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Review Article

DRUG DELIVERY AND ITS DEVELOPMENTS FOR PULMONARY SYSTEM

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ABSTRACT

Now a day's pulmonary drug delivery remains the favourite route for administration of various drugs. 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 of up to 100m^2 and it has particularly thin 0.1 μm - 0.2 μm absorptive mucosal membrane and good blood supply. Targeted drug delivery to the lungs has evolved to be one of the most widely investigated systemic or local drug delivery approach. As time goes on, the drug delivery systems (DDS) for the treatment of pulmonary diseases are increased due to 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, as well as increasing local drug activity while reducing systemic side effects and first-pass metabolism. Generally half of all pharmaceuticals are not soluble in water, but are soluble in lipid. As the lung is able to absorb both water and oil into the tissue, this is not a restriction of pulmonary delivery. This present review discusses the advantages, current challenges in drug delivery to lungs, and recent advances in new technologies, devices, formulation, and applications for pulmonary drug delivery system.

Key words: pulmonary delivery, MDI, Nebulizers, particle engineering, novel formulations.

INTRODUCTION

Pulmonary delivery of drugs 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 years 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 and its applications[1]. By facilitating the systemic delivery of large and small molecule drugs through inhalation into the lung, this advanced pulmonary technology provides an exclusive and inventive delivery alternative in favour of therapies which have to be currently administered by intravenous, intramuscular, and subcutaneous injection, or by oral delivery that causes adverse effects or the drugs are poorly absorbed and also they are associated with pain[2]. Devices used to deliver drugs by pulmonary route are based on one of three platforms are pressurized metered dose inhaler, nebulizer and dry powder[3]. In the treatment of obstructive respiratory diseases, pulmonary delivery can minimize systemic side effects, and it provides rapid response, and it minimizes the required dose.

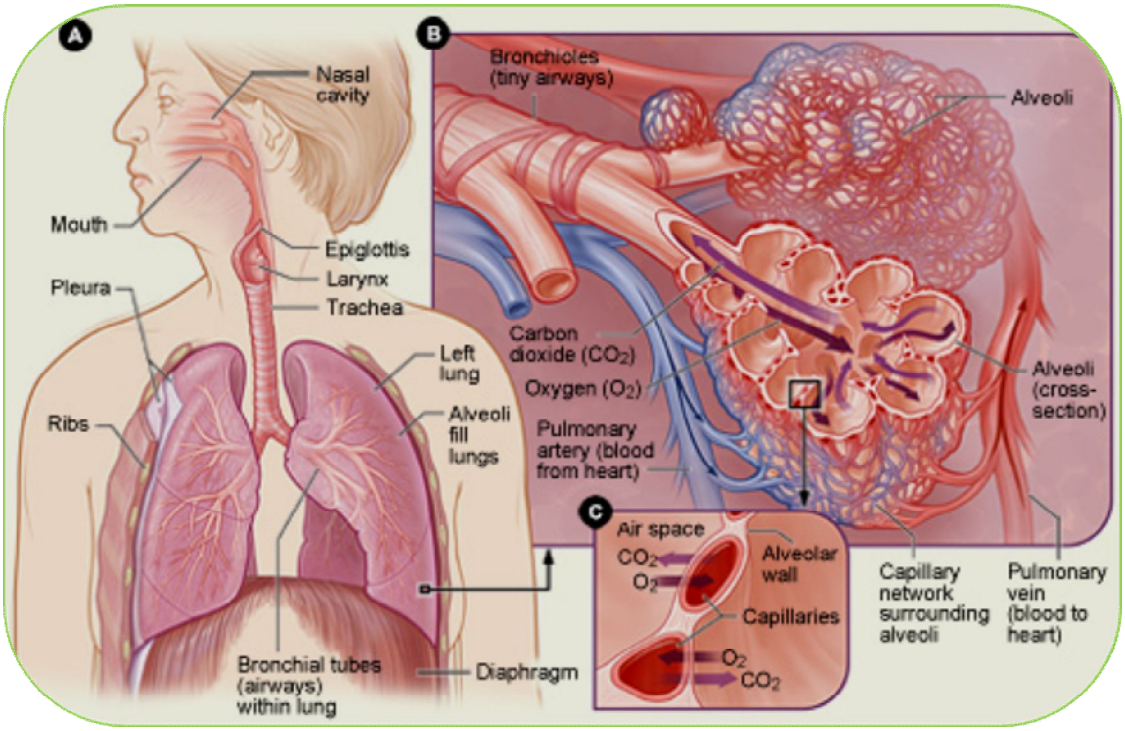

Fig. 1: Anatomy and physiology of pulmonary system[4]

ADVANTAGES OF PULMONARY DRUG DELIVERY[2,5]

- It provides a non-invasive method of delivering drugs into the bloodstream for those molecules that currently can only be delivered by injection. These include peptides and proteins, such as insulin for diabetes or interferon beta for multiple sclerosis and most of the drugs developed in recent years by biotechnology companies.
- Allow efficient drug targeting to the lungs for relatively common respiratory tract diseases such as asthma, emphysema, and chronic bronchitis.
- It gives very fast onset of action comparable to the i.v. Route and quicker than can be achieved with either oral delivery or subcutaneous injections.
- Inhaling helps to avoid gastrointestinal tract problems such as poor solubility, low bioavailability, gut irritability, unwanted metabolites, food effects and dosing variability.
- 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.
- In asthma and diabetes requires long term treatment if it is given by pulmonary drug delivery safety is maximum because rest of body not exposed to drug.

CHALLENGES IN PULMONARY DRUG DELIVERY[6,7]

Low Efficiency of inhalation system

The major challenge in pulmonary drug delivery is the low efficiency of the inhalation systems. Optimum aerosol particle size is very important for deep lung delivery, since if theparticles are too small, they will be exhaled, and if the particles are too large, they have an effect on the 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 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 conventional small molecule asthma drugs are crystalline in nature, and relatively moisture resistant in the dry macromolecules. 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.

Development in pulmonary drug delivery[6,8]

From the past 15 years, inhalation systems have been developed with the intention of making use of new technological concepts aiming for one or more of the following improvements moderately adapted from following key concepts.

Improvements regarding the fine particle fraction (FPF)

Inhalation system produces the particles size of 1-5 mm and fine particles, there by causes the good deposition in to lungs. A high batch to batch reproducibility of the FPF reduces the variability in lung deposition.

Improvements that affect particle velocity and reduce coordination problems

The system that produces the aerosol at a reduced velocity is chosen to avoid the oropharyngeal deposition. Systems that are not only release the aerosol for the period of the first 0.5 sec of the inhalation but also they generate the aerosol over a period longer than 1sec have been developed, because such type of systems reduces coordination problems for the patient. Coordination problems of patient are also reduced by breath actuated systems.

Improvements that reducing the cost by increasing the patient compliance

To get above type of improvement the type of aerosol system is selected depends on the factors like simple to use and robust, non fragile, small and easy to carry and do not require electricity or pressurized air.

Approaches to Pulmonary Drug Delivery[2]

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

1. Aerosol inhalation
2. Intratracheal instillation

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. In contrary to this, instillation process is much simple, not expensive and has non-uniform distribution of drugs.

RECENT ADVANCES IN PULMONARY DRUG DELIVERY INCLUDES

-Development in technologies for pulmonary drug delivery
-Development in pulmonary drug delivery devices
-Development in formulation of pulmonary drug delivery
-Development in applications of pulmonary drug delivery

Development in technologies for pulmonary drug delivery

Particle engineering for pulmonary drug delivery

With the rapidly growing popularity and sophistication of inhalation therapy, there is an increasing demand for tailor-made inhalable drug particles capable of affording the most efficient delivery to the lungs and the most optimal therapeutic outcomes. To cope with this formulation demand, a wide variety of novel particle technologies have emerged over the past decade. 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 application used for ` for both local and systemic drug deliveries[9,10].

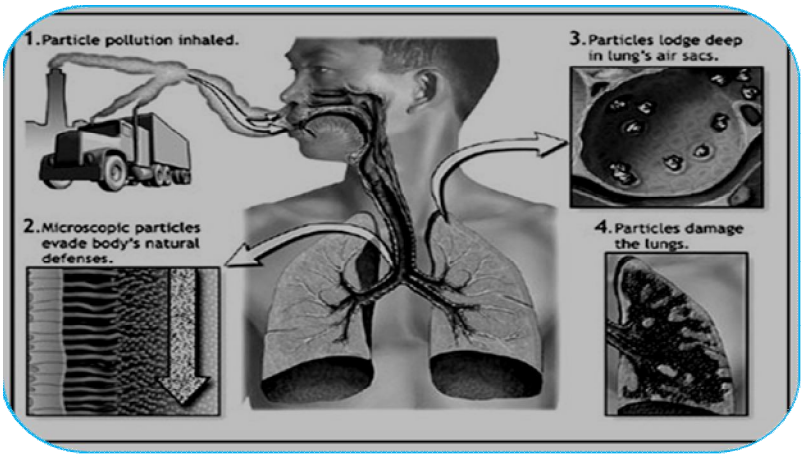

Fig. 2: Adverse health effects of inhaled particles. (The American Lung Association)[11]

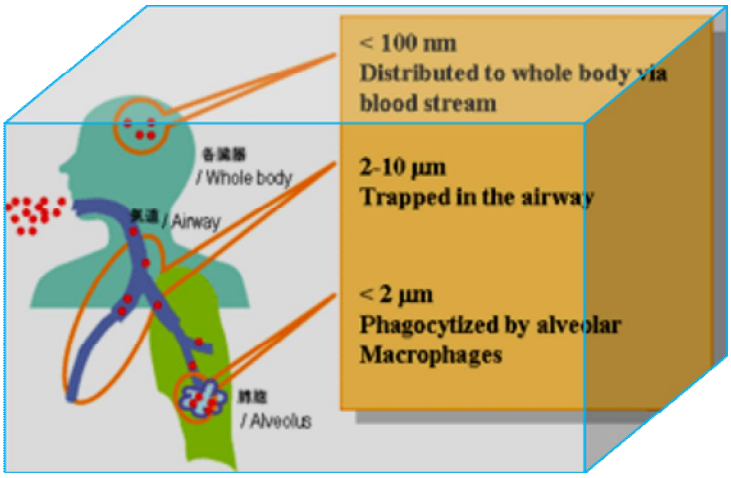

Fig. 3: In inhalation therapies, the deposition site of drug particles in lung is primarily determined by their size. Particle engineering including size control of the drug particles enables the targeting therapy in the pulmonary drug delivery[12].

Agglomerated vesicle technology for pulmonary drug delivery

In general inhalable formulations of various drugs have been developed to treat the systemic diseases via the lungs. But the problem with those inhalable formulations is they need repeated doses of drug to control the disease condition, since the inhaled drug cleared rapidly. And hence new technologies have been developed where inhaled particles are capable of controlled release of drug from the lungs. An important feature of these technologies is the large geometric size of the particles that makes it difficult for the lung macrophages to clear these particles, which results in longer residence times for the particles in the lungs. In an attempt to bring about modulation of release from long residence time particles, a novel concept was developed in the laboratory that has been termed as the Agglomerated Vesicle Technology (AVT). 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. Recent developments regarding the powder formulation aim at a reduction of the adhesive and cohesive forces between the particles to increase the FPF[13].

Recent advances in pulmonary drug delivery devices

Following types of inhalation devices are present

- **A)** Inhalation drug delivery system by- metered dose inhalers.
- **B)** Inhalation drug delivery system by - dry powder inhalers.
- **C)** Inhalation drug delivery system by - nebulizer.

A) Inhalation drug delivery system by metered dose inhalers[1,14]

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.

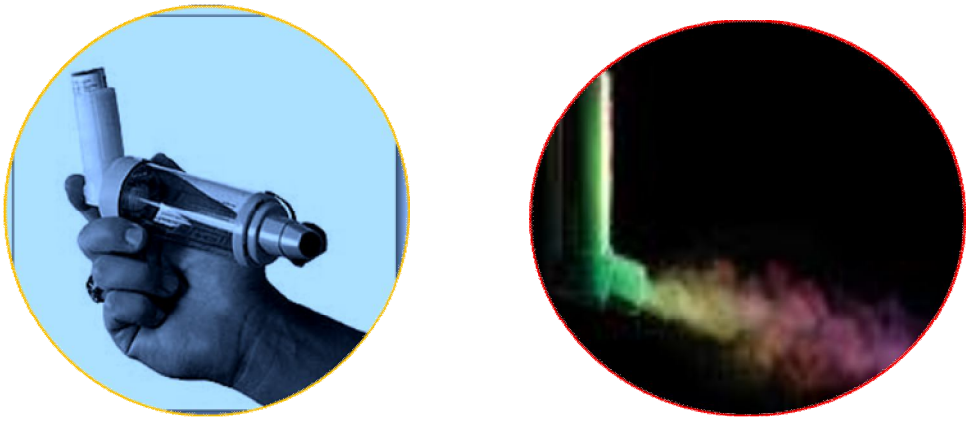

Fig. 4: MDI with a spacer

Trends in MDI technology[2,14]

- ❖ 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.
- ❖ Use of Spacers to improve patient coordination with MDI. Evidence indicates considerable intra and inter-subject variability for the inhalation technique.

- ❖ The Auto-haler TM is the first breath actuated or activated pressurized metered dose inhaler. Auto-haler 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.

Development of HFA MDI Formulations[14]

- ❖ At present there are only 2 drugs that have HFA-MDI formulations in the United States, namely albuterol and beclomethasone dipropionate, both of which use HFA 134a propellant.
- ❖ The HFA albuterol formulation was designed to be equivalent (in dose released and clinical effect) to the previous CFC MDI.
- ❖ The development of HFA-beclomethasone resulted in a redesign of the entire MDI metering-valve system and an improved particle size distribution.
- ❖ Lung deposition with the new formulation is in the 50–60% range.
- ❖ There are other HFA MDI drug formulations in various stages of development or approval, including the short-acting levalbuterol and the corticosteroid ciclesonide.

B) Inhalation drug delivery device by dry powder inhalers

The main advantages of dry powder systems include

- Product and formulation stability,
- The potential for delivering a low or high mass of drug per puff,
- Low susceptibility to microbial growth,
- Applicability to both soluble and insoluble drugs.

Current challenges facing the development of these systems for macromolecules include moisture control, efficient powder manufacturing, reproducible powder filling, unit dose packaging and development of efficient reliable aerosol dispersion and delivery devices. Currently there are two types[2,14,15];

- ➢ **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.
- ➢ **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.

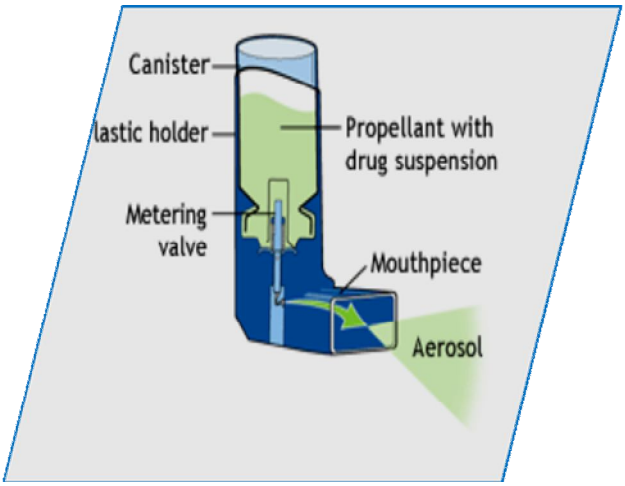

Fig. 5: Dry Powder Inhaler[16]

Trends in dry powder inhalation technology[17-19]

- ✓ Performance of the DPI can be altered through changes in the design of the device and also changes in the powder formulation. The forces involved in the process leads to the particle-particle interactions in the agglomerates and also the forces playing a role in the de-agglomeration process.
- ✓ Supercritical fluid technology is applied to improve the surface properties of the drug substance. Large porous particles have reduced inter-particulate forces due to their low density, the irregular surface structure and/or reduced surface free energy. Additionally, these particles are reported to have improved aerodynamic behaviour in the airways, whereas phagocytises 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.
- ✓ Air classifier Technology has been recently used in the devices to prevent agglomeration in devices.
- ✓ 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.

C) Inhalation drug delivery devices by nebulizer[2,7,20]

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. 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. Nebulizers are particularly useful for the treatment of hospitalized or non-ambulatory patients.

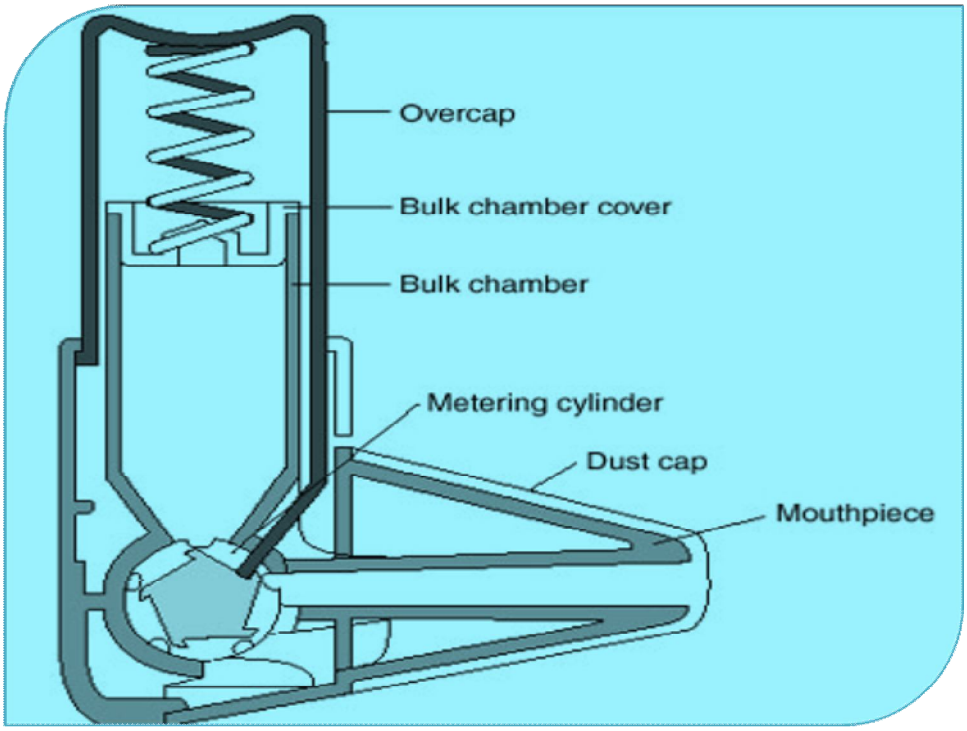

Fig. 6: Nebulizer[21]

Trends in nebulizer technology[14]

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

Depend upon generation of aerosol new technologies are classified 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 electro hydrodynamic breakup to generatethe aerosol- MysticTM (Battelle).
- Systems that apply condensation to generate the aerosol.

Fig. 7: Home nebulizers available in market which are known to be essential drug delivery machines. These help to clear the airways and prevent breathing problems. There are many home made nebulizers available.

Development in formulation of pulmonary drug delivery

Effective inhalable medications are formed by drug formulation. Formulation stability is another challenge in producing pulmonary drug delivery. Formulation is responsible for keeping drug in pharmacologically active state, 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. Here a formulation that is retained in the lungs for the desired length of time and avoids the clearance mechanisms of the lung might be necessary.

Strategies to increase nasal drug absorption

Although the intranasal route is efficient for topic, systemic and CNS delivery of a wide range of drugs, it cannot be applied for many others due to their low nasal bioavailability. Briefly, bioavailability of nasally administered drugs is particularly restricted by low drug solubility, rapid enzymatic degradation in nasal cavity, poor membrane penetration and rapid mucociliary clearance (MCC).

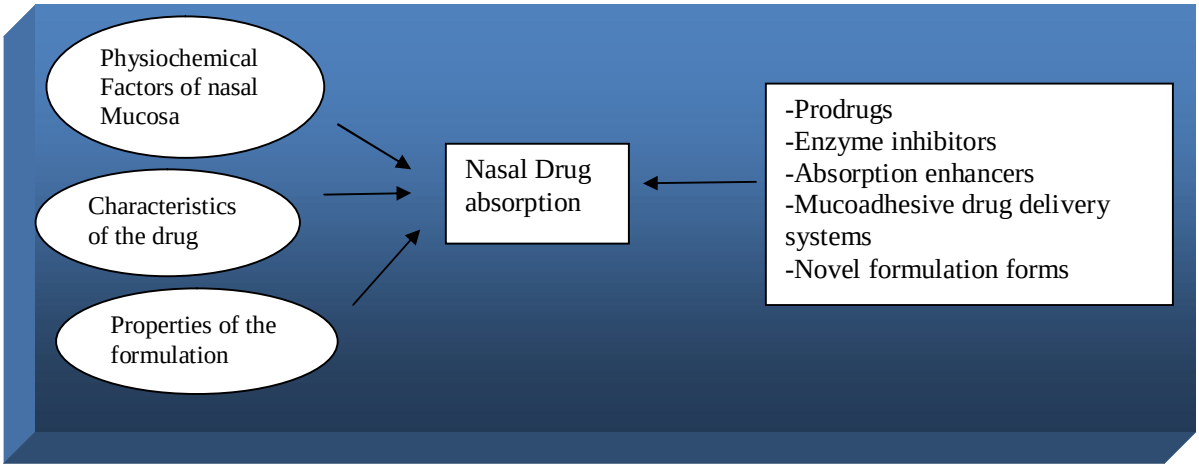

Fig. 8: Factors which affect the nasal drug absorption and practical strategies to overcome them[22]

1. Prodrugs[22,23]

The term 'pro-drug' was described by Albert in 1951 and it is used to explain compounds that undergo biotransformation prior to exhibiting their pharmacological effect. Over the years, prodrugs have been used to overcome drugs' bad taste, poor solubility, insufficient stability, incomplete absorption across biological barriers and premature metabolism to inactive or toxic species. Intranasal drugs are commonly administered as solutions or as powder formulations which need to undergo a dissolution process before absorption. Lipophilic drugs easily pass through bio-membranes, but they are poorly water soluble. Hence they have to be administered as a prodrug with higher hydrophilic character in order to make possible the production of an aqueous nasal formulation with a suitable concentration. Once in the blood stream, the prodrug must be quickly converted to the parent drug. In contrast, very hydrophilic polar drugs may not have ability to cross bio-membranes. Thereby, if they are administered as prodrugs with higher lipophilic character, the penetration through the membrane may increase.

For instance, L-Dopa is poorly soluble in water, so it is very difficult to develop a corresponding intranasal aqueous formulation with an effective dose. Kao et al. produced various prodrugs of L-Dopa and observed that their solubility enhanced significantly in comparison with the parent drug, allowing, hence, the development of adequate nasal formulations. Furthermore, their nasal administration resulted in a rapid and complete absorption to the systemic circulation, where quick conversion to L-Dopa takes place. Similar results were obtained for testosterone which is also poorly water-soluble.

2. Enzymatic inhibitors

Nasal mucus layer and nasal mucosa have a wide variety of enzymes. Hence they act as enzymatic barriers for nasal drug delivery. Various approaches have been used to avoid enzymatic degradation, including the use of proteases and peptidases inhibitors. For example, bestatine and comostate amylase are used as aminoptidases

inhibitors and leupeptine and aprotinin as trypsine inhibitors probably involved in the degradation of calcitonin. Furthermore, bacitracin, amastatin, boroleucin and puromycin have been used to avoid enzymatic degradation of drugs such as leucine enkephalin and human growth hormone[22].

3. Absorption enhancers

Small and large hydrophilic drugs may be poorly permeable across nasal epithelium and may show an insufficient bioavailability. Their absorption is greatly improved by administered in combination with absorption enhancers which induce reversible modifications on the structure of epithelial barrier by modifying the phospholipidic bilayer. In intranasal drug delivery, absorption enhancers most used are surfactants (laureth-9), bile salts, fatty acids (taurodihydrofusidate) and polymeric enhancers (chitosan, cyclodextrins, poly-L-arginine and aminated gelatin)[24-27].

4. Novel drug formulations

Several factors have been included in support of developing nasal formulations containing liposomes, microspheres and nanoparticles for intranasal drug delivery. In fact, it is not clear if those formulations increase drug absorption by transporting encapsulated drug across the membrane or just because they enhance the nasal retention time and stability of the drug. However, their use is in extensive growth and the results have been very capable.

i. Liposomes

Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments in which drugs and other substances might be included. In recent times, 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. Liposomal drug delivery systems present various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values. In fact, they have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has been attributed to the increasing nasal retention of peptides, protection of the entrapped peptides from enzymatic degradation and mucosal membrane disruption. Jain et al. incorporated insulin in liposomes coated with chitosan and carbapol and administered them intranasally to rats. The results demonstrated that this formulation was effective and that its mucoadhesive property is a viable option for a sustained release of insulin [20,28,29].

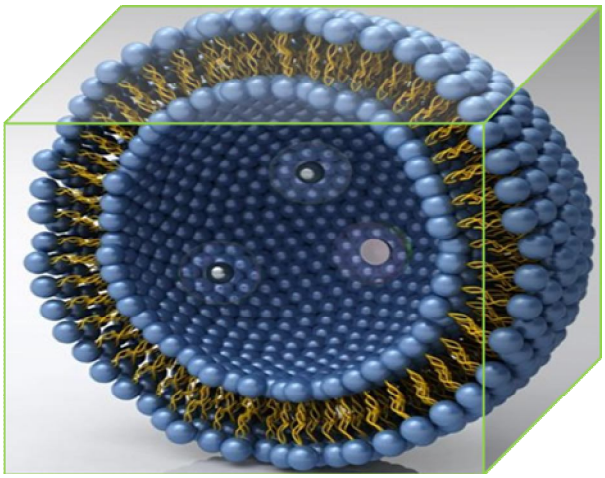

Fig. 9: Structure of liposomes[22]

ii. Nanoparticles

Nanoparticle systems are being investigated to improve drug delivery and intranasal drug administration. Nanoparticles are solid colloidal particles with diameters raging from 1-1000 nm. They consist of macromolecular materials and which are therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles can offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and in a limited quantity, since the tight junctions are in the order of 3.9-8.4 Å. There are several studies have been suggested that nanoparticle systems can be preferably suited as a vehicle for sustained release therapy. 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. nanoparticle systems are also suitable for the delivery of nasal vaccines [22,30].

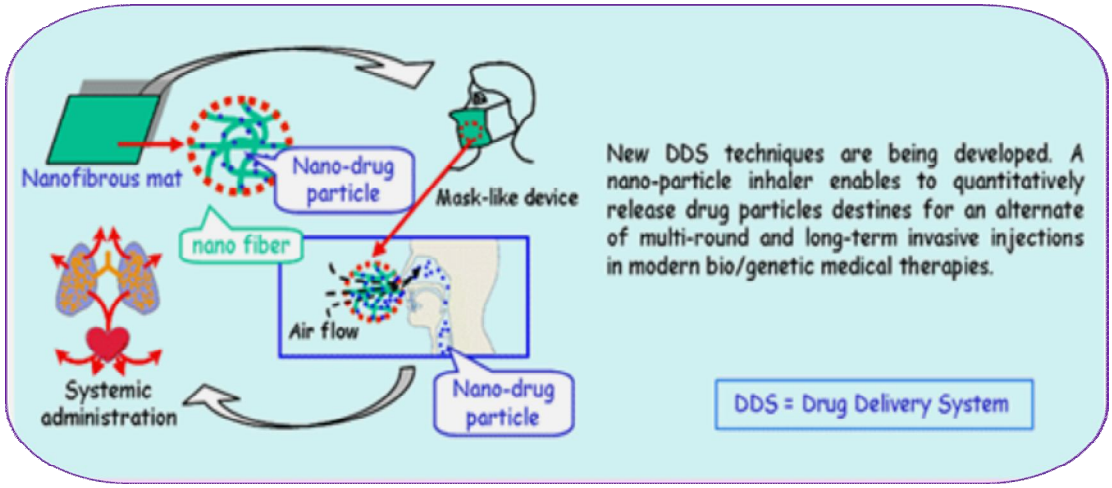

Fig.10: New technique for drug delivery[12]

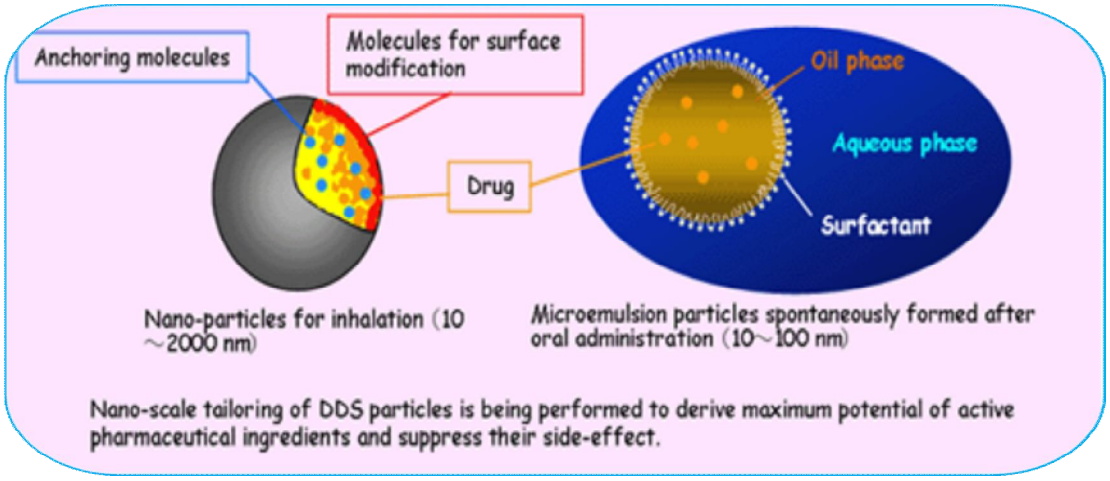

Fig.11: Tailoring of drug delivery systems particles supported by controlling of nano-scale structures[12]

iii. Microspheres

Microsphere technology has been widely useful in designing of formulations for nasal drug delivery. Microspheres are usually based on muco-adhesive polymers (chitosan, alginate), which provide various advantages for intranasal drug delivery. Moreover, microspheres may protect the drug from enzymatic metabolism and gives sustain drug release, thereby prolonging its effect. Wang et al. have investigated the aminated gelatin microspheres as a nasal drug delivery system for insulin. They have observed a considerable hypoglycemic effect when administered intra-nasally in dry powder form to rats, but no significant effect was achieved when given in a suspension. Gavine et al. have analyzed nasal mucosa after its exposure to microspheres of alginate/chitosan containing metoclopramide. They observed the opening of tight junctions in the epithelium and also observed that these spray-dried microspheres have promising properties as mucoadhesive nasal carriers. Many other similar studies have been carried out and positive results are found for nasal delivery of carbamazepine using chitosan microspheres, cyclodextrins using chitosan and alginate as mucoadhesive polymers and carvedilol using alginate mucoadhesive microspheres[22].

iv. Mucoadhesive drug delivery systems

MCC is one of the most important limiting factors for nasal drug delivery, because it reduces the time allowed for drug absorption. Thus, mucoadhesive drug delivery systems improving the nasal drug absorption, and also prolonging the contact time between drug and nasal mucosa. Mucoadhesion indicates the attachment of the drug delivery system to the mucus, involving an interaction between mucin and a synthetic or natural polymer called mucoadhesive. The sequential events that occur during this mucoadhesion include several steps. Firstly mucoadhesive systems absorb water from mucus layer and get wet and swelling. Following this, the polymer intimately penetrates into the mucus and, hence, localizes the formulation in nasal cavity, enhancing the drug concentration gradient across the epithelium. Mucoadhesives mostly used in intranasal drug delivery are chitosan, alginate and cellulose or its derivatives[22].

Development in applications of pulmonary drug delivery

1. Applications of pulmonary drug delivery in Asthma and COPD.

Asthma is a chronic long term lung disease that is categorized by inflammation and narrowing of airways. Asthma causes repeated periods of wheezing, chest tightness, shortness of breath, and coughing. The coughing often occurs at night or early in the morning. Asthma affects people of all ages, but it most often starts in childhood. COPD means chronic obstructive pulmonary diseases, which is correlated to smoking, chronic bronchitis and emphysema. 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[1,31].

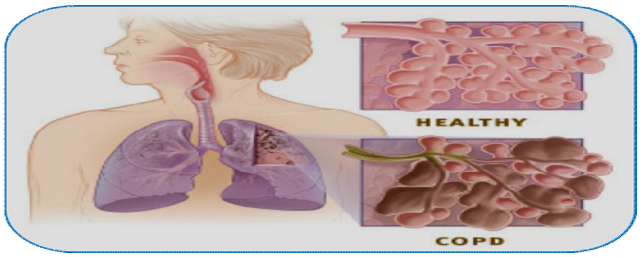

Fig.12: The dark brown areas show the bullae resulting from collapsed or deteriorated alveoli walls. These structures are removed in bullectomy[32]

2. Applications of pulmonary delivery in diabetes

Diabetes is a syndrome of disordered metabolism and unfortunate hyperglycemia resulting from a insufficiency 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 rebelliousness by up to half of the diabetics. Peptides and/or proteins are becoming more important in medication. When these are taken orally, they are degraded by the proteolytic enzymes in the gastrointestinal tract, and might be impervious 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 restricted to the parenteral route. Repeated injections are necessary due to the short half-lives of peptide/protein drugs. The first attempts at intrapulmonary delivery were made in the 1920s. Several companies are working on insulin inhalers than any other insulin delivery option[1,33].

Trade Name	Formulation	Particle Characteristic	Delivery System	Onset, minutes	Peak, hours	Duration, hours	Bioavailability, %
Exubera® (Pfizer)	Dry powder	< 5 µm aerodynamic diameter	Spacer device that propels dry powder via compressed air	10 - 20	2	6	10
AERx† (Novo Nordisk)	Liquid	< 5 µm particle diameter	Breath guidance system	10	2	5 - 8	13
AIR (Alkermes/Lilly)	Dry powder	10 - 20 µm geometric diameter; < 5 µm aerodynamic diameter	Breath-powered unit dose inhaler	13	¾	6 - 7	8 - 9
Technosphere Insulin (MannKind)	Crystalline dry powder	Ordered lattice array of 2 µm spherical particles	Commercially available asthma inhaler	10 - 13	⅓	3	16 - 26

Fig. 13: Comparison of insulin products[34]

3. Applications of pulmonary delivery in 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. Nitroglycerine is a drug of choice for angina pectoris, and is given through sublingual route. It is a coronary vasodilator. The immediate relief of angina is probably caused by a reduced demand of oxygen on the heart and the subsequent reduced cardiac work. 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[1].

4. Applications of pulmonary delivery In Pulmonary arterial hypertension

Pulmonary hypertension in the setting of chronic hypoxia due to underlying lung disease represents a challenging area for evaluation and management. Although chronic hypoxia is a recognized cause of pulmonary hypertension, it would rarely

lead to severe pulmonary hypertension. In 2004, the FDA approved Ventavis (iloprost), an inhaled treatment for pulmonary arterial hypertension, made by CoTherix (South San Francisco, CA, U. S. A.). In pulmonary arterial hypertension, severe restriction of blood vessels results in early death. Iloprost naturally dilates blood vessels[31,35].

5. Application of pulmonary drug delivery in cancer chemotherapy

Cancer is one of major disease which takes death of people. Lung cancer is the leading cause of cancer deaths globally, and inhaled chemotherapy seems a logical approach to treat lung cancer. A multicenter Phase I clinical trial is evaluating doxorubicin HCl inhalation solution in lung cancer patients. As many as 400 000 lung cancer patients could benefit from inhaled chemotherapy; a study is going on aerosolized paclitaxel solution to mice with lung tumors. The treatment significantly reduced lung tumors and prolonged survival. Aerosol delivery of the anticancer agent's difluoro methylornithine and 5- fluorouracil reduced lung tumours in mice 50 % and 60 %, respectively. Interleukin-2 stimulates immune function in cancer patients, but injections cause fever, malaise, and local swelling[31].

6. Inhaled drug delivery for tuberculosis therapy

One third of the world population is infected with tuberculosis (TB), and new infections occur at a rate of one per second. The recent increase in the emergence of drug-resistant strains of *Mycobacterium tuberculosis* and the dearth of anti-TB drugs is threatening the future containment of TB. New drugs or delivery systems that will stop the spread of TB and slow down or prevent the development of drug-resistant strains are urgently required. One of the reasons for the emergence of drug-resistant strains is the exposure of mycobacteria to sub-therapeutic levels of one or more antibiotics. Lung lesions containing large numbers of bacteria are poorly vascularized and are fortified with thick fibrous tissue; conventional therapy by the oral and parenteral routes may provide sub-therapeutic levels of anti-TB drugs to these highly sequestered organisms. Administering drugs by the pulmonary route to the lungs allows higher drug concentrations in the vicinity of these lesions. Supplementing conventional therapy with inhaled anti-TB therapy may allow therapeutic concentrations of drug to penetrate effectively into lung lesions and treat the resident mycobacteria[36].

7. Applications 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. Naturally occurring peptides calcitonin and parathyroid hormone, used to treat osteoporosis by regulating bone metabolism. For the peptides to become viable therapies, formulations must be developed that bypass the need for injection. Pulmonary delivery of calcitonin and parathyroid hormone appears likely in the near future. The recent introduction of a nasal formulation of calcitonin points to the feasibility of lung delivery. 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].

8. Application of pulmonary delivery of opioids as pain therapeutics

For pain management painful inject able are given. 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. In the past, the few studies evaluating pulmonary delivery of opioids for the management of severe pain has with limited success. Earlier attempts at systemic delivery of opioids through the lungs utilized standard jet nebulizer/compressor systems which have minimal efficiency for deep lung delivery. Studies are going on to introduce new molecules for management of pain trough 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 non-invasively severe pain in the postoperative setting and in malignant disease. So by giving pain killer via pulmonary route we can give parental efficacy with oral convenience to patients. So the pulmonary drug delivery is unproblematic to control pain[37].

9. Gene therapy via pulmonary route

Gene therapy holds great potential for the treatment of various acquired and inherited pulmonary diseases. Main aim of Gene therapy given by pulmonary route is for treatment of cystic fibrosis. Cationic-lipid-mediated CFTR gene transfer can significantly influence the underlying chloride defect in the lungs of patients with CFC. There are many problems to be overcome before clinical applications are practical. Some of these are safety, successful transfer of sufficient genetic material to appropriate tissue, adequate gene expression, maintenance of expression over time, and efficacy of expression[38].

10. Recent use of pulmonary drug delivery in transplantation

Inhalation route play a role very important role in transplantation. During lung transplantation, pulmonary vascular pressure and an intrapulmonary shunt have been shown to respond to inhaled nitric oxide and inhaled aerosolized prostacyclin. prostacyclin which is given by pulmonary route has also been described as an alternative to nitric oxide in the management of reperfusion injury after lung transplantation. Acute and chronic rejections are major problems compromising transplant and patient survival. Aerosolized cyclosporine is useful for reducing the risk of acute rejection[39].

CONCLUSION

Pulmonary drug delivery is a vital research area, which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various other diseases. There have been a number of significant achievements in technologies to express and deliver drugs by pulmonary route. However the issues for drug companies and patients concerning pulmonary delivery revolve around economic evaluations, approvals, administration and managed health care. Because the drug administration through pulmonary route is a complicated and complex process, which comprising not only on aspects from technology but also from physiology, clinical application or patient use. As these issues are resolved, pulmonary delivery will be probably regarded as one of the most important drug delivery alternative.

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