

Pulmonary Drug Delivery System

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Abstract: Pulmonary drug delivery is primarily use to treat conditions of the airways, delivering locally acting drugs directly to their site of action. These routes of drug delivery may give the advantages like small amount of drug, less adverse reaction and rapid onset of action. The human respiratory system is complicated organ system these system consist of two reagions conducting airways and respiratory region. The airway further divided in to many folds such as nasal cavity, nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles. The respiratory region consists of respiratory, bronchioles, alveolar ducts and alveolar sac. Pulmonary drug delivery may show that many molecule are absorbed through the deep lung in ton the bloodstream naturally with high bioavailability and without the need for enhancer used by other noninvasive route. In these inhalation therapy most common device use such as nebulizer which consist of two types such as Jet nebulizer and Ultrasonic nebulizer, Metered dose inhaler (MDI), and Dry powder inhaler(DPI). Pulmonary drug delivery is used for management of COPD and Asthma only but due to advancement in application nowadays Pulmonary drug delivery is useful to treat Diabetes, angina pectoris, cancer, bone disorders, tuberculosis, migraine acute lung injury and others. We also describe here the various evaluation parameter for pulmonary drug devices. In these review we study the pulmonary disease, different devices use on it, and there application with its evaluation parameter.

Key Words:- Pulmonary, lungs, Inhalers, asthma, COPD, Aplications.

INTRODUCTION

Pulmonary route was use to treatment of different respiratory diseases from the last decade. The inhalation therapies involved the use of leaves from plants, vapors from aromatic plants, balsams, and myhr. Through, around the turn of the 19th century, with the invention of liquid nebulizers, these newer treatments developed into valid pharmaceutical therapies. In the 1920 s adrenaline can introduce as a nebulizer solution, in 1925 nebulizer porcine insulin was use in investigational studies in diabetes, and in 1945 pulmonary delivery of the newly revealed

penicillin was investigate. steroids had been introduced in between 1950s for the treatment of asthma and nebulizers were enjoy widely use. In 1956 the pressured metered dose inhaler (pMDI) was placed, over the last 5 decades, helped by the advances in molecule design and drug discovery the pMDI was risen to become the major stay for the asthma treatment ¹. It may found that certain drugs taken by pulmonary route are readily absorbed by the alveolar region direct in to blood circulation. Pulmonary route having many advantages over other routes of supervision for the treatment of particular disease states, specifically lung associated bigger protein

molecules may degrade into the gastrointestinal situation and are excreted through the first pass metabolism into the liver which can be transferred through the pulmonary route if deposited in the respiratory passage of the lungs².

ANATOMY AND PHYSIOLOGY OF LUNGS³.

1) Lung regions:-

The respiratory tract starts at the nose and terminates deep in the lung at an alveolar sac. There are a number of schemes for categorizing the various regions of the respiratory tract.

2) Nasopharyngeal region:-

This is also referred to as the “upper airways”, which involves the respiratory airways from the nose down to the larynx.

3) Tracheo-bronchial region:-

This is also referred to as the “central” or “conducting airways”, which starts at the larynx and extends via the trachea, bronchi, and bronchioles and ends at the terminal bronchioles.

4) Alveolar region:-

This is also referred to as the “respiratory airways”, “peripheral airways” or “pulmonary region”, comprising the respiratory bronchioles, alveolar ducts and alveoli.

The term “pulmonary” can be misleading since some authors use it with reference to the whole lung, while others control its use to the alveolar region. In this chapter pulmonary refers to the whole lung. The use of “upper respiratory tract” (i.e. NP plus trachea) and “lower respiratory tract” is also common place.

Pulmonary epithelium:-

The lung contains more than 40 different cell types, of which more than six line the airways. The diversity of pulmonary epithelia can be illustrated by examining its structure at three principal levels.

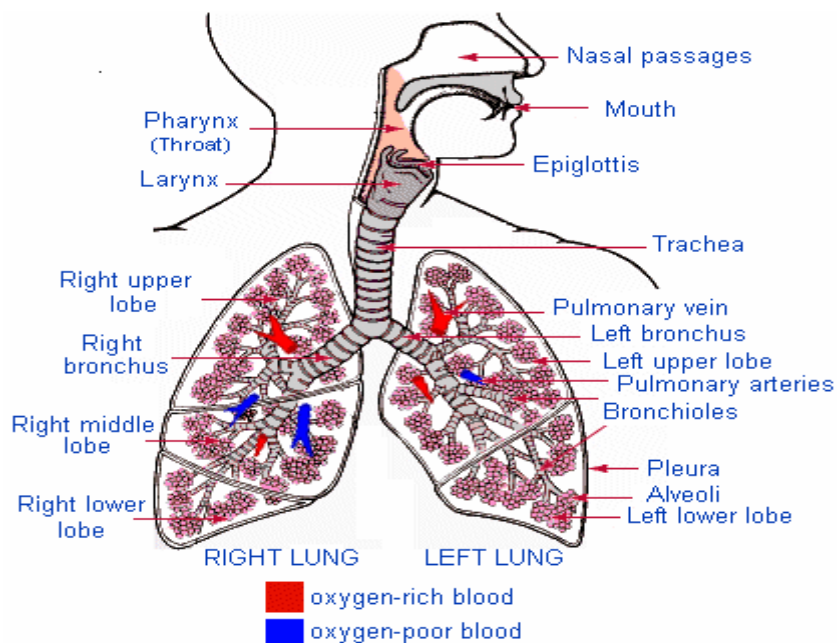


Fig 1: Different regions of the human respiratory tract

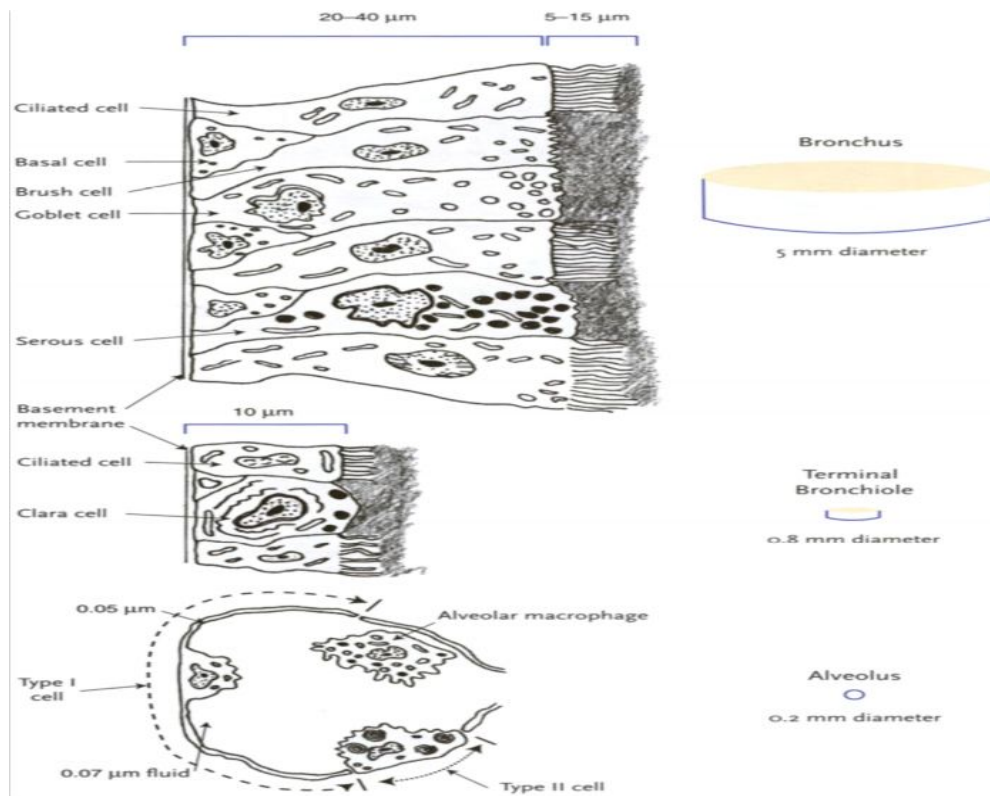


Fig 2: Pulmonary Epithelium

The bronchi:-

These are lined predominantly with ciliated and goblet cells. Some serous cells, brush cells and Clara cells are also present with few Kulchitsky cells.

The bronchioles:-

These are primarily lined with ciliated cuboidal cells. The frequency of goblet and serous cells decreases with progression along the airways while the number of Clara cells increases.

The alveolar region:-

This is devoid of mucus and has a much flatter epithelium, which becomes the simple squamous type, 0.1–0.5 μm thick. Two principal epithelial cell types are present:

- Type-I pneumocytes: Thin cells offering a very short airways-blood path length for the diffusion of gases and drug molecules. Type-I pneumocytes occupy about 93% of the surface area of the alveolar sacs, despite being only half as abundant as type-II cells.
- Type-II pneumocytes: Cuboidal cells that store and secrete pulmonary surfactant.

Alveolar macrophages account for ~ 3% of cells in the alveolar region. These phagocytic cells scavenge and transport particulate matter to the lymph nodes and the mucociliary escalator.

Ciliated cells:-

In the trachea bronchial region, a high proportion of the epithelial cells are ciliated such that there is a near complete covering of the central airways by cilia. Towards the periphery of the tracheobronchial region, the cilia are less abundant and are absent in the alveolar region. The ciliated cells each have about 200 cilia with numerous interspersed microvilli, of about 1–2 μm in length. The cilia are hair-like projections about 0.25 μm in diameter and 5 μm in length. They are submersed in an epithelial lining fluid, secreted mainly from the serous cells in the sub-mucosal glands. The tips of the cilia project through the epithelial lining fluid into a layer of mucus secreted from goblet cells. The cilia beat in an planned fashion to propel mucus along the airways to the throat.

FACTORS AFFECTING PULMONARY DRUG DELIVERY⁴

Mechanisms of particle deposition in the airways

Effective resistance mechanisms may have involved may reduces the burden of external particles enter the airways, and clearing those it may achieve something in being stored. Therapeutic aerosols are two-phase colloidal systems in that the drug is contained in a dispersed phase they may have a solid, liquid or combination of the two, based on the method and formulation of aerosol generation. Evidently for effective therapy, the drug must have obtain able to the lung in aerosol droplets or particles that deposit in the specific lung region and in sufficient quantity to be effective. The respiratory resistance mechanisms of mucociliary clearance and phagocytosis by macrophages may act upon insoluble particles. Aerosol particle dissolution they may slow and the drug may then subsequently to be subject to enzymatic deprivation before it reaches to its specific site of pharmacological action. Aerosols for pulmonary drug delivery are transported from the mouth.

Inertial impaction

This is the main deposition mechanism for particles $>1 \mu\text{m}$ in the upper tracheo-bronchial regions. A particle having a large momentum it may not able to follow the altering direction of the inspired air as it transferred the bifurcations and it will show result to collide with the airway walls as it continues on its original course.

Description of particle deposition mechanisms at an airway branching site⁵

Impaction it mainly occurs near the bifurcations, certainly the impaction of particles from tobacco smoke on the bifurcations may be one cause why these sites are often the foci for lung tumors. The prospect of inertial impaction will be dependents upon particle momentum, thus particles with higher densities or larger diameter and those travelling in airstreams of higher velocity will show superior impaction.

Sedimentation:-

By the settling under gravity the particles may deposited. It becomes highly important for particles that reach airways where the airstream velocity is relatively low, e.g. the bronchioles and alveolar region. The fraction of particles depositing by this mechanism it may dependent upon the time the particles use in these regions.

Brownian diffusion:-

This is of minor significance for particles $>1 \mu\text{m}$. Particles smaller than this size are displaced by a sequentially bombardment of gas molecules, which may results in particle collision with the airway walls. The chances of particle deposition by diffusion increases with the particle size decreases. Brownian diffusion is also more common in regions where airflow is very low or absent, e.g. in the alveoli. Another method of deposition, that of interception, is of important for fibers but it may not for drug delivery. Generally:-

- Particles bigger than $10 \mu\text{m}$ will have impact in the upper airways and are rapidly removed by swallowing, coughing and mucociliary processes.
- The particles in the size range $0.5\text{--}5 \mu\text{m}$ may break away from impaction in the upper airways and may deposit by sedimentation and impaction in the lower TB and A regions. If the aerosol particle size is between the 3 and $5 \mu\text{m}$ then deposition it mainly occur in the TB region. If the particles are smaller than the $3 \mu\text{m}$ then appreciable deposition in the A region is likely to occur.

Physiological factors affecting particle deposition in the airways³

Lung morphology:-

Each successful production of the tracheobronchial tree produces airways of falling diameter and length. Every bifurcation results in an increase possibility for impaction and the decrease in airway diameter is associated with a smaller displacement necessary a particle to make contact with a surface.

Inspiratory flow rate:-

When the inspiratory flow rate increases they enhance deposition by impaction in the first few generations of the TB region. The increase in flow not only increase particle momentum but also result in an increase in turbulence, mostly in the larynx and trachea, which itself will enhance impaction in the proximal tracheo-bronchial region.

Co-ordination of aerosol generation with inspiration:-

The energy of aerosol particles generated from pressurized metered dose inhalers (p MDIs, is largely govern by the pMDI formulation rather than the subject's IFR. pMDI aerosol droplets will be travelling at velocities of $2,500\text{--}3,000 \text{ cm s}^{-1}$. A failure to co-ordinate actuation of the p-MDI during the early on phase of the inspiratory plan will result

in near total particle impaction in the oropharyngeal area.

Tidal volume:-

An increased IFR will usually be connected with an enlarge in the volume of air inhaled in one breath, the tidal volume. Obviously an increase in tidal volume will result in penetration of aerosol particles deeper into the TB and A regions and a better chance for deposition inside these regions.

Breath holding:-

Increasing the time between the end of inspiration and the start of exhalation increase the time for sedimentation to occur. Breath-holding is normally used to optimize pulmonary drug delivery.

Disease states:-

Bronchial obstruction as seen in different pulmonary disorders may associated with the larger local airflows and turbulence and this will result in localized deposition in the larger airways of the trachea-bronchial region. The bronchoconstriction of asthma has a more influence on exhalation than inhalation and thus deposition by sedimentation may be superior than normal.

Pharmaceutical factors affecting aerosol deposition ⁴

Aerosol velocity:-

The aerosols formed by nebulizers and dry powder inhalers (DPIs) are transported into the lung by entrainment on inspired air. In difference, pMDIs generate aerosol droplets with velocities greater than the inspiratory airflow and therefore the aerosol will have a greater affinity to impact in the oropharyngeal region.

Size:-

Marketable devices do not lead to monodispersed particles and frequently the size distribution is extensive and the particles may show varying shapes. Consequently a number of terms are used to adequately characterize an aerosol sample:- The geometric standard deviation (GSD) is defined as the size ratio at 84.2% on the cumulative frequency curve to the median diameter. This assumes that the sharing of particle sizes is Lognormal. A monodisperse, i.e. ideal aerosol, has a GSD of 1, although in practice an aerosol with a GSD of <1.22 is describe as monodisperse while those aerosols with a GSD >1.22 are referred to as polydispersed or heterodispersed.

Shape:-

Particles which are non-spherical will have at smallest amount one physical dimension which is superior than the aerodynamic diameter. Ecological fibers 50 μm in length can reach the A region because they align with the inspired airflow. Such materials then impact in the airways by a procedure of interception with the airway walls.

Density:-

Particles having densities less than 1 g cm^{-3} (unit density) may have a mean physical diameter larger than the aerodynamic limit. Most micronized drugs for inhalation will contain particle densities around 1, although materials created by freeze-drying or spray-drying methods are likely to be appreciably less dense.

Physical stability:-

Therapeutic aerosols are often inherently actually unstable since they have a high concentration of particles and their close immediacy may lead to mutual repulsion or other inter-particulate reactions. Aerosol particles generate by DPIs may be hygroscopic and, during their passageway throughout the high humidity environments of the airways, may enlarge in size and thus have a greater chance of being prematurely deposited. It be supposed to not be assumed, however, that the uptake of water vapor will always occur.

Pulmonary delivery devices:-

Current inhalation devices are separated into three different categories, the refinement of the nebulizer and the evolution of two types of compact portable devices, dry powder inhaler (DPI) and metered-dose inhaler (MDI).

ADVANTAGES OF PULMONARY DRUG

DELIVERY

- 1) It is needle free pulmonary delivery.
- 2) It requires small and fraction of oral dose.
- 3) Low concentration in the systemic circulation are associated with reduced systemic side effects.
- 4) Rapid Onset of action
- 5) Avoidance of gastrointestinal upset
- 6) Degradation of drug by liver is avoided in pulmonary drug delivery ^{6,7}.

DISADVANTAGES OF PULMONARY DRUG

DELIVERY

- 1) Oropharyngeal deposition gives local side effect.
- 2) Patient may have difficulty using the pulmonary drug devices correctly

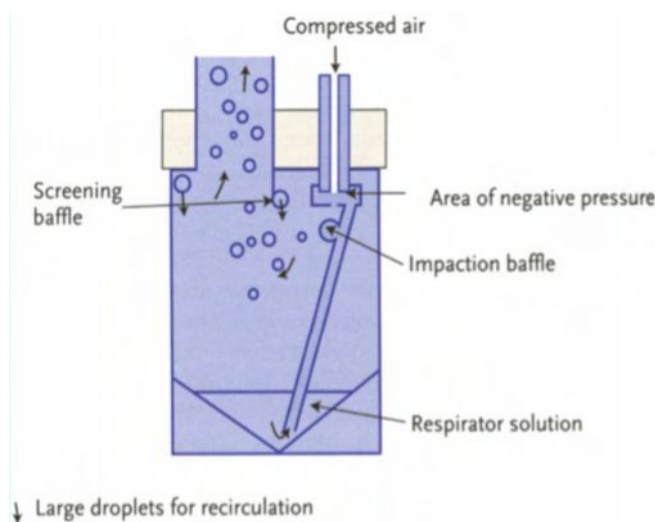


Fig 3: Air jet nebulizers

- 3) Drug absorption may be limited by the physical barrier of the mucus layer.
- 4) Various factors affect the reproducibility on drug delivery on the lungs, including physiological and pharmaceutical barrier.
- 5) The lungs are not only accessible surface for drug delivery complex but also delivery devices are required to target drug delivery.

RECENT TECHNOLOGIES OF PULMONARY DRUG DELIVERY

Nebulizer: Nowadays the many physicians are mostly use nebulizer for the treatment of acute asthma in an emergency care unit or for treating patients with severe asthma at home. In jet nebulizers, an aerosol is prepared by a high velocity air stream from a pressurized source directed against a thin layer of liquid solution. Ultrasonic nebulizers include the vibration of a piezoelectric crystal aerosolizing the solution. The nebulizer can transport more drugs to the lungs than MDI or DPI, the most common disadvantage of nebulizer are lack of possibility, higher costs of drug delivery as a result of the larger need for assistance from healthcare professionals, and the need for higher drug doses to achieve a therapeutic result ⁸.

Metered Dose Inhaler (MDI): These are the most common device for administration of aerosolized drugs. In this technique, a medication is mixed in a canister with a propellant, and the preformed mixture is expelled in exact measured amounts upon actuation of the device. Correct use of MDIs requires

that patients learn how to organize exhalation and inhalation with actuation of the device. By using the spacer device it may solve the problem moderately the bulky size of the device can be prevention for patients who have need of use of MDIs outside their homes. In near the beginning 1990, attempts were actively made to reformulate MDIs as a result of the mandatory ban on the use of propellant chlorofluorocarbons (CFCs), which have been concerned in the depletion of the Earth’s ozone layer. Optional propellants, such as hydrofluoroalkane 134a (HFA-134), have be extensively investigated for their potentials to change CFCs since 1990.

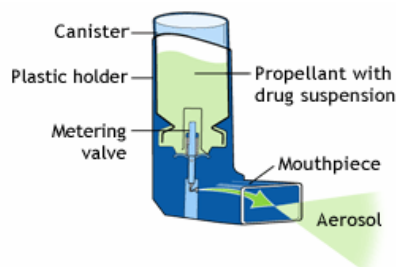


Fig 4: Metered-dose inhalers

Powder Inhaler (DPI): Dry powder systems use drug single or its blends with a suitable carrier, mainly as lactose, for delivery to the lungs. The three main factors Drug, Carrier, and device may affecting the act of pulmonary delivery of drugs. Unlike MDIs, delivery of medication with a DPI require minimum patient coordination and collaboration of breathing following actuation of the device. In addition, DPIs are small, portable devices that can be easily carried in a purse or pouch. There is also not require to use spacers. In addition, DPIs are devoid of environmentally injurious CFC propellants, as normally necessary in MDI formulation. Since both MDI and DPI have been exposed to afford comparable efficacy in delivering the similar drug and in view of the mandatory ban of CFCs use in MDIs by the United Nations, it is not shocking that DPIs have become increasingly significant as a pulmonary drug delivery system over the precedent decade. The aerosol drug delivery is undergo dramatic changes in both inhaler device and formulation aspects¹⁰. There is a rapid move from the traditional propellant-driven metered dose inhalers to the high presentation liquid atomizers and dry powder inhalers. The inhaler devices are particularly attractive as dry powders. Because of dry powder show the greater chemical stability than the liquids are use in atomizers. On the other hand, formulation and production of dry powders for inhalation can be difficult and challenging due to the potential physical instability of the powder.

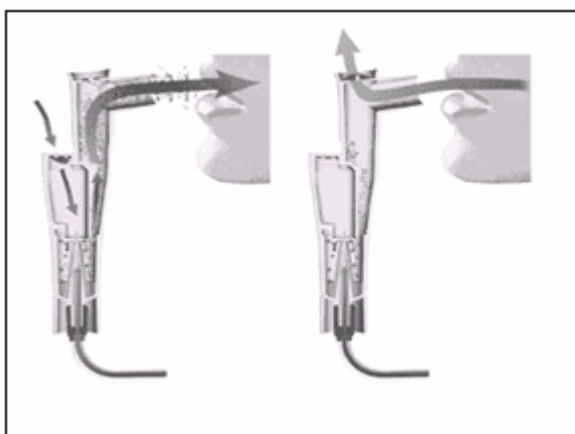


Fig.5: Dry Powder Inhalers

Advantages for Dry Powder Inhalers (DPIs):

Larger drug available for pay loads per puff. Blending is not require for it. Enables use of small, flow-rate independent inhalers, The particles readily disaggregate despite their small size. Enables improved lung deposition, de dose decrease variability

and potential for condensed dose through enhanced dispersibility.

EVALUATION OF PULMONARY

DRUG DELIVERY DEVICES

1) Cascade impactors

Cascade impactors determine the aerodynamic activities of aerosol particles by size-separating the dose in impactor plates. Cascade impactors give up valuable aerosol parameters such as the fine particle fraction (FPF) mass median aerodynamic diameter (MMAD). *In vitro* particle sizing data obtained from impactors plan first at scheming the quality of the pharmaceutical product and next at provide an analysis tool for product improvement. It is projected that outcome from cascade impactors forecast human lung deposition data as particle aerodynamic size determines aerosol deposition in the human respiratory tract. In wide-ranging the FPF thoroughly overestimates whole lung authentication in humans. Dimensions in cascade impactors are prepared at room temperature and at low absolute humidity, which is not representative of human airways' ambient circumstances.

e2) *In vitro*:-

In this respect, *in vitro* models for pulmonary drug delivery studies propose another as it convey up fewer moral questions but also because they allow a fast screening of drugs. In both cellular models, it is significant that epithelial cells form a tense monolayer in order to characterize the natural epithelial barrier. Monolayer tension and reliability are classically assessed by measuring Tran's epithelial electrical resistance (TEER) and potential difference crosswise the monolayer. Monolayers of lung epithelial cells permit the categorization of drug transport and evaluation of potential drug and formulation toxicity. Drug transport is classically calculated in the apical to basolateral direction, and vice versa, in order to ensure for active transport mechanisms.

3) Continuous cell cultures¹¹

Continuous cell cultures are supplementary reproducible and easier to utilize than primary cell cultures but they frequently do not have the differentiated morphology and the biochemical characteristics of the original tissue. There are a small number of cell lines resulting from alveolar epithelial cells. A549 is a type II alveolar epithelial cell line that originates from human lung adenocarcinoma. It can be very helpful in metabolic and toxicological studies but it is less interesting as a drug delivery model because A549 cells do not form stretched monolayers.

4) Primary cell cultures ¹²

The majority primary cell cultures used as models for pulmonary drug delivery and convey studies consist of alveolar epithelial cells. Type II pneumocytes for primary culture can be removed from the lung of different species. Human cells are the mainly representative of the clinical circumstances, but they are less available than cells from other mammals. Human type II pneumocytes are removed from normal lung tissue of patients undergoing partial lung resection. In culture, the cells experience segregation into type I-like cells, as indicated by morphological and histochemical change. In premature stages of the cell culture, the cells create elevated levels of surfactant protein C and little levels of caveolin 1, a marker of type I pneumocytes, and on the other hand at later stages. On day 8 of culture, the cells form a tight monolayer consisting mainly of type I cells and some interspersed type II cells, with TEER > 2000 Ω cm² and potential difference > 10 mV.

5) Air-interface cultures

Air-interface cultures (AIC) are models that permit aerosol particles to place straight onto semi-dry apical cell surface. Drug deposition and dissolution take place in a small volume of cell lining fluid, a circumstances that mimics more directly deposition on the lung surface *in vivo*. The AIC show greater similarity to airways epithelial morphology, with superior glycoprotein discharge, more prominent microvilli and the construction of a pseudo stratified layer of columnar cells, while the liquid-covered culture created a monolayer of cells.

6) In –vivo

Before new drugs are deliver to the human lungs, animal studies need to be passed out. The morals of any animal experiment require to be accepted by an Institutional Animal Care and Use Committee. Experiment perform in an animal model can afford information on drug declaration, metabolism, assimilation and kinetic profile as well as on drug and rats and guinea-pigs) are frequent formulation acceptability. So, non-human primates are use only in advanced research. By contrast, small rodents (mice, models for preliminary studies on pulmonary drug delivery because they can be used in large numbers. Mice have been used less often for assessing pulmonary release of systemically performing drugs because pharmacokinetic studies are not optimally perform in mice. Owing to its small size, one mouse can offer only one blood sample at a time (1 ml whole blood sample is withdrawn by cardiac puncture and mouse euthanasia must be done at each time point of the plasma drug concentration–time curve. Guinea-

pigs have been generally used as an animal form of allergic asthma and infectious diseases (e.g., tuberculosis) since the airway anatomy and the respond to inflammatory stimuli are similar to the human case. The dissimilar mammals do not show to present related mucociliary clearance and alveolar macrophage morphometry. In large mammals, the rate of mucus permission in millimetres per minute is elevated compared with small rodents. Though, huge mammals also have longer airways than minute rodents and thus, worldwide, the bronchial permission of inhaled particles is comparatively slow in humans (> 24 h). By contrast, bronchial clearance of particles is relatively quick and early in rats and mice. The number of macrophages per alveolus and the alveolar macrophage volume are superior in human and canine lungs than in small rodents' lungs.

7) Passive inhalation:-

During passive inhalation of aerosolised drugs, animals are kept awake and allowed to breathe normally. Aerosolised drugs are delivered using an aerosolisation chamber in whole body, head-only or nose-only exposure systems. The devices most frequently used for generating aerosols are nebulisers. Passive inhalation is principally used in the mouse and less frequently in larger animals (rat, guinea-pig, dog). This method is more representative of drug delivery to the human lungs than intratracheal instillation of large volumes of liquids. The drug concentration in the aerosol is determined by sampling the test atmosphere and quantifying the drug in the sample.

8) Whole body exposure system:-

In whole body aerosol exposure system, animals are placed in a sealed plastic box that is connected to a nebuliser or a generator of dry powder aerosol. Although this system allows a less stressful pulmonary drug administration to an important number of animals, there is potential drug absorption across the skin after deposition on the animal fur, from the nasal mucosa and from the gastrointestinal tract.

9) Head-only or nose-only exposure systems:-

In the head-only or nose-only exposure systems, the animal is attached to the exposure chamber and only the head or the nose is in contact with the aerosol. The systems can be designed for delivering drugs to one or to several animals. Compared with the whole body exposure system, the head-only or nose-only exposure systems offer several advantages. Skin exposure to the drug and its uptake by the transdermal route are avoided. The low volume of the aerosolisation chamber reduces the amount of drug needed to generate the aerosol. Potential drug

reactivity with excreta is avoided. Variable durations of animal exposure are possible in one single test.

10) Direct intratracheal administration:-

Dry powders can be delivered intratracheally using a powder-insufflator or by generating a powder aerosol. Although intratracheal administration is a simple method of pulmonary drug delivery, small changes in the method can lead to significant differences in site of drug deposition within the lung and, thereby, in systemic drug absorption. Deposition of the solution in the trachea, central and peripheral lobe sections was assessed after tissue grinding using albumin as a slowly diffusing marker. The use of a simple micro-syringe led to the deepest administration within the lung and to the highest bioavailability when the instillation was followed by the administration of a 3 ml air bolus. A spray-instillator, producing 25 – 30 µm solution droplets, led to more central deposition and lower bioavailability. Advantages of intratracheal administration of drugs include the perfect control of the drug dose delivered, the absence of drug losses in the instrumentation (except for liquid and powder aerosols), the bypassing of nasal passages and the possible targeting of different regions within the respiratory tract.

11) Intranasal administration:-

Intranasal administration is mostly known for local drug delivery to the nasal mucosa but it can also be used for intrapulmonary drug administration in mice. Intranasal administration is performed on the anaesthetised mouse kept in a vertical position. With the help of a micropipette, the solution is deposited on a nostril and is simply aspirated in respiratory airways during breathing. Use of a small volume of solution restricted drug administration to the nasal cavity but that the use of a larger volume of solution allowed a deeper administration to be reached in lung upper airways.

CURRENT APPLICATIONS OF PULMONARY DRUG DELIVERY

1) Application of pulmonary drug delivery in Asthma and COPD^{13,14}

Asthma is a chronic lung that disease is characterized by inflammation and narrowing of airways. Asthma causes recurring period so wheezing, shortness of breath, chest tightness and coughing. For treatment of asthma advances had done in drugs such levosalbutamol inhalers which show greater efficacy as compare tosalbutamol. COPD means chronic obstructive pulmonary diseases. For the

treatment of COPD tiotropium inhalers are present in market.

2) Recent role pulmonary delivery in patients on ventilators

Nowadays to improve inhalation coordination of patient devices are mostly used like Baby mask. This mask is attached to spacer for small tidal volumes and low inspiratory flow rates infant and young Children. We can easily give medication to child up to 2 years by using baby mask this is recent advancements in applications of pulmonary drug delivery.

3) Pulmonary delivery in cystic fibrosis

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

I) N-Acetylcysteine

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

II) Recombinant human deoxyribonuclease aerosol

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

III) Tobramycin-spray dried

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

4) New use of pulmonary delivery in diabetes

Diabetes is deficiency of insulin secretion or resistance. The most common form of this therapy is twice-daily subcutaneous injections of insulin. This type of treatment is painful and as a result encourages non compliance by up to half of the diabetics. Various companies are working on insulin inhalers than any other insulin delivery option. Insulin inhalers would work much like asthma inhalers. The products fall into two main groups the dry powder formulations and solution, which are delivered through different patented inhaler systems. E.g. Novel pMDI formulations for pulmonary delivery of proteins¹⁵⁻²⁰.

5) In migraine

Ergotamine is drug of choice for migraine. Many years ago, ergotamine via metered dose inhaler was used successfully to treat migraine headache²¹.

6) Angina pectoris

Angina pectoris is not a disease itself it is symptoms of myocardial ischemia it arises as a result of imbalance between oxygen supply and demand of myocardium. Nitroglycerine. Is drug of choice for angina pectoris has been given generally by sublingual route Isosorbide aerosol has also been reported useful in hypertensive crisis. In United States inhalation therapy for angina-pectoris is very well accepted²¹.

7) Role of pulmonary delivery in vaccination

While there was moderate interest in aerosol vaccination 15–20 years ago, progress to ward application has been modest seen. Nearly 100 vaccines are approved in the U. S. About half of these prevent respiratory infections, yet all are currently injected Recently inhaled measles vaccine given by nebulizer. As far back as the 1960, influenza experts tested aerosol flu vaccines¹⁸.

8) In emphysema

Emphysema is most popular respiratory disorder due to deficiency of Alpha 1 antitrypsin uncontrolled neutrophil elastase deficiency formed which leads to lung destruction and the formation of emphysema. Now a days recombinant AAT (rAAT) given intravenously(IV) is very well accepted treatment. Early evaluation of aerosolized AAT documented adequate alveolar fluid AAT and penetration into the lung inter stitium. Neutrophil elastase's inhibitor, secretory leukocyte protease inhibitor, has also been considered for protection against elastase in CF and patients with AAT deficiency.

9) Recent use of pulmonary drug delivery intransplantation

Inhalation route play a role very important role in transplantation. Acute and chronic rejections are major problems compromising transplant and patient survival. Aerosolized cyclosporine is useful for reducing the risk of acute rejection.²¹

10) In Pulmonary arterial hypertension

This is new use of pulmonary route in2004, the FDA approved Ventavis (iloprost), an inhaled treatment for pulmonary arterial hypertension. In pulmonary arterial hypertension, severe restriction of blood vessels results in early death.²²

11) In acute lung injury

Drug given by pulmonary route plays very important role in acute lung injury. Major complication of acute lung injury is Hypoxemia and it is often difficult to manage. Mediators such as nitric oxide and prostacyclin can improve oxygenation by increasing blood flow through ventilated areas. Prostaglandin E by continuous aerosol via a ventilator has also been shown to improve oxygenation.

12) Application of pulmonary drug delivery as a surfactant aerosol

In respiratory distress of premature infants and neonatal surfactant plays important role. There continues to be great appeal for the use of surfactant in adults because of the apparent success in neonates, but its use should not become practice until well controlled trials document clinically meaningful efficacy.

13) Gene therapy via pulmonary route

This is new research in application of pulmonary drug delivery .Main aim Gene therapy given by pulmonary route is treatment of cystic fibrosis. There are many problems to be overcome before clinical applications are practical. Some of these are safety, successful transfer of sufficient genetic material to appropriate tissue, adequate gene expression, maintenance of expression over time, and efficacy of expression.

14) Application of pulmonary drug delivery in cancer chemotherapy

Cancer is one of major disease which takes death of people. Lung cancer is the leading cause of cancer deaths globally, and inhaled chemotherapy seems a logical approach to treat lung cancer. Aerosol delivery of the anticancer agent's difluoro methyl ornithine and 5-fluorouracil reduced lung tumors in mice 50 %and 60 %, respectively. Interleukin-2 stimulates immune function in cancer patients, but injections cause fever, malaise, and local swelling²³.

15) Delivery of pentamidine by pulmonary route²⁴

Protozoan *Pneumocystis carinii*(PCP) is major cause of Pneumonia in Patients with acquired immunodeficiency syndrome . Aerosol pentamidine is not only useful in treating mild PCP and, but also for prophylaxis against PCP.

16) Delivery of Amphotericin by pulmonary route²⁵

Now days Amphotericin aerosol has been successfully used to treat various infections. Such use should not become clinical practice without good randomized controlled trials. Ribavirin aerosol has also been used for treatment or prophylaxis following bone

marrow transplantation but controlled trials are needed to better clarify efficacy.

17) Delivery of Gentamycin by pulmonary route

For chronic *Pseudomonas aeruginosa* (PA) infections in CF gentamycin given by pulmonary route play an important role. It was observed that daily inhalations of gentamycin delays the acquisition of chronic PA infections and decreases disease progression in children with zanamivir, made by GSK, was the first inhaled anti-viral medication approved by the FDA in 1999. For treatment of flu, the dose of dry powder inhalers is twice daily for 5 days²⁴.

18) Diagnostic application pulmonary drug delivery²⁶

Pulmonary drug delivery is not only useful for therapeutic purpose but also for diagnosis purpose. For example, inhalation of aerosols of methacholine and histamine is responsiveness in asthma.

19) Nicotine aerosol for smoking cessation

As we know that smoking is injurious to health. It is very difficult to ace such habit. From ancient times people smoke cigarette and get addicted with smoking. Primary reason for cigarette smoking is Nicotine addiction, and nicotine replacement is appealing as a means of reducing cigarette use to ultimately achieve cessation.

20) Inhaled drug delivery for tuberculosis therapy²⁷

Tuberculosis is most infectious diseases cause by *Mycobacterium tuberculosis*. Administering drugs by the pulmonary route to the lung allows higher drug concentrations in the vicinity of these lesions. Supplementing conventional therapy with inhaled anti-TB therapy may allow therapeutic concentrations of drug to penetrate effectively into lung lesions and treat the resident mycobacterium.

21) Pulmonary delivery of lower molecular weight Heparin²⁸

Now days, low molecular weight heparin is better as an alternative to unfractionated heparin because of improved pharmacokinetic profiles and reduced cost of therapy in the treatment of deep vein thrombosis and pulmonary embolism. Low molecular weight heparins are given by subcutaneous and intravenous routes. Administration of an anticoagulant drug directly to the pulmonary circulation would be ideal for the treatment of pulmonary embolism. A pulmonary formulation of LMWH will allow direct administration of the drug into the lungs, and consequently this formulation is likely to reduce the mortality from an attack of

pulmonary embolism. This pulmonary therapy is noninvasive because it is needle free.

22) Recent use of pulmonary delivery for bone disorders²⁹

Diseases such as osteoporosis and Paget's disease of bones can be treated by pulmonary delivery. The predicted increase in the number of patients with osteoporosis and the lack of ideal therapies dictates the need for better treatments. Clinical evidence from a variety of other peptides and proteins indicates that pulmonary delivery is safe, efficient, well tolerated and preferred by patients so pulmonary route is better option to treat bone disorders. Following are drugs used to treat osteoporosis are the naturally occurring peptides calcitonin and parathyroid hormone, which regulate bone metabolism.

23) Current use of pulmonary delivery of opioids as pain therapeutics³⁰

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

CONCLUSION

As discussed in this review, the pulmonary drug delivery field is truly one of the mostly popular areas in today's applied pharmaceutical research and its development. Certainly, still at this time, the more information is collected the more related questions are surfacing covering the area of lung physiology and diseases, lung deposition, intelligent inhalation devices, delivery of biopharmaceuticals. Absorption enhancement, controlled drug release in the lung and, last but not least. As more efficient pulmonary drug delivery devices and sophisticated formulations become available, physicians and health professions will have a choice of a wide variety

of device and formulation combinations that will target specific cells or regions of the lung, avoid the lung's clearance mechanisms and be retained within the lung for longer periods. The more efficient, user-friendly delivery devices may allow for smaller total deliverable doses, decrease unwanted side-effects and

increase clinical effectiveness and patient compliance. Some of the key determinants for successful dispersion of pharmaceutical powders suitable for inhalation are reviewed with an emphasis on the practical significance.

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