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REVIEW ARTICLE

Capsule based Dry Powder Inhalers: Current Practice And Future Direction

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ABSTRACT
Pulmonary drug delivery is currently the focus of accelerated research and development because of the potential to produce maximum therapeutic benefit to patients by directly targeting drug to the site of pathology in the lungs. There are large ranges of devices that are currently available, or under development, for clinical use. A major concern that is very relevant in day-to-day clinical practice is that inter and intra-patient variability of the drug dosage delivered to the deep lungs from the device design, and the patients inhalation profile. Since this time, changes in the drug delivery market and regulatory pressure have driven innovation of Capsule based DPI. This article takes a look at the market forces driving DPI innovation and focuses on a novel solution that has simplicity at the heart of its design, and which hopes to reduce the healthcare cost, as well as the needs of new markets.
***Keywords**: Asthma, Chronic obstructive pulmonary disease, Drug delivery, Dry powder inhaler, Technology assessment.*

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INTRODUCTION

The benefits of inhale therapy for the treatment of asthma and chronic obstructive pulmonary disease (COPD) have been recognized for many years. In comparison with oral or parenteral formulation, minute but therapeutic doses of drug are delivered topically into the airways where the active drug exerts its beneficial effects locally within the lungs. Unwanted systemic effects are minimised because the medication acts with maximum pulmonary specificity together with a rapid onset of action. Central to the success of inhale treatment has been the availability of efficient aerosol delivery system or inhalers.

Pressurised metered dose inhalers and dry powder inhalers (DPI) are the devices most commonly used for drug delivery in the treatment of asthma and COPD. However, a forceful and deep inhalation through the DPI is needed to de-aggregate the powder formulation into respirable particles as efficiently as possible in order to ensure that is delivered to the lungs. Although all patients are capable of generating enough flow to operate a DPI efficiently, the need to inhale forcefully, and therefore generate a sufficient inspiratory flow, remains a problem for young children and patients with severe airflow limitations. For this reason, DPIs are not recommended for use in children under the age of 5 years. Less well known is that DPIs should also not be used in patients with compromised respiratory function who often do not have the respiratory effort needed to ensure effective drug delivery from DPIs. At the same time that DPIs were introduced, there was an environmental concern that the chlorofluorocarbon (CFC) propellants used in Pressurised metered dose inhalers were contributing to irreparable damage to the ozone layer in the atmosphere. The pharmaceutical industry was, therefore, committed to the development of non-CFC propellants for used in Pressurised metered dose inhalers, and also the development of DPIs that did not require any propellants at all. Reformulation of Pressurised metered dose inhalers change to

hydrofluoroalkane propellants was challenging but resulted in drug formulation with favourable safety and tolerability profiles, although the need to reformulate inhaled corticosteroid (ICS) and long-acting beta-adrenergic bronchodilators (LABA) for use in Pressurised metered dose inhalers Presented particular technical difficulties, especially regarding the achievement of dose-content uniformity. Another important distinction between DPIs and Pressurised metered dose inhalers, particularly those delivering standard coarse (>2um) aerosol particles, is that with the latter inhalers no more than 20% of the emitted dose reaches the lungs. Conversely, DPIs have been associated with a pulmonary drug deposition rate that can be as high as 40% of the administered dose, provided patients use optimally- controlled inhalation flows through the device, otherwise lung deposition can be as low as ~15%. The high speed of inhalation flows needed from some DPIs may result in marked droplet deposition in the oropharynx (between 50% and 80% of the administered dose), with subsequent potential for local adverse effect such as oral candidiasis and dysphonia, and systemic drug absorption after swallowing. Bronchoconstriction is an uncommon adverse reaction following use of Pressurised metered dose inhalers, and is through to be cause by excipients, such as oleic acid, possibly in combination with the propellant, whereas DPIs contain no propellants or preservatives.[1-4]

Classification of DPI

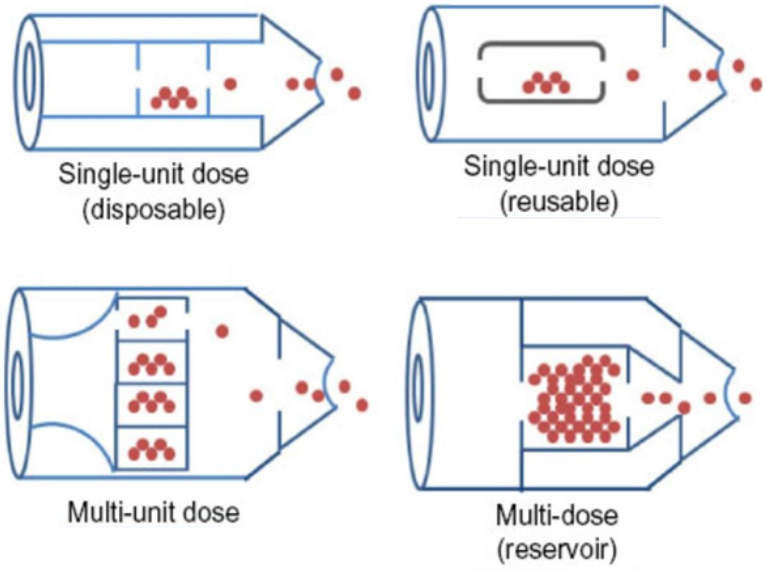

Fig. 1: Dry powder inhaler classified by number of doses [1]

The single-unit dose inhaler- Requires patient to load a single hard gelatine capsule containing the powder formulation into the device before each use. This is a very common type of DPI device.

Fig. 1(a): Single- dose DPIs [1]

Single-unit dose (disposable): Device containing a pre-metered amount of a single dose that is discarded after use. Inhalation medicine, from an economic perspective, the trend of the past two decades indisputably has been the introduction of a large number of generic devices of administration of ICS and beta-agonist for the treatment of asthma and COPD. In many countries, this development and the pressure on healthcare budgets have resulted in a significant switch from branded to generic medications and devices. The chronic nature of these asthma and COPD requires a lifetime of treatment, with a high costs. In addition, many new applications of inhale therapy (e.g. vaccination, rescue medications, enzyme, peptides) many require inhaler specifications that can not be achieved using classic inhaler technology and for several of these applications, disposable inhaler versions maybe preferred. By design, capsule-based DPIs seem most suitable as disposable and can also be developed as single- use devices. However,

disposable DPIs used in these setting still need to be simple and inexpensive, but also highly effective and reproducible.

Multi-unit dose: Devices deliver individual doses from pre-metered replaceable blisters, disks, dimples or tubes. The multi unit dose inhalers are likely to ensure greater dosage control and chemical stability of the formulation.

Fig. 1(b): Multi unit-dose DPI [1]

Multiple-dose (reservoir) –It contain a bulk amount of drug powder in the device with a built in mechanism to meter a single dose and individual doses are delivered with each activation.

Fig.1 (c): Multi-dose DPI [1]

This brief review focuses on recent improvements in capsule- based DPI technology and on the recent introduction of capsule-based disposable inhaler.

Inhalation aids

Spacers and valved holding chamber (VHCs) are used with Pressurised metered dose inhalers to increase the efficiency of aerosol delivery. A spacer is a tube or extension device that is placed at the interface between the patient and the Pressurised metered dose inhalers. VHCs such as AeroChamber Plus® Flow-Vu® have a one way valve at the mouthpiece end to allow inhalation and prevent exhalation into the chamber (fig. 2.).

Fig.2: Aerosol chamber [5]

VHC enables the patient to breath from a "standing aerosol cloud" that does not require breath coordination. These inhalation aids reduce the speed of the emitted aerosol and allow for the evaporation of propellant from larger droplets reducing oropharyngeal deposition and increasing deep lung deposition. However, they can also reduce the doses delivered from pMDI due to electrostatic precipitation. Newer spacer and VHCs are made of anti-static polymers that minimize adherence of the emitted particles to the inner walls of the spacers. New generation of spacers can indicate whether the patient is inhaling correctly or not, such as those that whistle when the patient is inhaling too quickly. [5-7].

Capsule -based DPI technology

Although therapeutic application of capsule -based DPIs began in the middle of last century with the introduction of the Aerohaler® for the delivery of antibiotics, the Spinhaler® introduce at the end of the

1960s, was the first DPI containing a powder formulation of the bronchoactive drug in device prior to use. Since then, DPI system have constantly evolved in technology and performance, a trend that still continues. DPI formulation may either be fine powder drug (particle size <5um) blends with larger carrier particles (generally lactose) to prevent aggregation and increase powder flow prior aerosolization, or it may consist of drug alone shown in (Fig. 3.)

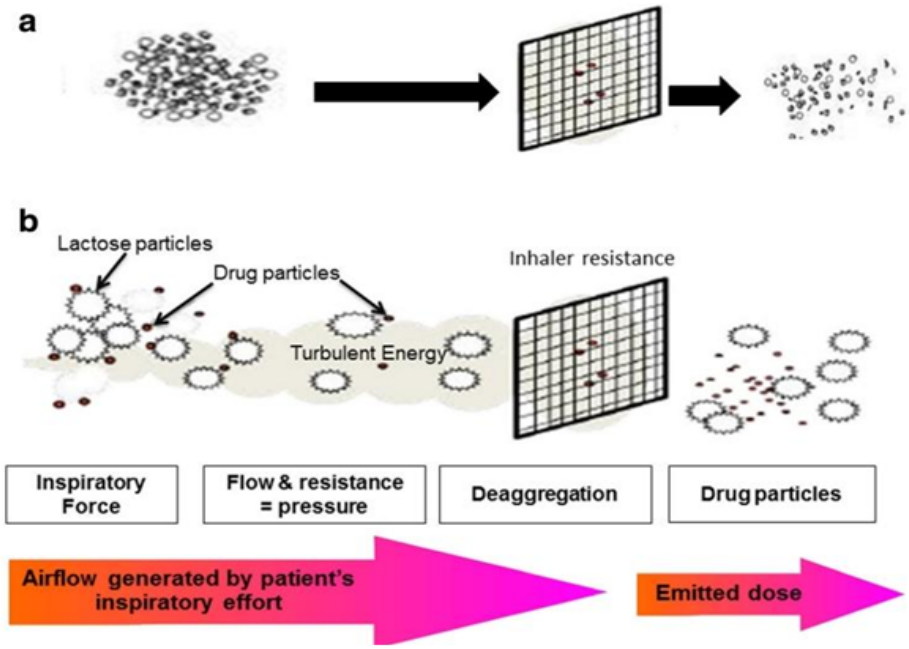

Fig 3: Schematic diagram of dry powder inhaler formulations and dispensing powder mechanism(a)Drug only formulation(drug agglomerates)(b)Carrier-based formulation. [8]

In all cases, the powder formulations travel along the airways to deposit in the targeted areas of the lung, and then dissolve to exert their pharmacodynamics effect or are absorbed to reach systemic targets. A drug particle size between 1 and 5um is needed for entry into the deep lung by inhalation and particle of 1-2 um are most suitable for reaching the small airways and alveolar epithelium.

The role of the technology in DPI devices is to disperse the powder mixtures into a repairable fine drug particle fraction by aerodynamic means. The aerodynamic behaviour of a DPI is affected by its design, dimension, and geometry of the functional engineered device part, such as the air-inlet /air-outlet, inhaler resistance, mechanisms of disaggregating powder mixtures (helicoids, sieves, cyclone channel) and emptying the dose (Venturi-effect, centrifugal forces, spinning /twisting). For instance, the air-inlet size has been a significant impact on powder dispersion at different inhalation flow rates by varying the inlet jet flow turbulence and particle interaction velocity. The performance of device can also be modified by the resistance to airflow, which has a direct impact on the peak inspiratory flow (PIF), acceleration rate, inhaled volume to reach PIF, and total inhalation time. [8-10]

Limitations of capsule -base DPI:

Handling -relate limitations:

Capsule- based DPI requires that single doses are individually loaded into the inhaler immediately before use: this is inconvenient for some patients and does not allow direct dose counting. The device then need to be primed by breaking the capsule, and then, depending on the patients breathing profile, the inhalation process must be continue or repeated until the capsule is emptied: this may result in under -dosing and high dose variability. In addition, the sequence of steps required to properly load the device may not be easy for children or elderly patients with diminished dexterity. However, the methodology used to investigate preference for and satisfaction with a particular inhaler was not validated, and preference was assessed over a limited time frame.

Technical limitations

It has been shown that the air inlet size and grid structure of the Aerolizer capsule-based DPI were found to impact significantly on aerosolization of the Carrier-based powder. More specifically, the powder contain in the capsule needs to be release through the spinning capsule will ejects the powder through the capsule holes. When the air flow increases, the capsule rotation speed will increase significantly,

which increases the centrifugal force hence facilitating the powder exist. In addition, the fine particle fraction is higher when the airflow rate is increased. Thus, at a flow rate <30 L/ min, greater variations in drug retain in the capsule can be observed compared with higher flow rates.

THE FUTURE OF CAPSULE- BASED DRY POWDER INHALER

The technology seems archaic by today's standard :a deep breath in would cause a ball to strike a centrifuge counting penicillin powder and shake the powder out into the airstream. However, the same device was later used to treat asthma, which set a precedent for future treatment of the disease. Today, throughout Europe, dry powder inhaler (DPIs) are used an estimated 40% of patient to treat asthma and chronic obstructive pulmonary diseases

Since this time, changes in the drug delivery market and regulatory pressures have driven innovation of DPIs forward: to date, there are dozens of different DPI devices commercially available, and the DPI market itself is worth approximately $18 billion. [11]

It has to be acknowledging that still more efficient aerosol device are needed, that formulations have to be safer and bioavailability has to be improved. Compared the results for inhaled proteins from different studies, showing that systemic bioavailability for compounds with mom weight (MWs) <10 kDa can vary from almost 0% to 100%, whereas for MWs >10 kDa, 60% is maximal. Therefore, bio availabilities are often too low for cost-effective and reliable treatment. Besides, pulmonary administration of one of the time, insulin, may be less relevant today because of the refinement of subcutaneous injection devices and new pharmacological strategies for patients with type 2 diabetes. These examples show how difficult it is to predict the future of DPI therapy. Many large pharmaceuticals may eventually appear be unsuitable for inhalation. Smaller molecules, on the other hand, such as levodopa, loxapine, and (locally acting) iloprost or sildenafil (MWs<< 1kDa) seem to have considerably greater future perspective. [12]

Currently, the treatment of infectious lung diseases with inhale antibiotics is in the spotlight. An advantage is deposition directly at the site of infection, which makes higher local concentrations also, could make drug-resistant organisms susceptible to the antibacterial drug again. Some inhaled dry powder antibiotics are on the market already (e.g. TOBI from Novartis and colobreathe from Forest Laboratories for CF therapy) or are expected to obtain approval soon (Ciprofloxacin DPI from Bayer HealthCare for bronchiectasis therapy). For all these drugs, classic capsule inhalers are used. Therapy for diseases such as TB is much more challenging because of the higher doses involved.[13-14]

For the future, the success of pulmonary TB treatment may depend on the development of efficient novel high-dose DPIs and synergistic drug combinations. Some studies with proven synergistic effect of antibiotic combinations have recently already been reviewed e.g. particularly for inhaled antibiotics, the need for good patient compliance with the instructions, minimizing patient errors, and good adherence to the therapy are prerequisites for an effective treatment. Also, the expectations for dry powder pulmonary vaccination are currently high. The advantages are improved stability (in dry state), no reconstitution needed (required sterile water).

New DPI design and development will benefit from computer -aided design. CFD and discrete element method may assist optimizing the flow field and particle behaviour inside, but Also ex-mouthpiece of the inhaler into the oral cavity.

Now 3D printing techniques facilitate rapid DPI prototyping and making casts of (upper) parts the respiratory tract based on high-resolution CT scan.

Future challenges and objectives for DPIs

Challenges/objective	Solutions
Reducing patient errors	Simple self-intuitive DPI design Minimal number of handling steps The same inhaler for all inhaled design
Improving patient compliance with the inhalation instructions	Simple self-intuitive DPI design Feedback on inhalation performance
Improving patient adherence to the therapy	Minimizing the number of inhalations per dose Simple, compact DPI design
Improving safety	No unnecessary excipients Disposable inhalers for special application Hygroscopic Vaccines Antibiotics
Improving efficacy	More powerful inhaler design (balancing between dispersion, and deposition forces)
Specialized inhalation	Patient (group) tailored DPI design
Reducing the costs of inhaled therapy	Simple and cheap (but effective) DPI design Simple drug formulation technologies

The needs of the DPI in market

The most successful DPI solutions will be those that match the changing needs of the drug delivery market as well as those of different patient groups, countries, cultures, diseases, etc. As retailed below:

Reusability and cost: single -Dose versus multi-dose.

As a DPI is used repeatedly by the same user, reusability is a key factor driving down the costs per dose. Single- dose inhalers, which rely on capsule to be loaded into the device, can cause difficulties for patients having to load up a capsule; there is a need, therefore, for more patients -friendly devices. Multi-dose DPs have also been developed to overcome some of the inherent limitations of single-dose inhalers. The AB Draco company (now a division of Astra Zeneca) pioneered the design of multi -dose DPIs with their Turbuhaler®.[15]

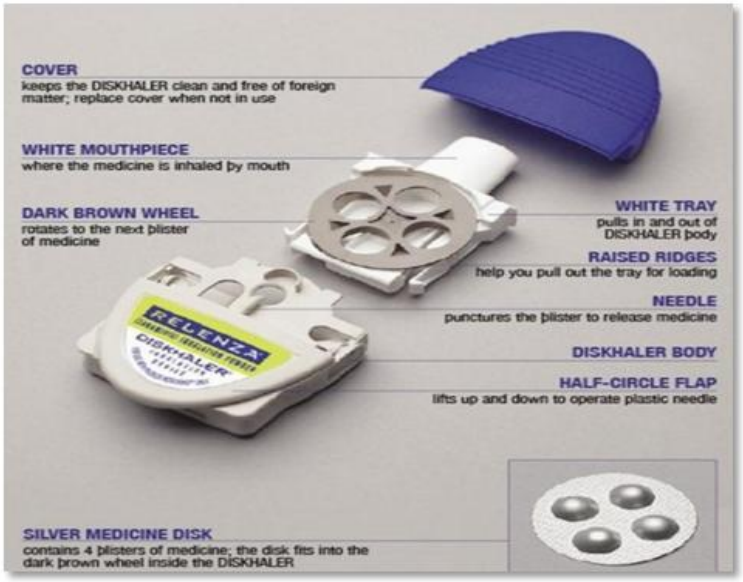

Fig. 4: Parts of Diskhaler [15]

In this device, the drug formulation is contained in a reservoir and can be dispensed into the dosing chamber by a twisting back and forth action at the lower end of the device.

Complexity & compliance

The way the patient uses inhaler can play a major role in ensuring a consistent dose to the patients lungs, therefore; capsule loading and inhalation techniques are critical elements that can affect the efficacy of a DPI. It is important that patients are correctly trained to use the inhaler by the healthcare provider. Easy -to-use devices and those that can be easily taught to patient compliance and an accurate and acceptable dosage regime: a device requiring only a few basic steps will therefore be easy for the patient to master. [16-17]

Filling Technology

The introduction and capsules has meant standardized filling technologies can be incorporated into the manufacturing process, thus meeting the needs of large-scale industrial filling of such devices, with millions of doses being manufactured yearly. Modern and accurate large-scale filling processes are also available to meet the needs of premetered devices. With the availability of the aforementioned filling technologies, it is realistic to manufacture and fill DPIs on a large scale to meet worldwide volume needs at acceptable costs.

Emerging Economics

In Asia and Latin America, asthma has been treated predominantly with Pressurised metered dose inhalers, which are considered to be a more cost effective proportion than DPIs. However, healthcare reforms in these regions are making asthma diagnosis and medication more available to patients, so it is anticipated that the DPI growth trend will spread to these areas. The availability of low-cost, patient friendly DPI options would encourage their use in emerging economics. [18]

CONCLUSION

The structure and design of inhaler have a major impact on the aerosol deposition to the lungs. An ideal inhaler should deliver precise and consistent doses to targeted region in the lungs and maintain the stability of the deliver drugs. DPIs are becoming more popular because of ease of use and the powder

stability. The future development of DPI devices will have to focus on simplicity of use, reliability, consistency, suitability for a large range of products and doses, cost effectiveness. It will be possible to adopt sophisticated technological approaches to solve the problems associated with efficient drug delivery to achieve local and systematic pharmacological effect.

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