Formulation

DELIVERY

Malvern Spraytec System

Consistency of Delivery is Key in Nasal Spray Treatments

Correct droplet size—a critical parameter in nasal sprays—ensures that patients' bodies absorb active ingredients as intended. | BY **PAUL KIPPAX** AND **ANNE VIRDEN**

From the drug maker's perspective, nasal sprays are an excellent choice for delivering locally acting drugs to relieve such conditions as sinus congestion and allergic rhinitis. They are also a valuable alternative to oral and injection delivery for vaccines, peptides and proteins. Absorption in the highly vascular nasal cavity is rapid. This route also avoids passage through the gastrointestinal tract and the risk of enzymatic degradation.

From the patient perspective, nasal sprays are a winner again: they are easy to use and readily accepted compared with several other delivery methods.

A critical parameter of nasal spray medications is the size of spray droplets. Droplet size impacts how an active ingredient is deposited in the nasal cavity and therefore how well it is absorbed by the body. The simple acts of storing a medication and shaking it before use can cause viscosity changes, which in turn can affect droplet size. The success of a nasal spray product therefore depends on achieving an optimal match between the drug formulation and the delivery device.

Difficult Task

Studying droplet size during the course of a spray event, however, is challenging: Actuation is typically complete in about a tenth of a second.

Laser diffraction analysis has proven itself up to the task. With data acquisition rates as high as 10 kilohertz, the top laser diffraction instruments are able to capture the fine detail of a droplet profile in real time, providing insight for the development of nasal spray formulations and delivery devices.

Droplet size affects a drug's deposition behavior in the nasal passages. A nasal spray product must deliver a uniform dose into the nasal passages, each time the product is used and throughout its lifetime.

In the United States, this delivery is ensured and validated via test methods specified by the Food and Drug Administration (FDA). The 2003 draft guidance document, *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (http://www.fda.gov/ cder/ guidance/5383DFT.pdf), outlines the testing required for nasal product studies in support of new drug applications and abbreviated new drug applications. It highlights the benefits of in vitro testing for assessing bioavailability and bioequivalence, and the correlation between certain physical characteristics and product performance. The link between particle size and pulmonary (as opposed to nasal) deposition is discussed, as is the use of laser diffraction and its recommendation for use in droplet size measurement. Consistent drug delivery during the lifetime of the product is critical and the document provides guidance on this aspect of performance.

Another FDA guidance document, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, and Controls Documentation* (July 2002), recommends that manufacturers test spray products near the point of container exhaustion to determine how performance tails off after delivery of the labeled number of doses. The ideal is to have uniform dose delivery right up to the point where the container is empty, although this is difficult to achieve in practice; a sharp drop-off is desirable. The FDA recommends that manufacturers measure spray content uniformity, droplet particle size, and drug particle size for each spray after the labeled number of doses has been dispensed. This information can be used to determine the optimum fill level for a nasal spray container.

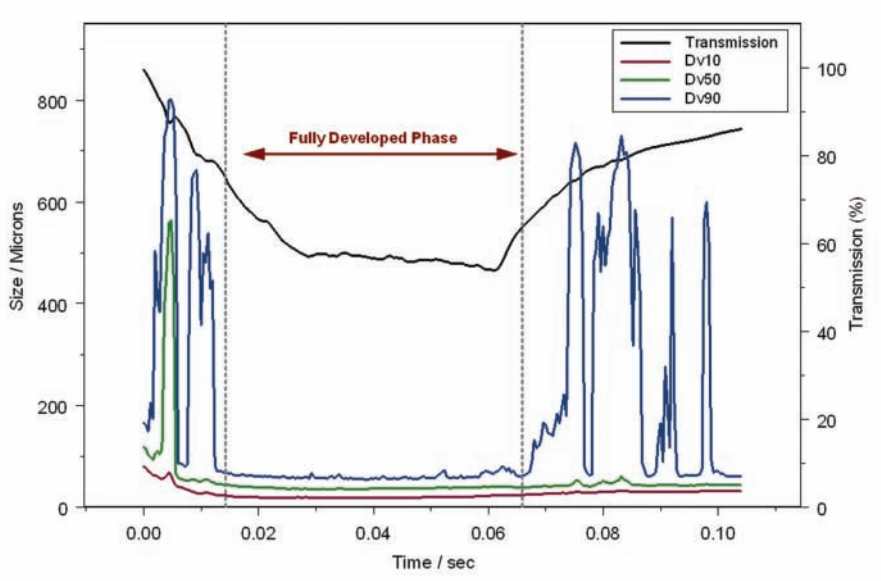

Figure 1: Changes in particle size observed during nasal pump spray actuation, measured using the Spraytec laser diffraction-based analyzer.

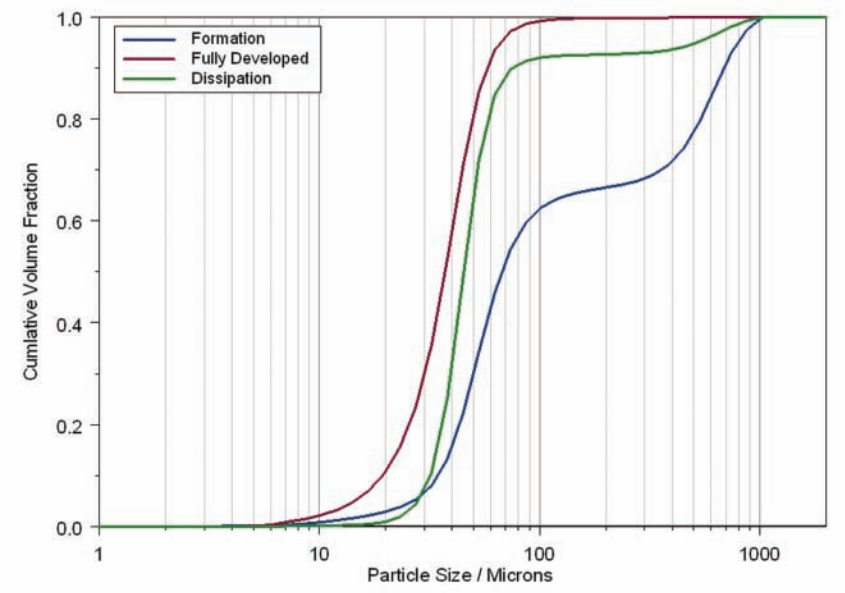

Figure 2: Average cumulative size distributions calculated for each phase of atomization observed during nasal pump spray actuation.

Laser Diffraction Characterizes Sprays

With the technique of laser diffraction, particle size is determined by measuring the diffraction pattern produced as light is scattered by the droplets that make up a spray plume. The intensity and angle of scattering correlate with droplet size, which can be calculated from the measured diffraction patterns using an appropriate scattering model.

A key feature of the technique for nasal spray applications is the speed of data acquisition—as high as 10 kilohertz for state-of-the-art systems. This speed permits real-time monitoring of the evolution of droplet size throughout the duration of the spray event, providing data for the study of atomization dynamics.

The measurement range for laser diffraction, 0.1 to 2000 microns, is also ideal because the droplet size of nasal sprays is typically 20 to 120 microns. Droplets smaller than this range tend to be drawn into the lung whereas larger droplets may be cleared from the nose very rapidly.

Figure 1 shows a typical particle size profile for a nasal spray actuation. Complete actuation of the nasal spray occurs in less than 130 milliseconds. But because measurements are made every 100 microseconds, the profile of the spray event is captured in detail: three distinct phases are visible.

At the start of the actuation is the formation phase, characterized by a relatively large droplet size, which is attributable to low initial flow through the spray pump nozzle. There is then a sharp decrease in particle size to a relatively steady value, which is maintained throughout the fully developed phase. During this period, flow through the nozzle is optimal and droplet size is at its most stable. At the end of the fully developed phase the metering chamber is almost empty and the flow rate decreases once more. This decrease causes a corresponding increase in droplet size. This final period is referred to as the dissipation phase.

FDA guidelines recommend that data from the fully developed phase be used for the characterization of nasal sprays, permitting statistically valid comparisons between different products. In the foregoing example, the fully developed phase is clearly identifiable and can be defined on the basis of a time window during which all the particle size parameters (Dv10, Dv50 and Dv90) are stable. Using this time window, researchers can determine averaged particle size data for each of the phases (see Figure 2) and asses the reproducibility of delivery during the fully developed phase, by repeatedly actuating the product.

Batch Release Testing

A nasal spray device, as mentioned previously, is expected to perform consistently when the labeled number of doses has been exceeded. The data shown in Figure 3 are taken from a study of this characteristic for a particular spray product.

Researchers measured the spray profiles from successive actuations of a

pump product, from the beginning life stage through end of life. Averaged particle size data for the fully developed phase were then calculated to assess consistency across the lifetime of the product. An automated actuator was used to ensure repeatable device operation throughout the experiment.

On the first actuation a slightly larger droplet size is measured; the recorded value of transmission is also higher at this point. Transmission is a measure of the proportion of light from the laser source which passes through the spray. High transmissions are therefore associated with low spray concentrations.

The data collected suggest that the pump was not fully primed before the start of these measurements. In subsequent actuations, the output of the pump is highly reproducible up to actuation 61, both in terms of particle size (Dv10, Dv50 and Dv90) and concentration (transmission). Beyond this point, particle size and transmission start to rise rapidly as the device runs low. The label claim number of doses in this case was 50.

The measurements made using laser diffraction can detect problems with the operation of the device. In the foregoing experiment, one of the actuations measured during the middle life stage (actuation 43) shows an increased particle size. This anomaly is associated with a significant increase in the measured transmission, indicating that the spray concentration is low. The particle size increase suggests that the metering chamber was not completely filled prior to this actuation.

Studying the spray characteristics of a device in this way allows assessment of the impact on bioavailability of pump operation up to and beyond the label claim dosage.

The combined study of droplet size and rheological measurements can be a valuable way of rationalizing differences in behavior between similar batches as formulation rheology can have a direct impact on atomization behavior.

Figure 4 shows viscosity data for two different batches of a standard nasal spray product. The viscosity of batch two is significantly lower than that of batch one. Viscosity data measured at low shear rates is particularly relevant for the prediction of storage instability. Suspensions having relatively low viscosities tend to be more prone to settling. In this case, the experimental results are consistent with the manufacturer's observations, as a problem with the batches was first detected as storage instability; batch two was less stable than batch one.

Droplet size data for both sprays were measured to assess the impact of this viscosity difference on product performance (Figure 5). The batch with lower viscosity produces finer droplets when atomized in the nasal spray and therefore may deposit differently in the nasal passages. ■

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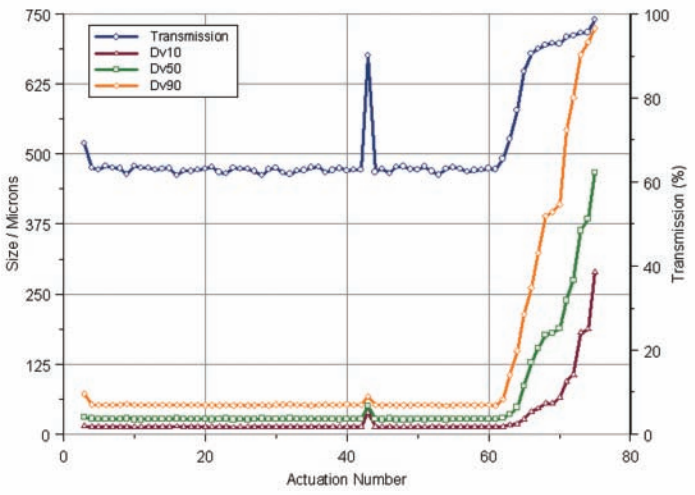

Figure 3: Changes observed in the Dv10, Dv50, Dv90 and transmission as a function of actuation number. All of the results relate to the stable phase of pump actuation.

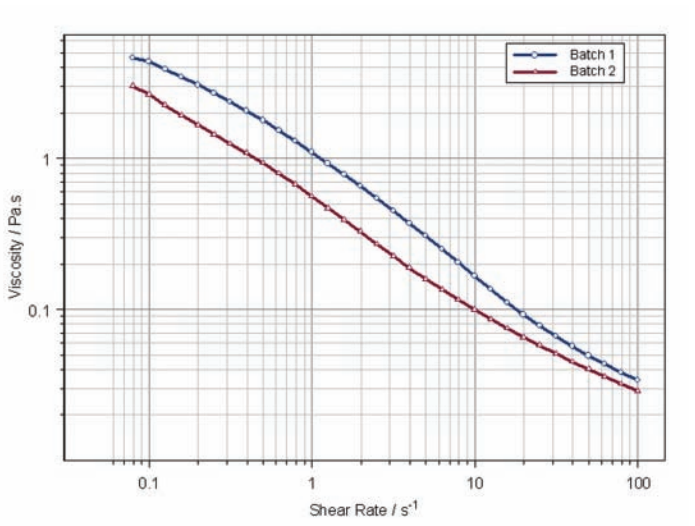

Figure 4: Viscosity data for two batches of a standard nasal spray formulation.

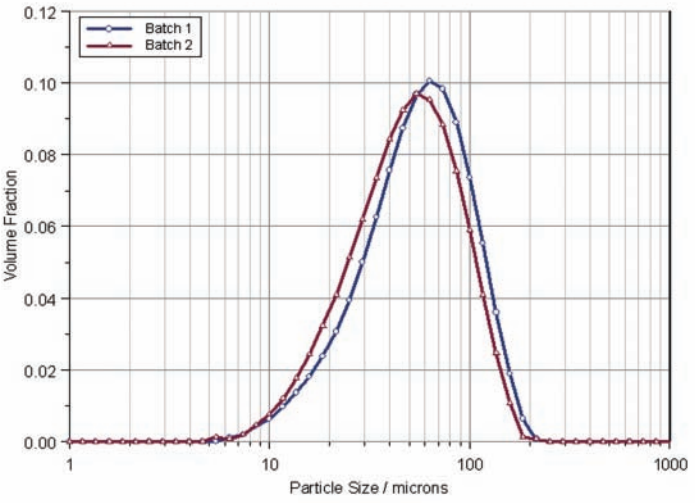

Figure 5: Droplet size data for a standard nasal spray formulation.

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