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Pulmonary Drug Delivery System: A Review

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Abstract

Growing attention has been given to the potential of pulmonary root as an alternative for noninvasive systemic delivery of therapeutic agents. Pulmonary drug delivery can be used as an alternative to oral delivery. The system can be best utilized for both local and systemic actions. Pulmonary Drug Delivery System (PDDS) is an important research area which impacts the treatment of illness including asthma, chronic obstructive pulmonary disease (COPD) and various other diseases. Inhalation gives the most direct access to the drug target. This route can be used to deposit the drug to the target site at the high concentration reducing the amount of drug given to the patient and help in reducing systemic side effects and first pass metabolism. Generally, half of all pharmaceuticals are not soluble in water, but are soluble in lipid. As the lungs can absorb both water and oil into the tissue this is not a restriction of pulmonary delivery.

Keywords

Pulmonary Drug Delivery System, COPD, Systemic, Inhalation

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INTRODUCTION

Pulmonary drug delivery systems (PDDS) have been used for decades to deliver drugs for treatment of respiratory disorders [1] as well as other disorders. The lungs provide a huge surface area of alveoli with rich capillary network which acts as an excellent absorbing surface for administration of drugs. Throughout the past several years, rapid onset of action and higher efficiency has been responsible for the success of pulmonary delivery system for symptomatic relief in treatment of asthma and chronic obstructive pulmonary disease (COPD). Research in the area of pulmonary drug delivery has gathered momentum in the last several years, with increased interest in using the lung as a means of delivering drugs systemically. Delivery of locally acting drugs directly to the site of action reduces the amount of dose needed to produce the pharmacological effect but now the lung has been studied as a possible route to administer the treatment of systemic diseases, like diabetes mellitus. The site of deposition that is on central or peripheral airways and whether the distribution of the inhaled drug is uniform or non-uniform may play a vital role in an inhaled drug's effectiveness [2].

Pulmonary delivery of drugs has become an attractive target in the health care industry as the lung is capable of absorbing pharmaceuticals either for local deposition or for systemic delivery. Some pharmaceuticals are not soluble in water but are soluble in lipids. As the lung is able to absorb both water and oil into the tissue, this is not a limitation of pulmonary delivery. Targeted drug delivery to the lungs has evolved to be one of the most widely investigated systemic or local drug delivery approaches [3].

Advantages of PDDS [4]

1. Pulmonary drug delivery has very negligible side effects since the rest of the body is not exposed to drug.
2. The onset of action is very quick.
3. Degradation of drug by liver is avoided.
4. Ability to nebulize protein-containing solutions.
5. The ability to nebulize viscous drug formulations for pulmonary delivery.
6. Increased drug delivery efficacy due to size-stable aerosol droplets with reduced hygroscopic growth and evaporative shrinkage.
7. It is needle free.

Disadvantages of PDDS [5]

1. Improper dosing may cause serious problems.
2. There is a chance of stability problems of formulations.
3. Some drugs may produce irritation or toxicity.
4. Some drugs may be retained in lungs and clearance of the drug may be difficult.
5. It is difficult in producing optimum particle size,

ANATOMY AND PHYSIOLOGY OF LUNGS

The human respiratory system is a complicated organ system of very close structure–function relationships. The system consisted of two regions such as the conducting airway and the respiratory region. The airway is further divided into many folds: nasal cavity and the associated sinuses, and the nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles. The respiratory region [6] consists of respiratory bronchioles, alveolar ducts, and alveolar sacs. The human respiratory tract is a branching system of air channels. The major task of the lungs is gas exchange, by adding oxygen to, and removing carbon dioxide from the blood passing the pulmonary capillary bed.

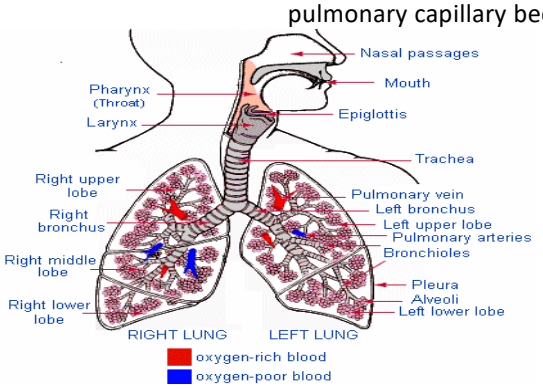

Figure 1: Anatomy of lungs

Lung regions

The respiratory tract starts at the nose and terminates deep in the lung at an alveolar sac. There are a number of schemes for categorizing the various regions of the respiratory tract.

Nasopharyngeal region

This is also referred to as the “upper airways”, which involves the respiratory airways from the nose down to the larynx.

Tracheo-bronchial region

This is also referred to as the “central” or “conducting airways”, which starts at the larynx and extends via the trachea, bronchi, and bronchioles and ends at the terminal bronchioles.

Alveolar region

This is also referred to as the respiratory airways, peripheral airways or pulmonary region, Comprising the respiratory bronchioles, alveolar ducts and alveoli.

Pulmonary epithelium

The lung contains more than 40 different cell types, of which more than six line the airways. The diversity of pulmonary epithelia can be illustrated by examining its structure at three principal levels.

The bronchi

These are lined predominantly with ciliated and goblet cells. Some serous cells, brush cells and Clara cells are also present with a few Kulchitsky cells.

The bronchioles

These are primarily lined with ciliated cuboidal cells. The frequency of goblet and serous cells decreases with progression along the airways while the number of Clara cells increases.

The alveolar region

This is devoid of mucus and has a much flatter epithelium, which becomes the simple squamous type, 0.1–0.5 µm thick. Two principal epithelial cell types are present:

Type-I pneumocytes: Thin cells offering a very short airways-blood path length for the diffusion of gases and drug molecules. Type-I pneumocytes occupy about 93% of the surface area of the alveolar sacs, despite being only half as abundant as type-II cells.

Type-II pneumocytes: Cuboidal cells that store and secrete pulmonary surfactant. Alveolar macrophages account for ~ 3% of cells in the alveolar region. These phagocytic cells scavenge and transport particulate

matter to the lymph nodes and the mucociliary escalator.

Ciliated cells

In the trachea bronchial region, a high proportion of the epithelial cells are ciliated such that there is a near complete covering of the central airways by cilia. Towards the periphery of the tracheobronchial region, the cilia are less abundant and are absent in the alveolar region. The ciliated cells each have about 200 cilia with numerous interspersed microvilli, of about 1–2 µm in length. The cilia are hair-like projections about 0.25 µm in diameter and 5 µm in length. They
are submersed in an epithelial lining fluid, secreted mainly from the serous cells in the sub-mucosal glands. The tips of the cilia project through the epithelial lining fluid into a layer of mucus secreted from goblet cells. The cilia beat in an planned fashion to propel mucus along the airways to the throat.

Barriers of pulmonary drug delivery system

The first requirement for drug absorption is for the active pharmaceutical ingredient (API, or drug) to reach the absorbing barrier. For the respiratory system, the drug has to be deposited on the luminal surface of the epithelial membrane and be absorbed before being cleared or degraded. Furthermore, adequate absorption of the API may also require controlling its release profile as it passes through multiple biological barriers. These barriers include: (1) the mucus layer, (2) epithelial layer, (3) interstitium and basement membrane, and (4) capillary endothelium.

The mucus layer is the first barrier. The deposited drug needs to be dissolved or transverse the mucus layer before degradation due to the enzymatic activity or clearance by mucociliary activity. Because the ciliary action is relatively fast in removing the drug from the absorption site, permeation enhancers must act rapidly to increase bioavailability. The understanding of mucus layer thickness and clearance rate is important to develop drug delivery strategies to overcome mucosal clearance mechanisms. In the lung, the thickness of the luminal mucus gel has been reported to be ~5–10 μm. The underlying, less viscoelastic sol layer, also known as the periciliary liquid, covers the cilia and has an additional 5–10 μ m thickness. However, other studies based on confocal fluorescence microscopy suggest that airway mucus may range in thickness from 5 to 55 μm. The nasal tract has a thin mucus layer which is readily accessible and considered highly permeable compared to other mucosal surfaces. In the nasal tract, the ciliary motion transports mucus with a flow rate of about 5 mm per minute, and the mucus layer is renewed approximately every 20 min.

The second barrier is the epithelial cell membrane. It is comprised of a layer of pseudostratified columnar cells interconnected via tight junctions. Most drugs are primarily absorbed via transcellular diffusion, permeating through the epithelial cell membrane. Small hydrophobic molecules can partition across biological membranes via a concentration gradient. Hydrophilic molecules generally require some sort of selective transport system to cross the lipid bilayer. Large and polar drugs may be absorbed by a paracellular mechanism, and the tight junction structure represents the barrier to paracellular absorption.

Once a drug molecule has passed through to the basolateral side of the epithelium, the next
barrier is the capillary endothelium for absorption into the blood. While this is not critical for locally acting drugs, it is important for systemically targeting APIs. Strategies used to overcome these barriers to absorption include Preventing degradation / metabolism; Enhancing barrier permeability via transient opening of tight junctions, Disruption of lipid bilayer packing / complexation / carrier / ion pairing; and Enhancing resident time/slowing down mucociliary clearance [7,8].

METHODS INVOLVED IN PRODUCTION OF DRUG PARTICLES FOR PULMONARY DELIVERY

Particle size plays an important role in the development of pulmonary drug delivery systems. The optimum particle size required for pulmonary delivery is 1- 5µm. Commonly used methods to achieve this particle size are micronization, spray drying, spray-freeze drying, supercritical fluid crystallization and double emulsion method [9-15].

1. Micronization

By using suitable solvent, crystals are formed which is then micronized to the required size. Energy requirement is huge for micronization. Polymorphic transformation and amorphous formation are the major problems in this process which makes the method unsuitable for many cases.

2. Spray drying

Spray drying is a process that involves conversion of liquid into dried particles. In this process liquid is sprayed into droplets and then dried by using a hot air chamber. Spray drying can produce uniform particle size. This major disadvantage of this method is it's not applicable for thermolabile drugs.

3. Spray freeze drying

Spray freeze-drying is a combination of spray drying and freeze-drying process. In this method there is no heating step. Sublimation mechanism is used to

remove the water from the particles. So, this method can be used for thermolabile drugs.

4. Supercritical fluid crystallization

Supercritical fluids are fluids (gases and liquids) at a temperature and pressure, above their critical points. At this critical point, the fluid exists as a single phase. These fluids have the advantage of both liquid and gas. Supercritical fluids are highly compressible at critical point.

This method may be divided into two types of namely precipitation from supercritical solutions and precipitation using supercritical fluid as non-solvents or anti-solvents. Carbon dioxide is widely used as supercritical fluid because of its applicability for heat sensitive materials.

5.Double emulsion/Solvent evaporation

This technique is commonly used for preparation of microspheres and nanoparticles. This method involves preparation of o/w emulsion and subsequent removal of oil phase. The o/w emulsions are prepared by emulsifying the oily phase containing the drug, polymer and organic solvent in an aqueous solution containing emulsifying agent. The solvent is removed by evaporation resulting in drug loaded polymeric nanoparticles.

Drug delivery carriers for pulmonary system

Drugs for pulmonary delivery require some carriers for targeted action in lungs. Carriers may help in reducing the side effects also. The carrier systems used for pulmonary drug delivery are given below.

1. Inert Carriers

If the dose of the drug is very less, it is difficult to dispense. To overcome the difficulty the drug is dispensed with the aid of bulk carriers. Lactose can be used as a carrier to provide accurate dose and to improve flow property.

2. Biodegradable Polymers

Biodegradable polymers can be used as carriers in pulmonary drug delivery to achieve sustained and controlled release. Biodegradable polymers such as polylactic acid and poly glycolic acid can be used as carriers.

3. Microparticles

Microparticles serve as a potential carrier for pulmonary drug delivery systems. Microparticles are hollow spherical particles with diameter of about 100 to 500µm in which the drug is encapsulated. Controlled and targeted delivery can be achieved by microparticles. Commonly used polymers are polylactic acid, polylactic-co-glycolic acid, albumin, gelatin, chitosan and dextran. Stability and higher drug loading can be achieved by microparticles.

4. Nanoparticles

Nanoparticles are particles ranging from diameter of 1 to 1000 nm. These particles may also be used as carriers for pulmonary route. Controlled and targeted delivery can be achieved by nanocarriers. Biodegradable polymers like poly ε-caprolactone, poly lactic acid, gelatin, chitosan is used to provide sustained action.

5. Liposomes

Liposomes are one of the carriers used in pulmonary drug delivery. These carriers may be helpful in increasing the residence time of drug to provide sustained release. Liposomes can be targeted to the alveolar surface which may be used to treat various lung diseases. The advantages of liposomes include improved stability, reduced side effects, targeted action and reduced local irritation. Liposomes have been used for treatment of neonatal respiratory distress syndrome. The increase in drug uptake by the lungs can be achieved by coating the liposomes with polysaccharide derivatives.

PULMONARY DRUG DELIVERY DEVICES

Pulmonary drug delivery devices can be divided into different categories [16-18], such as nebulizer, the metered-dose inhaler (MDI), the dry powder inhaler (DPI) etc.

Nebulizers

Nebulizers have been used for many years to treat asthma and other respiratory diseases. There are two basic types of nebulizers, jet and ultrasonic nebulizers. The jet nebulizer functions by the Bernoulli principle by which compressed gas (air or oxygen) passes through a narrow orifice creating an area of low pressure at the outlet of the adjacent liquid feed tube. This results in drug solution being drawn up from the fluid reservoir and shattered into droplets in the gas stream. The ultrasonic nebulizer uses a piezoelectric crystal vibrating at a high frequency (usually 1-3 MHz) to generate a fountain of liquid in the nebulizer chamber; the higher the frequency, the smaller the droplets produced. While these disposable nebulizers are inexpensive, the compressors supplying the air or oxygen are not. Most of the prescribed drug never reaches the lung with nebulization. The majority of the drug is either retained within the nebulizer (referred to as dead volume) or released into the environment during expiration. On average, only 10% of the dose placed in the nebulizer is deposited in the lungs.

Inhalers

The medicine inside an inhaler goes straight into the airways. Therefore, it needs much smaller dose than taking the medicine as a tablet or liquid by mouth. Inhalation represents an attractive, rapid, and patient friendly route for the delivery of systemically acting drugs, as well as for drugs that are designed to act locally on the lungs themselves. This concept is especially exciting now that the concept of an inhaled systemic macromolecule, one of the key factors for success in this area is the ability to control the combined powder and device properties. This is essential for the development of dry-powder inhaler (DPI) products yet remains a major technical hurdle to those wishing to succeed with this route and exploit the product opportunities arising from the numerous market drivers.

Metered Dose Inhalers

The MDI was a revolutionary invention that overcame the problems of the hand-bulb nebulizer, as the first portable outpatient inhalation device and is the most widely used aerosol delivery device today. The MDI emits a drug aerosol driven by propellants, such as chlorofluorocarbons (CFC) and more recently, hydrofluoroalkanes (HFAs) through a nozzle at high velocity (> 30 m s-1). MDIs deliver only a small fraction of the drug dose to the lung. Typically, only 10-20% of the emitted dose is deposited in the lung. The high velocity and large particle size of the spray causes approximately 50-80% of the drug aerosol to impact in the oropharyngeal region. Hand-mouth discoordination is another obstacle in the optimal use of the MDI. The delivery efficiency of an MDI depends on a patient's breathing pattern, inspiratory flow rate (IFR) and hand-mouth coordination. Increases in IFR result in decreases in total lung dose deposition and penetration into the peripheral airways. Fast inhalations (> 60 l min^{-1}) result in a reduced peripheral deposition because the aerosol is more readily deposited by inertial impaction in the conducting airway and oropharyngeal regions. When aerosols are inhaled slowly, deposition by gravitational sedimentation in peripheral regions of the lung is enhanced. Peripheral deposition has also been shown to increase with an increase in tidal volume and a decrease in respiratory frequency. As the inhaled volume is increased, aerosols are able to penetrate more peripherally into the lungs.

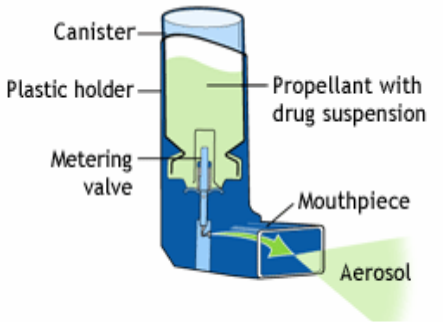

Figure 2: Metered-dose inhalers

Pressurized metered dose inhalers.

The pMDI is not available for all drugs or dosages, making it difficult for clinicians to prescribe the same type of device for diverse inhaled medications. This is exacerbated by the trend of many pharmaceutical companies not to release newer inhaled drugs as pMDIs. The design of the CFC propellant pMDI requires initial and frequent priming. Failure to prime

the device results in administration of a substantially lower dose than that prescribed. Unfortunately, frequent priming tends to waste drug to atmosphere. The greatest single limitation of the pMDI is the inconsistent dosing that occurs with incorrect use.This includes the impact of hand-breath asynchrony, excessive inspiratory flow velocity, nose-breathing, and the cold-Freon effect (the patient stops inhalation when the cold aerosol plume reaches the hypopharynx). For an aerosol device efficiently to deliver medication to the lower respiratory tract, most of the aerosol medication particles must be of a size for inhalation and deposition in the airway, generally 0.5-4.5um mass median aerodynamic diameter. Extended use of the pMDI beyond the labeled number of doses results in a "tailing-off" effect at the end of canister life. While the pMDI provides consistent dosing for the number of actuations listed on the drug label, after that the dose fluctuates between the nominal dose and a negligible dose. In the absence of a dose-counter, which is not provided with most pMDIs, the patient must count the number of doses taken to determine the effective life of the pMDI. The method of "floating" the pMDI canister in water to determine canister depletion is unreliable, and water entering the nozzle can reduce the emitted dose of subsequent actuations.

Dry powder inhalers (DPI)

Interest in DPIs as an effective, efficient, and environmentally friendly way of delivering drugs to the lung has accelerated in recent years. A fundamental difficulty with developing solid state aerosols, or DPIs, is managing both the ubiquitous and the transient forces contained in powder beds. Indeed, managing such particulate forces, for example via particle engineering techniques, is now central to successful DPI formulation and production. With DPIs, the drug aerosol is created by directing air through loose powder. Most particles from DPIs are too large to penetrate the lungs due to large powder agglomerates or the presence of large carrier particles (e.g., lactose). Thus, dispersion of the powder into respirable particles depends on the creation of turbulent air flow in the powder container. The turbulent airstream causes the aggregates to break up into particles small enough to be carried into the lower airways and also to separate the carrier from drug. Each DPI has a different air flow resistance that governs the required inspiratory effort. However, deposition in the lung tends to be increased when using high-resistance inhalers.

LATEST DEVELOPMENT IN INHALER TECHNOLOGY AND MARKETED INHALERS [19-21]

Handihaler

The Handihaler (BoehringerIngelheim) provides a good example of device life cycle management (LCM). The old Inhalator device had a blocky and unattractive design and no mouthpiece cover, while the newer Handihaler offers users a more pleasing shape for both to use.

The Aerogen pulmonary delivery technology

The technology being developed at Aero Gen consists of a proprietary aerosol generator (AG) that atomizes liquids to a predetermined particle size. These delivery platforms accommodate drugs and biopharmaceuticals formulated as solutions, suspensions, colloids, or liposomes used for systemic and local use

Technosphere Insulin (Mankind Corporation)

Technosphere insulin is a kind of lattice containing a dry-powder formulation of crystallized insulin in gelatin capsules. The insulin delivery mechanism uses a high-impedance inhaler with a powder deagglomeration system. Pharmacokinetics and pharmacodynamics studies have shown a very fast absorption (time to peak insulin level: 12-14 minutes, time to maximum metabolic effect: 20-40 minutes) and a short duration of action (2 to 3 hours). Bioavailability was proportional to the administered dose and the biopotency was around 15%. Technosphere/Insulin particles are optimized for inhalation into the deep lung. They are inhaled using the MedTone™ inhaler, a passive, high-resistance, low-flow, dry-powder delivery device. Technosphere/Insulin powder in 2.5-10 mg quantities is filled into single use cartridges that are inserted into the MedTone™ inhaler. The powder is discharged into the oral cavity simply by inhaling through the device mouthpiece. The inhaler does not require manual activation. Since it is activated by patient inhalation, it is not necessary to co-ordinate the timing of device activation and patient inhalation. Additionally, the MedTone™ inhaler is a small, compact device that is inconspicuous, easy to carry and use.

GyroHaler

The GyroHaler is a novel, cost-effective, multi-unit dose DPI device that has been designed to deliver formulations that act locally in the lung. The GyroHaler is designed to target the market occupied by the latest generation of multi-dose inhalers, such as GlaxoSmithKline's DiskusR, which are capable of storing and delivering up to 60 doses. GyroHaler is compact and easy to use and with a small number of moulded parts in order to allow short device development times and competitive manufacturing

costs. The device is intended to be disposable after one month and is designed to have aerosolisation characteristics competitive with existing marketed devices. In addition, the GyroHaler device offers aluminium foil blistered drug protection from moisture, oxygen and light.

Aspirair

Aspirair is a high-delivery-efficiency, user friendly "active" DPI, which delivers drugs via the lung to the systemic circulation in an efficient and effective manner. Typically purpose formulated powders deliver around 70% or greater fine particle dose (% of MD) from Aspirair. Unusual among DPIs is Aspirair's capability of delivering high ultra-fine particle doses (UFPD <3um) coupled with minimal deposition in the oropharynx. Aspirair is an "active" DPI powered using mechanically pressurized air thatacts as an energy source for powder de-aggregation using a miniature cyclone dispersion chamber. To Aspirair, the patient inserts a foil blister containing the dry-powder dose into the device, which pierces the blister. A charge of air is then compressed by the patient using a low torque, corkscrew-type manual pump. Finally, the patient inhales through the mouthpiece, triggering release of the charge of air, which passes through the blister, entraining the powder. The dose then flows into a vortex nozzle where shear and turbulent forces disperse the powder and slow down the air stream, so that a 'soft' aerosol emerges from the mouthpiece that is matched with the patient's inspiratory manoeuvre.

AERx system

This system uses a liquid insulin formulation and expels a single dose of aerosol of fine insulin particles though a disposable nozzle on a disposable dosage strip. The AERx® iDMS emits the aerosol by extruding the solution through the holes of the nozzle. It is a battery powered device utilizing a microprocessor to guide electronically the user to the optimal breathing pattern (flow rate and depth of breath). The system allows delivering metered dose of insulin and single unit increments. It is the size of a small book. As containing a liquid formulation, it requires cold storage. AERx is a high-performance system that delivers liquid formulations to and through the lung, for respiratory and systemic applications. It offers completely non-invasive therapy for small molecules and proteins that require frequent and/or long-term self-administration. The AERx system consists of a disposable prefilled AERx Strip with an integral nozzle, from which the drug is aerosolised via one of several delivery device options. The devices range from electromechanical versions (AERx) with precise dose titration and data management capabilities, to all-mechanical versions (AERx Essence) that deliver a pre-set dose in a single breath.

Exubera, developed by Nektar/Pfizer

Exubera was granted marketing approval by health authorities (EMEA in Europe and FDA in the US) in January 2006, for the treatment of type 1 (in association with basal insulin) and type 2 diabetes. The device uses insulin powder formulation, which consists of recombinant human insulin (60%) and excipients (mannitol, glycine, sodium and nitrate). The powder is packed in blister packs, each one containing 1 or 3 mg of insulin (about 28 and 84 IU) equivalent to 3 IU and 9 IU of subcutaneous insulin respectively which represents a 10% relative activity. The blister is inserted into a slot at the base of the device. Activation leads to compressing trapped air, puncturing the blister and releasing air through the blister at high velocity. Insulin particles (MMAD approximately 3 um) are aerolised into an inhalation chamber. Then, the subject inhales the respirable cloud with a full slow breath. The device is 23 cm long, but when it is folded, it has the size of devices used for asthma. Pharmacokinetics of inhaled insulin has shown a peak at about 55 minutes and a more rapid return to basal level than regular subcutaneous insulin.

Aerodose (Aerogen Inc./Nektar Therapeutics)

Aerodose is a system activated by breath which uses a liquid insulin formulation aerosolised in small droplets. Pharmacokinetics and pharmacodynamics studies have shown a time to peak insulin level shorter after insulin inhalation than after regular subcutaneous insulin (60-97 minutes vs 168-237 minutes) and an onset of action and a peak metabolic effect occurring earlier with inhaled insulin. Reproducibility was similar with inhaled or subcutaneous insulin.

Spiro System (Dina Pharmacy Inc/Elan Corporation)

Spiro System provides a dry-powder insulin formulation encapsulated in blister-disks via a breath-activated inhaler. After inhalation, peak insulin level was observed at 70 minutes and a doseresponse relationship was observed.

Aerosols

Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium. The drugs, delivery by aerosols are deposited in the airways by gravitational sedimentation, inertial impaction, and diffusion. Mostly larger drug particles are deposited by the first two mechanisms in the airways, while the smaller particles get their way into the peripheral region of the lungs by following diffusion. Although there is similarity in drug absorption from the lungs and the other mucosal surfaces, but due to the complexity in

aerosol-particle disposition, the aerosol administration further complicated by the hygroscopic properties of most therapeutic aerosols that allow the particle size to change drastically during the drug transport in the highly humid atmosphere of the respiratory tract. Other factors, which directly influence the aerosol deposition by the above three mechanisms, are aerodynamic size distribution of the aerosol particles, and the density of the aerosol particles. There are three commonly used clinical aerosols: jet or ultrasonic nebulizers, metered-dose inhaler (MDI), and dry-powder inhaler (DPI). Metered dose inhalers are the most frequently used aerosol delivery system. The dry-powder-inhalers are designed to deliver drug/excipients powder to the lungs.

APPLICATIONS OF PULMONARY DRUG DELIVERY SYSTEM [22,23]

1. Pulmonary drug delivery for the treatment of Asthma and COPD

Asthma is a chronic lung that disease is characterized by inflammation and narrowing of airways. Asthma causes recurring period so wheezing, shortness of breath, chest tightness and coughing. For treatment of asthma advances had done in drugs such levo-salbutamol inhalers which show greater efficacy as compared to salbutamol. For the treatment of chronic obstructive pulmonary diseases (COPD) titropium inhalers are present in the market.

2. Role pulmonary delivery inpatients on ventilators

Nowadays, to improve inhalation coordination of patient devices are mostly used like Baby masks. This mask is attached to a spacer for small tidal volumes and low inspiratory flow rates infants and young Childers. Medication can be given to a child up to 2 years by using a baby mask. This is recent advancements in applications of pulmonary drug delivery.

3. New use of pulmonary delivery in diabetes

Diabetes is deficiency of insulin secretion or resistance. The most common form of this therapy is twice-daily subcutaneous injections of insulin. This type of treatment is painful and as a result encourages noncompliance by up to half of the diabetics. Various companies are working on insulin inhalers than any other insulin delivery option. Insulin inhalers would work much like asthma inhalers. The products fall into two main groups the dry powder formulations and solution, which are delivered through different patented inhaler systems. E.g., Novel pMDI formulations for pulmonary delivery of proteins.

4. Role of pulmonary delivery in vaccination

While there was moderate interest in aerosol vaccination 15–20 years ago; progress toward application has been modest seen. Nearly 100 vaccines are approved in the U. S. About half of these prevent respiratory infections, yet all are currently injected. Recently inhaled measles vaccine given by nebulizer. As far back as the 1960, influenza experts tested aerosol flu vaccines.

5. Gene therapy via pulmonary route

Main aim Gene therapy given by pulmonary route is treatment of cystic fibrosis. There are many problems to be overcome before clinical applications are practical. Some of these are safety, successful transfer of sufficient genetic material to appropriate tissue, adequate gene expression, maintenance of expression over time, and efficacy of expression.

6. Pulmonary drug delivery in cancer chemotherapy

Lung cancer is the leading cause of cancer deaths globally, and inhaled chemotherapy seems a logical approach to treat lung cancer. Aerosol delivery of the anticancer agent's difluoro methyl ornithine and 5-fluorouracil reduced lung tumors in mice 50 %and 60 %, respectively. Interleukin-2 stimulates immune function in cancer patients, but injections cause fever, malaise, and local swelling.

7. Diagnostic application pulmonary drug delivery

Pulmonary drug delivery is not only useful for therapeutic purposes but also for diagnosis purposes. For example, inhalation of aerosols of methacholine and histamine is responsiveness in asthma.

8. Pulmonary delivery for bone disorders

Diseases such as osteoporosis and Paget's disease of bones can be treated by pulmonary delivery. The predicted increase in the number of patients with osteoporosis and the lack of ideal therapies dictates the need for better treatments. Clinical evidence from a variety of other peptides and proteins indicates that pulmonary delivery is safe, efficient, well tolerated and preferred by patients so pulmonary route is better option to treat bone disorders. Following are drugs used to treat osteoporosis are the naturally occurring peptides calcitonin and parathyroid hormone, which regulate bone metabolism.

Conclusion

Pulmonary drug delivery is one of the oldest drug delivery systems. But still now it is widely used due to its potential advantages. The drugs which produce gastrointestinal (GI) irritation can be administered by pulmonary route. One of the major hurdles in this system is achieving the optimum particle size, which determines the targeted delivery of drug to lungs. A number of methods like micronization, spray drying,

spray freeze drying, supercritical fluid crystallization and double emulsion are available to achieve the expected particle size. But still it requires further study to select the suitable methods and additives based on the nature of the drugs. Carriers like microparticles, nanoparticles, liposomes etc. can be used in pulmonary delivery. Although advanced technologies are available, in some cases, the product may fail to achieve its goal. To make an effective pulmonary drug delivery system, it is necessary for research professional to have thorough knowledge in the areas of disease condition being treated, lung anatomy and physiology, method of achieving optimum particle size, carrier suitability and drug delivery devices.

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