



DRUG DELIVERY TO THE LUNGS

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ABSTRACT

Drug delivery to the lungs is an innovative and challenging area in pharmaceutical research. Pulmonary drug delivery can be used as an alternative to oral delivery. These systems can be best utilized for both local and systemic actions. Pulmonary delivery may be used for wide range of drugs. This drug delivery system fetches interest because it can be used for water insoluble drugs also. More than 40% of new drugs have low bioavailability through oral route. Pulmonary route provides enhanced bioavailability, reduced toxic effect and targeted means of delivery. The important requirement of a pulmonary delivery system is to provide perfect deposition of drug in lungs. This can be achieved by preparing optimum size of the particles. The optimum size can be achieved by anyone of the techniques like micronization, spray drying, supercritical fluid crystallization or solvent evaporation. Carriers like microparticles, nanoparticles, liposomes can be used in lung targeting. Drug delivery devices also play important role in depositing the particles in lungs. This article focuses on the technologies, devices and carriers used in pulmonary drug delivery system.

Keywords: Lungs, pulmonary drug delivery, particle size, carriers, drug delivery devices.

1. INTRODUCTION

Low bioavailability is one of the major issues for many drugs.¹ Currently lots of approaches are involved to enhance the bioavailability. One such approach is pulmonary drug delivery which aids to increase the bioavailability and also to achieve targeting of drug to lungs.² Pulmonary delivery is an interesting area in pharmaceutical research to increase the drug efficacy, and also to reduce the possible side effects produced by other systems of drug delivery. Pulmonary delivery is not a new one. Already this system was widely accepted in ancient period for lung and other respiratory diseases. In 17th and 19th century inhalation therapy for TB was studied in Europe.³ Some drugs are readily absorbed by alveoli and directly enter the systemic circulation. Due to advancement of devices in pulmonary delivery, it is possible to deliver larger doses into the lung. Targeting of drugs to specific receptors in lung and to retain the drug for sustained action are the major challenges in pulmonary drug delivery systems.

When developing a pulmonary drug delivery system one of the important parameter to be considered is particle size. Optimum particle size is very important for targeting of drug to lungs. If the particle size is too small they will exhale and if it is too large, they may affect the oropharynx and larynx.⁴ Drug can be delivered by using carriers like cyclodextrins, microparticles, liposomes, nanoparticles etc.⁵

1.1. Anatomy & physiology of the respiratory system

The main function of the respiratory system is to inhale oxygen for blood which is supplied to all parts of the body and to exhale carbon dioxide.

The respiratory tract is divided into upper and lower parts. The upper respiratory tract consists of nose, nasal cavity and pharynx whereas the lower consists of larynx, trachea, bronchi and the lungs. The terminal parts of the bronchi are alveoli. The alveoli are the functional unit of lungs. Alveolar cells may be of type I or type II. Type I cells are small, non-phagocytic, membranous pneumocytes. These cells are approximately 5µm in thickness. Type II cells are large, granular, epithelial pneumocytes. These cells are approximately 10 to 15µm in thickness.⁶ The alveoli consist of surface active lining component which contains phospholipids. Presence of this surface active lining affects compound solubility and can produce interaction of drug with cell surfaces and receptors. The surface active lining possesses anti-inflammatory property.⁷

1.2. Mechanism involved in deposition of particles in lung^{8,9}

The mechanism involved in deposition of particles in lung may be impaction, sedimentation, interception or diffusion.

Impaction

Impaction occurs due to air flow changes. Usually impaction occurs in case of large size particles and it is extent in the bronchial region.

Sedimentation

Sedimentation occurs if the gravitational force is more than the air flow force. Sedimentation is settling of particles due to low air flow. This mechanism occurs in larger size particles. Particles of hygroscopic nature may enlarge in size as they pass through air passages and sediments.



Interception

Deposition by interception may occur due to physical size or shape of particles. Interception occurs in small airways.

Diffusion

Deposition may occur by diffusion if the particles size is less than the diameter of 0.5 micron. Brownian movement takes place in diffusion principle. Usually diffusion occurs when there is low air flow.

1.3. Advantages of pulmonary drug delivery^{10,11}

- Quick onset of action
- Ease and convenience of administration
- Avoids first pass metabolism
- Targeting can be easily achieved.
- Comparing to oral dose, pulmonary dose is less
- Reduced side effects
- Degradation of drug by liver can be avoided

1.4. Disadvantages of pulmonary drug delivery systems^{11,12}

- Improper dosing
- Stability problems
- Some drugs may produce irritation or toxicity
- Some drugs may be retained in lungs and clearance of the drug may be difficult
- Difficulty in producing optimum particle size
- Amount of drug delivered per puff is less which may be ineffective for certain Therapy

2. METHODS INVOLVED IN PRODUCTION OF DRUG PARTICLES FOR PULMONARY DELIVERY

Particle size plays an important role in development of pulmonary drug delivery systems. The optimum particle size required for pulmonary delivery is 1- 5µm. Commonly used methods to achieve this particle size are micronization, spray drying, spray-freeze drying, supercritical fluid crystallization and double emulsion method.

2.1. Micronization¹³

By using suitable solvent, crystals are formed which is then micronized to the required size. Energy requirement is huge for micronization. Polymorphic transformation and amorphous formation are the major problems in this process which makes the method unsuitable for many cases

2.2. Spray drying^{14,15}

Spray drying is a process that involves conversion of liquid into dried particles. In this process liquid is sprayed into droplets and then dried by using hot air chamber. Spray drying can produce uniform particle size. This major

disadvantage of this method is it's not applicable for thermolabile drugs.

2.3. Spray freeze drying¹⁶

Spray freeze-drying is a combination of spray drying and freeze drying process. In this method there is no heating step. Sublimation mechanism is used to remove the water from the particles. So this method can be used for thermolabile drugs.

2.4. Supercritical Fluid Crystallization^{17,18}

Supercritical fluids are fluids (gases and liquids) at a temperature and pressure, above their critical points. At this critical point, the fluid exists as a single phase. These fluids have advantage of both liquid and gas. Supercritical fluids are highly compressible at critical point.

This method may be divided into two types namely precipitation from supercritical solutions and precipitation using supercritical fluid as non-solvents or anti-solvents. Carbon dioxide is widely used as supercritical fluid because of its applicability for heat sensitive materials.

2.5. Double Emulsion/Solvent Evaporation¹⁹

This technique is commonly used for preparation of microspheres and nanoparticles. This method involves preparation of o/w emulsion and subsequent removal of oil phase. The o/w emulsions are prepared by emulsifying the oily phase containing the drug, polymer and organic solvent in an aqueous solution containing emulsifying agent. The solvent is removed by evaporation resulting in drug loaded polymeric nanoparticles. Examples of polymers used are PLA, PLGA etc.

3. DRUG DELIVERY DEVICES

For pulmonary route, drug delivery devices play an important role equivalent to that of formulation aspects. It is difficult to administer a formulation through pulmonary route without suitable drug delivery devices. The drug delivery devices are given below.

1. Metered Dose Inhalers
2. Dry Powder Inhalers
3. Nebulizers:

- Jet Nebulizers
- Ultrasonic Nebulizers

3.1. Metered Dose Inhalers (MDI)

A metered dose inhaler is a drug delivery device designed to provide fine droplets of medicament, usually with a particle size of less than 5µm. The formulation is filled in the device, and the dose required is released by actuator. MDIs contain propellants like chlorofluorocarbons and hydrofluoralkanes.²⁰ The major inconvenience of the MDI is patient must be educated to operate the device. Another problem in MDI is less quantity of drug can be



delivered in lungs. Generally 10–20% of the expelled dose is deposited in the lung.²¹

3.2. Dry Powder Inhalers (DPI)

The name itself indicates that the formulation is in solid form. Dry powder inhalers (DPIs) contain drug alone or mixed with suitable carriers. DPIs have potential advantages like stability, ease of handling and relatively cheap when compared to MDIs. There is no need of harmful propellants like CFC which may create environmental pollution. The DPIs may be designed for single or multi dose purpose. The powder can be filled in hard gelatin capsules.²² The capsule containing the dry powder is opened within the device. The remaining capsule residue must be thrown away after use. Again new capsule can be filled in the device for next dose.

3.3. Nebulizers

There are two types of nebulizer, namely jet and ultrasonic. In jet type nebulizer, liquid is converted and sprayed as fine droplets by use of compressed gas. Jet nebulizers contain baffles in the chamber which prevents the exit of large droplets from the device. The aerosol from a jet nebulizer comprises of sprayed droplets and solvent vapor. The disadvantages include time consumption, drug wastage etc. Only 10% of the dose is actually deposited in the lungs by jet type.²³

In ultrasonic type, aerosol droplets are produced through high frequency vibrations of a piezoelectric crystal. Requirement of assisting healthcare person and expense, limits this type of nebulizer usage.

4. DRUG DELIVERY CARRIERS FOR PULMONARY SYSTEMS

Drugs for pulmonary delivery require some carriers for targeted action in lungs. Carriers may help in reducing the side effects also. The carrier systems used for pulmonary drug delivery are given below.

4.1. Inert Carriers

If dose of the drug is very less, it is difficult to dispense. To overcome the difficulty the drug is dispensed with aid of bulk carriers. Lactose can be used as a carrier to provide accurate dose and also to improve flow property.²⁴

4.2. Biodegradable Polymers

Biodegradable polymers can be used as carrier in pulmonary drug delivery to achieve sustained and controlled release. Biodegradable polymers such as polylactic acid, poly glycolic acid can be used as carriers.²⁵

4.3. Microparticles

Microparticles serve as a potential carrier for pulmonary drug delivery systems. Microparticles are hollow spherical particles with diameter of about 100 to 500µm in which drug is encapsulated. Controlled and targeted delivery can be achieved by microparticles. Commonly used polymers are polylactic acid, polylactic-co-glycolic acid,

albumin, gelatin, chitosan and dextran. Stability and higher drug loading can be achieved by microparticles.²⁶

4.4. Nanoparticles

Nanoparticles are particles ranging from diameter of 1 to 1000 nm. These particles may also be used as carrier for pulmonary route. Controlled and targeted delivery can be achieved by nanocarriers. Biodegradable polymers like poly ε-caprolactone, poly lactic acid, gelatin, chitosan are used to provide sustained action.²⁷

4.5. Liposomes

Liposomes are one of the carriers used in pulmonary drug delivery. These carriers may be helpful in increasing the residence time of drug to provide sustained release. Liposomes can be targeted to the alveolar surface which may be used to treat various lung diseases. The advantages of liposome include improved stability, reduced side effects, targeted action and reduced local irritation. Liposomes have been used for treatment of neonatal respiratory distress syndrome. The increase in drug uptake by the lungs can be achieved by coating the liposomes with polysaccharide derivatives.²⁸

5. APPLICATIONS OF PULMONARY DRUG DELIVERY SYSTEMS

Applications of pulmonary drug delivery systems were presented in table 1.

6. CONCLUSION

Pulmonary drug delivery is one of the oldest drug delivery systems. But still now it is widely used due to its potential advantages. The drugs which produce GI irritation can be administered by pulmonary route. One of the major hurdles in this system is achieving the optimum particle size, which determines the targeted delivery of drug to lungs. Number of methods like micronization, spray drying, spray freeze drying, supercritical fluid crystallization and double emulsion are available to achieve the expected particle size. But still it requires further study to select the suitable methods and additives based on the nature of the drugs. Carriers like microparticles, nanoparticles, liposomes etc. can be used in pulmonary delivery. Although advanced technologies are available, in some cases, the product may fail to achieve its goal. To make an effective pulmonary drug delivery system, it is necessary for a research professional to have thorough knowledge in the areas of disease condition being treated, lung anatomy and physiology, method of achieving optimum particle size, carrier suitability and drug delivery devices.



Table 1: Applications of pulmonary drug delivery systems

Drug	Uses	Carriers	Method
Budesonide ²⁹	Anti-asthmatic	Microparticles	Spray drying/ Supercritical fluid crystallization
Rifampicin ³⁰	Anti-tuberculosis	Nanoparticles	Solvent evaporation
Isoniazid ³¹	Anti-tuberculosis	Nanoparticles	Multiple emulsion technique
Pyrazinamide ³¹	Anti-tuberculosis	Nanoparticles	Multiple emulsion technique
Naringin ³²	Combat oxidative stress	Microparticles	Spray drying
Capreomycin ³³	Anti-tuberculosis	Liposomes	Spray drying
Sumatriptan succinate ³⁴	Acute migraine	Nanoparticles	Reactive precipitation Spray drying
Tobramycin ³⁵	Antibiotics	Nanoparticles	Emulsion-based spray-drying
Doxycycline ciprofloxacin ³⁶	Antibiotics	Microparticles	Spray-drying
Salbutamol sulphate ³⁷	Anti-asthmatic	Microparticles	Spray drying
Amikacin ³⁸	Antibiotics	Microspheres	Freeze drying
Ketotifen fumarate ³⁹	Anti-inflammatory	Liposomes	Freeze drying
Tacrolimus ⁴⁰	Immunosuppressant	Liposomes	Spray drying
Ipratropium bromide ⁴¹	chronic obstructive pulmonary disease	Microspheres	Supercritical fluid crystallization
Erythromycin ⁴²	Antibiotic	Microparticles	Double emulsion/solvent evaporation

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