Pharmaceutical Particle Counting, Size Measurement and Chemical Analysis by SEM / EDX

Measurement and Characterisation Problem

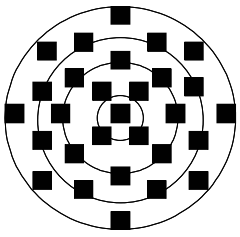
The particle and size distribution characteristics of a drug will often have an impact on the rate of delivery in the body. The regulatory bodies (e.g. FDA) have a stringent requirement of understanding the chemical and physical characteristics of drug particles and potential contaminants as part of the drug validation process.

Historically, optical light microscopy has been sufficient, however more recently the regulatory authorities are increasingly insisting on characterising finer particles and agglomerates unresolvable in transmission or reflection by optical microscopy. This shortcoming can be overcome by using Scanning Electron Microscopy (SEM).

Characterisation of Smaller Drug Particles

This application note details the laboratory's capabilities to mimic optical microscopy methods using SEM, and extend beyond the capability of optical techniques using manual or automated image collection and analysis. The SEM can automatically perform analysis down to a particle size of 2 µm, below this manual operation is required (ultimate resolution of SEM is 2 nm) with the advantage of chemical characterisation using EDX. The field of view is determined by the particle size range to be analysed. If multiple fields are to be analysed, as is commonplace within the pharmaceutical industry, a matrix of areas needs to be defined. An example of this is shown in figure 1.

Fig.1. Automated repeatable matrix of analysed areas on sample e.g. 100 areas covers 5% of a 35mm disk.



An example matrix of 29 magnified fields for particle counting across a sample

Suitable Substrates

The substrate on which the particles are deposited will affect the method used to discriminate between the substrate and the particles. Typical substrates for powders include:

- Microscope glass slides
- Organic filters e.g. Millipore
- Double sided sticky tape

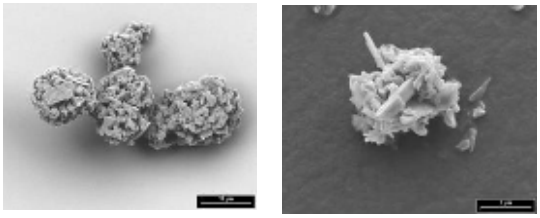


Fig.2. Example images of Ventolin™ drug particles (scale bar 10 µm left, 5 µm right)

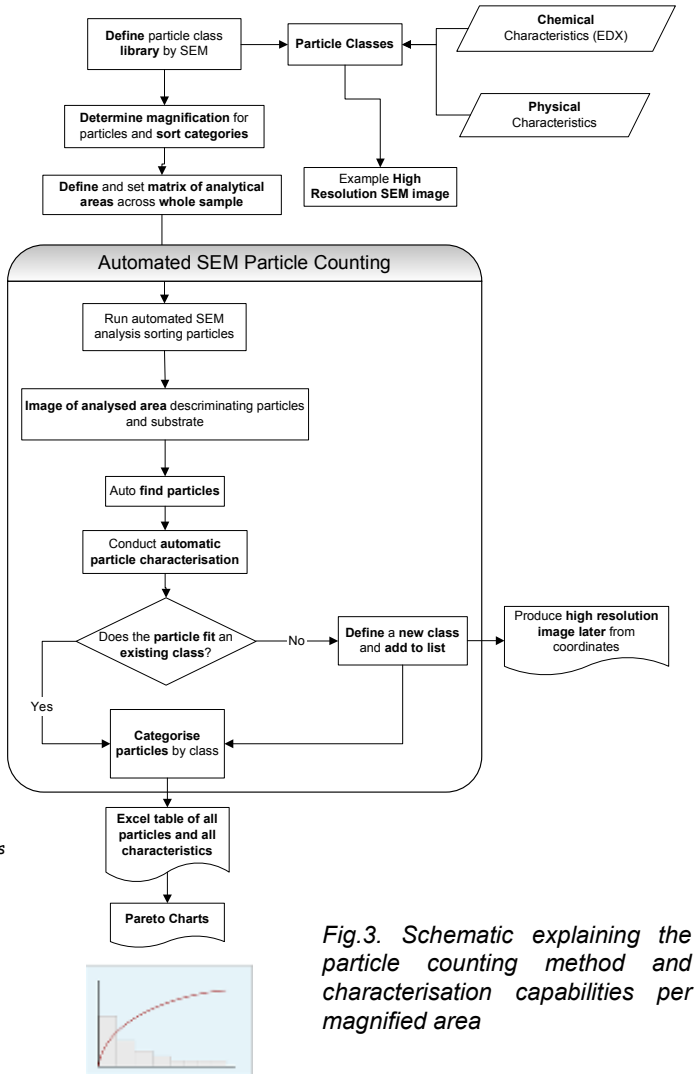


Fig.3. Schematic explaining the particle counting method and characterisation capabilities per magnified area

(* denotes UKAS accredited test)

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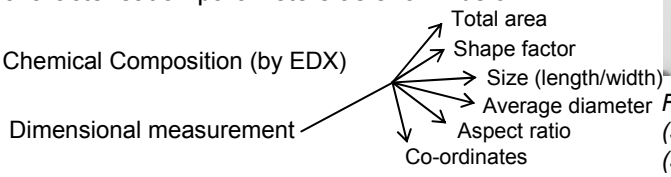
A schematic of the experimental process is shown in figure 3. The procedure allows the particles to be classified and a Pareto to be developed according to any parameter or combination of characterisation parameters as shown below:.



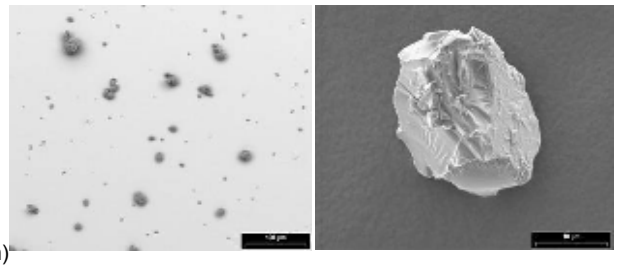


Fig.5. SEM images showing typical particle distribution (scale bar 100 µm) and contaminant fine glass particle (scale bar 10 µm)

Full or Semi-Automatic Particle Counting

The particle size range must be ≥ 2µm or else a semi-automated approach with some level of manual input is required. The procedure requires some initial standard SEM background work to obtain a library of particle types to be found in the sample.

Requirements of the fully-automated procedure

Particle size to be ≥2µm.

The particles must be distinguishable from the substrate using one of the SEM detectors.

Particle density should not be so high that many particles are overlapping or particles are agglomerates.

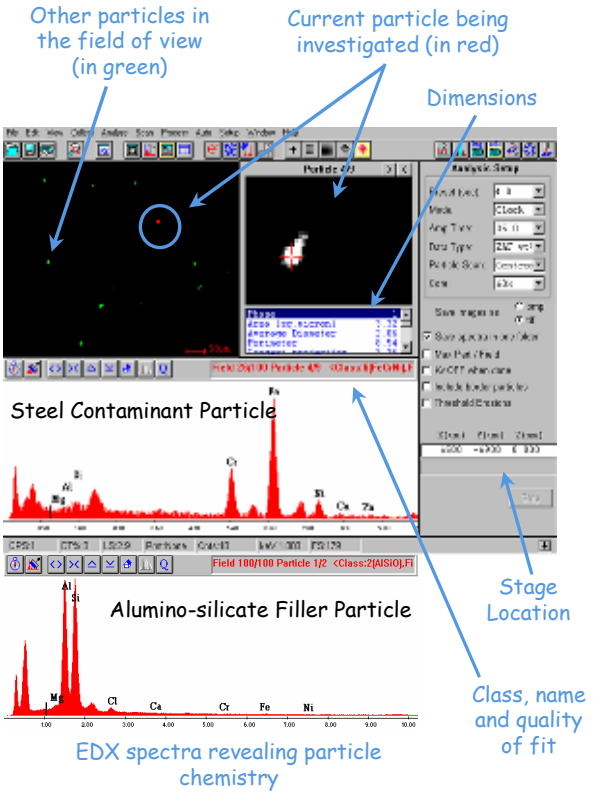


Fig.4. Typical output screen from automated analysis. Example EDX spectra are shown from two chemically distinct particles.

Fig.6. SEM / EDX Instrument used for particle counting

Measurement / Characterisation Solution

The SEM / EDX technique allows for the identification of the critical characteristics of particles. It offers the ability to gather information about finer particles than by optical microscopes and can readily distinguish between clusters and agglomerates of particles in addition to the chemical analysis available by EDX.

The strength of this analysis technique is its ability to gather statistically significant data on the size, morphology and composition of the particles in a time efficient manner, beyond the capabilities of conventional optical microscopy.

Talk to our experienced SEM staff to discuss your particle analysis needs.

Contact us today

Find out how we can help solve your problems in process improvement, process control and materials analysis

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