Academic Sciences International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 5, Issue 3, 2013

Review Article

# PULMONARY DRUG DELIVERY SYSTEM: REVIEW

**CHATURVEDI N.P.*, SOLANKI H.**

**Department of Pharmaceutics, IIT BHU, Varansi, India 221005. Email: neha_cvedi23@rediffmail.com.**

*Received: 24 Nov 2011, Revised and Accepted: 05 Jan 2013*

**ABSTRACT**

Growing attention has been given to the potential of pulmonary route as an alternative for non-invasive systemic delivery of therapeutic agents.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 drug delivery is an importantresearch area which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various other diseases. Inhalation gives the most direct access to drug target. This route can be used to deposit the drug to the target site at high concentration, reducing the amount of drug given to the patient and also help in reducing the systemic side effect and first pass metabolism. In the treatment of obstructive respiratory diseases, pulmonary delivery can minimize systemic side effects, provide rapid response and minimize the required dose since the drug is delivered directly to the conducting zone of the lungs. Generally half of all pharmaceuticals are not soluble in water, but are soluble in lipid. As the lung is able to absorb both water and oil into the tissue, this is not a restriction of pulmonary delivery. Carriers like micro particles, nanoparticles, liposomes can be used in lung targeting.This article focuses on the technologies, mechanism of drug deposition, devices, carriers and recent advances used in pulmonary drug delivery system.

**Keywords:** Inhaler, Pulmonary drug delivery, Dry powder inhaler, Meter dose inhaler, Nebulizer, Liposomes, Microspheres, Mucoadhesion, Nanoparticlesin Pulmonary Delivery

## INTRODUCTION

Pulmonary Route serves to be best alternative to the non-invasive administration for systemic delivery of therapeutic agent (mainly proteins and peptides)due to the fact that lungs could provide a large absorptive surface area (upto 100m$^2$)but extremely thin (0.1-0.2mm) absorptive mucosal membrane and good blood supply.The respiratory tract is one of the oldest routes used for the administration of drugs. Over the past decades inhalation therapy has established itself as a valuable tool in the local therapy of pulmonary diseases such as asthma or COPD (Chronic Obstructive Pulmonary Disease).

The latest and probably one of the most promising applications of pulmonary drug administration is:-

1) Its use to achieve systemic absorption of the administered drug substances.

2) Particularly for those drug substances that exhibit a poor bioavailability when administered by the oral route, as for example peptides or proteins, the respiratory tract might be a convenient port of entry.

Devices used to deliver drugs by pulmonary route are based on one of three platforms arepressurized metered dose inhaler, nebulizer and dry powder[3]. In the treatment of obstructive respiratory diseases, pulmonary delivery can minimize systemic side effects, and it provides rapid response, and it minimizes the required dose[1].

When developing a pulmonary drug delivery system one of the important parameter to be considered is particle size. Optimum particle size is very important for targeting of 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.[3] Drug can be delivered by using carriers like cyclodextrins, microparticles, liposomes, nanoparticles etc.[2,4]

## ADVANTAGES OF PULMONARY DRUG DELIVERY[5,6]

- It is needle free pulmonary delivery.
- It requires low and fraction of oral dose i.e. drug content of one 4 mg tablet of salbutamol equals to 40 doses of meter doses.
- Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug.
- Onset of action is very quick with pulmonary drug delivery.
- Inhaling helps to avoid gastrointestinal tract problems such as poor solubility, low bioavailability, gut irritability, unwanted metabolites, food effects and dosing variability.
- In asthma and diabetes requires long term treatment if it is given by pulmonary drug deliverysafety is maximum because rest of body not exposed to drug.
- Degradation of drug by liver is avoided in pulmonary drug delivery.

## LIMITATIONS

- Stability of drug in vivo.
- Transport.
- Targeting specificity.
- Drug irritation and toxicity.

Drug retention and clearance

## ANATOMY AND PHYSIOLOGY OF LUNGS[7]

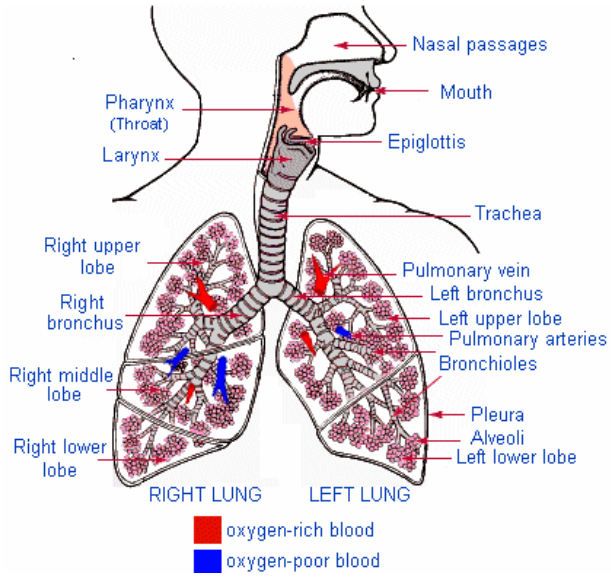



**Fig. 1: Different regions of the human respiratory tract**

The human respiratory system is a complicated organ system of very close structure–function relationships. The system consisted of two regions:

- The conducting airway
- The respiratory region.

The airway is further divided into many folds: nasal cavity and the associated sinuses, and the 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 gas exchange, by adding oxygen to, and removing carbon dioxide from the blood passing the pulmonary capillary bed.

**Lung regions:-**

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

**Nasopharyngeal region:-**

This is also referred to as the "upper airways", which involves the respiratory airways from the nose down to the larynx.

**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 ends at the terminal bronchioles.

**Alveolar region:-**

This is also referred to as the "respiratory airways", "peripheral airways" or "pulmonary region", Comprising the respiratory bronchioles, alveolar ducts and alveoli.

**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.

**The bronchi:-**

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

**The bronchioles:-**

These are primarily lined with ciliated cuboidal cells. The frequency of goblet and serous cellsdecreases with progression along the airways while the number of Clara cells increases.

**The alveolar region:-**

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

• Type-II pneumocytes: Cuboidal cells that store and secrete pulmonary surfactant.

Alveolar macrophages account for ~ 3% of cells in the alveolar region. These phagocytic cells scavenge and transport particulate matter to the lymph nodes and the mucociliary escalator.

**DRUG DELIVERY DEVICES[8]:**

For pulmonary route, drug delivery devices play an important role equivalent to that of formulation aspects. It is difficult to administer a formulation through pulmonary route without suitable drug delivery devices. The drug delivery devices are given below.

1. Metered Dose Inhalers

2. Dry Powder Inhalers

3. Nebulizers:

- Jet Nebulizers
- Ultrasonic Nebulizers

**Metered Dose Inhalers (MDI) [[1,8]]:**

Used for treatment of respiratory diseases such as asthma and COPD. They can be given in the form of suspension or solution.A metered-dose inhaler (MDI) is a complex system designed to provide a fine mist of medicament, generally with an aerodynamic particle size of less than 5 microns, for inhalation directly to the airways. They consist of a micronized form of the drug in a propellant under pressure with surfactants to prevent clumping of drug crystals. Lubricants for thevalve mechanism and other solvents are the other constituents. When the device isactuated, the propellant gets exposed to atmospheric pressure, which leads to aerosolisation 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. The fraction of drug to the airways ranges from 5 percent to 15 percent.


**Fig. 2: Metered Dose Inhalers (MDI)**

**Dry Powder Inhalers(DPI)[5,9,1]**

DPIs are bolus drug delivery devices that contain solid drug in a dry powder mix (DPI) that is fluidized when the patient inhales.Dry powder formulations either contain the active drug alone or have a carrier powder (e.g. lactose) mixed with the drug to increase flow properties of drug. DPIs are a widely accepted inhaled delivery dosage form, particularly in Europe, where they are currently used by approximately 40% of asthma patients. Lack of requirement of propellant is an advantage of DPIs over MDIs. The fraction of the drug delivered to the site of action by a DPI varies from 9% to 30% and varies among different commercially available products.


**Fig. 3: Dry Powder Inhalers**

Currently there are two types 9.10;

Unit-Dose Devices: Single-dosepowder inhalers are devices in whicha powder contained capsule is placedin a holder. The capsule is openedwithin the device and the powder isinhaled.

Multi-dose Devices: Multi-dosedevice uses a circular disk thatcontains either four or eight powderdoses on a single disk. The doses aremaintained in separate aluminiumblister reservoirs until just beforeinspiration.

**Nebulizers[5,11]**

Nebulizers are widely used as aerosolize drug solutions or suspensions for drug delivery to the respiratory tract and are particularly useful for the treatment of hospitalized patients.

- Delivered the drug in the form of mist.
- There are two basic types:

1) Air jet

2) Ultrasonic nebulizer

In ultrasonic nebulizers, ultrasoundwaves are formed in an ultrasonic nebulizerchamber by a ceramic piezoelectric crystalthat vibrates when electrically excited. Theaerosol produced by an air jet nebulizer isgenerated when compressed air is forcedthrough an orifice; an area of low pressureis formed where the air jet exists.Nebulizers are particularly useful for thetreatment of hospitalized or nonambulatorypatients.

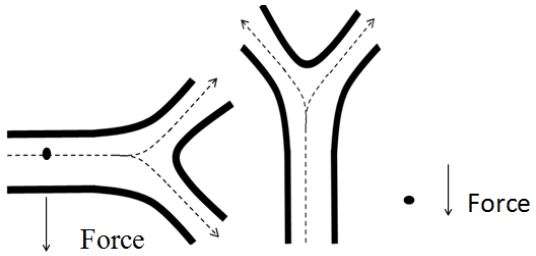
**Mechanism involved in deposition of particles in Lung [12,13]**

The drugs is deposited in the airways by:

- gravitational sedimentation,
- impaction,
- diffusion.

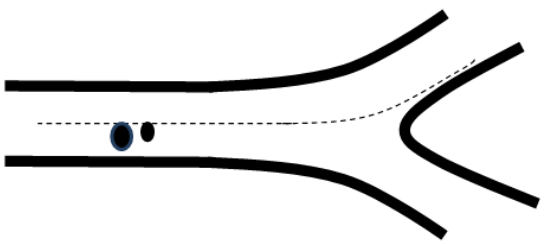
Mostly larger drug particles are deposited by first two mechanisms in the airways, while the smaller particles get their way into the peripheral region of the lungs by following diffusion.

**Sedimentation**



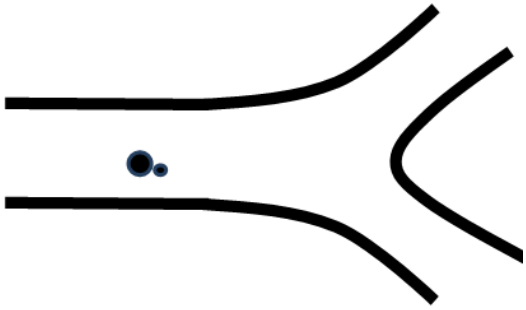

Gravitational force act on the particle. Sedimentation occurs if the gravitational force is more than the air flow force. Sedimentation is settling of particles due to low air flow. Lung airways have different orientation so deposition of particle will be different depending on the direction of the particle flow and direction of gravitational force.This mechanism occurs inlarger size particles. Particles of hygroscopic nature may enlarge in size as they pass through air passages and sediments.

**Impaction:**



Impaction occurs due to air flow changes. Impaction increases with particle size and flow rate. This type of deposition occursthroughout the lung. This is important, especially in the head airway where most of the large particles are screened out. Impaction occurs mostly in the upper generation airways due to high velocity

**Diffusion**



Caused by Brownian motion. Deposition may occur by diffusion if the particles size is less than the diameter of 0.5 micron. Diffusion is the deposition mechanism for small particles. Diffusion increases with decreasing particle size and flow rate. More deposition occurs in the alveoli region because longer residence time and smaller airway

**RECENT ADVANCES IN FORMULATION OF PULMONARY DRUGDELIVERY**

Effective inhalable medications are formed by drug formulation. Formulation stability isanother challenge in producing pulmonary drug delivery. Formulation is responsible forkeeping drug in pharmacologically active state, it must be efficiently delivered into thelungs, to the appropriate site of action and remain in the lungs until the desired pharmacological effect occurs. Several factors have been included insupport of developing nasal formulationscontaining liposomes, microspheres and nanoparticles for intranasal drug delivery. In fact, it is not clear if those formulations increase drug absorption by transporting encapsulated drug across the membrane or just because they enhance the nasal retention time and stability of the drug.However, their use is in extensive growth and the results have been very capable.

**Liposomes[14,15,16]**

Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments in which drugs and other substances might be included. In recent times, they have been investigated as a vehicle for sustained-release therapy in the treatment of lung disease, gene therapy and as a method of delivering therapeutic agents to the alveolar surface for the treatment of systemic diseases. Liposomal drug delivery systems present various advantages such asthe effective encapsulation of small and large molecules with a wide range of hydrophilicityand pKa values. In fact, they have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has beenattributed to the increasing nasal retention of peptides, protection of the entrapped peptides from enzymatic degradation and mucosal membrane disruption.

**Nanoparticles**

Nanoparticle systems are being investigated to improve drug delivery and intranasal drug administration. Nanoparticles are solid colloidal particles with diameters raging from 1-1000 nm. They consist of macromolecular materials and which are therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles can offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by Para cellular routeandin a limited quantity, since the tight junctions are in the order of 3.9-8.4 Å. There are several studies have been suggested that nanoparticle systems can be preferably suited as a vehicle for sustained release therapy.

Sustained release from therapeutic aerosol can prolong the residence of an administered drug in the airways or alveolar region, minimize the risk of adverse effects by decreasing its systemic absorption rate, and increase patient compliance by reducing dosing frequency. Nanoparticle systems are also suitable for the delivery of nasal vaccines**.[17,18]**

**Microspheres[17]**

Microsphere technology has been widely useful in designing of formulations for nasal drug delivery. Microspheres are usually based on muco-adhesive polymers (chitosan, alginate), which provide various advantages for intranasal drug delivery. Moreover, microspheres may protect the drug from enzymatic metabolism and gives sustain drug release, thereby prolonging itseffect.

**Mucoadhesive drug delivery systems**

MCC is one of the most important limiting factors for nasal drug delivery, because it reduces the time allowed for drug absorption. Thus, mucoadhesivedrug delivery systems improving the nasal drug absorption, and also prolonging the contact time between drug and nasal mucosa.Mucoadhesion indicates the attachment ofthe drug delivery system to the mucus, involving an interaction between mucin anda synthetic or natural polymer calledmucoadhesive. The sequential events thatoccur during this mucoadhesioninclude several steps. Firstly mucoadhesive systemsabsorb water from mucus layer and get wetand swelling. Following this, the polymer intimately penetrates into the mucus and, hence, localizes the formulation in nasal cavity, enhancing the drug concentration gradient across the epithelium.Mucoadhesives mostly used in intranasal drug delivery are chitosan, alginate and cellulose or its derivatives[17].

**CONCLUSION**

Pulmonary drug delivery is one of the oldest drug delivery systems. But still now it is widely used due to its potential advantages. The drugs which produce GI irritation can be administered by pulmonary route. One of the major hurdles in this system is achieving the optimum particle size, which determines the targeted delivery of drug to lungs. Inhalable nanocarrier systems offer numerous advantages, the decrease in particle size leads to an increase in surface area leading to enhanced dissolution rate, as well as relatively uniform distribution of drug dose among the alveoli.But still it requires further study to select the suitable methods and additives based on the nature of the drugs. Carriers like microparticles, nanoparticles, liposomes etc. can be used in pulmonary delivery. Although advanced technologies are available, in some cases, the product may fail to achieve its goal. Pulmonary route can be best utilizes 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 (around 50mg) in one breath is major challenge with DPI. Also to maintain stability of powder formulation is another problem associated with DPI.

**REFERENCES**

1. R. Sunitha. Drug Delivery And Its Developments For Pulmonary System: *Review Article.* International Journal of Pharmaceutical, Chemical And Biological Sciences .2011, 1(1), 66-82.
2. K.Masilamani. Drug Delivery To The Lungs. *Review Article.*Issn 0976 – 044x. Volume 10, Issue 2, September – October 2011; Article-017.
3. N. R. Labiris& M. B. Dolovich. Pulmonary Drug Delivery Part I: Physiological Factors Affecting Therapeutic Effectiveness Of Aerosolized Medications, Blackwell Publishing Ltd., *British Journal Of Clinical Pharmacolology,* 2003, 56(6): 588–599.
4. PandeyShivanand, ShuklaParidhi, Bhatt Sweta, ChoudharyVasanti, Viral D, V.Subhash, K.K Shailesh, Manish Goyani, N. P. Jivani. Microfine Dry Powder: Pulmonary Drug Delivery System, *Journal Of PharmacyResearch*, 2009, 2(7): 1159-1162.
5. Tangri P. Approaches To Pulmonary Drug Delivery Systems. International Journal Of Pharmaceutical Sciences And Research. 2(7):1616-1622.
6. Hindle M And Byron Pr. Dose Emissions From Marketed Dry Powdered Inhalers. Int J Pharm. 1999;116–169.
7. KarhaleAshish A., ChaudhariHiralal S., UghadePrajkta L., BaviskarDheeraj T., Jain Dinesh K. Pulmonary Drug Delivery System. International Journal Of Pharmtech Research Coden (Usa): Ijpriflssn : 0974-4304 Vol.4, No.1, Pp 293-305, Jan-Mar 2012.
8. Nimesh P. Patel, Arpan A. Patel AndMoin K. Modasiya. Aerosols: Pulmonary Drug Delivery System. International Journal Of Pharmaceutical And Chemical Sciences. Vol. 1 (1) Jan – Mar 2012.
9. Paul J. Atkins And Timothy M. Crowder.The Design And Development Of Inhalation Drug Delivery Systems.Modern Pharmaceutics By Marcel Dekker, P.1-31.
10. Ogden, Jill, Rogerson, C And Smith I.Issues In Pulmonary Delivery. In Scrip Magazine. 1996:56–60.
11. Michael T. Newhouse, "Encyclopedia Of Pharmaceutical Technology", Second Edition, Dekker, New York Informa Healthcare Usa. 2000;19:1279-1285.
12. PandeyShivanand*Et Al*. Local And Systemic Pulmonary Drug Delivery Of Small Molecules, *Journal Of PharmacyResearch*, 2009, 2(8): 1200-1202.
13. Mortonen, T., And Y. Yang. Deposition Mechanics Of Pharmaceutical Particles In Human Airways. In A.J.Hickey, Editor. Inhalational Aerosols: Physical And Biological Basis For Therapy. *Marcel Dekker*, New York.1996, 1–21.
14. Mcelvaney Ng, Hubbard Rc And Birrer P. Aerosol *A*-1 Antitrypsin Treatment For Cystic Fibrosis. Lancet. 1991;337:392–394.
15. Jain Ak, Chalasani Kb, KharRk, AhmedFj And DiwanPv. Muco-Adhesive Multivesicular Liposomes As An EffectiveCarrier For TransmucosalInsulinDelivery. J Drug Target, 2007;15:417-427.
16. Law Sl, Huang Kj, Chou VhyAndCherngJy. Enhancement Of Nasal Absorption Of Calcitonin Loaded In Liposomes. J Liposome Res.2001;11:164-174.
17. AnaísaPires. Intranasal Drug Delivery: How, Why And What For? J Pharm Sci. 2009;12(3):288 – 311.
18. Fernandez-Urrusuno R, Romani D,Calvo P, Vila-JatoJl And Alonso Mj. Development Of A Freeze Dried Formulation Of Insulin-Loaded Chitosan Nanoparticles Intended For Nasal Administration. S.T.P Pharma Sciences. 999;9:429-436.