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Review Article

Dry Powder Inhalers - An Overview

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ABSTRACT

The drug product encompasses the pharmacologic activity with the pharmaceutical properties. The ideal characteristics are physical and chemical stability, ease of processing, accurate and reproducible delivery to the target organs and availability at the site of action. A Dry powder inhaler (DPI) is a device that delivers medication to the lungs in the form of a dry powder. For the DPI, these goals can be met with a suitable powder formulation, an efficient metering system and a perfectly selected device. This review focuses on the dry powder inhaler formulation, evaluation, material methods and development processes. Most of the dry powder inhaler formulation encompasses micronized drug particles blended with larger carrier particles that promote the flow properties, reduce aggregation and help in dispersion. A combination of the physicochemical properties, particle size, shape, surface area and morphology affects the forces of interaction and aerodynamic properties, which in turn determine the fluidization, dispersion, delivery to the lungs and deposition in the peripheral airways. However the properties of free micronized powders often interfere with the drug handling and with drug delivery, reducing the dose consistency. Dry powder inhalers are evaluated by the drug product characterization studies such as the in vitro dose proportionality, effect of patient dose, priming etc. The development of the new designs of the DPI is governed by the driving forces such as the regulatory and pharmacopoeial requirements, delivery systems for the NCE, clinical factors and commercial factors.

Keywords: Dry Powder Inhaler, Micronization, Dose Consistency, Patient Complaints.

INTRODUCTION

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 (Peart J *et al., 2001)*. Inhaled drug delivery systems can be categorized into three main groups namely the pressurized metered dose inhalers, dry powder inhalers and nebulisers each group with a unique strength and weakness. The important of these, dry powder inhalers; enable the pulmonary delivery of higher dose, locally acting, such as sodium cromoglycate. They also offer an alternative delivery system to patients who are unable to synchronize the discharge and inhalation of MDIs. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales (Dolovich MB *et al.,* 2005; Barry PW *et al.,* 2003). Dry powder inhalers have a number of advantages over other methods of pulmonary drug delivery, for example, direct delivery of drug into deep lungs utilizing the patient's respiration and are increasingly being explored as a mechanism for the delivery of on the systemic drugs. Successful delivery of drugs into the deep lung depends on integration between powder formulations and the device performance. Licensing and marketing approval require that current DPIs demonstrate in vitro performance and in vivo efficacy and reliability.

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.

IDEAL DRY POWDER INHALERS

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

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Effective dosing

- ✓ Uniform dose through life
- ✓ Targeted and optimized delivery
  - controlled respirable fraction
  - 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
- ✓ Design optimized by the use of, for example, practical engineering, manufacturing innovation
- ✓ In-process controls for quality
- ✓ 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

FORMULATION

The particle size distribution affects the deposition of drug in the respiratory tract. However, before drug can be delivered to the lungs, drug particles must leave the DPI and separate from each other and from other components in the formulation. Thus, a DPI formulation must undergo flow, fluidization, and deaggregation. However, micronsize particles, particularly those resulting from high-energy operations such as jet milling, have high surface areas and surface energies, which result in poor flow and a high tendency to aggregate. Formulation strategies aim at alleviating these problems (Newman SP *et al.,* 2002).

Formulation development includes an array of processes in which an active pharmaceutical ingredient is incorporated into a drug product. While biological activity is a prerequisite for a successful dosage form, it is not the sole determinant. Factors such as stability, processibility, delivery, and availability to the target organ contribute to an efficacious pharmaceutical system. Optimization of these factors is a key development task, and the final product is often a compromise between pharmaceutical and practical (i.e. economic/engineering) considerations. Formulation development is challenging because molecules with pharmacologic activity often display poor physicochemical properties. In fact, the same molecular characteristics that confer pharmacologic activity (e.g. high receptor affinity) frequently limit a compound's pharmaceutical utility, making it difficult or even unsuitable for delivery (Di L *et al.,* 2003; Lipinski CA 2000). This is particularly true for many of the compounds that are identified by high-throughput screening methods (Lipinski CA 2000; Lipinski CA *et al.,* 2001). Development of pharmaceuticals for inhalation is a particular challenge, as it involves the preparation of a formulation and the selection of a device for aerosol dispersion. The lungs have lower buffering capacity than other delivery sites (eg, the gastrointestinal tract or the blood), which limits the range of excipients that could enhance delivery outcomes. An additional variable, unique to pulmonary delivery, is the patient, both in terms of inhalation mode and respiratory-tract anatomy and physiology (Timsina MP *et al.,* 1994). There are many more ways to administer an inhaled aerosol than there are to swallow a tablet. Variability in delivered dose to an individual or a population of patients can be substantial (Aswania O *et al.,* 2004; Cochrane MG *et al.,* 2000). Consequently, reproducible therapeutic effect is difficult to assure.

Treating respiratory diseases with inhalers requires delivering sufficient drug to the lungs to bring about a therapeutic response. For optimal efficacy, drug administration must be reliable, reproducible, and convenient. This goal can be achieved by combination of formulation, metering, and inhaler design strategies (Smyth HD *et al.,* 2005).

The formulation of DPI can be classified into three categories

- ✓ API production.
- ✓ Formulation of API with or without carriers.
- ✓ Integration of the formulation into device.

Production and classification of the primary API

The API requires an aerodynamic diameter of <5µm (J.N. Pritchard 2001), to avoid impaction and sedimentation in the upper respiratory tract. Particles of this size range, however, have high surface area to mass ratios, thus making them highly cohesive or adhesive and difficult to aerosalize. Generally, dry powder APIs for inhalation are prepared through the milling of larger crystalline materials however, the resultant crystals shape is irregular and may contain regions of both crystalline and amorphous material, resulting in unpredictable behaviour with respect to aerosalization performance and physical stability (P.M. Young *et al.,* 2004; G.H. Ward *et al.,* 1995). In an attempt to improve surface heterogeneity and produce particles with controlled size descriptors, techniques such as supercritical fluid technology (P.M. Young *et al.,* 2004; G.H. Ward *et al.,* 1995; J. Jung *et al.,* 2001), crystallization by ultrasonic precipitation (J.S. Kaerger *et al.,* 2004), and preparation of low density porous particles (H.K. Chan 2006) have been investigated. A common method of particle production is spray drying since it is a single step process resulting in primary API particles with spherical morphology, with a controllable size distribution. Interestingly it is important to highlight that all though spray drying may result in a more uniform geometry, the aerosilization efficiency may not necessarily be improved since the contact area between particles and their packing geometry will be directly related

to the energy required to disaggregate the particles during aerosilization.

Formulation of the API in binary or ternary systems

The clinical efficacy of DPI formulations is generally higher than that of the conventional dosage forms (M.P. Timsina *et al.,* 1994) with respiratory medicine dosage generally being an order of magnitude less than their tablet counterparts. Consequently the API is regularly formulated with a binary component such as coarse lactose, to improve flow, allow accurate metering and aid dispersion. However, as discussed above the API has a high surface area to mass ratio and therefore may adhere to the carrier with a greater energy than the energy available for dispersion, during the aerosolisation. As a consequence, carrier system tends to be inherently inefficient (Y. Kawashima *et al.,* 1998).

The ball mill (Hu G *et al.,* 2001) 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. Ball milling is very slow and the process is poorly scalable, which is why tumbling-ball mills are used only in the laboratory.

Integration of formulation in a DPI device

DPI device is the primary factor in developing a new DPI formulation. Knowledge about computational fluid dynamics is essential in designing DPI devices. CFD enables the analysis of particle flow, shear stress and potential particle impaction within the device. Subsequently this data may be applied to estimate the in vitro aerosolisation efficiency of a model API (I.J. Smith *et al.,* 2003).

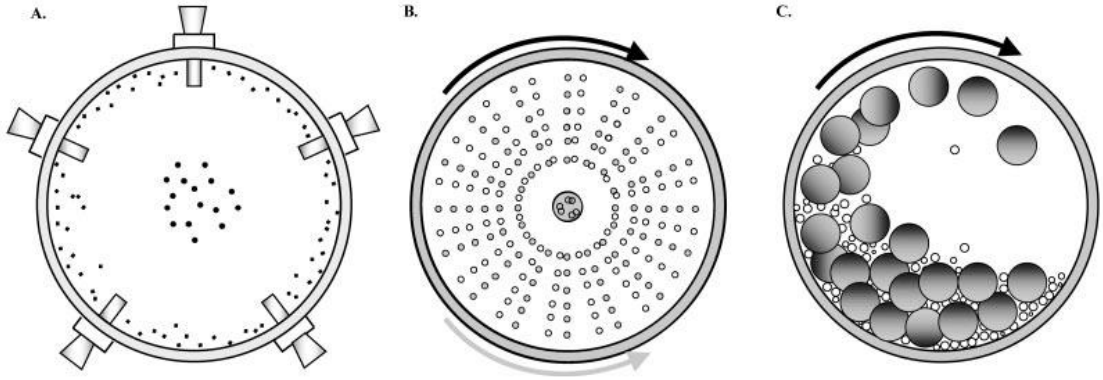

Fig. 1: Cross-sections of 3 mills commonly used to create micron-size particles.
A: Jet mill. B: Pin mill. C: Ball mill

Jet milling (Cheng YS *et al.,* 1985) (or air-attrition milling) is the most useful technique; it 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 a higher centrifugal force and are forced to the outer perimeter of the chamber. Small particles exit the mill through the central discharge stream. Depending on the nitrogen pressure and powder feed rate, particles down to 1 µm in diameter can be produced.

A pin mill (Drogemeier R *et al.,* 1996) uses mechanical impact to grind material, both by particle-particle and particle-solid collisions. A pin mill 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. Milled product is collected from the bottom. The pin mill can produce 1µm particles, but not as small as the jet mill. On the other hand, the pin mill's power consumption is lower than that of the jet mill.

Innovative powder formulations

Efficient delivery of drugs from DPIs depends not only on the device, but also on the drug formulation and the formulation of a DPI involves the production of suitable powders for effective respiratory deposition as well as formulation of powders with or without excipients. Historically, drug particles for inhalation have been produced by milling process and are then blended with a carrier like lactose to improve flow properties and dose uniformity (Dolovich, M 1992). Other carriers such as mannitol and trehalose (Timsina, M.P *et al.,* 1994) have also been reported to use in the DPI formulations (Stahl K *et al.,* 2002). The properties of such blends are a function of the principal adhesive forces that exists between the particles and the surface tension of the adsorbed moisture level layers (Podczeck, F 1997). In carrier mediated formulations, drug carrier adhesion is likely to effect the dispersion of drugs aerosolised via the inhaler devices (Hickey A.J *et al.,* 1994).

Insufficiency of traditional methods of powder production has lead to the development of alternative techniques which produce powders of specific size, density and morphology and with less cohesion and adhesion (Hickey A.J *et al.,* 1997). The dispersion of powder aerosols is also influenced by the geometric diameters of

the particles which are generally at odds with the

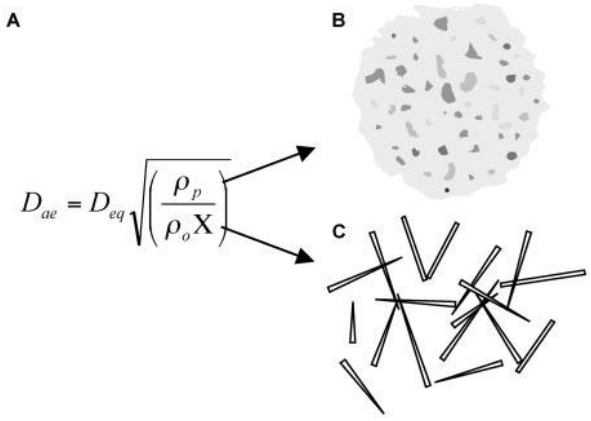

Fig. 2: Strategies for altering the aerodynamic diameter.

A: Aerodynamic diameter equation. B: Large, low-density porous particles.

C: Needle-shaped particles. Particles in both B and C are expected to have aerodynamic diameters smaller than their size would suggest.

Dae= aerodynamic diameter. Deq=unit density of equivalent volume sphere. ρp= particle density. ρo unit density. X= dynamic shape factor

efficiency of deposition in the lungs. A number of alternative techniques, including specialized spray drying, ultrasound assisted crystallization and supercritical fluid technology, in situ method have also been demonstrated (Hess, D.E *et al.,* 2005). Development of sustained released spray dried recombinant human insulin with hyaluronic acid is an existing example of formulation of proteins for DPIs (Surendrakumar K *et al.,* 2003). The underlying principle has been described as enhanced performance through particle engineering and recent particle engineering (Ostrander K.D *et al.,* 2000) has seen the development of highly porous particles with large geometric diameters but small aerodynamic diameters which by improving powdered dispersion can improve efficacy of DPIs (Edwards D.A *et al.,* 1997). A number of novel powder formulations have been demonstrated such as powder hale, (Staniforth J.N *et al.,* 1996) porous particles, pulmosphere, (Edwards D.A *et al.,* 1998) solidose, nanoparticles, (Blair, J *et al.,* 2000) surface modified patricles, (Ostrander, K.D *et al.,* 2000) engineered powder (Morton D 2006).Recently, respiratory delivery of proteins, interleukins and oligonuleotides, (Chet L.L 2007) gene therapy and vaccination was reported elsewhere. Inhalation of insulin from DPI formulation showed to increase systemic level of insulin and suppressed systemic glucose levels (Patton J.S 1996). Dry powder inhaler formulation of measles vaccine and beta glucuronidase was also reported. Pulmonary delivery of erythritol-based powder form of glucagon, a key regulatory element of glycogen metabolism has been demonstrated (Patton J.S *et al.,* 2002). Another study demonstrated that the bioavailability of inhaled calcitonin was more than double compared to that of the bioavailability of injected calcitonin (Endo K *et al.,* 2005). Pulmonary delivery of DPI for gentamycin (Banga A.K 2003), colistin sulphate (Crowther, L.N.R *et al.,* 1999) and tobramycin sulphate (Newhouse, M.T *et al.,* 1999) has been successfully investigated and inhaled delivery showed higher plasma concentrations compared to those achieved by nebulisation. The outcome of these investigations is indicative of expanding the DPI formulation for other drugs include protein-based compounds, biologics, for the treatment of systemic disorders.

DPI DESIGN ISSUES

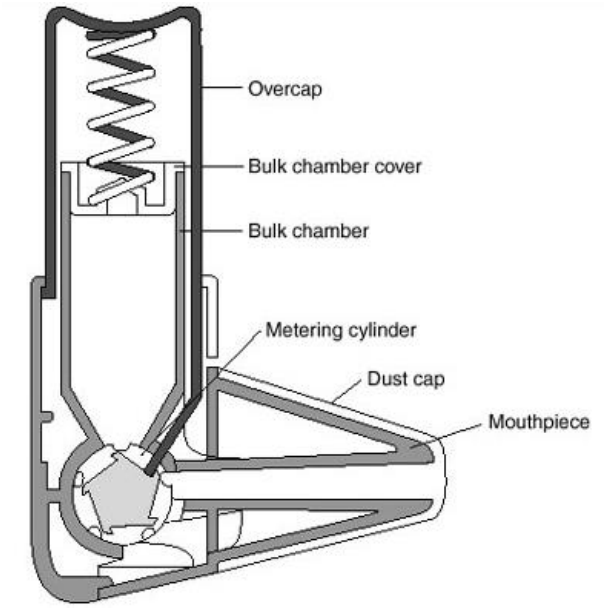

Fig. 3: DPI design

The design of DPI must be coordinated with the formulation of the drug. Inhaler design particularly the geometry of the mouth piece, is critical for patients to produce an air flow sufficient to lift the drug from the dose chamber or capsule, break up the agglomerates in a turbulent air stream, and deliver a dose to the lungs as therapeutically effective fine particles. The airflow generated by inhalation directly determines particle velocity and hence the ease with which particle are deagglomerated.

The materials used in the construction of DPIs (Personn G *et al.,* 1989) characteristics of the formulation (Carter PA *et al.,* 1998; Tobyn M *et al.,* 2004; M.P. Timsina *et al.,* 1994) effect electrostatic charge accumulation. Some formulations, as well as inhaler materials, accumulate and retain electrostatic charge more strongly than others, and this will affect both drug retention within these inhalers as well as delivered aerosol behaviour.

PRINCIPLE OF OPERATION

Most DPIs contain micronized drug blended with larger carrier particles, which prevents aggregation and helps flow. The dispersion of a dry powder aerosol is conducted from a static powder bed. To generate the aer-

Fig. 4: currently available DPI devices
(A) AerolizerTM, (B)EasyhalerTM, (C) TurbohalerTM, (D) DiskhalerTM,
(E) NovolizerTM, (F) RotahalerTM,(G) ClickhalerTM, (H) MAGhalerTM,
(I) SpinhalerTM, (J) HandihalerTM

osol, the particles have to be moved. Movement can be brought about by several mechanisms. 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. Thus, deposition into the lungs is determined by the patient's variable inspiratory airflow (Dunbar CA *et al.,* 1998; Smith IJ *et al.,* 2003 Newman S *et al.,* 1994). Inadequate drug/carrier separation is one of the main explanations for the low deposition efficiency encountered with DPIs (Dunbar CA *et al.,* 2000). Dose uniformity is a challenge in the performance of DPIs. This is a greater concern with powders than with liquids because of the size and discrete nature of the particulates. Various dispersion mechanisms (Zeng XM

et al., 2000) have been adopted for DPIs. While most DPIs are breath-activated, relying on inhalation for aerosol generation, several power-assisted devices (pneumatic, impact force, and vibratory) have been developed or are currently under development. These devices are being considered for the delivery of systemically active drugs that have narrow therapeutic windows. It is important to note that these "active" inhalers are not subject to the same limitations as passive inhalers and have airflow. Inadequate drug/carrier separation is one of the main explanations for the low deposition efficiency encountered with DPIs. Dose uniformity is a challenge in the performance of DPIs. This is a greater concern with powders than with liquids because of the size and discrete nature of the particulates. Various dispersion mechanisms have been adopted for DPIs. While most DPIs are breath-activated, relying on inhalation for aerosol generation, several power-assisted devices (pneumatic, impact force, and vibratory) have been developed or are currently under development. These devices are being considered for the delivery of systemically active drugs that have narrow therapeutic windows. It is important to note that these "active" inhalers are not subject to the same limitations as passive inhalers and have a different advantage/disadvantage profile. Moreover, it has been suggested that if shear and turbulence could be standardized by using a dispersion mechanism that is independent of the patient's breath, high delivery efficiency and reproducibility might be achieved. Thus, an active inhaler might provide formulation-independent delivery. There is no commercially available active-dispersion DPIs.

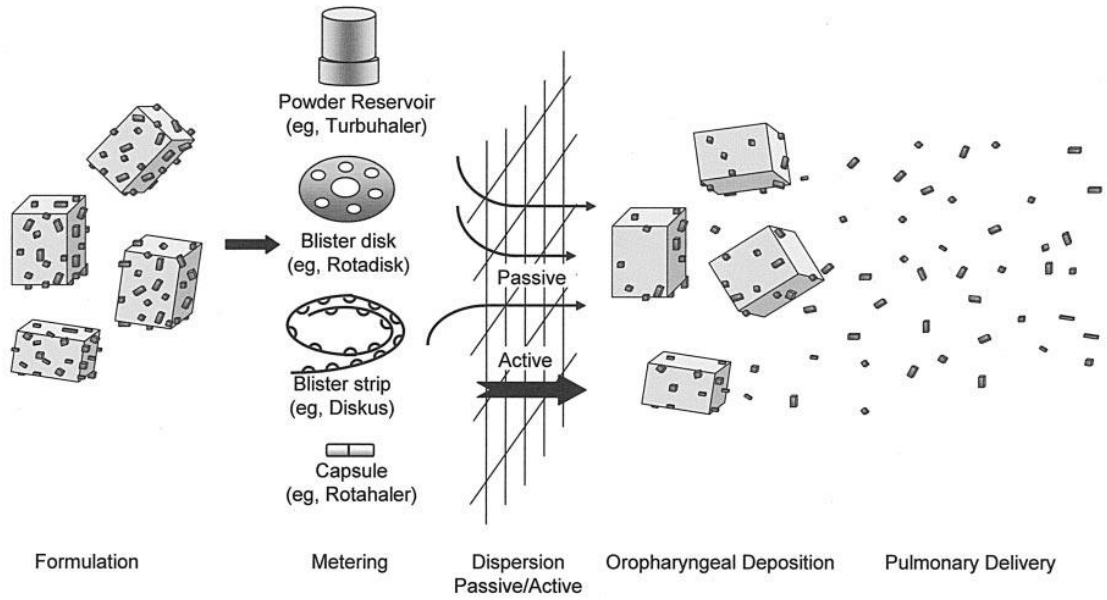

Fig. 5: Principle of dry powder inhaler design

EVALUATION

In vitro testing of Dry powder inhalers

In order for any drug to be safe and efficacious, the therapeutic entity must reach the site of action in an appropriate concentration and have acceptable impurity levels. For inhalation dosage forms, the amount of drug delivered as well as the aerodynamic particle size range being delivered must be tested. This aspect is determined by the mass of drug of a particular size range being delivered to the respiratory tract (Zeng XM *et al.,* 2000). Metered dose inhalers and dry powder inhalers are the most common portable devices used to deliver drugs to the lung. The operating principles of the two delivery systems are very different and this needs to be reflected by the in vitro methods employed to characterize these dosage forms (Norwood DL *et al.,* 1995). The design of pressurizes metered dose inhaler used by a number of pharmaceutical companies is fundamentally the same; MDIs consist of a metering valve, container, actuator, micronized drug, propellant and surfactant. The high vapour pressure propellant passing through the small exit orifice in the valve stem propels the drug to the patient in a deaggregated state; therefore the drug delivered to the patient is relatively independent of the patient's inhalation flow rate.

All pharmaceutical dosage forms must ensure that the drug delivered is safe and efficacious. In addition it is important that the in vitro test should be designed to stimulate the patient use as much as possible (Dalby R *et al.,* 2003). In the case of some of the inhalation dosage forms, more testing is necessary due to the uniqueness of the dosage form in order to develop, critically assess an ensured product quality. Product safety testing ensures that the correct drug is present with an acceptable level of impurities. The test typically performed as part of product safety are listed below

- Appearance
- Identity(chromatography and spectroscopy)
- Microbial limits
- Water content

- Extractives
- Drug related impurities
- Drug content per unit dose/dose delivery
- Particle size analysis/respirable dose
- Stimulated patient use
  - Through device use
  - Patient parameters/parallelisms
    - Flow rate
    - Inhalation volume
    - Environmental aspects
- Reusable Vs disposable reliability testing

ADAVANTAGES

Typical advantages of dry powder inhalers are

- Propellant freed design
- Less need for patient coordination
- Less need for patient cocordination
- Less potential for formulation problems (formulation stability)
- Less potential for extractables from device components
- Environmental sustainability

DISADVANTAGES

Typical disadvantages of dry powder inhalers

- Dependency on patient's inspiratory flow rate and profile
- Device resistance and other design issues
- Greater potential problems in dose uniformity
- Less protection from environmental effects and patient abuse
- More expensive than pressurized metered dose inhalers
- Not available world wide
- Development and manufacture more complex/expensive

CONCLUSION

The number of diseases that are being considered candidates for the aerosol therapy has increased substantially. Until recently, asthma was only the clear example of a disease that could be treated via aerosol delivery to lungs. We now consider it possible to treat not only asthma and chronic obstructive pulmonary diseases but also systemic disorders such as diabetes, cancer, neurobiological disorders and other pulmonary diseases such as cystic fibrosis and pulmonary infectious diseases.

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