# Particle size distribution and particle identification

## Introduction

**Particle size distribution (PSD) is an important characteristic of pharmaceutical products across all types of preparation, including solid oral drug products, semi-solids, aerosols, and sterile liquid products.**

An active pharmaceutical ingredient (API) can be present in formulations as particles ranging from nanocolloids to millimeters. The size and distribution of these particles play an important role in influencing the safety and efficacy of pharmaceutical products. PSD plays a role in a drug's efficacy, bioavailability and dissolution rate, the drug release rate in controlled-release formulations, the deposition of particles during aerosol use, as well as the long-term stability of the product during storage and use.

Laser diffraction is the most commonly used method for determining particle size thanks to its high accuracy and reproducibility. Here, we will see how the Hound, a unique device that combines light microscopy with Raman spectroscopy, makes particle identification even faster and just as reliable.

## Topical semi-solid drug delivery

In topical and transdermal drug delivery, particle size plays an important role in determining the pharmacologic properties of the product. For example, when the API is suspended in a vehicle, like a gel or cream, particle size interacts with the solubility of the vehicle to determine the dissolution rate.

Particle size also affects the rate, depth, and pathway of absorption through the skin. Ultimately, the choice of particle size in topical preparations can help to maximize drug efficacy at the site of action and minimize the risk of systemic adverse reactions.

Often drugs especially over the counter (OTC) medication may have more than one API. Maintaining the correct ratio is critical to ensure product consistency and efficacy. Clarifying or confirming the ratio becomes more challenging if the API particles are of similar size, and PSD alone may not be sufficient. Scientists have shown how the Hound can be used to determine the PSD in a topical acne treatment containing two APIs in a single formulation, and distinguish the APIs from one another.

The product was a cream containing 0.1% adapalene and 2.5% benzoyl peroxide. A thin layer was spread onto a gold-coated slide and a 1.6 x 1.6 mm area was automatically analyzed using optical imaging and Raman 532 nm laser spectroscopy. This revealed a count of 1,203 adapalene particles and 2,797 benzoyl peroxide particles within the sample area.

Hound was then able to produce cumulative particle size distribution analysis, showing the D50 and D90 values for adapalene, which indicated that adapalene particles were smaller and were also present in a narrower range of sizes than benzoyl peroxide (Figure 1).

Normally, a relatively large sample area would need to be surveyed due to the low concentration of adapalene in the sample. With the image-directed Raman spectroscopy capabilities of Hound, the analysis was complete in around three hours, which compares with a 17-hour analysis time with ultra-fast Raman spectroscopy on a sample area of this size.

This type of analysis could be useful for determining PSD and identity at all stages of semi-solid pharmaceutical formulation production, including development, quality control, and storage.

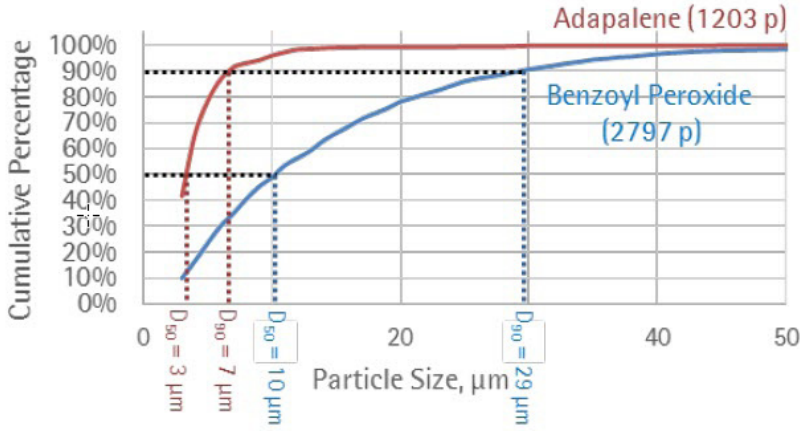


Figure 1: Cumulative particle size distribution for adapalene and benzoyl peroxide in a topical cream, as measured by the Hound.

## Aerosol drug delivery

In inhalation devices, such as asthma inhalers, manipulating particle size allows drug delivery to be targeted to specific regions of the airways to optimize the therapeutic response.

Different particle sizes will reach different regions of the airway. Bronchodilators are most effective when particle sizes are in the larger range, as the site of action is in the proximal airway. In contrast, fine particle sizes achieve wider dispersal within the lung and may be more effective for treating distal lung disease, such as with steroids.

Here we show how the Hound can be used to characterize particle size distribution for an inhaler containing both a bronchodilator (salmeterol) and a steroid (fluticasone).

The medication was actuated three times from a dry powder inhaler. The particles were sampled over a 1 x 1 mm area and analyzed using a 532 nm Raman laser. Data on 15,000 particles from 2-10 micrometers were acquired and compared to the Hound's integrated spectra library for identification. Overall, 452 of the particles contained API, and PSD analysis showed a much smaller average size for the bronchodilator (3.2 microns) compared with the steroid (6.0 microns). Since the PSD of the APIs overlap, it was important to have the Raman capabilities to distinguish the two particles and confirm the composition of the mixture (Figure 2).

In a similar study, we characterized the API distribution in a nasal spray containing a single API and an inert ingredient, cellulose, across a 4 x 4 mm sample area.

The concentration of API particles was very low, at 2%. To identify every particle by Raman would be impractical. Cellulose particles were more elongated, so by incorporating morphology characteristics to exclude cellulose particles, we were able to selectively identify particles in the sample. Identifying the particles with Raman determined the concentration of API at 34%. This allowed the PSD of 1,011 API particles to be analyzed within 4 hours, which is significantly faster than if a non-selective approach had been used, which would have taken around 66 hours to complete.

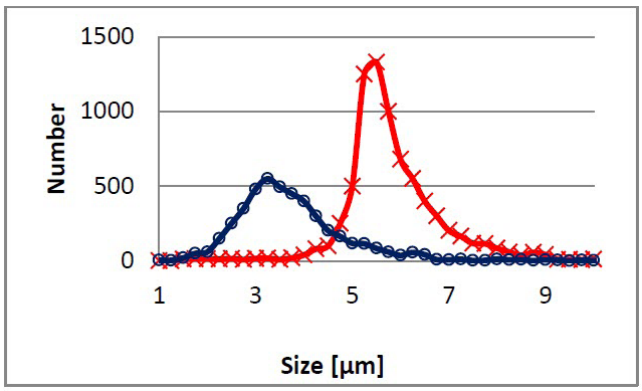


Figure 2: Particle size distribution of salmeterol (blue) and fluticasone (red) when actuated from a dry powder inhaler, as measured by the Hound.

## Summary

PSD methods that rely solely on size and shape may provide insufficient data to properly characterize an API in a mixture. The Hound (Figure 3) first uses bright- or dark-field imaging to automatically characterize each particle within the sample for size, shape, morphology, and fibrosity. Next, Hound uses Raman spectroscopy at 785 nm or 532 nm to capture the chemical signature of the particles and identifies them by comparing them to a built-in customizable database. The combination of the two techniques ensures that PSD can be performed on complex samples quickly, with an orthogonal analysis method to confirm identity.


Figure 3: Hound combines microscopy, Raman and Laser-Induced Breakdown Spectroscopy (LIBS) to count, size, and ID particles by their chemical or elemental fingerprints.

## References and further reading

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UNCHAINED LABS

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



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