Content Uniformity Verification by IR Laser Imaging

Application Note MIC421

Solid oral dosage forms are an analytical challenge.

The production of pharmaceutical tablets is a multi-stage process that includes powder processing, milling, granulating, mixing and compacting. Nevertheless, hundreds of thousands of tablets are produced per hour in modern, high-throughput production facilities.

Variations in the process parameters, however, can strongly influence the composition of the tablets and thus their quality. It is not only the total content of active ingredients and excipients that is important, but also their granularity and distribution within the tablet.

Pharmaceutical products naturally require maximum product uniformity to ensure consumer safety for each individual tablet. Therefore, an analytical method is required that captures all relevant quality parameters in a short time enabling complete characterization of a tablet's properties to optimize production processes and assure quality.

Spectroscopic Solutions to pharmaceutical Quality Control

The application of (Fourier transform) infrared spectroscopy in pharmaceutical quality control is already well established. In this process, the unique spectral infrared absorption signature is used for unambiguous chemical identification.

This principle can be transferred to the microscopic level, allowing the smallest structures to be chemically analyzed and identified with a spatial resolution of a few micrometers.

(FT-)IR microscopy therefore allows visualization of the distribution of (active) ingredients in a tablet, control of the uniformity of a coating, investigation of impurities, and many other applications that are usually grouped under the term "chemical imaging". Such chemical images are composed of thousands of IR spectra that contain a wealth of chemical information about the sample.

In this AppNote, we introduce the use of IR laser microscopy to understand the chemical composition of a tablet and the distribution of active ingredients.

I Want it All: Speed, Resolution, and Ease of Use.

To gain statistically significant information on the product properties, it is required to measure a large number of tablets. That makes the speed of measurement particularly important. To effectively use chemical imaging for development- production and qc-processes in solid-dosage form manufacturing, complete tablets must be analyzed in shortest time at micrometer level and with highest quality of results.

Although classical FT-IR microscopy can provide the necessary resolution, the analysis is limited to small areas investigated by ATR. For IR laser imaging, however, the situation is quite different. By using a sharp, single-frequency IR emission at very high power, contactless analysis in reflectance becomes feasible, decreasing measurement times drastically.

Up to 90,000 IR spectra are simultaneously acquired with one imaging camera detector, reducing analysis times by two orders of magnitude. As a result, hours become minutes and tablet analysis finally becomes widely applicable in routine applications.

By using modern machine learning methods, evaluation of data is also accelerated. Even huge amount of information can be processed efficiently and reliably by a dedicated classifier, that performs the analysis in a few seconds - fully automated of course.

Chemical Imaging of a Tablet's API distribution

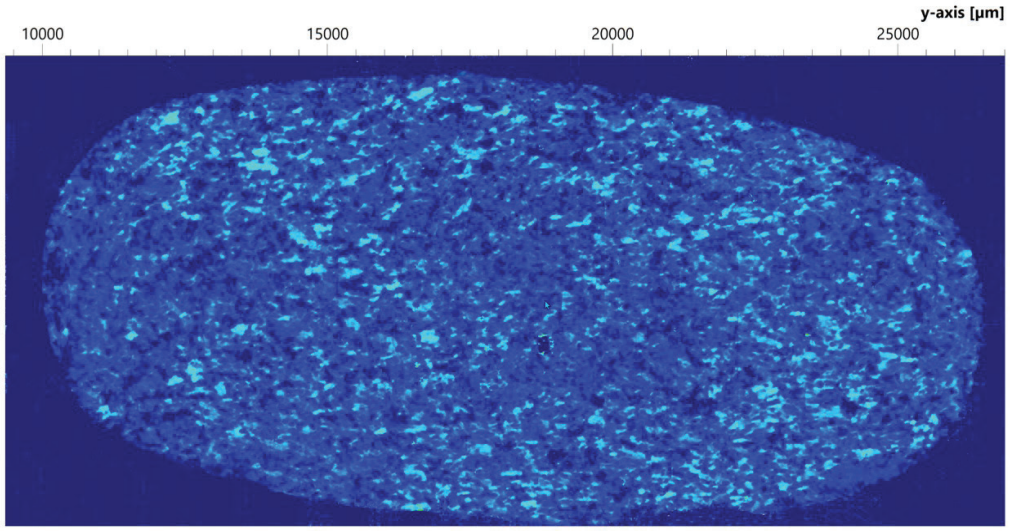
In the manufacturing process of a tablet, a constant and repeatable distribution of APIs and excipients must be achieved. Usually, a uniform distribution is desired, while deviations or impurities are indicators of process problems. As such, these deviations are often used to disguise falsified products of poor quality in forensic applications.

A commercially available tablet was used to demonstrate the exceptional applicability of IR laser imaging to quality control. Prior to the analysis, the surface of the tablet (Figure 1) was conditioned with a tablet mill. It was analyzed at a pixel resolution of 5 µm and across the full accessible IR laser range from 1800 cm^{-1} to 950 cm^{-1}. Measurement of the complete tablet took less than 10 minutes.

Fig. 1
Tablet ready for the analysis after treatment with a tablet mill.

The evaluation of the raw data (Figure 2) was then performed by a dedicated machine-learning classifier developed by Bruker. The "Tablet Analyzer" software allows to create product-specific models based on reference spectra of all components of a product. It automatically creates and trains a fully connected neural network for this particular composition. Once set up, the model can be applied by the push of a button and the analysis is automatically performed.

Fig. 2
Measurement of the tablet as displayed in OPUS.

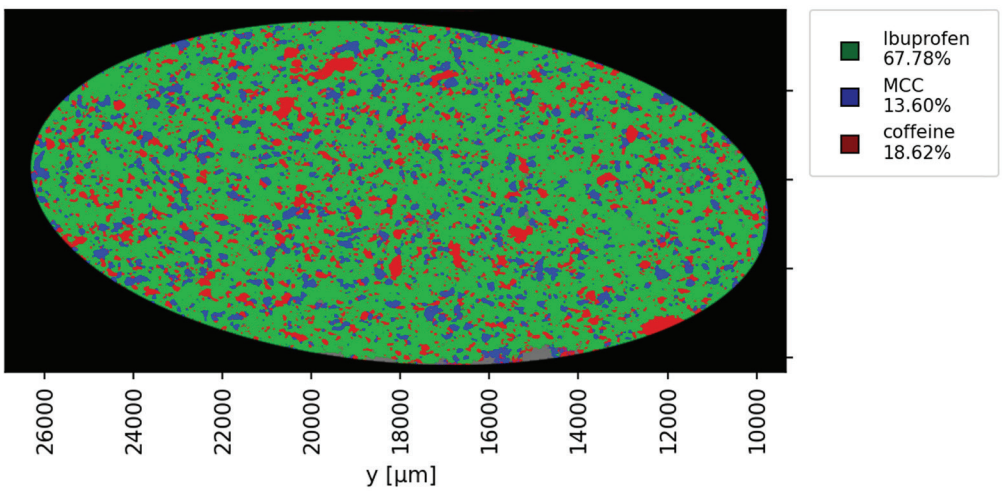


Complete analysis in a matter of minutes.

The result (Figure 3) shows a color-coded representation of the distribution of the individual components as well as the percentage of particles for each component. This high-quality chemical image was made possible by Bruker's patented spatial coherence reduction.

With this automatically generated chemical image, users can evaluate the distribution and granularity of the different ingredients. Additional quantitative and statistical information on granularity and mixing ratios is also available (Figure 4). In the case of ibuprofen, which is recognized as a tablet matrix, no statistical values are assigned. The user can document the analysis by generating a comprehensive report at the push of a button.

Fig. 3
Analysis result shown as a false color plot and particle size statistics.



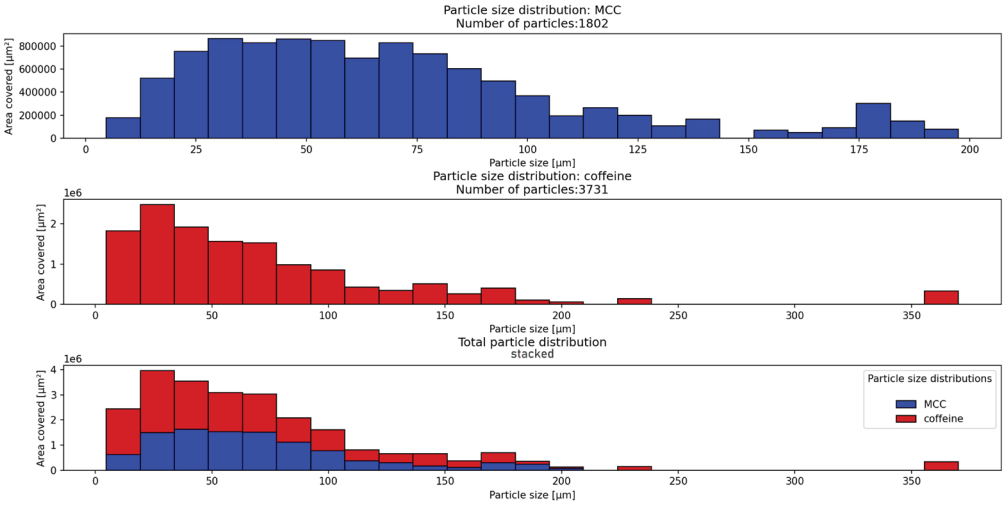


Fig. 4
Particle statistics received by the tablet analyzer.

Since a complete QCL spectrum was measured at each individual point (5 micrometer pixel), the spectral and spatial delineation of the individual ingredients is very specific. The differentiation of different ingredients thus becomes reliable and reproducible.

Foreign bodies or contaminants can easily be localized in the chemical images. They can then be identified by their full spectral signature using the FT-IR integration of the HYPERION II, which is available in parallel.

Summary: Innovation with Integrity

The methodology presented here, developed by Bruker, addresses known problems and limitations of pharmaceutical tablet imaging with true innovation. Utmost speed, reliability, and ease of use are achieved and far surpass previously available methods, making comprehensive tablet feasible for the first time.

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