Review Article CODEN: IJPRNK ISSN: 2277-8713
S. S. Upadhye, IJPRBS, 2015; Volume 4(5): 242-261 IJPRBS

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

A REVIEW ON PULMONARY DRUG DELIVERY SYSTEM

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Accepted Date: 05/10/2015; Published Date: 27/10/2015

Abstract: Targeting the drug delivery into the lungs has become one of the most important aspects of the systemic or the local drug delivery. The pulmonary tract tends to be considered as very attractive & promising route for the administration of the active substances intended to treat the local pulmonary for e.g., COPD [chronic obstructive pulmonary disease], asthma, microbial infections as well as the systemic diseases for e.g, diabetes. The human respiratory system is complicated organ system these systems consist of two reagions conducting airways & respiratory region. The airway is further divided into many folds such as the nasal cavity, oropharynx, nasopharynx, trachea, larynx, bronchioles & bronchi. The respiratory region consists of respiratory bronchioles, alveolar sac & alveolar ducts. This present review discusses the challenges in pulmonary drug delivery, advantages, different factors affecting pulmonary drug delivery, different pulmonary delivery devices, evaluation of pulmonary drug delivery devices and applications for pulmonary drug delivery system

Keywords: Targeting drug deliver, Pulmonary drug delivery, Asthma

PAPER-QR CODE

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How to Cite This Article:

S. S. Upadhye, IJPRBS, 2015; Volume 4(5): 242-261

INTRODUCTION

The inhalation delivery of the therapeutic agents though, has been known poorly understood from many years. But the pulmonary tract tends to be considered as the very promising & attractive route for the administration of the active substances that are intended to treat the local pulmonary for e.g., asthma, chronic obstructive pulmonary disease (COPD), microbial infections) as well as the systemic diseases [For e.g., Diabetes] From over the past decade certain drugs have been sold in the compositions suitable for forming the drug dispersion for the pulmonary delivery to treat the different conditions in the humans. Such a pulmonary drug delivery composition is designed to be delivered by the inhalation by the patient of the drug dispersion so that a active drug within the dispersion can reach the lung. It has been seen that certain drugs that are given by pulmonary route are readily absorbed through the alveolar region directly into the blood circulation. The pulmonary route possesses many advantages over the other routes of administration for the treatment of the specific disease states particularly the lung associated large protein molecules which degrade in the GI conditions & are eliminated by the first pass metabolism in the liver & can be delivered via the pulmonary route if deposited in a respiratory zone of the lungs. The devices used to deliver the drugs by the pulmonary route area are based on one of the 3 platforms nebulizer, pressurized metered dose inhaler & the dry powder .In the treatment of the disease the aerosol administration represents the valuable means by which the therapeutic agent may be delivered.[1-2]

ANATOMY AND PHYSIOLOGY OF THE LUNGS

Anatomy of the Lungs

The lungs are responsible for the gas exchange & supply of oxygen to all the cells. The lungs consist of the total of 5 lobes, the right lung consisting of the 3 & the left lung of 2 lobes. The interior of the lungs is comprised of the bronchi & smaller air passages, the alveoli, blood vessels & the lymph tissue. The bronchi are further divided into the primary & secondary bronchi & the bronchioles & lastly the alveoli. The lungs have over 300 million of the alveoli. Furthermore each alveolus is lined with the pulmonary capillaries, thus forming the vast network comprising over 280 billion capillaries thus giving rise to the vast surface area of almost 70 m^2 available as the blood-gas barrier. A alveolar gas exchange majorly occurs at the interface consisting of the alveolar epithelium, endothelium & the interstitial cell layers. A alveolar wall is made up of two types of alveolar epithelial cells, namely the [pneumonocytes] Type I & Type II. Between the capillaries & the alveolar epithelium, there exists the single endothelial layer. The distance between a alveoli & capillaries is so small of about 0.5 µm that owing to this extreme thinness of the blood-gas interface the gas exchange is facilitated by diffusion at the interface. The alveoli are coated with the layer of the alveolar fluids & mucus

which is majorly composed of the phospholipids & the surface proteins. This phospholipid surfactant layer at the alveoli reduces the surface tension & is essential for the proper functioning of the exchange of gas. These distal respiratory passages are supported by the thin layer of connective tissue. This layer is surrounded with different cells like the macrophages, fibroblasts, nerves, as well as the lymph vessels. This serves as an ideal location for the administration of the drugs with access to the pulmonary, as well as the lymphatic system [3,4]

Deposition of the Particles

Depending on the particle size of the formulation the deposition of particles in the different regions of the lungs is dependent. Based on the particle size, 3 different mechanisms of drug deposition are defined, namely the impaction, sedimentation & the diffusion . In the impaction, the aerosol particles pass through the oropharynx & the upper respiratory passages at a high velocity. Due to the centrifugal force, the particles collide with the respiratory wall and are deposited in the oropharynx regions. This mechanism is generally observed for dry powder inhalation [DPI] & metered dose inhalators [MDI] with particles sizes greater than 5 µm. In case of the DPI, the inspiratory effort of the patient plays an important role in the deposition. If the force of the inhalation is insufficient, the dry powder deposits in the upper airways owing to the mass of the particles & the inertial forces. For the MDI & despite the high speed of the generated aerosol the high particle sizes also tend to lead to the deposition of the particles mostly in the upper respiratory tract region. The gravitational forces are predominantly responsible for the sedimentation of the particles. The particles with sufficient mass & sizes between 1 to 5 µm are deposited in the smaller airways & bronchioles where they are deposited slowly provided the sufficiently long time span. Hence sedimentation is also influenced by the breathing pattern The slow breathing provides the sufficient time span for the sedimentation. Apart from the impaction & sedimentation the Brownian motion plays the major role in the deeper alveolar areas of the lungs. The Brownian motion of the surrounding molecules of the aqueous lung surfactant causes the random movement of the particles. Upon contact with the lung surfactant the dissolution of the API in the alveolar fluid is essential for the diffusion. Additionally the concentration gradient also influences the diffusion process. The particles smaller than 1 to 0.5 µm are deposited in the alveolar region while most of the particles owing to smaller sizes are exhaled. For the nanoparticulate systems the sedimentation is the most attractive method of the particle deposition. The nanoparticulate systems after being released from an aerosol form aggregates in the micrometer size range. These aggregates are believed to have the sufficient mass to sediment & stay in the bronchiolar region for the longer time & hence achieving the desired effect. Apart from the mechanisms, the parameters such as the particle size of the aerosol, particle geometry & morphology along with the surface properties, play an important role in the deposition phenomena. Furthermore the breathing

frequency & the holding of the breaths, air velocity, humidity & tidal volume also are the vital factors influencing the deposition. [5,6]

Clearance of the Particles

The upper airways [from the trachea till the tertiary bronchi] are lined with the thick mucus film

this acts as the protective layer in order to clear & trap the particles. The mucociliary movements clear the foreign particles immediately before they can move to the lower areas of the lung by either swallowing or coughing. In this region the clearance also depends on the number of cilia & the ciliary beat frequency as well as the quantity & quality of the mucus. In the deeper areas of the lungs that is, the alveolar region, the transport mechanism is believed to be more complex. The alveolar lining consists of the variety of proteins & lipids which act as the barrier for the transport of the molecules. Along with the alveolar linings the tight junctions present at the epithelial cell serves as the primary barrier for the transport to occur. The proteins transporter plays the vital role in the transport of the API via active absorption or passive diffusion depending on the nature & chemical structure of the API. The another important aspect in this region is the clearance of the molecules by the alveolar macrophages which needs to be taken into the consideration in the drug transport mechanisms. The molecules that are able to cross the barrier are either taken up by the cells & further absorbed into the systemic circulation or phagocytized by the alveolar macrophages. Therefore for understanding the uptake & clearance mechanisms of the drug formulation it is essential to understand the physiology of the lungs. In spite of the advances in the formulation development, there is still some lack of information with respect to the exact uptake transport & clearance of the particles in the alveolar epithelium & how the API molecules reach the systemic circulation. Although the several in vitro models have been established for studying the uptake & permeation of the APIs in the pulmonary epithelium [air-liquid interface models] there are still open questions with respect to the behavior of the cells in the diseased condition. The lungs being in contact with the air are susceptible to numerous disorders & diseases ranging from the respiratory infections to lifestyle & genetic diseases. The most common diseases include pulmonary hypertension, asthma, COPD [chronic obstructive pulmonary disorder], ARDS [acute respiratory distress syndrome] in infants, lung infections, chronic lung cancers, & cystic fibrosis, like pneumonia, tuberculosis [5,7-8]

CHALLENGES IN PULMONARY DRUG DELIVERY

Poor formulation stability for drug

The most traditional small molecule asthma drugs are crystalline & in the case of the corticosteroids relatively moisture resistant in the dry state. They are also rather stable in the

liquids as compared to most of the macromolecules which are unstable in the liquid state, amorphous & highly moisture sensitive in the dry state.

Less drug mass per puff

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

Improper dosing reproducibility

Following are the reasons for Poor dosing reproducibility like worsening of diseases, unstabality of formulation, problem in device, to get the maximum dose reproducibility the patient education plays an important role.

Low Efficiency of inhalation system

The efficiency of presently available inhalation systems has generally too low which is important challenge in the pulmonary drug delivery. The optimum aerosol particle size is very important for the deep lung delivery. The optimum particle size for the deep lung deposition is 1-5 mm. The aerosol system should have to produce the optimum size particles because if they are too small they will be exhaled. If the particles are too large, they affects on the oropharynx & larynx. [9]

ADVANTAGES OF PULMONARY DRUG DELIVERY SYSTEM

- It reduces evasion of first pass hepatic metabolism by absorbed drug
- It reduces extracellular enzyme levels compared to GI tract due to the large alveolar surface area
- It offers the potential for pulmonary administration of systemically active materials
- It provides local action within the respiratory tract
- It provides reduced dose
- It provides rapid drug action
- It allows for the reduction in systemic side-effects It can be employed as an alternative route to the drug interaction when two or more medications are used concurrently

DISADVANTAGES OF PULMONARY DRUG DELIVERY SYSTEM

- Necessitates frequent dosing

The duration of activity is often short-lived due to the rapid removal of drug from the lungs or due to drug metabolism. [10]

FACTORS AFFECTING PULMONARY DRUG DELIVERY

The Mechanisms of particle deposition in the airways

The Effective resistance mechanisms may have involved may reduces the burden of external particles enter the airways & clearing those it may achieve something in being stored. The therapeutic aerosols are 2-phase colloidal systems in that the drug is contained in the dispersed phase they may have the liquid, solid or combination of the two based on the method & formulation of the aerosol generation. Evidently for the effective therapy the drug must have obtain able to the lung in aerosol droplets or particles that deposit in the specific lung region & in sufficient quantity to be effective. The respiratory resistance mechanisms of the mucociliary clearance & phagocytosis by macrophages may act upon the insoluble particles. The aerosol particle dissolution they may slow & the drug may then subsequently to be subject to enzymatic deprivation before it reaches to its specific site of the pharmacological action. The aerosols for pulmonary drug delivery are transported from the mouth.

The Brownian diffusion

This is of minor significance for the particles >1 µm. The particles smaller than this size are displaced by the sequentially bombardment of gas molecules which may results in particle collision with the airway walls. With the particle size decreases the chances of particle deposition by diffusion increases. The Brownian diffusion is also more common in regions where airflow is very low or absent For example in the alveoli. The another method of deposition, that of interception, is of important for fibers but it may not for drug delivery. Generally:-

• The particles in the size range 0.5–5 µm may break away from impaction in the upper airways & may deposit by sedimentation & impaction in the lower TB & A regions. If the aerosol particle size is in between the 3 & 5 µm then deposition it mainly occur in the TB region. If the particles are smaller than the 3 µm then appreciable deposition in the A region is likely to occur.

• The particles bigger than 10 µm will have impact in the upper airways & are rapidly removed by coughing, swallowing & mucociliary processes.

The Inertial impaction

This is the main deposition mechanism for particles >1 µm in the upper tracheo-bronchial regions. The particle having the large momentum it may not able to follow the altering direction of the inspired air as it transferred the bifurcations & it will show result to collide with the airway walls as it continues on its original course.

The Sedimentation

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

The description of particle deposition mechanisms at an airway branching site

Near the bifurcations the impaction mainly occurs, certainly the impaction of particles from the tobacco smoke on the bifurcations may be one cause why these sites are often the foci for the lung tumors. The prospect of the inertial impaction will be dependents upon the particle momentum thus particles with the higher densities or larger diameter & those travelling in the airstreams of higher velocity will show superior impaction. [11-12]

PULMONARY DELIVERY DEVICES

The lung has served as the route of drug administration for around thousands of years. The origin of inhaled therapies can be traced back 4000 years ago to India, where people used to smoke the leaves of the Atropa belladonna plant to suppress cough. In the 19th & early 20th centuries asthmatics smoked asthma cigarettes that contained stramonium powder mixed with the tobacco to treat the symptoms of their disease. The development of the modern inhalation devices can be divided into 3 different categories, the refinement of the nebulizer & the evolution of 2 types of compact portable devices, MDI [the metered-dose inhaler] & the DPI [dry powder inhaler].[13]

Inhalers

The medicine inside an inhaler goes straight into the airways. Hence it needs much smaller dose than take the medicine as the tablet or liquid by mouth. The inhalation represents an rapid, attractive & patient-friendly route for the delivery of the systemically acting drugs as well as for drugs that are designed to act locally on the lungs themselves. This concept is especially exciting now that the concept of an inhaled systemic macromolecule, The one of the key factors for success in this area is the ability to control the device properties & combined powder. This is essential for the development of the DPI [dry-powder inhaler] products yet remains the major technical hurdle to those wishing to succeed with this route & exploit the product opportunities arising from the numerous market drivers:

• The rapid onset of action

• By improving patient compliance & acceptance for the non-invasive systemic route

• By reduction of side effects

• By differentiation of new product & competitive brand opportunities

• By product stability & expedition of regulatory approval through improved consistency of delivery

• By product lifecycle enhancement

• The new forms of inhaled therapeutics often requiring the high doses or greater efficiency & accuracy

• The attractive device form with convenient & easy operation & delivery

Metered-dose inhalers

The MDI was the revolutionary invention that overcame the problems of the hand-bulb nebulizer as the first portable outpatient inhalation device & is the most widely used aerosol delivery device today. The MDI emits the drug aerosol driven by the propellants such as CFC [chlorofluorocarbons] & more recently the HFAs [hydrofluoroalkanes] through the nozzle at high velocity [> 30 m s−1]. The MDIs deliver only the small fraction of the drug dose to the lung. Only 10–20% of the emitted dose is deposited in the lung typically. The high velocity & large particle size of the spray causes approximately 50–80% of the drug aerosol to impact in the oropharyngeal region. Hand-mouth discoordination is another obstacle in the optimal use of the MDI. The delivery efficiency of the MDI depends on the patient's breathing pattern, IFR [inspiratory flow rate] & hand-mouth coordination. A increase in the IFR result in decrease in total lung dose deposition & penetration into the peripheral airways. The fast inhalations [> 60 l min−1] result in the reduced peripheral deposition because the aerosol is more readily deposited by inertial impaction in the conducting airway & oropharyngeal regions. When the aerosols are inhaled slowly deposition by the gravitational sedimentation in the peripheral regions of the lung is enhanced. The peripheral deposition has also been shown to increase with an increase in the tidal volume & the decrease in the respiratory frequency. The aerosols are able to penetrate more peripherally into the lungs as the inhaled volume is increased. The period of breath holding on completion of the inhalation enables particles which penetrate the periphery to be deposited in that region instead of being exhaled during the expiratory phase. Hence the optimal conditions for inhaling the MDI aerosols are from the starting volume equivalent to the functional residual capacity actuation of the device at the start of the inhalation IFR of <60 l min−1 followed by the 10-s breath-hold at the end of the inspiration. [14]

Pressurized metered-dose inhalers

The pMDIs are not available for all drugs or dosages making it difficult for the clinicians to prescribe the same type of device for the diverse inhaled medications. This is exacerbated by the trend of many pharmaceutical companies that not to release newer inhaled drugs as pMDIs. The design of the CFC-propellant pMDI requires the initial & frequent priming. The failure to prime the device results in the administration of the substantially lower dose than that prescribed. Unfortunately the frequent priming tends to waste the drug to the atmosphere. The one of the greatest single limitation of the pMDI is the inconsistent dosing that occurs with incorrect use. This includes the impact of hand-breath asynchrony, nose-breathing, excessive inspiratory flow velocity & the cold-Freon effect [the patient stops inhalation when the cold aerosol plume reaches the hypopharynx]. To deliver medication for an aerosol device efficiently to the lower respiratory tract most of the aerosol medication particles must be of the size for inhalation & deposition in the airway generally 0.5-4.5µm mass median aerodynamic diameter. The patient must inhale the aerosol with the slow, deep inhalation to maximize the aerosol deposition in the airway, followed by the breath-hold to allow sedimentation of the medication particles. The extended use of the pMDI beyond the labeled number of doses results in the "tailing-off" effect at the end of the canister life. While the pMDI provides consistent dosing for the number of actuations listed on the drug label after that the dose fluctuates between the negligible dose & nominal dose. In the absence of the dose-counter which is not provided with most of the pMDIs the patient must count the number of doses taken to determine the effective life of the pMDI. The method of "floating" the pMDI canister in water to determine canister depletion is unreliable & water entering the nozzle can reduce the emitted dose of the subsequent actuations.[15,16]

Dry powder inhalers

The interest in the DPIs as an effective, efficient & environmentally friendly way of delivering the drugs to the lung has accelerated in the recent years. The fundamental difficulty with developing the solid state aerosols or DPIs is managing both the ubiquitous & the transient forces contained in the powder beds. Indeed managing such particulate forces for example via particle engineering techniques is now considered central to the successful DPI formulation & production. In the consequence much attention is currently focused on producing the "smart" formulations where it may be possible to achieve the excellent powder flow & low cohesive forces. However having an efficient & robust formulation technology in the laboratory is only the start on the road to producing the successful DPI product. The pharmaceutical scientists all too frequently meet major obstacles when they engage in the world of the DPI product design-not least because of the further complications of this area resulting from the plethora of DPI device designs. There is tremendous variation in the methods used to store & meter powders &

to generate the aerosol cloud. In the case of the DPI aerosol generation there is the great deal of the variation between different types of device in the electrostatic & fluid dynamic environment that the powder formulation experiences. With the DPIs the drug aerosol is created by directing the air through the loose powder. Most of the particles from DPIs are too large to penetrate into the lungs due to the large powder agglomerates or the presence of large carrier particles [For e.g. lactose]. Hence, dispersion of the powder into respirable particles depends on the creation of turbulent air flow in the container of the powder. The turbulent airstream causes the aggregates to break up into particles small enough to be carried into the lower airways & also to separate the carrier from the drug. Each DPI has the different air flow resistance that governs the required inspiratory effort. As the resistance of the device is higher, the more difficult it is to generate an inspiratory flow great enough to achieve the maximum dose from the inhaler. Hence, deposition in the lung tends to be increased when using high-resistance inhalers.[17-19]

Nebulizers

The nebulizers have been used for many years to treat the asthma & other respiratory diseases. There are 2 basic types of nebulizer, jet & ultrasonic nebulizers. A jet nebulizer functions by the Bernoulli principle by which the compressed gas [oxygen or air] passes through the narrow orifice creating an area of low pressure at the outlet of the adjacent liquid feed tube. This would result in drug solution being drawn up from the fluid reservoir & shattered into the droplets in the gas stream. The ultrasonic nebulizer uses the piezoelectric crystal vibrating at the high frequency [usually 1–3 MHz] to generate the fountain of liquid in the nebulizer chamber the higher the frequency, the smaller will be the droplets produced. The constant output jet nebulizers can aerosolize most drug solutions & provide large doses with very little patient coordination or skill. The treatments using these nebulizers can be time-consuming but are also inefficient, with large amounts of the drug wastage [50% loss with continuously operated nebulizers]. While these disposable nebulizers are inexpensive the compressors supplying the oxygen or air are not. Most of the prescribed drug never reaches the lung with nebulization. The majority of the drugs are either retained within the nebulizer [referred to as dead volume] or released into the environment during expiration. On an average only 10% of the dose placed in the nebulizer is actually deposited in to the lungs. The physical properties of the drug formulations may have an effect on the nebulization rates & the particle size. The viscosity, osmolarity, ionic strength, pH & surface tension may prevent the nebulization of some of the formulations. If the pH is too low or if the solution is hyper or hypo osmolar, the aerosol may induce the bronchoconstriction, coughing & irritation of the lung mucosa, as well the high drug concentrations may decrease the drug output with some nebulizers. The advances in technology have led to the recent development of the novel nebulizers that reduce the drug

wastage & improve the delivery efficiency. The enhanced delivery designs increase aerosol output by directing auxiliary air, entrained during inspiration through the nebulizer causing more of the generated aerosol to be swept out of the nebulizer & available for inhalation. The drug wastage during exhalation is reduced to the amount of the aerosol produced by the jet air flow rate that exceeds the storage volume of the nebulizer. The adaptive aerosol delivery monitors the patient's breathing pattern in the first three breaths & then targets the aerosol delivery into the first 50% of the each inhalation. This ensures that the aerosol is delivered to the patient during the inspiration only thereby eliminating the drug loss during the expiration that occurs with continuous output of the nebulizers. [18,20-21]

EVALUATION OF PULMONARY DRUG DELIVERY DEVICES

1. In –vivo Evaluation

Before the new drugs are delivered to the human lungs the animal studies need to be passed out. The moral of any of the animal experiment require to be accepted by an Institutional Animal Care & Use Committee. The experiment perform in an animal model can afford information on the drug declaration, assimilation, metabolism & kinetic profile as well as on drug & rats & guinea-pigs are frequent formulation acceptability. So the non-human primates are use only in advanced research.By the contrast the small rodents mice, models for preliminary studies on pulmonary drug delivery because they can be used in large numbers. For assessing pulmonary release of systemically performing drugs the mice have been used less often because the pharmacokinetic studies are not optimally performed 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 the cardiac puncture & mouse euthanasia must be done at each time point of the plasma drug concentration–time curve. The guinea pigs have been generally used as an animal form of allergic asthma & infectious diseases, since the airway anatomy & the respond to the inflammatory stimuli are similar to the human case. The dissimilar mammals do not show to present related mucociliary clearance & alveolar macrophage morphometry. In the large mammals, the rate of mucus permission in millimetres/ minute is elevated and compared with small rodents. Though the huge mammals also have longer airways than the minute rodents & thus worldwide, the bronchial permission of inhaled particles is comparatively slow in the humans [> 24 h]. By contrast the bronchial clearance of particles is relatively quick & early in rats & mice. The number of macrophages per alveolus & the alveolar macrophage volume are superior in human & canine lungs than in the small rodents' lungs.

2. In vitro Evaluation

In this respect, the in vitro models for the pulmonary drug delivery studies propose another as it convey up fewer moral questions but also because they allow the fast screening of drugs. It is

significant that epithelial cells form the tense monolayer in order to characterize the natural epithelial barrier in both cellular models. The monolayer tension & reliability are classically assessed by measuring the Tran's epithelial electrical resistance [TEER] & potential difference crosswise the monolayer. The monolayers of lung epithelial cells permit the categorization of the drug transport & evaluation of the potential drug & formulation toxicity. The drug transport is classically calculated in the apical to the basolateral direction & vice versa in order to ensure for the active transport mechanisms.

3. The Air-interface cultures

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

4. The Continuous cell cultures

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

5. The Primary cell cultures

For the pulmonary drug delivery the majority primary cell cultures used as models & convey

studies consist of alveolar epithelial cells. The Type II pneumocytes for the primary culture can be removed from the lung of different species. The human cells are the mainly representative of the clinical circumstances, but they are less available than the cells from other mammals. The human type II pneumocytes are removed from the normal lung tissue of patients undergoing partial lung resection. In the culture the cells experience segregation into type I-like cells as indicated by the morphological & histochemical change. In the premature stages of the cell culture the cells create elevated levels of the surfactant protein C & little levels of caveolin 1 the marker of type I pneumocytes & on the other hand at the later stages. On day 8 of the

culture the cells form the tight monolayer consisting mainly of type I cells & some interspersed type II cells with TEER > 2000 Ω cm2 & potential difference > 10 mV.

6. The cascade impactors

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

7. The direct intratracheal administration

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

8. The passive inhalation

During the passive inhalation of the aerosolised drugs the animals are kept awake & allowed to breathe normally. The aerosolised drugs are delivered using the aerosolisation chamber in the whole body, nose-only or head-only exposure systems. The devices most frequently used for generating the aerosols are nebulisers. The passive inhalation is principally used in the mouse & less frequently in the larger animals [dog rat, guinea-pig]. This method is more representative

of drug delivery to the human lungs than the intratracheal instillation of large volumes of liquids. The drug concentration in the aerosol is determined by sampling the test atmosphere & quantifying the drug in the sample.

9. The whole body exposure system

The animals are placed in a sealed plastic box that is connected to a nebuliser or a generator of dry powder aerosol, in the whole body aerosol exposure system. Although this system allows the 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 & from the GIT.

10. The intranasal administration

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

11. The head-only or nose-only exposure systems

The animal is attached to the exposure chamber & only the head or the nose is in contact with the aerosol in the head-only or nose-only exposure systems. The systems can be designed for delivering the drugs to one or to several animals. As compared with the whole body exposure system the head-only or nose-only exposure systems offer several advantages. The skin exposure to the drug & its uptake by the transdermal route are avoided. The low volume of the aerosolisation chamber reduces the amount of the drug needed to generate the aerosol. The potential drug reactivity with excreta is avoided. In one single test the variable durations of animal exposure are possible.[22-23]

DEVELOPMENT IN APPLICATIONS OF PULMONARY DRUG DELIVERY

1. In cancer chemotherapy

The cancer is one of the major disease which takes death of people. The lung cancer is the leading cause of the cancer deaths globally & inhaled chemotherapy seems the logical approach to treat the lung cancer. The multicenter Phase I clinical trial is evaluating doxorubicin HCl inhalation solution in the lung cancer patients. As many as 400 000 lung cancer patients could

benefit from the inhaled chemotherapy the study is going on aerosolized paclitaxel solution to mice with the lung tumors. The treatment significantly reduced lung tumors & prolonged the survival. The aerosol delivery of the anticancer agent's difluoro methylornithine & 5-fluorouracil reduced the lung tumours in the mice 50 % & 60 % respectively. The Interleukin-2 stimulates the immune function in the cancer patients but injections may cause malaise, fever & local swelling [24]

2. For bone disorders

By pulmonary delivery the diseases such as osteoporosis & Paget's disease of bones can be treated. The predicted increase in the number of the patients with osteoporosis & the lack of ideal therapies dictates the need for the better treatments. The clinical evidence from the variety of the other peptides & proteins indicates that the pulmonary delivery is efficient, safe, well tolerated & preferred by the patients hence, the pulmonary route is better option to treat the bone disorders. Naturally occurring peptides calcitonin & parathyroid hormone are used to treat the osteoporosis by regulating the bone metabolism. to become viable therapies for the peptides the formulations must be developed that bypass the need for the injection. The pulmonary delivery of the calcitonin & the parathyroid hormone appears likely in the near future. The recent introduction of the nasal formulation of calcitonin points to the feasibility of the lung delivery. The pulmonary formulation inhaled through the mouth that delivers calcitonin or the PTH into the deep lung should improve the bioavailability & the efficacy of the drugs [25]

3. Application of pulmonary delivery of opioids as pain therapeutics

Painful inject able are given for the pain management. The pain killer pulmonary opioid delivery is better alternative to avoid the pain associated with the inject able. The early clinical studies involving the inhaled opioids were focused in treatment of the dyspnoea & not the pain management, but they showed that the inhalation of various opioid compounds is safe, even in the severely ill patients. The advent of the specialized & efficient pulmonary drug delivery systems has facilitated the evaluation of the inhaled opioids such as the fentanyl & morphine for management of severe pain associated with the malignant disease or surgery. In the past the few studies evaluating the pulmonary delivery of the opioids for the management of severe pain has with the limited success. The earlier attempts at the systemic delivery of the opioids through the lungs utilized the standard compressor systems/jet nebulizer which has the minimal efficiency for deep lung delivery. The studies are going on to introduce the new molecules for the management of pain through pulmonary route, the studies with efficient pulmonary delivery systems, designed for the systemic drug applications conclusively show that

the inhaled opioids are completely, rapidly & reproducibly absorbed into the bloodstream. Thus the pulmonary route

has excellent potential for treating the noninvasively severe pain in malignant disease & in the postoperative setting. So by giving the pain killer through pulmonary route we can give parental efficacy with the oral convenience to the patients. So the pulmonary drug delivery is unproblematic to control pain [26]

4. Inhaled drug delivery for tuberculosis therapy

The one third of the world's population is infected with the tuberculosis [TB] & the new infections occur at the rate of one/ second. The recent increase in the emergence of the drug-resistant strains of the Mycobacterium tuberculosis & the dearth of the Anti-TB drugs is threatening the future containment of the TB. The new drugs or delivery systems that will stop the spread of TB & slow down or prevent the development of the drug-resistant strains are required urgently. For the emergence of the drug-resistant strains one of the reasons is the exposure of the mycobacteria to the sub-therapeutic levels of one or more antibiotics. The lung lesions containing the large numbers of bacteria are poorly vascularized & are fortified with the thick fibrous tissue, conventional therapy by the parenteral & oral routes may provide sub therapeutic levels of the anti-TB drugs to these highly sequestered organisms. By administering drugs by the pulmonary route to the lungs allows the higher drug concentrations in the vicinity of these lesions. Supplementing the conventional therapy with the inhaled anti-TB therapy may allow the therapeutic concentrations of drug to penetrate effectively into the lung lesions & treat the resident mycobacteria [24]

5. In Angina pectoris

The angina pectoris is symptoms of the myocardial ischemia & it is arises as the result of the imbalance between the supply of oxygen & myocardium demand. The drug of choice for angina pectoris is nitroglycerine & it is given through the sublingual route. It is the coronary vasodilator. The immediate relief of the angina is probably caused by the reduced demand of the oxygen on the heart & the subsequent reduced cardiac work. The aerosol form has been tested in the Europe & has been found comparable to the sublingual nitroglycerine. In particular, its efficacy has been found better than the nitroglycerine tablets in patients with dry mouth. The Isosorbide aerosol has also been reported of the use in hypertensive emergency [27]

6. In Pulmonary arterial hypertension

The pulmonary hypertension in the setting of the chronic hypoxia due to the underlying lung disease represents the challenging area for the management & evaluation. Although the

chronic hypoxia is the recognized cause of the pulmonary hypertension it would rarely lead to severe pulmonary hypertension. In 2004 the FDA approved Ventavis [iloprost], an inhaled treatment for pulmonary arterial hypertension, made by CoTherix [South San Francisco, CA, U. S. A.]. In pulmonary arterial hypertension, severe restriction of the blood vessels results in early death. Iloprost naturally dilates blood vessels [24,28]

7. In Asthma and COPD

The asthma is the chronic long term lung disease that is categorized by narrowing of airways & inflammation. The asthma causes repeated periods of chest tightness, wheezing, coughing & shortness of breath. The coughing often occurs at night or early in the morning. The asthma affects the people of all ages but it most often starts in the childhood. The COPD means chronic obstructive pulmonary diseases, which is correlated to emphysema, smoking & chronic bronchitis. Today's inhaled drug delivery market is conquered by the 3 main classes of drug such as corticosteroids, bronchodilators & anticholinergic. All these 3 classes of drugs are given by only pulmonary route. The Titropium inhalers are present in market to treat COPD. The levosalbutamol inhalers are present in the market to treat asthma. [24,27]

8. Gene therapy via pulmonary route

The gene therapy holds the great potential for the treatment of various inherited & acquired pulmonary diseases. The main aim of the gene therapy given by the pulmonary route is for the treatment of cystic fibrosis. The Cationic-lipid mediated CFTR gene transfer can significantly influence the underlying chloride defect in the lungs of the patients with CFC. There are many problems to be overcome before the clinical applications are practical. Some of these are safety, successful transfer of sufficient genetic material to appropriate tissue, maintenance of expression, adequate gene expression over time, and efficacy of expression [29]

9. In transplantation

The inhalation route plays the very important role in the transplantation. During the lung transplantation, the pulmonary vascular pressure & an intrapulmonary shunt have been shown to respond to the inhaled nitric oxide & inhaled aerosolized prostacyclin. The prostacyclin which is given by the pulmonary route has also been described as an alternative to the nitric oxide in the management of reperfusion injury after the lung transplantation. The Acute & chronic rejections are major problems compromising the transplant & patient survival. for reducing the risk of acute rejection the aerosolized cyclosporine is useful [30]

10. In diabetes

The diabetes is the syndrome of disordered metabolism & unfortunate hyperglycemia resulting from the insufficiency of the insulin secretion or resistance. The diabetes can cause the heart attack, stroke, kidney disease, blindness, nerve damage & other serious health problems. The most common form of this therapy is twice-daily the subcutaneous injections of insulin. This type of treatment is painful & as the result encourages the rebelliousness by up to half of the diabetics. The peptides or proteins are becoming more important in the medication. They are degraded by the proteolytic enzymes in the GIT when these are taken orally & might be impervious to the intestinal mucosa due to their hydrophilicity & large molecular size. As the result the systemic delivery of these macromolecular drugs & other diagnostic & therapeutic agents has been restricted to the parenteral route. The repeated injections are necessary due to the short half-lives of the peptide or protein drugs. The first attempts at the intrapulmonary delivery were made in the 1920s. Several companies are working on the insulin inhalers than any other insulin delivery option [27,31]

CONCLUSION

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

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