RECENT ADVANCES IN PULMONARY DRUG DELIVERY SYSTEM

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ABSTRACT
Pulmonary drug delivery system has been widely used in various diseases conditions like asthma, angina pectoris, diabetes, cancer, migraine, tuberculosis, acute lung injury and other. Pulmonary drug delivery system is a needle free technique. Pulmonary route has concerned as a tremendous scientific and biomedical importance in recent years due to its unique properties such as a large absorptive area and good blood supply. The aim of present review article is to discuss different era of pulmonary drug delivery systems like advances in development in technologies for pulmonary drug delivery, advancements in pulmonary drug delivery devices, advancements in formulation of pulmonary drug delivery, advancements in application of pulmonary drug delivery system and some important aspects of pulmonary drug delivery systems such as advantages, limitation, application and mechanism relating to pulmonary drug delivery system.

Keywords: pulmonary drug delivery system, dry powder inhaler, metered dosage inhaler, nebulizer.

INTRODUCTION
Pulmonary delivery of the drug has develop into an attractive target in the health care industry as the lung is capable of absorbing pharmaceuticals either for local deposition or for systemic delivery. The origin of inhaled therapies seen in back 4000 year ago to India, Where people smoked the leaves of the atropa belladonna plant to suppress cough. The development of an inhalation therapy which is efficient and safe depends not only on a pharmacologically active molecule, but also on a delivery system.[¹]

In recent years patients with respiratory diseases use various devices , which help the removal of mucus from the airways and the improvement of pulmonary function. The aim of the present study is to determine the effectiveness of the current devices of respiratory physiotherapy, as it comes from the review of literature. The current devices of physiotherapy for patients with respiratory diseases are presented as an alternative therapy method or a supplemental therapy and they can motivate patients to apply therapy by themselves. These devices seem to increase patient’s compliance to daily
treatment, because they present many benefits, as independent application, full control of therapy and easy use. In recent years, devices of respiratory physiotherapy have emerged which offer alternatives to standard chest physiotherapy which are less time-consuming and offer greater independence to the patient with chronic lung disease. According to recent literature, devices of respiratory physiotherapy are introduced as alternative therapy methods. In order to facilitate and improve mobilization of mucus from airways, through which better lung ventilation and improved pulmonary function can be achieved. These devices are safe and offer acceptable airway clearance to conventional chest physiotherapy.

Patients with chronic respiratory diseases prefer to use devices of respiratory physiotherapy because of their benefits, such as the independent application and the reduced cost of therapy. Aerosol treatments may be given while the patient is using these devices, if needed. The current devices of respiratory physiotherapy are: positive expiratory pressure, high frequency chest wall oscillation, oral high frequency oscillation, intrapulmonary percussive ventilation, incentive spirometry and the flutter device.\cite{2}

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**Fig 1: Anatomy and physiology of pulmonary system\cite{3}**

**Advantages of pulmonary drug delivery\cite{4-5}**

- It is needle free pulmonary delivery.
• It requires low and fraction of oral dose.
• Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug.
• Onset of action is very quick with pulmonary drug delivery.
• Degradation of drug by liver is avoided in pulmonary drug delivery.

Disadvantages of pulmonary drug delivery
• Oropharyngeal deposition gives local side effect.
• Patient may have difficulty using the pulmonary drug devices correctly.
• Drug absorption may be limited by the physical barrier of the mucus layer.
• Various factors affect the reproducibility on drug delivery on the lungs, including physiological and pharmaceutical barrier.
• The lungs are not only accessible surface for drug delivery complex but also delivery devices are required to target drug delivery.

Challenges in pulmonary drug delivery system<sup>[6]</sup>

Low efficiency of inhalation system
The major challenges in pulmonary drug delivery are the low efficiency of inhalation system. Optimum aerosol particle size is very important for deep lung delivery, since if the particles are too small, they will be exhaled, and if particles are too large, they have an effect on oropharynx and larynx. Optimum particle size for deep lung deposition is 1-5 mm.

Less drug mass per puff
Generally reasonable delivery of many drugs require milligram doses but to get an adequate effect through the pulmonary drug delivery with most existing systems, the amount of drug per puff delivered to the lower respiratory tract is too low less than 1000 mcg.

Poor formulation stability for drug
Most conventional small molecule asthma drugs are crystalline in nature, and relatively moisture resistant in the dry macro molecules. Whereas in the case of corticosteroids, which are unstable in the liquid state, amorphous, and highly moisture sensitive in the dry state.
Improper dosing reproducibility

The reasons for poor dosing reproducibility are degeneration of diseases, problem in device, and instability of formulation. To get maximum dose reproducibility patient education play important role.

Mechanism of deposition of particles and their becoming into the lungs after inhalation\[7-10\]

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 Particulate matter is the micron, or micrometer (10^-6 meter). The Particulate matter in an aerosol can range in size from 0.001 to greater than 100 microns in diameter. Particles intended to be administered by pulmonary route are generally categorized based on size:

- Coarse particles are larger than 2 microns in diameter
- Fine particles are between 0.1 and 2 microns in diameter
- Ultrafine particles are less than 0.1 micron

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

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 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 drug delivery systems for pulmonary administration. These systems can be broadly classified into immediate
release [e. G. Lactose-drug mixtures for dry powder inhaler (dpi) application] and controlled release systems (such as liposomes, micelles, nano- and microparticles based on polymers). Particulate drug carriers such as liposomes, microparticles and nanoparticles can be / have been used to improve the therapeutic index of new or established drugs by modifying drug absorption, reducing metabolism, prolonging biological half-life or reducing toxicity. Drug distribution is then controlled primarily by properties of the carrier and no longer by physico-chemical characteristics of the drug substance only. A careful design of such drug delivery systems, based on a thorough understanding of the clinical requirements for the disease conditions to be treated, lung architecture / physiology, appropriate selection of the carrier materials, production process and device, are key to successful delivery using advanced drug delivery systems such as liposomes and microparticles.[11-13]

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

Microparticles:

The terminology “microparticle” (size comprised between 1 and 999 μm) includes the microspheres (uniform sphere constituted of a polymeric matrix) and the microcapsules. Biodegradable microspheres, designed from natural or synthetic polymers, have been largely used as drug targeting systems via different routes. Hydrophilic and lipophilic molecules can be encapsulated or incorporated into microspheres. Compared to liposomes, microspheres have an in vivo and in vitro more stable physicochemical behavior and should allow a slower release and a longer pharmacological activity of the encapsulated drugs. Biodegradable microspheres are prepared by using varied polymers: albumin, chitosan, polysaccharide, poly (lacticco-
Glycolic acid, poly (lactic) acid, poly (butylcyanoacrylate) and poly (lactic-co-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.\cite{14}

**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, a carrier that has not been up to now much studied especially for pulmonary administration. However solid lipid Micro particles, 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 $\beta_2$-mimetic agent and thereby to prolong its duration of action. The active substance we chose to work with is salbutamol acetonide, 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 solid lipid Microparticles.\cite{15}

**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.[16]

**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 in rats have shown this method to indeed allow for minimal inhibitory drug concentrations 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 tuberculosis drugs, which may translate into a less frequent and attenuated drug treatment regimen.[17]

**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.\[18\]

**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 have proven to be non-toxic in acute human and animal studies. These results suggest that drug-liposome aerosols should be more effective for delivery, deposition and retention of water-insoluble, hydrophobic, lipophilic compounds in contrast to water soluble compounds. The development of liposomal formulations for aerosol delivery with jet nebulizers has expanded the possibilities for effective utilization of aerosol based therapies in the treatment of pulmonary diseases. The property of sustained release or depot effect of liposomes has been studied using different tracer molecules to monitor absorption and clearance of liposomes from the lung.\[19-21\]

The development of liposomal formulations, compatible with aerosol delivery with jet nebulizers, has also expanded the possibilities for more effective utilization of aerosol based therapies for the treatment of a variety of pulmonary diseases. Such utilization of liposomes, as aerosol delivery vehicles, has many reported potential advantages for clinical development, including aqueous compatibility facilitated intra-cellular delivery particularly to alveolar macrophages and lymphocytes and sustained pulmonary release to maintain therapeutic drug levels within the lung.\[22\]

**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.[23-24]

Several aerosol formulations designed with an external phase constituted of a propellant have been described. Propellants like hydrofluoroalkanes (HFAs) or propane have been suggested. Reverse microemulsions stabilized by lecithin and using propane and dimethylether as propellants have been also described. These microemulsions, characterized by mean geometric diameters ranged between 1 and 5 μm and by a respirable fraction up to 36%, showed high stability during more than 4 weeks at room temperature. Water-in-hfa emulsions stabilized by non ionic fluorinated surfactants have been also studied in order to administer drugs by pulmonary route and studied new reverse miniemulsions and microemulsions based on fluorinated surfactants intended for pulmonary delivery of drugs.[25]

Cyclodextrins complexation:

Cyclodextrins 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 Cyclodextrins, becoming higher soluble in an aqueous medium. β-Cyclodextrins seems to be the more used for pharmaceutical development, due to the size

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of its cavity, the complexation efficiency with drugs and their relatively low production costs. Cyclodextrins have been studied to encapsulate drugs and to be used in this application to target drugs into the lungs. Cyclodextrins are able to complex with testosterone, salbutamol or rolipram. Cyclodextrins can be used also in combination with other vectors. They are able to increase the encapsulation rate of drugs into microparticles and to modulate their releases. Principally, they were described and used by pulmonary route for their pulmonary absorption promoter of peptides and proteins like insulin or calcitonin.[26]

Recent advancements in pulmonary drug delivery devices:

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Inhalation techniques and devices[31]

1. Pressurized metered-dose inhaler:

The most common device for inhaled drug delivery is the Pressurized metered dose inhaler. The Pressurized metered dose inhaler consists of a pressurized canister and a chamber outfitted with a mouthpiece and protective cover. The canister contains a medication, a surfactant and/or a solvent, and a liquid propellant such as chlorofluorocarbon. Chlorofluorocarbon must be removed from Pressurized metered dose inhaler according to the Montreal protocol on substances that deplete the ozone layer. Environmentally friendly propellants such as hydrofluoroalkanes are rapidly replacing chlorofluorocarbon in Pressurized metered dose inhaler.
The inhaler itself is designed to deliver exact doses of medication. When the canister is pressed, a one-way metering valve is opened by the trigger mechanism in the activator body. The medication is aerosolized near the opening of the mouthpiece, at which point the patient must inhale it. The aerosol consists of droplets in varying diameters. When the medication is inhaled, large droplets are deposited in the mouth, pharynx, and larynx, whereas smaller droplets make their way toward the lower airways. Manufacturers of hydrofluoroalkanes–driven devices have improved the design characteristics and drug formulations to address some of the drawbacks of the older Pressurized metered dose inhaler. They have decreased the velocity and increased fine particle dose in an attempt to improve the therapeutic ratio of the drug. The new designs deliver a more consistent dose throughout the life of the canister, thus eliminating the tailoff effect (reduction of drug output as the device nears empty). Chlorofluorocarbon-driven devices deliver reduced doses when exposed to cold. Hydrofluoroalkane driven canisters deliver consistent doses even when exposed to temperatures as low as –20°C. The new generation of Pressurized metered dose inhaler produces a warmer spray, which should alleviate the cold freon effect (interruption of inspiration) experienced by some patients in the past, reliable and effective method of delivering inhaled medication, and, when used properly, their efficacy is at least equal to that of other inhalation devices. Their greatest disadvantage is complicated to use effectively. Several studies have revealed that a large number of patients are unable to master the technique.\[32\]

2. Spacing devices:
Spacing devices were designed to overcome the difficulties experienced when using Pressurized metered dose inhaler. Spacing devices are available in varying forms and sizes. The most efficient spacing devices have a holding chamber and a one-way valve that opens during inspiration and closes during expiration, preventing drug loss caused by poor coordination between actuation of the Pressurized metered dose inhaler and inspiration. Spacing devices also improve the deposition of medication in the lower Airways. Essentially, they slow down and suspend small droplets of aerosolized medication for approximately 1 to 2 seconds. This allows time for some of the propellant surrounding the particles of medication to evaporate; hence, the inhaled aerosol is made up of a greater proportion of particles small enough to reach the lower airways. The larger particles that would not reach the lungs remain within the spacing device, thus significantly reducing the deposition of medication in the oropharynx and thereby reducing adverse effects. The use of a spacing device is recommended for patients who take high doses of inhaled corticosteroids to prevent oropharyngeal candidacies. Patients who are unable to hold their breath for 4 seconds should use a spacing device with a one way valve, allowing the patient to obtain a suitable dose of medication in three to four tidal breaths. Patients who cannot make a tight seal around the mouthpiece—for example, someone suffering from facial paralysis—should use a spacer with a mask attachment. However, many patients find them embarrassing to use in public or cumbersome to carry spacing devices are therefore indicated as follows:

- To overcome difficulties of patients who are unable to use Pressurized metered dose inhaler correctly. (i.e., because of coordination problems, physical or mental handicaps, etc)
- To reduce the risk of adverse effects with inhaled respiratory medications. (especially when using high doses of inhaled corticosteroids)
- To decrease or eliminate coughing or arrested inspiration experienced by some patients
  When using chlorofluorocarbons-driven devices.
- To administer inhaled medication during severe exacerbations as recommended by the American thoracic society.
Two commonly used examples of spacing devices that have one-way valves are the aero chamber plus and the venta haler. Aero chamber plus vhc is a 145-ml rigid cylinder made of polyester. It has a rubber adapter that makes it compatible with most Pressurized metered dose inhaler and is available with a mouthpiece or a mask. The aero chamber plus with mouthpiece is also outfitted with an audible flow signal (flow signal whistle) that will sound if the patient inhales too quickly. The venta haler is an elliptical-shaped device made of rigid, transparent plastic with a capacity of 750ml. The venta haler was designed to fit glaxosmithk line products and therefore does not fit all Pressurized metered dose inhaler. [32-33]

![Image of aero chamber plus]

**Fig. 3: spacing devices.** [32-33]

3. Multidose dry powder inhalers:
Alternative methods of aerosol delivery that are effective and easy to use are increasingly in demand. Some patients also have difficulty using Pressurized metered dose inhaler correctly because of problems synchronizing the activation of the Pressurized metered dose inhaler and inspiration or because of reaction to the propellants used in Pressurized metered dose inhaler. Breath activated inhalers were developed in response to these problems. Dry powder inhalers are portable inspiratory flow driven devices that deliver dry powder formulations of inhaled drugs to the lungs. [34-35]
A) Turbuhaler:
The turbuhaler is a multi dose breath-actuated metered-dose inhaler that is comprised of components and a metal spring. The medication in the turbuhaler is in the form of a fine, additive free dry powder (eg, budesonide, terbutaline) with the exception of formoterol and symbicort (formoterol and budesonide combination), which also contains lactose powder. If the mechanism is activated a second time, either intentionally or inadvertently, the patient cannot inhale a double dose, as only a single dose is aligned at any time with the inhalation channel. The turbuhaler uses the force of inspiration to lift particles that are deposited onto a dosing disc within the container into the respiratory system. When a patient inhales through the turbuhaler, the fine powder medication moves through the inhalation channel toward a disaggregation zone, which consists of two spiral channels designed to create turbulent air flow in the mouthpiece (hence the name turbuhaler). This action further breaks each particle of fine powder into smaller, more therapeutically effective units (particles in diameter < 6 μm). Studies indicate that the minimum inspiratory flow rate needed to attain a therapeutic dose using the turbuhaler is 30l/min. Because of the low flows required, the turbuhaler (bricanyl) has been quite successfully used in the treatment of acute severe asthma in the emergency department.\[34,36\]
B) Diskhaler
The diskhaler delivers dry powder formulations of inhaled drugs such as salbutamol, salmeterol, and Beclomethasone in a lactose-based drug carrier. It consists of a case containing a rotating wheel onto which a metallic filmed medication disk containing four or eight blisters of medication is loaded. A blister is mechanically punctured by lifting the cover. The medication may then be inhaled through the mouth. Subsequent doses are available by rotating the cartridge. Each dose on the blister pack is individually numbered and appears in a small window on the device, allowing the patient to monitor the number of doses taken and how many remain. Every medication disk is hermetically sealed and must remain so to protect the powder medication from humidity that will cause it to clump. \[37\]

C) Diskus:
The diskus is a new multi dose Dry powder inhaler that contains 60 doses of medication in a lactose-based carrier. The diskus device currently carries all major classes of inhaled therapy (inhaled corticosteroids, short and long-acting \(\beta_2\) agonists, and combination therapy). The outside of the diskus comprises five main parts: an attached cover that
slides open, a thumb grip that uncovers the dose-release lever, a mouthpiece, and a dose counter. There are four wheels inside the diskus one wheel contains 60 doses of powder medication individually wrapped in blisters on a foil strip. The individual wrapping protects the powder from humidity and other environmental conditions. Sliding the dose-release lever peels the foil off the top of each dose as it is advanced to the mouthpiece. The peeled foil is then wound on to another wheel. The dose is then inhaled, and the empty blister advances to a fourth wheel. Once the diskus cover is closed, the lever is automatically returned to the starting position. The diskus provides a relatively consistent dose over a wider range of flow rates than the other Dry powder inhaler inspiratory flow between 30 and 90l/min ensures delivery of 90% of the dose.\textsuperscript{[36,38]}

![Diskus Diagram](image)

**Fig. 7: Diskus**

4. **Wet nebulization:**

Inhaled medication was delivered most commonly via wet nebulization, until recent years when more efficient portable devices became available. Nebulizers break down measured doses of medication in liquid form into a mist of small droplets, called an aerosol, which can then be inhaled through a mask or a mouthpiece. Wet nebulization requires the following:

- An energy source such as a compressor
- Compressed air or oxygen
- A mask or a mouthpiece
- A nebulizer
Compressed air or oxygen is more frequently used in hospitals that have large sources of these gases under pressure. Most patients will use a small portable compressor that is safe and effective for home use. The compressor is powered by electricity and functions by drawing the surrounding air through an external air inlet, forcing it through a small tube to a nebulizer. In the nebulizer, the driving gas is forced through a very small opening called a venturi, creating a low pressure zone. As a result of this fall in pressure, the liquid is sucked up from the reservoir through a capillary system, creating droplets. Only the smallest droplets leave the nebulizer, whereas the majority impact on the baffles and walls of the nebulizer and drip back into the reservoir. This process is repeated continuously for several minutes. During nebulization, the solution used to dilute the medication evaporates resulting in an increasing concentration of the medication. A small amount of solution will remain on the baffles and walls of the nebulizer (dead volume), even when nebulization continues until no more spray is produced. Because the drug concentration increases during nebulization, up to 50% of the drug may be left in the reservoir. Several factors will affect drug deposition in the lungs, including the output of the nebulizer and the patient’s breathing pattern. Drug output is affected by residual volume and gas flow. The latest nebulizers allow for an initial volume of 2 to 2.5 ml and leave a dead volume of about 0.5 ml gas flow affects the size of particles released from the nebulizer and the nebulization time. Studies have shown that optimal flow for most currently used nebulizers is between 6 and 10 l/min. Generally, it takes approximately 5 to 10 minutes to administer 2.5 ml of solution at this flow rate. Breathing should be slow and regular, with an occasional deep breath. Additionally, when inhaling nebulized medication, the patient must learn to breathe through the mouth to reduce drug deposits in the nose and pharynx. Contrary to popular belief, wet nebulization is not the most effective aerosol delivery system. In fact, only 1 to 5% of the output from most compressed air nebulizers is delivered to the lower branches of the bronchial tree. A large amount of the medication is lost to the air during the exhalation phase because aerosol output is constant during both inspiration and expiration. According to the nebulizer project group of the british thoracic society standards of care committee and the quebec pharmacology advisory board nebulizers are indicated for the following circumstances:
For those patients who are unable to use other types of inhalation devices, for example, those who suffer from physical or cognitive deficits.

In hospital settings for severe dyspnoea and when high doses of medication or oxygen must be administered once able to cooperate, individuals should be given another type of inhalation device and their technique should be reassessed.\[39]\]

Fig. 8: nebulizer

Recent applications of pulmonary drug delivery

1) Application of pulmonary drug delivery in asthma and chronic obstructive pulmonary diseases

Asthma is a chronic lung disease characterized by inflammation and narrowing of airways. Asthma causes recurring periods of wheezing, shortness of breath, chest tightness, and coughing. For treatment of asthma, advances have been made in drugs such as levosalbutamol inhalers, which show greater efficacy compared to salbutamol. For the treatment of chronic obstructive pulmonary diseases, tiotropium inhalers are present in the market.\[40,41]\]

2) Recent role of pulmonary delivery in patients on ventilators

Nowadays, to improve inhalation coordination of patient devices, baby masks are mostly used. This mask is attached to a spacer for small tidal volumes and low inspiratory flow rates in infants and young children. We can easily give medication to a child up to 2 years by using a baby mask. This is a recent advancement in the applications of pulmonary drug delivery.
3) Pulmonary delivery in cystic fibrosis

Nowadays cystic fibrosis is very common disease. Pulmonary delivery played an important role in the treatment of cystic fibrosis for decades. The main aim of aerosol system is to deliver drugs to infants and children’s. The following drugs are given by pulmonary route for management of cystic fibrosis.

(1) N-Acetylcysteine

The mucolytic agents N-acetylcysteine have been used by pulmonary route to help in sputum clearance. It will help to liquefy tenacious secretions and make their clearance easier. Recently newer mucolytic agent, nacystelyn, has been developed for delivery via a dry powder inhaler.

(2) Recombinant human deoxyribonuclease aerosol

Nowadays deoxyribonuclease is given by pulmonary route. Recombinant human deoxyribonuclease aerosol many used to liquefy secretions in cystic fibrosis patient.

(3) Tobramycin-spray dried

Tobramycin powders containing Nanoparticles for pulmonary delivery. Tobramycin is commonly used to treat patients with cystic fibrosis. Overall, evidence suggests improved lung function and probably reduced hospitalization when tobramycin is part of maintenance therapy in cystic fibrosis.

4) New use of pulmonary delivery in diabetes

Diabetes is deficiency of insulin secretion or resistance. The most common form of this therapy is twice-daily subcutaneous injections of insulin. This type of treatment is painful and as a result encourages non compliance by up to half of the diabetics. 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 pressurized metered-dose inhaler formulations for pulmonary delivery of proteins.

5) New use of pulmonary delivery in diabetes

Diabetes is a syndrome of disordered metabolism and inappropriate hyperglycemia resulting from a deficiency of insulin secretion or resistance. Diabetes can cause a heart attack, stroke, blindness, kidney disease, nerve damage and other serious health
problems. The most common form of this therapy is twice-daily subcutaneous injections of insulin. This type of treatment is painful and as a result encourages noncompliance by up to half of the diabetics. Peptides and/or proteins are becoming more important in medication. When taken orally, peptides and/or proteins are degraded by the proteolytic enzymes in the gastrointestinal tract, and might be impermeable to the intestinal mucosa due to their hydrophilicity and large molecular size. As a result, systemic delivery of these macromolecular drugs and other therapeutic and diagnostic agents has been limited to the parenteral route. Repeated injections are required due to the short half-lives of peptide/protein drugs. [42-47]

6) Angina pectoris

Angina pectoris is not a disease itself; it is symptoms of myocardial ischemia. It arises as a result of imbalance between oxygen supply and demand of myocardium. Nitroglycerine is drug of choice for angina pectoris and has been given generally by sublingual route; isosorbide aerosol has also been reported useful in hypertensive crisis. In United States inhalation therapy for angina-pectoris is very well accepted. [48]

7) In pulmonary arterial hypertension

This is new use of pulmonary route in 2004, the FDA approved vent avis, an inhaled treatment for pulmonary arterial hypertension. In pulmonary arterial hypertension, severe restriction of blood vessels results in early death. [49]

8) Inhaled drug delivery for tuberculosis therapy

Tuberculosis is most infectious diseases cause by mycobacterium tuberculosis. Administering drugs by the pulmonary route to the lung sallows higher drug concentrations in the vicinity of these lesions. Supplementing conventional therapy with inhaled antitb therapy may allow therapeutic concentrations of drug to penetrate effectively into lung lesions and treat the resident mycobacterium. [50]

9) Recent use of pulmonary delivery for bone disorders

Disease such as osteoporosis and paget’s disease of bones can be treated by pulmonary delivery. The predicted increase in the number of patients with osteoporosis and the lack of ideal therapies dictates the need for better treatments. 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. Following are drugs used to treat osteoporosis are the naturally occurring peptides calcitonin and parathyroid hormone, which regulate bone metabolism. [51]

10) Current use of pulmonary delivery of opioids as pain therapeutics

To avoid pain associated with inject able pain killer pulmonary opioid delivery is better alternative. Early clinical studies involving inhaled opioids were focused on treatment of dyspnoea and not pain management, but they showed that inhalation of various opioid compounds is safe, even in severely ill patients. The advent of specialized and efficient Pulmonary drug delivery systems has facilitated the evaluation of inhaled opioids, such as morphine and fentanyl, for management of severe pain associated with surgery or malignant disease. Studies are going on to introduce new molecules for management of pain through pulmonary route studies with efficient pulmonary delivery systems, designed for systemic drug applications, conclusively show that inhaled opioids are rapidly, completely and reproducibly absorbed into the bloodstream. Thus, the pulmonary route has excellent potential for treating noninvasively severe pain in the postoperative setting and in malignant disease. [52]

CONCLUSION

Pulmonary drug delivery devices has been played crucial role into the pharmaceutical field, because it is a needle free technique. In recent years, many diseases conditions like respiratory diseases, cardiac diseases, and larynx as well as pharynx disorders treat by administration of pulmonary drug delivery. As more efficient pulmonary drug delivery devices and sophisticated formulations become may available, physicians and health professions will have a choice of a wide variety of device and formulation combinations that will target specific cells or regions of the lung, avoid the lung’s clearance mechanisms and be retained within the lung for longer periods. Moreover, pulmonary drug devices which have allowed to small amount of the desire dose delivered to the effective body areas, decrease un-wanted site effects and escalate clinical effectiveness and patient compliance. Therefore, modernist technical era latest new pulmonary drug devices are most successive, very useful and effective devices rather than intravenous or any other route of the administration.
REFERENCES


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