INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION

国际创新药学院

Granulation

Course BSc (Pharm) or BSc (ATT)

Year 2024-2025 II

Module Medicines: Pharmaceutics 2 (MP2)

Lecturer Dr. Shi Du

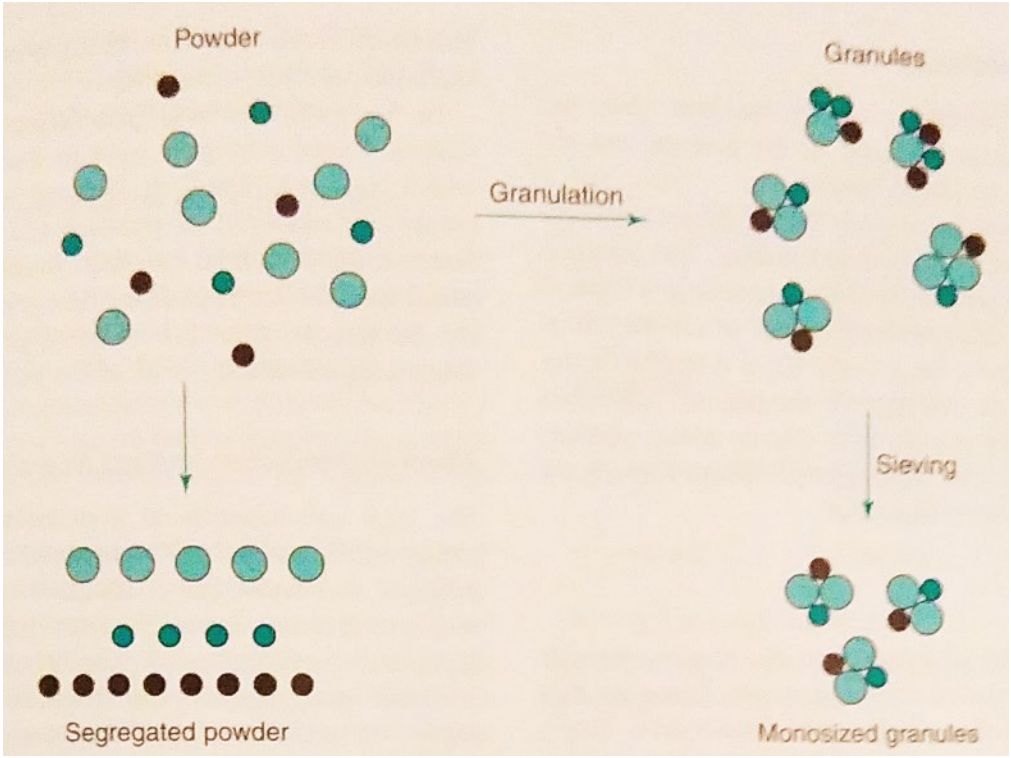
Learning Outcomes

1. Identify the importance of granulation within the tabletting process and the two main methods of granulation

2. Describe the stages of granulation and mechanisms of bonding within granule agglomerates

3. List the main types of equipment used for granulation and describe the principal machinery used

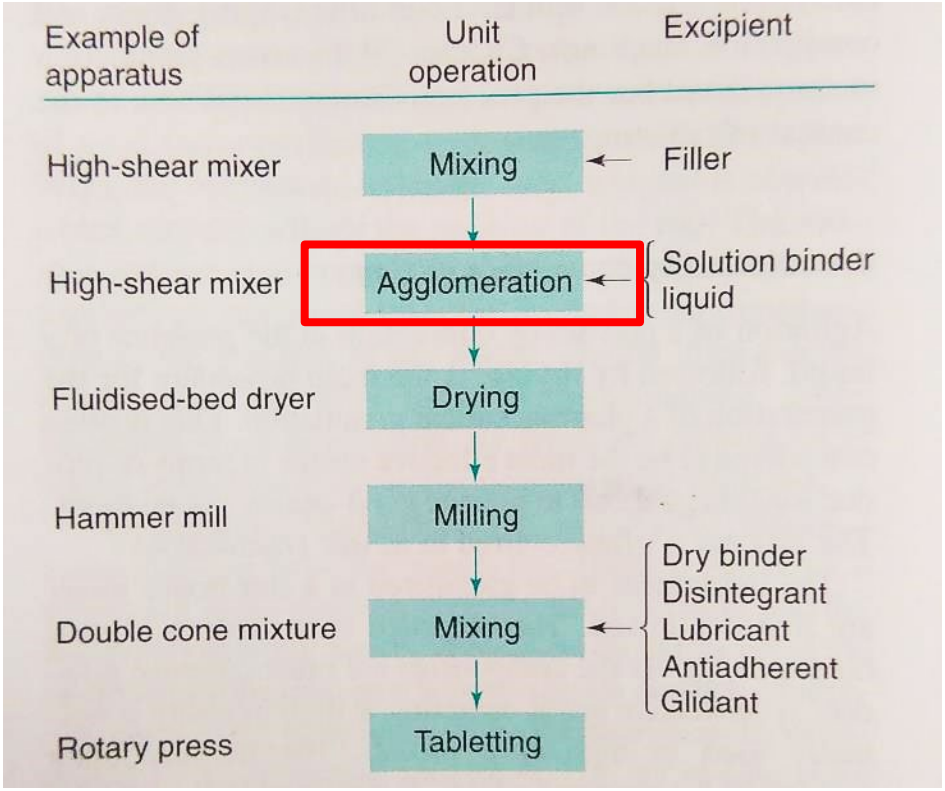
4. Explain the process of extrusion and spheronisation and its relevance to granulation processes



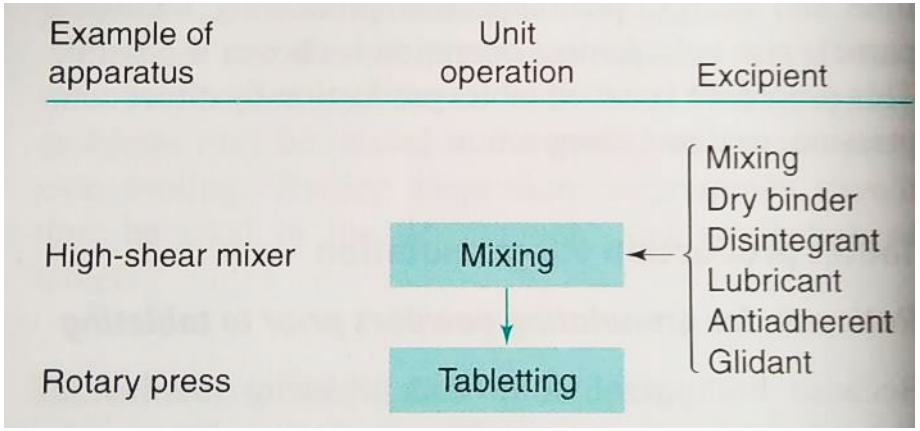
RCSI

Unit Operations in Tabletting

Tablet Production with Granulation



Tablet Production with Direct Compression



Granulation is the process in which primary powder particles are agglomerated to form larger multi-particulate entities called granules.

- Granulation can prevent powder segregation of the random mixture
- Granulation can improve powder flow properties
- Granulation can improve compaction in the tabletting process
- Granulation can improve safety for operators and reduce cross contamination on factory line

RCSI

Methods of Granulation

1. Dry granulation
   - Aggregation using high pressure
   - Two methods: Slugging and roller compaction
   - Slugging: Process where powders are pre-compressed into large tablets that are then milled into granules
   - Roller compaction: Squeeze powder between two rollers to make a sheet that is milled into granules

2. Wet granulation
   - Aggregation using a liquid binder called a granulating fluid
   - Granulating fluid: Non-toxic and volatile solvent (e.g. water, ethanol, isopropanol)
   - Fluid often contains a binder
   - Fluid removed in subsequent drying step

3. Hot melt granulation
   - Aggregation using binders with low melting points
   - Increase temperature to melt the binder
   - Cooling to room temp to re-solidify between particles

RCSI

Dry vs Wet Granulation: Differences in Manufacture Process

Dry Granulation	Wet Granulation
Mixing	Mixing
Application of pressure	Addition of granulating fluid
Milling and particle size separation	Agitation
Mixing	Drying
	Milling and particle size separation
	Mixing

Stages of Granulation

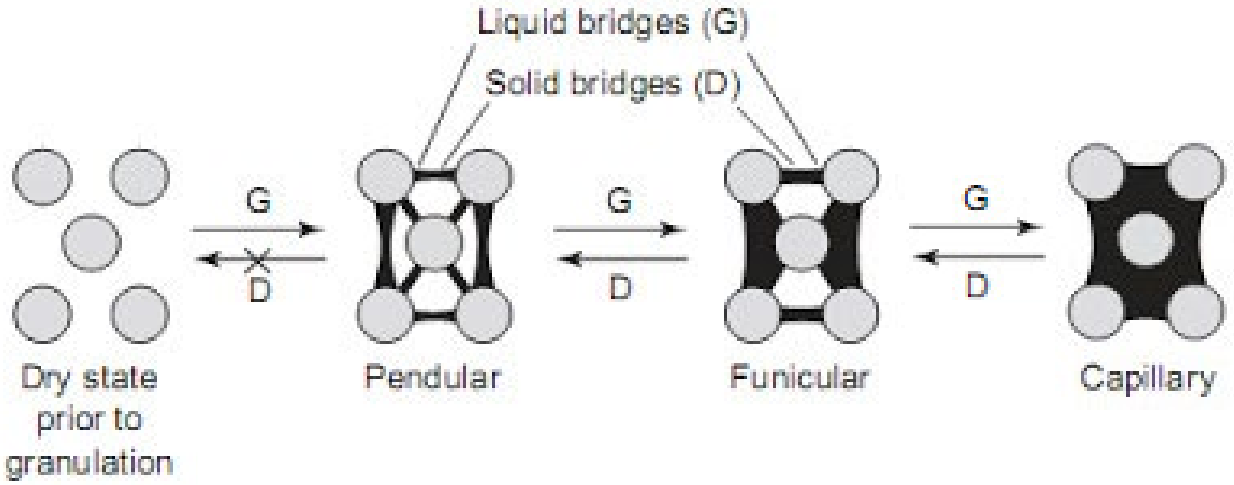
1. **Nucleation: Particle-particle contact and adhesion due to liquid bridges**
2. **Transition: Nuclei grow by more liquid bridges or by joining of two or more nuclei**
3. **Ball growth: Further large, spherical granule growth**

RCSI

Bonding Mechanisms in Granulation

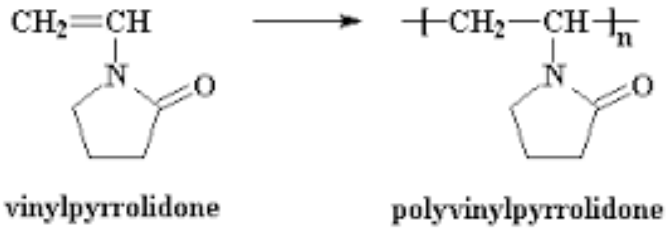
1. Adhesion and cohesion forces in immobile liquid films between powder particles
   - Thin immobile films reduce distance between particles
   - Resultant increase in contact area increases van der Waal's forces
   - Cohesion of slightly damp powders

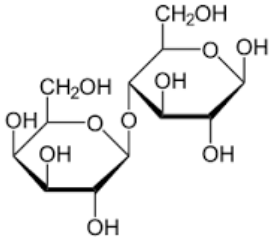
2. Interfacial forces in mobile liquid films
   - Liquid addition in wet granulation will distribute between particles in three stages
   - Pendular: Particles held together by lens-shaped rings of liquid
   - Funicular: Intermediate stage where liquid content increases
   - Capillary: Particles held by capillary suction at liquid-air interface
   - Granule tensile strength increases during stages by factor of approximately 3
   - Can also reach capillary stage by continued mixing of material in pendular stage
   - Liquid bridges replaced by solid bridges

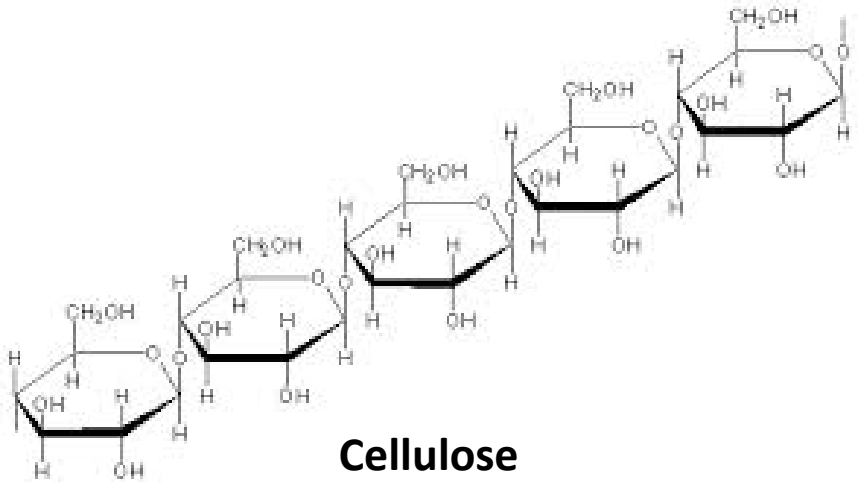


RCSI

Bonding Mechanisms in Granulation







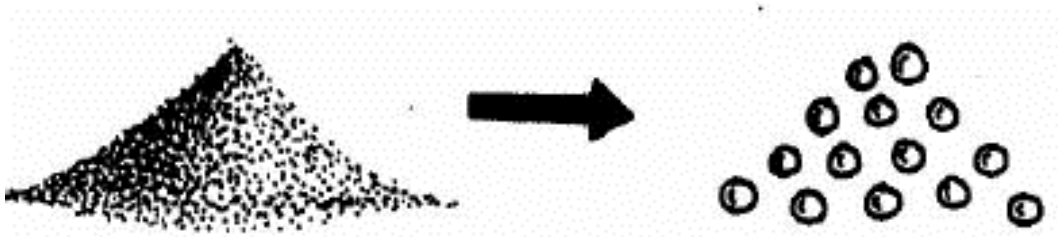
3. Formation of solid bridges
   - Binding agent within solvent hardens or crystallises during drying
   - Partial dissolution of solid particles by solvent followed by crystallisation on drying
   - Drying rate influences the size of solid bridges formed: Slower rate = larger crystals

4. Attractive forces in dry granulation
   - van der Waal's and electrostatic forces
   - Mechanical interlocking

RCSI

Granulating Equipment

1. Shear granulators
2. High-speed mixer-granulators
3. Fluidised-bed granulators
4. Roller Compaction
5. Spheronisers/Pelletisers
6. Spray dryers*



* Later Lectures

RCSI

High-speed Mixer-Granulators

- Used extensively in pharmaceutical granulation
  - Combine mixing and granulation in the one piece of equipment

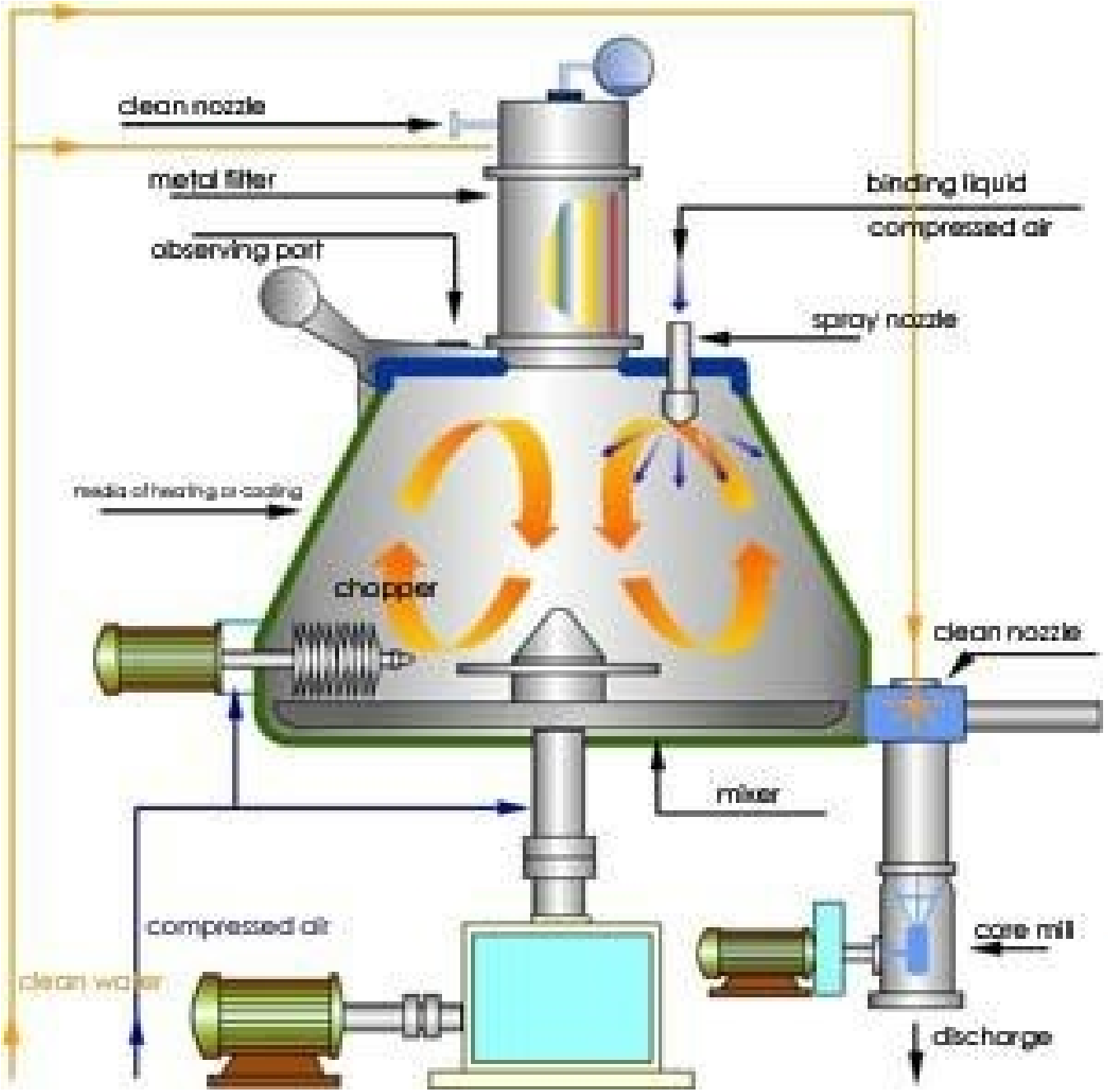
- Process
  1) Powders added into bowl and mixed by impeller
  2) Granulating fluid added into bowl
  3) Liquid mixed into powder by impeller to form a moist mass
  4) Chopper breaks up mass into bed of granular material
  5) Granules discharged

- Advantages
  - Mixing and granulation in one equipment
  - Large volumes of up to 1250 litres available
  - Very rapid- granulation occurs in minutes

- Limitations
  - Can form over-massed granules that are unusable
  - Sensitive to variations in raw materials

RCSI

High-speed Mixer-Granulators

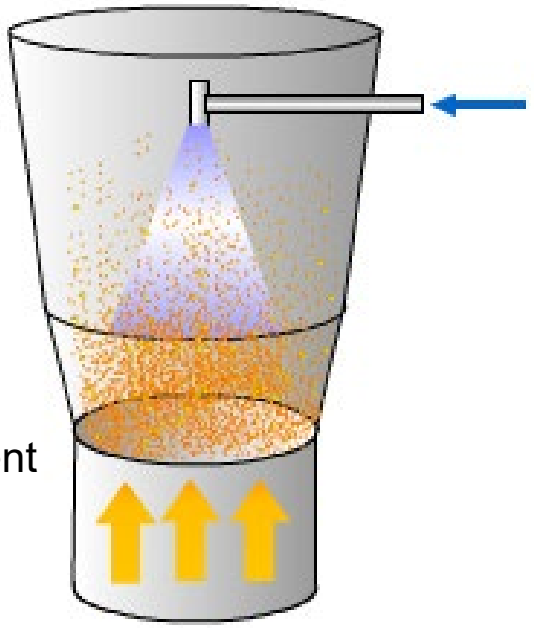


RCSI

Fluidised-bed Granulators

- Powder particles fluidised in a stream of air and granulated
  - Combine mixing, granulation and drying in the one piece of equipment

- Process
  1) Filtered air blown through bed of powder to mix ingredients
  2) Granulating fluid sprayed in from above the powder bed
  3) Fluidisation creates wet granules
  4) Heated air used to dry granules
  5) Granules discharged

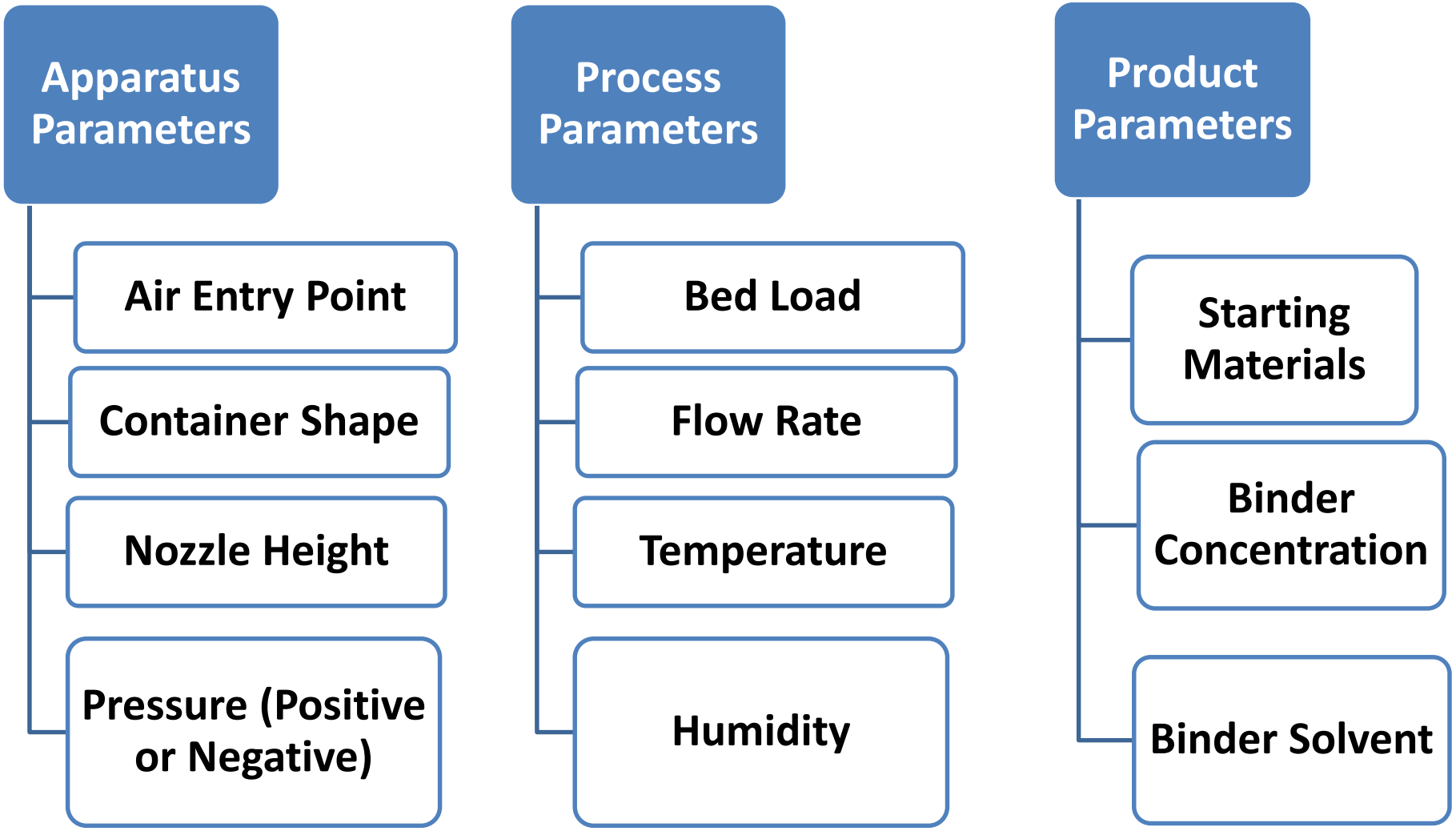


- Advantages
  - Mixing, granulation and drying in one equipment
  - Mixing by fluidisation very efficient
  - Large amounts of up to 1500kg available

- Limitations
  - Equipment is expensive
  - Lengthy optimisation of parameters required for different formulations
  - Unsuitable for thermosensitive drugs

RCSI

Fluidised-bed Granulators: Parameters influencing Granules



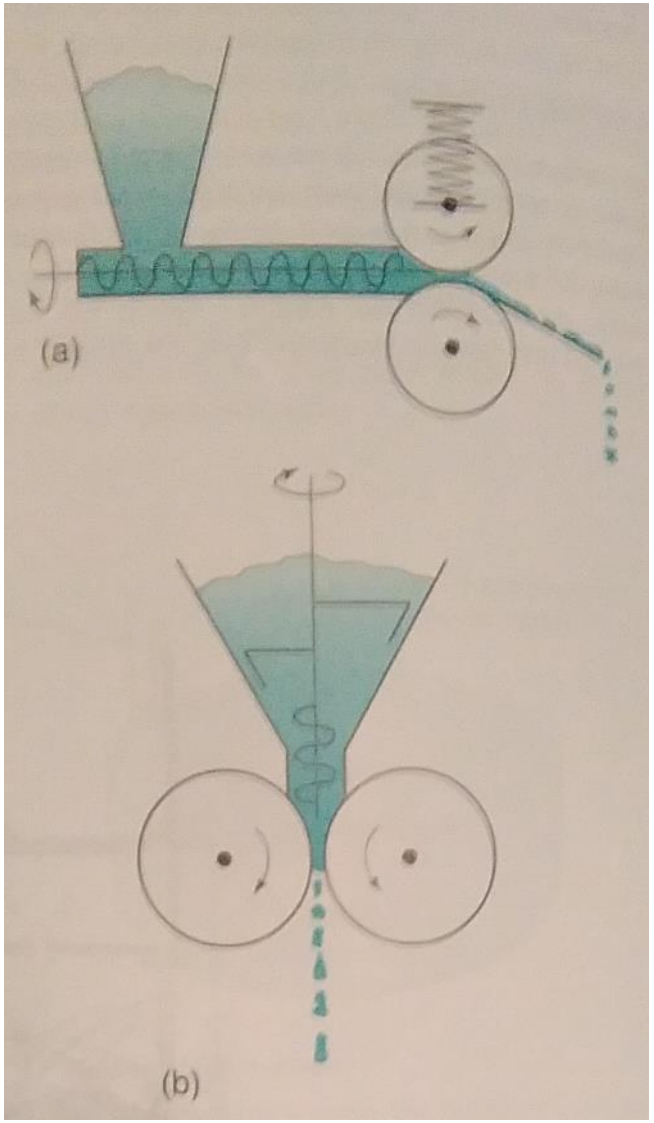
RCSI

Roller Compaction

- Gentler method of dry granulation than slugging
  - Slugging tends to make granules with poor re-compaction properties (“work hardening”)
  - Compressed sheet made by roller compaction has less severe application of pressure

- Process
  1) Powder mixture fed through two counter-rotating rollers
  2) Powder squeezed as it passes through to form a compressed sheet

- Advantages
  - Economical
  - Versatile- Modify flow rate, pressure and surface of rollers
  - Easy to scale up



RCSI

Spheronisers: Extrusion and Spheronisation

- Pelletisation/Spheronisation
  - Process of forming spherical agglomerates
  - Popular for controlled release formulations

- Process
  1) Powder mixture wetted with granulating fluid
  2) Extrusion of wet mass into rod-shaped granules of uniform diameter
  3) Spheronisation of granules

- Advantages
  - Versatile method for production of various types of spherical granules

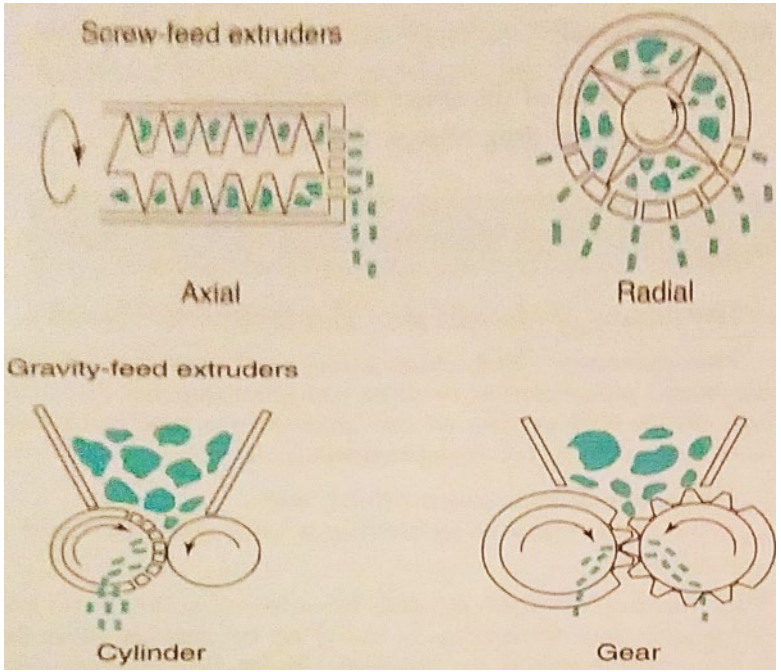
- Limitations
  - Labour intensive

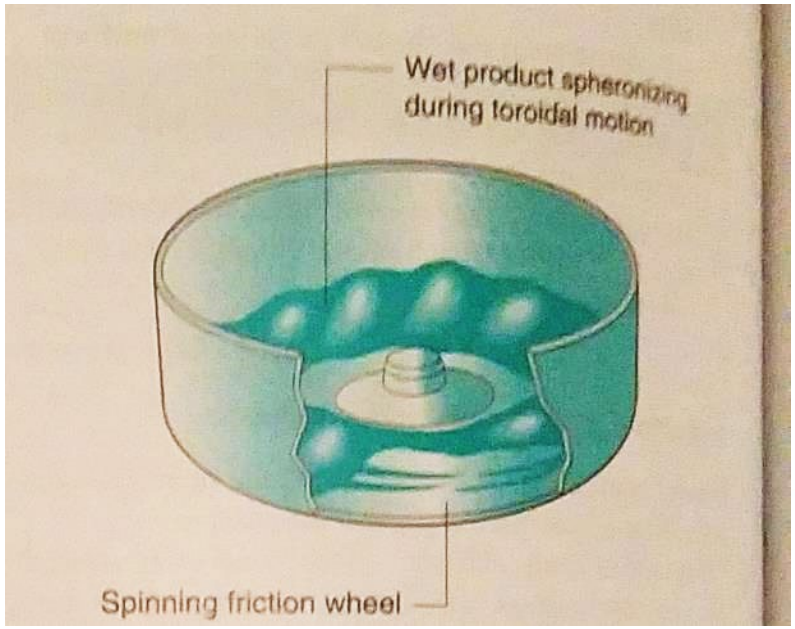
RCSI

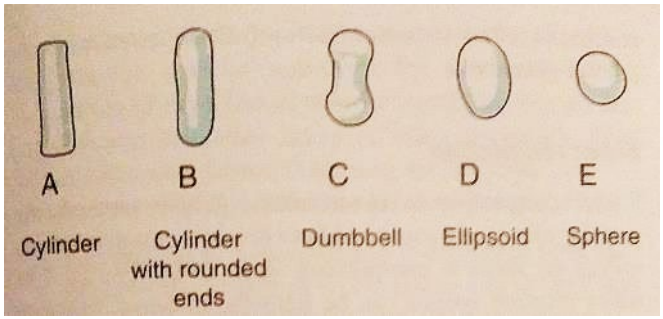
Spheronisers: Extrusion and Spheronisation

- Extrusion
  - Process of forcing a wet mass through a die of defined dimensions
  - Shapes powder into small cylindrical particles with uniform diameter
  - Powder must be able to undergo suitable plastic deformation
  - Extruders defined by feed mechanism

- Spheronisation
  - Round off the rods into spherical pellets
  - Spheroniser uses frictional forces to form pellets







RCSI

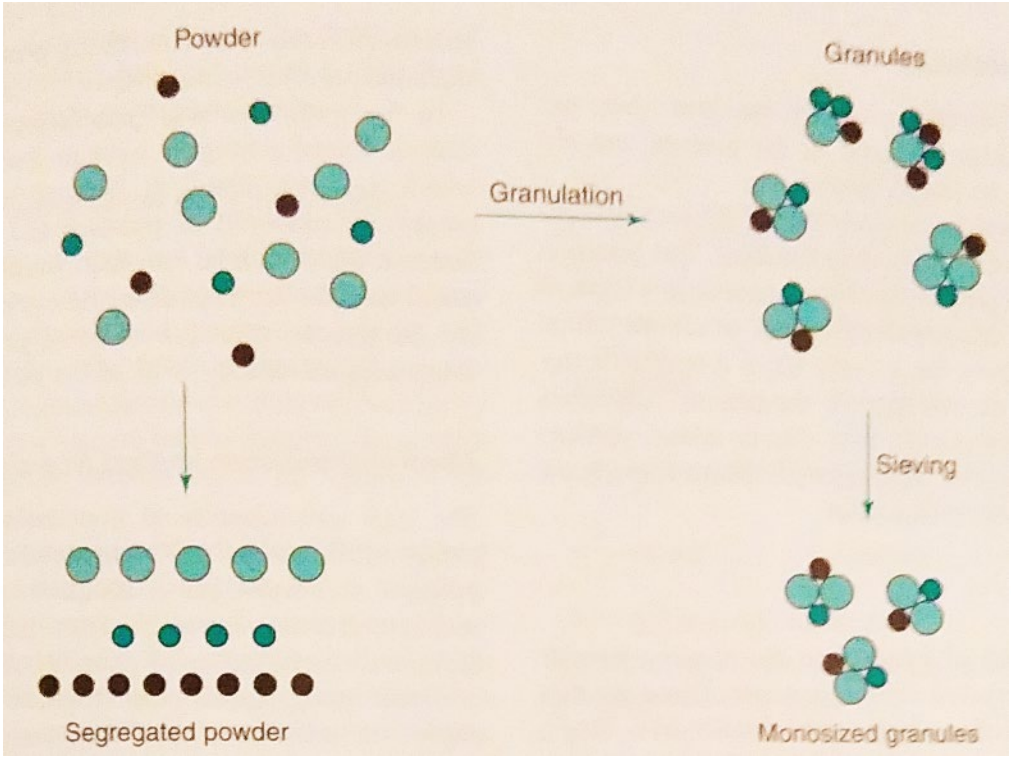
Learning Outcomes

1. Identify the importance of granulation within the tabletting process and the two main methods of granulation

2. Describe the stages of granulation and mechanisms of bonding within granule agglomerates

3. List the main types of equipment used for granulation and describe the principal machinery used

4. Explain the process of extrusion and spheronisation and its relevance to granulation processes



RCSI

Further Reading

- Aulton's Pharmaceutics Chapter
  - Granulation

RCSI