Industrial Pharmacy 1
Introduction
Particle size analysis

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Credit: Prof. Nizar Al-Zoubi

formula → active agent + inactive agent.

milling → عملية الطحن
↳ if there a difference in the size between the agents.
↳ after milling there are seiving (تنخيل)
↓
mixing.
(depending on formula).
↓
الخلط يكون
Bulk
(production.

steps:
1. milling.
2. seiving.
3. mixing.
4. granulation
↓
give the best dosage form from tablet or capsules.
↓
by addition a liquid.
5. Drying & compression.
6. milling
7. mixing.

Introduction

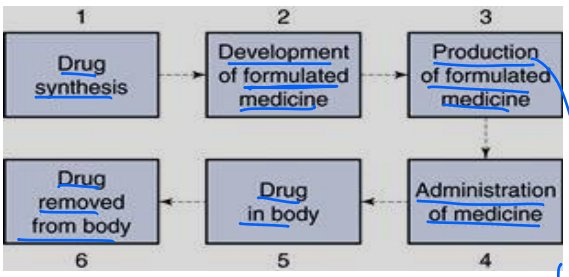
Categories of dosage forms

1. Solids: Powder, granulates, tablets, capsules

**** Powder, granules

1. Liquids: solutions, Suspensions, emulsions, etc
2. Semisolids: creams, ointments, etc.
3. Gaseous **

Particle size and the lifetime of a drug



* we can't mix a different size agent → seperation will happen.
* The formula also contain an excepient → have many functions.

*heat sensetive drugs ⟶ any drug contain protein. (insulin)

الطرق التقليدية لـ drying : oven

- تقنيات حديثة : frez drying

dosage form depending on manufacturing:

1. solid ⟶ powder, granules, tablet, capsules

لما بتحضر الـ capsules أو tablet إلى من powder or granules.

2. liquid.

3. semisolid

4. Gaseous. ⟶ anesthatic gases.

* شرب الأطفال الذي يتم حله عند الإستخدام:

(solid) powder ← as a dosage form عند عملية التصنيع

(liquid) suspension ← as a dosage form عند عملية الإستخدام also vial of injection.

drugs ⟶ naturaly
⟶ synthesis.

شرطين عشان الدوا يقدر يؤخذ الدواء:

1. it's give an action. ⟶ effective
2. Can remove from the body. ⟶ safe. (metabolism).

Function of excipient → 1. flowability.
(inactive agent.) → 2. important to give the stability and efficacy → 3. dosage form.

* granulation is a important step in potant drug.

Powders and granules

granules → aggregation of particles by using Binder.

- The term 'powder' when used to describe a dosage form describes a formulation in which a drug powder has been mixed with other powdered excipients to produce the final product.
- The function of the added excipients depends upon the intended use of the product (ex. Colors, flavors, sweetening agents may be added to powders for oral use).
- Granules which are used as a dosage form consist of powder particles that have been aggregated to form a large particle, which is usually 2 – 4 mm in diameter.

Powder → فعالة / excipient → غير فعالة

sphirical تكون granules

* مش شرط كلها نفس الحجم

Powders and granules

- Powders and granulated dosage forms are traditionally dispensed as:
  a. Bulk powders or granules for internal use (العبوة فيها كذا جرعة)
  b. Divided powders or granules (i. e. single preparation) for internal use (Sachet)
  c. Dusting powders for external use. (Baneocine (fine) → ما بتعمل irritation)
  d. Insufflations for administration to ear , nose or throat
  e. Antibiotic syrups to be reconstituted before use (liquid بعد الاستخدام (suspension))
  f. Powders for reconstitution into injections (added sline or water for injection when we use)
  g. Dry powder inhalers (→ asthmatic device.)

ملح انجليزي

antibiotic

Powders and granules

Advantages of powders and granules as a dosage form

1. Solid preparations are more chemically stable than liquid ones.
2. Powders and granules are a convenient form in which to dispense drugs with a large dose (ex. Mg trisilicate oral powder dose is 1 – 5 g).
3. Orally administered powders and granules of soluble medicament have a faster dissolution rate than tablets and capsules.

Powders and granules

Disadvantages of powders and granules

1. They are less convenient to carry than a small container of capsules and tablets (except laminated sachets).
2. The masking of unpleasant taste may be a problem.
3. They are not suitable for administration of potent drugs with a low dose.
4. They are not suitable for the administration of drugs which are inactivated in, or cause damage, to the stomach.

Powders and granules

Dispensed preparations:

Bulk powders

- The mixed ingredients are packed into a suitable bulk container, such as wide-mouthed glass jar.
- The constituents are usually relatively non-toxic medicaments with a large dose.

Divided powders

- Divided powders are similar formulations to bulk powders but individual doses are separately wrapped.
- Modern packaging materials of foil and plastic laminates have replaced paper wrapping.

Powders and granules

Bulk granules

- Segregation, If present in bulk powders, can be prevented by granulation.
- Bulk granules contain similar medicaments to powders (I.e. those with low-toxicity, high dose drugs).

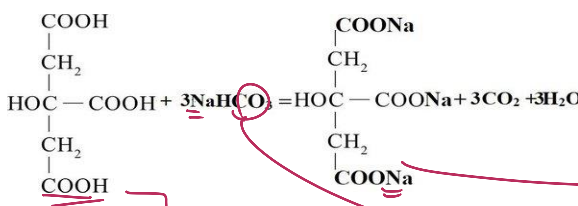
Divided granules

- These are granulated products in which amount sufficient for one dose is individually wrapped.
- Effervescent granules can be presented in this manner

Effervescent granules

- Effervescent pharmaceutical preparations generally contain acid substances and a source of CO_2 (carbonates or bicarbonates salts of sodium, potassium and calcium).

- Traditional acid materials are the citric and tartaric acid. However, ascorbic acid, fumaric acid and acetylsalicylic acid may be used.



citric acid.

Preparation of effervescent granules

Wet Granulation Methods

- The acid and carbonate parts of the effervescent formulation can be granulated either separately or as a mixture with water (crystal water of citric acid, liquid water, or water vapor), ethanol (possibly diluted with water), isopropanol, or other solvents.

Dry Granulation

- Granulation by slugging or roller compaction is suitable for active ingredients that cannot be wet granulated.

Powders and granules

Dusting powders

- Dusting powders contain ingredients used for therapeutic, prophylactic, or lubricant purposes and are intended for external use.
- Only sterile dusting powders should be applied to open wounds.
- Dusting powders for lubricant purposes or superficial skin conditions need not be sterile but they should be free from pathogenic organisms.
- Containers: glass, plastic or metal containers with a perforated lid.
- The powder must flow well from such a container, so that they can be dusted over the affected area.
- The active ingredients must therefore be diluted with materials having reasonably good flow properties, e.g. purified talc or maize starch.

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Powders and granules

Insufflations

- Insufflations are medicated powders which are blown into regions such as the ear, nose and throat using an insufflator.
- The use of traditional insufflations had declined because:
  1. – They are not very acceptable
  2. – Dose non-uniformity (if the drug has systemic activity).
- Some potent drugs are now presented in this way because they are rapidly absorbed when administered a fine powder via the nose.

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Powders and granules

Dry powder inhalers

- The use of dry-powder systems for pulmonary drug delivery is now extensive.

- This dosage form has developed into one of the most effective methods of delivering active ingredients to the lung for the treatment of asthma and chronic obstructive pulmonary disease.

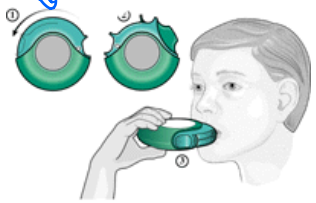

Figure 1: Diskus

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Powders and granules

Oral antibiotic syrups

- For patients who have difficulty in taking capsules and tablets, e.g. young children, a liquid preparation of a drug offers a suitable alternative.
- However many drugs, e.g. antibiotics, are physically or chemically unstable when formulated as a solution or suspension.
- The method used to overcome this instability problem is to manufacture the dry ingredients of the intended liquid preparation in a suitable container in the form of a powder or granules.
- When pharmacist dispenses the product, a given quantity of water is added to reconstitute.
- Shelf life of reconstituted syrup is 1-2 weeks.

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Powders and granules

Powders for injection → Content of excipient The least

- Injections of medicaments that are unstable in solution must be made immediately prior to use and are presented as sterile powders in ampoules.

لـ عشان يكون عندي فعالات كبير اثناء عملية التصنيع ← لأنها لازم تكون very sterial.

- Sufficient diluent, e.g. sterile water for injection, is added from a second ampoule to produce the required drug concentration.

should add normal saline. → to give isotonicity → عشان يكون pH الـ مقبول وما يعمل pain or shrink or swell for RBCs.

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Particle size analysis

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Particle size and the lifetime of a drug

Particle size influence :

- mixing (content uniformity for potent drugs, segregation)
- powder flow
- tabletability
- Bulk volume
- drug release into solution.
  - (e.g. griseofulvin, tolbutamide, spironolactone, indomethacin and nifidipine)
  - Nitrofurantoin optimal particle size is 150 µm
  - ** **practically insoluble** in water

Particle size and the lifetime of a drug

Particle size influence

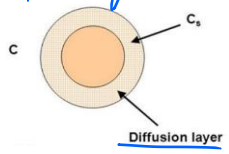
- The properties and behavior of various dosage forms:
  - suspensions: sedimentation rate, texture, taste, rheology
  - parenteral suspensions: *syringeability*, injectability and sustained release.
  - ophthalmic suspensions: irritation of the eye surface (small particle size is used)
  - inhalation aerosols: The position and retention of particles in the bronchopulmonary tract
  - topical formulation: grittiness (powder must be impalpable)

Effect of particle size on dissolution rate

Noyes & Whitney equation:

$$\frac{dM}{dt} = \frac{DS}{h}(C_s - C)$$

dM/dt: rate of dissolution
(Change of the dissolved amount with time)
C_S is the solubility of solute
C is the concentration of solute at time, t
Cs-C =concentration gradient
D is the diffusion coefficient of the solute in solution,
S is the surface area of the exposed solid ⇒ inversely proportional to particle size
h is the thickness of the diffusion layer.

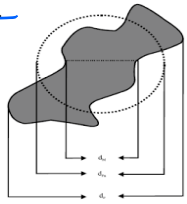


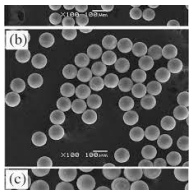
Particle size

- When determining the size of large solid usually we need to measure at **least three dimensions**.

- When determining the size of regular particles like spheres or cubes, it is possible to describe the size using one dimension (diameter or length).

- If the particles are mono-sized (have the same size) then it is possible to describe the particle size by measuring one particle.



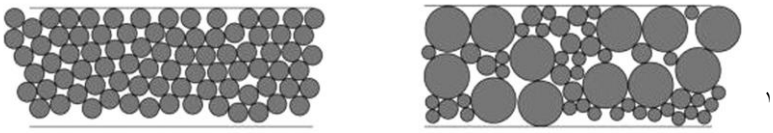


Particle size

- However powders generally are composed of particles that are:
  1. – irregular in shape
  2. – with different sizes
  3. – Are very small in size to allow measuring of dimensions .

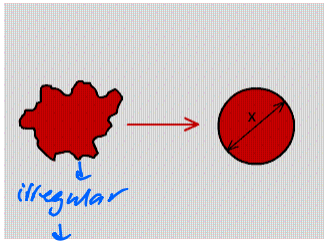
- In order to give good representation the size of relatively large number of particles should be determined.

(s) (p)



Particle size

- For these reasons it is impractical to measure more than one dimension.
- For this reason, solids are considered to approximate to a **sphere**, which can then be characterized by determining its diameter.
- This is an approximate representation of the particle size and is referred to as ***equivalent diameter*** of the particle.



Equivalent diameters

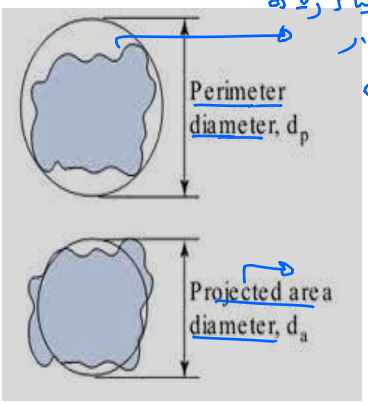
peri ← عشاء

Projected perimeter diameter (d_p)

- The diameter of a circle that has the same perimeter as the projected image of the particle.

Projected area diameter (d_a)

- The diameter of a circle that has the same area as the projected image of the particle.



Equivalent diameters

Feret's diameter (d_F)

- The mean distance between two parallel tangents to the projected particle perimeter

Martins diameter (d_M)

- The mean length of the chord separating the projected particle into two equal areas.

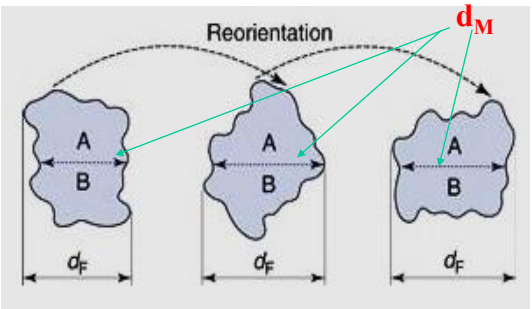


Fig. 10.3 Influence of particle orientation on statistical diameters. The change in Feret's diameter is shown by the distances, d_F; Martins diameter d_M corresponds to the dotted lines in the midpart of each image.

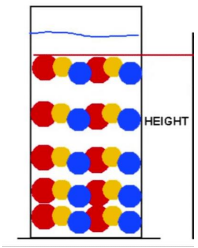
Equivalent diameters

Volume diameter (d_v)

- The diameter of a sphere that has the same volume as the particle.

Stokes diameter (d_{st})

- The diameter of a sphere that has the same sedimentation rate as the particles



Sieve diameter (d_s)

- The particle dimension that passes through a square aperture

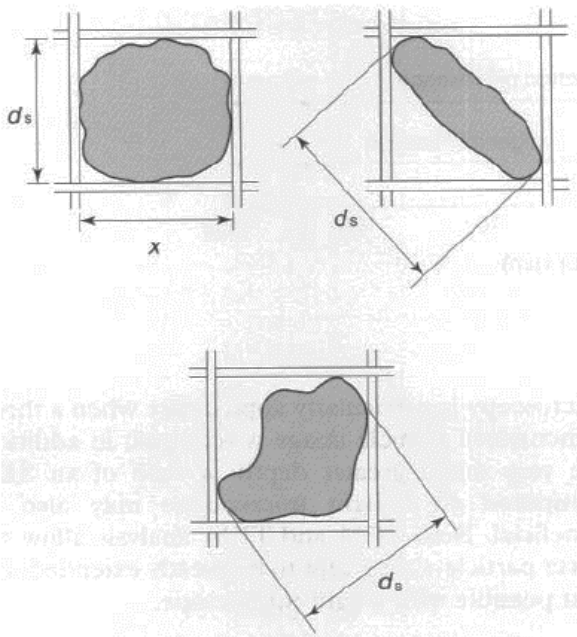
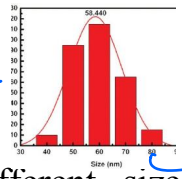


Fig. 10.7 Sieve diameter d_s for various shaped particles

Description of particle size

Mean particle size

- The mean particle size of an analyzed sample can be considered as a rough description for the size of sample.



Particle size distribution

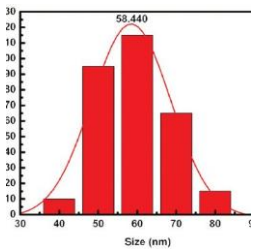
- The distribution of particles into different size ranges can be plotted in the form of histogram.
- A histogram presentation allows different particle size distributions to be compared.
- The value of the peak is the ***mode*** (highest frequency)

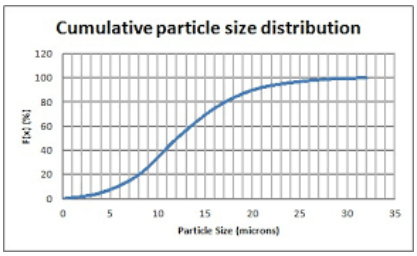
Presentation of size distribution

1) Frequency distribution data

2) Cumulative frequency distribution data

They are either under size or oversize





1) Frequency distribution data

Presentation of size distribution

Number and weight distributions

- Frequently, we are interested in obtaining data based on a weight, rather than a number distribution.
- This can be obtained directly by methods such as *sieving* and *sedimentation*.
- Number distribution can be **converted** to weight distributions and vice versa.

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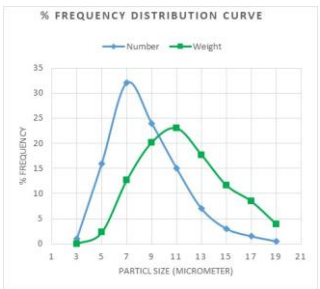
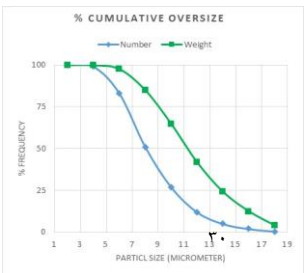
(1) size range	(2) Mean of size range, d (μm)	(3) Number of particles in each size range, n	(4) Percent n	(5) nd3	(6) Percent nd3 (Weight)	(7) Cumulative percent frequency undersize (Number)	(8) Cumulative percent frequency undersize (Weight)	(9) Cumulative percent frequency oversize (Number)	(10) Cumulative percent frequency oversize (Weight)
2.0-4.0	3	2	1	54	0.03	1	0.03	100	100
4.0-6.0	5	32	16	4000	2.31	17	2.34	99	99.97
6.0-8.0	7	64	32	21952	12.65	49	14.99	83	97.66
8.0-10.0	9	48	24	34992	20.16	73	35.15	51	85.01
10.0-12.0	11	30	15	39930	23.01	88	58.16	27	64.85
12.0-14.0	13	14	7	30758	17.72	95	75.88	12	41.84
14.0-16.0	15	6	3	20250	11.67	98	87.55	5	24.12
16.0-18.0	17	3	1.5	14739	8.49	99.5	96.04	2	12.45
18.0-20.0	19	1	0.5	6859	3.95	100	99.99	0.5	3.96
		Σ n = 200	100	173534	99.99				





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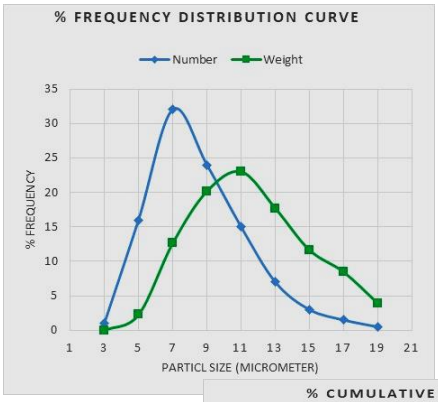

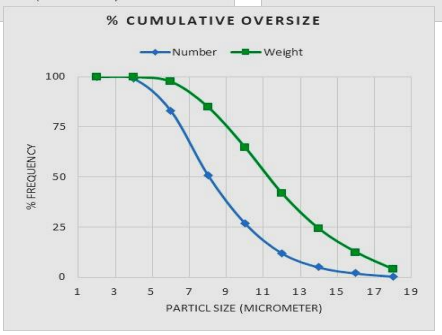

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Description of particle size

Types of distributions

- ***Normal distribution***: The mode separates the curve into two symmetrical halves.
- ***Positively skewed***: A frequency curve with an elongated tail towards the higher size range.
- ***Negatively skewed***: A frequency curve with an elongated tail towards the lower size range.
- ***Bimodal***: The frequency curve containing two peaks (two modes)

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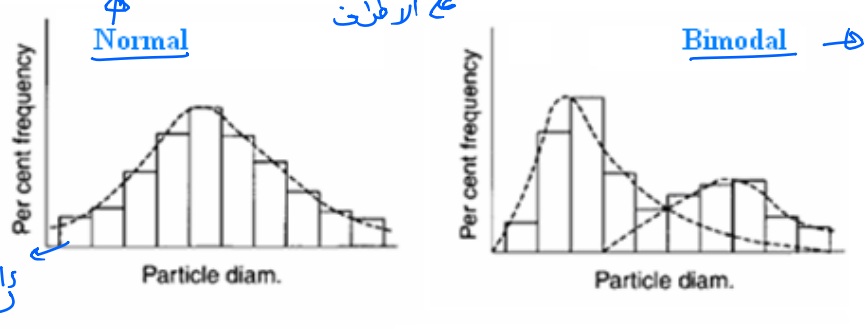

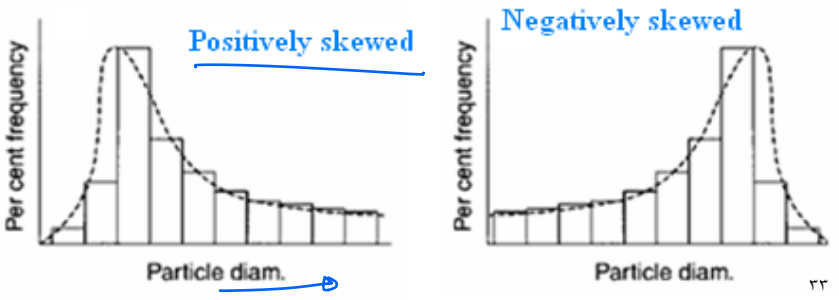

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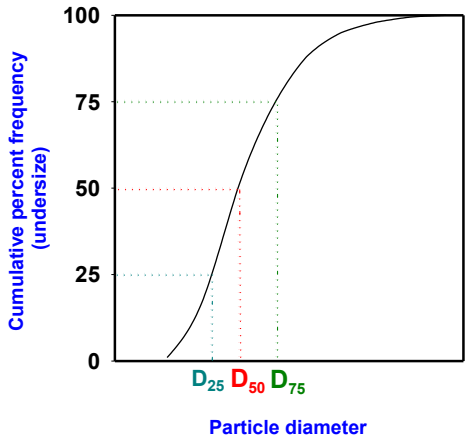
يعطيكم العافية زميلتكم
مرام الزيادي

Presentation of size distribution

Evaluation of degree of skewness

- The degree of skewness can be estimated by determining interquartile coefficient of skewness (*IQCS*)



$$IQCS = \frac{(D_{75} - D_{50}) - (D_{50} - D_{25})}{(D_{75} - D_{50}) + (D_{50} - D_{25})}$$

Cumulative frequency distribution curves.

Point D_{50} corresponds to the median diameter; D_{25} is the lower quartile point and D_{75} is the upper quartile point.

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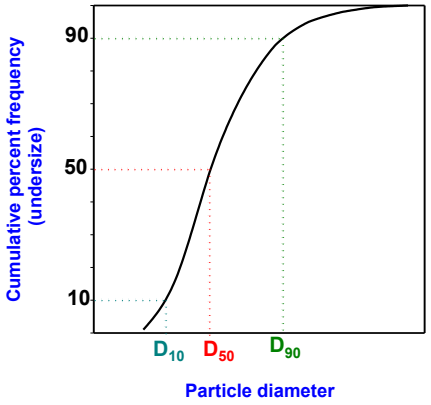
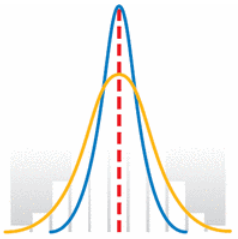
Presentation of size distribution

Evaluation of distribution width

- The size distribution width can be estimated by determining **Span**



$$Span = \frac{D_{90} - D_{10}}{D_{50}}$$



- **Note**: D_{90}, D_{50}, D_{10} are values corresponding to 90, 50 and 10% in the cumulative undersize curve.

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Particle size analysis methods

Microscope methods

Equivalent diameters

d_a, d_p, d_F and d_M can be determined

Range of analysis

- Light microscope (1 - 1000 μm)
- Scanning electron microscope (0.05 - 1000 μm)
- Transmission electron microscope (0.001 - 0.05 μm)

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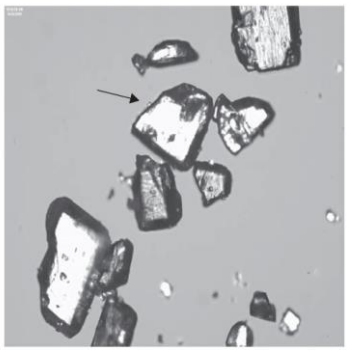

Image by light microscope

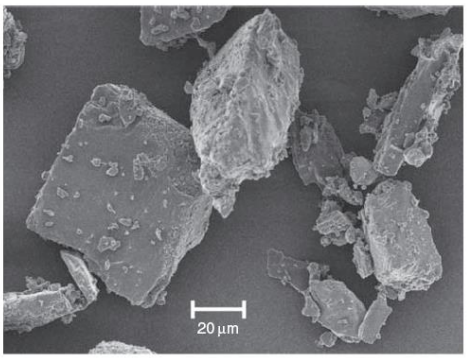

Image by scanning electron microscope(SEM)

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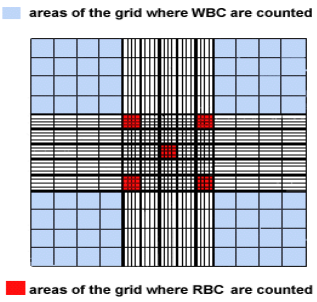
Particle size analysis methods

Microscope methods



Sample preparation

Techniques

- manual
- Semiautomatic
  - Particle comparator
  - Image shearing eyepiece (double prism arrangement)
- Automatic
  - A video camera is used to transform the image to a microprocessor where manipulations and calculations are done

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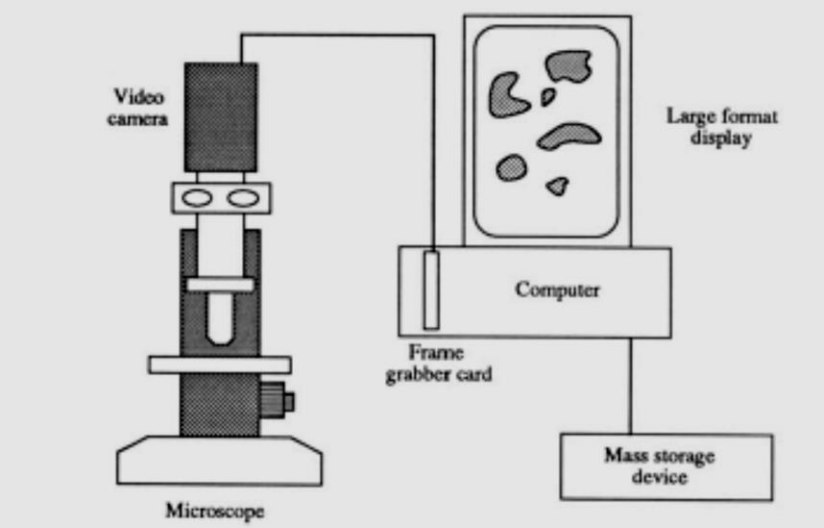

Figure 10.4. Typical image processing system.

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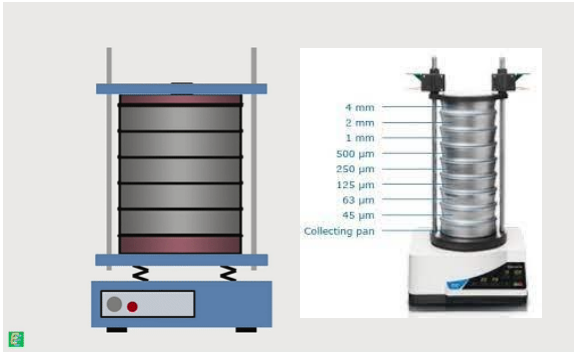
Particle size analysis methods

Sieve methods



Equivalent diameter

Sieve diameter (d_S)

Range of analysis

Available range: (5 - 125 000 µm)

ISO range: (45 - 1000 µm)

Sample preparation

Dry sieving: for non cohesive powders

Wet sieving: for suspensions and cohesive powders

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Particle size analysis methods

Sieve methods

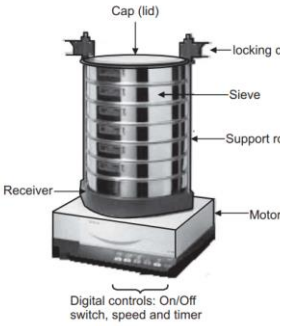
Techniques

1) Vibrated sieving:

- Uses a sieve stack (usually 6 –8 sieves)
- The Particles are retained on sieve mesh corresponding to the sieve diameter.

2) Air-jet sieving:

- Uses individual sieves starting from that of smallest aperture.
- Vacuum is applied to encourage particles to pass through sieves.



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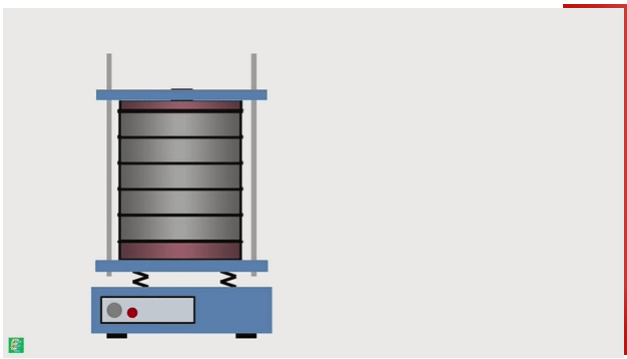

Vibrated sieving:

Air-jet sieving:

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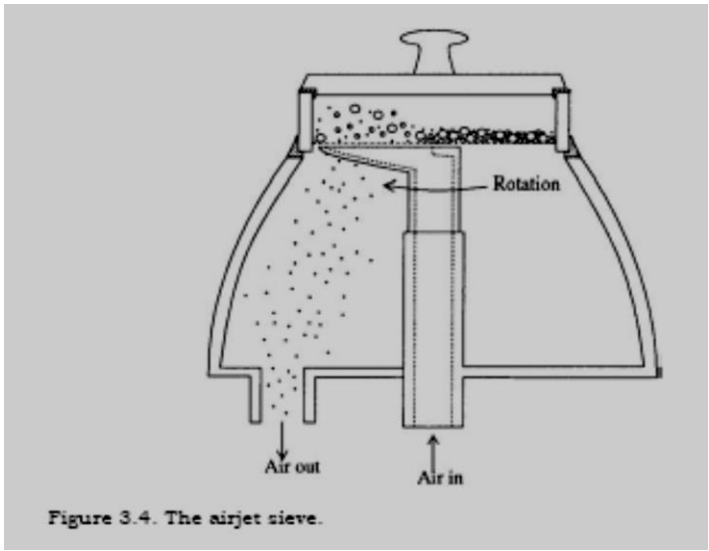

Figure 3.4. The airjet sieve.

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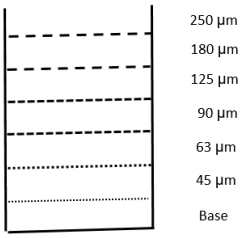
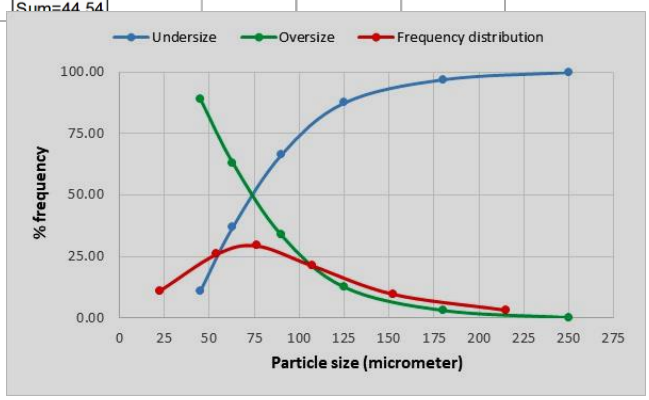
(1) Sieve size range (μm)	(2) mean of size range	(3) Sieve fractions		(4) Nominal aperture size (μm)	(5) % Cumulative undersize	(6) % Cumulative oversize
		wt (g)	wt%			
>250		0.02	0.04	250	99.96	0.04
180-250	215	1.32	2.96	180	96.99	3.01
125-180	152.5	4.23	9.50	125	87.49	12.51
90-125	107.5	9.44	21.19	90	66.30	33.70
63-90	76.5	13.1	29.41	63	36.89	63.11
45-63	54	11.56	25.95	45	10.93	89.07
<45	22.5	4.87	10.93	0	0	100
		Sum=44.54				





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Standards for powders based on sieving

- Standards for pharmaceutical powders are provided in **pharmacopoeiae**, which indicate the degree of coarseness or fineness depending on percentage passing or not passing through certain sieves.
- e.g. BP

Table 12.1 Powder grades specified in British Pharmacopoeia

Description of grade of powder	Coarsest sieve diameter (μm)	Sieve diameter through which no more than 40% of powder must pass (μm)
Coarse	1700	355
Moderately coarse	710	250
Moderately fine	355	180
Fine	180	—
Very fine	125	—

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Standards for powders based on sieving

- Some Pharmacopoeia define another size fraction, known as 'ultrafine powder'.
- In this case it is required that the maximum diameter of at least 90% of the particles must be no greater than 5 μm and that none of the particles should have diameters greater than 50 μm.

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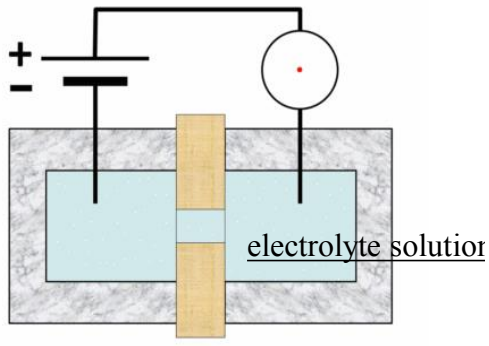
Particle size analysis methods

Electric stream sensing zone method (Coulter counter)

Equivalent diameter:

Volume diameter (d_v)



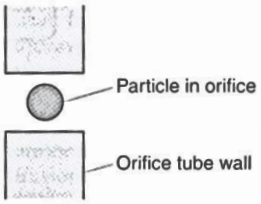


Fig. 10.13 Particle passing through the measuring aperture of an electrical stream sensing zone apparatus.

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Particle size analysis methods

Electric stream sensing zone method (Coulter counter)

Principle of measurement

- Powder samples are dispersed in an electrolyte solution to form a very dilute suspension.
- The particle suspension is drawn through an orifice where electrodes are situated on either side and surrounded by electrolyte solution.
- As the particle travels through the orifice, it displaces its own volume of electrolyte solution.
- The change in electrical resistance between the electrodes is proportional to the volume of the particle (volume of electrolyte displaced)

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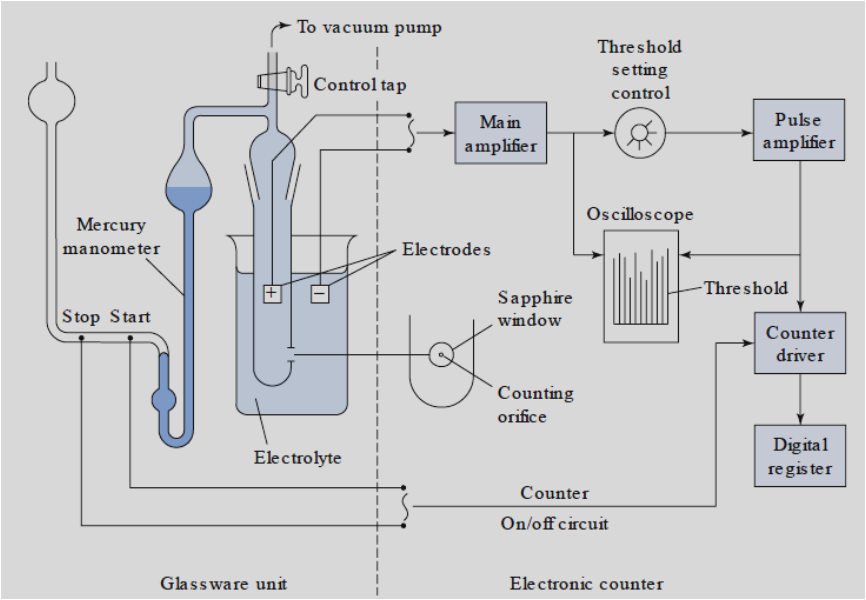


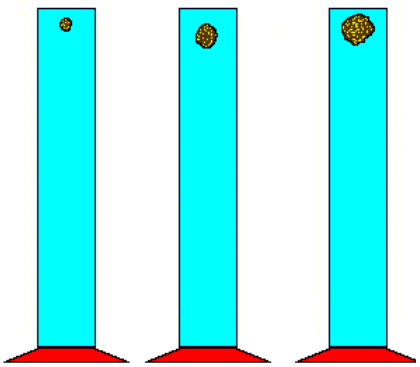
Diagram of electrical sensing zone apparatus

Particle size analysis methods

Sedimentation methods

Range of analysis

- for gravitational ~ 5 - 1000 μm
- for centrifugal ~ 0.5 - 50 μm



Particle size analysis methods

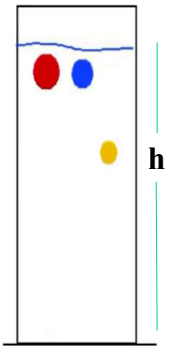
Sedimentation methods

Equivalent diameter: Stokes diameter (d_{st})

- Stokes equation:

$$d_{st} = \sqrt{\frac{18\eta h}{(\rho_s - \rho_f) g t}}$$

- $\mathbf{d_{st}}$ = Stokes diameter,
- η = viscosity of fluid,
- **h** = height or sedimentation distance,
- ρ_s = density of solid,
- ρ_f = density of fluid,
- **g** = the acceleration due to gravity,
- **t** = time

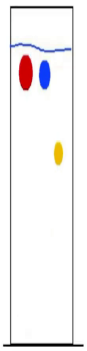


Particle size analysis methods

Sedimentation methods

Principles of measurement

- Particle size distribution can be determined by examining the powder as it sediments out.
- The powder is dispersed uniformly or introduced as a thin layer in a fluid.
- Techniques can be divided into two main categories.



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Sedimentation methods

Pipette method (Andreasen pipette)

- In this method known volumes of the suspension are withdrawn, at various time intervals, from bottom (lower set limit).
- The amount of solid is determined in each volume.
- The particle diameter corresponding to each time period is calculated from Stokes' law.
- The amount of solid determined for each time interval is the weight fraction having particles of sizes more than the size obtained by the Stokes' law for that time period.

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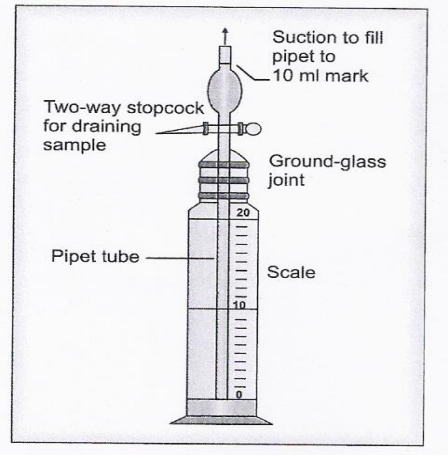

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- A suspension of 5 g of ZnO_2, density 5.60 g/cm^3, in 50 ml of water was prepared containing 2.75 g sodium citrate as deflocculating agent was transferred to Andreasen pipette (h = 20 cm) and volume made up to 550 ml using distilled water. The suspension was shaken and allowed to settle under the acceleration of gravity, 981 cm/sec^2, at 25◦C. the density of the medium is 1.01 g/cm^3, and its viscosity is 1 centipoise = 0.01 poise or 0.01 g/cm sec.

$$d_{st} = \sqrt{\frac{18\eta h}{(\rho_s - \rho_f) g t}}$$

Time (sec)	Particle size (µm)	Size range (µm)	Mean of size range (µm)	wt of sample collected (g)	wt (%)	Cumulative undersize (%)	Cumulative Oversize (%)
600	11.54	>11.54		0.7	14	86	14
1200	8.16	8.16-11.54	9.85	0.9	18	68	32
1800	6.66	6.66-8.16	7.41	1.5	30	38	62
2400	5.77	5.77-6.66	6.22	0.8	16	22	78
3000	5.16	5.16-5.77	5.47	0.6	12	10	90
3600	4.71	4.71-5.16	4.94	0.5	10	0	100
				Σ = 5			

- A suspension of 5 g of ZnO_2, density 5.60 g/cm^3, in 50 ml of water was prepared containing 2.75 g sodium citrate as deflocculating agent was transferred to Andreasen pipette (h = 20 cm) and volume made up to 550 ml using distilled water. The suspension was shaken and allowed to settle under the acceleration of gravity, 981 cm/sec^2, at 25◦C. the density of the medium is 1.01 g/cm^3, and its viscosity is 1 centipoise = 0.01 poise or 0.01 g/cm sec.

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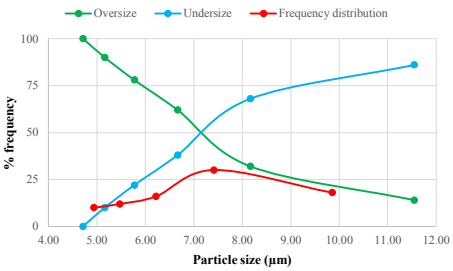
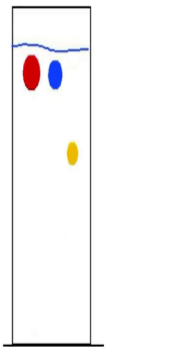
2400	5.77	5.77-6.66	6.22	0.8	16	22	78
3000	5.16	5.16-5.77	5.47	0.6	12	10	90
3600	4.71	4.71-5.16	4.94	0.5	10	0	100
				Σ = 5			





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Sedimentation methods

Balance method

The increase in weight of sedimented particles falling onto a balance pan suspended in the fluid is recorded with time. **Gravity**

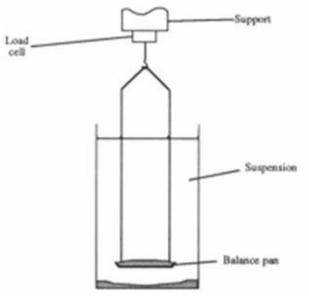
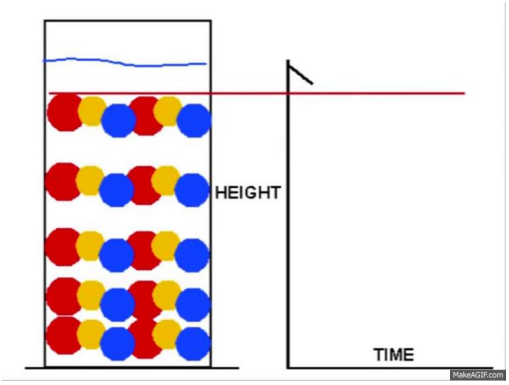


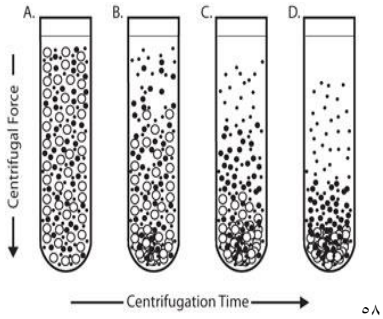
Figure 9.3. Sedimentation balance.



Sedimentation methods

Alternative technique

- It is the application of centrifugal sedimentation to make quicker the sedimentation of small particles.



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Particle size analysis methods

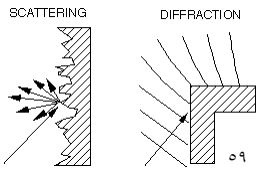
Laser light scattering methods

Equivalent diameters: Area diameter, d_a, volume diameter, d_v.

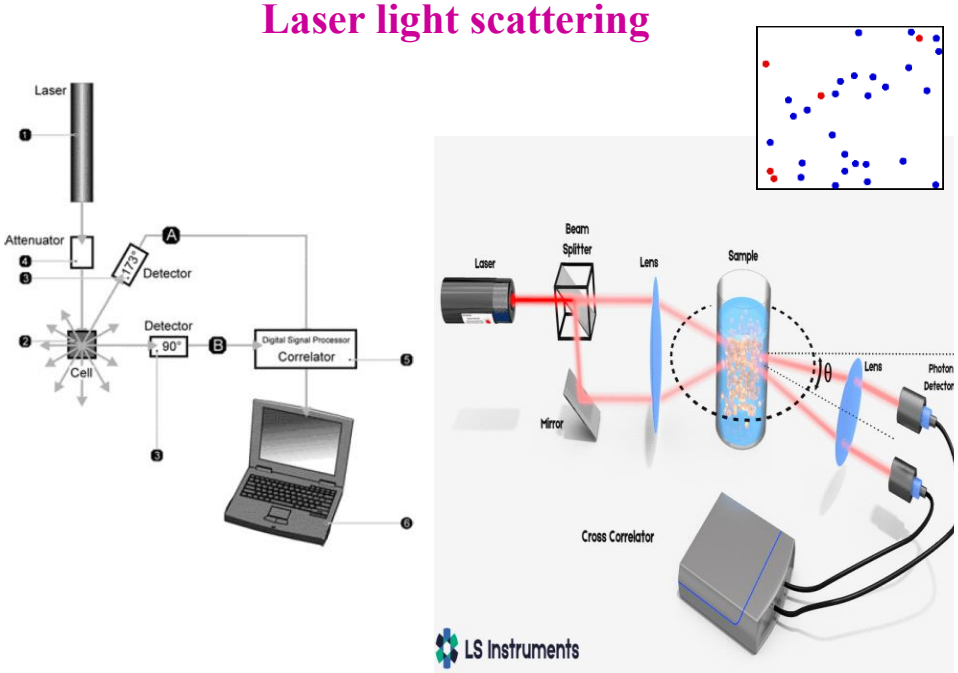
Principle of measurement: Interaction of laser light with particles

1) Fraunhofer diffraction

- This is based on forward scatter (small angle change) of laser light by particles, which is detected, amplified and analyzed by microprocessor.
- Range of analysis = 0.5 - 1000 nm
- Sample is liquid orair-suspendedd



Laser light scattering



Particle size analysis methods

Laser light scattering methods

2) Photon correlation spectroscopy (PCS)

- It is termed also Dynamic light scattering (DLS)
- This is based on the Brownian movement (random motion of small particles or macromolecules caused by the collisions with the smaller molecules of the suspending fluids) .
- Range of analysis ~ 0.001 - 1 μm
- PCS analyses the constantly changing patterns of laser light scattered or diffracted by particles in Brownian movement and monitors the rate
- Calculation of size is based on Stokes-Einstein equation:

$$D = \frac{1.38\times10^{-12}T}{3\pi\eta d}\, m^2 s^{-1} \qquad d_{st} = \sqrt{\frac{18\eta h}{(\rho_s - \rho_f)gt}}$$

- T = absolute temperature, d = diameter, η= viscosity of liquid,
- D = Brownian diffusion

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Selection of particle size analysis method

Factors to be taken into consideration:

1. Size range of powder
2. Amount of sample

   If sample is very small we can use microscopy but we can not use sieving
3. Speed of analysis
4. Accuracy of results
5. Cost
6. Physical nature of material (like Agglomeration and cohesiveness)

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Influence of particle shape

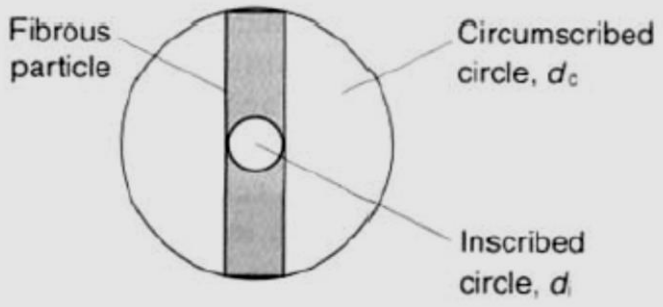

Fig. 10.6 A simple shape factor is shown which can be used to quantify circularity. The ratio of two different diameters (d_i/d_c) is unity for a circle and falls for acicular particles.

Circularity= di/dc

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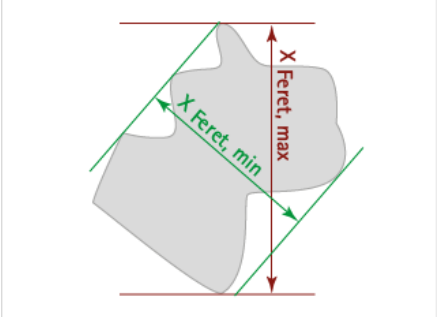
Particle shape descriptors

Aspect ratio

- The ratio of the minimum to the maximum Feret diameter is another measure for the particle shape.
- =df $_{min}$/df $_{max}$



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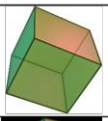
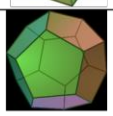
Particle shape descriptors

Sphericity

- The sphericity S is the ratio of the surface area of a sphere (with the same volume as the given particle) to the surface area of the particle:

Shape	Spherecity
Tetrahedron 	**0.671**
Cube 	**0.806**
Dodeca-hedron 	**0.910**

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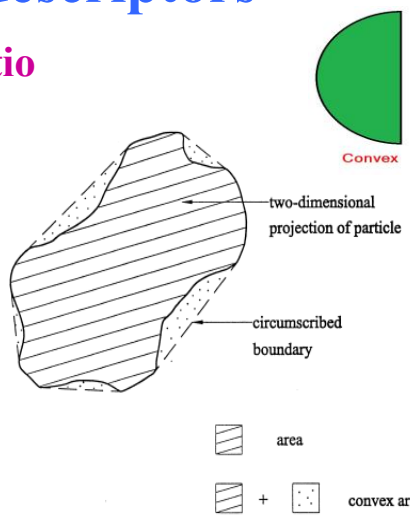
Particle shape descriptors

Convexity and fullness ratio

$$\text{convexity ratio} = \frac{\text{area}}{\text{convex area}}$$

$$\text{fullness ratio} = \sqrt{\frac{\text{area}}{\text{convex area}}}$$



Example:
Convexity ratio =4/2=2

fullness ratio= √4/2=1.414

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