



Assessing dry powder inhalers

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The performance characterisation of dry powder inhalers (DPI) recognises the importance of three factors: the device, the formulation and the patient.

Successful product development demands an understanding of how each of these shapes drug delivery, and how to test the product in a relevant way.

To enable what would otherwise be impractical, invasive and potentially dangerous testing, and to remove the huge variation and costs associated with human subjects, it is common practice to test inhalation devices and formulations using *in vitro* test apparatus. Industry standard test conditions and relevant parameters have been devised and published by the regulatory authorities and within the pharmacopoeias to enable accurate comparisons between data sets. For dry powder inhalers (DPIs) performance is a function of the applied breathing profile and this is reflected in the developed methodologies. However, while standardised protocols are an essential aspect of efficient research and routine equivalency testing, the recommended representative inhalation profile does not attempt to accurately reflect performance across the entire patient population.

This paper discusses the measurement parameters, potential variables and interactions between each of the three main factors in DPI drug delivery. Delivery mechanisms, test apparatus and pharmacopoeial test conditions are reviewed. We also look at a method for assessing the impact of 'non-standard', low flow rate profiles on product performance. More representative of geriatric, paediatric or chronically ill patients, low flow rate data can demonstrate whether or not patients with weaker inhalation profiles can access the DPI performance necessary to receive an efficacious dose.

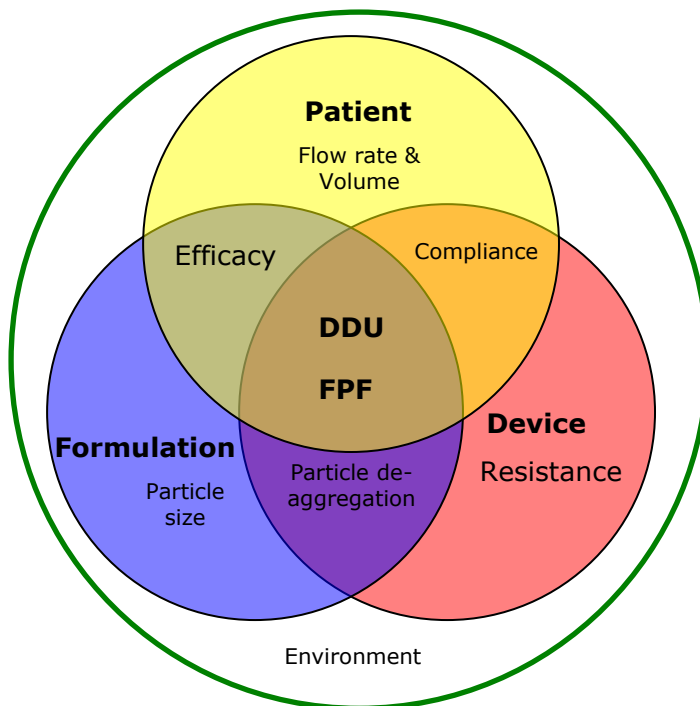


Figure 1: A simple model for dry powder inhaler (DPI) testing

An inhalation therapy model

There are three main factors involved in the most basic model of an inhalation therapy: the formulation containing the active pharmaceutical ingredient (API); the device used to deliver it; and the patient receiving it. As shown in figure 1, each of these plays an active role in consistent, efficacious treatment. In the case of dry powder inhalers (DPIs), potential particle cohesion and compaction issues caused by a high humidity environment must also be considered¹.

With DPIs the patient, device and formulation must consistently combine to successfully aerosolise the dose, delivering particles containing active pharmaceutical ingredient (API) in the correct size range for optimal *in vivo* deposition and absorption. Only particles below approximately five microns are likely to get beyond a patient's pharynx during inhalation and subsequently deposit in the lung. The percentage of these fine particles relative to the total number of aerosolised particles - the fine particle fraction (FPF) - is therefore a critical measure during *in vitro* inhalation testing. An understanding of how formulation properties, device design and patient compliance and capabilities impact FPF, and other key parameters, is crucial for effective DPI development and testing.

The device

Dry powder inhalers (DPI) may be used to deliver both locally-acting and systemic drugs. They are often classified into two types: pre-metered or single dose systems that use capsules, or blister packs, to predetermine the amount of medication available with each inhalation, and reservoir or device-metered, multi-dose systems where a mechanism within the device itself is used to measure out each dose. Most devices are defined as passive which means that patient inhalation draws the dose from the device and into the lungs; the strength of the breathing manoeuvre providing the only motive force for aerosolisation and delivery.

One of the main advantages of DPI technology is the automatic coordination of dose delivery with inhalation and the removal of any need for a propellant. In general, this makes them easier to use than a metered dose inhaler (MDI) and less likely to cause irritable side effects due to additives ^(2,3). In addition, DPIs offer better sterility and stability, and play to the strengths of an industry already fluent in dry powder formulation science. Following the Montreal Protocol's progressive phasing out of the chlorofluorocarbons (CFCs) used in propellants, propellant-free DPI delivery can offer a better alternative than reformulation for a metered dose inhaler (MDI) using hydrofluoroalkanes (HFAs) or other alternatives.

However, because DPIs rely on inspiratory effort to deliver active pharmaceutical ingredient (API), their use can be limited. Effort dependent drug delivery has the potential for poor repeatability⁴ especially in weaker patients, and training is required to ensure an effective and repeatable inhalation technique.

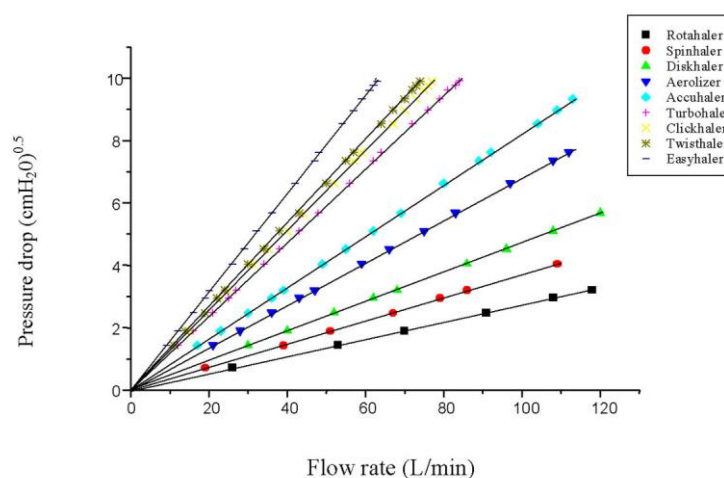


Figure 2: Resistance differences between dry powder inhalers

It is important to recognise that the resistance to flow that a DPI device presents is a function of its design (Figure 2). The air flow that a patient, inhaling with consistent strength, can generate through a DPI will therefore vary from device to device. A high resistance device will be associated with much lower air flows than one that presents much less resistance. Testing under representative conditions is essential to ensure that the flow rate induced by the patient's inhalation strength will adequately aerosolise a given formulation.

The formulation

Usually a DPI formulation consists of API and excipients, such as lactose. Ideally it would be API alone but because particle/particle interactions increase with decreasing size it is often not feasible to process, de-aggregate and aerosolise the typically fine API powder. To get around this, formulators use larger excipient particles as carriers. These carrier particles make the product easier to manufacture and handle, but must be stripped away from the dosage during aerosolisation, returning the API to its primary particle size for deposition in the lung.

A formulation will be compatible with a given device if the flow rate the patient can generate during inhalation de-aggregates the powder bed with sufficient energy to disperse the dose. Manipulation of the physical properties of the formulation is one way of achieving this goal, changing to a device with different flow resistance properties (e.g. shear forces) is an alternative.

The patient

Although using a DPI eliminates the difficulty of having to teach a patient to synchronise inhalation with device actuation, patient compliance remains an issue and some training on inhalation technique is still required.^(4,5) Furthermore as shown in table 1, the breathing pattern of a patient is influenced by their physical size and strength – often age associated - and their health. It is clear that geriatric and paediatric patients, or those with severely compromised respiratory capacity due to chronic or acute conditions, do not produce the same breathing profile as a healthy adult and might therefore struggle to produce the energy required to fully access a DPI dose.

	ASTHMATIC CHILD			ADULT ASTHMATIC			COPD		
Severity	MILD	MOD	SEV	MILD	MOB	SEV	MILD	MOD	SEV
N	101	20	8	7	10	13	34	36	25
Age	10.5 (4.2)	9.5 (3.6)	10.3 (3.2)	48.3 (14.7)	53.3 (19.7)	66.0 (10.0)	78.5 (10.2)	75.6 (9.4)	72.6 (9.9)
MDI	112 (16)	98 (24)	109 (18)	>120	111 (15)	106 (16)	102 (21)	100 (23)	95 (28)
Aerolizer	102 (22)	82 (26)	91 (16)	108 (16)	84 (22)	81 (23)	69 (21)	72 (24)	64 (22)
Diskus	87 (23)	71 (23)	80 (17)	92 (19)	71 (22)	70 (21)	60 (17)	63 (21)	56 (16)
Turbuhaler	72 (17)	58 (18)	66 (12)	76 (21)	56 (19)	54 (18)	47 (13)	48 (16)	43 (14)
Clickhaler	73 (16)	57 (16)	65 (11)	72 (21)	54 (18)	53 (18)	47 (13)	48 (17)	42 (14)
Twisthaler	58 (12)	47 (14)	53 (10)	60 (18)	45 (16)	44 (15)	39 (11)	40 (14)	35 (11)
Easyhaler	54 (11)	43 (14)	49 (7)	55 (13)	40 (12)	40 (12)	33 (10)	35 (13)	31 (10)

Table 1: Inhalation flows measured through a variety of inhalers

Ref: Chrystyn, H. (2009) *Effects of Device Design on Patient Compliance: Comparing the Same Drug in Different Devices; delivered at Respiratory Drug Delivery Europe 2009*

Failure to achieve the required air flow or duration can result in incomplete dispersion and a lower dose of API to the lung. The risk of partial or even total non-delivery can cause several problems. While patients suffering from an acute disease are likely to be able to tell when they have not received the correct dose, and have the opportunity to try again, those with a chronic condition would have no way of knowing that they were not receiving beneficial treatment. This can lead to slow but progressive deterioration in their condition. Alternatively, a patient might simply assume that the formulation was ineffective and become non-compliant. Either way, the result is poor patient health and higher costs to the healthcare system.

Standard test conditions

In a standard test set-up for measuring the aerodynamic particle size of DPI aerosols, a patient's inspiration is replicated *in vitro*, as far as possible within the constraints of the technology, using a vacuum pump connected to a critical flow controller. A cascade impactor is used as an aerodynamic size fractionator for the delivered particles. Whilst broadly representative of lung deposition it is important to recognise that a cascade impactor is not a lung model, since particle deposition in the lungs is a function of a number of complex factors, such as sedimentation and diffusion as well as impaction⁶. The same test set-up using a particle collection tube (figure 3) in place of the cascade impactor is used to determine DDU.

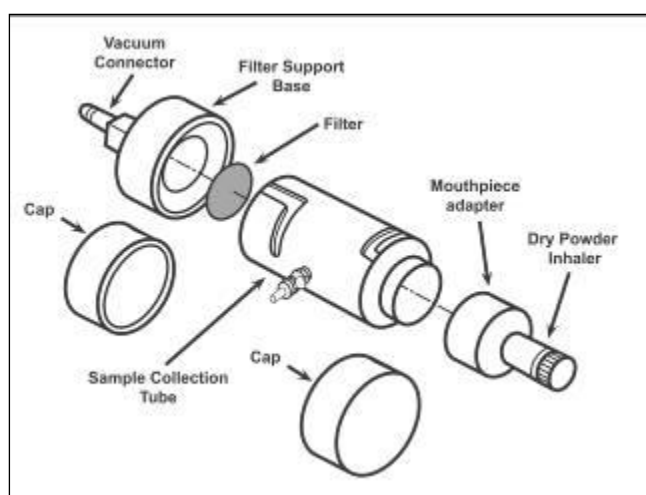


Figure 3: Schematic of a DPI sampling apparatus

Cascade impaction uses particle inertia to split the delivered dose into size fractions which are then analysed to generate an aerodynamic particle size distribution for the API. The flow rate and test time used are derived from figures that represent the strength and inhaled volume of a typical patient's inspiration; the method removing variables associated with the "patient". Standard test conditions based upon the flow profile of a typical adult have been agreed industry wide and published in pharmacopoeias and are widely used by manufacturers.

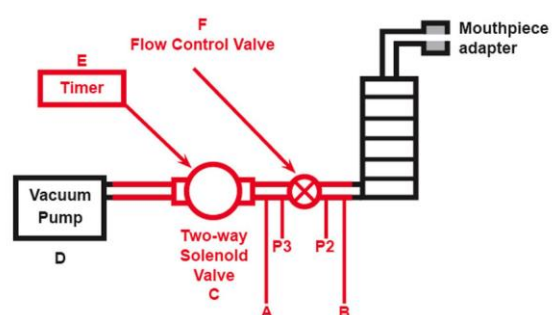


Figure 4: Diagrammatic representation of a system to measure aerodynamic particle size in DPIs

Cascade impactors used for inhaled product testing are constant flow rate devices, therefore requiring the production of a square-waved flow, rather than the approximate bell-shaped curve produced by a human breath profile. As shown in figure 4, a control valve is used to adjust the flow to give a 4kPa pressure drop over the device, as stipulated by the pharmacopoeias. The device is then replaced by a flow meter to determine the flow rate for all subsequent testing. As figure 2 shows, each device has a unique pressure drop / flow rate relationship influenced by its design. Low resistance DPIs can give very high flow rates and so the pharmacopoeias state an upper limit of 100 L/min. They also specify a total air volume of 4L for testing - although FDA guidelines set this at 2L, believing it to be more representative of a patient's forced inspiration volume. From the measured flow rate and specified air volume, test duration can be calculated. These pre-determined test conditions then apply for both DDU and aerodynamic particle size measurement testing.

Flow rate stability is critical for aerodynamic particle size measurements using a cascade impactor as the equipment's performance is itself dependent on air flow. The impact of fluctuations caused by variations in pump performance must be eliminated. This is done by ensuring that the pressure downstream of the flow control valve (P2, figure 4) is less than half of the upstream pressure (P3) giving a critical (sonic) flow condition across the valve.

Test equipment

Inhalation test equipment from Copley Scientific measure and record all the parameters required for determining air flow rate and maintaining constant, stable test conditions in accordance with pharmacopoeia recommendations.



Figure 5: Standard test set-up

Figure 5 shows a typical equipment set-up for DPI testing and includes a High Capacity Pump Model HCP5, a Critical Flow Controller TPK 2000 and an Andersen Cascade Impactor (ACI) with throat. An alternative impactor is the Next Generation Impactor (NGI) which is widely used throughout the pharmaceutical industry. The DPI being tested is connected to the inlet of the right-angled induction port (throat) with a mouthpiece adaptor. Particles greater than around 10 microns in diameter are removed from the aerosol cloud by a pre-separator placed between the induction port and the impactor inlet. Sample deposits are collected from each stage of the cascade impactor and analysed using high pressure liquid chromatography (HPLC).

Extended test conditions

While standard test conditions are ideal for comparative studies there is increasing interest in investigating DPI performance at lower flows that more accurately reflect the breathing profiles of weaker patients. Because cascade impactors rely on particle inertia, which is flow rate dependent, they naturally have a functional lower limit for flow rate. The Andersen Cascade Impactor (ACI), for example, was originally designed to provide calibrated performance for operation at 28.3L/min (1SCFM). Modified versions of the instrument have since been developed and calibrated for operation at 60 and 90 L/min but analysis becomes less accurate at conditions furthest away from these calibration points. Below 28.3 L/min, performance of the ACI is not well established, with little calibration data existing. However, the NGI is calibrated down to 15 L/min making it more suitable for low flow rate testing.



Figure 6: *Mixing inlet mounted on an ACI*

To achieve successful low flow rate DPI testing, it is possible to decouple flow rate through the inhalation product and impactor using a mixing inlet as shown in figure 6. Using this mixing inlet, the air flow from the inhaler is supplemented with a controlled stream of clean air through the side port. This way, the flow through the impactor is kept constant at a higher flow rate, ensuring good aerodynamic performance is maintained even when the flow rate through the device itself is low.

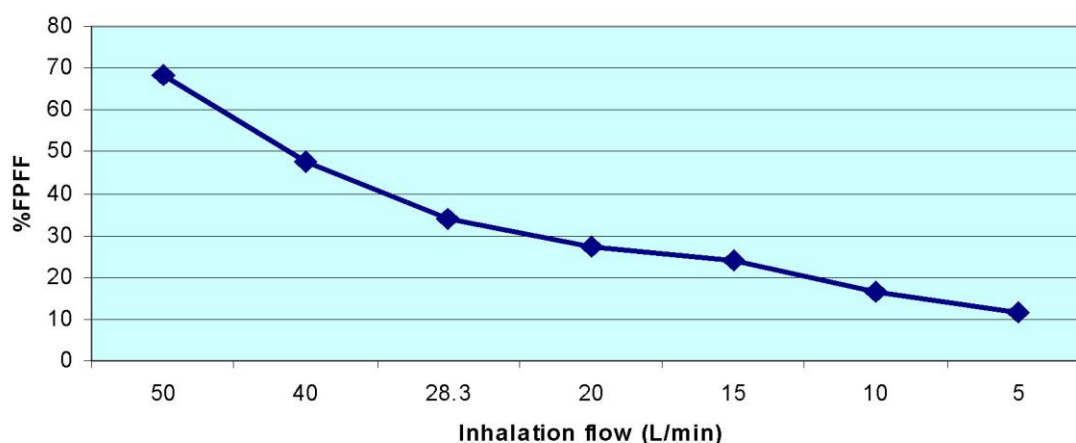


Figure 7: Effect of inhalation flow on %FPF for an example combination of dry powder inhaler and formulation [Adapted from Table 2, Nadarassan et al, 2007⁷]

Results shown in figure 7 clearly demonstrate the effects of lower inhalation flow rates on the %FPF in one example device/formulation combination. As flow rates drop, a reduction in FPF can be caused by failure to achieve aerosolisation to a suitable particle size and/or incomplete device emptying. Figure 6 results confirm that when this example device/formulation combination is used with low flow rates, there is an increased potential that the majority of API will be deposited in the mouth and throat rather than reaching the lung. This can lead to a loss of efficacy with each inhalation, which can ultimately lead to a loss of patient compliance, reduced efficacy and ineffective treatment in the long term.

Conclusion

DPI performance is dictated by the complex relationship between formulation, device and patient. Understanding these factors and how they influence key parameters such as delivered dose and fine particle fraction is essential for effective product development. Pharmacopoeias and guidance documents currently specify standardised test conditions to aid developers of inhalation technologies and formulations to provide comparative and repeatable test data.

These test conditions represent the approximate breathing profile of a typical adult patient, within the constraints of the *in vitro* test system, and successfully fulfil the need to reduce variation across device/formulation testing, providing valuable data for research and QC. Increasingly, however, there is interest in investigating how breathing profiles generated by the broader patient population impact drug delivery.

Copley Scientific leads the field of inhalation test equipment. The company not only supplies test set-ups specifically designed to easily reproduce results to Pharmacopoeial specifications, it also markets a mixing valve for low flow rate testing. This enables developers to extend their test protocols to include conditions representative of all patient types.

References

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