Scanning Electron Microscopy Services for Pharmaceutical Manufacturers

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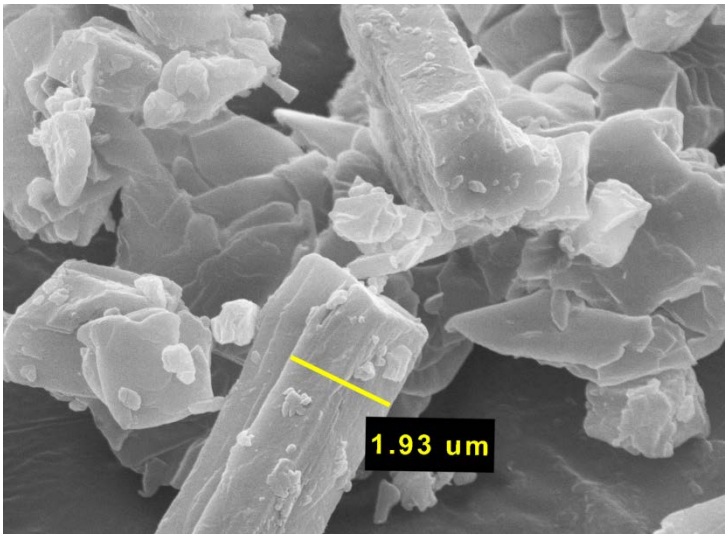
Scanning Electron Microscopy (SEM) Services for Pharmaceutical Manufacturers

“ Smaller particles in pharmaceutical manufacturing are increasing the need for SEM characterization. ”



Capsule containing Amoxicillin drug. Magnification: 6,000x

Today, all pharmaceutical and biopharmaceutical companies follow testing requirements which set standards for inspection of visible particulates, and also for examining the size and quantity of sub-visible particulates in final products. These quality control mechanisms are typically employed at the end of the production cycle, and are typically done via optical inspection. However, pharmaceutical developers and manufacturers are finding that they need the high resolution provided by a scanning electron microscope (SEM) to characterize, control, and elementally quantify the size and shape of these particles.

In particular, the continuing trend toward smaller particles for active pharmaceutical ingredients (API), and better quality of the final product, has pushed particle dimensions into the sub-micrometer regime, which is beyond the capability of optical measurement tools. [1]

This article will review some different types of unwanted particulate matter found in pharmaceutical products and the advantages of using scanning electron microscopy with energy dispersive spectrometry (SEM-EDS) as a means to fully characterize particle matter during the manufacturing process. In addition, periodic sampling of the final product for the active matrix and coating thickness will be presented.

Particle contamination

Particulate matter can range in size from sub-microns up to several hundreds of microns. In most cases, particle size distribution and total count are required. Foreign particles or particulate matter in drug powder products is an area of extreme concern. Unwanted particles should be controlled and their sources identified. Contamination due to an excessive amount of particulate matter in pharmaceutical products might lead to quality and safety problems. Particle contamination in manufacturing sites might even result in the suspension of production.

Scanning electron microscopy provides visual information about the organic and inorganic submicron particles (size, shape, and morphology), and also chemical identification based on the X-ray energy lines.

“ Costs associated with the investigation of contamination sources and development of a suitable cleaning process can be formidable. ”

Typical sources of particle contamination

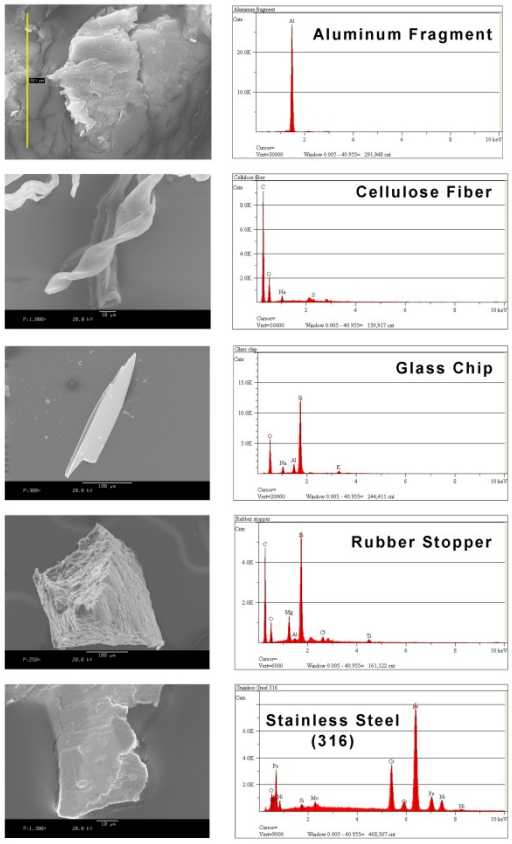


Figure 1. SEM Images and EDS Spectra of common pharmaceutical contaminants.

Depending on the nature of the sample (organic, inorganic, or metallic), and the type of information desired, the imaging and chemical characterization capabilities of SEM-EDS lead many pharmaceutical laboratories to use this technology to evaluate morphology, size, shape, and elemental composition of metallic and organic sub-visible particles.

Sources of particulate matter vary depending on the development process, equipment used, location, and overall facility cleanliness. But, even the cleanest rooms can produce particulate matter shed by gowns, gloves, skin, sample preparation equipment, and glassware. Containers and closures, specifically rubber closures, contribute particulate matter due to leaching, chemical reactions, friction, and changes in physical properties.

Some of the most common materials identified in pharmaceutical environments are stainless steel, silica, aluminum, salts, minerals, organic fluorinated compounds, and carbonaceous materials in varying sizes and shapes.[2] SEM Images and EDS spectra of some of these particles are shown in Figure 1.

Active Ingredients in Pharmaceutical Tablets

Pharmaceutical tablets are composed of a number of different materials, each of which is designed to improve performance. The Active Pharmaceutical Ingredient (API) is intended to act on the particular disease or the symptoms of the disease. The other components, referred to as excipients, act as fillers, bulking agents, tablet disintegrants, and tablet coatings (to protect the

core and to mask taste). Consistent performance of the tablets depends directly upon the amount of each excipient in the tablet.

During development, it is useful to have a means to investigate the distribution of excipients and API within the tablet itself. The use of EDS maps and BSE (Back Scattered Electron) images of tablet cross-sections are two related means of directly examining excipient and API distribution within a tablet. The example shown in Figure 2 highlights the quantitative methods using a multi-vitamin tablet as a test case using a backscatter image of the tablet cross-section along with the accompanying EDS map.[3]

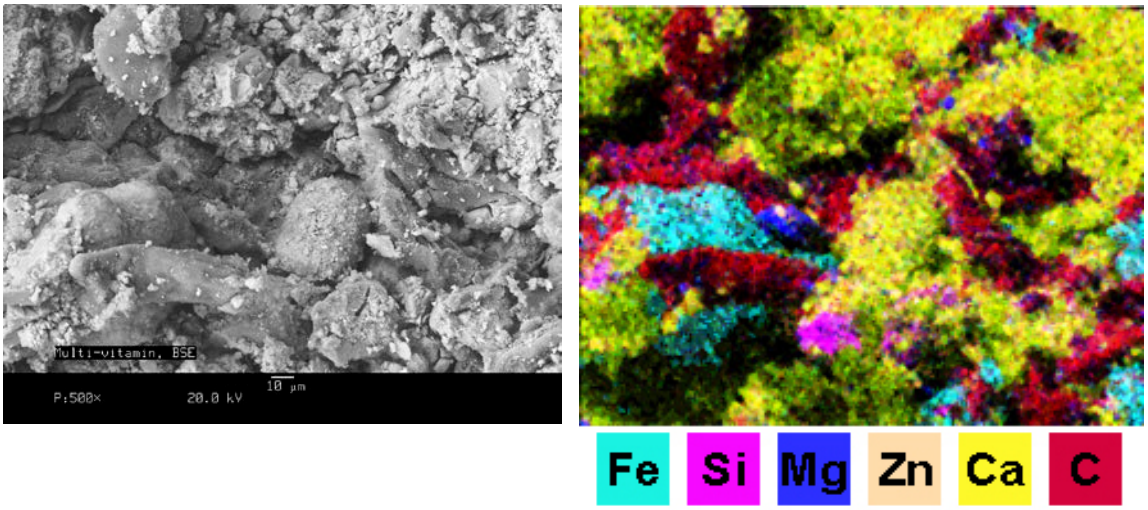


Figure 2. Backscattered Electron Image and EDS Map of a Multi-vitamin Cross-section

In addition to visually seeing all of the elements, the EDS system can provide quantification by percent of the total elements as shown in Table 1. Of note in the table is the incorporation of oxygen that was purposely excluded from the EDS map of Figure 2.

Elt.	Intensity (c/s)	Atomic %	Conc	Units
C	84.95	37.169	25.796	wt.%
O	93.39	49.951	46.179	wt.%
Mg	46.42	3.310	4.648	wt.%
Si	6.49	0.295	0.479	wt.%
Ca	233.44	8.133	18.834	wt.%
Fe	7.89	0.456	1.472	wt.%
Zn	6.54	0.686	2.593	wt.%
		100.000	100.000	wt.%

Table 1. Quantitative Analysis of the Multi-vitamin Tablet

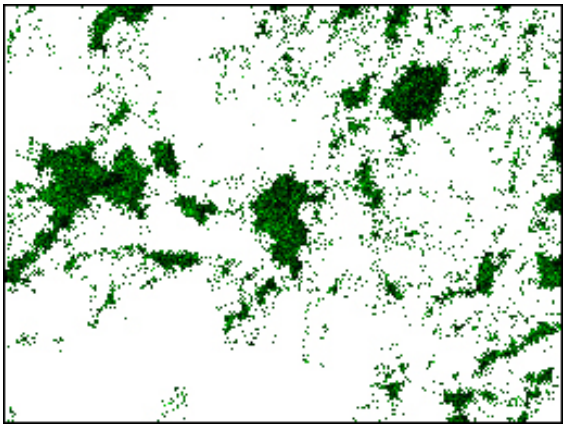


Figure 3. Oxygen (O) EDS Map of the Multi-vitamin in Fig. 2

Since oxygen bonds tightly with other elements to form oxides, it was left out of the comprehensive EDS map. Shown in Figure 3 is the oxygen element EDS map in green. It is interesting to note the various elements that the oxygen binds to by overlaying Figure 3 on top of Figure 2. As a note, the green that is shown in Figure 2, is the combination of the mutliple colors from the Iron (Fe), Zinc (Zn), and Calcium (Ca).

Quality Control

Besides monitoring for particulates in a production line, and quantifying the API within the tablet, another quality control check can be obtained by measuring thickness of the tablet's coating. Figure 4 shows the thickness value of a tablet coating from an Ibuprofen sample using a Back Scattered Electron (BSE) Image.

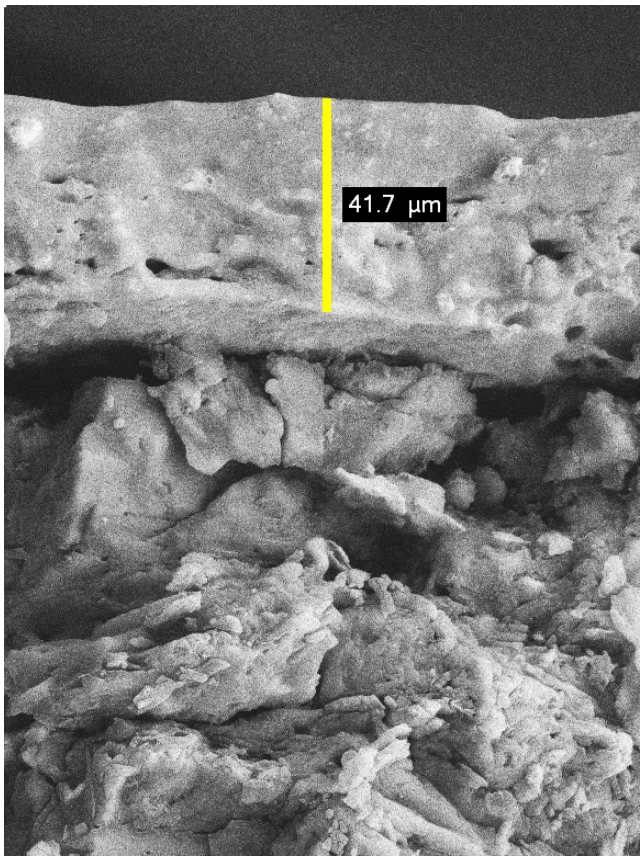


Figure 4. Coating Thickness of an Ibuprofen Tablet

Tablet coatings have numerous functions including strengthening, controlled release, ease of handling and packaging, protection of the tablet from moisture, improved taste, facilitate swallowing, and to provide tablet identity.

The adhesion of a coating to the tablet is influenced by the strength of the interfacial bonds between film and tablet. Poor adhesion results in peeling, which reduces film functionality. The mechanical protection provided by the coating can also be compromised by loss of adhesion, leading to the accumulation of moisture at the film-tablet interface. This could affect the stability of moisture sensitive drugs.

Summary

Implementing a SEM-EDS particle-characterization program is a key step towards optimizing the design and therapeutic effect of new pharmaceutical products, and controlling undesirable contamination. SEM imaging provides the resolution required to evaluate both the size and shape of nanometer scale particles. The large depth of focus of the SEM reveals fine surface detail, even over large, irregularly-shaped particles. SEM and EDS image-based particle

analysis provides qualitative and quantitative capabilities for nanoscale particles far beyond the capability of optical microscopy.

About our Analytical Testing Laboratory

> **“ Numerous clients have benefitted from our technical expertise and commitment to customer service. ”**

The Analytical Testing Laboratory of SEMTech Solutions in North Billerica, Massachusetts was established in 2007 as a provider of R&D, QA & QC services for those companies needing high resolution scanning electron microscopy. We serve as a resource of unbiased, independent analytical data and counsel. Over the last several years, we have seen a significant increase in the amount of pharmaceutical companies requesting SEM services for particulate analysis. Our SEM laboratory is equipped with all the capabilities as shown in this paper, along with Polarizing Light and Stereo Microscopes. Our lab manager, Dr. Ernie Dobi, has over 30 years of electron beam experience working across various fields.

References

1. Lich, B., Wilfen, U., 2009, When Size & Shape Matter, *Drug Discovery & Development*. Vol. 12 Issue 2, p. 26
2. Vicens, M.C., 2012, A New Picture of Particles, *Drug Discovery & Development*.
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