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DRY POWDER INHALERS: A REVIEW

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ABSTRACT

Now a day the pulmonary route serves as an excellent route for administration of various drugs by inhalation. Inhalation by pulmonary route is most successful, since it reduces the quantity of dose required from other routes of administration and it also avoids hepatic first pass metabolism only smaller fraction of drug gets metabolized by liver. Pulmonary route is utilized to treat different respiratory illness for since a long time. Inhaler is used to treat respiratory diseases like chronic inflammatory disorder such as asthma, chronic obstructive pulmonary disease and other lung diseases. The inhalation delivery can be done via nebulizers, metered dose inhalers and dry powders inhalers.

INTRODUCTION

Dry powder inhalers are the devices that deliver the drug to the lung through the respiratory tract[1]. DPIs are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema, COPD and diabetes mellitus[2]. The DPI formulation prepared by active pharmaceutical ingredients with carrier lactose most commonly corticosteroids used to deliver for lung disease. Excipients improves bulk properties of the formulation such as lactose, L-leucine, Nacl, Pluronic F127, mannitol, glucose, etc., are used to prepared dry powder. The particle sizes of the inhaled pharmaceuticals are very significant where to deposit in the respiratory tract[3]. If the particle size is large the inhaled particles deposit in mouth and throat. The particle size of the inhaled pharmaceutical is 1-5 µm[4]. The inhaled drug moves across air sacs of the lung prior to reaching the blood stream.

Why DPI is required?

Dry powder inhalers have propellant free nature, high patient compliance, high dose Carrying capacity, drug stability and protection with patents. The pharmaceutical engineering provides controlled drug particle size and altered excipient systems. One of the model drug-glucagon is administered for the lack of pancreatic hormones. Glucagon causes hepatic dysfunctions and metabolic disorders. Dry powders inhalers have the following advantages and disadvantages:

Advantages of dry powder inhalers:

- Propellant free
- Effectively exhibit local site of respiratory tract
- No liver metabolism
- Lowers adverse reactions
- Quick action
- Lung target drug delivery with 1-3m particle size
- Better drug carrying capacity
- Inhalation by long breath
- Loss of drug is higher during inhalation.30% of drug reaches the lung

- ❖ Big alveolar surface area gives good bioavailability
- ❖ Patient compliance very good, easy to carry
- ❖ Comfortable
- ❖ High dose carrying capacity
- ❖ Drug stability
- ❖ Rapid onset of action and predictable
- ❖ Lesser quantity of drugs to treat local diseases and systemic diseases

Disadvantages:

- ❖ Powder gets agglomeration with humidity
- ❖ Powder may not reach lung during inhalation
- ❖ Poor absorption with some systemic disease
- ❖ Unpredictable and variable dose

Classification of dry powder inhalers:

Dry powders inhalers can be classified into three main categories.They are:

i. First Generation Inhalers
ii. Second Generation Inhalers
iii. Third Generation Inhalers

Dry powder inhalers can be classified into three main categories. They are:

iv. First Generation Inhalers
v. Second Generation Inhalers
vi. Third Generation Inhalers

A. First Generation Inhalers: These are mainly breathe actuated single unit-devices.

e.g. a. spinhaler
b. cyclohaler

B. Second Generation Devices: These are mainly breathe actuated multi-unit and multiple dose devices

a.Multi-unit: e.g.ellipta
b. Multiple dose:e.g.turbohaler

C.Third Generation Devices:

These are the active devices
e.g.a. Easyhaler
b. Exubera
c. Taper

Applications of pulmonary drug delivery:

Dry powder inhalers have been used in the Management of respiratory diseases such as asthma, emphysema, bronchitis and chronic obstructive pulmonary disease.

- ❖ Treatment of diabetes mellitus.
- ❖ Respiratory delivery to treat cystic fibrosis with N-acetylcysteine recombinant human deoxyribonuclease aerosol and tobramycin
- ❖ Angina effectively treating with nitroglycerin, isosorbide aerosol through pulmonary route.
- ❖ Surfactant aerosol and gene therapy carried out with respiratory route.
- ❖ The novel drug delivery advances liposomes, nanoparticles, microsphere and mucoadhesive exist in the applications of pulmonary route.

Dispersion of dry powder inhalers:

Dry powder inhalers: Powdered aerosol[5] is the modern drug delivery of inhaled pharmaceuticals aerosols. The difficulties are manufacturing powder aerosols and measured quantity of fine particles.

DPI operation is classified as active and passive:

- Active operations are carried out with the help of external mechanical energy.
- Passive operations are carried out with patient single large breath.

The dispersion taken place to manage inter particulate forces that binded with the particles in the bulk dry powder and dispersed become individual particles with an inhalation Vander wallforce lowers when particle size is increased in dry powder inhaler. The right temperature and humidity is essential for DPI performance[6-7]. If formulation is cohesive the dispersion is decreased.

Dry powder inhaler devices for respiratory medicines:

- ➢ DPI devices such as aerolizer, diskus, ellipta, flex haler, handihaler, press air, Rota haler, turbuhaler, twist haler, breezhaler, spin haler, easy haler, totadisk, novelizer, and exubera are mainly used[8-9].

- The dry powder is filled into the capsules. Capsules are kept into the chamber[10]. The moving mechanism splits the capsules into head and body then powder will be drawn out of capsules.
- The need of the DPI drug delivery is to excel consistent, efficient dose delivery, correct use of device, patient compliance and treatment efficacy.

Some of the commonly used Dry powder inhaler devices are as follows:

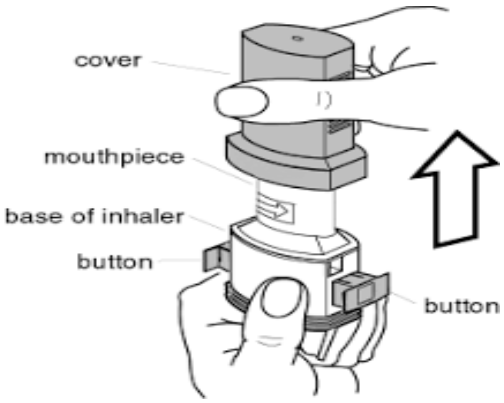

Figure 1:**AEROLIZER**

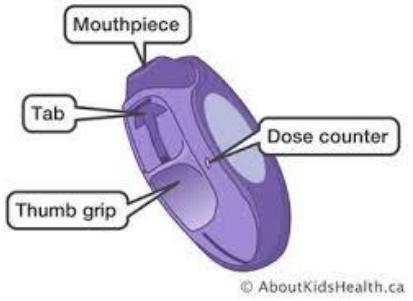

Figure 2:DISCUS APPARATUS

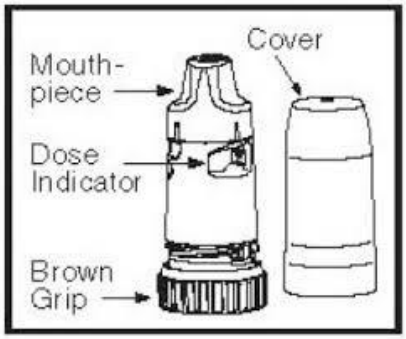

Figure 3:FLEXHALER

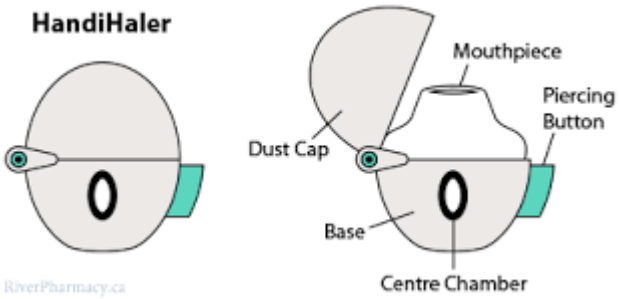

Figure 4:HANDIHALER

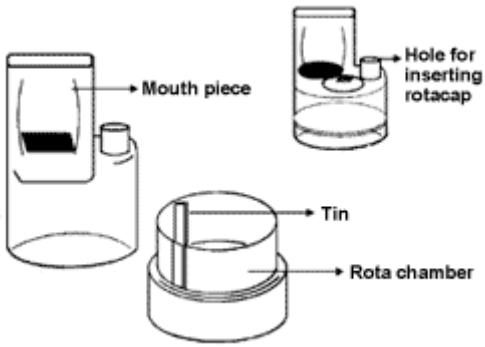

Figure 5:ROTAHALER

Respirable particles: The optimal particle size of respirable particles is 1-5µm. Systemic particle of less than 2µm is needed for drug deposition[11-13]. In oropharyngeal region, particle size greater than 5µm deposits then improves systemic effects. The particle deposition in the lung depends upon aerodynamic particle nature such as particle size, particle density, particle shape, hygroscopicity and electrical charge.

Formulation design: The DPI formulations, used quickly, require less patient coordination. Drug is exposed only to pulmonary region in the body, so side effects are very negligible and avoids hepatic metabolism of a drug. DPI therapy produces rapid and predictable onset of action[14].

CAUTION: DPI is prescribed for child with age more than 4 years, since children aged less than 4 years may not generate sufficient respiratory flow.

Sustained release formulation: Microencapsulation methods are useful to produce sustains release inhalation formulations [15]. Sustained release inhaled pharmaceuticals provide reduction of dosage frequency, lesser side effects, given once daily

are economic and patient compliance. The polylactic acid, poly lactide coglycolide and Eudragit is 100 polymers are useful to produce sustain release microparticles

Drug deposition:

Pulmonary delivery is more attractive for systemic delivery since this region is rich in blood supply and allows fast absorption and fast onset of action. Particles with 5µm deposit in the bronchial region of the respiratory tract and particle size of 1-3µm range reaches the alveoli Drugs with poor oral permeability may be well absorbed in lungs[16]. The transit of particle takes place throughout the airway of the lung by the mechanism of impaction, sedimentation [17-19], electrostatic deposition and diffusion. The amount of drug deposited in the lungs varies according to deliver device. Lung deposition may be evaluated by use of radio labelled substances including measurement of particle size to determine the percentage of drug in the respirable range.

Active Pharmaceutical Ingredient Preparation

- To create particles in the respirable size range (⬍ 5µm i n diameter), the drug particle size must be reduced in a separate unit operation. There are several options for reducing the particle size, and it may be necessary to evaluate several methods to find the one that works best for the specific drug.
- The first size-reduction technique the formulation scientist will typically turn to is milling. Thereare many different mills, the most commonly used mills are:

Jet milling[20](or air-attrition milling):

- It is the most usefultechnique which reduces particle size via high-velocity particle-particle collisions.
- Unmilled particles are introducedinto the milling chamber. High-pressure nitrogen is fedthrough nozzles and accelerates the solid particles to sonicvelocities. The particles collide and fracture.
- While flyingaround the mill, larger particles are subjected to a highercentrifugal forces and are forced to the outer perimeter ofthe chamber.
- Small particles exit the mill through the central discharge stream.

Depending on the nitrogen pressure and powder feed rate, particles down to 1 m in diameter can be produced.

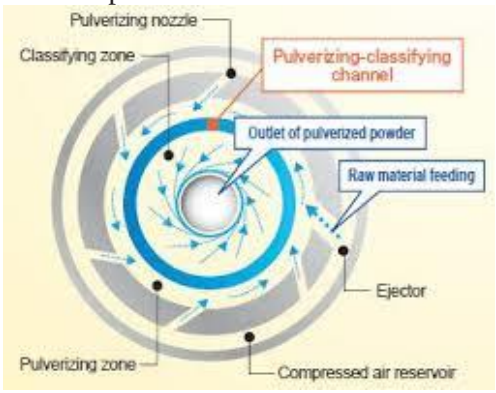

Figure 6: jet mill

Pin mill:

- A pin mill uses mechanical impact to grind material,both by particle-particle and particle-solid collisions.
- Apin mill is equipped with a series of concentrically mountedpins located on a spinning rotor and stationary stator plate.
- Powder is fed to the milling chamber and transportedthrough the milling chamber by centrifugal force.
- Milledproduct is collected from the bottom. The pin mill canproduce 1- but not as small as the jet mill.
- On the other hand, the pin mill's power consumption islower than that of the jet mill.

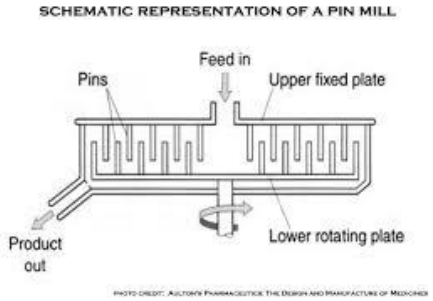

Figure 7: Pin mill

m particles,133

Ball mill:

- The ball mill is essentially a rotating cylinder loaded with drug and "milling

media" (i.e, balls that grind the drug between each other as they tumble inside the mill).

- The size and material of the milling media can be varied[21].
- Ball milling is very slow and the process is poorly scalable, which is why tumbling-ball mills are used only in the laboratory.

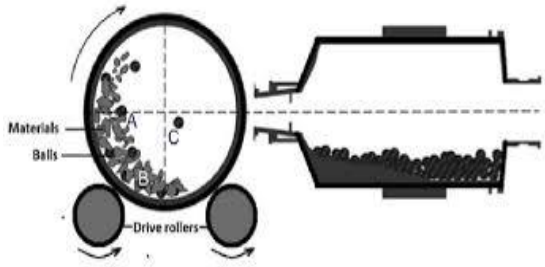

Figure 8: Ball mill

Particle engineering for inhalation:

The micronized dry powder inhaler formulation can be prepared by following methods:

- co-precipitation of drug and carrier by lyophilization,
- specialized spray drying,
- spray freeze drying,
- ultra sound assisted crystallization,
- flash crystallization,
- controlled precipitation and
- supercritical fluid technologies.

Micronization is the process used to decrease the particle size of less than 5µm and create a large surface area to mass ratio. Spray drying is the one step constructive process that provides greater control over particle size, shape and micronization is destructive process [22].

Formulation of Dry powder Inhalers: The most common approach for the for a DPI formulation is to blend the fine drug particles with an inert carrier (most usually lactose) consisting of coarser particles.

During the blending the fine drug particles adhere to the surface of the carrier particles forming adhesive mixtures.

The dispersion of drug particles from the adhesive mixtures upon inhalation is a three - step process including:

i. Fluidization of the powder in the airstream
ii. Detachment of primary and agglomerated particles
iii. Breakup of agglomerates into primary particles

Assessment of drug delivery:

- Content uniformity is the major challenge in DPI formulation. The common formulation challenges depend on the final drug-carrier characteristics such as flow property, aggregation, bridging, particle size, particle shape, amorphous content, particle size distribution [23], dose delivery through inhaler and performance stability.
- Stability and dosing performance of the DPI depends upon the formulation and composition of DPI.
- During pharmaceutical manufacturing, powders are frequently transported by a vibrating surface such as a belt feeder or vibrating conveyor. Carriers acts as bulking agent and prevent the loss of drug during aerosolization.

Novel inhalation delivery systems:

- Reduced dosing frequency, improved patient compliance and reduction of side effects are advantage of sustain release formulations for pulmonary drug delivery[24].
- At present 30%of inhaled drugs only reach the systemic circulation. This increases the number of doses and frequency of administration [25-26].
- Spray drying is the process of that yields particle size of above 2µm. Drug release modifiers such as chitosan are used in spray drying process and exhibits sustain release properties.
- Chitosan is bio compatible and biodegradable polymer used in pharmaceuticals. The muco adhesive property of chitosan exhibits adhesion

in the mucus membrane of the respiratory tract[27].

- Pulmonary targeting can be achieved by prolonging pulmonary residence time either by reducing release from drug particle, reducing release from drug delivery system or by initiation of biological interaction.

Inhalable microparticles:

Modified solvent evaporation method is one of the best methods to produce inhalable microparticles. The polymeric aqueous solution is employed in the preparation of microspheres are polylactic acid, polylactic co-glycolic acid, eudragit RL 100, eudragit RS 100, ethyl cellulose, hydroxy propyl methyl cellulose, gelatin, chitosan and alginate. Differential scanning calorimetry is used to employ structure of micro particles. The microparticles evaluated for drug loading, percentage, entrapment efficiency, tapped density and In vitro drug release by diffusion analysis. The emulsifiers are used to produce controlled release products such as polymer coated microparticles [28].

Drug delivery devices:

i. Inhaler device has major influence on the performance of the dosage form. Inhalers are small hand held devices where medicine is released as spray into the mouth, reaches the lung directly.
ii. The selection of inhalation devices based upon the formulation and capacity to handle the device by the patient.DPIs have device metered[29] an internal reservoir containing sufficient formulation for multiple doses that are metered by the device itself during actuation by the patient.
iii. Several devices are available in the market for aerosolization and each device is unique in its own way of delivering drug. The devices are made as pre metered or device metered dry powder inhaler and both can be driven by patient inspiration alone or with some type of power-assistance.
iv. Differentiation of device design causes variation in performance based on the capacity of patient's inspiratory flow rate.

Physico-chemical characterization:

a. The DPIs must be characterized to find out its physicochemical properties with the suitable analytical method.
b. Crystallinity of the drug particles can be examined by X-ray diffractometer and by differential scanning colorimetry.
c. Water content in the blend can measured by using Automatic Karl-Fischer Titrator [30].
d. Particle size and its distribution can be measured by laser diffraction techniques and photo correlation spectroscopy.
e. Particle morphology can be measured by scanning electron microscopy and dynamic and static image analyzers.
f. Raman imaging systems are used for measurement of particle size, crystallinity and shape.
g. Dosage unit sampling apparatus is used for sampling and testing of dry powder inhaler.
h. Drug content and solubility can be analyzed by LC-MS, HPLC, UV or other suitable system.
i. Aerosol velocity can be determined by laser droplet velocimeter.

DRY POWDER CHARACTERIZATION:

Particle size distribution:

The particles of different sizes are called polydisperse particles. The inhaled pharmaceuticals are mostly polydisperse. The distribution of particle sizes calculated are studied as frequency and count distributions, the log normal distribution, cumulative mass and volume distribution. The total mass of an aerosol are calculated from its mass median diameter and the number of particles unit/volume[31].

Particle deposition: The inhaled pharmaceutical aerosol deposits in the respiratory tract. Inhalation flow rate also affects particle deposition. The parameters used to determine impaction are flow velocity, linear dimension, particle diameter and Cunningham

slip correction factor governed by Reynolds number. The modern deposition models of different lung regions typically are empirical models, lagrangian dynamic models and eulerian dynamic models. Empirical model is simple. The equation of empirical model fits with the in vivo data of lung deposition of aerosols [32].

Target of aerosol deposition:

If particles settle by sedimentation then those particles get deposited in alveolar regions [33]. Inter subject variability is also factor of lung deposition of inhaled pharmaceutical aerosols. The particle size of 1-3m is useful in achieving lung targeting. There is variation of lung deposition of aerosol with diseased lungs and effect of age on deposition.

The movement of aerosol particles:

Aerosol mechanics help us to study the movement of the single aerosol particle in a fluid. The determination of particle in a fluid flow is simplified as the spherical is particle size assumption and the particle density is more than surrounding fluid density. The fluid forces such as buoyancy force, magnus force, lift force, basset force and pressure force are significant if fluid density is greater than particle motion, concept of aerodynamic diameter, effect of induced electrical charge, space charge and effect of humidity on electrostatic charge research is required for the determine the importance of inhaled pharmaceutical aerosols[34].

Vander Waals adhesive forces:

The determination of the origin of the adhesive forces is helpful to design target drug delivery [35]. The source of the intermolecular potential energy lies in the quantum mechanical electromagnetic interaction between the electrons and protons of the molecules called Vander Waals forces. There are equations for understanding origin adhesive forces. The DPI mechanics is complex there is complicate measurement mechanics involved in initial and final states of the powder.

TABLE 1:PUBLISHED INHALABLE FORMULATIONS

Generic name	Reference
capreomycin	Thaigarajan et al
Salbutamol sulphate	K.Satish kumar et al
Meloxicam potassium	Edit Benke et al
Fluticasone propionate/salmeterol	Barbra P Yawn et al
Ciprofloxacin	Daniela Traini et al
Insulin	Bernd W. Muller et al

Inhaler testing:

The cascade impactor is one of the best instruments to evaluate the aerosol emitted from a DPI. The various sizes of dry powder particle deposition at the various regions of respiratory tract is determined in vitro by cascade impactors [36-37]. The Anderson cascade impactor mimics the role of particle size deposition at respiratory tract. The invitro cascade impact or data correlates with in vivo clinical study. United States pharmacopeia and European Pharmacopeia describes the Andersen eight stage impactor (USP apparatus 1), Marple miller impactor (USP apparatus 2), twin impinge (metal and glass), multistage liquid impinger, cascade impactor classify aerosol particles and droplets based on aerodynamic diameters [38-39]. The coordination of aerosol generation and inspiration is required to improve lung deposition.

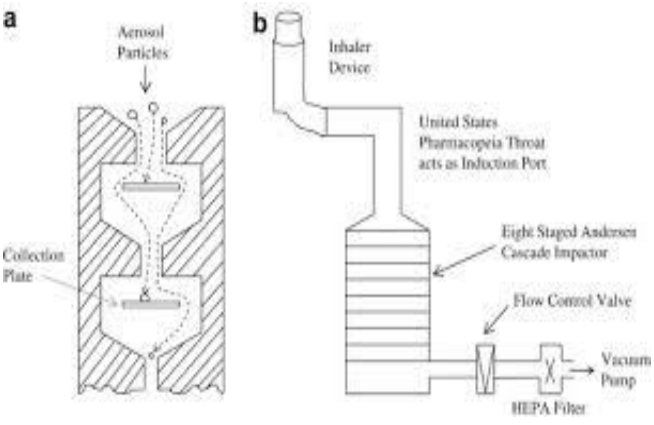

Figure 9: CASCADE IMPACTOR

CONCLUSION:

Dry powder inhaler aerosols contains sustained release microparticle producing effective delivery. At this period of time, they are many achievements of developing sustained release microparticles of inhaled aerosols. The novel drug delivery system is fully control to local lung disease and systemic diseases. Inhalation is the preferable way to drug delivery to the respiratory tract for the treatment of respiratory disease. The choice of inhaler device is most important in the treatment of asthma and COPD. The extensive research should be taken on pharmaceutical dry powder to solve the problems associated with content uniformity, reproducibility and efficacious drug delivery to achieve local and systemic effects. The pharmaceutically improved delivery of dry powder inhaler formulation and ease of application causes better compliance towards patients, physicians and pharmacists.

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