

Nasal Spray Chemically Specific Particle Size Distribution Analysis

Chemically Specific Sizing

Particle size of active pharmaceutical ingredient (API) directly correlates to bioavailability and drug efficacy. For inhalers and nasal sprays, API particle size is important for availability to sites of action within the respiratory tract. The API particle size distribution should be stable to ensure reproducible bioavailability within the storage period. FDA recommends a thorough characterization of particle size distributions when the performance of a drug product depends on particle size. Therefore there is a need for fast, detailed and highly reproducible particle characterization techniques.

Chemically Specific Particle Size Distribution in Nasal Spray Sample

A sample of nasal spray was deposited on a microscope slide. 4x4 mm area was analysed in automated regime using Single Particle Explorer instrument. Microscopic images were taken, particles were counted and their sizes were measured and chemical composition was identified through Raman spectroscopy. During initial analysis it was determined that the relative amount of API particles in the sample is 2% with the other 98% of particles being cellulose. With such a low relative amount of API particles it is required to analyse a total of 50000 particles in order to have results for 1000 API particles. Such analysis is very time consuming and therefore there is a need to selectively analyse only API particles. A comprehensive comparison of API and cellulose particles shows that these two classes of particles have very distinct physical characteristics. As can be seen in Figures 1 and 2. API particles are generally darker and more spherical than cellulose particles. Based on these physical characteristics, illumination, image processing parameters as well as targeted particle sphericity were optimized for the selective particle recognition to focus on primarily API particles. Settings for Raman analysis were optimized for high throughput analysis.

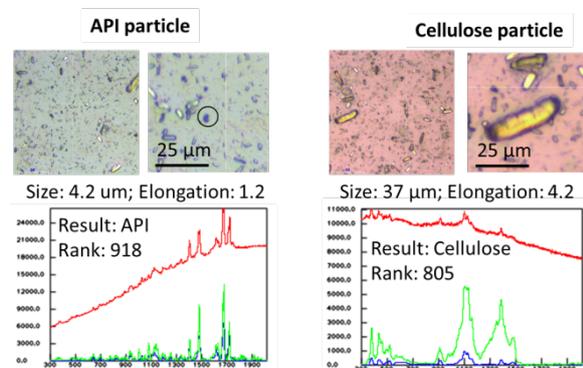


Fig. 1: Images and Raman spectra of API and cellulose particles. API particles are much darker and rounder than cellulose particles.

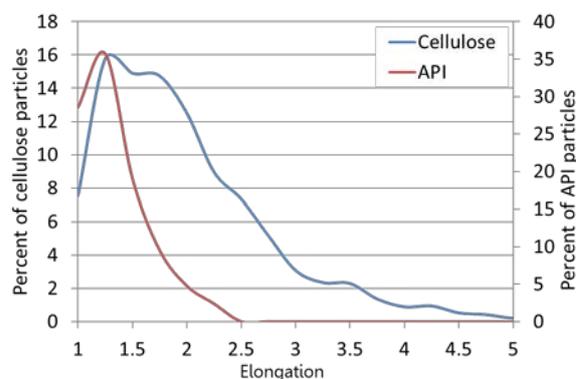


Fig. 2: Shape (elongation) distribution of API and cellulose particles. Elongation values for API particles do not exceed 2.5, whereas cellulose particles have elongation values up to 5.

As the result analysis selectivity increased to 34%, therefore it was only necessary to analyse 3000 particles to get the results for 1000 API particles. As the result 1011 API particles were analysed in just 4 hours. The size distribution was then inferred from the analysis and can be seen in Figure 3.

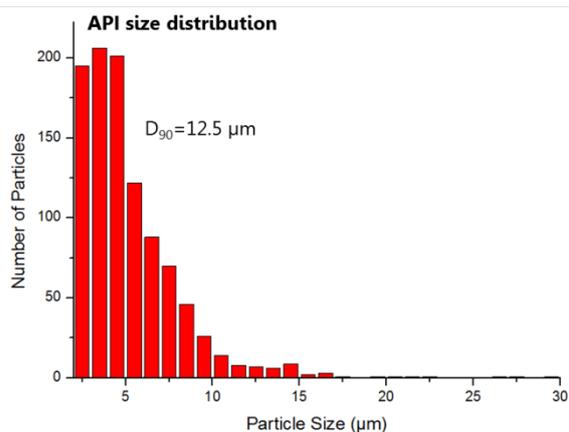


Fig. 3: Size distribution of 1011 API particles analysed in 4 hours. Average API particle size is 5.2 µm; D90 = 12.5 µm.

Conclusions

Here we used an automated image guided spectroscopy for rapid determination of the size distribution of API particles present in nasal spray. This technique allows adjusting particle recognition parameters to analyse only particles of the interest without a need to screen an entire sample when it is not necessary. This approach can provide chemically specific particle size distribution within a couple of hours for thousands of particles. With this method Single Particle Explorer can provide rapid reliable characterization of samples for development of formulations as well as for quality control and product monitoring within the storage period.