

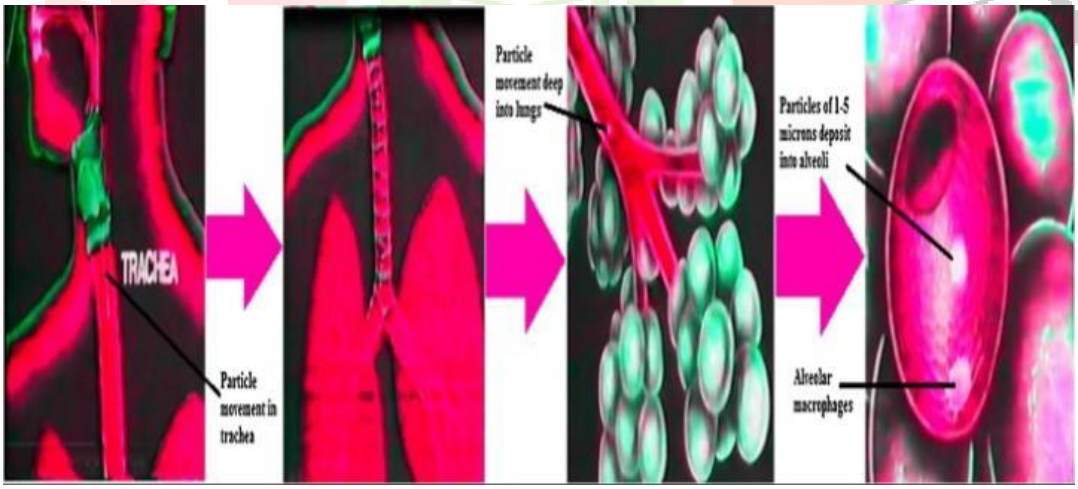

Fig 1: mechanism of pulmonary drug administration

Advantages of drug delivery via the pulmonary route

Pulmonary delivery is expanding a category of drugs called ‘‘inhalables,’’ defined as respiratory and systemic therapies administered simply by inhaling. Inhalables offer several advantages over injectables, transdermal or oral methods of delivery

- Provide a non-invasive method of delivering drugs into the bloodstream for those molecules that currently can only be delivered by injection. These include peptides and proteins, such as insulin for diabetes or interferon beta for multiple sclerosis and most of the drugs developed in recent years by biotechnology companies.
- Enable effective drug targeting to the lungs for relatively common respiratory tract diseases such as asthma, emphysema, bronchiectasis and chronic bronchitis.
- Provide for very rapid onset of action similar to the i.v. Route and quicker than can be achieved with either oral delivery or subcutaneous injections.
- Inhaling helps avoid gastrointestinal tract problems such as poor solubility, low bioavailability, gut irritability, unwanted metabolites, food effects and dosing variability.
- Reduction of dosage i.e. Drug content of one 4 mg tablet of salbutamol equals to 40 doses of meter doses.

Pulmonary delivery the best route of Drug Delivery

While injection has served as the primary means of delivering macromolecules produced by biotechnology, many non-invasive routes have been explored as alternatives. Oral delivery remains the most common method of delivery for most small molecule drugs. However, oral delivery most often does not work for macromolecules because proteins are digested before they have an opportunity to reach the bloodstream. The skin offers an even less naturally permeable boundary to macromolecules than the gastrointestinal tract. Thus, passive transdermal delivery of proteins and peptides using technology has not succeeded. Peptides and proteins can be shot through the skin into the body using high-pressure ‘‘needle-less’’ injection devices. The devices, which inject proteins like insulin, have been available for years, however they have failed to impress doctors or patients due to the associated discomfort. Nasal delivery is inefficient in terms of the amount of drug actually delivered to the body and to increase its efficiency, penetration enhancers must be added that may cause local irritation. In contrast, research has shown that many molecules are absorbed through the deep lung into the bloodstream naturally with relatively high bioavailability and without the need for enhancers used by other non-invasive routes.

Approaches to Pulmonary Drug Delivery

The drugs can be administered by pulmonary route utilizing two techniques ;

1.Aerosol inhalation

2. Intratracheal instillation

By applying aerosol technique, we could achieve more uniform distribution with greater extent of penetration into the peripheral or the alveolar region of the lung, but this costs more and also faced with difficulty in measuring the exact dose inside the lungs. In contrary to this, instillation process is much simple, not expensive and has non-uniform distribution of drugs.

Following types of inhalation devices are present:

A. Inhalation drug delivery system by- metered dose inhalers
B. Inhalation drug delivery system by- dry powder inhalers

C. Inhalation drug delivery system by- nebulizer

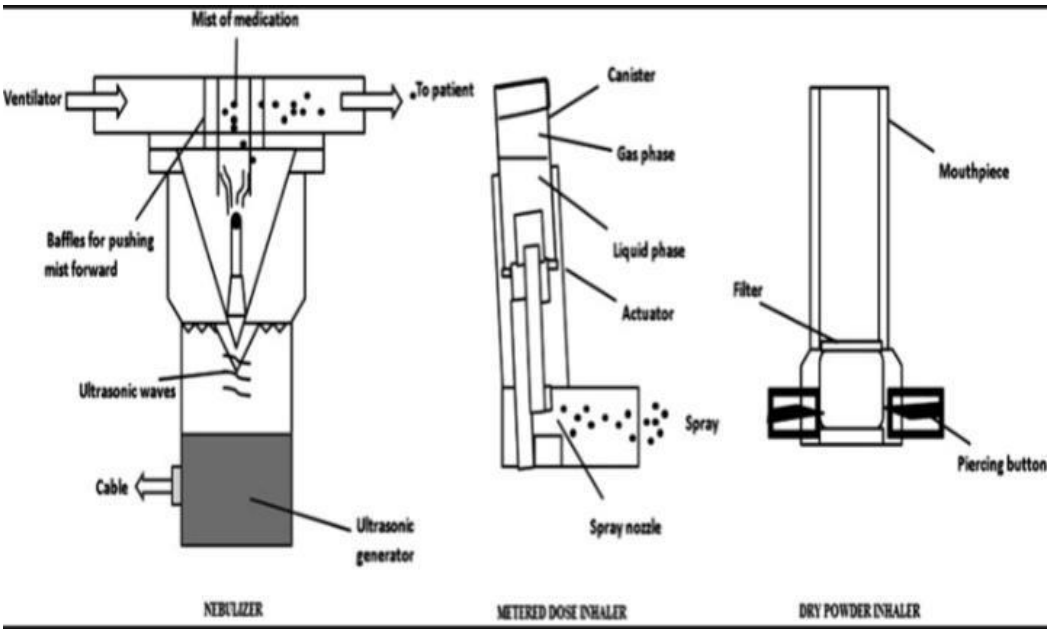

Fig 2: Inhalation devices

A) Inhalation drug delivery system by metered dose inhalers:
A metered-dose inhaler (MDI) is a complex system designed to provide a fine mist of medicament, generally with an aerodynamic particle size of less than 5 microns, for inhalation directly to the airways for the treatment of respiratory diseases such as asthma and COPD.8-11

Trends in MDI technology:

There has been much interest in the differences in effects of Enantiomer of many medications and beta agonist adrenergic bronchodilators have received much attention. Recently levo salbutamol active enantiomer of salbutamol is present in market which is free from termers and palpitation that seen in salbutamol.

Use of Spacers to improve patient coordination with MDI.

The Autohaler TM is the first breath actuated or activated pressurized metered dose inhaler. Autohaler solve the key problem of the pressurized metered dose inhaler (pMDI), does not rely on the patient's inspiratory effort to aerosolize the dose of medication unlike dry powder inhalers.

B) Inhalation drug delivery device by dry powder inhalers:

Dry powder aerosols are frequently highly soluble and quickly dissolve in the fluid layer lining the surface of the deep lung before passing through the thin cytoplasm of the type I alveolar cells the interstitial space and capillary endothelium. The main advantages of dry powder systems include product and formulation stability, the potential for delivering a low or high mass of drug per puff, low susceptibility to microbial growth, and applicability to both soluble and insoluble drugs. Current challenges facing the development of these systems for macromolecules include moisture control, efficient powder manufacturing, reproducible powder filling, unit dose packaging and development of efficient reliable aerosol dispersion and delivery devices.

Currently there are two types;

- Unit-Dose: Devices Single-dose powder inhalers are devices in which a powder contained capsule is placed in a holder. The capsule is opened within the device and the powder is inhaled.
- Multi-dose Devices: Multi-dose device uses a circular disk that contains either four or eight powder doses on a single disk. The doses are maintained in separate aluminum blister reservoirs until just before inspiration.

Device name	**Company**
Monohaler	Pfizer
PDS	Inhale
Ultrhalre	Aventis
mDPI	Sky pharma
Turbocpsin	PH &T
Flowcaps	Hovione

Table no 1: Examples of DPI New Devices

Device name	**Company**
Disc (multi unit dose)	Dey labs
Spiros (multi unit dose)	Dura
Tape, pfeiffer (multi unit dose)	Astra
Prohaler (multi dose)	Valois
Airboost (multi dose)	3B
Kholer inhaler (multi dose)	IB
Bulkhaler, Mikrohaler miat (multi dose)	Astra medical
Swisshaler (multi dose)	Createchnic
Monohaler (unit dose)	Astra

Table no 2:Examples of DPI devices that have been abandoned

Trends in dry powder inhalation technology:

- Changes in the performance of the DPI can be achieved either through changes in the design of the device through changes in the powder formulation, the forces governing the particle-particle interactions in the agglomerates and the forces playing a role in the de-agglomeration process 9, 10.
- Supercritical fluid technology is applied to improve the surface properties of the drug substance. Large porous particles have reduced inter-particulate forces because of their low density, the irregular surface structure and/or reduced surface free energy. Moreover, these particles are claimed to have improved aerodynamic behavior in the airways, whereas phagocytosis of the deposited particles in the alveoli is reduced. In another approach, smaller porous particles (3-5 mm) have been used to improve de-agglomeration and lung deposition 11, 12.
- Changes in device technologies are few new developments really aim at an increase of the de-agglomeration forces generated during the inhalation.
- Air classifier Technology has been recently used in the devices to prevent agglomeration in devices 12.
- Modified form of Air classifier technology is multiple air-classifier technology. In this technology multiple classifier chambers are placed in a parallel arrangement, which further increases the dose that can be aerosolized. 10-12

C) Inhalation drug delivery devices by nebulizer:

Mainly there are two general types of nebulizer systems, the ultrasonic and the air jet. In ultrasonic nebulizers, ultrasound waves are formed in an ultrasonic nebulizer chamber by a ceramic piezoelectric crystal that vibrates when electrically excited. These set up high energy waves in the solution, within the device chamber, of a precise frequency that generates an aerosol cloud at the solution surface. The aerosol produced by an air jet nebulizer is generated when compressed air is forced through an orifice; an area of low pressure is formed where the air jet exists. Nebulizers are particularly useful for the treatment of hospitalized or non-ambulatory patients 13-15.

Trends in nebulizer technology:

- Recent developments in liquid aerosol technology combine the advantages of mDIS and nebulizers are called metered dose liquid inhalers. The major advantage that all these systems aim for is a reduced velocity of the aerosol. Liquid inhalers applying the concept of a low velocity aerosol are often referred to as 'soft mist inhalers'.
- Wet nebulization aims at the generation of monodisperse aerosols, the absence of propellants in the formulation by applying aqueous drug formulations, a reduction in the residual volume after nebulization and an improved portability compared with nebulizers.

Formulations

pMDIs account for two-thirds of sold inhalers, however, due to technological advancements and environmental concerns, DPIs emerged as the preferred medical device for the treatment of a diverse range of respiratory disorders. Many DPIs contain powder mixtures of coarse carrier particles and micronized drug particles with aerodynamic particle diameters of 1–5 µm. It is estimated that only 10–15% of the drug reaches the deep lung while 20% of the drug is lost in the oropharyngeal sphere and 65% is not released from the carrier due to interparticulate adhesive forces. Lechanteur and Evrard have reviewed carrier-free particles, which are characterized by a sugar-based core encompassed by a corrugated shell layer produced by spray drying [3]. Special attention is given to the relation between the morphology (characterized by a corrugated surface) and lung deposition performance.

A different approach to overcoming the limitations of conventional carrier-based dry powders was followed by Benke et al.

They report the development of an interactive physical blend of a surface-modified carrier and spray-dried meloxicam potassium with suitable shape and size for pulmonary delivery. The nonsteroidal anti-inflammatory drug was used with the intention to provide local anti-inflammator effects to decrease the progression of cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD). In vitro and in silico studies resulted in high lung deposition, confirming that the interparticle interactions were indeed reduced in the novel formulation.

Rashid and co-workers, on the other hand, followed the traditional approach and formulated a lactose carrier-based dry powder formulation of glucagon for pulmonary delivery [5]. They investigated L-leucine and magnesium stearate as dispersibility enhancers and found the highest fine particle fraction (FPF) for the formulation to contain Mg stearate (36%) and large carrier lactose, whereas leucine was not a suitable excipient for the pulmonary delivery of glucagon.

Liquid formulation of fluticasone instead of dry powders were studied by Dogbe et al., in order to improve the biopharmaceutical performance of the drug [6]. The study compares liposomes and cyclodextri(CyD) complexes in vitro and in vivo in mice. The in vitro tests showed no cytotoxic effects of either formulation. Fluticasone liposomes resulted in up to 30-times higher lung concentration in comparison with free drug after intranasal administration. Fluticasone hydroxypropyl-cyclodextrin complexes also showed higher lung accumulation than the free form after inhalation, however, this effect was not as pronounced as those observed with the liposomes.

Lung compatibility of formulation excipients/polymer

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. 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. 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. These are some vital issues, which can be properly rectified through suitable models.

Challenges in Pulmonary Drug Delivery

- Low Efficiency of inhalation system
- Less drug mass per puff
- Poor formulation stability for drug
- Improper dosing reproducibility

Recent advances in Pulmonary Drug Delivery:

A formulation that is retained in the lungs for the desired length of time and avoids the clearance mechanisms of the lung is necessary. Various techniques are used to improve the current formulation techniques such as;

- Micronization via jet milling,
- Precipitation,
- Spray drying

Recent Formulations of Pulmonary Drug Delivery

- Insulin by Aerosol
- Nicotine Aerosol for Smoking Cessation
- Aerosols for Angina.
- Alpha 1 Antitrypsin
- Gene Therapy via Aerosol
- In Cancer chemotherapy
- Pentamidine Aerosol
- Gentamycin aerosol
- Ribavirin Aerosol
- Pulmonary delivery of lower molecular weight Heparin.
- Controlled delivery of drugs to lungs
- Pulmonary delivery of drugs for bone disorder

Liposomes

Liposomes, as a pulmonary drug delivery vehicle, have been studied for years and used as a means of delivering phospholipids to the alveolar surface for treatment of neonatal respiratory distress syndrome. More recently, they have been investigated as a vehicle for sustained-release therapy in the treatment of lung disease, gene therapy and as a method of delivering therapeutic agents to the alveolar surface for the treatment of systemic diseases.

Large Porous Particles

Pulmospheres are the new type of aerosol formulation is the large porous hollow particles,. They have low particle densities, excellent dispersibility and can be used in both MDI and DPI delivery systems. These particles can be prepared using polymeric or nonpolymeric excipients, by solvent evaporation and spray-drying techniques. Pulmospheres are made of phosphatidylcholine, the primary component of human lung surfactant. The large size of Pulmospheres allows them to remain in the alveolar region longer than their nonporous counterparts by avoiding phagocytic clearance.

Biodegradable polymers

Biodegradable polymer microspheres are currently being studied as sustained release pulmonary drug Carriers. Polymers such as polylactic acid are used in medical. Applications such as sutures orthopedic implants and medical Dressings, and poly glycolic acid have been investigated.

Propellants used in pulmonary drug delivery devices:

Recently HFA propellants are a new alternative for CFC propellants in pulmonary drug delivery devices.

Inhaled Antibiotics

Seven publications in this special issue cover various aspects of the inhalation of anti-infectives to treat lung infections. Inhaling antibiotics allows for high target site concentrations, whilst minimising systemic exposure and toxicity. Nonetheless, only a handful of antibiotics are currently marketed as nebulisable solutions or dry powders, and almost exclusively for the use in CF. Future inhaled antibiotic trials should therefore focus on disease areas outside of CF, e.g., non-CF bronchiectasis,drug-resistant non-tuberculous mycobacterial infections, ventilator-associated pneumonia, post-transplant airway infections and tuberculosis (TB). Therefore, an increased number of drugs as well as novel drugs must be studied as well as other formulations. Banaschewski and Hofmann have reviewed research into completed inhaled development programs, as well as ongoing research into inhaled therapies for both non-TB mycobacterial lung disease and TB. They conclude that preclinical and clinical studies have shown that inhalation therapy, complementary to current guidance-based therapy strategies, are clinically beneficial for all types of mycobacterial infections. However, an open-minded approach should be followed to continue investigating potential additions to the Antibacterial therapeutic arsenal.In two papers, Sibum and colleagues report the formulation, characterization and stability testing of high-dose dry powders of isoniazid with little or no excipient for the treatment of TB .Initially, isoniazid was jet milled and spray dried with and without the excipient L-leucine. However, milling isoniazid did not yield a suitable formulation and spray drying the pure drug resulted in particles too large for pulmonary administration. When 5% L-leucine was added, respirable particles could be produced by spray drying but their storage stability was poor at higher relative humidity .The stability was later improved by using trileucine instead of L-leucine. The optimal formulation contained 3% trileucine w/w and had a maximum fine particle dose of 58 mg when a nominal dose of 80 mg was dispersed from the Cyclops dry powder inhaler .In a case also using isoniazid, Wyszogrodzka-Gaweł et al. developed a the ranostic approach to TB treatment and diagnosis that allows for imaging of the lungs by MRI .Metal-organic framework (MOF) Fe-MIL-101-NH nanoparticles were loaded with isoniazid using factorial design of spray-drying with poly(lactide-co-glycolide) and leucine. The formulation thus obtained had MRI contrast capabilities, aerodynamic properties suitable for lung delivery, modified drug release and was taken up by macrophages.

Rossi and co-workers, in an attempt to treat mycobacterial lung infections, studied inhalable antibiotic powders targeting alveolar macrophages . Their sodium hyaluronate-based formulation contained two antibiotics (i.e., rifampicin and isoniazid) and the efflux pump inhibitor, verapamil and was produced by spray drying. The sub-micron-sized particles had a high fine particle fraction, showed a sustained release profile, were not toxic towards macrophages and achieved more than 80% reduction in bacterial viability in susceptible and resistant M. tuberculosis strains in vitro. Isoniazid was introduced in 1952. Bedaquiline, on the other hand is a relatively novel oral anti-TB drug that was approved in the US in 2012 by fast-track accelerated approval and is on the World Health Organization's List of Essential Medicines. Bedaquiline, however, has a black-box warning of increased risk of death and arrhythmias. Hence, Momin et al. developed inhalable bedaquiline dry powder particles with the intention of reducing the systemic side-effects .Bedaquiline was processed by spray drying and the resulting micro particles were stable during one-month of storage. Spray-dried bedaquiline was non-toxic in respiratory epithelial cell cultures and effectively inhibited the growth of M. tuberculosis in vitro Antimicrobial peptides (AMPs) are being considered as alternatives to conventional antibiotics. AMPs do not only have direct antimicrobial activity, but also modulate the immune system and wound repair, making them of interest in CF therapy. Forde and colleagues studied whether prodrugs of AMPs (pro-AMPs) can be delivered by VMN and whether modifications of pro-AMP had an effect on the delivery .Nebulization did not alter AMPs' physical characteristics and antimicrobial activity. Approximately 25% of the nominal dose was delivered in a spontaneous breathing setting, with higher delivery rates observed in a mechanically-ventilated model. These results demonstrated the feasibility of AMP delivery using a VMN and also that the prodrug modification is not detrimental.

Pulmonary Delivery of Biopharmaceuticals

Vaccines against bacterial diseases may directly reduce antibiotic use through reduction of disease incidence. Thus, immunisation has the potential to reduce antibiotic use. Vaccine delivery via mucosal surfaces is an interesting alternative to parenteral vaccination and in many cases resembles the route taken by the microorganism when entering the body.

Inhaled Anti-Cancer Treatment

Another disease that could benefit from the advantages that inhalation therapy offers in terms of reduced systemic drug burden is lung cancer. Parvathaneni et al. in their study investigated the anti-tumour effects of liposomally-encapsulated pirfenidone in vitro .Pirfenidone, a repurposed anti-fibrotic drug, was encapsulated in cationic liposomes. The formulation was successfully aerosolized by a jet nebulizer and showed promising anti-tumour effects in various human lung cell lines compared to free pirfenidone.

In Vitro and In Silico Deposition and Drug Disposition

Particle deposition in the lungs is associated with the breathing patterns of the patient and also pathophysiological changes due to lung diseases. In their study, Farkas and colleagues measured realistic inhalation profiles of mild, moderate, and severe COPD patients and simulated the deposition patterns of the Symbicort Turbuhaler in comparison to data generated from healthy control subjects .They found an association between the amount of drug deposited within the lungs and disease severity. The results from this study suggest that to receive a similar lung concentration, severe COPD patients would require much higher doses than healthy individuals. Tailoring the shape and size of fiber-like aerosols to achieve targeted pulmonary drug delivery with increased deposition efficiency is an interesting concept. Shachar-Berman et al. calculated the transport and deposition characteristics of fibers under physiological inhalation conditions in silico using computational fluid dynamics (CFD) simulations .Aerosol deposition was quantified as a function of the equivalent diameter (dp) and geometrical aspect ratio (AR). They found that high AR fibres in the narrow range of dp = 6–7 µm mainly deposited in the upper airways, whereas fibres in the range of dp = 4–6µm penetrated all the way to distal lung regions. To prolong the duration of the effect in the lungs, increasing the drug's affinity to lung tissue is an important strategy for drug development. However, differences in lung structure and blood flow affect local pulmonary drug disposition. Himstedt and co- workers studied regional lung distribution of four drugs (i.e., salmeterol, fluticasone propionate, linezolid and indomethacin) after intravenous administration in rats . In addition, a semi-mechanistic model was employed to describe the observed tissue drug concentrations. The in silico model was able to explain the pulmonary pharmacokinetics of the two neutral and one basic model drug based on their tissue specific affinities (Kp) and organ blood flow. The pulmonary PK of indomethacin, however, could not be modelled, suggesting that acidic drugs have different pulmonary PK characteristics. In their paper, Salomon et al. studied the activity of carnitine transporter OCTN2, which is associated with asthma and other inflammatory lung diseases. They studied freshly isolated human alveolar type I (ATI)-like epithelial cells in primary culture and several respiratory epithelial cell models .[H]-acetyl-l-carnitine uptake and pharmacological inhibition was determined in ATI-like, NCl-H441, A549 and Calu-3 cells. It was concluded that OCTN2 is involved in the cellular uptake of acetyl-l-carnitine at the alveolar epithelium, however none of the tested cell lines are optimal surrogates for primary cells in carnitine transport studies. Antimicrobial peptides (AMPs) are being considered as alternatives to conventional antibiotics. AMPs do not only have direct antimicrobial activity, but also modulate the immune system and wound repair, making them of interest in CF therapy. Forde and colleagues studied whether prodrugs of AMPs (pro-AMPs) can be delivered by VMN and whether modifications of pro-AMP had an effect on the delivery .Nebulisation did not alter AMPs' physical characteristics and antimicrobial activity. Approximately 25% of the nominal dose was delivered in a spontaneous breathing setting, with higher delivery rates observed in a mechanically-ventilated model. These results demonstrated the feasibility of AMP delivery using a VMN and also that the prodrug modification is not detrimental.

Environmental Exposure and Toxicity Studies

Pulmonary drug delivery research is usually mainly concerned with administering aerosols to the lungs. The non-deposited, exhaled dose, however, can be a significant health hazard in both clinical and homecare settings. In two publications, McGrath and colleagues used nebulised albuterol sulphate solution when they investigated fugitive aerosol emissions from two commercially available nebulisers in combination with an open or valved facemask or using a mouthpiece with and without a filter and during high flow nasal cannula (HFNC, see below for more on HFNC) therapy . respectively. It was shown that the MMAD of the fugitively-emitted aerosols was less than 1 µm, while the initially generated aerosols were between 2 and 5 µm. A facemask combination resulted in the highest time-averaged

fugitively-emitted aerosol concentrations, whereas a filter on the exhalation port of the mouthpiece yielded the lowest concentrations. In the HFNC study, fugitive aerosol emissions were influenced by the interface type, patient and supplemental gas-flow rate, with fugitive aerosol MMAD decreasing with an increasing flow rate. These findings are important in developing policy and best practice for risk mitigation from fugitive emissions. 'Foamy' alveolar macrophages (FAM) may be indicators of drug-induced phospholipidosis. Currently, orally administered amiodarone is used to induce pulmonary phospholipidosis. Patel et al. in their study investigated if pulmonary delivery of amiodarone in rats could be established as a novel phospholipidosis-induced FAM model in comparative inhalation toxicology. A high dose of aerosolised amiodarone caused transient pulmonary inflammation, however, only oral delivery resulted in FAM.

High Flow Nasal Cannula Therapy

High flow nasal cannula (HFNC) is widely utilized to support critically ill adults, paediatrics and neonates. Through the continuous delivery of oxygen at high flow rates that meet or exceed patients' inspiratory flow, HFNC improves oxygenation, respiratory rates, patient comfort, and tolerance during therapy. As HFNC becomes more widely employed, the technique is also being considered for aerosol drug delivery. Ji et al. have identified the ratio of nasal cannula gas flow to patient inspiratory flow as a primary independent predictor of inhaled dose. When the ratio was <1, the inhaled dose was higher than those with ratio > 1. The inhaled dose was also more consistent with quiet and distressed breathing with ratio < 1 .In a separate study, Alcoforado and co-workers observed that both flow and active heated humidity inversely impacted aerosol delivery through HFNC. Nonetheless, aerosol administration across the range of commonly used flows can provide measurable levels of lung drug deposition in healthy adult subjects .Ji and colleagues retrospectively analysed study data on HFNC- delivery epoprostenol (iEPO), utilised to improve oxygenation in mechanically ventilated patients with severe hypoxemia comorbid with pulmonary hypertension or right heart dysfunction .Their data suggest that iEPO via HFNC can improve oxygenation in adult patients and supports the need for a larger prospective randomised control trial to further evaluate the efficacy of iEPO via HFNC.

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. 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.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.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.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 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 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.

Future Scope

Despites the many challenges faced by pulmonary drug delivery system, several peptide and protein drugs are currently investigated for potential systemic absorption through pulmonary system, and that includes insulin, calcitonin, luteinizing-hormone-releasing hormone (LHRH) analogs, granulocyte colony-stimulating factor (rhG-CSF), and human growth hormone (hGH). Despite considerable clinical experience with aerosolized macromolecules, there have been no serious safety issues to date, nor have there been significant problems with throat irritation or cough.

CONCLUSION

Given the advances in pulmonary delivery technology, the issues for drug companies and patients concerning pulmonary delivery revolve around economic evaluations, approvals, administration and managed health care. As these issues are resolved, pulmonary delivery will doubtless become regarded as one of the leading drug delivery alternatives. In this Special Issue, a cross-section of current research in the field of pulmonary drug delivery is published. There is still a lot of work to be done in the areas of inhaler devices and formulation development, particularly, with regards to dry powder and colloidal systems. A severe limitation in this field of research is the small number of excipients FDA/EMA-approved for inhalation. Topical delivery of antibiotics appears to be an area that has attracted a lot of interest in recent years and is likely to make an even bigger impact in the treatment of pulmonary infections in the future. Moreover, viral lung diseases such as COVID-19 are a challenge and delivering antivirals by inhalation might be an approach worth considering. In addition to infectious diseases, conditions such as lung cancer are being actively researched in the context of inhalation drug delivery. The respiratory route can also be utilised to achieve mucosal vaccination against bacterial or viral infections. Furthermore, there is a tangible shift from lab-based experiments towards in silico studies, e.g., in the areas of deposition modelling and physiology-based pharmacokinetic modelling. In the foreseeable future, however, the computer-based approached will need to be based on real-life data generated in actual experiments in the lab or the clinical setting. In the context of data generation, scientists should focus on novel techniques to study the fate of inhaled drugs, in order to allow in vivo/in vitro correlations and predictions.

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