APPLICATION NOTE

FEI COMPANY™
TOOLS FOR NANOTECH

Imaging and Analysis for Drug Formulations

Any sample, all data

Typical applications in the method development and QC lab include analysis of:

- *Drug excipient homogeneity*
- *Particle shape and size*
- *Shelf life analysis*

Quanta systems will help you with:

- *More Information – Determine high resolution structure and composition using a wide range of signals and detectors.*
- *Better information – Examine specimens in unaltered condition. Eliminate coating interference and charging artifacts.*
- *Less work – Eliminate drying, fixing, coating or other preparation procedures.*
- *Wider range of samples – Examine wet, outgassing, non-conductive samples.*
- *Dynamic experiments – Observe response to changes in humidity, temperature, mechanical force*

FEI's Quanta Series Scanning Electron Microscope/Focused Ion Beam (SEM/FIB) systems provide you with a broad range of easy-to-use imaging and analytical capabilities essential to developing and maintaining manufacturing processes that meet industry GMP requirements. Chemical, microbial, and thermal stability, as well as flow, compaction and dissolution properties are essential process and material characteristics in pharmaceutical production. All depend, to some extent, on structure and composition at the micrometer scale and below. Although a variety of techniques exist to help you monitor these properties in a production setting, initial validation during process development and the interpretation of anomalous results from production measurements often require the high-resolution imaging and analysis capabilities of an electron microscope. The use of ESEM (Environmental SEM) technology in FEI's Quanta SEMs provides additional analytical capabilities while at the same time eliminating much of the sample preparation required by conventional SEMs.

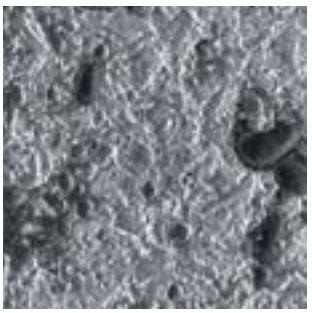
Quanta systems allow you to shorten development and validation cycles for new processes providing faster time-to-market for new products. Also enabling rapid and intuitive monitoring of batch to batch variations resulting in fast correction of production problems for higher process yields.

Formulated Products: Drug Excipient Homogeneity

It is essential to understand how well the ingredients of the formulation are blended in the various stages of the production process, and to analyze the distribution of the active ingredients within the excipient matrix in the final product. For those formulations that allow characterization based on elemental information, the combination of secondary electron imaging, backscattered electron imaging and X-ray analysis permits such an evaluation in a single tool. The use of ESEM enables immediate imaging of the non-conductive material without coating. ESEM technology also allows accurate X-ray analysis even in the absence of coatings.

Surface Characterization

When analyzing formulated products, you are confronted with the need to evaluate and control a wide variety of material characteristics many of which require accurate, unobscured observations of surface form and structure. The wide variety of signals generated in the SEM imaging process permits the selection of an imaging mode that best fits the analytical task. Secondary electrons (SE) provide high resolution and emphasize topography. Backscattered electrons (BSE) bring out material contrast. Characteristic X-rays show the location of specific elements. Quanta observes non-conductive materials without the interference of conductive coatings. Low voltage operation enhances near surface information. Wide field images permit rapid surveys of relatively large areas. No matter what your need, the Quanta has an imaging mode to fit - any sample, all data.



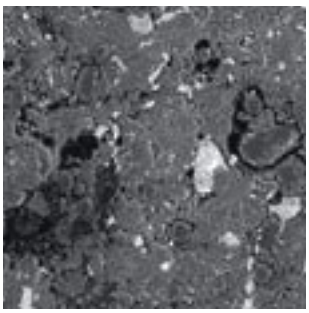
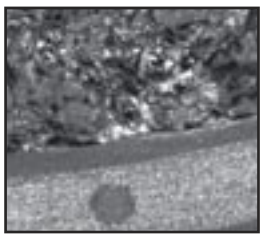
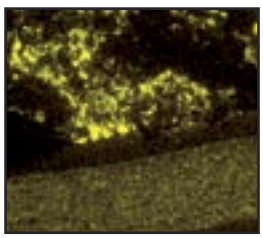


Image Left: This is a formulated paracetamol sample with enhanced imaging of the surface details with secondary electron information.

Image Right: This is the same sample shown in the left image but with backscatter electron image information of exactly the same area showing the material contrast. Note that the heavier elements appear brighter in the image.

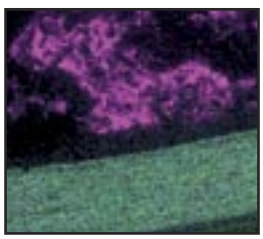


This is a backscatter electron image of a formulated ibuprofen sample showing a part of the core as well as the coating. Below are further images showing the characteristics of elements in ibuprofen samples. These are color coded for easy identification and concentration of the various elements in the sample.



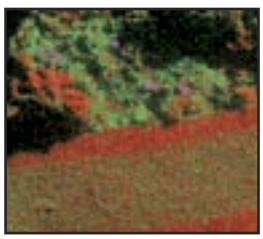
The element magnesium is highlighted in yellow within the sample.

Magnesium



The elements of Silicon, Titanium and Calcium are highlighted in this sample.

Silicon
Titanium
Calcium



The elements Carbon, Oxygen and Sodium are highlighted in this sample.

Carbon
Oxygen
Sodium

Enabling Technologies

The ESEM detector actually uses gas in the sample chamber to amplify the secondary electron signal. SE that escape from the sample surface are accelerated by the detector field. They collide with and ionize gas molecules creating additional electrons. The process repeats resulting in proportional, low-noise, cascade amplification of the original secondary electron signal. Any charge accumulating at the sample surface is neutralized by the ions created in the amplification process.

X-ray analysis in a gaseous environment is complicated by the scattering of beam electrons after they pass the final aperture. The greater the distance between the aperture and the sample, the farther the scattered electron can land from the intended beam spot, where they can generate X-rays that are not characteristic of the intend beam location. In the Quanta's unique Gaseous Analytical Detector (GAD) the final aperture is located very close to the sample surface where it limits the size of the "skirt" created by scattered electrons and improves the accuracy and spatial resolution of the x-ray analysis.

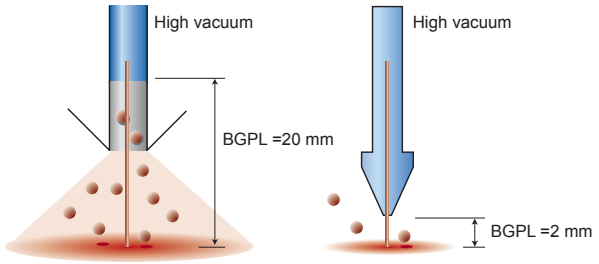
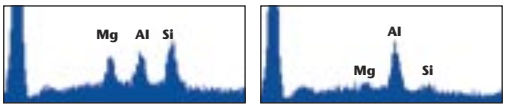


Image Left: Typical low-vacuum analytical geometry with long Beam Gas Path Length (BGPL).
Image Right: Proprietary ESEM analytical geometry with short BGPL.

Here below you see two graphs showing the improved accuracy in Energy Dispersive Spectroscopy (EDS) under low vacuum conditions. The graph on the left shows spurious EDS peaks from adjacent layers in a typical low vacuum EDS dectection system without a Gaseous Analytical Dectector (GAD). The graph on the right shows that by using the GAD, that the Silicon and Titanium peaks are spurious peaks from the adjacent layer.

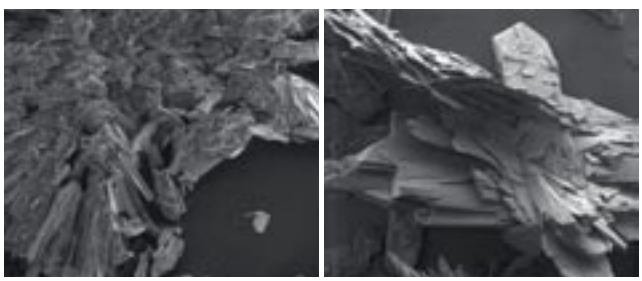


Raw Materials: Particle Size, Shape, and Aggregate

Particle size, shape and aggregation are primary determinants of dissolution behavior and drug bioavailability. Also these parameters govern the flow characteristics within the production process. As such they must be carefully controlled. While bulk techniques exist for characterizing size distribution in production they generally do not have the imaging capability required to determine shape and aggregation. Smaller particles and tighter size and shape distribution provide faster dissolution and absorption and more predictable dissolution rates. Sub-micrometer and even nanometer size particles are not uncommon. These are well beyond the resolution capabilities of optical microscopy. Quanta has the resolution needed for even the smallest particles and the dynamic range as well as the depth of focus to look at large particles as well.

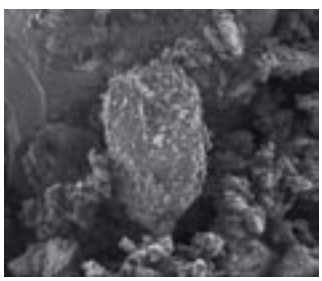
Enabling Technology

Particle characterization can involve observations of particles both from a dry powder and from a particle suspension. Typically a particle suspension is diluted and filtered to obtain a sample that can be analyzed in an SEM. From a dry powder the sample can be directly dispersed on a sample holder. For a conventional SEM the particles as well as the filtration medium must be dried and coated before analysis, obscuring the fine surface details that can be important for understanding milling and mixing processes. ESEM technology provides the ability to analyze size, shape and aggregation without coating, or even drying the filter before introduction into the SEM sample chamber.



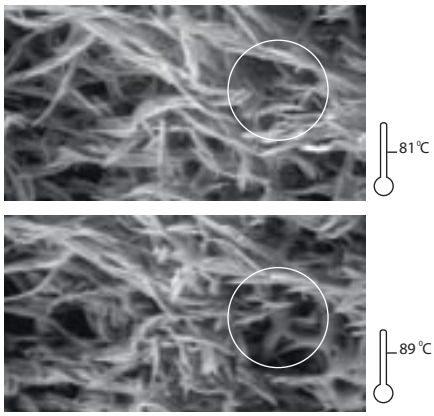
These images are of an active compound drug crystal directly after two crystallization processes. The images show the differences in the shape and size of the crystals.

Image of formulated particles for inhalation used in a dry powder inhaler are shown here. The resolution reveals the small active compound particles on the larger carrier particles.



Shelf Life Analysis

A key issue in pharmaceutical formulation development is understanding of how the product behaves in various ambient conditions. The Quanta scanning microscope enables a fast, intuitive understanding of product behavior based on morphological changes when the temperature or relative humidity is changed. The temperature of the sample can be controlled directly from the microscope user interface.



Both images above show the behavior of active compound crystals during heating. The Quanta allows you to control the temperature thru the user interface enabling you to directly observe the morphological changes.

Enabling Technology

The heating stage provides the heating capability to allow direct observation of the morphological changes of the sample for temperatures up to 1000°C. The peltier cooling stage permits the hydration/dehydration experiments by controlling the sample temperature from -30°C to + 30°C from ambient. Only ESEM permits sample chamber pressures high enough to maintain water in a liquid state. Its differential pumping system and multiple pressure limiting apertures permit pressures as high as 2600 Pa in the sample chamber while maintaining high vacuum conditions in the electron source and column regions. All dynamic experiments can be monitored and recorded digitally in real-time.

For a direct morphological evaluation of hydration/dehydration behavior of the product, the sample temperature in combination with the water vapor gas pressure within the sample chamber can be controlled to set the relative humidity of the ambient atmosphere near the sample anywhere between 0% and 100%.

These images show the dramatic changes in the crystal morphology before and after a hydration and dehydration cycle.

IQ/OQ

In order to support your installation qualification and operation qualification requirements, FEI supports a fully documented installation procedure using an installation and acceptance test document.

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