International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

A Comprehensive review on Pulmonary Drug Delivery System

Vaibhav S. Wagh, Dr. Atish S. Mundada
Department of pharmaceutics ,SNJB´s ShrimanSureshdada Jain College Of Pharmacy,Chandwad Pin -423101(Nashik)

Submitted: 08-05-2023 Accepted: 20-05-2023

ABSTRACT
The delivery of drugs to the lungs is now an essential aspect of both local and systemic drug delivery. To this end, numerous techniques and drug delivery devices have been developed in recent years to facilitate this process. The current primary approaches to drug targeting involve directly applying drugs into the lungs via inhalation therapy, utilizing pressurized metered dose inhalers (pMDI) or dry powder inhalers (DPI). Intratracheal administration is frequently the first step in lung drug delivery in vivo. Effective drug carriers are necessary to convey an appropriate drug dosage to the lungs, and these can include solid, liquid, or gaseous excipients. Pharmaceutical carriers such as liposomes, nano and microparticles, cyclodextrins, microemulsions, micelles, suspensions, or solutions have all demonstrated success in targeting drugs to the lungs. The use of micro-reservoir type systems provides significant benefits, including high loading capacity and the ability to control the size and permeability of the carrier system, allowing for regulation of drug release kinetics. These systems enable the use of a relatively small number of vector molecules to deliver significant amounts of the drug to the target site. This review explores the approaches and devices necessary for administering drugs into the lungs.

KEYWORDS :-
Targeting drug delivery, drug delivery devices, pressurized metered dose inhalers, Liposomes, microparticle

I. INTRODUCTION :-

The success of a treatment greatly depends on the delivery techniques and optimal drug concentration, as doses above or below the recommended range can be toxic or ineffective. The limited progress in treating severe diseases has highlighted the need for a multidisciplinary approach to deliver therapeutic agents to targeted tissues. Improved drug efficacy and treatment can be achieved through innovative strategies that control pharmacokinetics, pharmacodynamics, immunogenicity, and biorecognition. These interdisciplinary approaches, including polymer science, pharmaceutical technology, bioconjugate chemistry, and molecular biology, are known as advanced drug delivery systems. Existing and developing drug delivery/targeting systems can be effectively utilized to minimize drug degradation and loss, prevent harmful side effects, and increase drug bioavailability. Nanotechnology has been widely recognized for over two decades for its potential to enhance drug delivery and targeting, while new advancements in drug delivery strategies are reducing toxicities and improving treatment efficacy.

Drugs are commonly delivered to the respiratory tract to treat airway diseases like bronchial asthma and cystic fibrosis. This method can result in a rapid onset of activity, making it highly desirable for delivering bronchodilator drugs. Additionally, delivering smaller doses locally reduces the potential for adverse systemic effects and drug costs. The pulmonary route is also useful when a drug is poorly absorbed orally, or when it is rapidly metabolized orally. The avoidance of first-pass metabolism in the liver may also be advantageous, although the lung itself has some metabolic capability. The lung's large surface area, abundance of capillaries, and thin air-blood barrier also make it a potential route for delivering drugs with systemic activity, such as proteins and peptides like insulin and growth hormone.

ANATOMY AND PHYSIOLOGY OF RESPIRATORY TRACT :-

The respiratory system plays a vital role in delivering oxygen to the body's cells and removing carbon dioxide. Oxygen and carbon dioxide are exchanged between the air, blood, and body tissues through respiration. The upper respiratory tract includes the nose, nasal cavity, and pharynx, while the lower respiratory tract consists of the larynx, trachea, bronchi, and lungs. The trachea divides into bronchi, which branch into smaller bronchioles within the lungs, ultimately leading to the alveoli. The alveoli are responsible for gaseous exchange, making them the functional units of the lungs.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

The trachea is a continuation of the larynx and serves as a passageway for air from the larynx to the bronchi and then into the lungs. It begins at the edge of the larynx and divides into two bronchi that continue into each lung. The bronchi divide into smaller bronchioles, which branch in the lungs to form passageways for air. The terminal parts of the bronchioles are the alveoli, which are the functional units of the lungs where gaseous exchange takes place. The trachea is approximately 10-11cm long and located mainly in the median plane in front of the oesophagus, extending downward to about the level of the 5th thoracic vertebra.

The bronchi are lined with ciliated columnar epithelium and are composed of the same tissue as the trachea. As the bronchi subdivide into smaller airways, the cartilages become irregular in shape and are absent at the bronchiolar level. The smaller airways include bronchioles, terminal bronchioles, alveolar ducts, and finally, alveoli. Each lung contains approximately 300 million alveoli, which have a large surface area (~100 m2) for efficient gas exchange. The blood barrier between the alveolar space and the pulmonary capillaries is very thin to facilitate rapid gas exchanges.

BRONCHIAL BLOOD CIRCULATION :-

The bronchi and smaller air passages are supplied with blood by branches of the right and left bronchial arteries, while venous return occurs mainly through the bronchial veins. On the right side, the bronchial veins empty into the azygos vein and on the left side into the superior intercostal vein. Although the lungs receive the entire cardiac output, only the alveolar region and respiratory bronchioles are supplied by the pulmonary circulation. Blood flow to the larger airways, from the trachea to the terminal bronchioles, is through the systemic circulation, and these airways receive only about 1% of the cardiac output. The role of bronchial circulation in delivering drugs to distal or nonventilated areas of the lungs is unclear. The bronchial blood flow may increase up to 30% of cardiac output in conditions such as bronchiectasis. However, the influence of bronchial circulation on the efficacy of inhaled drugs or their distribution in the lung has not been studied in humans yet.

ADVANTAGES OF DRUG DELIEVERY VIA PULMONARY ROUTE :

Pulmonary delivery is a growing field that includes inhalable drugs for respiratory and systemic therapies. Compared to injectables, transdermal, or oral methods, inhalable have advantages such as fast onset of action, targeted delivery, and convenience.

- Non-invasive drug delivery method for molecules like peptides and proteins that can currently only be injected.
- Effective targeting of drugs to the lungs for respiratory diseases such as asthma, emphysema, bronchiectasis, and chronic bronchitis.
- Rapid onset of action similar to intravenous administration and faster than oral or subcutaneous injection.
- Avoidance of gastrointestinal tract issues such as poor solubility, low bioavailability, and dosing variability.
- Potential reduction of drug dosage, e.g., a 4 mg tablet of salbutamol equals 40 doses of metered-dose inhaler.

The respiratory system can be affected by various diseases, including those caused by genetic factors, infections, and air pollutants. Some common respiratory disorders are asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), lung cancer, pneumonia, bronchiolitis, common cold, cough, pulmonary hypertension, and respiratory diseases .

MECHANISM OF DEPOSITION OF PARTICLES:

The size distribution of aerosol particles can be modified through various techniques, such as using different types of aerosol generators or controlling environmental factors like temperature and humidity. The size of the aerosol particles plays a critical role in determining where in the respiratory tract they deposit, as well as their overall effectiveness in delivering drugs to the lungs. Fine particles have been found to have greater efficiency in delivering drugs to the lungs compared to larger particles, which tend to deposit in the upper airways.

. Particles intended to be administered by pulmonary route are generally categorized based on size:

· Coarse particles are larger than 2 microns in diameter

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

· Fine particles are between 0.1 and 2 microns in diameter
· Ultrafine particles are less than 0.1 micron Most aerosol particles are poly disperse.

ADVANTAGES OF DRUG DELIEVERY VIA PULMONARY ROUTE

The category of drugs known as "inhalables" is a growing area in pulmonary delivery. These drugs are administered through inhalation and provide several advantages compared to other delivery methods, such as injectables, transdermal or oral methods.

One of the benefits of inhalables is that they offer a non-invasive way to deliver drugs into the bloodstream, particularly for molecules that can only be delivered through injection. This includes peptides and proteins, such as insulin for diabetes or interferon beta for multiple sclerosis, as well as many drugs developed by biotechnology companies in recent years.

In addition, inhalables allow for effective targeting of drugs to the lungs, which is particularly useful for treating common respiratory tract diseases like asthma, emphysema, bronchiectasis and chronic bronchitis. Inhalables also have a very rapid onset of action, similar to the intravenous route, and quicker than can be achieved with either oral delivery or subcutaneous injections.

By inhaling drugs, patients can avoid problems associated with gastrointestinal tract issues, such as poor solubility, low bioavailability, gut irritability, unwanted metabolites, food effects, and dosing variability. Finally, inhalables can reduce the dosage needed for effective treatment, as the drug content of one 4 mg tablet of salbutamol is equivalent to 40 doses of metered doses.

Principal Mechanism Of Respiratory Deposition :-

The process of depositing inhaled particles into the various regions of the respiratory system is a complex one that is influenced by a multitude of factors. Some of the factors that can affect respiratory deposition include
Respiratory deposition is influenced by a variety of factors such as breathing rate, mouth or nose breathing, lung volume, respiration volume, and the health of the individual. In addition, the constantly changing hydrodynamic flow field caused by bifurcations in the airways can also impact respiratory deposition

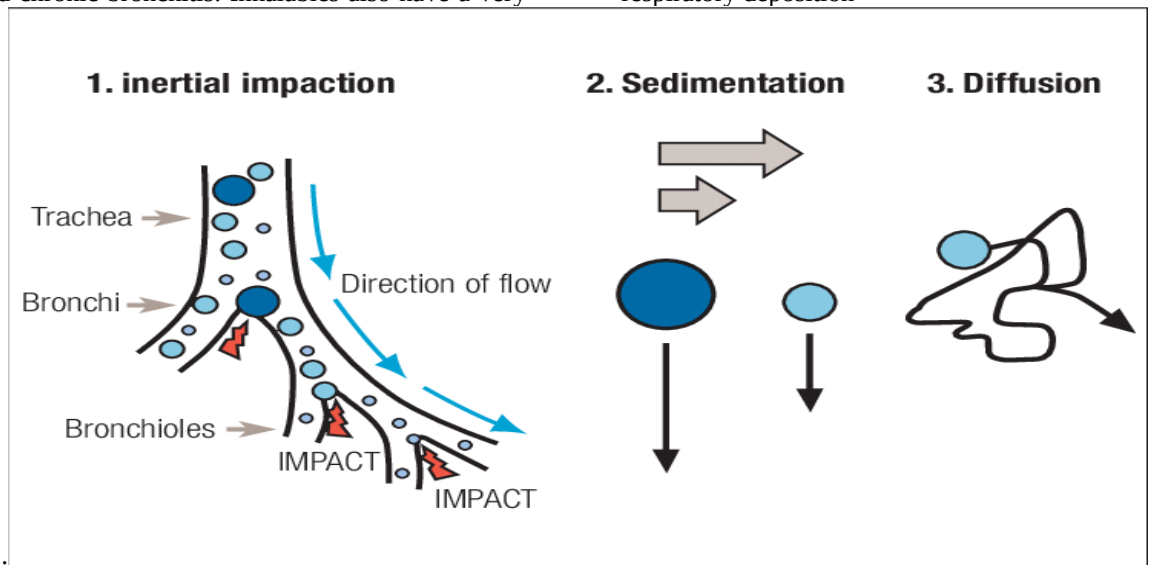

Fig-Principle of particle deposition

The deposition of particles in the respiratory system can occur via different mechanisms depending on the particle size, airflow, and location in the respiratory system. These principal mechanisms include

Impaction-

As airflow changes occur due to bifurcations in the airways, particles suspended in the airflow tend to continue along their original path due to inertia and may collide with an airway surface. The extent of this mechanism depends heavily on the aerodynamic diameter of the particles, as the stopping distance for very small

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

particles is quite low. Larger particles in close proximity to airway walls near the initial airway bifurcations tend to undergo impaction. Consequently, the highest level of deposition by impaction takes place in the bronchial region. On a mass basis, impaction is responsible for the majority of particle deposition.

Sedimentation-

Sedimentation is the settling out of particles in the smaller airways of the bronchioles and alveoli, where the air flow is low and airway dimensions are small. The rate of sedimentation is dependent on the terminal settling velocity of the particles, so sedimentation plays a greater role in the deposition of particles with larger aerodynamic diameters. Hygroscopic particles may grow in size as they pass through the warm, humid air passages, thus increasing the probability of deposition by sedimentation

Interception-

Interception is another mechanism of particle deposition that occurs when a particle comes into contact with an airway surface as a result of its physical size or shape. In contrast to impaction, particles that undergo interception do not deviate from their air streamlines. Interception is more likely to occur in smaller airways or when the air streamline is in close proximity to an airway wall. The most significant deposition by interception takes place with fibers, which have a greater tendency to come into contact with airway surfaces due to their length. Additionally, fibers have relatively small aerodynamic diameters in relation to their size, which allows them to penetrate into the smallest airways.

Diffusion-

Diffusion is a significant mechanism of deposition for particles with aerodynamic diameters less than 0.5 microns, and its efficiency is influenced primarily by the geometric size of particles, rather than their aerodynamic size. Diffusion is the net movement of particles from a region of higher concentration to a region of lower concentration, driven by Brownian motion. Brownian motion is the random, erratic motion of a particle as a result of the constant impact of air molecules. Diffusional deposition is more prevalent when particles have just entered the nasopharynx, and is also likely to occur in the smaller airways of the pulmonary (alveolar) region, where air flow is low.

Absorption -

The pulmonary membrane naturally allows for the permeation of small molecule drugs as well as many therapeutic peptides and proteins. Inhaled drugs face a significant barrier in the form of the lung epithelium, which is thick (50-60 μm) in the trachea but thins to an extremely thin 0.2 μm in the alveoli. The transition from trachea, bronchi, and bronchioles to alveoli involves a significant change in cell types and morphology. The lungs are more permeable to macromolecules than any other entry point into the body. Peptides and proteins are among the most promising therapeutic agents, as they can be inhaled instead of injected, leading to better compliance. Modified peptides that inhibit peptidase enzymes have shown high bioavailability when administered through the pulmonary route. Small molecules can also exhibit prolonged absorption if they possess high solubility or are highly cationic.

While rapid absorption of molecules can be beneficial in many medical applications, there are scenarios where it may be preferable to slow the absorption of an inhaled small molecule. This could be done to extend its local activity within the lungs or to regulate its absorption into the body. Inhaling very insoluble molecules that dissolve slowly can result in their retention in the lungs for prolonged periods, ranging from hours to even days. Slow dissolution rates from relatively insoluble, lipophilic particles contribute to the extended absorption period of compounds like Fluticasone propionate, amphothericin B, and all-trans retinoic acid from the lungs. One can also use slow-release particles such as nanoparticles and liposomes to regulate the rate of absorption.

APPROACHES IN PULMONARY DRUG DELIVERY :-

Targeted drug delivery to the lungs is one of the most extensively researched approaches for local or systemic drug delivery. Drug delivery systems (DDS) are increasingly used for the treatment of pulmonary diseases due to their potential for localized therapy within the lungs. This approach enables drugs to be deposited in specific disease sites at higher concentrations, thereby reducing the overall drug quantity given to patients (approximately 10-20% of the oral dose) while increasing local drug activity and minimizing systemic side effects and first-pass metabolism. To fully exploit the advantages presented by the lungs and address some of the encountered challenges, researchers have focused on particulate DDS for

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

pulmonary administration. These systems can be broadly classified into immediate release (e.g., lactose-drug mixtures for dry powder inhaler (DPI) application) and controlled-release systems (such as liposomes, micelles, nano- and microparticles based on polymers)

The field of biotechnology has yielded numerous therapeutic proteins, also referred to as biomolecules, macromolecules, biotherapeutics, or biologicals. Many of these compounds are administered through injection or intravenous methods to prevent degradation in the gastrointestinal tract. However, patients often avoid these routes due to their pain, inconvenience, and high cost. Pulmonary delivery provides a patient-friendly and non-invasive alternative to injections, offering a more efficient and effective way to deliver drugs while also improving patient compliance.

The use of particulate drug carriers, such as liposomes, microparticles, and nanoparticles, can improve the therapeutic index of established or new drugs by modifying drug absorption, reducing metabolism, prolonging biological half-life, or reducing toxicity. With such carriers, drug distribution is primarily controlled by carrier properties and no longer only by the physico-chemical characteristics of the drug substance. The careful design of drug delivery systems (DDS) based on a thorough understanding of clinical process, and device are key to successful drug delivery using advanced DDS such as liposomes and microparticles.requirements for the disease, lung physiology, selection of carrier materials, production

Microparticles –

The term "microparticle," referring to particles with sizes ranging from 1 to 999 µm, encompasses microspheres and microcapsules, both of which are uniform spheres made of a polymeric matrix. Biodegradable microspheres, made from natural or synthetic polymers, have been widely used as drug targeting systems through different administration routes. Hydrophilic and lipophilic molecules can be encapsulated or incorporated into microspheres. Compared to liposomes, microspheres exhibit more stable physicochemical behavior in vitro and in vivo and can lead to slower release and longer pharmacological activity of the encapsulated drugs. Biodegradable microspheres can be made from various polymers, including albumin, chitosan, polysaccharide, poly(lactic-co-glycolic) acid, poly(lactic) acid, poly(butylcyanoacrylate), and poly(lactic-co-lysine graft lysine).

Sustained release microparticles:

Currently, sustained release formulations for pulmonary delivery have not yet been marketed despite the increasing interest in this research field. However, the control of drug delivery in the respiratory tract can be achieved by using suitable carriers that have appropriate drug release characteristics. Liposomes have been extensively studied as carriers for sustained release, as they can provide sustained release of incorporated active substances. However, liposomes have some disadvantages, including high production costs and relative instability during storage and nebulization, which can lead to disruption and loss of entrapped substances. Polymeric microspheres have also been successfully tested as sustained release drug delivery systems, but their safety is still uncertain.

Nanoparticles-

Nanoparticles have similar characteristics to microspheres, as they are made up of polymers or lipids and can either bind drugs at their surface or encapsulate them. In the latter case, a controlled release can protect the drug against enzymatic degradation and modify its bioavailability. These drug delivery systems can be designed for in vivo applications, including molecules with therapeutic activities and radiocontrast agents, or in vitro as a support for molecules intended for diagnosis. Different authors have reviewed the manufacturing and encapsulation methods for drugs and the feasibility of modifying the surfaces of these carriers. Targeting studies of these drug delivery systems via the pulmonary route have mainly been conducted by encapsulating insulin.

Sustained release Nanoparticles

A potential advantage of delivering antibiotics through inhalation is the ability to directly target infected lung tissue while maintaining lower systemic drug concentrations and toxicity. Preliminary studies in rats have shown that pulmonary delivery of para-amino salicylic acid (PAS) can result in minimal inhibitory drug concentrations (MIC) in lung tissue with lower systemic tissue drug concentrations. Polymeric and lipid nanoparticles are promising delivery systems due to their large size and low density, which allows them to deposit in the alveolar region and avoid elimination from the lungs. The porous shell surface of these nanoparticles also allows for slow,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

sustained release of TB drugs, potentially resulting in a less frequent and less intense drug treatment regimen.

Micelles-

A successful drug delivery system should demonstrate optimal drug loading and release properties, long shelf-life, and low toxicity. Colloidal systems like micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticles consisting of small particles of 10–400 nm diameter, have shown promise as carriers in pulmonary drug delivery systems. Drugs can be trapped in the core of a micelle and transported at concentrations even greater than their intrinsic water solubility. A hydrophilic shell can form around the micelle, effectively protecting the contents. Additionally, the outer chemistry of the shell may prevent recognition by the reticuloendothelsial system and early elimination from the bloodstream. A further advantage of micelles is that their size and shape can be modified, and chemical techniques using cross-linking molecules can improve their stability and temporal control. Micelles can also be chemically altered to selectively target a wide range of disease sites

Liposomes:-

The use of liposomal drug formulations for aerosol delivery has several advantages, including sustained release to maintain therapeutic drug levels, improved intra-cellular delivery, and aqueous compatibility. Additionally, drug-liposomes may reduce local irritation and toxicity both locally and systemically. Many drug-liposomal formulations have shown increased potency with reduced toxicity. Studies have shown that liposomal aerosols, including CsA, are non-toxic in acute human and animal studies. Therefore, drug-liposome aerosols may be more effective for delivering, depositing, and retaining water-insoluble, hydrophobic, and lipophilic compounds in contrast to water-soluble compounds

The use of liposomal formulations for aerosol delivery with jet nebulizers has increased the potential for effective utilization of aerosol-based therapies in treating pulmonary diseases. The sustained release or depot effect of liposomes has been studied using tracer molecules to monitor the absorption and clearance of liposomes from the lungs. Liposomal formulations compatible with aerosol delivery through jet nebulizers offer potential advantages for clinical development, including aqueous compatibility, facilitated intracellular delivery, particularly to alveolar macrophages and lymphocytes, and sustained pulmonary release to maintain therapeutic drug levels within the lungs.

Microemulsions-

The use of emulsions and microemulsions as drug delivery systems for pulmonary treatments has numerous advantages, provided that non-toxic surfactants are used. Some surfactants used for the treatment and prevention of acute respiratory distress syndrome (ARDS) can also act as drug targeting systems. However, these surfactants should not interfere with the therapeutic acNumerous aerosol formulations have been developed that use a propellant as the external phase. Propellants such as hydrofluoroalkanes (HFAs) and propane have been suggested for this purpose. Some formulations use reverse microemulsions stabilized by lecithin, with propane and dimethylether as propellants. These microemulsions have mean geometric diameters ranging from 1 to 5 µm, and a respirable fraction of up to 36%. They remain stable for more than four weeks at room temperature. Other formulations use water-in-HFA emulsions stabilized by non-ionic fluorinated surfactants, which have been studied for pulmonary drug delivery. Recently, new reverse miniemulsions and microemulsions based on fluorinated surfactants have been developed for pulmonary drug delivery of the drug. Although few emulsions or microemulsions have been studied for pulmonary drug delivery, they offer several advantages over other drug targeting systems. They are easy to manufacture and allow for maximum drug incorporation, with close to 100% encapsulation due to the drug being soluble in one phase. Reverse emulsions and microemulsions, in particular, are promising for solubilizing large amounts of hydrophilic drugs due to their physicochemical characteristics.

A variety of aerosol formulations have been developed with an external phase consisting of a propellant, such as hydrofluoroalkanes (HFAs) or propane. Reverse microemulsions stabilized by lecithin and using propane and dimethylether as propellants have also been reported. These microemulsions have a mean geometric diameter ranging between 1 and 5 µm and a respirable fraction of up to 36%. They have shown high stability for more than four weeks at room temperature. In addition, water-in-HFA emulsions stabilized by non-ionic fluorinated surfactants have

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

been studied for drug delivery via the pulmonary route. New reverse miniemulsions and microemulsions based on fluorinated surfactants have also been investigated for pulmonary drug delivery. It is important to note that the propellants and surfactants used in these formulations should not be toxic and should not interfere with the therapeutic activity of the drugs

Cyclodextrins

Cyclodextrins (CDs) are oligosaccharides composed of six, seven, or eight units of glucopyranose, known as α-, β-, and γ-CDs, respectively. When a drug is completely or partially included into the cavity of CDs, it can form non-covalent bonds with CDs, making the drug more soluble in an aqueous medium. β-CD is widely used in pharmaceutical development due to the size of its cavity, high complexation efficiency with drugs, and relatively low production costs. CDs have been investigated for their potential to encapsulate drugs and target them to the lungs. Testosterone, salbutamol, and rolipram have been complexed with CDs. Additionally, CDs can be used in combination with other drug delivery systems

PULMONARY DELIVERY DEVICES

The use of the lungs as a route for drug administration has been known for thousands of years. In India, people smoked the leaves of the Atropa belladonna plant 4000 years ago to suppress cough. In the 19th and early 20th centuries, asthma sufferers smoked asthma cigarettes containing stramonium powder mixed with tobacco to relieve their symptoms. The development of modern inhalation devices can be classified into three categories: the refinement of the nebulizer, and the evolution of two types of portable devices, the metered-dose inhaler (MDI) and the dry powder inhaler (DPI). Various pulmonary delievery devices are listed below

Nebulizers-

Nebulizers have been used to treat respiratory diseases, including asthma, for many years. There are two primary types of nebulizers: jet and ultrasonic nebulizers. The jet nebulizer operates based on the Bernoulli principle, where compressed gas (air or oxygen) passes through a narrow orifice, creating a low-pressure area at the outlet of the adjacent liquid feed tube. This action draws the drug solution up from the fluid reservoir and breaks it into droplets in the gas stream. The ultrasonic nebulizer, on the other hand, uses a piezoelectric crystal vibrating at a high frequency (usually 1–3 MHz) to create a fountain of liquid in the nebulizer chamber. The frequency of vibration affects the droplet size, with higher frequencies producing smaller droplets.

Constant output jet nebulizers are capable of aerosolizing most drug solutions and require little patient coordination or skill, delivering large doses. However, these nebulizers are inefficient and time-consuming, resulting in significant drug wastage (up to 50% loss with continuously operated nebulizers). While disposable nebulizers are relatively inexpensive, the compressors used to supply air or oxygen are not. Unfortunately, the majority of the prescribed drug never reaches the lungs through nebulization. Most of the drug either remains within the nebulizer (known as dead volume) or is released into the environment during exhalation. Typically, only around 10% of the drug placed in the nebulizer is deposited in the lungs. The physical properties of drug formulations can also affect nebulization rates and particle size. Factors such as viscosity, ionic strength, osmolarity, pH, and surface tension can impede the nebulization of certain formulations. Additionally, if the solution is too acidic or too hyper- or hypo-osmolar, the aerosol may cause bronchoconstriction, coughing, and lung mucosa irritation. Moreover, high drug concentrations may reduce the drug output with certain nebulizers.

Inhalers:

Inhalers are a highly effective method for delivering medicine straight to the airways, requiring smaller doses compared to tablets or liquids taken orally. This method is attractive for delivering drugs that act locally on the lungs or systemically throughout the body. An exciting concept in this area is the delivery of inhaled systemic macromolecules. Successful development of dry-powder inhaler (DPI) products requires precise control of both the powder and device properties, which remains a significant technical challenge for those seeking to take advantage of the many market opportunities in this field.

Advantages of Inhalers :-

There are several advantages of using inhalers in pulmonary drug delivery:

- Targeted delivery: Inhalers allow for direct delivery of drugs to the lungs, where they are needed. This results in a more targeted and effective treatment for respiratory conditions.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

- Rapid onset of action: Inhalers deliver drugs directly to the site of action, resulting in a rapid onset of action. This is especially important in emergency situations, such as asthma attacks.

Lower doses: Inhalers require lower doses of medication compared to oral or intravenous routes, as the drug is delivered directly to the lungs.

- Reduced side effects: Since inhalers require lower doses of medication, they also result in fewer systemic side effects, such as nausea or vomiting.
- Portable and convenient: Inhalers are small and portable, making them easy to carry and use on-the-go. They are also simple to use and require minimal coordination, making them ideal for elderly or paediatric patients.
- Improved compliance: Inhalers have been shown to improve patient compliance with treatment regimens, as they are easy to use and can be integrated into daily routines.

Overall, inhalers provide a safe, effective, and convenient method for delivering drugs to the lungs for the treatment of respiratory condition

Metered-dose inhaler :-

Metered-dose inhalers (MDIs) are a type of inhaler used for delivering medication to the lungs. They are commonly used for the treatment of asthma, chronic obstructive pulmonary disease (COPD), and other respiratory conditions.

The following are some advantages of using MDIs:

1. Accurate Dosage: MDIs are designed to deliver a precise amount of medication with each puff, making it easier to achieve the desired therapeutic effect.
2. Convenient: MDIs are portable and easy to use, making them a convenient option for patients who need to take their medication on-the-go.
3. Fast-Acting: MDIs deliver medication directly to the lungs, allowing for quick and effective relief of respiratory symptoms.
4. Reduced Side Effects: Because the medication is delivered directly to the lungs, the dose required is usually lower than that needed with oral medications, which can help reduce the risk of systemic side effects
5. .Cost-Effective: MDIs are often less expensive than other inhaler devices, making them a more cost-effective option for patients.

Overall, MDIs offer several advantages in the delivery of pulmonary medication, making them a popular choice for patients and healthcare providers alike.

Pressurized metered-dose inhalers:

Pressurized metered dose inhalers (pMDIs) are a type of inhaler device used for pulmonary drug delivery. They consist of a canister containing a medication under pressure, a metering valve, and an actuator mouthpiece. When the patient activates the inhaler, the metering valve releases a precise dose of medication in the form of a fine aerosol mist, which is then inhaled into the lungs.

One of the main advantages of pMDIs is their convenience and portability. They are small and easy to carry around, making them a popular choice for patients who need to take their medication on the go. They are also relatively easy to use, requiring minimal coordination and effort from the patient.

Another advantage of pMDIs is their ability to deliver medication directly to the lungs, bypassing the digestive system and reducing the risk of side effects associated with oral medications. They can be used to deliver a wide range of medications, including bronchodilators, corticosteroids, and combination therapies.

However, pMDIs can be challenging to use correctly, particularly for patients with poor hand-lung coordination. They require proper technique and timing to ensure that the medication is effectively delivered to the lungs. Some patients may also experience irritation or other side effects from the propellant used to deliver the medication.

Dry powder inhalers-

Dry powder inhalers (DPIs) are devices used to deliver medications in a dry powder form directly to the lungs. The powder is usually contained in capsules or blisters, and the device is activated by the patient inhaling through the mouthpiece. DPIs are popular because they do not require propellants or refrigeration, are easy to use, and are portable.

Some of the advantages of DPIs include:

1. No need for coordination: Unlike MDIs, DPIs do not require coordination between pressing the canister and inhaling, making them easier to use for some patients, such as children and elderly individuals.
2. No propellants: DPIs do not require propellants, which means they do not contain

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

any chlorofluorocarbons (CFCs) or hydrofluoroalkanes (HFAs) that can be harmful to the environment.
3. Portable: DPIs are small and portable, which makes them convenient for patients to carry with them and use as needed.
4. Long shelf life: DPIs have a longer shelf life compared to other inhaler types, as they do not contain propellants that can deteriorate over time.
5. Accurate dosing: DPIs deliver a consistent and accurate dose, which is important for patients who require precise dosing for their medication to be effective.
6. Variety of medications available: Many different types of medications can be delivered through DPIs, including bronchodilators, corticosteroids, and combination therapies.

Overall, DPIs offer many advantages over other types of inhalers and are a popular choice for patients with respiratory conditions such as asthma and COPD.

LATEST DEVELOPMENT IN INHALER TECHNOLOGY

There have been several recent developments in inhaler technology aimed at improving drug delivery efficiency and patient convenience. Here are some of the latest advancements:

Smart inhalers: These are inhalers that can connect to a smartphone app or other electronic device to track medication usage, remind patients when to take their medication, and provide feedback on inhalation technique.

Breath-actuated inhalers: These inhalers release medication automatically when the patient takes a deep breath, eliminating the need for hand-breath coordination and ensuring that the full dose is delivered to the lungs.

3D-printed inhalers: These inhalers are made using 3D printing technology, which allows for customized designs that can be tailored to individual patient needs and preferences.

Nanoparticle inhalers: These inhalers use tiny particles to deliver medication directly to the lungs, potentially improving drug absorption and reducing side effects.

Biologic inhalers: These inhalers deliver large molecules, such as antibodies, directly to the lungs, allowing for targeted therapy for respiratory diseases like asthma and COPD.

Overall, these advancements in inhaler technology are improving the efficacy and convenience of pulmonary drug delivery, ultimately leading to better health outcomes for patients with respiratory disease

SMART INHALER :-

Smart inhalers are inhalers that are equipped with sensors to monitor the usage and effectiveness of the medication. They connect to mobile devices to provide real-time feedback, reminders, and data on usage patterns. This technology can improve adherence, optimize treatment plans, and enhance patient outcomes

BREATH -ACTUATED INHALER :-

Breath-actuated inhalers (BAIs) are a type of inhaler that releases medication automatically when the patient inhales, without the need for pressing a button or coordinating their breathing with the device. This feature makes them particularly useful for patients with poor inhalation technique or those who have difficulty using traditional inhalers. BAIs typically use a dry powder formulation, which can be more stable than liquid formulations and therefore have a longer shelf life. They also have the potential to deliver higher doses of medication to the lungs compared to traditional inhalers.

The operation of a BAI involves the inhalation of air through the device, which triggers the release of a predetermined dose of medication. This ensures that the medication is delivered only when it is needed, reducing the risk of overuse or underuse. Some BAIs also feature dose counters, which allow patients to track the number of doses remaining in the device and ensure they are using it correctly.

BAIs have been shown to improve adherence to medication regimens and can be particularly beneficial for patients with chronic obstructive pulmonary disease (COPD) or asthma. They are also being integrated with digital health technologies, such as smartphone apps, to provide real-time monitoring and feedback to patients and healthcare providers

3D PRINTED INHALER

3D printing technology has been applied to the development of inhalers to improve drug delivery in patients. One of the advantages of 3D printing is the ability to create complex shapes and precise geometries, allowing for personalized inhaler designs. Additionally, 3D printing enables the production of inhalers with unique features

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

such as customized dosage, inhalation flow rate, and medication release profiles.

In 3D printed inhalers, the dose is deposited onto a cartridge or blister strip which is inserted into the inhaler. The inhaler device is designed to fit the patient's mouth and respiratory system, and can be customized for individual patients. This technology allows for more precise dosing and personalized inhaler design, which can improve the effectiveness of the medication and reduce side effects.

However, the development of 3D printed inhalers is still in its early stages and faces regulatory challenges. The safety and efficacy of these inhalers need to be demonstrated through clinical trials before they can be widely adopted. Nevertheless, 3D printed inhalers have the potential to revolutionize the field of respiratory drug delivery and provide more effective and personalized treatment options for patients

NANOPARTICLE INHALER :-

Nanoparticle inhalers are a type of inhaler that delivers medication in the form of nanoparticles. These inhalers use nanotechnology to create drug particles that are smaller than those used in traditional inhalers. The smaller particle size allows for better distribution and absorption of the medication in the lungs, leading to more effective treatment.

One of the most promising applications of nanoparticle inhalers is in the treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). By delivering medication in the form of nanoparticles, these inhalers can improve the efficiency and effectiveness of treatment, reducing the frequency and severity of symptoms.

Some examples of nanoparticle inhalers currently in development include liposomal inhalers, which use lipid nanoparticles to deliver drugs directly to the lungs, and nanofiber inhalers, which use electrospun nanofibers to create a high surface area for drug delivery.

While still in the early stages of development, nanoparticle inhalers hold great promise for the future of respiratory disease treatment, offering improved drug delivery and more effective symptom management

BIOLOGIC INHALER :-

A biologic inhaler is a type of inhaler that is used to deliver large molecule drugs, also known as biologics, to the lungs. Biologics are typically proteins or other complex molecules that cannot be taken orally and must be delivered directly to the bloodstream or targeted tissues.

Biologic inhalers are designed to deliver these drugs to the lungs using technologies such as dry powder inhalers, metered dose inhalers, or nebulizers. These inhalers are capable of delivering the biologic drug in a controlled and precise manner, which is essential for achieving the desired therapeutic effect while minimizing side effects.

Biologic inhalers are used to treat a variety of respiratory conditions, including asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. Some of the biologics delivered via inhalers include monoclonal antibodies, growth factors, and enzymes. These drugs are highly effective in treating respiratory conditions but can be difficult to deliver to the lungs due to their complex molecular structures.

Overall, biologic inhalers represent an important advancement in the treatment of respiratory diseases and offer new therapeutic options for patients who have not responded to traditional treatments. However, as with any new technology, ongoing research and development are needed to optimize the delivery of biologics via inhalers and to further improve patient outcome

RECENT ADVANCES IN NEBULIZER TECHNOLOGY :-

Recent advances in nebulizer technology aim to improve drug delivery efficiency, reduce drug wastage, and provide a more convenient and patient-friendly experience. Some of the notable advances in nebulizer technology include:

Vibrating Mesh Technology: Vibrating mesh technology nebulizers use a mesh with thousands of small holes that vibrate at high frequency to generate an aerosol mist. This technology offers advantages such as reduced treatment time, smaller particle size, and increased drug delivery efficiency.

Adaptive Aerosol Delivery: This technology monitors a patient's breathing pattern and adjusts the aerosol delivery to coincide with the first half of each inhalation, reducing drug wastage during exhalation.

Breath-Enhanced Nebulizers: These nebulizers use an auxiliary air supply to enhance aerosol output and improve drug delivery efficiency. They work by directing auxiliary air, entrained during inspiration, through the nebulizer, causing more of the generated aerosol to be swept out of the nebulizer and available for inhalation.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

Electronic Nebulizers: These nebulizers use electronic controls to optimize drug delivery and reduce treatment time. They can be programmed to deliver a specific dose of medication or to adjust the aerosol output based on the patient's breathing pattern

HANDIHALER:-

HandiHaler is a dry powder inhaler (DPI) device designed to deliver medication directly to the lungs for the treatment of chronic obstructive pulmonary disease (COPD). It is an easy-to-use device with a user-friendly design that enables patients to take their medication independently, improving their quality of life.

The HandiHaler device is composed of two parts: the inhaler and the capsule containing the medication. The inhaler has a mouthpiece, which the patient inhales through, and a transparent window, which allows the patient to see if the capsule is empty after use. The capsule is loaded into the inhaler, and when the patient inhales, the medication is released from the capsule and carried to the lungs.

One of the advantages of the HandiHaler is that it delivers medication in a consistent and controlled manner, ensuring that the right amount of medication is delivered to the lungs. Additionally, it is small and portable, making it easy for patients to carry with them and use on-the-go.

The HandiHaler is also designed with patient safety in mind. The inhaler has a safety mechanism that prevents the device from being used when the capsule is not properly loaded, and the capsule itself is easy to load and dispose of safely.

DISKHALER:-

The Disk inhaler, also known as the Diskhaler, is a dry powder inhaler that delivers medication directly to the lungs. It consists of a circular plastic device that holds medication in the form of small blisters. The patient opens the device and inhales the medication through a mouthpiece, which is activateda sliding lever. The Diskhaler is designed to be simple to use, portable, and effective in delivering medication. It is commonly used to treat respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). The Diskhaler has advantages over other inhaler devices, including its reliability, ease of use, and low environmental impact

GYROHALER:-

The Gyrohaler is a type of dry powder inhaler that was developed by AstraZeneca. It is designed to deliver a precise and consistent dose of medication to the lungs. The Gyrohaler uses a unique spinning disk technology that disperses the powder medication into fine particles for inhalation. The spinning disk is operated by a user-friendly twisting mechanism that is easy to use.

The Gyrohaler has several advantages over other dry powder inhalers, including its ability to deliver a consistent and accurate dose, as well as its ease of use. It also has a low resistance to airflow, which makes it easier for patients with respiratory issues to use.

The Gyrohaler has been used to deliver several types of medications, including bronchodilators and corticosteroids, and has been approved for use in several countries around the world. Its unique spinning disk technology has also been adapted for use in other types of inhalers, including the Aerolizer and the Twisthaler..

MARKETED INHALER

There are several recently marketed inhaler and nebulizer devices that have gained popularity.

One example of a recently marketed inhaler is the ProAir Digihaler. It is a digital inhaler that uses sensors to track medication use and provide personalized insights to help patients manage their asthma. It also provides real-time dose tracking and reminders for when to take the next dose.

Another example is the Ellipta inhaler, which is designed to deliver long-acting bronchodilators for patients with COPD. It has a unique dose counter and a one-click opening mechanism that simplifies its use for patients.

As for nebulizers, the PARI Trek S is a portable nebulizer that allows for effective aerosol treatment on the go. It is small, lightweight, and can be used with a rechargeable battery or AC power.

Another example is the AeroEclipse II Breath Actuated Nebulizer (BAN). It delivers medication only when the patient inhales, improving medication delivery efficiency and reducing drug waste

PROAIR DIGIHALER® :-

ProAir Digihaler is a recent inhaler device that utilizes digital technology to help patients manage their asthma symptoms. It is a breath-activated metered-dose inhaler that uses a small sensor to detect inhaler use and sends data to a

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

mobile app via Bluetooth. The app records the date, time, and location of inhaler use, as well as any symptoms and triggers experienced by the patient. This information can then be shared with healthcare providers to help them make more informed treatment decisions.

ProAir Digihaler also includes a built-in dose counter and a visual indicator to let patients know when they need to refill their inhaler. The inhaler is designed to be used with ProAir's albuterolsulfate medication, which is a bronchodilator used to treat asthma and other respiratory conditions.

The use of digital technology in inhaler devices like ProAir Digihaler can help patients better manage their asthma by providing them with real-time data on their symptoms and medication use. It also allows healthcare providers to monitor patient adherence and adjust treatment plans as needed

ELLIPTA® :-

Ellipta is a type of dry powder inhaler (DPI) designed for the delivery of medication directly into the lungs. It is a multi-dose inhaler that contains a pre-loaded blister strip of medication, which is pierced by the inhaler when activated by the patient. The inhaler delivers a fine powder of the medication into the patient's airways, where it is absorbed quickly and effectively.

One of the unique features of the Ellipta inhaler is its breath-activated mechanism. The inhaler is activated when the patient takes a deep breath in, which triggers the release of the medication. This helps to ensure that the patient receives the full dose of medication with each use, as they must take a proper inhalation to activate the device.

The Ellipta inhaler is used for the treatment of various respiratory conditions, including asthma and chronic obstructive pulmonary disease (COPD). It is available in several different formulations, including combinations of long-acting beta-agonists and corticosteroids. The inhaler is designed for ease of use, with a simple one-step activation process and a clear dose counter to track the remaining doses. Overall, the Ellipta inhaler is an effective and convenient option for patients with respiratory conditions who require regular medication.

PARI TREK S®:-

The PARI TREK S is a portable nebulizer that is designed for on-the-go use. It is small and compact, weighing less than a pound, and can easily fit into a backpack, purse, or briefcase. The device is battery-operated, which makes it ideal for traveling or use outside of the home.

One of the unique features of the PARI TREK S is its breath-enhanced technology. This means that the device only releases medication during inhalation, making it more efficient and effective than traditional nebulizers. The device also produces very small particles, which can reach deeper into the lungs and provide better treatment for respiratory conditions.

The PARI TREK S comes with a reusable nebulizer cup and mouthpiece, which can be easily cleaned and sterilized. It also has a built-in battery, which can provide up to 50 minutes of continuous use. The device is compatible with a variety of medications, including bronchodilators, corticosteroids, and antibiotics.

Overall, the PARI TREK S is a convenient and effective option for those who need nebulizer treatments on-the-go. Its small size and breath-enhanced technology make it a popular choice among patients with respiratory conditions.

AEROECLIPSE II®:-

The AeroEclipseII is a small, handheld nebulizer that uses vibrating mesh technology to deliver medication to the lungs. It is designed to be used by people with respiratory conditions such as asthma, COPD, and cystic fibrosis.

The device is portable, lightweight, and easy to use, making it a convenient option for people who need to take their medication on the go. It operates quietly and quickly, delivering medication in as little as 6 minutes. The AeroEclipse 2 has a large medication cup, which means it can hold more medication and reduce the need for frequent refilling.

One of the key benefits of the AeroEclipse 2 is its ability to produce consistently small particles, which can improve medication delivery to the lungs. The device also features a one-way valve system that prevents medication from escaping during exhalation, reducing medication waste and improving overall efficiency.

Overall, the AeroEclipse 2 is a reliable and effective nebulizer option for people with respiratory conditions who need to administer medication via inhalation

II. CONCLUSION:-

The pulmonary route of drug administration has gained attention for its potential

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1119-1134 www.ijprajournal.com ISSN: 2249-7781

as a non-invasive method for systemic delivery of therapeutic agents. The lungs offer a large absorptive surface area of up to 100 m .A thin absorptive mucosal membrane (0.1 µm – 0.2 µm), and good blood supply. Pulmonary drug delivery may be a promising alternative to oral or intravenous administration, reducing the incidence of side effects associated with high serum drug concentrations. Inherently small size and surface modification properties of inhalable drugs offer opportunities for innovative controlled drug release and pulmonary cell targeting therapeutic platforms. Integrating pulmonary delivery may improve targeting, release, and therapeutic effects of drugs and needle-free inhalation vaccines. Novel devices with improved delivery features, metered dosing, and deep lung penetration may increase the efficiency of protein delivery to the lungs. Efficient dosing has been improved by eliminating hold-up in new devices, using particles designed to penetrate the deep lung, and improving aerosol characteristics. The approaches and devices in pulmonary drug delivery systems are more prominent compared to other drug delivery systems, emphasizing the importance of considering their development in the overall therapeutic performance of the system.

REFERENCE

[1]. Pfutzner A., Mann A.E., Steiner S.S. TechnosphereTM/insulin – A new approach for effective delivery of human insulin via the pulmonary route. Diabetes TechnolTher2002;4:589-94.Cole J.L. and Hansen C.J., "Analytical ultra-centrifugation as a contemporary biomolecular research tool". J Biomol Tech, Vol 10, pp 163-176,(1999).

[2]. Brange J., Whittingham J., Edwards D., Zhang Y.S., Wollmer A., Brandenburg D., Dodson G, and Finch J., "Insulin structure and diabetes treatment". Curr Sci, Vol 72, pp 470-476,(1997).

[3]. Brange J. and Volume A., "Insulin analogues with improved pharmacokinetic profiles". Adv Drug Delivery Rev, Vol 35, pp 307-335,(1999). Exubera package insert. FDA website. January 2006.

[4]. Cefalu WT, Skyler JS, Kourides IA, et al. Inhaled insulin Study Group. Inhaled human insulin treatment in patients with type 2 diabetes mellitus. Ann Intern Med 2001;134:203-7.

[5]. Perera AD, Kapitza C, Nosek L, et al. Absorption and metabolic effect of inhaled insulin: Intrapatient variability after inhalation via the Aerodose® insulin inhaler in patients with type 2 diabetes. Diabetes Care 2002;25:2276-81.

[6]. Kim D, Mudaliar S, Chinnapongse S, et al. Dose-response relationships of inhaled insulin delivered via the Aerodose® insulin inhaler and subcutaneously injected insulin in patients with type 2 diabetes. Diabetes Care 2003;26:2842-7.

[7]. Rave K, Nosek L, Heinemann L, et al. Inhaled micronized crystalline human insulin using a dry powder inhaler. Doseresponse and time action profiles. Diabet Med 2004;21:763-8.

[8]. Schuster J, Rubsamen R, Lloyd P, et al. The AERx? aerosol delivery system. Pharm Res;14:35,4-7,(1997).

[9]. Farr S.J., McElduff A., Mather L.E., et al. Pulmonary insulin administration using the AERx? system: Physiological and physicochemical factors influencing insulin effectiveness in healthy fasting subjects. Diabetes TechnolTher2000;2:185-97.

[10]. Azria M., "Treatment with calcitonin for osteoporosis". Ann Rheum Dis, Vol 55, pp 700-714,(1996).

[11]. International Pharmaceutical Aerosol Consortium, 1997. Ensuring patient care-the role of the HFC MDI.

[12]. Metered dose pressurized aerosols and the ozone layer. European Resp. J. 3:495-497, (1990)

[13]. Groneberg DA, Nickolaus M, Spinger J, Doring F, Daniel H, Fischer A. Localization of peptide transporter PEPT2 in the lung: implications of pulmonary oligopeptide uptake. Am J Pathol. 2001;158:707–14.

[14]. Groneberg DA, Eynott PR, Döring F, Dinh QT, Oates T, Barnes PJ, et al. Distribution and function of the peptide transporter PEPT2 in normal and cystic fibrosis human lung. Thorax. 2002;57:55–60.

[15]. Groneberg DA, Witt C, Wagner U, Chung KF, Fischer A. Fundamentals of pulmonary drug delivery. Resp Med. 2003;97:382–87.

[16]. Tuncer DI, Nevin C. Controlled Delivery of Peptides and Proteins. Curr Pharm Des. 2007;13:99–117.

[17]. Sangwan S, Agosti JM, Bauer LA, Otulana BA, Morishige RJ, Cipolla DC, et al. Aerozolized protein delivery in asthma: amma camera analysis of regional deposition and perfusion. J Aerosol Med. 2001;14:185–95.
[18]. Scheuch G, Siekmeier R. Novel approaches to enhance pulmonary delivery of proteins and peptide. J Physio Pharmacol. 2007;58:615–25.
[19]. Siekmeier R, Scheuch G. Systemic treatment by inhalation of macromolecules:- principles, problems and examples. J Physio Pharmacol. 2008;59:53–79.
[20]. Flume P, Klepser ME. The rationale for aerosolized antibiotics. Pharmacother. 2002;22:71–9.
[21]. Mastrandrea LD, Quattrin T. Clinical evaluation of inhaled insulin. Adv Drug Deliv Rev. 2006;58:1061–75.
[22]. Expectoration of Phlegm. Molecules 2020, 25, 3064-3076, https://doi.org/10.3390/molecules25133064.
[23]. Foster, W.M.; Langenback, E.; Bergofsky, E.H. Measurement of tracheal and bronchial mucus velocities in man: relation to lung clearance. J. Appl. Physiol. 1980.
[24]. Woods, A.; Andrian, T.; Sharp, G.; Bicer, E.M.; Vandera, K.K.A.; Patel, A.; Mudway, I.; Dailey, L.A.; Forbesa, B. Development of new in vitro models of lung protease activity for investigating stability of inhaled biological therapies and drug delivery systems. Eur. J. Pharm. Biopharm. 2020, 146, 64-72.
[25]. Patton, J.S.; Fishburn, C.S.; Weers, J.G. The lungs as a portal of entry for systemic drug delivery. Ann. Am. Thorac. Soc. 2004, 1 338-344.
[26]. Olsson, B.; Bondesso, E.; Borgstrom, L.; Edsbäcker, S.; Eirefelt, S.; Ekelund, K.; Gustavsson, L.; HegelundMyrbäck, T. Pulmonary drug metabolism, clearance, and absorption. In: Controlled Pulmonary Drug Delivery. Smyth, H.; Hickey, A. Ed.; Springer, New York, NY, USA, 2011; pp. 21-50, https://doi.org/10.1007/978-1-4419-9745-6_2.
[27]. Eriksson, J.; Sjögren, E.; Lennernäs, H.; Thörn, H. Drug absorption parameters obtained using the isolated perfused rat lung model are predictive of rat in vivo lung absorption. AAPS J. 2020, 22, 71-83
[28]. Ruge, C.A.; Kirch, J.; Lehr, C.M. Pulmonary drug delivery: from generating aerosols to overcoming biological barriers-therapeutic possibilities and technological challenges. Lancet Respir. Med. 2013, 1, 402-413.
[29]. Movia, D.; Prina-Mello, A. Preclinical development of orally inhaled drugs (oids)-are animal models predictive or shall we move towards in vitro non-animal models? Animals (Basel) 2020, 10, 1259-1275.
[30]. Derendorf, H. Excessive lysosomal ion-trapping of hydroxychloroquine and azithromycin. Int. J.Antimicrob. Agents 2020, 55, 106007-106013..
[31]. Borghardt, J.M.; Weber, B.; Staab, A.; Kunz, C.; Formella, S.; Kloft, C. Investigating pulmonary and systemic pharmacokinetics of inhaled olodaterol in healthy volunteers using a population pharmacokinetic approach. Br. J. Clic. Pharmacol. 2011, 81, 538-552.
[32]. Bartels, C.; Looby, M.; Sechaud, R.; Kaiser, G. Determination of the pharmacokinetics of glycopyrronium in the lung using a population pharmacokinetic modelling approach. Br. J. Clin. Pharmacol. 2013, 76, 868-879.
[33]. Weber, B.; Troconiz, I.F.; Borghardt, J.M.; Staab, A.; Sharma, A. Model-based evaluation of single and multiple dose pharmacokinetics of inhaled tiotropium in healthy volunteers and implications for systemic exposure studies. Respiratory Drug Del. Europe 2015, 2, 249-254.
[34]. Edsbäcker, S.; Johansson, C.J. Airway selectivity: an update of pharmacokinetic factors affecting local and systemic disposition of inhaled steroids. Basic Clin. Pharmacol. 2006, 98, 523-536..
[35]. Lin, Z.; Li, M.; Wang, Y.S.; Tell, L.A.; Baynes, R.E.; Davis, J.L.; Vickroy, T.W.; Riviere, J.E. Physiological parameter values for physiologically based pharmacokinetic models in food-producing animals. Part I: Cattle and swine. J. Vet. Pharmacol. Ther. 2020, 43, 385-420..
[36]. Boger, E.; Evans, N.; Chappell, M.; Lundqvist, A.; Ewing, P.; Wigenborg, A.; Fridén, M. Systems pharmacology

approach for prediction of pulmonary and systemic pharmacokinetics andreceptoroccupancyhttps://doi.org/10.33263/BRIAC113.1009910118https://biointerfaceresearch.com/ 10114of inhaled drugs. CPT Pharmacometrics Syst. Pharmacol. 2016, 5, 201-210,.

[37]. Bäckström, E.; Hamm, G.; Nilsson, A.; Fihn, B.M.; Strittmatter, N.; Andrén, P.; Goodwin, R.J.; Fridén, M. Uncovering the regional localization of inhaled salmeterol retention in the lung. Drug Deliv. 2018, 25, 838-845, https://doi.org/10.1080/10717544.2018.1455762.

[38]. Ashish, K.; Hiralal, C.; Prajkata, U.; Dheeraj, B.; Dinesh, K. Pulmonary drug delivery system. Int. J.Pharm.Tech. Res. 2012, 4, 293-305.

[39]. Kadam, P.; Kanekar, H.; Khale, A. Pulmonary drug delivery system: current practices and applications. World J. Pharm. Res. 2014, 3, 204-229.

[40]. Shaikh, S.; Nazim, S.; Khan, T.; Shaikh, A.; Zameeruddin, M.; Quazi, A. Recent advances in pulmonary drug delivery system: A review. Int. J. Appl. Pharm. 2010, 2, 27-33.

[41]. Cheng, Y.S. Mechanisms of pharmaceutical aerosol deposition in the respiratory tract. AAPS PharmSciTech. 2014, 15, 630-640.

[42]. Groneberg, D.A.; Witt, C.; Wagner, U.; Chung, K.F.; Fischer, A. Fundamentals of pulmonary drug delivery. Respir. Med. 2003, 97, 382-387.

[43]. Thulasiramaraju, T.V.; Kumar, B.T.; Babu, M.N. Pulmonary drug delivery system: An overview. AJRBPS2013, 1, 16-34.

[44]. Shah, N.D.; Shah, V.V.; Chivate, N. Pulmonary drug delivery: a promising approach. J. Appl. Pharm. Sci.2012, 2, 33-37.

[45]. Ibrahim, M.; Verma, R.; Contreras, L.G. Inhalation drug delivery devices: technology update. Med Devices (Auckl) 2015, 8, 131-139, https://doi.org/10.2147/MDER.S48888.

[46]. Alipour, S.; Montaseri, H.; Tafaghodi, M. Preparation and characterization of biodegradable paclitaxel loaded alginate microparticles for pulmonary delivery. Colloid Surface B. 2010, 81, 521-529.

[47]. El-Sherbiny, I.M.; El-Baz, N.M.; Yacoub, M.H. Inhaled nano-and microparticles for drug delivery. Glob. Cardiol. Sci. Pract. 2015.

[48]. Abdelaziz, H.M.; Gaber, M.; Abd-Elwakil, M.M.; Mabrouk, M.T.; Elgohary, M.M.; Kamel, N.M.; Kabary, D.M.; Freag, M.S.; Samaha, M.W.; Mortada, S.M.; Elkhodairy, K.A. Inhalable particulate drug delivery systems for lung cancer therapy: Nanoparticles, microparticles, nanocomposites and nanoaggregates. J. Control Release 2018, 269, 374-392, https://doi.org/10.1016/j.jconrel.2017.11.036.

[49]. Goel, A.; Baboota, S.; Sahni, J.K.; Ali, J. Exploring targeted pulmonary delivery for treatment of lung cancer. Int. J. Pharm. Investig. 2013, 3, https://doi.org/10.4103/2230-973X.108959.

[50]. Lee, W.H.; Loo, C.Y.; Traini, D.; Young, P.M. Inhalation of nanoparticle-based drug for lung cancer treatment: advantages and challenges. Asian J. Pharm. Sci. 2015, 10, 481-489.

[51]. Hitzman, C.J.; Elmquist, W.F.; Wattenberg, L.W.; Wiedmann, T.S. Development of a respirable, sustained release microcarrier for 5-fluorouracil I: In vitro assessment of liposomes, microspheres, and lipid coated nanoparticles. J. Pharm. Sci. 2006, 95, 1114-1126.

[52]. Williams III, R.O.; Barron, M.K.; Alonso, M.J.; Remuñán-López, C. Investigation of a pMDI system containing chitosan microspheres and P134a. Int. J. Pharm. 1998, 174, 209-222..

[53]. Wang, H.; Xu, Y.; Zhou, X. Docetaxel-loaded chitosan microspheres as a lung targeted drug delivery system: in vitro and in vivo evaluation. Int. J. Mol. Sci. 2014, 15, 3519-3532.

[54]. Kim, I.; Byeon, H.J.; Kim, T.H.; Lee, E.S.; Oh, K.T.; Shin, B.S.; Lee, K.C.; Youn, Y.S. Doxorubicin-loaded highly porous large PLGA microparticles as a sustained-release inhalation system for the treatment of metastatic lung cancer. Biomaterials 2012, 33, 5574-5583.

[55]. Wu, D.; Wang, C.; Yang, J.; Wang, H.; Han, H.; Zhang, A.; Yang, Y.; Li, Q. Improving the intracellular drug

concentration in lung cancer treatment through the co-delivery of doxorubicin and miR-519c mediated by porous PLGA microparticle. Mol. Pharm. 2016, 13, 3925-3933..

[56]. Zhu, L.; Li, M.; Liu.; X.; Du, L.; Jin, Y. Inhalable oridonin-loaded poly (lactic-co-glycolic) acid large porous microparticles for in situ treatment of primary non-small cell lung cancer. Acta Pharm. Sin. B 2017, 7, 80-90..

[57]. Umeyor, C.E.; Kenechukwu, F.C.; Uronnachi, E.M.; Osonwa, U.E.; Nwakile, C.D. Solid lipid microparticles (SLMs): an effective lipid based technology for controlled drug delivery. Am. J. Pharmtech Res. 2012, 2, 1-18.

[58]. Levet, V.; Rosière, R.; Merlos, R.; Fusaro, L.; Berger, G.; Amighi, K.; Wauthoz, N. Development of controlled-release cisplatin dry powders for inhalation against lung cancers. Int. J. Pharm. 2016, 515, 209-220.

[59]. Gidwani, B.; Vyas, A. A comprehensive review on cyclodextrin-based carriers for delivery of chemotherapeutic cytotoxic anticancer drugs. Biomed. Res. Int. 2015, 2015, 1-15,