RECENT ADVANCES IN NASAL FORMULATIONS AND DEVICES USED IN PULMONARY DRUG DELIVERY

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ABSTRACT
Pulmonary drug delivery has gained tremendous scientific interest in recent years and has progressed within the context of treatment for lung diseases. Lung is an attractive environment for bio molecules, which are highly susceptible to enzymatic degradation in the gastrointestinal tract as well as hepatic degradation. Pulmonary route is a non-invasive administration for systemic delivery of therapeutic agents (mainly peptides and proteins). Lungs provide a large absorptive surface area but extremely thin (0.1 µm – 0.2 µm) absorptive mucosal membrane and good blood supply. Intra tracheal administration is a first approach in lung drug delivery in vivo. In inhalation therapy most common devices used were nebulizer, Metered dose inhaler (MDI), and Dry powder inhaler (DPI). Pulmonary drug delivery is used for management of COPD and Asthma. Last few years techniques and new drug delivery devices intended to deliver drugs into the lungs have been widely developed. Pulmonary drug delivery can also be used to treat Diabetes, angina pectoris, cancer, bone disorders, tuberculosis, migraine acute lung injury and others. Liposomes, nano and micro particles, cyclodextrins, micro emulsions, micelles, suspensions, or solutions are all examples of the pharmaceutical drug carriers that have been successfully used to target drugs into lungs. This review discusses the approaches and devices required to be administer drug into the lungs.

Key words: Asthma, Lungs, Nanoparticles, Nebulizer, Non-invasive, Pulmonary drug delivery.
1. INTRODUCTION

The pulmonary route has been used for local administration of drugs to treat lung diseases such as asthma and chronic obstructive pulmonary disease (COPD) [1]. Pulmonary drug delivery allows local drug targeting and administration of low doses and decreased drug concentrations systemically which results in reduced systemic side effects. Corticosteroids, antibiotics, β2-agonists, mucolytics and new classes of drugs are under investigation for direct administration to the lungs. Drugs are generally delivered to the respiratory tract for the treatment or prophylaxis of bronchial asthma and cystic fibrosis. The administration of a drug at its site of action results in rapid onset of activity, which is highly desirable when delivering bronchodilator drugs for the treatment of asthma. Smaller doses can be administered locally compared to delivery by the oral or parenteral routes. Thereby reducing the potential incidence of adverse systemic effects and reducing dosage costs. The pulmonary route is also useful in several aspects like, where a drug is poorly absorbed orally e.g. sodium cromoglicate, where it is rapidly metabolized orally e.g. isoprenaline. The effect of first pass metabolism in the liver may also be avoided.

The lungs can be used as a route for delivering drugs having systemic activity. It offers large surface area, abundance of capillaries and the thinness of the air-blood barrier. This has been exploited in the treatment of migraine with ergotamine. Recent studies have demonstrated the potential for delivering proteins and peptides such as insulin and growth hormone through the airways [2]. Systemic chemotherapy in primary or metastatic lung cancer showed low clinical efficacy. It is related to low drug penetration locally in the tumour. Aerosolised chemotherapy would increase exposure of the lung tumour to the chemotherapeutic agent, minimising systemic side effects [3]. Local drug administration is pulmonary gene therapy where DNA or RNA interference is also delivered. Potential applications include treatment of gene disorders such as inflammatory diseases such as asthma, cystic fibrosis, and COPD, infections and cancer [4, 5].

1.1. ADVANTAGES OF PULMONARY DRUG DELIVERY [6].

- Provides local action within the respiratory tract
- Provides rapid drug action
- Provides a non-invasive method of delivering drugs into the bloodstream.
- Allow efficient drug targeting to the lungs for respiratory tract diseases such as asthma, emphysema, and chronic bronchitis.
Inhaling helps to avoid gastrointestinal tract problems such as poor solubility, low bioavailability, gut irritability, food effects, unwanted metabolites and dosing variability.

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.

Reduces evasion of first pass hepatic metabolism by absorbed drug

Offers the potential for pulmonary administration of systemically active materials

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**Fig No.1: Anatomy of Human Respiratory System**

2. MECHANISM OF DEPOSITION OF PARTICLES INTO THE LUNGS

Aerosols are suspensions of solid or liquid particles in a gas. Most aerosol particles are polydisperse. They have a wide range of particle sizes that must be characterized by statistical measures.

The particulate portion of an aerosol is referred to as particulate matter. Particulate matter is a generic term applied to chemically heterogeneous discrete liquid droplets or solid particles. The Particulate matter in an aerosol is in size range from 0.001 to greater than 100 microns in diameter. Particles intended to be administered by pulmonary route are generally categorized based on size:

- Coarse particles > 2 microns in diameter
- Fine particles are between 0.1 and 2 microns in diameter
ultrafine particles < 0.1 micron

2.1. PRINCIPLE MECHANISMS OF RESPIRATORY DEPOSITION [7-12].
The deposition of inhaled particles in the different regions of the respiratory system is very complex, and depends on many factors. Some of the factors influencing respiratory deposition include:

- Breathing rate
- Lung volume
- Respiration volume
- Mouth or nose breathing
- Health of the individual
- Bifurcations in the airways result in a constantly changing hydrodynamic flow field.

Depending on the particle size, airflow, location in the respiratory system, particle deposition occurs via one of the following principal mechanisms:

2.1.1. Impaction
Bifurcation in the airways causes the airflow changes, so the suspended particles tend to travel along their original path due to inertia and impact on an airway surface. This mechanism is highly dependent on aerodynamic diameter. The stopping distance for very small particles is quite low. Impaction occurs mostly in case of larger particles that are very close to airway walls, near the first airway bifurcations. So deposition by impaction is greatest in bronchial region.

2.1.2. Sedimentation
Sedimentation is the process of settling out of particles in the smaller airways of the bronchioles and alveoli, where the air flow is low and airway dimensions are small. The rate of sedimentation is dependent on the terminal settling velocity of the particles. So sedimentation plays a greater role in the deposition of particles with larger aerodynamic diameters. Size of Hygroscopic particles increases as they pass through the warm, humid air passages, thereby increasing the probability of deposition by sedimentation.

2.1.3. Interception
Interception occurs when a particle contacts an airway surface due to its physical size or shape. Particles that are deposited by interception do not deviate from their air streamlines.
which is observed in impaction. Interception occurs mostly in small airways or when the air Stream line is close to airway wall. Interception is most significant for fibres, which easily contact airway surfaces do to their length. Fibres have small aerodynamic diameters relative to their size, so they can reach the smallest airways.

2.1.4. Diffusion
This is the primary mechanism of deposition for particles less than 0.5 microns in diameter. It is governed by geometric size rather than aerodynamic size. Brownian motion is the random wiggling motion of a particle due to constant bombardment of air molecules. Diffusion is the transport of particles from a region of high concentration to a region of lower concentration due to Brownian motion. Diffusional deposition occurs mostly when the particles enters the nasopharynx, and is also most likely to occur in the smaller airways of the alveolar region where air flow is low.

2.1.5. Absorption
Pulmonary membrane is permeable to small molecule drugs and for many therapeutic peptides and proteins. The epithelium of the lung is the significant barrier to absorption of inhaled drugs. The thickness is 50–60 µm in the trachea, but abdicates in thickness to an extremely thin 0.2 µm in the alveoli. The lungs are more permeable to macromolecules than any other portal of entry into the body. Some of the therapeutic agents include peptides and proteins, which could be inhaled instead of injected, thereby improving compliance. Small molecules can exhibit prolonged absorption if they are highly soluble or if they are highly cationic. Though rapid absorption of molecules has many medical uses, there are certain situations where one might want to slow the absorption of an inhaled small molecule or either to keep it prolonged acting locally in lung, or regulate its absorption into the body. Very insoluble molecules that slowly dissolve from the inhaled particle may stick in the lung for many hours. Fluticasone propionate, Amphotericin B, and all-trans retinoic acid are absorbed from the lungs over a period of hours, due in part to their slow dissolution rate from relatively insoluble lipophilic particles. Formulation of drugs in slow release particles such as nanoparticles and Liposomes can also be used to control absorption rate.
3. FACTORS WHICH AFFECT THE NASAL DRUG ABSORPTION AND PRACTICAL STRATEGIES TO OVERCOME THEM:

![Diagram showing factors affecting nasal drug absorption]

**Fig No. 2: Factors which affect the nasal drug absorption**

4. PULMONARY CLEARANCE [13]

The primary function of the pulmonary defensive system is to respond to inhaled particles and to keep the respiratory surfaces of the alveoli clean and available for respiration. The elimination of particles that are deposited on the lower respiratory tract is the important defence mechanism to prevent adverse interactions of aerosols with lung cells.

Insoluble particulates are cleared by several pathways. These pathways get impaired in certain diseases and are thought to depend on the nature of the administered material. Swallowing, expectoration and coughing are the sequence of clearance mechanisms operating in the naso/oropharynx and tracheobronchial tree. Soluble particles can also be cleared by dissolution with subsequent absorption from the lower airways. The rate of particle clearance from these regions differs significantly and its prolongation can have serious effects causing lung diseases from the inhaled toxic compounds. It is now recognized that the lungs are the site for the uptake, accumulation, and metabolism of numerous endogenous or exogenous compounds. All metabolizing enzymes are found in smaller amounts in the lungs. The rate at which a drug is cleared and absorbed from the respiratory tract depends on the following factors.

- Biopharmaceutical factors (particulates vs. drug in solution),
- The mucociliary clearance rate,
Drug release rate,
The physicochemical properties of the drug (molecular weight, partition coefficient, charge),
Site of deposition along the airways.

5. MUCOCILIARY CLEARANCE [13]
It is a physiologic function of the respiratory tract to clear locally produced debris, excessive secretions, or unwanted inhaled particles. It consists of ciliated epithelial cells reaching from the naso/oropharynx and the upper tracheobronchial region down to the most peripheral terminal bronchioles. An efficient clearance mechanism involves beating of the cilia, together with mucus secreted by the goblet cells. For normal mucociliary clearance to occur it is necessary that the epithelial cells are intact, the ciliary activity and the rheology of mucus are normal, and that the depth and chemical composition of the periciliary fluid layer is optimal. By altering the volume of mucus secretion, the mucus viscosity and elasticity, or the ciliary beat frequency, mucociliary escalator can be impaired. In smokers, in patients with chronic bronchitis, and in acute asthmatics, it is reported that Mucociliary clearance gets impaired. Certain diseases are known to enhance clearance rates.

6. NOVEL DRUG FORMULATIONS
Nasal formulations containing Liposomes, microspheres and nanoparticles have been used in recent 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.

6.1 Liposomes
Liposomes are phospholipids vesicles composed of lipid bilayers enclosing one or more aqueous compartments in which drugs and other substances are included. They have been investigated as a vehicle for sustained-release formulations 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 system has various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values. They have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has been
attributed to increase nasal retention of peptides, provides protection to the entrapped peptides from enzymatic degradation and mucosal membrane disruption. Insulin incorporated in liposomes coated with chitosan and carbopol, when administered them intranasally to rats. The results demonstrated that this formulation was effective and that its mucoadhesive property is a good option for a sustained release of insulin [14, 16, 17].

6.2. Nanoparticles
Nanoparticles are solid colloidal particles with diameter ranging from 1-1000 nm. They consist of macromolecular materials which are therapeutically active and can also be used as adjuvant in vaccines in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles offer several advantages due to their small size. However only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and also in a limited quantity. Since the tight junctions are in the order of 3.9-8.4 Å [38].

Advantages of Nanoparticles

✓ Preferably used as a vehicle for sustained release formulations.
✓ Sustained release from a therapeutic aerosol can prolong the residence of an administered drug
✓ Minimize the risk of adverse effects
✓ Decreasing its systemic absorption
✓ Reduces dosing frequency.
✓ Increased patient compliance
✓ Suitable for the delivery of nasal vaccines [15, 18].

6.3. Microspheres
Recently Microsphere technology has been widely useful in designing of formulations for nasal drug delivery. Microspheres are usually based on muco-adhesive polymers (xanthan gum, Carbopol, polyacrylates, cellulose derivatives etc.,), which provide various advantages for intranasal drug delivery. Nasal/ Pulmonary microspheres also protect the drug from enzymatic metabolism which occurs due to harsh environment in GIT and gives sustain drug release, thereby prolonging its effect. Aminated gelatin microspheres as a nasal drug delivery system for insulin has been investigated by Wang et al., They observed a considerable hypoglycaemic effect when administered intra-nasally in dry powder form to rats. But there is
no significant effect when given in a suspension. Gavine et al. have analyzed nasal mucosa after its exposure to microspheres of alginate/chitosan containing metoclopramide. They observed the opening of tight junctions in the epithelium and also observed that these spray-dried microspheres have promising properties as mucoadhesive nasal carriers. Many other similar studies have been carried out and positive results are found for nasal delivery of carbamazepine using chitosan microspheres, cyclodextrins using chitosan and alginate as mucoadhesive polymers, Gentamycin using HPMC and carvedilol using alginate mucoadhesive microspheres [15].

6.4 Micelles
A successful drug carrier system needs to demonstrate optimal drug loading and release properties, long shelf-life and low toxicity. Micelle contains drugs entrapped in the core and transported at concentrations even greater than their intrinsic water solubility. A hydrophilic shell can form around the micelle, effectively protecting the contents. In addition, the outer chemistry of the shell may prevent recognition by the reticulo endothelial system, and therefore early elimination from the bloodstream. Colloidal systems, such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticles dispersions consisting of small particles of 10–400 nm diameter showed as great promising carriers in pulmonary drug delivery systems. A feature that makes micelles more attractive is that their size and shape can be changed. Chemical techniques using cross linking molecules can improve the stability of the micelles and their temporal control. Micelles may also be chemically altered to selectively target a broad range of disease sites [37].

6.5. Mucoadhesive drug delivery systems
It is one of the most important limiting factors for nasal drug delivery, because it reduces the time allowed for drug absorption. Thus, mucoadhesive drug delivery systems improving the nasal drug absorption, and also prolonging the contact time between drug and nasal mucosa. Mucoadhesion as a strategy improves systemic drug delivery via the nasal route. Mucoadhesion indicates the attachment of the drug delivery system to the mucus, involving an interaction between mucin and a synthetic or natural polymer called mucoadhesive. The sequential events that occur in mucoadhesion include.

- Firstly the mucoadhesive system absorbs water from mucus layer and get wet and swells.
Secondly, the polymer intimately penetrates into the mucus and localizes the formulation in nasal cavity, enhancing the drug concentration gradient across the epithelium. Mucoadhesives are mostly used in intranasal drug delivery are hydrogels, hydrophilic polymers, polyacrylates, starch, chitosan, alginate and cellulose derivatives [15].

7. RECENT TECHNOLOGIES OF PULMONARY DRUG DELIVERY. [19]

![Inhaler for pulmonary drug delivery](image)

**Fig No. 3: Inhaler for pulmonary drug delivery**

7.1. Nebulizer [41, 42]

Nebulizers are being widely used by many physicians for the treatment of acute asthma in an emergency care unit or for treating patients with severe asthma at home. There are two types of nebulizers jet nebulizer and ultrasonic nebulizer. In jet nebulizers, aerosol is prepared by high velocity air stream from a pressurized source directed against a thin layer of liquid solution. Ultrasonic nebulizers include the vibration of a piezoelectric crystal aerosolizing the solution. These nebulizers can transport more drug to the lungs than MDI or DPI.

**Disadvantages**

- Lack of possibility,
- Higher costs of drug delivery,
- Larger need for assistance from healthcare professionals,
- Higher drug doses to achieve a therapeutic result.
7.2. Metered Dose Inhaler (MDI)[39,40]
These are the most common device used for administration of aerosolized drugs. In this, the medication is mixed in a canister with a propellant, and the preformed mixture is expelled in exact measured amounts upon actuation of the device. Patients should learn correct use of MDIs how to organize exhalation and inhalation with actuation of the device. By using the spacer device it may solve the problem moderately. In the beginning 1990, attempts were made to reformulate MDIs due to mandatory ban on the use of propellant chlorofluorocarbons (CFCs), which have been concerned as the cause of depletion of the Earth’s ozone layer. Optional propellants, such as hydrofluoroalkane 134a (HFA-134), have be extensively investigated for their potentials to change CFCs.

7.3. Dry Powder Inhaler (DPI)
Dry powder systems use a single drug or its blends with a suitable carrier, mainly as lactose for delivery to the lungs. The three main factors in this system include Drug, Carrier, and device. Delivery of medication with a DPI requires minimum patient coordination and
The collaboration of breathing following the actuation of the device. DPIs are small, portable devices that can be easily carried in a purse or pouch. Use of spacers is not required in this system likewise in MDI’s. In addition, DPIs are devoid of environmentally injurious like CFC propellants, which are necessary in MDI formulation. In the view of the mandatory ban of CFCs use in MDIs by the United Nations, DPIs have become significantly increased as a pulmonary drug delivery system over the precedent decade. The aerosol drug delivery has undergone dramatic changes in both inhaler device and formulation aspects. The inhaler devices are more attractive as dry powders. Dry powder showed the greater chemical stability than the liquids which are used in atomizers. On the other hand, formulation and production of dry powders for inhalation is difficult and challenging due to the potential physical instability of the powder.

Fig No. 6: Powder Inhaler (DPI)

8. CURRENT APPLICATIONS OF PULMONARY DRUG DELIVERY

8.1. Pulmonary drug delivery in Asthma and COPD [20]

Asthma is a chronic lung disease that is characterized by inflammation and narrowing of airways. Asthma causes recurring period of wheezing, chest tightness, shortness of breath, and coughing. Advances in treatment of asthma had done in drugs such levosalbutamol inhalers which show greater efficacy as compare to salbutamol. For the treatment of COPD, tiotropium inhalers are presently found in market.

8.2. Application of pulmonary delivery in patients on Ventilators

Baby masks are used to improve inhalation coordination of patient devices. This mask is attached to spacer for small tidal volumes and low inspiratory flow rates infant and young Childers. It can be used to give medication to children up to 2 years by using baby mask.
8.3. Pulmonary delivery in cystic fibrosis
Pulmonary delivery played an important role in the treatment of Cystic Fibrosis for decades. The main aim of formulating the aerosol system is to deliver drugs to infants and children. The following drugs are given by pulmonary route for management of cystic fibrosis.
- N-Acetylcysteine,
- Recombinant human deoxyribonuclease aerosol,
- Tobramycin- Spray dried Tobramycin powders containing Nanoparticles.

8.4. Use of pulmonary devices in diabetes
Deficiency of insulin secretion or resistance leads to Diabetes. The common therapy available now is twice-daily subcutaneous injections of insulin. This type of treatment is very painful and as a leads to non compliance by diabetic patients. Various companies are working on insulin inhalers than any other insulin injection. The newly developed Insulin inhalers would work similar to asthma inhalers. The products fall into two main groups the dry powder formulations and solution, which are delivered through different patented inhaler systems. E.g. Novel pMDI formulations for pulmonary delivery of proteins [21-26].

8.5. Role of pulmonary delivery in vaccination
There was moderate interest in aerosol vaccination 15–20 years ago. Progress towards application of pulmonary devices in vaccination has been modestly developed. Nearly 100 vaccines are approved in the U. S. About half of these prevent respiratory infections. Yet all are currently injected recently inhaled measles vaccine given by nebulizer [24].

8.6. In migraine
Ergotamine is drug of choice for migraine. Many years ago, ergotamine via metered dose inhaler was used successfully to treat migraine headache [27].

8.7. Recent use of pulmonary drug delivery intrans Plantation
Pulmonary route play a role very important role in transplantation. Acute and chronic rejections are major problems compromising transplant and patient survival. Aerosolized cyclosporine was found to be useful for reducing the risk of acute rejection [27].

8.8. Emphysema
Emphysema is a respiratory disorder that occurs due to deficiency of Alpha 1 antitrypsin uncontrolled neutrophil elastase deficiency. It leads to lung destruction and the formation of
emphysema. Recombinant AAT (rAAT) is given intravenously (IV) and it is very well accepted treatment. Early evaluation of aerosolized AAT reported adequate alveolar fluid AAT and penetration into the lung interstitum. Neutrophil elastic’s inhibitor, secretory leukocyte protease inhibitor, has also been considered for protection against elastase in CF and patients with AAT deficiency.

8.9. Angina pectoris
Angina pectoris is not a disease by itself but its symptoms of myocardial ischemia arises as a result of imbalance between oxygen supply and demand of myocardium. Nitroglycerine is the drug of choice for angina pectoris. It is given generally by sublingual route. Isosorbide aerosol has also been reported useful in hypertensive crisis. In United States inhalation therapy for angina-pectoris is very well accepted [27, 43].

8.10. In Pulmonary arterial hypertension
This use of pulmonary route has been approved by FDA. Ventavis (iloprost), an inhaled for treatment of pulmonary arterial hypertension. In pulmonary arterial hypertension, severe restriction of blood vessels results in early death [28].

8.11. As a surfactant aerosol
Surfactant plays important role in respiratory distress of premature infants and neonatal. There continues to be great appeal for the use of surfactant in adults because of the apparent success in neonates. But its use should be limited until well controlled trials document clinically meaningful efficacy.

8.12. In acute lung injury
Major complication of acute lung injury is Hypoxemia and it is often difficult to manage. Drug given by pulmonary route plays very important role in acute lung injury. Smooth muscle relaxants such as nitric oxide and Mediators like prostacyclin can improve oxygenation by increasing blood flow through ventilated areas. Prostaglandin E by continuous aerosol through ventilator has also been shown to improve oxygenation.

8.13. Use of pulmonary route for Gene therapy
Gene therapy is given by pulmonary route in the treatment of cystic fibrosis. There are many problems to be overcome before clinical applications are practical. Some of these are safety,
successful transfer of sufficient genetic material to appropriate tissue, adequate gene expression, maintenance of expression over time, and efficacy of expression.

Lung cancer is the leading cause of cancer deaths globally. Inhaled chemotherapy seems to be a logical approach to treat lung cancer. Aerosol delivery of the anticancer agents like difluoro methyl ornithine and 5-fluorouracil reduced lung tumors in mice up to 50% and 60%, respectively. Interleukin-2 stimulates immune function in cancer patients, but injections cause fever, malaise, and local swelling [29].

8.15. Delivery of pentamidine by pulmonary route [30]
Pneumonia is mainly caused due to Protozoan Pneumocystis carinii (PCP) in Patients with acquired immunodeficiency syndrome. Aerosol pentamidine is not only useful in treating mild PCP and, but also for prophylaxis against PCP.

8.16. Delivery of Gentamycin by pulmonary route:
Gentamycin is given by pulmonary route for chronic Pseudomonas aeruginosa (PA) infections in CF. It was observed that daily inhalations of Gentamycin delays the acquisition of chronic PA infections and decreases disease progression in children. Zanamivir, made by GSK, was the first inhaled anti-viral medication approved by the FDA in 1999. For treatment of flue, dose of dry powder inhalers is twice daily for 5 days [30].

8.17. Nicotine aerosol for smoking cessation
Smoking is injurious to health. It is very difficult to control such habit. From ancient times people smokes cigarette and get addicted with smoking. Primary reason for cigarette smoking is Nicotine addiction, and nicotine replacement is appealing as a means of reducing cigarette use to achieve cessation.

8.18. Delivery of Amphotericin by pulmonary route [31]:
Amphotericin aerosol has been successfully used to treat various infections. Such use should not become clinical practice without good randomized controlled trials. Ribavirin aerosol has also been used for treatment or prophylaxis for bone marrow transplantation but controlled trials are needed to better clarify efficacy.
8.19. Diagnostic application pulmonary drug delivery [32]
Pulmonary drug delivery is not only used for therapeutic purpose but also for diagnostic purpose. For example, inhalation of aerosols of methacholine and histamine is responsiveness in asthma.

8.20. Inhaled drug delivery for tuberculosis therapy [33]
Tuberculosis is most infectious diseases caused by Mycobacterium tuberculosis. Administration of drugs through pulmonary route to the lung allows higher drug concentrations in the vicinity of these lesions. Supplementing conventional therapy with inhaled antiTB therapy may allow therapeutic concentrations of drug to penetrate effectively into lung lesions and to treat the resident mycobacterium.

8.21. Pulmonary delivery of lower molecular weight Heparin [34]
Low molecular weight heparins (LMWH) are better alternative to unfractionated heparin because of improved pharmacokinetic profiles and reduced cost of therapy in the treatment of deep vein thrombosis and pulmonary embolism. Low molecular weight heparins are given by subcutaneous and intravenous routes. Administration of an anticoagulant drug directly to the pulmonary circulation would be ideal for the treatment of pulmonary embolism. A formulation of LMWH will allow direct administration of the drug into the lungs. In addition this formulation is likely to reduce the mortality from an attack of pulmonary embolism. This pulmonary therapy is non-invasive.

8.22. Use of pulmonary delivery for bone disorders [35]
Pulmonary delivery used to treat disease such as osteoporosis and Paget’s disease of bones can. The predicted increase in the number of patients with osteoporosis and the lack of ideal therapies dictates the need for better treatments. Clinical evidences proved that other peptides and proteins indicate that pulmonary delivery is safe, efficient, well tolerated. In addition it is preferred by patients so pulmonary route is better option to treat bone disorders.

8.23. Delivery of opioids as pain therapeutics [36]
Pulmonary opioid delivery is better alternative to avoid pain associated with injectable pain killers. Clinical studies involving inhaled opioids were focused on treatment of dyspnoea and non pain management. But they showed that inhalation of various opioid compounds is safe, even in severely ill patients. By the use of specialized and efficient pulmonary drug delivery
devices, facilitated the evaluation of inhaled opioids, such as morphine and fentanyl, for management of severe pain associated with surgery or malignant disease. Studies are going on to introduce new molecules for management of pain trough pulmonary route. Studies with efficient pulmonary delivery systems, designed for systemic drug applications, conclusively show that inhaled opioids are rapidly, completely and reproducibly absorbed into the bloodstream. Thus, the pulmonary route has excellent potential for treating noninvasively severe pain in the postoperative setting and in malignant disease.

CONCLUSION
As discussed in this review, the pulmonary drug delivery is one of the mostly popular areas in today's applied pharmaceutical research and development. A wide variety of Controlled release formulations have been administered to the lung by oral inhalation for the treatment of various disease states. Pulmonary drug delivery would be the promising step rather than the traditional drug delivery systems. As more efficient pulmonary drug delivery devices and sophisticated formulations are available. Physicians and health professions will have a choice of using a wide variety of devices and formulation combinations that will target specific cells or regions of the lung, avoid the lung's clearance mechanisms and retains drug within the lung for longer periods. Pulmonary drug delivery can minimize systemic side effects, provide rapid response and minimize the required dose in the treatment of obstructive respiratory diseases. Several techniques have been developed to improve the Quality of pulmonary drug delivery system without affecting their integrity. Because of advancement in applications of pulmonary drug delivery it is useful to treat multiple diseases. So pulmonary drug delivery is the best route for administration as compared to the other routes. The efficiency of drug dosing into the lungs has been improved by the elimination of holdup in new devices, particles designed to penetrate into the deep lung and device configurations. From the review, we conclude that the approaches and devices in pulmonary drug delivery system are most prominent when compared to other drug delivery system.

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