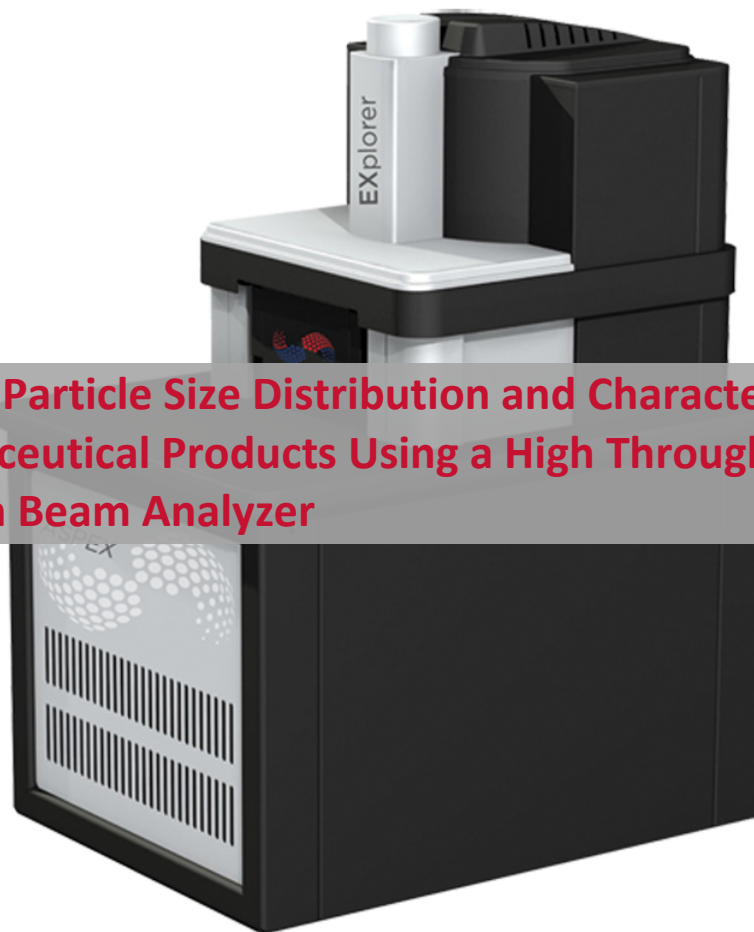




# ASPEX

The Power to Perceive



## Foreign Particle Size Distribution and Characterization in Pharmaceutical Products Using a High Throughput Electron Beam Analyzer

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## Introduction: A Quality By Design Approach

In an effort to meet FDA recommendations, pharmaceutical manufacturers and contract research facilities are adopting the Quality by Design (QbD) approach to assess the quality and safety of solid and parenteral drug products with respect to foreign particles. The QbD approach, which can be applied during developmental studies, or through routine quality control, is based on the idea that the manufacturers of drug products, devices, and formulation components are expected to understand their processes thoroughly. This concept can be incorporated in pharmaceutical companies by using analytical testing techniques that will allow the monitoring and understanding of every step of the manufacturing process. By successfully implementing the QbD approach, manufacturers can identify and improve areas that may constitute a risk of contributing foreign particulate material to the drug product delivered dose.

In general, pharmaceutical products are required to be essentially free of visible foreign particles. For parenterals, the USP General Chapter <788> specifies light obscuration and microscopy as the methods for the counting and sizing of particles in the  $\geq 10\mu\text{m}$  and  $\geq 25\mu\text{m}$  size range. In addition, there is a large variety of techniques for particle analysis, including infrared spectroscopy, raman microprobe, light obscuration, laser diffraction, optical microscopy, and scanning electron microscopy. All of these techniques have advantages and limitations, and the final decision for the most appropriate testing technique lies on each facility. In this case, the use of automated Scanning Electron Microscopy-Energy Dispersive Spectrometry (SEM-EDS) is illustrated as part of the QbD approach to monitor the particle content in the components of an asthma kit.

## Particle Characterization Techniques

The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) has published several reviews that summarize various particle analysis technologies commonly used for the particle analysis of orally inhaled and nasal drug products (OINDP).

Fourier transform infrared spectroscopy (FTIR) is a technique mostly used to identify organic, polymeric, and some inorganic materials. When using FTIR, particles must be harvested individually, preventing the technique to be used for particle enumeration.

Raman microprobe is typically used as a complimentary method to FTIR. Even though Raman microprobe systems can be automated, they have no utility for the study of metals and fluorescent materials. Both vibrational techniques are used to physically characterize solids.

Light obscuration is used for fast particle counting. This technique is dependent on particle shape and is prone to sizing errors when testing non-spherical or high aspect ratio particles.

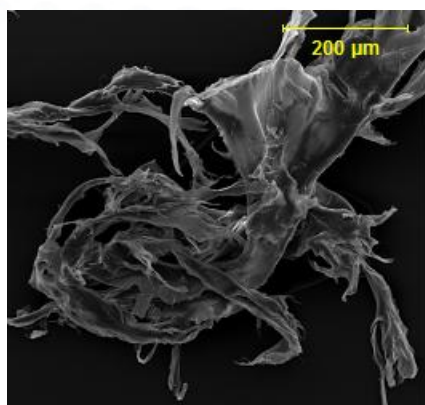
Optical Microscopy is a reliable technique that allows the direct visualization of particles. Low depth field makes this technique impractical for particles smaller than 5 microns.

SEM-EDS is used to perform size, shape, and elemental composition analysis of particles at low micron and submicron range. It has limited applicability to the detection of submicron organic materials.

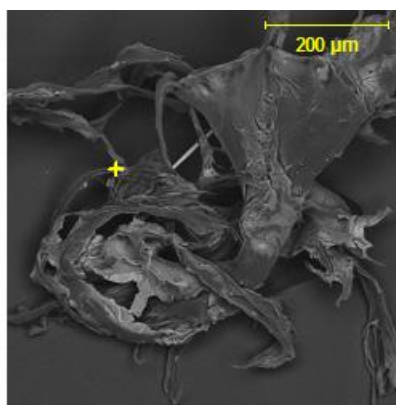
For this study, the ASPEX Personal Scanning Electron Microscope (PSEM) with Automated Feature Analysis (AFA) software was used to evaluate the components of a pharmaceutical asthma product for particulate content and composition. As a guideline, the limits for the subvisible particles allowed specified in the USP <788> were used. Samples collected from different lots were carefully prepared in a particle limiting environment. Enumeration and characterization of particulate material from the packaging, encapsulated powder, and the exterior of the inhalable device was performed. Particle size distribution data combined with compositional information was utilized to identify potential sources of contamination and improve process quality.

SEM-EDS Technology

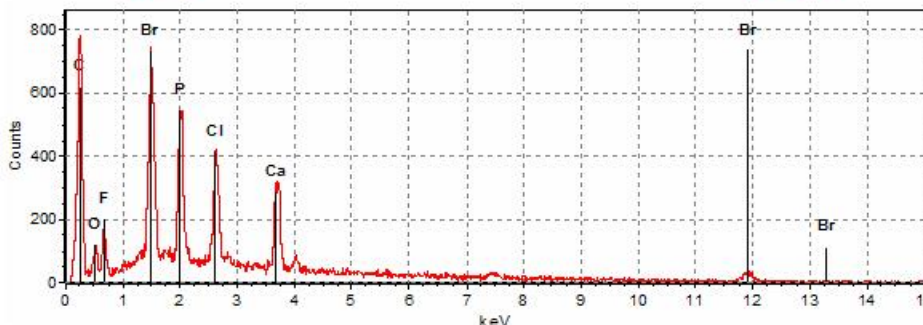
Scanning Electron Microscopy (SEM) combined with Energy Dispersive Spectrometry (EDS) is a powerful combination of analytical techniques for the evaluation of particulate matter. The SEM-EDS is powerful instrument that combines three types of signals for a full detailed sample analysis. The first component is Secondary Electron (SE) imaging, which is used to obtain surface information for a qualitative description of the sample. Surface defects, porosity, and the three-dimensional structure can be evaluated using high-resolution imaging. The second component is Backscatter Electron (BSE) imaging which is commonly used for the automation of the SEM-EDS analysis. BSE imaging displays compositional contrasts based on the atomic number of the various elements present in the sample. The Backscatter Electron signal is used to find features during the automated analysis. The third component of the SEM-EDS system is the Energy Dispersive Spectrometer (EDS). Nowadays, Silicon Drift Detectors (SDD) have been incorporated in almost every SEM-EDS platform, resulting in state-of-the-art equipment capable of providing high throughput particle analysis. The SDD provides chemical composition and their relative proportions on the sample. Data is typically displayed as the number of X-rays received and processed by the detector (counts per seconds) vs. the energy levels of the counts.



**SED**



**BSED**



**EDS (Chemical Composition)**

## Method Development

### *Compositional Contrast*

A sample preparation method was developed in order to analyze both organic and inorganic particles in a single analysis. All the samples were prepared by filtering a solution containing the particles washed from the different components of the asthma kit. Through a polycarbonate filter membrane (0.2 micron pore size). Preliminary evaluation showed that the majority of the particles were of organic nature (carbonaceous). Since the polycarbonate filter membrane has a similar backscatter signal than these particles, a sputter coater was used to deposit a thin layer of gold on each filter membrane prior to filtration. The gold provided a backscatter signal contrast ideal for the detection of organic particles. In addition, other materials such as silica, aluminum, and stainless steel have sufficient contrast with gold for the automated detection. As mentioned before, the automated analysis is dependent on the backscatter signal contrast between the substrate and the elements present in the sample.

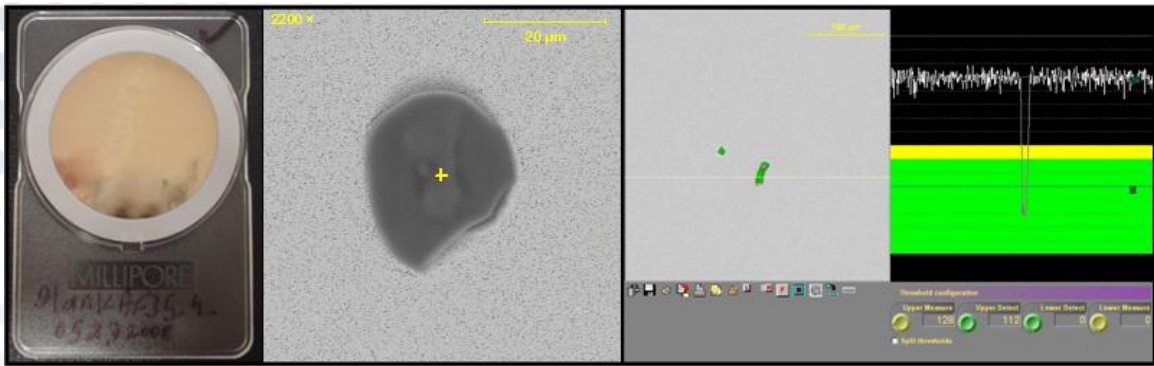


Figure 2: Backscatter contrast between the particle and filter membrane. Gold coated filter membranes provide a bright surface for the detection of darker particles.