Characterizing carrier-free DPI formulations

Using laser diffraction and morphological imaging to examine aerosolization performance of carrier-free inhalation powders

Janne Raula, Esko Kauppinen, Deborah Huck, Paul Kippax, and Anne Virden
Aalto University, Malvern Instruments

Dry powder inhaler (DPI) developers are increasingly interested in tackling the powder engineering challenges presented by carrier-free formulations. While carrier formulations solve a number of handling and aerosolization problems, they also result in increased material deposited in the patient's mouth and throat through sedimentation and impaction compared to carrier-free medications. Carrier-free formulations, on the other hand, can be tricky due to the cohesive forces between the fine active pharmaceutical ingredient (API) particles.

At particle sizes below 10 μm, especially in the <5 μm range required for deposition in the lung, the strength of inter-particle forces of attraction rises exponentially, dramatically increasing the likelihood of agglomeration. Successful carrier-free delivery, therefore, requires modification of the properties of the fine API particles to reduce the cohesive forces between them [1]. One potential strategy involves reduction of the contact area between particle surfaces by increasing surface roughness for example; alternatively, developers may choose to reduce particle surface energy [2].

A combination of two complementary characterization techniques, laser diffraction and image analysis, delivers data on particle size and morphology that can accelerate and optimize the development of carrier-free dry powders by improving understanding of how a process like particle coating affects the dispersion characteristics of the formulation. Laser diffraction enables the examination of powder entrainment and dispersion, while image analysis enables the study of powder structure before and after delivery.

Laser diffraction

Laser diffraction delivers volume-based size distributions for particles from 0.1-2,000 μm, comfortably covering the entire range of interest for inhaled formulations. In laser diffraction, particles illuminated in a collimated laser beam scatter light over a range of angles. Large particles generate a high scattering intensity at relatively narrow angles to the incident beam, while smaller particles produce a lower intensity signal but at much wider angles.

Laser diffraction analyzers record the pattern of scattered light using an array of detectors and calculate the particle size distribution of the sample from it using an appropriate model of light behavior, preferably Mie theory as recommended by ISO13320. In addition, if the user correctly specifies the path length of the laser through the sample, the analyzer can calculate the sample concentration using Beer-Lambert's Law by measuring the change in laser light transmission caused by the presence of the particles. The technique is widely used within the pharmaceutical industry, and USP <429> provides a good introduction to its capabilities and the process of method development.

Non-destructive and suitable for either wet or dry samples, laser diffraction offers a faster particle sizing technique than cascade impaction and requires less manual labor. Automated, standard operating procedure-driven operation, developed over the last decade, streamlines the analytical process to the point of push button routine measurement, significantly reducing operator-to-operator variability, with extremely high reproducibility and repeatability. Laser diffraction provides data for the entire formulation, not just the active, making it complementary to conventional particle size distribution (PSD) measurement of DPI formulations by cascade impaction.

The technique has several advantages for measuring PSD during delivery of inhaler formulations, which can help developers optimize the formulation/device combination. First, the instrument's measurement speed allows for real-time particle size measurement throughout the duration of the drug delivery event. Laser diffraction also allows the simultaneous measurement of particle concentration and particle size within the aerosol plume, providing detailed information for the dynamic study of dispersion behavior.

The technique also maintains a history of particle size and concentration for every actuation, showing how both parameters change over the several hundred millisecond duration of the drug aerosolization.

Image analysis

Image analysis quantifies the size and shape of particles in a sample by analyzing individual 2D images of each particle. Advances in computing power and digital camera technology have revolutionized this method over recent years, accelerating sharp image capture and the data analysis required to convert the images into size and shape distributions for the sample.

Compared with manual microscopy, the conventional approach for shape quantification, image analysis is much faster, taking minutes rather than hours, far less manually intensive, and more statistically relevant because it can analyze a much larger particle population. The best image analysis systems for particle characterization are now fully automated and can record microscope-quality images of hundreds of thousands of particles, ranging from 0.5 to 10,000 mm in size within minutes.

As with conventional microscopy, developers can visually analyze images of individual particles or discrete, well-defined populations if desired by drawing them from the database of images collected. For DPI research, for example, analysts may want to study only the fine particle fraction or only agglomerated material, which they can accomplish by classifying the data according to size or shape respectively. This capability makes image analysis a powerful tool for troubleshooting and for root cause analysis applications and, during early stage research, the overlaying of size data with shape information drives more sophisticated product development than is possible with size information alone.

Assessing the effects of particle coating on surface structure

In an effort to develop a carrier-free formulation of salbutamol sulfate, developers coated the salbutamol with L-leucine [3]. Previous studies have shown that very small L-leucine crystals enhance the flowability and dispersion properties of fine API particles by introducing a degree of surface roughness on an otherwise relatively smooth surface [4, 5], and the goal for this study was to investigate links between the proportion of L-leucine applied, the resulting changes in API particle shape and surface topology as determined by image analysis, and dispersion behavior in a DPI as determined by laser diffraction [3].

First, the researchers used image analysis to obtain data on the circularity of samples of commercially available micronized salbutamol sulfate (MSS) and of salbutamol sulfate particles coated with various proportions of L-leucine. The sample proportions included 97% salbutamol/3% leucine (designated "S97L03"), 91% salbutamol/9% leucine (S91L09), and 82% salbutamol/18% leucine (S82L18).

A circularity close to 1 indicates particles with a 2D projection approaching that of a perfect sphere, while circularities closer to 0 indicate more irregular shapes. Data generated by an automated image analysis-based particle characterization system show that circularity of the drug particles decreases with increasing L-leucine content (Fig. 1). Samples containing 18% L-leucine have a more complex elongated shape than those with just 3% L-leucine, which are almost spherical, with a circularity value close to 1. MSS exhibits the lowest overall circularity value, with the images indicating that it contains a significant number of rod-shaped particles.

Scanning electron microscope observations confirm that the four samples exhibit significantly different particle shape and surface topography (Fig. 2) [6].

Figure 1

Circularity distributions for coated and uncoated samples of salbutamol

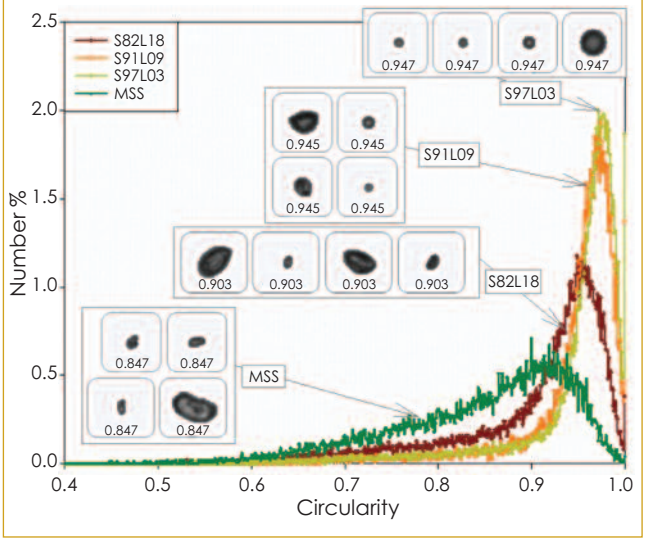
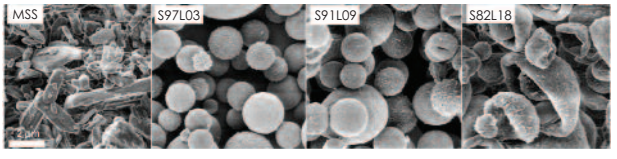


Figure 2

SEM images of micronized salbutamol sulfate (MSS) and L-leucine coated salbutamol sulfate powders



Investigating drug delivery characteristics

The next step involved the evaluation of the aerosolization characteristics of the samples using a laser diffraction system with a high data acquisition speed of 1 complete particle size distribution every 400 ms. Data recorded for flow rates of 30, 60, and 90 L/min show good, reproducible dispersion from a passive device to a respirable size of under 10 μm at each flow rate for all three of the coated samples (Fig. 3), with the proportion of the emitted dose in the <10 μm range varying from 78 to 93%. The MSS particles, however, exhibit flow rate dependent behavior, with very poor dispersion at 30 L/min, rising to more acceptable performance at 90 L/min.

Concentration profiles for the samples, calculated by the laser diffraction analyzer at a flow rate of 60 L/min, highlight the significance of the coating for entrainment behavior between the coated and uncoated materials (Fig. 4). All of the coated materials demonstrate rapid entrainment, giving a high initial particle concentration that is likely to be beneficial for API delivery to the lungs. Of these samples, however, the S82L18 appears to release most efficiently; the peak relevant to the initial entrainment phase is high, and the area under the curve is also markedly greater than for either of the other two coated samples, suggesting the delivery of a larger quantity of material.

Emitted mass data, measured by weighing the inhaler and capsule before and after each actuation, confirm the superior properties of the S82L18, which in general has the highest emitted mass of all those tested at each flow rate (Table 1). For all samples, emitted mass increases with flow rate, with variability in emitted mass tending to be higher at low flow rates, which provide relatively little energy for entrainment and dispersion of the dose.

The uncoated MSS sample exhibits a much lower initial powder concentration, with delivery continuing at a relatively low concentration until the end of the measurement and a high variability in emitted mass at all flow rates. These results suggest that break-up of the MSS powder bed held within the capsule is relatively slow and offer further evidence of the poor dispersion properties of the material.

Figure 3

Flow rate dependence of the volume of material below 10 μm in size for each formulation

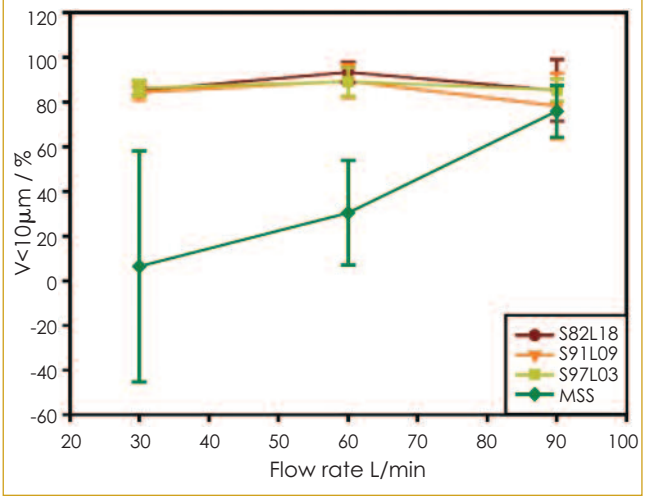


Figure 4

Concentration (Cv) profiles for samples at a flow rate of 60 L/min

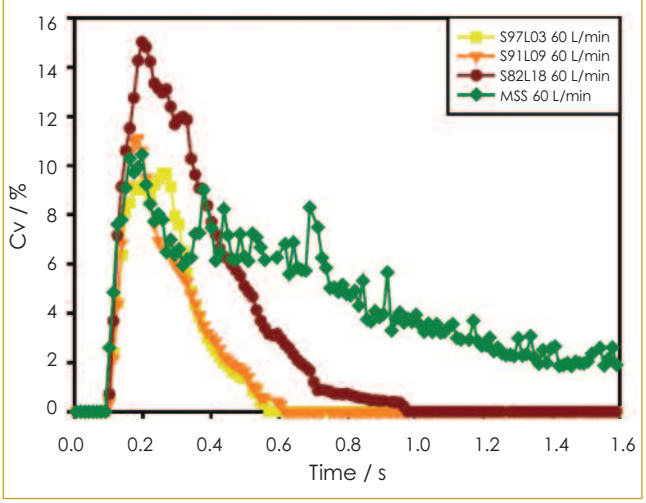


Table 1

Average emitted mass for each formulation at 30, 60, and 90 L/min, as calculated over 3 device actuations

Flow rate	Emitted mass (mg)							
	S97L03		S91L09		S82L18		MSS	
(L/min)	Average	%RSD	Average	%RSD	Average	%RSD	Average	%RSD
30	4.43	14.60	5.03	8.46	6.99	7.39	4.72	32.21
60	6.54	17.48	6.28	5.15	9.00	10.38	6.67	12.59
90	7.39	7.65	8.45	3.35	9.96	6.81	9.06	24.88

The laser diffraction data confirm that nano-crystal coating improves the dispersion improves the dispersion behavior of the drug powder. The data also confirm that amount of powder emitted from the device increases as the L-leucine concentration increases. Combining the laser diffraction data with the image analysis data, which shows decreasing roundness of the particles with increasing amounts of L-leucine, allows the researchers to determine quickly that roundness and the emitted dose are inversely related and to adjust the formulation for the optimal amount of L-leucine.

In addition to formulation development benefits, laser diffraction techniques also transfer easily into the process arena, with on- and in-line instruments providing a well-established, reliable process analytical technology (PAT) solution for continuous monitoring at both pilot and manufacturing scale.

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Janne Raula is Senior Research Associate and Esko Kauppinen is Professor in the Department of Applied Physics, Aalto University, Finland. Deborah Huck is Product Technical Specialist, Morphological Imaging Systems; Paul Kippax is Product Manager, Diffraction Products; and Anne Virden is Product Technical Specialist, Diffraction, Malvern Instruments, Enigma Business Park, Grovewood Road, Malvern, Worcestershire, WR14 1XZ, UK. Tel: +44 1684 892456.