

Research Article

APPROACHES AND DEVICES USED IN PULMONARY DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Targeting drug delivery into the lungs has become one of the most important aspects of systemic or local drug delivery. Consequently, in the last few years, techniques and new drug delivery devices intended to deliver drugs into the lungs have been widely developed. Currently, the main drug targeting regimens include direct application of a drug into the lungs, mostly by inhalation therapy using either pressurized metered dose inhalers (pMDI) or dry powder inhalers (DPI). Intratracheal administration is commonly used as a first approach in lung drug delivery in vivo. To convey a sufficient dose of drug to the lungs, suitable drug carriers are required. These can be solid, liquid, or gaseous excipients. Liposomes, nano and microparticles, cyclodextrins, microemulsions, micelles, suspensions, or solutions are all examples of this type of pharmaceutical carrier that have been successfully used to target drugs into lungs. The use of micro reservoir type systems offers clear advantages, such as high loading capacity and possibility of controlling size and permeability, and thus of controlling the release kinetics of the drugs from the carrier systems. These systems make it possible to use relatively small numbers of vector molecules to deliver substantial amounts of a drug to the target. This review discusses the approaches and devices required to be administer drug into the lungs.

Keywords: Targeting drug delivery, drug delivery devices, pressurized metered dose inhalers, Liposomes, microparticles.

INTRODUCTION

Drugs are generally delivered to the respiratory tract for the treatment or prophylaxis of airways disease, such as bronchial asthma and cystic fibrosis. The administration of a drug as its site of action can result in rapid onset of activity, which may be highly desirable, for instance when delivering bronchodilator drugs for the treatment of asthma. Additionally, smaller doses can be administered locally compared delivery by the oral or parenteral routes, thereby reducing the potential incidence of adverse systemic effects and reducing drug costs. The pulmonary route also useful where a drug is poorly absorbed orally, e.g. sodium cromoglicate, or where it is rapidly metabolized orally, e.g. isoprenaline. The avoidance of first pass metabolism in the liver may also be advantageous, although the lung itself has some metabolic capability.

The lung may be used as a route for delivering drugs having systemic activity, because of its large surface area, the abundance of capillaries and the thinness of the air-blood barrier. This has been exploited in the treatment of migraine with ergotamine, studies have demonstrated the potential for delivering proteins and peptides such as insulin and growth hormone via the airways.¹

Anatomy and Physiology of Human Respiratory Tract:

The respiratory system works with the circulatory system to deliver oxygen from the lungs to the cells and remove carbon dioxide, and return it to the lungs to be exhaled. The exchange of oxygen and carbon dioxide between the air, blood and body tissues is known as respiration. Healthy lungs take in about 1 pint of air about 12–15 times each minute. All of the blood in the body is passed through the lungs every minute. The respiratory tract is divided into two main parts: the upper respiratory tract, consisting of the nose, nasal cavity and the pharynx; and the lower respiratory tract consisting of the larynx, trachea, bronchi and the lungs (Figure 1). The trachea, which begins at the edge of the larynx, divides into two bronchi and continues into the lungs. The trachea allows air to pass from the larynx to the bronchi and then to the lungs. The bronchi divide into smaller bronchioles which branch in the lungs forming passageways for air. The terminal parts of the bronchi are the alveoli. The alveoli are the functional units of the lungs and they form the site of gaseous exchange.

The trachea or wind pipe is a continuation of larynx and extends down words to about the level of the 5th thoracic vertebra where it divides (bifurcates) at the carina into the right and left bronchi, one bronchus going to each lung. It is approximately 10-11cm long and lies mainly in the median plain in front of the esophagus. (Figure 2)

The bronchi are composed of same tissue as the trachea. They are lined with ciliated columnar epithelium. The bronchi progressively subdivide into bronchioles, terminal bronchioles, alveolar ducts and finally alveoli. Towards the distal end of the bronchi the cartilages become irregular in shape and are absent at bronchiolar level.

Alveoli are small and there are approximately 300 million of them in each lung. Although alveoli are tiny structures, they have a very large surface area in total (~100 m²) for performing efficient gas exchange. The blood barrier between the alveolar space and the pulmonary capillaries is very thin to allow for rapid gas exchange.²

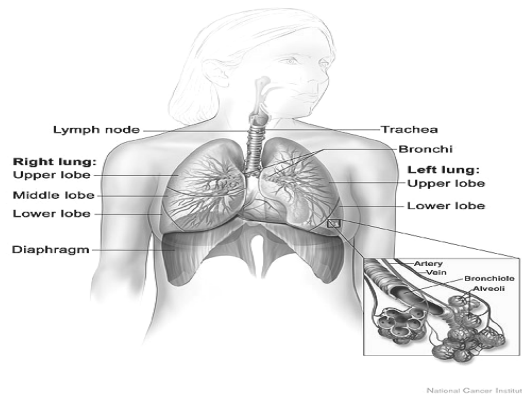


Figure 1: Human Respiratory System

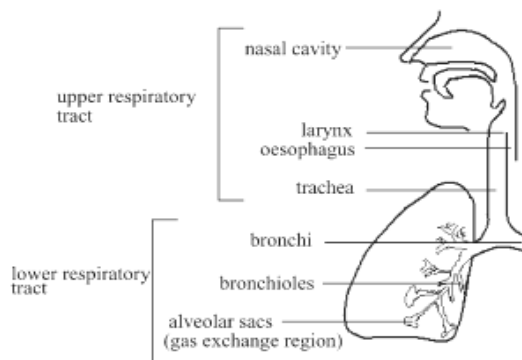


Figure 2: Schematic illustration of the human respiratory system shows the upper respiratory and lower respiratory tracts.

Bronchial blood circulation:

The supply to the walls of the bronchi and smaller air passages is through branches of the right and left bronchial arteries and the venous return is mainly through the bronchial veins. On the right side they empty into the azygos vein and on the left into the superior intercostals vein. The lung receives the entire cardiac output and thus is the best perfused organ in the body. However, only the alveolar region and respiratory bronchioles are supplied by the pulmonary circulation. Blood flow to the larger airways (trachea to terminal bronchioles) is via the systemic circulation and these airways receive approximately 1% of the cardiac output. The role of the bronchial circulation in distributing aerosolized drugs to regions distal from the original site of deposition or to nonventilated regions of the lung is unknown. The endobronchial circulation is recirculated to the peripheral airways and lung parenchyma via the bronchial veins and right atrium. Bronchial blood flow is augmented in diseases, such as bronchiectasis, from 1% to as much as 30% of cardiac output. In sheep, bronchial blood flow increased with antigen- and histamine-induced bronchoconstriction. Theoretically, inhaled drugs that are absorbed into the circulation from the tracheobronchial regions can be redistributed downstream and peripheral to airway obstructions, into otherwise poorly accessible areas of the lung which may aid in the drug's efficacy. Thus far, no experimental work in humans has been done to investigate the role of bronchial circulation in lung distribution of inhaled medications or its influence on their efficacy.³

The respiratory system is susceptible to a number of diseases, and the lungs are prone to a wide range of disorders caused by genetic factors, infection and pollutants in the air. The most common problems of the respiratory system are:

- Asthma
- Bronchiolitis
- Chronic obstructive pulmonary disease (COPD)
- Common cold
- Cough
- Cystic fibrosis (CF)
- Lung cancer
- Pneumonia
- Pulmonary hypertension
- Respiratory diseases of newborns.

Mechanism of Deposition of particles and their becoming into the lungs after inhalation:

Aerosols are suspensions of solid or liquid particles in a gas (usually air). The particulate portion of an aerosol is referred to as particulate matter (PM). Particulate matter is a generic term applied to chemically heterogeneous discrete liquid droplets or solid particles. The metric used for describing PM is the micron, or micrometer (10^{-6} meter). The PM in an aerosol can range in size 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 are larger than 2 microns in diameter
- Fine particles are between 0.1 and 2 microns in diameter
- Ultrafine particles are less than 0.1 micron

Most aerosol particles are poly disperse. They have a wide range of particle sizes that must be characterized by statistical measures. In some cases, such as with an ink jet printer, it is desirable to have a mono disperse aerosol with particles of equal size.

PRINCIPAL MECHANISMS OF RESPIRATORY DEPOSITION

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

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

Impaction-

Each time the airflow changes due to a bifurcation in the airways, the suspended particles tend to travel along their original path due to inertia and may impact on an airway surface. This mechanism is highly dependent on aerodynamic diameter, since the stopping distance for very small particles is quite low. Impaction occurs mostly in the case of larger particles that are very close to airway walls, near the first airway bifurcations. Therefore, deposition by impaction is greatest in the bronchial region. Impaction accounts for the majority of particle deposition on a mass basis.

Sedimentation-

Sedimentation is the 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. Hygroscopic particles may grow in size as they pass through the warm, humid air passages, thus increasing the probability of deposition by sedimentation.

Interception-

Interception occurs when a particle contacts an airway surface due to its physical size or shape. Unlike impaction, particles that are deposited by interception do not deviate from their air streamlines. Interception is most likely to occur in small airways or when the air streamline is close to an airway wall. Interception is most significant for fibers, which easily contact airway surfaces due to their length. Furthermore, fibers have small aerodynamic diameters relative to their size, so they can often reach the smallest airways.

Diffusion-

Diffusion is the primary mechanism of deposition for particles less than 0.5 microns in diameter and is governed by geometric rather than aerodynamic size. Diffusion is the net transport of particles from a region of high concentration to a region of lower concentration due to Brownian motion. Brownian motion is the random wiggling motion of a particle due to constant bombardment of air molecules. Diffusional deposition occurs mostly when the particles have just entered the nasopharynx, and is also most likely to occur in the smaller airways of the pulmonary (alveolar) region, where air flow is low.⁴⁻⁷

Absorption-

The pulmonary membrane is naturally permeable to small molecule drugs and to many therapeutic peptides and proteins. The epithelium of the lung, the significant barrier to absorption of inhaled drugs, is thick (50–60 μm) in the trachea, but diminishes in thickness to an extremely thin 0.2 μm in the alveoli. The change in cell types and morphology going from trachea, bronchi, and bronchioles to alveoli is very dramatic. The lungs are far more permeable to macromolecules than any other portal of entry into the body. Some of the most promising therapeutic agents are peptides and proteins, which could be inhaled instead of injected, thereby improving compliance. Particularly, peptides that have been chemically altered to inhibit peptidase enzymes exhibit very high bioavailabilities by the pulmonary route. Small molecules can exhibit prolonged absorption if they are highly soluble or highly cationic.

Although the rapid absorption of molecules has many conceivable medical uses, there are situations when one might want to slow the absorption of an inhaled small molecule, either to keep it acting longer locally in lung, or to regulate its absorption into the body. Very insoluble molecules that slowly dissolve from the inhaled particle may stick in the lung for many hours or even days. 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. Encapsulation in slow release particles such as nanoparticles and liposomes can also be used to control absorption.⁸⁻⁹

APPROACHES IN PULMONARY DRUG DELIVERY

Targeted drug delivery to the lungs has evolved to be one of the most widely investigated systemic or local drug delivery approaches. The use of drug delivery systems (DDS) for the treatment of pulmonary diseases is increasing because of their potential for localized topical therapy in the lungs. This route also makes it possible to deposit drugs more site-specific at high concentrations within the diseased lung thereby reducing the overall amount of drug given to patients (10–20 % of the per oral quantity), as well as increasing local drug activity while reducing systemic side effects and first-pass metabolism.

To further exploit the other advantages presented by the lungs, as well as to overcome some challenges encountered, scientists developed interests in particulate DDS for pulmonary administration. These systems can be broadly classified into immediate release [e. g. lactose-drug mixtures for dry powder inhaler (DPI) application] and controlled release systems (such as liposomes, micelles, nano- and microparticles based on polymers).

Particulate drug carriers such as liposomes, microparticles and nanoparticles can be / have been used to improve the therapeutic index of new or established drugs by modifying drug absorption, reducing metabolism, prolonging biological half-life or reducing toxicity. Drug distribution is then controlled primarily by properties of the carrier and no longer by physico-chemical characteristics of the drug substance only. A careful design of such DDS, based on a thorough understanding of the clinical requirements for the disease conditions to be treated, lung architecture / physiology, appropriate selection of the carrier materials, production process and device, are key to successful delivery using advanced DDS such as liposomes and microparticles.¹⁰⁻¹²

The biotechnology discoveries unleashed a wave of therapeutic proteins, also known as biomolecules, macromolecules, biotherapeutics, and biological. Most are administered via injection or intravenous methods to avoid degradation in the gastrointestinal tract. Patients, however, fear and avoid injections and IV treatments, which are painful, inconvenient, and expensive. Pulmonary delivery offers a patient-friendly, non-invasive alternative to injections and can also be a more efficient and effective way to deliver a drug and achieve patient compliance.

Microparticles:

The terminology “microparticle” (size comprised between 1 and 999 μm) includes the microspheres (uniform sphere constituted of a polymeric matrix) and the microcapsules. Biodegradable microspheres, designed from natural or synthetic polymers, have been largely used as drug targeting systems via different routes. Hydrophilic and lipophilic molecules can be encapsulated or incorporated into microspheres. Compared to liposomes, microspheres have an in vivo and in vitro more stable physicochemical behavior and should allow a slower release and a longer pharmacological activity of the encapsulated drugs. Biodegradable microspheres are prepared by using varied polymers: albumin, chitosan, polysaccharide, poly (lactico-co-glycolic) acid, poly (lactic) acid, poly (butylcyanoacrylate) and poly (lactico- lysine graft lysine).

Pulmonary administration of aerosolized microspheres allows a sustained and prolonged release of drugs for respiratory or non respiratory diseases, in this last case, the drug being protected against the enzymatic hydrolysis. Microspheres can be produced following different requirements such as the morphology, the size and the porosity by varying different technological parameters during their preparation. Microspheres are less hygroscopic and are then less liable to swell in the presence of moisture located into the lungs.¹³

Sustained release microparticles:

Up to now sustained release formulations for pulmonary delivery have still not been marketed inspite of the increasing interest in this research field. The control of the drug delivery in the respiratory tract may be achievable by employing suitable carriers, possessing appropriate drug release characteristics. In this purpose liposomes have been the most studied

carriers. They proved to be able to provide a sustained release to the incorporated active substances but they present some disadvantages, i.e a high production cost a relative instability during storage and during nebulisation that can lead to disruption and loss of entrapped substance. Polymeric microspheres have also been successfully tested as sustained release drug delivery system but their safety still remains uncertain. That is the reason why we decided to focus on Solid Lipid Microparticles (SLMs), a carrier that has not been up to now much studied especially for pulmonary administration. However SLMs present several advantages: they can be considered as physiologically compatible, physicochemical stable and allowing a large-scale production at a relative low production cost. The aim of this work was to produce a drug carrier able to provide a sustained release to a β 2-mimetic agent and thereby to prolong its duration of action. The active substance we chose to work with is salbutamol acetonide (SA), a derivative of salbutamol that have been synthesized in order to get a more lipophilic substance and thereby to allow a more effective incorporation of this drug into SLMs.¹⁴

Nanoparticles:

Nanoparticles present the same characteristics than the microspheres, they are also constituted of polymers or lipids and drugs bound either at the surface of the particles either encapsulated into the vector. In this last case, a protection against the enzymatic degradation and a modified bioavailability of the drug can be envisaged and increased by a controlled release. These targeting systems can be designed for in vivo applications including molecules with therapeutic activities and radio contrast agents or in vitro as a support for molecules intended for diagnosis. Manufacturing and encapsulating methods for drugs and the feasibility of modifying the surfaces of these vectors have been reviewed by different authors. Drug targeting studies using these vectors by pulmonary route have been essentially conducted by encapsulating insulin.¹⁵

Sustained release Nanoparticles:

A pulmonary drug delivery system to treat tuberculosis offers a number of advantages over current oral medications. By delivering antibiotics via inhalation, the infected tissues of the lung are directly targeted while maintaining lower systemic drug concentrations and toxicity. Preliminary studies on pulmonary delivery of para-amino salicylic acid (PAS) in rats have shown this method to indeed allow for minimal inhibitory drug concentrations (MIC) to be reached in lung tissue with much lower systemic tissue drug concentrations. In addition, previous studies on the use of polymeric nanoparticles for drug delivery have shown that it is possible to encapsulate and deliver a range of proteins and drug molecules.

Lipid and polymeric nanoparticles shells are promising candidates for this delivery method because of their large size and low density, which causes them to deposit in the alveolar region (where there is good contact with the bloodstream) and avoid elimination from the lungs. In addition, the porous shell surface allows for the slow, sustained release of TB drugs, which may translate into a less frequent and attenuated drug treatment regimen.¹⁶

Micelles:

A successful drug carrier system needs to demonstrate optimal drug loading and release properties, long shelf-life and low toxicity. 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 show great promise as carriers in pulmonary drug delivery systems. Drugs can be trapped in the core of a micelle 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 reticuloendothelial system, and therefore early elimination from the bloodstream. A further feature that makes micelles 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.¹⁷

Liposomes:

The utilization of liposomal drug formulations for aerosol delivery has many potential advantages, including aqueous compatibility, sustained pulmonary release to maintain therapeutic drug levels and facilitated intra-cellular delivery

particularly to alveolar macrophages. Furthermore, drug-liposomes may prevent local irritation and reduce toxicity both locally and systemically. Increased potency with reduced toxicity is characteristic of many drug-liposomal formulations. Liposomal aerosols (including CsA) have proven to be non-toxic in acute human and animal studies. These results suggest that drug-liposome aerosols should be more effective for delivery, deposition and retention of water-insoluble, hydrophobic, lipophilic compounds in contrast to water soluble compounds.

The development of liposomal formulations for aerosol delivery with jet nebulizers has expanded the possibilities for effective utilization of aerosol based therapies in the treatment of pulmonary diseases. The property of sustained release or depot effect of liposomes has been studied using different tracer molecules to monitor absorption and clearance of liposomes from the lung.¹⁸⁻²⁰

The development of liposomal formulations, compatible with aerosol delivery with jet nebulizers, has also expanded the possibilities for more effective utilization of aerosol based therapies for the treatment of a variety of pulmonary diseases. Such utilization of liposomes, as aerosol delivery vehicles, has many reported potential advantages for clinical development, including: aqueous compatibility facilitated intra-cellular delivery particularly to alveolar macrophages and lymphocytes and sustained pulmonary release to maintain therapeutic drug levels within the lung.²¹

Microemulsions:

The emulsions and microemulsions are dosage forms showing numerous advantages providing that the surfactants used are not toxic. Anyway, more and more exogenous surfactants, used for treatments and as a precaution for acute respiratory distress syndrome (ARDS), are used as solutions or suspensions drug targeting systems. Therefore, these allow envisaging at once a respiratory treatment and a drug delivery system. These surfactants are considered as effective drug targeting systems if they don't interfere with the therapeutic activity of the drug.

Very few emulsions or microemulsions have been studied to administer drugs by the pulmonary route. However, these dosage forms show numerous advantages compared to other drug targeting systems: easiness to be manufactured and maximum of drug to be incorporated. Indeed, the drug being soluble into one phase, this one will be located preferentially into this phase, leading to an encapsulation close to 100%. Due to their physicochemical characteristics, reverse emulsions and microemulsions should allow to solubilize a large amount and a lot of hydrophilic drugs.²²⁻²³

Several aerosol formulations designed with an external phase constituted of a propellant have been described. Propellants like hydrofluoroalkanes (HFAs) or propane have been suggested. Reverse microemulsions stabilized by lecithin and using propane and dimethylether as propellants have been also described. These microemulsions, characterized by mean geometric diameters ranged between 1 and 5 μm and by a respirable fraction up to 36%, showed high stability during more than 4 weeks at room temperature. Water-in-HFA emulsions stabilized by non ionic fluorinated surfactants have been also studied in order to administer drugs by pulmonary route and studied new reverse miniemulsions and microemulsions based on fluorinated surfactants intended for pulmonary delivery of drugs.²⁴

Cyclodextrins:

Cyclodextrins (CDs) are the result of the association of oligosaccharides and are formed of six, seven or eight units of glucopyranose (α -, β - or γ -CD, respectively). Following the complete or partial inclusion of the drug into the cavity, the drug can interact by non covalent bonding with CDs, becoming higher soluble in an aqueous medium. β -CD seems to be the more used cyclodextrins for pharmaceutical development, due to the size of its cavity, the complexation efficiency with drugs and their relatively low production costs. CDs have been studied to encapsulate drugs and to be used in this application to target drugs into the lungs. CDs are able to complex testosterone, salbutamol or rolipram. Cyclodextrins can be used also in combination with other vectors. They are able to increase the encapsulation rate of drugs into microparticles and to modulate

their releases. Principally, they were described and used by pulmonary route for their pulmonary absorption promoter of peptides and proteins like insulin or calcitonin.²⁵

PULMONARY DELIVERY DEVICES

The lung has served as a route of drug administration for thousands of years. The origin of inhaled therapies can be traced back 4000 years ago to India, where people smoked the leaves of the *Atropa belladonna* plant to suppress cough. In the 19th and early 20th centuries, asthmatics smoked asthma cigarettes that contained stramonium powder mixed with tobacco to treat the symptoms of their disease. The development of modern inhalation devices can be divided into three different categories, the refinement of the nebulizer and the evolution of two types of compact portable devices, the metered-dose inhaler (MDI) and the dry powder inhaler (DPI). The advantages and disadvantages of each system will be discussed below and are summarized in. More detailed reviews of inhalation technology have been previously published.²⁶

Nebulizers:

Nebulizers have been used for many years to treat asthma and other respiratory diseases. There are two basic types of nebulizer, jet and ultrasonic nebulizers. The jet nebulizer functions by the Bernoulli principle by which compressed gas (air or oxygen) passes through a narrow orifice creating an area of low pressure at the outlet of the adjacent liquid feed tube. This results in drug solution being drawn up from the fluid reservoir and shattered into droplets in the gas stream. The ultrasonic nebulizer uses a piezoelectric crystal vibrating at a high frequency (usually 1–3 MHz) to generate a fountain of liquid in the nebulizer chamber; the higher the frequency, the smaller the droplets produced.

Constant output jet nebulizers can aerosolize most drug solutions and provide large doses with very little patient coordination or skill. Treatments using these nebulizers can be time-consuming but are also inefficient, with large amounts of drug wastage (50% loss with continuously operated nebulizers). While these disposable nebulizers are inexpensive, the compressors supplying the air or oxygen are not. Most of the prescribed drug never reaches the lung with nebulization. The majority of the drug is either retained within the nebulizer (referred to as dead volume) or released into the environment during expiration. On average, only 10% of the dose placed in the nebulizer is actually deposited in the lungs.²⁷

The physical properties of drug formulations may have an effect on nebulization rates and particle size. The viscosity, ionic strength, osmolarity, pH and surface tension may prevent the nebulization of some formulations. If the pH is too low, or if the solution is hyper- or hypo-osmolar, the aerosol may induce bronchoconstriction, coughing and irritation of the lung mucosa. As well, high drug concentrations may decrease the drug output with some nebulizers. (Figure 3)

Advances in technology have led to the recent development of novel nebulizers that reduce drug wastage and improve delivery efficiency. Enhanced delivery designs increase aerosol output by directing auxiliary air, entrained during inspiration, through the nebulizer, causing more of the generated aerosol to be swept out of the nebulizer and available for inhalation. Drug wastage during exhalation is reduced to the amount of aerosol produced by the jet air flow rate that exceeds the storage volume of the nebulizer. Adaptive aerosol delivery monitors a patient's breathing pattern in the first three breaths and then targets the aerosol delivery into the first 50% of each inhalation. This ensures that the aerosol is delivered to the patient during inspiration only, thereby eliminating drug loss during expiration that occurs with continuous output nebulizers.²⁸⁻²⁹

Inhalers:

The medicine inside an inhaler goes straight into the airways. Therefore it needs much smaller dose than took the medicine as a tablet or liquid by mouth. Inhalation represents an attractive, rapid and patient-friendly route for the delivery of systemically acting drugs, as well as for drugs that are designed to act locally on the lungs themselves.

This concept is especially exciting now that the concept of an inhaled systemic macromolecule, One of the key factors for success in this area is the ability to control the combined powder and device properties. This is essential for the development of dry-powder inhaler (DPI) products, yet remains a major technical hurdle to those wishing to succeed with this route and exploit the product opportunities arising from the numerous market drivers:

- Rapid onset of action
- Improving patient acceptance and compliance for a non-invasive systemic route
- Reduction of side effects
- Differentiation of new product and competitive brand opportunities
- Expedition of regulatory approval through improved consistency of delivery and product stability
- Product lifecycle enhancement
- New forms of inhaled therapeutics often requiring high doses and/or greater efficiency and accuracy
- Attractive device form with convenient and easy operation and delivery



Figure 3: Nebulizer

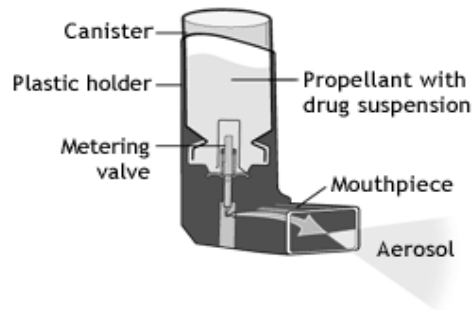


Figure 4: Metered-dose inhaler

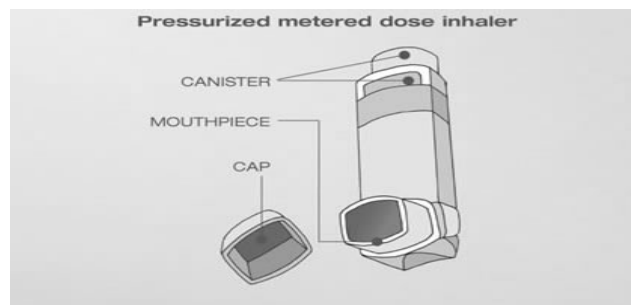


Figure 5: Pressurized metered-dose inhaler

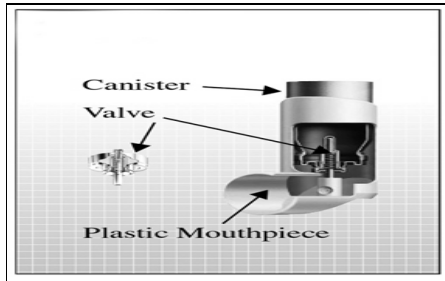


Figure 6: Dry powder inhaler



Figure 7: Handihaler



Figure 8: MedTone™ inhaler with single use cartridge containing Technosphere®/Insulin powder



Figure 9: AERx Essence delivery system

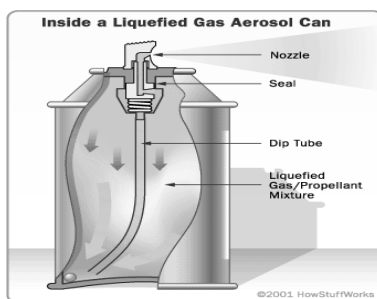


Figure 10: Aerosol

Metered-dose inhalers:

The MDI was a revolutionary invention that overcame the problems of the hand-bulb nebulizer, as the first portable outpatient inhalation device and is the most widely used aerosol delivery device today. The MDI emits a drug aerosol driven by propellants, such as chlorofluorocarbons (CFC) and more recently, hydrofluoroalkanes (HFAs) through a nozzle at high velocity ($> 30 \text{ m s}^{-1}$). MDIs deliver only a small fraction of the drug dose to the lung. Typically, only 10–20% of the emitted dose is deposited in the lung. The high velocity and large particle size of the spray causes approximately 50–80% of the drug aerosol to impact in the oropharyngeal region. Hand-mouth discoordination is another obstacle in the optimal use of the MDI. (Figure 4)

The delivery efficiency of an MDI depends on a patient's breathing pattern, inspiratory flow rate (IFR) and hand-mouth coordination. Increases in IFR result in decreases in total lung dose deposition and penetration into the peripheral airways. Fast inhalations ($> 60 \text{ l min}^{-1}$) result in a reduced peripheral deposition because the aerosol is more readily deposited by inertial impaction in the conducting airway and oropharyngeal regions. When aerosols are inhaled slowly, deposition by gravitational sedimentation in peripheral regions of the lung is enhanced. Peripheral deposition has also been shown to increase with an increase in tidal volume and a decrease in respiratory frequency. As the inhaled volume is increased, aerosols are able to penetrate more peripherally into the lungs. A period of breath holding on completion of inhalation enables particles which penetrate the periphery to be deposited in that region, instead of being exhaled during the expiratory phase. Thus, the optimal conditions for inhaling MDI aerosols are from a starting volume equivalent to the functional residual capacity, actuation of the device at the start of inhalation, IFR of $<60 \text{ l min}^{-1}$ followed by a 10-s breath-hold at the end of inspiration.³⁰

Pressurized metered-dose inhalers:

The pMDI is not available for all drugs or dosages, making it difficult for clinicians to prescribe the same type of device for diverse inhaled medications. This is exacerbated by the trend of many pharmaceutical companies not to release newer inhaled drugs as pMDIs. The design of the CFC-propellant pMDI requires initial and frequent priming. Failure to prime the device results in administration of a substantially lower dose than that prescribed. Unfortunately, frequent priming tends to waste drug to atmosphere.³¹

The greatest single limitation of the pMDI is the inconsistent dosing that occurs with incorrect use. This includes the impact of hand-breath asynchrony, excessive inspiratory flow velocity, nose-breathing, and the cold-Freon effect (the patient stops inhalation when the cold aerosol plume reaches the hypopharynx). For an aerosol device efficiently to deliver medication to the lower respiratory tract, most of the aerosol medication particles must be of a size for inhalation and deposition in the airway, generally $0.5\text{--}4.5\mu\text{m}$ mass median aerodynamic diameter. The patient must inhale the aerosol with a slow, deep inhalation to maximize aerosol deposition in the airway, followed by a breath-hold to allow sedimentation of the medication particles. Extended use of the pMDI beyond the labeled number of doses results in a “tailing-off” effect at the end of canister life. While the pMDI provides consistent dosing for the number of actuations listed on the drug label, after that the dose

fluctuates between the nominal dose and a negligible dose. In the absence of a dose-counter, which is not provided with most pMDIs, the patient must count the number of doses taken to determine the effective life of the pMDI. (Figure 5) The method of “floating” the pMDI canister in water to determine canister depletion is unreliable, and water entering the nozzle can reduce the emitted dose of subsequent actuations.³²

Dry powder inhalers-

Interest in DPIs as an effective, efficient and environmentally friendly way of delivering drugs to the lung has accelerated in recent years. A fundamental difficulty with developing solid state aerosols, or DPIs, is managing both the ubiquitous and the transient forces contained in powder beds. Indeed, managing such particulate forces, for example via particle engineering techniques, is now considered central to successful DPI formulation and production. (Figure 6)

In consequence, much attention is currently focused on producing “smart” formulations, where it may be possible to achieve excellent powder flow and low cohesive forces. However, having an efficient and robust formulation technology in the laboratory is only a start on the road to producing a successful DPI product.³³

Pharmaceutical scientists all too frequently meet major obstacles when they engage in the world of DPI product design – not least because of the further complications of this area resulting from the plethora of DPI device designs. There is tremendous variation in the methods used to store and meter powders and to generate the aerosol cloud. In the case of DPI aerosol generation, there is a great deal of variation between different types of device, in the fluid dynamic and electrostatic environment that the powder formulation experiences.³⁴

With DPIs, the drug aerosol is created by directing air through loose powder. Most particles from DPIs are too large to penetrate into the lungs due to large powder agglomerates or the presence of large carrier particles (e.g. lactose). Thus, dispersion of the powder into respirable particles depends on the creation of turbulent air flow in the powder container. The turbulent airstream causes the aggregates to break up into particles small enough to be carried into the lower airways and also to separate carrier from drug. Each DPI has a different air flow resistance that governs the required inspiratory effort. The higher the resistance of the device, the more difficult it is to generate an inspiratory flow great enough to achieve the maximum dose from the inhaler. However, deposition in the lung tends to be increased when using high-resistance inhalers.³⁵

Latest development in Inhaler technology and marketed inhalers:

Handihaler:

The Handihaler (Boehringer Ingelheim) provides a good example of device life cycle management (LCM). The old Inhalator device had a blocky and unattractive design and no mouthpiece cover, while the newer Handihaler offers users a more pleasing shape both to use and to see, as well as protection to the mouthpiece. (Figure 7)

Technosphere® Insulin (Mankind Corporation):

Technosphere® insulin is a kind of lattice containing a dry-powder formulation of crystallized insulin in gelatin capsules. The insulin delivery mechanism uses a high-impedance inhaler with a powder deagglomeration system. Pharmacokinetics and pharmacodynamics studies have shown a very fast absorption (time to peak insulin level: 12-14 minutes, time to maximum metabolic effect: 20-40 minutes) and a short duration of action (2 to 3 hours). Bioavailability was proportional to the administered dose and the biopotency was around 15%.³⁶

Technosphere®/Insulin particles are optimized for inhalation into the deep lung. They are inhaled using the MedTone™ inhaler, a passive, high-resistance, low-flow, dry-powder delivery device. Technosphere®/Insulin powder in 2.5-10 mg quantities is filled into single use cartridges that are inserted into the MedTone™ inhaler. The powder is discharged into the oral cavity simply by inhaling through the device mouthpiece. The inhaler does not require manual activation. Since it is activated by patient inhalation, it is not necessary to co-ordinate the timing of device activation and patient inhalation. (Figure 8) Additionally, the MedTone™ inhaler is a small, compact device that is inconspicuous, easy to carry and use.³⁷

GyroHaler:

The GyroHaler is a novel, cost-effective, multi unit-dose DPI device that has been designed to deliver formulations that act locally in the lung. The GyroHaler is designed to target the market occupied by the latest generation of multi-dose inhalers, such as GlaxoSmithKline's DiskusR, which are capable of storing and delivering up to 60 doses.

GyroHaler is compact and easy to use and with a small number of moulded parts in order to allow short device development times and competitive manufacturing costs. The device is intended to be disposable after one month and is designed to have aerosolisation characteristics competitive with existing marketed devices. In addition the GyroHaler device offers aluminium foil blistered drug protection from moisture, oxygen and light.

GyroHaler technology could be used to deliver a range of locally acting products in an efficient, cost-effective and patient-friendly manner. The GyroHaler concept was created with the key market drivers for these products in mind, not only to facilitate development of Vectura's own product pipeline, but also to license the technology to third parties for the development of other leading respiratory products. In this respect, Vectura's engineers and scientists have experience in working in close collaboration with partners further to adapt the device design and formulation attributes to meet the potential branding and performance requirements for specific products, while building on a common foundation of core technology, intellectual property and know-how.³⁸

Aspirair:

Aspirair is a high-delivery-efficiency, user friendly "active" DPI, which delivers drugs via the lung to the systemic circulation in an efficient and effective manner. Typically purpose formulated powders deliver around 70% or greater fine particle dose (% of MD) from Aspirair. Unusual among DPIs is Aspirair's capability of delivering high ultra-fine particle doses (UFPD <3µm) coupled with minimal deposition in the oropharynx.

Aspirair is an "active" DPI powered using mechanically pressurised air that acts as an energy source for powder de-aggregation using a miniature cyclone dispersion chamber. To Aspirair, the patient inserts a foil blister containing the dry-powder dose into the device, which pierces the blister. A charge of air is then compressed by the patient using a low torque, corkscrew-type manual pump. Finally the patient inhales through the mouthpiece, triggering release of the charge of air, which passes through the blister, entraining the powder. The dose then flows into a vortex nozzle where shear and turbulent forces disperse the powder and slow down the air stream, so that a 'soft' aerosol emerges from the mouthpiece that is matched with the patient's inspiratory manoeuvre.

These characteristics together with other attributes such as: precise dose-to-dose repeatability and low variability of delivered dose; high payload capability for small (and large) molecules; robust and cost-effective construction; convenient small size; simple operation; delivery independent of inspiratory flow rate with slow aerosol velocity; performance approaching full dispersion of the primary particles; and excellent dose stability (from foil blisters), all make Aspirair an attractive proposition for the delivery of small-molecule drugs for systemic delivery. The device is also highly appropriate of course in macromolecule delivery and for lung diseases where a high degree of control is required.³⁹

AERx system:

This system uses a liquid insulin formulation and expels a single dose of aerosol of fine insulin particles through a disposable nozzle on a disposable dosage strip. The AERx®iDMS emits the aerosol by extruding the solution through the holes of the nozzle. It is a battery powered device utilizing a microprocessor to guide electronically the user to the optimal breathing pattern (flow rate and depth of breath).⁴⁰⁻⁴¹ The system allows delivering metered dose of insulin and single unit increments. It has the size of a small book. As containing a liquid formulation, it requires cold storage.

AERx is a high-performance system that delivers liquid formulations to and through the lung, for respiratory and systemic applications. It offers completely non-invasive therapy for small molecules and proteins that require frequent and/or long-term self administration. The AERx system consists of a disposable prefilled AERx Strip with an integral nozzle, from which drug is aerosolised via one of several delivery device options. As seen in figure 1, the devices range from electromechanical versions (AERx) with precise dose titration and data management capabilities, to all-mechanical versions (AERx Essence®) that deliver a pre-set dose in a single breath. (Figure 9)

Marketed AERx based formulations:

- AERx HCQ
- AERx Liposomal Ciprofloxacin
- AERx insulin Diabetes Management System
- AERx Smoking Cessation
- AERx Liposomal Treprostinil

Exubera®, developed by Nektar/Pfizer

Exubera® was granted marketing approval by health authorities (EMA in Europe and FDA in the US) in January 2006, for the treatment of type 1 (in association with basal insulin) and type 2 diabetes. The device uses insulin powder formulation, which consists of recombinant human insulin (60%) and excipients (mannitol, glycine, sodium and nitrate). The powder is packed in blister packs, each one containing 1 or 3 mg of insulin (about 28 and 84 IU) equivalent to 3 IU and 9 IU of subcutaneous insulin respectively which represents a 10% relative activity. The blister is inserted into a slot at the base of the device. Activation leads to compressing trapped air, puncturing the blister and releasing air through the blister at high velocity. Insulin particles (MMAD approximately 3 µm) are aerosolised into an inhalation chamber. Then, the subject inhales the respirable cloud with a full slow breath. The device is 23 cm long, but when it is folded, it has the size of devices used for asthma. Pharmacokinetics of inhaled insulin has shown a peak at about 55 minutes and a more rapid return to basal level than regular subcutaneous insulin.⁴²⁻⁴³

Aerodose® (Aerogen Inc./Nektar Therapeutics)

Aerodose® is a system activated by breath which uses a liquid insulin formulation aerosolised in small droplets. Pharmacokinetics and pharmacodynamics studies have shown a time to peak insulin level shorter after insulin inhalation than after regular subcutaneous insulin (60-97 minutes vs 168-237 minutes) and an onset of action and a peak metabolic effect occurring earlier with inhaled insulin. Reproducibility was similar with inhaled or subcutaneous insulin.⁴⁴⁻⁴⁵

Spiro System (Dina Pharmacy Inc/Elan Corporation)

Spiro System provides a dry-powder insulin formulation encapsulated in blister-disks via a breath-activated inhaler. After inhalation, peak insulin level was observed at 70 minutes and a dose-response relationship was observed.⁴⁶

Aerosols:

Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium. The drugs, delivery by aerosols are deposited in the airways by: gravitational sedimentation, inertial impaction, and 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.⁴⁷

Although there is similarity in drug absorption from the lungs and the other mucosal surfaces, but due to the complexity in aerosol-particle disposition, the aerosol administration further complicated by the hygroscopic properties of most therapeutic aerosols that allow the particle size to change drastically during the drug transport in the highly humid atmosphere of the respiratory tract. Other factors, which directly influence the aerosol deposition by above three mechanisms, are aerodynamic size distribution of the aerosol particles, and the density of the aerosol particles. (Figure 10)

There are three commonly used clinical aerosols: jet or ultrasonic nebulizers, metered-dose inhaler (MDI), and dry-powder inhaler (DPI). The metered-dose inhalers are most frequently used aerosol delivery system. The dry-powder-inhalers are designed to deliver drug/excipients powder to the lungs.

Almost all aerosols were using a CFC (chlorofluorocarbon) propellant but in mid-nineties efforts were made to consider an alternative to ozone depleting CFC by other classes of environmental friendly propellants such as hydrofluoroalkanes (HFAs: HFA -134a and HFA-227). These HFA compounds contain no chlorine, which infact causing the ozone depletion effect. The safety and efficacy of these new introduced propellants were investigated to meet the requirements of American and

European regulatory agencies. In most cases, these two propellants met the safety conditions and found that they have safety compliance as of their predecessor CFC propellant.⁴⁸⁻⁴

CONCLUSION:

Growing attention has been given to the potential of a pulmonary route as an non-invasive administration for systemic delivery of therapeutic agents due to the fact that the lungs could provide a large absorptive surface area (up to 100 m^2) but extremely thin ($0.1\ \mu\text{m} - 0.2\ \mu\text{m}$) absorptive mucosal membrane and good blood supply. Pulmonary drug delivery of inhalable drugs may be a promising alternative to oral or intravenous administration, thus decreasing the incidence of side effects associated with a high drug serum concentration. Nevertheless, their inherently small size and surface modification properties enable further opportunities for innovative controlled drug release and pulmonary cell targeting therapeutic platforms. The integration of pulmonary delivery has the potential to improve the targeting, release, and therapeutic effects of drugs and needle-free inhalation vaccines with significant potential capability of overcoming the physicochemical and biological hurdles. However, it is important to remember that it is the performance of the system as an ensemble that is paramount for optimal therapeutic performance. It is therefore essential that the approaches and devices are given the same weighting in the development process. Novel devices with improved delivery features and metered dosing (similar to currently available metered dose inhalers) might overcome the administration difficulties and increase the efficiency of protein delivery to the deep lung. The efficiency of drug dosing into the lungs has been improved by the elimination of hold-up in new devices, particles designed to penetrate into the deep lung and device configurations to improve aerosol characteristics. From the review, we conclude that the approaches and devices in pulmonary drug delivery system is most prominent with compare to the other drug delivery system.

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