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CAPSULE-BASED DRY POWDER INHALERS, AN OPTIMAL SOLUTION FOR DIFFERENT INSPIRATIONAL RATES

There is a wide range of devices available to deliver inhalation therapies, but there is increasing interest in the use of dry powder inhalers (DPIs) due to improved engineering and powder formulations. In this article, Gabriela Dujovny, Scientific Business Development Manager, Qualicaps, looks at the advantages and disadvantages of the DPIs currently available and reports on a study of dry powder inhalation aerosolisation performance at different flow rates.

There are several routes available for drug administration, of which the most popular have been oral and injectable. Advances in drug delivery technology have led to the development of several non-invasive, self-administered forms that offer excellent alternatives to these more traditional routes. For example, inhalation technology of medicines offers significant and unique benefits as the delivery of the active compounds targets the lungs directly, minimising side effects from systemic distribution and allowing for a lower dose together with a rapid onset of action.

It is the preferred route for drug administration in chronic respiratory diseases, primarily asthma and chronic obstructive pulmonary disease (COPD); although besides the treatment of respiratory diseases, inhalation drug delivery is also being investigated for a wide range of potential systemic therapies, such as insulin, oxytocin, antibiotics, vaccines and drugs (including peptides and proteins) for neurological disorders.

Pulmonary drug delivery technologies are based on developing simple, easy-to-use, cost effective devices. These devices should provide consistent drug delivery, with high lung penetration and a multiple dosage capacity. Portable devices can be essentially grouped into two main categories: pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). DPIs are gaining market share and are forecasted to become the dominant player by 2018 (Figure 1).[1] This growth is due to new developments along with improved device engineering and more adequate powder formulations. In addition, DPIs are activated by the patient's inspiratory airflow and subsequently are breath-actuated, therefore eliminating the dependence on hand-mouth co-ordination required with pMDIs.

> "One of the most important characteristics of micro-dispersed particles generated after inspiration is their particle size."

DPIs currently available on the market include:

- Single-dose capsule DPIs, e.g. Aerolizer, Novartis, Basel, Switzerland; Handihaler, Boehringer-Ingelheim, Ingelheim am Rhein, Germany
- Multi-dose devices:
  - Those devices with a bulk drug reservoir which is metered by the patient during use, e.g. Turbuhaler, AstraZeneca, London, UK; Twisthaler, Schering, Kenilworth, NJ, US.

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- Those with pre-metered dispensed doses packaged inside blisters, Diskus (Accuhaler® in the UK), GSK, Brentford, UK.

Each inhaler type has advantages and disadvantages that must be considered with regard to drug delivery performance.

FACTORS THAT AFFECT DPI DRUG DELIVERY PERFORMANCE & EFFECTIVENESS

The effectiveness of powder drug delivery to the lungs depends on several factors:

- Powder formulation
- Inspiratory airflow rate generated by the patient
- Device intrinsic resistance to airflow defined as the turbulence produced inside the device to generate the respirable inhalation aerosol
- Humidity, that can affect the dose delivery from the DPI.

The inspiratory airflow generated by the patient represents the only active force able to produce the micro-dispersion of the powder formulation for inhalation. One of the most important characteristics of micro-dispersed particles generated after inspiration is their particle size.

Inhaled drug particles will deposit in different regions of the respiratory tract according to their particle size: particles of 1-5 µm will deposit in the respiratory airways – the target area of therapeutic application – while particles >5 µm will predominately deposit in the oropharynx. This relates to particle dynamic behaviour and describes the main mechanisms of aerosol deposition:

- **Inertial impaction:** which mainly influences the deposition of larger particles where the ability to follow the respiratory flow is reduced proportionally to velocity of flow. This occurs mainly with large or high-velocity particles, i.e. those with high inertia, that are unable to follow the airstream when it changes direction, thus impacting on the airway wall, usually the upper part of the airways.
- **Sedimentation:** process proportional to the aerodynamic particle size and to the period during which the particles remain in the lungs.[2,3] Therefore, a short retention at the end of respirable airways increases the likelihood of lung deposition.[4]
- **Diffusion:** particles smaller than 0.5 µm may not deposit at all, since they move by Brownian motion and settle very slowly.

In order to de-agglomerate powder particles from a bond on larger carrier molecules (such as lactose) into a respirable dose, a sufficient flow rate must be achieved in the DPI device.

On the other hand, stronger air flows cause a higher grade of impaction, resulting in higher rates of oropharyngeal deposition. Therefore, lung deposition in most DPIs depends considerably on the patients' inspiratory flow rate and the particular device's intrinsic resistance.

The intrinsic resistance to airflow through the device is an important determinant of the final flow rate resulting in the inhaler. It defines how much inspiratory flow should be created in the device to release the correct amount of the delivered drug. However, flow resistance differs from device to device, and the recommended evaluation to determine the correct flow rate for a particular DPI is *in vivo*/*in vitro* testing of the device.

To calculate the correct flow rate to be tested, it is necessary to establish the flow rate that produces a drop in pressure with the device of approximately 4 kPa, comparable with that found *in vivo* when using a particular inhaler under study with its specific resistance.[5] The efficacy of DPIs depends on the strength and duration of a single inhalation by the user. The duration of the test is set on the basis of the total air volume typically inhaled in one adult breath, adjusted to be four litres in the case of the EurPh and two litres in the case of the USP.

DPI devices have different intrinsic degrees of resistance to flow, i.e. some require more effort to inhale than others. A low-resistance device presents less resistance to airflow, meaning that it may be easier to use and therefore more effective for patients. Conversely, in high-resistance devices, patients need to apply greater effort to generate the necessary inspiratory flow to allow for an optimum drug delivery.[6]

However, the dependency of a DPI on inspiratory flow rates involves contradictory aspects that can generate a conceptual misunderstanding that comes into play when deciding which DPI is more convenient for the patient in real life. It has been shown that a higher intrinsic resistance of a DPI needs stronger inspiratory capacity, but reduces oropharyngeal deposition of the particles because the impaction of particles in larger airways is diminished.

Although low-resistance devices are associated with the concept of "the most effective DPIs", they require inspiratory abilities sufficient enough to de-agglomerate the medication formulation into particles suitable for lung deposition (micro-dispersion)[7] and frequently cannot be achieved by those affected with a disease-induced airflow limitation.[8] A patient capable of reaching a flow rate of more than 60 L/min is considered ideal for use of most DPI devices.[9]

The other factor that can affect DPI performance and effectiveness of drug delivery is humidity, which can cause clumping of the particles and reduce the de-agglomeration of the respirable aerosol. For example, reservoir-based DPIs have chambers

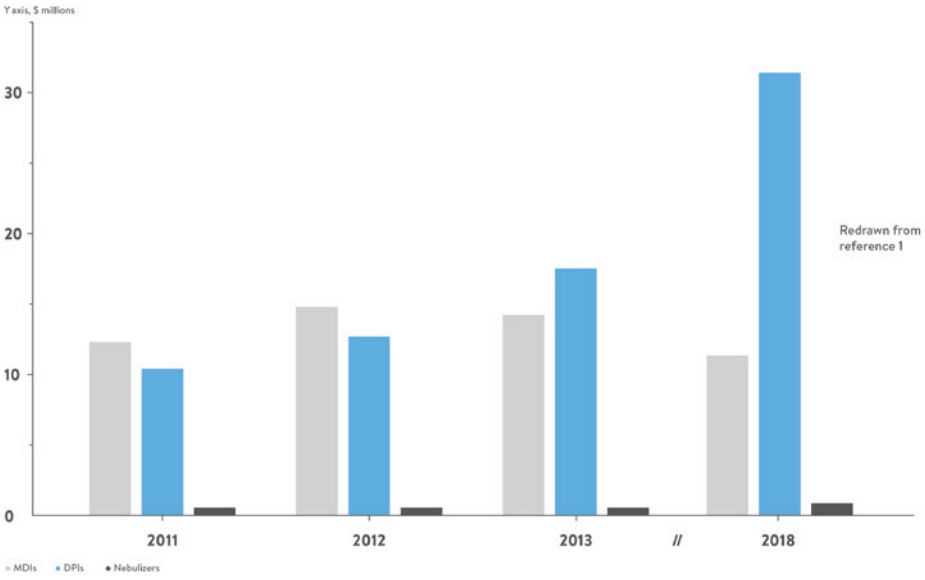
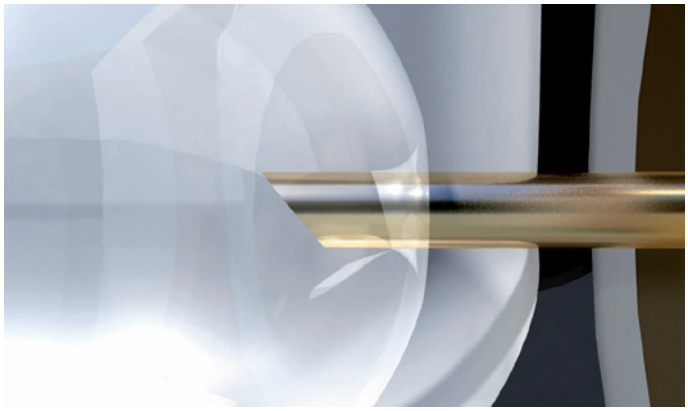


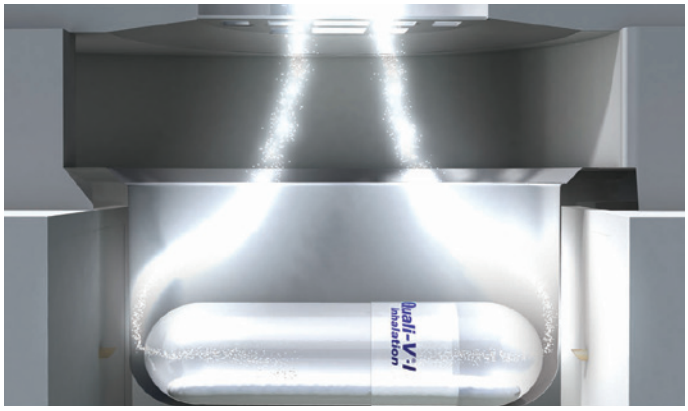
Figure 1: Global market for pulmonary drug delivery technologies, a comparison in the growth in the 3 main types.

1) Device opening

2) Puncturing



3) Aerosolization



4) Patient inspiration

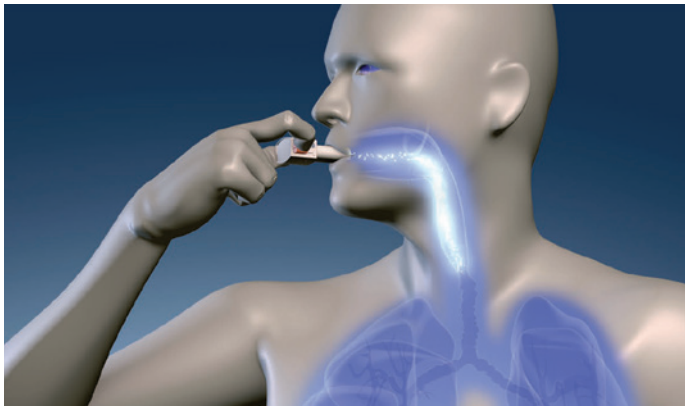


Figure 2: Steps followed by capsuled-base DPIs inhalation.

containing multiple doses for dispensing and offer less protection from humidity in the environment than capsules, so they must be stored in dry conditions.

In contrast, two-piece, hard-shell capsules are an established dosage form for DPI systems, in which they are used as a single-dose container for a powdered drug,[10] protected within blisters and thus unaffected by changes in ambient humidity. Capsule-based DPIs are loaded before each inhalation and punctured within the device, so that the powder is evacuated from the shell with minimum retention (Figure 2).

USING CAPSULES FOR DPI DEVICES

The first marketed product in a capsule-based DPI used gelatin capsules. However, they have a well-known drawback of becoming brittle as they lose moisture when exposed to low humidity, because water acts as a plasticiser for the shells. To minimise this issue drastically, capsules were developed from another polymer, hypromellose (HPMC), which is not dependent on moisture content to maintain its structure. This resulted in

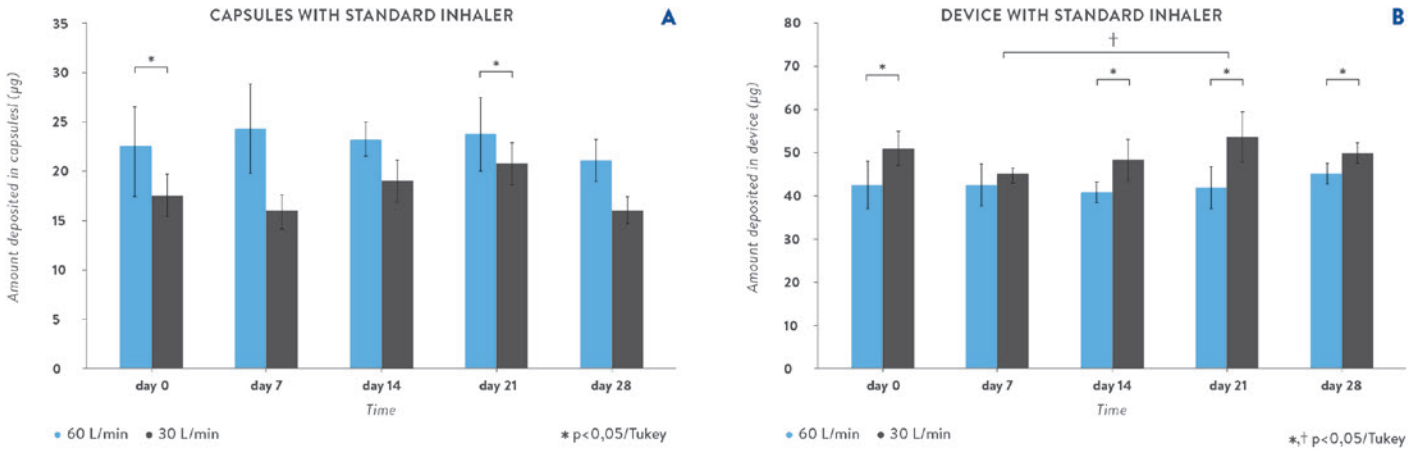


Figure 3: Deposition of salbutamol sulphate remaining in (A) capsules and (B) device, following aerosolisation at 60 L/min and 30 L/min from a 2-pin standard inhaler (Mean ± SD, n=6). * indicates significance between 30 and 60 L/min. # - indicates significance between different time points at 60 L/min. † indicates significance between different time points at 30 L/min.

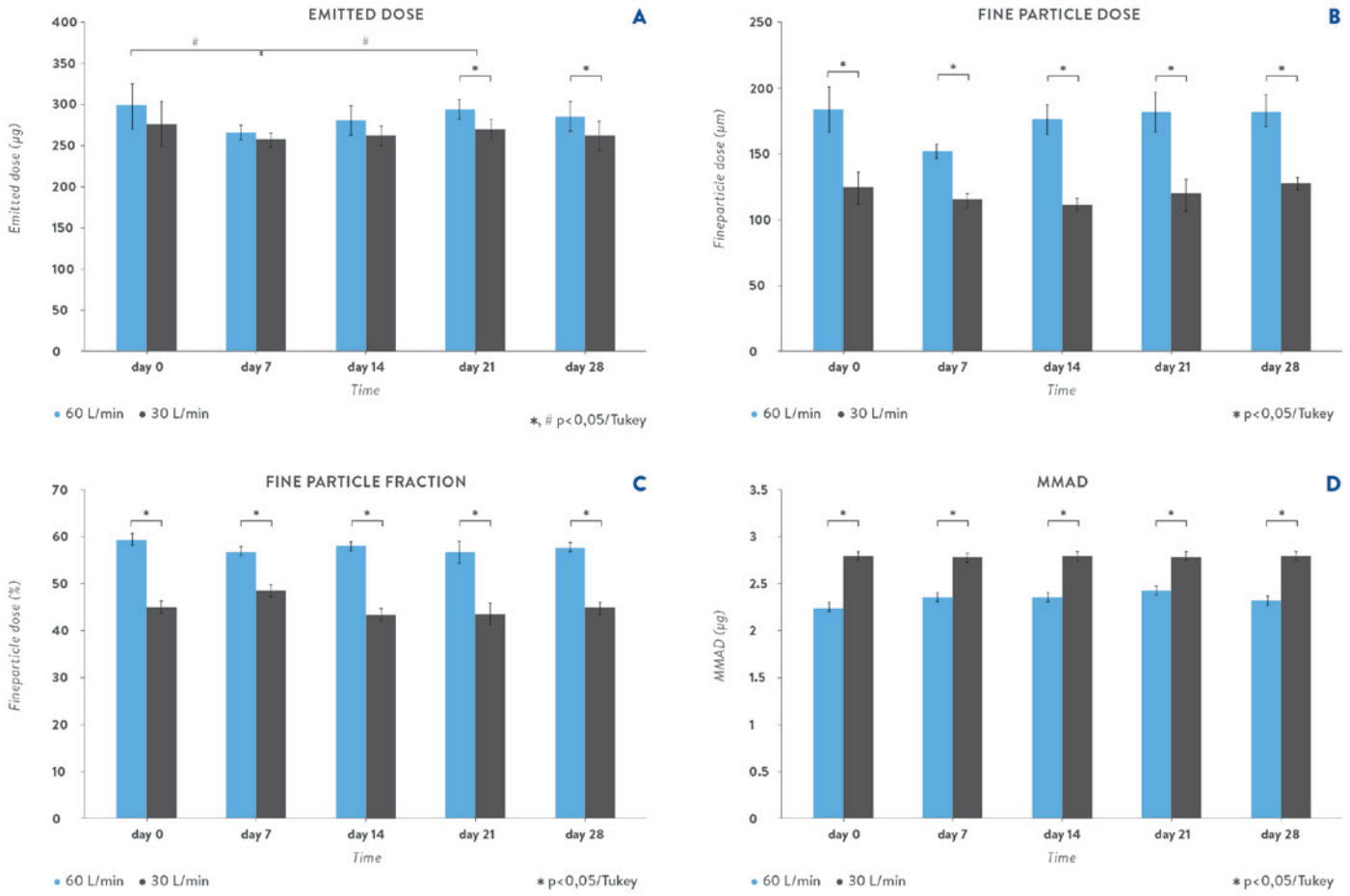


Figure 4: (A) Emitted dose (µg), (B) Fine particle dose (µg), (C) Fine particle fraction (%), (D) MMAD (µm) of salbutamol sulphate at 30 and 60 L/min from a 2-pin standard inhaler (Mean ± SD, n=6). * indicates significance between 30 and 60 L/min. # indicates significance between different time points at 60 L/min.

Quali-V® (HPMC) capsules launched by Qualicaps® in 2002,[11] that were later specifically tailored for the inhalation application and branded as Quali-V®-I.

The grade of HPMC chosen for these capsules had the correct hydroxypropyl/methyl ratio and the correct molecular weight distribution to ensure exceptional puncturing and cutting properties. Their moisture content of 4.5-6.5% is lower than that of gelatin capsules (13-16%), thus providing a capsule suitable for moisture-sensitive active ingredients. These capsules can be dried down to lower moisture contents if required without affecting their physical properties.

STUDY: DRY POWDER INHALATION AEROSOLISATION PERFORMANCE AT DIFFERENT FLOW RATES

The aim of the study* was the investigation of the aerosolisation properties of a dry powder formulation composed of inhalation-grade lactose and micronised salbutamol, in Quali-V®-I (size 3) capsules, using a standard low resistance 2-pin inhaler device RS01 (Plastiape Spa, Osnago, Italy) at different flow rates (30 and 60 L/min) in order to assess the ability of patients to effectively use the device with various degrees of airway obstruction.

Preparation of inhalation-grade lactose mixed with micronised salbutamol (50:1 w/w), *in vitro* drug deposition and analysis of Salbutamol were performed.[12] The capsules were dispersed through a 2-pin DPI RS01 low-resistance inhaler and punctured. *In vitro* impaction measurements were taken for the two formulations at 30 and 60 L/min to determine the influence of a sub-optimal air flow rate on the aerodynamic properties of the RS01 low-resistance inhaler.

The key aerosolisation parameters were evaluated. The emitted dose (ED) was calculated as the total mass of drug depositing in the mouthpiece, induction port, pre-separator and new generation impactor (NGI) stages. The fine particle dose (FPD) was determined as the mass of drug deposited in the NGI with aerodynamic diameters ≤ 3.99 µm for 30 L/min and 4.46 µm for 60 L/min.

The fine particle fraction percentage (% FPF) of each dose was the ratio of the drug mass depositing in the NGI over the emitted dose. Mass median aerodynamic diameter (MMAD) was calculated by subjecting the inertial impaction data to log-probability analysis. Mass of drug remaining in capsule and device were measured.

Comparing capsules and device:

- Less deposition of the drug was observed in capsules with 30 L/min compared with 60 L/min (Figure 3A). Neither a significant increase nor decrease can be observed at both the flow rates with time.
- A significant difference in the deposition of salbutamol in the standard inhaler was observed between the flow rates (Figure 3B).

Comparing ED, FPD, FPF & MMAD:

- There was no significant difference in the aerosolisation parameters of salbutamol across different weeks of analysis (Figure 4).
- There was a significant difference between the different flow rates used (30 and 60 L/min) for: ED, FPD, FPF and MMAD (Figures 4A–D).

- A higher flow rate (60 L/min) indicated more FPD and FPF with lower MMAD when compared with the lower flow rate (30 L/min) (Figures 4B–D).

CONCLUSIONS OF THE STUDY

- The results indicate significant differences in powder retention with higher deposition at 60 L/min within capsules and 30 L/min in the device.
- In addition, the ED, FPD, FPF was significantly greater at 60 L/min compared to 30 L/min at each time point.
- This demonstrates the important relationship between inhalation, therapeutic dose and lung deposition.
- However, despite these differences there was very little significant variability when comparing each flow rate over time. Hence, there is very good dose reproducibility, which is important for ensuring equivalent doses are administered during the treatment cycle.

Integration of all the above data highlights that there is a link between the emitted dose (especially particle size under 5 µm), total lung deposition and ultimately clinical response.

In its standard version, the RS01 is a low-resistance device reaching a pressure drop of 4 kPa at 100 L/min. The results obtained showed that this capsule-based device was useful even at lower flow rates than 60 L/min; it is therefore suitable for use on a wide range of patients. However, for acute asthma or COPD (low-respiratory capacity in patients), there are other capsule-based DPIs with a high-resistance to airflow, such as HandiHaler, that work properly for inspiratory flow rates of less than 50 L/min to produce a pressure drop of 4 kPa, recommended to obtain powder de-agglomeration.[12, 13]

On the other hand, previous studies using the multi-dose device inhalers Diskhaler and Easyhaler showed salbutamol FPF values of 30.5% and 32.1% for 60 L/min and 90 L/min in the case of Diskhaler and 36.0% for 60 L/min using Easyhaler.[14] In comparison, data obtained in the present study showed that for a flow rate of 30 L/min, FPF was approximately 40%, which is higher than those provided by studies referenced in the following bibliography. Overall, data demonstrated that HPMC capsules specifically designed for inhalation (marketed as Quali-V®-I) represent an ideal option for DPI devices.

** This research was conducted in its entirety by Imran Y. Saleem, PhD, School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK, and sponsored by Qualicaps®.*

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