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DRY POWDER INHALERS FOR PULMONARY DRUG DELIVERY SYSTEM

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ABSTRACT

Pulmonary drug delivery remains the preferred route for administration of various drugs. Dry Powder Inhalers are found to be good alternatives to metered-dose inhalers (MDIs) has accelerated recently in a bid to find effective products that do not use chlorofluorocarbon propellants. A wide range of Dry powder inhalers (DPIs) devices are currently available on the market to deliver drugs into lungs with a view to maximize drug delivery with low variability and high efficacy. For the good DPI formulation particle size of API must be present in size range about 1-10 µm for maximizing its effect and also guarantee that the patient gets the same dose every time at different airflow rate. DPI are formulated using four types of formulation strategies such as; Carrier Free, Drug Carrier, Drug Additive, Drug Carrier Additive. In the last decade many patents have been filed claiming improvement in aerosol performance of dry powder inhalers through the use of (i) incorporation of fines of carrier particles to occupy active sites on the surface and use of hydrophobic carriers to facilitate deaggregation through reduced surface energy and particle interaction (ii) reducing aerodynamic diameters through particle engineering and incorporating drug into porous or low particle density, and/or (iii) preparing less cohesive and adhesive particles through corrugated surfaces, low bulk density, reduced surface energy and particle interaction and hydrophobic additives.

KEYWORDS : *inhalation therapy, pulmonary drug delivery, carrier lactose, physico-chemical characterization; particle size.*

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INTRODUCTION [1, 2, 3]

Rapid development in pulmonary drug delivery by inhalation aerosols in the past decade has led to novel invention of aerosol delivery devices and new formulation technologies capable of producing particles of defined characteristics for improved delivery. It is mainly used for systemically acting drugs such as peptide and protein, as well as for drugs that are designed to act locally on the lungs themselves for the treatment of asthma,

Chronic Obstructive Pulmonary Diseases (COPD) or Cystic Fibrosis (CF). Small doses of drugs are delivered direct to their site of action, leading to a rapid onset of action and a low incidence of side effects. For almost 8,000 years asthmatics inhaled medicine by smoking it. This changed in the 1930s with the invention of the electric nebulizer and again in the 1950s with the invention of the metered dose inhaler (MDI). A third option that has been slowly gaining momentum is the Dry Powder Inhaler (DPI). Dry Powder inhalers are versatile delivery systems which may require some degree of dexterity to operate, although one of the objectives of recent developments has been to simplify their operation. Typically they dispense a metered quantity of powder in a stream of air drawn through the device by the patient's own inspiration. In the design of a new powder inhaler consideration must be given to optimizing the formulation of the powder containing the drug substance to ensure chemically stable and consistent doses over a range of inhalation conditions; and design of powder inhaler itself to produce a convenient device that is comfortable and easy for the patient to use.

Pulmonary drug delivery by Dry Powder Inhalers (DPIs), got too much importance now a days, by virtue of its propellant free nature, high patient compliance, high dose carrying capacity, drug stability and patent protection, has encouraged rapid development in recent past to realize full potential of lungs for local and systemic treatment of disease.

IDEAL PROPERTIES OF DRY POWDER INHALERS [4]

For designing an ideal DPI delivery system, several characteristics would be important for both clinical efficacy and patient acceptance.

The following are the characteristics required from an ideal dry powder inhaler:

Effective dosing

- Uniform dose
- Targeted, optimized, and with multiple-dose capability delivery
- controlled respirable fraction
- The ideal particle size would be 2-5 um for optimal drug delivery.
- Inhalation of dose-independent aerosol generation
- Bolus of aerosol available at the beginning of an inhalation
- Operable at low inhalation flow rates

Efficient device

- Good environmental production
- In-process controls for quality
- Cost effective
- Compact, portable, cheap and reusable
- Clear comparative data for complaint

Easy to use

- Simple operation
- Dose counter
- Dose-ready indicator
- Patient feedback of dose administration

Pulmonary drug delivery system is mainly classified into three classes

1. **Nebulizer:** [5]

In this system, aerosols are generated from solution or suspension of drug in an appropriate solvent. Nebulizers are very efficient at creating mists of extremely fine droplets with good pulmonary deposition. Its devices which is widely used to deliver aerosol therapy, especially in children. A nebulizer works by taking some liquid medicine and blasting compressed air or oxygen through it at a high speed, turning it into a mist that is then inhaled into the patient's lungs. They use an electronic air compressor to build up this pressure.

- **Advantages of Nebulizer** [6]

1. High doses of medication can be used.
2. Multiple drugs can be used in single system, it can be used for combination therapy if drug are compatible with each other.
3. Effective with tidal breathing.
4. High dose and dose modification is possible
5. Easy formulation handling, requires less co-ordination of patient and Drug concentration can be adjusted if desired

6. It can be used in very young or very old, debilitated patients or those in acute distress
7. It works with low inspiratory flows or volumes

- **Disadvantages of Nebulizer** [7]

1. Equipment is large which is difficult to transport portability issue.
2. Variability in performance between different nebulizers.
3. Pressurized gas source is requiring in jet.
4. Possibility of drug degradation with ultrasonic stimulation and temperature rise.
5. An external power source is needed, either electricity or compressed gas, making it less portable
6. They are generally less portable and are more expansive
7. With inadequate cleaning, medicine can be easily contaminated

2 Pressurized Metered Dose Inhaler (pMDI) [7, 8]

pMDI are the device in which medication is mixed into the canister with a propellant and the performed mixture is expelled in precise measured amounts upon actuation of the device. A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. A metered dose inhaler is a handheld device that delivers a specific amount of medication in aerosol form, rather than as a pill or capsule. The MDI consists of a pressurized canister inside a plastic case, with a mouthpiece attached. With an MDI, you press on the device while inhaling the COPD medication directly into your lungs. Its portability makes it easy to use anywhere, anytime. MDIs use a chemical propellant to push medication out of the inhaler

- **Advantages of pMDI:** [5,6]

1. Easy to handle.
2. Highly portable and unlike the nebulizers, no drug preparation is necessary
3. Accurate metering performance, Dose to Dose reproducibility is high.
4. Capacity of large number of does at low cost

- **Disadvantages of pMDI:** [5,6]

1. Limited to the treatment of upper airway conditions because of it emits the dose at high velocity, which makes premature deposition in the oropharynx.
2. Need for coordination of MDI actuation and patient inhalation.
3. Drug content/dose is problematic if pMDI not shaken in case of suspensions.
4. Contains propellant such as Chlorofluorocarbon (CFC) which depletes the ozone layer and also increases the risk of skin cancer, cataract, immune suppression, and global warming
5. pMDI is limited to certain drugs that are stable in a propellant.
6. High pharyngeal deposition might be possible.

3) DPI

Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. DPIs have a number of advantages over other methods of pulmonary drug delivery, for example, direct delivery of drug into the deep lungs utilizing the patient's respiration and are increasingly being explored as a mechanism for the delivery of systemic drugs. Successful delivery of drugs into the deep lungs depends on the integration between powder formulations and the device performance

Advantages of Dry Powder Inhaler [9]

As DPIs has been motivated by the desire for alternatives to pMDIs, so advantages of DPI over pMDI is given as follows;

1. Require little or no coordination of actuation and inhalation.

Incorrect use of pMDIs is still a prevalent problem. It was found that poor coordination of actuation and inhalation caused decreased asthma control in a substantial proportion of patients treated with corticosteroid pMDIs. Whereas DPIs are activated by the patient's inspiratory airflow, they require little or no coordination of actuation and inhalation. This has frequently resulted in better lung delivery than was achieved with comparable pMDIs.

2. *Formulation Stability.*

Since DPIs are typically formulated as one-phase, solid particle blends, so they are preferred as stable formulation. Dry powders are at a lower energy state, which reduces the rate of chemical degradation and the likelihood of reaction with contact surfaces. By contrast, pMDI formulations, which include propellant and co solvents, may extract organic compounds from the device components.

3. *Propellant-free design.*

pMDI contains propellants such as chlorofluorocarbons and hydrofluoroalkanes which are ozone-depleting and greenhouse gases respectively. Production of CFC propellants was banned from 1st January 1996 in order to stop the depletion of ozone layer. So pMDI were replaced by DPI which do not contains propellant. So DPI's are environmental friendly formulation.

Other advantages of DPI are as follows;

1. High drug dose carrying capacities. DPIs can deliver a range of doses from less than 10 mg to more than 20 mg via one short inhalation Minimal extrapulmonary loss of drug due to low oropharyngeal deposition, low device retention and low exhaled loss.
2. As the drug is deposited in lungs, DPI's having fewer side effects as the rest of body is not exposed to drug.
3. Less potential for extractable from device components.
4. Short treatment type

Disadvantages of Dry Powder Inhaler

1. Requires moderates to high inspiratory flow
2. Can result in high pharyngeal deposition
3. Can't able to deliver for all medication

FORMULATION STRATEGIES FOR DRY POWDER INHALER [2]

Efficacy of DPI is mainly depends on flow property of powder which is mainly affected by strong interparticle forces which make the cohesive bulk powder agglomerate. There are three types of interparticle forces, the van der Waals force, the electrostatic force and the capillary force. The van der Waals force becomes noticeable when the particles are sufficiently close (0.2–1.0 nm) to one another and when the particles are small (20 µm or less). Surface roughness, geometrical structure and deformation of individual particles can significantly change the van der Waals force. Electrostatic force can occur by the potential difference when particles of different work functions are brought into contact. The resulting Coulomb attraction makes the powder adhesive. Capillary force comes from fluid condensation in the gaps between particles in close contact, resulting in the formation of liquid bridges between particles. High capillary force comes at the expense of electrostatic force, which diminishes with increasing moisture.

To overcome these difficulties different types of formulation strategies for DPI are as follows Fig. 1

A. Carrier Free
B. Drug Carrier
C. Drug Additive
D. Drug Carrier Additive

A. Carrier Free

In carrier free strategy, active therapeutic ingredient is in the form of a single compound, multi-compound composite or encapsulated particles. There are various production techniques ranging from crystallization and milling, spray drying, supercritical fluid. Crystallization and milling were found unsuitable for preparing pulmonary drugs because they cannot produce optimal particle shape, narrow particle size distribution, low surface energy and avoidance of amorphous material. The inhalation drug particle must have aerodynamic particle size less than 5 µm.

B. Drug Carrier

It is difficult to dispense 1µg to 1 mg of doses of drug into the small blisters for dry powder inhalers. Also it is challenging to entrain powder by inhalation because the desired particles are between 1 and 5µm.So the drug molecules are mixed with larger particle to make them flow better and also to increase the volume of each dose. The geometric size of these carrier particles

can range from 50 to 100 µm. Coarse particles in the bed of fine particles, if mobilized, can act as an additional agitator or turbulence promoter to aid the fluidization of fine particles. Also it bulked up mixture is much easier to dispense in doses containing very small doses of active ingredient. Disadvantage of this strategy includes; carriers generally deposit in the mouth along with many drug particles adhered to them which leads to less drug reaching the lungs. Also poor detachment of drug particles from the surface of the carrier particles, resulting in poor delivery efficiency.

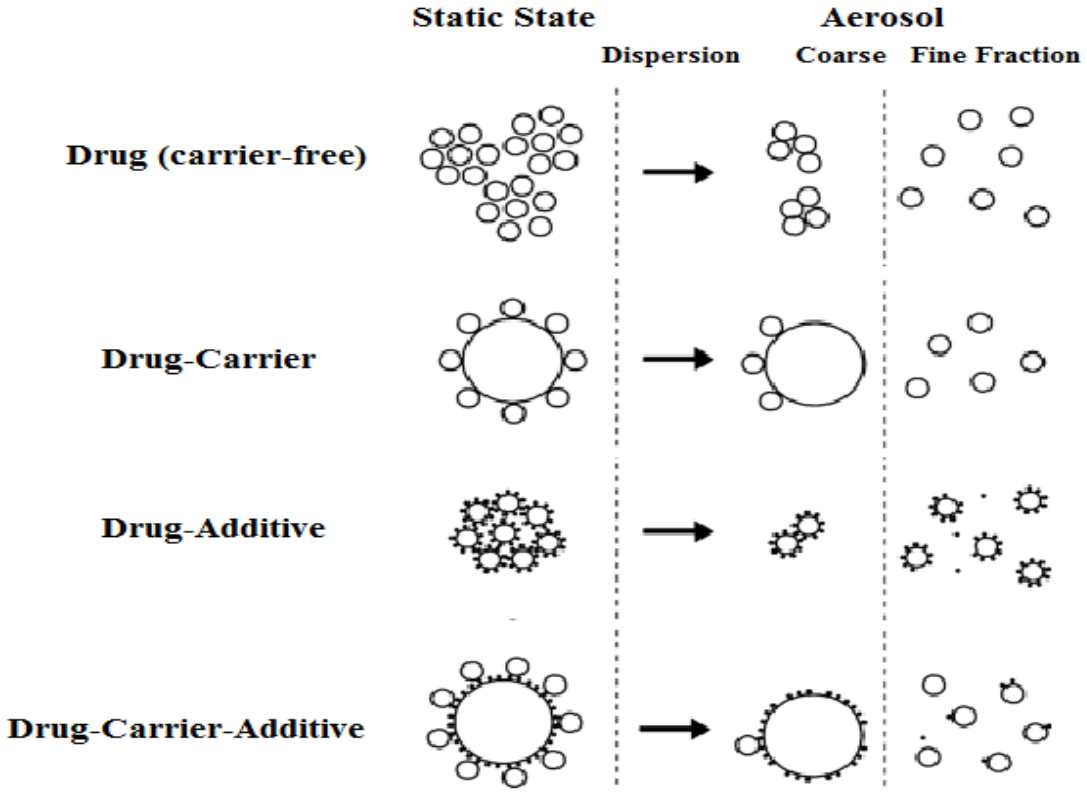

Fig. 1: Different types of formulation strategies for Dry Powder Inhaler [1, 2]

C. Drug Additive:

The addition of finer particles can also improve the fluidization quality of drug fine powders. Van-der Waals attraction is mainly depend on the particle-particle distance so by enlarging the separation distance will substantially reduce the adhesive force and consequently improves the fluidization behavior of fine particles and also improve the flow property of drug. Additives such as submicron silica (0.5–3 wt. %), alumina (29 nm), aerosol 200 (12 nm) were used.

D. Drug Carrier Additive:

An additional particle type may be added to the formulation to improve drug delivery. This additive may be a fine particle such as a fine particle of the same composition as the carrier, which could function as a physical spacer, or possibly by occupying high-energy sites such as clefts in the carrier surface. The most common example of this type of system is the use of fine lactose in a lactose carrier system. An increase in the fraction of

lactose fines has resulted in improved detachment of drug particles from the carrier particle.

Formulation Of DPI [07, 11, 12]

Formulation of DPI mainly includes three steps;

1. API production.

2. Formulation of API with or without carriers.

3. Integration of the formulation into device.

1. API Production

The important requirement of API in case of DPI is particle size. Particle size of drug should be less than 5 µm. It should be in the range of 1-5 µm. Generally the drug particle size is not well controlled during bulk drug production. The drug particle size must be reduced in a separate unit operation to achieve aerodynamic particle size of drug. There are various size reduction techniques such as milling, spray drying, and supercritical fluid extraction.

Various types of mills used for size reduction of drugs but few of them are suitable for DPI to reduce the size in the range of 1-5 µm such as fluid-energy mills, air jet mill; high-peripheral-speed mills, such as the pin-mill; and the ball mill. Basic designs are shown in Fig. 2

Air Jet mill reduces particle size via high-velocity particle-particle collisions. Unmilled particles are introduced into the milling chamber with help of Venture pressure. High-pressure nitrogen or air is fed into grinding chamber through nozzles and accelerates the solid particles to sonic velocities, air pressure is known as grinding presure. The particles collide and fracture. While flying around the mill, larger particles are subjected to higher centrifugal forces and are forced to the outer perimeter of the grinding chamber. Small particles exit the mill through the central discharge stream.

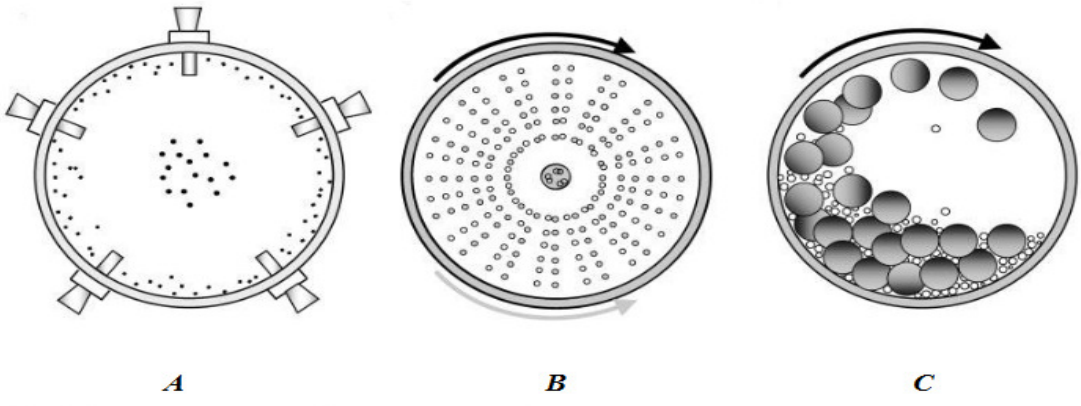

Fig. 2 Cross-sections of 3 mills commonly used to create micron-size particles.

A: Jet mill. B: Pin mill. C: Ball mill [12]

A pin mill uses mechanical impact to grind material, both by particle-particle and particle-solid collisions which can produce 1 µm particles. It is equipped with a series of concentrically mounted pins located on a spinning rotor and stationary stator plate. Powder is fed to the milling chamber and transported through the milling chamber by centrifugal force. The ball mill is a rotating cylinder loaded with drug and balls that grind the drug between each other as they tumble inside the mill.

In spray-drying, the drug is dissolved in water or solvent and sprayed as fine mist into a heated expansion chamber. The droplets dry, leaving behind tiny particles of drug that are collected at the bottom of the chamber.

2. Formulation of API with or without carriers.

The role of carrier in DPI is enhancing the flow property of powder and also aerosol performance

of the cohesive drugs and fine lactose. After drug and carrier (s) have individually been brought to their desired forms, they are combined in the blending process. Inadequate mixing can cause poor dose uniformity. In many cases, inadequate mixing cannot be overcome simply by increasing the mixing time. Mixer selection, rotation speed, capacity, and fill level are all parameter for optimization which affects the blend homogeneity. Different powders may have different mixing requirements, depending on the forces present between the various particles. For low concentration (drug-carrier ratio) blends, geometric dilutions are necessary pre-blending steps.

There are high energy active sites on the surface of the coarse carrier particles thereby leading to a strong adherence of the drug particles to the coarse carriers (Particle size > 20 µm). Addition of fine carrier particles (Fines < 10 µm) saturates the active sites of coarse carrier particles partially to which, then, micronized drug is attached. Hence, drug adheres to passive sites i.e. less energy sites and facilitates the deaggregation of the micronized drug during inhalation leading to enhanced respirable fraction.

3. Integration of the formulation into device.

After the formulation has been blended, it is filled into capsules, multi-dose blisters, or reservoirs for use with the inhaler device. The filling process is automated and depends on the nature of the metering system.

Carriers used in DPI [2, 13, 14]

Dry powder formulations for inhalation are often composed of fine drug particles and inert coarse carrier particles. The fine drug particles adhere to the carrier surface. Interactions between Carrier and Drug particles are mainly dependent on the physicochemical characteristics of the interacting particles such as; particle size, shape, surface morphology, contact area, hygroscopicity of drug and carrier particle.

Lactose is the most widely used carrier as it is approved and generally accepted as safe by most regulatory agencies. Several other compounds such as mannitol, sucrose and sorbitol, glucose, and more recently cyclodextrin, raffinose, trehalose and xylitol have been suggested as possible alternatives to lactose. Alternatives are required if the drug is chemically incompatible with lactose. Spray dried lactose–polyethylene glycol composite particles have also been suggested for use as a carrier particle.

General Equirements for Carrier [15- 21, 27, 28]

Two contradictory requirements must be fulfilled for dry powder formulation. On the one hand, adhesion between carrier and drug must be sufficient for the blend drug and carrier to be stable. On the other hand adhesion drug and carrier have to be weak enough to enable the release of drug from carrier during patient inhalation. Then, the drug will be able to reach the lungs. Particle adhesion force is equivalent in magnitude to the force required for particle detachment. Techniques often used to determine interparticle forces within the powder system include vibration, centrifugation, impact separation and more recently atomic force microscope (AFM). Other requirements are given as follows;

1. Carrier should not react with drug and device.
2. Carrier should be compatible with drug.
3. Improving transport and the proportion of drug that reaches to the lungs.
4. Improving stability of the drug *in vivo*.

Lactose is the most commonly used carrier in DPI formulations nowadays due to availability of it in various inhalation grades with different physical and chemical properties. The advantages of lactose are its low and well studied toxicity profile, physical and chemical stability, compatibility with most of drug substance, broad

availability and low price makes it suitable candidate for DPI's Carrier. [10]

The role of particle size of lactose [25]

The particle size of lactose is one of the most important parameters for DPI's. Lactose are studied extensively for the efficacy of DPI,s [22, 23]. The particle size of lactose influences various parameters like flow, specific surface area, bulk and tapped density, emitted dose and fine particle dose fraction. In general a decrease in particle size will decrease the flow and increase the specific surface area and hence increases the absorption capacity at the site of action. A reduction in mean particle size increases the aerosolisation of various drugs [22, 23]. A reduction in particle size increases the fluidization energy and this could explain the increase of the amount of drug particles that will get into the lung [24].Fine lactose particles have been reported to be of influence for the fine particle mass of drug. In Figure 3 the effect of addition of micro fine lactose and milled lactose to sieved lactose on the fine particle fraction is given. It can be seen that the addition of micronized or milled fines increase the fine particle fraction of Albuterol[9, 25].

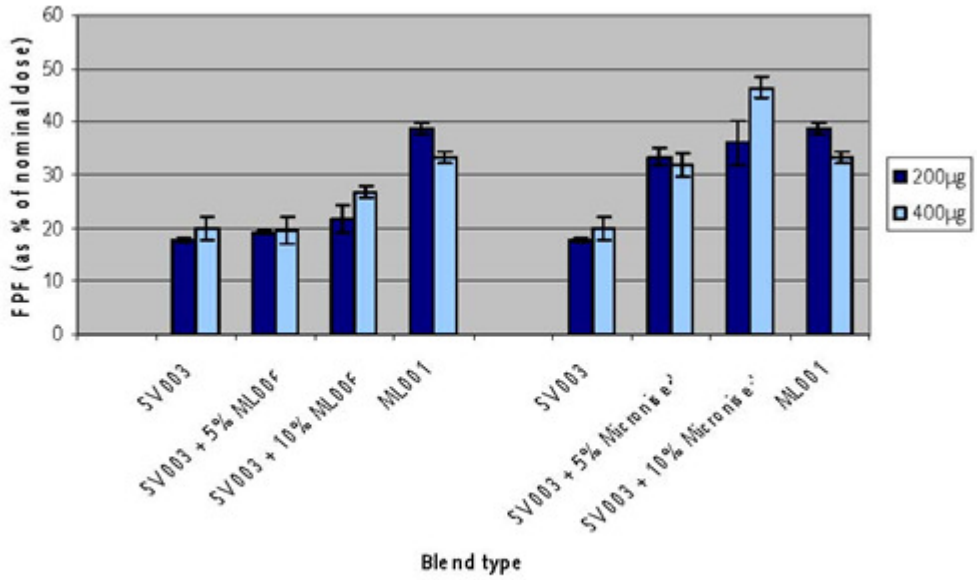

***Figure 3**: Effect of addition of fine lactose on the fine particle fraction (FPF) of Albuterol*

Flow, bulk and tapped density are important for filling the formulation into the device. The requirement to fill low dose of powder into a device (10-20 mg) makes it important to have these parameters under control. Presence of micronized lactose has an influence on the residue of powder that stays into the mouthpiece. This is depicted in figure 4[9]. As a higher amount of powder stays into the mouthpiece the final dose into the lung is lower.

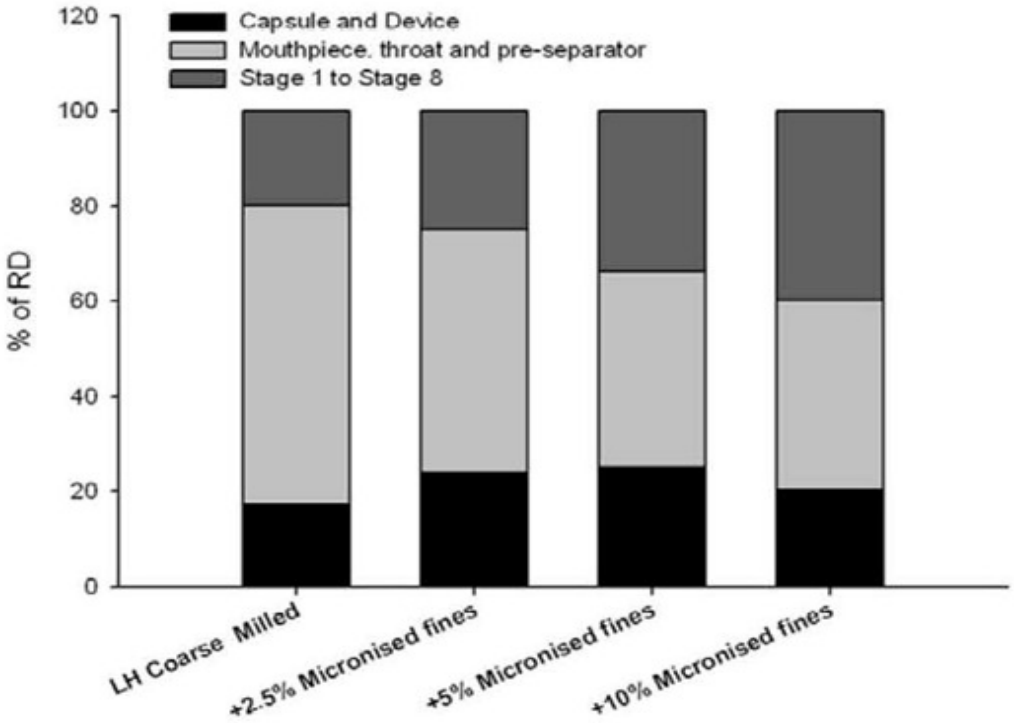

Figure 4: *Effect of addition of micronized lactose and the residueof active in different stages after inhalation.*

Therefore, some literatures refer for the optimization of lactose as carrier base particles for better inhalation and dosing purpose.

Modified Lactose for application in DPIs

Some of the researcher did extensively study on Lactose as it is one of the best carrier for Dry Powder Inhalers. Some common basics in lactose engineering are as follows

Shape modification [10, 26, 27.28]

It was concluded that engineered crystal growth under controlled conditions can enhance the potential inhalable fraction of drug from dry powder inhalers. The use of elongated crystals of lactose was also found to produce a higher inhalation efficiency of albuterol sulfate which was extensively studied by Zeng XM et el .

Surface modification by micronization

Surface smoothing of lactose particle resulted in balanced drug-carrier adhesion force so that the drug-carrier particles could be emitted together and efficiently separated in airflow after emission resulting into better performance for DPI's. [29] There are number of lactose grades for inhalations were studied. Appropriate carrier and drug-to-lactose blending ratio were selected based on drug content and emitted dose uniformity. Aerosol performance was characterized by Andersen cascade impaction in means of Fine particle dose monitoring and Emitted dose. Study done by Helena Schiavone and co-workers on blend formulations of SEDS (solution enhanced dispersion by supercritical fluids) budesonide and albuterol exhibited a significant drug content uniformity (7–9% RSD) improvement over micronized drug blends (16–20% RSD). SEDS formulations demonstrated higher emitted dose and reduced emitted dose variability (10–12% RSD) compared to micronized powders (21–25% RSD) in case of Turbospin, albeit without significant enhancement of the fine particle fraction.[30]

Thus; co-micronization with fine lactose is an efficient and simple strategy to formulate a powder for inhalation with enhanced aerosolization properties, especially for highly cohesive drug substance in dry powder inhalers.

Some other techniques include

Composite lactose Engineering and Engineered lactose-mannitol mixture [10]

Where Lactose particles were prepared by fusing sub units of lactose in saturated lactose slurry, to obtain a larger sized carriers molecule and used for inhalation of salbutamol sulfate. Composite carriers give improved drug aerosol performance. It was suggested that composite based carriers are a potential route to control drug-carrier adhesion forces and variability thus allowing more precise control of formulation performance, this study was extensively done by Young PM and his co-workers . [31]

In other study Mannitol and lactose were co-crystallised to prepare crystals with more desirable characteristics than either lactose or mannitol alone for application as carriers in the formulations of salbutamol sulfate DPIs. Evaluation in In-vitro showed that crystallized carriers shown more efficient delivery of salbutamol sulphate compared to other formulations which contain other commercial grade of carriers. This study was extensively done by Kaialy W and co-workers. [32]

Micronized Lactose and Granulation technology

Recently it was reported and studied that granulation technology can be used for loading drug on micronized Lactose Carrier molecule. This help for better fine Particle dose monitoring and more emitted dose fraction. [25]

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