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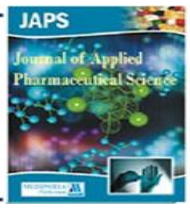


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# Pulmonary Drug Delivery: A Promising Approach

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**ABSTRACT**

Pulmonary drug delivery has attracted tremendous scientific and biomedical interest in recent years and has progressed considerably within the context of local treatment for lung diseases, by virtue of enhanced local targeting and reduced systemic side effects with the administration of minute drug dosages. Furthermore, with the high surface area and permeability of the lung, the 21st century has seen a paradigm shift to inhaled therapy for systemic use. But the pulmonary tract tends to be considered as very promising and attractive route for the administration of active substances intended to treat local pulmonary e.g., asthma, chronic obstructive pulmonary disease (COPD), microbial infections) as well as systemic diseases. (e.g., diabetes) Recent progress within biotechnology has generated a group of novel protein and peptide drugs to which administration to the respiratory tract, to obtain systemic delivery seems advantageous compared to e.g. parenteral or gastrointestinal administration (tablets, capsules etc.). The low metabolic activity in the lungs allows systemic delivery without liver passage Hence lung is an attractive environment for biomolecules, which are highly susceptible to enzymatic degradation in the gastrointestinal tract (ventricle and guts) as well as hepatic degradation (first pass metabolism).

**Keywords:** Pulmonary drug delivery, Dry powder for inhalation, Asthma, Chronic obstructive pulmonary disease.

## INTRODUCTION

Pulmonary drug delivery has attracted tremendous scientific and biomedical interest in recent years and has progressed considerably within the context of local treatment for lung diseases, by virtue of enhanced local targeting and reduced systemic side effects with the administration of minute drug dosages. Furthermore, with the high surface area and permeability of the lung, the 21st century has seen a paradigm shift to inhaled therapy for systemic use (Young *et al*., 2008). The inhalation delivery of therapeutic agents has been known, though poorly understood, for many years. But the pulmonary tract tends to be considered as very promising and attractive route for the administration of active substances intended to treat local pulmonary (e.g., asthma, chronic obstructive pulmonary disease (COPD), microbial infections) as well as systemic diseases (e.g., diabetes) (Jaspart *et al*., 2007). A wide variety of agents has been administered to the lung via oral inhalation, for the treatment of diverse disease states. The most frequent use of inhalation therapy is for the treatment of obstructive airway diseases using drugs such as short and long-acting β sympathomimetics, corticosteroids, and anticholinergic agents. However, the respiratory route has been receiving increased attention since the early 1990s as an alternative to parenteral drug delivery, most notably for the delivery of inhaled insulin (Hickey *et al*., 2004) and also for peptide and protein therapeutics.

## ASTHMA

Worldwide, more than 300 million people suffer from asthma or Chronic obstructive pulmonary disorder (COPD). Asthma is one of the most common chronic diseases worldwide and affects 22 million persons in the United States (Asthma Focus, 2005). Asthma is the most common chronic disease in childhood, affecting an estimated 6 million children, and it is a common cause of hospitalization for children in the United States (Asthma Focus, 2005).

## PULMONARY DRUG DELIVERY

The human lung consists of 5 lobules and 10 bronchopulmonary segments. Arranged adjacent to each segment are lung lobules composed of 3–5 terminal bronchioles. Each bronchiole supplies the smallest structural unit of the lung, the acinus, which consists of alveolar ducts, alveolar sacs, and alveoli. Alveolar epithelial type I cells represent the principle cell type lining the surface of the alveoli. The major functions of these cells, which cover 93% of the alveolar space, are to provide a surface for gas exchange and to serve as a permeability barrier. Alveolar epithelial type II cells have a much smaller surface area per cell and they represent 16% of the total cells in the lung. They play a basic role in synthesis, secretion and recycling of surface-active material (lung surfactant).

The alveolar blood barrier in its simplest form consist a single epithelial cell, a basement membrane, and a single endothelial cell. While this morphologic arrangement readily facilitates the exchange, it can still represent a major barrier to large molecules. Before entering the systemic circulation, solutes must traverse a thin layer of fluid, the epithelial lining fluid. This layer tends to collect at the corners of the alveoli and is covered by an attenuated layer of surfactant. Unlike the larger airways, the alveolar region is lined with a surface active layer consisting of phospholipids (mainly phosphatidylcholine and phosphatidylglycerol) and several key apoproteins. The surfactant lining fluid plays an important role in maintaining alveolar fluid homeostasis and permeability, and participates in various defense mechanisms. Recent studies suggest that the surfactant may slow down diffusion out of the alveoli. The respiratory airways, from the upper airways to the terminal bronchioles, are lined with a viscoelastic, gel-like mucus layer 0.5–5.0 mm thick. The secretion lining consists of two layers: a fluid layer of low viscosity, which surrounds the cilia (periciliary fluid layer), and a more viscous layer on top, the mucus. The mucus is a protective layer that consists of a complex mixture of glycoprotein's released primarily by the goblet cells and local glands. The mucus blanket removes inhaled particles from the airways by entrapment and mucociliary transport at a rate that depends on viscosity and elasticity. The lung tissue is highly vascularized, which makes pulmonary targeting difficult because of fast absorption of most drugs (especially lipophilic and low molecular weight drugs) (Manca, 2009).

Small molecules such as β2 agonists e.g. Salbutamol (Ventolin®), Terbutaline (Bricanyl®), Salmeterol (Serverent®), Formeterol Oxis®), and glucocorticoids e.g. Budesonide (Pulmicort®) and Fluticasone (Flutide®), for local administration in the lungs, are all part of successful treatment of respiratory disease such as asthma, rhinitis and chronic obstructive pulmonary disease (COPD).

However, recent progress within biotechnology has generated a group of novel protein and peptide drugs to which administration to the respiratory tract, to obtain systemic delivery seems advantageous compared to e.g. parenteral or gastrointestinal administration (tablets, capsules etc.). For example, the low metabolic activity in the lungs allows systemic delivery without liver passage Hence lung is an attractive environment for biomolecules, which are highly susceptible to enzymatic degradation in the gastrointestinal tract (ventricle and guts) as well as hepatic degradation (first pass metabolism). However, respiratory system in itself restricts the entrance of particulate matter by various means: e.g. geometry of the airways and clearance mechanisms of the lungs. Consequently inhalation particles have to be aerodynamically optimized to reach absorption sites in the alveolar epithelium (Elversson, 2005).

Studies on the delivery of drugs to or via the respiratory tract have been carried out in the recent 25 years. This route can offer considerable advantages and disadvantages over other drug administration ways as listed below,

### Advantages

- Provides local action within the respiratory tract
- Provides rapid drug action
- Provides reduced dose
- Allows for a reduction in systemic side-effects It can be employed as an alternative route to drug interaction when two or more medications are used concurrently
- Reduces extracellular enzyme levels compared to GI tract due to the large alveolar surface area
- Reduces evasion of first pass hepatic metabolism by absorbed drug
- Offers the potential for pulmonary administration of systemically active materials

### Disadvantages

The duration of activity is often short-lived due to the rapid removal of drug from the lungs or due to drug metabolism.

- Necessitates frequent dosing (Ozer, 2007).

### Uptake of inhaled drug after inhalation therapy

There are several advantages in delivering drugs, to the lungs including a non invasive method of delivery; the surface area of the lung is between 80 m2 and 140 m2, which is about half the area of a tennis court. In addition, in most pulmonary regions, the thickness of the alveolar epithelium is only between 0.1 μm and 0.2 μm. The total distance between epithelial surface and blood in the alveolar area is between 0.5 μm and 1.0 μm which are much less than in the bronchial system (distance between mucus surface and blood: 30 μm–40 μm). Thus, it appears that pharmaceuticals after deep inhalation and deposition in the peripheral (i.e. alveolar)

region of the lung can be rapidly absorbed. Pulmonary delivery therefore has the advantage, compared to nasal delivery, that it is possible to obtain a sufficiently high absorption without the need of enhancers (WO/2003/086516). Another advantage is that these drugs are not subject of a hepatic first pass effect after their absorption as shown in figure 2.

On the other hand, the human lung has different defense mechanisms to prevent aerosol particles penetrating into the deep lung. Primarily, the oropharyngeal region and the bronchial tree are excellent filters to eliminate aerosol particles from the inhaled air and particles deposited on ciliated epithelium are subject to mucociliary transport to the gastrointestinal tract.

Therefore, to deliver a drug into the deep lung, one has to surmount these filters. However, even after deposition in the alveolar region of the lung, a number of mechanisms inhibit the absorption of inhaled pharmaceuticals. There are a number of absorption barriers (i.e. mucus layer, alveolar lining fluid layer, macrophages and other cells, alveolar epithelium and basement membrane) which act to varying extents by inhibiting drug permeation into the circulation, there exists competing cellular uptake pathways (e.g. particle phagocytosis by macrophages), and of course proteolytic degradation can limit the amount of intact drug available for absorption. The function of these barriers can be impaired by very different substances and consequently the absorption of drugs can be increased, for example, by the use of absorbance enhancers (e.g. cyclodextrins, detergents and bile acids). Furthermore, proteolytic degradation can be inhibited by protease inhibitors (e.g. nafamostat mesilate and aprotinin) and phagocytosis by macrophages reduced by packaging of substances into porous particles. In principle, absorption kinetics of inhaled substances depend on their molecular weight (small molecules are more rapidly absorbed than larger ones), pH-value, electrical charge, solubility and stability of the inhaled substance.

The other target regions within the lung for inhalable drugs are the large and small bronchial airways. Different pulmonary diseases are located in these parts of the respiratory tract. The most relevant are: asthma, chronic obstructive pulmonary disease (COPD) and bronchial tumors. To treat these diseases locally, one has to deliver the drugs specifically to this region. However, a minor proportion of drugs can also be absorbed into systemic circulation after such a tracheobronchial deposition. In contrast to the inhalation of drugs for systemic treatment, the inhalative therapy of asthma and COPD by means of nebulizers and metered dose inhalers (MDI) has been clinically established for many years and the treatments involve generally low molecular weight molecules in formulations free of stabilizers and absorption enhancers (Scheuch *et al*., 2006).

**Parameters determining particle deposition in deep lung**

Different biophysical parameters determine regional drug deposition in the human lungs:

- Aerodynamic particle behaviour (e.g. size, density, hygroscopicity, shape, electrical charge).
- Breathing pattern of the patients (e.g. flow rate, ventilation volume, end-inspiratory breath holding).
- Time of aerosol pulse injection into the breathing cycle.
- Anatomy of the respiratory tract.

Of these factors, aerosol particle size and size distribution are the most influential on aerosol deposition. The aerodynamic particle diameter (AD) is the diameter of a sphere with a density of 1 g/cm3 that has the same aerodynamic behaviour as the particle which shall be characterized. In that way, aerosol particles with different density and shape can be characterized depending on their aerodynamic properties (Scheuch *et al.*, 2006).

**Aerodynamic particle behavior**

The size of the particles is a critical factor affecting the site of their deposition, since it determines operating mechanisms and extent of penetration into the lungs. Aerosol size is often expressed in terms of aerodynamic diameter (AD). The aerodynamic diameter is defined as the equivalent diameter of a spherical particle of unit density having the same settling velocity from an air stream as the particle in question. Thus, particles that have higher than unit density will have actual diameters smaller than their AD. Conversely, particles with smaller than unit density will have geometric diameters larger than their AD. Aerosol size distributions may be characterized as practically monodisperse (uniform sizes) or polydisperse (non-uniform sizes).

The upper airways (nose, mouth, larynx, and pharynx) and the branching anatomy of the tracheobronchial tree act as a series of filters for inhaled particles. Thus, aerosol particles bigger than 100 μm generally do not enter the respiratory tract and are trapped in the naso/oropharynx. The particles must be very fine, for example having a aerodynamic diameter of less than 10 μm. Particles having aerodynamic diameters greater than 10 μm are likely to impact the walls of the throat and generally do not reach the lung. Particles having aerodynamic diameters in the range of 5 μm to 0.5 μm will generally be deposited in the respiratory bronchioles whereas smaller particles having aerodynamic diameters in the range of 2 to 0.05 μm are likely to be deposited in the alveoli (Manca, 2009). Particles in the ambient air are transported by different physical mechanisms. The relevant mechanisms for therapeutic aerosols are diffusion by Brownian motion (particles in the size range of <0.5 μm), sedimentation by the gravitational force (particles in the size range of >0.5 μm) and impaction (size range >3 μm).

**Mechanism of drug deposition:**

The mechanisms by which particles deposit in the respiratory tract includes *impaction* (inertial deposition), *sedimentation* (gravitational deposition), *Brownian diffusion*, *interception*, and *electrostatic precipitation*. The relative contribution of each depends on the characteristics of the inhaled particles, as well as on breathing patterns and respiratory tract anatomy. All mechanisms act simultaneously, but the first two mechanisms are most important for large-particle deposition within the airways (1 mm, AD, 10 mm). *Diffusion*, however, is the main determinant of deposition of smaller particles in peripheral regions of the lung. *Impaction* occurs when a particle's momentum prevents it from changing course in an area where there is a change

in the direction of bulk air flow. It is the main deposition mechanism in the upper airways, and at or near bronchial branching points. The probability of *impaction* increases with increasing air velocity, breathing frequency, and particle size. *Sedimentation* results when the gravitational force acting on a particle overcomes the total force of the air resistance. Inspired particles will then fall out of the air stream at a constant rate. This is an important mechanism in small airways having low air velocity. The probability of *sedimentation* is proportional to residence time in the airway and to particle size, and decreases with increasing breathing rate.

*Diffusion* occurs when the collision of gas molecules with small aerosol particles exerts discrete non-uniform pressures at the particles' surfaces, resulting in random *Brownian motion*. The effectiveness of *Brownian motion* in depositing particles is inversely proportional to particle diameters of those particles, 0.5 μm, and is important in bronchioles, alveoli, and at bronchial airway bifurcations. Molecule-size particles may deposit by *diffusion* in the upper respiratory tract, trachea, and larger bronchi (Manca, 2009).

**Respiratory patterns**

The pattern of respiration during aerosol exposure influences regional deposition, since breathing volume and frequency determine the mean flow rates in each region of the respiratory tract, which, in turn, influence the effectiveness of each deposition mechanism. Turbulence tends to enhance particle deposition, the degree of potentiating depending on the particle size. Rapid breathing is often associated with increased deposition of larger particles in the upper respiratory tract, while slow, steady inhalation increases the number of particles that penetrate to the peripheral parts of the lungs slow breathing, with or without breath-holding, showed a broad maximum deposition in the ciliated airways (tracheobronchial region). The pulmonary maximum occurred between 1.5 μm and 2.5 μm with breath-holding and between 2.5 μm and 4μm without breath-holding. Rapid inhalation showed similar trends: the tracheo-bronchial region maximum falls and shifts to between 3 μm and 6 μm. Pulmonary deposition sharpens and occurs between 1.5 μm and 2 μm with breath-holding, and between 2 μm and 3 μm without breath-holding. When the above considerations are taken into account, the ideal scenario for aerosol would be (Manca, 2009):

- Aerosol AD smaller than 5 μm, to minimize oropharyngeal deposition
- Slow, steady inhalation and
- A period of breath-holding on completion of inhalation.

**Pulmonary clearance**

The primary function of the pulmonary defensive response to inhaled particles is to keep the respiratory surfaces of the alveoli clean and available for respiration. The elimination of particles deposited in the lower respiratory tract serves an important defense mechanism to prevent potentially adverse interactions of aerosols with lung cells. Insoluble particulates are cleared by several pathways, which are only partially understood. These pathways are known to be impaired in certain diseases and are thought to depend on the nature of the administered material. Swallowing, expectoration, and coughing constitute the first sequence of clearance mechanisms operating in the naso/oropharynx and tracheobronchial tree.

A major clearance mechanism for inhaled particulate matter deposited in the conducting airways is the mucociliary escalator, whereas uptake by alveolar macrophage predominates in the alveolar region. In addition to these pathways, 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 consequences, causing lung diseases from the toxic effects of inhaled compounds. It is now well recognized that the lungs are a site for the uptake, accumulation, and/or metabolism of numerous endogenous or exogenous compounds. All metabolizing enzymes found in the liver are also found in the lung, although in smaller amounts. The rate at which a drug is cleared and absorbed from the respiratory tract depends on the dynamic interaction of several factors, predominantly (Manca, 2009):

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

**Mucociliary clearance**

Mucociliary clearance 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. Beating of the cilia, together with mucus secreted by the goblet cells, contributes to an efficient clearance mechanism. 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. Thus, the mucociliary escalator can be impaired by altering the volume of mucus secretion, the mucus viscosity and elasticity, or the ciliary beat frequency. Mucociliary clearance is known to be impaired in smokers, in patients with chronic bronchitis, and in acute asthmatics. Certain diseases have the opposite effect that of enhancing clearance rates (Manca, 2009).

The controlled release of drugs for pulmonary delivery is a research field which has been so far rather unexploited but is currently becoming increasingly attractive. The development of controlled release formulations for inhalable drugs has been widely investigated since several years. However, up to now, sustained release formulations for pulmonary delivery have not been marketed yet in spite of the increasing interest in this research

(Jaspart *et al.*, 2007). There are many advantages to developing sustained release formulations for pulmonary drug delivery, including reduced dosing frequency, improved patient compliance and reduction in side effects (Seville *et al.*, 2008). The reduction of the dosing frequency is of great concern for a number of pulmonary disorders including asthma and chronic obstructive pulmonary disease (COPD). In particular, long acting β2-adrenergic receptor agonists with glucocorticoids used for the relief of asthma- and COPD-related bronchospasm have a plasma half life that constrain the patient to an administration of the drug every 5.5 hours. A controlled release formulation leading to a prolonged duration of action of more than 8 hours would prevent nocturnal exacerbation in bronchial asthma. Controlled release formulations are widely used in oral or parenteral formulations but have not been established for pulmonary applications.

Current research approaches include the use of liposomes, micro- and nanosuspensions and dry powder formulations. In this purpose the liposomes have been the most extensively investigated carriers. They can be prepared with lung endogenous phospholipids as surfactants, with a wide range of size and are able to incorporate both hydro and lipophilic drugs. Liposomes proved to be able to impart a sustained release profile to the incorporated substances but they also present some disadvantages, i.e., a high production cost, a relative instability during storage and nebulisation that can lead to their disruption and to the premature loss of entrapped substances. Therefore liposomal dry powder formulations are currently getting more attractive **(**Seville *et al.*, 2008).

Polymeric microspheres have also been successfully tested in vitro as well as in vivo as sustained release drug delivery system. They are more physicochemical stable than liposomes, both in vitro and in vivo, allowing thus a slower release of encapsulated drugs. Their main disadvantage is that their safety still remains uncertain. It was showed that pulmonary administration of PLA microspheres to rabbits led to histological damages assessed in terms of pulmonary haemorrhage, eosinophilia and neutrophil infiltration. Inflammation can, however, be avoided using large porous particles. To date, the commercial use of such products is thus difficult. For similar reasons it is also difficult to aerosolize a particle suspension in a way to ensure a constant delivered dose to the lung. Therefore, dry powder formulations have attracted attention.

The formulation typically contains structural components of the particle as well as agents allowing the release of the drug over an extended period of time. These include lipids, proteins, sugars or synthetic polymers such as poly (vinyl alcohol) or polyesters. In particular, PLGA has been widely used, as it is considered biodegradable and weakly toxic (Jaspart *et al.*, 2007). Spray-drying technology also offers the potential to incorporate a range of excipients into the formulation. In addition, spray-dried powders that exhibit sustained drug release properties may be generated through the inclusion of drug release modifiers such as hydroxypropyl methylcellulose (HPMC), glyceryl behenate and polylactic acid, chitosan, etc. Leucine-HPMC is the promising excipient combination that can be employed in a wide range of applications, including sustained release preparations. Indeed, this combination has received considerable attention for the formulation of spray-dried powders for pulmonary drug delivery (Pilcer *et al*., 2010).

## CONCLUSION

A wide variety of agents has been administered to the lung via oral inhalation, for the treatment of diverse disease states. Controlled release formulations are widely used in oral or parenteral formulations but have not been established for pulmonary applications, which would be the promising step towards the pulmonary drug delivery instead of traditional drug delivery systems. Also, it would be an alternative to parenteral drug delivery, most notably for the delivery of inhaled insulin and also for peptide and protein therapeutics. Such drug delivery system will also provide bypass way for hepatic first pass metabolism of many potent drugs and reduce drug induced toxicity or adverse drug reactions. Thus, it concludes that further research is necessary for pulmonary drug delivery in the treatment of life threatening disorders; as most promising, advanced and attractive economic drug delivery system.

## REFERENCES

Young P, Salama R, Traini D, Chan H., Preparation and characterization of controlled release co-spray dried drug–polymer microparticles for inhalation 2: Evaluation of in vitro release profiling methodologies for controlled release respiratory aerosols, Eur. J. Pharm. Biopharm. 2008; 70, 145-152.

Dalby R, Suman J., Inhalation therapy: technological milestones in asthma treatment, Adv. Drug Deliv. Rev. 2003; 55, 779-791.

Jaspart S, Bertholet P, Piel G, Dogne J, Delattre L, Evrard B, Solid lipid microparticles as a sustained release system for pulmonary drug delivery, Eur. J. Pharm. Biopharm. 2007; 65, 47-56.

Hickey A, Thompson D., Pharmaceutical Inhalation Aerosol Technology, 2004; 2nd ed. USA: Marcel Dekker.

Management of Chronic FAMOUS ASTHMATICS Asthma - An Update, Asthma Focus. 2005; I (2), 1-8.

Joshi J, editorial consultant, Handbook on asthma management, 2004; CIPLA Ltd., Mumbai.

Tripathi KD, Essentials of Medical pharmacology, 2003; 5, 198-199.

Elversson J., Spray-dried powders for inhalation: particle formulation and formulation concepts (dissertation), Faculty of pharmacy: Uppsala University. 2005; 11-15.

Ozer A, Alternative applications for drug delivery: Nasal and pulmonary routes, Nanomaterials and Nanosystems for Biomedical Applications. 2007; 99-112.

Alagusundaram M., Deepthi N., Ramkanth S., Dry Powder Inhalers - An Overview, Int. J. Res. Pharm. Sci. 2010; 1(1), 34-42.

Scheuch G, Kohlhaeufl M, Brand P, Siekmeier R., Clinical perspectives on pulmonary systemic and macromolecular delivery, Adv. Drug Deliv. Rev. 2006; 58, 996-1008.

Seville P, Learoyd T, Burrows J, French E. Chitosan-based spray-dried respirable powders for sustained delivery of terbutaline sulfate, Eur. J. Pharm. Biopharm. 2008; 68, 224-234.

Pilcer G., Amighi K., Formulation strategy and use of excipients in pulmonary drug delivery. Int. J. Pharm. 2010; 392, 1-