MICRONIZATION *at its Finest*

Particle Size Characterization of Individual Components in Co-Micronization Blends of APIs with SPES Technology

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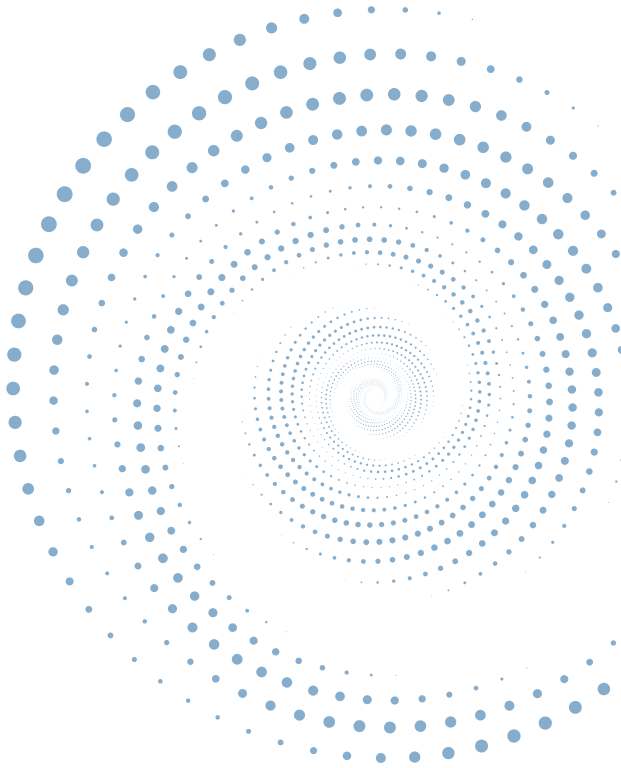
ABSTRACT

Active Pharmaceutical Ingredients (APIs) often require particle size control and solubility enhancement with excipients to increase dissolution rates and solubility for APIs to be bioavailable. **Microsize** utilizes co-micronization with jet mills to produce micronized blends of APIs and excipients that have superior content uniformity, particle size control, and enhanced bioavailability. **EOS Instruments** is the producer of the Classizer™ ONE, an advanced particle analyzer based on the SPES (Single Particle Extinction and Scattering) technology which can analyze individual components in API blends. SPES optically classifies particles by measuring the complex field scattered in the forward direction, one particle at a time. The multiparametric SPES data and its analysis using a Principal Component Analysis (PCA) software extracts particle size distributions (PSDs), refractive indices (RIs), and numerical concentrations of individual components in blends. API/excipient and API/API blends were prepared by co-micronization and characterized by the Classizer™ ONE to demonstrate the technologies.

KEY TAKEAWAYS

- **APIs frequently need particle size control and excipients to improve bioavailability**
- **Co-micronization is an effective way to micronize and blend APIs and excipients**
- **The SPES technology can characterize the size and optical properties of individual components in blends**



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INTRODUCTION

The solubility and dissolution rates of Active Pharmaceutical Ingredients (APIs) can be increased by blending micronized excipients that increase solubility with micronized APIs. Blending micronized materials together is not trivial due to cohesive forces that cause poor mixing. Co-micronization overcomes poor mixing by producing uniform micronized API/excipient blends by feeding pre-blended, unmilled materials or co-feeding individual components into spiral jet mills (Figure 1). The powders are injected into the mill by pressurized gas (typically air or nitrogen), and they are further accelerated by gas from nozzles positioned around a ring inside the mill. The accelerated particles collide and fracture into smaller particles. The smaller particles exit the mill when the particles are small enough to overcome the centrifugal force and the radial drag becomes the dominant force. The particle size distribution (PSD) can be controlled by adjusting the gas pressure and the feed rate and the Dv90 values are typically less than 20 µm. The spiral jet mills blend the APIs and excipients together in a vortex as they are micronized, creating a homogenous blend.

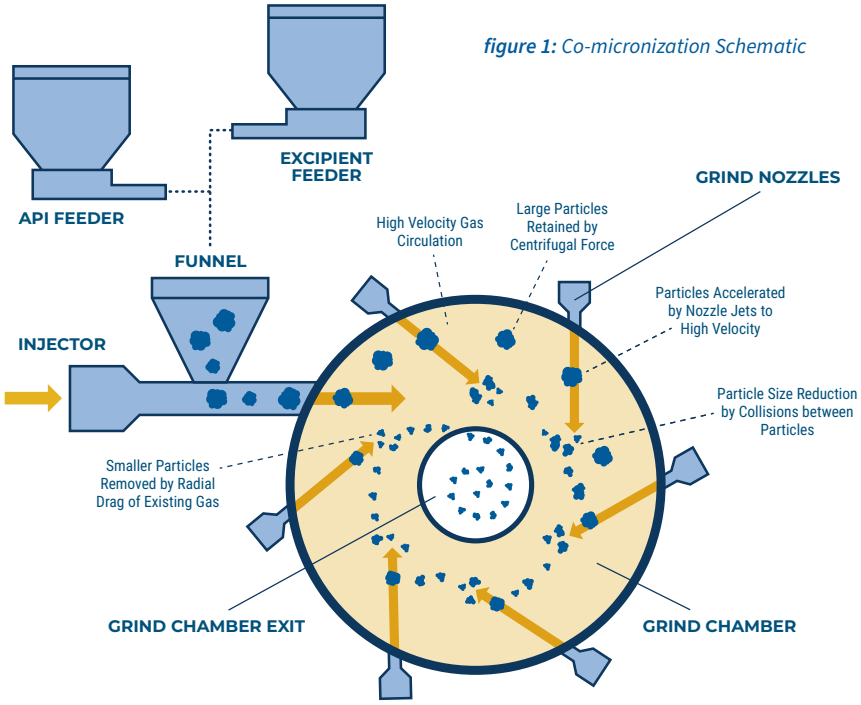

figure 1: *Co-micronization Schematic*

Quantifying the particle size distribution (PSD) of the individual components is critical to understanding the quality attributes of the blend and ultimately the drug product. In this white paper, we employ the Classizer™ ONE based on SPES technology to measure and show that for certain blends, SPES can resolve the PSD of individual components in the mixture.

The patented technology called SPES – Single Particle Extinction and Scattering – is a laser scattering technology that obtains multiparametric data for particles in the 200 nm – 20 µm range [1, 2]. As illustrated in Figure 2, the liquid sample is circulated through a cuvette where the laser is focused. Each particle passing in the volume illuminated by the laser will scatter light, which in the forward direction impinges on the SPES sensor. This sensor retrieves the real and imaginary components of the electric field scattered by each particle, from which the two parameters used to build the two-dimensional EOS Clouds are obtained (Figure 3):

- C_{ext}, the extinction cross section; for large particles, it can be thought of as their shadow
- α, the particle's polarizability, proportional to its optical volume

Both parameters depend on particle size and refractive index (RI), which can be derived for each individual population on the EOS Clouds by fitting an appropriate theoretical model – a compact *Mie* dielectric sphere – to the data. Particles that differ in size and/or RI will populate different regions of the EOS Clouds.

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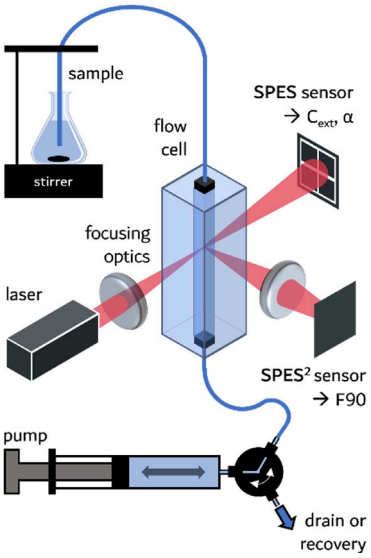

figure 2: The patented SPES sensor measures the complex fields scattered by single particles, illuminated by the laser focused on the cuvette. From this signal the software obtains the two optical parameters, α and C_{ext}. While not employed here, the intensity scattered at 90° is also measured for each particle.

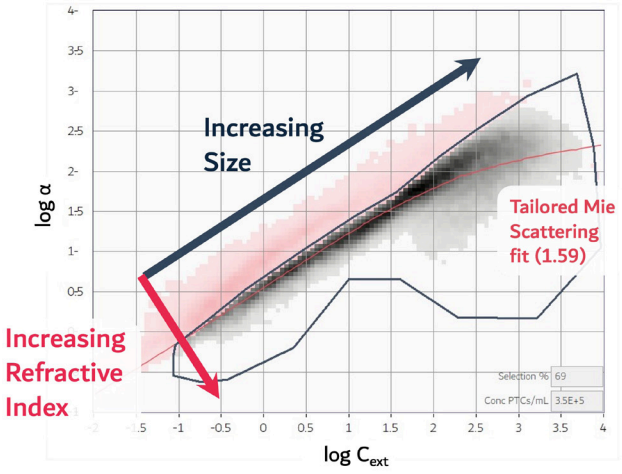

figure 3: The EOS Cloud is a two-dimensional histogram in logarithmic scales of the particles counted with a given a and C_{ext}. Here, as an example, we plot the EOS Cloud of the 95:5 Diphenhydramine HCl / SYLOID® blend. The black is the selected population corresponding to the Diphenhydramine HCl. The red line is its effective refractive index measured (1.59). The red pixels of the Cloud outside the selection, correspond to the SYLOID® population. Thanks to SPES the two populations can be fully isolated and selected separately.

INSTRUMENTS AND METHODS

Co-micronization

Co-micronization trials were conducted on a 4" spiral jet mill at 90 PSI with unmilled API/excipient and API/API pre-blends. Diphenhydramine HCl/SYLOID® (50:50, 95:5, 99:1), Diphenhydramine HCl/Hypromellose (25:75), and Diphenhydramine HCl/Acetaminophen (50:50) were selected for the trials. The individual components were also separately jet milled under the same conditions as the blends. Appropriate amounts of unmilled APIs and excipients were added to an 8 oz container and pre-blended with a Turbula mixer for ten minutes. The unmilled pre-blends were hand fed into a Microsize custom-made 4" spiral jet mill equipped with a 27" combination poly w/ PTFE membrane filter sleeve. The manifold and injection pressures were set to 90 PSI.

Characterization of APIs – size, optical properties, and concentration

The APIs were measured with a Classizer™ ONE unit equipped with a syringe pump. For each sample, 30 mg of powder was suspended into 10 mL of Isopar G with 2% lecithin. Blanks were measured to ensure negligible background. The suspensions were vortexed (1 minute), ultrasonicated (10 minutes), and vortexed again (1 minute) before being diluted for the measurement. Dilution factors ranged from 5 (Hypromellose) to 500 (SYLOID®), in a volume of 10 to 20 mL of pure Isopar G. The stability of the suspensions was verified for up to 20 minutes with the Continuous Flow Analysis add-on of Classizer ONE's software. Samples were run in triplicate and each measurement took approximately 5 minutes. The quantitative size, concentration, and refractive index values of the individual components in blends were obtained from the EOS Clouds.

Principal Component Analysis

The Principal Component Analysis (PCA) software was used to separate individual components of blends to extract semi-quantitative information. For each blend, the PCA was first trained on Clouds of its individual components and later used to analyze the blend. PCA was run on analytical triplicates to ensure reliability of its results. PCA results consist of images representing the largest variation across the dataset and, for each measurement, a semi-quantitative scalar value (the Principal Component) quantifying the contribution to the variation of that measurement.

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RESULTS

Diphenhydramine HCl/SYLOID® (50:50, 95:5, 99:1), Diphenhydramine HCl/Hypromellose (25:75), and Diphenhydramine HCl/Acetaminophen (50:50) blends were co-micronized in a 4" spiral jet mill at 90 PSI. The individual components were also separately milled under the same conditions. The materials were characterized by the Classizer™ ONE for RI and PSD (volumetric, Dv, and numeric, Dn), the results are shown in Table 1.

Table 1. RI and PSD results

Blends and Individual Components within the Blends	RI	Dv10 (µm)	Dn10 (µm)	Dv50 (µm)	Dn50 (µm)	Dv90 (µm)	Dn90 (µm)
100% SYLOID®	1.45	1.6	0.68	3.6	1.07	5.5	2.68
Diphenhydramine HCl/SYLOID® (50:50) Co-Micronized Blend	1.46	1.6	0.58	4.0	0.93	6.3	2.43
Diphenhydramine HCl	1.60	2.8	0.36	5.7	0.75	9.6	3.30
SYLOID®	1.45	1.6	0.65	3.8	1.12	6.0	2.61
Diphenhydramine HCl/SYLOID® (95:5) Co-Micronized Blend	1.56	3.1	0.41	6.9	1.11	12.1	3.66
Diphenhydramine HCl	1.59	3.4	0.51	7.1	1.44	12.0	4.54
SYLOID®	1.45	1.8	0.67	3.8	1.26	5.9	3.13
Diphenhydramine HCl/SYLOID® (99:1) Co-Micronized Blend	1.59	4.1	0.42	8.1	1.50	13.4	5.50
Diphenhydramine HCl	1.59	4.2	0.55	8.1	1.80	13.3	5.87
SYLOID®	1.45	2.0	0.66	3.9	1.34	5.7	3.44
100% Diphenhydramine HCl	1.59	4.1	0.47	7.6	2.21	12.1	6.20
Diphenhydramine HCl/ Hypromellose (25:75) Co-Micronized Blend	1.53	3.7	0.43	8.6	0.87	14.2	3.32
100% Hypromellose	1.51	1.2	0.36	6.0	0.54	13.3	1.10
Diphenhydramine HCl/ Acetaminophen (50:50) Co-Micronized Blend	1.61	4.6	0.42	8.5	1.35	13.3	5.95
100% Acetaminophen	1.64	1.7	0.28	5.0	0.42	8.7	0.89

RESULTS (cont.)

Spiral jet milling and co-micronization produced materials that had Dv90 and Dn90 values < 15 µm, which demonstrated that the materials were micronized. The EOS Clouds of the Diphenhydramine HCl/SYLOID® blends distinguished the particle sizes and optical properties of the individual components.

The differences between the RIs (1.45 for SYLOID® and 1.59 for Diphenhydramine HCl) allowed the PSD of each individual component in the 50:50, 95:5, and 99:1 Diphenhydramine HCl/SYLOID® blends to be determined. See Figures 4 and 5 for a representative example of the 95:5 blend.

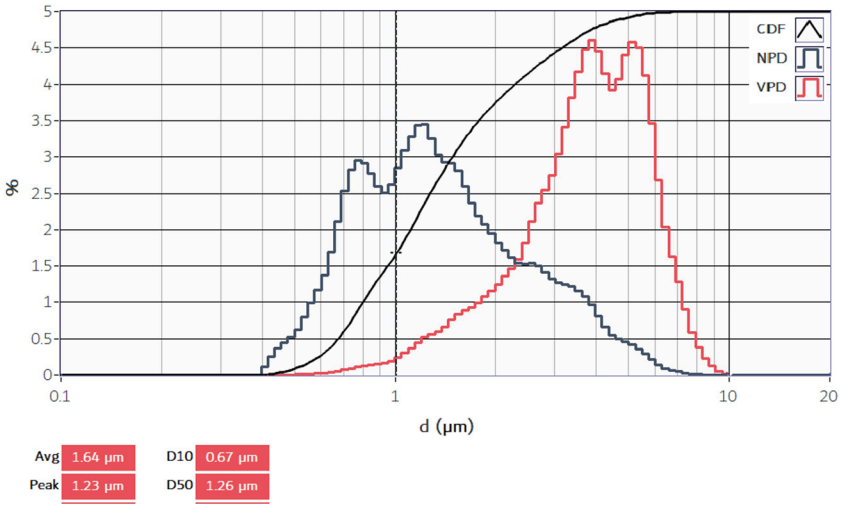

figure 4: *The numeric (black) and volumetric (red) PSDs of the upper SYLOID® population in the 95:5 Diphenhydramine/SYLOID® blend, obtained with the selection reported in Figure 3.*

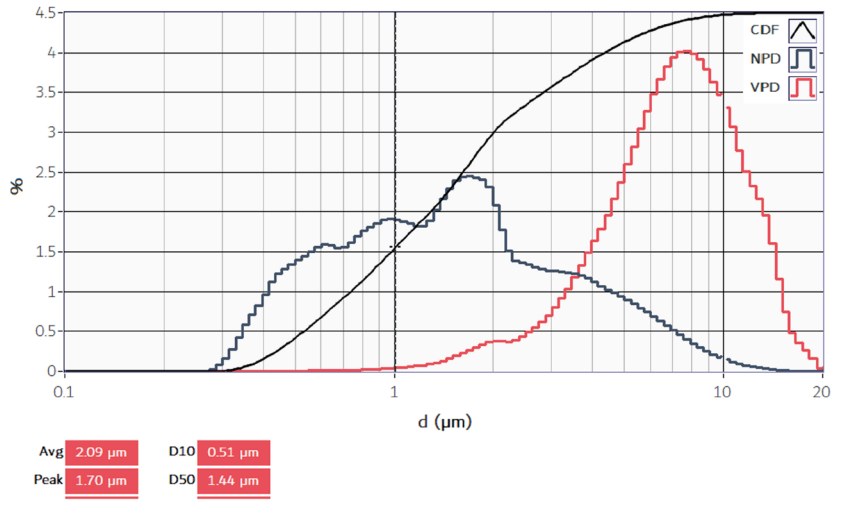

figure 5: *The numeric (black) and volumetric (red) PSDs of the lower Diphenhydramine in the 95:5 Diphenhydramine SYLOID®/ blend, obtained with the selection reported in Figure 3.*

The PCA analysis results for Diphenhydramine HCl/SYLOID® (50:50, 95:5, 99:1), Diphenhydramine HCl/Hypromellose (25:75), and Diphenhydramine HCl/Acetaminophen (50:50) co-micronized blends are shown in Figure 6. The PCA qualitatively measured the contribution of the two components in all of the blends studied. The three different Diphenhydramine HCl/SYLOID® ratios were identified, including the 99:1 ratio, which demonstrates its sensitivity.

The PCA was effective even when there was a considerable overlap between populations (similar RIs), as in the case of the Diphenhydramine HCl/Hypromellose and the Diphenhydramine HCl/Acetaminophen blends. The SPES technology deconvoluted the optical fingerprint of each component by utilizing the two-dimensional nature of the data.

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RESULTS (cont.)

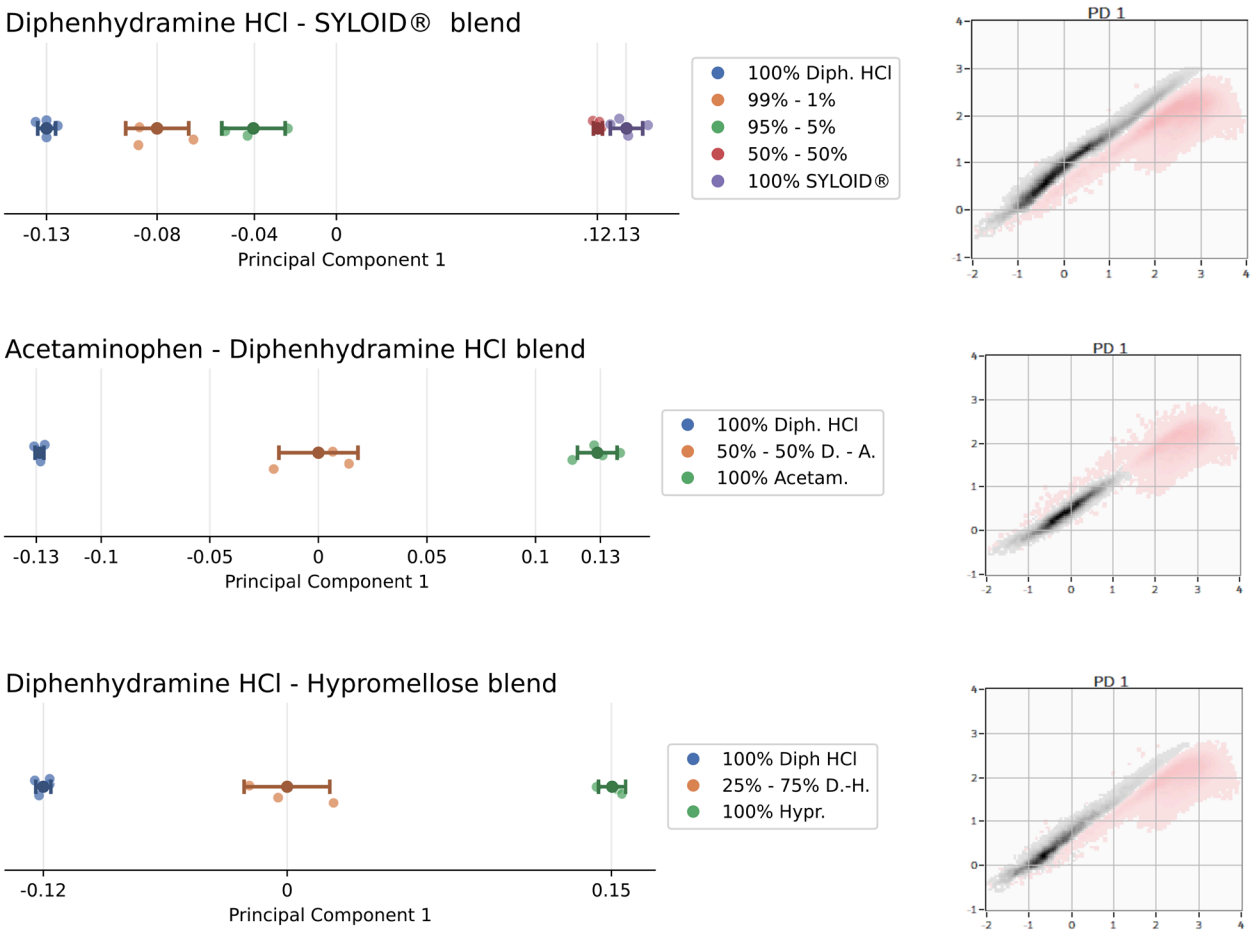

figure 6: Results of the PCA analysis for the blends studied, alongside their associated Principal Directions. Each Principal Direction found the differences between the Clouds of the individual components in the blend.

CONCLUSION

Co-micronization of API/excipient and API/API blends produced micronized materials. SPES technology, utilized by the Classizer™ ONE, successfully characterized the refractive indexes (RIs) and particle size distributions (PSDs) of the blends. The difference between the RI of SYLOID® and Diphenhydramine HCl allowed the individual PSD of the components in the blends to be determined. The Principal Component Analysis (PCA) software qualitatively measured the quantities of the materials in the blends.

REFERENCES

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1. Potenza, Marco AC, Tiziano Sanvito, and Alberto Pullia. "Measuring the complex field scattered by single submicron particles." Aip Advances 5.11 (2015).

2. Villa, S., et al. "Measuring shape and size of micrometric particles from the analysis of the forward scattered field." Journal of Applied Physics 119.22 (2016).