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Review Article

SUSTAINED RELEASE AEROSOL FOR PULMONARY DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The onset of action is rapid in Pulmonary Drug Delivery System (PDDS), since drug directly target at the local site of the respiratory airway. Therefore lesser risk of side effect is the advantage of PDDS to produce local effects in asthmatic condition. Overcome of poor gastrointestinal absorption, avoidance of first pass metabolism in the liver, needle free (painless) at the same time could achieve rapid onset of action are advantages with PDDS to produce systemic effects during diabetes. The design of novel polymeric material plays a major role in the development of controlled release formulation for the treatment of pulmonary diseases. The controlled drug delivery to the lung with polymeric nanoparticle is more significant in drug therapy. The well established analytical methods are necessary to evaluate the physicochemical properties of the PDDS. This review discusses concise view on the development of sustained release PDDS for optimum therapeutic effect.

Keywords: Pulmonary drug delivery, Sustained release, Aerosol, Aerodynamic diameter, Spray drying, Freeze drying.

INTRODUCTION

Currently the respiratory diseases are used to treat effectively through PDDS and clinically produce more beneficial effects over other route of drug administration. The inhalation of aerosol deposits the drug in pulmonary region, produces local effect and also produces the targeted drug delivery to the respiratory diseases. The pharmacological benefits of pulmonary drug delivery includes lesser systemic exposure, reduced side effects, rapid onset of drug action and desired site of action. The right dose is delivered at target specific or site specific, therefore unnecessary add up of doses are reduced[1,3]. The duration of action is short with the use of inhalation medications and more number of drug administration is required per day. This leads to poor control over pharmacological action of drugs at various sites of the lung [4,5]. The controlled release drug delivery system offers separate line of respiratory research in pharmaceutics. Hence the next level of pulmonary drug administration includes, controlled release of aerosolized formulation of improved efficacy and patient's safety of the drug.

Aerosol exposure in the biology of lung

Aerosol preparations are stable dispersion or suspension of solid materials and liquid droplets in gaseous medium. The particle kinetic[6] is most significant in aerosols. The aerosol must release the drug that should reach into alveolar sacs of the airways of the lung. The anatomy of the human respiratory system is complex in nature. The lung constitutes about 40 different cell types[7,8]. Lungs have large surface area [9,10]for absorption around 80-140m^2, in that 70m^2 being in intimate contact with capillariesand have good vascularisation. The lung mucosal membrane thickness is 0.1µm to 0.2µm. The essential functions of the airway include warming, humidifying and cleaning of inhaled air. It divides into conducting airway and respiratory region. 85% of total lung volume consists of respiratory region; 6-10 % of lung volume consists of conducting airways. The remaining part of lung consists of nervous and vascular tissue. The conducting airways further divides into nasal cavity and the associated sinuses, nasopharynx, oropharynx, larynx, trachea, bronchi and bronchioles. The mucus is coated on the walls of the conducting airways. Mucin is the major component present in the mucus. It is secreted by goblet and submucosal gland cells. The respiratory region is divided into bronchioles, alveolar ducts and alveolar sacs. It has good blood supply. The surfactant lining presents in the alveoli prevents the collapse of alveoli during breathing. Epithelial lining fluid, epithelium, endothelium, interstitium and basement membrane, lymphatic system, alveolar macrophages, surfactants secreted by type II cells, mucocilliary clearance, and pathophysiological changes such as hypersecretion, inflammation, and epithelial disruption controls the absorption through pulmonary route[11].

Aersol inhalation (oral and intrnasal application) and intratracheal instillation are two techniques used to administer drug through pulmonary route. The uniform distribution and greater penetration into the peripheral or the alveolar region of the lung. Finding exact dose invivo is costlier and difficult. At the same time intratracheal instillation technique achieve simple instillation process, non expensive and has non-uniform distribution of drugs. The site of deposition of an inhaled drug in the lung alters the residence time. Drug penetration depends on particle size[12], particle charge, solubility and liphophilicity. Both hydrophilic and lipophilic drugs are absorbed through the lung. Low molecular substances such as nicotine and its derivatives are well absorbed in lung. The gastrointestinal route difficulties such as poor solubility, low bioavailability, unwanted metabolites, food effects and dosing variability are avoided in pulmonary route of drug delivery. Lung exhibit lower metabolic activity compared with intestinal wall and liver.

Pulmonary drug delivery system (PDDS)

The small amount of drug is sufficient to prevent disease, adverse effects are less when compared through systemic absorption, rapid and predictable onset of action is the advantages of PDDS [13]. The aerosols used for clinical application are ultrasonic nebulizer, pressurized metered dose inhaler (pMDI) and dry powder inhaler (DPI). Nebluiser with vibrating mesh technology [14-16]is used for aerosol generation. Vibrating nebuliser is superior than pneumatic and ultrasound driven nebulisers. Propellants are used in pMDI and drug excipients powder used in the design of DPI. DPIs are small portable devices. Turbuhaler and Diskhalers are examples of DPI devices. Among PDDS dry powder inhaler (DPI) increasingly popular, since it is free from propellant such as chlorofluorocarbon[17,18], solid dosage forms, chemically stable, breath actuated and patient friendly. DPI prepared by batch crystallisation from suitable solvent then micronized to attain the respirable particle size range of 1-5um. Alternate methods spray drying [19], freeze drying [20] and super critical fluid technology are used to manufacture the DPI. pMDI also used for nasal and pulmonary application. Spacers are used for pulmonary application and it is used to remove non-respirable particles by impaction on the walls of the spacer. Actuators of 3M drug delivery system are more effective and efficient to produce respirable fraction in pMDI.

Drug Deposition

The laws of aerosol kinetics deals with dynamic actions of aerosol particles. The mechanisms involved in depositing aerosol particles into the lung including inertial impaction, sedimentation (gravitational deposition), Brownian diffusion, interception and electrostatic precipitation. Larger drug particle deposited by sedimentation and inertial impaction. The smaller particles

deposited in the periphery of the lung by diffusion process. The aerodynamic size distribution and the density aerosol particles influence directly to these three mechanisms. The reason is that the respiratory system is designed as a series of filters to prevent environmental aerosols to get into the deep lung and to keep the lung surface clean. The first ones, the oropharyngeal region and the bronchial tree are excellent filters to eliminate aerosol particles from the inhaled air and particles deposited on the ciliated epithelium of the bronchial tree are subject of mucociliary transport to the gastrointestinal tract. Therefore, to deliver a drug into the deep lung one has to overcome these filters. The drug administered through pulmonary route is rapidly absorbed. But larger drug molecules yield low bioavailability due to enzymatic degradation and or low mucosal permeability [21,22]. The bioavailability enhanced by using permeation enhances such as surfactants, fatty acids and saccharides, chelating agents and enzyme inhibitors such as protease inhibitors. Syringe is used to deliver a small amount of solution in to trachea. This technique is rapid quantifiable method in pulmonary drug delivery. Drug deposition takes place in small absorptive area and it is localized. Powder formulations are administered by the method called insufflation.

Pulmonary absorption

The respirable aerodynamic particle size range of 0.5-5μm [23] (500-5000nm) is considered optimum for uptake of macrophages in the alveolar region. Phagocytosis done in carrier particles and loss of drug molecule. The rapid phagocytosis targeting is the useful tool for sustained drug release in lung. Lung barriers[24] in drug absorption through pulmonary route are epithelial lining fluid thickness of 10μm in central airways, and 0.05 μm in alveoli, heterogeneous composition of cell types in epithelium and endothelium, interstitial and basement membrane drained by lymphatic vessels and lymphatic system, alveolar macrophages of defence phagocytic cells, surfactant secreted by type II cells, mucocilliary clearance from trachea to bronchioles, mucus prodution and pathophysiological changes such as hypersecretion, inflammation and epithelial disruption.

Passive diffusion, transcellular diffusion (lipophilic compounds), paracellular diffusion take place with hydrophilic compounds. Transport mechanisms such as carrier mediated transport, vesicle mediated transcytosis, and efflux transports are occurred in pulmonary absorption. Lung has thin barrier with large surface area, higher systemic bioavailability, drugs are better absorbed. Therefore faster absorption occurred in lung after inhalation, challenge is the formulation should stay in local site of the lung and release the drug for the prolonged period of time. Polar drugs are better absorbed, and faster absorption with fewer metabolisms are advantages in comparison of lung versus gastrointestinal tract absorption properties. In general lung metabolism rates are low, expression of esterase is similar in lung and liver, Phase I activities generally 10% in lung compared to liver.

Drug Products of PDDS

PDDS target to cure the diseases such as diabetes [25,26], angina pectoris, cancer [27,28], bone disorders, migraine, tuberculosis, acute lung injury, malarial vaccines [29], thrombosis and emphysema [30] and others. Degradation of drug by liver is avoided in pulmonary drug delivery[31]. Three main classes of drugs namely bronchodilators, corticosteroids, and anticholinergic are most important in the class of inhaled drugs. Asthma affects people of all ages, but most often starts in childhood. The mucolytic agent nacystelyn, has been developed for delivery via a dry powder inhaler. Novel pressurised metered dose inhaler formulations for pulmonary delivery of proteins [32-34]. Ergotamine metered dose inhaler is used to treat migraine and head ache. Measles vaccine given by nebulizer. Ventavis (iloprost), an inhaled treatment for pulmonary arterial hypertension, made by CoTherix, United States of America (USA). Prostaglandin E1 by continuous aerosol via a ventilator has also been shown to improve oxygenation. Zanamivir, made by GlaxoSmithKline, was the first inhaled anti-viral medication approved by the Food and Drug Administration, USA, inhalation of aerosols of methacholine and histamine is widely used to assess nonspecific bronchial responsiveness in asthma. Ribavirin aerosol is the novel sustained released microspheres for pulmonary drug delivery. Aradigm has developed AERx pulmonary technology, which helps in delivering morphine and insulin into the lungs. Alkermes designed an inhalation technology, which enable to deliver efficient dry powder of small molecule of peptide and protein drug particles to the deep lungs. Nektar Therapeutic and Pfizer started dosing first diabetic patients for the phase III clinical trial for inhalable insulin Exubera [35]. The protein peptides such as insulin, calcitonin, luteinizing-hormone-releasing hormone analogs, granulocyte colony-stimulating factor, and human growth hormone are in investigation for systemic application through pulmonary drug delivery system.

Manufacturing methods

The simple dry powder inhalers prepared by blending drug of particle size 1-5μm with coarse lactose 30-60μm. The lactose serves as carrier[36,37]. and bulking agent. Lactose improve flowability, improving dosing accuracy, minimizing the dose variability and easier to handle during manufacturing[38,39]. process. Physicochemical alteration in these carrier leads to change in deposition nature of drug [40]. So carriers such as lactose, sucrose should be designed to improve to attain optimum deposition profile of drug[41]. The inertness of the carrier, easy adhesion during blending, easy separation with inhalation are the preferable qualities of the carrier molecules. The crystallinity of lactose plays a major role in the formulation. The solid respirable colloidal particles prepared by spray drying process [42,43]. Thermolabile substances such as proteins and peptide are processed through spray drying [44]. The uniform particle structure can be obtained by spray drying process [45]. Spray freeze drying is the combination of spray drying and freeze drying processing steps. Spray freeze drying is the advance particle engineering method used to prepare controlled respirable aerosolized particles. Super critical fluid technology[46,47]. is the controlled crystallization of drugs from dispersion of super critical fluid carbondioxide. Sustained release microsphere of controlled particle size is prepared by solvent evaporation method [48]. Single emulsion solvent evaporation method [49] and microemulsion method [50]. are other methods used to prepare nanoparticles of respirable particle size.

Particle Engineering

Particle size in inhalation considered as aerodynamic diameter not geometric diameter. Particle retention of the lung depends on particle size distribution[51]. The particle size required to reach the alveolar duct is 1-5 μm. The particle size of 0.5 micrometer is exhaled, deposited or both by random brownian motion in distal regions. The Aerodynamic diameter d_{aer} of individual particle is $d_{aer} = (\rho / F)^{0.5} d$. Where: d is mass median particle diameter as measured by light microscopy, ρ is particle density, and F is the dynamic shape correction factor. Ten stage cascade impactor [52] instrument is commonly used to evaluate the sizing of aerosols, recommended by United States and European pharmacopeia. Anderson cascade impaction studies used to calculate Mass Median Aerodynamic Diameter (MMAD). The MMAD of the particles is defined from this graph as the particle size at which the line crosses the 50% mark. The Geometric Standard Deviation (GSD) is calculated as $GSD=(X/Y)^{0.5}$, where X and Y are the particle sizes at which the line crosses the 84.13% mark and the 15.87% mark, respectively. Fine particle fraction (FPF) is defined as the mass fraction of particles smaller than a certain aerodynamic diameter. The twin impinger is used to estimate FPF value. The fine particle mass is the total mass of the particles that are in fine particle range. Example is 1-5μm drug fine particle range in dry powder inhaler.

Sustained Release PDDS

Now nanomedicine fulfils the quality of novel formulation and its action throughout tissue, cell, and sub cellular level. Nanotechnology also modifies the duration of drug action and intensity of drug action [53,54]. The site and rate of drug release with tailored dose of controlled release formulations can be prepared with nanoparticle system [55,56]. Polymeric nanoparticle is capable to prepare the successful prolonged release and cell specific targeted drug delivery [57]. The manufacturing methods for drug loaded polymeric

nanoparticles signifies physicochemical and release characters of the formulation. The nature of manufacturing techniques depends upon the drug and nature of the ingredients present in the final composition of the nanoformulations [58,59]. The drug release rate of nanoparticles altered by interaction of nanoparticles with biological matters such as protein, and cells.

The carrier systems are applied to formulate the controlled release formulation for lung route. Chitosan [60-62] is non toxic, biodegradable and biocompatiblesustained release carrier. Single emulsion solvent evaporation and spray drying are the most preferable method to manufacture the polymeric nanoparticles. Spray drying with fine particle fraction in the range of 25-40% is used for dry powder inhaler [63]. The advantages of these nanocarriers [64,65] provides uniform distribution of drug in alveoli, improved solubility of drug, reduction of dosing frequency achieve sustained action, lesser side effects, improved patient compliance etc. Liposomes are controlled release drug delivery vehicles for lung [66] and extensive research was carried out for pulmonary delivery. The lung surfactant Alveofact is the first pharmaceutical liposomal product [67]. The liquid state liposomes are delivered by nebuliser [68-70] as the aerosol to the lung. In this liquid state leakage of encapsulated drug may cause disadvantage, so recently research has been carried out on liposomal dry powder formulations [71,72]. The agglomerated liposomes [73] prepared for modulated pulmonary drug delivery by Ananth V.A. et al. The respirable nanoparticles prepared for controlled release by jet milling process [74]. Aerosol successfully delivers the drug to lower airways of the lung, such as insulin loaded chitosan [75,76]nanoparticles. The research investigations broadly carried out in pulmonary gene delivery for various clinical applications[77-79]. Formulation of dry powder inhaler consists of colistin [80], azithromycin [81], and tobramicin [82] are establish success in the treatment of cystic fibrosis. Hugh D.C.Smyth et.al, prepared the respirable, swellable, biocompatible controlled release microparticle [83] of curcumin loaded poly (D,L-lactic-co-glycolic acid) PLGA by using single emulsion solvent evaporation method [84] and aeroslization study done with next generation impactor. Hirota K. et al., prepared drug loaded PLGA microparticle [85] for inhalation. Drug loaded PLGA nanoparticles encapsulated in microspheres based on PEG-Chitosan graft copolymer. PLGA is selected based on its characteristics such as biocompatibility, biodegradability, and very minimal toxicity nature [86].

CONCLUSION

At present sustained release medications for pulmonary route is not available in the market, even the research carried out several years before. The extensive research goes on various drug delivery system for pulmonary are liposomes, micro and nanomedicines and dry powder inhaler (DPI) of controlled release products. The alteration of chemical composition of polymer leads to sustained action of pulmonary delivery of pharmaceutical products. The sustained release aerosol offers unique opportunities and challenges in the development of pulmonary drug delivery system and continues to be an active area of research. The future of controlled release PDDS is very promising and fascinating. Thus its concludes that further research is most significant for PDDS especially for the treatment of life threatening disorders.

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