Review Article

Dry Powder Inhaler: An Advance Technique for Pulmonary Drug Delivery System

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ABSTRACT

A growing attention has been given to the potential of a pulmonary route. Pulmonary Drug Delivery represents an attractive, needle free, rapid and patient-friendly route used for drugs with poor to no bioavaibility when administered via the oral route which can pass the alveolar membrane. It is mainly classified into three classes; Nebulizer, pMDI, DPI. DPIs are an alternative to pMDI that delivers medication to the lungs in the form of a dry powder. Particle Size of API must be present in size range about 1-10 μm which 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. Dry powder for inhalation is often composed of fine drug particles and inert coarse carrier particles such as lactose. The dispersion of a dry powder aerosol is conducted from a static powder bed. When the patient takes breathe, air is introduced into the powder bed creates turbulence and leads to fluidization of static powder blend and enters the patient's airways where the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact in the oropharynx and are cleared. Lung Deposition Study is carried out by Twin Stage Impingner. The inhalation device is important in achieving adequate delivery of inhaled drug to lung which mainly classified based on dose type into Single-unit and Multi-dose reservoirs.

Keywords: pMDI, DPI, Inhalation Device.

INTRODUCTION [1, 2]

Pulmonary Drug Delivery System serves as major route of drug administration for thousand of year. Ancient inhalation therapies include the use of leaves from plants, vapors from aromatic plants, balsams, and myrrh. 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).

Advantages of Pulmonary Drug Delivery System. [1, 2, 3]

1. Needle free and non invasive drug delivery system.
2. Drug is directly deposited in the lung, so minimizes the dose requirement and has negligible side effect as the rest of body is not exposed to drugs.
3. Respiratory tract provide a large surface area which is highly permeable for absorption of drug into the blood so gives quick onset of action.
4. The large protein molecules which might degrade in gastrointestinal tract and eliminated by first pass metabolism are given by pulmonary route which avoid the first pass metabolism.

Pulmonary drug delivery system is mainly classified into three classes;

1. **Nebulizer:** [4]

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.

a. Advantages of Nebulizer[5]

1. High doses of medication can be used.

2. Multiple drugs can be used in single system.
3. Easy formulation handling and requires less co-ordination of patient.

b. Disadvantages of Nebulizer[6]

1. Equipment is large which is difficult to transport.
2. Variability in performance between different nebulizers.
3. Need for external power source.

2. pressurized Metered Dose Inhaler (pMDI)[6,7]

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. Advantages of pMDI: [1, 4, 5]

1. Easy to handle.
2. Accurate metering performance.
3. Capacity of large number of does at low cost.

b. Disadvantages of pMDI: [1, 4, 5]

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. Require careful co-ordination of actuation and 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
5. pMDI is limited to certain drugs that are stable in a propellant.

3. Dry Powder Inhaler

Dry powder inhalers have advanced significantly over the past 10–15 years. A Dry powder inhaler (DPI) is a device that delivers medication to the lungs in the form of a dry powder. The dry powder platform comprises devices that generate an aerosol directly from 1-5 µm size drug powder, or mixtures with excipients such as Lactose Monohydrate. The development of DPIs has been motivated by the desire for alternatives to pMDIs, to reduce emission of ozone-depleting and greenhouse gases chlorofluorocarbons and hydrofluoroalkanes respectively that are used as propellants. DPIs are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD although DPIs have also been used in the treatment of diabetes mellitus.

a. General Requirements of DPI. [8, 9]

DPIs have to meet the following requirements;

i. *Particle Size of API:* Active Compound must be size about 1 to 10 µm. Such micro fine particles can be obtained by micronization, controlled precipitation from suitable solvent or by spray drying if the process conditions are suitable.
ii. *Drug content uniformity:* It is important that each capsule or blister in a single-dose system contain the same amount of powder and medication while in a multi-dose system; the reservoir must release the same amount of powder and drug every time.
iii. *Content uniformity at different airflows:* The dose has to be released in exactly the same way at low breathing and at a high breathing rate.
iv. *Stability of powder against humidity and temperature:* Major ingredient of DPI is lactose which must be protected against particle size growth. The main property responsible for particle size growth is an undesired combination of temperature and relative humidity which is controlled by storage in the correct packaging is important for stability.
v. *Flowability:* Almost all active ingredients have poor flowability; the good flow has to be supplied by the carrier.

b. Advantages of Dry Powder Inhaler[3, 4, 10]

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 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.
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 range from less than 10 mg to more than 20 mg
2. Minimal extrapulmonary loss of drug due to low oropharyngeal deposition, low device retention and low exhaled loss.
3. Less potential for extractable from device components.

c. Formulation Strategies for Dry Powder Inhaler[1]

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 (Fig. 1) are used as follows

i. *Carrier Free:* In carrier free strategy, active therapeutic ingredient is in the form of a single compound, multi-compound composite or encapsulated particles. The inhalation drug particle must have aerodynamic particle size less than 5 μm.
ii. *Drug Carrier:* It is difficult to dispense 1μg to 1 mg of doses of drug into the small blisters for dry powder inhalers. So the drug molecules are mixed with larger particle to make them flow better and also to increase the volume of each dose. 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. 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.
iii. *Drug Additive:* The addition of finer particles can also improve the

fluidization quality of drug fine powders. Additives such as submicron silica (0.5–3 wt. %), alumina (29 nm), aerosol 200 (12 nm) were used.

iv. *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.

d. Formulation. [6, 11, 12]

Formulation of DPI mainly includes three steps;

i. API Production

Particle size of drug should be less than 5 µm. It should be in the range of 2-5 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. There are various size reduction techniques such as milling, spray drying, and supercritical fluid extraction.

There are 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 2-5 µm such as fluid-energy mills, such as the jet mill; high-peripheral-speed mills, such as the pin-mill; and the ball mill.

Jet mill reduces particle size via high-velocity particle-particle collisions. Unmilled particles are introduced into the milling chamber. High-pressure nitrogen is fed through nozzles and accelerates the solid particles to sonic velocities. 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 chamber. Small particles exit the mill through the central discharge stream.

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. Final milled product is collected from bottom. 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.

ii. 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. 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 preblending steps.

iii. 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.

iv. Carriers used in DPI [1, 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. API usually present in a low concentration, with a drug to carrier ratio of 1:67.5 (w/w). 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. 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.

i. General Requirements for Carrier.[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 of drug and carrier has to be weak enough to enable the release of drug from carrier during patient inhalation. 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*.
5. Increasing the specific delivery of drug to target tissues.

v. Principle of dry powder inhaler design.[6, 11]

The dispersion of a dry powder aerosol is conducted from a static powder bed. To generate the aerosol, the particles have to be moved. Movement can be brought about by several mechanisms viz.; Passive and Active. Passive inhalers employ the patient's inspiratory flow. When the patient activates the DPI and inhales, airflow through the device creates shear and turbulence; air is introduced into the powder bed and the static powder blend is fluidized and enters the patient's airways. There, the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact in the oropharynx and are cleared (Fig. 2)

For aerosol generation, several power-assisted devices (pneumatic, impact force, and vibratory) have been developed or are currently under development. These are called as active-dispersion DPIs which are no commercially available.

vi. Lung Deposition Study

Five mechanisms govern particle deposition in lung airways as follows

i. *Inertial impaction:* defined as inertial deposition of a particle onto an airway surface. It happens principally close to the airway bifurcations of the large conducting airways.
ii. *Gravitational sedimentation:* occurs in the small conducting airways where the velocity of the air is low and for particle below 5µm in size.
iii. *Diffusion:* occurs in small airways and alveoli where the airflow is very low and for sub micrometer-sized particles (below 0.5) and are subject at Brownian motion.
iv. *Interception:* is important only for fibers (asbestos) and aggregates. For such particles, deposition may occur when a particle contacts an airway wall, even though its centre of mass might remain on a fluid streamline.
v. *Electrostatic attraction:* electrostatic charges enhance deposition by increasing attractive forces to airway surfaces, in particular for fresh generated particles.

Lung deposition study is carried out by Twin Stage Impingner apparatus.

vii. DPI Device[15, 16]

The primary inhaler parts are same for all type of devices on the market and many in development. Dry Powder Inhaler device consists of; powder formulation, dose measuring system, powder deagglomeration principle and mouthpiece (Fig. 3)

Ideal Characteristics for DPI Device[16]

1. Device should be easy to use and convenient to carry.
2. Contain multiple doses
3. Protect the drug from moisture.

4. Accurate and uniform delivery of doses over wide range of inspiratory flow rate.
5. Consistent dose delivery throughout the life of the inhaler.
6. Minimum adhesion between drug formulation and devices.

CONCLUSION

Dry Powder Inhaler is promising route for Pulmonary Drug Delivery System which is given by oral inhalation as DPI having numerous advantages over pMDI. DPIs generally consist of drug having size range 1-5µm and carrier particles having 50-150 µm. Generally Lactose is mostly preferable carrier. Lung deposition occurred by Active and Passive mechanism can be studied by using Twin Stage Impingner apparatus.

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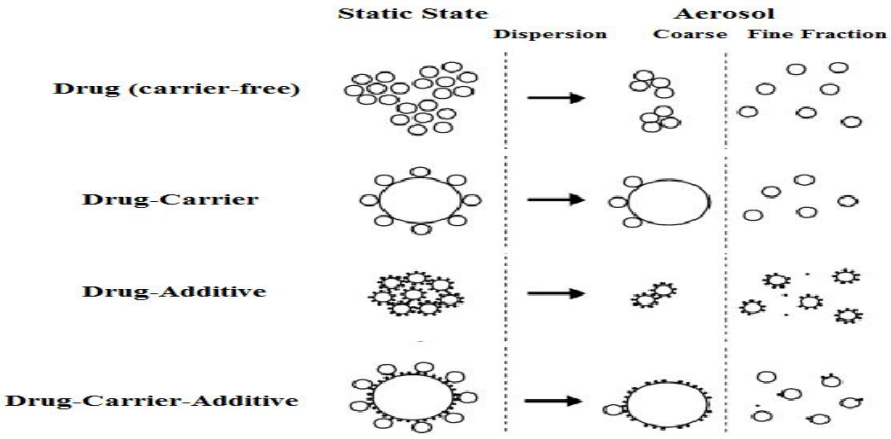

Fig. 1: Different types of formulation strategies for Dry Powder Inhaler[1]

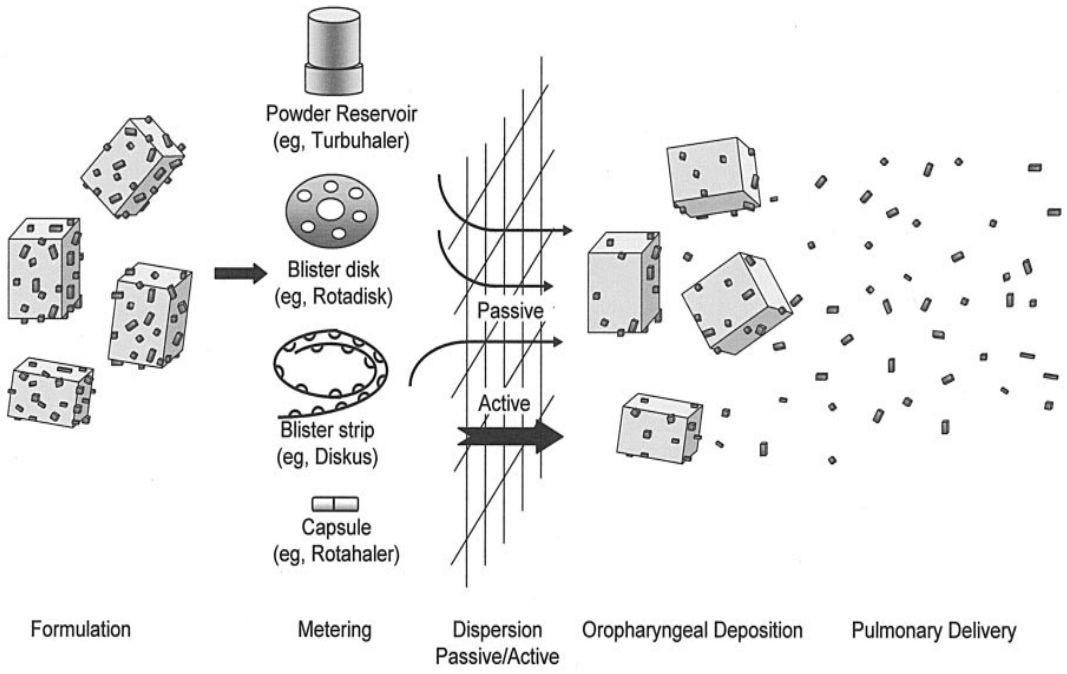

Fig. 2: Principle of dry powder inhaler design.[6]

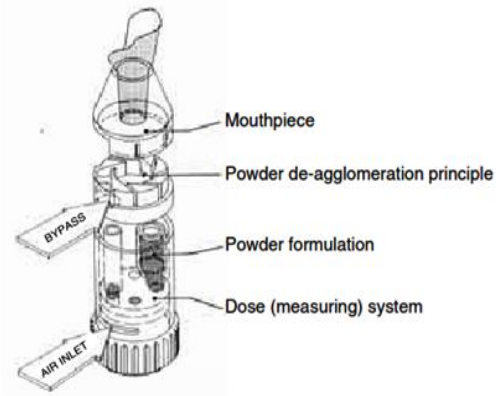

Fig. 3: Primary functional design elements of dry powder inhaler[10]

REFERENCES

1. Derek Ivan Daniher, Jesse Zhu; Review Dry powder platform for pulmonary drug delivery; Particuology. 2008;6:225–238.
2. Siraj Shaikh, Sayyed Nazim, Tarique Khan, Afsar Shaikh, Mohammad Zameeruddin and Aamer Quazi. Recent Advances In Pulmonary Drug Delivery System: A Review. International Journal of Applied Pharmaceutics. 2010;2(4):27-31.
3. http://www.kem.edu/dept/clinical_pharmacology/ACCP_Day1/Session%202/Dr%20Misra%20-%20RECENT%20ADVACNCES%20IN%20LIPOSOMAL%20DPI%20FOR%20PULMONARY%20D.pdf
4. Richard J. Malcolmson and Jonathan K. Embleton. Dry powder formulations for pulmonary delivery. Reviews research focus, PSTT. 1998;1(9):394-398.
5. http://nanoparticles.org/pdf/Gardner.pdf, David L. Gardner; Factors to Consider in Developing a Dry Powder Inhaler;
6. Martin J Telko and Anthony J Hickey; Dry Powder Inhaler Formulation. Respiratory Care. 2005;50(9):1209-1227.
7. http://dspace-unipr.cilea.it/bitstream/1889/1080/1/C.Parlati_PhDThesis.pdf, Chiara Parlati; Respirable Microparticles Of Aminoglycoside Antibiotics For Pulmonary Administration.
8. www.lactose.com, Dry powder inhalers, Access on 01/02/2012.
9. Manfred Keller and Rudi Muller-Walz. Dry Powder For Inhalation, United State Patent Application Publication, Publication No.- US2011/0114092 A1, Publication Date- May 19, 2011.
10. Ian Ashurst, Ann Malton, David Prime and Barry Sumby. Latest advances in the development of dry powder inhalers. Reviews-research focus PSTT. 2000;3(7):246-256.
11. Alagusundaram M, Deepthi N, Ramkanth S, Angalaparameswari S, Mohamed Saleem TS, Gnanaprakash K, Thiruvengadarajan VS and Madhusudhana Chetty C. Dry Powder Inhalers - An Overview. International Journal Research Pharmaceutical Science. 2010;1(1):34-42.
12. Mahavir B. Chougule, Bijay K. Padhi, Kaustubh A. Jinturkar and Ambikanandan Misra. Development of Dry Powder Inhalers; Recent Patents on Drug Delivery & Formulation. 2007;1(1):11-21.
13. Imran Saleem and Hugh Smyth. Carriers in Pulmonary Dry Powder Drug Delivery. Future Drug Delivery. 2006:34-36.
14. Saint-Lorant G, Leterme P, Gayot A and Flament MP. Influence of carrier on the performance of dry

powder inhalers. International Journal of Pharmaceutics. 2007;334:85–91.
15. Newman SP and Busse WW. Review Evolution of dry powder inhaler design, formulation, and performance. Respiratory Medicine. 2002;96:293-304.
16. Nazrul Islam and Ellen Gldaki. Mini Review Dry Powder Inhalers (DPIs)- A review of device reliability and innovation. International Journal of Pharmaceutics. 2008;360:1-11.