INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION

国际创新药学院

Mixing and Flowability

Course	BSc (Pharm) or BSc (ATT)
Year	2024-2025 II
Module	Medicines: Pharmaceutics 2 (MP2)
Lecturer	Dr. Shi Du

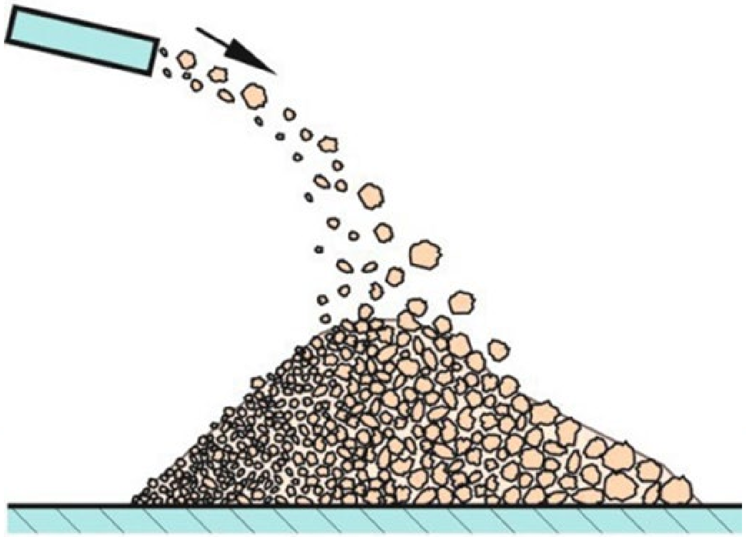
Learning Outcomes

1. Explain the essential concepts of mixing including the types of mixtures and appropriate sampling of mixes

2. List and describe the main methods of mixing used in oral solid dosage form manufacture

3. Describe powder flowability in terms of characterisation of packing geometry, powder flow and methods to improve powder flowability

4. Explain the concept of powder segregation and the main methods used to reduce segregation



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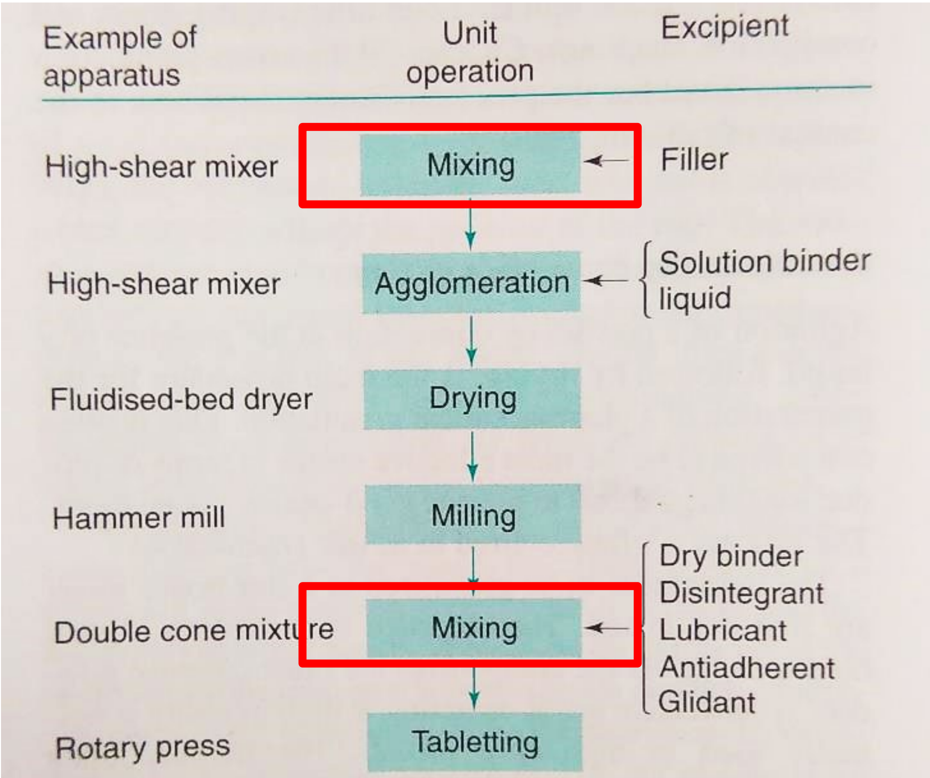
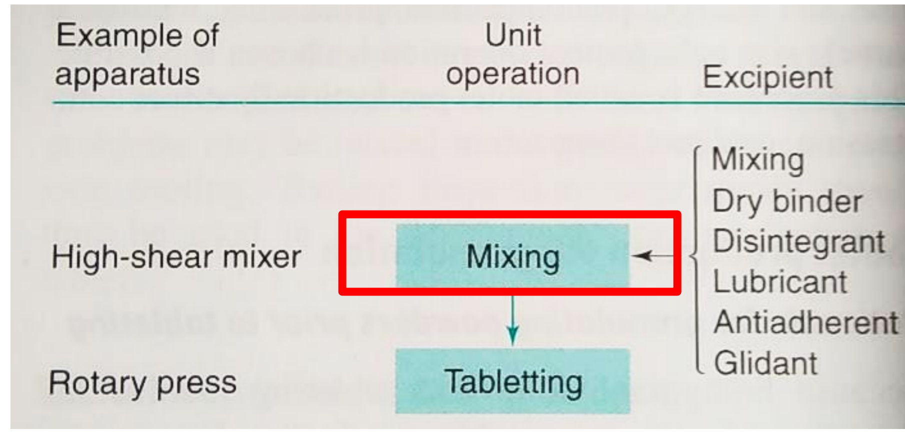
Unit Operations in Tabletting

Tablet Production with Granulation



Tablet Production with Direct Compression



Almost no solid dosage forms contain only one ingredient and as a result, mixing is a critical process to consider for effective blending of the active and other excipients.

- Ensure even distribution of all components of the dosage form-> Uniformity of content
- Ensure an even appearance of the final dosage form-> Acceptability
- Important for drug liberation from the dosage form-> Disintegration; modified release

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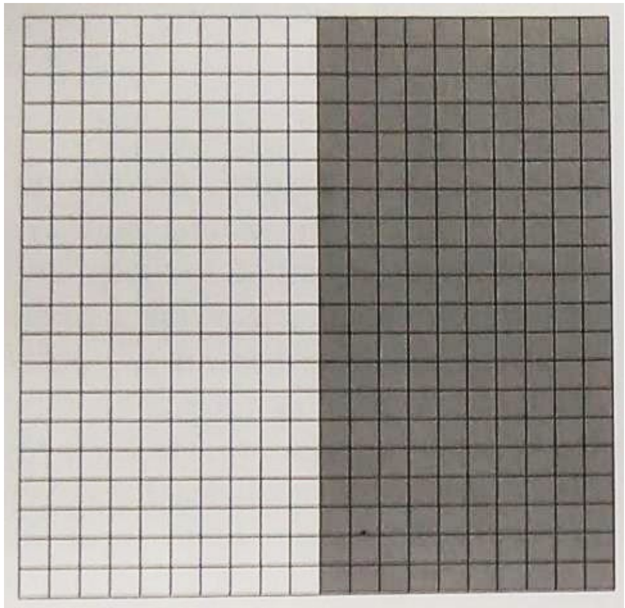
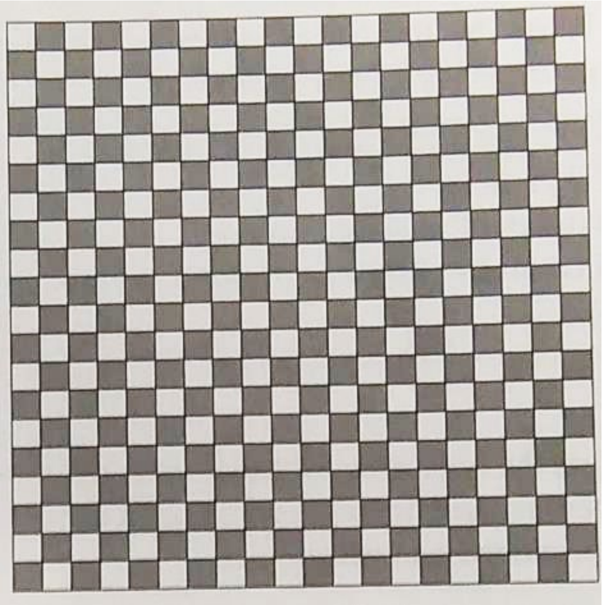
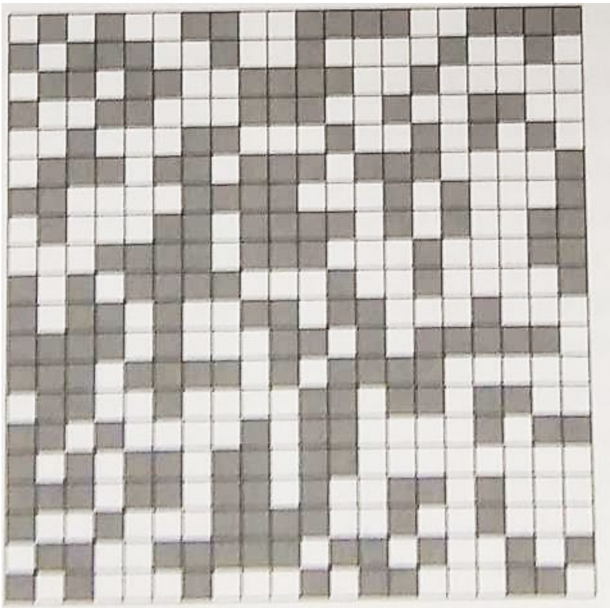
Mixing: Essential Concept



Segregated Powder



“Perfect” Mix



Random Mix

Random Mix-> Consider the probability that:

a) **Selection of a particular type of particle is the same at all positions in the mix (e.g. API)**
b) **The proportion of this particle to other ingredients in this position is equal to that in the total mix (e.g. Ratio of API:Diluent)**

Mixing: Types of Mixtures

1. Positive mixture
   - Components mix spontaneously and irreversibly by diffusion
   - Occurs as a function of time
   - Will occur w/o energy input; input of energy can speed up process
   - Applicable in general for miscible liquids and gases

2. Negative mixture
   - Components tend to separate out following mixing
   - Energy input must be sufficient to counter this tendency
   - Applicable in general for suspensions and emulsions

3. Neutral mixture
   - Static in behaviour: no tendency to form spontaneously but also unlikely to separate following formation of mixture
   - Energy input required to mix but not required to maintain mixture
   - Further energy input, however can cause segregation (demixing)
   - **Applicable in general to solids and semi-solids**

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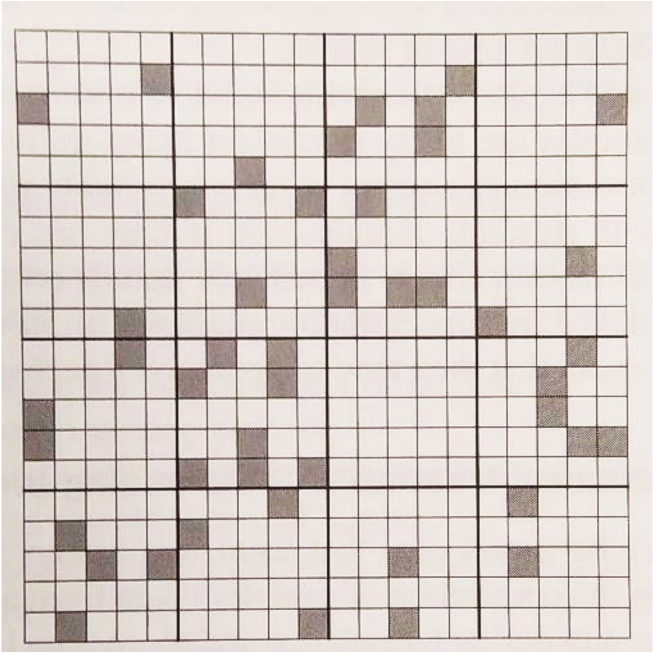
The Concept of Mixing: Scale of Scrutiny and Dosage Unit

- Evaluation of the degree of mixing is important!
  - Determine the extent of mixing at a given time
  - Discover the time at which sufficient mixing has occurred
  - Assess efficiency of process
  - Compare different mixing processes

- Scale of scrutiny
  - Refers to the minimum weight or volume of a sample of the mixture that must be analysed to guarantee the sufficient extent of mixing
  - Relates to the dosage unit of the solid dosage form

- Example: 200mg tablet containing 10mg ezetimibe
  - Need to be assured that every 200mg of powder in process contains 10mg of active
  - Scale of scrutiny is 200mg for sampling and QC

- Key aim when formulating tablets-> Minimise variation between samples in random mix
  1. Select an appropriate scale of scrutiny
  2. Select an appropriate particle size
  3. Select an appropriate method of mixing



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Powder-Mixing Equipment

1. Tumbling mixers/blenders
2. Agitator mixers
3. High-speed mixer-granulators
4. Fluidised-bed mixers

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Powder-Mixing Equipment: Tumbling Mixers

- Operation
  - Powder in steel drum that is rotated about an axis
  - Different shapes of drum
  - Mixing occurs primarily by shear and diffusive mechanisms
- Advantages
  - Useful for free-flowing powders
- Limitations
  - Does not mix poorly flowing powders-> Inefficient shear
  - Can cause powder segregation due to vibratory action
- General use
  - Mixing step prior to tabletting
  - Blending of lubricants, glidants or external disintegrants with granules

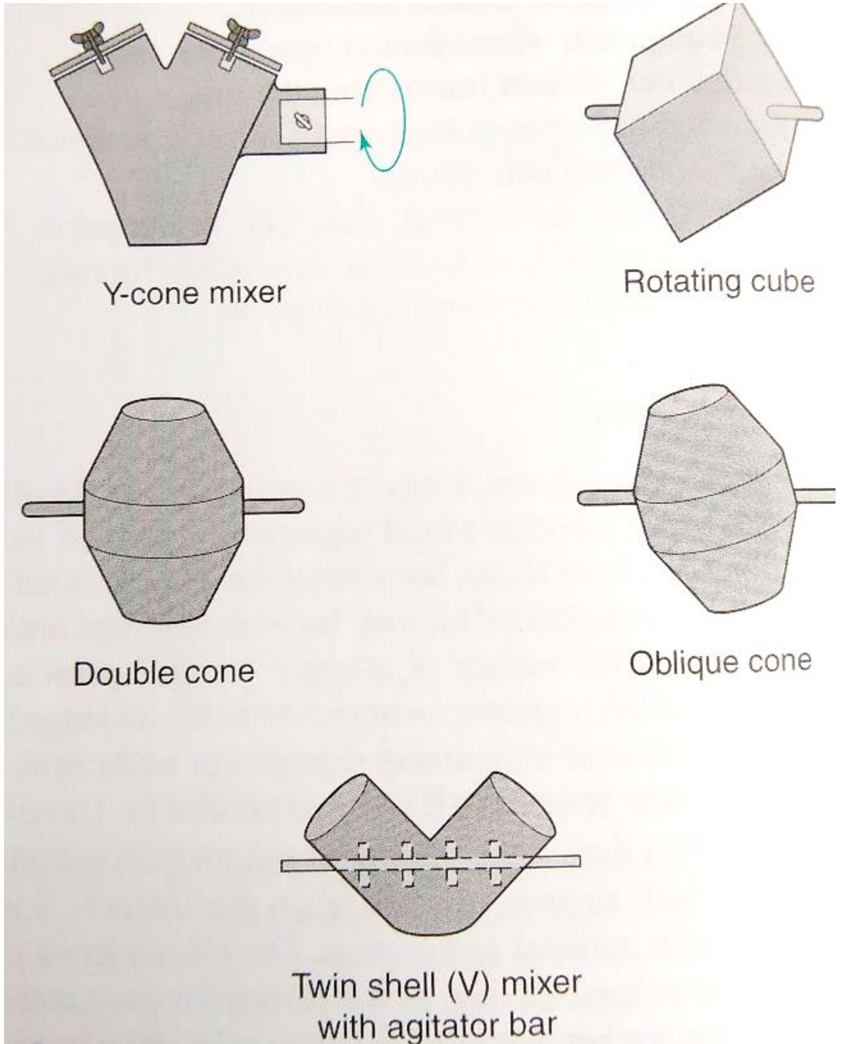

Fig. 12.6 Different designs of tumbling mixers.

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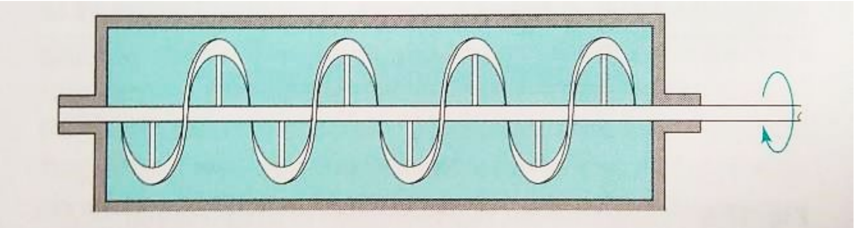
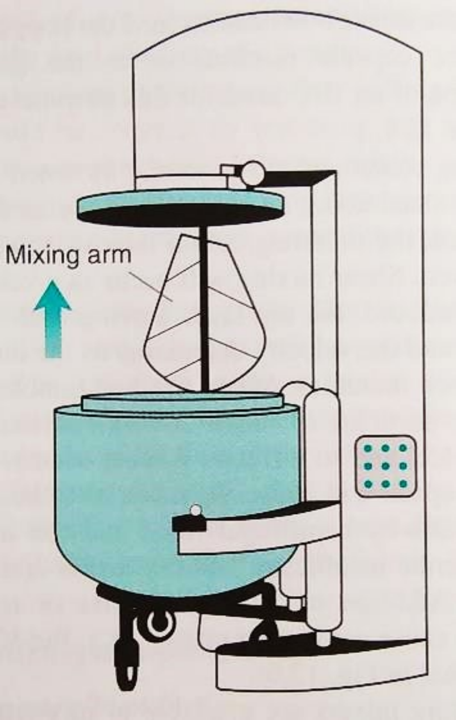
Powder-Mixing Equipment: Agitator Mixers

- Ribbon agitator
  - Convective mixing by use of helical blade
  - Better than tumblers for poor-flow powders or those prone to segregation



- Planetary mixer
  - Mixing blade on a rotating arm-> Convective and diffusive
  - Double rotatory effect



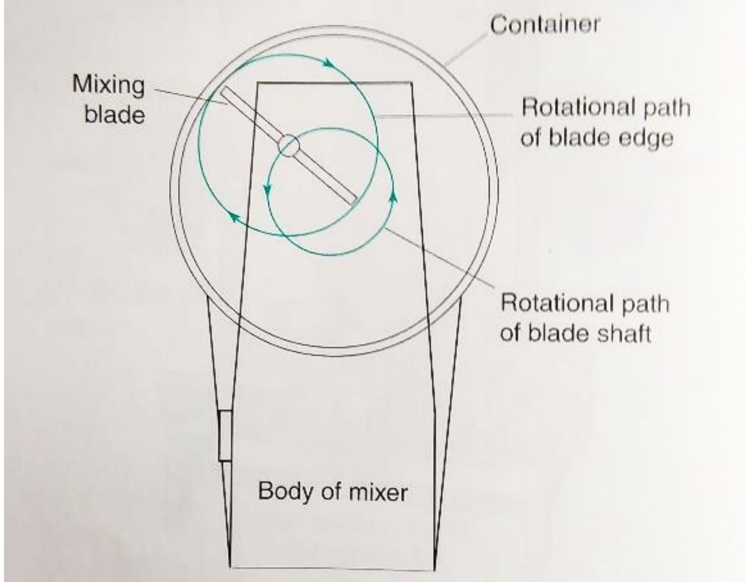


Fig. 12.12 Planetary mixer – top view, showing path of paddle.

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Powder-Mixing Equipment

- Mechanisms of mixing
  a) Convective mixing-> Transfer of relatively large groups of particles from one part of the powder bed to another
  b) Shear mixing-> Layer of powder bed moves over another and mixing occurs at interface
  c) Diffusive mixing-> Movement of individual particles due to expansion of void spaces between adjacent particles in the powder bed

- In general, all three mechanisms occur to some extent in a mixing process
  - Depends on instrument, mixing conditions and powder flowability

- General considerations in mixing processes
  - Quantity of API usually much less than that of other excipients-> Geometric dilution procedures
  - Volume fill of equipment-> Avoid over- and under-filling
  - Formulation and choice of predominant appropriate mixing mechanism

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Powder Flowability: Adhesion & Cohesion

- The presence of relative molecular forces of attraction have a resultant effect on a particle's tendency to stick to itself or to other materials
  - Cohesion-> Attraction between "like" substances (i.e. powder particles stick to powder particles; poor flow)
  - Adhesion-> Attraction between "unlike" surfaces (e.g. powder to container surface; better flow)
  - Attractive forces include van der Waal's, surface tension and electrostatic forces

- Particle size, shape and density influence powder cohesive forces and bulk powder flow
  - How?

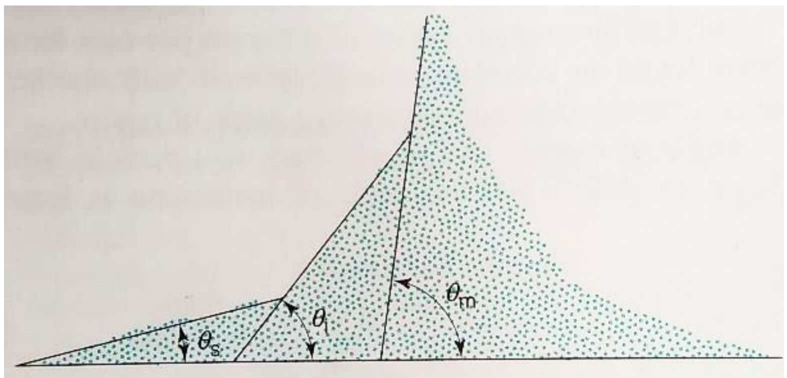
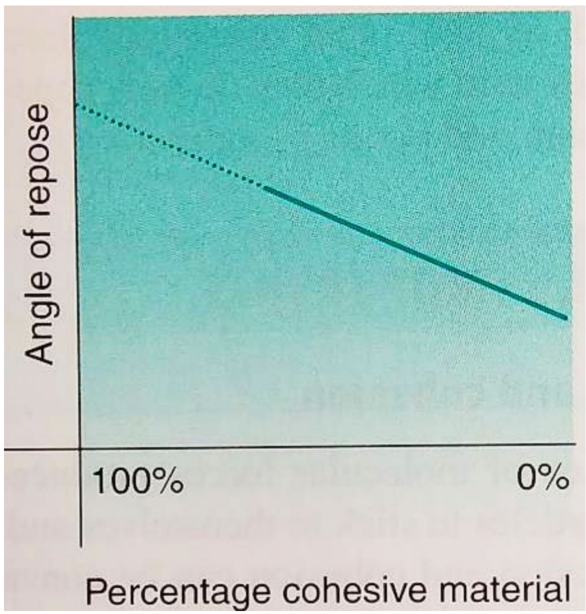
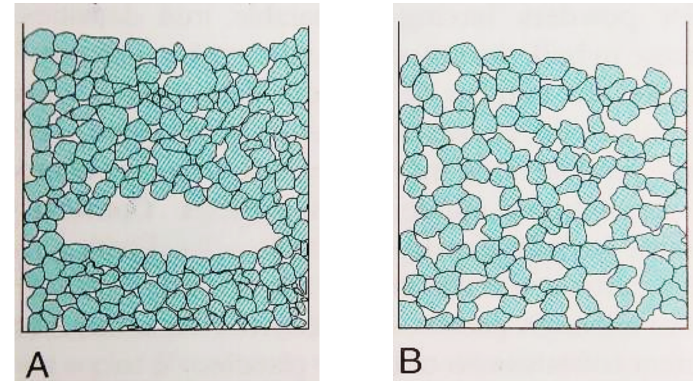


Fig. 13.3 Cohesive powder poured in a heap and showing different angles of repose: θ_m maximum angle formed by cohesive particles θ_s shallowest angle formed by collapse of cohesive particle heap, resulting in flooding. In some cases a third angle, θ_i is identifiable as an intermediate slope produced by cohesive particles stacking on flooded powder.



Powder Flowability: Packing Geometry

- Gravitational forces, adhesive and cohesive forces will influence how a powder will fill a defined volume
  - Resultant packing geometry of the particles is due an equilibrium between the forces
  - This equilibrium can be disturbed and “reset” by the application of energy (e.g. vibration)
  - The result? Differences in packing volume



- Packing geometry can be characterised by the measurement of porosity and bulk density
  - Useful for free-flowing powders

- Three types of density for pharmaceutical powders
  1. True density-> The density of the material itself excluding voids or interparticulate pores
  2. Bulk density-> The mass of the powder divided by the bulk volume; takes macroscopic interparticulate voids into account
  3. Tapped density-> The mass of the powder divided by the tapped volume; it is used in the estimation of powder flowability and compressibility

$$\rho_b = m/v$$

ρ_b = Bulk Density
m = Mass
v = Volume

For powders with a similar true density, an increase in bulk density means a decrease in porosity

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Powder Flowability: Factors affecting Packing Geometry

- Particle size and distribution
  - Powders with a wider size range are generally more compact and have higher degree of cohesion
  - Why?
- Particle shape and texture
  - Influence the minimum porosity and the formation of powder arches or bridges
- Surface properties
  - Influences attractive forces between particles
- Handling and processing
  - Prior to flow

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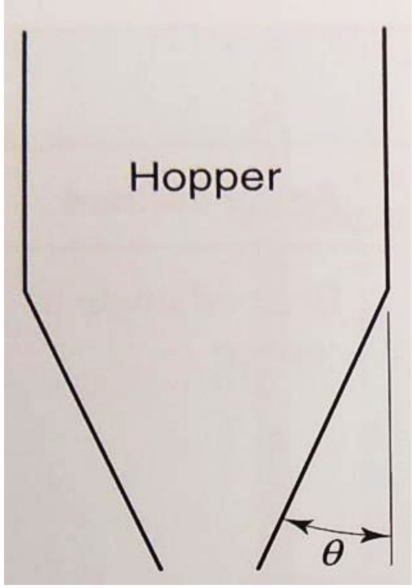
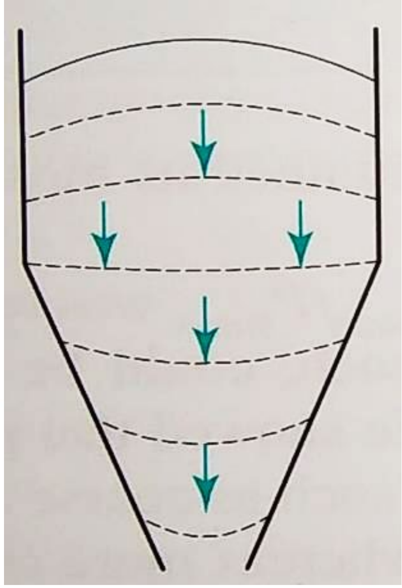
Powder Flowability on an Industrial Scale: Hoppers

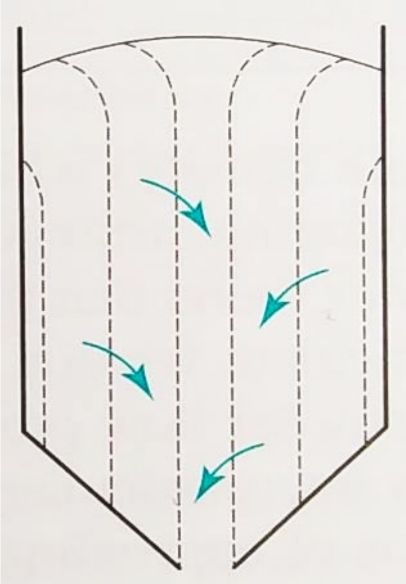
- Hopper
  - Tank that stores bulk powders
  - Used for transfer between processes and to encourage powder flow
  - Powder flows through an orifice in the base of the cylindrical container

- Flow through a hopper
  - Mass flow-> “First in, first out” for freely flowing powders
  - Funnel flow-> “Last in, first out” for poorly flowing powders (“rat-hole”)

- Factors affecting flow rate through hopper orifice
  - Orifice diameter
  - Hopper width
  - Hopper wall angle







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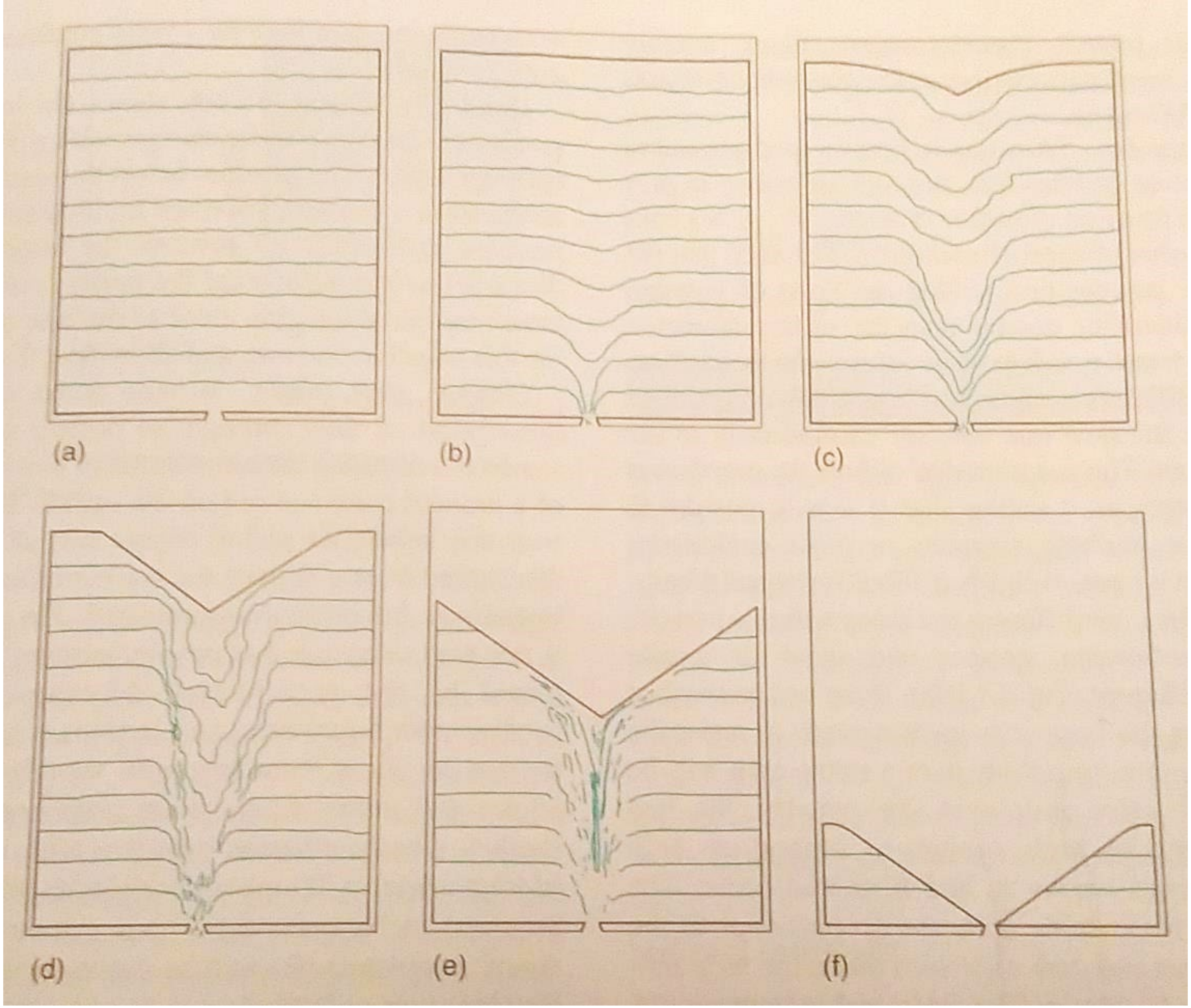
Powder Flowability: Powder Flow through an Orifice



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Powder Flowability: Characterisation of Flow

1. Angle of repose
   – Indirect method
   – Quantify angle between powder heap and flat surface
   – Lower angle means better flow

Table 24.14 Angle of repose as an indication of powder flow properties

Angle of repose (degrees)	Type of flow
<20	Excellent
20–30	Good
30–34	Passable*
>40	Very poor

2. Bulk density measurement
   – Indirect method
   – Measure ease at which powder consolidates
   – Obtain initial bulk density ("poured density") and bulk density after tapping ("tapped density")
   – Carr's Index and Hausner Ratio

$$Compressibility\ Index = 100 \times \left(\frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}} \right)$$

$$Hausner\ \ Ratio = \left(\frac{\rho_{tapped}}{\rho_{bulk}} \right)$$

Table 13.2 Relationship between powder flowability and % compressibility

% Compressibility range	Flow description
5–15	Excellent (free-flowing granules)
12–16	Good (free-flowing powdered granules)
18–21	Fair (powdered granules)
23–28	Poor (very fluid powders)
28–35	Poor (fluid cohesive powders)
35–38	Very poor (fluid cohesive powders)
>40	Extremely poor (cohesive powders

3. Hopper flow rate
   – Direct method
   – Measure time taken for known mass of powder to flow through orifice

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Powder Flowability: Improving Flow

1. Alter particle size and size distribution
   - Coarser powders flow better in general

2. Alter particle shape and texture
   - More spherical particles flow better
   - Smoother surfaces flow better

3. Alter surface forces
   - Reduce generation of electrostatic charge and surface tension on particle surface
   - Charge-> Minimise powder transport; earth containers to neutralise charge
   - Surface tension-> Control humidity

4. Add excipients
   - Use of flow activators-> Glidants (e.g. colloidal silica)
   - Reduce cohesion and adhesion

5. Alter process conditions
   - Use of vibration-assisted hoppers
   - Use of force feeders-> Vibrating baffles at the base of hoppers; rotating paddles after exit from hopper

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Powder Segregation (Demixing)

- Essentials
  - The separation of components within a powder mixture
  - Important factor to consider for bulk powder transfer and storage

- Why does segregation happen?
  - Monosized populations of powder samples are very rare (see lecture on Particle Tech)
  - Different particles will have different size, shapes and densities
  - Particles with similar properties tend to congregate together

- Segregation is influenced by three main effects
  1. Particle size-> Main cause in solid powders; percolation, trajectory and elutriation segregation
  2. Particle shape-> Influences flow properties of a particular component; high flowability of one component relative to another
  3. Particle density-> Influences downward motion due to gravity or other force; not usually important for pharmaceutical powders

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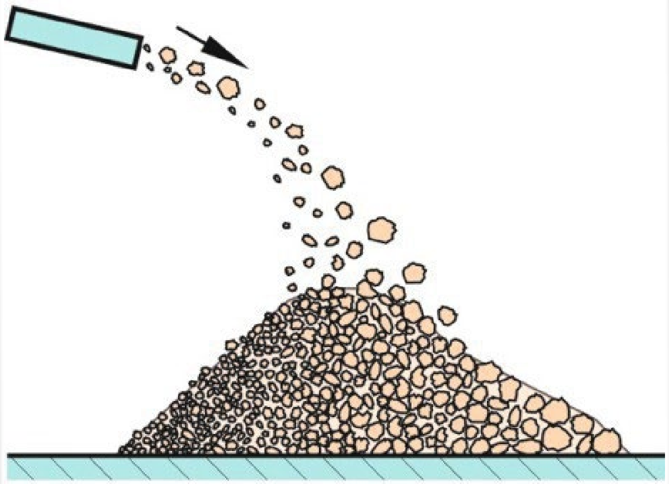
Powder Segregation: Particle Size Effects

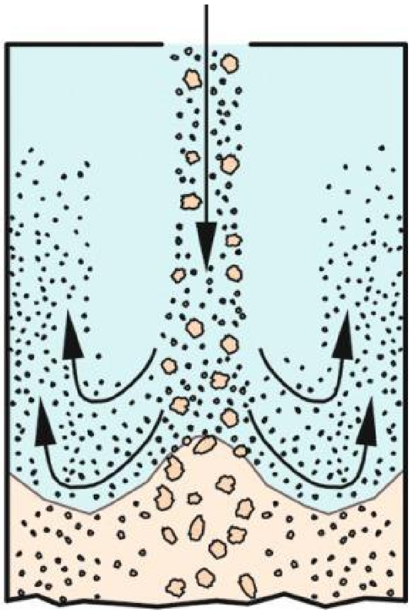
Percolation segregation

- Smaller particles pass through voids between larger particles
- Smaller particles congregate at bottom of container



Trajectory segregation

- Larger particles have greater kinetic energy
- Larger particles travel further along a path before their movement stops
- Larger particles pushed to borders



Elutriation segregation (Fluidisation segregation)

- Air turbulence created in process keeps smaller particles afloat
- Smaller particles later settle on larger powder bed
- "Dusting out"

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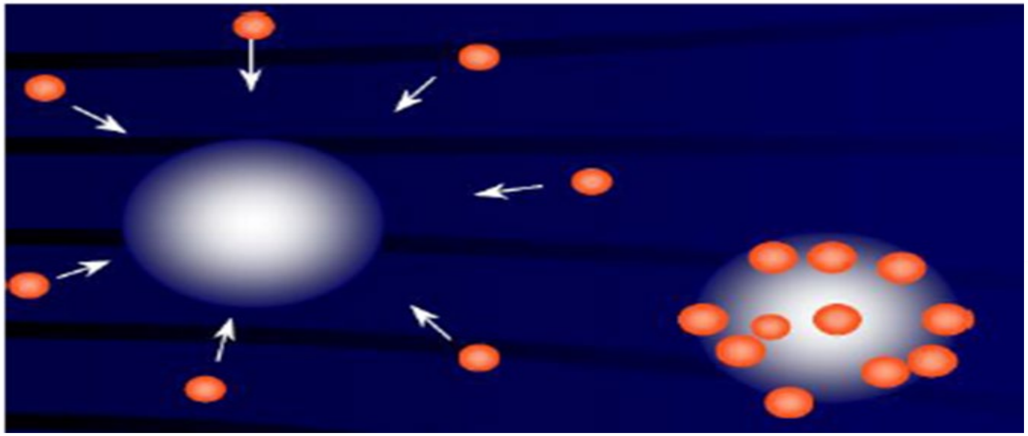
Prevention of Powder Segregation

- Various methods employed to reduce segregation
  a) Particle size reduction/milling and separation of a particular size before mixing
  b) Controlled crystallisation of crystal habit and polymorph
  c) Selection of excipients with similar density of particles
  d) Granulation creates granular units composed of all ingredients that are of a uniform size
  e) Reduce vibration and powder movement within the tabletting processes where possible
  f) Use of “ordered mixing”

- Ordered mixing
  – Use of larger “carrier” particles that micronised particles will adhere to
  – Larger particle and adsorbed particles essentially move as one larger particle-> Less segregation and improved flow properties
  – Important for direct compression tabletting processes
  – Requires uniformity of carrier particle size, sufficient ratio of carrier:small particle and reduced vibration and movement where possible



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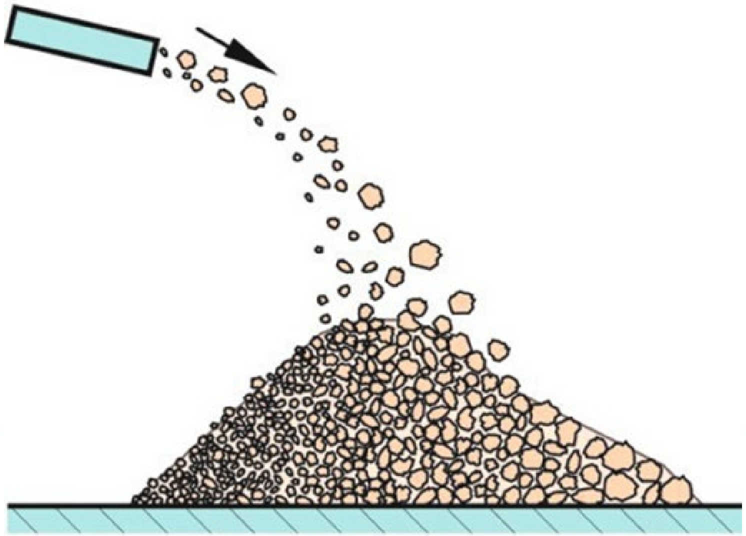

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Further Reading

- Aulton's Pharmaceutics Chapters
  - Mixing
  - Powder Flow

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