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Pulmonary drug delivery-Determining attributes

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Abstract

Pulmonary diseases are one of the significant conditions and influence the lifestyle for a majority of the population in today's world. From ancient times, inhalational drug delivery is being utilised to target the lungs for the management and treatment of pulmonary diseases with reduced side effects. Factors like the physiology of the respiratory system, selection of devices, particle characteristics, and formulation characteristics affect the efficiency of inhalational drug delivery. The precise usage of the inhaler device is indispensable for the efficient delivery of drugs. The characteristic particle impacts the region of drug deposition and in turn influences drug dissolution. Drug dissolution is also affected by the physiological aspect of the respiratory tract, which is concerned primarily in disease states. Formulation type and characteristics decide the release mechanism and influences the inhalational pattern. Liposomes, nanoparticles, microparticles, micelles, dendrimers, etc. can be utilised for passive and active targeting of drugs to the lungs. Inhalational drug delivery can be harnessed to deliver therapeutic agents to systemic circulation for diseases apart from pulmonary diseases. The inhalational drug delivery techniques and devices are being continuously researched upon and reworked to acquire better drug loading with minor loss during drug delivery. The review focuses on the significance and factors associated with pulmonary drug delivery.

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INTRODUCTION

Pulmonary disease or lung disease constitutes diseases or disorders that affects the lungs and its associated structures in breathing effectively. It may be caused due to bacterial, viral or fungal infections or may be due to environmental factors. According to WHO report 2017, Lung disease deaths in India constitutes about 10.9% and is ranked about 4 in deaths caused by respiratory diseases. The primary illness includes Chronic Obstructive Pulmonary Disease, Asthma, Bronchitis, Emphysema, Pneumonia, Acute respiratory Distress, Interstitial lung disease and Lung cancer.

Pulmonary drug delivery comprises devices, systems or formulations by which drugs are delivered to lungs either for the treatment of respiratory ailments or for systemic delivery for other diseases. Currently, pulmonary drug delivery is achieved by inhalation of drugs orally or nasally and can be used for local and systemic action. They have a profound advantage that the drug reaches directly to the systemic circulation and hence achieve higher bioavailability. It provides an effective non-invasive method and can also bypass the first-pass metabolism. But

the efficiency and stability of the inhalation system still constitutes a significant problem.

History of inhalational therapy

Inhalational therapy or respiratory therapy is the intake of medications through nose or mouth for therapeutic purposes. It has been using it for the treatment of pulmonary diseases from ancient times/ for more than 2000 years. The new inhalational technique was done as burning incense in a room or fumigating odorous material and evolved odour will give relief to respiratory troubles and calmness. Ancient Egyptians started using inhalation for the treatment of oral, pharyngeal and chest problems. There is evidence for inhalational therapy by Babylonian civilisation, Greek medicine, Romans, Persian physicians, Arabs and even in ancient India.

Philip Stern rationalised the new inhalation therapy in 1764 as a method to directly deliver therapeutic agents to the lungs. Drugs can be inhaled by one or other means according to nature and form of the drug. The most ancient method of drug inhalation is by sniffing or smelling directly from hands. Later on, vapour inhalation straight from a vessel or with the help of sprayer was utilised for delivery of drugs.

At the beginning of the industrial revolution, physicians started inventing inhalation therapies and experimented with inhalation devices. At first, simple tools were modified through which inhalations can be taken slowly and was mainly utilised for the general anaesthesia. The development of newer techniques and devices used the inhalational therapy for respiratory diseases, especially for asthma, COPD etc. (Stein and Thiel, 2017). Sales-Girons invented first powered or pressurised inhaler where liquid particles were converted to fine droplets with pressure. This type of systems was referred to as atomiser. Later on, the baffles were attached to atomisers, which in-turn reduced the droplet size, which can deposit directly to the lungs and was referred to as nebulisers. (Crompton, 2006).

The use of dry powders instead of liquid and vapour was introduced by Ira Warren in 1852 and got quickly popularised along with atomisers and nebulisers. The atomisers, nebulisers and Dry powder inhalers uses breath driven delivery of drugs and the quantity of drugs reached into the lungs depends on the breathing ability of the patient. Development of metered-dose inhalers resolves this issue which was designed to deliver a specific amount of drug on applying pressure. Spacer devices were later on developed to ensure the effective delivery of drugs to lungs by MDI even with normal breathing (Crompton, 2006). The modern era of science has seen various developments in the inhalational therapy in terms of devices, pressurising system, and dosing units concerning atomisers, nebulisers, pMDI and DPI.

Inhalers for pulmonary drug delivery

Even though there are different techniques and devices for inhalational therapy, pMDI, DPI and nebulisers are the most commonly used ones to deliver the active pharmaceutical ingredients. The selection of tool depends on the method of medication dispensing, targeting technique (active or passive), frequency of administration (single dose or multiple doses), formulation aspects and refillability of devices. The main factor in the effectiveness of device selection comes about when the patient has the proper knowledge in necessity and manner of using inhalational tools for their therapy.

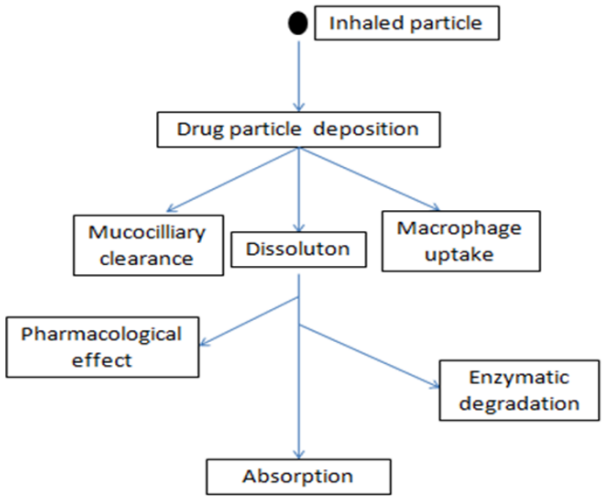

Figure 1: Fate of inhaled particles

Pressurised metered-dose inhalers

The pressurised metered-dose inhalers (pMDI) are compact, portable pressure-driven inhaler device most widely used to deliver therapeutic agents in the treatment of asthma and COPD. The medicament is dispensed as a suspension in the propellant mixture, and a trigger or actuation can only achieve the delivery. The pMDI actuation generates aerosol with high velocity and larger particles of size 25μm. Consequently, particles settle down by impaction in the oropharyngeal region, and only 10-20% reaches the lungs. Additionally, patients should breathe a slow, deep inhalation followed by breath-hold is required for efficient delivery of medicaments from pMDI's. (Myrdal *et al.*, 2014).

The pMDI's consists of several components, namely container, propellants, drug formulation, metering valve and actuator. Every vessel or container is manufactured from an inert and robust material such

as glass, stainless steel and aluminium. The coating can be provided to prevent adhesion of drugs to the container. Propellants are a significant component in pMDI's, and their selection is substantial for adequate working. The most commonly used propellants have constant vapour pressure, and hence chlorofluorocarbons (CFC) makes a satisfactory choice. Due to the environmental impact of fluorocarbons, it is being replaced with hydrofluoroalkanes (Rönmark *et al.*, 2018). The drug is formulated as a suspension in a surfactant solution, and physicochemical properties of formulation decide the particle size distribution of DPI. The metering valve is another significant component which have a volume range of 25μl-100μl and helps in dose precision. The nozzle diameter in the actuator determines the particle size in an aerosol which is an essential parameter in lung deposition. The meticulous design of the formulation and device components is required for the efficient delivery of smaller particles directly into the lungs (Vallorz *et al.*, 2019).

pMDI can be designed for single or multi-dose delivery with modifications in the actuator and metering valve. The increased and efficient airway deposition can be achieved by using spacers, which aids in the formation of smaller droplets and collecting larger ones. Use of spacer also helps in standard dosage delivery. The newer technologies assisted the advancement of pMDI to breath-actuated MDI, which overcomes the poor patient coordination and incorporation of electronic logging increases patient compliance (Myrdal *et al.*, 2014; Tosh *et al.*, 2018).

Dry powder inhalers

Dry powder inhalers are developed to overcome the limitations with pMDIs and nebulisers. They are breath-actuated devices where the drug is loaded as a powder in capsules or blister. Before the delivery, capsule or blister gets punctured and requires proper inspiratory flow rate for efficient drug delivery. The particles will be in capsule or blister as loose aggregates with or without a carrier system and should have an aerodynamic diameter of <5mm. Even though it requires a sufficient inspiratory flow rate; it can be used in the drug delivery for the treatment of asthma and COPD. The device and formulation are designed to produce larger dispersion forces to create deagglomerated particles. Thus deliver an aerosolised stream of finer particles (Usmani, 2019).

DPIs are classified based on the mechanism of powder dispersion, several loaded doses, patients adherence and coordination to device usage. There are three types of DPI available: single-dose, multi-dose and reservoir based design. Single unit dose DPI's contains drug powder mixture in a capsule whereas in multi-dose system drug is loaded to different blisters, with each blister being pierced with each rotation. Single-dose DPIs largely depended on the patient's inspiratory flow rate. The reservoir-based system has predetermined dose delivery system and delivers specific dose during each actuation. Multi-dose DPIs and reservoir system constitute the second generation DPIs. The modern DPIs are power-driven or assisted DPIs that doesn't depend on patients inhalation rate, and rather drug delivery is mediated with battery impellers or vibrating piezoelectric crystals. (Chandel *et al.*, 2019).

Nebulisers

Nebulisers are used in an emergency setting or in case of children or in elderly where liquid formulation of drugs is transformed to aerosols with the help of an external force. The aerosolised particles will have sufficient size to deliver drugs to the lungs. The aim of the nebuliser is to give drugs for a shorter duration and the required particle size is achieved by atomisation process. Fluid output for aerosolisation and droplet size is determined by the flow rate, viscosity, temperature, surface tension and also depends on the design of nebuliser. Higher flow rate, lower viscosity & surface tension are required for generating adequate droplet size (Chandel *et al.*, 2019).

In nebulisers, aerosolisation of the liquid formulation can be accomplished by baffles, ultrasonic waves or by compressed air. Based on the aerosolisation principle, nebulisers are divided into pneumatic nebulisers, ultrasonic nebulisers and jet nebulisers. Mesh nebulisers which are a newer version are compact and can be used with any type of formulation.

The fate of inhaled particles

The respiratory system consists of two zones- conducting zones (upper respiratory tract) and respiratory zone (lower respiratory tract). The whole respiratory system constitutes a large surface area and is provided with an abundant blood supply makes a good route for drug absorption for local and systemic action. The particles once inhaled will travel through the respiratory tract and will deposit in various regions of the stretch. The drug deposited on to the epithelium will either get absorbed to systemic circulation or get enzymatically degraded or cleared out by specific respiratory defence mechanisms. The respiratory system is lined with mucous and is associated with various barriers-mechanical, chemical and immunological. The collective fate of any inhaled particles is diagrammatically repre-

sented in Figure 1 (Newman, 2005). The efficient delivery of drugs to the lungs has to overcome these barriers.

Particle deposition

The particle deposition of inhalational drug delivery system is mainly by inertial impaction, Diffusion (Brownian movement) and Gravitational sedimentation. Ancillary mechanisms include interception, adsorption and electrostatic precipitation. Factors which influences the mechanism of deposition can be categorised as aerodynamic particle behaviour, airway geometry and breathing pattern. Particle size, shape, charge, density and hygroscopicity constitute the particle characteristics. The deposition mechanism further depends on the flow rate of the inhalational drug delivery (Cheng, 2014).

Particle size

The aerodynamic diameter is an independent parameter determining the particle deposition in the lungs and affects the local action. Geometric diameter and density of the particle has effects on the aerodynamic diameter since it measures the settling time in the air compared to a spherical particle. Particle size and size distribution influences the mechanism and region of deposition. Particles in the size range of 0.1-1μm will deposit into smaller airways and alveoli by Brownian diffusion because they have high particle velocity and hence can quickly move within the respiratory tract. The deposition to central airways, i.e. to lungs and lower bronchial airways is by gravitational sedimentation. It can be achieved by particles with size range 1-5μm where particles settle in response to gravity. Particles of size higher than 5μm will settle down in the mouth and other thoracic regions by inertial impaction because a more massive particle can't change the direction of respect to airflow in the respiratory tract. For efficient lung deposition to occur, particles should be in the range of 0.5-5 μm with slower inhalation (Borghardt *et al.*, 2018). The quality and efficiency of the aerosol depends on the particle size distribution and is evaluated by the Polydispersity index parameter. The monodisperse powder has lower PDI, but, it produces superior effect than polydisperse powder. The interception, adsorption and electrostatic precipitation depend on particle velocity along with the particle size (Peng *et al.*, 2016).

Particle shape

The inhaled particles may not always be spherical and accordingly different shapes has respective drag and velocity with correspondingly minimal settling velocity, which influences the aerodynamic diameter. The shape of particles consequently has a well-connected impact on drug deposition in the human respiratory tract. The particle shape and deviation from spherical particles can be assessed by the parameters elongation ratio, flatness ratio, roundness (first-order descriptor), shape factor, angularity (second-order descriptor) and surface factor (third-order descriptor). (Peng *et al.*, 2016).

Elongation ratio describes how irregular and elongated the particle is. Higher the ER value (e.g., needle-shaped particles) more irregular and has more surface roughness and has exceptional aerodynamic behaviour, hence deposit more to lower regions of the lung. For micron-sized or submicron-sized particles, shape factor ascertains the effect on lung deposition. Shape factor value can range from -1 to 1 and lower the shape factor more the surface roughness and more irregularity from the spherical particles (Sturm, 2012) .

Particle charge

Particle charge has an influence on the aerosol deposition in the lungs due to the repulsive forces between the particles, thus enhancing the distribution respiratory tract. The electrostatic charge also enhances particle retention in the respiratory tract. Influence of particle charge is significant in upper airways where the deposition occurs by impaction but becomes prominent in lower airways due to large surface area. Particle charge and size can be acclimatised for deposition in distinct regions of the lung (Chow *et al.*, 2007).

Particle density

Along with particle size and particle charge, particle density also has an essential role in aerosol dynamics. Aerodynamic diameter is dependent on particle density and dynamic shape factor which relates to particle electric mobility diameter. The particle optical property is also secondarily reliant on frequency as refractive index increases by particle density. Particles with a smaller size which deposit by diffusion is independent of density whereas particles which deposit by sedimentation depends on density. Particles with high density and smaller geometry have more deposition than those with lower density and larger particle size (Katrib *et al.*, 2005).

Particle hygroscopicity

The Hygroscopic aerosol particles tend to grow in size as it moves down through the physiologically humid respiratory tract. The variation in the relative humidity and temperature in respective regions of the respiratory tract affects the particle size, and as a result, the quantity, mechanism and area of depo-

sition will vary (Winkler-Heil *et al.*, 2014)

Breathing pattern

The nature of breathing determines the lung function and hence the breathing pattern is considered as a factor affecting lung deposition. Effect of breathing pattern can be assessed by the measuring tidal volume and respiratory frequency, which in turn will vary with particle size. Larger tidal volume and lower flow rate results in higher particle deposition since the particle gets longer (Solanki *et al.*, 2018).

Airway geometry

The anatomy of the airway has an impact on the particle flow rate and region of particle deposition. The pathological conditions alter the anatomy of respiratory tract resulting in the variation in particle deposition. In general, larger particles with higher inspiratory airflow deposit more by impaction in narrower airways with more extensive branching (Kourmatzis *et al.*, 2018).

Pulmonary drug dissolution

Once the inhaled particle deposit into the lungs, it must dissolve with the pulmonary tissues to reach the systemic circulation. For the pulmonary ending to take place, the drug has to circumvent various physiological barriers. The physiological barriers are the significant parameter and are in turn dependent on particle size, relative humidity and temperature.

The inhalant particles have to interact with barriers primarily, to undergo pulmonary dissolution. The respiratory tract is lined with airway surface liquid or mucus with varied thickness in different regions of the respiratory tract. It consists of high molecular weight glycoproteins with anti-microbial, anti-protease and anti-oxidant activity. Mucus provides visco-elastic properties to the respiratory tract and aids in mucociliary clearance (Ibrahim and Garcia-Contreras, 2013). The deposited drugs have to transverse through the mucus layer, withstanding the drug degradation.

The conducting region of the respiratory tract constitutes pseudostratified ciliated epithelium, and the respiratory area is lined with squamous epithelium which constitutes the second barrier in drug dissolution. With transcellular diffusion, paracellular transport, vesicle-mediated transcytosis and carrier-mediated transport, tight junctions connect the cells and transportation of drugs. Except for carrier-mediated transport, other transport mechanisms are passive methods. Active transport is carried out with the aid of transporter molecules, and there are mainly seven families of transporter molecules (Ibrahim and Garcia-Contreras, 2013).

Basement membrane forms an integral barrier consisting of specialised extracellular matrix and has a predominant function, especially in the disease states of asthma, COPD etc. The basement membrane modulates the movement of molecules, fluids, cells or proteins through the interstitium to capillary. The particle then passes through the capillary endothelium to reach the systemic circulation. The basement and the capillary membrane has more significant in the case of particles with systemic effects.

Mucociliary clearance

Mucociliary clearance is a primary innate defence mechanism involving a combined function of cilia movement and gel-sol mucus production. Mucociliary action helps in the removal of local respiratory debris, unwanted secretions and inhaled foreign particles. The changes in the quality of mucus or the cilia movement lead to the impairment of mucociliary clearance. Hence it is a critical factor in the treatment of diseases as in asthma, COPD, Emphysema where the function of mucociliary function is altered. Positively charged particles have more affinity towards the negatively charged mucus, altering the absorption of such particles (Munkholm and Mortensen, 2014).

Macrophage uptake

The macrophage clearance is significant in alveoli where mucociliary clearance is absent, and particles reaching too deep lungs, especially in alveoli get degraded or get eliminated by the alveolar macrophages. Macrophage uptake is slower and rarely occurs because most of the particles get dissolved in the alveolar fluid. Also, particles with a size less than 100nm go off non-identifiable and will be ingested by alveolar epithelial cells directly to the lymphatic system (Fröhlich, 2017).

Pulmonary drug absorption

The pulmonary absorption is characteristic to distinct particles whether they produce a local or systemic effect. In locally acting drug, pulmonary absorption translates as a pathway to the clearance of the particles and occurrence of side effects. For systemic acting drugs, drug absorption is a significant step as it decides the pharmacological effect of drugs (Kleinstreuer, 2014).

The particle is transported through the pulmonary epithelium by transcellular diffusion, paracellular transport, vesicle-mediated transcytosis and carrier-mediated transport. Except for carrier-mediated transport, other transport mechanisms are passive methods. Active transport is carried out by one of seven transporter molecule families in the pulmonary tract. It includes the family of

Solute-carrier transporters (Organic Cation Transporters and Organic Anion Transporters) and ABC transporters which regulates the absorption of various macromolecules. Vesicle-mediated transport is involved in the uptake of macromolecules through alveolar epithelial cells (Kleinstreuer, 2014).

Considering the physicochemical nature of drugs, those that are highly lipophilic are absorbed by passive diffusion. In contrast, smaller hydrophilic molecules are absorbed through the paracellular pathway, i.e. in between the tight junctions. The increased absorption rate is seen in the alveolar region compared to other conducting regions.

Enzymatic degradation

Drugs that bypasses the clearing mechanisms and gets absorbed into lung tissues undergoing metabolism. Even though there are metabolism enzymes through the conducting airways and alveoli, the enzymes present in the lungs have limited activity compared to gastric and hepatic enzymes. The dominant metabolising phase I enzyme present in the lungs is the Cytochrome P450 family of enzymes. It can metabolise any inhaled macromolecules (El-Sherbiny *et al.*, 2015). Also, the pulmonary tract has Flavin. Flavin contains monooxygenase, monoamine oxidase, esterases, epoxide hydrolase and aldehydes dehydrogenase. The Flavin mono-oxygenase is involved in the metabolism of fatty acids, steroids and other lipophilic molecules. Esterases are prominent in alveolar cells and are involved in the metabolism of peptides and proteins.

The phase II enzymes exhibited in the lungs consists of UDP- glucuronosyltransferases (UGTs), sulfotransferases (SULTs), glutathione (GSH) S-transferases (GSTs), and N-acetyltransferases (NATs). Metabolising enzymes influences the duration and intensity of the therapeutic action of drugs for pulmonary diseases.

Particulate carriers for drug targeting to lungs

Drug targeting is a drug delivery principle where drug moiety is targeted to a specific site of action which will amplify the drug action solely for the disease organs, tissues or cells. The drug targeting improves drug efficacy, lower side effects and reduce treatment costs. The drug targeting to any system can be achieved by two techniques: passive targeting and active targeting. Direct administration of pharmacological moiety to the disease site has also been achieved.

Passive targeting is a non-selective form of targeting utilising the Physico-chemical factors and physiological conditions of cells or tissues associated with a disease condition. The pharmacological moiety is formulated in such a way that it will be targeted to act on the affected site. The physical factors like temperature, magnetic property, redox and ultrasound sensitivity are utilised to induce the effect of drugs. The drug-carrier complex may be distributed throughout the body, but the pharmacological impact will be limited to a specific site. The active targeting includes the conjugation of drug-carrier complex with ligands such as peptides, nucleic acids, antibodies, vitamins or simple molecules which has higher affinity towards the specific receptors present on the cells.

Drug targeting to lungs can be either done by inhalation or through the intravenous route, inhalation route being most effective in maximum deposition and hence enhanced absorption of pharmacologically active moiety. Drug targeting to lungs is a function of physicochemical properties of drugs, Anatomy of the respiratory system, the physiological condition of lungs, which also affects absorption and distribution of drugs into the lungs. The factors responsible for lung targeting are considered. They are formulation design and drug-target to lung as a combined effect of formulation characteristic and inhaler design.

Particulate carriers have been used for both local and systemic therapy for various respiratory diseases and the carrier systems aids in boosting the stability, cellular uptake and site-specific targeting. Carrier systems at micrometre and nanometre range such as liposomes, polymeric Nanoparticles, Microparticles, dendrimers and polymeric micelles have been studied for inhalational drug delivery.

Liposomes for pulmonary drug delivery

Liposomes accounts for one of the flexible lipid-based drug delivery systems for inhalation. Liposomes are versatile and biocompatible delivery system as it is composed of natural and synthetic phospholipids with neutral or anionic in charge. Liposomal drug delivery diminishes the mucociliary clearance, thus boosting the residence time and drug potency (Osman *et al.*, 2018). Although liposomal delivery has advantages, it has a significant drawback of weak instability in systemic circulation as it is easily recognised and taken up by the mononuclear phagocytic system, which can be beneficial in fewer cases. Novel technologies are being developed for passive and active targeting of liposomal drug delivery to the pulmonary region.

Stealth liposomes, where the liposomes encapsulated with drugs or the drug alone is conjugated with Polyethylene glycol strands attaining a lower recognition to the immune system. The fabrication of Stealth liposomes also alters the physicochem-

ical nature of drug encapsulated. Formulation of multi vascular liposome enhances the circulatory time and helps in attaining a sustained release of drugs. The surface conjugation with thermosensitive ligand moieties helps in specific targeting and is mainly utilised for active targeting (Bulbake *et al.*, 2017).

Nanocarriers for Pulmonary drug delivery

Even though nanoparticles has higher uptake in lungs, it has dominance in targeting drugs to alveoli than other regions. The various nanocarriers being researched includes polymeric nanoparticles, nano micelles, lipid nanoparticles and nanocapsules. Likewise, in liposomes, fabrication of stealth nanoparticles increases the circulation time and hence increasing the bioavailability. The drug presence can also be prolonged by fabricating with biodegradable polymers, thus assisting in maintaining a sustained release of drugs.

Polymeric nanoparticle makes a versatile choice for improving the therapeutic index of the drug by increasing the stability of drug and residence time. Formulation with biodegradable polymers makes it even more versatile. Physicochemical, chemical properties of the drug can be adapted by the selective choice of polymers, surfactants and solvents. The lipid based nanoparticles chiefly consists of liposomes, solid lipid nanoparticles (SLN) and lipid-coated nanoparticles.

Lipid Nanoparticles are preferable, especially in the delivery of chemotherapeutic drugs which provides biocompatibility, enhance the efficacy of the drug and also improves the site-specific targeting. Lipid nanocarriers have also been widely used for protein and gene delivery by inhalation for pulmonary and systemic effect. Solid lipid nanocarriers are nanocarriers made up of phospholipid and is favorable compared to other lipid carriers due to improved biocompatibility, enhanced drug loading and stability. In pulmonary drug delivery, the use of surfactants occasionally creates a hindrance (Kaur *et al.*, 2012).

Metal Nanoparticles made up of iron, gold and zinc has been developed for the active targeting in pulmonary drug delivery. The main drawback in the metal nanoparticle is the development of toxicity on prolonged usage (Kaur *et al.*, 2012).

Microparticles for pulmonary drug delivery

The microparticles hold resemblance in the behaviour with nanoparticles and are capable of delivering drugs to deep lungs without getting exhaled as it has suitable aerodynamic diameter. (El-Sherbiny *et al.*, 2015). For effective delivery of drugs to lungs, the particle size of about1-5μm is appropriate, and deviation from this range may be ineffective in proper targeting of drugs. The microparticles with lower density have less macrophage clearance and hence makes it suitable for sustained release formulation. Even though microparticles have meagre drug release properties, it benefits with increased drug loading and entrapment assisting in lowering the drug dose. The variability in polymers also helps to formulate it as sustained and controlled release formulation.

Polymeric Micelles for pulmonary drug delivery

Polymeric micelles are self assembling nano sized structure amphiphilic block co-polymers moulded to form an inner hydrophobic core and an outer hydrophilic shell. Minuscule sized shells can enhance the solubility of hydrophobic drugs and incorporated into it and also enables to evade from rapid excretion. Consequently, the biocompatibility, drug loading and stability of the drug is enhanced, and surface engineering allows it for specific targeting (Patra *et al.*, 2018). The shell counters the opsonisation, adsorption with protein molecules furthermore summons the bioavailability of polymeric micelles. Additionally, the size of the polymeric micelles can be modulated with altering the chemical nature of polymers fabricating into unilamellar and multilamellar micelles.

Dendrimers for pulmonary drug delivery

Polymeric macromolecules expands to form an extensively branched framework providing with characteristic central core and branches towards the periphery. Dendrimers can incorporate both hydrophilic and hydrophobic polymers either in the core or in the periphery of the polymer branches through. Dendrimers can passively detour through the barriers in the airway and easily uptaken by macrophages. Therefore, Dendrimers makes a suitable choice for passive and active targeting (Mehta *et al.*, 2019).

CONCLUSION

Numerous researches are being carried out for developing newer inhalational devices and method of administration to target drugs effectively and to decrease the side effects. The study on particle characteristics aids in developing effective formulations providing sustained and controlled release of drugs. The development of powder formulation is far beneficial rather than inhalation device development. Inhalational drug delivery has immense prospect to bring forth drug action in the respiratory tract and systemic circulation.

Conflict of Interest

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