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A REVIEW ON CONCEPT AND VIGILLANCE OF PULMONARY DRUG DELIVERY SYSTEM

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ABSTRACT

Pulmonary drug delivery is primarily used to treat condition of the airways delivery locally acting drugs directly to their site of actions. Delivery of anti-asthmatic and other locally acting drug directly to their site of action reduces the dose needed to produce a pharmacological effect. While the low concentration in the systemic circulation may an also reduce the side effects, provide the rapid response and minimize the required dose since the drug is delivered directly to the conducting zone of the lungs is a needle free several technique have been developed. The overall drug delivery depends on its efficacy, quality, safety and to achieve such a attributes. New dispersible formulations and drug aerosol delivery devices for inhalable peptide, protein and various small molecules become of increasing interest for the treatment of systemic and respiratory diseases. The important requirement pulmonary delivery system is a provide perfect deposition of drug in lung this can be achieved by preparing optimum size of the particles. Pulmonary route as an Non-invasive administration for systemic delivery and therapeutics agents (mainly peptide and protein) due to the fact that the lungs could provide a large absorptive surface area but extremely thin (0.1µm and 0.2µm) absorptive mucosal membrane and good blood supply. Aerosol administration of peptide-based drug also play important role in the treatment of pulmonary and systemic disease and the unique cellular properties of airway epithelium offers a great potential to deliver new compounds. As the relative contribution from the large airways to large alveolar space are important availability. It's a treatment of illness, asthma, include chronic obstructive pulmonary disease etc. which maximum patient comfort and compliance.

KEYWORDS:- Pulmonary drug delivery system, delivery devices, lungs, particles, airways, clearance, aerosol.

INTRODUCTION

Pulmonary route used to treat different respiratory diseases from last decade the inhalation therapies involved the use of leaves from aromatic plant, basams and myhrr. Pulmonary drug delivery is primarily used to treat conditions of the airways delivering locally acting drug directly to their site of action.[1] The type of drug application in the therapy of the diseases is a clear from of targeted drug delivery. The latest and probably one of the most promising applications of the pulmonary drug administration is

1. It is use to achieve systemic absorption of the administered drug substance.
2. Particularly for those drug substance that exhibit it a poor bioavability when administered by the oral route, as for e.g. Peptide or protein, the respiratory tract might be a convenient port of entry.[2]

Advances in the use of lungs as a portals for delivery of medication to the blood stream have greatly expanded the potential application of pulmonary delivery. This advance technology was initially applied to the systemic delivery of large molecules such as insulin, interferon-b or q-1 proteins inhibitor.[3]

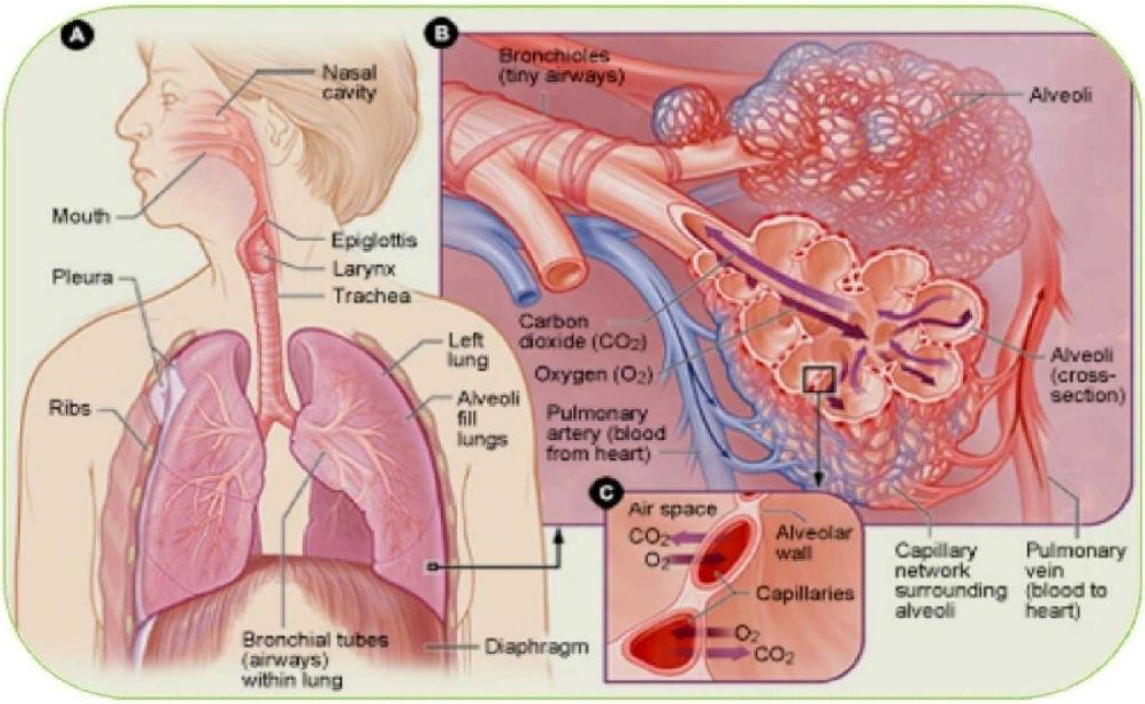

Fig. no. 1: Respiratory tract.

Anatomy and physiology of lungs

The human respiratory system is complicated organ system of very close structure function and relationship.[4]

The system consist of region.

1. Conducting airway
2. Respiratory region

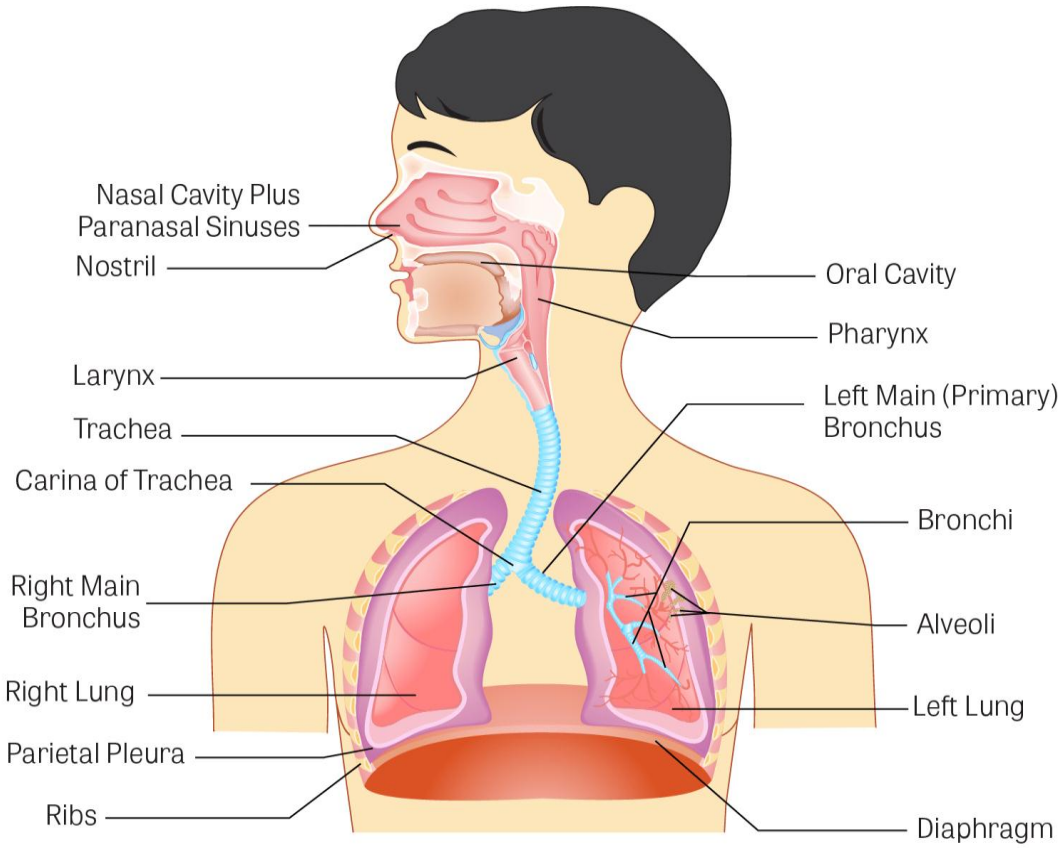

Fig. no. 2: Anatomy and Physiology of lungs.

The airway is further divided into, any folds, nasal cavity and the associated sinuses and the nasopharynx, oropharynx, larynx, trachea, bronchi and bronchioles. The respiratory region consist of respiratory bronchioles, alveolar ducts and alveolar sacs, the human respiratory tracts is branching system of air channels with approximately bifurcations from the mouth to the zero alveoli, The major task of the lung is gas exchange, by adding oxygen to and removing carbon dioxide from the blood passing the pulmonary capillary bed.[4,5]

Fig. no. 3: Lung region.

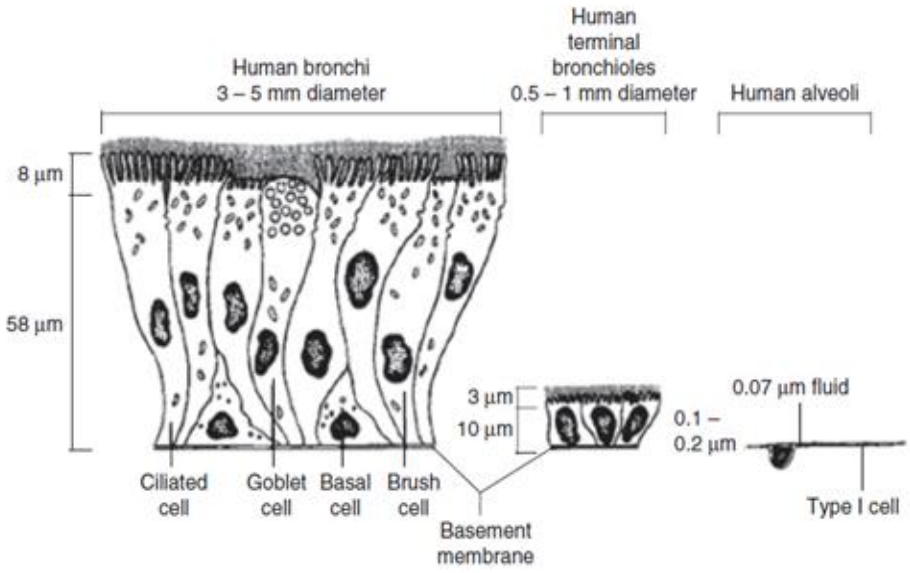

Fig. no. 4: Type of cell present in lung.

Bronchi

1. Cillated cells
2. Goblet cells
3. Brush cells
4. Clarae cells

Bronchioles

1. Cleated cells
2. Clara cells

Alveolli

1. Type 1 – Premocytes

2. Type 1 – Pneuocytes

Factors affecting an pulmonary drug delivery system[6,7]

1. Mechanism of particle disposition in the airways.

a. Inertial impaction
b. Sedimentation
c. Brownian diffusion

2. Physiological factor affecting partial disposition in the airway

a. Lung morphology
b. Inspiratory flow rate
c. Co-ordination of aerosol generation with inspiration
d. Tidal volume
e. Breath holding
f. Disease states

3. Pharmaceutical factor affecting aerosol disposition

a. Aerosol velocity
b. Size shape
c. Density
d. Physical stability

Mechanism involved in deposition of particles in lungs[8,9]

1. Impaction

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

2. Sedimentation

Occurs if the gravitational force is more than air flow force. Sedimentation is settling of particles due to low air flow. This mechanism occurs in larger size particles, particles are hydroscopic nature may enlarge in size as they pass through air passage and sedimentation.

3. Interception

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

4. Diffusion

May occurs by the diffusion in the particle size is less than the diameter of 0.5micron. Brownian movement take [place in diffusion principle. Usually diffusion occurs when there is low air flow.

Advantages[10]

1. Avoid first pass metabolism.
2. Reduced side effect.
3. Comparing oral dose, pulmonary dose is less.
4. Quick onset of action.
5. Degradation of drug by liver can be avoided.

Disadvantage[11]

1. Some drug may produce irritation and toxicity.
2. Stability problems.
3. Difficulties in producing optimum particle size.
4. Amount of drug delivered per putt is less effective for certain theory.

Disorder of lungs[10,11]

1. Acute bronchitis
2. Chronic
3. Bronchiectasis
4. Asthma
5. Pulmonary hemorrhage
6. Pulmonary emphysema
7. Pulmonary edema

Challenges

1. Low efficiently of inhalation system.
2. Less drug mass per puff.
3. Poor formulation stability for drug.
4. Improper dosing reproducibility.

Formulation approaches[12]

Pulmonary delivered drugs are rapidly absorbed except large macromolecules drug. Which may yield low bioavability due to enzymatic degradation and/or low mucosal permeability. Pulmonary bioavability of drugs could be improved by including various permeation enhancers such as surfactant, fatty acid and saccharides, chelating agent and enzyme inhibitors such as protease inhibitors. The most important tissue is the protein stability in the formulation, the dry powder formulation may need to buffers to maintain the pH, and surfactant such as Tween to reduce any chance of Aggregation. The stabilizers such as sucrose are also added in the formulation prevent denaturation during prolonged storage. Pulmonary bioavability largely depends on the physical properties of delivered the protein and it is not the same for all peptide and protein drugs. Insulin liposomes are one of the apporoaches in the controlled release aerosol preparation. Intratracheal delivery of insulin liposome (dipalomytialphosphatidyl choline, cholesterol) have significantly enhance the desired hypoglycemic effect. The coating of disodium fluorescein by hydrophobic lauric acid is also an effective way to prolonged the pulmonary residence time by increasing the dissolution half time. In another method, pulmonary absorption properties were modified for protein/peptide drug (rhGCSF) in conjugation with polyethylene glycol (PEGlation) to enhance the absorption of the protein drug by using intratracheal instillation delivery in rat.

Aerosols

Aerosol preparations are stable dispersions or suspension of solid material and liquid droplets in a gaseous medium. The drugs delivery by aerosol is deposited in the airway by gravitational sedimentation, inertial impaction and diffusion. Mostly larger drug particles are deposited by first two mechanisms in the airways, while the smaller particles get their way into the peripheral region of lungs by following diffusion.

1. Aerosol inhalation
   a. Metered-dose inhaler
   b. Dry powder inhaler
   c. Jet or ultrasonic Nebulizers
2. Intraarterial inhalation

By applying aerosol technique, we could achieve more uniform distribution with greater extent of penetration into peripheral or the alveolar region of the lung. But this more and also

faced with difficulty in measuring the exact dose inside the lungs.in contrary to this, installation process is much simple, not expensive and has non-uniform distribution of drugs.

Classification[13]

Pulmonary drug targeting includes delivery of aerosol directly to the respiratory epithelium, epithelial cells (macrophages) by inhalation. The design of molecules or formulations is an important factor to be considered to promote retention or clearance from the lung. Depending on the mode of drug releasing action. Pulmonary drug delivery system are broadly classified into major three types.

1. Immediate release system (excipient drug mixture such as lactose drug mixture).
2. Controlled release a system (liposomes, Micelles, Nano and Microparticles based on polymer).
3. Sustained release system (Microsphere based on polymer).

Previous treatment

a. Inhalers (Used in asthma)[14,15,16]

Three types of inhalers are most commonly used by people with asthma. the three types of inhalers are Metered Dose Inhalers (MDIs), Dry Powder inhalers (DPIs) and Nebulizers. Metered Dose Inhalers contain one type of bronchodilating drug described above in liquid form. The Dry Powder Inhaler is the second most used type of inhaler and its contains in a Dry Powder form.

i. The MDI uses a chemical propellant force in order to push the drug out of the inhaler and into the lungs. the propellant force has been provided by a chemical called Chlorofluorocarbons when pressure is applied to the inhaler, the drug is converted into a mist form and these small particles can be easily inhaled into the lungs. One drawback of MDIs is the Hand-Lung coordination that is required to effectively deliver the medicine to the lungs. In order to preeurize to liquid form of the drug and thus transform the drug into an aerosol ,an effective inhalable form, one must press the canister portion of the inhaler while simultaneously breathing in. The hand-lung coordination is very hard to do for most people and dose not allow for the maximum amount of drug to be delivered to the lungs these patient see lower effectiveness. This can improved with a piece of equipment called as a spacer.

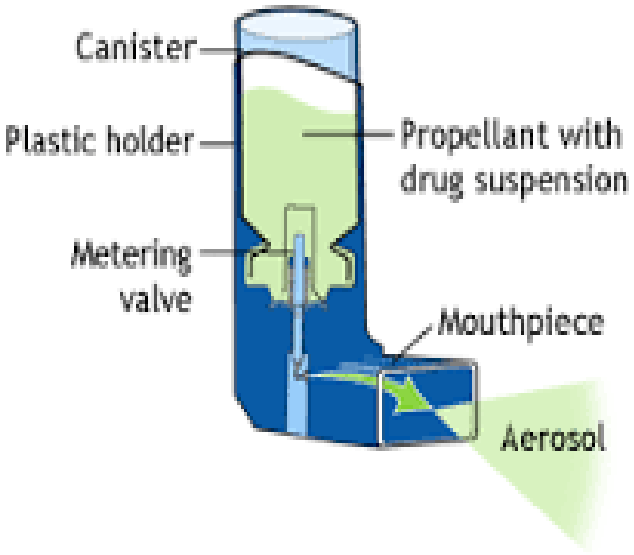

Fig. no. 5: Metered dose inhaler.

ii. The second type of inhaler in the Dry Powder Inhaler and is also used by many people suffering from Asthma in this from of drug delivery the drug is supplied in a powder from and will be broken into a small particles in aerosol from upon the inhalation by the patient. the DPI uses the inspiration forces of breathing in order to deliver the medication from the inhaler to the lungs.

Adv:- Environmental sustainability with a propellant free design.

Little or no patient coordination required

Formulation stability

Disadvantage:- Deposition efficiency dependent on patient inspiratory airflow

Potential for dose uniformity problems

Development and manufacturing more complex and expensive.

iii. The third type of inhaler is the nebulizer, the nebulizer is bulky, big, non-portable machine that uses air in order to create the aerosol from of medication. Air is passed through the liquid medication present in the nebulizer which in the nebulizer which in turn forms small particles of drug in aerosol form. The nebulizer is primarily used in emergency situations, when medication delivered to the lungs must be precise an exact in order to save a person's life and prevent an asthma attack from worsening.

a. Diabetes[17,18]

i. **Injection aids:-** Use push button system and spring loaded-syringe holder and stabilizing guides to aid needle and syringe injections.

ii. **Insulin pens:-** Is suitable and conveniently portable. include dials to manage dosage and plunger to deliver insulin under the skin.

iii. **Insulin jet injector:-** High pressure air mechanism applied to send fine spray to skin.

iv. **Subcutaneous infusion sets:-** Insulin is injected into a catheter that stays in plays in tissue directly beneath the skin.

v. **External insulin pumps:-** External pump is sets to provide a steady dose of insulin continuously throughout the day. The pump is connected to the body by narrow flexible plastic tubing that ends with a needle inserted just under the skin. The devise provides constant blood glucose monitoring.

The most common site of injection are the abdomen, back of the upper arms, the upper buttocks or hips, and the outer sides of thighs. These sites are preferred because there is a layer of fat just below the skin tom absorb the insulin but very few nerves and thus less discomfort.

However , these injection may still be troublesome and patient compliance low, so pulmonary drug delivery is a potentially better treatment. Pulmonary drug delivery and the inhalation of drug particles would be noninvasive and a more convenient alternative for providing insulin.

b. Lung cancer[19,20]

There are several option already use for the treatment of lung cancer.

i. **Surgery:-** If the disease is localized (hasn't spread) doctor can remove the tumor from lungs. These procedure requires that part of or entire lobes of the lungs be removed, decreasing lung capacity and function.

ii. **Chemotherapy:-** If surgery is not a viable option, chemotherapy is used. Chemotherapy is the delivery of cancer fighting chemicals either intravenously or orally. Chemotherapy causes many undesirable side effects.

iii. **Adjuvant Chemotherapy:-** Adjuvant chemotherapy is the combined treatment of surgery followed by chemotherapy.

iv. **Radiotherapy:-** This treatment exposes the patient to ionizing radiation in hopes of killing the cancerous cells. The treatment has been shown to be effective, but its biggest problem is that is it not selective it kills all cell, cancerous or not.

c. Chronic obstructive pulmonary disease[21]

i. Medication via MDI (Inhaler)

Bronchodialators: Taken to relax the muscle lining the lungs, making the airways more flexible during the respiration.

Glucocorticosteroids: Taken to reduce inflammation in the lungs and used usually in more serious cases COPD.

Rehabilitation

A programmed designed by medical professionals that may modify a patients lifestyle and diet choices, introduce exercise routines, and offer counselling and therapy sessions.

ii. Oxygen therapy

Oxygen is delivered to a patient during session in which pure oxygen in delivered through tubes or mask, to improve overall oxygen absorption by the system and organs and behalf of the patient.

iii. Surgery

Usually a last resort for patient suffering from suffering COPD that have not seen improvement under other methods of treatment.

Bullectomy:- Damaged alveoli walls yield larger cavities called bullae. Bullectomy involves the removal of very large bullae to free the lungs and facilitate breathing. The dark brown show the bullae resulting from collapsed or deteriorated alveoli walls. These structures are removed in bullectomy.

Lung Volume reduction Surgery (LVRS): damaged lung tissue is extracted from lungs.

Lung Transplant: Potential for many serious complications.

Current trend in pulmonary drug delivery technology

a. Particle engineering for pulmonary drug delivery[22,23,24]

Particle engineering is science that combines the principles of microbiology, chemistry, formulation science, aerosol and powder science, nanotechnology etc. advancement in inhalation therapy, has led to the generation of novel particle technologies, for drug formulation administered to through respiratory route. This has necessitated the use of new potent medicines for various pulmonary disorder such has asthma COPD and various infectious disease through accurate and consistent dosing inhalation devices. The particle

engineering technology has increase the fraction of the formulated dose range drugs including bronchodilators. Steroids and anti-infectives, proteins/peptide and eventric oxide to reach to the targeted site.

b. Agglomerated vesicle technology for pulmonary drug delivery[22,23,25]

This are micronized particles in which agglomerates of core nanoparticles are chemically linked with either permanent such as carbonyl or cleavable such as a disulfide or ester bonds. Such cleavage between the links can be controlled to modulate the drug release, it is an expansion of liposomal based system. Ciprofloxacin is one such example produced by this technology.

Current trend in pulmonary drug devices

a. Metered dose inhalers (MDI)[26]

A metered dose inhaler is a drug delivery system that produces a medicament in the from of fine having aerodynamic particle size of less than 5microns for direct inhalation to the airways.it is use for the treatment of the respiratory disease such asthma and COPD. these device can be categorized in two types such as , accurately metering device (e.g. Spray, pump, pressurized metered dose inhalers (pMDIs), Unit/Bi-doses)and non or poorly metering devices.

b. Dry powder inhalers (DPI)

Three general types of DPIs are available in the market depending upon the dose size.

c. Unit dose devices[27]

Single-dose powder inhaler consists of a powder containing capsule place in a holder which gets open within the device and the powder is inhaled. The used capsule residue shall be replaced by a new capsule for the next dose.

d. Multi dose devices[28]

Multi-unit dose devices utilize individually prepared and sealed drug doses.

e. Air classifier technology in devices[29]

Air-classifier technology system consist of a classifier, also called as cyclone chamber.it is based on the principle of de-agglomeration of rotating particles by applying high inertial forces.

f. Multiple air classifier technology[30]

It is the modified form of air classifier technology involving parallel arrangement of multiple classifier chambers to increase the dose of aerosolization.

g. Nebulizers[31]

Previously three general types of nebulizer system were known and available in the market viz. ultrasonic, piezo mesh and air jet (pneumatic) pneumatic nebulizers are further categorized in to two types such as concentric and cross flow nebulizers now days never technique have introduced nebulizer that have replaced the classical nebulizer by adaptive aerosol delivery(AAD) technology wet nebulization methodologies.

Current trend in pulmonary drug delivery formulation

a. Nano aerosols[32]

It is pulmonary targeted drug delivery system for the treatment of lung disease such as lung cancer, respiratory, systemic infection and gene delivery for the treatment of cystic fibrosis and to deliver drug effectively to the lungs due to the inherent characteristics of the aerosol and the rout of administration loaded first line anti tubercular drug, isoniazid in chitosan-TPP nanoparticles that show controlled targeted drug delivery to the lungs in order to enhance bioavability and to reduced dose frequency.

b. Liposomes[13]

Several studies on anti-tubercular (ATD) loaded liposomal formulation have revealed their sustained and targeted release ion the lungs with minimum biodistribution through the systemic circulation.

c. Lactose carrier systems[33]

Recent advances in inhalation therapy have introduce lactose as an efficient carrier for respiratory drug formulation. Lactose carrier system consists of smaller subunits of lactose which must be evaluated of drug-carrier adhesion. Variation in drug-carrier forces and influence on drug aerosol performance prior to their use. Drugs blended with a coarse carrier system (63-90µm), such as lactose (α-lactose monohydrate) serves to be one of the recently used system for dry powder inhaler device due to its favorable toxicological data and easy avability. Its possess favorable size, shape and floe properties which add to its selection criteria.

d. Large porous particles[34,35]

Pulmoshperes are the new type of porous hallow aerosol made up of phosphatidylcholine, the primary component of human lung surfactant. Their large size allows them to remain the alveolar region longer than their nonporous counterparts thus avoiding their phagocytic clearance. For e.g., large porous insulin particles shows more duration of systemic effects thus decreasing blood glucose level for 90 h as a compared to only 4 h in case of small nonporous insulin particles of testosterone shoe high systemic bioavability as compared to conventional particle size. Formulated pulmosheres of rifampicin, an anti-tuberculosis antibiotic, for extended release of drug into lung and systemic circulation.

e. Biodegrable polymers[36,37]

Now days microspheres made pf biodegradable polymers such as PLA and PGA is being studied as sustained release pulmonary drug carriers.

Evaluation parameter of pulmonary drug delivery[38,39]

IN-VITRO

In vitro model is used in this method, it is important that epithelial cells from a light monolayer in order to represent the natural epithelial barrier. monolayer tightness and integrity are classically assessed by measuring Trans Epithelial Electrical Resistance (TEER)and potential difference across monolayer. monolayer of lung epithelial call allow characterization of drug transport, assessment of potential drug and formulation toxicity.

IN-VIVO

Animal study is carried out to get information on drug deposition. Metabolism, absorption and kinetic profile as well as drug and formulation tolerability. non-human primates are used in advance research by contrast, small rodent (mice, rats and guinea pigs)are common models for initial studies on pulmonary drug delivery. Human branching is symmetric, in contrast monopodial branching of non-human primates mammals. Different mucocilliary clearance, Large mammal have longer airways than small rodents.

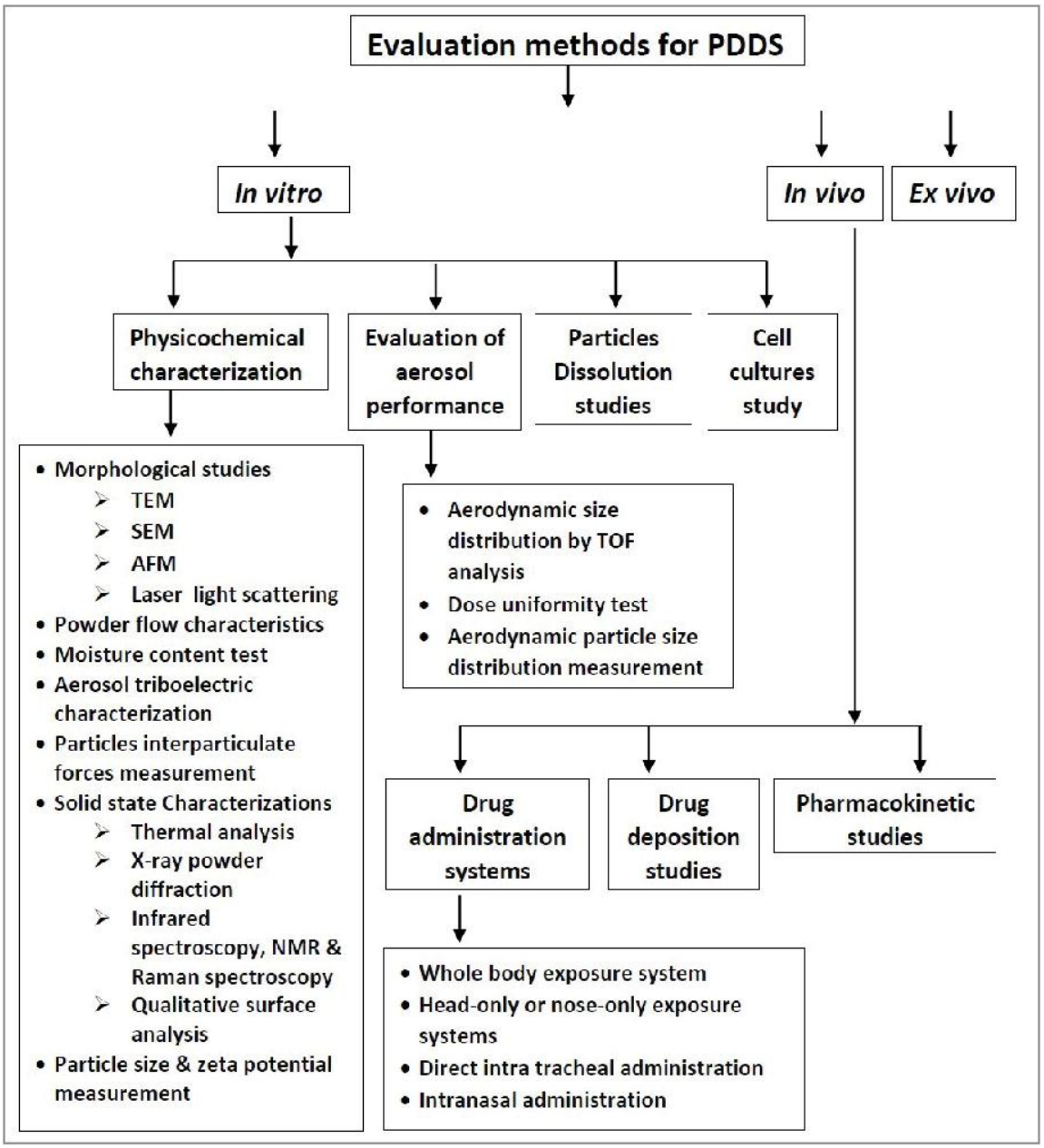

Fig. no. 6: Evaluation method of pulmonary drug delivery.

CONCLUSION

Pulmonary drug delivery is one of the oldest drug delivery systems. It plays important roles in the treatment of various respiratory systemic disease and displays an attractive area of future drug development, it is provide a large surface area for absorption, thin alveolar epithelium permitting rapid absorption. Absence in first pass metabolism. Rapid onset of action and high bioavability. The system is used for achieving the optimal particle size which determines the targeted delivery of drugs to the lungs carriers like microparticles, nanoparticles, liposomes etc., can be used to in pulmonary drug delivery. The various advanced technologies are available to make the effective pulmonary drug delivery system.

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