When blending two or more bulk solid ingredients to form a product, achieving a homogenous distribution is essential. This is particularly true where particle size, density, and shape are the primary causes of nonhomogeneity. These differences can cause blend segregation and ingredient agglomeration.

When such a blended product fails to meet homogeneity specifications, examining the “failed” product’s structure at the particle level is sometimes necessary to determine the cause of failure. While several optical and electron microscopy methods have the ability to take high-resolution pictures of samples, these methods are tedious, time-consuming, and require extensive sample preparation. The results are typically limited to grayscale, two-dimensional cross-sectional images that can be difficult to interpret — the methods are unable to capture the sample’s three-dimensional structural features. This is particularly critical when the sample is inhomogeneous, and a two-dimensional picture may not accurately represent the sample’s actual structure.

A more thorough, three-dimensional examination determining a sample’s composition as a function of position is usually described as chemical imaging or chemical mapping. Chemical imaging requires an instrument that combines a microscope, a spectroscope, and a rasterization stage (in which the instrument converts the collected data into a graphical computer image). A spectroscope identifies a material’s chemical composition by shining light at a sample and analyzing how the light interacts with the sample, resulting in a graph-like image called a spectrum. The sample absorbs, transmits, and reflects (or scatters) fractions of the light. The absorbed light is re-emitted after a certain amount of time, depending on the material. The reflected, transmitted, and re-emitted light has different spectra than the light shone on the sample to begin with, and these spectra can be used to determine the material’s chemical composition at any given point within the sample.

Until recently, this process required lengthy measurements and expensive equipment, but smaller and faster equipment now allows the user to operate the system at, say, a manufacturing line, to quickly examine a blend’s structure while the process is running. Such capability allows for early diagnosis and can even help prevent a failure from occurring in the first place.

In the past two decades, chemical imaging equipment has used several different spectroscopy methods, including energy-dispersive, near-infrared (NIR), and Raman. Energy-dispersive spectroscopy uses X-rays to quantify a material’s composition at the atomic level and can only be used to determine an ingredient’s spatial distribution when that ingredient is the only ingredient containing a given atom. NIR spectroscopy uses light in the near-infrared region of the electromagnetic spectrum but is limited somewhat by poor chemical specificity (ability to distinguish between substances) and resolution. Raman spectroscopy analyzes only the light scattered by the sample, looking for evidence of the Raman effect (changes in wavelength with respect to the light shone, indicating the sample’s chemical composition). Raman spectroscopy provides higher chemical specificity and resolution than NIR and is also less affected by the sample’s physical characteristics, such as particle size and shape. This makes Raman imaging a powerful tool for studying a material’s structure.

To explain how Raman imaging determines a material’s structural composition, we’ll use an instrument called the mPAT LAB from a company called H₂Optx (www.h2optx.com) as an example. This instrument can achieve spatial resolution (in the XY plane) as low as 10 by 10 microns, which is smaller than the primary particle size of most powders. One of the instrument’s best features is that it incorporates an automated grinder, which can shave layers off a sample during a production run, enabling the user to scan multiple layers and compose a three-dimensional map of the sample structure.

The operator mounts the sample on a moving stage and grinds the sample to the desired depth. The stage then moves the sample to a camera screen, which scans the sample with the desired resolution and takes a Raman spectrum from each position. The instrument then analyzes the Raman spectrum using the classical least squares mathematical method, which compares the sample’s measured
spectrum with the spectra of reference samples of pure ingredients to calculate each ingredient’s concentration at each position.

In the simplest and most common analysis, the instrument assigns each ingredient a different color and colors each pixel in the scanned image to match the ingredient that dominates the sample at that position, generating an image that represents the ingredients’ spatial distribution. The instrument carries out this process for multiple layers in the sample, creating a three-dimensional, multicolor map, as shown in Figure 1, with each color representing a particular ingredient. The instrument can also generate a quantitative summary to show the general ingredient distribution for each layer or for the sample as a whole.

Another way of looking at the sample’s microstructure is to map an individual ingredient’s distribution in terms of particle size, as shown in Figure 2. The figure shows an ingredient’s particle-size distribution in intervals of less than 50 microns (Figure 2c), 50 to 250 microns (Figure 2d), and greater than 250 microns (Figure 2e).

The main disadvantage of Raman imaging is the method’s low quantum yield — only a small fraction of the light results in a Raman effect. This means that the method requires a long integration time (the time needed to take the spectrum measurement). The method can take between 1 and 2 hours to scan and generate an image.
of a 4-by-4-centimeter sample area using up to 20 layers. The time depends on the integration time, the number of layers analyzed, and the depth of profiling desired. While this disadvantage is vanishing quickly as laser and detector technologies advance, this can pose a practical limit to the number of samples an instrument can meaningfully analyze and raises the question of whether the samples analyzed are statistically representative of the material stream.

Fortunately, you can couple Raman imaging with other analysis methods to allow for statistically significant sampling. For example, you can use another type of spectroscopy — transmission-infrared spectroscopy, which analyzes infrared light transmitted through a material sample — as a quick method (usually taking about a minute) to characterize a sample’s total composition and filter out samples of interest (those with an unusually high or low ingredient concentration). Then you can analyze those samples using the slower Raman method, which can detect common causes of off-target ingredient amounts, such as inefficient blending, segregation, or agglomeration.

Using this technique, you should eventually be able to correlate material attributes and process variables to product structure and performance. This analysis can aid in the Quality by Design manufacturing approach that’s strongly encouraged by the FDA. For example, if one ingredient in a pharmaceutical tablet is cohesive and tends to agglomerate, understanding the effects of formulation and process parameters on the active ingredient domain size within a tablet and on the tablet’s dissolution performance (how the tablet dissolves) can help you improve your process.

During some blending processes, shearing action can cause low-melting-point ingredients to soften and coat other ingredients, often affecting a tablet’s dissolution performance and hardness. During wet granulation, moisture affinity variations between ingredients can cause nonuniform ingredient distribution in different-sized granules, often affecting product quality. Using chemical imaging, you can examine these and other effects to determine the root causes of your quality issues.

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