BIO & PHARMA ANALYTICAL TECHNIQUES

Chapter 5 Particle Size Analysis

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Chapter Description

- Aims
  - Discuss theory, principles and application of analytical techniques used in material characterisation, pre-formulation development, manufacturing process and storage stability.

- Expected Outcomes
  - Explain the definition of particle analysis, focusing on the particle size
  - Discuss on the influence and significance of particle analysis in pharmaceutical industry
  - Differentiate the advantages and disadvantages of each method in particle analysis

- References

  - Gunzler H. & Williams A. (2002). Handbook of Analytical Techniques. Wiley-VCH, Weinheim, Germany.
  - Mullertz, A., Perrie, Y. and Rades, T. (2016) Analytical Techniques in the Pharmaceutical Sciences (Advances in Delivery Science and Technology). Springer, United States.

What is Particle?

- A particle is an extremely **small constituents of matter / object** to which can be ascribed several physical properties.
- In relation to a pharmaceutical drug, *particle relates to a network of drug molecules bound to each other in a more or less structured manner - forming solid "clusters" (particles) such as powders.*
- Tablets and capsules used for pharmaceutical products are **"made of" particles of various particle sizes** in the form of powders.
- **Particle analysis = powder analysis**
- Particle analysis might be related to the active pharmaceutical ingredient (**API**), but also to the **excipients.**

Particle Characterisation

Analytical Purpose	Analytical Technique	Results
Structural Analysis	Optical microscopy SEM, TEM, BET	Size Detection of large particle Surface morphology (bulk & single) Porosity Surface area
Solid state Analysis	DSC Spectroscopy - Raman, IR, NIR Hot Stage microscopy	Polymorphism
Particle Size	Sieve, LD	
Rheological	Rheometer	Viscosity

- Particle size, shape, surface area and flowability characteristics → **critical properties** for a large number of pharmaceutical processes.

- The **higher rate of solubilization** - influenced by the small particle size, by a saturation effect of an API

- Only the **combination of the results** of different techniques will enable the developer to understand the system and to draw conclusions for factors such as physical stability.

- Thus, **appropriate techniques have to be selected** from a large variety of existing technologies.

Importance of Particle size

- **Particle Size Distribution** is a very important parameter as there is an **optimal size for each application**.
- Particle size can affect: **"Processability"** of powder (API, excipients) – flow, mixing, compaction…
- Particle size may also affect a **formulation's behaviour** during processing and its **content uniformity** (critical).
- For ex, the widespread operation of **direct compression** tableting; particle size can influence **segregation behaviour.**
- It is also affect the **consistency of composition and tablet weight.**

- **Size distribution** is also an important parameter which allows **understanding the heterogeneity** of particle sizes in a mixture.

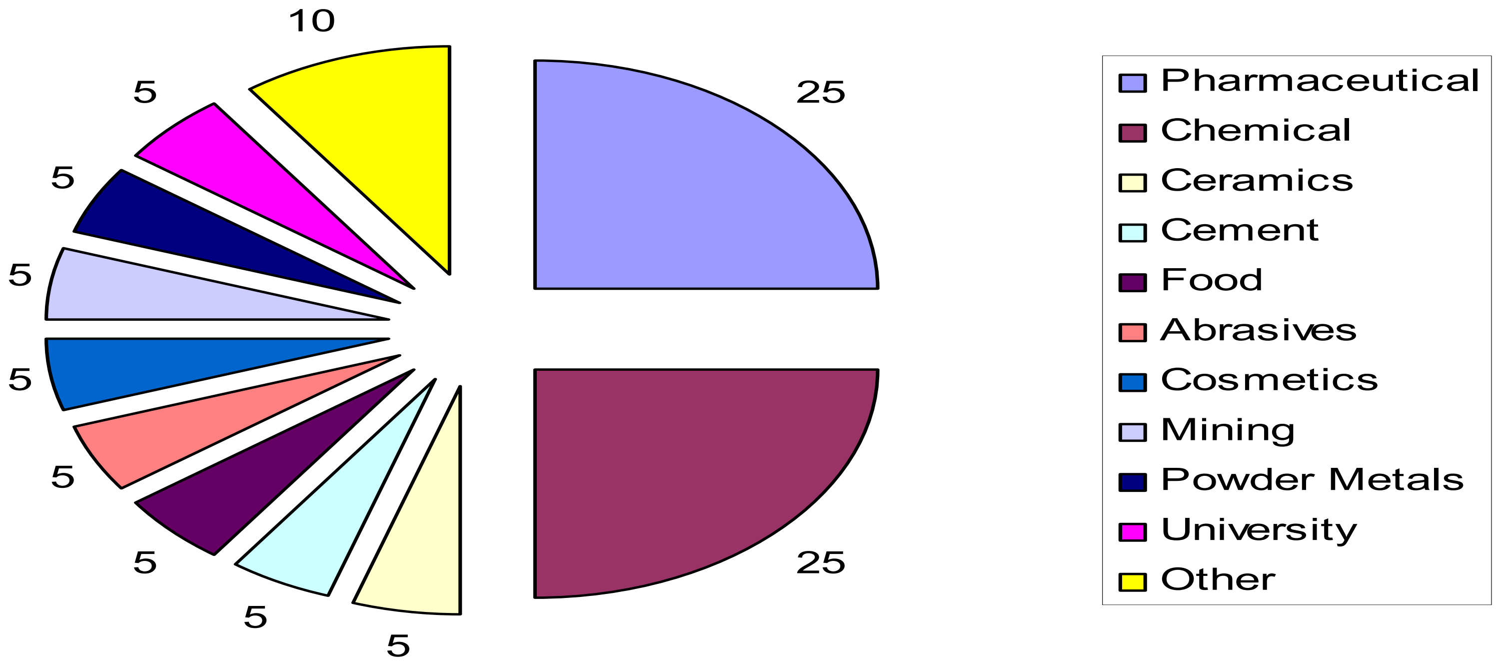
- A particle sample is **mono disperse** if all particles present the **same size**, whereas, a sample of particles that have **variable sizes** is known as **poly disperse**.

Importance of Particle Size?

The particle size distribution → **direct influence on material properties** such as:

1. Reactivity or dissolution rate – e.g. catalysts, tablets.
2. Stability in suspension – e.g. sediments (bioavailability)
3. Efficacy of delivery – e.g. asthma inhalers
4. Texture and feel
5. Appearance – e.g. powder coatings.
6. Flow ability and handling
7. Viscosity – e.g. nasal sprays
8. Packing density and porosity

Who cares about particle size?



Particle Size Analysis

Pharmaceutical particle size analysis, also known as particle sizing, determines the mean particle size within a powder sample.

Measurement of pharmaceutical particulate size is important for meeting compliance with international standard regulatory bodies.

Particle size analysis standards are used to calibrate the analytical equipment used to measure pharmaceutical particle

Laser diffraction and **sieving**: commonly-used methods of pharmaceutical particle size analysis.

Methods For Determining Particle Size

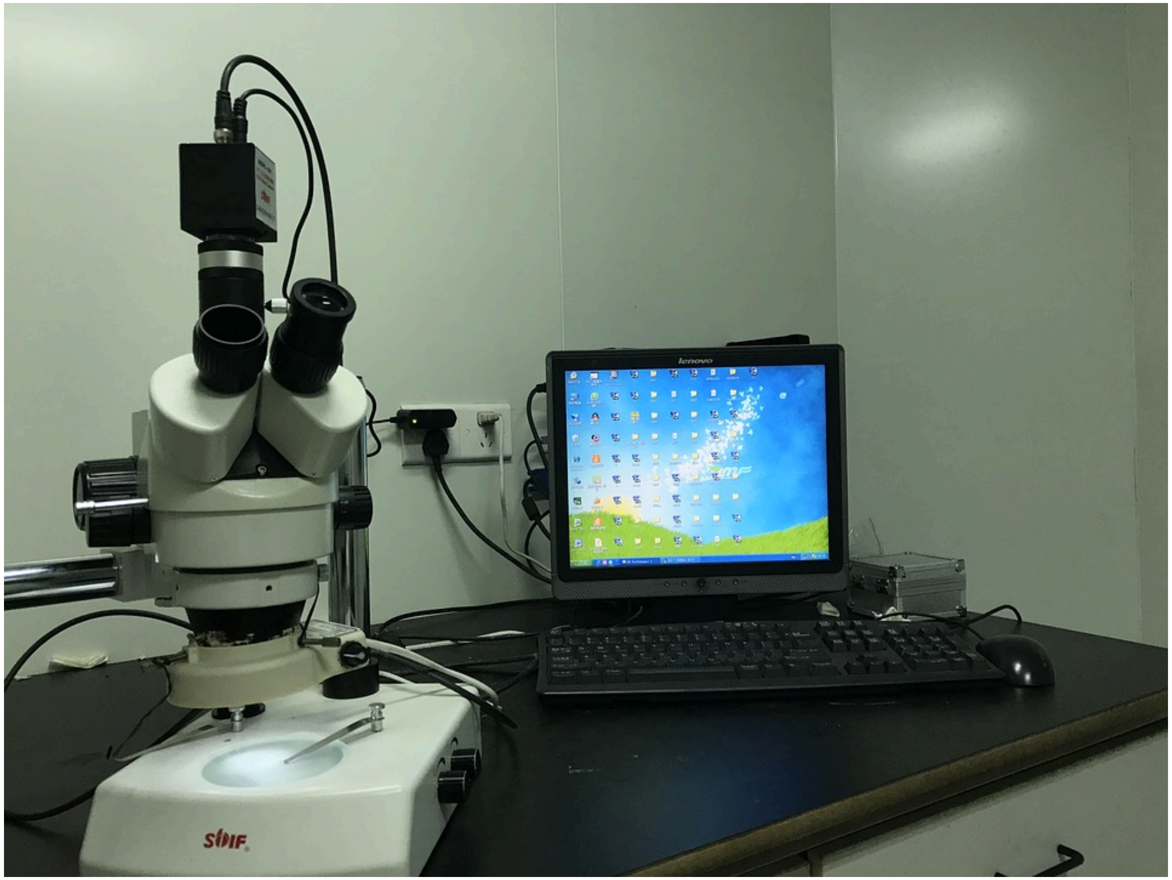
- Methods for determining the particle size:
  - Miscroscopy
  - Sieving
  - Laser/Light Diffraction Method

Method 1: Microscopy

- **Microscopy Optical microscopy** (1-150µm)
- to describe **morphological appearance, shape, size** of particles and their distribution in APIs and excipients. Microscopic investigations can generally be applied to particles of **1µm and larger.**

- **Electron microscopy** (0.001µ- 0.1nm)
- Examine each particle individually → as an absolute measurement of particle size.
- For submicron particles → either TEM or SEM

High Resolution Optical Microscope



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Electron Microscope

Scanning Electron Microscopy (SEM)

Transmission Electron Microscopy (TEM)

Manual Optical Microscopy

Advantages	Disadvantages
• Economical method • Each particle examined – detect aggregates, 2D shape, colour, melting point. • Permanent record – photograph • Small sample sizes required	• Time consuming • No information on 3D shape • Certain amount of subjectivity associated with sizing – operator bias

Transmission (TEM) and Scanning Electron Microscopy (SEM)

Advantages:

- Particles are individually examined
- Visual means to see sub-micron specimens
- Particle shape can be measured

Disadvantages:

- Very expensive
- Time consuming → sample preparation
- Materials such as emulsions difficult/impossible to prepare

METHOD 2: Sieving

- A sieve analysis: a practice used to **assess the particle size distribution** of a granular material.

- A sieve analysis can be performed on any type of non-organic or organic granular materials.

- Ex: sands, crushed rock, clays, granite, soil, **a wide range of manufactured powders**, grain and seeds - to a minimum size depending on the exact method.

- **Most common technique - simple**.

- Sieve analysis is performed - a **nest or stack of sieves** (each lower sieve has **a smaller aperture size).**

- Sieves → **aperture size** / **mesh size /** sieve number.

- Mesh size is No. **of wires per linear inch.**

- Approx. size range : 5µm - 3mm

- **Purpose:**
  - determine the percentage of different grain sizes,
  - determine the distribution of the coarser, larger-sized particles, and finer particles.

Two main types of sieving:

1. Mechanical Sieving

carried out by stacking the sieves in ascending order of aperture size and placing the powder on top of the sieves.

2. 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.

Advantages

- Easy to perform
- Wide size range
- Inexpensive

Disadvantages

- Less reproducibility
- Irregular/agglomerated particles

SIEVE SIZE

(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

METHOD 3: LIGHT/LASER DIFFRACTION

- **Laser diffraction (LD)**: a laser beam pass through the particles and the light scattered by them is collected over a range of angles in the forward direction.
- Using beam diffraction phenomenon (Fraunhofer diffraction)
- The light-scattering effect caused by the interaction of a laser beam with particles is measured by an array of detectors.
- The size distribution of the particles can be calculated using the principle that the angle of diffraction of the light is inversely proportional to the particle size.
- Similarly to sieve analysis particle characteristics other than size cannot be measured.

Advantages

- Non-intrusive: uses a low power laser beam.
- Fast : typically <3minutes to take a measurement and analyse.
- Precise and wide range - up to 64 size bands can be displayed covering a range of up to 1000,000:1 in size.
- Absolute measurement (no calibration is required).
- Simple to use.

Disadvantages

- expensive
- assuming spherical particles
- must be a difference in refractive indices between particles and suspending medium

Factors affected for particle size analysis

1. Nature of the material
2. Cost
3. Specification requirements
4. Time restriction

APPLICATION IN PHARMACEUTICAL INDUSTRY

Control of the API Starting Material

- The development of a drug product begins already with the quality control of the starting material.
- Often times micronized API is used as starting material for top-down processes in order to avoid clogging of the equipment.
- Clogging can occur in high pressure homogenizers in the tiny homogenization gap, or in continuously operated ball mills at the media screen, which separates the milling media from the
- It is often coupled with microscopic techniques to confirm the results.
- The objective is to test the **consistency of the particle size of the starting material.**

APPLICATION IN PHARMACEUTICAL INDUSTRY

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.

CONCLUSION OF THE CHAPTER

- **Particle size 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.
- 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**.

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Any Question?

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