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PULMONARY DRUG DELIVERY SYSTEM: AN OVERVIEW

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ABSTRACT
Targeting drug delivery into the lungs has become one of the most important characteristics of systemic or local drug delivery. From centuries lung has served as a route of drug administration. Pulmonary drug delivery is an important research area which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various other diseases. 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 0.1 µm – 0.2 µm absorptive mucosal membrane and good blood supply. In these inhalation therapy most common devices used such as nebulizer, Metered dose inhaler (MDI), and Dry powder inhaler (DPI). This article focuses on recent improvement in the technologies, devices, formulation and applications of pulmonary drug delivery system.

KEYWORDS: *Pulmonary drug delivery, Dry powder inhaler, Meter dose inhaler, nebulizer, Asthma, Chronic obstructive pulmonary disease*

INTRODUCTION

Pulmonary route have been use to treat different respiratory diseases from the last decade. From centuries, the inhalation therapies involved the use of leaves from plants, vapours from aromatic plants, balsams, and myrrh. Through, around the turn of the 19th century, with the invention of liquid nebulizers, these newer treatments developed into valid pharmaceutical therapies. In the 1920 s adrenaline can proposed as anebulizer solution, in 1925 nebulizer porcine insulin have been use in investigational studies in diabetes, and in 1945 pulmonary delivery of the newly revealedpenicillin was investigated. From 1950s steroids had been used for the treatment of asthma. In 1956 the pressured metered dose inhaler (pMDI) was placed,over the last 5 decades, there are some advancement occurs inmolecule design and drug discovery. The pMDI wasrisen to become the major stay for the asthmatreatment.(1) The pulmonary route has used widely in the recent times due to its unique properties such as a large absorptive area of up to 100m^2; ultimately thin 0.1 µm - 0.2 µm absorptive mucosal membrane and good blood supply. Pulmonary route have many advantages over other routes of administration to treat the specific disease states, particularly lung associated large protein molecules which degrade in the gastrointestinal conditions and are removed by the first pass metabolism in the liver can be delivered via the pulmonary route if deposited in the respiratory zone of the lungs.(2,3) There are several devices used totransport drug by pulmonary route area based on one ofthreeplatforms pressurized metered dose inhaler, nebulizer and drypowder.(4)

ANATOMY AND PHYSIOLOGY OF LUNGS

1) Lung regions:-

The respiratory tract starts at the nose and end in the lung at an alveolar sac.A large amount of molecules can be absorbed into the bloodstream through the enormous surface area of lung. When a breath of air is inhaled, it movesdown the trachea and the conducting airways to reach the alveolar epithelium. The various regions of the respiratory tract are categorised by a number of schemes.

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2) Nasopharyngeal region:-
This is also referred to as the "upper airways", which involves the respiratory airways starting from the nose and down to the larynx.

3) 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 terminates at the terminal bronchioles.

4) Alveolar region:-
This is also referred to as the "respiratory airways","peripheral airways" or "pulmonary region", consisting the respiratory bronchioles, alveolar ductsand alveoli.(5)

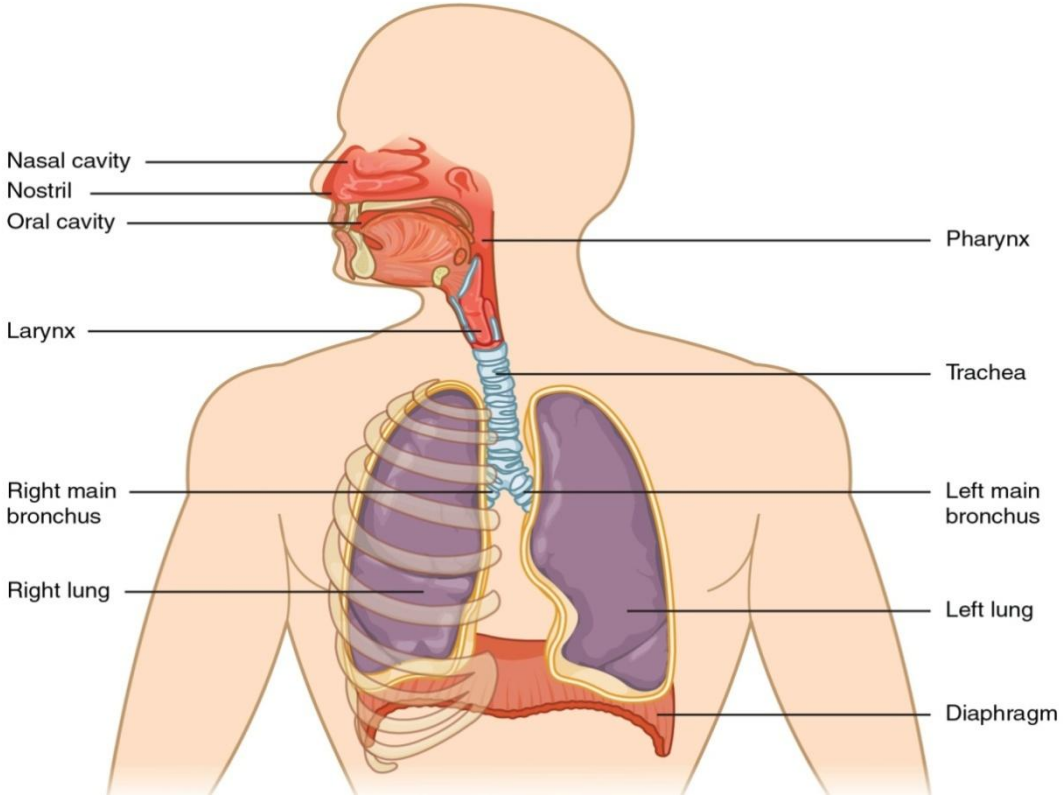

Fig 1: **Pulmonary system**

The term "pulmonary" can be evasive sincesome authors use it with reference to the wholelung, while others control its use to the alveolar region. The use of "upper respiratory tract"(i.e. NP plus trachea) and "lower respiratory tract"is also common place.

Pulmonary epithelium:-
There are more than 40 different celltypes present in lungs, of which more than six line the airways. The range of pulmonary epithelia can beexplained by examining its structure at threeprincipal levels.

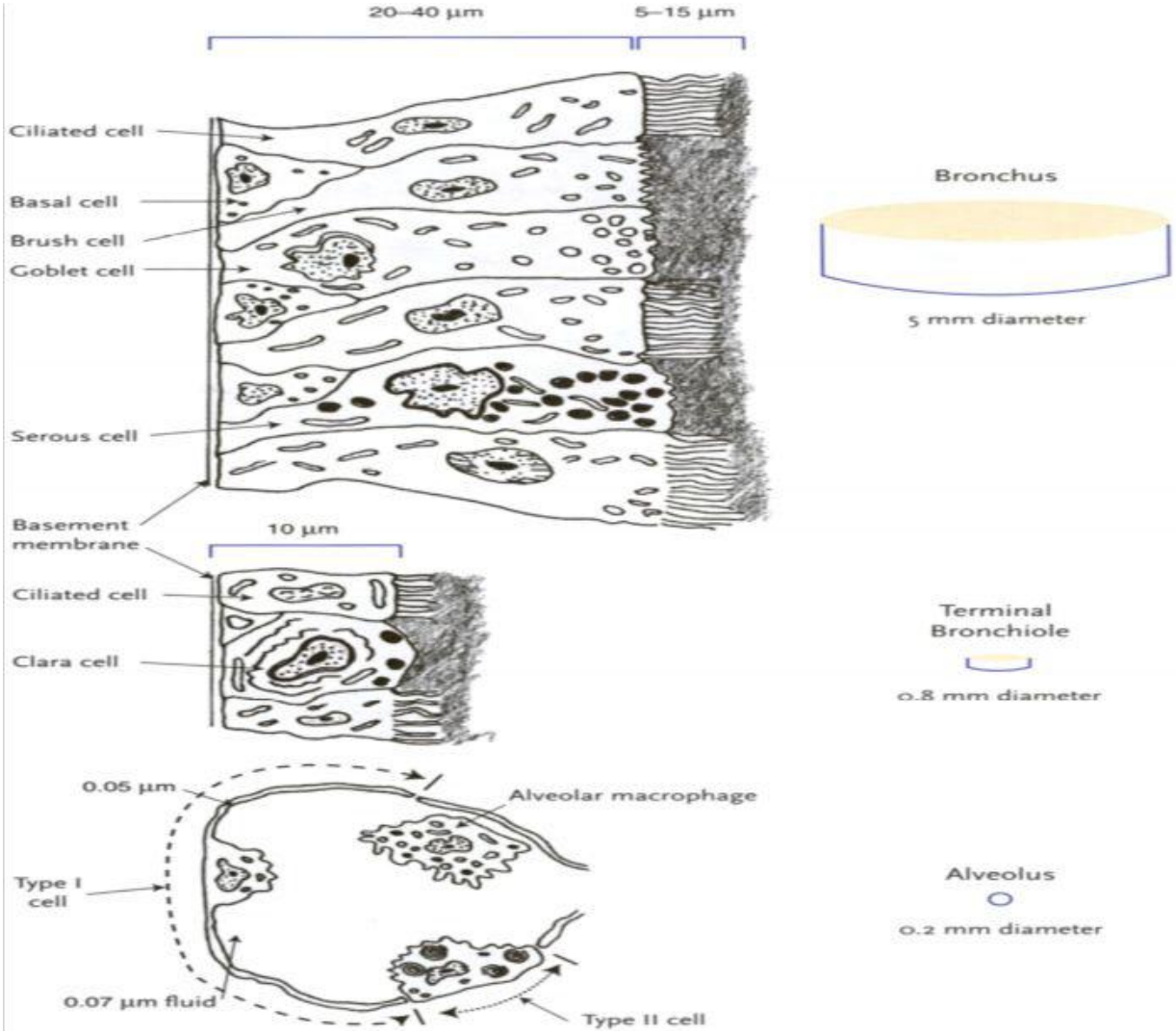

Fig 2: Pulmonary Epithelium

The bronchi:-

These are lined primarily with ciliated and goblet cells. There are some cells present such asserous cells, brush cells and Claracells are also present with few Kulchitsky cells.

The bronchioles:-

These are mainly lined with ciliated cuboidalcells. The frequency of goblet and serous cellsdiminishes with improvement along the airways while thenumber of Clara cells enhances.

The alveolar region:-

This is free from mucus and has a much flatterepithelium, which becomes the simple squamous type,0.1–0.5 µm thick. There are two main epithelial cell typesare present:

1. Type-I pneumocytes: Thin cells presenting a very shortairways-blood path length for the diffusion of gases and drug molecules. About 93% of the surface area of the alveolar sacs occupied Type-I pneumocytes, bydespite being only half as abundant as type-II cells.
2. Type-II pneumocytes: Cuboidal cells are those that store andsecrete pulmonary surfactant.3% of cells in thealveolar region occupied by alveolar macrophages. These phagocytic cells forage andtransfer particulate matter to the lymph nodes and themucociliary escalator.

Ciliated cells:-
In the tracheobronchial region, a large amountof the epithelial cells are ciliated such that there is anear complete covering of the central airways by cilia. Towards the circumference of the tracheobronchial region,the cilia are less abundant and are absent in thealveolar region. The ciliated cells each have about 200 cilia with numerous dispersed microvilli, of about1–2 μm in length. The cilia are hair-like projectionsabout 0.25 μm in diameter and 5 μm in length. The ciliated cells are mainly secreted from the serous cells in the sub-mucosalglands and submersed in an epithelial lining fluid. The sharp end of the cilia extends through theepithelial lining fluid into a layer of mucus secretedfrom goblet cells. The cilia beat in aplanned way to propel mucus along the airways to the throat.

ADVANTAGES

1. Imparts local action within the respiratory tract.
2. Provides rapid onset of action.
3. Provides decreased dose.
4. Reduces systemic side-effects. It can beused as an alternative route to drug interaction when more than two medications are used concurrently.
5. Due to the large alveolar surface area it reduces extracellular enzyme levels in comparison to GI tract.
6. Decreases elusion of first pass hepatic metabolism byabsorbed drug.
7. It is needle free pulmonary delivery.
8. It requires small amount of oral dose.
9. Absence of gastrointestinal upset.
10. Decomposition of drug by liver is avoided inpulmonary drug delivery.
11. Liposomal drug formulations remain stable when nebulised.
12. Ability to nebulise protein-containing solutions.

DISADVANTAGES

1. Local side effect provided by Oropharyngeal deposition.
2. Patient may have some difficulties using the pulmonarydrug devices properly.
3. Drug absorption may be restricted by the physicalbarrier of the mucus layer.
4. The reproducibility of drugdelivery on the lungs affected by several factors including physiological andpharmaceutical barrier.
5. The lungs are not only approachable surface for drugdelivery complex but also delivery devices arerequired to target drug delivery.
6. The duration of activity is often short-lived due to the rapid elimination of drug from the lungs or due to drug metabolism.
7. Necessitates frequent dosing.(6,7,8)

CHALLENGES IN PULMONARY DRUG DELIVERY

Low Efficiency of inhalation system:
Nowadays, efficiency ofthe available inhalation systems are generally toolow which is important challenge in pulmonary drug delivery.

Appropriate aerosol particle size is very important for deep lungdelivery. The optimum particle size for deep lung deposition is 1- 5 mm.Aerosol system should have to produce perfect size particlesbecause they are too small, they will be exhaled. Oropharynx and larynx are affected due to large particle size.

Less drug mass per puff:
To get adequate effect with the pulmonary drug delivery, practical delivery of many drug which require milligram doses but with most existing systems, the total amount of drug per puff delivered to the lower respiratory tract is too low that is less than 1000 mcg.

Poor formulation stability for drug:
Most conventional small molecule asthma drugs are crystalline and inthe case of corticosteroids, comparatively moisture resistant in the dry state. They are also moderately stable in liquids as compared to most macro molecules, which are unstable in the liquid state, amorphous, and highly moisture sensitive in the dry state.

Improper dosing reproducibility:
There are some reasons for poor dosing reproducibility such as worsening of diseases, problem in device, unstability of formulation. Patient education play important role to get maximum dose reproducibility.(9)

PULMONARY DRUG DELIVERY DEVICES

Nebulizers
From centuries nebulizers have been used for the treatment ofasthma and other respiratory diseases. There are twobasic types of nebulizers:

1. **Jet nebulizer:** The working of jet nebulizer is based on the Bernoulli principle by which compressed gas (air or oxygen) passes through a small orifice and generating 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 dispersed into droplets in the gas stream.

2. **Ultrasonicnebulizer:** The ultrasonic nebulizeruses a piezoelectric crystal vibrating at a highfrequency (usually 1-3 MHz) to generate a fountainof liquid in the nebulizer chamber;, the smallerdroplets produced due the higher frequency, thecompressors supplying the air or oxygen are expensive while the disposable nebulizers are inexpensive.Most of the prescribed drug never reaches the lungwith nebulization. During expiration, majority of the drug is eitherretained within the nebulizer (referred to as deadvolume) or released into the environment. On average, only 10% of the dose placedin the nebulizer is actually deposited in the lungs.(10) A large amount of drugs can be transported to the lungs through nebuliser than MDI or DPI. The mostcommon drawback of nebulizer are lack ofpossibility, excessive costs of drug delivery as a result ofthe larger need for assistance from healthcare professionals, and the need for higher drug doses toachieve a therapeutic result. (11)

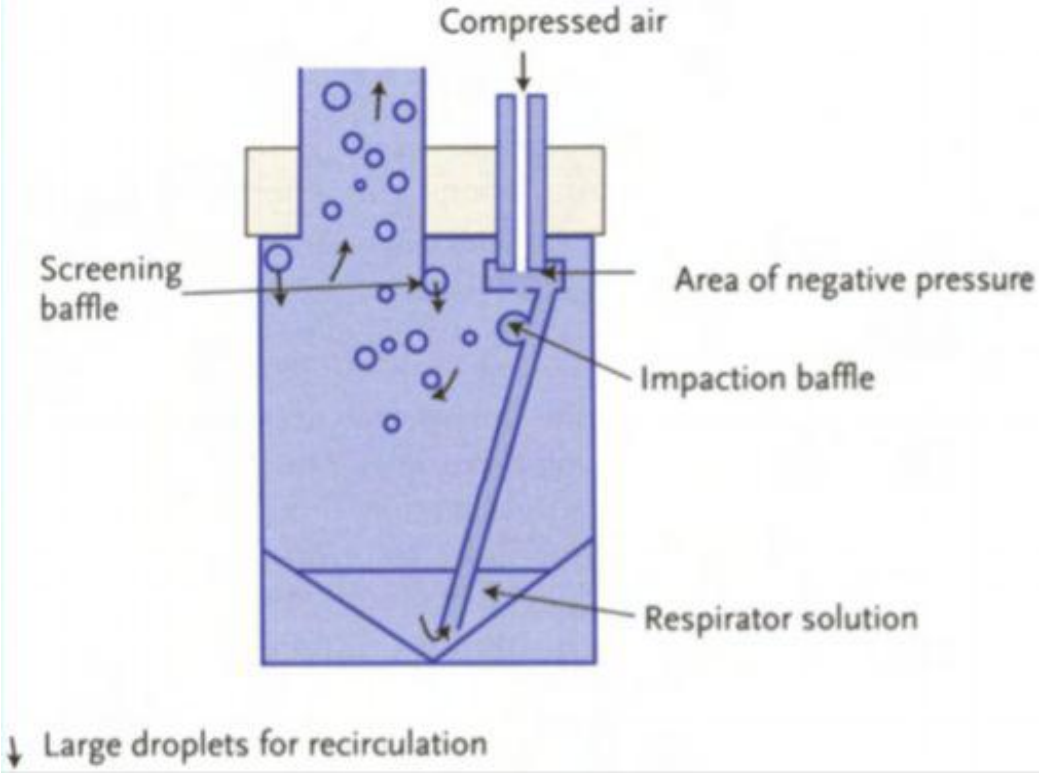

Fig 3: Air jet nebulizer

Metered Dose Inhalers (MDIs)

The MDI was a revolutionary development thatovercame the problems of the hand-bulb nebulizer,asthe first portable outpatient inhalation device and isthe most extensively used aerosol delivery device today. The MDI secrete a drug aerosol driven by propellants, such as chlorofluorocarbons (CFC) and morerecently, hydrofluoroalkanes (HFAs) through anozzle at high velocity (> 30 m s-1). MDIs deliveronly a small amount of drug dose to the lung.Mostly, only 10-20% of the emitted dose isdeposited in the lung. Approximately 50-80% of the drug aerosol impacts in theoropharyngeal region due to the high velocity and large particle size of the spray. Hand-mouth discoordinationis another impediment in the optimal use of the MDI. The Patient's breathing pattern, inspiratory flow rate(IFR) and hand-mouth coordination is responsible for efficient delivery of MDI. The total lung dose deposition andpenetration into the peripheral airways decreases with increase in inspiratory flow rate. Fastinhalations (> 60 l min-1) result in a decreasedperipheral deposition because the aerosol is moreeasily deposited by inertial impaction in the conducting airway and oropharyngeal regions. Deposition bygravitational sedimentation in peripheral regions ofthe lung is enhanced by slow inhalation of aerosols. Peripheral deposition hasbeen also shown to increase with a decrease in respiratory frequency and an increase in tidalvolume. Asthe inhaled volume is increased, aerosols are able topenetrate more peripherally into the lungs.(12) The method of "floating" the pMDIcanister in water to determine canister depletion isunpredictable, and water entering the nozzle can lessenthe emitted dose of successive actuation. (13)

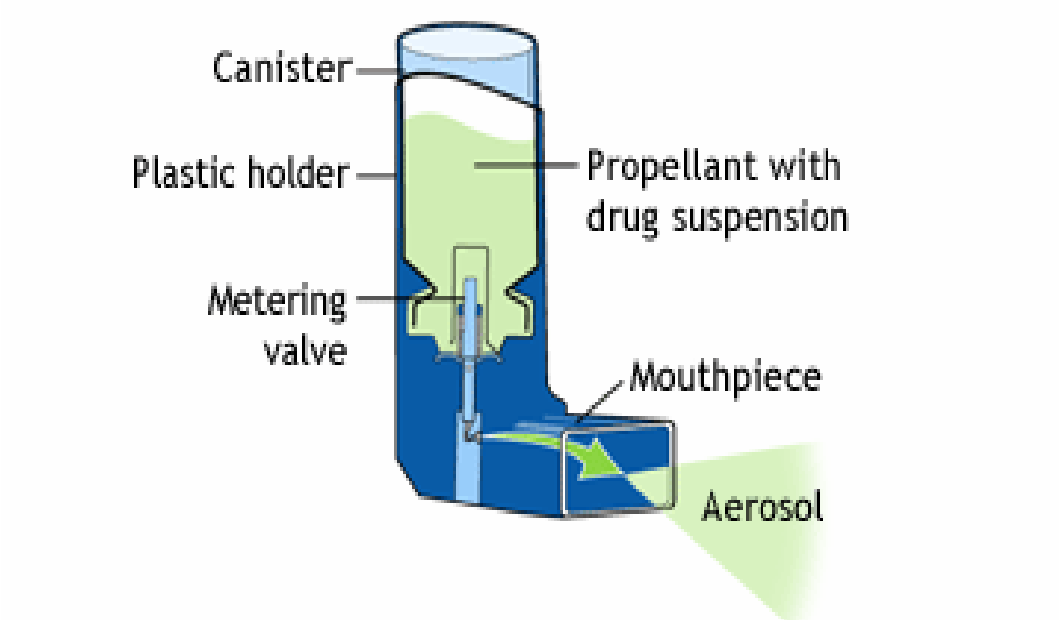

Fig 4: Metered-dose inhaler

Dry Powder Inhalers (DPIs**)**

For the delivery of drug to the lungsDry powder systems uses drug as single or its mixture with a suitable carrier, mainly as lactose. The pulmonarydelivery of drugs is affected by three main factors that are drug, carrier and device. Unlike MDIs, deliveries of medication with a DPI require minimum patientcoordination and collaboration of breathing ensuringactuation of the device. In addition, DPIs are small,portable devices that can be easily carried in a purse or pouch. Thisis also not requiring touse spacers. Moreover, DPIs are free from environmentally injuriousCFC propellants, as normally necessary in MDIformulation. Since both MDI and DPI have beenexposed to afford comparable efficacy in deliveringthe similar drug and in view of the mandatory ban ofCFCs use in MDIs by the United Nations, it is notshocking that DPIs have become increasingly significant as a pulmonary drug delivery system overthe precedent decade. The aerosol drug delivery isundergo dramatic changes in both inhaler device andformulation aspects.(14) There is a rapid move from thetraditional propellant-driven metered dose inhalers to the high presentation liquid atomizers and dry powderinhalers. The inhaler devices are particularly attractiveas dry powders. Dry powder shows thegreater chemical stability than the liquids that are used inatomizers. On the other hand, due to the potential physical instability of the powder formulation and production of dry powders for inhalation can bedifficult and challenging.

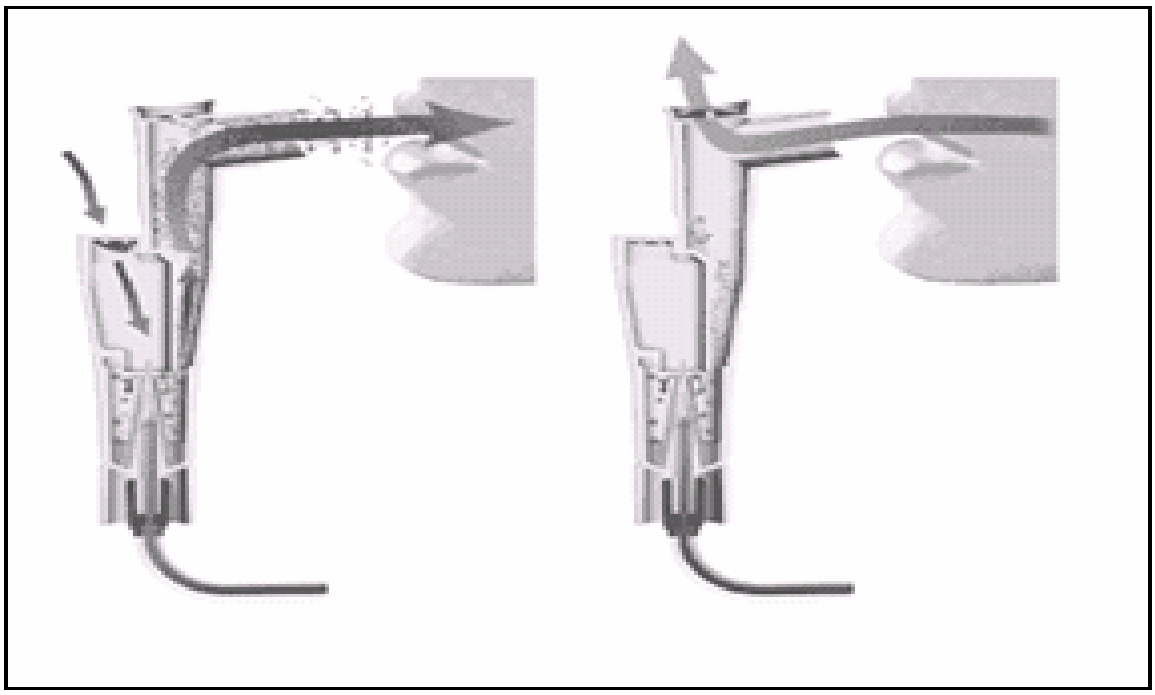

Fig.5: Dry Powder Inhaler

Recent Formulations of Pulmonary Drug Delivery:

1. In Cancer chemotherapy
2. Insulin by Aerosol
3. Nicotine Aerosol for Smoking Cessation
4. Aerosols for Angina
5. Alpha 1 Antitrypsin
6. Pentamidine Aerosol
7. Pulmonary delivery of lower molecular weight Heparin
8. Gentamycinaerosol
9. Gene Therapy via Aerosol
10. Controlled delivery of drugs to lungs
11. Pulmonary delivery of drugs for bone disorders
12. Treatment of Migraine
13. Aerosol Vaccination.
14. Aerosols in Transplantation
15. Pulmonary arterial hypertension
16. Acute Lung Injury
17. Surfactant Aerosol
18. Amphotericin B
19. Ribavirin Aerosol
20. Zanimivir R/C with revolizer for swine flu.
21. Aerosols used in clinical investigations of disease
22. Inhaled Drug Delivery for Tuberculosis Therapy
23. Pulmonary delivery of lower molecular weight Heparin.
24. Pulmonary delivery of opioids as pain therapeutics(15,16)

CONCLUSION

From thousands of years, the lung has served as a route of drug administration for various drugs. Pulmonary drug delivery is an important research area which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various diseases. As more systematic pulmonary drug delivery devices and sophisticated formulations become may available. Physicians and health professions will have a choice of a large variety of devices and formulation combinations that will target specific cells or regions of the lung, avoid the lung's clearance mechanisms and be retained within the lung for longer periods. It is a needle free delivery system. In the recent past years, several techniques have been developed to improve the quality of pulmonary drug delivery system without affecting their integrity. It is useful for multiple diseases because of advancement in applications of pulmonary drug delivery so pulmonary drug delivery is the best route of administration.

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