The abbreviated impactor measurement concept

A potentially faster and more precise way to assess quality of inhaled drug products

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The Quality by Design (QbD) initiative [1] provides a significant opportunity for the pharmaceutical industry to re-appraise how it builds quality into orally inhaled products (OIPs). QbD involves rigorous definition of how critical quality attributes (CQAs) relate to the knowledge, design, and control spaces that map OIP performance [2]. Aerodynamic particle size distribution (APSD) qualifies as a CQA for *in vitro* inhaler performance because of its relationship with particle deposition in the respiratory tract [3]. APSD measurements, therefore, serve an important purpose in the context of OIP quality control (QC) [4]. However, traditional multistage cascade impaction methods for measuring APSD require a great deal of labor [5], and operator inconsistency can make them subject to measurement variability [6].

Abbreviated testing methods have the potential to alleviate some of these problems, but several past attempts have failed to gain wide acceptance. The Twin Impinger [7] and Fisons 2-stage metal impactor [8] offered the earliest concepts for abbreviated testing and appeared as apparatuses A and B respectively in the European Pharmacopeia up to the 4th Edition (2002). In the mid 1990s, guidance for reducing the 8-stage Andersen Cascade Impactor (ACI) to abbreviated formats for pMDI and DPI assessments [9] appeared, but the regulators were not receptive to reducing size resolution in cascade impactor (CI) measurements at that time [10, 11]. Furthermore, the suggested apparatus configurations proposed at the time lacked theoretical support.

The single stage impactor (SSI) option developed in 1997 to validate the time-of-flight-based Aerodynamic Particle Sizer (APS) spectrometer, which arguably qualifies as a two-stage abbreviated impactor, has demonstrated the ability to provide comparable performance with full resolution CIs for a few pMDI-based formulations [12]. However, the SSI works as part of the complete APS package and not as a stand-alone apparatus [13].

In the past year or so, Trudell Medical International and Copley Scientific have developed the abbreviated impactor measurement (AIM) concept as a viable alternative to full resolution cascade impactor (CI) measurement [14]. This new method of abbreviated cascade impaction has demonstrated the potential both to improve decision making in QC and to make the testing process itself more efficient.

Theoretical aspects of the AIM concept

A typical full resolution multi-stage CI such as the ACI or the Next Generation Pharmaceutical Impactor (NGI) does not represent an analogue of the human respiratory tract [15] due to the fact that regional particle deposition in the respiratory tract does not sharply resolve into multiple size-related fractions. Rather, a CI size fractionates incoming aerosol into discrete size bands that relate to individual stage collection characteristics [16]. On this basis, operators may choose metrics to characterize impactor-measured APSD that optimize precision instead of obtaining full resolution APSD data that likely offers less precision due to stages that collect little active pharmaceutical ingredient (API) [6].

In its simplest form, the AIM concept involves eliminating all stages from a multi-stage CI except those required to establish fine and coarse particle fractions [17] (Fig. 1). Where appropriate, the pre-separator is also included to eliminate over-size particles. AIM testing retains the induction port as specified in the pharmacopoeial methods [16]. By reducing the number of stages, the AIM concept reduces the 7 or 8 data points associated with the typical full resolution APSD to the 2 mass fractions assigned to fine (FPF) and coarse (CPF) particles. Multiplying the total mass captured by the impactor by the FPF gives the fine particle mass (FPM); multiplying total mass by the CPF produces the coarse particle mass (CPM). When the appa-

Figure 1

Impactor-measured APSD fractionated into fine (FPM) and coarse (CPM) components

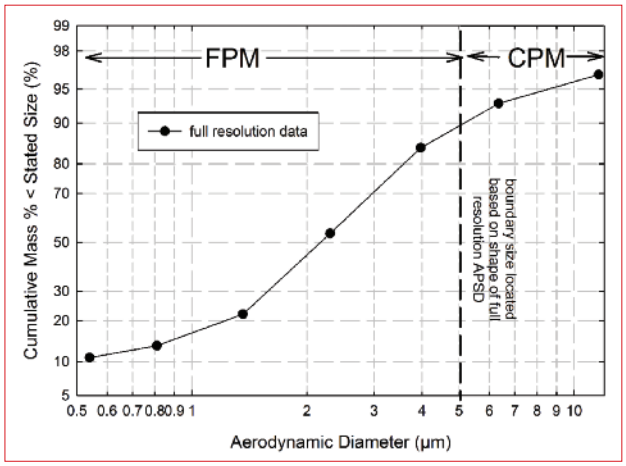
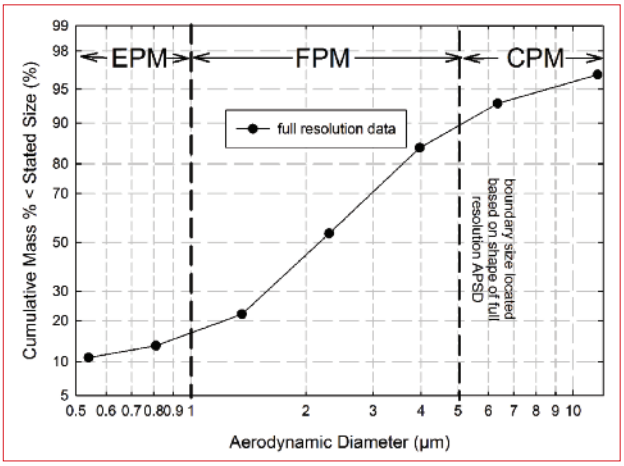


Figure 2

Augmentation of AIM concept to include extra-fine fraction



ratus includes the induction port and pre-separator, summing the FPM and CPM gives the mass that actually enters the abbreviated impactor.

To match the specification provided in the European Pharmacopeia [18], operators can fix the boundary between the two fractions at 5.0 µm aerodynamic diameter. However, for determining product QC, this value does not necessarily have to relate to clinical performance in terms of likely lung deposition location. Indeed, examination of a large database of currently marketed OIP has shown recently that the ratio of CPM/FPM sensitively indicates shifts in APSD [19]. Moreover, this sensitivity increases as the boundary size approaches the mass median aerodynamic diameter (MMAD) for the drug product of interest.

Furthermore, the sum of CPM and FPM captures changes in the amplitude of the full resolution APSD that affect the area under the curve when expressed in terms of the differential mass-weighted function

$$\left(\left[\sum_{i=1}^{i=n} m_i/(CPM+FPM\right]\right)$$

versus d_{ae}, where m_i is the mass on stage 'i' of an 'n'-stage system [19], a feature independent of size-related shifts in APSD.

Analysts may also want to incorporate a third sub-fraction encompassing extra fine particles (EPM) as a refinement (Fig. 2), especially for solution-based pMDI formulations where the bulk of the aerosol entering the CI often approaches 1.0 µm aerodynamic diameter [17]. Although this augmentation provides more information about the overall shape of the APSD, the CPM/FPM ratio provides adequate information by itself, especially with the boundary fixed close to the MMAD for these formulations, so using EPM as a QC metric is unnecessary.

The stage grouping method incorporates error associated with each stage into the aggregate API mass assigned to the group, and the stages that collect low amounts of API have a higher variability that adds significantly to the group error [19]. Improvements in measurement precision obtained through AIM should translate into better decision making capability in the QC environment.

Despite the potential advantages of AIM-based systems, full resolution APSD measurements still have a role. Complete APSDs provide guidance in product pharmaceutical development and help to rationalize the outcomes of clinical development programs. Furthermore, analysts still need a definitive OIP APSD specification as the benchmark against which to evaluate shifts in CPM/FPM or CPM + FPM in the product QC environment.

Experimental aspects

Recent reviews of full resolution impactor method variability [5, 6] have highlighted the complexity and difficulty of these measurements, and current experimental proposals are backed by ongoing data-supported theoretical assessments that add necessary rigor to the development of AIM-based methods as practical tools, especially for OIP QC [19]. Manufacturers of CI equipment have begun to develop several different abbreviated systems based on these new studies for users to evaluate [17].

The Fast Screening Impactor (FSI) from MSP Corporation, a 2-stage abbreviated system based on a modified NGI pre-separator, avoids possible pitfalls of AIM equipment created by eliminating compo-

nents from a full resolution CI. Removing those components may simply relocate the typically small internal losses in the abbreviated apparatus that would normally be retained but not accounted for in the full resolution version.

A range of inserts for the FSI provides a 5 µm cut-off diameter for flow rates from 30-100 L/min at 5 L/min intervals, achieving this flexibility by varying the nozzle sizes of the single stage impactor contained within the body of the device. Nozzles can also be manufactured to provide other specified cut-off diameters, e.g., 4.7 µm, which corresponds with Stage 2 of the ACI at 28.3 L/min. A filter collector located below the pre-separator body collects the fine fraction.

Modifying the NGI by using deep cups to make selected stages non operational can convert it into an abbreviated 2- or 3-stage system. In addition, an insert for the stage 1 nozzle can reduce jet diameter to a desired size limit for the stage cut-point. Alternatively, inserting special exhaust- or inlet-carrying- 'O'-cups in successive stages of the impactor can create an abbreviated NGI [20]. Using a nozzle insert, size fractionation takes place at the first stage, with the coarse fraction captured at that stage and the fine fraction transported via the first exhaust cup to a filter located immediately below. The cleaned gas flow then returns to the NGI via the second exhaust cup. Currently, no data have been published concerning the performance of these abbreviated NGI systems.

Some proof of concept data already exists for 2 slightly different 3-stage versions of a short stack ACI, with one study involving dry particles and the other evaporating particles [21-23]. The Fast-Screening Andersen (C-FSA) impactors from Copley Scientific (Fig. 3) are the first abbreviated instruments based on the non-viable ACI. Two recent proof of concept studies using a version of the C-FSA and a similar but slightly modified version of an ACI (the T-FSA) developed at Trudell Medical International focused on pMDI-produced aerosols (Fig. 4). The T-FSA includes a non-operating ACI stage '0' inserted to provide comparable functional dead space before the first size-separating stage.

Both studies investigated the potential for non-ideal behavior associated with particle bounce, internal losses and, in the second study, differences in evaporation behavior. The first study evaluated both the C-FSA and T-FSA with pMDI-based formulations, first with a formulation producing dry particles (Flovent-HFA fluticasone proprionate at 125 µg/actuation) and the second involved a formulation containing 8% ethanol (Qvar beclomethasone dipropionate at 100 µg/actuation) producing evaporating particles.

Figure 3

Copley C-FSA

Figure 4

Trudell version of the FSA with an additional stage to collect extra-fine particles as well as a non-operating stage 0 to retain similar dead space to full resolution ACI for sampling aerosols containing volatile species

The use of surfactant- or grease-coated collection plates proved essential to minimize particle bounce and re-entrainment (Fig. 5) because the increased inertia of particles that would otherwise be collected by previous stages in the full resolution configuration enhances non-ideal behavior in abbreviated systems. With coated collection plates, both reduced impactors proved substantially equivalent to the full resolution ACI (Fig. 6).

Similar behavior will likely occur with other AIM-based systems derived from full resolution CIs by the removal of non-operating stages. Interestingly, the small but measurable wall losses associated with stages in the full ACI that were removed to create the abbreviated designs transferred to the lower stage in the abbreviated impactors, but the effect resulted in only about a 2% increase in EPM. In the follow-on study, the introduction of additional dead space in the T-FSA compared with the C-FSA improved agreement with the ACI in terms of FPM by providing similar conditions for ethanol evaporation (Fig. 7).

These validation experiments indicate that both fast screening ACI designs have the potential for use with other pMDI-delivered formulations. Currently, plans are under way within the Impactor Sub-Team of the European Pharmaceutical Aerosol Group (EPAG) to extend the database associated with proving the utility of all types of AIM-based systems with a range of different OIP types.

In practice, implementing AIM will necessitate evaluation of the suitability of OIPs on a formulation-by-formulation basis with a chosen system to establish substantial equivalency with full resolution (benchmark) CI data. This process, which will likely be essential to achieve regulatory acceptance for routine QC use in production, is best undertaken as a key part of the product development process.

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Figure 5

Collection of FP particles onto uncoated collection plates in the C-FSA

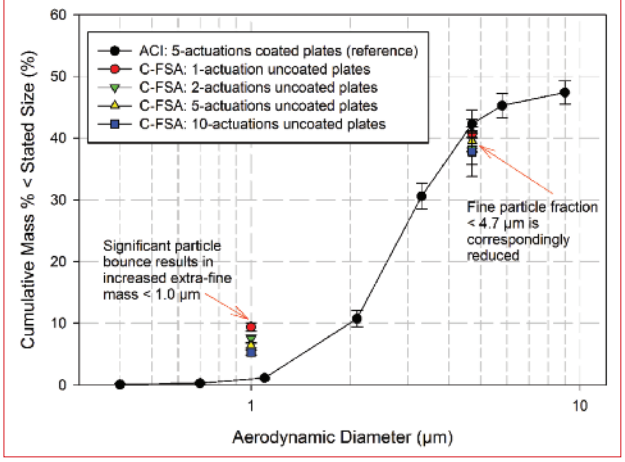


Figure 6

Collection of FP particles onto surfactant-coated collection plates in the C-FSA

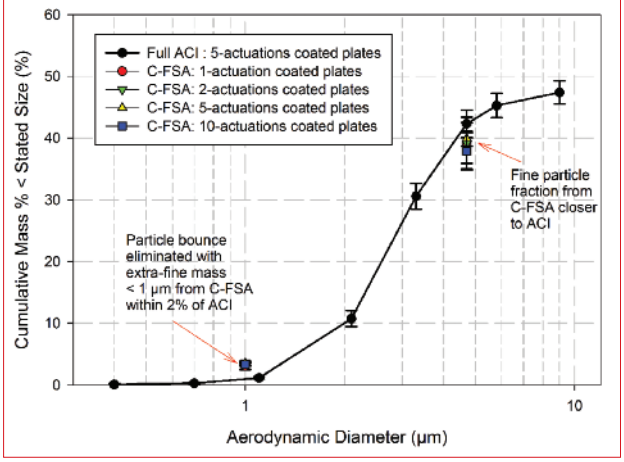
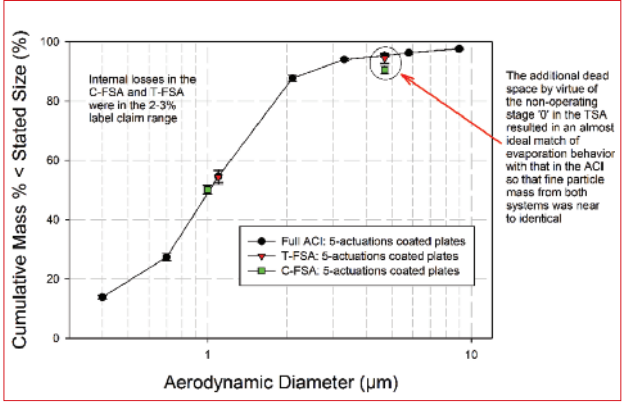


Figure 7

Comparison of C-FSA and T-FSA to ACI for ethanol-containing BDP particles



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