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PULMONARY DRUG DELIVERY SYSTEM: AN OVERVIEW

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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 prominently describes the formulation approaches and devices required to be administer drug into the lungs.

KEYWORDS

Targeting drug delivery, Respiratory mechanisms, Formulation approach, Drug delivery devices and Pressurized metered dose inhalers.

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INTRODUCTION

The respiratory tract is one of the oldest routes used for the administration of drugs. Over the past decades inhalation therapy has established itself as a valuable tool in the local therapy of pulmonary diseases such as asthma or COPD (Chronic Obstructive Pulmonary Disease). This type of drug application in the therapy of these diseases is a clear form of targeted drug delivery. Currently, over 25 drug substances are marketed as inhalation aerosol products for local pulmonary effects and about the

drugs are in different stages of clinical development. The drug used for asthma and COPD eg.- β_2 -agonists such as salbutamol (albuterol), Terbutalinformoterol, corticosteroids such as budesonide, Flixotide or beclomethasone and mast-cell stabilizers such as sodium cromoglycate or nedocromil. The latest and probably one of the most promising applications of pulmonary drug administration is

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

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 for 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.

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).

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 (lactic-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 B2-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 systematically. 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.

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

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.

PULMONARY DRUG DELIVERY DEVICES

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. 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

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

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.

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.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 0.5-4.5µm mass median aerodynamic diameter. 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. 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.

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. 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 (BoehringerIngelheim) 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.

The AeroGen pulmonary delivery technology

The technology being developed at AeroGen consists of a proprietary aerosol generator (AG) that atomizes liquids to a predetermined particle size. These delivery platforms accommodate drugs and biopharmaceuticals formulated as solutions, suspensions, colloids, or liposomes used for systemic and local use

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.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 pressurized 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.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.

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

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.

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.

The Direct Haler Pulmonary Delivery Flat form

- Direct Haler™ Pulmonary is an innovative and new device for dry powder each pre-metered, pre-filled pulmonary dose has its own Direct Haler™ Pulmonary device.
- The device is hygienically disposable and is made of only 0.6 grams of Polypropylene. Direct Haler™ Pulmonary offers effective, accurate and repeatable dosing in an intuitively easy-to-use device format.
- The powder dose is sealed inside the cap with a laminate foil strip, which is easily torn off for dose-loading into the Powder Whirl chamber, before removing the cap and delivering the dose.

NEWER DEVELOPMENT

- Dr Reddy's launched 'Dose Counter Inhalers' in India on Friday, April 16, 2010, as an innovation

- in the metered dose inhaler (MDI) space with launch of 'Dose Counter Inhalers (DCI) for the first time in India. This first MDI in India that gives patients an advance indication of when the inhaler is going to be empty. DCI is a new drug delivery device with a single device having 120 metered doses. There is a window in the inhaler that changes color from green to red.
- Green indicates the inhaler is full and red indicates the inhaler is empty. Half green and half red in the window indicate it's time to change the inhaler.

SEVILLE - THE FUTURE OF INHALATION TECHNOLOGY

Licensed to Aradigm's, the *Seville* technology was invented at the University of Seville, Spain. It is a

novel and patent protected aerosol generation technology. Air and liquid simultaneously flow through a single orifice, causing the formation of aerosols that are significantly smaller than the orifice dimensions, ensuring that the nozzle does not become blocked. Compared with existing liquid technologies, the aerosolized drug output per inhalation should be considerably higher -about ten times that of most nebulizers. Unlike AERx technologies, the *Seville* technology will be developed with a multi-dose reservoir, allowing many dose deliveries before having to reload or discard the device. The Aradigm's *Seville* technology is in early development but has the potential to improve.

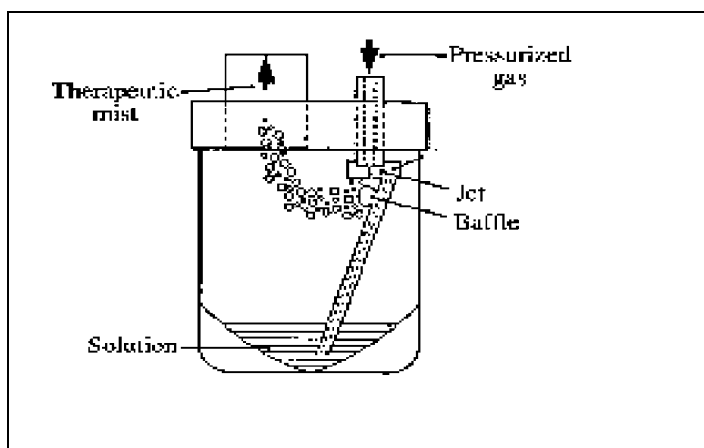


Figure No.1: Air Jet Nebulizers

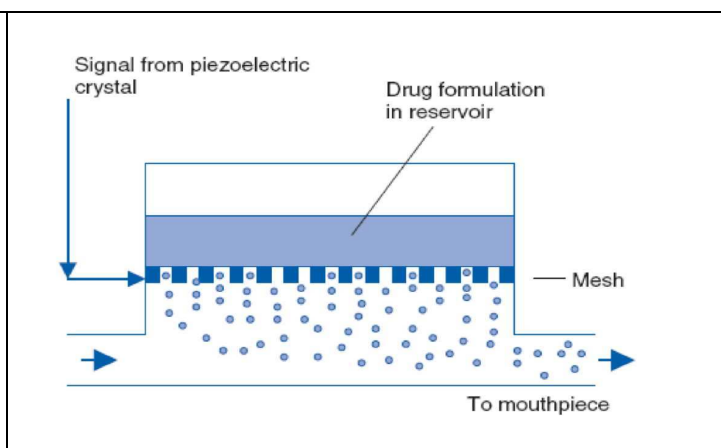


Figure No.2: Ultrasonic Nebulizers



Figure No. 3: Nebulizer

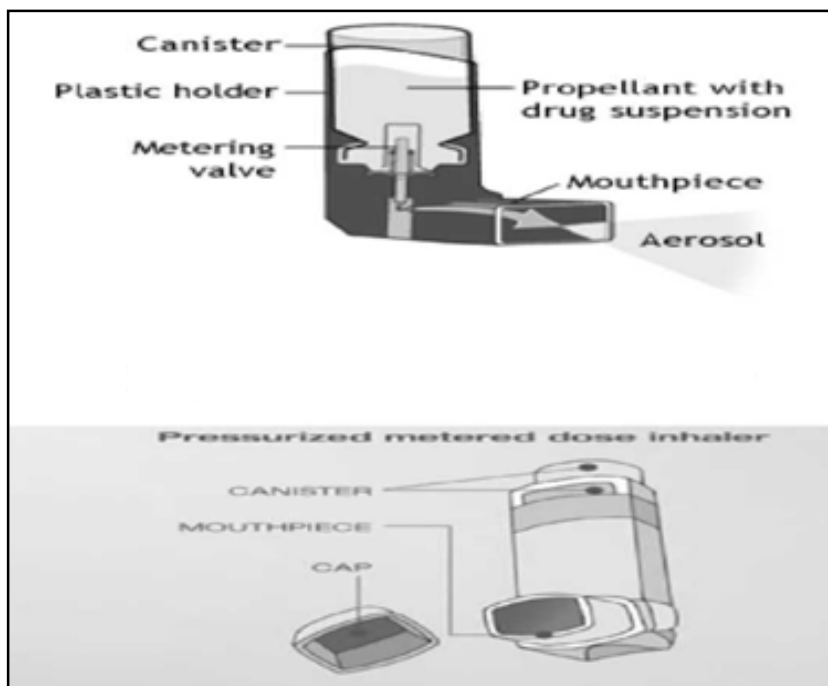


Figure No.4: Metered Dose Inhaler

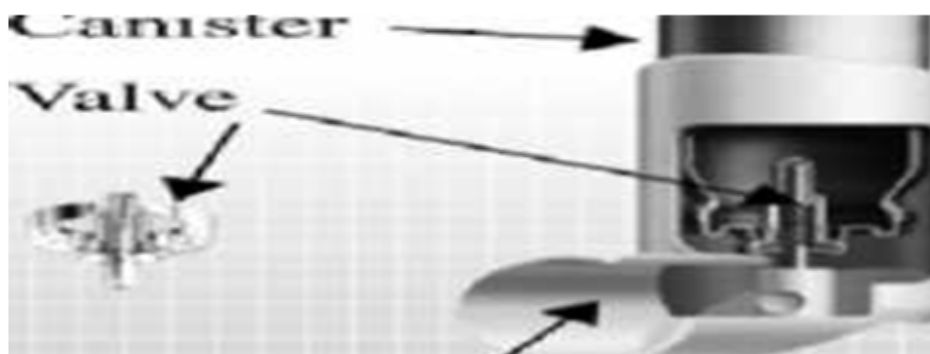


Figure No. 5: Dry Powder Inhaler



Figure No.6: AERx Essence delivery system

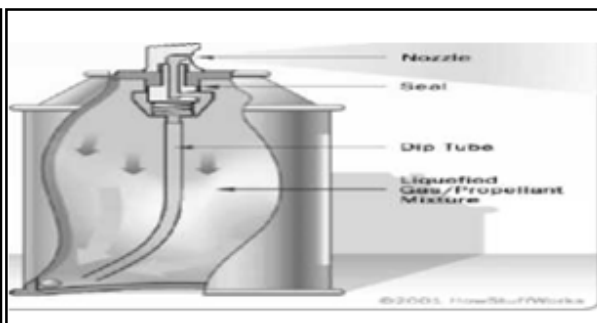


Figure No.7: Aerosol



Figure No.8: Metered Dose Inhalers




Advair	Floventrota disk	Serwevent
		

Figure No.9: Dry Powder Inhalers



Figure No.10: Handihaler



Figure No.11: Aeronob portable nebulizer



Figure No.12: Techno Sphere® Insulin

AERx-essence	AERx-sophisticated	AERx-strip

Figure No.13: AERx system

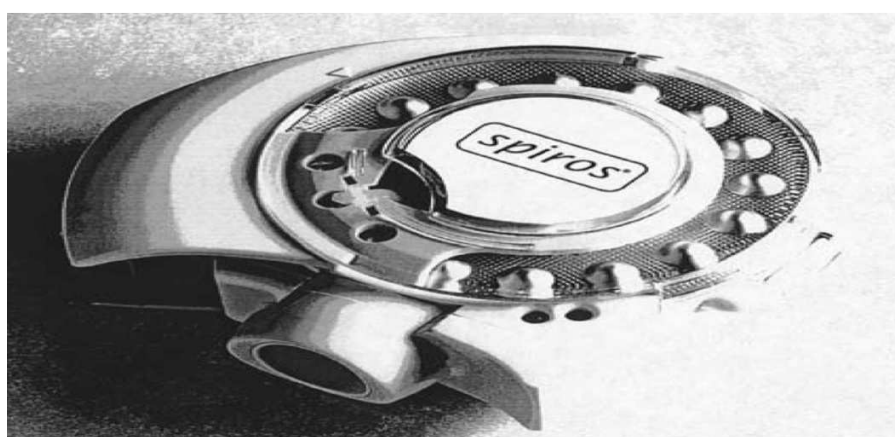


Figure No. 14: Spiro System

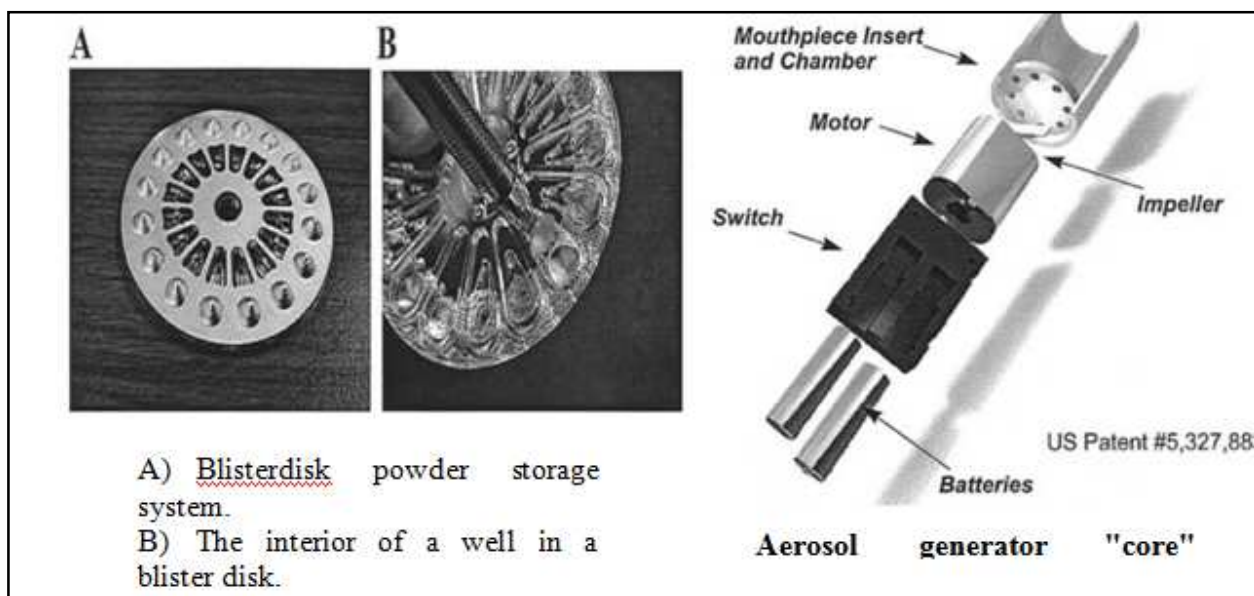


Figure No. 15: Aerosol Technology

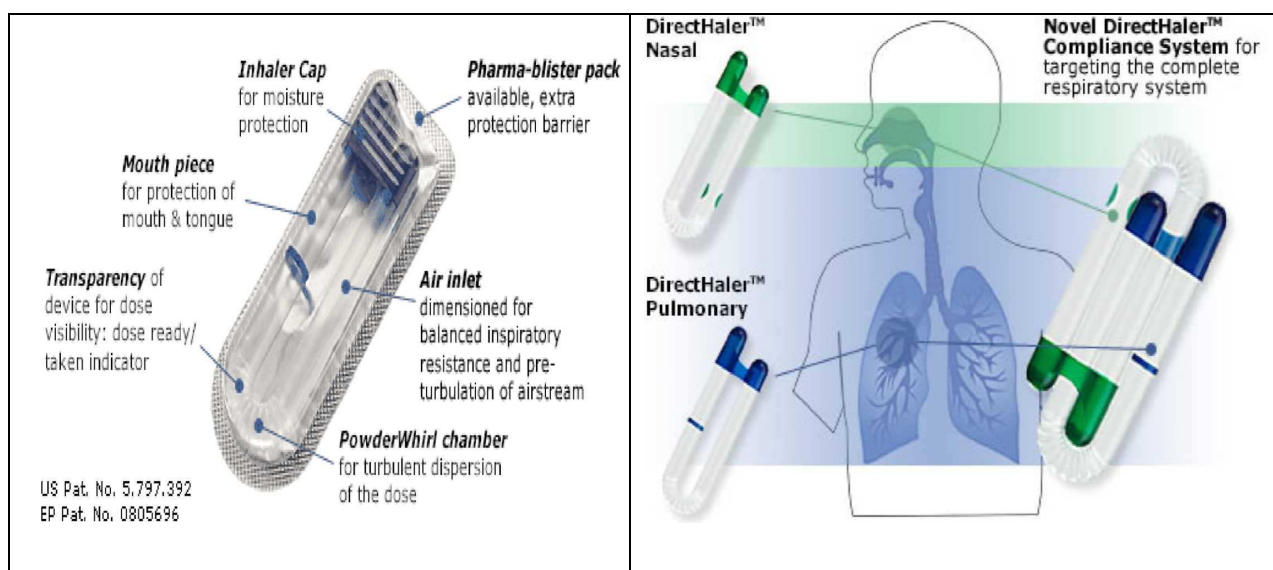


Figure No.16: Direct Haler Pulmonary Delivery Flat form



Figure No.17: Dose Counter Inhalers

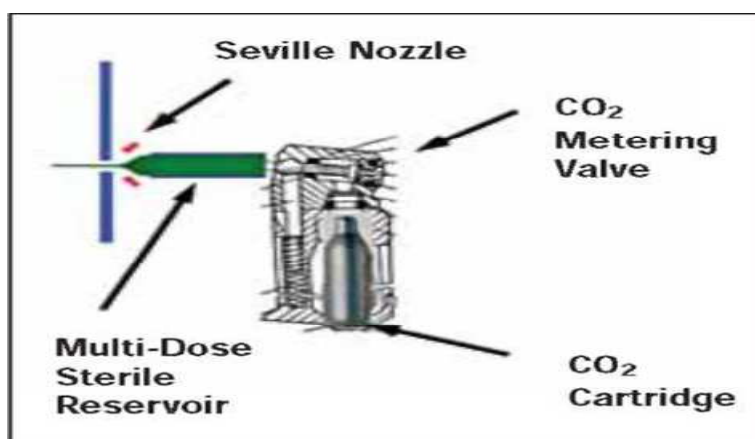


Figure No.18: Aradigm's Seville Technology

CONCLUSION

The lung has served as a route of drug administration for thousands of years. Now a day's pulmonary drug delivery remains the preferred route for administration of various drugs. Pulmonary drug delivery is an important research area which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various diseases. Inhalation gives the most direct access to drug target. In the treatment of obstructive respiratory diseases, pulmonary delivery can minimize systemic side effects, provide rapid response and minimize the required dose since the drug is delivered directly to

the conducting zone of the lungs. It is a needle free several techniques have been developed in the recent past, 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 for multiple diseases. So pulmonary drug delivery is best route of administration.

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