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PULMONARY DRUG DELIVERY SYSTEM – AN OVERVIEW

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ABSTRACT

Pulmonary route have-been used to treat various respiratory diseases for this centuries. These routes of drug delivery may give the advantage like a small amount of drug, less adverse reaction and rapid on set of action. Pulmonary drug delivery can be used as best and suitable alternative to oral delivery. These systems can be best utilized for both local and systemic action it is needle free technique have been developed in the recent post to improve the quality of pulmonary drug delivery system without affecting their integrity. In this section discussed on nowadays advances in the devices formulation and application of pulmonary drug delivery system.

KEYWORD: Pulmonary drug delivery devices, application.

INTRODUCTION

Millions of people are affected by pulmonary diseases and their populations are continuously increasing worldwide. The efficacy of pulmonary drug and its treatment can be achieved from the new ideas on controlling the pharmacokinetics, pharmacodynamics, immunogenicity, and biorecognition. The recent strategies of pulmonary drugs based on interdisciplinary perspective such as polymer science, pharmaceutical science, bioconjugate chemistry science, and molecular biology, are often called novel/advanced drug delivery systems. Different drug delivery/drug targeting systems already exist and currently under development can be efficiently used to minimize the drug degradation and loss, to prevent harmful side effects and to increase drug bioavailability. These include chronic obstructive pulmonary disease (COPD), tuberculosis,[1] lung cancer,[2] cystic fibrosis, pulmonary hypertension, asthma and various others which are complex human airway disorders. These diseases cause a strongest lung inflammatory component along with inflammatory cytokine production, cell infiltration, and airway hyper-reactivity. In this regard, growing meditation has been given to the probable of a pulmonary route as a non-invasive administration for systemic and local delivery of therapeutic agents, because the high permeability and large absorptive surface area of lungs, and suitable blood supply.[1-3] Pulmonary route has gained increase important in the recent times due to its unique properties such as a large absorptive area of up to 100m2 extremely thin 0.1m-0.2m absorption mucosal membrane and good blood supply in 19th century inhalation therapy is used for TB treatment, some drug is readily absorbed by alveoli and directly enter in systemic circulation. The alveolar epithelium of the distal lung has been shown to be an absorption site for most of the therapeutics and various macromolecules.[4-7] In the 1920 adrenaline was introduce as a nebulizer solution, and in 1925 nebulization porcine insulin was use in investigational studies in diabetes and in 1945 pulmonary delivery of the newly revealed Penicillin was investigate.[8] Till now, pulmonary drug delivery was confined to asthma and COPD therapy, however with the Advent of various technological advancements the latest and most promising application of pulmonary drug delivery is done on other therapeutic areas such as diabetes virus, infection cancer etc., administration of drug to the alveolar region achieves systemic absorption which provide to be the most successful work in this field for example, development of inhalational insulin formulation lowers the blood glucose levels various other involve the development of peptide and protein such as calcitonin, recombinant human granulocyte colony stimulating factor, luteinizing human-releasing hormones (LH-RH) antagonist and growth hormone for systemic absorption, apart from drug delivery to the lungs this route also serves to target drug to the brain. When developing a pulmonary drug delivery one of the important parameters to be considered is particle size is very important for targeting of the drug of lung. if the particle size too small they will exhale and if it is too large, they may affect the oropharynx and larynx. The drug can be delivered by using carriers like cyclodextrin microparticles, liposomes nanoparticle.[9,10,11]

Advantages Of Pulmonary Drug Delivery[12]

- Inhaled drug delivery Put drug where it is needed.
- It requires low and fraction of oral dose i.e., drug content of one 4mg tablet of salbutamol equal to 40 dose of meter doses.

- 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 i.e., an inhaled dose usually taken a min of 17-30 min as compare to an oral dose of bronchodilator which may take 2-3 hrs. to powerful effective.
- It requires low and fraction of oral dose avoid the first pass metabolism.
- The dose needed to produce in a pharmacological effect can be reduced.
- In asthma and diabetes required long term treatment if it is given by pulmonary drug delivery safety is maximum become the rest of the body not exposed to the drug.
- Avoidance of gastrointestinal upset.
- Bioavailability of larger drug molecule can be improved by means of the absorption enhance.
- Bioavailability of smaller drug molecule is very good.
- Convenient for long-term therapy, as compared to parenteral medication of drug.
- Less in evasive and shows increase patient compliance.

Disadvantages of Pulmonary Drug Delivery

- Drug absorption of pulmonary drug can be limited by the physical barrier of the mucus layer.
- Or pharyngeal deposition given local side effect.
- Various factor effects the reproducibility on drug delivery on the lungs, including physiological and pharmaceutical barrier.
- The lungs not only accessible surface for drug delivery complex but also delivery devices are required to Target drug delivery.
- Difficult in producing optimum particle size.
- Same drug may produce irritation and toxicity.

Anatomy and Physiology of Pulmonary Drug Delivery System

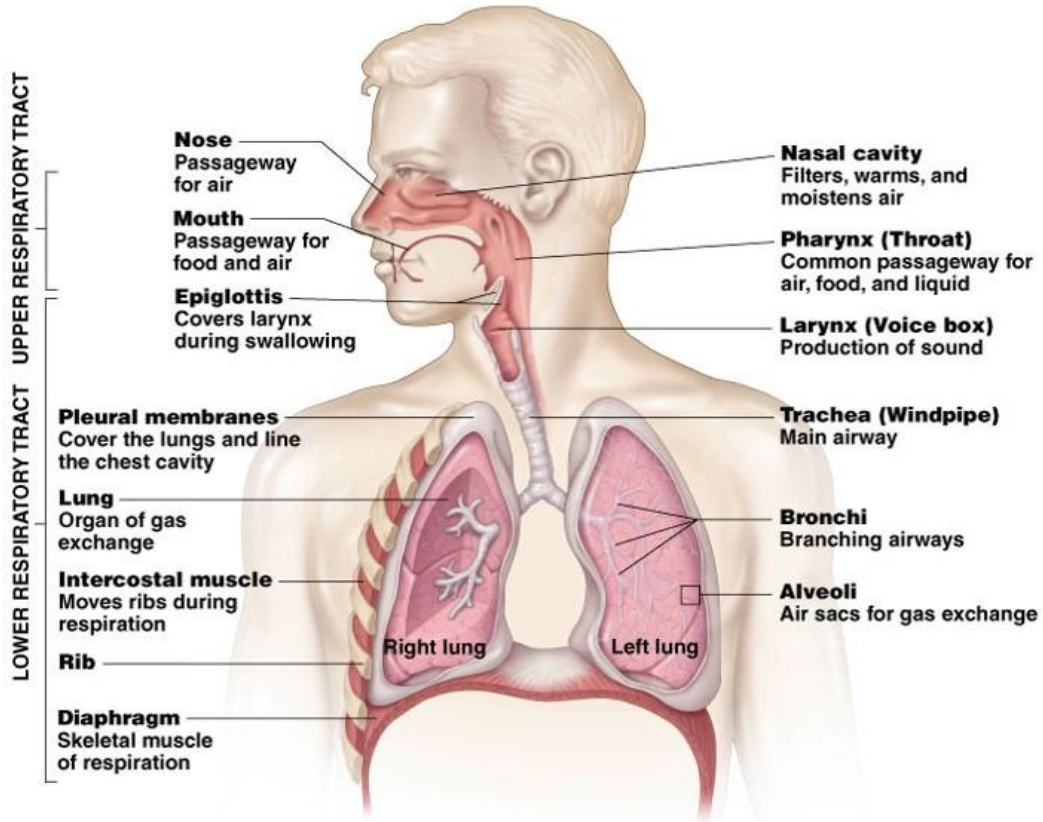


Figure 1: (Different regions of the human respiratory tract).

The respiratory system works with the circulatory system to deliver oxygen from the lungs to the cells and remove CO2 and return it to the lungs to be exhaled. The exchange of oxygen and CO2 between the air, blood and body tissues is understood as respiration. Healthy lungs absorbed in about 1 pint of air about 12–15 times each minute. All of the blood within the body is passed through the lungs every minute.[13]

1) Lung Region

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

2) Nasopharyngeal Region

This is also mentioned because the "upper airways", which involves the respiratory airways from the nose right down to the larynx.

3) Tracheobronchial Region

This is also mentioned because the "central" or "conducting airways", which starts at the larynx and extends via the trachea, bronchi, and bronchioles and ends at the terminal bronchioles.

4) Alveolar Region

This is also mentioned because the "respiratory airways", "peripheral airways" or "pulmonary region", Comprising the respiratory bronchioles, alveolar ducts and alveoli.

The term "pulmonary" are often misleading since some authors use it with regard to the entire lung, while others control its use to the alveolar region. During this chapter pulmonary refers to the entire lung. The utilization of "upper respiratory tract" (i.e.NP plus trachea) and "lower respiratory tract" is additionally common place.

Pulmonary Epithelium

The lung contains quite 40 different cell types, of which quite six line the airways. The range of pulmonary epithelia are often illustrated by examining its structure at three principal levels.

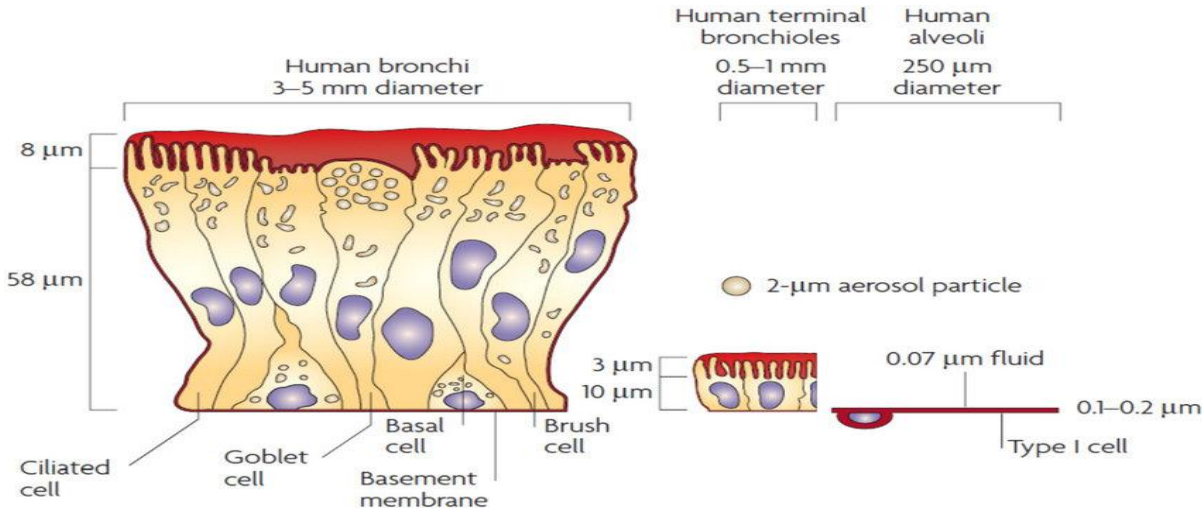


Figure 2: (Pulmonary epithelium).

The bronchi

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

The bronchioles

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

The alveolar region

This is devoid of mucus and features 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 really short airways-blood path length for the diffusion of gases and drug molecules. Type-I pneumocytes occupy about 93% surface area of the alveolar sacs, despite being only half as abundant as type-II cells.

- **Type-II pneumocytes**

Cubical cells that store and secrete pulmonary surfactant. Alveolar macrophages account for 3% of cells within the alveolar region. These phagocytic cells scavenge and transport particulate to the lymph nodes and therefore the mucociliary escalator.

Ciliated cells

In the trachea bronchial region, a high proportion of the epithelial cells are ciliated such 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 within the alveolar region. The ciliated cells each have about 200 cilia with numerous interspersed microvillus, of about 1–2 µm long. The cilia are hair-like projections about 0.25 µm in diameter and 5 µm long. They are submersed in an epithelial lining fluid, secreted mainly from the serous cells within the sub-mucosal glands. The ideas of the cilia project through the epithelial lining fluid into a layer of mucus secreted from goblet cells. The cilia hammer in a planned fashion to propel mucus along the airways to the throat.[13,14,15]

Factors Affecting Pulmonary Drug Delivery

Mechanisms of particle deposition within the airways

Effective resistance mechanisms may have involved may reduce the burden of external particles enter the airways, and clearing those it's going to achieve something in being stored. Therapeutic aerosols are two-phase colloidal systems there in the drug is contained during a dispersed phase they will have a solid, liquid or combination of the 2 supported the tactic and formulation of aerosol generation. positively for effective therapy, the drug needs have obtained ready to the lung in aerosol droplets or particles that deposit within the specific lung region and in sufficient quantity to be effective. The respiratory resistance mechanisms of mucociliary clearance and phagocytosis by macrophages may influenced insoluble particles. Aerosol particle dissolution they will slow and the therefore the drug may then subsequently to be subject to enzymatic deprivation before it reaches to its specific site of pharmacological action.

Inertial impaction

This is the most deposition mechanism for particles >1 μm within the upper tracheobronchial regions. A particle having an outsized momentum it is going to unable to follow the altering direction of the inspired air because it transferred the bifurcations and it'll show result to hit airway walls because it continues on its original course.

Particle deposition mechanisms at an airway branching site (Description)

Impaction it mainly occurs near the bifurcations, certainly the impaction of particles from tobacco smoke on the bifurcations could also be one cause why these sites are often the foci for lung tumors. The prospect of inactive effect is going to be dependents upon particle momentum, thus particles with higher densities or larger diameter and those travelling in airstreams of upper velocity will show superior impaction.

Sedimentation

Sedimentation by the settling under gravity the particles can deposited. It becomes highly important for particles that reach airways where the airstream velocity is comparatively low, e.g., the bronchioles and alveolar region. The fraction of particles depositing by this mechanism it going to dependent upon the time the particles use in these regions.

Brownian diffusion

Brownian diffusion of minor significance for particles 1 μm. particles smaller than this size are displaced by a sequentially bombardment of gas molecules, which can lead to particle collision with the airway walls. Brownian diffusion is also more common in regions where airflow is very low or absent, e.g., in the alveoli. Another method of deposition, that of interception, is of important for fibers but it going to not for drug delivery. Generally -

- Particles more than 10 μm will have impact within the upper airways and are rapidly removed by swallowing, coughing and mucociliary processes.
- This particles within the size range 0.5–5 μm may break free from impaction within the upper airways and should deposit by sedimentation and impaction within the lower TB and A regions. If the aerosol particle size is between the three and 5 μm then deposition it mainly occurred within the TB region. If the particles are smaller than the 3 μm then appreciable deposition in the A region is likely to occur.

Physiological factors affecting particle deposition in the airways

Lung morphology

Every successful production of the tracheobronchial tree produces airways of falling diameter and length. Every bifurcation leads to a rise possibility for impaction and therefore the decrease in airway diameter is related to a smaller displacement necessary a particle to form contact with a surface.

Inspiratory flow rate

When the inspiratory flow rate increase and they enhance character by influence in the first few generations of the TB region. The enhancement in flow not only enhancement particle momentum but also result in an enhancement in turbulence, mostly in the larynx and trachea, which itself will enhance impaction in the proximal tracheobronchial region.

Co-ordination of aerosol generation with inspiration

The energy of aerosol particles generated from pressurized metered dose inhalers p MDIs, is essentially govern by the p MDI formulation instead of the subject's IFR. P MDI aerosol droplets will be travelling at velocities of 2,500–3,000 cm s-1. A failure to co-ordinate actuation of the p-MDI during the early on phase of the inspiratory plan will result in near total particle impaction in the oropharyngeal area.

Tidal volume

An increased IFR will usually be connected with an enlarge within the volume of air inhaled in one breath, the tidal volume. Obviously a increase in tidal volume will end in penetration of aerosol particles deeper into the TB and A regions and a for better chance for deposition inside these regions.

Breath holding

Increasing within the time between the end of inspiration and the start of exhalation enhancement of time for sedimentation to occur. Breath-holding is generally wont to optimize pulmonary drug delivery.

Disease states

Bronchial interrupt as seen in different pulmonary deformation may associated with the larger local airflows and turbulence and this will result in localized nature in

the larger airways of the trachea-bronchial region. The bronchoconstriction of asthma features a more influence on exhalation than inhalation and thus deposition by sedimentation could also be superior than normal.

Pharmaceutical factors affecting aerosol deposition
Aerosol velocity
The aerosols constituted of nebulizers and dry powder inhalers are transported into the lung by entrainment on inspired air. In difference, p MDIs generate aerosol droplets with velocities greater than the inspiratory airflow and thus the aerosol will have a greater affinity to impact within the oropharyngeal region.

Size
Marketable devices don't cause to monodispersed particles and regularly the dimensions distribution is extensive and therefore the particles may show varying shapes. Consequently, number of terms are used to adequately characterize an aerosol sample. The geometric variance (GSD) is defined because the size ratio at 84.2% on the cumulative frequency curve to the median diameter. A monodisperse, i.e., ideal aerosol, features a GSD of 1, although in practice an aerosol with a GSD of 1.22 are mentioned as poly dispersed or hetero dispersed.

Shape
Particles which are non-spherical will have at slightest one physical dimension which is superior than the aerodynamic diameter. Ecological fibers 50 μm long can reach the neighborhood because they align with the inspired airflow. Such materials then impact within the airways by a procedure of interception with the airway walls.

Density
Particles having densities but less than 1 g cm−3 (unit density) may have a mean physical diameter larger than the aerodynamic limit. Those micronized drugs used for inhalation will contain particle densities around one, although materials created by freeze-drying or spray drying methods are likely to be appreciably less dense

Physical stability
The aerosols are frequently vested actually unstable because they need a high concentration of particles and their close immediacy may cause mutual repulsion or other inter-particulate reactions. Aerosol particles generate by DPIs could also be hygroscopic and, during their passageway throughout the high humidity environments of the airways, may enlarge in size and thus have a greater chance of being prematurely deposited. It be alleged to not be assumed, however, that the uptake of water vapor will always occur.

Pulmonary delivery devices
Current inhalation devices are separated into three different categories, the refinement of the nebulizer and therefore the evolution of two sorts of compact portable devices, dry powder inhaler (DPI) and metered-dose inhaler (MDI).

What is the challenge
- The major challenge in the development of inhalable compound is limited understanding of the relationship between pharmacokinetic (PK) and pharmacodynamic (PD) effects in the lunge.
- To ensure a predictable reproducible lunge dose and clinical effects with each treatment while minimizing side-effects and to achieve this at reasonable cost.
- The patient in present the most important barrier to meeting this challenge o Natural lunge defense mechanisms evolved to stop entry of inhaled partials and to eliminate them once deposited.
- Pulmonary drug delivery is much more complex than taking a tablet. Improper dosing reproducibility.
- Most traditional drugs are crystalline, within the case of corticosteroids, and highly moisture sensitive drugs are unstable. Less drug mass per puff.
- To take adequate effect with the pulmonary drug delivery practical delivery of the many drug which require milligram doses but with most existing systems, the entire amount of drug per puff delivered to the lower respiratory tract is just too low but 1000 mcg. Low Efficiency of inhalation system.
- Aerosol system should need to produce optimum size particles because they're too small, they are going to be exhaled. If the particles are too large, they affected on the oropharynx and larynx. (0.5-1mm).[15,16]

IDEAL Characterstics of Therapeutic Aerosol
- Contain a safe and efficacious drug.
- Contain minimal quantities of inert excipients.
- Monodisperse, small particle size.
- Low velocity after generation.
- High concentration and rate of generation.
- Highly reproducible characteristics.
- Low bioburden (solids) or sterile (liquids).

Drug Delivery Devices
For Pulmonary route, drug delivery devices play an important role equivalent to the formulation to that formulation. It is difficult to administer a formulation through a pulmonary route without suitable drug delivery devices. The drug delivery devices are given below:
1. Metered dose inhaler
2. Dry powder inhaler
3. Nebulizer

1) Metered dose inhaler

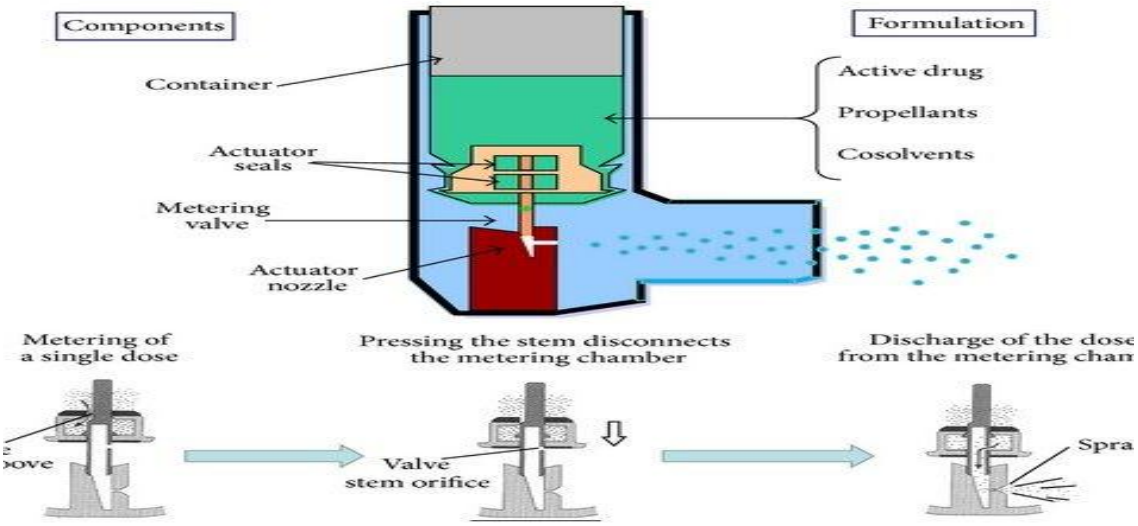


Figure 3: (metered dose inhaler).

The metered dose inhaler, known as MDI in short form, it is a pressurized inhaler that delivers medication by using a propellant spray. It is composed of four essential components:

- The base formulation (drug, propellant, excipients, etc.)
- The container,
- The metering valve and actuator (or mouthpiece).

It is a drug delivery device which provides the fine droplets of a medicament having the particle size of fewer than 5 micrometers. It is used for the treatment of respiratory diseases such as asthma and COPD. They can be given from suspension or solution. In case of suspensions formulations, the substances that are insoluble within the propellant and solvent are dispersed within the suitable propellant vehicle. Solution formulations of MDIs restrained the active ingredient dissolved during a pure mixture of propellants. MDIs contains the propellant like chlorofluorocarbons and hydrofluoroalkanes. They contain a micronized sort of the drug during a propellant struggling with surfactants to stop clumping of drug crystals. Lubricants for the valve mechanism and other solvents are the opposite constituents. When the device is actuated, the propellant gets exposed to atmospheric pressure, which leads to aerosolization of the drug. As it travels through the air, the aerosol warms up resulting in evaporation of the propellant that reduces the particle size to the desirable range.

How to use the MDI,

- Shaken of the inhaler well before use is most important. (3 to 4 shakes)
- Remove the cap
- Breathe out, away from your inhaler
- Bring the inhaler to your mouth. Place it in your mouth between your teeth and shut your mouth around it.
- Start to breathe in slowly. Press the highest of your inhaler once and keep inhaling slowly until you've got taken a full breath.
- The inhaler removed from your mouth, and hold your breath for about 5-15 seconds, then breath out. The major problems arise of the MDIs is patient must be educated to operate the device. Another problem in MDIs is the less quantity of drug can be delivered into the lungs.[17-22]

2) Dry powder inhaler

It's a versatile system that requires some degree of dexterity. The name itself indicates that formulation id solid form. It contains the active drug alone or has a carrier powder mixed with the drug to increase the flow properties of a drug. Dry powder inhaler has a greater stability, ease of handling, and relatively cheap when compared to metered dose inhaler. A dry powder inhaler (DPI) may be a device that delivers medication to the lungs within the sort of a dry powder. DPIs are normally used to treat respiratory illnesses, such as asthma, bronchitis, emphysema and COPD although DPIs have additionally been utilized as a part of the treatment of diabetes mellitus. DPIs are a different option for p MDI, DPI is mainly classified into Active and Passive. Majority of DPIs are passive breath- actuated devices. They depend on the patient inspiration to operate. Device metered in which the drug is contained in reservoir within the device which pre-measures every dose on actuation.[23,24,25,26]

They can be designed for a single or multi-dose purpose

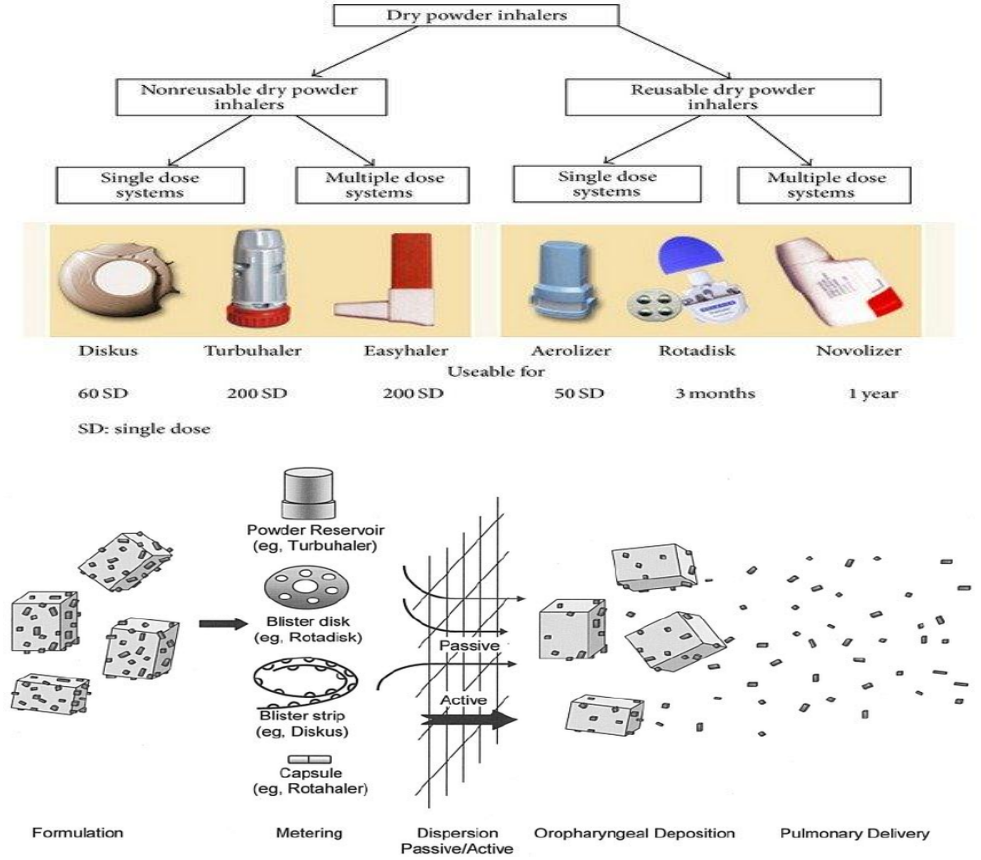


Figure 4: (dry powder inhaler).

Unit-Dose Devices

Single-dose/unit devices powder inhalers are devices in which a powder inclusive capsule is placed in a holder. The capsule is opened within device and powder is inhaled. It consists of,

Spin haler

It works similar to Rota haler, except that outer sleeves slide down to pierce the capsule and propellant disperse the drug.

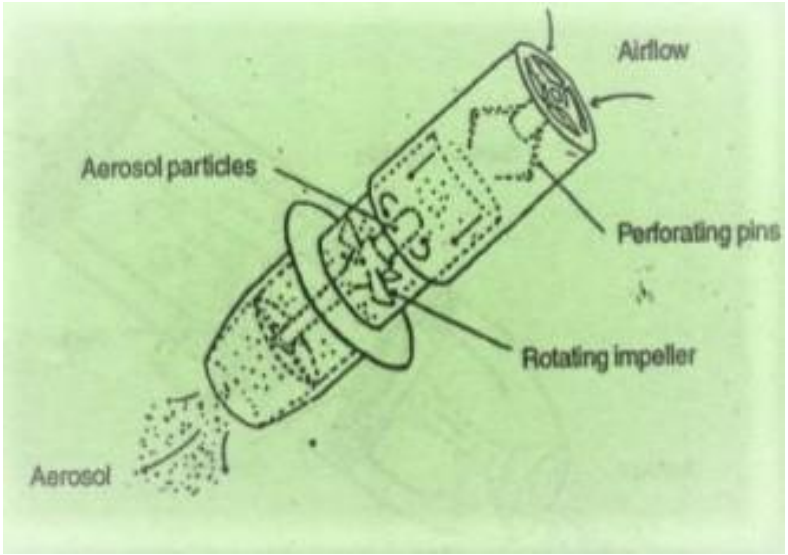


Figure 5: (spin haler).

Rota haler

Insert a capsule into the Rota haler, the colored end first, twists the Rota haler to break the capsule. Inhale deeply to get powder into the airway. Several breaths may be required, does not require the coordination of the aerosol.

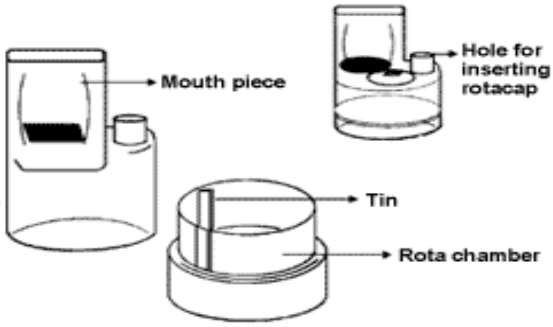


Figure 6: (Rota haler).

Multi-dose Devices

The multi-dose device uses a circular disk that contains either four or eight powder doses on a single disk. The doses are preserved in isolated aluminum bleb reservoirs until just before inspiration. It consists of …

Turbuhaler

It is a dry powder inhaler available in an easy use format. It can overcome the need for both a carrier and loading individual doses. Turbuhaler are commonly-used dry powder inhaler devices for patients with respiratory disease. Their effectiveness is limited in part by the patient's ability to use them correctly. This has led to numerous studies being conducted over the last decade to assess the correct use of these devices by patients and health care professionals,[23,26]

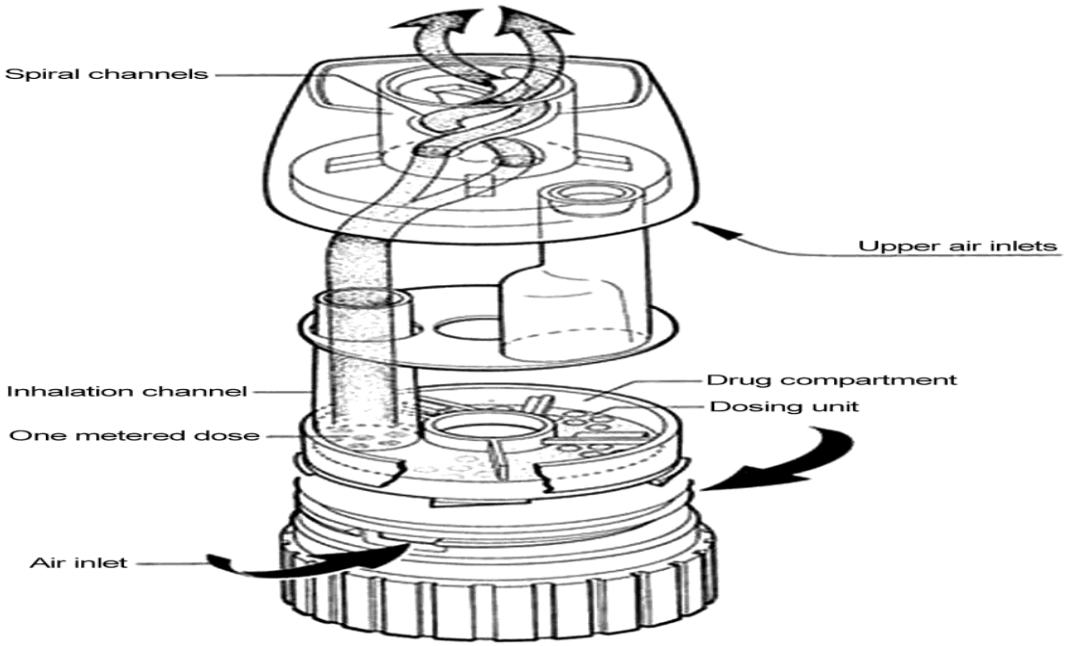
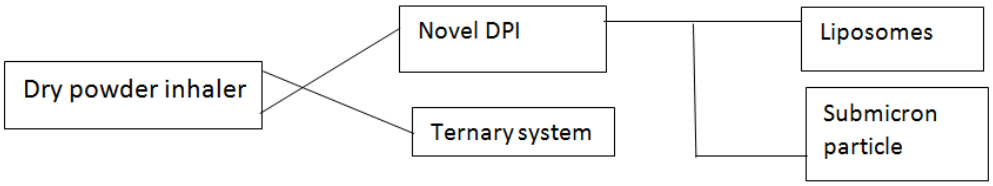


Figure 7: (turbuhaler).

Disc haler

Classification of DPI formulations:



3) Nebulizer

Nebulizers have been used in inhalation therapy around the early 19th century. In the available of marketed respiratory solution are normally composed of drug dissolved in aqueous, isotonic solvent systems that may contain preservatives to reduce microbial growth. There

are two traditional devices: air-jet and ultrasonic nebulizers. For a typical jet nebulizer, compressed air passes through a narrow hole and entrains the drug solution from one or more capillaries mainly by momentum transfer. The nebulizer is used as aerosolizing drug solution or suspensions for drug delivery for the respiratory tract and is particularly used for the treatment of a patient. It is commonly used in treating cystic fibrosis, asthma, and another respiratory disease.[27] But nebulization has many well-documented disadvantages, including extended administration time, high cost, low efficiency, poor reproducibility and great variability, risk of bacterial contamination and constant cleaning requirements, and sometimes the need for bulky compressors or gas cylinders.[28]

A nebulizer is formulated by -

- The pharmaceutical solution technology- parenteral products
- Formulated in water
- Co-solvents
- pH above 5

There are two types of the nebulizer, namely jet and ultrasonic,

a) Jet nebulizer

In jet nebulizer, the liquid is converted and sprayed into fine droplets by use of compressed gas, for the prevention of exits of a large droplet from the device the baffles are used in a jet nebulizer. Disadvantage:

- Time consumption
- Drug wastage

b) Ultrasonic nebulizer

In ultrasonic type, aerosol droplets are produced through high-frequency vibrations of a piezoelectric crystal, for that the ultrasound waves are formed in it.[27,28]

CONCLUSION

The many diseases that are being opinion candidates for the aerosol therapy has increased substantially. While at the latest, asthma was only the clear example of a disease that could be treated via aerosol delivery to lungs. We now consider it possible to treat not only asthma and chronic obstructive pulmonary dis-eases but also systemic disorders such as diabetes, cancer, neurobiological disorders and other pulmonary diseases such as cystic fibrosis and pulmonary infec-tious disease. But administration of drug via pulmonary route is a difficult and complex process, comprising not only aspects from technology but also from physiology, clinical application or patient use. This demonstrate that for different diseases or even for each individual drug, the required conditions for optimal administration differ substantially and that a perfect inhaler suitable for all types of drugs and diseases is a fiction.

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