The Abbreviated Impactor Measurement (AIM) and Efficient Data Analysis (EDA) concepts: Why they are important and how to work with them

This article summarizes the potential for implementing either or both AIM and EDA into the existing methods for aerodynamic size characterization of OIP aerosols

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Introduction

The Abbreviated Impactor Measurement (AIM) and Efficient Data Analysis (EDA) concepts have been developed in parallel, as ways in which to improve the collection and analysis of data associated with the size characterization of aerosols emitted from orally inhaled products (OIPs). This article explains why they are both important developments and provides advice on ways to implement either or both concepts.

The AIM concept: An overview

The background for the AIM concept and some ways of implementing abbreviated cascade impactor measurements were presented in three previous issues of Inhalation magazine.[1-3] Since this time, the options available for creating AIM-based systems have greatly expanded from potentially using the Twin Impinger, to working with reduced versions of both Andersen non-viable (ACI) and viable (ACVI) cascade impactors, the Fast Screening Impactor (FSI) and modified versions of the Next Generation pharmaceutical Impactor (NGI). Summaries of a series of experimental method development and validation studies undertaken by various laboratories were given at a special symposium led by the European Pharmaceutical Aerosol Group (EPAG) and held as part of the Drug Delivery to the Lungs 21 meeting in December 2010.[4-9] Since then, many other articles have appeared in which a variety of AIM-based systems have been evaluated successfully with all types of OIPs.[10-17] Several important learning points have emerged from these investigations:

1. Stringent precautions are necessary to prevent particle bounce in abbreviated impactors;

2. To get equivalent results, it is important to match the dead-space upstream of the first impaction stage of the abbreviated impactor to that of the full resolution system before its initial impaction stage, if the product being tested contains volatile species, such as ethanol;

3. Matching the overall dead-space of the abbreviated system and the full resolution impactor is important to achieve comparable flow rate rise times in dry powder inhaler (DPI) testing; in this context, it should be noted that the full resolution results are not inherently "correct," but they are the stakeholder-recognized benchmark for the comparisons;

4. From the standpoint of avoiding the need to acquire and maintain additional equipment, it may be desirable to develop the abbreviated impactor using the same components from the parent full resolution system. However, the Fast Screening Impactor that has no parent full resolution appara-

tus has also been used successfully with the NGI as the reference full resolution cascade impactor (CI).

The potential for bias associated with the removal of intermediate stages caused by decreased or no overlap in the stage collection efficiency-aerodynamic diameter profiles has been examined theoretically for both NGI- and ACI-based abbreviated systems. These assessments came to the conclusion that stage collection efficiency curve-related bias is insignificantly small for all except the most accurate work with near-to-monodisperse aerosols whose geometric standard deviation is ≤ 1.2.[18,19] Because all currently marketed OIPs generate polydisperse aerosols, this source of potential error can therefore be ignored.

Given the choice of abbreviated systems available (Figure 1), the selection of any particular AIM platform will ultimately depend on the familiarity of the testing laboratory with the equipment and its limitations and preference in (semi)automation. In addition, the nature of the product being evaluated (metered dose inhaler (MDI) with or without spacer/valved holding chamber, DPI or nebulizing system) will be an important consideration that dictates important operating variables, in particular the chosen flow rate-time profile through the apparatus.

The EDA concept: An overview

Efficient Data Analysis was designed specifically to address OIP quality control (QC) decisions with respect to the CI-measured aerodynamic particle size distribution (APSD), where the general goal is to confirm that the batch in question is of suitable quality to be released commercially.[20] This process necessarily takes the form of sampling a relatively small number of units, measuring properties of the aerosols generated by these samples and making a decision concerning the quality of the sampled batch. This practice leads to three primary considerations:

1. The properties measured should be relevant for detecting significant abnormalities from the expected APSD;

2. The measurements should possess sufficient precision and accuracy over the range of interest;

Figure 1

Examples of the various options for AIM-based measurements

FSA with 1.0 and 5.0 µm stage cut-point sizes
— Copley Scientific

"Trudell" FSA with empty stage 0 for MDIs having low volatile co-solvents

FPD
—Westech Instument Services

Twin impinger
— Copley Scientific

FSI
—MSPCorp.

3.The decision process based on the measurements should reliably make correct inference about the quality of the batch by appropriately minimizing and balancing the risk of decision errors. Such errors would include judging a batch suitable when it is not suitable and conversely judging a batch unsuitable when it is actually suitable.

In the EDA approach, the process of data acquisition from either an AIM-based or full resolution-based CI system is simplified to its maximum extent; namely the determination of the size fractions related to large particle mass (LPM) and small particle mass (SPM) of the fraction of the dose that enters the apparatus and passes through the size-fractionating stages.The sum of LPM and SPM is the impactor-sized mass (ISM) and the metric LPM/SPM defines the ratio of the two sized mass fractions. The following statements describe the logic that drove the selection of the two EDA metrics:[12]

1. Both can be easily obtained;

2. The ratio metric, LPM/SPM, is highly correlated with the mass-weighted mean of the APSD (represented customarily by the mass median aerodynamic diameter (MMAD), but independent of the area under the curve (AUC) of the differential mass-weighted APSD;

3. The other metric, ISM, is related to the AUC of the APSD, but independent of the mean of the distribution.

In the past three years, much work has been undertaken to show unambiguously that these metrics taken together are sensitive to shifts in both the amplitude in terms of mass of active pharmaceutical ingredient (API) and displacement in terms of aerodynamic diameter (Figure 2) that may arise with approximately unimodal APSDs that are typically generated from all types of OIPs.[20-22] (The reader is referred to the cited references for comprehensive explanations of the methods that were used.)

Table 1 illustrates the type of improvement in decision-making that is possible with EDA compared with the "classical" stage groupings procedure,

Figure 2

Possible movements to a unimodal OIP APSD

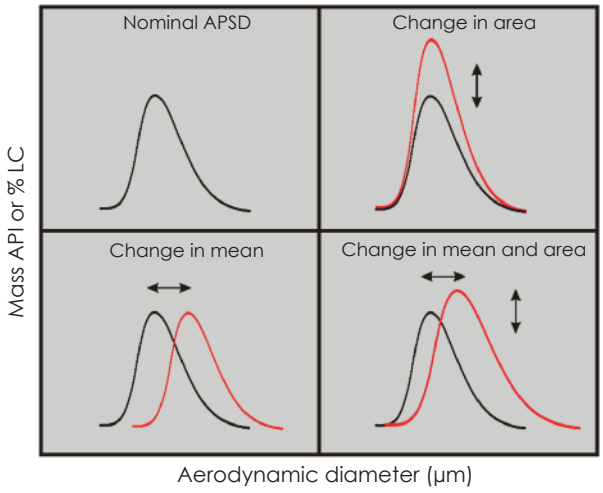


Table 1

Simulation results for various scenarios showing type I and type II error rates for EDA and stage groupings approaches and the relative type 1 error rates for grouped stages compared to EDA; Results from Groups 2-4 are combined to yield the overall grouped-stage decision (i.e., if any of the Groups 2-4 fails, the overall decision is fail)

Grouping distribution percentiles	Prediction interval (%)	Error rates: *LPM/SPM* ratio Type I	*LPM/SPM* ratio Type II	Grouped stages Type I	Grouped stages Type II	Relative Type I Error rates: Grouped stages vs. EDA
10, 90	95	6.57	0.03	22.82	0	3.47
	99	10.86	0.01	30.51	0	2.81
	99.9	17.01	0.01	41.82	0	2.46
5, 95	95	8.48	0.04	23.08	0	2.72
	99	13.89	0.01	32.39	0	2.33
	99.9	19.66	0.01	43.09	0	2.19
1, 99	90	9.61	0.09	20.95	0.09	2.18
	95	12.24	0.08	26.05	0.02	2.13
	99	17.38	0.05	39.03	0	2.25
	99.9	20.81	0.02	48.04	0	2.31

based on a large, simulated database (30,000 CI profiles modelled on the characteristics of real CI results) that represent the gamut of possibilities for OIP aerosols. In stage grouping, the mass entering the full resolution CI is typically assigned to three contiguous groups. Group 2 corresponds to the proximal stages, representing the coarse mass fraction whose aerodynamic diameter is approximately > 5.0 µm. Group 3 comprises the middle stages and the fine particle fraction between approximately 1.0 and 5.0 µm aerodynamic diameter. Group 4 contains the distal stages plus back-up filter representing the extra-fine fraction approximately < 1.0 µm aerodynamic diameter. Group 1 (not analyzed) contains the non-sized fraction of the OIP emitted mass that is captured before the size-fractionating stages.

Type I and II errors (which could also be considered "misclassifications") arise out of the uncertainty in the estimation of the true value of a quality attribute associated with the batch being tested. In Table 1, type I and type II errors represent false rejection and false acceptance of the product, respectively. Specifically, Table 1 shows comparisons at different combinations of distribution percentiles that might be used to set grouping acceptance limits (e.g., 5th and 95th versus 1st and 99th percentiles), as well as different prediction intervals for the outcomes (e.g., 95% versus 99.9% prediction intervals). It is clearly evident that the AIM metrics provide more discriminating results than stage groupings in connection with type I errors while providing comparable outcomes in connection with the relatively small rate of type II errors that arise.

Another way of looking at EDA compared with stage groupings is by evaluating the degree to which either option predicts the location of the MMAD for each APSD from a blinded database containing many hundreds of CI determinations from marketed OIPs. These products included CFC-suspension pressurized metered dose inhalers (MDIs), HFA-suspension and solution MDIs and dry powder inhalers (DPIs) that Tougas et al.[20] used for their assessments. Figures 3 and 4 illustrate the much-closer correlation achievable between actual MMADs and the corresponding predicted values than can be achieved using either stage groups 2 (coarse) or 4 (extra-fine) for an HFA-suspension MDI and an HFA-solution MDI, respectively. Product codes in these figures refer to designations assigned to blind the identity of a specific OIP and are consistent with descriptors used in previous publications.[20-22]

The other two groupings are unable to offer any information about the location of the MMAD value for a given APSD; group 1 because it comprises non-sized material; and group 3 (fine particle fraction) because its value is confounded by movement in API mass associated with shifts in MMAD in either direction to and from its neighboring groupings. In summary, both approaches to assess EDA demonstrate the potential for superior decision-making by adopting this concept in the process of batch disposition in product quality control.

Figure 3

Comparison between predicted (by metric) versus actual MMAD from CI data: HFA suspension MDI product code w9k201

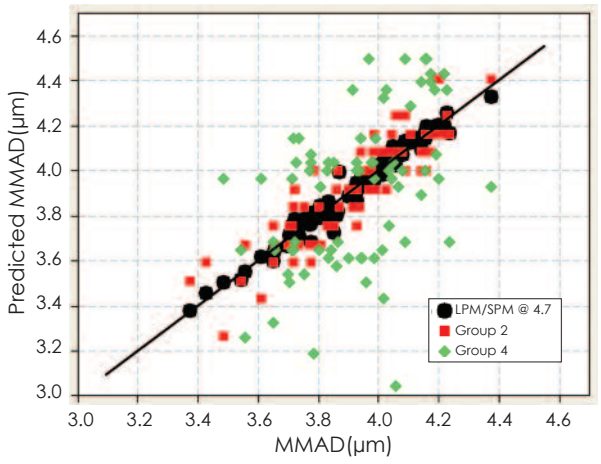
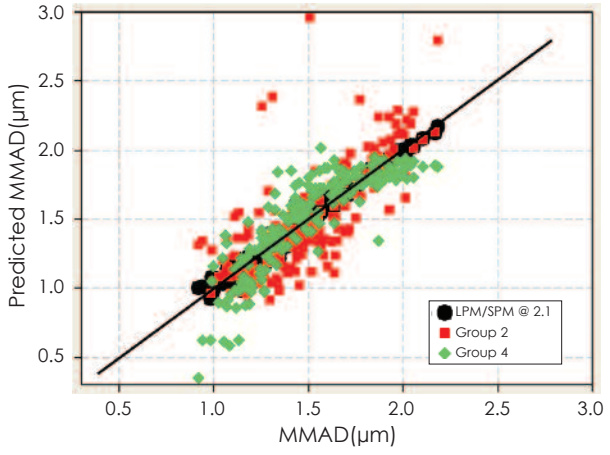


Figure 4

Comparison between predicted (by metric) versus actual MMAD from CI data: HFA solution MDI product w9j801



AIM and EDA in the product life cycle: The right approach for the task in hand

EDA can be used with either full resolution CI or abbreviated impactor data, depending upon the stage in the product life cycle. Table 2 summarizes the advantages of the three available options.

Importantly, there is flexibility in the use of these potentially simpler and more capable methods for assessing OIP aerosol aerodynamic particle size. Table 3 defines considerations that are suggested for evaluation at various stages in the OIP life cycle; from product characterization and screening in early development through the development stages before commercialization, in quality control

Table 2

Options for AIM and EDA in the OIP life cycle

AIM	EDA with AIM	EDA with full resolution CI
Simpler apparatus	Similar sensitivity to APSD changes compared to current methods	Complete APSD – useful in diagnosis in event of OOS/OOT with AIM system
Fewer samples for assay	More sensitive measures of APSD shifts than with stage groupings from full resolution CI	
Greater mass of API per sample than with single stages in full resolution CI, therefore improved sensitivity per inhaler actuation	Potential for fewer false-rejection results in batch release	
Less recovery solvent volume (*Green Chemistry*-compatible)		
Less time to make measurement	Less time per measurement in data processing with potential for more powerful experiment designs improving "coverage" of the batch	

Table 3

Applications for full resolution- and AIM-based CI measurements with EDA in the OIP product lifecycle

	OIP APSD measured for . . .		
	…Product characterization and development	**…Product quality control**	**…*In vitro* assessment for equivalence comparisons**
Impactor sytem to use	Full resolution CI for initial screening candidate formulations, then AIM-QC on short-listed candidates	AIM-QC, supported by full resolution CI (e.g. in the context of OOS investigation)	Full resolution or AIM-pHRT (potential use for comparison with HRT deposition data) With an anatomically correct or idealized inlet if possible
Proposed metrics to use	Initially *EPM*, *FPM* and *CPM* with size ranges related to likely deposition in the HRT; later EDA metrics to develop QC specification	EDA metrics, namely *SPM* and *LPM* with boundary near to *MMAD: LPM/SPM* and *ISM (SPM + LPM)*	Full profile comparisons or *EPM, FPM* and *CPM* with size ranges related to likely deposition in the HRT
Statistical approaches	A number of approaches related to the APSD characterization and the development of the product specification	Tests to detect significant changes in APSD	Generic statistical equivalence testing

for lot release and/or *in vitro* comparisons in support of clinical batches.[23]

An AIM-Quality Control system (AIM-QC) is typically developed for use in the OIP development quality control environment, where the abbreviated impactor is modified with minimal changes to the parent CI measurement system (e.g., use of a standard Ph.Eur./USP induction port). There may only be one stage to size-fractionate large from small particle fractions in order to determine the EDA metrics LPM/SPM and LPM + SPM. Also, the size boundary between the two will likely be chosen to suit the APSD of the product aerosol (i.e., close to its MMAD). In contrast, an AIM-potential Human Respiratory Tract (AIM-pHRT) system is appropriate where it is deemed advantageous to compare CI-based data more closely with clinical measures, in particular with regional lung deposition. This type of abbreviated apparatus may therefore have an anatomically correct or idealized anatomic inlet and there will likely be at least two size-fractionating stages to size-separate the incoming aerosol into coarse particle mass (CPM), fine particle mass (FPM) and extra-fine particle mass (EPM) components. The boundary sizes between CPM and FPM and between FPM and EPM will likely be chosen close to 5.0 and 1.0 µm aerodynamic diameter, respectively. These limits are based on the likelihood of linking CPM, FPM and EPM to upper airway deposition, lung deposition in the conducting airways, and deposition in the distal lung including the alveolar sacs, with the attendant possibility of exhalation without deposition, respectively.[24]

Concluding remarks

This overview summarizes the potential that exists to implement either or both AIM and EDA concepts into the existing framework of methods for the aerodynamic size characterization of aerosols from OIPs. The authors are in the final stages of publishing a handbook[25] covering both approaches, together with background information related to the more general topic of Good Cascade Impactor Practice (GCIP). In addition to providing the background theory associated with each concept, this book contains a wealth of case studies that are based on data from marketed OIPs. The information presented in this article has been derived from some of its content.

References

1. Mitchell, J.P., Nagel, M.W. and Copley, M. The abbreviated impactor measurement concept:A potentially faster and more precise way to assess quality of inhaled drug products. Inhalation. 2009;3(3):26-30.

2. Copley, M., Mitchell, J., McAulay, E. and Russell-Graham, D. Implementing the AIM concept. Inhalation. 2010;4(1):7-11.

3. Mitchell, J.P., Tougas, T.P., Lyapustina, L, et al. on behalf of IPAC-RS. Abbreviated Impactor Measurement (AIM) and Efficient Data Analysis (EDA) Concepts: A partnership for the assurance of oral inhaled product (OIP) quality. Inhalation. 2010;4(6):6-10.

4. Russell-Graham, D., Cooper, A., Stobbs, B., McAulay, E., Bogard, H., Heath, V. and Monsallier, E. Further evaluation of the Fast-Screening Impactor for determining fine particle fraction of dry powder inhalers. Drug Delivery to the Lungs-21, The Aerosol Society, Edinburgh, UK, 2010;21:374-377.

5. Després-Gnis, F. and Williams, G. Comparison of Next Generation Impactor and Fast-Screening Impactor for determining fine particle fraction of dry powder inhalers. Drug Delivery to the Lungs-21, The Aerosol Society, Edinburgh, UK, 2010;21:386-389.

6. Rogueda, P., Morrical, B. and Chew, Y.D. Comparison of NGI and the Fast Screening Impactor (FSI) for suitability for analytical drug development. Drug Delivery to the Lungs-21, The Aerosol Society, Edinburgh, UK, 2010;21:394-397.

7. Sheng, G. and Watanabe, W. Feasibility of Fast Screening Impactor as a screening tool. Drug Delivery to the Lungs-21, The Aerosol Society, Edinburgh, UK, 2010;21:390-393.

8. Svensson, M. and Berg, E. Measuring the fine particle dose using inter-stage filters in the NGI – an overview of two methods. Drug Delivery to the Lungs-21, The Aerosol Society, Edinburgh, UK, 2010;21:382-385.

9. Tservistas, M., Uhlig, M. and Mitchell, J. Assessment of abbreviated impactor measurement (AIM) methods for nebulizer characterization. Drug Delivery to the Lungs-21, The Aerosol Society, Edinburgh, UK. 2010; 21:378-381.

10. Chambers, F.E. and Smurthwaite, M. Comparative performance evaluation of the Westech Fine Particle Dose (FPD) impactor. In: Dalby RN, Byron PR, Peart J, Suman JD, Young PM (eds), Respiratory Drug Delivery 2012. Davis HealthCare International Publishing, River Grove, IL, USA, 2012:553-557.

11. Keegan, G.M. and Lewis, D.A. Rapid prototype screening with the Copley Fast Screening Andersen (FSA). In: Dalby RN, Byron PR, Peart J, Suman JD, Young PM (eds), Respiratory Drug Delivery 2012, Davis HealthCare International Publishing, River Grove, IL, USA, 2012: 469-472.

12. Keegan, G.M. and Lewis, D.A. Formulation-dependent effects on aerodynamic particle size measurements using the Fast Screening Andersen (FSA). In: Dalby RN, Byron PR, Peart J, Suman JD, Young PM (eds), Respiratory Drug Delivery 2012, Davis HealthCare International Publishing, River Grove, IL, USA, 2012: 465-468.

13. Pantelides, P.N., Bogard, H., Russell-Graham, D., Cooper, A.D. and Pitcairn, G.R. Investigation into the use of the Fast Screening Impactor as an abbreviated impactor measurement (AIM) tool for dry powder inhalers. In: Dalby RN, Byron PR, Peart J, Suman JD, Young PM (eds), Respiratory Drug Delivery-Europe 2011, Davis Healthcare International Publishing, River Grove, IL, USA, 2011:391-395.

14. Daniels, G.E. and Hamilton, M. Assessment of early screening methodology using the reduced Next Generation and Fast Screening Impactor systems. In: Dalby RN, Byron PR, Peart J, Suman JD, Young PM (eds), Respiratory Drug Delivery-Europe 2011, Davis Healthcare International Publishing, River Grove, IL,USA, 2011:327-330.

15. Hamilton, M. and Daniels, G. Assessment of early screening methodology using the Next Generation and Fast Screen Impactor systems. Drug Delivery to the Lungs-22, The Aerosol Society, Edinburgh, UK 2011:355-358.

16. Sheng, G., Zhang, J., Simmons, R. and Watanabe, W. Fast Screening Impactor (FSI) as a Prescreening Tool for MDIs and Nebulizers. In: Dalby RN, Byron PR, Peart J, Suman JD, Farr SJ, Young PM (eds), Respiratory Drug Delivery 2010, Davis Healthcare International Publishing, River Grove, IL, USA, 2010:637-640.

17. Mitchell, J.P., Copley, M., Sizer, Y., Russell, T. and Solomon, D. Adapting the Abbreviated Impactor Measurement (AIM) concept to make appropriate inhaler aerosol measurements to compare with clinical data: A scoping study with the "Alberta" Idealized Throat (AIT) inlet J. Aerosol Med. Pulmon. Deliv. 2012;25(4):188-197.

18. Roberts, D.L. and Mitchell, J.P. Influence of stage efficiency curves on full-resolution impactor data interpretation. Drug Delivery to the Lungs-22, The Aerosol Society, Edinburgh, UK, 2011;181-184.

19. Roberts, D.L. and Mitchell, J.P. Influence of stage efficiency curves on interpretation of abbreviated impactor data. Drug Delivery to the Lungs-22, The Aerosol Society, Edinburgh, UK, 2011;177-180.

20. Tougas, T.P., Christopher, D., Mitchell, J.P., Strickland, H., Wyka, B., Van Oort, M. and Lyapustina, S. Improved quality control metrics for cascade impaction measurements of orally inhaled drug products (OIPs). AAPS PharmSciTech. 2009;10(4):1276–1285.

21. Tougas, T. Efficient data analysis in quality assessment. In: Dalby RN, Byron PR, Peart J, Suman JD, Young PM (eds), Respiratory Drug Delivery-Europe 2011, Davis Healthcare International Publishing, River Grove, IL, USA, 2011:209-213.

22. Christopher, D. and Dey. M. Detecting differences in APSD: Efficient data analysis (EDA) vs. Stage grouping. In: Dalby RN, Byron PR, Peart J, Suman JD, Young PM (eds), Respiratory Drug Delivery-Europe 2011, Davis Healthcare International Publishing, River Grove, IL, USA, 2011:215-224.

23. Tougas, T.P., Christopher, D., Mitchell, J.P., Lyapustina, S., Van Oort, M., Bauer, R. and Glaab, V. Product lifecycle approach to cascade impaction measurements. AAPS PharmSciTech. 2011;12(1):312-322.

24. Rudolph G, Köbrich R. and Stahlhofen W. Modeling and algebraic formulation of regional aerosol deposition in man. J Aerosol Sci. 1990;21(S1):S403–S406.

25. Tougas, T.P., Mitchell, J.P. and Lyapustina, S.L. (Editors). Good Cascade Impactor Practices, AIM and EDA for Orally Inhaled Products. Springer, N.Y. in press.

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