Dry Powder Inhalers: Recent Advancements and Innovations


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Introduction

The pulmonary route of administration is a non-invasive, rapid, and effective approach to delivering therapeutic agents both locally and systemically (1). The pulmonary route allows for the administration of drugs in a better manner as the surface area to the volume ratio is very high which improves the bio-availability, thus giving a higher therapeutic effect.

Dry Powder Inhalers or DPIs are the systems that are used to deliver particle-type formulation of an API for local and systemic action through the oral-pulmonary route. The driving force which carries away particles comes from the inspiratory flow of the patient. They provide high physicochemical stability and a higher dose availability to patients. Currently, more than 40 such products are available in the market.

Dry powder inhalers consist of an overcap, a bulk chamber, a metering cylinder, and a mouthpiece. They can be categorized into unit and multi-dose dry powder inhalers. Capsules are used in unit dose inhalers where the capsule cover is left behind and the single dose is dropped into the device to be aerosolized and administered. Multi-dose inhalers have blister packs containing several doses in them. The drug dispersion occurs due to inspiratory flow which causes turbulence and deagglomeration of particles so that they can be delivered well.

DPIs, currently available in the market, are known to majorly lack aerosolization performance as the bioavailability of the drug which is administered ranges from 9% to 80%. The primary issues generally quoted for the above-mentioned statement are: i) agglomeration of particles and ii) insufficient inspiratory airflow to achieve the desired driving force. Thus, to combat these problems, several new-age DPI systems were launched to improve the DPI's device quality for better efficacy (2).

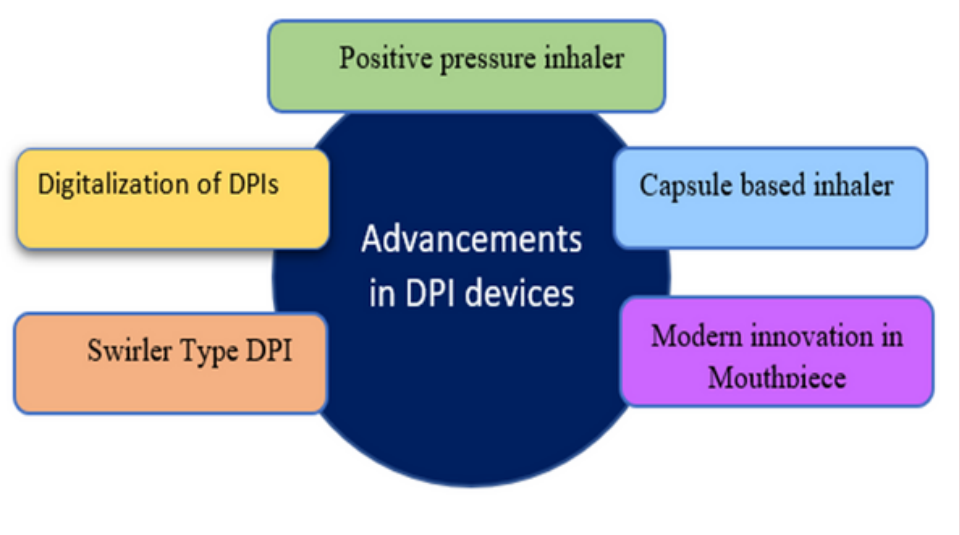

Figure 1: Advancements in DPI devices

Positive-Pressure Inhalers

In the case of children, the efficiency of the DPI is very low as an adequate inspiratory flow of the drug does not occur. The efficiency is known to lie between 5% to 30% according to the in-vivo (3) and in-vitro (4)(5)(6) studies performed on several dry powder inhalers Children under the age of 6 tend to obstruct the flow of the dose with their tongues or cheeks which decreases the content of the drug by 90% (7). Despite training the paediatrics to take the dose accurately, a huge population is seen to exhale back into the simulation, thus affecting the aerosolization to a large extent due to moisture exposure (8).

To avoid such complications, a positive-pressure dry powder inhaler for children with a vertical aerosolization chamber has been introduced. Since it is made of stainless steel, sticking of the contents to the wall of the chamber i.e. internal loss of drug is minimized, which ensures that the Emitted Dose (ED) variability and flow rate are low. This vertical orientation also helps in loading a bigger powder mass without compensating for the aerosolization performance (8).

In addition, several such in-vitro studies were done by adding a 3-Dimensional rod array interface. Rods of 0.5 mm diameter were placed in a 3-4-3 pattern in a parallel staggered form preventing the straight flow of particles to deagglomerate them with minimal losses incurred. This was fairly optimized for both active and passive DPIs. Incorporating these rods at the open end of air-jet DPI does not substantially increase the complexity and the expense of rods. For these inhalers depending on the resistance posed by the patient actuation timing can be changed which helps in delivering 750ml of air volume (8).

Capsule-based Inhalers

Most of the blister or capsule-based DPIs use needles that break and aerosolize the particle into fine form but instead of needles, hollow capillaries are used. During actuation, a high inlet speed jet is formed which produces a fine aerosol making it efficient for delivery. The same device is designed such that positive pressure sources are used, making it easy for children and infant (9).

A) When the capillary pierces the capsule at opposite ends:
Four capillaries of 0.6 mm each are connected near an outlet (aerosol propelling out of the device) and one capillary is at the opposite end. When the actuation is done, air flows into the device due to which the particle travels and comes in contact with the capillary and aerosol formation is observed.

B) Capillary piercing on the same side:
Two capillaries of 0.6 mm and 0.89 mm are attached one over the other as the air inlet chamber is vertically attached. Particles vibrate and get aerosolized after passing through these capillaries which are then given out from the outlet.

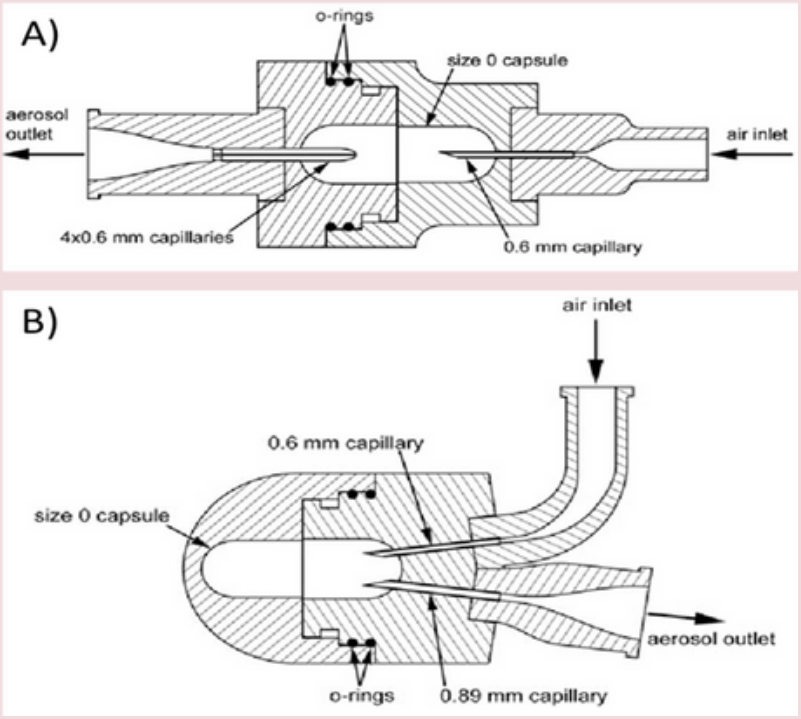

Fig 2. A) Piercing opposite ends B) Piercing on the same side (9)

Modern Innovations in the Mouthpiece of DPI
A study was conducted in which four mouthpieces with different geometries were designed using 3-D modeling application software (ProE, Creo R7.0). Later they were fabricated using 3-D printers. Four prototypes were made by mounting these modified mouthpieces to one of the commercially available DPIs i.e., Diskus™ (GlaxoSmithKline) (10).

These are the few geometries which were designed also shown in the figure:
a) Prototype I – Original device with no mouthpiece.
b) Prototype II – Airflow is rotated in a helical flow path.
c) Prototype III – Segregation of airflow in six streams and by changing the area of cross-section by placing them radially.
d) Prototype IV – Swirl motion of airflow is created by the addition of conical wall and a spiral passage as it enters mixing chamber, decrease in the momentum is seen and flow disperses widely with radial velocity as it exits mouthpiece.

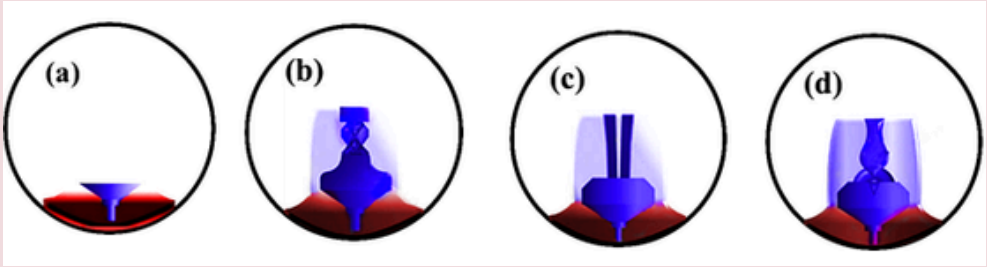

Fig 3.0 Geometries of different prototypes showing flow passage inside mouth piece
Author compiled; Adapted From (10)

To study the distribution and flow of particles after actuation, the following experiments and tests were done:

1. Particle Imaging Velocimetry to help in visualizing the velocity of particles from different prototypes
2. Anderson Cascade Impaction which focuses on the aerosol performance by calculating the Fine Particle Fraction (FPF)

The results obtained from the experimental study proved that aerodynamic characteristics affect the rate of air flow and functioning of the mouthpiece of the DPIs, thus improving efficacy of the device. It was also identified that the rotation speed of particles should be kept uniform to ensure smooth movement through the device.

Swirler-Type DPI

To have a maximum drug amount reaching the lungs, it is essential that the particles need to be deagglomerated into their finest form and aerosolized well such that the aerodynamic properties of the API particles are improved to achieve maximum bioavailability. The DPI was designed such that it had: 1) a multiple-dimpled inner chamber, 2) one-sided tangential inlets, and 3) a wall and grid (called a flow straightener). The dimples on the chamber cause an effect on the particle wall impaction and swirl-flow field. For a particle size greater than 50µ, spherical dimples are preferred as they have a balanced impact angle distribution while rectangular dimples cause a low swirl intensity but higher turbulence level. This helps in deagglomerating the particles such that the API is released from their carrier particles and is administered. The tangential inlets help in inducing a particle wall impaction causing the particles to collide against the dimples continuously. Lastly, the grid is useful in uniformly straightening the flow of the swirl formed, affecting the axial velocity, and improving the frequency of particle-wall impaction. The above-mentioned facts were proven by increasing the particle sizes of the DPI, where particle wall impaction had an insignificant effect near the inlets. Thus, the grid was seen to significantly straighten the swirl flow and affect the rate of particle wall impaction. Further, the mouth constriction has decreased the turbulence kinetic energy which helps in decreasing the depositional loss in extra-thoracic volume. The optimization of the Swirler-type Dry powder inhaler (DPI) was done using computational fluid dynamics and discrete phase modeling (11).

Digitalization of DPI

Technology is the key factor governing the existence of DPIs. Digitalization can play a major role in improving patient and drug-device interaction for better drug delivery. Incorporating these ideas helps companies to track patient activity and the clinical efficacy of their devices. It

may also help to collect data so that further studies can be done to improve the inhalation technique, widening the scope of treatment. Multiple application-supported DPIs are also being launched which can make a dosing schedule with reminders and alarms for patients. The technique of administration can thus be improved by making the DPI more useful and further feedback mechanisms can be developed (12).

Table 1: Marketed Digitalized DPIs
Author compiled; Adapted from (12)

Brand Name	Characteristics	Company	Year
Enerzair® Breezhaler®	Recording date and time, records inhalation acoustic and send reminders	Novartis ResMed	2020
HeroTracker® Sensor	Records actuation, dose reminders	Aptar Pharma	2020
Digihaler®	Dose reminders and scheduling	Glenmark Pharmaceuticals Ltd	2019
Hailie® sensor	Audio-visual reminders, records of date and time of actuation	Adherium Ltd.	2018

Conclusion

As per the FDA guidelines, for devices like DPIs, CGMP (current good manufacturing practices) requirements should be followed to ensure safe use of these medical devices. Further, the desired QTPPs (quality target product profile) like aerodynamic characteristics, stability, purity etc should also be tested before release of the marketed device. This article throws light upon the breakthroughs and innovations coming in with various ongoing studies on DPIs, but at the same time, the reproducibility of these experiments in a large forum needs analysis. Optimization of devices for a particular drug will not necessarily be sufficient. We need a universal device that supports most of the drugs administered via the pulmonary route as each drug has a different particle shape, size, and characteristics(13).

Conversion from in-vitro to in-vivo is a long and tedious process as the delivery not only depends on the formulation but also varies from person to person, showing that this preliminary data requires future studies. It is obligatory to study these innovations in terms of load effects, realistic inhalation waveforms, and intersubject variability in pulmonary delivery.

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Fun & frolic

UNSCRAMBLE THE GLOBAL PHARMACEUTICAL PACKAGING COMPANIES

ANSWER KEY (fron page 20)

1. APTAR
2. SNAPSIL CORPORATION
3. CREDENCE MEDSYSTEMS
4. PACKSYS GMBH
5. NEMERA
6. RONDO
7. HUHTAMAKI FLEXIBLE PACKAGING
8. SMART SKIN TECHNOLOGIES

GUESS THE PACKAGING & ITS USE:

ANSWER KEY (from page 32)

A. Miat ® monodose nasal insufflator

B. Aptar Pharma's Opthalmic squeeze dispenser

C. SFM Medical Devices Nextaro's Two component plastic solution and a patented screw system for reconstitution of lyophilised pharmaceutical components.

D. Virbac's All In One Contactless Multidose Delivery Cap for single injection of multiple doses of veterinary medicines.

E. Dosea smart label, a digital, smart, ultrathin label that provides communication and alarm systems in integrated printed electronic circuits.