

PARTICLE CHARACTERISATION IN EXCIPIENTS, DRUG PRODUCTS AND DRUG SUBSTANCES

AUTHOR: HILDEGARD BRÜMMER, PhD, CUSTOMER SERVICE MANAGER, SGS LIFE SCIENCE SERVICES, GERMANY

Particle characterization has significance in many industries. For the pharmaceutical industry, particle size impacts products in two ways: as an influence on drug performance and as an indicator of contamination. This article will briefly examine how particle size impacts both, and review the arsenal of methods for measuring and tracking particle size. Furthermore, examples of compromised product quality observed within our laboratories illustrate why characterization is so important.

INDICATOR OF CONTAMINATION

Controlling the limits of contaminating particles is critical for injectable (parenteral) solutions. Particle contamination of solutions can potentially have the following results:

- Adverse direct reactions: e.g. particles are distributed via the blood in the body and cause toxicity to specific tissues or organs, or particles of a given size can cause a physiological effect blocking blood flow e.g. in the lungs.

- Adverse indirect reactions: particles are identified by the immune system as foreign material and immune reaction might impose secondary effects.

In order to protect a patient and to guarantee a high quality product, several chapters in the compendia (USP, EP, JP) describe techniques for characterisation of limits. Some of the most relevant chapters are listed in Table 1.

Particle characterisation of drug substances, drug products and excipients is an important factor in R&D, production and quality control of pharmaceuticals. It is becoming increasingly important for compliance with requirements of FDA and European Health Authorities.

TABLE 1. RELEVANT CHAPTERS IN COMPEDIA RELATING TO PARTICLE SIZE

COMPENDIUM		TITLE
EP	2.9.19	Particulate contamination - Sub-Visible Particle
EP	2.9.31	Particle Size Analysis by Laser Light Diffraction
EP	2.9.37	Optical Microscopy
EP	2.9.38	Particle - Size Distribution Estimation by Analytical Sieving
USP	<766>	Optical Microscopy
USP	<786>	Particle Size Distribution Estimation by Analytical Sieving
USP	<788>	Particulate Matter in Injections
USP	<789>	Particulate Matter in Ophthalmic Solutions
USP	<811>	Powder Fineness
JP	3.04	Particle Size Determination by optical microscopy for morphological appearance and shape of individual particles
JP	6.03	Particle Size Distribution Test Preparation
JP	10	Laser Diffraction Measurement of Particle Size
JP	11/12	Powder Particle Size Determination

PARTICLE SIZE AND DRUG PERFORMANCE

Particle size of drug substances and pharmaceutical excipients have an influence on chemical and physical behaviour. Particle size is therefore relevant for the behaviour of powders, granulates, creams, emulsions, liquids, etc. in relation to:

- Bioavailability
- Flowability
- Adhesive strength
- Drying properties
- Solubility
- Filterability
- Thermal conductivity

Size analysis becomes particularly important with new drug delivery formats such as liposomes and nanoparticles. Size

analyses of these products are essential to achieving a homogeneous product, while optimal particle size and shape is product dependent.

Particle testing is specifically required during stability testing, prior to release of the drug into the market. In our laboratories, we have observed a few cases of altered solid products during stability testing.

- A decrease in particle size during stability testing resulting in higher weight as humidity adsorption increased.
- Prolonged storage influenced crystal growth and modification of the active ingredient. This growth was confirmed

by microscopy.

- Prolonged storage caused a decrease in particle size resulting in increased agglutination.
- Prolonged storage caused a change in particle size of a drug, negatively impacting content uniformity. The effect is especially important in cases of low API to excipient ratio.

Similar examples can be related to liquid products.

- An emulsion separated into two phases due to an increase of particle size.
- Changes in particle size of eye drops were determined to have an influence on bioavailability and biocompatibility.

PARTICLE SIZE ANALYSIS

Several techniques are available for testing of particles. Table 2 gives an overview of available techniques and the range they work within.

TABLE 2. CURRENTLY AVAILABLE PARTICLE SIZE ANALYSIS TECHNIQUES AND PARTICLE SIZE RANGE

TECHNIQUE	MIN [μM]	MAX [μM]
Laser Diffraction Measurement by Malvern Mastersizer 2000	0.02	2000
Scanning Electron Microscopy	0.5	5000
Optical Microscopy	1	10
Time of Flight	5	250
Air-Jet-Sieving	20	500
Mechanical Sieving	35	4000

The most common method for particle size distribution is the **Laser Diffraction Measurement**. The laser diffraction method is suitable for highly accurate determination of particle sizes in a range of 0.02 μm to 2000 μm . The technique is based upon the beam diffraction phenomenon (Fraunhofer diffraction). In

practice the particles are passed through a focused laser beam, and these particles scatter light at an angle that is inversely proportional to their size. The angular intensity of the scattered light is then measured by a series of photosensitive detectors.

In our laboratory, we use this instrument for dry powders as well as for well-dispersed samples and solutions (e.g. slurries or samples that need to be measured wet in order to achieve good particle distribution). Typical diagram of a particle size distribution investigation is shown in Figure 1.

FIGURE 1. EXAMPLES OF PARTICLE SIZE DISTRIBUTION:

0.2 – 1 mm

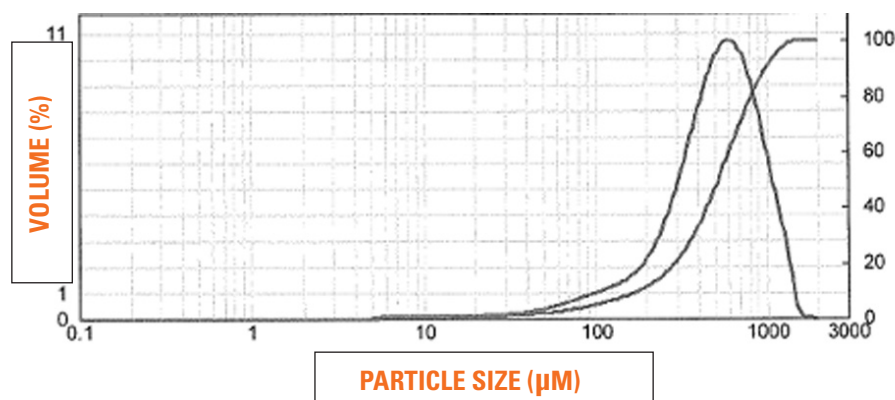
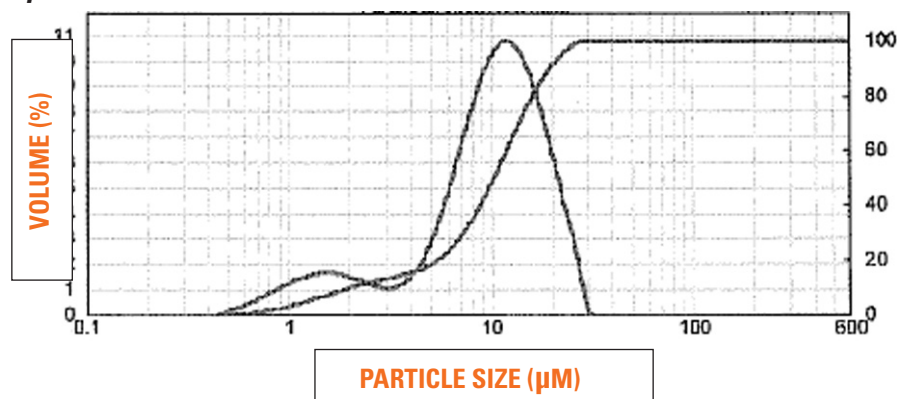


FIGURE 1. EXAMPLES OF PARTICLE SIZE DISTRIBUTION:**5 – 20 μm** 

In this example, two particle size classes (e.g. 0.1 – 1 mm and 5 – 20 mm) are shown. The actual measurement of the number of particles in a given range and the cumulative curve is represented.

For larger particles, analytical sieving methods can be used. The European Pharmacopeia classifies powders according to their fineness. Table 3 summarizes the different types of

powders. Our laboratory has established tests for various powders and granulates.

TABLE 3. POWDER CLASSIFICATION ACCORDING TO EUROPEAN PHARMACOPEIA

TYPE	%	SIEVE NUMBER	%	SIEVE NUMBER
Coarse powder	> 95	1400	≤ 40	355
Moderately fine powder	> 95	355	≤ 40	180
Fine powder	> 95	180	≤ 40	125
Very fine powder	> 95	125	≤ 40	90

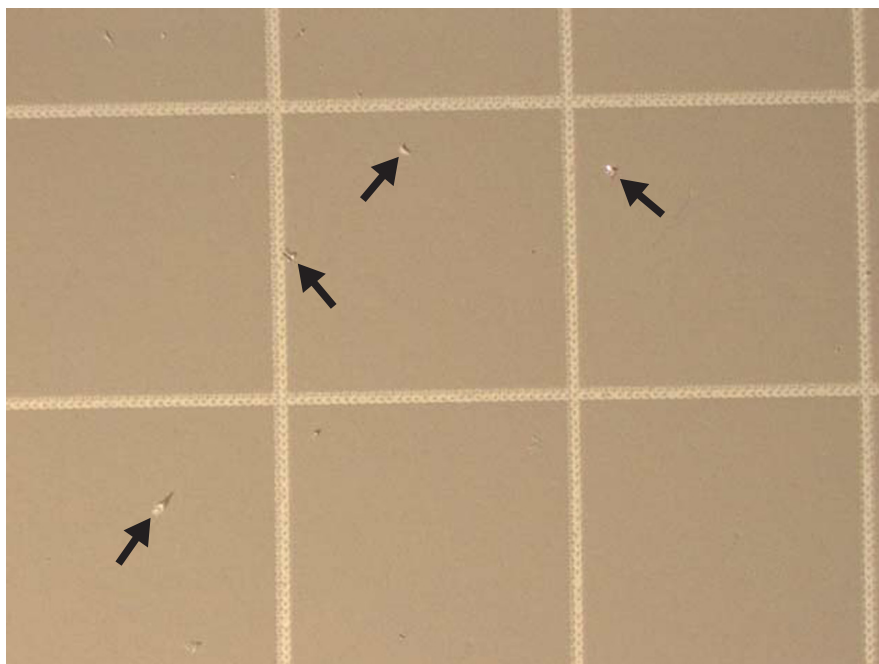
There are two main types of sieving: Mechanical Sieving and Air-Jet-Sieving. Mechanical sieving is carried out by stacking the sieves in ascending order of aperture size and placing the powder on top of the sieves. With Air-Jet-Sieving, the powder is fluidized and collected by application of negative pressure. A wide range of sieve sizes are described in USP, EP and JP. In general, our laboratories conduct mechanical sieving for particles larger than 75 μm and for smaller particles air-jet sieving or sonic sieving.

Should further characterisation of particles be required, optical microscopy methods

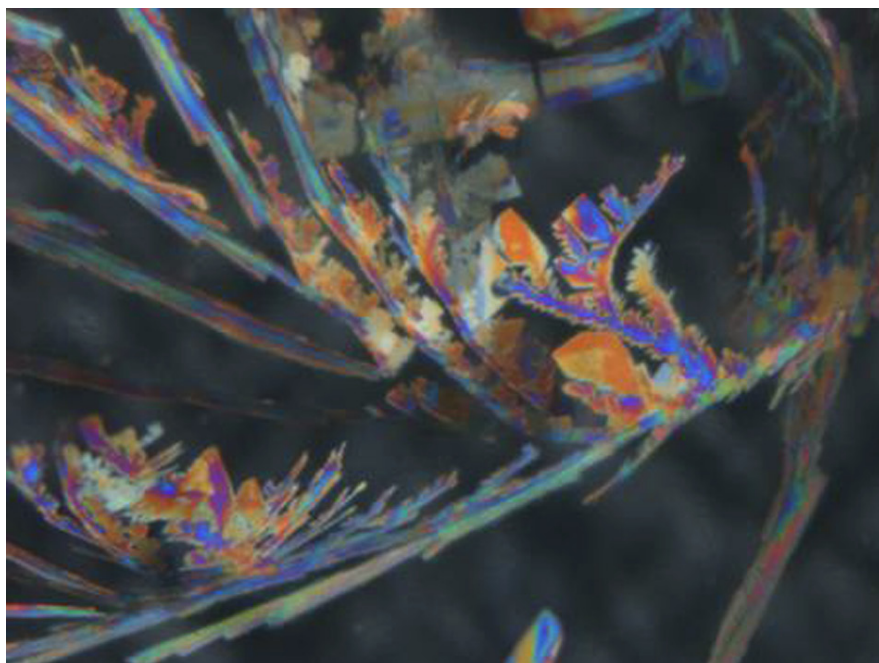
can be used to gain more information on the shape and structure of the particles. We utilize microscopy to describe morphological appearance, shape, size of particles and their distribution in APIs and excipients. Microscopic investigations can generally be applied to particles of 1 μm and larger. Optical microscopy is particularly useful for characterisation of particles that are not spherical.

In order to measure particle size, an ocular micrometer is inserted and a calibrated stage micrometer is placed at the centre of the microscope stage and fixed in place. The ocular is adjusted to

the focus point of the stage micrometer scale. Then the distance between the scales of the two micrometers is determined and the particle size is calculated. Particle number can also be calculated by counting particles within the grid of the micrometer. Figure 2 illustrates a typical field of a membrane filter carrying the particulate matter in a parenteral solution. Several particles of different shape are marked by an arrow.

FIGURE 2. PARTICULATE CONTAMINATION IN A PARENTERAL SOLUTION

Optical microscopy can also be used to investigate particles surfaces for re-crystallization of drug products (e.g. patches). Typical recrystallization of an API observed during stability storage is shown in Figure 3.

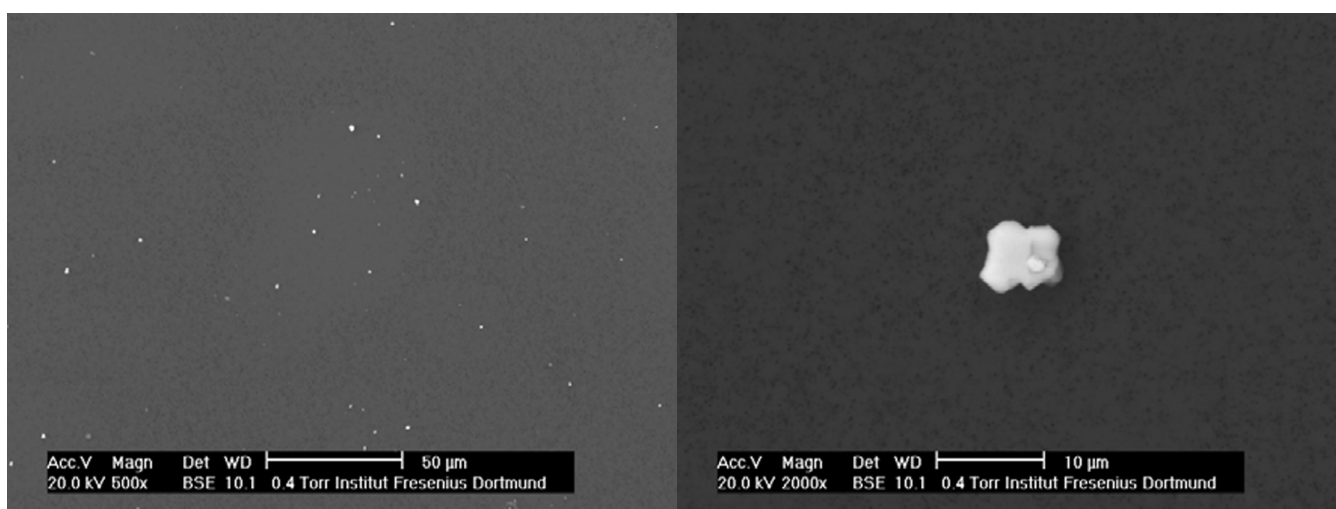
FIGURE 3. RECRYSTALLIZATION OF AN API ON A PARTICLE SURFACE

The Environmental Scanning Electron Microscopy (ESEM), with integrated Energy Dispersive X-ray microanalysis (EDX) for high resolution imaging and element analysis, is a new generation scanning electron microscope (SEM). ESEM allows for collecting information regarding particle size and shape. Consequently, this technique could be used for stable nanosuspensions for intravenous injections. In addition, single particles can be isolated and evaluated regarding to shape.

While for conventional SEMs, samples must be suitable for high-vacuum and electroconductive. In contrast, using ESEM, damp samples, greasy/fatty and isolating materials can be observed at high resolutions and analysed without the otherwise necessary preparations. The image is achieved by secondary electrons (SE - topography contrast) or by back scattered electrons (BSE - material contrast). The EDX system applied allows for detecting elements of atomic number of 5 (boron) or higher.

Typical pictures of a filter surface and a selected particle are shown in Figure 4. On the left, an overview image is shown with the distribution of particles (bright spots). By EDX it is possible to determine the elemental composition of each particle. On the right a detailed image of one selected particle is depicted which shows its crystalline morphology.

FIGURE 4. PARTICLES VIEWED WITH ESEM (ENVIRONMENTAL SCANNING ELECTRON MICROSCOPY)



ANALYSIS OF VISIBLE AND SUBVISIBLE PARTICLES

Prior to any analytical investigation, methods for visual examination of injections and infusions are established. Testing these particles involve a special system consisting of a black and white panel and a white-light source with defined intensity of illumination.

For the determination of particulate contamination, we have established two procedures in our laboratory: "Light Obscuration Particle Count Test (method 1)" and "Microscopic Particle Count Test (method 2)." In some cases, we utilize both methods in order to achieve conclusive determination against the EP/

USP requirements. Unfortunately, not all preparations can be tested by method 1. Solutions with reduced clarity, containing air bubbles or increased viscosity must be tested using method 2.

SUMMARY

Particle analysis is an increasingly important parameter in API and excipient characterisation. Depending on the formulation, various techniques and approaches are available. Pharmacological behaviour of drug product can be influenced by changes in particle size and structure. In addition, information

concerning potential contamination of injections and infusions is required as part of the safety assessment of the drug. Therefore, an intensive study of API and excipient particle size, from the drug development to manufacturing, can facilitate the development of safe, stable and efficient products.

SGS Life Science Services offers the techniques reviewed in the article for particle characterisation. With the established techniques and experience in particle analysis, SGS's scientific staff is able to deliver a high quality particle analysis on your product.

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CONTACT INFORMATION

EUROPE

BELGIUM

+32 10 42 11 11
be.pharmaqc@sgs.com

FRANCE

+33 1 41 06 95 93
fr.pharmaqc@sgs.com

GERMANY (TAUNUSSTEIN)

+49 6128 744 245
de.pharmaqc@sgs.com

GERMANY (BERLIN)

+49 30 3460 7500
de.pharmaqc@sgs.com

ASIA

INDIA

+91 44 2254 2601
in.pharmaqc@sgs.com

THAILAND

+662 294 7485 9
th.pharmaqc@sgs.com

SINGAPORE

+65 677 53 034
sg.pharmaqc@sgs.com

CHINA

+86 21 6115 2197
cn.pharmaqc@sgs.com

TAIWAN

+886 2 2299 3279 ext 2500
tw.pharmaqc@sgs.com

NORTH AMERICA

CANADA

+ 1 905 364 3757
ca.pharmaqc@sgs.com

USA (FAIRFIELD, NJ)

+ 1 888 747 8782
us.pharmaqc@sgs.com

USA (LINCOLNSHIRE, IL)

+1 847 564 8181
us.pharmaqc@sgs.com

WWW.SGS.COM/PHARMAQC