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PULMONARY DRUG DELIVERY - AN EMERGING TOOL FOR HERBAL DRUG DELIVERY SYSTEMS

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ABSTRACT

Respiratory diseases are increasing day by day due to air pollution. Treatment of respiratory diseases using oral route of administration suffers disadvantage of first pass metabolism and requires larger dose of drugs. To overcome this problem targeted drug delivery is gaining much importance which reduces dose of a medicines and adverse effects. The pulmonary drug delivery system offers several merits over other drug delivery systems and therefore, this delivery route has been in prime focus for various applications like local and systemic therapeutics delivery. Pulmonary drug delivery can be used as an alternative to oral delivery. Pulmonary drug delivery is an important research area and is getting popularized for the treatment of pulmonary disease because it can directly deliver the drug to the lungs. Generally, most of the pharmaceuticals are not having good solubility in water but they are easily soluble in lipids, as in case of lungs both water soluble as well as lipid soluble drugs are absorbed by the tissues so this is not a restriction of pulmonary delivery. Carriers like micro particles, nanoparticles, liposomes can be used in lung targeting. Advances in device technology have led to the development of more efficient delivery systems capable of delivering larger doses

and finer particles into the lung. The overall development of drug delivery system depends on its efficacy, quality, and safety and to achieve such attributes there is a need of reliable evaluation methods to test them. Herbal medicines are now a day preferred for the treatment of pulmonary diseases due to safety and efficacy. They are also having less side effects and wider acceptance. This review discusses different pulmonary drug delivery and herbal drugs via pulmonary drug delivery route for the treatment of various respiratory diseases. This review reflects about the human respiratory system, herbal dosage forms and devices used for delivery of drug.

Keywords: Pulmonary drug delivery, herbal drugs, respiratory diseases

INTRODUCTION:

The effectiveness of a treatment depends on how the drug is given and how much of it is needed. New improvements to the system help get rid of things that are not needed and build up new ways to treat the disease. The traditional way of giving medicine has problems like low bioavailability, first-pass metabolism, unwanted side effects, a lack of selectivity, and invasive methods that patients don't want to do. Pulmonary drug delivery is an important target, as the lungs can absorb drugs either for local deposition or systemic delivery. Various dosage forms are available for the delivery of drugs through the pulmonary route **[1]**.

The hieroglyphs carved in Egypt in 1500 BC serve as evidence that inhalation is one of the oldest methods of drug delivery **[2, 3]**. For centuries, the pulmonary approach has been used to deliver pharmacologically active agents to treat local diseases of the respiratory tract, such as asthma, chronic obstructive pulmonary disease, infections of the respiratory tract, etc. **[4]**. About four thousand years ago, Indians inhaled medications to treat various diseases such as cough, asthma, and wheezing. Atropa-belladonna leaf was smoked for the suppression of cough, and asthmatic patients smoked stramonium powder with tobacco to get relief from the disease **[3]**.

The pulmonary route is widely used to treat local diseases of the respiratory tract like asthma and chronic obstructive pulmonary disease. Leaves of plants, vapors from aromatic plants, balsams, and myrrh are used for ancient inhalation therapies. In the 1920s, adrenaline was administered as a nebulizer solution for experimental studies in diabetes. Penicillin was investigated for pulmonary delivery in 1945, and in 1956, pressurised metered dose inhalers were introduced. Through inhalation, a smaller dosage can be delivered directly to the lung with reduced side effects **[5]**. Pulmonary drug delivery is becoming more important for both local and systemic drug delivery because of its large surface area, ability to

bypass hepatic metabolism, and low enzymatic activity **[6]**. The trend for use of natural and herbal drugs has been increasing in recent years, with 74% of active 121 compounds being used to develop important medicines such as digitoxin, ephedrine, and reserpine derived from medicinal plants. Practitioners make decoctions from the various plant parts for consumption in traditional medicine systems **[7]**.

Over a period, researcher has focused on deliver of herbal medicines through pulmonary route **[5]**. Herbal medicines are preferred over allopathic drugs because of less side effects, safe and effective treatment and for many diseases modern medicines have failed to treat. Even chronic diseases can effectively be treated using herbal medicines. The pulmonary drug delivery system for herbal medicines is useful because it is advantageous in delivering the herbal drug at the site of action which minimizes the toxic effects with the increase of bioavailability **[2, 8]**.

By modifying drug absorption, reducing metabolism, prolonging biological half-life, or reducing toxicity the therapeutic index had improved using liposomes, microparticles and nanoparticles of herbs **[9]**.

Drug delivery mode preferred in global market in 2012 indicated 21 % use of Pulmonary route and Pulmonary and other diseases are now being treated by pulmonary drug delivery **[10]**.

THE HUMAN RESPIRATORY SYSTEM:

Respiration is known as the exchange of oxygen and carbon dioxide between the air and the blood tissue. Respiratory system works as delivery of oxygen from the lungs to the cells and removal of carbon dioxide, and then return it to the lungs to be exhaled **[9]**.

The respiratory tract mainly divided into 2 parts The upper respiratory tract

-The lower respiratory tract

Organs of upper respiratory tract includes nose, nasal cavity, and pharynx. While the lower respiratory tract includes larynx, trachea, two bronchi (One bronchus to each lung), bronchioles and smaller air passage, two lungs and their coverings, the pleura, intercoastal muscles and the diaphragm **[9]**.

Passing of air is allowed by trachea from the larynx to the bronchi upto lungs. Respiratory tract consists of airways distal to the bronchioles and the alveoli, where rapid exchange of oxygen and carbon dioxide takes place during respiration. From larynx to trachea towards the 5^{th} thoracic vertebra where it divides into two parts as carina and bronchi. One bronchus which is about 10-11 cm long is going to each lung. There are more than 40 different cells gets composed to form lungs. This close structure-function

relationship makes this system a complex organ system **[9]**.

Lung has a large surface area (70-140 m2) for drug absorption and the thickness of alveolar epithelium is 0.1-0.5 µm**.** These two parameters attract researcher to focus on pulmonary route for drug delivery **[10]**.

When drugs are delivered through pulmonary route, the particles are deposited in lung by three mechanism that is impaction, sedimentation, and diffusion. Deposition of drug is dependent on the diseased state of lungs. Due to inflammation or bronchoconstriction, deposition will occur in upper airway. Increased airflow will also lead to impaction in upper airway. Sedimentation usually occurs in the lower airflow region of deep lung so it is considered as secondary deposition mechanism **[6]**.

The deposition of particles in lung depends on the aerodynamic diameter of particle. Particle size more than 6 µm are predominantly deposited in the extrathoracic region. Smaller particle size <1 µm being mostly exhaled out of the lung while particle sizes of 1–5 µm aerodynamic diameters are better size for the distribution of drug throughout the lungs. A highly permeable deep lung is found to be an attractive option for the systemic delivery of drugs **[10]**.

Due to genetic factors, pollutants in the air and infection lungs are prone to wide range of disorders like Asthma, Bronchiolitis, Chronic obstructive pulmonary diseases, Cough & Cold, Cystic fibrosis, Lung cancer, Pneumonia, Pulmonary hypertension, Respiratory diseases of new born.

PULMONARY ROUTE:

The pulmonary route is an alternative to oral and non-invasive administration for the systemic delivery of therapeutic agents. It can be used to treat pulmonary diseases such as asthma, COPD, and bronchitis. This system can perform local as well as systemic actions **[11]**.

The drug can be administered through the pulmonary route in two ways: intranasal administration and oral inhalation administration. Intratracheal instillation is the most common method used in labs, delivering a small amount of drug solution or dispersion to the lungs with a syringe. This method is simple and inexpensive, while the aerosol method uses uniform drug distribution with good penetration capacity. The aerosol technique is costly, and the exact dose required is not calculated, which are some disadvantages faced by this technique **[1]**.

MECHANISM OF RESPIRATORY DEPOSITION [9]

There are 5 principal mechanism for deposition of herbal drug which is depending on the particle size, air flow and location in the respiratory system namely

Impaction, Sedimentation, Interception, Diffusion and Absorption.

Impaction

Impaction is a mechanism that causes suspended particles to travel along their original path due to inertia and impact on an airway surface due to bifurcation in the airways. This mechanism is highly dependent on the aerodynamic diameter and is particularly important for the bronchial region, as it accounts for the most particles deposited on the mass basis. **Sedimentation** It is described as the settling of particles in the bronchioles and alveoli's smaller airways, where there is a low airflow and the airway dimensions are small. Because the rate of sedimentation depends on how fast the particles settle at the end, sedimentation has a bigger effect on the deposition of bigger particles. When hygroscopic particles move through warm, humid air passages, they are more likely to settle and form deposits.

Interception

When particle contact on an airway surface due to its size or shape, interception occurs. The deposited particles do not deviate from their air streamlines just like impaction. It occurs either in small airways or when the air streamline is close to an airway wall. Fibres which can easily contact airway surfaces due to their length are most significant for interception. These fibres can often reach the smallest airways because of the smallest aerodynamic diameter they have.

Diffusion

For deposition of particles less than 0.5 μm in diameter, diffusion is the primary mechanism which is governed by geometric instead of aerodynamic size. Because of Brownian motion, diffusion is the net transport of particles form higher to lower concentration. Due to constant bombardment of air molecules, random wiggling motion occurs in Brownian motion. When the particles have just entered the nasopharynx then diffusional deposition occurs and which is most likely occurs in the smaller airways where flow of air is low.

Absorption

The small molecule drugs are naturally permeable to pulmonary membrane. There is very dramatic change in types of cells and morphology going from trachea to alveoli. If the small molecules are highly soluble or highly cationic then it can exhibit prolonged absorption. Some herbs required slow absorption due to their long-acting ability in the body.

ADVANTAGES OF PULMONARY ROUTE OF DRUG DELIVERY [4, 12]

- Large surface area (70-140 m^2) of lungs provides rapid absorption of drug.
- The alveolar epithelium is very thin, which promotes rapid uptake of drug in blood stream. Rate and extent of

absorption will be more in pulmonary drug delivery which minimizes quantity of administered dose

- It offers rapid drug delivery to the systemic circulation due to large surface area.
- Compared to oral route, low enzymatic activities are observed in lungs which minimizes drug metabolism. Even it overcomes first pass metabolism.
- Compared to systemic route of drug delivery, it is a non-invasive route which provides more patient compliance.
- Due to large number of arterioles available in the epithelium of alveolar sacs, blood supply will be more which helps in rapid absorption of drug.
- It has been reported that the particles with diameters less than 250 nm show minimal uptake by the phagocytic defence of the respiratory tract.
- It improves the distribution of tissue macrophages.
- It enhances the solubility and bioavailability of drugs.
- It improves the stability and pharmacological activity.
- It provides protection from physical and chemical degradation.
- It improves the pharmacokinetic effect, efficacy and therapeutic index.

DISADVANTAGES OF PULMONARY ROUTE OF DRUG DELIVERY: [13]

- Complex drug delivery devices are required to delivery drug to the airways which makes therapy costly.
- Proper control of aerodynamic diameter of particle is essential to deliver it to the required site in the lungs.
- It is difficult to deliver drug in reproducibly. Even it is difficult to control the dose of the drug delivered.
- Requires complex formulation procedures compared to traditional dosage forms.
- Mucus layer may produce barrier in the drug absorption. Irritant drugs can not be delivered through pulmonary route.
- Mucociliary clearance reduces drug retention in the lungs. Slowly absorbing drugs can produce challange when delivered through pulmonary route.
- Physical conditions of airway may affect the delivery and absorption of drug.

IMPORTANCE OF HERBAL DRUG DELIVERY: [12]

- It is more effective and widely available throughout the world.
- It shows better patient compliance and patient tolerance.
- Pharmacological action is improved by this drug therapy.
- It shows no or less side effects which is major advantage of this drug therapy.

DOSAGE FORMS FOR PULMONARY DRUG DELIVERY:

Microparticles:

Micro particle includes the microspheres and the microcapsules. Microspheres are uniform sphere constituted of a polymeric matrix. Micro particles size generally ranges between 1 and 999µm. Biodegradable microspheres are prepared from natural or synthetic polymers like albumin, chitosan, polysaccharide, poly (lacticco-glycolic) acid, poly lactic acid, poly butyl cyanoacrylate. Molecules which are soluble in water or oils/ lipids can be encapsulated or incorporated into microspheres. Micro particles generally have a stable physiological behavior and shows slow release of drug and good pharmacological activity in comparison of liposomes. They generally deposit in the deep lung and do not aggregate under shear force, so they are frequently used in pulmonary drug delivery system. Drugs which are in the form of aerosolized microspheres allows a sustained and prolonged release for respiratory or nonrespiratory diseases through pulmonary administration. Different morphology, size and porosity of microspheres can be produced by making some small changes during their preparation. Microspheres do not absorb moisture and are less liable to swell in the respiratory tract **[14]**.

Different drugs such as corticosteroids, insulin, and chemotherapeutics have been formulated within polymeric micro particles. Insulin-PLGA micro particles have been developed and showed a prolonged residence time extended from 6-48 hrs. Compared to free insulin **[15]**. There are many methods and techniques used in the formulation of micro particles:

- Spray drying
- Emulsion Polymerization
- Solvent evaporation/Solvent Extraction
- Hot Melt Microencapsulation
- Phase separation
  - Spray freeze drying method
  - Fluidized Bed Coating
  - Supercritical fluid technology
  - Chemical and thermal cross-linking

Nanoparticles

Nanoparticles possess somewhat some same characteristics as microspheres, only size of particles differ from each other. Polymers or lipids constitute to form nanoparticles, but drug is either encapsulated or bounded on the surface. If the drug is encapsulated, it can be protected against enzymatic degradation

and its bioavailability can also be increased by controlled release. Nanoparticles can be used for both in vivo and in vitro **[16]**.

Many chemical processing technologies have been used to produce nanostructured materials suitable for pulmonary delivery. Nanoparticle pharmaceuticals offer several advantages over formulations containing larger particles. For example, as the size of a particle decreases, a greater number of its molecules will find at its surface rather than inside the particle.

Even anticancer drugs are used efficiently in the treatment of lung cancer through pulmonary route as it reduces systemic toxicity, 5-flurouracil has been formulated in the lipid coated nanoparticles which shows sustained release and proves to be potent drug in treatment of lung cancer. Recently, Nano-in-macro (SIMANIM) particles have been developed and applied for pulmonary delivery of antibodies **[17]**.

Nanoparticles Based Systems for Pulmonary Applications [18]:

1) **Solid lipid Nanoparticles**

   The lipids used are completely tolerated by the body and are less toxic and as a result more acceptable for pulmonary drug delivery. Phospholipids, physiological lipids and primary triglycerides are some constituents of the nanoscale aqueous suspension of SLN. Phospholipids are present in the lungs which helps in proper functioning of breathing mechanism. Drugs are generally incorporated through SLN for pulmonary administration.

2) **Polymeric nanoparticles**

   In pulmonary drug delivery polymers are gaining importance and even many polymers have been studied. Poly lactic acid, alginate, chitosan, gelatine base are some polymers which are commonly used. They possess many advantages such as long shell life, Protect drug from degradation, High encapsulation of drug, and long lasting drug delivery. In one of the studies Hydroxybenzyl alcohol an anti-inflammatory compound is incorporated in polyoxalate was prepared using PGLA based nanoparticle. These were given through intratracheal route in a mice model suffering from ovalbumin induced asthma. This showed the results of fall in the levels of cytokinins. This nanoparticles of polyoxalate have the potential for the treatment of asthma and airway inflammation.

   Advantages [19, 20]: of these include easy method of preparation, protection the drug from degradation, Nontoxic, increased therapeutic efficacy and better

Bioavailability, Due to small size it can easily penetrate through capillaries and give sustain release at the target site, Adverse effects can be prevented, Clearance time is longer, sustain release for a prolong period of time, Due to small size dissolution is faster. **Disadvantages [19, 20]**: of the Nano particle based formulation include pulmonary inflammation and carcinogenicity, unavailability of Safety data of humans, Drug which is loaded in nanoparticles can be loss due to nebulization, Sometimes it induce toxic effects on release of drug from Nano carriers

Liposomes:

Liposomes are considered a novel drug delivery system, especially for pulmonary applications, as it is prepared primarily from phospholipids, which are already present in lungs. Generally, cholesterol, phospholipids lung surfactants etc. are used in preparation of liposomes. Alveofact® which is a purified bovine surfactant was introduced as first liposomal product in 1990s, for treatment of acute respiratory distress in infants. Usage of liposomes shows several advantages but most important is it shows sustain release properties which results in maximum therapeutic effect more a longer period **[18]**. Liposomes act as drug carrier in which drug is entrapped **[21]**.

The complex of Drug-liposomes may prevent local irritation and reduce toxicity, these characteristics are commonly seen in many formulations. While conducting clinical and non-clinical studies, usage of liposomal aerosols has proven to be non-toxic and can be considered more effective for delivery, deposition and retention of water insoluble, hydrophobic, lipophilic compounds in contrast to water soluble compounds. Aerosol delivery of liposomal formulation which are being developed, can be delivered with the help of jet nebulizers, and have possibilities for effective results in treatment of pulmonary disease **[14]**.

Advantages of Liposome includes increase in efficacy and therapeutic index of the drugs like actinomycin-D, reduction in toxicity of the drugs which are encapsulated and non-toxic in nature, flexible, completely biodegradable and nonimmunogenic **[21]**. **Disadvantages of liposome include** very low solubility in the respective medium, less stable in nature, Problems like leakage and fusion are seen if proper encapsulation does not take place, and half life is short **[21]**.

Micelle

Micelle is considered as drug carrier system with long shell life and low toxicity. Particle size generally ranges from should 10–400 nm diameter is considered as good carriers in pulmonary delivery systems. Generally, core of micelle is used to trap the drug in it, a shell hydrophilic in nature can be formed

around it to protect the contents in it. Size and shape of micelle can be changed **[14]**. Micelles may also be chemically altered to selectively target a broad range of disease sites **[20]**.

Micelle consists of both hydrophilic and hydrophobic segments and amphiphilic molecules in the aqueous solution. Micelle is formed at critical micelle concentration. In this field many drugs loaded micelles were designed for different purposes, one of them were Jones and Leroux who designed beclomethasone dipropionate loaded polymeric micelles. This helped to treat asthma and chronic pulmonary obstructive disease by administrating it to the lungs in inhalation dosage form. Some beneficial results were achieved due to bulky outer hydrophilic shell of polymeric micelle which helped to evade the mononuclear phagocytic system. This proved it is beneficial in delivering hydrophobic corticosteroids. These drugs cannot penetrate through mucus layer to reach the target site, this made the treatment a failure in the past. Inflamed tissues of the lungs to gluccocorticosteroids can be targeted by the micelles used for pulmonary delivery **[22]**.

Advantages of micelle includes stability of Hydrophobic drugs, protection of drugs from getting eliminated by phagocytic system, less toxic and can be removed easily by renal filtration, Solubility of the drugs increases if encapsulated inside the micelles, for example Paclitaxel water solubility increases when it is encapsulated in micelle though it is water insoluble drug. **Disadvantages includes** less stable in blood stream; Drug leakage can occur if micelle concentration is reduced due to dilution of blood **[23]**.

Microemulsions

Micro emulsion is a thermodynamically mixture of surfactant or mixture of immiscible liquid controlled by surfactant **[24]**. Surfactant present in the micro emulsion are nontoxic in nature. Surfactants do not interfere with the therapeutic activity of the drug and hence considered as effective drug targeting system. Less number of micro emulsions have been reported to be used through pulmonary route. It is more advantageous in compared to other targeting systems as they are easy to prepare, and more amount of drug can be incorporated. Micro emulsion should allow to solubilize large number of hydrophilic drugs due to their physiochemical characteristics **[14]**. **Advantages of micro emulsion includes l**ong shell life, stable in nature, can solubilize drugs which are insoluble in water and hydrophobic solvents, and hydrophilic and lipophilic drugs, minimize side effects and reduce drug dosing, Patient compliance, microemulsions are reversible in nature **Disadvantages : includes s**tability can be influenced by environmental parameters, high melting

substance have limited solubility capacity in micro emulsions, large concentration for surfactant is required **[24]**.

Cyclodextrins

Six, seven or eight units of glucopyranose (α-, β- or γ-CD, respectively) results to form Cyclodextrins. Generally, drugs are complete or partial inclusion into the cavity, which leads to high solubility in the aqueous medium due to interaction between cyclodextrin and drug through non-covalent bonding. Size of its cavity, the complexation efficiency with drugs and their relatively low production costs are some of the reasons due to which β-CD is the most used cyclodextrins for pharmaceutical development. CDs targets lungs as they are encapsulated with the drug, they are available in different combination with other vectors. They allow sustain release of drugs and can increase the encapsulation rate of drugs into micro particles. They are widely used as carrier in the pulmonary route. They are known as pulmonary absorption promoter of peptides and proteins like insulin when they are used through pulmonary route **[14]**.

First-pass metabolism can be avoided by administration through lungs, effective drug absorption in the lungs, good blood supply and low enzymatic activity. Faster onset of drug action, decreased clearance, increased drug adsorption and solubility, and increases stability of chemically unstable drugs are some the advantages seen in cyclodextrins. Inhalation powders also consists of complexes of cyclodextrins which shows effective result without lowering the drug deposition in the lungs **[25]**.

Aerosols

Most efficient way to deliver drugs to the lungs is through administration of aerosols **[26]**. The drugs, delivered by aerosols is deposited in the airways by: gravitational sedimentation, inertial impaction, and diffusion. Mostly larger drug particles are deposited in two mechanisms in the airways, while the smaller particles get their way into the peripheral region of the lungs by following diffusion. Physicochemical characteristics, deposition site in the airways and biological defences such as mucociliary transport and resident airway macrophages decides the fate of inhaled aerosol particles. The three commonly used clinical aerosols include Jet nebulizers and ultrasonic nebulizers, Metered dose Inhaler and Dry powder inhaler **[27]**.

1. **Nebulizers:**

Asthma and other respiratory diseases are treated with the help of nebulizers for many years. Jet and ultrasonic are two different types of nebulizers. The jet nebulizer is driven up by the compressed gas which passes through a small opening creating an area of low pressure at the outlet. Jet nebulizer is based on Bernoulli principle which results to form small droplets in the

gas steam from the drug solution which is drawn from the fluid reservoir. The ultrasonic nebulizer uses a piezoelectric crystal. Normally it vibrates at a high frequency. The higher the frequency, the smaller the droplets produced in the nebulizer chamber.

Usage of these nebulizers leads to large amounts of drug wastage during treatment and even it is time consuming and inefficient. Large amount of drug is released in the environment during expiration or retained in the nebulizer itself leading to drug wastage. To overcome these difficulties of drug wastage and inefficiency, novel nebulizers have been developed **[26]**. Some properties like particle size and nebulization rates may leads to changes in the physical properties of the pulmonary formulations. Nebulization of some formulations can be affected by viscosity, osmolality, ionic strength, pH, and surface tension **[28]**. **Advantages of nebulizer are c**oordination or specific inhalation technique is not required, nebulizer is suitable for infants or patients who are not able to use other devices. **Disadvantages** are large amount of drug wastage, inefficient, contents are easily degraded, time consuming **[26]**.

2. Metered-dose inhalers:

Problems of the hand-bulb nebulizer were overcome by the invention of MDI. Small fraction of the drug dose was delivered to the lung by the MDIs. They can be given in the form of solution and suspension. Only 10–20% of the emitted dose was able to get deposited in the lungs. Hand-mouth coordination, patient's breathing pattern and inspiratory flow rate (IFR) are some of the reasons on which efficacy of MDI device depends on. When IFR increases, more drug is diffused in the peripheral airway and very less dose is deposited in the lungs. Slow inhalation leads to gravitational sedimentation in the peripheral region of lung while fast inhalations lead to less peripheral deposition **[28]**. To eliminate difficulties of coordination, Breath actuated MDIs have also been developed. These inhalers do not improve lung deposition nor do help patients who stop inhaling the moment of actuation, still patients prefer it **[26]**. **Advantages of MDI include** delivery of specified amount of dose, small size and convenience, Degradation of drug is not easy to take place, Quick to use, multiple doses can be given through it. **Disadvantages with this system include** Difficulty to deliver high doses, Range of drugs used for delivery is limited and Coordination of patients **[26]**.

3. Dry powder inhalers:

DPIs is used in delivering drugs to the lungs and is considered as an effective, efficient, and environmentally friendly way of delivery. The drug particle size less than 5µm is used **[24]**. Drugs especially proteins

are delivered to lungs with the help of device like DPIs **[1]**. Due to presence of large carrier particles or large powder agglomerates in the DPIs, they are unable to penetrate into the lungs. Creation of turbulent air flow is important for dispersion of the powder into respirable particles in the powder container. This turbulent airstream helps in breaking down of large particles into small enough to be carried into the lower part of respiratory tract and helps in separation of carrier and drug. Resistance in air flow is different with each DPI. It is difficult to generate an inspiratory flow required to achieve maximum dose from the inhaler if the resistance is higher in the device. Usage of high resistance inhalers tends to increase deposition in the lungs **[26]**. **Advantages of DPI include** Compact in size, Easy to carry from place to another, Its usage is very easy, No coordination between hands and legs is required, Less formulation problems, Less chemical degradation And **Disadvantages include a**ggregates of powder form due to humidity which makes capsule soft, If the patient exhales in the inhaler little amount of dose is lost, Dependent on the inspiratory flow rate, and Greater potential problems in dose uniformity **[26]**.

CHALLENGES OF THE PULMONARY DRUG DELIVERY SYSTEM [29]:

Generally inhaled drugs faced two main problems low bioavailability and short half-life. This can lead to severe side effects and optimal therapeutic effect. The main causes behind these major problems are:

1) Pulmonary Clearance
2) Enzymatic degradation
3) Rapid system adsorption

Pulmonary Clearance Mechanism:

Defence system present in our body prevents foreign bodies to enter in, similarly respiratory defence mechanism acts in the same way to maintain respiratory system healthy and sterile. When aerosol particles enter the respiratory system, its defence mechanism eliminates the particle to interact with the lungs leading to the failure of the treatment. Clearance mechanism of the aerosol inhaled particles is mostly dependent on the target site where it must be deposited within the lungs.

1. Mucociliary clearance

It is the type of defence mechanism present in the respiratory upper tract, lined with epithelial cells consisting of two layers: goblet cells and ciliated cells. These two types of cells together are known as mucociliary escalator. The ciliated cells consist of two layers; mucus layer and periciliary layer and covered with airway surface liquid. Inhaled particles with enters in and gets deposited in the spaces between trachea and bronchi are eliminated by mucociliary escalator by coughing or swallowing. Generally particles having size more than 6μm are eliminated by

mucociliary escalator. Smaller particles do not get eliminated by mucociliary escalator and easily reach the epithelium and gets deposited in the alveolar region, where it remains for long time in lungs or gets dissolved. The balance between mucociliary escalator gets disturb during any inflammation or infection in lungs, it increases the elimination of the drug inhaled particles by decreasing the effectiveness and retention time of the drug.

2. Alveolar macrophage clearance

This clearance mechanism is situated deep down in the alveoli. Alveolar macrophages are present in large numbers in the lungs, they are nothing but phagocytic cells derived from monocytes. To keep alveolus free from foreign particles it is clean by 12-14 alveolar macrophages. Particle size ranging from 1.5-3 μm are taken up by the macrophages. The particles having size less than this can easily escape from the alveolar macrophages and can provide a controlled release in the lungs. The half-life of the inhaled drugs cannot exceed a few hours in the alveoli which results in increasing the frequency of dosing. This happens due to presence of alveolar macrophages in the alveoli.

Enzymatic degradation

Inhaled drug particles can easily undergo enzymatic degradation in the lungs and can result to a failure therapy or ineffective. Cytochrome P450 families are the primary detoxification enzyme in the lung which provide defence from the foreign particles. Many isoforms of cytochrome are also present in the lungs which are degrade broad spectrum of inhaled drugs, pollutant, toxicants, etc. Budesonide, ciclesonide, salmeterol, and theophylline are some inhaled drugs which are enzymatically degraded in the lung. Enzymatic degradation significantly influences a drug's bioavailability though it has low metabolic rate in comparison to other organs like liver.

Rapid systemic absorption

Rapid systemic absorption is another challenge faced by inhaled drugs. Lung's large surface area, good epithelial permeability and high vascularity are some areas used to describe rapid systemic absorption. Site of action is the main parameter on which optimal absorption of the inhaled aerosol relies either locally or systemically. When an inhaled drug is absorbed and terminated in the lung, therefore an ideal local effect is achieved. When the inhaled drug is systemically absorbed from the lung into blood stream, a systemic effect is achieved. The transfer of drugs from environment to blood starts by the interaction between the drug and the surfactant after deposition on the mucosa of trachea airways. Drug’s nature plays important role in the interaction and determines whether the drug is absorbed or eliminated.

When small lipophilic drugs and lung surfactant meets each other it improves its solubility and increases the rate and extend of the absorption. Exactly below the lung surfactant there is a thick lining which allows drug to diffuse to the epithelium and enter the main blood stream. Active and passive transport mechanism are part of systemic drug absorption. Drug nature, molecular weight and the targeted site are parameters on which the mechanism of drug absorption across epithelium depends. Small lipophilic and hydrophobic drugs are absorbed within 12 minutes from the lung into the systemic circulation via passive diffusion, while small hydrophilic drugs are absorbed within 65 minutes, through the tight junction have been reported in some studies.

CHALLENGES FOR DELIVERY OF HERBAL DRUG VIA PULMONARY ROUTE:

Delivery of herbal drugs via pulmonary route having challenges because respiratory system is a complex system. There are two main reasons behind that are;

A. Removal or inactivation of the inhaled material which have been deposited.

B. Patient must have to use the inhaler device correctly.

Until the 2nd half of the 20th century, pulmonary drug delivery was unsuccessful because of poor understanding of issues related to both lung defence mechanism and partly use of inhaler [30].

The limited understanding of the pharmacokinetic and pharmacodynamic effects on the lungs is the major challenge in the development of inhalable herbal compounds **[31]**.

Converting a promising prototype inhaler into a commercial successful product and then to secure an approval of product, collecting the clinical data is also a challenge **[31]**.

To prepare a reproducible lung dose with reasonable cost and with low side effects is also a challenge **[31]**.

It requires sufficient drug water solubility to enhance bioavailability of inhaled drugs from the lungs. Rather than higher dose, it requires low potency of inhaled drug. Because of this solubility of drug is essential and it highlights the need to design strategies to enhance water solubility significantly. It is also mandatory to maintain the required concentration of drug in lining fluid compartment above the MIC as long as possible. By efficient clearance mechanism of lung, systemic absorption across the air-blood barrier can disturb this goal **[32]**.

Lung clearance is also a challenge after deposition of drug. There are two clearance pathways for drug across the respiratory epithelium;

- Mucociliary system (mucociliary clearance)

- Alveolar macrophage (Alveolar clearance)

Hydrophilic molecules pass through extracellular pathways while lipophilic molecules pass through airway epithelium. The deposited drug in via alveolar region may be phagocytosed and either absorbed in pulmonary region or cleared by alveolar macrophages. After phagocytosis, the insoluble particles in macrophages are deposited in alveolar region which may be cleared by lymphatic system or move to ciliated airway to complete the process which may take few weeks to months **[10]**.

CONCLUSION:

Pulmonary drug delivery is one of the oldest drug delivery systems. But still now it is widely used due to its potential advantages. Lungs offer a vast variety of advantages over conventional oral drug delivery. The large surface area and the elimination of the first past effect makes the absorption of drugs in the lungs faster. The knowledge related to effects of variety of factors, such as the basic nature of therapeutic agents, cellular aspects, properties of delivery system, aerosol administration mechanisms, lung deposition pattern and type of drug delivery devices help the pharmaceutical scientist in successful development of pulmonary drug delivery system. This review discusses the general overview for using pulmonary drug delivery systems for delivery of herbal drugs. Which includes it's advantages, challenges, disadvantages, which type of herbs can be used, which type of devices are required to deliver the drugs, etc.

Various dosage forms used in pulmonary drug delivery system are developed. Carriers like micro particles, nanoparticles, liposomes etc. can be used in pulmonary delivery. Lipid-based colloidal systems namely, SLN and liposomes, have an added advantage owing to their physiological components in the formulation. Biodegradable polymeric nanoparticles may exhibit a sustained release effect. The micro particles offer a variety of opportunities such as protection and masking, better process ability, improve bioavailability, decreasing dosing frequency, improve stability, this approach facilitates accurate delivery of small quantities of potent drugs; reduced drug concentrations at sites other than the target organ or tissue; and protection of labile compounds. Various dosage forms are of no use until they evaluated based on different criteria. Non clinical studies of these particles are carried out using various model. Pulmonary route can be best utilized by the researcher if they have thorough knowledge of the disease behind treated, lungs anatomy, deposition mechanism, delivering device used. DPI offers several advantages like its simplicity in use, cheapness, robustness, ease of use but do

deliver large amount of powder in one breath is major challenge with DPI.

The global market has brought different types of herbal medicines worldwide. Now a days herbal medications are obtained from Indian herbs, Chinese herbs, Arabic herbs, and Western herbs. The combination between the herbal drugs and pulmonary delivery system has established the attractive therapy to cure the patients from the variety of disease.

The use of herbal drugs which provides less or no side effects is the one of the major advantages of it. These drugs can be directly targeted to the lungs which provides good therapeutic action and it avoid the first pass metabolism.

This delivery system is becoming one of the attractive drug delivery systems because the lung provides the direct access to the blood stream. For the absorption of medications, lung provides large surface area with relatively low enzymatic and controlled environment. Deposition of aerosol influenced by airway geometry, humidity, lung clearance, and presence of lung diseases and therefore it affects the therapeutic effectiveness of inhaled medications. Therefore, this drug delivery system is used for treatment of various diseases like asthma, COPD, cancer, cystic fibrosis.

The novel devices like MDI, pMDI, nebulizers are very useful for the targeted delivery of herbal drugs. These devices might have overcome the administration difficulties. These devices are improving the drug dosing efficiency, and the smaller particles can easily penetrate to the lungs.

From the review, we can conclude that delivering the herbal drugs by this pulmonary route is very prominent, easily applicable compare to the other drug delivery systems.

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