ACCELERATING INHALED PRODUCT TESTING

Implementing Quality by Design sets a tough challenge for those involved in developing and manufacturing inhalation products, providing an impetus to revisit and refine the analytical tools in routine use. Cascade impaction is a core analytical method in this field, an essential tool for measuring the aerodynamic particle size of all inhaled formulations. It can, however, be time consuming and labour intensive. While taking quite different approaches, both the Abbreviated Impactor Measurement (AIM) concept and semiautomation for impactor drug recovery are intended to address these issues. Jolyon Mitchell, Trudell Medical International, and Mark Copley, Copley Scientific, review the evidence

A survey of its members by the QbD (Quality by Design) sub-team at EPAG (the European Pharmaceutical Aerosol Group), pointed to the "increased amount of work needed during development" as being the greatest barrier to adopting QbD.[1] With QbD (the revised way of working enshrined in ICH Q8, Q9 and Q10), quality is designed into the product from the outset rather than being tested post-manufacture. Achieving this goal requires an improved understanding of both the product and the manufacturing process at an early stage. For the inhalation community, QbD is especially challenging for a number of reasons. One complicating factor is that the performance of an inhalation product is a function of both the device and the formulation, in combination. A second is the influence of the patient's operating technique. The lack of real-time analytical tools is problematic for manufacturing control, while the failure in many cases to establish clear in vitro-in vivo correlations makes it more difficult to target clinical performance. Against this backdrop, the industry is becoming increasingly receptive to new or refined analytical approaches that reduce the burden (time and cost) of accessing pertinent information.

Cascade Impaction

The central role of cascade impaction in the analytical toolkit for inhaled products is largely attributable to the fact that, unlike all other particle sizing methods, this one provides a mass-weighted distribution based on aerodynamic size for the active ingredient, rather than for the complete formulation. For inhaled drug delivery, in vitro particle size measurements are, in broad terms, used to target in vivo deposition performance. Cascade impactors cannot simulate the complex deposition characteristics of the lung, but rather fractionate a sample with particles in the sub-10 micron range on the basis of size.[2] Analysis of the resulting series of samples, typically by HPLC, determines the APSD (aerodynamic particle size distribution.)

Multistage cascade impactors operate on the principle of inertial impaction whereby separation occurs because of differences in inertia — a function of particle size and velocity. Sample-laden air is drawn through a series of stages, each made up of a plate with

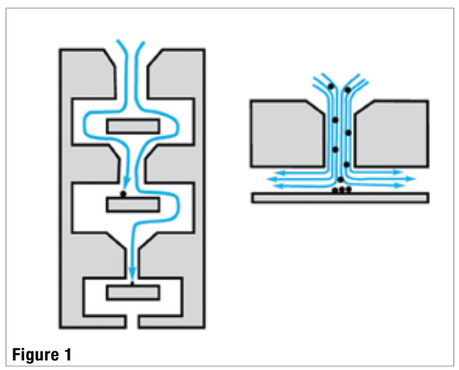

Figure 1

Figure 1: Schematic showing principle of operation of a cascade impactor

"THE AIM CONCEPT AND SEMI-AUTOMATION ARE BRINGING NEW SOLUTIONS FOR RAPID SCREENING AND QC"

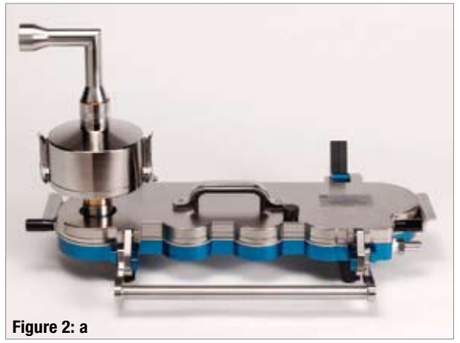

Figure 2: a

Figure 2: b

a specific nozzle arrangement and a collection surface. With each sequential stage, total nozzle area decreases; so, as airflow remains constant, particle velocity progressively increases. At each stage, therefore, smaller particles acquire sufficient inertia to break free from the air stream and impact on the collection surface (Figure 1). One benefit of cascade impaction is that it directly measures aerodynamic particle size, an intuitively sensible parameter for inhalation applications. Furthermore, there are commercially available cascade impactors that fractionate sensitively in the size range of greatest interest for pulmonary deposition. The ACI (Andersen Cascade Impactor) and the more recent NGI (Next Generation Pharmaceutical Impactor) both have five stages with cut-off diameters in the 0.5–5.0 micron range. Particles <5 micron make up the FPD (fine particle dose), and generally speaking are assumed to deposit in the lung. Usually, this is the design intent of the inhalation product. Unfortunately, these advantages are offset by a number of limitations, the main drawback being measurement time and the amount of labour involved in sample work up.[3] Operated manually, a conventional multistage impactor will normally yield only 5–8 complete measurements per day. Furthermore, operator-to-operator variability can introduce significant variation in the results, compromising data integrity.

Automation Strategies

Automation is a well-established and continuing trend for many analytical techniques, and cascade impaction is no exception. Many of the individual steps necessary for testing are simple and highly repetitive. Labour-saving devices that can perform these tasks fulfil several functions including

- enhancing reproducibility by limiting the potential for operator-to-operator and regional variability
- debottlenecking lab throughput
- reducing the risk of repetitive strain injury
- freeing up analyst time for more productive activities.

The complexities of cascade impaction make complete start-to-finish automation difficult, although equipment developers continue to work towards this goal. A more usual approach is to semiautomate discrete steps separately.

Sample preparation involves recovering deposited material from all surfaces of the impactor and any associated accessories, followed by dissolution of that material in a suitable solvent, ready for HPLC analysis. This is an arduous process, known to be the major source of error in cascade impaction measurements. Automation is therefore an attractive option. Some of the simplest tools provide controlled, reproducible washing of small items, such as the induction port (Figure 2). The operator charges the port with a known quantity of solvent and then loads it onto a machine that agitates the sealed unit for a defined period. At the other end of the spectrum are systems such as the Andersen and NGI sample recovery systems (A-SRS and N-SRS, respectively).

With the A-SRS and N-SRS, the analyst dismantles the cascade impactor and places all components (including the induction port, mouthpiece adapter and collection plates/cups) into their respective holders on the sample recovery bed. The unit then automatically sets up a closed liquid loop rinsing cycle for each component that ultimately delivers samples to septum-sealed HPLC vials for subsequent analysis. Such systems cut sample preparation times to around 10 minutes, increasing productivity by up to a factor of four.[4]

Designing New Impactors

Modifying the design of an impactor to simplify the analytical process is another approach. Ease-of-use was always a significant element when developing the NGI, itself the first impactor designed specifically to meet the express needs of the pharmaceutical industry. With a horizontal planar layout and a tray that enables the simultaneous removal of all seven collection cups (Figure 2), the NGI meets the design aim of a manual cycle time of less than 30 minutes, and more easily lends itself to automation. Even when manually operated, the NGI is

Figure 2: The NGI with induction port attached a) closed and b) open

Figure 3

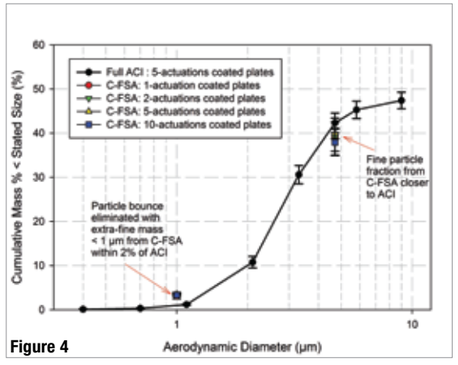

Figure 4

preseparator (if used) — retain their original function, which is to stop the initial surge of aerosol from a metered dose inhaler and/or larger aggregates from a dry powder inhaler entering the impactor. Cutting the number of stages significantly reduces the amount of sample recovery and work up, and replaces the full resolution aerodynamic particle size distribution with just two metrics: fine (small) and coarse (large) particle fraction (FPF and CPF) or mass (FPM and CPM).

Deciding where to set the boundary between these two fractions is clearly important. A figure of 5 microns would match, for example, the specification for FPF defined in the European Pharmacopoeia when the purpose is to provide data indicative of likely particle deposition in the respiratory tract.[6] However, it is vital to appreciate that it is more important to establish a technique that can sensitively differentiate between samples than to have a boundary value that is clinically relevant. Examination of a large database of oral inhaled formulations currently on the market confirms that the ratio of CPM:FPM is a sensitive metric of shifts in APSD.[7] Moreover, sensitivity increases as the boundary size approaches the MMAD (mass median aerodynamic diameter) for the drug product of interest. A boundary figure set on the basis of the MMAD for a given formulation may therefore prove to be the best choice.

Potentially, the accuracy and precision of FPM and CPM should be at least as good with AIM systems as that of equivalent metrics derived by grouping results from multistage cascade impaction, as the confounding of mass-based metrics that arises when stages are grouped is eliminated.[7] When doing multistage cascade impaction, the number of doses fired into the instrument is minimized, within the constraint of reaching the HPLC limits of detection for the active ingredient for every each stage. With a multistage unit, errors associated with the first and last stages tend to be relatively large, because of the very small amount of material collected.[7,8] AIM systems eliminate this problem altogether. Fewer actuations per measurement may also be possible, given the reduced number of aliquots to be recovered.

Practical AIM Concept

Whereas some might argue that reintroducing single/twin stage impactors takes the industry backwards rather than forwards, new options for the practical implementation of the AIM concept are underpinned by the very latest impactor theory. New designs and experimental proposals are being augmented by data-based theoretical assessments that bring rigour to development activities. Also, there is no expectation that these new options will completely displace conventional multistage impaction, which gives more detailed information and provides a benchmark against which AIM systems are assessed.

around 60% more productive than the ACI.[4] More recently, the idea of simplifying analysis by separating the sample into just a very few fractions has generated significant interest. Multistage cascade impaction is essential for detailed characterization, and can be particularly useful for rationalizing clinical behaviour, but may be unnecessary for QC and early screening work. For these applications, accurate and precise determination of a 'fine' and 'coarse' fraction may be sufficient. This is the heart of the AIM (Abbreviated Impactor Measurement) concept.

Figure 3: The fast screening Andersen impactor

Figure 4: A comparison of results obtained with an AIM system and conventional ACI using a pMDI producing dry particles

AIM Concept

In its simplest form, the AIM concept eliminates all stages from a multistage cascade impactor, except those required to split the dose into a fine and coarse fraction.[5] Multistage impactor components — such as the induction port and

Commercially available abbreviated systems associated with the NGI include the Fast Screening Impactor (FSI, MSP Corp., St Paul, MN, USA) a single-stage solution based on a modified NGI preseparator. A conventional NGI can also be modified for AIM through the use of deep cups that make selected stages non-operational, or by using special exhaust 'O' cups.[9] As yet, however, there is little published data concerning the performance of any of these systems.

An alternative option is the use of a short stack version of the ACI, such as the Fast-Screening Andersen impactor (C-FSA) from Copley Scientific (Figure 3). For this instrument, proof-of-concept studies are in place following recent work by Mitchell *et al.*[10,11] Experiments were done using the commercially available C-FSA and a slightly modified version developed at Trudell Medical International (T-FSA) that includes a non-operating stage 'O' from an ACI. Inserting this additional stage provides comparable functional dead space before the first size-separating stage.

In an initial study, the C-FSA and T-FSA were evaluated with pressurized metered dose inhaler (pMDI)-based formulations producing representative dry (Flovent — HFA; 125 µg/actuation fluticasone propionate [FP]) particles. The second investigation was undertaken with a formulation containing 8% ethanol that produces evaporating particles (Qvar; 100 µg/actuation beclomethasone dipropionate [BDP]). A focus for both studies was the potential for non-ideal behaviour: particle bounce, internal losses and, in the second study, differences in evaporation behaviour. Using a surfactant or grease-coated collection plates proved to be essential to minimize particle bounce and re-entrainment. Recently, it has been discovered that a glass microfibre filter saturated with surfactant is even more effective at eliminating bounce altogether. This problem is exacerbated in AIM systems owing to the increased inertia of particles usually collected by previous stages in a multistage unit. With these precautions in place, both the AIM systems gave results equivalent to a conventional ACI (Figure 4), confirming their suitability for pMDI characterization. Plans are under way within the European Pharmaceutical Aerosol Group (EPAG) Impactor sub-team to extend this work and prove the utility of all types of AIM-based systems with a wider range of inhaled product types.

Conclusion

The changing regulatory framework promotes a QbD approach that requires developers and manufacturers to understand product performance in a very detailed way. The feasibility of achieving this goal, and the amount of work required, is a major concern for the inhalation community. Aerodynamic particle size is a critical quality attribute for all inhaled products, routinely measured using the technique of cascade impaction, which gives detailed information specifically relating to the active ingredient. This technique, although uniquely valuable, can be time-consuming and manually intensive, so tools that accelerate and streamline measurement are to be welcomed.

Options for semiautomating cascade impaction have widened during the last decade, the best systems now delivering four-fold productivity increases compared with manual operation. Introduction of the AIM concept brings new solutions for QC and screening that have the potential to precisely measure fine and coarse particle fractions, while simultaneously reducing the analytical burden. While multistage cascade impaction remains an essential technique for the characterization of all inhalation products, setting the benchmark for aerodynamic particle size measurement, these new technologies have a valuable and complementary role to play in minimizing the ongoing analytical spend, from development through to QC. **Pharma**

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