

# Sub Micron Particle Size and Shape Characterization by SEM

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## ABSTRACT

In the pharmaceutical industry, SEM may be used as a qualitative tool for the analysis of drug substance and drug product in order to obtain information on the shape and surface structure of the material. These analytical capabilities can be essential to developing and maintaining manufacturing processes that meet industry GMP requirements.

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. SEM plays an important role in the characterization of nanoscale and sub-micron particles. 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.

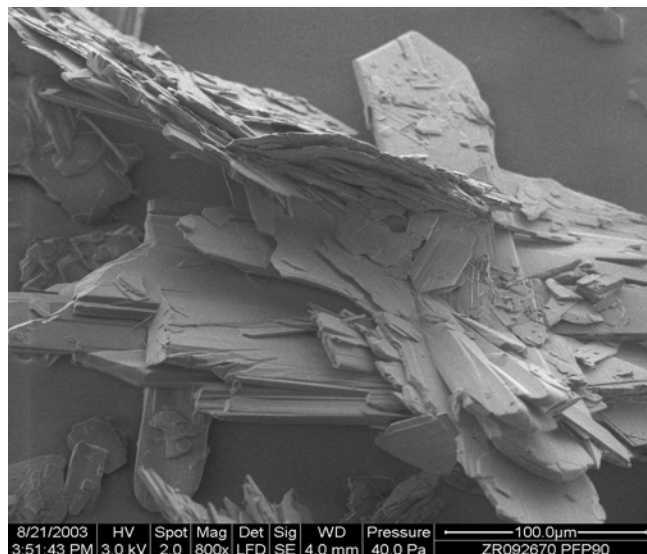


Image of an active compound drug after crystallization process for qualitative particle characterization. (fig 1)

## 1 PARTICLE CHARACTERIZATION AND SIZE DISTRIBUTION

A variety of techniques exist to monitor these properties in a production setting. However, 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 provides additional analytical capabilities while at the same time eliminating much of the sample preparation required by conventional SEMs.

Other bulk techniques exist for characterizing size distribution in production although 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 in active drug formulations. Sub-micrometer and even nanometer size particles are not uncommon.

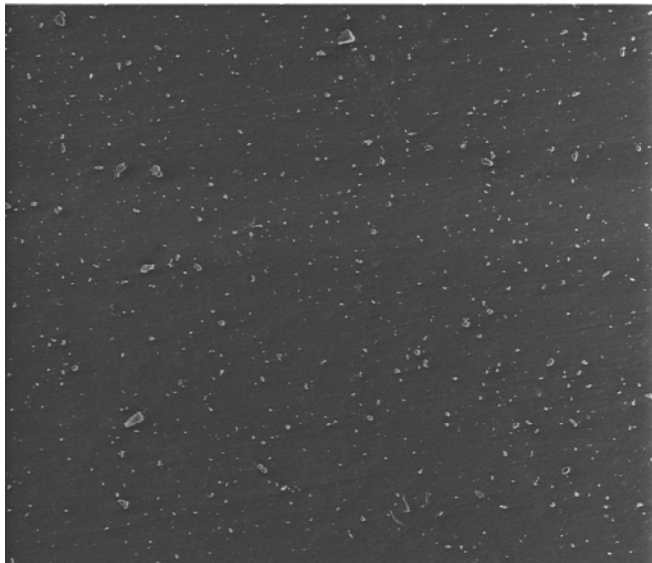
These are well beyond the resolution capabilities of optical microscopy. SEM has the resolution needed for smaller particles and the dynamic range as well as the depth of focus to look at large particles as well.

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.

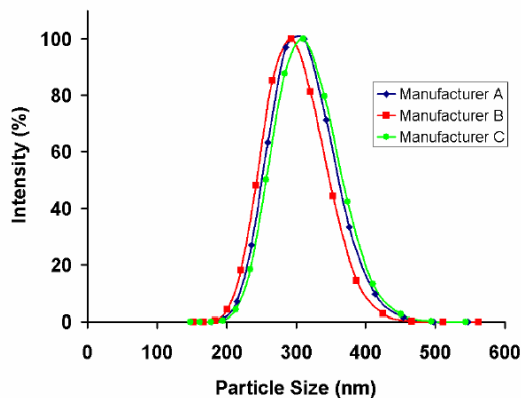
For a conventional SEM the particles as well as the filtration medium must be dried and coated before analysis, obscuring the fine surface details that can be important for understanding milling and mixing processes. Environmental SEM (ESEM) technology provides the ability to analyze size, shape and aggregation without coating, or even drying the filter before introduction into the SEM sample chamber.

### 1.1 Quantitative and Qualitative Analysis

More than just qualitative analysis, SEM plays an important role in the quantitative analysis for characterization of size, shape and distribution of nanoscale and sub-micron particulate systems. Furthermore, the technique can serve as an absolute reference standard to support the development of QC particle size distribution techniques.

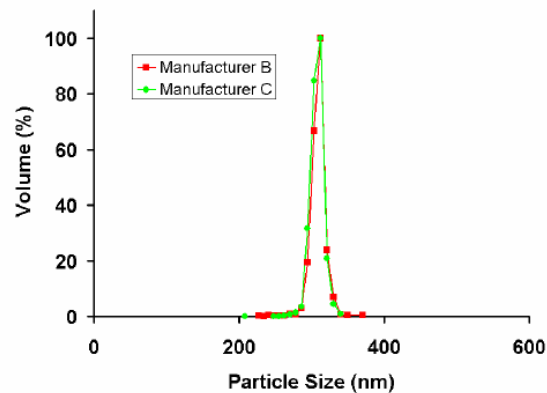


SE Image of broad profile pharmaceutical product (fig 2)



Laser diffraction data (fig 3)

For this poster, a study has been done to verify SEM particle characterization results versus the calibration standards provided by the standards manufacturers, as well as to characterize products with broad particle size distribution.



SEM-image analysis based data (fig 4)

In literature, the particle size distribution analysis of nanoscale and sub-micron polystyrene latex spheres has been described. Since these products are characterized by a narrow distribution, only a limited number of particles need to be analyzed which allowed the use of elaborate manual procedures in the SEM analysis of these products.

However, once the size distribution of the product gets broader and more particles need to be counted, the automation offered by the use of SEM technology becomes particularly beneficial.

## 2 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.

## 3 SURFACE CHARACTERIZATION

When analyzing formulated products, there is often a 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.

Non-conductive materials can be observed without the interference of conductive coatings. Low voltage operation can also enhance near surface information while wide field images permit rapid surveys of relatively large areas.

#### **4 ENVIRONMENTAL SEM**

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 intended beam location. With a 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.

#### **DISCUSSION**

SEM combined with Image Analysis is a promising technique for generating particle distribution profiles as well as surface characteristics with the possibility to visually re-evaluate the data by re-assessing the particle.

The technique holds promise for characterization of the size and shape of unknown products with relatively wide distribution profiles from the nanometer to the micron range.

SEM systems with ESEM capabilities can allow shortened development and validation cycles for new processes and provide faster time-to-market for new products. Rapid and intuitive monitoring of batch to batch variations is also made possible resulting in fast correction of production problems for higher process yields.

#### **REFERENCES**

- [1] Internal standard method for size calibration of sub-micrometer spherical particles by electron microscope, Technical Note 010B, June 15 (2003) Duke Scientific corporation.
- [2] Particle size analysis – Image analysis method; Part 1: static image analysis method, ISO 133220-1