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A Review on Pulmonary Drug Delivery System

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ABSTRACT

Drug delivery to the lungs is an innovative and challenging area of pharmaceutical research. It is primarily used to treat conditions of the airways, delivering locally acting drugs directly to their site of action. These routes of drug delivery may give the advantages like a small amount of drug, less adverse reaction and rapid onset of action. Pulmonary drug delivery can be used as an alternative to oral delivery. These systems can be best utilized for both local and systemic actions. Pulmonary delivery may be used for a wide range of drugs. It is a needle-free technique. The origin of inhaled therapies seen in back 4000 years ago to India, where people smoked the leaves of the Atropa belladonna plant to suppress a cough. In the 19th and early 20th centuries, asthmatics smoked asthma cigarettes that contained stramonium powder mixed with tobacco to treat the symptoms of their disease. But the administration of drugs by the pulmonary route is technically challenging because oral deposition can be high, and variation in inhalation techniques can affect the quantity of a drug delivered to the lungs. Pulmonary drug delivery remains the preferred route for administration of various drugs. It is an important research area which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease, and various diseases. Due advancement in application nowadays Pulmonary drug delivery is used to treat Diabetes, angina pectoris, cancer, bone disorders, migraine, tuberculosis, acute lung injury and others. In this article, we summarize the outline of this dosage form.

INTRODUCTION[1,2,3]:

Pulmonary drug delivery is not a new one, Already this system was widely accepted in the ancient period for lung and other respiratory diseases. In 19th-century inhalation therapy is used for TB treatment, some drugs are readily absorbed by alveoli and directly enter into systemic circulation. Due to this advanced of devices in pulmonary delivery, it is possible to deliver large dose into the lungs.

Over the decade certain drugs have been sold in compositions suitable for forming drug dispersion for pulmonary delivery to treat various conditions in humans. There are many advantages of pulmonary drug delivery system over the route 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. This advanced technology was initially applied to the systemic delivery of large molecules, such as insulin, interferon-b, or a1 proteinase inhibitor.

When developing a pulmonary drug delivery system one of the important parameters to be considered is particle size. Optimum particle size is very important for targeting of the drug to lungs. If the particle size is 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 cyclodextrins, microparticles, liposomes, nanoparticles etc.

ADVANTAGES OF PULMONARY DRUG DELIVERY SYSTEM:

1. It is needle-free pulmonary delivery.
2. It having a very negligible side effect since the rest of the body not exposed to a drug.
3. The onset of action is very quick.
4. Degradation of a drug by the liver is avoided.
5. It requires low and fraction of oral dose.
6. Avoid the first pass metabolism.
7. The dose needed to produce a pharmacological effect can be reduced.

8. In asthma and diabetes requires long-term treatment if it is given by pulmonary drug delivery safety is maximum because the rest of the body not exposed to the drug.

9. Avoidance of gastrointestinal upset.

10. Bioavailability of smaller drug molecule is very good.

11. Bioavailability of larger drug molecule can be improved by means of the absorption enhancer.

12. Convenient for long-term therapy, compared to parenteral medication.

DISADVANTAGES OF PULMONARY DRUG DELIVERY SYSTEM:

1. Improper dosing.
2. Stability of drug in vivo.
3. Some drug may produce irritation and toxicity.
4. Difficulty in producing optimum particle size.
5. Some drugs may be retained in lungs and clearance of the drug may be difficult.
6. Targeting specificity.
7. Difficult to transport.
8. Difficult to use
9. Drug absorption may be limited by the physical barrier of the mucus layer.

ANATOMY AND PHYSIOLOGY OF PULMONARY DRUG DELIVERY[4,5,6] :

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

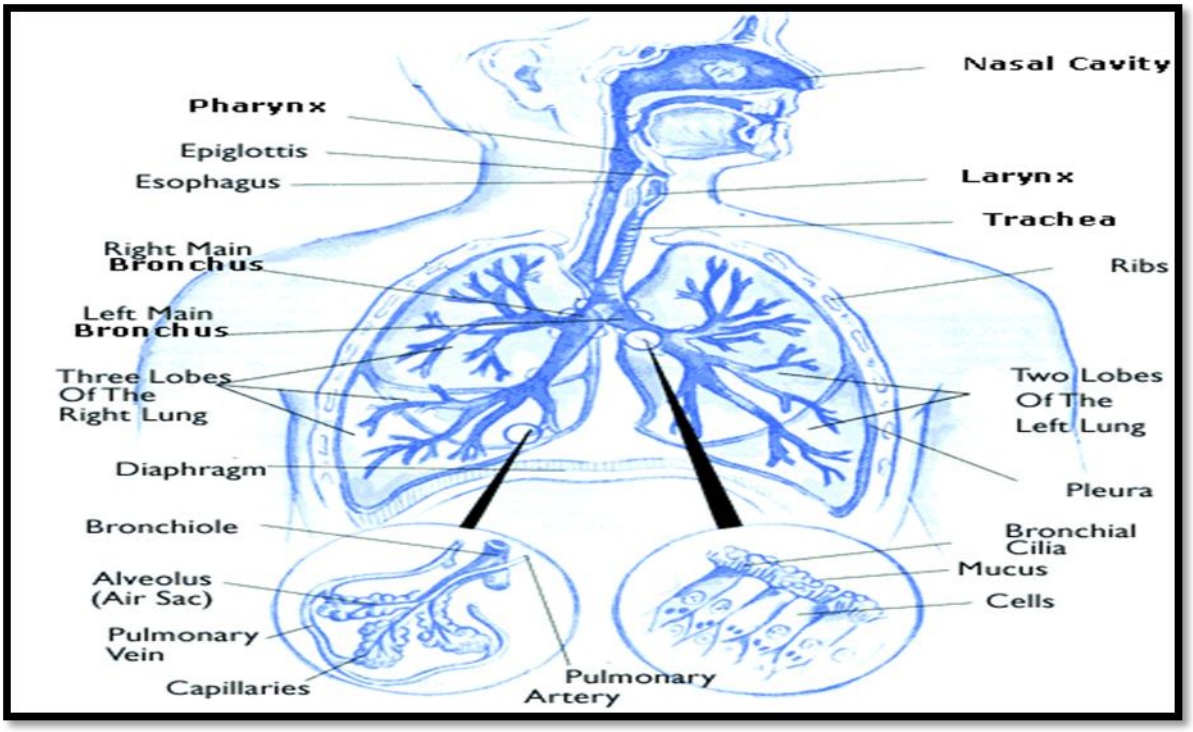


Figure 1: Different regions of a human respiratory tract

The human respiratory system consisted of two regions,

1. Conducting airway

2. Respiratory region.

The airways are further divided into various types, i.e. nasal cavity, associated sinuses, nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles.

The respiratory region 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 the gas exchange, by adding oxygen to and removing carbon dioxide from the blood passing the pulmonary capillary bed.

1. Lungs: The respiratory tract starts at the nose and terminates deep in the lungs at an alveolar sac.

2. Nasopharyngeal region: It is an "upper airways", which involves the respiratory airways from the nose down to the larynx.

3. Trachea–bronchial region: This is also referred to as "conducting" or "central airways", which start at the larynx and extends via the trachea, bronchi, and bronchioles and ends at the terminal bronchioles.

4. Alveolar regions: This is referred to as "respiratory airways", "peripheral airways" or “pulmonary regions”, Comprising the respiratory bronchioles, alveolar ducts, and alveoli.

5. 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.

6. The bronchi: These are lined predominantly with ciliated and goblet cells. Some serous cells, brush cells and Clara cells are also present with few Kulchitsky cells.

7. 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.

FACTORS AFFECTING ON PULMONARY DRUG DELIVERY SYSTEM[7,8]:

Mechanism of particle disposition in the airways,

- Inertial impaction
- Sedimentation
- Brownian diffusion

➢ **Physiological factors affecting particle deposition in the airways:**

- Lung morphology
- Inspiratory flow rate
- Co-ordination of aerosol generation with inspiration
- Tidal volume
- Breath holding

- Disease states

➢ **Pharmaceutical factors affecting aerosol deposition:**

- Aerosol velocity
- Size shape
- Density
- Physical stability

FORMULATING APPROACHES OF PULMONARY DRUG DEVICES[9,10,11]:

Pulmonary delivered drugs are rapidly absorbed except large macromolecules drugs, which may yield low bioavailability due to enzymatic degradation and\or low mucosal permeability.

By using permeation enhancers such as surfactants, fatty acids, and saccharides, cheating agent and enzyme inhibitors such as protease inhibitors we can improve the pulmonary bioavailability.

In this formulation the protein stability has a most important issue: the dry powder formulation may need buffers to maintain ph, and a surfactant such as a tween to reduce the chance of protein aggregation. For the prevention of denaturation during prolonged storage, the stabilizers such as sucrose are added.

Insulin liposomes are one of the recent approaches to the controlled release of pulmonary preparation. Intratracheal delivery of insulin liposomes has significantly enhanced the desired hypoglycemic effect.

The drug can be administered by pulmonary route using two techniques,

- Aerosol inhalation
- Intratracheal Instillation

We could achieve more uniform distribution with greater extent of penetration into the peripheral or alveolar region of the lungs by applying the aerosol techniques, but in that cost is high and we can be faced the difficulty in measuring the exact dose inside the lungs. The

second installation technique is simple and not expensive and has a non-uniform distribution of drugs.

DRUG DELIVERY DEVICES[12,13,14,15]:

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

✓ Jet nebulizers

✓ Ultrasonic nebulizers

1. Meterded dose inhaler:

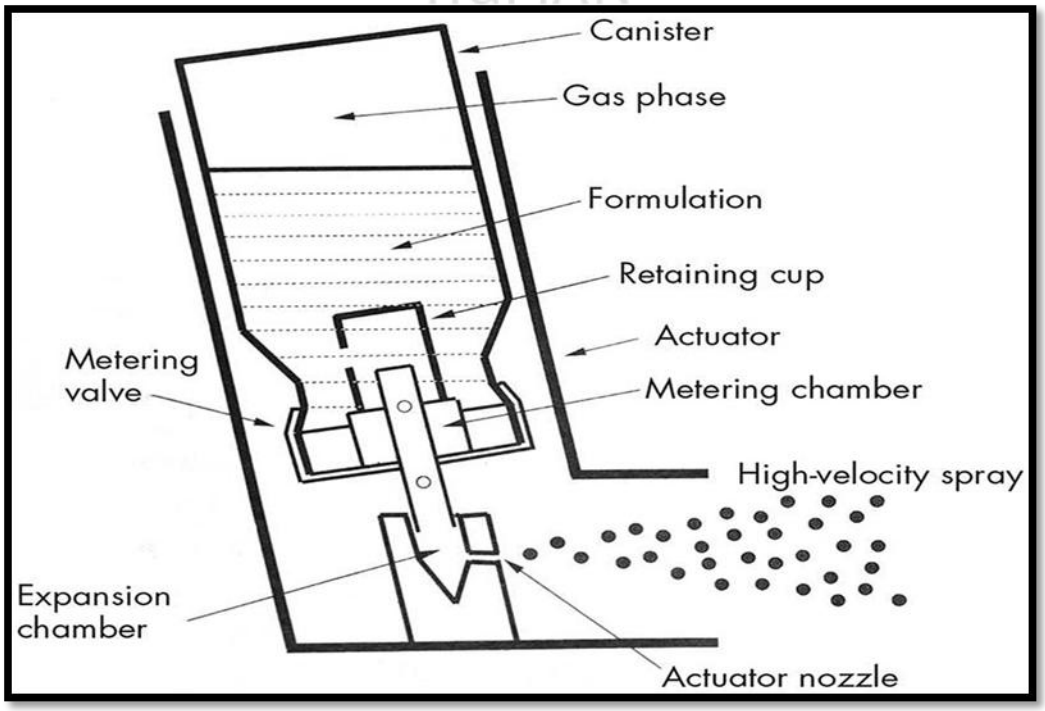


Figure 2: Metered dose inhaler

The metered- dose inhaler, called an MDI for short, 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 in the propellant and solvent are dispersed in the suitable propellant vehicle. Particle size, the solubility of active ingredient and surfactants or dispersing agents are the important factors to be considered in formulating MDI suspension formulations. Solution formulations of MDI consist of the active ingredient dissolved in a pure or mixture of propellants. Solution aerosol is relatively easy to formulate provide the ingredients are soluble in the propellant-solvent system. MDIs contains the propellant like chlorofluorocarbons and hydrofluroalkanes. They consist of a micronized form of the drug in a propellant under pressure with surfactants to prevent clumping of drug crystals. Lubricants for the valve mechanism and other solvents are the other 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 leading to evaporation of the propellant that reduces the particle size to the desirable range.

How to use the MDI,

- Shake the inhaler well before use (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 close your mouth around it.
- Start to breathe in slowly. Press the top of your inhaler once and keep breathing in slowly until you have taken a full breath.
- Remove the inhaler from your mouth, and hold your breath for about 10 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.

The key component parts of the pressurized metered- dose inhaler are given below.

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 is a bolus drug delivery devices that contain the solid drug in a dry powder mix that fluidized when the patient inhales. 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. There is no need for harmful propellent like CFC. They can be designed for a single or multi-dose purpose.

The principle of dry powder inhaler is given below,

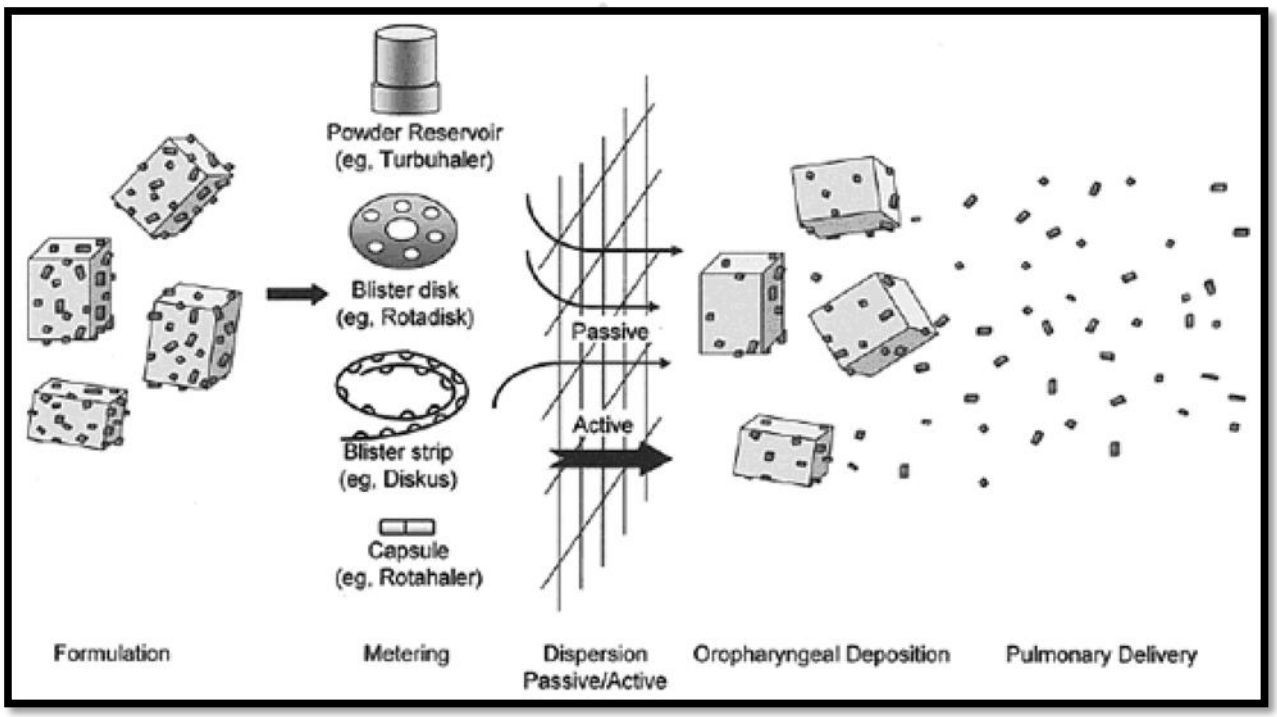


Figure 3: Principle of a dry powder inhaler

Unit-Dose Devices:

Single-dose powder inhalers are devices in which a powder containing capsule is placed in a holder.

The capsule is opened within device and powder is inhaled.

It consists of,

- **Spinhaler:**

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

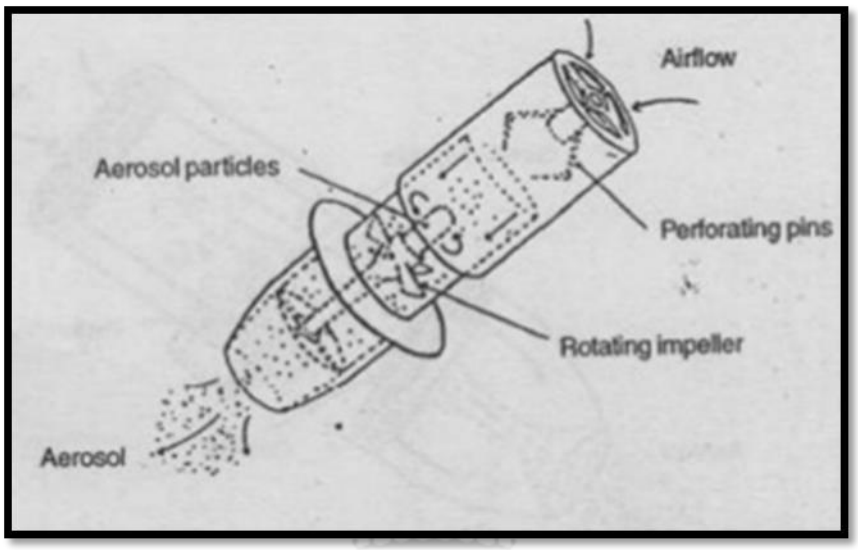


Figure 4: Spinhaler

- **Rotahaler:**

Insert a capsule into the rotahaler, the colored end first, twists the rotahaler 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.

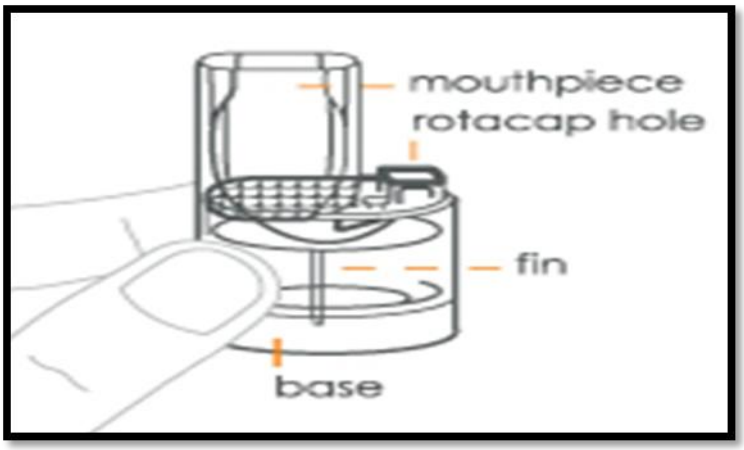


Figure 5: Rotahaler

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 maintained in separate aluminum blister reservoirs until just before inspiration.

It consists of,

- **Turbohaler:**

It is a dry powder inhaler available in an easy to use format. It can overcome the need for both a carrier and loading individual doses.

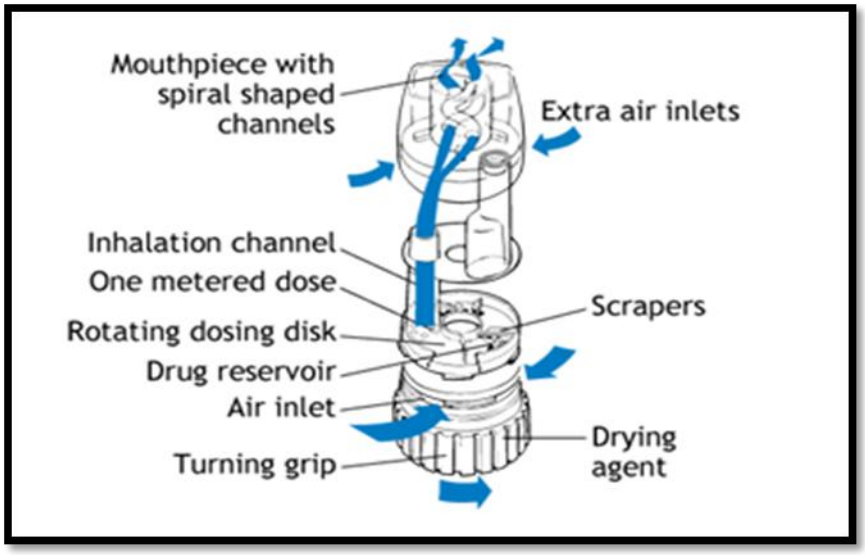
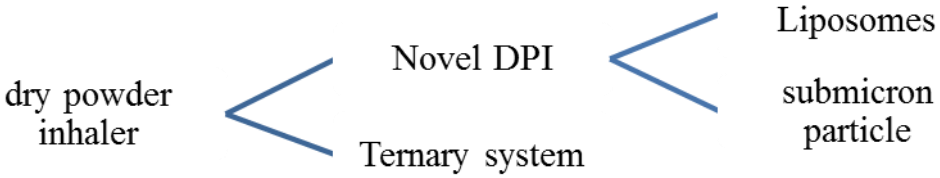


Figure 6: Turbohaler

- **Dischaler**

➢ Classification of DPI formulations:



3. Nebulizer:

The nebulizer is widely used as aerosolizing drug solution or suspensions for drug delivery to the respiratory tract and is particularly used for the treatment of a hospitalized patient. It is commonly used in treating cystic fibrosis, asthma, and another respiratory disease.

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,

i) **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

ii) **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.

Working principle of piezoelectric crystal effect,

Ultrahigh frequency current

↓

Piezoelectric transducer

↓

Ultrahigh frequency vibrations

↓

Disk vibrations

↓

Couplant (water bath)

Features of ultrasonic nebulizers:

- More expensive
- Heats up during operation, less noise
- Less Rx time
- Large average particle size
- Large output rate
- 0.5 to 3 micron-90% of the particle within range.

RECENT ADVANCES IN PULMONARY DRUG DELIVERY:

The pulmonary drug delivery formulation is retained in the lungs for the desired length of time and it can avoid the clearance mechanism of lungs. For improving the current formulation the various techniques are used,

- Liposomes

- Precipitation
- Spray drying using various excipient i.e.lipid and polymer
- Micronization via jet milling
- Carrier system like lactose
- Insulin by Aerosol
- Nicotine Aerosol for Smoking Cessation
- Aerosols for Angina.
- Alpha 1 Antitrypsin
- Gene Therapy via Aerosol
- In Cancer chemotherapy
- Pentamidine Aerosol
- Gentamycin aerosol
- Ribavirin Aerosol
- Pulmonary delivery of lower molecular weight Heparin.
- Controlled delivery of drugs to lungs

APPLICATION OF PULMONARY DRUG DELIVERY SYSTEM:

Table 1: Different applications of pulmonary drug delivery system

Drug	Use	Carriers	Method
Budenoside	Anti-asthmatic	Microparticles	Spray drying/ Supercritical fluid crystallization
Rifampicin	Anti-tuberculosis	Nanoparticles	Solvent evaporation
Isoniazid	Anti-tuberculosis	Nanoparticle	Multiple emulsion techniques
Pyrazinamide	Antituberculosis	Nanoparticle	Multiple emulsion techniques
Naringin	Combat oxidative stress	Microparticle	Spray drying
Tobramycin	Antibiotics	Nanoparticles	Emulsion-based spray drying
Erythromycin	Antibiotic	Microparticles	Double emulsion\solvent evaporation
Amikacin	Antibiotic	Microspheres	Freeze drying

FUTURE SCOPE:

The pulmonary drug delivery can face the many more challenges, in that protein and peptides drugs are currently investigated for potential systemic absorption through pulmonary system, and that includes calcitonin, luteinizing-hormone-releasing-hormone(LHRH) analogs, granulocytes colony-stimulating factor (rhG-CSF), human growth hormone, insulin. Despite considerable clinical experience with an aerosolized macromolecule, there have been no serious safety issue to date, and not have there been a significant problem with throat irritation or a cough.

CONCLUSION:

Pulmonary drug delivery is one of the oldest drug delivery systems. But still, now it is widely used due to its potential advantages. It is the important drug delivery system which impacts the treatment of illnesses, including asthma, chronic obstructive pulmonary disease, and various diseases. The drug which produces GI irritation can de administer by the pulmonary route. This system is used for achieving the optimal particle size which determines the

targeted delivery of drugs to the lungs. Carriers like microparticles, nanoparticles, liposomes etc; can be used in pulmonary drug delivery. The various advanced technologies are available to make the effective pulmonary drug delivery system. In that dry powder inhaler have several advantages like simplicity in use, cheapness, robustness, ease of use but do deliver a large amount of powder (around 50mg) in one breath is a major challenge with DPI. So pulmonary drug delivery is the best route of administration as compared to other routes.

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