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Review Article

RECENT ADVANCES IN PULMONARY DRUG DELIVERY SYSTEM: A REVIEW

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ABSTARCT

The lung has served as a route of drug administration for thousands of years. Now a day's pulmonary drug delivery remains the preferred route for administration of various drugs.

In this article, we summarize the rationale behind the advances of pulmonary drug delivery system. Pulmonary drug delivery is an important research area which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various other diseases. Inhalation gives the most direct access to drug target. In the treatment of obstructive respiratory diseases, pulmonary delivery can minimize systemic side effects, provide rapid response and minimize the required dose since the drug is delivered directly to the conducting zone of the lungs .It is a needle free several techniques have been developed in the recent past, to improve the Quality of pulmonary drug delivery system without affecting their integrity. This article focuses on recent advances in the technologies, devices, formulation and applications of pulmonary drug delivery system.

Key words: Inhaler, Aerosol, Pulmonary drug delivery, Dry powder inhaler, Meter dose inhaler,nebulizer, Fine particle fraction.

INTRODUCTION

Pulmonary route have been used to treat various respiratory diseases for centuries. Ancient inhalation therapies included the use of leaves from plants, vapors from aromatic plants, balsams, and myhrr. However, around the turn of the 19th century, with the invention of liquid nebulizers, these early treatments developed into legitimate pharmaceutical therapies. In the 1920 s 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 recently discovered penicillin was investigated. steroids had been introduced in the mid 1950s for the treatment of asthma and nebulizers were enjoying widespread use. In 1956 the pressured metered dose inhaler (pMDI) was introduced, over the past 5 decades, helped by the advances in molecule design and drug discovery the pMDI has risen to become the main stay of asthma treatment .[1]

Over the decade certain drugs have been sold in compositions suitable for forming drug dispersion for pulmonary delivery to treat various conditions in humans. Such pulmonary drug delivery compositions are designed to be delivered by inhalation by the patient of a drug dispersion so that the active drug within the dispersion can reach the lung. It has been found that certain drugs given by pulmonary route are readily absorbed through the alveolar region directly into blood circulation. Pulmonary route possesses many advantages over other routes of administration for the treatment of specific disease states, particularly lung associated large protein molecules which degrade in the gastrointestinal conditions and are eliminated by the first pass metabolism in the liver can be delivered via the pulmonary route if deposited in the respiratory zone of the lungs. Devices used to deliver drug by pulmonary route area based on one of three platforms pressurized metered dose inhaler, nebulizer and dry powder .In the treatment of disease, aerosol administration represents a valuable means by which a therapeutic agent may be delivered.[2]

IDEAL CHARACTERSTICS OF THERAPEUTIC AEROSOL

Contain a safe and efficacious drug.

Contain minimal quantities of inert excipients.

Monodisperse, small particle size

Low velocity after generation

High concentration and rate of generation

Highly reproducible characteristics

Low bioburden (solids) or sterile (liquids)

ADVANTAGES OF PULMONARY DRUG DELIVERY

Inhaled drug delivery puts drug where it is needed.

It requires low and fraction of oral dose i.e. drug content of one 4 mg tablet of salbutamol equals to 40 doses of meter doses.

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.

In asthma and diabetes requires long term treatment if it is given by pulmonary drug delivery safety is maximum because rest of body is not exposed to drug.[3]

CHALLENGES IN PULMONARY DRUG DELIVERY

Low Efficiency of inhalation system

Efficiency of presently available inhalation systems has generally too low which is important challenge in pulmonary drug delivery. Optimum aerosol particle size is very important for deep lung delivery. Optimum particle size for deep lung deposition is 1-5 mm. Aerosol system should have to produce optimum size particles because they are too small, they will be exhaled. If the particles are too large, they affects on the oropharynx and larynx.

Less drug mass per puff

To get adequate effect with the pulmonary drug delivery practical delivery of many drug which require milligram doses but With most existing systems, the total amount of drug per puff delivered to the lower respiratory tract is too low less than 1000 mcg .

Poor formulation stability for drug

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.

Improper dosing reproducibility

Following are reason for Poor dosing reproducibility like worsening of diseases', problem in device, unstabality of formulation. To get maximum dose reproducibility patient education play important role. [1]

RECENT ADVANCES IN PULMONARY DRUG DELIVERY INCLUDES

Recent Advances in technology of pulmonary drug delivery

Recent advances in pulmonary drug delivery devices

Recent Advances in formulation of pulmonary drug delivery

Recent Advances in applications of pulmonary drug delivery

Key concept responsible for advances in pulmonary drug delivery

Over the past 15 years, inhalation systems have been developed that make use of new technological concepts aiming for one or more of the following improvements partly adapted from following key concepts.

Improvements regarding the fine particle fraction (FPF)

Inhalation system that produces particles of 1-5 mm size and fine particle fraction so that good deposition in to lungs. A high batch to batch reproducibility of the FPF to reduce variability in lung deposition.Monodisperse inhalation sysytem, to target the deposition in the lung.

Improvements that affect particle velocity and reduce coordination problems

To avoid oropharyngeal deposition, Systems that produces the aerosol at a reduced velocity is preferred. Systems that not only release the aerosol during the first 0.5 *s* of the inhalation but also generate the aerosol over a period longer than 1 *s* such type of system reduces coordination problems for the patient . coordination problems of patient is reduced by breath actuated systems.

Improvements that reducing the cost by increasing the patient compliance

To get above type of improvement following type of aerosol system is selected Systems that are simple to use and robust, non fragile , small and easy to carry and do not require electricity or pressurized air.[4]

RECENT TECHNOLOGIES USED IN PULMONARY DRUG DELIVERY

Particle engineering for pulmonary drug delivery

Recent advances in inhalation therapy have sparked considerable biomedical interest in the development of novel particle technologies for respiratory drug formulation. Introduction of new potent medicines in various therapeutic areas such as asthma, chronic obstructive pulmonary disease (COPD) and various infectious diseases has necessitated an accurate and consistent dosing with inhalation devices. There are many emerging inhalation products with new absorption mechanisms and/or rapid onset of action for systemic therapies. Controlled and sustained release with composite particles is another applications used for ` for both local and systemic drug deliveries.[5,6]

Agglomerated vesicle technology for pulmonary drug delivery

These particles are of multimicron sized chemically linked agglomerates of core nanoparticles. The links between the nanoparticles can be either permanent (e.g. carbonyl) or cleavable (e.g. disulfide or ester). Complex agglomerate structures can be achieved by scheduling the application of linker agents. The release rate of drugs from the assembly can be modulated by controlling the extent of cleavage of the links. One envisions the structure of the agglomerate during cleavage being controlled by the location of the permanent and cleavable links in the agglomerate experiments on the release of ciprofloxacin from these agglomerates in vitro are presented. Recent developments regarding the powder formulation aim at a reduction of the adhesive and cohesive forces between the particles to increase the FPF.[7]

RECENT ADVANCES IN PULMONARY DRUG DELIVERY DEVICES

Following types of inhalation devices are present

Inhalation drug delivery system by- metered dose inhalers

Inhalation drug delivery system by —dry powder inhalers

Inhalation drug delivery system by -nebulizer

A) Inhalation drug delivery system by- metered dose inhalers

A metered-dose inhaler (MDI) is a complex system designed to provide a fine mist of medicament, generally with an aerodynamic particle size of less than 5 microns, for inhalation directly to the airways for the treatment of respiratory diseases such as asthma and COPD.

Advances in MDI Technology and Use Enantiomer Preparations of Inhaled Drugs

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. Similarly that the (R)enantiomer of albuterol is mainly responsible for bronchodilator while the (S)-enantiomer may stimulate airway reactivity. Data suggest, however, that after aerosol delivery, the systemic absorption for (R)-albuterol is faster than for (S)-albuterol and that, conversely, the lung retention of (S)-albuterol is longer, which may be detrimental.

Generic proliferation of devices and medications

Nowadays new MDI and nebulizer brands are introduced regularly in pharma market. Even for those who watch this field, it is not unusual to hear a new, unfamiliar brand name regularly. One trend has been the move to generic MDIs and to over the counter availability. These are introduced in the literature by comparing them with well-known older devices. Often, documentation that generic brands or new devices are comparable to older ones is difficult to come by, so comparisons showing pharmacokinetic equivalency are useful.

New technologies to improve patient's inhalation coordination with MDI

Spacers are used to improve patient coordination with MDI. Both adults and children often have difficulty coordinating the inhalation effort with the timing of the aerosol puff. Evidence indicates considerable intra and intersubject variability for the inhalation technique. [8,9]

Flow gate valve technology in spacers

Certain company s spacer present in market which is static free with valve mechanism which increases drug dose reaching to lungs. Valves opens during inhalation and closed during exhalation this ensures that the residual dose is retained in spacer for subsequent inhalation[3]

The autohaler modified form of pMDI

The Autohaler TM is the first breath actuated or activated pressurized metered dose inhaler . Autoihaler solve the key problem of the pressurized metered dose inhaler (pMDI) viz. coordination of actuation with inhalation and does not rely on the patient's inspiratory effort to aerosolize the dose of medication unlike dry powder inhalers .Autohaler is modified form of pressurized metered dose inhaler. [3]

B) Inhalation drug delivery device by dry powder inhalers

Today there are essentially two types of DPIs, those that use drug filled into discrete individual doses, e.g., either a gelatin capsule or a

foil–foil blister, and those that use a reservoir of drug that meters out doses when required. Both are now widely available around the globe and are gaining broad acceptance.

Unit-Dose -Devices Single-dose powder inhalers are devices in which a powder containing capsule is placed in a holder. The capsule is opened within the device and the powder is inhaled. The capsule residue must be discarded after use and a new capsule inserted for the next dose

Multidose Devices - Multidose device uses a circular disk that contains either four or eight powder doses on a single disk. This typically would be treatment for one to two days. The doses are maintained in separate aluminum blister reservoirs until just before inspiration. This device is a true multidose device, having 60 doses in a foil–foil aluminum strip that is opened only at the point just prior to patient inspiration.[10,11]

New developments in dry powder inhalation technology

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, or . described extensively, the forces governing the particle–particle interactions in the agglomerates and the forces playing a role in the deagglomeration process .Recent developments regarding the powder formulation aim at a reduction of the adhesive and cohesive forces between the particles to increase the FPF. 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 behavior 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 deagglomeration and lung deposition.

Changes in device technologies are few new developments really aim at an increase of the deagglomeration forces generated during the inhalation. It is well known that if the more efficient the force is, higher the FPF will be. A main classification parameters in the new device developments is whether or not the powder deagglomeration is power assisted (active devices) or depends on the kinetic energy of the inhalation flow generated by the patient (passive devices). Regarding the passive devices, recently two DPI devices were introduced that apply impaction forces for the generation of the aerosol. [12]

Air-classifier technology in devices

This is another most important technology used in recent devices for pulmonary drug delivery. The inhaler contains a classifier (cyclone) chamber in which high inertial forces are applied onto the rotating particles. Moreover, the action of these forces on the larger agglomerates is sustained because they remain in the classifier for a certain period of time, which can be controlled by the classifier design and by the choice of carrier-size fraction. Air-classifier technology system one contains a cyclone chamber for particle deagglomeration. Modified form of Airclssifier technology is multiple air-classifier technology.

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. Another interesting point in this development is that the authors managed to develop a disposable DPI. The concept of a disposable inhaler is interesting because it reduces the chance of microbial contamination.

C) Inhalation drug delivery devices by nebulizer

Mainly there are two general types of nebulizer systems, the ultrasonic and the air jet. In ultrasonic nebulizers, ultrasound waves are formed in an ultrasonic nebulizer chamber by a ceramic piezoelectric crystal that vibrates when electrically excited. These set up high energy waves in the solution, within the device chamber, of a precise frequency that generates an aerosol cloud at the solution surface. The aerosol produced by an air jet nebulizer is generated when compressed air is forced through an orifice, an area of low pressure is formed where the air jet exists. A liquid may be withdrawn from a perpendicular nozzle (the Bernoulli Effect) to mix with the air jet to form droplets. A baffle (or baffles) within the nebulizer is often used to facilitate the formation of the aerosol cloud. Carrier air can be used to generate the "air jet." alternatively, compressors may be used to generate the air stream. Nebulizers used today for drug delivery to the respiratory tract and are particularly useful for the treatment of hospitalized or nonambulatory patients.[13]

Recent developments in liquid aerosol technology combine the advantages of MDIs and nebulizers is called metered dose liquid inhalers' as we know that the CFC propellants were replaced by HFAs in MDIs and the classical nebulizer area was extended with the adaptive aerosol delivery (AAD) technology in the 90s of the past century, several' .These systems try to combine the advantages that MDIs and nebulizers offer, and to get rid of the many disadvantages they suffer from. The major advantage that all these systems aim for is a reduced velocity of the aerosol. This feature is of paramount importance because it will reduce oropharyngeal deposition and increase the lung deposition. Liquid inhalers applying the concept of a low velocity aerosol are often referred to as 'soft mist inhalers'. Further developments in the field of wet nebulization aim 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.[14]

Depend upon generation of aerosol new technologies areclassified into four groups

Systems that force the liquid through a nozzle - Respimat , AERxTM, MedSpray

Systems that use a vibrating mesh or perforated plate - Aerodose. TouchsprayTM technology.

Systems that use electrohydrodynamic breakup to generatethe aerosol- MysticTM (Battelle)

Systems that apply condensation to generate the aerosol.[4]

RECENT ADVANCES IN FORMULATION OF PULMONARY DRUG DELIVERY

Effective inhalable medication are produced by drug formulation. Formulation stability is another challenge in producing pulmonary drug delivery. Formulation is responsible for keeping drug pharmacologically active, it must be efficiently delivered into the lungs, to the appropriate site of action and remain in the lungs until the desired pharmacological effect occurs. Depending upon disease condition effective formulation release drug, such as insulin for diabetes, must be deposited in the lung periphery to ensure maximum systemic bioavailability. . Thus, a formulation that is retained in the lungs for the desired length of time and avoids the clearance mechanisms of the lung may be necessary. Research into dry powder formulations has been an area of growth in recent years and will be the focus of this section. Various techniques are used to made advances in dry powders formulation for inhalation involves either ,micronization via jet milling, precipitation, or spray drying using various excipients, such as lipids and polymers, or carrier systems like lactose.

Lactose carrier systems

Recent advances in inhalation therapy have sparked considerable biomedical interest in the development of novel particle technologies for respiratory drug formulation .The cohesive powders with poor flow arises if the surface electric forces associated with the particles exceed the gravitational force acting upon them'. To overcome this problem, the drug is blended with a coarse carrier system (30–100 μm), such as lactose. At present, marketed dry powder inhalers contain either the drug alone or mixed with a bulk carrier, usually lactose (α-lactose monohydrate). Lactose has an established safety profile and improves the flow

properties of the formulation necessary for reproducible filling and promoting dosing accuracy

Liposomes

Liposomes, as a pulmonary drug delivery vehicle, have been studied for years and used as a means of delivering phospholipids to the alveolar surface for treatment of neonatal respiratory distress syndrome. More recently, they have been 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.

Sustained release from a therapeutic aerosol can prolong the residence of an administered drug in the airways or alveolar region, minimize the risk of adverse effects by decreasing its systemic absorption rate, and increase patient compliance by reducing dosing frequency. A sustained-release formulation must avoid the clearance mechanisms of the lung, the mucociliary escalator of the conducting airways and macrophages in the alveolar region.

Table 1: Shows the advantages and disadvantages of the different technologies of dry powder inhalaton[4]

Name of technology	Advantages	Disadvantage
For particale medication of powder formulation in dry powder inhalers. Supercritical technology	Smooth surface with decreased cohesive and adhesive forces, pure highly crystalline drug obtained,increases FPF.Decreases batch to variability	Difficult to scale up and Costly technology .
Pulmosphere and large porus particale technology of powder formulation in dry powder inhalers.	improved processing , deagglomeration and improved aerodynamic behavior	Expensive technology and non approved excipients necessary.
Air classifier technology and eclipse technology in passive devices.	Economic simple high FPF possible and high sustaines deagglomeration forces possible.	Requires adequate formulations and risk of polution of system.
pulmonary inhaler, aspirair,spiros technology in active devices.	Mainly studied with insulin and holding chamber allowed for slow inhalation.	dependant on battery and losses in holding chambers

Table 2: Show the advantages and disadvantages of the different technologies of metered dose liquid inhalers

Name of the Technology	Advantage	Disadvantage
AeroDose (Aerogen) (2) eFlow (Pari) (3) Omron NE-U03, NE-U22 Tecchnologies in vibrating mesh nebulizers of metered dose liquid inhaler	Significant improvement compared with MDI nebulizer and Well-controlled monodisperse aerosol and Aerosol generation independent of inspiratory flow rate	Comlex and expensive electronics in the device and dependent on battery or external energy source
1) AERx (Aradigm) (2) MedSpray Tecchnologies in Capillary wave break-up nebulizers of metered dose liquid inhaler	I. Significant improvement compared with MDI and nebulizer in both technologies and both rechologies monodisperse aerosol	Expensive and complex device
	II. No coordination problems for patient seen with AERX Technology	Dependent on Electronics
	Low shear forces in nozzle with minimum resistance, and therefore, low pressures and Complete dose	High pressure on liquid

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 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. After intratracheal administration into rats, only 8% and 12.5% of macrophages contain Pulmospheres particles immediately and 48 h after inhalation, respectively, compared with 30% and 39% of macrophages containing nonporous particles during a similar time interval.

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 orthopedic implants and 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 has not yet been established for lung delivery.[14,15,16,17,18,19]

Advances in propellants used in pulmonary drug delivery devices

Recently HFA propellants are a new alternative for CFC propellants in pulmonary drug delivery devices. Generally the higher vapor pressures of the HFAs (particularly 134a) have the potential to generate aerosols of higher quality than the "old" CFC formulations. However, except in a few notable instances, potential product improvements have been sacrificed for development costs and time as per market need.[20]

RECENT TREND IN APPLICATIONS OF PULMONARY DRUG DELIVERY

New applications of pulmonary drug delivery[22, 23, 24,25,26,27,28,29,30]

Apart from asthma and COPD recentaly pulmonary drug delivery is used for following indication

Insulin by Aerosol

Treatment of Migraine

Nicotine Aerosol for Smoking Cessation

Aerosols for Angina.

Aerosol Vaccination.

Alpha 1 Antitrypsin

Aerosols in Transplantation

Pulmonary arterial hypertension

Acute Lung Injury

Surfactant Aerosol

Gene Therapy via Aerosol

In Cancer chemotherapy

Pentamidine Aerosol

Amphotericin B

Gentamycin aerosol

Ribavirin Aerosol

Zanimivir R/C with revolizer for swine flue.

Aerosols used in clinical investigations of disease

Inhaled Drug Delivery for Tuberculosis Therapy

Pulmonary delivery of lower molecular weight Heparin.

Controlled delivery of drugs to lungs

Pulmonary delivery of drugs for bone disorders

Pulmonary delivery of opioids as pain therapeutics

CONCLUSION

There have been a number of significant achievements in technologies to express and deliver drugs by pulmonary route. Improvements in the aerosol's velocity, particle size, or moment of release have been achieved. But drug administration via pulmonary route is a difficult and complex process, comprising not only aspects from technology but also from physiology, clinical application or patient use.. This shows that for different diseases or even for each individual drug, the required conditions for optimal administration differ substantially and that a perfect inhaler (plat-form) suitable for all types of drugs and diseases is a fiction.

Advantages of DPIs such simple and cheap devices, their robustness, portability, easy of use as high FPF but systems that can disperse larger amounts of powder (upto 50 mg) within one breath is Major challenges that remain for dry powder inhalation. To maintain stability of powder formulation is another challenge associated with DPI.

As compare to classic nebulizers or MDIs the new liquid inhalation systems are certainly better option but many liquid aerosol generation systems require an external energy source and contain complex electronics. Due to this there is increase failure risk and reduce the freedom of the patient. Further relevant aspects are the dependency of the device's performance on the physicochemical characteristics of the liquid formulation . Advancements in pulmonary drug delivery should not only focus on only one technological aspects, but also need to focus on other aspects.

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