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DISSOLUTION TESTING - Exploring the Link Between Particle Size & Dissolution Behavior for OINDPs

INTRODUCTION

In the development of orally inhaled and nasal products (OINDPs), a primary focus is achieving deposition at the preferred site within the pulmonary system or nasal cavity. The particle size or droplet size of the delivered drug has a strong influence on this aspect of performance, explaining the reliance on particle size measurement within OINDP research. However, as OINDP performance is refined, more attention is being paid to the path of the drug molecule following deposition. The speed of drug uptake into the bloodstream directly impacts its pharmacodynamic effect and bioavailability and consequently the clinical efficacy and safety of a product. It is therefore becoming increasingly important to have a greater understanding of dissolution behavior at the site of deposition, especially when it comes to demonstrating bioequivalence, a defining element of a generic submission.

Here, we review current trends in dissolution testing within the context of understanding particle size, which impacts clinical studies and ultimately generic submissions. The experimental work we present demonstrates the correlation between active pharmaceutical ingredient (API) specific particle size information and dissolution performance and illustrates the potential value of Morphologically Directed Raman Spectroscopy (MDRS), a relatively new analytical technique. By efficiently measuring the particle size and extent of aggregation of defined components within an OINDP
formulation, MDRS provides data that can be used to assess the dissolution behavior of APIs, even in the presence of particular excipients.

LOOKING BEYOND DEPOSITION

The central task of OINDP development, whether innovator or generic, is to identify a formulation/device combination that will successfully deliver the required dose of active ingredient to the preferred deposition site within the lung or nasal cavity. In the case of slowly dissolving drugs, it is also important to optimize the dissolution kinetics in order to ensure that absorption occurs before the drug is cleared from the site of deposition. Principally, this relies on engineering a product that will produce particles of closely defined particle size under the conditions of clinical use. However, a lack of *in vivo* equivalence is often seen, even in cases where the particle size distribution of the formulations being developed have been shown to be very similar, indicating that other properties not captured by traditional *in vitro* assays are important.

Focusing on pulmonary delivery, an aerodynamic diameter of 5 microns is routinely taken as the upper size limit for deposition in the lung, although more finely sized particles may be more effective for deposition in the deep lung. In reality, the emitted aerosol particle size is a polydisperse distribution, and a full understanding of the particle size distribution and extent of aggregation of the components is critical to achieving bioequivalence. The difficulties of achieving this goal, coupled with the fact that the delivered particles are so small, has meant there has been little focus on the *in vivo* dissolution behavior of OINDPs. In addition, there is, as yet, no standard dissolution testing technique, and considerable disagreement on the approach to dissolution testing that is most relevant. However, this situation is beginning to change.

The FDA's critical path initiative, which was introduced in 2004 to ease the translation of new therapies into commercially available efficacious drugs, indicates that a complete understanding of the particle size distribution of formulation components may be a leading indicator of *in vivo* outcomes.[1] Its application to suspensions highlights some central issues with respect to demonstrating bioequivalence. One is the need for component-specific particle size information, rather than a comparison of the overall formulation, a need that underlines the specificity limitations of microscopy. Another is that a significant number of submitted comparisons between Test and Reference products are challenged on the basis of precision and accuracy. Understanding the comparability of the particle size distribution *in vitro* can prevent undesirable outcomes *in vivo* and directly expedites the commercialization of a new product - a highly valuable
outcome.

This need to rigorously demonstrate bioequivalence is one of the reasons for an increased interest in OINDP dissolution testing. Because the speed of drug uptake into the bloodstream directly influences its bioavailability, understanding the impact of particle size and other particle properties on post-delivery dissolution behavior is important for demonstrating bioequivalence as part of an Abbreviated New Drug Application (ANDA). In addition, dissolution testing is becoming more of a focus in the development of innovator products. Here, controlling and meeting performance targets is an increasingly demanding task due to the desire to deliver less-soluble, larger molecule active components within OINDPs.

In summary there is a growing awareness of the need to consider the dissolution behavior of OINDPs and to learn how to control it by manipulating routinely measured parameters, such as particle size.

DISSOLUTION TESTING FOR OINDPS

The complexity of drug uptake within the pulmonary region presents certain unique challenges for OINDP dissolution testing. Dissolution testing for oral solid dosage is well established; however, the amount of liquid present in the stomach is substantial compared with the volume in the lung. The generation of relevant OINDP dissolution data relies on realistically recreating the

saturated sink conditions that apply during pulmonary dissolution during *in vitro* testing. Furthermore, there is no consensus on the dissolution media that should be used for OINDP dissolution or how best to introduce the sample into the dissolution apparatus.

Dissolution apparatus commonly used for OINDP testing, such as paddle apparatus, custom-built flow through apparatus and diffusion controlled cell systems, are all based on the USP <711> recommendations for oral solid form dissolution testing.[2] However, methods are modified to realistically simulate the conditions within the pulmonary region. Dissolution apparatus customized for OINDP analysis incorporates a semi-permeable membrane, designed to mimic the wall of the lung, through which the dissolved components must pass. Dissolution profiles are then determined using high-performance liquid chromatography (HPLC), or online UV analysis, to analyze collected samples of dissolution media.

A detailed review of dissolution test methods is beyond the scope of this article, but in broad terms, methods presented in the literature vary in terms of the following:[3]

-The type of sample used – whether the bulk formulation is tested or just the size fraction likely to deposit in the region of interest

-Apparatus design

-The formulation of the dissolution medium used for testing

-Data analysis and treatment

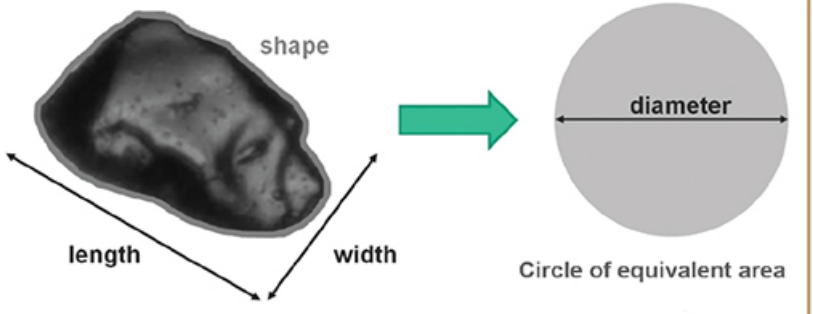
An official compendial method for dissolution testing methodologies has yet to be agreed, and the need for one is still open to question. In the absence of a direct regulatory requirement, monograph, or standardized method for dissolution testing, it is helpful to consider whether alternative techniques can be used to reliably infer *in vivo* dissolution behavior. The establishment of a robust correlation between particle size and dissolution behavior, for example, potentially meets the need to robustly demonstrate bioequivalence while at the same time minimizing dissolution testing.

CORRELATING PARTICLE SIZE TO DISSOLUTION BEHAVIOR

The bioavailability and therapeutic action of OINDPs depend on absorption of the API rather than the bulk formulation. Therefore, the development of relevant correlations between particle size and dissolution behavior relies, in the first instance, on measuring the primary particle size distribution and extent of aggregation of the API alone. This is a complicating factor when it comes to gathering the particle size information required to assess dissolution, especially given that the current component-specific methods applied to particle size analysis of OINDP, such as cascade impaction, destroy the particles within the formulation during the analysis process, making assessments of the degree of agglomeration (or dispersion) of the API more difficult to achieve. MDRS is a proven technique for generating component-specific information and efficiently addresses this issue.

Analytical systems that combine automated imagining with Raman spectroscopy, such as the Morphologi G3-ID (Malvern Instruments, Malvern, UK) provide the chemical identification capabilities needed to deliver component-specific particle size distribution data. At the same time, such systems offer substantial improvements in accuracy and efficiency over conventional microscopy, significantly reducing analysis times and avoiding the subjectivity associated with manual methods. Automated imaging uses advanced optics to rapidly collect two-dimensional images of a particle population that has been dispersed representatively on a plate. Smart software builds up number-based distributions of defined descriptors of particle size and shape from the measured dimensions of individual images (Figure 1).

FIGURE 1

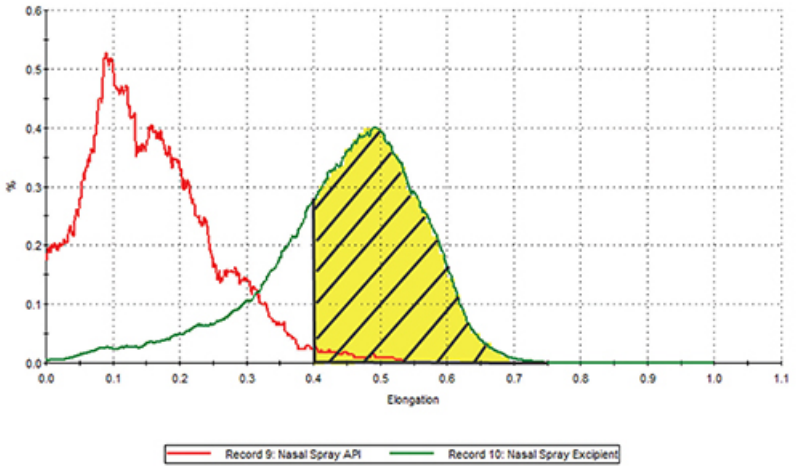


Morphological imaging uses advanced optics to collect images of particles. Particle dimensions are used to generate size and shape distributions for a sample.

Using automated imaging, the particles in a sample can be classified into discrete populations through the application of size and shape filters. The addition of Raman spectroscopy enables chemical identification of groups with distinct morphological features, or alternatively, the secure differentiation of particle populations that are morphologically similar. Either step enables the

generation of a component-specific particle size distribution. As many API and excipient particles within OINDPs are morphologically similar, separating components with Morphologically Directed Raman Spectroscopy is often the key to achieving the specificity required for relevant analysis. Figure 2 illustrates the application of Morphologically Directed Raman Spectroscopy in a multicomponent OINDP.

FIGURE 2



Particle shape (elongation) distribution data for excipient and API in a nasal spray analyzed using MDRS show that shape descriptors can be used to identify the majority of excipient particles. Particles in the non-shaded region require chemical identification to allow them to be identified as either API or excipient.

Size and shape analysis reveals that the components within this product are morphologically distinct, to a significant extent. On the basis of elongation, a shape parameter derived from the ratio of particle length to width, the sample can be divided into two distinct particle populations. However, there is an overlap. Particles with an elongation ratio in excess of 0.4 can be confidently identified as excipient while those of lower elongation, though likely to be API, cannot be reliably designated as such. In this example, Raman spectroscopy enables the initial association of specific morphological features with the API and is then used to definitively differentiate particles that are morphologically similar. Using dimensions for all the particles identified as API enables the generation of an API-specific particle size distribution.

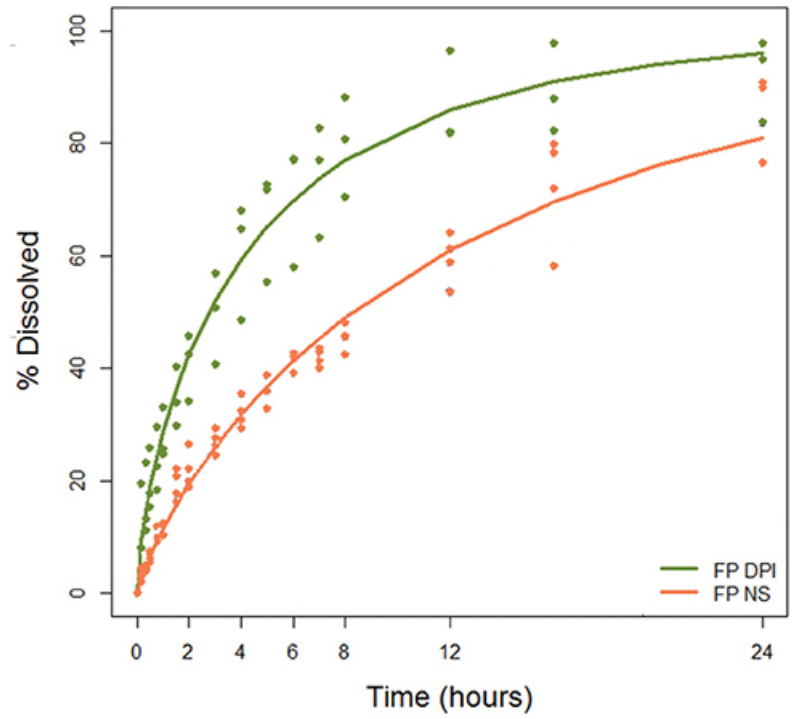
CASE STUDY: MEASURING THE RELATIONSHIP BETWEEN PARTICLE SIZE & DISSOLUTION BEHAVIOR

In a recent collaborative project, Malvern Instruments, Next Breath (a company that specializes in OINDP research), and the University of Florida used MDRS to assess whether component-specific particle size data could be correlated directly with dissolution rates. Particle size distribution was measured for a widely used inhaled API - Fluticasone Propionate - using the Morphologi G3-ID. As the device used to aerosolize an inhaled drug influences the delivered particle size, experiments were carried out using a DPI and a Nasal Spray (NS). Particle size was measured post-actuation for each device/API formulation.

Dissolution testing was carried out using the Modified Transwell™ method at the University of Florida, courtesy of Dr. Gunther Hochhaus.[4] A glass microfiber filter was used as the dissolution membrane, and a Sodium Dodecyl Sulfate (SDS) type surfactant was incorporated within the dissolution media to promote a more representative simulation of hydrophobic drug dissolution in the lung. The dissolution data gathered were fitted to a Weibull probability distribution model, and the time required to dissolve 63% of the drug (T63) was determined for each device/formulation combination.

Figure 3 shows the dissolution profile for Fluticasone Propionate, delivered with a DPI and an NS. The dissolution profiles are substantially different, with DPI delivery being associated with more rapid dissolution than NS delivery.

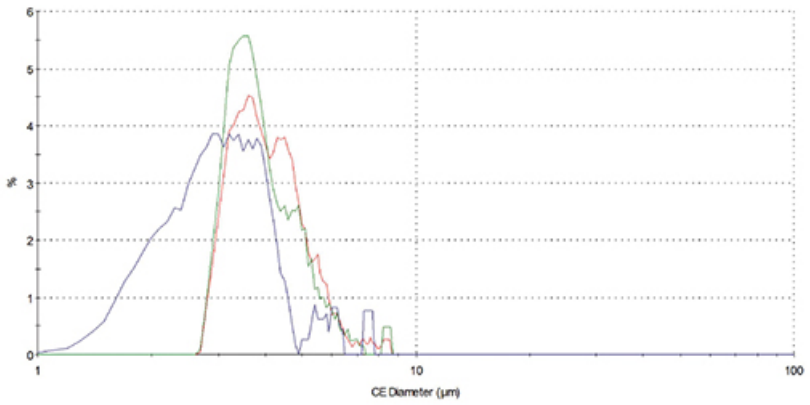
FIGURE 3



Dissolution profiles for Fluticasone Propionate delivered by DPI and Nasal Spray. The delivery device substantially impacts the dissolution rate of the drug.

Figure 4 compares the particle size distribution for Fluticasone Propionate delivered by DPI and by NS. The DPI-delivered samples have a finer particle size distribution than the dose delivered by NS, a finding that directly correlates with the observed dissolution data. The DPI delivers Fluticasone Propionate with a finer particle size, which dissolves more rapidly.

FIGURE 4



FP delivered using a DPI (blue curve) has a finer particle size compared to that observed using a NS (red and green curves).

In addition to being able to measure the particle size of the API within each formulation, the particle size and shape data provided by the Morphologi G3-ID system can also be used to classify particles as being either primary particles or agglomerates.[5] The data obtained are provided in Table 1 and confirm that the extent of agglomeration within the NS formulation is higher than in the DPI formulation. This too may help account for the difference in dissolution rate.

The data presented here highlight a number of important aspects of OINDP dissolution testing, including the impact of delivery device on dissolution behavior and the need for repeat analysis to account for natural variations in the actuation process. The most significant finding, however, is the suggestion that MDRS can be used successfully to generate data that correlate directly to dissolution rate. This is because the technique enables the secure differentiation of API from other ingredients in the formulation, thereby providing access to particle size distribution data specifically for the component of interest.

TABLE 1				
	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)	% Aggregate
FP DPI	2.0	3.3	5.4	27%
FP NS	3.2	4.1	5.7	36%

LOOKING AHEAD

A greater understanding of the behavior of OINDP formulations post deposition is increasingly required, both to refine performance and, for generic manufacturers, to ensure bioequivalence. MDRS is a useful tool for *in vitro* OINDP testing that provides the chemical identification required to generate component-specific particle size data for APIs within a formulation. The data presented here shows how the results delivered by the technique can be correlated with dissolution data, and may therefore provide a means of assessing product bioavailability.

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