The liability of fine particle dose (FPD)

Can we rely on the fine particle dose metric alone for quality control?

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The following is the first in a series of articles by the Cascade Impaction Working Group of the International Pharmaceutical Aerosol Consortium for Regulation and Science (IPAC-RS) concerning the limitations of metrics commonly used in the assessment of aerodynamic particle size distributions (APSDs) of orally inhaled products (OIPs). The current article concerns the surprisingly limited utility of the fine particle dose metric in quality control. The next article in this series will continue the theme of scrutinizing metrics used to make batch disposition decisions, with a focus on the stage grouping metrics favored by the United States Food and Drug Administration (FDA). These articles are written to educate: to dispel common misconceptions, to raise awareness of risks and to encourage scientists to scrutinize current practices. These articles should not be mistaken for regulatory guidance documents.

Introduction

Fine particle dose (FPD), the active pharmaceutical ingredient (API) mass less than 5 µm aerodynamic diameter, is a commonly used metric in the assessment of aerodynamic particle size distributions (APSDs) of orally inhaled products (OIPs). In particular, for products marketed in Europe, both the European Pharmacopoeia[1] and the European Medicines Agency (EMA)[2] recommend use of FPD (referred to as "fine particle mass" by the EMA) for quality control (QC) of OIPs. Similarly, in their 2006 guidance on the quality of inhaled pharmaceutical products, Health Canada defaults to the use of fine particle mass less than 5 µm to characterize inhaler APSDs in the context of assessing product quality.[3] Each document clearly presents FPD as the primary metric for characterizing the APSD of an OIP, acknowledging only via caveat that "additional criteria may be appropriate" if FPD alone is insufficient for APSD characterization. However, as discussed in the following article, FPD is generally quite poorly suited to the quality control of APSDs. This matter should be of concern to regulators, drug manufacturers and patients alike. Our aim is therefore to stimulate discussion regarding the purpose of APSD testing in QC and the importance of using appropriate metrics.

The liability of fine particle dose (FPD)

The liability of relying on FPD in the QC environment can be quickly illustrated with the following example. Imagine that you work in QC and that you are tasked with determining the suitability of a newly manufactured batch of an OIP for release to the European market. In this scenario, your job is to determine whether the performance of the current batch is sufficiently similar to that of the clinical batches previously used to demonstrate the safety and efficacy of the product, as defined by the approved specifications.

In this case, the product in question is a solution pressurized metered dose inhaler (pMDI). Figure 1 summarizes the typical performance of this pMDI as well as that of the newly manufactured batch. In panel A, the 200 mass-weighted APSDs shown in gray illustrate the typical performance of the product while the sole distribution highlighted in red is the APSD of the current batch. The same APSDs are presented in cumulative form in Panel B. Individual FPD values determined

for each APSD are shown in Panel C with the same color-coding and these FPD values are also summarized with a box-and-whisker plot to show the mean and quartiles of the data set. It is worth noting that these APSDs are not simulated data; they are real QC test results for an actual marketed product (see sidebar for more detail).

So let's return to the task at hand: you need to determine whether the current batch should be released to the European market. Essentially, you need to determine whether you manufactured what you intended to manufacture. At a glance, it appears that this should be a trivial decision. The APSD of the newly manufactured batch visually stands out from the other 200 APSDs. Moreover, examination of the cumulative plots (Panel B) of the APSDs reveals that the product's mass median aerodynamic diameter (MMAD) is typically between 1-2 µm, whereas the current batch has an MMAD of about 3.5 µm. Even in the absence of product specifications (which were not provided by the pMDI manufacturer), the current batch clearly does not perform as intended. Simply put, you intended to manufacture a product whose performance is summarized by the gray data, but you have failed to do so.

It appears that disposition of the batch should be a straightforward matter: the batch does not perform as intended and should therefore be rejected. Unfortunately, if you were to rely on FPD alone to assess this product's performance, you would have reached the opposite conclusion.

Looking further at the FPD data for these distributions (Panel C), we see that the current batch's FPD does not stand out at all from the pool of typical FPD values. In fact, the FPD for the current batch is just inside the lower quartile of the data set, meaning that it is within the bounds that define the central 50% of FPD values for this product. Although we do not know the precise FPD specification limits for this product, it is safe to assume that an FPD value between the upper and lower quartiles of this data set would conform to any realistic FPD specification. Otherwise, the manufacturer would be rejecting at least one out of every four batches (specifically every batch whose FPD falls below the lower quartile, which comprise 25% of the tested batches), and very likely some batches above the upper quartile as well. Frankly, this would be an absurd and utterly unsustainable practice.

In summary, the purpose of performing APSD testing on the current pMDI batch was to determine whether you had manufactured what you intended to manufacture, and, in the face of compelling evidence to the contrary, FPD clearly "thinks" that you succeeded. It is hard to understand the value of APSD testing that concludes this batch is just like all of the others. Moreover, what is the point of training scientists, of qualifying chromatography systems, of calibrating balances and flow meters, and of mensurating cascade impactor stages, if you ultimately rely on FPD to control your product?

Figure 1

Panel A: The APSD of a single, newly-manufactured pMDI batch (red) is superimposed on 200 typical APSDs (gray) for comparison. Panel B: The same APSD data as Panel A, displayed as cumulative distributions. Panel C: FPD values for each APSD with accompanying box-and-whisker plot.

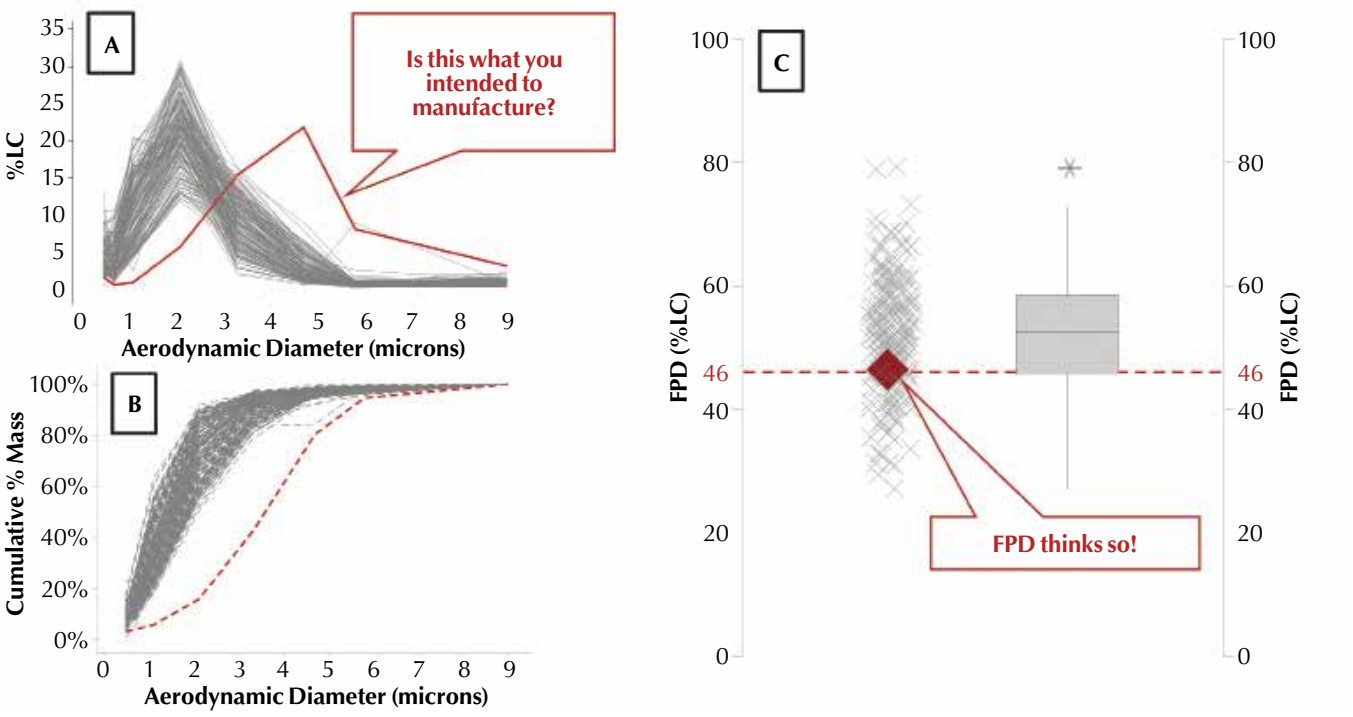
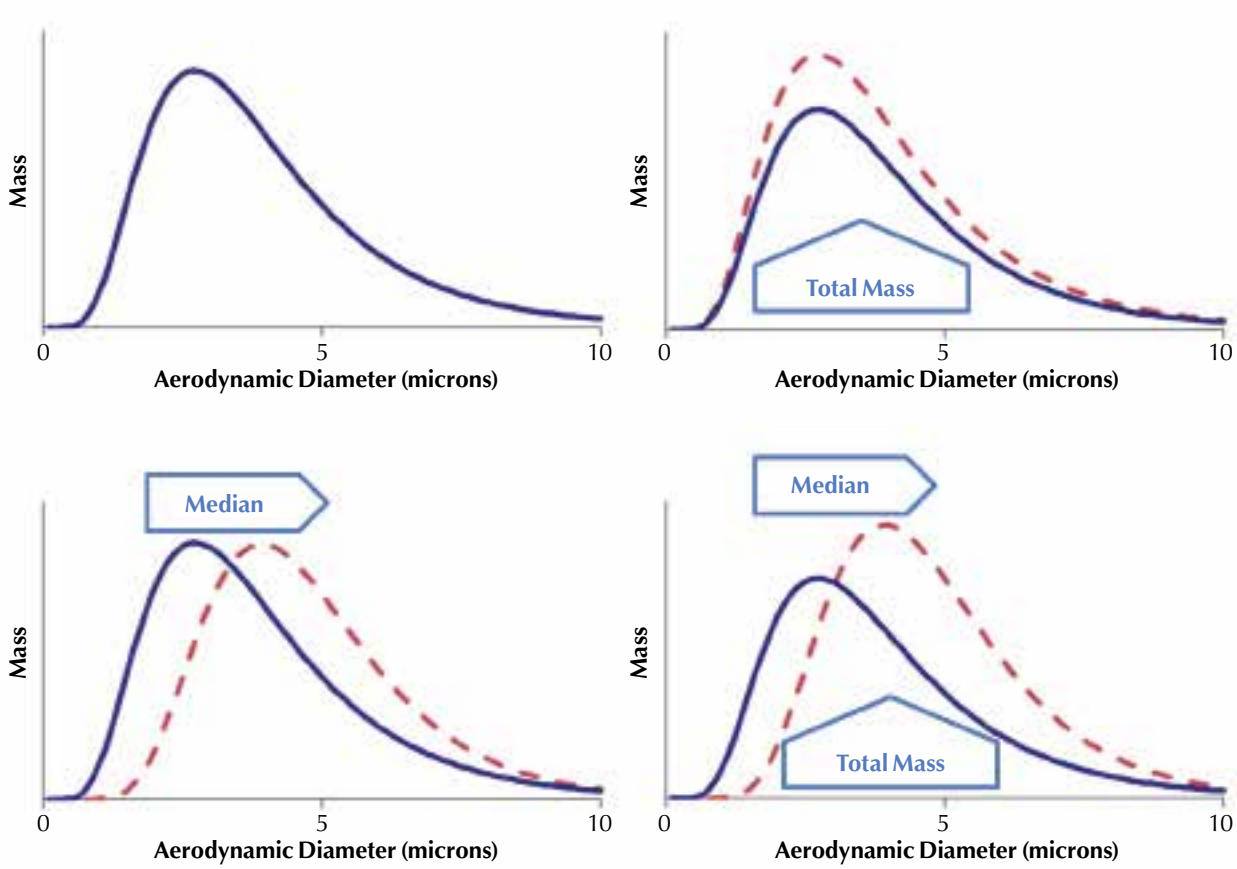


Figure 2

An APSD has two orthogonal dimensions: mass and size. For quality control of the APSD of an OIP, the testing and metrics must be sensitive to changes in both dimensions.



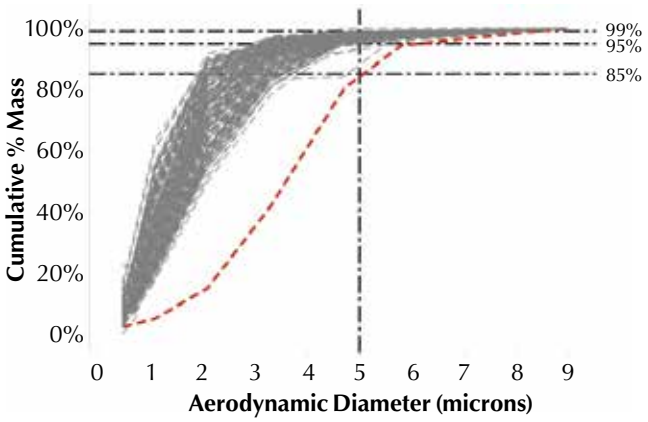
Why does fine particle dose fail?

So why does FPD fail to pick out such a glaring outlier in this example? Why is the metric not sensitive to such a large shift in the APSD? There are two key reasons. First, it needs to be understood that APSD data have two orthogonal dimensions: mass and aerodynamic size. An APSD can undergo changes in either dimension separately, or in both dimensions simultaneously, as illustrated in the examples shown in Figure 2. For example, changes in the delivered dose (i.e., mass per actuation) might impact only the mass dimension of the APSD. On the other hand, a change in the formulation composition could impact only the size dimension of the APSD. And, of course, some factors (or combinations of factors) could simultaneously impact both the size and mass dimensions of a product's APSD. The bottom line is that to adequately control an APSD, *QC testing must be sensitive to changes in either dimension.* In more general terms, a system of metrics attempting to describe a distribution must account for both the x- and y-dimensions. This is fundamentally challenging with only a single metric.

The chosen boundary of 5 µm is a further limitation of FPD in the QC environment. The cumulative distributions from the example (provided again in Figure 3) help illustrate this limitation. Looking at the typical product performance defined by the gray data, we can see that the FPD typically accounts for 95-99% of the size-fractionated mass for this product. In other words, virtually the entire APSD is contained within the FPD. A critical consequence of this is that large shifts in the size dimension of the APSD (significant coarsening, for example) will elicit only small changes in the FPD. In the present example, the APSD of the newly manufactured pMDI batch (red data) is dramatically coarser than those of the historical batches, as reflected

Figure 3

Cumulative APSDs of a solution pMDI product. The APSD from a new batch (red line) is juxtaposed with APSDs from 200 typical batches (gray). Reference lines show the 5 µm FPD cut-off for each set of data.



by an MMAD in excess of 3 µm. This represents a dramatic and readily observable departure from the 1-2 µm MMAD range typically observed for this product. However, this large shift in the size dimension of the APSD has resulted in only a slight decrease in FPD from > 95% to roughly 85%. The small drop in FPD is clearly just the tip of the iceberg. In short, FPD is remarkably insensitive to changes in the aerodynamic size of the aerosol.

Context and implications

So what does this mean? Some may doubt the significance of this example, questioning, in particular, the clinical relevance of shifts in MMAD. If a 1 µm shift in MMAD is deemed to have no clinical significance, why should we care if such shifts are detected by FPD? This argument completely misses the point of QC testing. The disparity between the current batch's APSD and those of previous batches tells us that something has gone wrong, that something in either the formulation, the process or the device components is not as it should be. Whatever the cause of this unexpected outlier APSD, it reflects that the product or the process is not under control and the root cause(s) should be determined. This is true regardless of whether there are clear implications regarding efficacy and/or safety for the patient. This concept is fundamental to quality control, within the pharmaceutical industry and beyond.

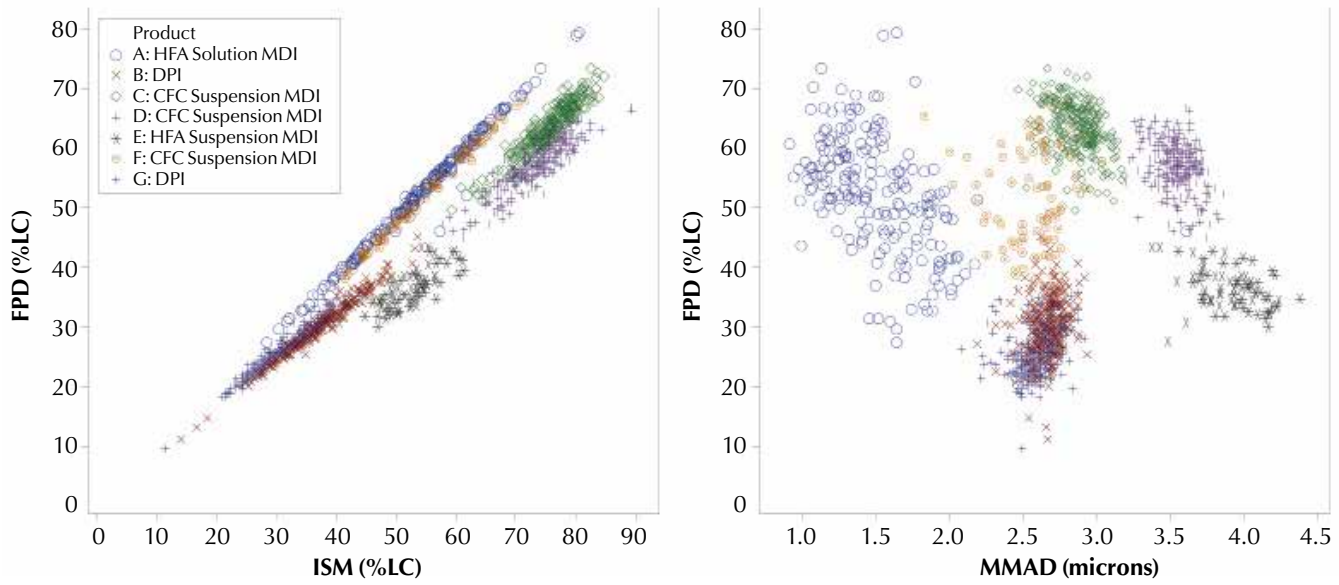
Stepping back, it is important to appreciate what the preceding example represents. It is natural to question whether the phenomenon illustrated here is a common occurrence or whether this data set represents an isolated peculiarity. The key lesson from this example—the insensitivity of FPD to changes in the size dimension of APSDs—is not limited to a specific OIP. Indeed, a recent publication by our group demonstrates just how poorly suited FPD is to the QC environment, using APSD data from four different OIPs.[4] As in the example here, the authors observed that FPD is remarkably insensitive to APSD size changes. Building on this published work, the two graphs in Figure 4 summarize individual APSD data from eight OIPs. The first graph plots FPD values versus impactor-sized mass (ISM). The second graph plots the same FPD values versus their corresponding MMADs. Note that each data point is a single measurement from an individual inhaler. The pMDI featured in the prior example is included as Product A. Two observations are immediately obvious from these graphs: FPD correlates very strongly with ISM, and not at all with MMAD. Each of these observations is true for each individual OIP and also for the combined data set.

The strong correlation between FPD and ISM shown in the left graph arises from the fact that the FPD constitutes the vast majority of the ISM. The dependence of ISM on FPD is, in fact, so great that they cannot be used as separate metrics. In other words, *using both metrics (ISM and FPD) would offer no improvement in QC decision-making compared to the use of either metric alone.*

Meanwhile, the lack of correlation between FPD and MMAD, laid bare in the right graph, confirms that, for these eight OIPs, the vast majority of their size-fractionated mass is finer than the 5 µm FPD boundary. This may seem like a simple restatement of the previous point (that FPD and ISM are essentially one and the same), but it reinforces an important message: that FPD does not reliably detect shifts in MMAD. Even for Product E (an HFA suspension MDI) whose MMAD is closest to the 5 µm boundary, shifts in MMAD from roughly 3.5 µm to 4.4 µm fail to impact the FPD.

Figure 4

FPD for eight different OIPs plotted against ISM (left panel) and MMAD (right panel). Each data point represents an individual APSD determination from the IPAC-RS blinded database (see sidebar for details).



The APSD data from these additional OIPs confirm that the fundamental limitations of the FPD metric are, in fact, universal and are not unique to the unpalatable example highlighted in the previous figures.

Summary

In this article, the insensitivity of FPD to shifts in inhaler APSD is clearly illustrated. In addition to highlighting the liability of relying on FPD alone for control of an APSD, the underlying causes have been discussed. Moreover, data from eight different products are examined to demonstrate the broad relevance of this phenomenon. The conclusion is clear: due to the insensitivity of FPD to APSD size, FPD cannot be used alone as a metric for APSD quality control. FPD can be used to control the mass-dimension of the APSD, but it must be used in conjunction with an orthogonal metric that is sensitive to changes in the size-dimension (such as MMAD). Importantly, supplementing FPD with metrics such as ISM or material balance (total mass ex-inhaler), neither of which are sensitive to APSD size changes, is not sufficient. The implications of this observation extend beyond the realm of QC testing. Indeed, any study relying solely on FPD to compare APSDs may equate aerosols that are, in fact, significantly different.

In the next article of this short series, we intend to place impactor stage groupings (currently favored by the US FDA[5] as a quality control measure for OIP APSD) under similar scrutiny. Fine Particle Dose, as we have seen, essentially represents a single, very large grouping of stages, and the resulting weakness is that it fails to detect large differences between APSDs. In QC, this can result in misclassifications where batches are inappropriately released. Conventional Stage Groupings, on the other hand, typically split the size-fractionated mass into three groups. As such, the grouping approach does not suffer the inherent limitations of FPD. However, as the reader will see, the manner in which the stage groupings are typically used introduces a different risk, wherein batches may be incorrectly rejected. As members of the IPAC-RS Cascade Impaction Working Group, we contend that neither FPD nor stage groupings are reliable metrics for making batch disposition decisions. Moreover, given the potential impact to patients and their medicines, we believe drug developers and the authorities who regulate them have a responsibility to address these shortcomings.

The IPAC-RS APSD Database

The APSD data used in this manuscript originate from QC testing of actual OIPs. The blinded IPAC-RS database includes APSD data for 34 OIPs, which are either commercially marketed or in late development (Phase IIB or later), from seven manufacturers. To ensure blinding and confidentiality, APSD data were submitted to the IPAC-RS secretariat. For each product, the APSD data consist of API recoveries from individual impactor components (e.g., induction port, stages, filter, etc.) expressed as a percent of the product label claim. More information regarding the database can be found at:

https://wayback.archive-it.org/7993/20170405182408/https:/www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_rpt2.pdf

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