Dry Powder Inhaler a Review

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ABSTRACT

Present review is about Dry Powder Inhaler (DPI). Interest in DPIs as an effective, efficient and environmentally friendly way of delivering drugs to the lung has accelerated in recent years. Dry powder inhaler can meet these goals only with a suitable powder formulation, an efficient metering system, and a carefully selected device. When a DPI is actuated; the formulation is fluidized and enters the patient’s airways. Under the influence of inspiratory airflow, the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact on the oropharyngeal surfaces and are cleared. Successful delivery of dry powder aerosols to the lung requires careful consideration of the powder production process, formulation and inhaler device.

Keywords: Dry powder inhaler, Carrier particle, Fluidization, Fine particle fraction, inspiratory flow, aerodynamic diameter

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INTRODUCTION

Inhalation drug delivery has been used for many years for the delivery of pharmacologically active agents to treat respiratory disease. Traditional asthma therapy with bronchodilators, steroids, mast cell stabilizers, and anticholinergic drugs has primarily used the pressurized metered-dose inhaler (MDI). However, this delivery system is now under increasing threat because of the environmental concerns regarding chlorofluorocarbon (CFC) propellants. A range of alternative devices, such as dry powder inhalers, which do not contain propellants, are being evaluated and developed [1]. Dry powder inhalers contain the drug in a powder formulation, where drug particles (< 5 μm) are blended with a suitable large carrier (e.g. lactose) to improve flow properties and dose uniformity and drug powders are delivered into the deep lung via a device known as dry powder inhaler (DPI). Powder de-agglomeration and aeroionisation from these formulations are achieved by the patient’s inspiratory airflow [2]. In a DPI, the aerosol needs to be generated from the powder formulation by patient 's own effort. For achieving this, a high turbulence is needed to break the large agglomerates of the drug into smaller, finer and inhalable particles. Turbulence is generated by creating resistance to air flow in the DPI device and the effort required to generate adequate flow rates is dependent on the extent of resistance. Whereas the flow rates required to be generated vary among various available DPIs, a flow rate of 60-90 L/min is generally required [3].

Principles of Operation

Most DPIs contain micronized drug blended with larger carrier particles, which prevents aggregation and helps flow. To generate the aerosol, 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 air-flow. 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 [4]. Figure 1 shows the principles of DPI design.
The formulation typically consists of micronized drug blended with larger carrier particles, dispensed by a metering system. An active or passive dispersion system entrains the particles into the patient’s airways, where drug particles separate from the carrier particles and are carried into the lung [4].

Formulation Aspects

Dry powder formulations either contain the active drug alone or have a carrier powder mixed with drug. 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 [5]. The requirement to use micronized drug with small(ideally less than 5 μm) particle achieved good aerodynamic properties of the dispersed powder is confounded by the need to develop formulation that fill easily and accurately. It is also important that changes in the physical nature of the formulation on transporation and storage not adversely affect during formulation development. The inclusion of carrier can aid in the handling of the formulation and may impart some aerodynamic benefits also. The goal of delivering micronized powders is a challenging one. Because, these type of powder are highly cohesive. Their high interparticulate forces make them difficult to deaggregate, hence need for high inspiratory flowrate and turbulent airflow within DPI. Incorporation of carrier may aid the deaggregation process, but it can also lead to problem absorption of atmospheric moisture. Controlled temperature and humidity studies of salts form and lactose(or other suitable carrier)combination are essential during formulation development [6]. Various techniques were develop to improve formulation performance by development of tertiary excipient like magnesium stearate and leucine. The inclusion of magnesium stearate in the DPI formulation as a ternary additive helped in improving the performance of the formulations [7]. Magnesium stearate can form film layers which can adhere to drug-excipient particles and can interfere with inter-particle bonding as a result of hydrophobic coating [8]. The use of leucine also in the DPI formulation as a ternary additive has help ed in improving the performance of the DPI formulations. This is possibly due to antiadherent action of the material [9].

Carriers Used in Dry Powder Inhaler

Carrier particles are used to improve drug particle flow ability, thus improving dosing accuracy and minimizing the dose variability observed with drug formulations alone while making them easier to handle during manufacturing operations. With the use of carrier particles, drug particles are emitted from capsules and devices more readily, hence, the inhalation efficiency increases. Design of the carrier particle is important for the development of DPIs. Carrier particles should have several characteristics such as physico-chemical stability, biocompatibility and biodegradability, compatible with the drug substance and must be inert, available and economical. [10] Lactose is the most common and frequently used carrier in DPI formulations accordingly nowadays various inhalation grades
of lactose with different physico-chemical properties are available on the market. The advantages of lactose are its well-investigated toxicity profile, physical and chemical stability, compatibility with the drug substance, its broad availability and relatively low. Lactose, in particular alpha-lactose monohydrate, is typically used as 'the' carrier in dry powder inhalers [11]. Due to several drawbacks of lactose and modified lactose as a carrier for dry powder inhalers, there is an urgent need to find suitable alternative carriers for better drug dispersibility in DPI. Alternative carriers like mannitol, glucose, sorbitol, maltitol and xylitol as potential carriers in DPI formulations. Of all the sugars evaluated, mannitol seemed to be a promising carrier for DPIs whereas sorbitol, maltitol and xylitol sugars were not able to generate desirable FPF due to their hygroscopic nature [12]. Carriers like crystallized mannitol (Pearlitol 110 C), spray-dried mannitol (Pearlitol 100 SD), crystallized maltitol (Maltisorb P90) and spray-dried lactose (Lactopress SD 250) for two drugs: micronized terbutaline sulfate and micronized formoterol fumarate, it was found that crystallized forms of the carrier offered lower adhesion and better release of the active ingredient than spray-dried forms. The crystallized mannitol produced maximal fine particle dose [13].

**Basic Design of Dry Powder Inhaler Devices**

The inhalation device is important in achieving adequate delivery of inhaled drug to lungs. The device should be easy to use, inexpensive and portable. The device must provide an environment where the drug can maintain its physicochemical stability and produce reproducible drug dosing. The device should be designed to deliver high fine particle fraction (FPF) of drugs from the formulations. However, devices with higher resistance need a higher inspiratory force by the patients to achieve the desired air flow. This could be difficult for patients with severe asthma and for children and infants [14]. Dry powder inhaler devices are classified by dose type into single-unit dose, multi-dose reservoirs, and multi-unit dose, as illustrated schematically in Fig. 2. In a single-unit dose device, the drug is formulated as a micronized drug powder and carrier system and supplied in individual gelatine capsules, which are then inserted into the inhaler for a single dose and removed and discarded after use. There are two types of multi-dose devices, reservoir type devices and multi-unit dose devices [15].

The multi-dose reservoir type device stores the formulation in bulk, and has a built-in mechanism to meter individual doses from the bulk upon actuation. Newer devices of this type attempt to address issues such as reducing the flow rate dependent dose emission and of moisture ingress into the reservoir from patient exhalation or environmental humidity during the life of the product as these are common issues with the reservoir type device. The multi-unit dose device uses factory metered and sealed doses packaged in a manner that the device can hold multiple doses without having to reload. Typically, the packaging consists of replaceable disks or cartridges, or strips of foil-polymer blister packaging that may or may not be reloadable. This pre-packaged does have the advantage of being protected from the environment until use, and ensuring adequate control of dose uniformity [16]. A comprehensive and comparative review of commercially available DPIs and their classification is given below.
Figure 2: Illustration of four dose design options available for dry powder inhalers. [15]

Unit-Dose Devices

The Spinhaler® (Aventis) was the first dry powder device, described in 1971. It has a mechanism for piercing the capsule. The cap of the capsule fits into an impeller, which rotates as the patient breathes through the device, projecting particles into an airstream (Fig. 3). Shear force and relative motion are the predominant mechanisms of powder deggregation [17].

Figure 3: Schematic presentation of the Spinhaler® [18]

A similar DPI, the Rotahaler® (GlaxoSmithKline) has a mechanism for breaking the capsule into two pieces. The capsule body containing the dose falls into the device, while the cap is retained in the entry port for subsequent disposal. As the patient inhales, the portion of the capsule containing the dug experiences erratic motion in the airstream,
causing dislodged particles to be entrained and subsequently inhaled. Particle deaggregation is mainly caused by turbulence promoted by the grid upstream of the mouthpiece. A FPF of 26% has been reported for this low resistance device [17].

In the Aerolizer® (Novartis), the capsule is pierced on each side by four piercing pins. During inhalation, the capsule whirls and the particles are dispersed by turbulence generated by a spinning motion. Deagglomeration of the powder occurs through its passage through a plastic grid [17].

The Handihaler® (Boehringer Ingelheim) operates by dispensing drug contained in a capsule via a rumbling motion once the capsule has been opened by piercing pins. The particles are dispersed through the turbulence generated by a plastic grid at the time of inhalation. This device seems more complex as it requires at least 7 distinct steps to deliver the dose. For some patients, 2 inhalations are required to completely empty the capsule and achieve the therapeutic dose [18].

Multi-Dose Devices

Multi-dose DPIs have been developed, either as multi-unit dose or as multi-dose reservoir devices. Inhalator M® (Boehringer Ingelheim) has a rotating drum magazine for the storage of six capsules. The capsule is pierced at both ends and remains stationary while emptying occurs by fluidization due to the high pressure drop across the capsule. Deaggregation is caused by shear stress and collision [17].

The Diskhaler® (GlaxoSmithKline) employs individual doses packaged in blister packs on a disk cassette. Following piercing, inspiratory flow through the packaging depression containing the drug induces dispersion of the powder (Fig.4). The aerosol stream is mixed with a bypass flow entering through two holes in the mouthpiece that, together with a grid, gives rise to turbulence that promotes deagglomeration.

![Figure 4: Schematic presentation of the Diskhaler®](image-url)
The Diskus® (GlaxoSmithKline) is quite similar except that it contains a foil strip with 60 single dose blisters (Fig.5). FPF have been reported to be approximately 23-30% for these two low resistance devices [17].

One of the more sophisticated multidose reservoir systems is the Turbuhaler® (AstraZeneca). It contains 200 doses of small pellets of micronized drug that disintegrate into their primary particles during metering and inhalation. One dose can be dispensed into the dosing chamber by a simple back-and-forth twisting action on the base of the reservoir (Fig.6). Scrapers actively force drug into conical holes which cause the pellets to disintegrate. Fluidization of the powder is done by shear force as air enters the inhaler. Particle deagglomeration occurs by turbulence (from a series of tortuous channels), impaction on the bottom of the mouthpiece and high shear stress in the swirl nozzle of the mouthpiece. This device of medium resistance has presented an FPF of 39-45%. The advantages of the reservoir systems are their relative ease and low cost of manufacture and the ease of including a large number of doses within the device [19].
Novel Dry Powder Inhalers

The large dependence on high inspiratory flow rates for the operation of the first dry powder inhalers led to the development of new technologies based on passive and active powder dispersion mechanisms. In both cases, the objective is to facilitate de-agglomeration of drug particles, resulting in greater lung deposition. Devices using passive mechanisms include Novolizer® (Meda, Sweden) and Airmax® (Yamanouchi, Netherlands) The air classifier technology has been described as the most efficient passive powder dispersion mechanism currently used in dry powder inhalers. In this case, multiple supply channels generate a tangential airflow that results in a cyclone within the device during inhalation. Novolizer® uses this technology and, when compared to Turbuhaler®, showed a greater degree of budesonide deposition in the lung and lower drug deposition rates in the oropharynx. A similar mechanism is used in the Airmax®. This inhaler has a separator within which the airflow generates a cyclone similar to that observed in the Novolizer®, and this device also has greater efficacy than Turbuhaler® with respect to total drug that is delivered to the lungs, according to studies with salbutamol and budesonide. [20]

The technology of dry powder inhalers has developed to use energy as a key element in the process of particle de-agglomeration. Storage of mechanical energy in systems based on springs or compressed-air chambers was one of the alternatives found in some devices. Exubera® (Nektar Therapeutics, USA), for example, uses an air chamber that is actuated by the patient through a kind of manual pump. The effectiveness of this device, which was designed for aerosolizing insulin. Battery-powered, electrically driven systems have also become attractive options. Spiros® is a dry powder inhaler that operates appropriately even at very low inspiratory flow rates, exactly because it uses this principle to operate a twin-blade impeller that aerosolizes the drug.

Advancements in these inhalers also include new types of powdered formulations of drugs through the production of microparticles by spray-drying techniques, resulting in
porous particles, with low geometric diameter and high potential for lung deposition. Similar porous particles may be coupled to long-sized carrier molecules to reach the lungs with similar efficacy. Drug encapsulated liposomes are also a prospect of further improvement of drugs used in these devices [20].

Table 1: DPI devices currently available on the market [22]

<table>
<thead>
<tr>
<th>Device</th>
<th>DPI type</th>
<th>Company</th>
<th>Delivery method</th>
<th>Drug(s)</th>
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<tbody>
<tr>
<td>Aspirair</td>
<td>Multi-dose</td>
<td>Vectura</td>
<td>Powder/Active</td>
<td>Apomorphine hydrochloride</td>
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<td>Single dose</td>
<td>Innoveta Biomedics Ltd</td>
<td>Powder/Active</td>
<td>/</td>
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<tr>
<td>Actispher</td>
<td>Single dose</td>
<td>Britania</td>
<td>Powder/Active</td>
<td>/</td>
</tr>
<tr>
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<td>Multi-unit</td>
<td>Chiesi</td>
<td>Reservoir</td>
<td>/</td>
</tr>
<tr>
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<td>Multi-unit</td>
<td>Direct-Haler</td>
<td>Pre-metered</td>
<td>/</td>
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<td>Multi-dose</td>
<td>SkyPharma</td>
<td>Reservoir</td>
<td>Salbutamol sulphate</td>
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<td>Norton Healthcare</td>
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<td>Formoterol</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Budesonide</td>
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<td>PH&amp;T</td>
<td>Capsule</td>
<td>/</td>
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<td>Vaccines</td>
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<td>Certihalor</td>
<td>Multi-dose</td>
<td>Novartis</td>
<td>Powder</td>
<td>Formoterol</td>
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</table>

Physico-Chemical Characterization or Evaluation of Dry Powder Formulation

The DPIs must be characterised to find out its physicochemical properties with the suitable analytical method. Crystallinity of the drug particles can be examined by X-ray diffractometer and by thermograms of differential scanning colorimetry [23]. Water content in the blend can be measured by using Automatic Karl-Fischer Titrator [24]. Particle size and its distribution can be measured with laser diffraction techniques and photo correlation spectroscopy. Particle morphology can be measured by scanning electron microscopy and dynamic and static image analysers. Recently, Raman imaging systems are used for the measurement of particle size, crystallinity and shape. Dosage unit sampling apparatus (DUSA) is used for sampling and testing of dry powder inhaler. Drug content and solubility can be analysed with LC-MS, HPLC, UV or other suitable system. Total delivered
dose and dose uniformity, particle size and shape are determined by scanning electron microscope. Aerosol velocity can be determined by laser droplet velocimetry.\textsuperscript{[25]} Aerodynamic diameter is the diameter of a sphere of unit density that has the same terminal settling velocity as the particle under consideration and it is required to study on deposition mechanisms. Bulk density, Tap density, and Carr’s index have to be determined to evaluate powder flowability. A stability study has to be carried out for the final formulations as per ICH guidelines. Drug contents and thermal behaviour of the formulation should be monitored during the stability studies. Aerodynamic time of flight and image analysis was also used to determine particle size of the powder. Magnetic resonance imaging was utilised to explains the inter and intra subject variation in oropharyngeal deposition \textsuperscript{[26]}.

DPI design enable the dose to be dispensed independent of inspiratory flow rate between 30 L/min and 90 L/min. DPIs with medium resistance to airflow are designed to operate at an optimum rate of 60 L/min. The next generation impactor (Copley Scientific, UK), Anderson cascade impactor (Copley Scientific, twin impinger or aerosizer are used to determine particle size distribution, to estimate respirable fraction and for the aerosolization and deposition properties in vitro \textsuperscript{[27]}. The blend is dispensed from a suitable inhaler device into an apparatus with suitable volumetric flow rate at suitable time interval. These apparatus are able to discriminate sufficiently between the different formulation and inhalers used. Solvent (ethanol) is used to rinse the device to find out the drug content accurately. The multistage cascade impactors were used to determine the mass-weighted aerodynamic particle-size distribution and the data was used to calculate the mass median aerodynamic diameter of the samples \textsuperscript{[28]}.

CONCLUSIONS

Dry powder inhalation can be considered as an attractive drug delivery system, both for drug that are to be administered for local therapy in the lung, as well as for drugs that act systematically and for which the lung is only port of entry to the body. The System used at present still require significant improvement in various areas .However such improvement can only obtained when a profound understanding of the powder formulation, inhaler design and functioning aerodynamic behaviour of particles and inspiratory flow of the patients exist. This require further research both with regard to formulation and device as well as the experimental techniques and methods that provide relevant data when evaluating inhaler system. Novel devices with improved delivery features and metered dosing (similar to currently available metered dose inhalers) might overcome the administration difficulties and increase the efficiency of protein delivery to the deep lung.

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