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Recent Advanced Approaches in Pulmonary Drug Delivery System: A Review

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Abstract: *The lung has served as a route of drug administration for thousands of year. Now a day's pulmonary drug delivery remains the preferred route for administration of various drugs. 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 plant, balsam and myrrh. The pulmonary route has gained increasing importance in the recent time due to its unique properties such as a large absorptive area of up to 100m^2; extremely thin 0.1μm to 0.2μm absorptive mucosal membrane and good blood supply. Pulmonary drug delivery is an important research area which impacts the treatment of illness including asthma, chronic obstructive pulmonary diseases and various other diseases. Inhalation gives the most direct access to drug target in the treatment of obstructive respiratory diseases, pulmonary delivery can minimize systemic side effect, provide rapid response and minimize the required dose since the drug is delivery directly to the conducting zone of the lung it is a needle free several technique have been developed in the recent past, to improve the quality of pulmonary drug delivery system without affecting their integrity. New dispersible formulation and drug aerosol delivery device for inhalable peptide, protein and various small molecules have in the past decades, become of increase interest for treatment of systemic and respiratory diseases by different technologies, device, formulation and application of pulmonary drug delivery system.*

Key Words: *pulmonary drug delivery, lungs, aerosol, dry powder inhaler, meter dose inhaler, nebulizer, fine particle fraction*

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I. Introduction

The pulmonary route has gained increasing importance in the recent times due to its unique properties such as a large absorptive area of up to 100m^2; extremely thin 0.1μm – 0.2μm absorptive mucosal membrane and good blood supply. Devices used to deliver drug by pulmonary route area based on one of three platforms pressurized metered dose inhaler, nebulizer and dry powder. Pulmonary route processes 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 lung.

Pulmonary routes have been used to treat various respiratorydiseases for century. Ancient inhalationtherapy includes the use of leave from plants, vapors from aromatic plat, balsam and myrrh. In the 1920 adrenalin was introduce as the nebulizer solution , in 1925 nebulizer porcine insulin was use in experimental studies in diabetes, and in 1945 pulmonary delivery recently discover penicillin was investigate. Steroid had been introduced in mid-1950 for the treatment of asthma and nebulizer enjoy wide spread use. In 1956 the pressure metered inhaler (PMDI) was introduce , over the past 5 decades , helped by advance in molecules design and drug discovery the PMDI has risen to become the main stay of asthma treatment.

Over the decades 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 four 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 lung by fascinating the systematic delivery of large and small molecules drugs through inhalation deep into the lung, this advanced pulmonary technology provides 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 or respiratorydiseases. these include, but also extend well beyond, the traditional and long available (although still underutilized) therapies for asthma and chronic obstructive pulmonary disease(OPD) 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 advances technology was initially applied to the systematic delivery of large molecules, such as insulin, interferon-b, or a1 proteinase inhibitor. [11,20]

ADVANTAGE OF DRUG DELIVERY VIA PULMONARY ROUTE:

Pulmonary drug delivery expanding a category of a drug called inhalation, defined as respiratory and systemic therapies administration smiley by inhaling. Inhalable offer several advantages over injectable, Transdermal or oral method of delivery.

- Provide a non-invasive method of delivery drug into the bloodstream for those molecules that currently can only be delivered by injection. These include peptide and protein, such as insulin for diabetes or interferon beta for multiple sclerosis and most of the drug developed in recent year by biotechnology companies.
- Enable effective drug targeting to the lungs for relatively common respiratory tract diseases such as asthma, 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 injection.
- Inhaling help avoid gastrointestinal tract problem such as poor solubility, gut irritability, unwanted metabolite, food effect and dosing variability.
- Reduction of dosage that is drug content of one 4mg table of salbutamol equal to 40 dose of meter dose.
- Inhaled drug delivery puts drug where it is needed.
- It requires low and fraction of oral dose that is drug content of one 4mg tablet of salbutamol equal to 40 dose of meter dose.
- Pulmonary drug delivery having very negligible side effect since rest of body is not exposed to drug.
- Onset of action is very quick with pulmonary drug delivery.
- Degradable of drug by liver is avoided in pulmonary drug delivery.
- In asthma and diabetes requires long term treatment if it is given by pulmonary drug delivery safety is maximum because rest of body is not exposed to drug. [10]

CHALLENGES IN PULMONARY DRUG DELIVERY:

- Low efficiency of inhalation system
- Less drug mass per puff
- Poor formulation stability for drug
- Improper dosing reproducibility [10]

LUNG COMPATIBILITY OF FORMULATION EXCIPIENT/POLYMER:

The important attention to be given in the development of pulmonary drug delivery system is the compatibility of polymer used in the design of the particulate carrier. The safety of these polymers must be first determined and their compatibility with lung fluid is of great concern. The polymer use to prolong the release rate for chronic use may accumulate in the lungs, especially in the lung periphery, which is not served by mucociliary clearance. Chronic inhalation of carrier particle has been shown to induce depletion of surfactant with subsequent requirement of phagocytic cell. The chances of presence of residual solvent in the final product lead to pulmonary toxicity. Therefore, processing technique and formulation component must be thoroughly screened in order to avoid the design of dry powder inhalation formulation, such as a sugar, and cyclodextrin can cause bronchoconstriction in many of the hypersensitive individual. Chronic use of protein and other carrier, such as absorption enhancer and enzyme inhibitor, can produce immunogenicity local irritation, and toxicity increased permeability may also allow transport of other toxin and antigen across the epithelial barrier. These are some vital tissue, which can be properly rectified through suitable model. [11]

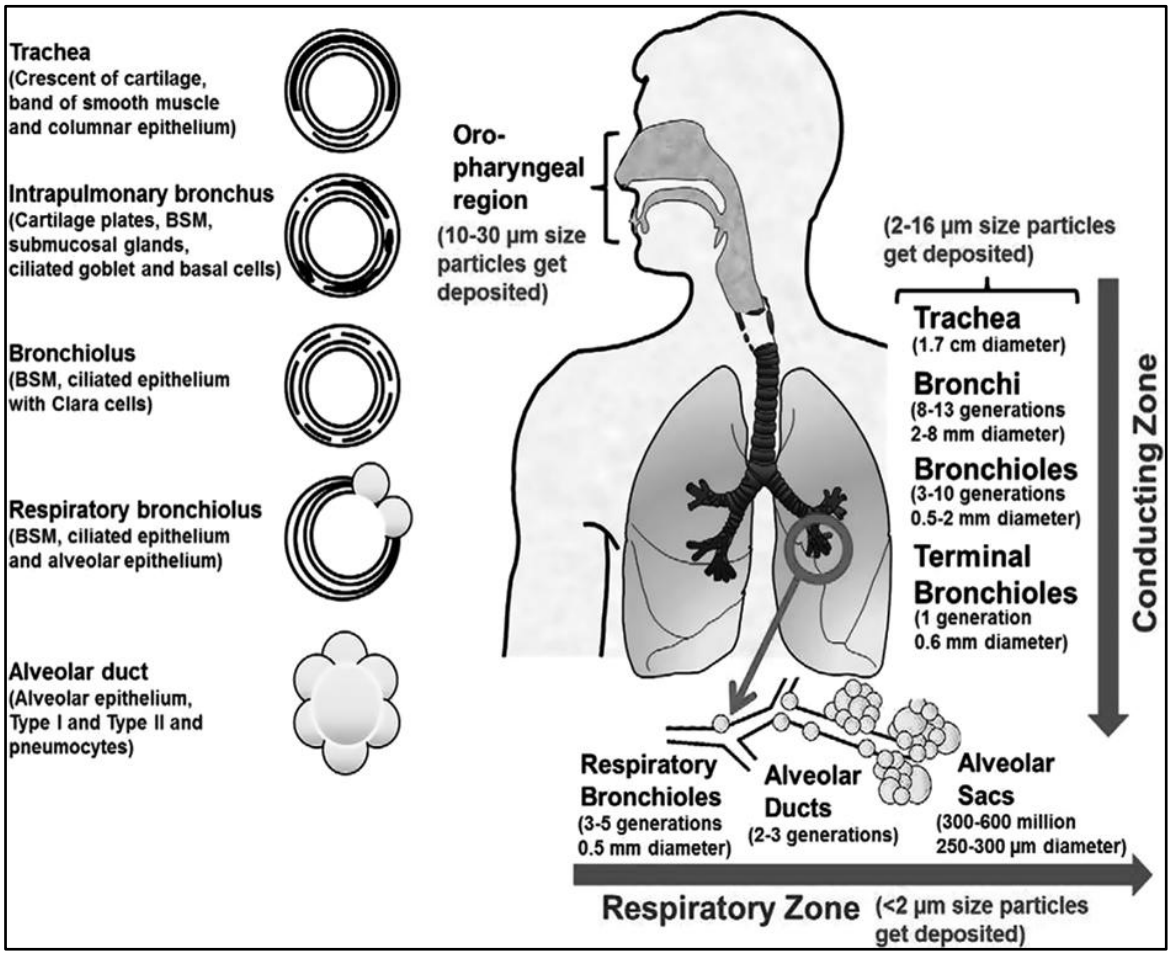
TECHNIQUE OF MAKING PARTICULATE MATTER FOR LUNG DELIVERY:

Many conventional techniques have been reported to produce DPI formulation. However, these methods have number of limitation, such as particle size, size distribution, shape and poor control over powder crystallinity. This problem can be rectified by specialized milling technique. Jet milling of drug under nitrogen gas with new nanojet milling instrument is the most suitable for pulmonary drug delivery.

→ Spray drying technique
→ Spray freeze drying method
→ Supercritical fluid technology

→ Solvent precipitation method
→ Double emulsion / solvent evaporation technique
→ Particle replication in nonwettingtemplate [11]

MECHANISM AND WAY OF PULMONARY DRUG ADMINISTRATION:



Over the last decades, the systemic absorption of a broad range of therapeutic agent after pulmonary application has been demonstrated in animal as well as human. 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, oralinhalative administration administration for better result can be expected as it allow to administer very small particle with a concentration loss of only 20% in comparison with 85% by nasal route. Oralinhalative Administration can again be classified as intratracheal instillation and intratracheal inhalation. The most common method used in laboratory is the intratracheal instillation, a small Amount of drug Solution or dispersion is delivered in to the lungs by a special syringe. This provides a fast & 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 bioavability,especially with method.However,intratracheal instillation is not a physiological route for Application and result obtained from these studies may not be transferable to aerosol application in human. On the contrary, inhalation method use aerosols 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 lung. The disposition of drug by aerosols administration in the pulmonary airways mainly take place by three mechanism:- gravitational sedimentation ,inertial impaction and diffusion . if the drug particle size is comparatively bigger then disposition take place by first two mechanism where, either sedimentation occur 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 aspect and ventilator parameter size of the particle or droplet and the geometry is a quite important they size of particle or droplet in term of diameter along with the surface electrical charge

,shape of the particulate matter if it is a fiber and hygroscope also having profound influence on drug disposition through pulmonary route. The term mass median aerodynamic diameter is used and it depends on size, shape, and density of the particulate system. [(4)]

II. Recent Technologies Used In Pulmonary Drug Deliverry:

Particles engineering for pulmonary drug delivery:

Recent advance in inhalation therapy have sparked considerable biomedical interest in the development of novel particle technologies for respiratory drug formulation. Introduction of new potent medicine in various therapeutic areas such as asthma, chronic obstructive pulmonary disease (COPD) and various infectiousdiseases has necessitated an accurate and consist dosing with inhalation device. There are many emerging inhalation product with new absorbance mechanism and rapid onset of action for systemic therapies. Controlled and sustained release with composite particle is another application used for both local and systemic drug delivery.

Liposome:

Liposomes for pulmonary delivery have attracted a marked interest owing to the ability of liposome vesicles to entrap therapeutic molecules and, following inhalation, localize the drug effect in the pulmonary system for a prolonged duration. This had been reported to enhance the therapeutic benefit of the drug and reduce the potential of systemic adverse effects.

Large porous particles:

Large porous particles can be useful vehicles for the sustained delivery of drugsto the lungs, for reasons briefly described below. They can also be useful fordelivery of drugs rapidly into the lungs or bloodstream, potentially at relatively high drug doses, for reasons described in the following section. Prepared in dry powder form, they can finally be designed to provide room-temperature stability. This breadth of potential carries with it formulation challenges that demand flexibility, particularly in terms of porous particle composition. Using a spray-drying process described later, we seek to prepare large porous particles, for currentApplications, as mixtures of pharmaceutical excipient and drug. Both drug and excipient are distributed throughout the porous particle matrix at ratios chosen to meet the targeted drug dose, drug stability, and drug release kinetics. Drug fractions ranging from less than 1% by weight to nearly 100% have been achieved in formulations prepared to date. Given that excipient clearance from the lungs is an important concern, we ideally choose excipients that are either endogenous to the human lung or approved for pulmonary or other routes of delivery to humans. Examples of excipient in each class include the lung lipid dipalmitoylphosphatedy1choline (dppc) and the sugar lactose.

Drug choice obviously greatly influences excipient selection. Currently wedevelop large porous particle formulations of small molecules, such as albuterol sulfate for asthma, and large proteins such as growth hormone for growth Scanning electron micrograph of large porous particles. The chemistry of each of these drugs will dictate a different solid state with each excipient matrix, impacting on particle morphology and shelf-life stability. It will also influence the kinetics of particle dissolution and drug release in the lungs. Particle chemistry also determines the ability to achieve sustained release of drugs through the physical and chemical integrity of the particle matrix. Sustained-release formulations require relatively insoluble particle matrices thatrelease drugs over prolonged periods of time. Equally important as particle chemistry for pulmonary drug delivery isparticle size, since standard (small nonporous) particles are cleared soon after deposition in the lungs by mucociliaryaction in the airways and macrophage uptake in the alveolar region of the lungs. Large porous particles have the potential to avoid phagocytic clearance in the peripheral regions of the lungs, thus prolonging the duration of meaningful sustained drug delivery. For a variety of reasons related to excipient choice and practicality, we currently develop our sustained-release pulmonary formulations with release times up to about a day. We also research delivery matrices for longer times. Formulation factors influencing drug release from the particle matrix include drug load, water uptake by the particle, particle matrix integrity, drug distribution within the particle, and specific excipient-drug interactions.

Bio-degradable polymer:

The same durability properties which make plastics ideal for many applications such as in packaging, building materials and commodities, as well as in hygiene products, can lead to waste-disposal problems in the case of traditional petroleum-derived plastics, as these materials are not readily biodegradable and because of their resistance to microbial degradation, they accumulate in the environment. In addition in recent times oil prices have increased markedly. These facts have helped to stimulate interest in biodegradable polymers and in particular biodegradable biopolymers. Biodegradable plastics and polymers were first introduced in 1980s. There are many sources of biodegradable plastics, from synthetic to natural polymers. Natural polymers are

available in large quantities from renewable sources, while synthetic polymers are produced from non-renewable petroleum resources.

Propellant drug used in pulmonary drug device:

Recently HFA propellants are new alternative CFC propellants in pulmonary drug device. [11, 20]

RECENT ADVANCE IN PULMONARY DRUG DEVICES:

Following types of inhalation devices are present

1. Inhalation drug delivery system by-metered dose inhalers
2. Inhalation drug delivery system by-dry powder inhalers
3. Inhalation drug delivery system by- nebulizer.

Inhalation drug delivery system by-metered dose inhalers:

A metered dose inhaler (MDI) is a complex system designated to provide a fine mist of medicament, generally with an aerodynamic particle size of less than 5micron, for inhalation directly to the airways for the treatment of respiratory disease such as asthma and COPD.

Inhalation drug delivery system by-dry powder inhalers:

Today they are essentially two types of dpi,those that use drug filled into discrete individual dose,e.g.., either a gelatin capsule or a foil-foil blister and those that use a reservoir of drug that meter out doses when required ,both are now widely available around the globe and gaining broad acceptance.

Inhalation drug delivery system by- nebulizer:

Mainly there are two types of nebulizer system, theultrasonic and the air jet, in 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 though an orifice , an area of low pressure is formed where the air jet exists. A liquid may be with drown from a perpendicular novel to mix with the air jet to form a droplet. A baffle within the nebulizer is obtained used to facilitate the formation the aerosol cloud.

Carrier air can be used to generate the air jet. Alternatively compressor may be used to generate the air stream. Nebulizerused today for drug delivery to the respiratory drug and are particularly uses full for the treatment of hospitalized or non-ambulatory patient. [11, 20]

RECENT FORMULATION OF PULMONARY DRUG DELIVERY:

- Insulin by aerosols.
- Nicotine aerosol for smoking cessation.
- Aerosols for angina.
- Alpha 1 antitrypsin.
- Gene therapy via aerosols.
- In cancer chemotherapy.
- Pentamidine aerosols.
- Gentamycin aerosols.
- Ribavirin aerosols.
- Pulmonary delivery of lower molecular Wight heparin.
- Controlled delivery of drug to lungs.
- Pulmonary delivery of drug for bone disorders [1].

RECENT APPLICATION OF PULMONARY DRUG DELIVERY:

Apart from asthma and COPD recently pulmonary drug delivery is used for following indication.

- Treatment of migraine
- Aerosols vaccination
- Pulmonary arterial hypertension
- Acute lung injury
- Surfactant aerosols
- Gene therapy via aerosols
- In cancer chemotherapy
- Amphotericin B
- Inhaled drug for tuberculosis therapy
- Pulmonary delivery of opioids as pain therapeutics[6]

IMPORTANCE OF PULMONARY DRUG DELIVERY IN FEATURE:

Despites the many challenges face by pulmonary drug delivery system, several peptides and protein drugs are currently investigated for potential systemic absorption through pulmonary system, and that includes insulin, luteinizinghormones releasing analoguegranulocyte colony stimulating factor, and human growth hormone. Despite considerable clinical pertinence with aerolitemacromolecules, there have been no serious safety issue to date, nor have there been significant problem with throat irritation or cough.(6)

III. Conclusion

Given the advance in pulmonary delivery technologies, the issue for Drug Company and patient concerning delivery revolve around economic evaluation, approval, and administration and managed healthcare. As this issue is resolve pulmonary delivery will doubtless become regardless as one of the leading drug delivery alternatives**.**

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