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STRATEGIES FOR APPROACHES IN PULMONARY DRUG DELIVERY SYSTEM: AN REVIEW

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ABSTRACT

Pulmonary drug delivery has attracted tremendous scientific and biomedical interest in recent years and has progressed considerably within the context of local treatment for lung diseases by virtue of enhanced local targeting and reduced systemic side effects with the administration of minute drug dosages. These routes of drug delivery may give the advantages like small amount of drug less adverse reaction and rapid onset of action. The human respiratory system is complicated organ system these system consist of two reagions conducting airways and respiratory region. The airway further divided into many folds such as nasal cavity, naso pharynx, oropharynx, larynx, trachea, bronchi, and bronchioles. The respiratory region consists of respiratory, bronchioles, alveolar ducts and alveolar sac. Metered dose inhaler, dry powder inhaler and nebulizer. Pulmonary drug delivery is used for management of asthma only but due to advancement in application now a days Pulmonary drug delivery is useful to treat diabetes, angina pectoris, cancer, bone disorders, tuberculosis, migraine acute lung injury and others. The low metabolic activity in the lungs allows systemic delivery without liver passage. Hence lung is an attractive environment for bio molecules, which are highly susceptible to enzymatic degradation in the gastrointestinal tract as well as hepatic degradation.

KEYWORDS: Lungs, Aerosols, nebulizer, Metered dose inhaler, dry powder inhaler.

INTRODUCTION

Drugs are generally delivered to the respiratory tract for the treatment or prophylaxis of airways diseases, such as bronchial asthma and cystic fibrosis. The pulmonary route is also useful where a drug is poorly absorbed orally, e.g. sodium cromoglycate or where it is rapidly metabolized orally, e.g. isoprenaline. The avoidance of first-pass metabolism in the liver may also be advantageous, although the lung itself has some metabolic capability. New dispersible formulations and drug aerosol delivery devices for inhaleable peptides, proteins and various small molecules have, in the past decade, become of increasing interest for the treatment of systemic and respiratory diseases. This advanced technology was initially applied to the systemic delivery of large molecules, such as insulin, interferon-*b*, proteinase inhibitor. 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 or by oral delivery that causes adverse effects or is poorly absorbed.

First, inhalable 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. Inhale Therapeutic Systems, Inc. (San Carlos, California.) is pioneering advanced pulmonary drug delivery technology to provide a convenient and pain-free alternative to injection for systemic delivery of peptides and proteins. Feedback from patients in the clinical trials and extensive market research support the view that inhalable drugs will be welcome alternatives to injections. Second, inhalable enable effective drug targeting to the lungs for relatively common respiratory tract diseases such as asthma, emphysema, bronchiectasis and chronic bronchitis. This direct delivery most often results in a better treatment outcome while potentially requiring less drug than if given systemically either orally or by injection. Third, inhalable 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. More rapid delivery could benefit treatments for pain, seizures, panic/anxiety attacks, hypertensive crises, anaphylaxis nausea, cardiovascular conditions , and Parkinson lock up dictions where speed is important. Fourth, inhaling instead of taking pills can help avoid gastrointestinal tract problems such as poor solubility, low bioavailability, gut irritability, unwanted metabolites, food effects and dosing variability.[1-5]

Anatomy

The respiratory tract can be considered as comprising trachea, bronchi, bronchioles alveolar regions. The upper respiratory tract comprises the nose, throat, pharynx and larynx, the lower tract comprises the trachea, bronchi, bronchioles and the alveolar regions. Simplistically, the airways can be described by a symmetrical model in which each airway divides into two equivalent branches or generations. In fact, the trachea branches into two main bronchi of which the right bronchus is wider and leaves the trachea at a smaller angle than the left, and hence is more likely to receive inhaled material. Further branching of the airways ultimately results in terminal bronchioles shown in Fig.1. These divide to produce respiratory bronchioles, which connect with alveolar ducts leading to the alveolar sacs.

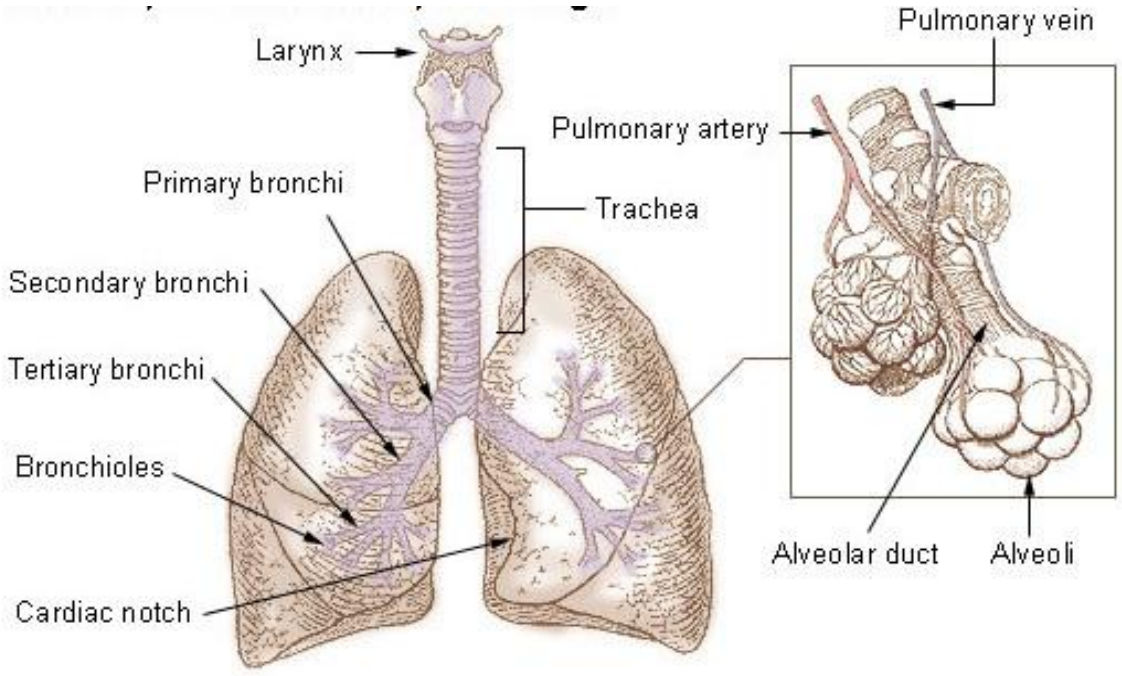

Fig. 1

Alveolar Epithelium

Epithelium measures approximately 100m^2 in adults It is made up of approximately 500,000,000 tiny air sacs, 300 *m*m in diameter, called alveoli. These are enveloped by an equally large capillary network and it is a cross this enormously large and extremely thin (0.1–0.2 *m*m) membrane that gas exchange and the transcytosis of large and small molecules occurs. The alveolar epithelium is composed of a thin, non-ciliated, non mucus covered cell layer consisting mainly of type I and type II fixed alveolar cells. A thin epithelial lining fluid, mainly surfactant, covers the type I and II alveolar epithelial cells. Type I pneumocytes make up most of the epithelial surface. It is the large, thin, type I pneumocytes that are the primary

site of pulmonary protein absorption. The type II pneumocytes, lying in niches between type I cells, are the main source of surfactants and also replace type I cells as they undergo apoptosis (programmed cell death) after about 120 days.[6-9]

Particle deposition in the airways

Aerosols require a size less than about 5 or 6µ , with less than 2µ being preferable for alveolar deposition larger particles or droplets are deposited in the upper respiratory tract and are rapidly cleared from the lung by the muco ciliary action, with the effect that drug becomes available for systemic absorption and may potentially cause adverse effects. Steroid aerosols of sufficiently large size may deposit in the mouth and throat, with the potential to cause oral candidiasis. The size of aerosolized drug may be especially important in the treatment of certain conditions where penetration to the peripheral airways is particularly desirable, for instance the treatment and prophylaxis of the alveolar infection Pneumocystis carinii. There are three main mechanisms responsible for particulate deposition in the lung shown in Fig.2.

1. Gravitational sedimentation,
2. Impaction
3. Diffusion.

Gravitational sedimentation

$$V = \frac{p\, gd^2}{18n}$$

From Stokes' law, particles settling under gravity will attain a constant terminal settling velocity *v* where *p* is particle density, *g* is the gravitational constant, *d* is particle diameter and *n* is air viscosity. Thus, gravitational sedimentation of an inhaled particle is dependent on its size and density, in addition to its residence time in the airways. Sedimentation is an important deposition mechanism for particles in the size range 0.5-3 µ, in the small airways and alveoli, for particles that have escaped deposition by impaction. By the settling under gravity the particles may deposited. It becomes highly important for particles that reach airways where the airstream velocity is relatively low, e.g. the bronchioles and alveolar region. The fraction of particles depositing by this mechanism it may dependent upon the time the particles use in these regions.

Diffusion

Collision and bombardment of small particles by molecules in the respiratory tract produce Brownian motion. The resultant movement of particles from high to low concentrations causes them to move from the aerosol cloud to the airways walls. The rate of diffusion is inversely proportional to the particle size, and thus diffusion is the predominant mechanism for particles smaller than 0.5 µ.

Impaction

This deposition mechanism is particularly important for large particles having a diameter greater than 5 µ, and particularly greater than 10 µ, and is common in the upper airways, being the principal mechanism for deposition in the nose, mouth, pharynx and larynx and the large conducting airways. With the continuous branching of the conducting airways, the velocity of the airstream decreases and impaction becomes a less important mechanism for deposition.[10-15]

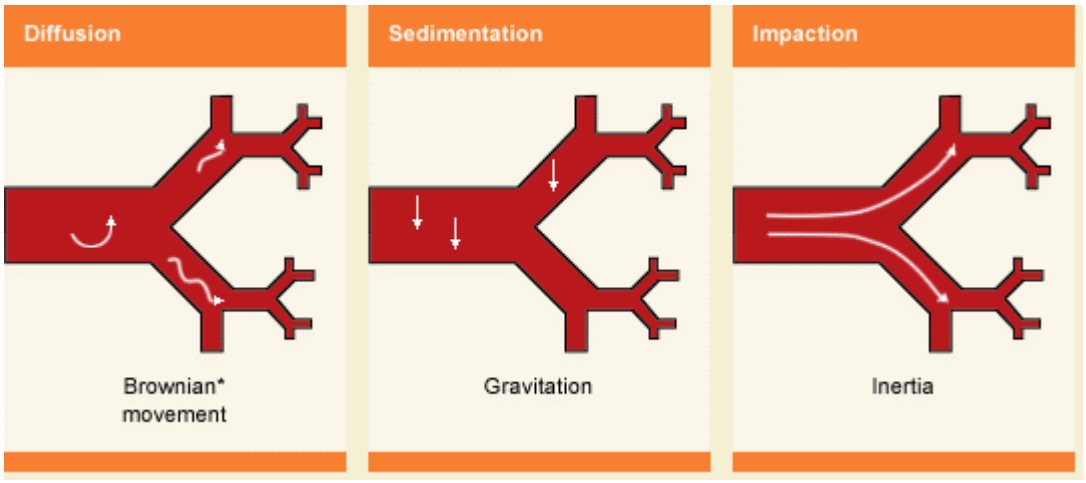

Fig. 2

Clearance of inhaled particles and drug absorption

Particles deposited in the ciliated conducting airways are cleared within 24 hours and ultimately swallowed. Alveolar macrophages engulf such particles and may then migrate to the bottom of the muco ciliary escalator, or alternatively particles may be removed via the lymphatics. Hydrophobic compounds are usually absorbed at a rate dependent on their oil/water partition coefficients, whereas hydrophilic materials are poorly absorbed through membrane pores at rates inversely proportional to molecular size.[16-20]

Strategies in Pulmonary Delivery

1. Metered-dose inhalers

In the mid-1950s the first pressurized metered dose inhaler (MDI) was developed for the administration of bronchodilator drugs locally to the lung. It was a major advance for the treatment of asthma since it made aerosol medications readily available in an inexpensive small multi dose device. Drug is either dissolved or suspended in a liquid propellant mixture together with other excipients including surfactants and presented in a pressurized canister fitted with a metering valve shown in Fig.3. A predetermined dose is released as a spray on actuation of the metering valve. When released from the canister the formulation undergoes volume expansion in the passage within the valve and forms a mixture of gas and liquid before discharge from the orifice. The high speed gas flow helps to break up the liquid into a fine spray of droplets. The metering valve of an MDI permits the reproducible delivery of small volumes (25-100 μl) of product. Unlike the non-metering continuous-spray valves of conventional pressurized aerosols, the metering valve in MDIs are used in the inverted position shown in Fig.4. Depression of the valve stem allows the contents of the metering chamber to be discharged through the orifice in the valve stem and made available to the patient.

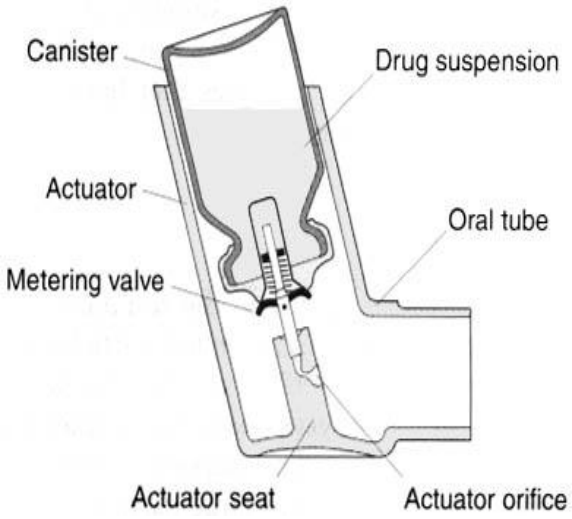

Fig. 3

Pressurized aerosols may be formulated as either solutions or suspensions of drug in the liquefied propellant. Solution preparations are two-phase systems. However, the propellants are poor solvents for most drugs. Cosolvents such as ethanol or isopropanol may be used,

although their low volatility retards propellant evaporation. Canisters are filled by liquefying the propellant at reduced temperature or elevated pressure.

In cold filling, active compound, excipients and propellant are chilled and filled at about -30°C.

Additional propellant is added at the same temperature and the canister sealed with the valve. In pressure filling, a drug/propellant concentrate is produced and filled at effectively room temperature and pressure usually slightly chilled to below 20°C. The valve is crimped on to the canister and additional propellant is filled at elevated pressure through the valve, in a process known as gassing. Pressure filling is most frequently employed for inhalation aerosols. However, no ozone-sparing replacement propellant has the properties high boiling point 23.7°C of CFC-11, which is a major problem for the pharmaceutical industry.

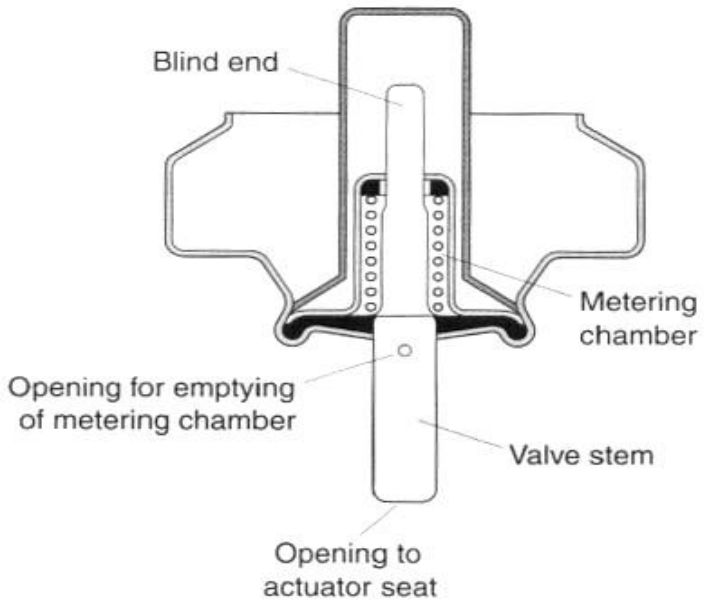

Fig. 4

The major advantages of MDIs are their portability, low cost and disposability. Many doses (up to 200) are stored in the small canister and dose delivery is reproducible. The inert conditions created by the propellant vapour together with the hermetically sealed container, protects drugs from oxidative degradation and microbiological contamination. The world aerosol market has grown due to the increased incidence of asthma and chronic obstructive pulmonary disease (COPD) as well as due to an increased number of patients receiving aerosol medications as the drug formulation-device combination of choice. Until recently,

companies developed pulmonary drug delivery systems primarily to dispense drugs to the airways of the lung for local lung applications. For the systemic delivery of most drugs, however, currently marketed aerosol delivery systems are inadequate due to the following

Low System Efficiency to be commercially feasible for the administration of costly proteins and peptides, the overall efficiency of presently available systems has remained generally too low. Correct aerosol particle size is very important for optimum deep lung delivery. Studies have established that these particles should range from one to three microns in aerodynamic diameter for optimum lung deposition efficiency. If the particles are too large, they impact in the oropharynx and larynx. If they are too small, they will be exhaled. Most existing MDI systems can only deliver a small fraction (about 10–20%) of the dispensed drug in the correct particle size for deep lung deposition although, recently developed 1*m*m solution aerosols from corticosteroid MDIs have achieved lung deposition efficiencies of 60% or more.

Poor Dosing Reproducibility for a variety of reasons, the dosing reproducibility of many existing systems is too variable for systemic delivery of most macromolecule drugs. Physicians and patients alike have tolerated the highly variable dosing of inhaled asthma medications for years because the drugs have a wide therapeutic window and optimizing the drug dose is usually a matter of trial and error.

Poor Formulation Stability for Macromolecules existing aerosol systems are not designed to protect the formulations of delicate macromolecules. Most traditional small molecule asthma drugs are crystalline and, in the case of corticosteroids, relatively moisture resistant in the dry state. They are also rather stable in liquids as compared to most macromolecules, which are unstable in the liquid state, amorphous, and highly moisture sensitive in the dry state.

2. Dry powder inhalers

In dry powder inhaler (DPI) systems, drug is inhaled as cloud of fine particles. The drug is either preloaded in an inhalation device or filled into hard gelatin capsules or foil blister discs which are loaded into a device prior to use. The main advantages of dry powder systems include product and formulation stability (even at room temperature or above), 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. To produce particles of a suitable size preferably less than 5 µm, drug powders for use in inhalation systems are usually micronized. The high energy powders produced have poor flow properties because of their static, cohesive and adhesive nature. The flowability of a powder is affected by physical properties,

including particle size and shape, density, surface roughness, hardness, moisture content and bulk density. Unit-dose DPI is the Rota haler, which is a simple two-piece device shown in Fig.5. The gelatin capsule is inserted into an orifice at the rear of the device and when the two sections are rotated a fin on the inner barrel pulls the two halves of the capsule apart[21-23]. During inhalation, the freed half of the capsule spins, dispersing its contents, which are inhaled through the mouthpiece.

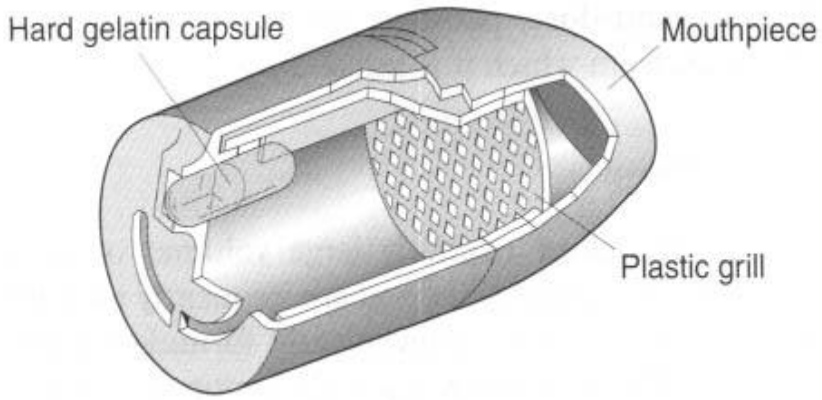

Fig. 5

3. Nebulizers

Where the therapeutic dose is too large for delivery with these alternative systems. Nebulizers also have the advantage over metered- dose and dry powder systems in that drug may be inhaled during normal tidal breathing through amout hpiece or face-mask, and thus they are useful for the patients such as children, the elderly and patients with arthritis, who experience difficulties with MDIs.[26] There are two categories of commercially available nebulizer such as jet and ultrasonic.

Jet nebulizers also called air-jet or air-blast nebulizers use compressed gas oxygen from a compressed gas cylinder, hospital air-line or electrical compressor to convert a liquid usually an aqueous solution into a spray. The jet of high-velocity gas is passed either tangentially or coaxially through a narrow Venturi nozzle, typically 0.3-0.7 mm in diameter.

In ultrasonic nebulizers the energy necessary to atomize liquids comes from a piezoelectric crystal vibrating at high frequency. At sufficiently high ultrasonic intensities a fountain of liquid is formed in the nebulizer chamber.[24-25]

CONCLUSION

A wide variety of agents has been administered to the lung via oral inhalation for the treatment of diverse disease states. Further research efforts are needed to ensure the safety of long term in vivo applications and the development of scale up from laboratory to industry in order to reach within a few years, the safety and large-scale production at affordable costs of innovative lung delivery technologies. It would be an alternative to parenteral drug delivery most notably for the delivery of inhaled insulin and also for peptide and protein therapeutics. Such drug delivery system will also provide bypass way for hepatic first pass metabolism of many potent drugs and reduce drug induced toxicity or adverse drug reactions. It concludes that further research is necessary for pulmonary drug delivery in the treatment of life threatening disorders; as most promising, advanced and attractive economic drug delivery systems.

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