INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION

国际创新药学院

Particle Technology

Course BSc (Pharm) or BSc (ATT)

Year 2024-2025 II

Module Medicines: Pharmaceutics 2 (MP2)

Lecturer Dr. Shi Du

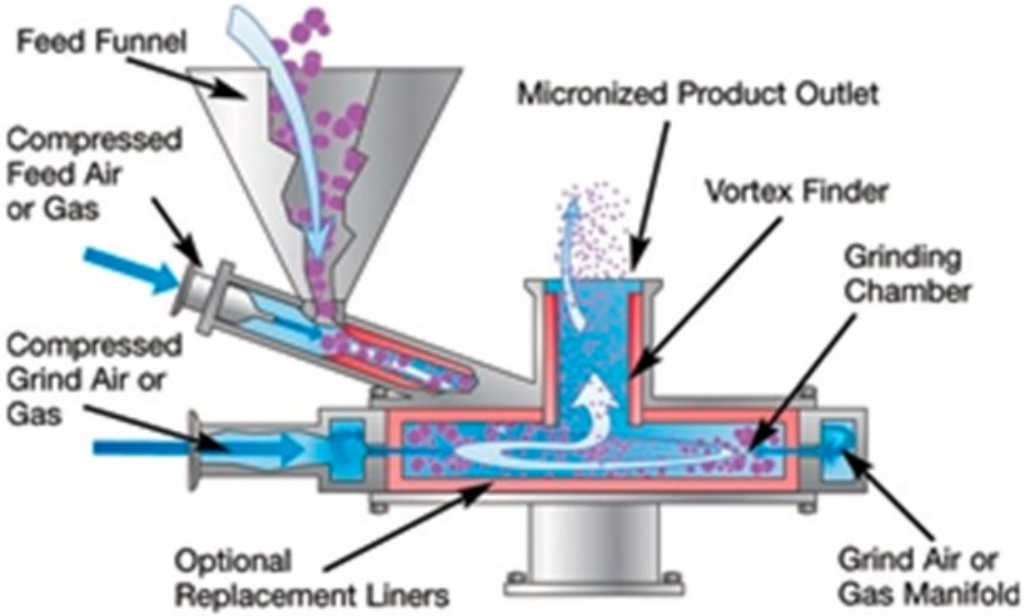
Learning Outcomes

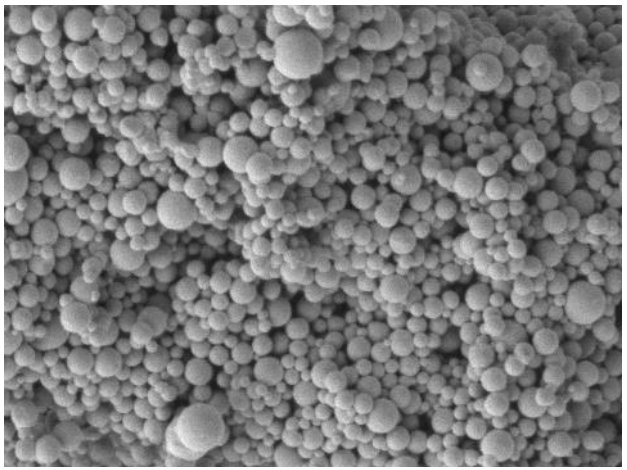
1. Explain the importance of particle technology and particle size analysis to the manufacture of oral solid dosage forms

2. Explain the principal methods of particle size analysis and the definitions of equivalent diameters used to characterise particle size

3. List and describe the main methods of particle size reduction used in oral solid dosage form manufacture

4. Explain the concept of particle size separation and list the main methods of separation

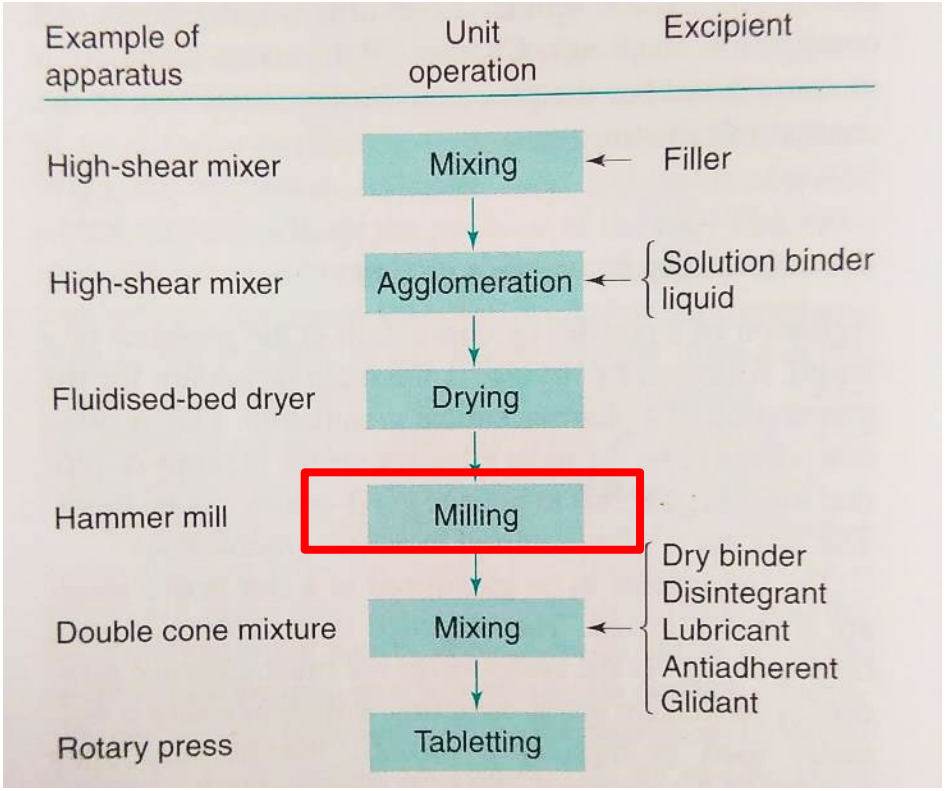




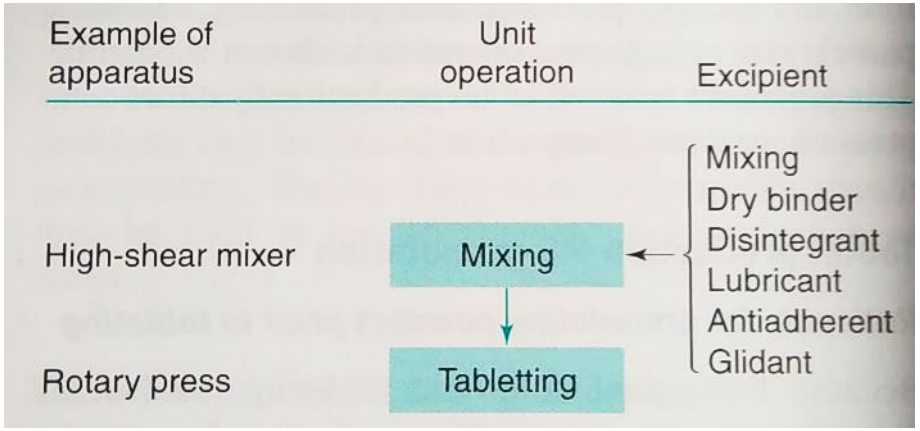
RCSI

Unit Operations in Tabletting

Tablet Production with Granulation



Tablet Production with Direct Compression

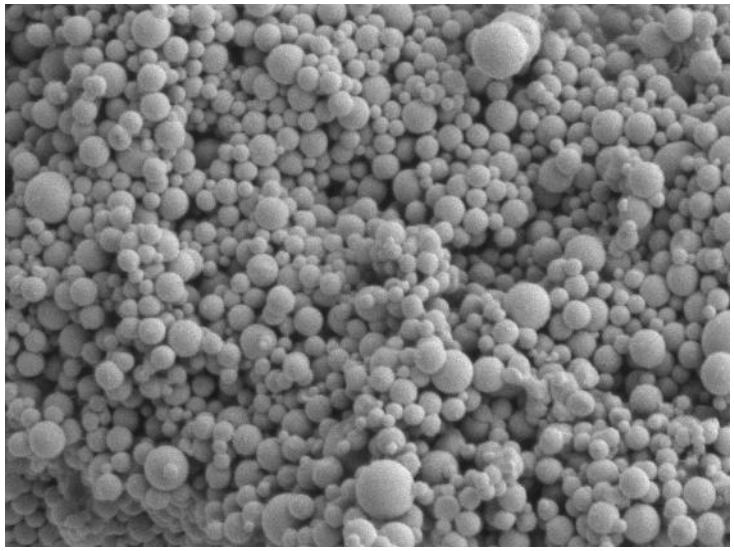


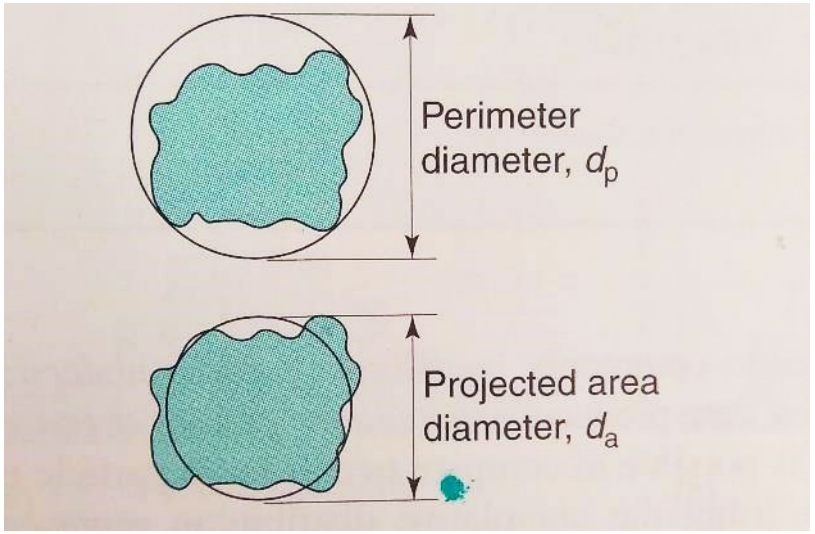
Particle size is a critical factor to consider in solid dosage form manufacture: Tablets (and capsules) are produced by using equipment that controls the mass of active ingredient(s) and other excipients by volumetric filling.

- Particle size affects powder flow and filling of this equipment
- Particle size reduction can facilitate mixing of ingredients
- Particle size important post oral administration

RCSI

Particle Size Characterisation





- A solid particle is often related to an approximate sphere from which a diameter can then be determined
  - Allows for standardisation and comparison between particles of different shapes
  - This approximation is referred to as an equivalent diameter
  - Examples of hypothetical spheres include those that relate to perimeter or to the area of the particle

RCSI

Particle Size Distribution

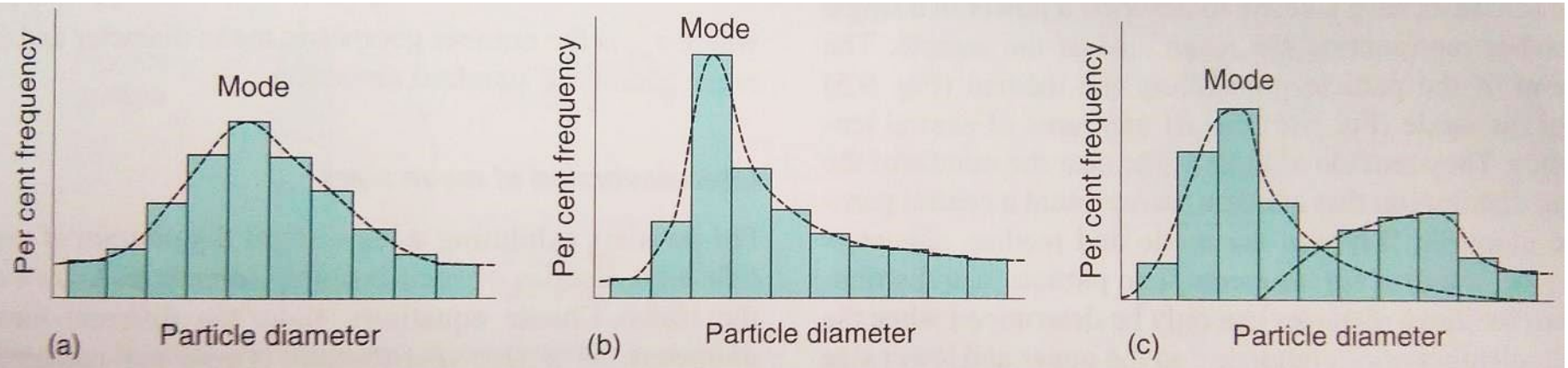


Fig. 9.4 Frequency distribution curves corresponding to (a) a normal distribution, (b) a positively skewed distribution and (c) a bimodal distribution.

- Particle size distribution is described as a frequency distribution
  - Monosized-> Particle Population can be described by a single (equivalent) diameter
  - Monosized populations are very rare-> Thus, we use frequency distribution plots
  - Plots based on standard or logarithmic scales

- Methods of particle size analysis
  1. Sieve methods
  2. Microscopic methods
  3. Light scattering
  4. Coulter counter

RCSI

Particle Size Analysis: Sieve Analysis

- Essential concepts
  - Measures sieve diameter: Width of minimum square aperture through which a particle will pass
  - Size range 5-125,000μm
  - Pass powder through sieves of known apertures
  - Sieve stack-> Coarse-fine particles

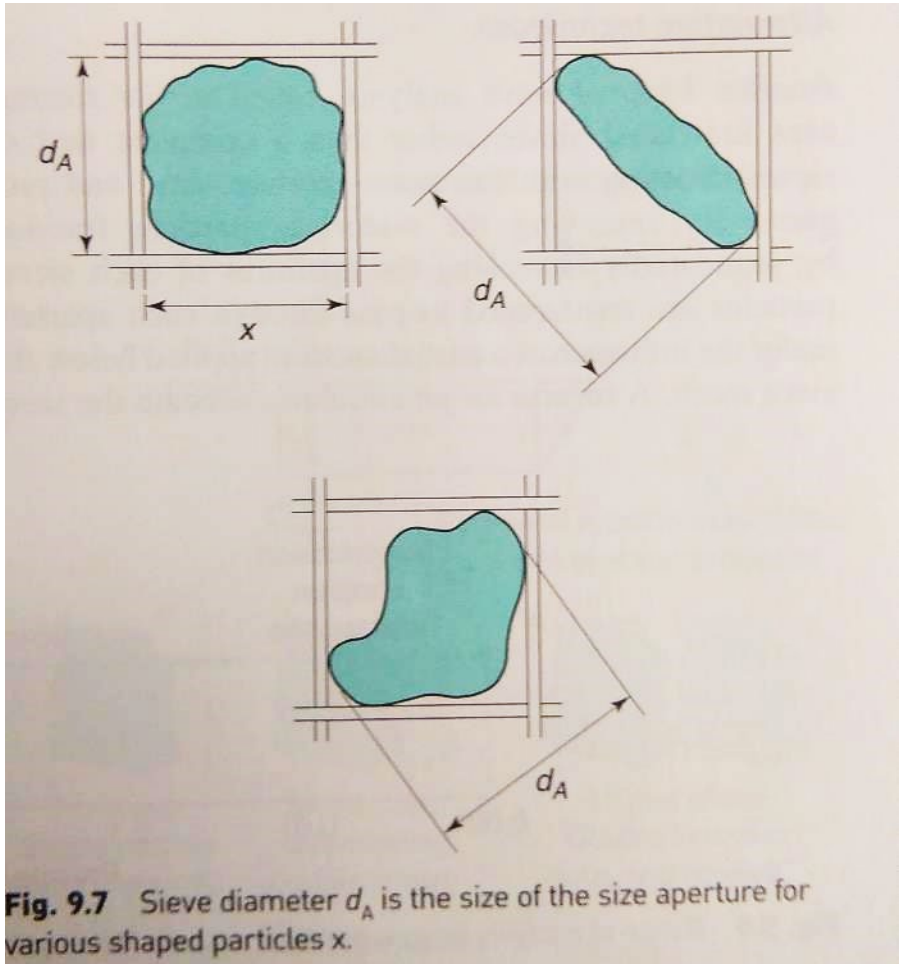
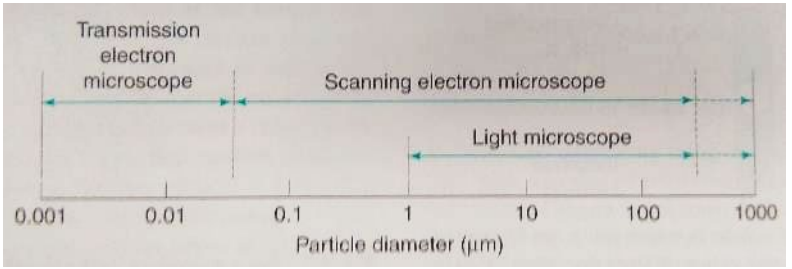


Fig. 9.7 Sieve diameter d_A is the size of the size aperture for various shaped particles x.

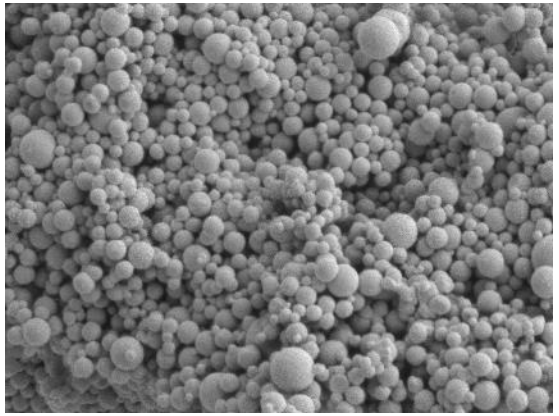
RCSI

Particle Size Analysis: Microscopic Methods

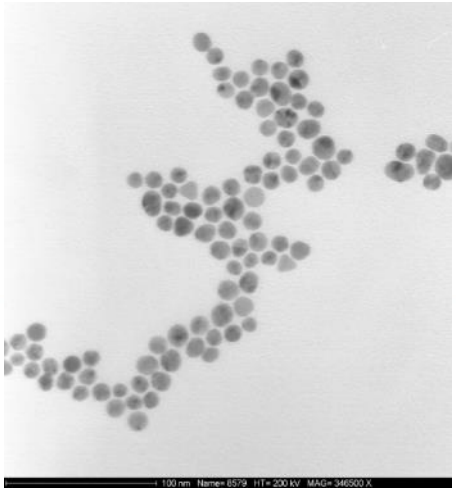
- Light microscopy
  - Equivalent diameters based on particle area and perimeter
  - Compare to calibrated scales
  - Automation possible



- Scanning electron microscopy (SEM)
  - Fine resolution of particles
  - Determination of particle shape and surface characteristics



- Transmission electron microscopy (TEM)
  - Ultra-thin specimens-> Cut with a diamond blade to see cross-sectional ultrastructure



TEM: Darwich et al 2011

RCSI

Particle Size Reduction: Essential Concepts

- Size reduction (Comminution)
  - Size reduction essentially involves the propagation of cracks by application of localised stresses in the particle
  - Cracks are generally propagated through weak points in the solid structure (e.g. Impurities, discontinuities)

In general, brittle materials are easier to reduce in size

- Surface hardness: Mohs' Scale
  - A scale that characterizes the scratch resistance of various minerals through the ability of a harder material to scratch a softer material
  - Ranges from 1 (e.g. talc) to 10 (e.g. diamond)
  - Harder materials resist size reduction
  - Important for energy requirements and for machinery fatigue

RCSI

Particle Size Reduction: Essential Concepts

- Size reduction and energy requirements
  - There is a relationship between energy applied (E) and the size reduction achieved
  - In general, increasing E will increase size reduction
  - E can also induce polymorphism and amorphous solids (see lecture on Physical Form on Tablet Behaviour)

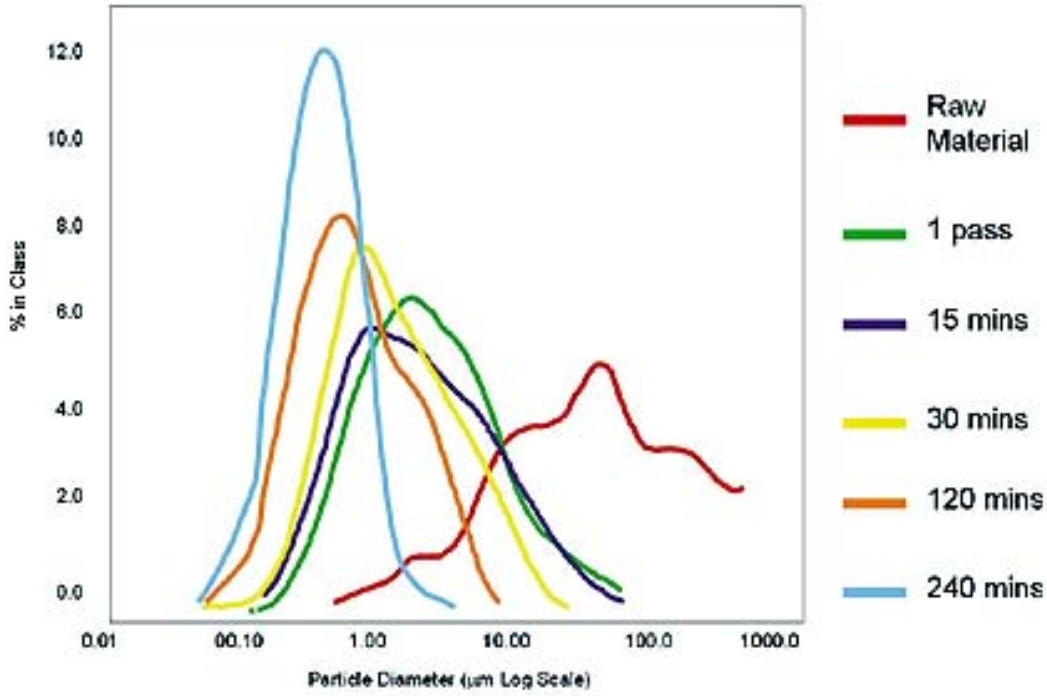
- Energy required is proposed to depend on:
  - Increased surface area-> Free surface energy
  - Size reduction ratio
  - Natural flaws in the material

- In practice, particle size reduction is quite energy-inefficient
  - Estimated that as little as 2% of E actually affects particle size reduction

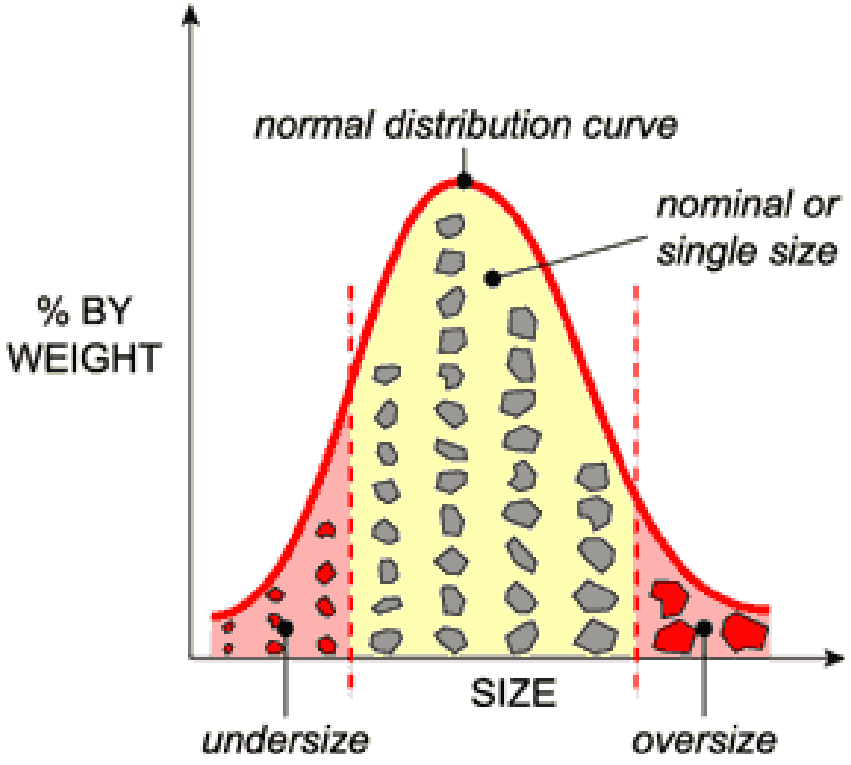
- Distribution of remaining energy?
  - Elastic deformation
  - Plastic deformation without fracture
  - Crack initiation
  - Deformation of machine parts
  - Friction-> Interparticulate and particle-machinery
  - Energy losses-> Heat, sound, vibration

RCSI

Particle Size Reduction: Effects on Size Distribution



AGGREGATE PARTICLE DISTRIBUTION



RCSI

Milling Methods and Equipment

- Milling
  - Milling is particle size reduction by mechanical means

- Methods of particle size reduction

1. Cutting->	Cutter mill
2. Impact->	Hammer mill; Vibration mill
3. Compression->	Mortar and pestle; End-runner mill; Edge-runner mill; Roller mill
4. Attrition->	Roller mill
5. Impact & attrition->	Ball mill; Fluid energy mill

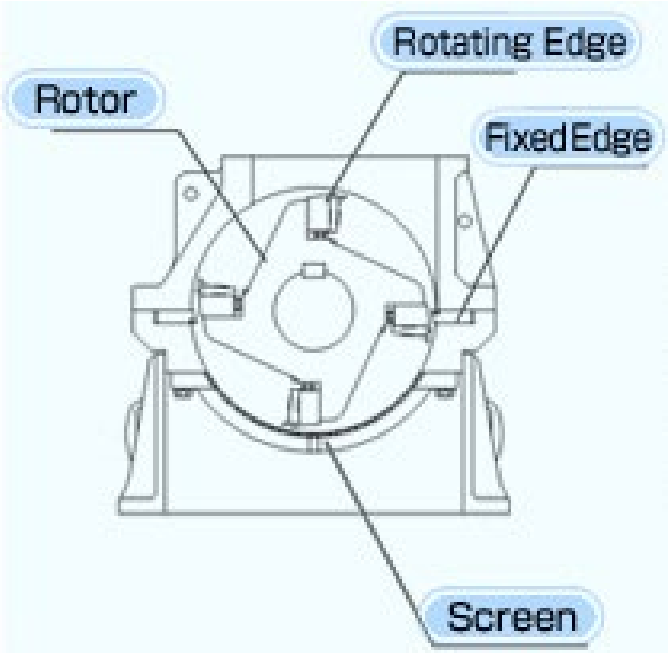
Compressive

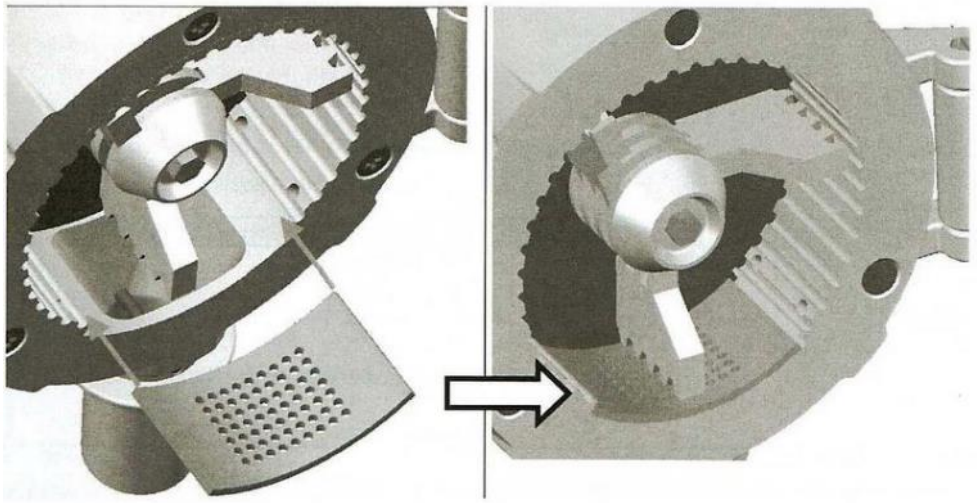
Shear
(Attrition)

RCSI

Cutter Mill

- Particle fracture between two sets of knives
  - Series of stationary and rotating knives
- High shear rates
  - Particle size reduction 100μm-100mm
- Uses
  - Dry granulation

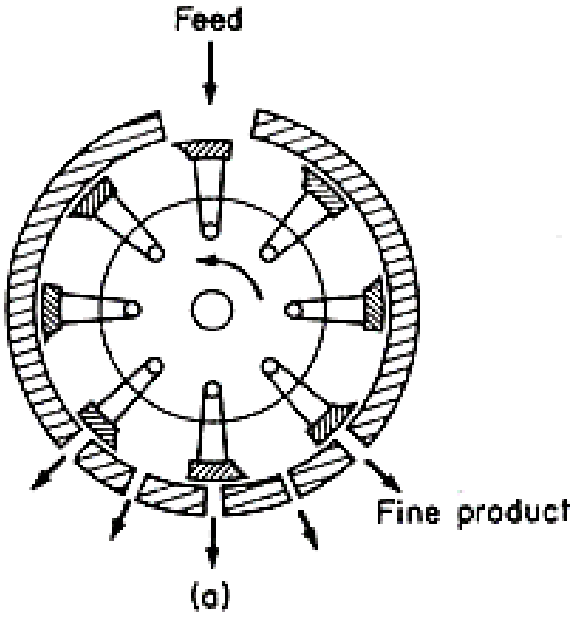




RCSI

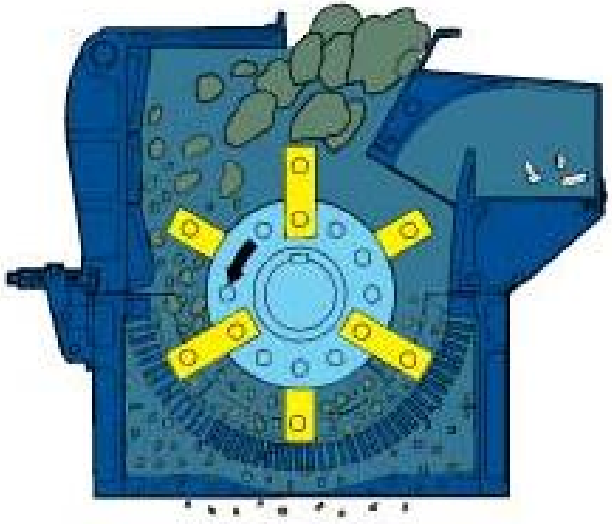
Hammer Mill

- Particle fracture by collision with hammers
  - Hammers mounted on a rotating shaft
  - High strain rates-> Brittle fracture induced in most materials
  - Hammer faces are versatile (e.g. flat, knife-edged)
  - Particle size 10-10,000μm (reported)
  - Generally, particles are in larger size range
  - Narrow size distribution



- Inefficient
  - Large amount of heat produced
  - Used with cooling jacket
  - Unsuitable for temperature-sensitive drugs

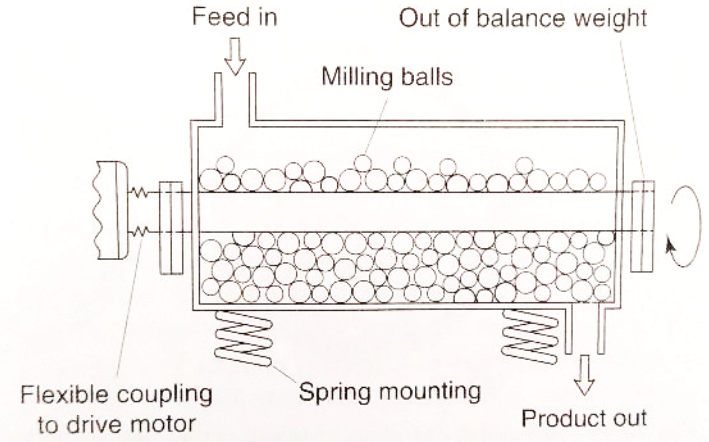
- Uses
  - Mixing
  - Wet grinding
  - Ointment milling
  - Dry crystalline grinding

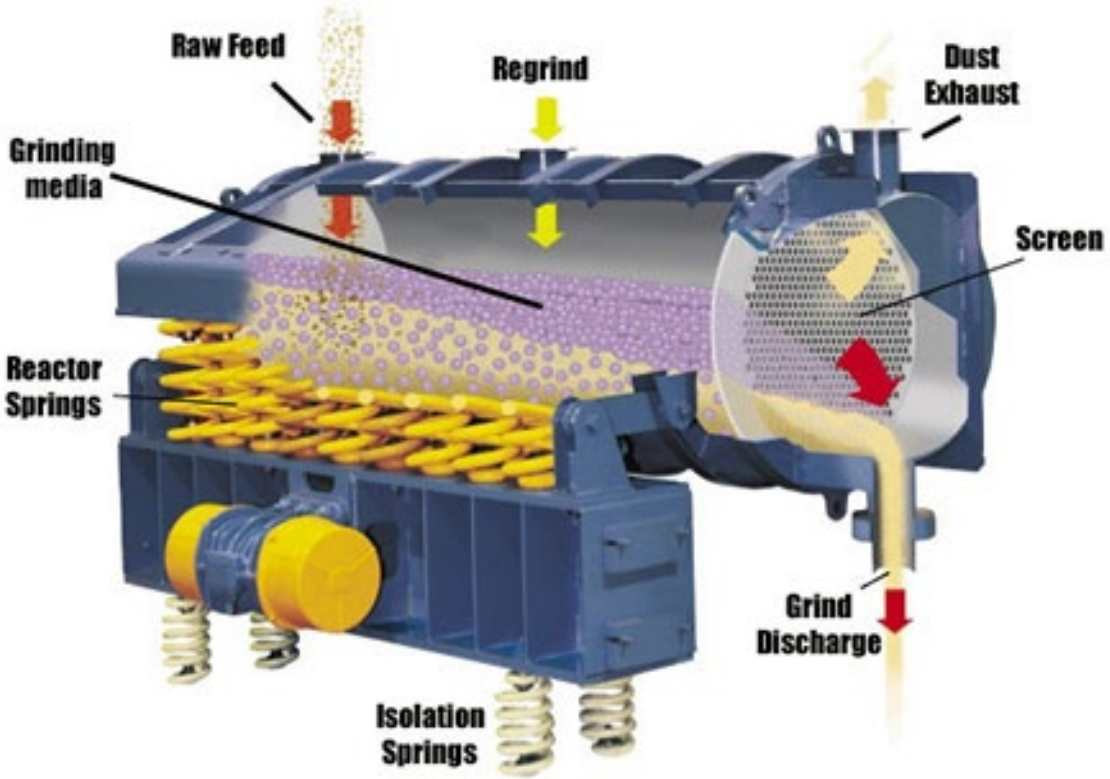


RCSI

Vibration Mill

- Particle fracture by collision with steel or porcelain balls
  - 80% of volume of drum contains balls
  - Vibration accelerates balls
  - Can mill to 1μm
  - Suitable for wet grinding

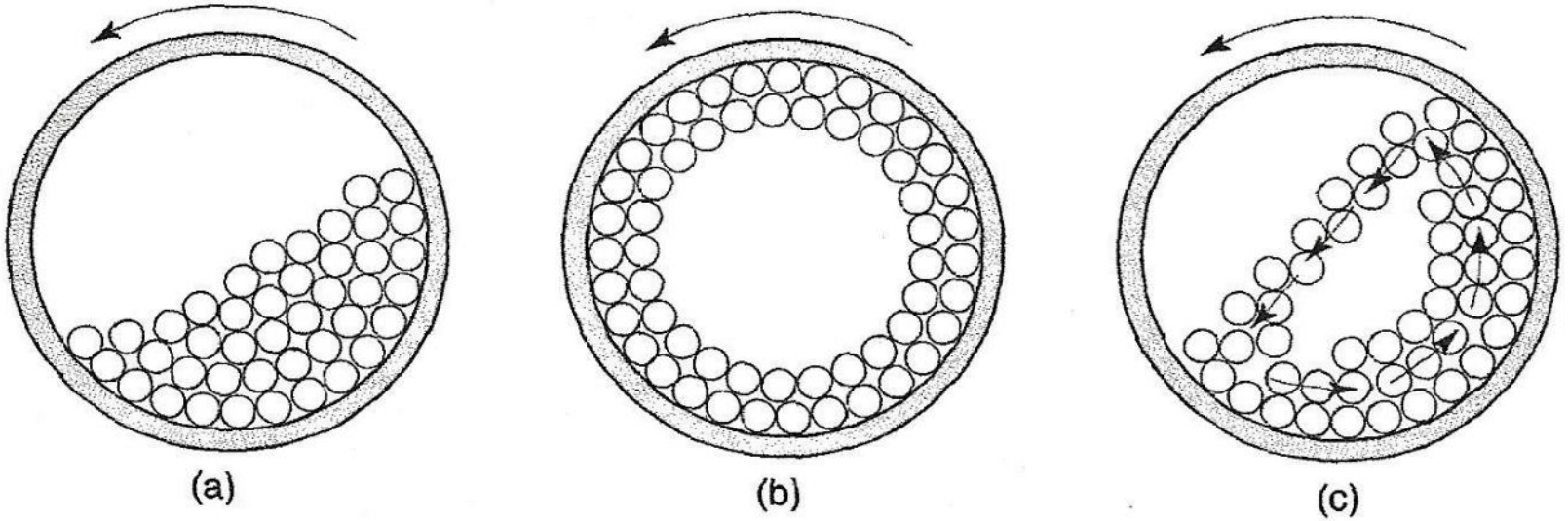




RCSI

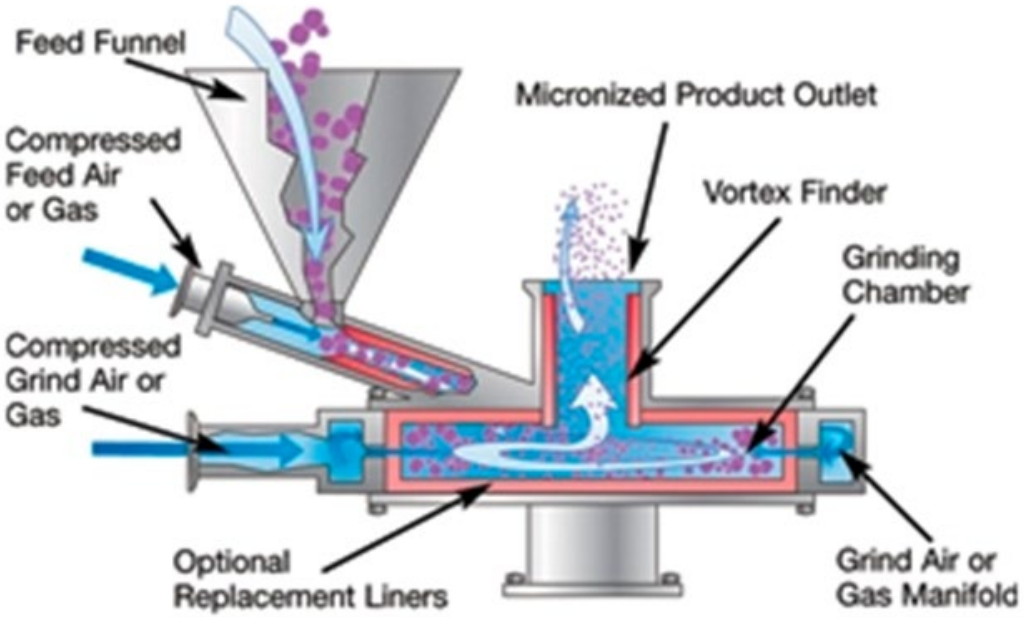
Ball Mill

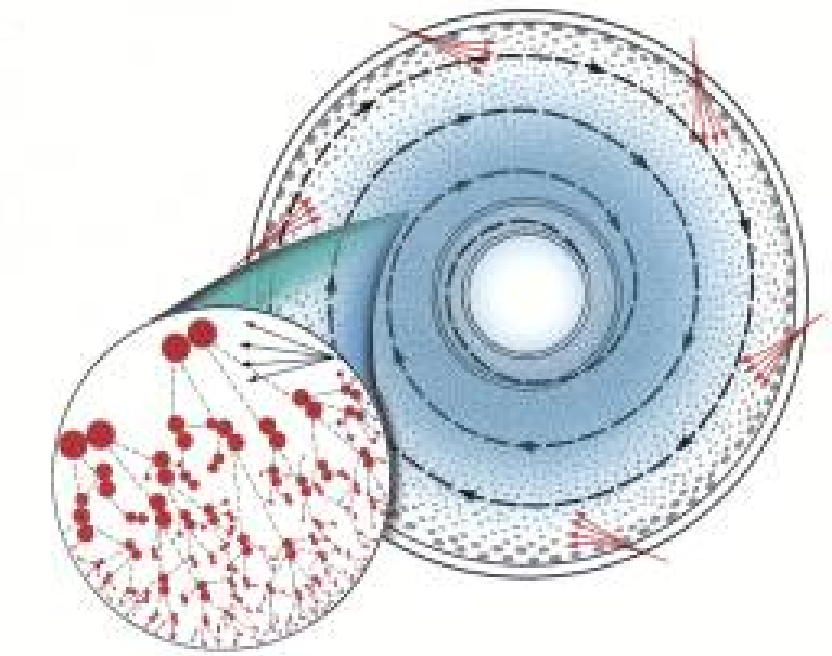
- Rotating hollow cylinder with balls inside
  - Particle fracture by collision and attrition with metal or porcelain balls
  - Balls occupy 30-50% of cylinder volume
  - Ball size range-> Smaller balls generally reduce size of smaller particles and larger balls generally reduce size of larger particles
  - Volume of powder important-> Avoid cushioning and abrasive damage
  - Rotational speed of cylinder is most important factor-> Aim for “cascading”
  - Particle size reduction 1-100μm



RCSI

Fluid Energy Mill





- Particle fracture by collision and attrition with other particles
  - Feed material blown through a circular chamber
  - High velocity fluid (usually compressed air) enters chamber
  - Particles accelerated by rotating fluid
  - Fluid creates zones of turbulence to induce particle size reduction
  - Particle size reduction 1-10,000μm

RCSI

Particle Size Reduction: Selection of Method

Table 10.1 Selection of size reduction mills according to particle properties and product size required

Mohs' 'hardness'	Tough	Sticky	Abrasive	Friable
(a) Fine powder product (< 50 μm)				
1–3 (soft)	Ball, vibration (under liquid nitrogen)	Ball, vibration		Ball, vibration, pin, fluid energy
3–5 (intermediate)	Ball, vibration			Ball, vibration, fluid energy
5–10 (hard)	Ball, vibration, fluid energy		Ball, vibration, fluid energy	
(b) Coarse powder product (50–1000 μm)				
1–3 (soft)	Ball, vibration, roller, pin, hammer, cutter (all under liquid nitrogen)	Ball, pin		Ball, roller, pin, hammer, vibration
3–5 (intermediate)	Ball, roller, pin, hammer, vibration, cutter			Ball, roller, pin, vibration, hammer
5–10 (hard)	Ball, vibration		Ball vibration, roller	
(c) Very coarse product (> 1000 μm)				
1–3 (soft)	Cutter, edge runner	Roller, edge runner, hammer		Roller, edge runner, hammer
3–5 (intermediate)	Edge runner, roller, hammer			Roller, hammer
5–10 (hard)	Roller		Roller	

Particle Size Separation

- Particle size separation is the isolation of a desired size range for separate handling or subsequent processing

- Size separation efficiency
  - Related to particle, fluid properties, and method used
  - Describes efficacy in dividing powder into undersized and oversized fractions
  - In a continuous size separation process, the production of these fractions depends on mass flow rates of the feed material

- Methods of powder separation
  1. Sieving
  2. Sedimentation-> Gravitational; centrifugal
  3. Elutriation-> Fluid flow opposes particle movement
  4. Cyclone-> Centrifugal elutriation

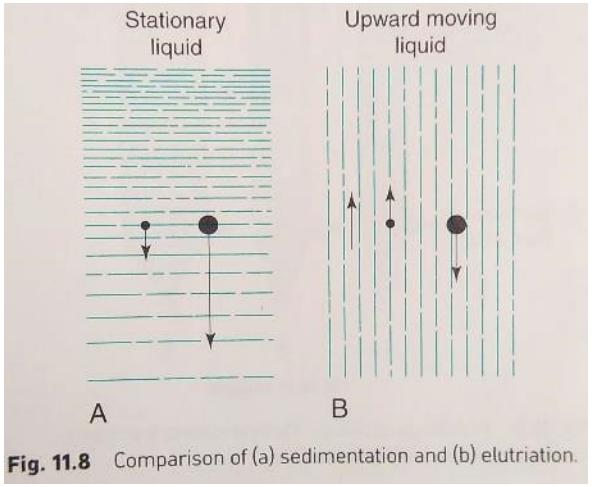


Fig. 11.8 Comparison of (a) sedimentation and (b) elutriation.

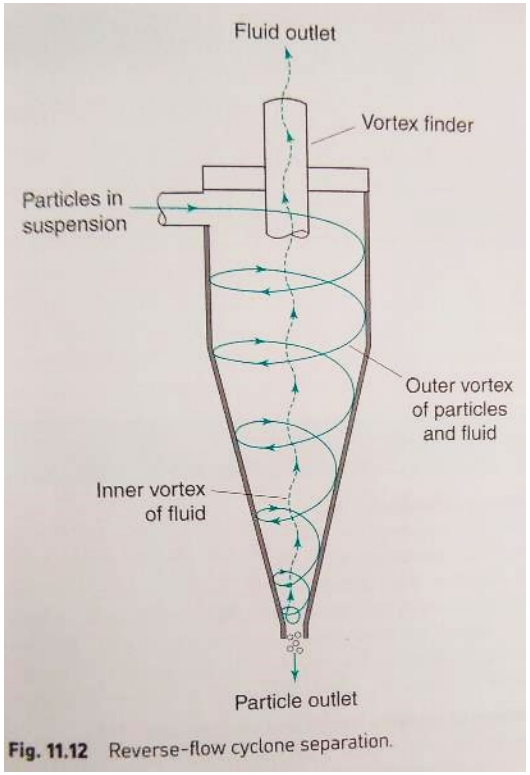


Fig. 11.12 Reverse-flow cyclone separation.

RCSI

Particle Size Separation: Powder Grades

Table 11.1 Example of powder grades specified in pharmacopoeias

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	–

Some pharmacopoeias define another size fraction, known as *ultrafine powder*, in which the maximum diameter of at least 90% of the particles must be no greater than 5 μm and none of the particles should have diameters greater than 50 μm.

RCSI

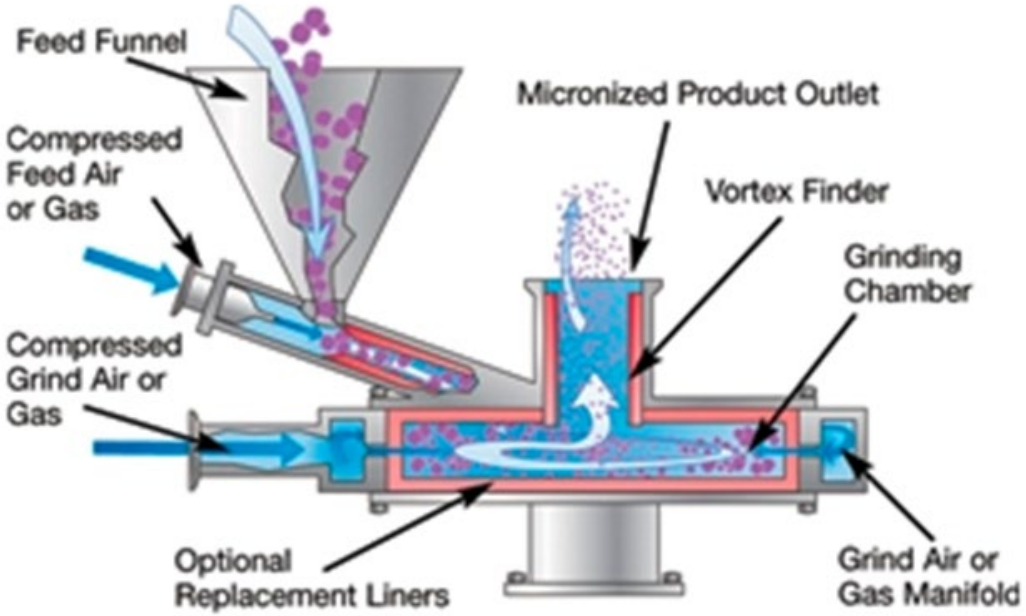
Learning Outcomes

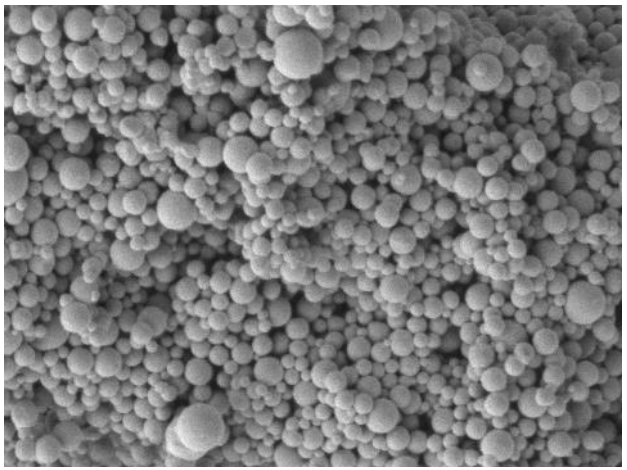
1. Explain the importance of particle technology and particle size analysis to the manufacture of oral solid dosage forms

2. Explain the principal methods of particle size analysis and the definitions of equivalent diameters used to characterise particle size

3. List and describe the main methods of particle size reduction used in oral solid dosage form manufacture

4. Explain the concept of particle size separation and list the main methods of separation





RCSI

Recommended Reading

- Aulton's Pharmaceutics Chapters
  - Particle Size Analysis
  - Particle Size Reduction
  - Particle Size Separation

RCSI