Chemically specific particle size distribution for nasal spray with Hound

Introduction

Particle size of an active pharmaceutical ingredient (API) directly correlates to its bioavailability and efficacy. For inhalers and nasal sprays, API particle size is important for drug availability at specific sites of action in the respiratory tract. The particle size distribution should be stable to ensure reproducible bioavailability throughout the shelf life of the product. The FDA recommends a thorough characterization of particle size distribution in cases such as this. A formulation may contain particles other than the API particles, so there is a need for fast, detailed, and highly reproducible particle characterization techniques.

Hound will count, size and determine the chemical or elemental composition of particles (Figure 1). Hound uses Raman spectroscopy paired with a database of known compounds to identify the chemical composition of particles. Once the chemical composition of a particle is known, a chemically specific particle size distribution can be created. In this application note, Hound measures the particle size distribution for a nasal spray formulation with two types of particles present.

Figure 1: Hound images, counts, sizes and identifies sub-visible and visible particles.

Methods

A nasal spray containing a single API was deposited on a gold-coated slide. A 4 x 4 mm area was analyzed automatically with Hound. Hound automatically counted the particles present and measured size and shape through image analysis, then determined the chemical composition of each particle with Raman spectroscopy. The Raman spectra for each particle was compared to reference spectra for the API and cellulose, an inactive ingredient. Due to a significantly lower concentration of API particles compared to cellulose particles, API particles were selectively analyzed to minimize the total number of analyzed particles.

A comprehensive analysis showed that the API and cellulose particles have distinct physical characteristics. Illumination, image processing parameters, and targeted particle sphericity were optimized for selective particle recognition of API particles. Settings for Raman analysis were optimized for reliable high throughput analysis.

Results

An initial analysis determined that the relative amount of API particles in the sample was 2%, while the other 98% of particles were cellulose. API particles were found to generally be darker and more spherical than cellulose particles (Figure 2). The elongation distribution is much lower for API particles with values falling under 2.5 compared to cellulose particles with values up to 5 (Figure 3). By optimizing analysis parameters to select for these darker and rounder particles, this selective analysis method increased the relative amount of API particles detected in the sample to 34% (versus 2% originally). To achieve the analysis target of 1,000 API particles, 3,000 particles were individ-

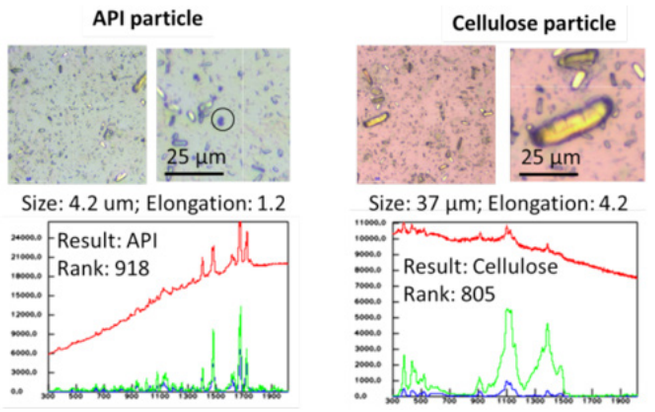

Figure 2: **Left:** Images of API particles and Raman spectra for a particle showing the matched reference spectra for the API. **Right:** Images of cellulose particles and Raman spectra for a particle showing the matched reference spectra for cellulose. Overall, API particles are much darker and rounder than cellulose particles.

ually analyzed in total. Of the 3,000 particles analyzed, 1,011 were determined to be API particles based on their Raman spectra. Analyzing these 3,000 particles took 4 hours. Through selective analysis for API particles, the total time to analyze 1,000 API particles was significantly reduced and most cellulose particles were eliminated prior to individual particle analysis.

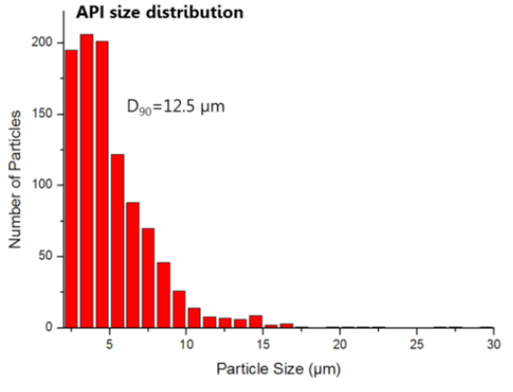

Figure 4: Size distribution of 1,011 API particles analyzed by Hound in 4 hours. Average particle size is 5.2 µm and D90 is 12.5 µm.

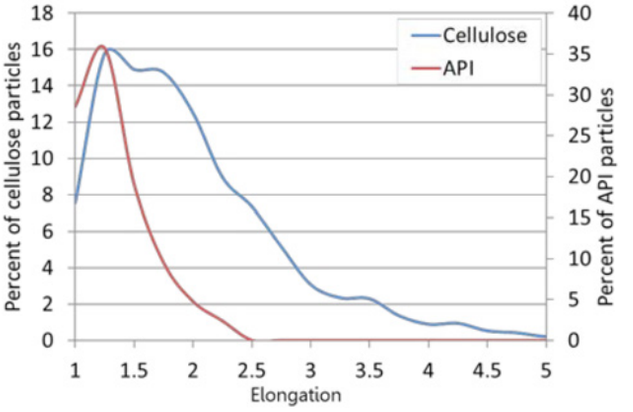

Figure 3: Elongation distribution of API and cellulose particles. Elongation values for API particles are lower than those for cellulose particles, which is useful for selective analysis.

The size distribution of the 1,011 API particles analyzed is shown in Figure 4. API particles had an average size of 5.2 µm and a D90 of 12.5 µm. Cellulose particles were excluded in this size distribution through selective analysis followed by Raman spectroscopy to determine particle composition. Without the selective analysis capabilities of Hound, this API-specific size distribution would have taken over 66 hours.

Summary

Hound was used for rapid determination of the size distribution of API particles present in nasal spray, despite the presence of significantly more cellulose particles than API particles. By adjusting particle recognition parameters on Hound, it was possible to focus on particles of interest without screening all particles in a sample. Hound can provide rapid reliable characterization of samples for formulation development, quality control, and product monitoring throughout the storage period of the drug.

Unchained Labs
6870 Koll Center Parkway
Pleasanton, CA 94566
Phone: 1.925.587.9800
Toll-free: 1.800.815.6384
Email: info@unchainedlabs.com

© 2018 Unchained Labs. All rights reserved. The Unchained Labs logo, The Hound and Hound logo is a trademark and/or registered trademarks of Unchained Labs. All other brands or product names mentioned are trademarks owned by their respective organizations.

Rev A