Gateway ANALYTICAL

White Paper

Analysis of Multi-Component Engineered Particles for Inhalation by Raman Chemical Imaging

One of the most promising trends in inhaled therapies over the past few years is the creation of particles that contain multiple active ingredients. Some studies have suggested that two, or even three, APIs deposited in the same location in the lung may have a synergistic effect.

Combination of the active ingredients within individual particles allows developers to create inhaled therapies that can achieve consistent localized delivery, and co-localization of topically delivered medicines can enhance efficacy at the molecular and cellular levels. The increased efficacy of these products may enable the use of lower doses, leading to safer drugs.

The specialists who engineer these products need a method for spatially resolved, chemically-specific analysis in order to verify the composition of the particles, which is critical for process optimization, quality control, and to meet regulatory requirements.

A solution to this problem required a team of expert scientists who have proven success developing creative solutions to analytical problems. Raman chemical imaging (RCI) experts at Gateway Analytical were up to the challenge and developed a proprietary, novel method of determining the ratio of each component drug within single particles and whether those particles contain the desired polymorphs.

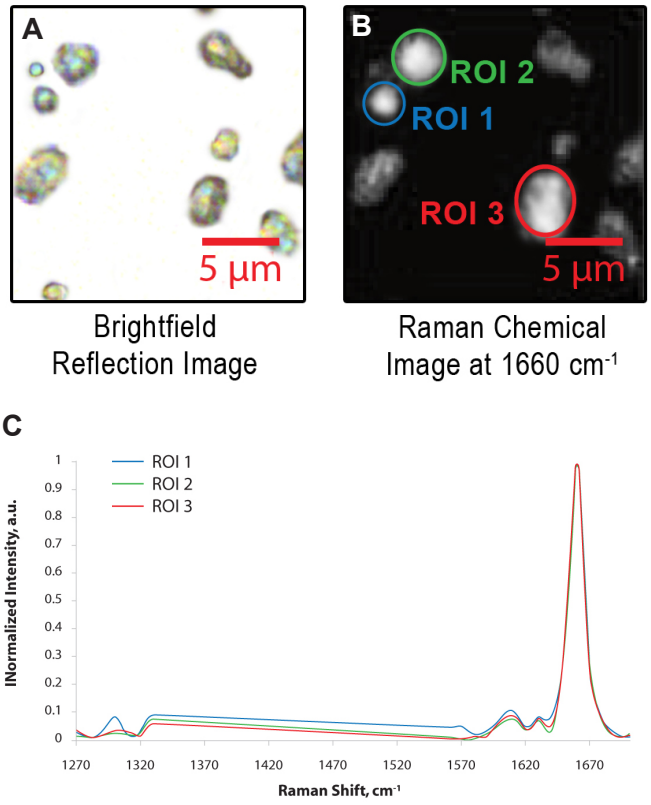

Figure 1. (A) Brightfield reflectance image and (B) processed RCI image of particles showing the regions of interest (ROI 1, ROI 2, ROI 3) and (C) their respective Raman spectra.

Analytical Requirements for Multiple API Particles

Selection of the optimal technique for production of the combination particles requires a high level of engineering expertise and accurate data on particle composition during the development process. RCI plays a key role in allowing analysts to characterize both the chemical composition and the particle size distribution (PSD) of the engineered particles in order to verify the consistent delivery of the proper ratio of drugs to the proper site in the lung.

In addition, developers must document the reproducibility and stability of the formulations created with this technology to support regulatory applications. The 1998 draft guidance on MDI and DPI drug products emphasizes the need for reproducible dose delivery and specifies that, “Appropriate acceptance criteria and tests should be instituted to control those drug substance parameters considered key to ensuring reproducibility of the physicochemical properties of the drug substance.”

Determining the technique that will create the most reproducible particles requires repeated analysis of drug composition and PSD with a technique that can distinguish between APIs combined within a single particle and those that have simply aggregated together.

Also, because different polymorphs of APIs have differing dissolution rates, engineers must ensure that the crystallization process consistently produces particles with the desired type of polymorph for each API, in addition to a consistent ratio of the component APIs. The stability of the crystals must also be assessed to ensure that the types of API polymorphs and the API/API ratio within each particle remain the same over time.

However, the draft guidance was produced prior to the advent of multiple API particles for inhalation and assumes that the formulations contain a jet-milled drug substance that can be isolated for analysis. None of the analytical tests suggested in the draft guidance for verification of the critical parameters is capable of differentiating APIs, much less different polymorphs, within individual particles.

Advantages of the New Combination Products

Combination inhalers have been around for decades, with the Duo-Medihaler isoproterenol hydrochloride and phenylephrine bitartrate MDI introduced in 1962, and the first combination DPI, the Seretide (Advair) fluticasone/salmeterol dry powder inhaler in 1999.

Most combination inhalers on the market today combine a bronchodilator, often a long-acting beta agonist (LABA), with an inhaled corticosteroid (ICS) for maintenance therapy, and sometimes also a long-acting muscarinic antagonist (LAMA). Most of these products contain jet-milled active ingredients mixed with excipients: suspension MDIs may contain suspension agents and surfactants; dry powder formulations generally include milled lactose as a carrier.

Any differences in the PSD of each of the active ingredients will almost certainly result in differences in deposition, preventing co-deposition of each active in the correct ratio in each region of the lung. Even if the PSDs were identical, both MDI and DPI formulations are affected by numerous factors that may cause imbalances.

In suspension MDIs, for example, one API may have more of a tendency than the other to stick to the canister or may have more of a tendency to flocculate. One component of a dry powder formulation may have more surface energy or may be more hygroscopic than the other, leading to differences in how each detaches from the carrier or aggregates with other particles.

Combination formulations also often contain significantly more of one API than the other, so that small differences in delivery may result in large changes in the delivered API ratio; for example, each dose of the Combivent MDI is designed to deliver 18 µg of ipratropium bromide and 103 µg of albuterol sulfate, and one version of the Advair Diskus is designed to deliver 50 µg of salmeterol xinafoate and 250 µg of fluticasone propionate.

Engineered combination particles can minimize these sources of variability. As long as the ratio of the two APIs is consistent from particle to particle, the ratio of the APIs deposited in the lung will always remain the same.

The Raman Chemical Imaging Method

In order to verify the amount of each component in the combination particles, the analyst begins by creating a spectral library for reference, taking into account factors such as fluorescence and Raman scattering signal strength to determine the Raman spectrum of each of the individual APIs. RCI can detect spectral shifts as small as 2 cm^{-1}, which allows the analyst to include spectra for polymorphs of each API in the library.

Once those spectra have been acquired, the technician prepares a slide with a sample of the combination particle formulation, either by actuating the MDI or by using a dry powder dispersion unit if necessary. If the analyst wants to examine only the respirable fraction of the particles, the inhaler can be actuated into a cascade impactor and a sample collected from the appropriate stage.

After proper set-up, the RCI microscope collects data from randomly selected fields of view (FOVs) across the slide and then overlays the spectral information collected from hundreds of FOVs with an optical image, correlating the data on a pixel-by-pixel basis. A 5 µm particle, for example, may be represented within a 30 pixel x 30 pixel field, with a spectrum collected for each pixel. By associating different colors with the spectra of the different drugs, the resulting image can provide a visual representation showing the presence of each of the active ingredients within each particle **(Figure 1)**.

The Raman signal is proportional to the amount of each API in the particle, so the operator is able to create a calibration curve by analyzing the Raman spectra from particles with known ratios of API. Once that calibration curve has been determined, the system can determine the relative distribution of actives in the given sample.

The system automatically generates a binary mask image and calculates the particle size distribution to assist the operator in visually identifying aggregates and agglomerates. The analyst can also identify stand-alone particles that may have resulted from a failure of co-crystallization and that contain only a single component.

Using this method during development of multiple component particles for inhalation provides a high degree of confidence that the final formulation is the most stable possible, as well as data necessary for determining the design space for Quality by Design (QbD) purposes.

This work was performed in collaboration with Dipesh Parikh, Shyam Karki and David Hipkiss from Prosonix Ltd, Magdalen Centre, Oxford Science Park, Oxford, OX4 4GA, UK.