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# IMPORTANCE OF INHALABLE MICROPARTICLES FOR ANTI ASTHMA AND ITS METHOD OF PREPARATION

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## ABSTRACT

The current study's objectives included maximizing microparticle properties, describing lung deposition, drug release, evaluating cytotoxicity, conducting *in vitro* and *in vivo* studies to determine their pharmacological effects, and evaluating inhalable microparticles carrying anti-asthmatic drugs for both specific and non-specific bronchial inflammatory asthma response. The pulmonary route results in systemic drug release, requires a lower dose, has rapid drug release, fewer first-pass hepatic metabolism and side effects. A synopsis of current developments in inhalable microparticles that have been documented in publications and patents released in the last few years has been offered as a consequence. Recent developments in inhaler technology and major problems in pulmonary drug administration have been briefly explored. Inhaling anti-inflammatory drugs is the most common treatment for inflammatory diseases of the airways, such as asthma. The shape, melting point, size distribution, drug content and drug entrapment %, flow property, in-vitro drug release, and comparative drug release tests with commercial dosage forms of the resulting microparticles were all evaluated. Inhalable microparticles created using a variety of techniques, including emulsion polymerization, dry coating, air suspension, spray drying, and spray freeze-drying.

**KEYWORDS:** Anti-Asthma, Pulmonary drug delivery, Inhalable Microparticles, Mechanisms and preparation.

## 1. INTRODUCTION

Asthma is a chronic, multifaceted condition that affects the lower airways and results in coughing, wheezing, trouble breathing, and heaviness in the chest. Chronic inflammation and airway hyperreactivity are its defining features. The pathogenesis of asthma is complex.[1] Patients typically have reduced airflow and decreased expiratory volume. Additionally, it makes the bronchi hyperresponsive and irritates the respiratory tract. These are not asthma-specific.[2] Inhaled medications are most frequently used to treat asthma and chronic obstructive pulmonary disease (COPD).[3]

The incidence of asthma has increased by 75% since 1994, and the most recent estimates from the World Health Organization place its number at 300 million. Since corticosteroids and other controller medicines have effective anti-inflammatory properties and effectively block a number of inflammatory responses that cause airway hyperresponsiveness, they are frequently used to treat asthma.

Asthma epidemiology, pathophysiology, and aetiology, as well as comparisons and contrasts between asthma in children and adults. The usual classifications employed in large population-based research are complicated by variations in asthma severity, age at which it first manifests, allergic phenotypes versus non-allergic phenotypes, and kind of airway inflammation.[4]

Because certain epidemiological definitions are more sensitive than others, these conditions can lead to misclassification of asthma status. A more sensitive definition of current asthma, for example, is "wheezing breathing in the last 12 months without a cold."[5]

Inhaled medications help asthma sufferers manage their symptoms and lead normal, busy lives.

Inhaled medication administration provides a focused pharmacological therapy for respiratory illnesses. The quick clearance of inhaled medications in the lungs, however, restricts their therapeutic efficacy. Because they can keep the drug load in the lungs and gradually release the drug locally at therapeutic levels, carriers offering prolonged drug release in the lungs can improve the therapeutic results of inhaled medications.

Risks for commonly inhaled particles with geometric diameters between 1 and 3 m and mass densities close to 1 g/cm3 include particle agglomeration in the dry powder inhaler and quick clearance by macrophages in the lung lumen. By designing particles with large geometrical diameters (> 5 m) and low mass densities

(0.4 g/cm3), these limitations could be addressed.[6] High porosity particles (LPPs) have big geometrical sizes that aid in particle dispersion and tiny aerodynamic sizes that come from low particle densities, which effectively allow LPPs to dodge impaction in upper airways and penetrate deeply into the lungs. Big porous particles may be more resistant to phagocytosis by alveolar macrophages due to their large geometric sizes in addition to having better flow properties.[7,8]

Asthmatics may require the usage of an inhaler on a daily basis. The frequency of their symptoms, as well as the numerous types of inhalers accessible, will influence how they should be treated.[9]

## 2. Recent innovations in inhaler technology

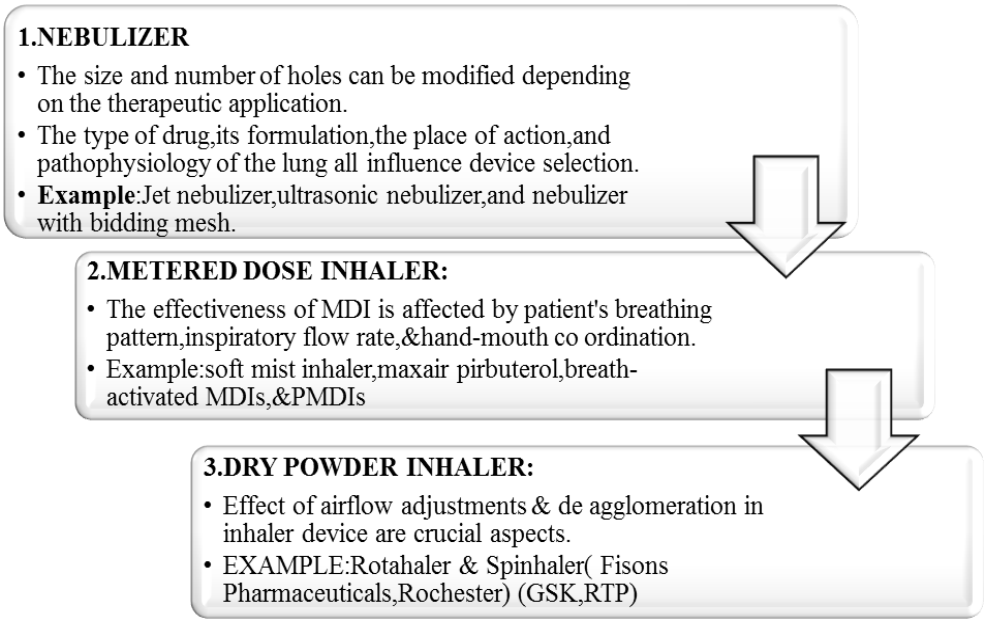


**Fig. 1: Types of inhaler technology.**

## 3. New technology used to treat asthma includes:

Because they preferentially deposit in the deep lung and do not clump together when subjected to shear force, these formulations' nanoparticles, microparticles, Micells, Cyclodextrins, and liposomes are frequently employed for pulmonary administration. Polymeric microparticles have been used in the development of numerous medications, such as corticosteroids, insulin, and chemotherapeutics.[10]

Polymeric microparticles have been widely used as a pulmonary delivery vehicle for therapeutic pharmaceuticals due to its many advantages, including the regulated release of encapsulated medications and simplicity of administration in a minimally intrusive way. However, employing small microparticles and nanoparticles (1–5 µm in diameter) for effective pulmonary drug administration offers difficulties since they are susceptible to alveolar macrophage removal and mucociliary clearance in the lungs. on the other hand, big microparticles (10–20 µm in diameter) with a low density (i.e., high porosity) are good for deep lung administration because their size prevents them from being cleared by alveolar macrophages.[11]

## 4. Particles deposition site

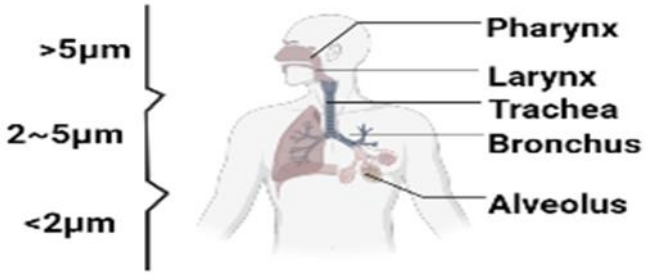


**Fig. 2: Diagram of particle deposition site.**

Particle Stratification Pattern The amount of particles that have accumulated in the respiratory system is determined by the patient's physiological conditions, such as breathing patterns and overall lung health, as well as the physicochemical characteristics like shape, size, bulk density, hygroscopicity, and moisture content of the inhaled particles.[12,13]

Following inhalation of the particles, Brownian diffusion, impaction caused by inertial forces, and gravity-induced deposition are the main mechanisms for deposition. Smaller particles (1-5µm) settle in the bronchiolar region, while bigger particles (>5 µm) settle in the upper respiratory tract. Brownian diffusion also deposits particles bigger than 1 µm in deeper alveolar areas, whereas exhalation expels particles less than 0.5 µm.[14,15]

**5. Superior to other methods for pulmonary administration. The benefits of medication administration via particulates include:**

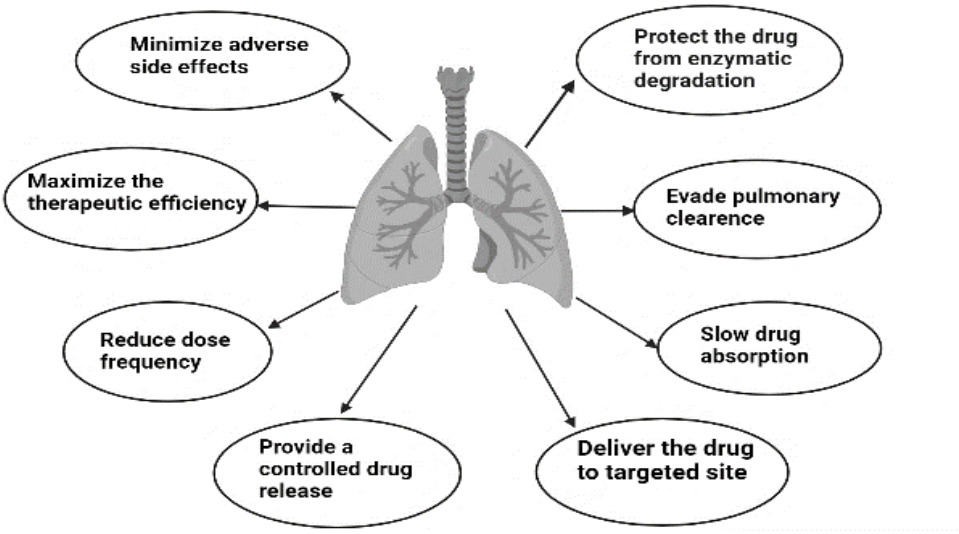


**Fig. 3: Benefits of microparticles for pulmonary administration.**

**6. Application of pulmonary medication delivery systems based on microparticles for the treatment of various respiratory illnesses.**

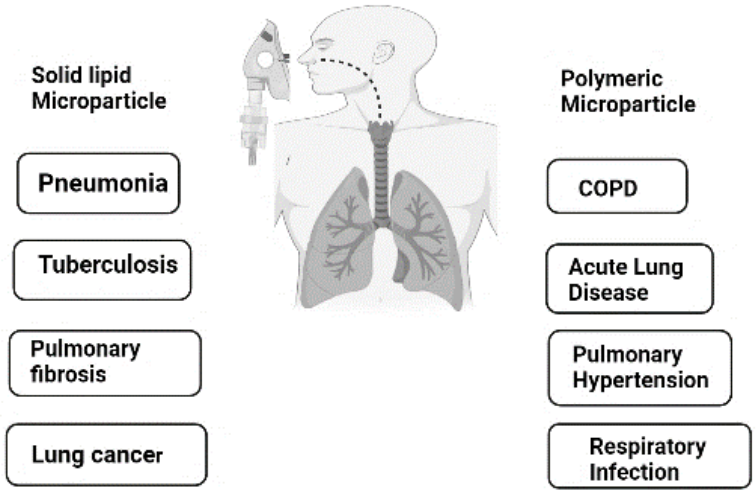


**Fig. 4: Application of microparticles for treatment of various respiratory illness.**

**7. Mechanism of respiratory drug deposition**

- **Diffusion:** When gases move from a high-pressure to a low-pressure area, they disperse. By transferring gas between the alveoli and lung capillaries, this includes both internal and exterior respiration. The movement of cells and capillaries inside internal tissues is known as interior respiration. Perfusion describes the blood flow to tissues and organs.

Alveoli receive blood from capillaries, allowing carbon dioxide and oxygen to spread. Until equilibrium is attained, where the concentration gradient on both sides of the membrane is equal, diffusion continues. Since the body constantly needs oxygen and constantly emits carbon dioxide, the respiratory system is constantly working to achieve equilibrium. The respiratory system's diffusion is in charge of supplying the body's cells with oxygen so they can produce energy and removing carbon dioxide as waste.[16]

- **Sedimentation:** This is a physical phenomena that occurs when particles in the airway are there for a long enough period of time and have enough mass to be deposited by the force of gravity. This is more prevalent in the last five generations of bronchial tubes, when slower airflow results in prolonged residence times.[17]

- **Impaction:** Aerosol particles follow a trajectory as they move through the airway as a result of this physical phenomenon, as opposed to the respiratory tract's contours. 2 Particles with enough momentum, which is the result of their mass and velocity, are affected by centrifugal force and collide with the airway wall as the airflow suddenly changes direction. The first 10 generations of the bronchial tree, where the air flow is turbulent and moving quickly, are where this mostly happens. This effect predominantly affects particles larger than 10 m, which are primarily kept in the oropharyngeal area, especially if the drug is administered using dry powder inhalers (DPI) or metered-dose inhalers (MDI).[18]

- **Interception:** A particle is intercepted when it physically contacts the surface of the airway due to geometrical characteristics. For pure interception, it is assumed that the particles move in a Brownian motion with very little inertia and inertia settling.

The particle makes contact because of its physical size rather than deviating from its original air streamline. For elongated particles, like fibres, which are long in one dimension but have small enough diameters to reach the narrow airways, interception is particularly crucial since it depends on the ratio of particle size to airway diameter.

- **Electrostatic deposition:** Electrically charged particles need electrostatic attraction to exist. When numerous mutually charged particles push these particles in the direction of the airway wall, they can deposit. A charged particle can also be drawn to a neutral surface by image forces in the absence of mutual repulsion. The particle itself generates an image force that is equivalent to its own charge but acts in the opposite direction. Only when the particle is in close proximity to the surface are image forces generated, which are weaker than coulombic forces. Particles that have just being created have more surface reactivity than older aerosols. When compared to older paricles, these newly created particles may be more charged, which leads to higher deposition.[19]

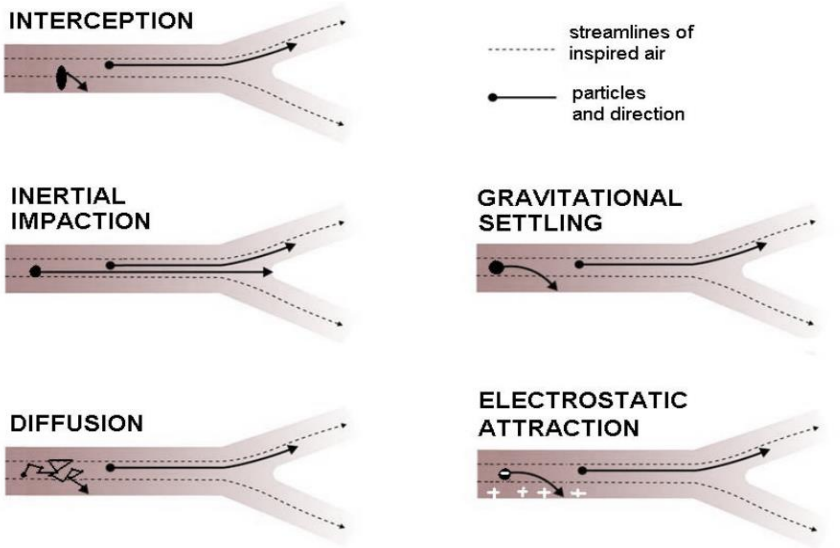


**Fig. 5: Mechanism of respiratory drug deposition.**

**Table 1: Representative conventional drugs for asthma.**

| Drug name | Drug type | Benefits | Disadvantages |
|---|---|---|---|
| Beclomethasone Dipropionate | Inhaled Corticosteroid | Reduce airway swelling | Dry mouth, irritated throat, voice changes |
| Budesonide | Inhaled | Prevents allergic reaction | Nasal dryness, |

| | | | |
|---|---|---|---|
| | Corticosteroid | | Nausea, vomiting |
| Theophylline | Xanthine derivative | Relaxes airway muscles | Nausea, abdominal pain,headache, diarrhea |
| Salmeterol xinafoate | Long acting beta agonist | Prevents brancho constriction | Hives, headache, blurred vision |
| Montelukast sodium | Leukotriene receptor agonist | Prevents branchospasm | Numbness, pain in the arms or legs, sinus pain |
| Fluticasone furoate | Inhaled Corticosteroid | Reduce airway swelling | Dysphonia, oropharyngeal Candidiasis |
| Mometasone | Inhaled Corticosteroid | Reduce airway swelling | Dysphonia, oropharyngeal Candidiasis |

## 8. Inhalable microparticles preparation method


**Fig. 6: List of preparation of inhalable microparticles.**

1. **Emulsion polymerization technique:** Emulsion polymerization is a simple method for dispersing monomers in an aqueous phase after 533tabilizing them with surfactants. The resulting microparticles with a High yields are produced by low polydispersity indices.[20]

2. **Dry coating method:** After being lyophilized, lactose and the generated microparticles are both fed to the MechanofusionTM equipment chamber at the same time. This equipment is made up of a revolving chamber with a speed range of 200 to 1600 rpm, a stationary blade, and a scrapper. Lactose, which is easily deposited inside the lung, has microparticles on its surface.[21]

3. **Air suspension technique:** Dale E. Wurster created the air suspension technique in 1940; it is sometimes referred to as the Wurster procedure. Wurster coating is the method of encapsulating various particles using differential airflow to produce cyclic material movement in a fluidized bed.[22]

4. **Spray drying technique:** Compared to earlier technologies, this method marks a turning point for the pharmaceutical business. It is an efficient dehydration technique that can be quickly customised. The inlet-outlet temperature, nozzle diameter, mixing of air or solution volume, pressure, feed rate, and atomizer type are some examples of the variables that have an impact on the size and shape of the microparticles.[23]

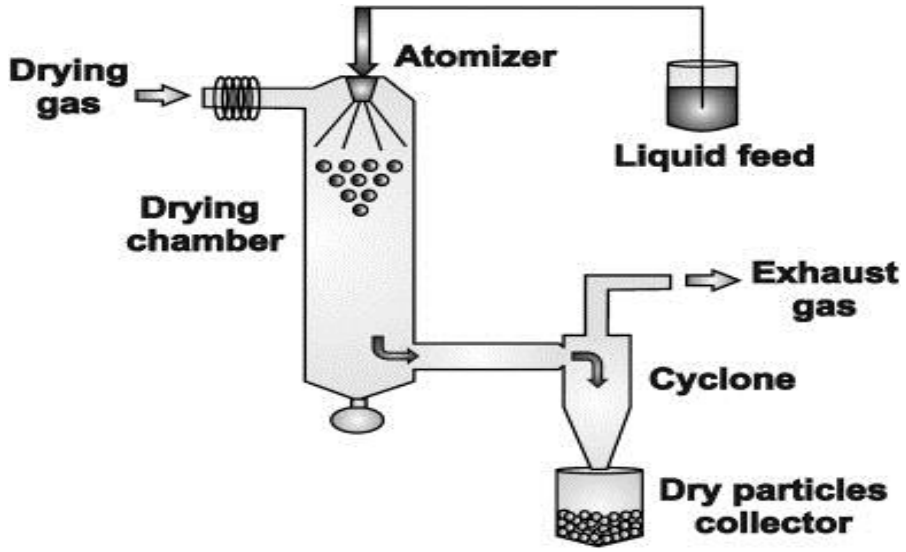


**Fig. 7: Schematic diagram of spray drying.**

5. **Spray freeze-drying method:** Spray-freeze drying is an excellent choice for materials that are extremely sensitive to heat, particularly lipid microparticles, which cannot endure heat for long periods of time during a standard drying technique. The microparticles are immobilised in a glassy matrix of polysaccharide in this approach, which protects them from various stresses such as freezing and dehydration. However, a crystallisation inhibitor is used to keep the microparticles and polysaccharide amorphous.[23]

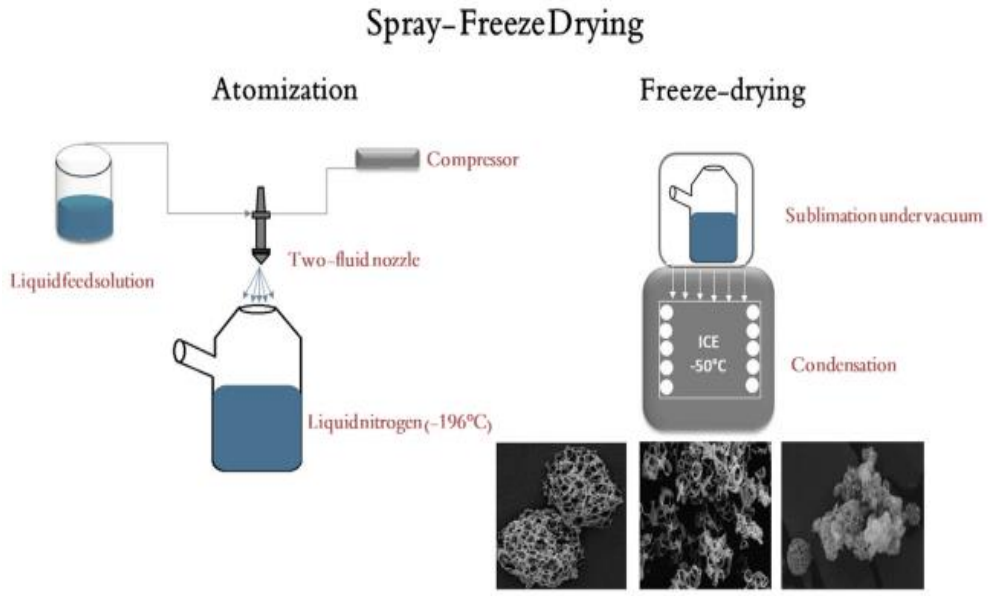


**Fig. 8: Schematic diagram of Spray- freeze drying.**

9. **Chracterization**

1. **Morphology:** The size of microparticles has a big impact on how well they work in vivo. Particles larger than 100 nm remain at the administration site until phagosomal clearance. Between 10 and 80 nm, there is the greatest lymphatic absorption and node accumulation.[24]

2. **Particle size analysis:** Coulter counters or the laser light diffraction (LD) method are typically used to gauge the size of microparticles that are 3 m or greater. The span-value of the distribution makes it possible to compare the results using the LD values d0.1, d0.5, and d0.9. The following equation is used to calculate the Span-value, which represents the size

**Span=d0.9/d0.1/d0.5**

2.1. **AFM, or atomic force microscopy:** AFM is a method that uses surface profiling to reveal details about the surface of nanoscale microparticles.[25]

**2.2. Coulter counter:** In the particle examination of microparticles for intravenous usage, a Coulter counter is highly useful. because it provides a precise particle number per volume unit for a range of particle sizes.[26]

**2.3. Image analysis:** To more precisely establish the shape, image analysis employing microscopic imaging techniques (such as scanning electron or light microscopy) is useful. The aspect ratio (AR), Feret-diameter, and roundness are used to describe the shape. P is the perimeter, and A is the projection area, so R = P 2 4A calculates the degree of roundness (R). AR = Dmax is used to compute the aspect ratio. The orthogonal diameter Do closest to Dmax is the largest. Cascade impactors can be used to study the aerodynamic size distribution, which is a sign of particle deposition during inhalation (powders, aerosols, and sprays). Particle size and density, in addition to shape, have an impact on the flow during deposition.[25]

**3. Physicochemical properties**

**3.1. Density:** Density has an impact on a particle's ability to float as well as its subsequent disintegration or enlargement. This value can be determined using the use of helium gas in pycnometric analysis. 20.[27]

**3.2. Porosity:** How water is absorbed, swollen, reconstituted, and released is significantly influenced by the porosity of microparticles. Mercury porosimeters can be used to directly monitor this parameter.[28]

**3.3. Flowability and Compressibility studies:** For particles utilised in dry environments, flowability, Carr's index, Hausner ratio, and angle of repose are important considerations. The official pharmacopoeias' recommendations may be followed for these tests(For instance, the United States and European Pharmacopoeias).[29]

**3.4. Mechanical test:** A texture analyzer can determine the tensile strength and elasticity of microparticles by measuring compression force in relation to distance, calculating maximum compression force and hardness, and then evaluating the mechanical resistance of the shell or matrix structure.[28]

**3.5. Swelling:** To analyse how dry particles behave in various scenarios, an equilibrium swelling study can be done. The swelling index (S%) can be calculated by multiplying the original particle diameter (di) by the initial particle diameter following reconstitution (ds).

$$S\ (\%) = di/di\ 100\ ds$$

**3.6. Wetting property:** Contact angle measurements can be used to determine the excipients' wetting properties.[29,30]

**3.7. Efficacy of drug entrapment:** The real loading and entrapment (encapsulation) efficiencies can be used to determine the success of drug loading: The true drug loading is as follows: DL (%) = drug (mg) (drug + polymer) (mg) 100 (3) Typically, the entrapment efficiency value is determined using the following formula: EE (%) = drug content entangled (mg) 100 mg is the theoretical medication concentration. (4) The process's nature and circumstances, as well as other variables, all have an effect on the optimal entrapment efficiency (100%). [31]

**4. Drug administration:**

**4.1. In vitro: Multiparticulate dissolution test:** USP 42-NF 37 recommends various procedures for dissolving multiparticulate formulations. The equipment and size are determined by how effectively the dose form functions in the medium and volume. When sink conditions are available, a reciprocating cylinder (USP Apparatus 1), a compendial rotating basket (USP Apparatus 2), or a flow-through cell (USP Apparatus 4) can be used to test non-disintegrating coated beads. Depending on the pH, ionic-character polymers behave differently. There are various pharmacopoeial approaches that can be performed to demonstrate whether drug release is independent of or dependent on the medium's ionic strength. The pH of the medium varies depending on the application, ranging from 1.2 to 7.5 in a hydrochloric acid, phosphate, or acetate solution.[32]

**4.2. *In vivo* :Drug administration systems:** In a whole-body exposure system, animals are placed inside a sealed plastic chamber that is connected to a dry powder aerosol generator or a nebulizer.[33] When compared to other exposure methods, pulmonary administration is less stressful,[34] although animals can also absorb certain drugs through their skin, noses, and gastrointestinal tracts. Only the animal's head or nose comes into touch with the aerosol when the animal is secured in an exposure chamber using a head-only or nose-only exposure device. Because of the system's unique architecture, it is feasible to administer to one or more animals. It offered several advantages over other types of exposure, including the capacity to prevent drug uptake via the skin and avoid drug exposure through the skin.[35] Despite the availability of commercial exposure systems, some handmade head-only or nose-only aerosol exposure system models have been developed and tested[36] Fluids are injected into the trachea using oral gavage needles and the MicroSprayer®[37 ] By creating powder aerosol or utilising a powder-insufflator, dry powders can be injected intratracheally. This is an

easy way to deliver pulmonary medications. Some advantages of this exposure system include control over medication dose delivery, the absence of drug loss in the exposure device, the avoidance of nasal passages, and the capacity to target different respiratory organ regions. For Powder insufflators are used to treat both respiratory and non-respiratory disorders, including COPD, asthma, pulmonary embolism, lung cancer, tuberculosis, diabetes, osteoporosis, and cancer.

It was also reported that immune stimulant and immune suppressant medications were administered. In addition to local nasal drug delivery, animals can receive intrapulmonary drug administration via intranasal administration.[38-39]

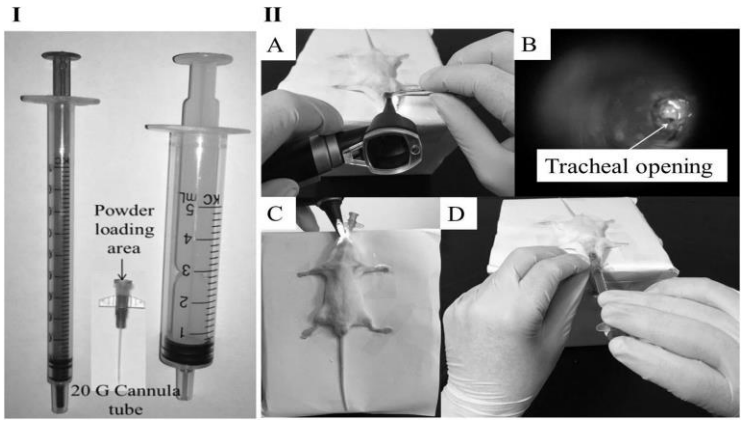


**Fig. 9: Administration via the trachea.**

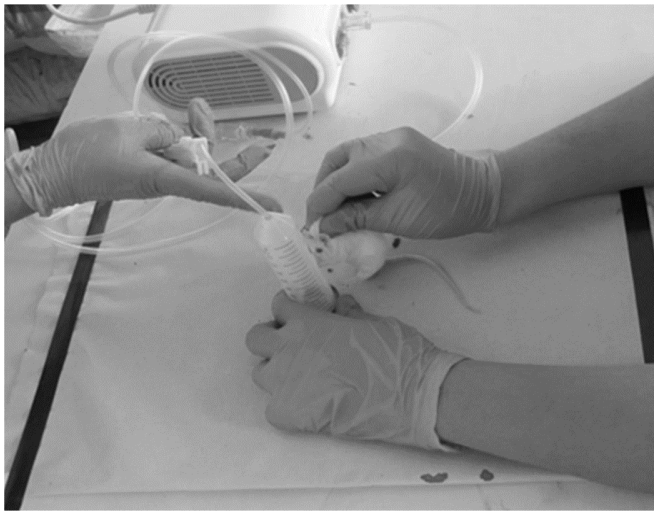

**Fig. 10: Administering Inhalable Microparticles to Mice Using a "Nose-Only" Inhalation Apparatus.**

**4.3. Studies relating to drug deposit:** When assessing the composition and efficiency of devices for pharmaceutical aerosols, The distribution of the drug in the lung and how much is deposited there are important considerations. Both invasive and non invasive methods can be used to measure the drug deposition in test animals. The non invasive method is useful because it offers in vivo pharmacokinetic information on when to administer a medicine. Dolovich investigated the concepts and uses of PET, gamma scintigraphy, and single-photon emission computed tomography (SPECT) as animal imaging techniques investigations. Such imaging techniques have been used to address inhalation toxicity and pulmonary medication delivery with success. When non-invasive methods are insufficient to sufficiently test the medication, invasive approaches, It is possible to utilise, such as bronchoalveolar lavage (BAL), for insoluble, inert particles.[40]

**4.4. Pharmacokinetic studies:** Using compartmental or non-compartmental techniques, pharmacokinetic parameters are calculated after a medication has been inhaled. By adding physiologically based pharmacokinetics, It is possible to create a mathematical model that describes how a specific medicine is distributed (PBPK).[41]

## CONCLUSION

The development of particles with the ideal physicochemical properties would allow for effective dry powder aerosolization and deposition in the deep lungs. As noted in this review, picking the right particle preparation methods is equally crucial. Despite technical

difficulties, this area has recently acquired popularity, and more advancements are anticipated with a better understanding of the physicochemical characteristics of particles and the biology of the respiratory system. To establish novel medication delivery systems for the lungs, characterisation tools must be developed in order to assess these inhalation products. Using the current compendial and standardised testing methods, which include becoming more and more necessary as time goes on. With a deeper grasp of product testing and characterization techniques, a viable pulmonary medication delivery system can be created.

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