WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 6, 204-229. Review Article ISSN 2277 – 7105

PULMONARY DRUG DELIVERY SYSTEM: CURRENT PRACTICES AND APPLICATIONS

Praful Kadam*, Hema Kanekar and Anubha Khale

H. K. College Of Pharmacy, Jogeshwari (West), Mumbai-400 102

Article Received on
05 June 2014,

Revised on 30 June 2014,
Accepted on 25 July 2014

***Correspondence for Author**
Praful Kadam
H. K. College Of Pharmacy, Jogeshwari (West), Mumbai-400 102.

ABSTRACT

Pulmonary route of drug delivery is gaining much importance in the present day research field as it enables to target the drug delivery directly to lungs, both for local and systemic treatment. It has 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 $100m^2$) but extremely thin (0.1µm – 0.2µm) absorptive mucosal membrane and good blood supply. Respiratory system mainly consists of three regionsnasopharyngeal region, tracheo-bronchial region and Alveolar region.For this region's most commonly used devices are nebulizers, metered-dose inhalers, and dry powder inhalers, they can be used for protein and peptide drugs.Pulmonary drug delivery is used not only for management of pulmonary disease but also for treatment of diabetes, angina pectoris, cancer, bone disorders, genetic disorders. This review discusses about basic anatomical principles, basis of drug absorption from lungs, mechanism of drug deposition, method to manufacture pulmonary drug delivery system and its quality requirement. The current practices such as administration of drug carriers through liposomes, nano and microparticles, cyclodextrins, micro emulsions, micelles, suspensions, or solutions are included and these pharmaceutical carriers can be further explored to target drugs into the lungs for treatment of various ailments.

KEY WORDS: nebulizers, metered-dose inhalers, dry powder inhalers, diabetes, anginapectoris, cancer, liposomes, etc.

INTRODUCTION

Inhaled therapies have existed for at least 5005 years[1]. The Ebers papyrus from ancient Egypt (1554 BC) describes how the breathless may be treated by the inhalation of the vapour of black henbane. There was not a specific inhaler device, instead the leaves would be thrown on two hot bricks, causing the alkaloids to vaporize and the patient was to inhale the free vapour. In ancient Greece Hippocrates (460-377 BC), who gave the word 'asthma', employed an apparatus which consisted of a pot, the lid of which had an opening for the reception of a reed, through which the vapour escaped and was inhaled through the open mouth: the latter being protected from scalding by moist sponges[2]. In India the Ayurveda practice of making inhalation of stramonium and hemp using pipe was practiced. The first "powered" or pressurized inhaler was invented in France by Sales-Girons in 1858[3]. However, around the turn of the 19th century, with the invention of liquid nebulizers, these early treatments developed into legitimate pharmaceutical therapies. In the 1920s adrenaline was introduced as a nebulizer solution, in 1925 nebulizer porcine insulin was used in experimental studies in diabetes, and in 1945 pulmonary delivery of the penicillin was investigated. Steroids had been introduced in the mid1950s for the treatment of asthma and nebulizers were enjoying widespread use[4].

Pulmonary route have been used to treat various respiratory diseases for centuries. New dispersible formulations and drug aerosol delivery devices for inhalable peptides, proteins and various small molecules become of increasing interest for the treatment of systemic and respiratory diseases[5]. Indeed, a major advantage of therapy via the lungs is the potentially improved therapeutic index, that is, the ratio of therapeutic benefit to adverse effects. The drugs can be administered by pulmonary route utilizing two techniques: aerosol inhalation (also used in intranasal applications) and intratracheal instillation[6]. By applying aerosol technique, we could achieve more uniform distribution with greater extent of penetration into the peripheral or the alveolar region of the lung, but this costs more and also faced with difficulty in measuring the exact dose inside the lungs[7]. In contrary to this, instillation process is much simple, not expensive and it has non-uniform distribution of drugs[8]. Drug–device combinations must aerosolize the drug in the appropriate particle size distribution and concentration to ensure optimal deposition and dose in the desired region of the lung[9].

Anatomy and physiology of lungs

In order to understand the proper mechanism of deposition of drugs, it is important to understand the anatomy and physiology of lungs. Air enters the respiratory passages via the nose or mouth at the entrance to the nasal passage then next to the pharynx.The air, in essence oxygen, then passes through the larynx and trachea to enter the chest cavity. The larynx, or voice box, is located at the head of the trachea, or windpipe. In the chest cavity, the trachea branches off into two smaller tubes called the bronchi which enter the hilus of the left and right lungs. The bronchi are then further subdivided into bronchioles. These, in turn, branch off to the alveolar ducts which lead to grape like clusters called alveoli found in the alveolar sacs. The anatomy of the respiratory system is shown in Figure 1 below. The walls of alveoli are extremely thin (less than 2μm) but there are about 300 millions of alveoli (each with a diameter about 0.25 mm). If one flattens the alveoli, the resulted surface can cover about 100 m^2 [10].

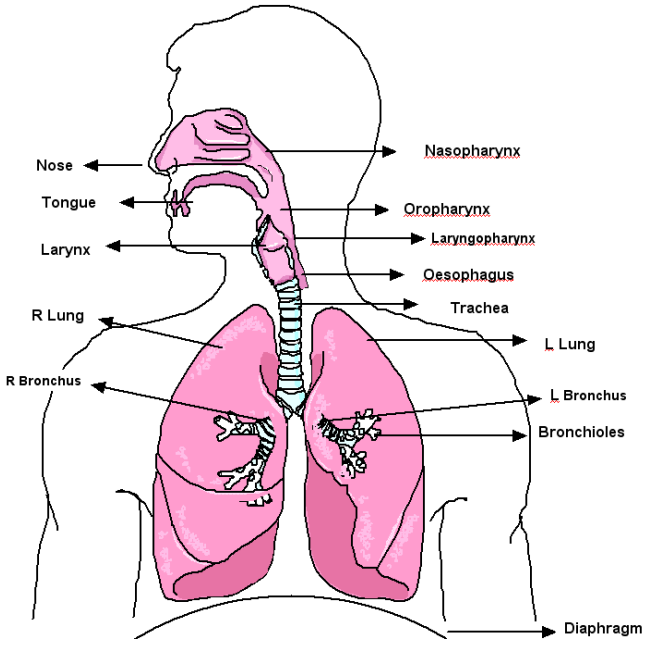

Fig.1. Anatomy of respiratory system

Pharmacokinetics of pulmonary acting drug

The optimal absorption characteristics of a pulmonary drug depend on the site of drug action. For pulmonary acting drug, absorption from the lungs determines the therapeutic effect profile (onset, intensity, and duration of action) of the drug. The lung appears to play a minimal role in drug metabolism; however, it plays a significant role in the distribution and accumulation of a variety of endogenous and exogenous compounds. The mechanism determining the distribution into the lung tissue is suggested to be simple diffusion followed

by association with tissue components, such as partitioning into membranes and subcellular organelles. The metabolism of many endogenous compounds such as serotonin, norepinephrine, bradykinin, and encephalin, occurs in the endothelial cells of the lung, whereas most xenobiotic metabolizing enzymes (i.e. phase I and II enzymes) are located within the epithelial cells (mainly the Clara cells and alveolar type II cells). An inhaled drug substance may be eliminated from the lung by mucociliary or cough clearance to the gastrointestinal tract, by passive or active absorption into the capillary blood network, or by metabolism in the mucus or lung tissue. This mechanism may act in parallel and are responsible for the disposition and dissipation of the initially high local drug concentration in the lung over timeas shown in figure 2. Since elimination by absorption and metabolism, and pharmacodynamics activity requires the drug to be in solution, dissolution of drug becomesa rate determining step for absorption[11].

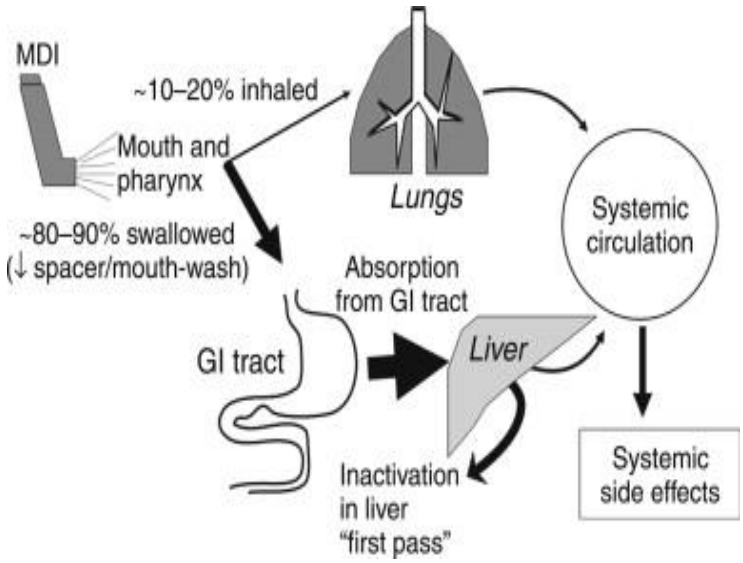

Fig.2. Pharmacokinetics of inhaled drug

Challenges in pulmonary drug delivery

For the development of pulmonary drug delivery devices, there need to study the various challenges which are involved in the pulmonary delivery of drug. These challenges are explained as follows,

1. Low Efficiency of inhalation system

For efficient drug delivery particle size is the most important factor,if the particles are too large, they impact in the oropharynx and larynx. If they are too small, they will be exhaled. Most existing MDI systems can only deliver a small fraction (about 10–20%) of the dispensed drug in the correct particle size for deep lung deposition although, recently

developed 1µm solution aerosols from corticosteroid pMDI have achieved lung deposition efficiencies of 60% or more.

2. Less drug mass per puff

With most existing systems, the total amount of drug per puff delivered to the lower respiratory tract is too low less than 1000 mcgto enable practical delivery of many macromolecules which require milligram doses.

3. Poor formulation stability for drug

Existing aerosol systems are not designed to protect the formulations of delicate macromolecules.Most traditional small molecule asthma drugs are crystalline and, in the case of corticosteroids, relatively moisture resistant in the dry state. They are also rather stable in liquids as compared to most macromolecules, which are unstable in the liquid state, amorphous, and highly moisture sensitive in the dry state.

4. Improper dosing reproducibility

For a variety of reasons, the dosing reproducibility of many existing systems is too variable for systemic delivery of most macromolecule drugs. Physicians and patients alike have tolerated the highly variable dosing of inhaled asthma medications for years because the drugs have a wide therapeutic window and optimizing the drug dose is usually a matter of trial and error. In the case of the bronchodilators, the rapid improvement characterized by easier breathing has enabled patients to know whether or not they have used the proper inhalation technique and dose.[12]

Mechanisms of Particle Deposition In The Airways

Main mechanisms responsible for particulate deposition in the lungs are gravitational sedimentation, impaction and diffusion.

Gravitational sedimentation

This is the physical phenomenon by which particles with sufficient mass are deposited due to the force of gravity when they remain in the airway for a sufficient length of time. This predominates in the last 5 bronchial generations, where the air speed is slow and the residence time is therefore longer. Gravitational sedimentation of an inhaled particle is dependent on its size and density, in addition to its residence time in the airways.

Sedimentation is an important deposition mechanism for particles in the size range 0.5-3µm, in the small airways and alveoli, for particles that have escaped deposition by impaction.

Inertial impaction

This is the physical phenomenon by which the particles of an aerosol tend to continue on a trajectory when they travel through the airway, instead of conforming to the curves of the respiratory tract. Where a bifurcation occurs in the respiratory tract, the airstream changes direction and particles within the airstream, having sufficiently high momentum, will impact on the airways' walls rather than follow the changing airstream. This deposition mechanism is particularly important for large particles having a diameter greater than 5µm, and particularly greater than 10µm, and is common in the upper airways, being the principal mechanism for deposition in the nose, mouth, pharynx and larynx and the large conducting airways. With the continuous branching of the conducting airways, the velocity of the airstream decreases and impaction becomes a less important mechanism for deposition.

Brownian diffusion

Collision and bombardment of small particles by molecules in the respiratory tract produce Brownian motion. The resultant movement of particles from high to low concentrations causes them to move from the aerosol cloud to the airways walls. The rate of diffusion is inversely proportional to the particle size, and thus diffusion is the predominant mechanism for particles smaller than 0.5µm[13].

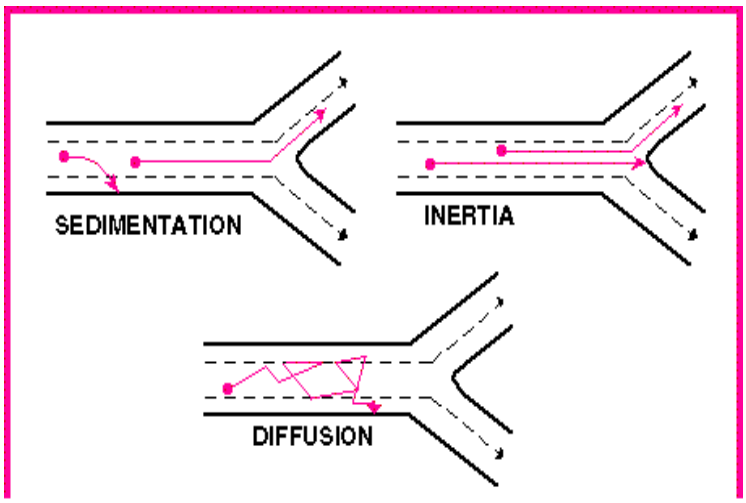

Fig.3. Mechanisms of particle deposition in the airways

Pulmonary drug delivery devices

The drugs can be administered by pulmonary route utilizing two techniques[14];

Aerosol inhalation

Intratracheal instillation

Aerosol technique have more uniform distribution with greater extent of penetration into the peripheral or the alveolar region of the lung, but this costs more and also faced with difficulty in measuring the exact dose inside the lungs. In contrary to this, instillation process is much simple, not expensive and has non-uniform distribution of drugs.

Aerosols

Aerosols are the dosage forms containing therapeutically active ingredients that are packaged under pressure in a sealed container and are released as a fine mist of spray upon activation of a suitable valve system. There are of three types[15] based on the states of matter present. These are:

1. Two-phase system. (Gas and liquid)
2. Three-phase system. (Gas, liquid, solid or liquid)
3. Compressed gas system.

Each of the aerosol system has following basic components[16]

1. Propellants
2. Containers
3. Product concentrate (containing API)
4. Valve and Actuators

Propellants

For pressurized metered dose inhalations propellants perform the essential function of expelling the material from the container by supplying the necessary pressure within the aerosol system. They are liquefied or compounded gases having vapour pressures exceeding employed to obtain the necessary delivery and spray characteristics of the aerosol. The commonly used propellants in aerosol systems are hydrocarbons, especially the fluorochloro derivatives of methane and ethane, the butanes, pentanes and compressed gases are used

.

Containers

Aerosol containers are usually made up of glass, plastic, metal or combination of these materials. Glass containers (uncoated glass container and plastic coated glass container) must

be precisely engineered to provide maximum in pressure, safety and impact resistance. Plastics (eg.Polyethylene naphthalate, Polyethylene terephthalate, etc.) must be employed to coat the glass to improve safety characteristics or to coat metal containers to improve corrosion resistance and enhances the stability of formulation. Metals include stainless steel, aluminium and tin-plated steel. Aerosol containers are made of metal(stainless steel, aluminium or tin-platedsteel), glass or plastic or a combination ofthese materials. The containers must be sodesigned that they provide the maximum inpressure safety and impact resistance.

Product concentrate (containing API)

For satisfactory bioavailability the active ingredients should have the majority of particles under 10μm in size in the case of inhalation aerosols and not more than 100μm for other types of aerosols.

Valves and Actuators

The valve regulates the flow of the active ingredient(s) and propellant from the container and determines the spray characteristics of the aerosol. It must be manufactured from materials which are inert to the contents of the aerosol. The commonly used materials are rubber, plastic, aluminium and stainless steel. Dispersing of potent medication at proper dispersion/ spray approximately 50 to 150 mg ±10 % of liquid materials at one time use of same valve. The actuator is fitted to the aerosol valve stem is a device which on depression or any other required movement opens the valve and directs the spray to the desired area.

Manufacturing of pharmaceutical aerosol

As explained earlier, fluorinated hydrocarbon gases may be liquefied by cooling below their boiling point or by compressing the gas at room temperature. These two features are used in the filling of aerosol containers with propellant.

Cold filling method

Two methods are involved In the first method, the product concentrates are chilled to temperature of – 30 to – 40^0 F. The chilled product concentrates are added to the chilled aerosol container. The chilled propellant is added through an inlet valve present under side of the valve of the aerosol container. In the second method, both the p product concentrate and the propellant are chilled to –30 to –40^0 F. Then the mixture is added to the chilled container.

In both the above methods, after the aerosol containers are filled, the valves are set in its place and the filled aerosol containers are passed through a water bath in which the contents of the containers are heated to 130^0 F to test for leaks and strength. Then the containers are air dried, capped and labelled. Cold filling method is advantageous for the filling of metering valve containing aerosol container. The pressure filling method is more prominent than cold filling method as most of the formulations cannot be cooled to very low temperatures[17].

Pressure filling method

By the pressure method, the product concentrate is quantitatively placed in the aerosol container, the valve assembly is inserted and crimped into place, and the liquefied gas, under pressure, is metered into the valve stem from a pressure burette. The desired amount of propellant is allowed to enter the container under its own vapour pressure. When the pressure in the container equals that in the burette, the propellant stops flowing. Additional propellant may be added by increasing the pressure in the filling apparatus through the use of compressed air or nitrogen gas. The trapped air in the package may be ignored if it does not interfere with the quality or stability of the product, or it may be evacuated with a special apparatus. After the container is filled with sufficient propellant, the valve actuator is tested for proper function. This spray testing also rids the dip tube of pure propellant prior to consumer use. Pressure filling is used for most pharmaceutical aerosols. It has two advantages over cold filling: there is less danger of moisture contamination of the product, and less propellant is lost in the process[18].

Qualitycontrol of pharmaceutical aerosols

Quality control of pharmaceutical aerosols includes the testing of propellant, valves, actuator, dip tubes, containers, weight checking, leak testing and spray testing[19].

1) Valves, actuators and dip tubes

The test for valves requires 25 valves and placed on suitable containers then containers were filled with specific test solutions. A button type actuator with 0.02 inch orifice is attached. The containers are placed in a suitable atmosphere at a temperature of 25 ± 1^0C· When the products have attained the temperature of 25 ±1^0C, the filled containers are actuated to fullest extent for 2 seconds. This procedure is repeated for a total of 2 delivered from each 25 test units. The valve delivery per actuation in µl=$\frac{\text{Individual delivery weight in mg}}{\text{Specific gravity of test solution}}$

For valve delivering: 54µl or less, the limits are ± 15% 55 to 200µl, the limits are ± 10% Out of the 50 individual deliveries, if four or more are outside the limits for the specified valve

delivery, the valves are rejected, if three individual deliveries are outside the limits, another twenty five valves are sampled and the test is repeated. The lot is rejected if more than one delivery is outside the specifications. If two deliveries from one valve are beyond the limits another twenty five valves should be taken then the lot is accepted if not more than one delivery is outside the specifications.

Containers

Containers must be examined for defects in linings. Quality control aspects of containers include degree of conductivity of electric current as measure of exposed metals. Glass containers examined for flaws. The dimensions of the neck and other parts must be checked.

Weight checking

Weight checking is carried out periodically by adding empty tarred containers to filling lines which after filling with product concentrate are removed and reweighed. Same procedure is used for checking weight of the propellant.

Leak test

Leak testing is carried out by checking the crimping of the valve. For metal containers this is accomplished by measuring the "crimp" dimensions. Final testing of valve closure is done by passing filled containers through the water bath.

Spray testing

Spray testing is serves to clear the dip tube of pure propellant and pure concentrate, and to check any defects in the valve and the spray pattern.

Evaluation tests of pharmaceutical aerosols

The final packed aerosol containers are evaluated for the following tests in order to ensure the patient's safety and to assure the quality of the aerosol dosage form. These are as:

1. Flammability and combustibility for the packaging container

   It includes Flame projection and Flame extension.
2. Performance test for product

   It includes the following tests

1. Aerosol Valve Discharge Rate

   This is determined by taking an aerosol product of known weight and discharging the content for given period of time, change in weight per time dispensed is checked.

2. Spray patterns

   This method involves the impingement of sprays on a piece of paper that has been treated with dye-talc mixture. It gives a record of the spray pattern

3. Dosage with metered valves

   Two points must be considered; reproducibility of dosage each time the valve is depressed and amount of medication actually received by the patient.

4. Net contents

   The tarred cans that have been placed onto the filling line are reweighed and the difference in weight is equal to the net content.

5. Foam stability

   The methods include visual evaluation, time for a given mass to penetrate the foam, etc.

6. Particle size determination

   Cascade impactor and light scattering decay methods are used for particle size determination.

3. Biologic testing

Therapeutic activity and Toxicity are considered in Biologic testing.

Therapeutic Activity

1. For Inhalation Aerosols: The determination of therapeutic activity is dependent on the particle size.

2. For Topical Aerosols: Therapeutic activity of aerosol products are determined by applying the therapeutically active ingredients topically to the test areas and the amount of therapeutically active substances absorbed is determined. Toxicity study: For Topical Aerosols: The topically administered aerosols are checked for chilling effect or irritation in the skin. When aerosol are topically applied, thermistor probe attached to the recording thermometer are used to determine the change in skin temperature for a given period of time.[20]

Aerosols are delivered mainly by three delivery systems:

A) Inhalation drug delivery system by - Metered Dose Inhalers (MDI).

B) Inhalation drug delivery system by - Dry Powder Inhalers (DPI).

C) Inhalation drug delivery system by – Nebulizer.

Metered dose inhaler

The pressurized metered dose inhaler (MDI) is the most widely used device for aerosol therapy. Over 70 million patients in the world use one, either alone or with a spacer fitted[21]. The device incorporates a disposable canister, where the drug formulation is stored which can be replaced for a new one at any time. A pMDI combines an aluminium canister mounted in a plastic actuator. The four basic components that can be found in all pMDI arethe formulation canister; the metering valve; the actuator, and the container[22] as shown in the figure 4. The formulation is made up by the drug, the propellants and often contains surfactant and other excipients. Propellants most commonly used are chlorofluorocarbons (CFCs): trichlorofluoromethane, dichlorodifluoromethane and dichlorotetra-fluoroethane, usually mixed.

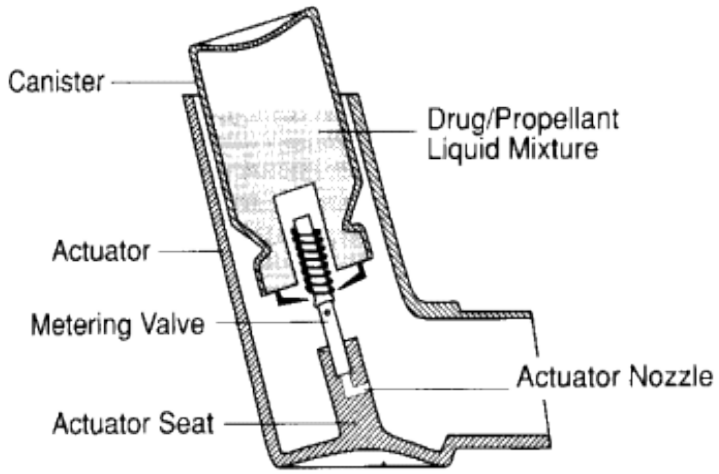

Fig.4. Meter dose inhaler

Trends in MDI technology:

1. There has been much interest in the differences in effects of Enantiomer of many medications, and beta agonist adrenergic bronchodilators have received much attention. Recently levo salbutamol active enantiomer of salbutamol is present in market which is free from termers and palpitation that seen in salbutamol.
2. Use of Spacers (figure 5) to improve patient coordination with MDI.

Fig.5. Spacer

3. The Autohaler TM is the first breath actuated or activated pressurized metered dose inhaler. Autohaler solve the key problem of the pressurized metered dose inhaler (pMDI), does not rely on the patient's inspiratory effort to aerosolize the dose of medication unlike dry powder inhalers.

Advantages

1. It is Compact and Portable device.
2. It multidose (approximately 200 doses) device and also inexpensive.
3. It will give sealed environment (no degradation of drug) and reproducible dosing.

Disadvantages

1. For pMDI, Inhalation technique and patient co-ordination required.
2. In this involve high oral deposition and give maximum dose of 5 mg.
3. Limited range of drugs available

Marketed product

Asthalin Inhaler 100mcg (Salbutamol)

It is used as bronchodialtor and it contains active ingredient salbutamol, manufactured by Cipla Pharmaceuticals.

Dry powder inhaler

Dry powder inhalers have been widely used to deliver medicinal powders into the lungs for local or systemic treatments. These portable devices provide single- or multidoses via oral inhalation, depending on the design of the powder reservoir and metering components.

Particles inevitably undergo triboelectrification from contacts with each other and with surfaces inside the inhaler during aerosolization. The drug is either preloaded in an inhalation device or filled into hard gelatine capsules or foil blister discs which are loaded into a device prior to use. DPIs have several advantages over MDIs. DPI formulations are propellant free and do not contain any excipient, other than a carrier - which is almost invariably lactose. The conventional DPI uses the energy supplied by the patient's inspiration to dispense and disperse a premetered quantity of drug substance. To produce particles of a suitable size (preferably less than 5 µm), drug powders for use in inhalation systems are usually micronized. The high-energy powders produced have poor flow properties because of their static, cohesive and adhesive nature. The flowability of a powder is affected by physical properties, including particle size and shape, density, surface roughness, hardness, moisture content and bulk density[23]. Currently there are two types (figure 6);

Unit-Dose: Devices Single-dose powder inhalers are devices in which a powder contained capsule is placed in a holder. The capsule is opened within the device and the powder is inhaled[24].

Multi-dose Devices: Multi-dose device uses a circular disk that contains either four or eight powder doses on a single disk. The doses are maintained in separate aluminium blister reservoirs until just before inspiration[25].

Fig.6. Unit and multi dose dry powder inhaler

Trends in dry powder inhalation technology

1. Changes in the performance of the DPI can be achieved either through changes in the design of the device through changes in the powder formulation, the forces governing the particle-particle interactions in the agglomerates and the forces playing a role in the de-agglomeration process.
2. Supercritical fluid technology is applied to improve the surface properties of the drug substance. Large porous particles have reduced inter-particulate forces because of their low density, the irregular surface structure and/or reduced surface free energy. Moreover, these particles are claimed to have improved aerodynamic behaviour in the airways, whereas phagocytosis of the deposited particles in the alveoli is reduced. In another approach, smaller porous particles (3-5 mm) have been used to improve de-agglomeration and lung deposition.
3. Changes in device technologies are few new developments really aim at an increase of the de-agglomeration forces generated during the inhalation.
4. Air classifier Technology has been recently used in the devices to prevent agglomeration in devices.
5. Modified form of Air classifier technology is multiple air-classifier technology. In this technology multiple classifier chambers are placed in a parallel arrangement, which further increases the dose that can be aerosolized.

Advantages

1. This device is compact, portable and breathe actuated.
2. It is easy to use.
3. For administration no hand-mouth co-ordination is required.

Disadvantages

1. In this respirable dose dependent on inspiratory flow rate.
2. Humidity may cause powders to aggregate and capsules to soften.
3. Dose will lost if patient inadvertently exhales into the DPI.
4. Most DPIs contain lactose.

Marketed product

Combihale™ It is used in the treatment of asthma and is available in two combinations, Combihale™ FF (Formoterol + Fluticasone) and Combihale™ FB (Formoterol + Budesonide), manufactured by Dr Reddy's Laboratories.

Nebulizer

Nebulizers are regulated as medical devices by the U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH). They are tested in accordance with applicable standards for medical device electrical safety, electromagnetic compatibility, environmental temperature and humidity, shock and vibration as well as for their biocompatibility of materials. Nebulizers are designed to be used with a broad range of liquid formulations. Drugs for use with nebulizers are approved by the FDA and the Center for Drug Evaluation and Research (CDER). Historically, drug solutions for inhalation were approved based on studies using standard jet nebulizers ranging in efficiency from 6–12%. The use of more efficient nebulizers created the risk of delivering inhaled dose above the upper threshold of the therapeutic window, increasing the risk of side effects and toxicity. Consequently, the FDA requires that the drug label of new liquid formulations identify the nebulizers used in the clinical studies. Because drug delivery varies with different nebulizer types, it is important to use the nebulizer cited on the drug "label" when possible. At the very least, clinicians should be aware of the relative performance of the "label" nebulizer[26].

Jet nebulizers

Jet nebulizers (also called air-jet or air-blast nebulizers) use compressed gas (air or oxygen) from a compressed gas cylinder, hospital air-line or electrical compressor to convert a liquid (usually an aqueous solution) into a spray. In a jet nebuliser the driving gas passes through a very narrow hole, known as a venturi, from a high pressure system (fig.7). At the venturi the pressure falls and the gas velocity increases greatly producing a cone shaped front. This passes at high velocity over the end of a narrow liquid feed tube or concentric feeding system creating a negative pressure at this point. As a result of this fall in pressure, liquid is sucked up by the Bernoulli Effect and is drawn out into fine ligaments. The ligaments then collapse into droplets under the influence of surface tension. This primary generation (atomisation) typically produces droplets 15–500 m in diameter. Coarse droplets impact on baffles while smaller droplets may be inhaled or may land on internal walls returning to the reservoir for renebulisation. Baffle design has a critical effect on droplet size.

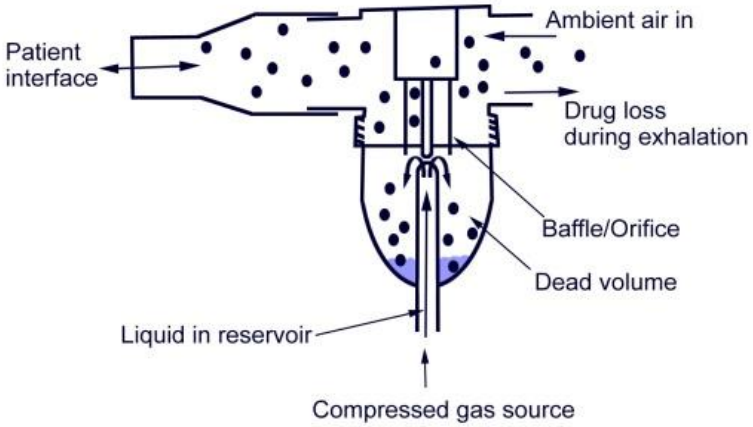

Fig.7. Jet nebulizer

Ultrasonic nebulizer

The ultrasonic nebulizer uses a rapidly vibrating piezoelectric crystal to produce aerosol particles. Ultrasonic vibrations from the crystal are transmitted to the surface of the drug solution where standing waves are formed. Droplets break free from the crests of these waves and are released as aerosol. The size of droplets produced is inversely proportional to two thirds of the power of the acoustic frequency. Like jet nebulisers, baffles within the nebuliser remove large droplets and much of the aerosol produced impacts on these, falling back into the drug reservoir[27].

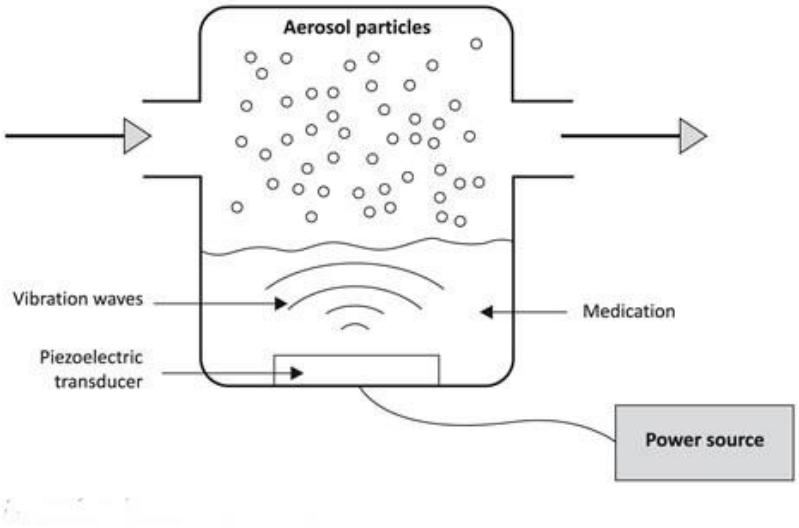

Fig.8. Ultrasonic nebuliser

Trends in nebulizer technology:

1. Recent developments in liquid aerosol technology combine the advantages of pMDI and nebulizers are called metered dose liquid inhalers. The major advantage that all these systems aim for is a reduced velocity of the aerosol. Liquid inhalers applying the concept of a low velocity aerosol are often referred to as 'soft mist inhalers'.
2. Wet nebulization aims at the generation of monodisperse aerosols, the absence of propellants in the formulation by applying aqueous drug formulations, a reduction in the residual volume after nebulization and an improved portability compared with nebulizers.

Advantages

1. For administration of drug no specific inhalation technique or co-ordination required.
2. It will aerosolize most drug solutions and delivers large doses.
3. It is suitable for infants and people too sick or physically unable to use other devices.

Disadvantage

1. This is time consuming, nonportable and relatively expensive device.
2. Contents easily contaminated.
3. In this delivery system having poor delivery efficiency and drug wastage.

Intratracheal inhalation

Intratracheal inhalation is used frequently for the exposure of animals to particles, both soluble and insoluble. It is a relatively inexpensive method of administration that allows for the instantaneous delivery of a known amount of test material, suspended in a small volume of vehicle, directly to the lung, or even to a single lobe within the lung. Because it administers the material directly to the lower respiratory tract, it avoids deposition in the nasal passages and/or on the fur as can occur in nose-only or whole-body inhalation exposure systems, thus making it very useful for studying the effects of test materials on the lower respiratory tract. This method is particularly well-suited for the administration of highly toxic or radioactive materials, as the dose is confined to a small volume, eliminating the need for decontamination of large pieces of equipment.

Intratracheal inhalation has a number of characteristics which could make it a useful tool in studying the effects of inhaled materials. Like other inhalation exposure systems, it delivers the test material to the lungs with an even distribution. The intratracheal inhalation system is also considerably smaller than even many small whole-body and nose-only inhalation

systems, so that a smaller amount of test material would be needed to achieve a given aerosol concentration. Additionally, the intratracheal inhalation system is closed, with all air and test material remaining enclosed within the relatively small apparatus and being passed through a filter before exhaust, thus facilitating its use in the study of highly toxic or radioactive substances[28].

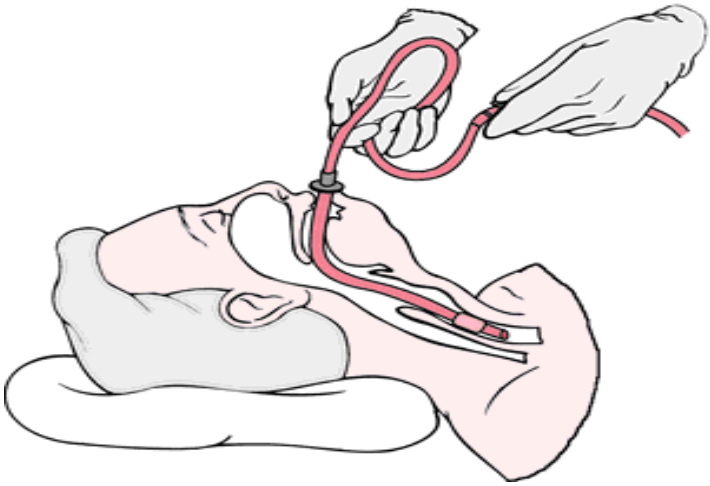

Fig.9. Intratracheal inhalation

Applications of pulmonary drug delivery

1. Asthma and Chronic Obstructive Pulmonary Disease (COPD)

Asthma is a chronic inflammation of the airways with reversible episodes of obstruction, caused by an increased reaction of the air- ways to various stimuli. This is a group of debilitating, progressive, and potentially fatal lung diseases that have in common increased resistance to air movement, prolonged expiratory phase of respiration, and loss of the normal elasticity of the lung tissue[29]. Today's inhaled drug delivery market is conquered by the three main classes of drug such as bronchodilators, corticosteroids, and anticholinergic. All these three classes of drugs are given by pulmonary route only. levosalbutamol inhalers are present in the market to treat asthma. Titropium inhalers are present in market to teat COPD[30].

2. Diabetes

Diabetes is a syndrome of disordered metabolism and unfortunate hyperglycaemia resulting from an insufficiency of insulin secretion or resistance. Various companies are working on insulin inhalers than any other insulin delivery option. Insulin inhalers would work much like asthma inhalers. The products fall into two main groups the dry powder formulations and solution, which are delivered through different patented inhaler systems. E.g. Novel pMDIformulations for pulmonary delivery of proteins[31].

3. Angina pectoris

Angina pectoris is symptoms of myocardial ischemia and it is arises as a result of imbalance between oxygen supply and demand of myocardium. An aerosol form has been tested in Europe and has been found comparable to sublingual nitroglycerine. In particular, its efficacy has been found better than nitroglycerine tablets in patients with dry mouth. Isosorbide aerosol has also been reported of use in hypertensive emergency[32.]

4. Pulmonary arterial hypertension

Pulmonary hypertension in the setting of chronic hypoxia due to underlying lung disease represents a challenging area for evaluation and management. In 2004, the FDA approved "Ventavis" (iloprost), an inhaled treatment for pulmonary arterial hypertension, made by CoTherix (South San Francisco, CA, U.S.A.)[33].

5. Lung cancer chemotherapy

Lung cancer is the most malignant cancer today. Lung cancer is one of the most lethal cancers and the second most common cancer in both men and women[34]. A study is going on with respect to aerosolized paclitaxel solution to mice with lung tumours. The treatment significantly reduces lung tumours and prolongs survival. Aerosol delivery of the anticancer agent's difluoro methylornithine and 5- fluorouracil reduces lung tumours in mice 50 % and 60 %, respectively. Interleukin-2 stimulates immune function[35].

6. Bone disorders

Disease such as osteoporosis and Paget's disease of bones can be treated by pulmonary delivery. Clinical evidence from a variety of other peptides and proteins indicates that pulmonary delivery is safe, efficient, well tolerated and preferred by patients so pulmonary route is better option to treat bone disorders. A pulmonary formulation inhaled through the mouth that delivers calcitonin or PTH into the deep lung should improve the bioavailability and efficacy of the drugs[36].

7. Opioids as pain therapeutics

For pain management painful inject able are given. To avoid pain associated with injectable pain killer,pulmonary opioid delivery is better alternative[37]. Inhaled opioids are rapidly, completely and reproducibly absorbed into the bloodstream. Thus, the pulmonary route has excellent potential for treating noninvasively severe pain in the postoperative setting and in malignant disease[38].

8. Gene therapy via pulmonary route

Gene therapy holds great potential for the treatment of various acquired and inherited pulmonary diseases. Main application of Gene therapy admininstered by pulmonary route is for the treatment of cystic fibrosis. Cationic-lipid mediated CFTR gene transfer can significantly influence the underlying chloride defect in the lungs of patients with CFC[39].

Recent advances in pulmonary drug delivery

Liposomes

Liposomes are one of drug delivery systems known pharmaceutically as vesicles. They can be prepared from phospholipids with or without cholesterol in a wide range of sizes, from 20 nm to 10 pm, and structurally have one or more lipid bilayers, separated by aqueous compartments, surrounding an aqueous core. Liposomes seem particularly appropriate for delivery of drugs to the lungs as they can be prepared from materials endogenous to the lung as components of lung surfactant. The rate and extent of pulmonary uptake of liposomes are a function of their composition, significantly faster rates occurring when liposomes contain phosphatidylglycerol[40]. More recently, it is being investigated as a vehicle for sustained-release therapy in the treatment of lung disease, gene therapy and as a method of delivering therapeutic agents to the alveolar surface for the treatment of systemic diseases[41].

Large porous particles

Pulmospheres are the new type of aerosol formulation is the large porous hollow particles,. They have low particle densities, excellent dispersibility and can be used in both MDI and DPI type of delivery systems. These particles can be prepared using polymeric or nonpolymeric excipients, by solvent evaporation and spray-drying techniques. Pulmospheres are made of phosphatidylcholine, the primary component of human lung surfactant. The large size of Pulmospheres allows them to remain in the alveolar region longer than their nonporous counterparts by avoiding phagocytic clearance. For example, in one of the study, it was found that after intratracheal administration into rats, only 8% and 12.5% of macrophages contain Pulmospheres particles which were found and 48 hours respectively after inhalation, whereasapproximately 30% and 39% of macrophages contained nonporous particles when administered during a similar time interval. Inhalation of large porous insulin particles resulted in elevated systemic levels of insulin and suppressed systemic glucose levels for 96 hours, whereas small nonporous insulin particles had this effect for only 4 hours. High systemic bioavailability of testosterone was also achieved by inhalation delivery of

porous particles with a mean diameter (20µm) approximately 10 times that of conventional inhaled therapeutic particles[42].

Biodegradable polymers

Apart from Liposomes, **biodegradable polymer microspheres** are currently being studied as sustained release pulmonary drug carriers. Polymers such as polylacticacid used in medical applications such as sutures, orthopaedic implants,medical dressings and poly glycolic acid have been investigated. Although a limited amount of research has been published in this area, the sustained-release profiles achieved with corticosteroids appear promising. However, the toxicity of this type of formulation needs to be established in humans for promising lung delivery of these microspheres[43].

Polymeric nanoparticulate system

The main role of polymeric nanoparticles in drug delivery system is to carry the drug molecules, to protect drugs from degradation, and to control drugrelease. Therapeutically used **polymeric nanoparticles** are composed of biodegradable or biocompatible materials, such as poly (ε-caprolactone) (**PCL**), poly(lactic acid)(**PLA**), poly(lactic-co-glycolic acid) (**PLGA**), alginic acid, gelatin and chitosan. Due to their biocompatibility, surface modification capability, and sustained-release properties, polymeric nanoparticles are intensively studied using various important pulmonary drugs. These pulmonary drugs include antiasthmatic drugs, antituberculosis drugs, pulmonary hypertension drugs, and anticancer drugs[44].

Solid lipid nanoparticles in pulmonary delivery

Solid lipid nanoparticles (SLNs) are made from solid lipids (i.e., lipids solid at room temperature), surfactant(s) and water. Since the beginning of 1990s, the SLNs have been focused on an alternative to polymeric nanoparticles. The advantages of drug release from SLNs in the lung are control of the release profile, achievement of a prolonged release and having a faster in vivo degradation compared to particles made from PLA or PLGA. In addition, SLNs proved to possess a higher tolerability in the lungs compared to particles made from some polymeric materials. Their being published on the pulmonary applications of SLNs as local delivery carriers for small molecules or as systemic delivery carriers for macromolecules[45].

Submicron emulsions in pulmonary Delivery

Until now, the submicron emulsion system has not yet been fully exploited for pulmonary drug delivery and very little has been published in this area. Cationic submicron emulsion loaded with Mycobacterium tuberculosis Ag85B DNA vaccine was explored for the pulmonary mucosal vaccination. Emulsion systems have been introduced as alternative gene transfer vectors to liposomes[46].

CONCLUSION

Pulmonary drug delivery is a developed technology in which medication is inhaled through the lungs and enters the bloodstream through the alveolar epithelium. Pulmonary drug delivery provides a simple way of systematic delivery with greater efficiency. The delivery device plays a major role in the efficiency of pulmonary delivery, and therefore recently many improvements have been made in the development of new devices and existing devices. The devices most commonly used for respiratory delivery, including nebulizers, metered-dose inhalers, and dry powder inhalers, these can be made adaptable for delivery of protein and peptide drugs. The choice of device will depend on the drug, the formulation, the site of action, and the pathophysiology of the lungs. One of the major challenges in this system is achieving the optimum particle size, which is utmost requirement for the targeted delivery of drug to lungs. Lung serves as important organ for major contribution of research in this area and it can be help to achieve safer pulmonary drug delivery in the treatment of chronic diseases.Thus understanding of challenges and overcoming, it coupled with anatomical and biopharmaceutical fundamentals helps in minimising the technical gaps and hence promote the future advancement in formulation of new developed strategy for pulmonary drug delivery.

REFERENCES

1. Lachman L., Lieberman H. and Kang J.: The Theory and Practice of Industrial Pharmacy. Varghese Publishing House, Second Edition, 1976.
2. Sanders M.: Inhalation Therapy an Historical Review. Primary Care Respiratory Journal; 2007; 16(2): 71-81.
3. Hugh C., Anthony J.: Controlled Pulmonary Drug Delivery. Springer, CRC Publisher, 2011.

4. Shaikh S., Nazim S., Khan T., Shaikh A., Zameeruddin M. and Quazi A.: Recent Advances in Pulmonary Drug Delivery System: A Review. International Journal of Applied Pharmaceutics; 2010; 4: 273.
5. Swarbrick J: Encyclopedia of PharmaceuticalTechnology. Informa Healthcare, Third Edition2007.
6. Aulton M., Taylor K.: Aulton's Pharmaceutics the Design and Manufacture of Medicines. Churchill Livingstone, Third Edition, 2007.
7. Sunitha R., Suria Prabha K.and Muthu P.: Drug Delivery And Its Developments For Pulmonary System. International Journal of Pharmaceutical, Chemical and Biological Sciences; 2011; 1(1): 66-82.
8. Patil J. et.al.: Pulmonary Drug Delivery Strategies - A Concise, Systemic Review. Lung India (Official Publication of Indian Chest Society); 2012; 29(1): 44-49.
9. Labiris N. and Dolovich M.: Pulmonary Drug Delivery- Part II: The Role of Inhalant Delivery Devices and Drug Formulations in Therapeutic Effectiveness of Aerosolized Medications. British Journal of Clinical Pharmacology; 2003; 56:600–612.
10. Waugh A.: Ross and Wilson Anatomy and Physiology in Health and Illness. Elsevier Health Sciences, Eleventh Edition, 2010.
11. Olsson B., Et Al.: Pulmonary Drug Metabolism and Clearance. Controlled Pulmonary Drug Delivery-Advances In Delivery Science and Technology. CRC Publisher; 2011; pg 21-50.
12. Tangri P. And Khurana S.: Approaches To Pulmonary Drug Delivery Systems. International Journal of Pharmaceutical Science and Research; 2011; 2(7): 1616-1622.
13. Tena A. and Clara P.: Deposition of Inhaled Particles In The Lungs. Elsevier España; 2012; ARBR-606:1-7.
14. Jain K.: Drug Delivery System. Human Press, 2008.
15. Indian Pharmacopeia, Aerosol Therapy. 2010; pp1-25.
16. US Pharmacopeial Convention, Inc. The United States Pharmacopeia. 23rd Ed. Rockville, MD: US Pharmacopeial Convention, Inc.; 2009.
17. Nash R. and Wachter A.: Pharmaceutical Process Validation. Marcel Dekker, Inc, Third Edition 2003.
18. Allen L., Popovich N. and Ansel H.: Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems.Lippincott Williams and Wilkins; 9th Edition, 2010.
19. Pokar H., Patel K. And Patel M.: Review On: Pharmaceutical Aerosol. Internationale Pharmaceutica Sciencia; 2012; 2: 58-66.

20. Lahakar S.: An Overview On: Pharmaceutical Aerosol. International Research Journal of Pharmacy; 2012; 3(9): 68-75.
21. Terzano C.: Pressurized Metered Dose Inhalers and Add-On Devices. Pulmonary Pharmacology and Therapeutics; 2001; 14: 351–366.
22. Oliveira R., Teixeira S., Silva L., Teixeira J. and Antunes H.: Study of A Pressurized Metered-Dose Inhaler Spray Parameters In Fluent. World Congress on Engineering; 2010 Vol. II; 978-988.
23. Ruzer L. and Harley N.: Aerosols Handbook Measurements Dosimetry and Health Effects; CRC Press, 2nd Edition, 2013, Pp-1-30.
24. Clark A.: Aerosol Science and Technology-Medical Aerosol Inhalers: Past, Present, And Future. Wiley-VCH, South San Francisco, 2007: 22:4, 374-391.
25. Chrystyn H.: The Diskus®: A Review of its Position Among Dry Powder Inhaler Devices. International Journal of Clinical Practice. 2007, 61, 6, 1022–1036.
26. O'Callaghan C. And Barry P.: The Science of Nebulised Drug Delivery. Thorax an International Journal of Respiratory Medicine;1997; 52 (Suppl 2):S31–S44.
27. Hickey A.: Pharmaceutical Inhalation Aerosol Technology. Marcel Dekker,Inc., Second Edition, 2004.
28. Osier M. and Oberdorster G.: Intratracheal Inhalation vs. Intratracheal Instillation: Differences in Particle Effects. Fundamental and Applied Toxicology1997; 40: 220 - 227.
29. Harrison E: National Respiratory Care Handbook. Jones and Bartlett Publishers, 2011.
30. Mcelvaney, G., Hubbard, C. and Birrer, P.: Aerosol A-1 Antitrypsin Treatment for Cystic Fibrosis. Lancet; 1991; 337: 392–394.
31. Kordella T.: The Future Of Insulin: Pills, Patches, And Puffs Are Slowly Coming Down The Pipelin. From Diabetes Forecast, American Diabetes Association; March 2003.
32. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021780s000MedR.pdf
33. Robyn J. and Barst M.: Recent Advances in the Treatment of Pulmonary Artery Hypertension. ACC Current Journal Review; 1998:61-63.
34. Goel A., Baboota S., Sahni J., and Ali J.: Exploring Targeted Pulmonary Delivery For Treatment Of Lung Cancer. International Journal of Pharmaceutical Investigation; 2013; 3(1): 8–14.
35. Kinnula V., Cantell K. and Mattson K.: Effect of Inhaled Natural Interferon Alpha on Diffuse Bronchioalveolar Carcinoma. European Journal of Cancer; 1990; 26:740–741.
36. Patton J.: Pulmonary Delivery Of Drug For Bone Disorders-Advance Drug Delivery Review, 2000; 42(3): 239-248.

37. Vadivelu N., Mitra S. and Narayan D..: Recent Advances in Postoperative Pain Management. Yale Journal of Biology and Medicine;2010, 83:11-25.
38. Stephen J. and Babatunde A.: "Pulmonary Delivery Of Opioids As Pain Therapeutics", Advanced Drug Delivery Reviews; 2006, 58, 1076–1088.
39. Driskell R. and Engelhardt J.: Current Status of Gene Therapy For Inherited Lung Diseases. National of Health Public Access; 2003; 65: 585–612.
40. Taylor K. and Newton J.: Liposomes for Controlled Delivery of Drugs tothe Lung. Thorax an International Journal of Respiratory Medicine; 1992; 47:257-259.
41. Schreier H., Gonzalez-Rothi R. and Stecenko A.: Pulmonary Delivery of Liposomes. Journal of Controlled Release; 1993; 24(1-3): 209–223.
42. Edward D. Et Al.: Large Porous Particles for Pulmonary Drug Delivery. Science Magazine; 1997; 276(5320): 1868-1871.
43. Malika Skiba, Et Al. Development of Cyclodextrin Microspheres for Pulmonary Drug Delivery, Journal of Pharmacy Pharmaceutical Sciences; 2005; 8(3): 409-418.
44. Mansour H., Yun-Seok Rhee, Xiao Wu: Nanomedicine in Pulmonary Delivery. International Journal of Nanomedicine;2009; 4: 299–319.
45. Almeida AJ, Souto E. Solid Lipid Nanoparticles as a Drug Delivery System For Peptides And Proteins. Advanced Drug Delivery Reviews; 2007; 59(6):478–490.
46. Anthony Moran Astec Project Ltd "Next Generation Of Automated Pulmonary Drug Delivery System", Ondrugdelivery Lt, Aug 2007.