A practical method for eliminating type I and type II errors when assessing the suitability for continued use of a cascade impactor

Both effective diameter and jet-to-plate criteria are required but the approach is easy

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Introduction

Cascade impactors are among the key pieces of analytical equipment in routine use for assessing the quality of inhalable drug products. The difficulty of calibrating impactors with particles of a known size makes the cascade impactor rare among analytical instruments. In a Good Manufacturing Practice (GMP) environment, the aerodynamic performance of the impactor must be known before the impactor is released for use in the laboratory. The calibration of new instruments is ideally obtained from a published calibration with particles. However, this calibration is laborious and available only at laboratories with specialized equipment, making it impractical for evaluating used impactors. Consequently, once the impactor has been in service, the user needs to make a decision about its continued use without being able to measure experimentally the current state of the particle size fractionation ability of the impactor.

This situation has led to a surrogate measurement, namely optical quantification of stage nozzle diameters (stage mensuration), as the preferred method of assessing instrument calibration. Early practitioners of this method, however, found themselves faced with the common problem of nozzles on a stage that were smaller (or larger) than the manufacturer's individual nozzle specification for a new impactor. Although it may have been logical to assume that the presence of a single nozzle diameter out of specification on a stage with typically hundreds of nozzles would not change the stage performance, the absence of a scientific rationale for accepting such a stage often resulted in the conclusion that the stage was not suitable for continued use in the laboratory.

Roberts and Romay[1] first posed the fundamentally based "effective diameter" as a proper averaging of the individual nozzle diameters and linked this metric with the aerodynamic performance of the instrument. This averaging method eliminated the error of disqualifying an acceptable impactor (a Type I error). Although the averaging approach is a scientifically supported basis for evaluating mensuration data, the method may not detect an unacceptable stage in some instances.

Roberts and Mitchell[2] recently showed that it is possible for the effective diameter to be within the required range even when there are nozzles that are too small to cause impaction on the collection surface. The so-called "jet-to-plate" criterion posed by these authors identifies such nozzles and other unusual nozzle possibilites, and when applied to the question of impactor suitability, will eliminate the error of qualifying an unacceptable impactor (a Type II error).

In this article, we summarize the theory and practice of applying *both* the "effective diameter test" and the "jet-to-plate test" to the question of the suitability for continued use of a cascade impactor. The overall goal is to help users eliminate both Type I and Type II errors when assessing impactor suitability. Perhaps surprisingly, no data other than that already gathered by optical stage mensuration is required to apply *both* tests, allowing the impactor user community, with no additional measurements, to ensure that impactors in use are aerodynamically equivalent to a new impactor.

Philosophy of suitability and the science of impactors

An impactor is suitable for continued use if, and only if, its aerodynamic performance is in the same range as that allowed for a new impactor. This point is basic, but because it is philosophical in nature, it is open to debate. Indeed, users of cascade impactors sometimes ask themselves whether an observed flaw in an impactor will actually show any differences in the mass-per-stage measured when testing a familiar inhalable drug product.

This thought process as a test for suitability of the impactor must be rejected because the lack of noticeable change in the mass of the active pharmaceutical ingredient (API) on one or more impactor stages can be caused by any number of possibly offsetting factors. These can include random method errors, variability in the inhaler device performance and uncertainties in instrumental measurements.

Because the goal of testing is to determine if the inhalable drug product is operating properly, each tool (including the impactor) used in the measurement of mass of API per stage needs to be known to be operating correctly and used correctly. That is the only way to ensure that the test result (mass per stage) truly reflects the performance of the inhalable drug product. Like any other piece of analytical equipment, the impactor must be known to be functioning as designed before results obtained with it can be considered reliable.

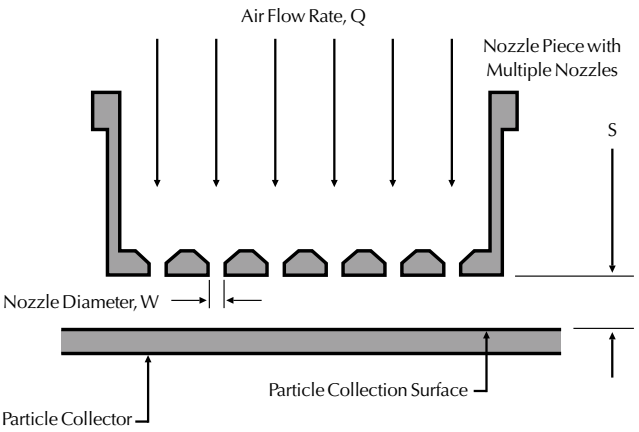
In this context, it is important that those who test inhalable drug products are aware that the science of cascade impaction is known, even if they are not experts themselves in cascade impaction. The performance of an impactor depends primarily on its flow rate, its nozzle diameters, and the distance from the nozzle exit to the particle collection surface, as first quantified by Marple.[3] Subsequent development of the theory of impactors led to criteria for the necessary separation distance between nozzles in a multi-nozzle impactor stage.[4] Impactors designed according to these principles[5, 6] exhibit sharp stage efficiency curves with the 50% "cut-point" diameter (D_{50}) in accord with the key dimensionless parameter known as the Stokes number. Readable summaries of key impactor design principles are readily available.[7-9]

Type I errors—How *not* to reject a good impactor

When quantification of the nozzle diameters by optical inspection first came to the forefront in the year 2000 as a method of ensuring suitability of used impactors (e.g., USP 24, General Chapter <601>),[10] no criteria were given to evaluate the data. At that time, many in the industry took the position that a single nozzle outside the specification of a new impactor would disqualify the impactor for continued use. Such a conclusion often would lead to an expensive, written report on the impact that this flaw may have had on impactor data taken since the previous optical inspection.

Figure 1

Definition of the "Jet-to-Plate" Parameters for Cascade Impaction



Although there was an intuitive understanding that a single nozzle should not be a significant problem,[11] Roberts and Romay were the first to articulate quantitatively how to average the nozzle diameters properly before applying the test of aerodynamic similarity to the used impactor.[1] This averaging method is a particularly valuable tool when only a few nozzle diameters are outside the specifications that apply to a new impactor. The averaging proposed by Roberts and Romay yields the "effective diameter," D_{eff}, so named because the stage is operating aerodynamically as if all of the nozzles were this size:

$$D_{eff} = (D^*)^{2/3} (\overline{D})^{1/3} \quad (1)$$

In Equation 1, D* is the area-mean nozzle diameter, and $\overline{D}$ is the area-median nozzle diameter of a given multi-nozzle stage; a user calculates these quantities directly from the optical stage mensuration data. When D_{eff} is in the range allowed for the nozzle diameters for a new impactor stage, the 50% cut-point (D_{50}) will be in the same range as that of a new impactor stage.

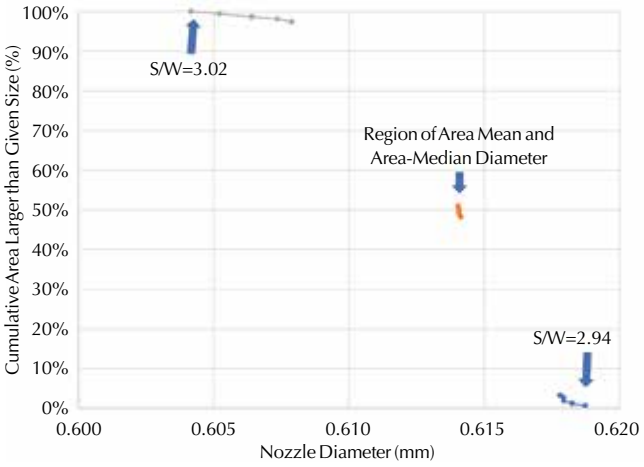
This concept of impactor suitability has been further refined, first by Roberts[12] and then by Roberts and Mitchell.[13] These authors addressed the approximations of the Roberts and Romay analysis and showed that for the substantial majority of inhalable drug products, the mass of API captured on each stage is rather insensitive to the shape of the stage capture efficiency curve. That result means that the D_{50} value of the stage is a sufficient characterization of the stage, a conclusion that supports the use of D_{eff} as a necessary criterion for suitability of a used impactor.

Type II errors—How *not* to accept a bad impactor

Although the concept of effective diameter has been in common practice for more than a decade, it only recently became clear that this criterion alone would be

Figure 2

Key Aspects of Nozzle Size Distribution when Testing Both D_{eff} and S/W



insufficient in some cases.[2] Figure 1 helps explain the most intuitive reason that this outcome is possible. For impaction to take place, it is the ratio of the separation distance, S, to the nozzle diameter, W, that matters to proper aerodynamic performance of an impactor stage (S/W).[7] If this ratio S/W gets too large (as if the collection surface were a long way away), the air jet slows substantially before hitting the collection surface, slowing the forward momentum of the particles and eventually eliminating impaction completely. For example, if a nozzle becomes partially occluded in use, W decreases, thereby increasing S/W eventually to a point that particles passing through this nozzle fail to impact the collection surface.

Roberts and Mitchell[2] explained there are several situations where it is possible for a group of nozzles to fail the S/W specifications that apply to a new impactor stage and therefore would not be detected by D_{eff}. Consequently, it is possible for a used impactor to satisfy the D_{eff} test at the same time as failing the S/W test, making the used impactor fail the test of aerodynamic similarity to a new impactor.

Specifications for the ratio of S/W are known for the Next Generation Impactor™ (NGI) and can be estimated for the Andersen Cascade Impactor (reference 12, Tables 4 and 5). In practice, measuring the value of S can be difficult, but the diameters (W) of all nozzles are known because of the stage mensuration data. Because the particle-capture efficiency under a given nozzle depends primarily on the nozzle diameter and secondarily on the distance to the nozzle surface, it is sufficient to use the *nominal design value* of S, or the values of S measured by the manufacturer when the impactor is new, to compute S/W. This approach is well justified when S/W is between 2 to 5 and possibly as large as 1 to 10.[2]

*With this approach, the **only** experimental data one needs to perform the "S/W test" are the individual nozzle diameters determined during optical stage mensuration.*

Since there is a reasoned method of deriving an "average" or "effective" nozzle diameter that characterizes the multi-nozzle stage, as described for D_{eff} and Type I errors, one has to ask whether there is a reasoned average value of S/W that could apply to a multi-nozzle stage. There is no such analytical result because the dependence of capture efficiency on the ratio S/W derives from a numerical solution of the applicable differential equations governing the fluid flow and particle motion. Therefore, the proper qualification policy is to ask whether *each* nozzle is within the S/W design specifications and then to use the result to quantify the impact if one or more nozzles are outside of the S/W specification.[2] In these (likely rare) cases, the S/W criterion provides an objective method of quantifying the impact, an aspect heretofore absent from used impactor quality assessements.

Examples of the D_{eff} and S/W test

Very often, users find that the effective diameter and S/W calculated from the optical inspection data of a used impactor are within the same range specified for a new impactor. Roberts and Romay[1] reported optical data for NGI-0030 after one year of use. For stage 5 of this impactor, the effective diameter was 0.614 mm (acceptable range 0.598 mm to 0.618 mm) even though one nozzle was slightly larger than that allowed in a new impactor. None of the nozzles after one year of use were smaller than that allowed for a new impactor. So, we anticipate that "all is well" even when we apply the S/W test along with the D_{eff} test. Indeed, from their Table 7, the S/W values for all 152 nozzles of stage 5 can be calculated to lay between 2.94 and 3.02, where we used for this calculation the nominal value of S (1.824 mm; Table 4 of reference 12). This range is well within the specification for S/W values (2.2 to 3.8; also given in Table 4 of reference 12). So, this stage satisfies both the D_{eff} and the S/W criteria, ensuring that by continuing to use it, one would not be discarding a good impactor nor accepting a bad impactor.

If we were assessing only the effective diameter, only the mid-range of the nozzle size distribution will typically be important. But when looking also for the Type II error (unacceptable values of S/W), the key portions of the nozzle diameter distribution include the "fringes" as well as the mid-range (Figure 2). This simple graphical representation of the optical inspection data communicates readily the role of D_{eff} and S/W in avoiding Type I errors and Type II errors when judging used cascade impactors.

Further insights can be drawn regarding the role of D_{eff} and S/W by examining a complete set of optical inspection data for a more recently used impactor. Users typically will receive a Certificate of Mensuration for the instrument providing the "descriptive statistics" of the nozzle dimensions for each stage. These descriptive statistics typically include the area-mean diameter, the area-median diameter and the effective diameter (Table

Table 1

Descriptive Statistics from Optical Inspection of NGI Stages 3 to 7

	Stage 3	Stage 4	Stage 5	Stage 6	Stage 7
Area-Mean Diameter*	2.181	1.202	0.600	0.317	0.204
Area-Median Diameter	2.181	1.203	0.601	0.317	0.204
Effective Diameter	**2.181**	**1.202**	**0.600**	**0.317**	**0.204**
Acceptance Range	2.165 to 2.205	1.197 to 1.217	0.598 to 0.618	0.313 to 0.333	0.196 to 0.216
Meets Criterion?	Yes	Yes	Yes	Yes	Yes

*All dimensions are in millimeters

1). Because Stages 1 and 2 of the NGI only have 1 and 6 nozzles, respectively, the typical descriptive statistics are not generated and these stages are therefore omitted from the following discussion.

The D_{eff} values for Stages 3 through 7 are each within the acceptance range for the stage. Therefore, each stage meets the D_{eff} criterion, and the instrument would be suitable for use in the laboratory under current practices. It is noted that the D_{eff} values for most of the stages are centered within the acceptance range except for Stage 5, where D_{eff} is closer to the lower limit. The area-mean diameter equals the area-median diameter on stages 3, 6 and 7, but these quantities differ by 0.001 mm on stages 4 and 5. The difference in the area-mean and area-median diameters for stages 4 and 5 indicates that the nozzle distributions on these stages are not symmetric around a central value. It is therefore more likely that an atypical nozzle (outlier) may be present on either of these stages. However, as discussed below, this observation is not necessarily reliable, particularly for the lower stages (with greater than 200 nozzles) where the descriptive statistics are not useful for detecting the presence of a few atypical nozzles.

To further explore the distribution of nozzle diameters on this used NGI, Table 2 presents the count of nozzle diameters in five size ranges around the nominal nozzle diameter for the same stages 4 through 7 represented in Table 1. [We omit discussion of stage 3 because the nozzle diameters for stage 3 are all within the diameter range requirement for all individual diameters for a newly manufactured stage]. As observed in Table 2, stages 4 through 7 each contain several nozzles with diameters that are more than 0.010 mm from the nominal value, which is outside of the range specified for a newly manufactured impactor. Evaluation of D_{eff} alone would not indicate whether one or more of these nozzles is outside of the dimensional specification for S/W. For Stage 4, which has less than 100 nozzles on the stage, the presence of a single nozzle not meeting the S/W specification would not be detectable with D_{eff}, but may be detectable by comparison of the area-mean and area-median diameters, where a difference of greater than 0.003 mm is a clear indication of an atypical nozzle on the stage.

The presence of an atypical nozzle diameter for Stage 4 has a high chance to be detected by comparison of the area-mean and area-median diameters, but stages with more nozzles make this comparison less reliable. For example, in the case of Stage 7, if the five nozzles in Table 2 with diameters smaller than 0.010 mm from the nominal value were completely occluded (diameter of "0"), then the area-mean, area-median and effective diameters calculated for the stage (Table 1) would be unchanged! Calculation of the S/W ratio for each nozzle using all measured diameters and the nominal S value shows that no atypical nozzles are present on any stage (Table 3).

Table 2

Number of Nozzles in Each Range Larger than and Smaller than the Nominal Nozzle Diameter

Nozzle Size Range	Number of Nozzles in Range			
	Stage 4	Stage 5	Stage 6	Stage 7
>-0.010 mm	4	19	3	5
-0.003 mm to -0.010 mm	35	133	393	178
Nominal ± 0.002 mm	13	0	0	447
+0.003 mm to +0.010 mm	0	0	0	0
>+0.010 mm	0	0	0	0
Total Nozzles	**52**	**152**	**396**	**630**

Table 3

Summary of S/W Results from Mensuration Data

	Stage 3	Stage 4	Stage 5	Stage 6	Stage 7
Nominal S (mm)	6.555	3.621	1.824	1.001	1.000
Minimum S/W	3.00	3.00	3.02	3.13	4.83
Maximum S/W	3.01	3.04	3.10	3.22	5.17
Acceptance Range	2.70 to 3.30	2.60 to 3.40	2.20 to 3.80	2.10 to 4.10	3.65 to 6.05
Meets Criterion?	Yes	Yes	Yes	Yes	Yes

The D_{eff} metric allows for the conclusion of acceptability of a used impactor to be made when the assumption that all nozzles on the stage are functioning within the design criteria is met. However, as shown in the examples above, the descriptive statistics of the mensuration results used to calculate D_{eff} are not sufficient to prove that the condition for all individual nozzles has been met. Therefore, evaluation of the calculated S/W values using the measured diameters obtained during mensuration provides a simple and necessary test for whether the aerodynamics of the impactor stages are within that allowed for a new impactor. In this way, the test of the S/W criteria avoids a Type II error that could be made if the decision were based on the D_{eff} criterion alone.

Conclusions

Impactors operate on known aerodynamic principles. Consequently, the criterion for continued use must be that the aerodynamics of the used impactor are in the same range as those of allowed for a new impactor. Proper aerodynamics are obtained when *both* the D_{eff} and the S/W criteria are met. Both of these tests can be made by quantitative measurement of the nozzle diameters (stage mensuration). Therefore "stage mensuration" data are sufficient for performing the D_{eff} test and the S/W test. Together these tests will help users avoid Type I errors (via the D_{eff} test) and Type II errors (via the S/W test), leading to high confidence that appropriate decisions are being made for keeping or rejecting used impactors.

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