Chemically specific particle sizing for topical formulations with Hound

Introduction

The particle size distribution of the active pharmaceutical ingredients (API) in a topical semisolid formulation correlates to biological performance. The distribution of API particle size should be stable to ensure reproducible bioavailability throughout the storage period of the cream. A topical formulation may have multiple APIs, creating a need for fast, detailed, and highly reproducible chemically specific particle characterization techniques.

Hound can count, size and determine the chemical or elemental composition of particles (Figure 1). Hound uses Raman spectroscopy and/or Laser-Induced Breakdown Spectroscopy paired with a database of known compounds to identify the chemical or elemental composition of particles. In this application note, Hound is used to measure the particle size distribution of two APIs in a single topical formulation.

Methods

A thin layer of a cream containing 0.1% adapalene and 2.5% benzoyl peroxide gel was spread on a gold-coated slide. A 1.6 X 1.6 mm area was analyzed automatically with the Hound by capturing images of the particles in the cream then analyzing the particles individually. Hound analyzed 4,000 particles in this sample area.

Figure 1: Hound images, counts, sizes and identifies particles with Raman and/or Laser-Induced Breakdown Spectroscopy.

The Hound automatically counted the particles and measured particle size by imaging, then determined the chemical composition of each particle with Raman spectroscopy. A 532 nm laser at 12% intensity for 3 seconds was used for Raman spectroscopy and the resulting spectra were compared to reference spectra for adapalene, benzoyl peroxide, and inactive ingredients. Illumination and image processing parameters were optimized for accurate particle recognition in the cream sample. Settings for Raman analysis were optimized for reliable high throughput analysis.
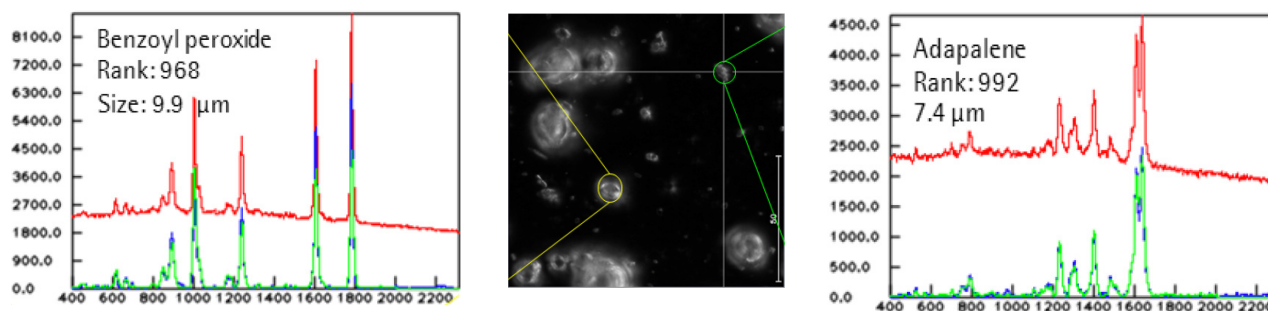

Figure 2: Darkfield image of benzoyl peroxide and adapalene particles and examples of the resulting raw Raman spectra (red), processed Raman spectra (blue) and reference match (green).
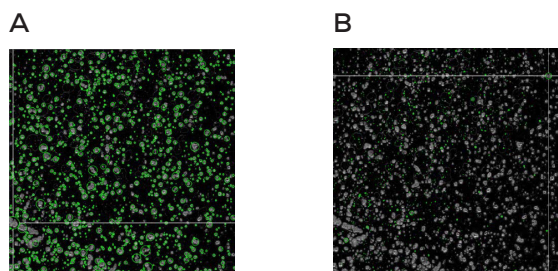
A

B

Figure 3: **(A)** 50x dark field image of a 1.6 X 1.6 mm area of a cream sample with benzoyl peroxide particles marked in green. **(B)** The same 50x dark field image with adapalene particles marked in green.

Results

The two APIs in this cream, benzoyl peroxide and adapalene, exhibit very clear Raman spectra (Figure 2). Adapalene particles were found to be significantly less abundant and smaller than benzoyl peroxide particles (Figure 3). Within the sample area analyzed, 1,203 adapalene particles and 2,797 benzoyl peroxide particles were identified based on Raman spectroscopy. Once particles were identified as either adapalene or benzoyl peroxide, cumulative size distributions of each particle type was determined. D_{50} and D_{90} values
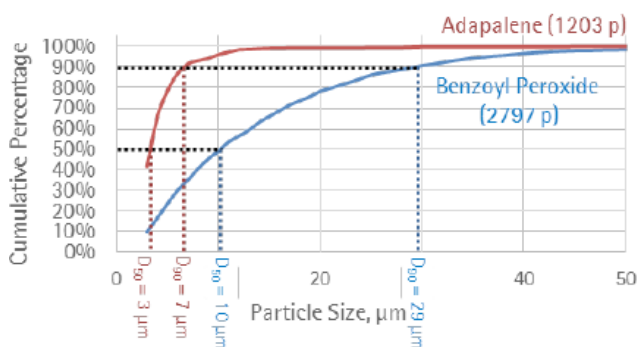

Figure 4: Cumulative particle size distribution of 1,203 adapalene particles and 2,797 benzoyl peroxide particles with D_{50} and D_{90} values displayed.

for adapalene were 3 μm and 7 μm, respectively, while benzoyl peroxide had higher D_{50} and D_{90} values of 10 μm and 29 μm, respectively (Figure 4).

To determine the particle size distribution of adapalene at the low concentration of 0.1%, a relatively large area of sample needed to be scanned. The automated image collection and analysis features and the image directed Raman spectroscopy of Hound allowed for a rapid method for determining particle size distributions of multiple APIs in a single sample. Total analysis time on the Hound was 3 hours. In comparison, using ultra-fast Raman imaging of an area of identical size (1.6 X 1.6 mm) would take a minimum of 17 hours (950 spectra per second).

Summary

Using the automated image directed spectroscopy feature of Hound, precise API characterization including the number, size, and chemical identity of particles present in a topical formulation was conducted rapidly and with minimal hands on time. Hound can provide chemical specific particle size distribution analysis within a few hours for thousands of particles, allowing for rapid and reliable characterization of samples for development of formulations, quality control, and product monitoring during storage.

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