Understanding the links between drug delivery route and *in vitro* test methods

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In vitro tests are widely used, from R&D through to QC, to improve the efficacy of drug delivery and confirm product consistency. Ensuring a drug reaches its intended site of action in vivo, in an appropriate state, is a crucial first step towards meeting clinical performance goals. Drugs may be delivered by the gastrointestinal tract; or via the rectal and vaginal mucosal membranes; through the surface of the skin; or by inhalation via the nose or lungs. In each case the requirements for effective delivery are different and the tests applied to assess drug performance differ accordingly.

In this introductory white paper we review the drug product characteristics that define the success of delivery via any given route, and the tests used to measure them. A key focus is the link between the mechanisms of drug delivery and the test conditions applied.

Different routes, different challenges

A clear taxonomic guide for the classification of pharmaceutical dosage forms can be found in Chapter <1151> of the US Pharmacopoeia (USP) entitled "Pharmaceutical Dosage Forms". The top tier of this taxonomy is route of administration, a factor which has a defining influence on the formulation of a product and the testing strategies applied in its development and manufacture. Delivery route is determined early in the drug development process and is strongly influenced by the type of disease being treated, the intended therapeutic effect, and the nature of the active drug substance.
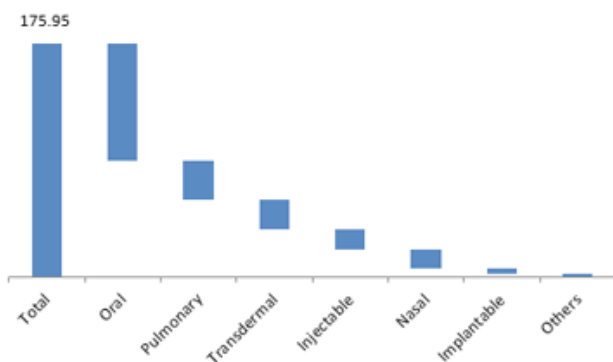
Figure 1: Global drug delivery technologies market, by mode of administration (USD Bn) [1]. Oral and injectable administrations took over 55% of the market share in 2015. The two modes represent the widest range of drugs in the pharmaceuticals market and, worldwide, are the most affordable methods.

Where a drug is specified for local action, for example, to rapidly ease breathing during an asthma attack or to alleviate eczema, then clearly this may mitigate towards a certain route, in this case pulmonary delivery and topical skin application, respectively. For systemic action, the options are broader, though physiology and the ability to quickly achieve a therapeutic effect may indicate one route above another. The commercial attractions of deriving efficiency gains from reformulation and a switch in delivery route may also be a factor. The gastrointestinal route is a highly effective way of delivering many systemic drugs, as evidenced from the fact that two thirds of all medicines prescribed today are oral solid dosage (OSD) forms. However, the drug substance must be sufficiently robust to avoid breakdown in the gastrointestinal tract; a criterion not met by many biopharmaceuticals.

In general terms, testing strategies focus on and quantify those aspects of the drug delivery process that are critical or rate limiting, for the specific product type. A drug required to act locally is not necessarily, or even desirably, absorbed into the blood stream. As a result testing focuses on getting the drug substance to the site of action – the delivery of drug particles to the lung, in the case of inhalers, for example, or the release of an active from a cream/emulsion matrix in the case of semisolids. Systemic drug administration, in contrast, relies on establishing a therapeutically effective concentration of drug in the blood or lymphatic system. This is potentially a more complex, multi-step process involving consideration of the rate of release from the product matrix and diffusion of the drug through specific biological barriers.

Adequately assessing a drug product for any given delivery route therefore calls for an understanding of the factors that will determine its efficacy, and identification of appropriate *in vitro* test methods to generate relevant data. The responsibility

for ensuring pharmaceutical products are safe, of adequate quality, and efficacious lies with the various national regulatory bodies, which are supported in their roles by the Pharmacopoeias. The USP and the European Pharmacopoeia (Ph. Eur.), define the standards with which the drug formulation shall comply, and the methods by which compliance will be judged, providing extensive support for test selection and optimisation.

Gastrointestinal delivery

OSD forms, such as tablets and capsules, are the most popular product type for the delivery of drugs via the gastrointestinal tract, though liquid medicines are a widely used alternative. The prevalence of OSDs is largely attributable to ease of administration and high patient acceptability, but physical and chemical stability is also an important feature. With these products the amount of drug introduced into the body is relatively easily controlled, by the patient taking a tablet containing a defined dose, but the rate of delivery may be less so, depending on the technology used. Controlled release products are precisely engineered to deliver a drug over an extended time period and maintain a consistent concentration *in vivo.*

Tablets are comprised of a mixture of active drug substances and excipients, usually in powder form, which are blended and then compressed to form the finished tablet. The quantity of active drug tends to be very low with the bulk consisting of: diluents, binders or granulating agents; glidants and lubricants to ensure efficient tableting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavours to enhance taste; and pigments to make the tablets visually attractive. A polymer coating is often applied to make the tablet easier to swallow and more resistant to environmental degradation, and to control release rate. Capsules differ from tablets in that they contain the drug formulation in a polymeric shell, typically hard gelatin. The associated manufacturing process therefore involves capsule filling rather than compression, a factor that directly influences the excipients used in the formulation. However, testing strategies for the two product types are closely similar.

Characteristics impacting product performance and the speed of drug delivery

Product stability is crucial for tablets and capsules which must be delivered to the patient intact, to ensure consistent dosing, and have a practical shelf life. Once the tablet has entered the body then its break down profile influences the rate of release, bioavailability and absorption of the drug. This process involves disintegration of the original OSD form, followed by dissolution of the resulting, smaller particles to produce a solution that can diffuse into the bloodstream.

Core testing requirements

Friability testing: Friability is the tendency for a tablet to chip, crumble or break and is one of the parameters used to quantify the physical integrity and stability of an OSD. Optimal friability gives the tablet sufficient physical stability for transport and storage while at the same time allowing it to break down readily in the gastrointestinal tract.

Methods and equipment for the friability testing of uncoated tablets are detailed in Ph. Eur. Chapter 2.9.7 and USP Chapter <1216>. Testing involves weighing a sample of tablets, rotating them in a drum of closely defined specification (the Roche friability drum) at a set speed, removing any loose dust/chips that have broken off from the tablets, and then reweighing the sample. The percentage weight loss quantifies friability, with a figure of <1% usually taken as the limit of acceptability.

For harder tablets and capsules, and for granules and spheroids, the level of attrition that occurs in standard test equipment is insufficient to give a meaningful result. Here alternative testing strategies are required, as described in Ph. Eur. Chapter 2.9.41, to apply a higher degree of abrasive action. With the equipment described in Method B: Oscillating Apparatus, for example, the horizontal shaking movement of an oscillating arm causes samples to rub against and collide with one another, and with the internal surfaces of the sample container, to promote breakage.

Hardness testing: Hardness, more correctly defined as breaking force (USP) or crushing strength (Ph. Eur.), is used alongside friability to quantify the physical stability of an OSD. Excessive hardness may result in long disintegration times and poor dissolution performance, while low hardness may be associated with high percentage defective figures and unacceptable weight variation.

Hardness testing is described in Ph. Eur. Chapter 2.9.8 and USP Chapter <1217> and involves placing the tablet between two platens or jaws, one attached to a load cell, the other to a motor which provides the mechanical drive. During testing the motorised jaw presses the tablet against the fixed jaw which measures the force at which the tablet breaks.

Disintegration testing: Disintegration is the first step in the breakdown of the tablet/capsule *in vivo*. Conditions within the gastrointestinal tract vary from patient to patient and assessment of the extent of disintegration can be subjective but the apparatus and methods described in Ph. Eur. Chapter 2.9.1 and USP Chapter <701> provide a reproducible and standardised method for assessment for all OSD forms.

Figure 2: A simple apparatus for standardised, reproducible disintegration testing

During disintegration testing the tablet or capsule is held in a tube within a basket assembly which moves up and down in a vessel containing a defined volume of simulated gastric fluid, held at 37°C (see figure). A plastic disc inserted in the tube, along with the sample, assists disintegration. The lower end of the tube is covered by a sieve mesh and the tablet is deemed to have passed the test if no residue remains on this mesh after a certain time period; 30 minutes is typical for ordinary tablet; 60 minutes for enteric coated tablets.

Dissolution testing: Dissolution testing is the primary *in vitro* method for investigating and comparing the bioavailability associated with different OSDs i.e. the amount of drug that the product makes available to the body. Measurements of dissolution rate support the optimisation of bioavailability and consequently therapeutic efficacy, and are also used to assess bioequivalence, for generic products, and for the confirmation of batch to batch equivalence, in QC.

The progressive optimisation of dissolution testing for different OSD forms has led to the introduction of a range of different apparatuses and techniques as detailed in Ph. Eur. Chapter 2.9.3 and USP Chapter <711>. Factors that influence the results obtained include: the composition and de-aeration state of the dissolution media; the precise physical dimensions of the test apparatus; and the test conditions applied, most especially whether these ensure that the tablet is dissolving into sink conditions i.e. that dissolution is not inhibited by a high localised concentration of drug substance. Furthermore dissolution rate can change as the tablet dissolves since this process naturally reduces the exposed surface area. Intrinsic dissolution testing is a distinct method which directly addresses this issue via constant surface area testing.

The most common apparatuses used for dissolution testing are Basket (Apparatus 1) and Paddle (Apparatus 2). A dissolution tester consists of a cylindrical vessel that holds the simulated gastric juice dissolution media, and is partially immersed in a water bath to maintain the dissolution apparatus at 37°C. In the Basket method, the tablet or capsule is contained in a cylindrical mesh basket, whereas in the Paddle method, it simply sinks to the bottom of the vessel below a paddle (see figure). During testing, the basket or paddle is rotated at a specified speed, and samples of the dissolution media are extracted at predefined time intervals to determine the percentage of dissolved drug present, typically via HPLC. These results enable the generation of a dissolution profile, a plot of drug release as a function of time. Other techniques specified in the USP for dissolution testing include: Reciprocating Cylinder (Apparatus 3), Flow-Through Cell (Apparatus 4) and Reciprocating Holder (Apparatus 7). These are not routinely required except for highly specialised dosage forms.

Figure 3: The most common types of dissolution testing apparatus are Apparatus 1 (Basket) and Apparatus 2 (Paddle)

Dermal delivery – topical and transdermal

Pharmaceutical products applied directly to the skin may be designed for topical action or for systemic delivery, and the test methods applied are differentiated accordingly. The majority of topical drugs are classified as semisolids, a group of products which includes creams, ointments, lotions and gels. These are typically hydrocarbon-based systems or oil in water emulsions incorporating additional ingredients such as emulsifiers, stabilisers, pH buffers, preservatives, absorption promoters and perfumes, and are applied to the skin for immediate relief.

In contrast, transdermal drug products (TDPs), most often patches, are designed to release an active ingredient through the skin into the bloodstream, over a prolonged period. Primary examples are products for hormone delivery and smoking cessation. Transdermal patches contain a reservoir of drug which is held within a physical device incorporating multiple polymeric membranes and layered matrices. These control the rate of release of the drug from the product, which is held in close contact with the skin by an adhesive.

Transdermal products enjoy a high degree of patient acceptance/compliance and are easy to use. In addition, semisolids are often formulated to deliver a moisturizing effect, which can enhance topical relief and efficacy, while TDPs offer the important advantages of avoiding first-pass metabolism in the gastrointestinal tract and enabling controlled release over a prolonged period. However, the skin is a highly efficient barrier against the outside environment so ensuring that a drug substance reaches the intended site of action can be a defining challenge for systemic delivery.

Characteristics impacting product performance and the speed of drug delivery

Transdermal products are subject to both product quality and performance testing. Product quality tests assess general physical attributes while performance tests focus on the release of the drug substance from the formulation matrix. For semisolids, product quality tests are detailed in USP Chapter <3> and address issues such as apparent viscosity, which impacts ease of use, and product uniformity over the defined shelf life. Performance testing involves measurement of the amount of drug released and the rate of release from the emulsion.

Product quality tests for TDPs include the measurement of tack and adhesion, which is crucial for keeping the product in place and, as for semisolids, are detailed in USP Chapter <3>. TDP performance is more complex to assess. For absorption into the blood stream the drug must diffuse out of the layered matrix of the product then through the layers of the skin to reach the capillaries that provide access to the blood stream. Diffusion from the product is controlled by the design of the patch while the rate of diffusion through the skin is influenced by physical and chemical properties of the drug such as: liposolubility; molecular weight; and electronic structure. Methods for testing TDPs have consequently been expanded beyond the simple measurement of dissolution rate across a solid-liquid interface to include the kinetics of membrane transfer.

Core testing requirements

Semisolids

Performance tests for semisolids are now detailed in (proposed) USP Chapter <1724> which describes three different apparatuses for the determination of drug release: Vertical Diffusion Cell (VDC); Immersion Cell; and Flow Through Cell (Apparatus 4). Of these the VDC is emerging as the preferred option, due to its simplicity and reproducibility.

Figure 4: 7 and 20 ml VDC designs are available for testing different volumes of semisolids.

A VDC comprises a sample holder and a reservoir containing the receptor medium, which is typically maintained at 32°C to approximate normal skin conditions (37°C for vaginal preparations). These two parts are separated by a membrane

which contains the test sample while at the same time keeping it in contact with the receptor medium. Over time – a typical test period is 6 hours - the drug substance diffuses from the sample, through the membrane into the receptor medium. As with dissolution testing, the extraction and analysis of samples of receptor medium therefore enables the generation of a drug release profile. Topping up the receptor reservoir as sampling proceeds keeps the sample in contact with receptor medium at all times, maintaining the diffusion process.
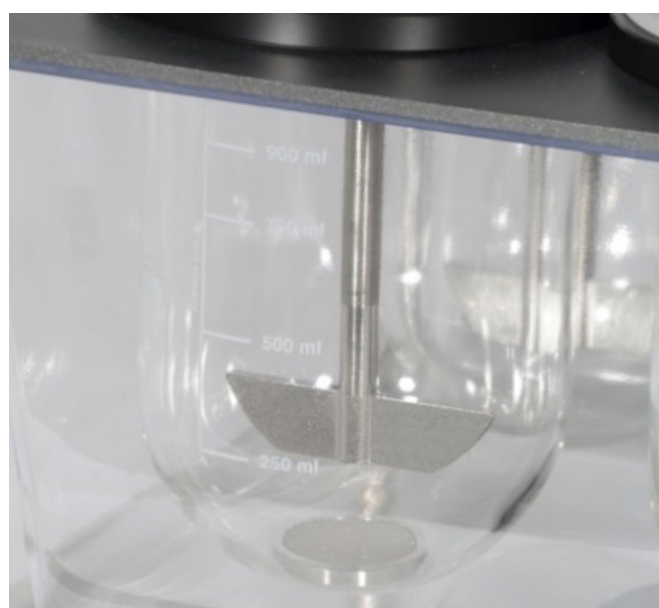
TDPs

Compendial methods for measuring the drug release performance of TDPs are closely analogous to the techniques used for OSD dissolution testing with three alternative apparatuses to choose from: Paddle over Disk; Rotating Cylinder; and Reciprocating Holder (Ph. Eur only). The Paddle over Disk method is a modified version of dissolution test Method 2 (Paddle Method) and increasingly preferred on account of its simplicity. It is described in USP Chapter <724> Method 5 and Ph.Eur.Chapter 2.9.4. Method 1.

Delivery via the rectal and vaginal mucosal membranes

Delivering drugs via the rectal or vaginal mucosal membranes advantageously avoids digestion in the gastrointestinal tract, in the same way as transdermal or inhaled drug delivery. Suppositories, solid formulations that are inserted into the body cavity, are the most common form of product for delivery via this route and share many of the same attributes as tablets. They may be hydrophilic or lipophilic in nature, depending on the intended application, and can be used to achieve topical action or for systemic drug delivery, the delivery of contraceptives being a primary application. However, suppositories have relative low patient acceptability and convenience, and drug absorption can be relatively unpredictable.

Suppositories contain an active drug substance formulated in a solid matrix. Hydrophilic products are formulated with a water-soluble base such as polyethylene glycol and, once

Figure 5: Methods for performance testing for TDPs use modified OSD dissolution testing apparatus and include: Rotating Cylinder (left) and Paddle over Disk (right).

The Paddle over Disk method makes use of standard dissolution testing apparatus, together with a disk assembly comprising a stainless steel screen and holder. Different disks are available for testing differently sized patches. The TDP is mounted onto the disk, release side up, using a suitable adhesive, and the disk assembly is then placed at the bottom of the dissolution vessel which is filled with preheated, degassed media held at 32°C to simulate skin conditions. During testing the paddle is rotated at a defined speed and samples are extracted from the dissolution vessel to determine a release profile for the drug substance.

inserted into the body, disintegrate and then dissolve into the rectal or vaginal fluids. Lipophilic suppositories, on the other hand, have a greasy base such as cocoa butter, which melts at body temperature to release the drug.

Characteristics impacting the success and speed of delivery

As with OSD forms, suppositories reliably introduce a defined dose of drug into the body, so it is the rate of release that is less easily controlled and the focus of testing. For hydrophilic products disintegration is an important part of the drug release process, while for lipophilic formulations softening

and melting times are key; no single method of drug release testing is suitable for all types of suppositories.

Core testing requirements

The suppository is a more common and accepted dosage form in Europe than in the USA, which may explain why Pharmacopoeial references to specific test methods for suppositories, are mainly confined to the Ph. Eur. The rate of dissolution of hydrophilic suppositories can be measured using the standard Paddle, Basket or Flow Through methods described in USP Chapter <711> and Ph.Eur. Chapter 2.9.3. The European Pharmacopoeia 8th Edition also includes a disintegration method for these products in Chapter 2.9.2. To quantify disintegration a sample is inserted into a cylindrical sample holder that is immersed in a glass vessel contained within a water bath controlled at 37°C. Every 10 minutes, during testing, the sample is inverted through 180 degrees to promote disintegration which should occur within a predetermined time.

Figure 6: Disintegration testing apparatus for hydrophilic suppositories can also be used to measure the softening times of lipophilic products.

Methods described for measurement of the dissolution rate of lipophilic suppositories include a modified Basket method, a Paddle method using a sinker and a modified Flow Through Cell with dual chamber which is described in Ph. Eur. Chapter 2.9.42. The softening time of lipophilic suppositories can be measured using the same apparatus as for hydrophilic disintegration testing but with alternative attachments, as described in Ph. Eur. Chapter 2.9.22.

Inhaled delivery

Pulmonary drug delivery is the most popular choice for the topical treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), while nasal drug delivery is used routinely for the treatment of allergies, rhinitis, colds and flu. However, like other parenteral delivery methods both inhaled routes avoid digestion of the drug substance and may also be used for systemic therapies. Antibiotics may be delivered via the lung, for example, while migraine treatments are able to rapidly reach the central nervous system via the dense blood vessel network at the back of the nasal cavities.

A primary point to recognise about inhaled drug delivery routes is that the dose delivered to the patient is not precisely controlled. Rather it is a function of features of the inhalation device, of the formulation, and of the physiology and inhalation technique of the patient. This differentiates inhalation from any other delivery route, as well as defining the testing landscape for orally inhaled products (OIPs).

The successful delivery of drugs to the lungs calls for the generation of particles of a respirable size and several different types of product are used. Dry powder inhalers (DPIs) contain the drug substance (or a combination of drug substances) in powder form either in isolation or mixed with larger excipient particles, typically lactose. As the patient inhales, air is drawn through the drug dose, aerosolising it and dispersing the particles, which are then pulled into the lung. Ensuring adequate dispersion using only the energy provided by the inhalation manoeuvre of the patient is the defining difficulty in developing DPIs with high drug delivery efficiency.

Metered dose inhalers (MDIs), in contrast, deploy an active drug delivery method, using a propellant to atomise a fixed volume of liquid solution or suspension. This means that inhalation and dose release are not naturally coordinated, so with these products the efficiency of drug delivery may be compromised by the patient failing to inhale at an optimal point. This issue of technique is routinely addressed through the use of spacers or valved holding chambers or novel breath-actuation mechanisms.

Nebulisers, the third general classification of OIPs, continuously atomise a drug formulation, once loaded, and the patient inhales the formulation by breathing normally through a mask. This arguably makes them the easiest inhaled product to use, however, nebulisers are far from being the most convenient as they are relatively large and deliver a dose over a relatively long timescale. With both MDIs and nebulisers there also remains the challenge of designing device and formulation to ensure consistent, well-controlled dispersion.

Characteristics impacting the success and speed of delivery

As delivered dose is not directly controlled in inhaled drug delivery it is one of the primary metrics measured to assess efficiency and clinical efficacy. The other critical characteristic for OIPs is particle size, since this influences deposition behaviour in the lungs. Generally speaking particles greater than 10 microns will fail to deposit in the lung, but will instead remain in the mouth and throat, whilst particles less than 5 microns will reach the deep lung and be therapeutically available due to the presence of receptors. This requirement for very fine particles to penetrate the defences that keep harmful material out of the lung explains why drug release *in vivo* has historically been considered a secondary issue, with particles in this size range typically assumed to dissolve relatively rapidly, even in the sub-optimal dissolution conditions of the lung.

Beyond these broad requirements specific tests vary from product to product, reflecting differences in the way each delivers a drug. With nebulisers, for example, there is an additional requirement to measure the amount of drug substance delivered as a function of time. The impact of patient physiology is also reflected in some tests with nebulisers characterised under conditions that reflect the inhalation profiles of the intended patient group – neonate, infant, child or adult – and DPIs tested at flow rates that correspond with the resistance to inhalation that they present.

Core testing requirements

Delivered dose

The delivered dose is the total amount of drug emitted from the inhaled product and, in the case of MDIs and DPIs, is measured using a Dosage Unit Sampling Apparatus (DUSA) in accordance with the methods described in USP Chapter <601> and Ph. Eur. Dosage Forms 0671. Separate chapters describe specific test methods for nebulisation - USP Chapter <1601>/ Ph. Eur. Chapter 2.9.44 - while draft guidance for the testing of MDIs with spacers and VHCs is presented in draft USP Chapter <1602>.

To measure delivered dose, the inhaled product is fired into the DUSA through which air is drawn at a defined flow rate using a vacuum pump. The DUSA consists of a sample collection tube with a filter at one end. The delivered dose is collected on the filter and the amount of drug substance within it is then determined from a chemical assay, typically by HPLC.

The principle way in which the various methods for the measurement of delivered dose differ is the test conditions applied during dose capture, most especially test flow rate, which reflects the delivery mechanism of the device. For an MDI, testing is carried at a constant flow rate of 28.3 L/min while for DPIs the flow rate applied is that which results in a 4kPa pressure drop across the device. DPIs with a higher resistance to air flow are therefore tested at lower flow rates than DPIs that are easier to inhale through. This is to ensure that the data gathered is more representative of the performance that will be observed in the clinic.

With nebulisers a sinusoidal breathing pattern is used to simulate use, with the dose being collected similarly on a filter. The dimensions of this pattern – total volume, frequency and inhalation to exhalation ratio – depend on the patient group (i.e. neonate, infant, child or adult) for which the product is intended. Furthermore the measurements made include the active substance delivery rate and the total active substance delivered by emptying the reservoir of the nebuliser. Delivered dose testing for MDIs with VHCs and spacers is also carried out under tidal breathing conditions.

Aerodynamic particle size distribution (APSD) measurement

Compendial methods for the measurement of particle size specify the technique of cascade impaction. Unlike other particle sizing techniques, cascade impaction generates a particle size distribution for the drug substance, rather than the formulation as a whole, and, has the added advantage of measuring aerodynamic particle size, a parameter of intuitive relevance in the specification of OIPs. The Pharmacopoeias recommend several commercially available impactors for testing MDIs and DPIs, but the three most widely used
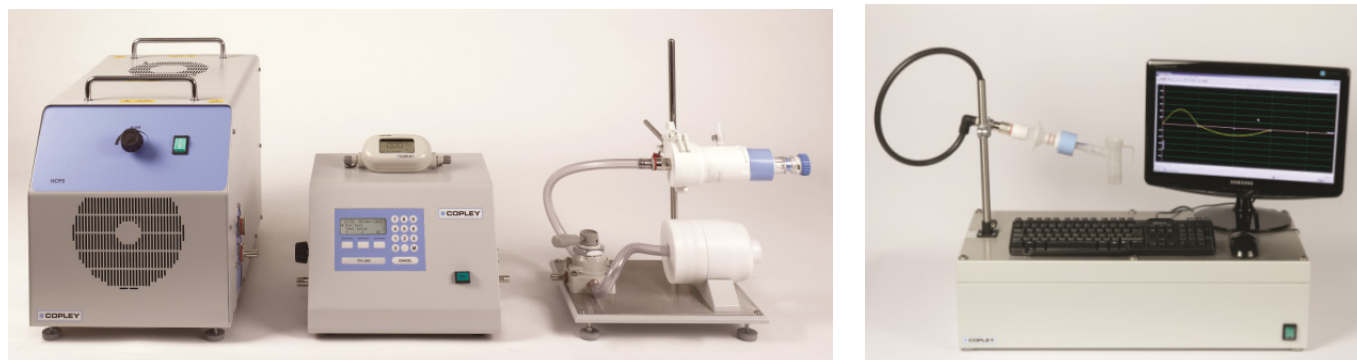

Figure 7: DUSA set-ups vary for different OIPs. A standard set-up for DPIs (left) and nebulisers (right) is shown here.

Figure 8: The MSLI, NGI and ACI are all referenced in compendial methods for determining the APSD of OIPs but the NGI and ACI are the instruments of choice for the majority of testing.

impactors - common to both Ph.Eur. Chapter 2.9.18 and USP Chapter <601> - are: the Andersen Cascade Impactor (ACI); Next Generation Impactor (NGI); and Multi-Stage Liquid Impinger (MSLI). In the case of Ph.Eur. Chapter 2.9.44 and USP Chapter <1601> for nebulisers, only the NGI features due to its lower range of calibration flow rates.

A full description of the technique of cascade impaction lies beyond the scope of this paper – see reference [2] - but in summary APSD measurement involves firing the OIP into the cascade impactor which then separates the dose on the basis of particle inertia, a function of particle size and velocity. Once the separation is complete the particle mass on each stage is recovered using a suitable solvent and then analysed, usually by HPLC to determine the amount of drug present, and generate an APSD for the drug substance.

A key feature of cascade impactors is the separation performance that they deliver is flow rate dependent, because of the correlation between particle inertia and velocity. This means a constant, well-defined and known air flow rate must be applied during testing. The flow rates specified are usually identical to those used for delivered dose testing for each device, for obvious reasons, except for when a sinusoidal pattern is specified. For nebulisers APSD measurement is carried out at 15 L/min, a figure deemed representative of the flow during normal tidal breathing while MDIs with spacers and VHCs are tested at the standard flow rate for MDIs – 28.3 L/min or a flow rate appropriate to the patient category – under 'worst case' and 'optimal' conditions which are simulated by manipulating the delay between firing the dose and sampling the resulting aerosol.

Final thoughts

Understanding the factors that influence the clinical efficacy of different pharmaceutical products provides insight into why different *in vitro* methods are applied to test them, and

the criticality of specific test conditions. *In vitro* methods are crucial, from R&D through to QC, because of their ability to cost-efficiently provide information for the development of new drugs and the confirmation of product quality. Optimisation remains an ongoing challenge and tests are refined on an ongoing basis with new introductions helping to enhance *in vitro in vivo* relationships and thereby improve relevance.

This is especially true for 'newer' drug delivery methods such as inhalation. Ultimately the more reliably an *in vitro* method can quantify the critical aspects of drug delivery, for any product, the greater its value in accelerating products to market and ensuring ongoing manufacture to the very highest standards.

References

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[2] Copley, M. (2007) Understanding cascade impaction and its importance for inhaler testing. Copley Scientific.

For more information on any aspect of inhaled product testing please refer to: Quality Solutions for Inhaler Testing 2015 Edition, Copley Scientific.

For more information on testing for all other pharmaceutical products discussed in this paper please refer to: Quality Solutions for the testing of Pharmaceuticals 2016 Edition, Copley Scientific.

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