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PULMONARY DRUG DELIVERY SYSTEM.

ROHIT GHOGARE[1]

PROF.SANTOSH WAGHMARE[2]

DR.HEMANT KAMBLE[3]

student,department of pharmaceutics,loknete shri.dadapatil pharate college of pharmacy,mandavgan pharate,shirur,pune,maharashtra[1]

professor and principle,department of pharmacy,loknete shri.dadapatil pharate college of pharmacy,mandavgan pharate,shirur,pune,maharashtra[2,3]

ABSTRACT: The pulmonary route of drug delivery is becoming increasingly important in modern research since it allows for site-specific and systemic medication delivery to the lung. The review was written with the intention of discussing the technical, physiological, and efficacy features of the innovative pulmonary route of drug targeting and various delivery devices, including metered dosage inhalers (MDI), dry powder inhalers (DPI), nebulizers, etc. The review also focuses on the excipient compatibility, devices, methods of producing particle dosages, evaluation, and improvements in the delivery of pulmonary drugs, as well as the mechanisms of pulmonary drug administration. From the entire study, it can be inferred that various pulmonary delivery systems have a degree of specificity for dosage formulations and are an essential tool for delivering medications to the target site.

INTRODUCTION:

The term "pulmonary drug delivery" refers to the process of delivering a medicine through the respiratory system. In the case of brochodialating medications, this is favourable since the drug will deliver directly to the area where its action is necessary, resulting in a faster drug effect and the ability to administer a low dose of the drug through this delivery mechanism, reducing side effects.

Oral administration of medications reduces absorption of substances like sodium carmoglicate. Additionally, the liver is where some medicines, like isoprenaline, are processed. These medicines can be given via the pulmonary route.

For millennia, pulmonary routes have been utilised to treat a variety of respiratory illnesses. Balsams, myrrh, aromatic plant vapours, and leaf material from plants were all used in early inhalation therapies. The development of liquid nebulizers, however, around the turn of the 19th century allowed these early remedies to become accepted pharmaceutical therapies.

Adrenaline was first made available as a nebulizer solution in the 1920s, porcine insulin was used in experimental diabetes research in 1925, and pulmonary penicillin delivery was studied in 1945. In the middle of the 1950s, steroids had been developed for the treatment of asthma, and nebulizers were in general use. The pressurised metered dosage inhaler (pMDI) was first launched in 1956, and during the last 50 years, with the aid of developments in drug discovery and molecular design, it has evolved into the mainstay of asthma treatment. Over the past ten years, a number of medications have been sold in forms that can be formed into drug dispersion for pulmonary delivery to treat a variety of human conditions.

Such pulmonary drug delivery compositions are made to be inhaled by the patient in order to administer a drug dispersion and enable the active medication to reach the lung. It has been discovered that some medications administered via the pulmonary route are easily absorbed through the alveolar region and enter the bloodstream right away. For the treatment of particular disease states, the pulmonary route has many advantages over other delivery methods. In particular, lung-associated large protein molecules that break down in 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. Systemic delivery via the lung also has advantages because it allows drugs to be delivered directly into the bloodstream.

It enables the delivery of compounds that are currently only possible through injection. Given that the lungs have a large surface area through which molecules can be absorbed and transported directly into the bloodstream, there has been an increase in interest in the potential of the pulmonary route as a non-invasive administration for systemic delivery of therapeutic agents (primarily peptides and proteins). The conducting airways have 12-23 branches, and their surface area is 0.8 m2. Could provide adults with a good blood supply, a thin absorptive mucosal barrier (0.1-0.2 mm), and a high absorptive surface area (up to 100 m2). Despite the immense potential of recent developments, the complexity of the human respiratory system's anatomical structure and the influence of disposition exerted by respiration make pulmonary administration of peptides and proteins challenging.

Given that the lung is capable of absorbing medications for local or systemic distribution, pulmonary drug delivery has emerged as an appealing target and is of enormous scientific and biological interest in the field of health care research. The control of airway tone and the creation of fluid for the airway lining are two important functions of the respiratory epithelial cells. In this regard, due to the lungs' high permeability, large absorptive surface area (roughly 70-140 m2 in adult humans with an incredibly thin absorptive mucosal membrane), and good blood supply, pulmonary routes have received increasing attention as a non-invasive administration for systemic and local delivery of therapeutic agents.

Most medicines and different macromolecules have been demonstrated to be absorbed by the alveolar epithelium of the distal lung. Additional benefits over peroral uses include the relatively low enzymatic activity, quick drug absorption, and ability to override first-pass metabolism. As has already been mentioned, administering medications via the pulmonary route can effectively cure several systemic diseases as well as localised respiratory conditions. This covers the administration of oxytocin, insulin, and human growth hormones systemically, as well as the topical therapy of pulmonary hypertension, pulmonary infections, and asthma. This is the case for many biotherapeutics that are currently administered intravenously, such as growth hormones, glucagons, and insulin, all of which may be administered to people by inhalation if the efficiency of inhalation were to increase.

Inhalation therapy relies heavily on knowledge of the transport and deposition of inhaled aerosols. Here, we discuss problems pertaining to the pulmonary drug delivery system's technical, physiological, and effective features. Transepithelial transport and pulmonary administration methods were also covered in this review. Polymer dosage options and different delivery methods have also been compiled.

THE PERFECT FEATURES OF THERAPEUTICAL AEROSOL:

1. Contain a safe and efficacious drug.
2. Contain minimal quantities of inert excipients.
3. Monodisperse, small particle size
4. Low velocity after generation
5. High concentration and rate of generation
6. Highly reproducible characteristics
7. Low bioburden (solids) or sterile (liquids)

PULMONARY DRUG DELIVERY BENEFITS:

1. Inhaled drug delivery puts drug where it is needed.
2. 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.
3. Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug.
4. Onset of action is very quick with pulmonary drug delivery.
5. Degradation of drug by liver is avoided in pulmonary drug delivery.
6. 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

DIFFICULTIES IN PULMONARY DRUG DELIVERY:

Low Inhalation System Efficiency

The efficiency of currently available inhalation systems is typically too low, which is a significant obstacle in the delivery of pulmonary drugs. The ideal aerosol particle size is crucial for delivery to the deep lungs. Particle sizes between 1 and 5 mm are ideal for deep lung deposition. The ideal size of particles should be produced by the aerosol system because if they are too small, they will be exhaled. The oropharynx and larynx are affected by excessively big particles.

Less drug mass per puff

Several drugs that need milligramme quantities must be administered practically to have an appropriate effect with pulmonary drug delivery, although The average present system delivers less than 1000 mcg of medication overall every puff to the lower respiratory tract, which is far too little.

Poor formulation stability for drug

The majority of conventional small molecule asthma medications are crystalline, and in the case of corticosteroids, they exhibit a fair amount of moisture resistance when dry. In contrast to most macromolecules, which are unstable in the liquid state, amorphous, and extremely moisture sensitive in the dry state, they are also quite stable in liquids.

Improper dosing reproducibility

the reasons are as follows: Poor dosage repeatability can cause diseases to worsen, device issues, and formulation instability. Patient education is essential to achieving the highest level of dosage repeatability.

THE LUNG'S STRUCTURE AND FUNCTION:

Airways

The conducting airways and the respiratory area are the two functional divisions of the human respiratory system. The throat, larynx, trachea, bronchi, and bronchioles, along with the nasal cavity and its associated sinuses, filter and condition the inspired air through the conducting airways.

The flow of blood

Blood travels to and from the lungs via the bronchial and pulmonary circulatory systems. The systemic circulation includes the bronchial circulation, which is highly pressurised. It absorbs around 1% of the cardiac output and conditions the inspired air while supplying oxygenated blood and nutrients to the lymph nodes, pulmonary blood vessels, and airways (from the trachea to the terminal bronchioles).

Major components of the lung – barriers to drug absorption

Epithelium

The tight ciliated barrier that the airway epithelial cells create keeps the airways free of debris stuck in the mucus, prevents the indiscriminate leakage of water and solutes into the airways, secretes components for the fluid and mucus layer that lines the airways, repairs epithelial damage, and controls the response of inflammatory cells, blood vessels, and smooth muscle.

Endothelium

The biggest capillary endothelial surface in the body, capillary endothelium makes up around 40% of the overall cellular content of the lung, making it unique among other tissues.

Alveolar macrophages

On the alveolar surface are the alveolar macrophages. The defensive mechanisms against inhaled bacteria and particles that have made it to the alveoli depend heavily on these phagocytic cells.

Interstitium and basement membrane

The lung's interstitium, which is made up of a variety of cells (fibroblasts, myofibroblasts, pericytes, monocytes, lymphocytes, and plasma cells), collagen, elastic fibers, and interstitial fluid, is the extracellular and extravascular space between cells in the tissue.

Lymphatic system

The pulmonary lymphatic system helps to remove fluid and protein that has filtered into the interstitium of the lung tissue from the vascular compartment and prevents fluid buildup in the lungs.

Epithelial lining fluid

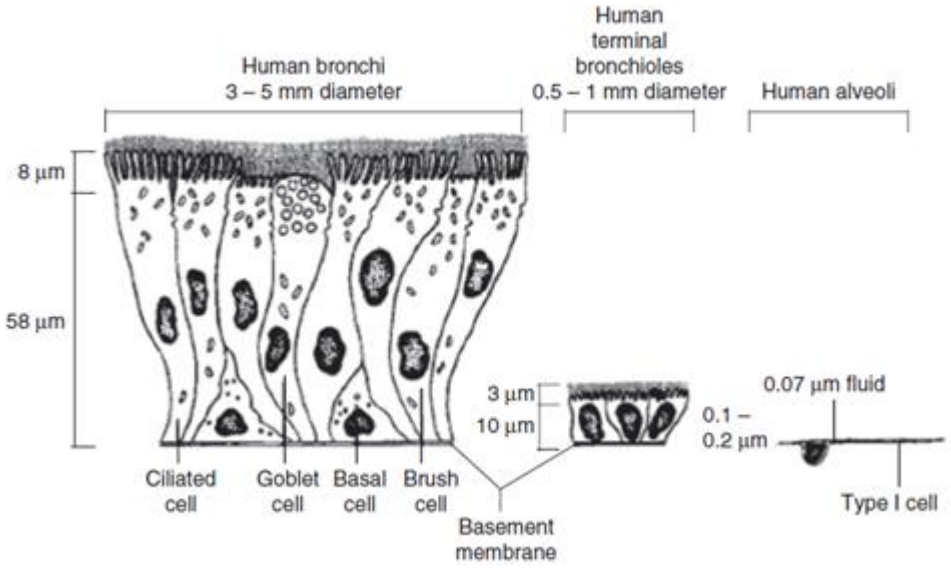
Before having any therapeutic effect, solid medication particles administered to the respiratory system must be wetted and dissolved. Despite the lung's close to 100% humidity, the epithelial lining fluid's volume is rather tiny.

Surfactant

The alveolar type II cells that make up the lung secrete a special blend of phospholipids and proteins that are only found in the surfactant.

Mucociliary clearance

Probably the most significant mechanical host defence in the lung is the mucociliary clearance. The mucus is swept from the nasal cavity and lungs, respectively, into the throat where it is swallowed, by the synchronised movements of cilia. Clearance rates of 3 to 25 mm/min have been observed in the nose in healthy persons.



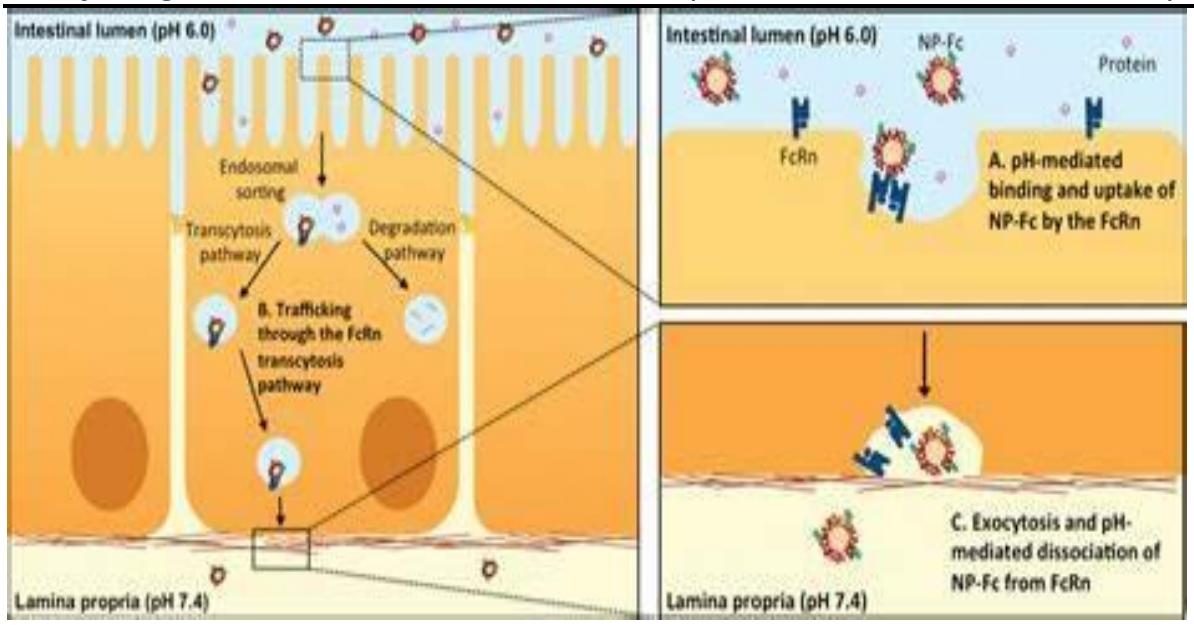
The relative cell size and the thickness of the surface fluid are shown in a schematic image of a lateral view of epithelial cells in the various lung regions of a human.

TRANSEPITHELIAL DRUGS TRANSPORT:

The creation of medication delivery systems for pulmonary applications necessitates a thorough understanding of the lung in both healthy and pathological states. There are more than 40 different types of cells in the lung. The human respiratory system is a complicated organ system with a close link between structure and function. The respiratory system and the conducting airways are the two most important parts of this system. The nasal cavity and its accompanying sinuses, as well as the nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles, are other segments of the airway. Alveolar ducts, alveolar sacs, and respiratory bronchioles make up the respiratory area.

Large quantitative discrepancies between these two regions' transepithelial drug transport along the respiratory epithelium are present. Lower regional blood flow and a smaller surface area in the upper airways hinder medication delivery. Additionally, this area has a high filtering capacity and can filter out up to 90% of drug delivery particles. The mucus layer, which covers the walls of the conducting airways, accumulates chemicals that are further inhaled. Goblet and submucosal gland cells release mucus, which is a gel-like film with mucin as its main constituent. The presence of ciliated cells in this area also causes the mucus to be propelled upward and out of the lung, cleaning it of foreign matter.

A narrower airway and alveolar space, on the other hand, makes up more than 95% of the lung's surface area and is directly related to the systemic. However, the narrower airway and alveolar space, which makes up more than 95% of the lung's surface area and is directly linked to the systemic circulation via the pulmonary circulation, accounts for much more of the lung's surface area. In addition, the size of holes and tight junction depth of alveolar and endothelial cells, as well as the pulmonary blood-gas barrier system, are the most likely factors that control transepithelial drug transport.



BIOLOGICAL MODELS FOR ASSESSMENT OF PULMONARY DRUG ABSORPTION:

In vivo animal models

The fate of a medication and its metabolites in the body are revealed by in vivo pharmacokinetic studies on animals by measuring the drug concentration in plasma or tissues. Accurate in vivo pharmacokinetic studies in animals are crucial to establishing in vitro-in vivo connections since there is a dearth of data on human absorption. Following pulmonary drug administration, plasma is taken and drug content is tested to evaluate the rate of lung absorption and bioavailability.

There are several models for this:

1. Passive inhalation.
2. Head only or nose only inhalation systems
3. Direct intratracheal administration
4. Intranasal administration

Isolated and perfused lungs or Ex vivo models

Lung-specific pharmacokinetic events can be studied without taking into account systemic distribution, metabolism, or elimination by using isolated and perfused lung models. The permeability barriers, interactions between various cell types, structural and cellular integrity of the lung tissue, as well as metabolic activity, are all preserved in these models.

Cell culture models

Mechanistically assessing pulmonary cellular integrity and physiological functions is challenging due to the airway epithelium's inaccessibility and heterogeneous makeup. Precise dosing and sampling, as well as a known local drug concentration and surface area of exposure, are crucial criteria that must be repeatable and controllable for studies on drug transport processes. As a result, numerous in vitro absorption models using airway and alveolar epithelial cell cultures of both animal and human origin have been developed.

Cell culture models are of three types:

a) Continuous cell cultures.
b) Primary cell cultures.
c) Air interface cultures.

MECHANISMS AND WAYS OF PULMONARY DRUG ADMINISTRATION:

The medicine can be taken via the pulmonary route in two main ways: first, intranasal administration, which has anatomical restrictions such a smaller airway lumen, and second, oral inhalative delivery.

Since oral inhalative administration enables the administration of extremely small particles with a concentration loss of only 20% as opposed to 85% via nasal route, significantly better effects can be anticipated. Again, intratracheal instillation and intratracheal inhalation can be used to categorise oral inhalative delivery. Intratracheal instillation is the technique that is most frequently employed in laboratories. A small amount of drug solution or drug dispersion is injected into the lungs using a specialised syringe during intratracheal instillation. This offers a quick and measurable way to administer medication to the lungs. A relatively small absorptive region is used to achieve localised drug deposition. Therefore, the instillation technique is far more straightforward, affordable, and has uneven medication distribution.

Intratracheal instillation has frequently been employed in preclinical animal research to evaluate the pulmonary absorption and systemic bioavailability, particularly with reference to the accurate dose and efficacy connected with this approach. The results from these research could not be applicable to aerosol applications in human beings because intratracheal instillation is not a physiological route for application.

Contrarily, the inhalation method makes use of the aerosol technique, which allows for a more uniform dispersion and deep penetration. The expense of this procedure is higher, and it is challenging to determine the precise dose in the lungs. Three mechanisms—gravitational sedimentation, inertial impaction, and diffusion—are primarily responsible for the drug deposition following aerosol administration in the pulmonary airway. The first two mechanisms—sedimentation caused by gravity force or inertial impaction caused by hyperventilation—take place if the drug particle size is relatively larger. Smaller particle sizes are deposited primarily through a diffusion mechanism, which is based on Brownian motion.

The size and geometry of the particles or droplets are very essential, in addition to the lung morphological characteristics and ventilatory factors. Drug deposition via the pulmonary route is significantly influenced by the size of the particle or droplet in terms of diameter as well as the surface electrical charges, form of the particulate matter if it is a fibre, and hygroscopy. The size, shape, and density of the particle system all affect what is referred to as the mass median aerodynamic diameter.

In fact, the three principal mechanisms of particle deposition in the respiratory tract rely on the size of the inhaled particles.

-The act of **impaction** is the inertial deposit of a particle onto the surface of an airway. It mostly happens at or near airway bifurcations, most frequently in extrathoracic and large conducting airways, where flow velocities are high and where quick changes in the bulk airflow's direction frequently occur, producing a lot of inertial forces. The likelihood of impaction rises as air velocity, breathing rate, particle size (>5 m), and density rise.

-In the small conducting airways where the air velocity is low, **gravitational sedimentation** is a key process for the deposition of particles that are over 0.5 m in diameter and under 5 m in diameter.

-While it reduces as the breathing rate rises**, deposition** owing to gravity increases with larger particle sizes and longer residence lengths. Particles that are submicron in size (particularly those that are smaller than 0.5 m) start to move randomly due to the action of the air molecules around them. Particle deposition by

diffusion may then be caused by this Brownian motion, especially in narrow airways and alveoli where bulk airflow is relatively low.

PULMONARY DRUGS DELIVERY DEVICES CURRENT TECHNOLOGIES:

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

Bymetered dosage inhalers for the delivery of drugs by inhalation

A metered-dose inhaler (MDI) is a sophisticated device used to deliver a small mist of medication directly into the airways for the treatment of respiratory conditions like asthma and COPD. This mist typically has an aerodynamic particle size of less than 5 microns.

Modernization of MDI Technology and Use of Inhaled Drug Enantiomer Preparations

Beta agonist adrenergic bronchodilators have drawn a lot of attention due to their different enantiomeric effects on a variety of drugs. Levo salbutamol, the active enantiomer of salbutamol, has recently entered the market and lacks the termers and palpitations associated with salbutamol. Similar to how albuterol's (R)enantiomer primarily acts as a bronchodilator while (S)enantiomer may increase airway responsiveness. However, data indicate that (R)albuterol is more quickly absorbed into the body following aerosol delivery than (S)albuterol, and that (S)albuterol's lung retention is longer, which may be harmful.

Generic proliferation of devices and medications

New MDI and nebulizer brands are now frequently introduced in the pharmaceutical market. Even for individuals who follow this industry, hearing a brand name that is new or unfamiliar frequently is not unusual. The transition to generic MDIs and their availability over the counter has been one trend. These are explained in the literature by making a comparison to well-known, earlier technology. Comparisons demonstrating pharmacokinetic equivalency are helpful because it is frequently difficult to find evidence that generic brands or new technologies are comparable to older ones.

New technologies to better coordinate patient inhalation with MDI

In order to help patients better coordinate with MDI, spacers are used. Children and adults frequently struggle to time the effort required to inhale with the aerosol puff. The inhalation approach appears to have significant intra- and inter-subject variability.

Flow gate valve technology in spacers

A specific brand of static-free spacer with a valve mechanism that improves medicine dose reaching the lungs is currently available on the market. The remaining dose is kept in the spacer for successive inhalations because valves open during inhalation and close during exhale.

The autohaler modified form of pMDI

The Autohaler TM is the first pressurised metered dose inhaler that is activated by breathing. The primary issue with pressurised metered dosage inhalers (pMDI), viz. Unlike dry powder inhalers, the autohaler coordinates actuation with inhalation. It also does not rely on the patient's inspiratory effort to aerosolize the drug dose. The autohaler is a modified version of a pressurised metered dose inhaler.

B) Inhalation drug delivery device by dry powder inhalers

There are essentially two types of DPIs available today: those that employ medication that is put into discrete individual doses, such as a gelatin capsule or a foil-foil blister, and those that use a reservoir of medication that metre out doses as needed. Both are now easily accessible worldwide and are growing popularity. Devices that incorporate a holder for a powder-containing capsule are known as unit-dose devices or single-dose powder inhalers. The mechanism opens the capsule, releasing the powder for inhalation. Multidose Devices - Multidose devices employ a circular disc that holds either four or eight powder doses on a single disc.

The disc must be destroyed after usage, and a fresh capsule must be inserted for the subsequent dose. Usually, this would be a one- to two-day treatment. Until immediately before inspiration, the doses are kept in separate aluminium blister reservoirs. With 60 doses packed into a foil-foil metal strip that is only opened at the point of patient inspiration, this device is a real multidose device.

Innovations in the field of dry powder inhalation

A change in the device's design, a change in the powder's composition, or both can be used to alter the DPI's performance. Recent innovations in the powder formulation aim at a reduction of the adhesive and cohesive forces between the particles to raise the FPF. These forces influence the particle-particle interactions in the agglomerates and the forces playing a role in the deagglomeration process.

Utilizing supercritical fluid technology, the medicinal substance's surface qualities are improved. Due to their low density, irregular surface structure, and/or low surface free energy, large porous particles have reduced inter-particulate forces. Additionally, it is claimed that these particles exhibit enhanced aerodynamic behaviour in the airways while reducing phagocytosis of the deposited particles in the alveoli. Another strategy has attempted to utilise smaller porous particles (3-5 mm) to enhance lung deposition and deagglomeration.

A few recent improvements in device technology actually aim to increase the deagglomeration forces produced during inhalation. It is common knowledge that the higher the FPF, the more effective the force. Whether the powder deagglomeration is power aided (active devices) or dependent on the kinetic energy of the inhaling flow produced by the patient is one of the primary classification characteristics in the new

device advancements (passive devices). Regarding the passive devices, two DPI devices that apply impaction pressures for the production of the aerosol have recently been introduced. 12

Airclassifier technology in devices

This is another another crucial technological advancement found in more modern pulmonary medication delivery devices. High inertial forces are supplied to the revolving particles in the classifier (cyclone) chamber of the inhaler. The longer the larger agglomerates stay in the classifier, which may be controlled by the classifier's design and the choice of carrier-size fraction, the more sustained the action of these forces on them is. One air-classifier technology system has a cyclone chamber for deagglomerating particles. Multiple air-classifier technology is a modified version of air-classifier technology.

Technologically advanced airclassifiers

This method allows for the parallel placement of numerous classifier chambers, which enhances the amount of dosage that may be aerosolized. The authors' success in creating a disposable DPI is another intriguing aspect of this discovery. A disposable inhaler is an intriguing idea because it lessens the possibility of germ contamination.

Nebulizer-based inhalation medication delivery systems

The ultrasonic and the air jet are the two main types of nebulizer systems. A ceramic piezoelectric crystal that vibrates when electrically energised creates ultrasound waves in the ultrasonic nebulizer chamber. These create precise frequency, high energy waves in the solution that travel through the device chamber and produce an aerosol cloud on the surface of the solution. A nebulizer that uses air jets creates aerosol. An area of low pressure develops where an air jet is present when compressed air is driven through an opening.

The Bernoulli Effect describes how a liquid can be pulled out of a perpendicular nozzle and combine with the air jet to produce droplets. To help the aerosol cloud form, the nebulizer frequently contains a baffle (or baffles). The "air jet" can be produced using carrier air, but it can also be produced using compressors. Today's nebulizers are used to administer medications to the respiratory system, and they are especially helpful when treating patients who are in hospitals or who are not ambulatory.

LUNG COMPATIBILITY OF FORMULATION EXCIPIENTS/POLYMERS:

The compatibility of polymers employed in the construction of particle carriers is a crucial consideration in the development of pulmonary medication delivery systems. Prior to being used, the safety of these polymers needs to be established, and their compatibility with lung fluid is a major worry. The polymers that are employed to slow the rate of release for chronic use may build up in the lung, particularly in the peripheral lung, which is not cleared by mucociliary action. It has been demonstrated that long-term inhalation of carrier particles causes surfactant depletion and phagocytic cell recruitment. The potential for residual solvent to be present in the finished product causes lung toxicity.

In order to prevent the hazardous effects, production methods and formulation ingredients must be carefully checked. Many hypersensitive people experience bronchoconstriction when exposed to carriers like sugars and cyclodextrins that are utilised in the formulation of dry powder inhalation products. Proteins and other carriers can cause immunogenicity, local irritability, and toxicity when used repeatedly. These carriers include absorption enhancers and enzyme inhibitors. Other poisons and antigens may be transported over the epithelial barrier as a result of increased permeability. These are some serious problems that can be effectively fixed with the right models.

Techniques for preparing particles for delivery to the lungs:

It has been observed that many traditional methods can create DPI formulations. However, these techniques have a number of drawbacks, including poor control over powder crystallinity and restrictions in particle size, size distribution, form, and shape. Specialized milling processes can solve these issues. The best way to make nanoparticles for pulmonary medication delivery is to jet-mill a drug under nitrogen gas using a novel nanojet milling device. Here, some of the key methods are briefly covered.

The spray-drying method

Spray drying is a cutting-edge method for producing pharmaceuticals that is effective in creating solid-state respirable colloidal particles. In the 1980s, spray drying was investigated as an alternate technique for creating fine particles for pulmonary delivery. This procedure involves pumping the feed solution to the nozzle, where the nozzle gas atomizes it once it has been delivered at room temperature. In order to remove water moisture from the system and create dry particles, the atomized solution is then dried by a prepared drying gas in a dedicated chamber. This approach shows greater promise for creating particles larger than 2 m.

According to reports, this technology has superior control over particle creation and can therefore be applied to large-scale production with ease. Because mechanical high-energy input is avoided in this method, it is also appropriate for thermolabile materials like proteins and peptides. More significantly, spray-drying may produce particles with a consistent shape.

Spray freeze drying method

In the early 1990s, this approach was investigated for use in the pharmaceutical industry. It is a cutting-edge particle engineering technique that combines the drying processes of freeze-drying and spray-drying. The medication solution is sprayed into liquid nitrogen to use as a freezing medium, then it is lyophilized. At temperatures below ambient, this approach generates nearly 100% yield, light, porous particles with a high fine particle fraction, and increased aerosol performance. Insulin and plasmid DNA are examples of thermolabile proteins and peptides that can be packaged into dry powder inhalation products. However, this is a pricey procedure that is only appropriate for expensive medications.

Supercritical fluid technology

The controlled crystallisation of pharmaceuticals from dispersion in supercritical fluids, such as carbon dioxide, is the key component of this technique. For the synthesis of inclusion complexes, liposomes, microparticles, and nanoparticles in the pharmaceutical industry. This process is utilised to create protein- and peptide-containing particulate pulmonary drug delivery systems and to enhance the formulation qualities of some medication candidates.

Solvent precipitation method

Sono-crystallization and micro-precipitation using opposing liquid jets are two components of this technique. By using direct controlled crystallisation, it is possible to create crystalline drug particles with a limited size distribution. Antisolvents can be used to quickly precipitate inhalable particles from aqueous solutions. Ultrasonic radiation has recently been used to regulate precipitation. Sono-crystallization was used to create a number of anti-asthmatic medications.

Double emulsion/solvent evaporation technique:

With this technique, an oil/water emulsion is created, and the oil phase is then eliminated through evaporation. Drug-loaded polymeric nanoparticles are created when the organic solvent diffuses from the polymer phase into the aqueous phase and subsequently evaporates. By using this technique, biodegradable polymers have undergone extensive research as respiratory solid medication nanoparticle carriers.

Replication of particles in nonwetting templates

Dr. Joseph DeSimone and his team developed the top-down particle fabrication technique known as Particle replication in non-wetting templates (PRINT). This method enables the loading of small organic medicines, proteins, peptides, oligonucleotides, siRNA contrast agents, radiotracers, and fluorophores into uniform-sized organic micro- and nanoparticles with total control over size, shape, and surface functionality.

PARTICULATE MATTER CHARACTERIZATION:

Understanding and control of nanoparticle manufacturing and uses must be established through nanoparticle characterisation. The size of the newly produced particles serves as the major characteristic of NPs.

Targeting NPs to the target brain requires particles with a very small size (1000nm), low charge, and a hydrophilic surface since these particles have a long half-life in blood circulation and are not recognised by the mononuclear phagocytic system (MPS).

Characterization is accomplished using a variety of methods, many of which are derived from materials science.

Common techniques are:

* Electron microscopy [TEM,SEM]
* Atomic force microscopy [AFM]
* Dynamic light scattering [DLS]
* Differential scanning colorimetry [DSC]
* X-ray photoelectron spectroscopy [XPS]
* Powder x-ray diffractometry [XRD]
* Fourier transform infrared spectroscopy [FTIR]
* Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry [MALDI-TOF]
* Coulter current method
* Microelectrophoresis

* Zeta potential
* Cascade Impaction
* Ultraviolet-visible spectroscopy
* Dual polarisation interferometry and
* Nuclear magnetic resonance [NMR]

NEW DEVELOPMENTS IN PULMONARY DRUGS DELIVERY FORMULA:

Pharmaceutical formulation creates effective inhalable medications. Another difficulty in producing pulmonary medication administration is formulation stability. The formulation is in charge of ensuring that a drug remains pharmacologically active; this means that it must be effectively delivered into the lungs, to the site of action, and must stay in the lungs until the desired pharmacological effect materialises. To provide maximum systemic bioavailability, an effective formulation release medicine, such as insulin for diabetes, must be deposited in the lung periphery depending on the illness situation. Therefore, a formulation that avoids the lung's clearance systems while staying in the lungs for the correct amount of time may be required.

This section will concentrate on research into dry powder formulations, which has been an area of growth in recent years. Advances in dry powder formulation for inhalation are made using a variety of techniques, including micronization via jet milling, precipitation, or spray drying with a variety of excipients, like lipids and polymers, or carrier systems, like lactose.

Lactose carrier systems

Recent developments in inhalation therapy have generated a great deal of biomedical interest in the creation of innovative particle technologies for the formulation of respiratory drugs. If the surface electric forces connected to the particles are stronger than the gravitational force acting on them, cohesive powders with poor flow will result. The medicine is combined with a coarse carrier system (30-100 m), such as lactose, to get around this issue. Currently, the medication is either present alone or combined with a bulk carrier, typically lactose (-lactose monohydrate), in commercialised dry powder inhalers. Lactose has a well-established safety profile and enhances the formulation's flow characteristics, which are required for repeatable filling and enhancing dosage precision.

Liposomes

For the treatment of neonatal respiratory distress syndrome, liposomes have been researched for many years as a mechanism of delivering phospholipids to the alveolar surface. They have lately received attention for their potential use in gene therapy, sustained-release therapy, and the delivery of therapeutic substances to the alveolar surface for the treatment of systemic illnesses. An given drug's time in the airways or alveolar region can be prolonged by sustained release from a therapeutic aerosol. This can also reduce the risk of side effects by slowing the rate of systemic absorption and improve patient compliance by reducing the frequency of dose. A sustained-release formulation must stay away from the lung's clearing systems, the conducting airways' mucociliary escalator, and the alveolar region's macrophages.

Large porous particles

The enormous porous hollow particles that make up pulmospheres, a novel type of aerosol composition, are large. They are suitable for both MDI and DPI delivery systems, have low particle densities, and have great dispersibility. These particles can be created via solvent evaporation, spray-drying, or excipients that are either polymeric or nonpolymeric. Phosphatidylcholine, the main element of human lung surfactant, makes up pulmospheres. The enormous size of Pulmospheres enables them to resist phagocytic clearance and stay in the alveolar region longer than their nonporous counterparts. Only 8% and 12.5% of macrophages after intratracheal injection to rats have Pulmospheres particles immediately after inhalation and 48 hours later, compared to 30% and 39% of macrophages that contain nonporous particles during the same time period.

Biodegradable polymers

Biodegradable polymer microspheres are being investigated as sustained release pulmonary medication carriers in addition to liposomes. Researchers have looked into polymers like polylactic acid, which is used in medical applications like sutures, orthopaedic implants, and dressings. The sustained-release profiles achieved with corticosteroids seem promise, despite the paucity of studies in this field. For lung delivery, the toxicity of this kind of formulation hasn't yet been determined.

ADVANCES IN PROPELLANTS USED IN PULMONARY DRUG DELIVERY DEVICES:

HFA propellants have recently emerged as a fresh substitute for CFC propellants in pulmonary medicine delivery devices. Compared to the "classic" CFC formulations, the greater vapour pressures of HFAs, especially 134a, have the potential to produce aerosols of superior quality. Except in a few notable cases, possible product enhancements have been foregone in favour of saving money and time throughout development in order to meet market demands.

A RECENT TREND IN PULMONARY DRUGS DELIVERY APPLICATIONS

New applications of pulmonary drug delivery
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
* Gentamycin aerosol
* Ribavirin Aerosol
* Zanimivir 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:

Technologies for drug delivery and expression by the lungs have made a lot of important advances. The moment of release, particle size, and aerosol velocity have all improved. However, administering drugs via the pulmonary route is a challenging and complex process that involves not only technological but also physiological, clinical, and patient use aspects. This demonstrates that there is no such thing as a perfect inhaler (plat-form) ideal for all types of medications and diseases. Instead, the necessary circumstances for effective delivery vary significantly for different diseases or even for each specific drug.

Another difficulty with DPI is maintaining powder formulation consistency. The modern liquid inhalation systems are unquestionably a better option than traditional nebulizers or MDIs, but many of these devices

require an external power supply and include sophisticated circuitry. As a result, the patient's independence is diminished and the likelihood of failure increases. The performance of the device is dependent on the physicochemical properties of the liquid formulation, among other pertinent factors. Technology shouldn't be the only thing that's the focus of improvements in pulmonary drug delivery; other factors also need to be taken into consideration.

Additionally, there is a lot of room for investigation and evidence of good agreement between in-vitro, ex-vivo, and in-vivo tests used to predict drug absorption from the intact animal, which may provide a strong foundation for advancement in nanomedicine strategies for pulmonary drug delivery in the future.

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