

**A REVIEW ON-PULMONARY DRUG DELIVERY SYSTEM**Swapnil M. More*¹ and Sagar S. Kale¹¹Asst Prof, Sahyadri College of Pharmacy Methwade Sangola.Article Received on
01 Dec. 2020,Revised on 22 Dec. 2020,
Accepted on 11 Jan. 2021DOI: <https://doi.org/10.17605/OSF.IO/29J6A>***Corresponding Author****Swapnil M. More**Asst Prof, Sahyadri College
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Sangola.**ABSTRACT**

Pulmonary drug delivery has attracted tremendous scientific and biomedical interest in recent years and has progressed considerably within the context of local treatment for lung diseases, by virtue of enhanced local targeting and reduced systemic side effects with the administration of minute drug dosages. Furthermore, with the high surface area and permeability of the lung, the 21st century has seen a paradigm shift to inhaled therapy for systemic use. Because of limitations associated with the conventional treatment of various chronic diseases a growing attention has been given to the

development of targeted drug delivery systems. Pulmonary route of drug delivery gaining much importance in the present day research field as it enables to target the drug delivery directly to lung both for local and systemic treatment. Pulmonary tract tends to be considered as very promising and attractive route for the administration of active substances intended to treat local pulmonary e.g., asthma, chronic obstructive pulmonary disease (COPD), microbial infections). Among the different respiratory cells, the ciliated epithelial cells of the larger and smaller airways and the type I and type II pneumocytes are the key players in pulmonary drug transport. With their diverse cellular characteristics, each of these cell types displays a unique uptake possibility. Hence, the better understanding of complexes and challenges facing the development of pulmonary drug delivery system offer an opportunity to the pharmaceutical scientist in minimizing the clinical and technical gaps.

KEYWORDS: Dry powder inhaler, lung deposition, pulmonary route, targeted drug delivery, Meter dose inhaler, nebulizer, Fine particle fraction.

INTRODUCTION

Pulmonary route have been used to treat various respiratory diseases for centuries. Ancient inhalation therapies included the use of leaves from plants, vapors from aromatic plants,

balsams, However, around the turn of the 19th century, with the invention of liquid nebulizers, these early treatments developed into legitimate pharmaceutical therapies. In the 1920 s adrenaline was introduced as a nebulizer solution, in 1925 nebulizer porcine insulin was used in experimental studies in diabetes, and in 1945 pulmonary delivery of the recently discovered penicillin was investigated. steroids had been introduced in the mid 1950s for the treatment of asthma and nebulizers were enjoying widespread use.

In 1956 the pressured metered dose inhaler (pMDI) was introduced, over the past 5 decades, helped by the advances in molecule design and drug discovery the pMDI has risen to become the main stay of asthma treatment.^[1]

The respiratory tract is an attractive route for the administration of therapeutics and genomics. The past decade has been marked by intensive research efforts on pulmonary drug delivery (PDD) for local and systemic drug and gene delivery including diagnostic agents because it has several advantages over other routes of administration.^[2,3] Various pharmaceuticals, biopharmaceuticals, anesthetics, smoke or steam have been successfully inhaled for medical purposes for centuries.^[4] Over the years inhalation therapy has established itself as a valuable tool in the local therapy of pulmonary diseases such as asthma, chronic obstructive pulmonary disease (COPD)^[4], cystic fibrosis (CF), and pulmonary hypertension.^[5] The local application of therapeutic agents to the respiratory system has several advantages over other routes of administration, i.e., a large surface area available for absorption, high to blood flow, highly vascularized tissue, rapid absorption, avoidance of first pass effect, avoidance of the effects of gastric stasis and pH, smaller doses required than by the oral route to achieve equivalent therapeutic effects useful for local treatment and systemic distribution.^[6,7] Site-specific delivery facilitates a reduction of the therapeutic dose to be administered, and thus, decreases the associated adverse effects.^[7] In addition, inhalation represents a non-invasive alternative for systemic delivery of biopharmaceuticals, which are labile to gastric acid, and thus, improves patient compliance.^[8] The efficiency of inhalation therapy depends on the delivery system, the devices used and the fate of the delivered medication in the respiratory tract. Once the therapeutic agent has been deposited in the lung, elimination is instantly initiated, decreasing the initial high local concentrations of the therapeutic agent in lung tissue.^[8,9] Because the concentration of the drug can decrease quickly, it often requires multiple daily inhalations which can cause difficulty for the patient's compliance.^[10]

Advantages

Provides local action within the respiratory tract

- Provides rapid drug action
- Provides reduced dose
- Allows for a reduction in systemic side-effects It can be
- Employed as an alternative route to drug interaction when two or more medications are used concurrently Reduces extracellular enzyme levels compared to GI tract
- Due to the large alveolar surface area Reduces evasion of first pass hepatic metabolism by
- Absorbed drug Offers the potential for pulmonary administration of
- Systemically active materials

Disadvantages

The duration of activity is often short-lived due to the rapid removal of drug from the lungs or due to drug metabolism. Necessitates frequent dosing^[11]

Anatomy and Physiology of Human Respiratory Tract

For the development of new PDD systems, one should have detailed knowledge of lung anatomy and physiology. The respiratory tract is mainly divided into two regions i.e., the upper airway and the lower airway with the line of division being the junction of the larynx and trachea.^[12] The upper airway acts as an air transport system and consists of the nose, mouth, pharynx and larynx. The lower respiratory tract consists of the tracheobronchial, gas-conducting airways and the gas exchanging acini. The lower airway is divided into three zones: conducting, transitional, and respiratory zones. The conducting zone is responsible for the bulk movement of air and blood. In the central airways, air flow is rapid and turbulent and no gas exchange occurs. The transitional zone has a limited role in gas exchange.^[12,13] The respiratory zone mainly comprises of respiratory bronchioles and alveoli, where the actual gas exchange takes place.^[13] Figure 1.1 shows a schematic representation of the lung. The bronchial tree trunk begins with the trachea, which bifurcates to form the main bronchi: the left and right primary bronchi. Each primary bronchus divides into still smaller secondary bronchi. The secondary bronchi branch into many tertiary bronchi that further branch several times, ultimately giving rise to tiny bronchioles that sub-divide many times, finally forming terminal bronchioles and respiratory bronchioles. Each respiratory bronchiole sub-divides into several alveolar ducts that end in clusters of small thin-walled air sacs called alveoli, which open into a chamber called the alveolar sac.^[14] Two physical changes occur while

moving from the trachea to the alveolar sacs in the airways that are important in influencing airway function. Firstly, the airway diameter decreases with the respiratory branches, e.g., a tracheal diameter (d) is 1.8 cm compared to an alveolar diameter of 0.04 cm. This permits adequate penetration of air to the lower airways for a given expansion of the lungs. Secondly, the surface area of the airways increases with each generation, to the extent that the total lung area at the level of the human alveolus is in the order of 140 m^2 .^[14] Alveoli are the terminal air spaces of the respiratory system and are the actual site of gas exchange between the air and the blood. About 100 million alveoli are found in each lung.^[15] Each alveolus is a thin-walled polyhedral chamber of approximately 0.2 mm in diameter. Gases taken up by inhalation need to cross alveolar epithelium, the capillary endothelium and their basement membranes to reach blood; the distance makes up around 500 nm length.^[14] So, the alveolus, providing increased surface area, becomes principal site of gas exchange in the airways.^[16] The human lung consists of five lobules and ten broncho-pulmonary segments. The luminal surface of the airways is lined by ciliated cells, which are the most common and numerous cell types

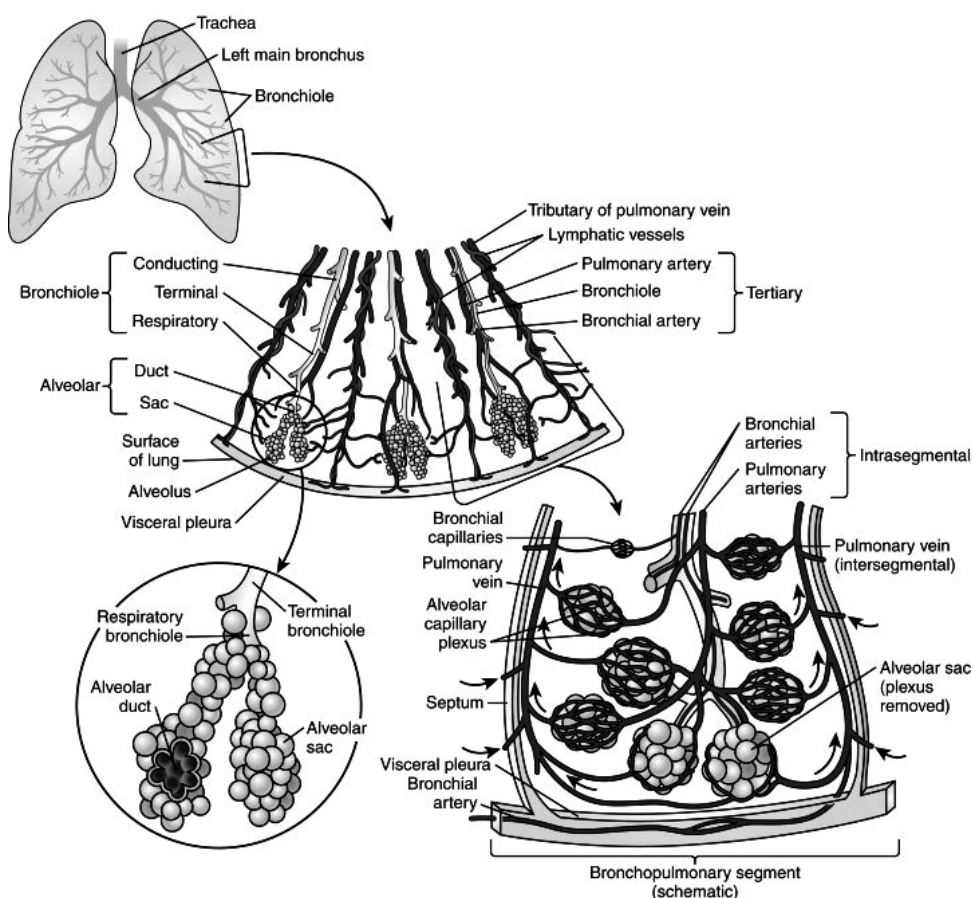


Figure 1.1: Internal structure and organization of lungs.^[17]

Mucus cells are intermingled among the ciliated cells. The walls of the conducting airways are coated by an adhesive, viscoelastic mucus layer (thickness: 5–55 μm) which is secreted by the mucus cells. The major components of mucus are glycoproteins and water.^[18] This mucus fulfils important functions, i.e., the protection of the respiratory epithelium from dehydration, the water in the mucus promotes saturation of inhaled air, mucus contains antibacterial proteins and peptides, such as defensins and lysozyme that inhibit microbial colonization of the airways, and mucus is also involved in airway protection from inhaled xenobiotics or chemicals. Clearance of mucus from the lung is driven by the motion of the ciliated cells ‘mucociliary escalator’, which generates a mucus flow rate of ~ 5 mm/min. Thus, the mucus blanket is replaced every 20 minutes in healthy subjects.^[18] The mucociliary escalator serves as an important protective mechanism for removing small inhaled particles from the lungs. The composition, thickness, viscosity and clearance of the mucus is often altered in patients suffering from airway diseases such as asthma, COPD and CF. The alveolar epithelium is composed of Type I and Type II alveolar cells and occasional brush cells. The Type I pneumocytes are thin cells, cover most of the surface of the alveoli (95% of the surface area) and the Type II pneumocytes are cuboidal secretory cells are interspersed among the Type I cells.^[19] The alveolar space is coated by a complex surfactant lining that reduces surface tension to minimize the work of breathing and prevents collapse of the alveoli during expiration.^[17] The majority of insoluble particles deposited in the upper airways are eliminated by mucociliary clearance.^[20] The most prominent defense mechanism of the respiratory region is macrophage clearance. The particles deposited in the deeper lung will be taken up by alveolar macrophages, which slowly migrate out of the lung, either following the broncho-tracheal escalator or the lymphatic system. The blood supply to the lung is provided by a pulmonary circulation and a systemic circulation. A drug delivered to the lower airways can enter the systemic circulation by absorption into the alveolar capillaries of the pulmonary vascular bed.^[17,19]

Cellular Aspectsof Pulmonary Drug Transport

The transepithelial transport of compounds along the respiratory epithelium from the upper airways with nasopharynx, trachea and large bronchi to the lower respiratory tract with small bronchioles and alveoli is characterized by large quantitative differences. In this respect, the transport in the upper airways is limited by a smaller surface area and lower regional blood flow. Also, the upper airways possess a high filtering capacity and remove 70 ^90% of pressurized particles. In contrast, the smaller airways and alveolar space account for more

than 95% of the lung's total surface area.^[21] Also, this compartment is directly connected to the systemic circulation via the pulmonary circulation.

There are two major cell types found in the alveolar epithelium: type I and type II pneumocytes. Whereas type I cells have a very thin cell body with long membranous extensions, occupying an area of about 95% of the alveolar surface^[22], the type II pneumocytes are characterized by a more cuboidal morphology and cover about 5% of the total alveolar surface.^[23,24] Studies on the subcellular morphology of type I cells revealed the presence of endocytotic vesicles which may function as carriers in the absorption processes of larger proteins such as insulin (5.7 kDa).^[25,26] Although type II pneumocytes express a variety of transport proteins, it is generally accepted that their main functions are the production of surfactant proteins and the differentiation into type I cells after epithelial barrier injuries. The pulmonary blood-gas barrier consists of a thick and a thin side, which are composed of the alveolar epithelium, the capillary endothelium, and the intervening extracellular matrix (basement membranes of the two cell layers).^[27]

Out of the two cell types involved in the blood-gas barrier, the type I cells display most likely the rate-limiting step concerning the uptake of compounds into the pulmonary circulation as previous studies reported a 103 times lower permeability for substances such as sucrose in comparison to endothelial cells.^[28] This is based on the difference in pore size between alveolar cells (0.6 μ m) and endothelial cells (4 μ m)^[29] and the tight junctions depth which is 0.2617 μ m (significantly) higher than the tight junctions depth of the capillary endothelial cells (0.1667 μ m).^[30]

In contrast to these conditions at the blood-gas barrier, three other different types of tight junctions have been identified for extra- and intrapulmonary airways.^[31] Most importantly, they differ in the degree of luminal μ bril interconnections which are sparsely interconnected in type I, more densely interconnected in type II and most densely interconnected in type III tight junctions. While the type I is almost exclusively found between extrapulmonary airway ciliated cells, the type II is primarily present in smaller airways and between Clara cells and the type III between mucous cells^[31] with a secretory cycle-associated change in permeability. This dependence upon the secretory cycle, which is leakier when the mucous cells are in a state of active secretion has also been reported for other cell types such as mammary gland epithelial cells.^[32] It is most likely that the regional differences in tight junction morphology are

directly linked to the transepithelial transport capacities of water and ions in contrast to actively transported larger molecules.

RECENT ADVANCES IN PULMONARY DRUG DELIVERY DEVICES

Following types of inhalation devices are present

Inhalation drug delivery system by- metered dose inhalers

Inhalation drug delivery system by - dry powder inhalers

Inhalation drug delivery system by -nebulizer

Pressurized Metered-Dose Inhalers

Traditional asthma therapy has primarily used the pMDI. Since the 1950s, they have been the backbone of inhalation therapy (33). In a pMDI, a propellant pressurized to a liquid state is holding the drug either in a suspended or dissolved form. Metered release of the fluid through a valve causes expansion and evaporation of propellant leaving the drug in the form of a high velocity aerosol. Rapid release of the propellant into the valve stem along with the actuator seating forms an expansion chamber where propellant starts to boil (Figure 1.). The liquefied propellant serves both as a source of energy for expelling the formulation from the valve in the form of rapidly evaporating droplets and as a dispersion medium for the drug and other excipients.

How to use the MDI,

Shake the inhaler well before use (3 to 4 shakes)

- Remove the cap
- Breathe out, away from your inhaler
- Bring the inhaler to your mouth. Place it in your mouth between your teeth and close your mouth around it. Start to breathe in slowly. Press the top of your inhaler once and keep breathing in slowly
- Until you have taken a full breath. Remove the inhaler from your mouth, and hold your breath for about 10 seconds, then
- Breath out.

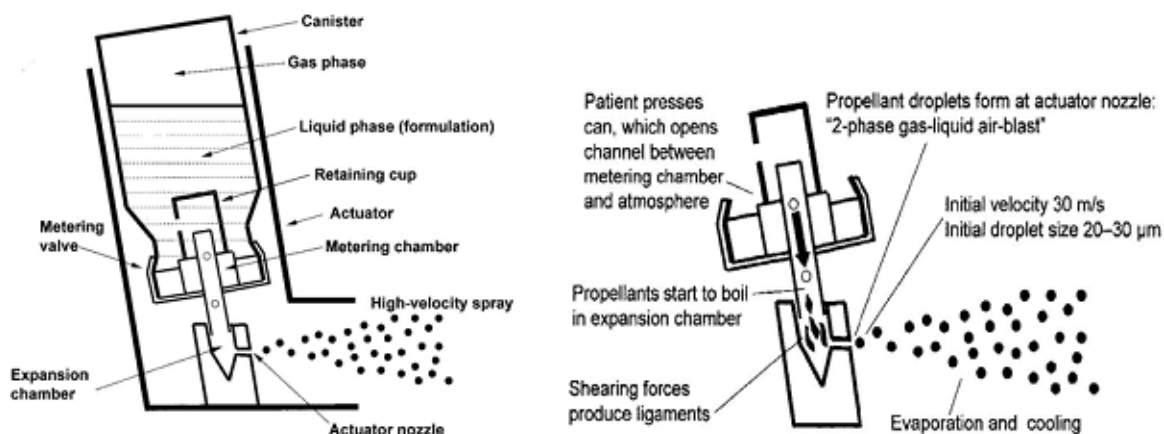


Figure 1: Schematic representation of a typical pressurized metered-dose inhaler.^[33]

The essential components of an MDI are the container, the metering valve, and the actuator. Usual valve volumes range from 25-100 μl , which deliver a drug dose of about 50 μg to 5 mg.

Nebulizers

Nebulizers have been used in inhalation therapy since the early 19th century. Marketed respiratory solutions are generally composed of drug dissolved in aqueous, isotonic solvent systems that may contain preservatives to reduce microbial growth. There are two traditional devices: air-jet and ultrasonic nebulizers. For a typical jet nebulizer (Figure 2), compressed air passes through a narrow hole and entrains the drug solution from one or more capillaries mainly by momentum transfer. Large droplets impact on baffles and gets refined to the size required, while droplets with smaller size run in a streamline flow of air bypassing the impact on baffles.^[36] Approximately 50-60% of the particles produced are in the respirable range.

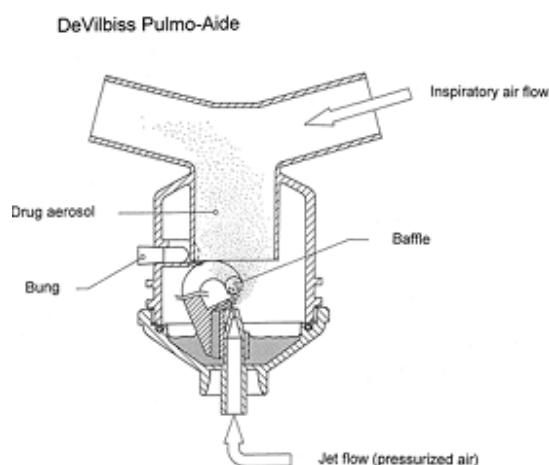


Figure 2: Schematic presentation of a jet nebulizer.^[34]

Dry Powder Inhalers

All DPIs have four basic features: a dose-metering mechanism, an aerosolization mechanism, a deaggregation mechanism, and an adaptor to direct the aerosol into the mouth. DPIs are subject to strict pharmaceutical and manufacturing standards by regulatory bodies, the most challenging of which is the demonstration of device reliability in terms of delivered dose uniformity and delivered dose deposition.^[35] Indeed, comparative *in-vitro* data for a generic product versus the innovator product must be provided on the complete individual stage particle size distribution profile using a multistage impactor/impinger with various impaction stages, such as the NGI.^[35]

For DPIs, the dose received by the patient is dependent on four interrelated factors^[36]

1. The properties of the drug formulation, particularly powder flow, particle size and drug carrier interaction
2. The performance of the inhaler device, including aerosol generation and delivery
3. Correct inhalation technique for deposition in the lungs
4. The inspiratory flow rate

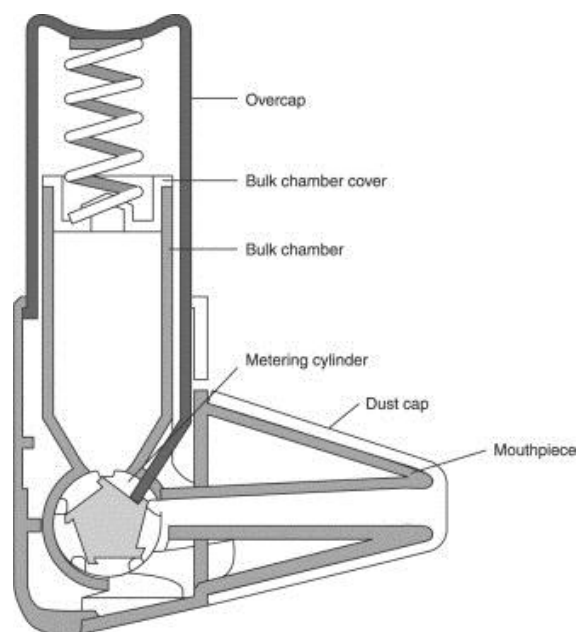


Fig no 3: Dry Powder Inhalers.^[37]

A similar DPI, the Rotahaler® (GlaxoSmithKline) breaks the capsules into two, the body part falling inside the device and the cap being retained in the entry port. As the patient inhales, the portion of the capsule containing the drug experiences erratic motion in the airstream, causing dislodged particles to be entrained and subsequently inhaled. Turbulence due to grid

upstream of the mouthpiece deaggregates particles. A FPF of 26% has been reported for this low resistance device.^[37]

Devices for generating particles.^[38,39]

Device	Particle size (mm)	Particle size uniformity
Metered-dose inhaler	1 [^] 35	Heterogeneous
Jet nebulizer	1.2 [^] 6.9	Heterogeneous
Ultrasonic nebulizer	3.7 [^] 10.5	Heterogeneous
Spinning disc	1.3 [^] 30	Monodisperse
Dry powder	Flow-related	Heterogeneous
Vibrating orifice	0.5 [^] 50	Monodisperse

Mechanisms and Ways Of Pulmonary Drug Administration

Over the last decade, the systemic absorption of a broad range of therapeutic agents after pulmonary application has been demonstrated in animals as well as humans. Through pulmonary route, the drug can be administered by two primary modes: first, intranasal administration, which has anatomical limitation, such as narrower airway lumen, second, oral inhalative administration. By oral inhalative administration far better results can be expected as it allows to administer very small particles with a concentration loss of only 20% in comparison with 85% by nasal route. Oral inhalative administration can again be classified as intratracheal instillation and intratracheal inhalation. The most common method used in laboratory is the intratracheal instillation. In the intratracheal instillation, a small amount of drug solution or dispersion is delivered into the lungs by a special syringe. This provides a fast and quantifiable method of drug delivery to the lungs. The localized drug deposition is achieved with a comparatively small absorptive area. So, the instillation process is much simple, non-expensive, and has non-uniform drug distribution.

In preclinical animal studies, intratracheal instillation has frequently been used to assess the pulmonary absorption and systemic bioavailability, especially with regard to the precise dosing and effectiveness associated with this method.^[40] However, intratracheal instillation is not a physiological route for application, and results obtained from these studies may not be transferable to aerosol applications in humans. On the contrary, inhalation method uses aerosol technique by which we can get more uniform distribution with great penetration. However, this method is more costly and difficult to measure the exact dose in lungs. The deposition of drug by aerosol administration in the pulmonary airway mainly takes place by three mechanisms:-gravitational sedimentation, inertial impaction, and diffusion. If the drug particle size is comparatively bigger, then, deposition takes place by first two mechanisms

where, either sedimentation occurs due to gravitational force or inertial impaction occurs due to hyperventilation. When the particle size is smaller they deposit mainly by diffusion mechanism, which in turn is based on the Brownian motion. Apart from the pulmonary morphological aspects and ventilatory parameters size of the particles or droplets and the geometry is quite important. The size of particle or droplet in terms of diameter along with the surface electrical charges, shape of the particulate matter if it is a fiber and hygroscopy also having profound influence on drug deposition through pulmonary route.^[41] The term mass median aerodynamic diameter is used and it depends on size, shape, and density of the particulate system.

Techniques of Making Particulate Matter For Lung Delivery

Many conventional techniques have been reported to produce DPI formulations. However, these methods have number of limitations, such as particle size, size distribution, shape and poor control over powder crystallinity. These problems can be rectified by specialized milling techniques. Jet-milling of drug under nitrogen gas with new nanojet milling instrument is the most suitable method for creating nanoparticles meant for pulmonary drug delivery. Here, some of the important techniques are discussed in brief.^[41]

Spray Drying Technique

Spray drying is an advanced pharmaceutical manufacturing process used to efficiently produce respirable colloidal particles in the solid state.^[42,43] Spray drying was explored in the 1980s as an alternative means of producing fine particles for pulmonary delivery. In this process, the feed solution is supplied at room temperature and pumped to the nozzle where it is atomized by the nozzle gas. The atomized solution is then dried by preheated drying gas in a special chamber to remove water moisture from the system, thus forming dry particles. This method is more promising in producing the particles of above 2- μm size. This method is reported to have better control on particle formation and hence can be easily translated to large scale production. This process is also suitable for thermolabile materials, such as proteins and peptides, because mechanical high- energy input is avoided in this process. More importantly, spray-drying can result in uniform particle morphology.^[44,45]

Spray Freeze Drying Method

This method was explored for pharmaceutical application in early 1990s. It is an advanced particle engineering method, which combines spray-drying and freeze-drying processing steps. It involves spraying the drug solution into liquid nitrogen as a freezing medium

followed by lyophilization.^[46] This method produces light and porous particles and high fine particle fraction with improved aerosol performance and almost 100% yield at subambient temperatures^[47] Thermolabile protein and peptide substances, such as insulin^[48] and plasmid DNA^[49] can also be formulated into dry powder inhalation products. However, this is an expensive process restricted for only expensive drug.

Supercritical Fluid Technology

The basic feature of this process is the controlled crystallization of drugs from dispersion in supercritical fluids, carbon dioxide. This method has been used in the pharmaceutical field for production of microparticles, nanoparticles, liposomes, and inclusion complexes. This method is used for the production of particulate pulmonary drug delivery systems containing proteins and peptides, and also used to improve the formulation properties of certain drug candidates.^[50,51]

Solvent Precipitation Method

This method involves sono-crystallization and micro-precipitation by opposing liquid jets. Crystalline drug particles with narrow size distribution could be prepared by direct controlled crystallization^[52] Inhalable particles can be produced by rapid precipitation from aqueous solutions using antisolvents. Recently, ultrasonic radiation has been applied to control the precipitation. Various antiasthmatic drugs were prepared using the sono-crystallization technique.

Double Emulsion/Solvent Evaporation Technique

This method involves preparation of oil/water emulsion with subsequent removal of the oil phase through evaporation. The organic solvent diffuses out of the polymer phase and into the aqueous phase, and is then evaporated, forming drug- loaded polymeric nanoparticles. By this method, biodegradable polymers have been intensively investigated as carriers for respiratory solid drug nanoparticles.

Particle Replication In Nonwetting Templates

Particle replication in non wetting templates (PRINT) is top-down particle fabrication technique developed by Dr. Joseph DeSimone and his group. This technique is able to produce uniform-sized organic micro- and nanoparticles with complete control of size, shape, and surface functionality, and helps in loading of small organic therapeutics, proteins, peptides, oligonucleotides, RNA contrast agents, radiotracers, and fluorphores.^[53-55]

CONCLUSIONS

It can be concluded from the whole literature that pulmonary drug targeting offers several advantages which can improve drug's efficacy and reduce unwanted systemic side effects. It provides a large surface area for absorption, thin alveolar epithelium permitting rapid absorption, absence of first-pass metabolism, rapid onset of action and high bioavailability. Since pulmonary disorders are engulfing a major portion of population every day, it has been a major issue of discussions and debates. Various new technologies for pulmonary drug delivery as well as novel targeting methodologies have directed researchers to focus upon this route as a more preferred one for targeting various pulmonary disorders.

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