كلية: الصيدلة	مقرر: التكنولوجيا الصيدلانية
الرمز: PHPT 638	مدرس المقرر: د. بشير القاسمي

Solid-state properties

Pharmaceutical technology

Dr. Basheer Al-kasmi

Lecture 1

States of matter

1. Solid (unique)
2. Liquid
3. Gas (vapour)

The strength of interaction between two molecules

1. Hydrogen bonds: electrostatic attraction (hydrogen atom - electronegative atom)

2. van der Waals forces:
   attraction (positive pole - negative pole)

Crystallization

molecules are packed in a defined order, and this same order repeats over and over again throughout the particle

Crystal ~ melting point

Crystal producing

1. Molten sample: Cooling below the melting point.
2. Solution: supersaturated by:

- Evaporation
- Cooling
- Anti-solvent

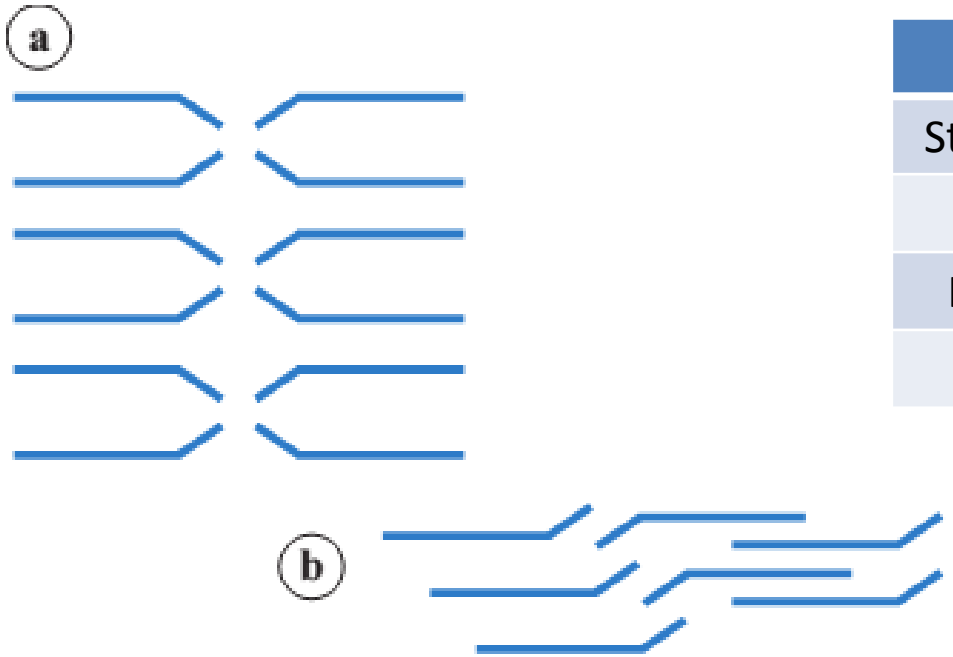
Polymorphism

Packing in other pattern according to crystallinity conditions.

The change in conditions could be a different in:

solvent, stirring, or impurities

Polymorphism



Form B
Strong lattice (higher density)
Higher melting point
Hard to remove a molecule
Low dissolution rate

Polymorphism

Monotropic polymorphism:

- Only one polymorphic form is stable (highest melting point).
- Other: metastable form (stable for days or months)

Enantropic polymorphism

- Under different conditions (temperature and pressure) the material can reversibly transform between alternative stable forms.

Polymorphism exambles:

Chloramphenicol palmitate:
α-polymorph: Stable form, β-polymorph: metastable
α produces lower serum levels than β

Paracetamol:
Form: more compressible

Hydrates and solvates

Crystallization: trap solvent within the lattice

Solvent: water ⟶ Hydrate

Solvent: other than water ⟶ solvate

Monohydrate:1 molecules of water to 1 molecule of drug

Dihydrate: 2 molecules of water to 1 molecule of drug

Trihydrate : 3 molecules of water to 1 molecule of drug

Hydrates vs Anhydrous:

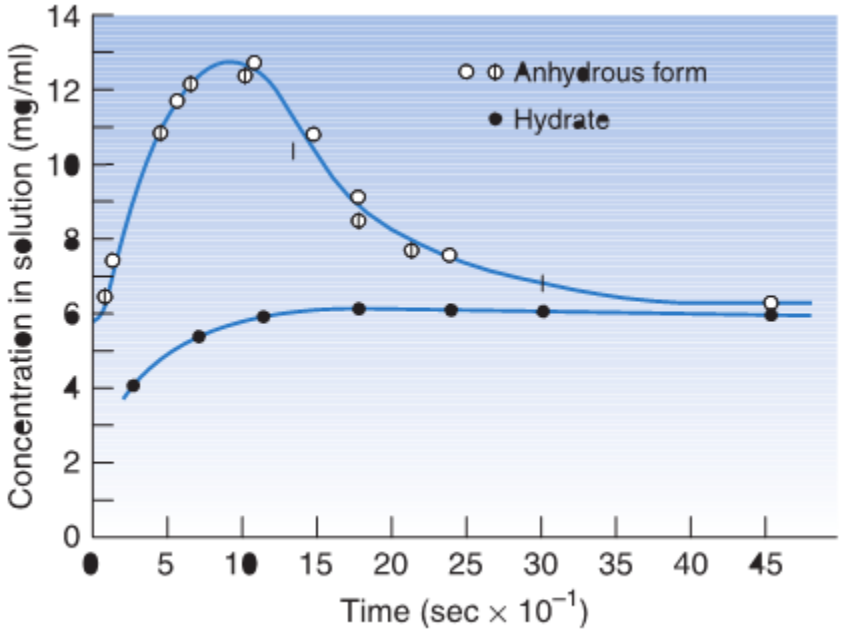
Theophylline (hydrate):

hydrogen bond = lattice together = slower dissolution rate.

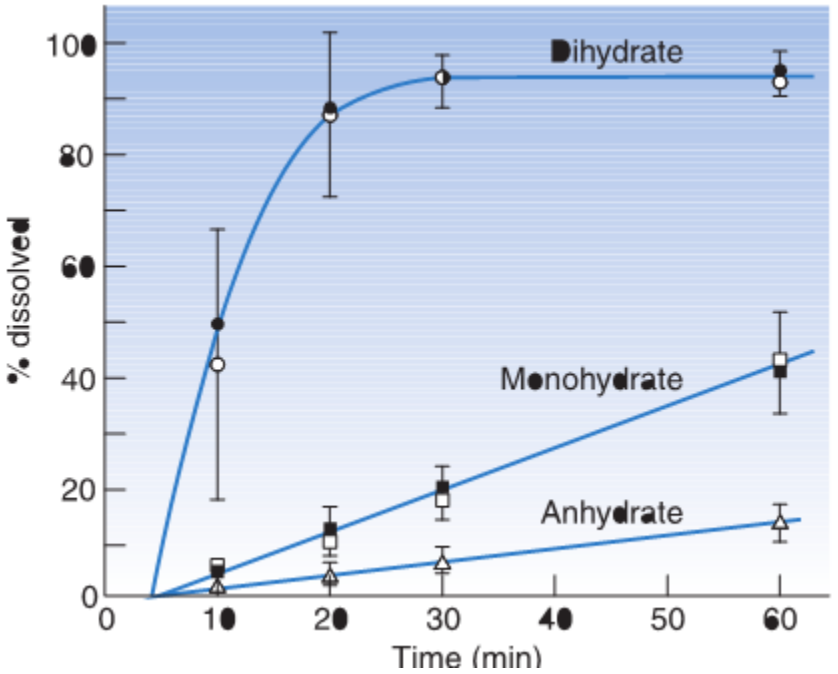
Erythromycin (hydrate)

water as a wedge pushing two molecules apart = preventing the interaction between the molecules = higher dissolution rate

Hydrates vs Anhydrous:



Theophylline



Erythromycin

Amorphous state:

molecules are not packed in a repeating long-range ordered fashion

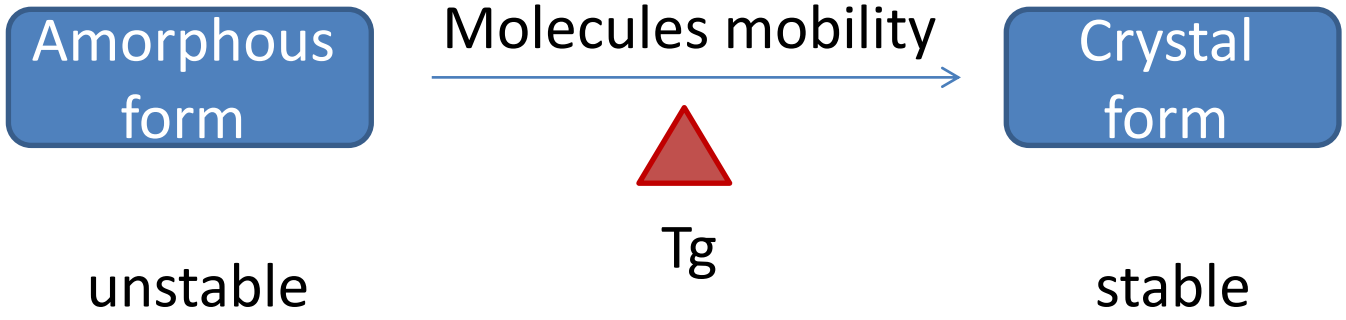
crystals have a melting point (the break-up of the crystal lattice), whereas the amorphous form does not (as it does not have a crystal lattice to break)

Amorphous producing:

1. Polymer (Semi-crystal): naturally
2. Solidifcation process was too fast (spray-dried)
3. crystal broken (milling).

Amorphous: unstable and will revert back to the crystal

Amorphous State:



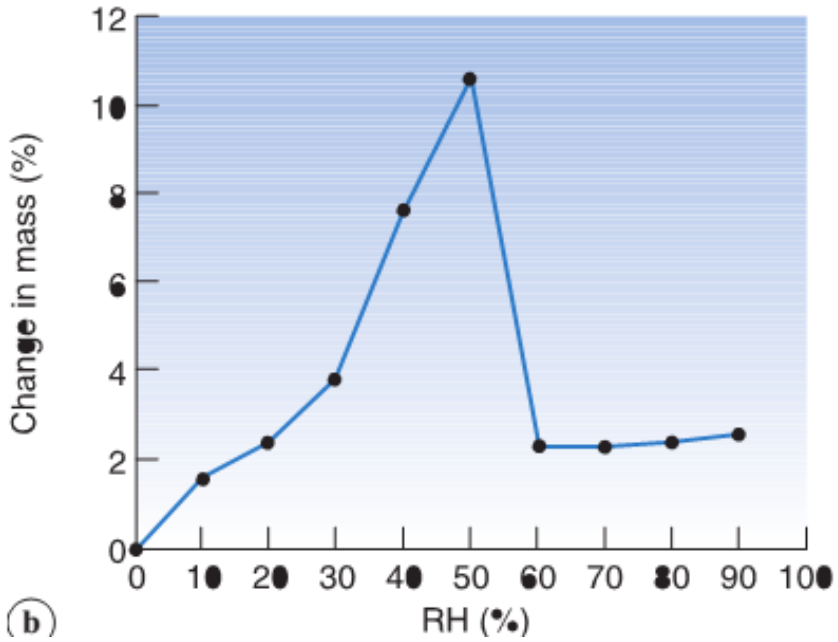
Glass transition temperature (Tg): Temperature at which amorphous transfer from glassy (brittle) to rubbery state.

It can be lowered by adding a small molecule of plasticizer like water

Amorphous vs Crystal:

Amorphous
No melting point
Transfer to crystal above Tg
Higher dissolution rate
Absorb larger quantities of water vapour (more degraded by hydrolysis)

Amorphous state:



Lactose amorphous

Lactose crystal

Crystal habit

Each changes in internal packing of a solid will give changing in the external shape of a crystal. The external shape is called the crystal habit.

Effect: dissolution rate and flowability

Crystal habit

Sphere:

radius 20 μm
volume 33,515 μm^3
surface area 5,027 μm^2

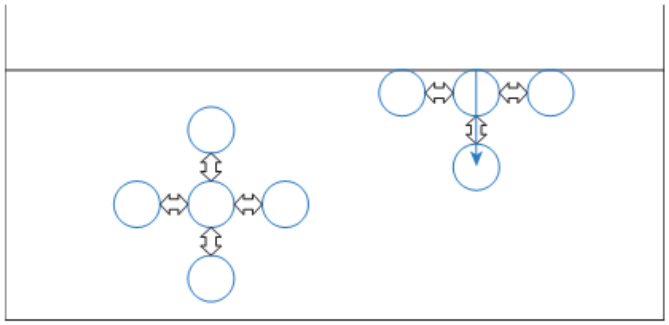
Cube:

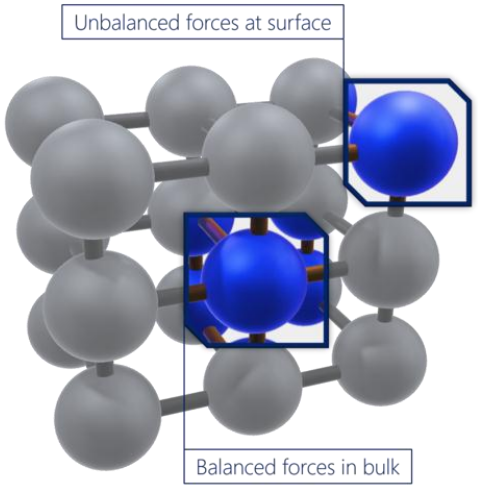
length, width and
thickness 32.2 μm
volume 33,386 μm^3
surface area 6,221 μm^2

Needle:

length 335 μm, width
and thickness 10 μm
volume 33,500 μm^3
surface area 13,600 μm^2

Surface tension vs surface energy





Liquid: surface tension, same for all surface
Solid: surface energy, every crystal face, edge and defect have different surface energy

Surface energy

Molecules at the surface of a material have a net inward force exerted on them from the molecules in the bulk

any interaction starts by an initial contact between two surfaces

Example: wetting solid by liquid

Surface energy

It changes in the same drug according to:

- habit
- polymorphic form , amorphous forms have surface energy greater than crystal
- the presence of a solvate or hydrate

Surface energy determining

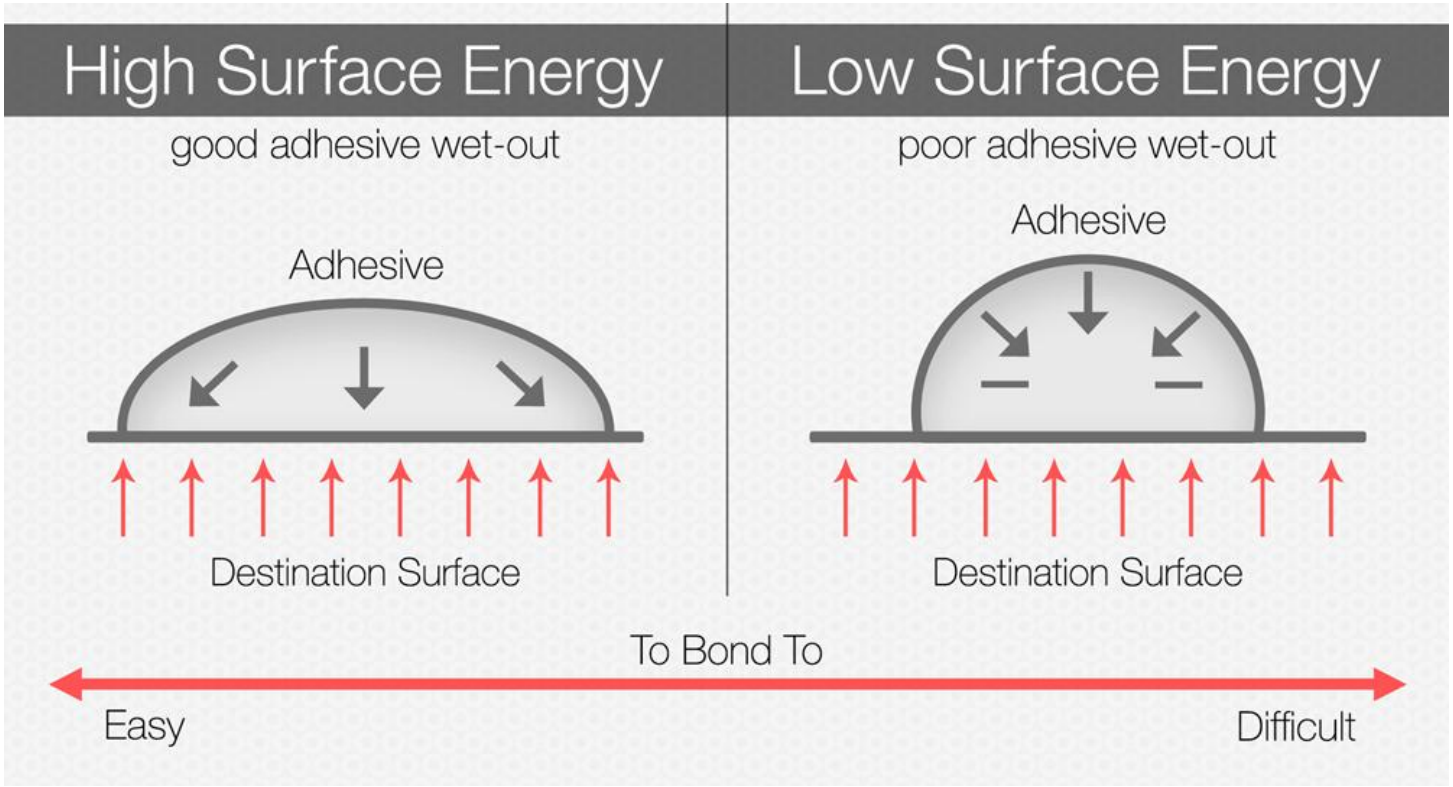
measure the contact angle between drop of liquid onto the solid surface

0 degrees = Perfect wetting of a solid by a liquid

Powders present problems as it is not possible to place a drop of liquid on the surface so powder compact before add liquid.

Disadvantage: compaction may well change the surface energy of the powder.

Surface energy determining



Surface energy determining Inverse phase gas chromatography

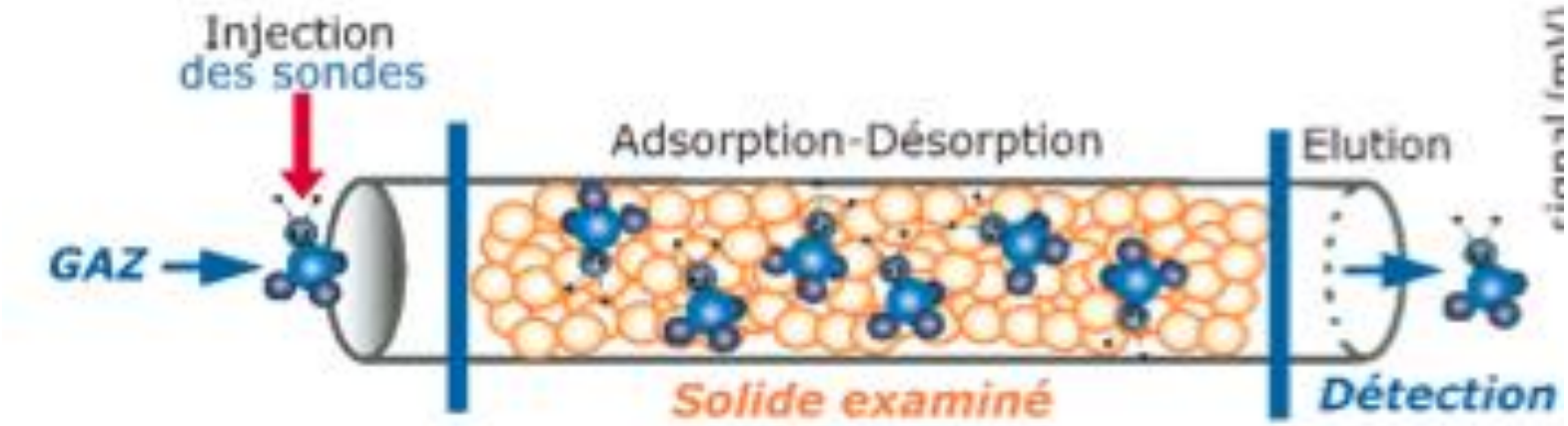
study the interaction between the powder and a vapour.

A column is packed with a powder and a test sample is injected into a constant flow of gas (hexane) through the column, which is held at constant temperature.

The test sample will be slowed to different extents based on the extent of interaction between them and the powder in the column

From the retention time of test sample, surface energy is determined

Surface energy determining
Inverse phase gas chromatography



THE END

Particle size analysis

Pharmaceutical technology

Dr. Basheer Al-kasmi

Lecture 2

The effect of particle size

Uniformity of drug content:

Powders with different particle sizes have different flow and packing properties.

Dissolution rate of drug:

reducing the size of particles will generally increase the rate of dissolution, which can have a direct impact on bioavailability

Dimensions:

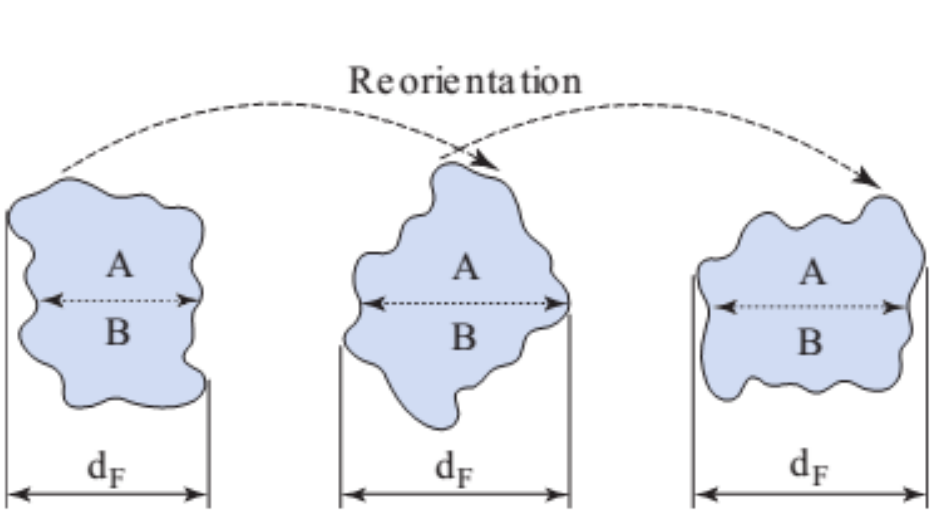
Description	Majority of particles (µm)
Coarse powder	350 <
Medium fine powder	350–100
Fine powder	100–50
Very fine powder	50–10
Micronized powder	< 10 µm

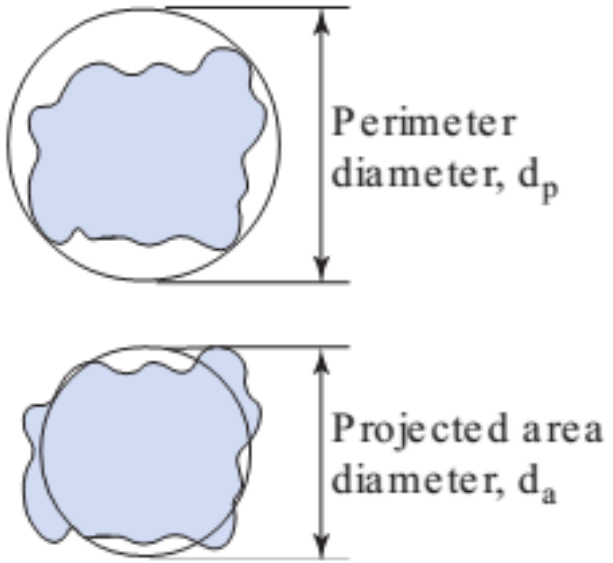
Dimensions:

Describing the size of irregularly shaped particles require measurement of no ewer than three dimensions

To overcome the problem of describing a three-dimensional particle with a single number,
we employ the concept of the equivalent sphere

Dimensions (Equivalent sphere diameters):





Range of equivalent diameters of particles measured (known as the size fraction) (μm)	Mean diameter of each size fraction (μm)	Number of particles in each size fraction (frequency)	Percent particles in each size fraction (% frequency)	Number of particles in the sample smaller than the mean diameter of each size fraction	Cumulative percent frequency smaller than the mean diameter of each size fraction (cum. % undersize)	Number of particles in the sample larger than the mean diameter of each size fraction	Cumulative percent frequency larger than the mean diameter of each size fraction (cum. % oversize)
<9.9	–	0	0.0	0	0	2200	100.0
10–29.9	20	100	4.5	50	2.3	2150	97.7
30–49.9	40	200	9.1	200	9.1	2000	90.9
50–69.9	60	400	18.2	500	227	1700	77.3
70–89.9	80	800	36.4	1100	50.0	1100	50.0
90–109.9	100	400	18.2	1700	77.3	500	22.7
110–129.9	120	200	9.1	2000	90.9	200	9.1
130–149.9	140	100	4.5	2150	97.9	50	2.3
150>		0	0.0	2200	100.0	0	0.0

Particle size distribution:

Histogram:

Graphical representation of a particle diameter range and their frequency.

Allows different particle size distributions to be compared

The peak frequency value, known as the mode

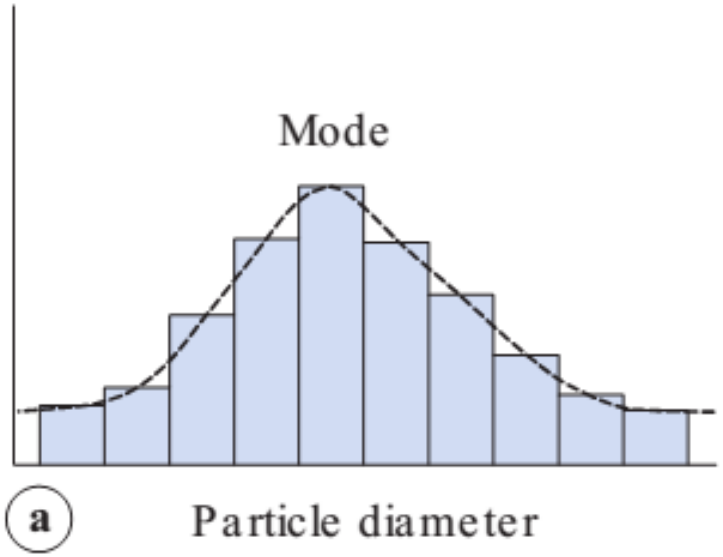
Particle size distribution

Histogram:

Normal distribution:

- Particles are normally distributed symmetrically about a central value

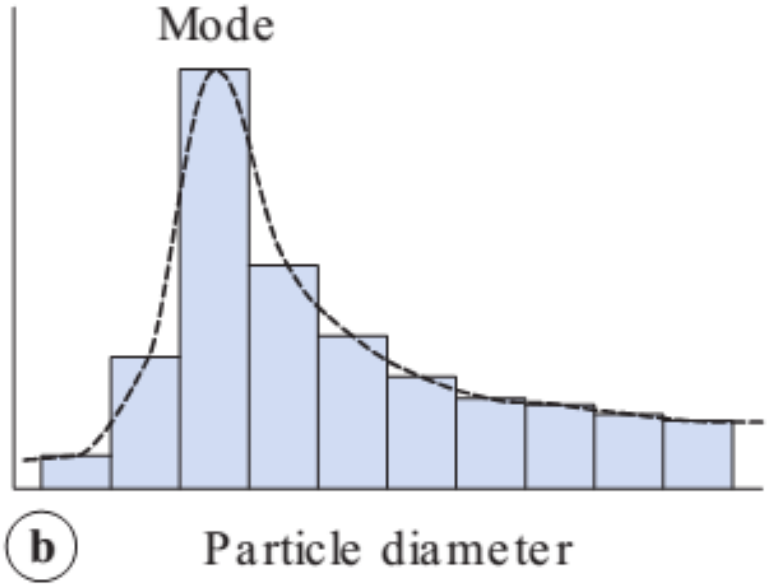
- Mode separates the normal curve into two identical halves,



Particle size distribution Histogram:

Skewed distribution:

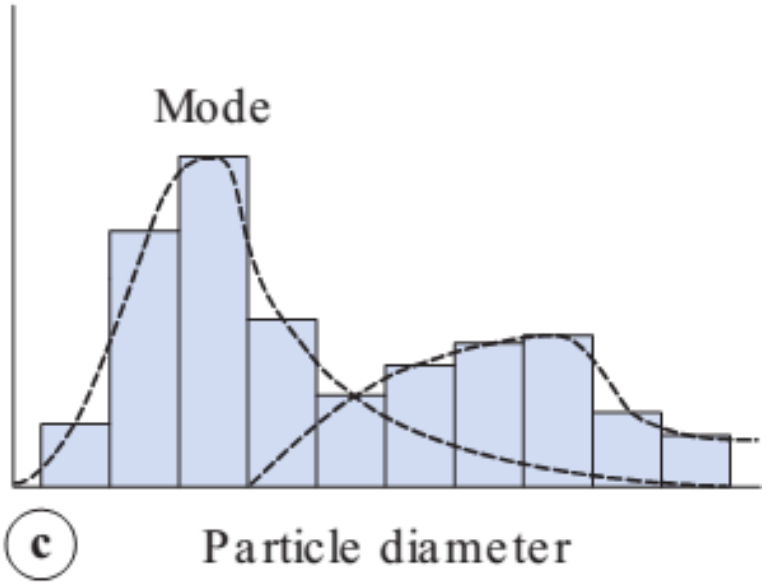
- Large proportion of fine or coarse particles
- Positively skewed: frequency towards higher size ranges
- These skewed distributions can sometimes be log normal distributions



Particle size distribution Histogram:

Bimodal distribution:

- Milling
- Unmilled produces a mode towards the highest particle size
- Milled produces new mode which appears lower down the size range.



Particle size distribution
Cumulative percent:

Cumulative percent frequency undersize:

Begins with the coarsest particles

Cumulative percent oversize:

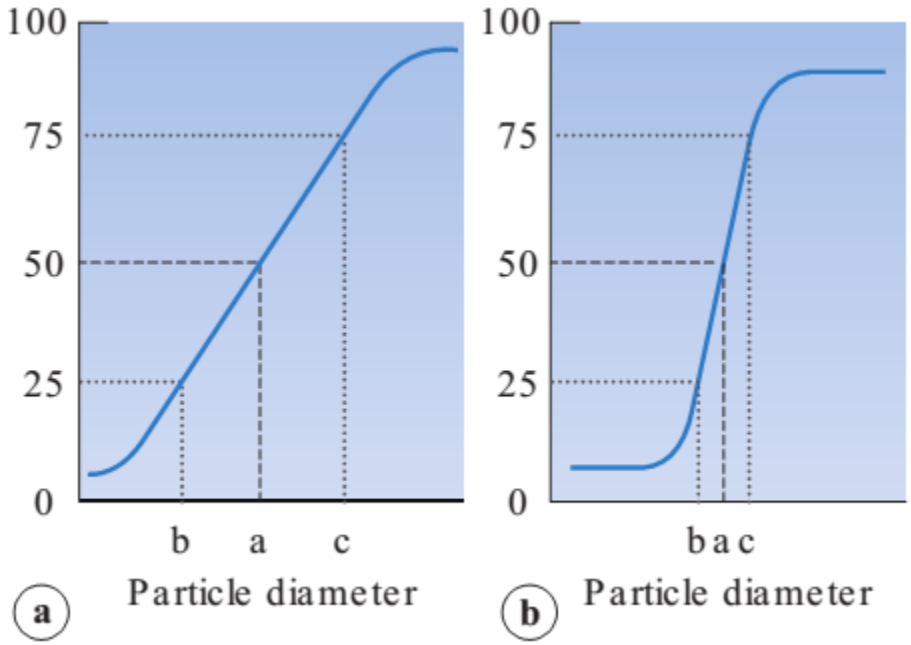
Begins with the finest particles.

Particle size distribution

Cumulative percent :

The median:
The point that separates the cumulative frequency curve into two equal halves.

The lower and upper quartile points at 25% and 75% divide the upper and lower ranges of a symmetrical curve into equal parts



Statistical methods to summarize size distribution data:

Interquartile Coefficient of Skewness (IQCS)

$$\mathrm{IQCS} = \frac{(c-a)-(a-b)}{(c-a)+(a-b)}$$

The IQCS can take any value between −1 and +1.

If the IQCS is zero then the size distribution is practically symmetrical between the quartile points.

Particle size analysis methods: Sieve methods

Range: 5 to 125 000 µm

For Dry powders

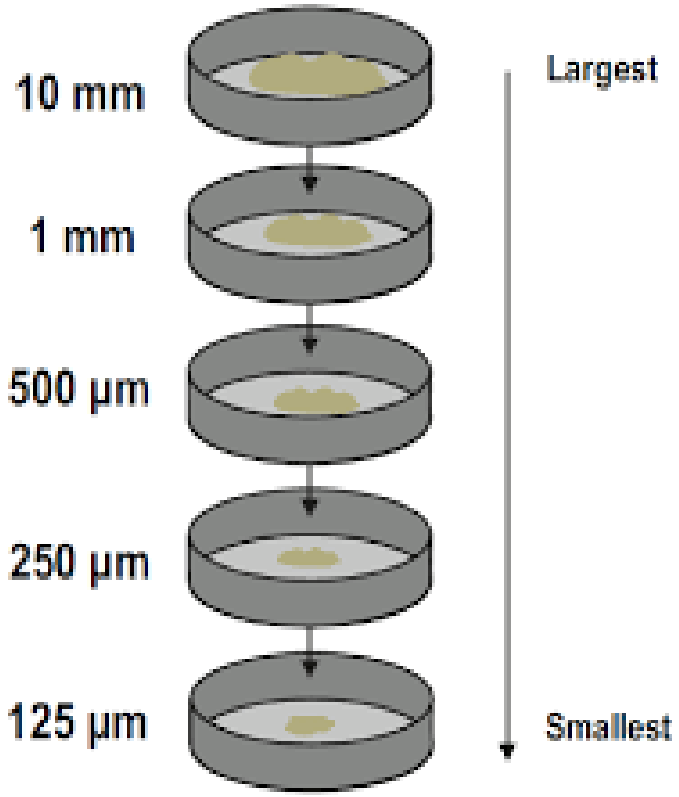
U.S. Mesh Size: the number of openings in one square inch of a screen.

Example: 40 US mesh = 425 µ

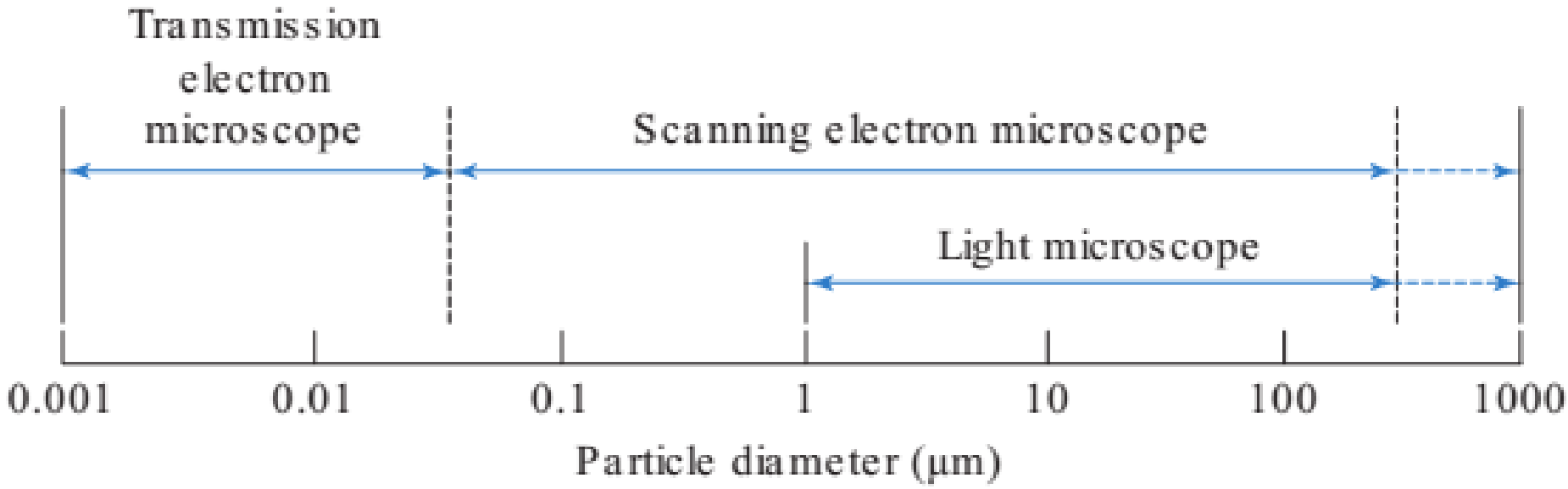
60 US mesh = 250 µ

80 US mesh = 165 µ

Particle size analysis methods: Sieve methods



Particle size analysis methods: Microscope methods



The end

Particle size reduction

Pharmaceutical technology

Dr. Basheer Al-kasmi

Lecture 3

Influence of size reduction on size distribution

The lower particle size limit of a milling operation is dependent on

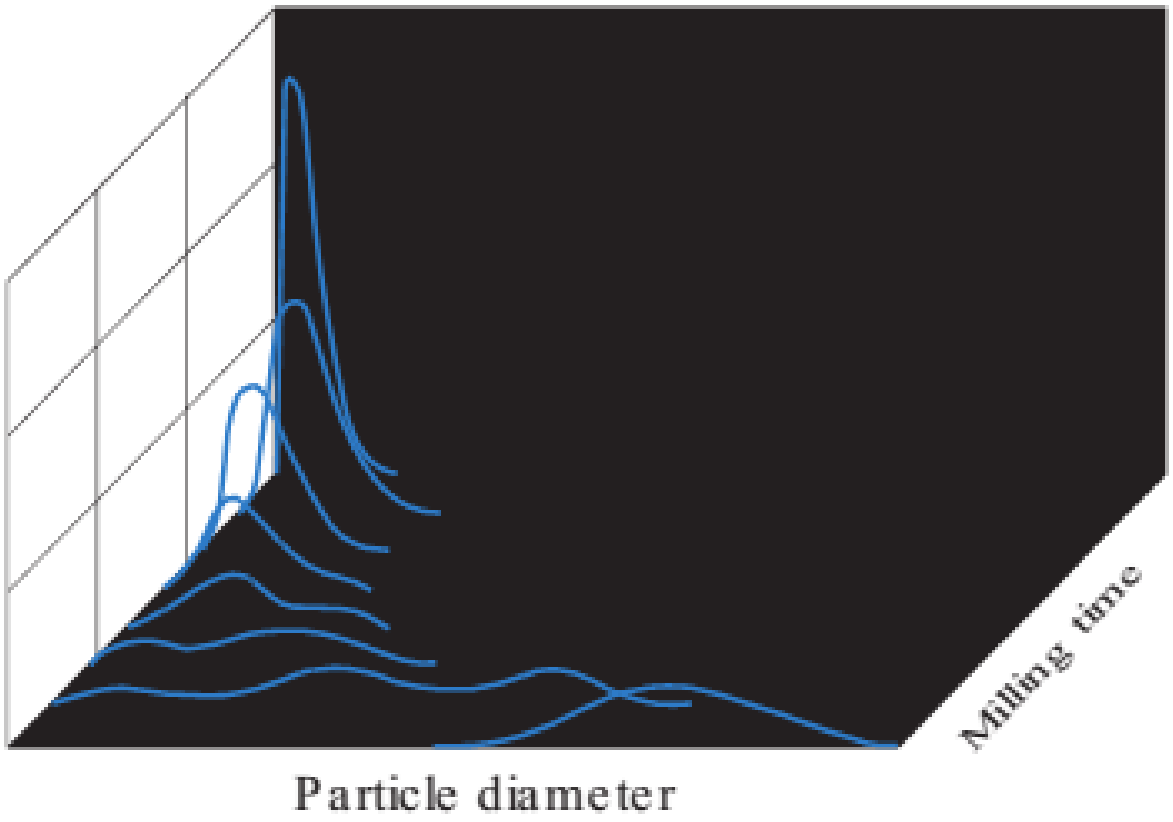
- The energy input size reduction (comminution) force
- Material properties.

Influence of size reduction on size distribution

Normal, size distribution was transformed into a size-reduced bimodal population

If milling is continued the unimodal population reappears, as the energy input is not great enough to cause further fracture of the finest particle fraction

Influence of size reduction on size distribution



Influence of size reduction on size distribution

Between Particle diameters below approximately 5 µm, an interactive cohesive forces between the particles are arised.

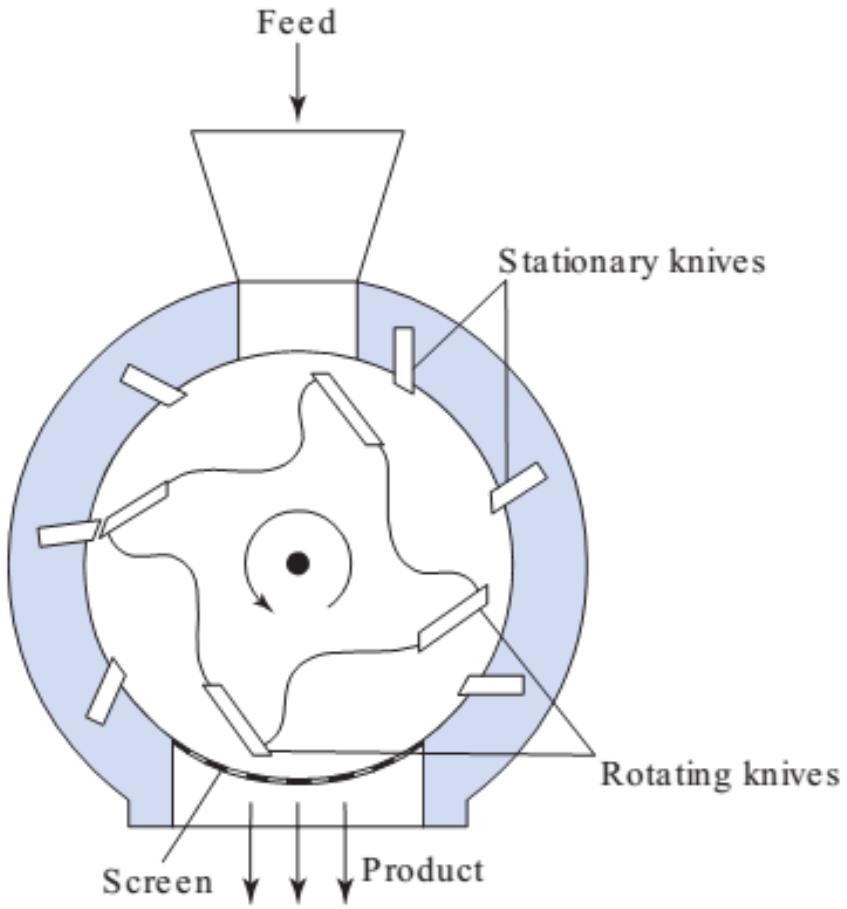
If comminution force of the used method is not great enough to cause further fracture, then the Particle (below 5 µm) agglomerate as opposed to particle fracture and size reduction ceases

Size reduction methods

1. Cutting methods
2. Compression methods
3. Impact methods
4. Attrition methods

Cutting methods

The shear rates present in cutter mills are useful in producing a coarse degree of size reduction of dried granulations prior to tableting



Compression methods

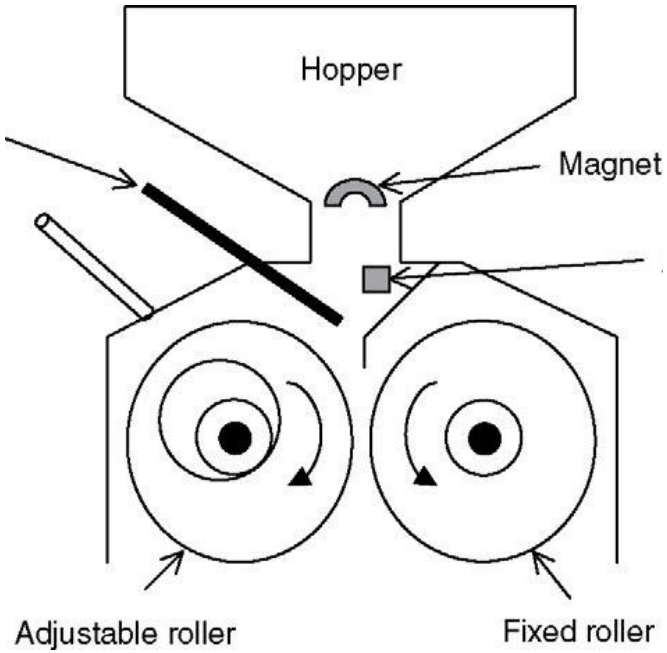
Runner mills
Size reduction by compression can be carried out on a small laboratory scale during development using a mortar and pestle.

Attrition methods

Roller mill

Produce size reduction of solids in suspensions, pastes or ointments

Two or three porcelain or metal rollers are mounted horizontally with an adjustable gap, which can be as small as 20 µm

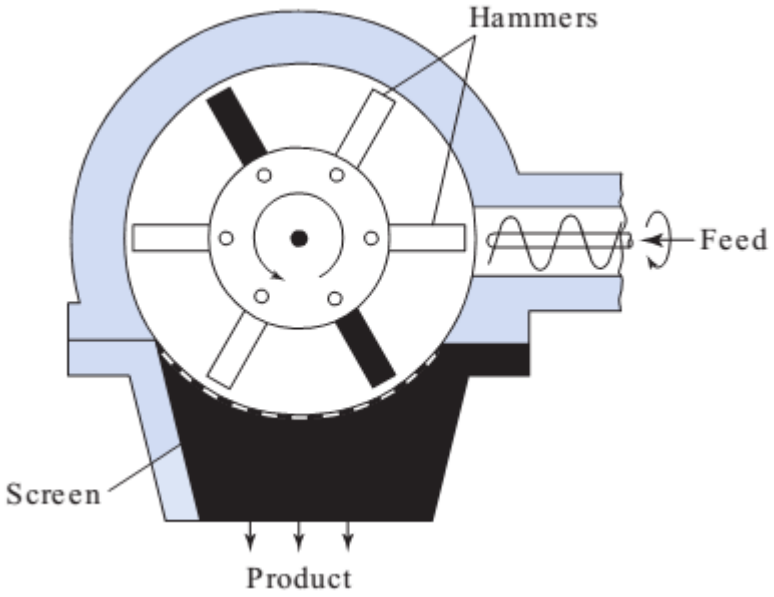


Impact methods

Hammer mill

The angular velocity of the hammers is so high that most particles undergo brittle fracture

Hammer mills tend to produce powders with narrow size distributions

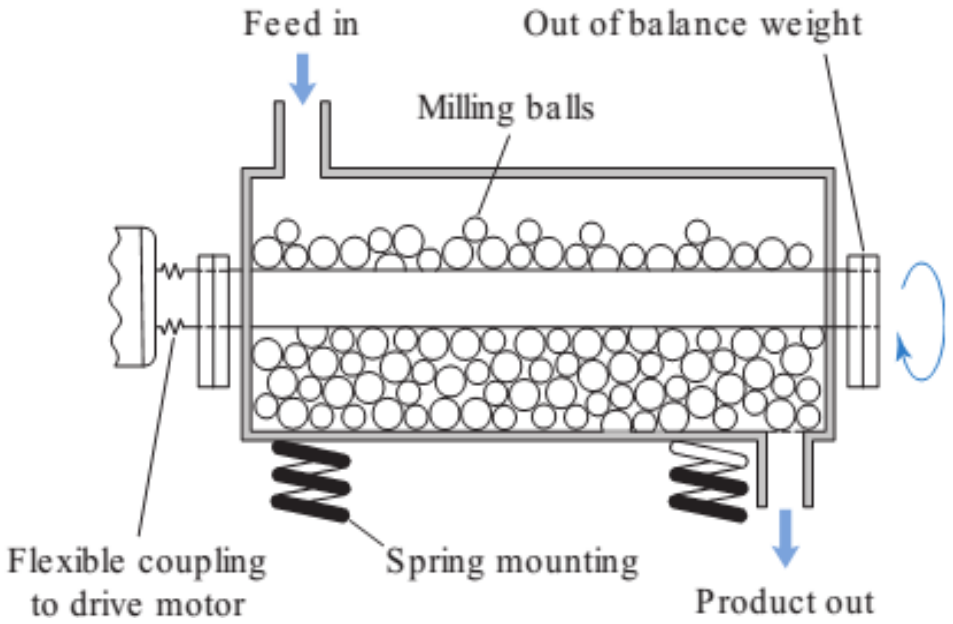


Impact methods

Vibration mill

Vibration mills are filled to approximately 80% total volume with porcelain or stainless steel balls

During milling the whole body of the mill is vibrated and size reduction occurs by repeated impact



Combined impact and attrition methods

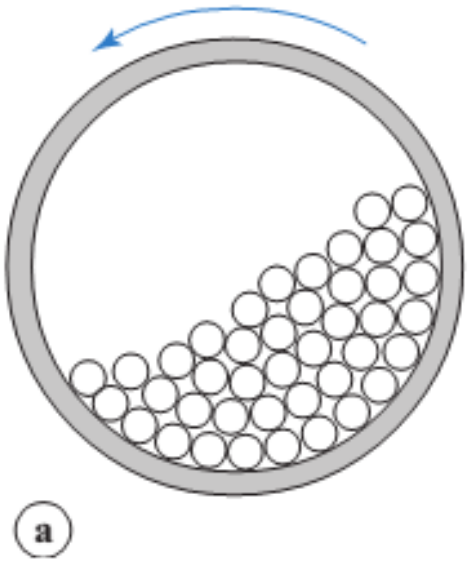
Ball mill

contains balls that occupy 30–50% of the total volume.

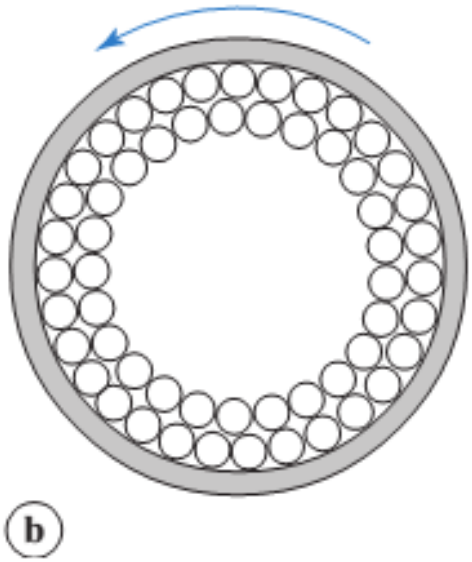
may contain balls with many different diameters as this helps to improve the process, as the large balls tend to break down the coarse feed materials and the smaller balls help to form the ne product by reducing void spaces between balls

Combined impact and attrition methods

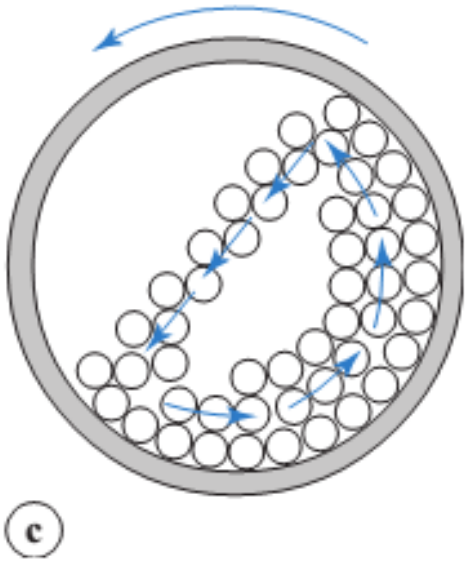
Ball mill



Low angular velocities
size reduction is minimal



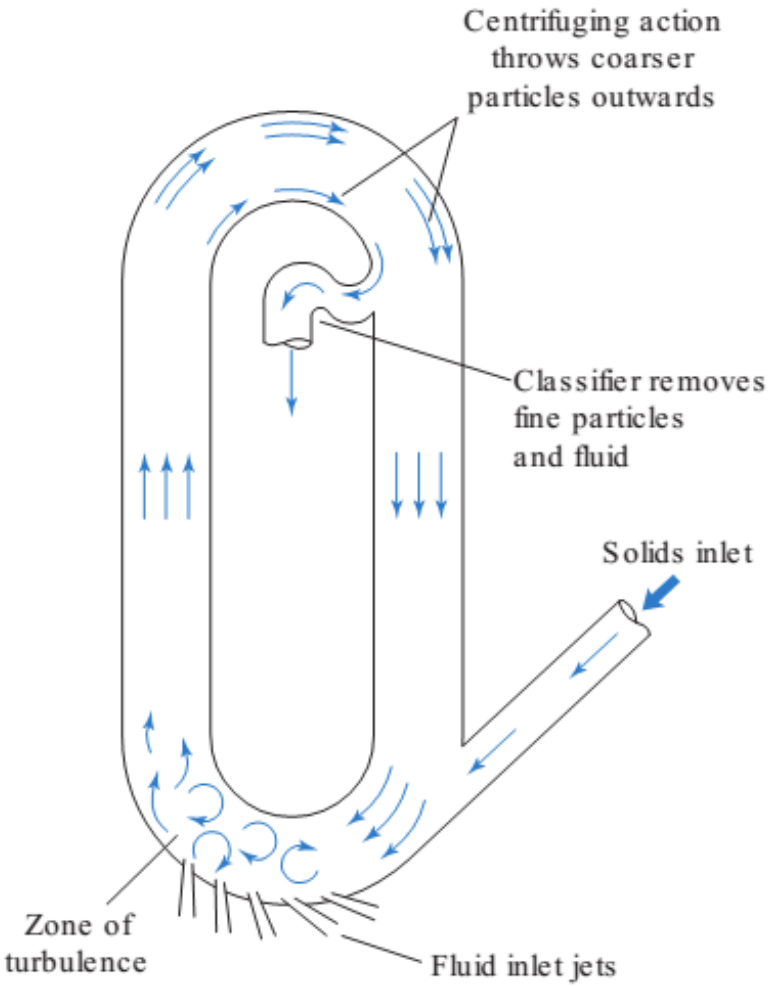
High angular velocities
no size reduction



30 rpm
most efficient

Combined impact and attrition methods

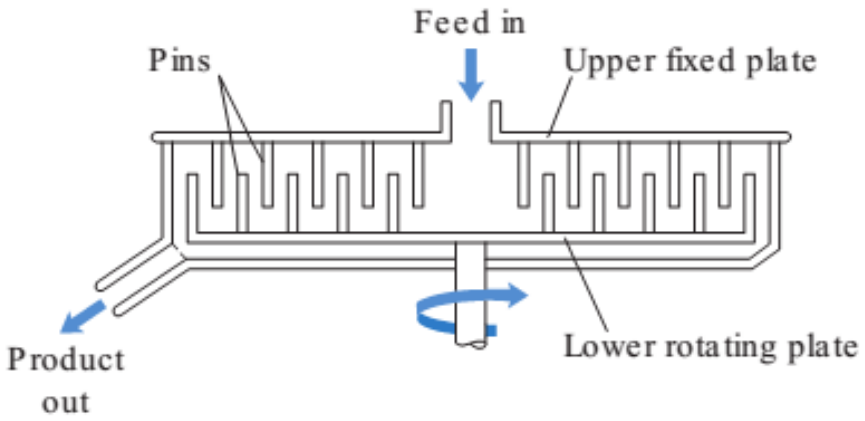
Fluid energy mill (jet mill or micronizer)



Combined impact and attrition methods

Pin mill

Two discs with closely spaced pins rotate against one another at high speeds.



Particle size reduction occurs by impaction with the pins and by attrition between pins.

Selection of particle size reduction method

Particle shape and proportion of fine particles may vary so that other properties of the powder will be altered

the cost of size reduction increases as particle size decreases, it is economically undesirable to mill particles to a finer degree than is necessary.

Selection of particle size reduction method

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, fuid energy
3–5 (intermediate)	Ball, vibration			Ball, vibration, fuid energy
5–10 (hard)	Ball, vibration, fuid energy		Ball, vibration, fuid 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	Roller, hammer	Roller, hammer	
3–5 (intermediate)	Roller, hammer			Roller, hammer
5–10 (hard)	Roller		Roller	

The end

Mixing

Pharmaceutical technology

Dr. Basheer Al-kasmi

Lecture 4

Mixing definition:

Unit operation that aims to treat two or more components, initially in an unmixed or partially mixed state, so that each unit (particle, molecule, etc.) of the components lies as nearly as possible in contact with a unit of each of the other components.

Perfect mixing:

Ideal situation of mixing

This situation is not normally practicable, is actually unnecessary and, indeed, is sometimes undesirable (Lubricant mixing).

Types o mixtures:

1. Positive mixtures
2. Negative mixtures
3. Neutral mixtures

Positive mixtures:

Gases or miscible liquids which mix spontaneously and irreversibly by diffusion (perfect mix).

No energy required with positive mixtures

Energy will shorten the time required to obtain the desired degree of mixing.

Materials which mix by positive mixing do not present any problems during product manufacture

Negative mixtures:

The components will tend to separate out.

Required energy to re-dispersed the components

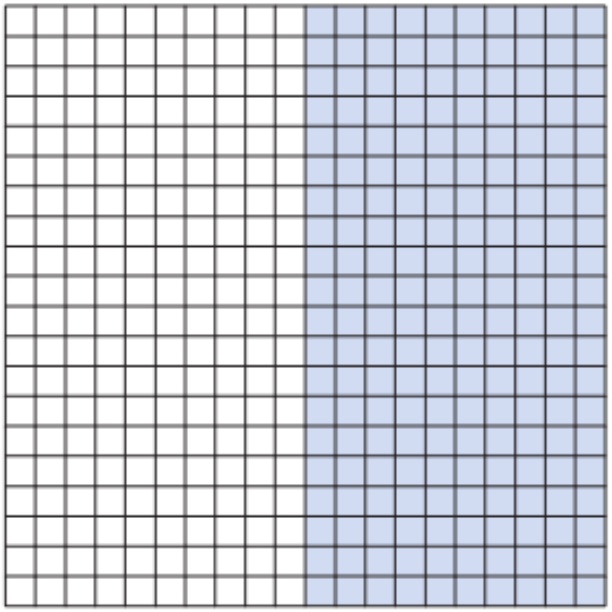
e.g. with a suspension formulation where there is a dispersion of solids in a liquid of low viscosity. Solid tend to separate very slowly.

Neutral mixtures:

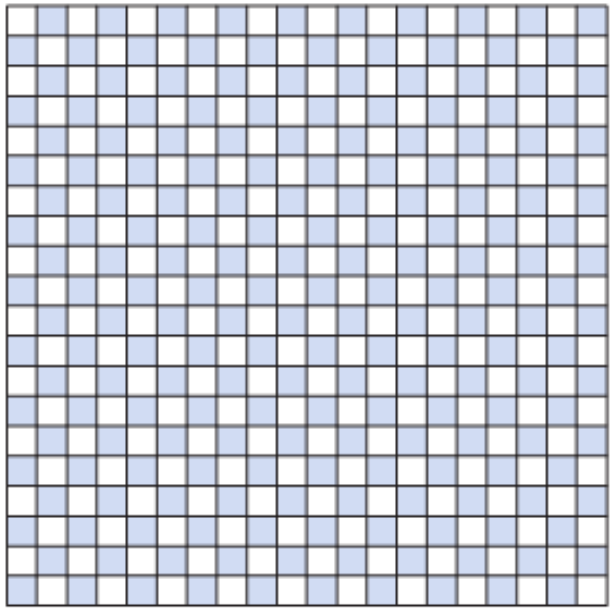
Neutral mixtures are said to be static in behaviour, i.e. the components have no tendency to mix spontaneously or segregate spontaneously once work has been input to mix them.

Examples of this type of mixture include mixed powders, pastes and ointments. Neutral mixes are capable of demixing, but this requires energy input

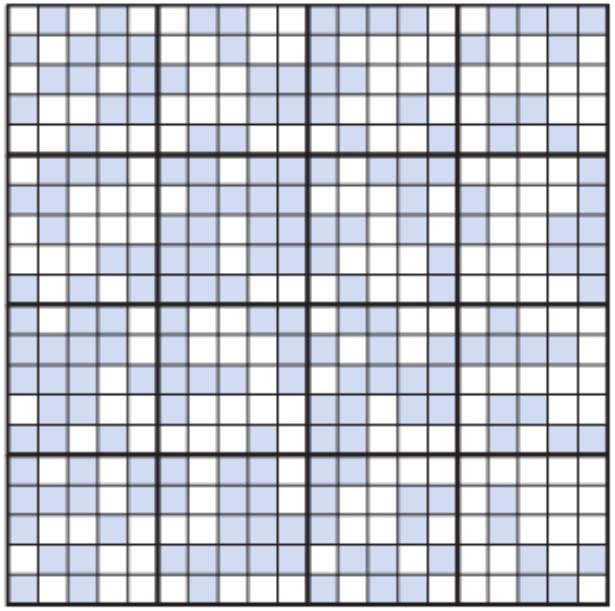
The mixing process:



Complete segregation
probability $1 \text{ in } 10^{60}$
after prolonged mixing



Perfect mixing
Probability $1 \text{ in } 10^{60}$



Random mixing
Practically

Random mix:

If any two adjacent particles are selected from the random mix shown:

- The chance of picking two coloured particles = 1 in 4 (25%)
- The chance of picking two white particles = 1 in 4 (25%)
- The chance of picking one of each = 2 in 4 (50%).

Random mix:

a mix where the probability of selecting a particular type of particle is the same at all positions in the mix and is equal to the proportion of such particles in the total mix

Random mixture: as the number of particles in the sample increases, then the closer will be the proportion of each component to that which would occur with a perfect mix

Scale of scrutiny:

The weight/ volume of the dosage unit which dictates how closely the mix must be examined/ analysed to ensure it contains the correct
dose/ concentration

The number of particles contained in the scale of scrutiny will depend on the sample weight, particle size and particle density, and will increase as the sample weight increases and the particle size and density decrease

Table 11.1 Number of particles of a minor active constituent present in samples taken from a 1:1000 random powder mix with different numbers of particles in the scale of scrutiny

Sample number	Number of particles in scale of scrutiny		
	1000	10000	100000
1	1	7	108
2	0	10	91
3	1	15	116
4	2	8	105
5	0	13	84
6	1	10	93
7	1	6	113
8	2	5	92
9	0	12	104
10	1	13	90

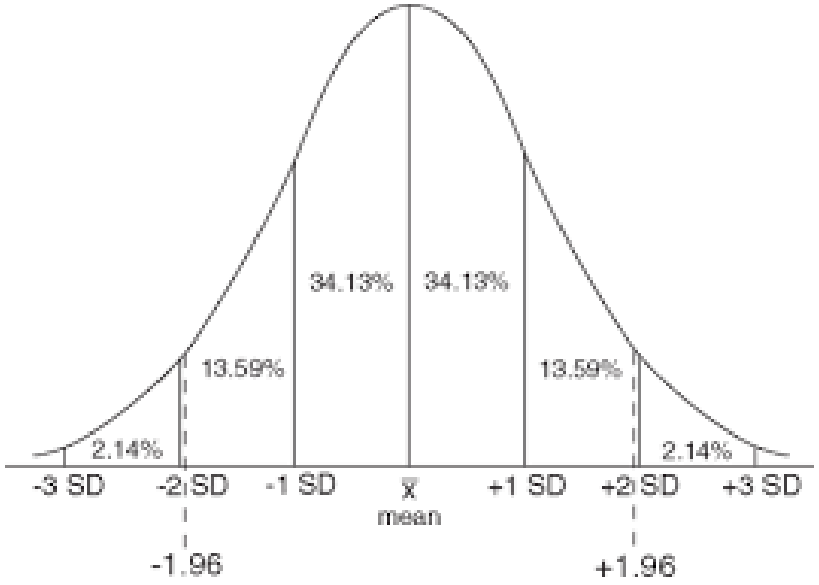
Scale of scrutiny:

The lower the proportion of active component present in the mixture, the more difficult it is to achieve an acceptably low deviation in active content.

The more particles there are present in a unit dose/ scale of scrutiny, the lower the likely deviation in content.

Scale of scrutiny:

The active component should not deviate by more than ± 5%



p is the proportion of the drug in the total mix and n is the total number of particles in the sample.

$$SD = \sqrt{\frac{p(1-p)}{n}}$$

Scale of scrutiny:

p: 0.5

it is required that 99.7% of samples contain within ± 5% of p

$$3 \times \mathrm{SD} = p \times (\%\ \text{acceptable deviation}/100)$$

$$\frac{0.5 \times 0.05}{3} = \sqrt{\frac{p(1-p)}{n}}$$

n= 3600

Scale of scrutiny:

Imagine it is necessary to produce a tablet weighing 50 mg which contains 50 µg of a potent steroid, and that the product specification requires 99 7% o tablets to contain between 47.5 µg and 52.5 µg o the steroid. If the mean particle density of the components is 1.5 g/cm3 (1500 kg/m3), what particle size should the steroid and excipients be?

Scale of scrutiny:

P= 0.001, % deviation allowed = (2.5/50) × 100 = 5%

n= 3.6×10^6

50 mg tablet contain at least 3.6×10^6 particles

Each particle weigh: $50/3.6\times10^{6}\text{mg}=1.39\times10^{-5}\text{mg}=1.39\times10^{-11}\text{kg}$

particle volume: $1.39\times10^{-11}/1500\text{m}^3=9.27\times10^{-15}\text{m}^3$

volume of a particle: $4\ \pi\ r^3/3$

$$r<1.30\times10^{-5}\ \text{m}$$

$$\text{d}\ <26\,\mu\text{m}$$

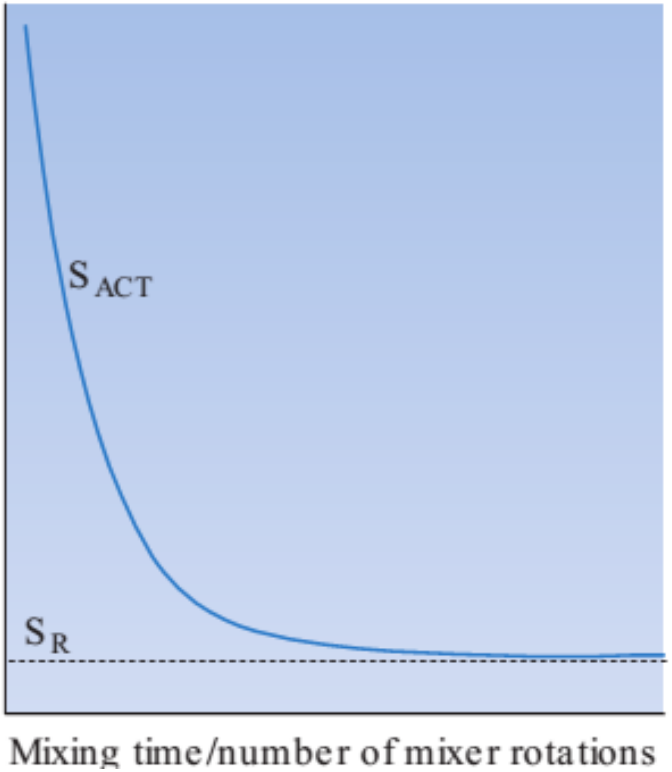
Evaluation of the degree of mixing:

Mixing index: $M = \frac{S_R}{S_{ACT}}$

S_{ACT} : content SD from a mix under investigation

S_R : content SD from a fully random mix

A minimum of 10 samples is usually analysed, these being removed from different depths into the mixer and from the middle and sides.



Mechanisms of mixing and demixing:

- Convection mixing
- Shear mixing
- Diffusion mixing

All three mixing mechanisms are likely to occur in a mixing operation

Mechanisms of mixing and demixing:

Convection mixing:

Transfer of relatively large groups of particles from one part of the powder bed to another, e.g. as might occur when a mixer blade or paddle moves through the mix.

This type of mixing tends to produce a large degree of mixing fairly quickly

Mechanisms of mixing and demixing:

Shear mixing

when a ‘layer’ of material flows over another ‘layer’ resulting in the layers moving at different speeds and therefore mixing at the layer interface.

e.g. high-shear or tumbling mixers (mixer induces velocity gradients within the powder bed and hence ‘shearing’ of one layer over another)

Mechanisms of mixing and demixing:

Diffusive mixing

When a powder bed is forced to move or flow, it will ‘dilate’, i.e. the volume occupied by the bed will increase.

This arises because the powder particles become less tightly packed and there is an increase in the air spaces or voids between them

particles pass through the void spaces created either under gravitational forces (e.g in a tumbling mixer) or by forced movement (e.g in a fluidized bed)

Powder segregation (demixing)

It may occur during transfer to filling machines or in the hopper of a tablet/ capsule/ sachet filling machine.

It return to differ in size, shape, density and surface properties of particles

Particle size effects

Percolation segregation: Smaller particles tend to fall through the voids between larger particles and thus move to the bottom of the mass

Trajectory segregation: During mixing, larger particles move greater distances than smaller particles.

Dusting out segregation: During mixing, very small particles (‘dust’) in a mix may tend to be ‘blown’ upwards by turbulent air currents as the mass tumbles, and remain suspended in the air. When the mixer is stopped or material discharge is complete, these particles will sediment and subsequently form a layer on top of the coarser particles

Particle density effects

If components are of different density, the more dense particles will have a tendency to move downwards, even if their particle sizes are similar in size.

Percolation segregation, Trajectory segregation

Often materials used in pharmaceutical formulations have similar densities and density effects are not generally too important

Particle shape effects

Spherical particles exhibit the greatest flowability and therefore are more easily mixed and segregate

irregular or needle-shaped particles may become interlocked, decreasing the tendency to segregate once mixing has occurred.

Non-spherical particles will also have a greater surface area to weight ratio, which will tend to decrease segregation by increasing any cohesive effects but will increase the likelihood of ‘dusting out’.

Approaches to minimize segregation

- Sieving to remove fines or lumps
- Milling of components
- Selection of excipients which have a density similar to the active component
- Granulation of the powder mix (size enlargement)
- Reducing the extent to which the powder mass is subjected to vibration or movement after mixing
- Using filling machine hoppers designed so that powder residence time is minimized
- Using equipment where several operations can be carried out without transferring the mix, e.g. a fluidized-bed drier
- Production of an ‘ordered’ mix

Ordered mixing:

if one powder is sufficiently small (micronized) it may become adsorbed onto ‘active sites’ on the surface of a larger ‘carrier’ particle (as lactose or sucrose) and exhibit a great resistance to being dislodged.

Useful in direct compression and inhaler formulations

Segregation in ordered mixes:

Ordered unit segregation: The carrier particles vary in size which may separate by percolation.

Displacement segregation: if another component competes for sites on the carrier it may displace the original adsorbed material which may then segregate due to its small size.

Saturation segregation: there are insufficient carrier particle

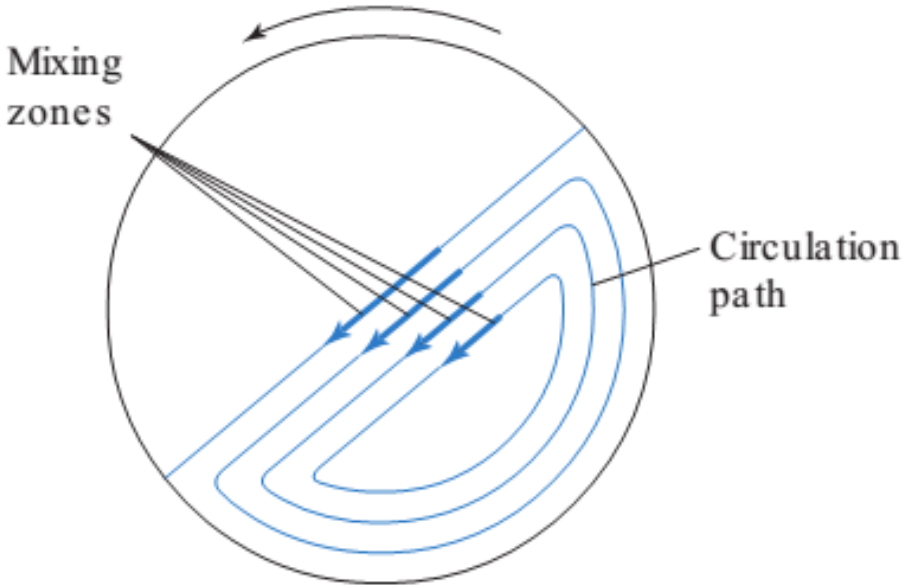
Practical considerations:

1. Sequentially building up the amount of material in the mixer.
2. Preblend the active component with a diluent in a smaller mixer prior to transferring it to the main mixer.
3. The volume of powder in the mixer is appropriate
4. Mixers should be suitably earthed to dissipate the static charge and the process should be carried out at a relative humidity approximately 40%.

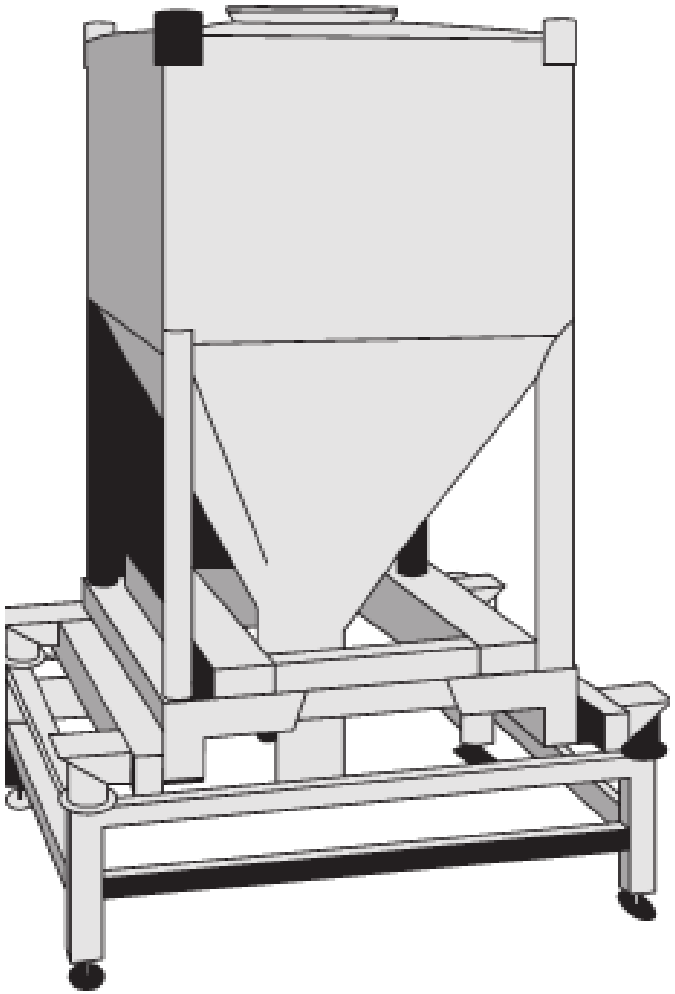
Powder-mixing equipment:

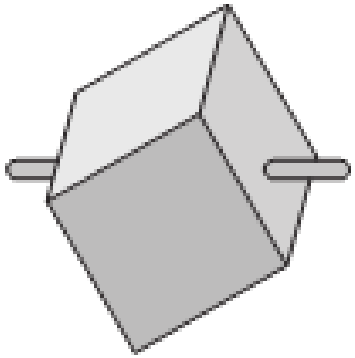
1. Tumbling mixers /blenders:

mixing/blending granules or free- flowing powders depending on Shear mixing.

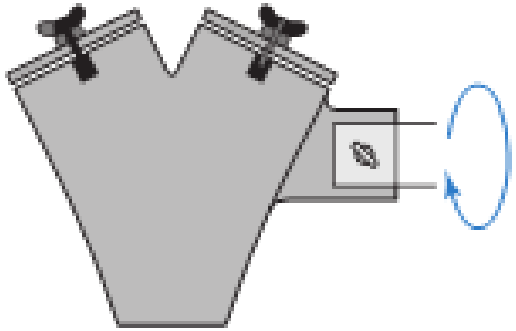


Tumbling mixers /blenders:





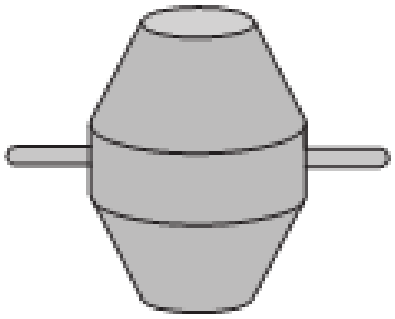
Rotating cube



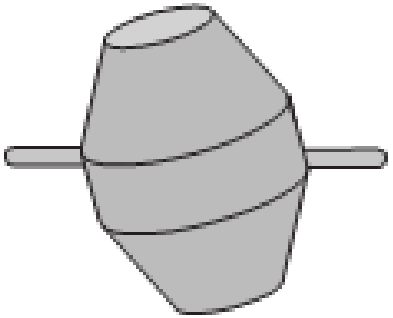
Y-cone mixer

- Typical intermediate bulk container.

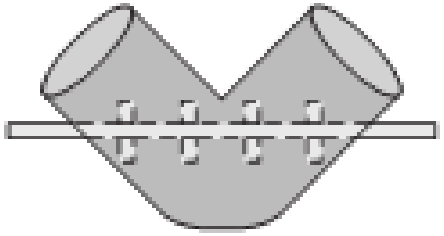
Tumbling mixers /blenders:



Double cone



Oblique cone



Twin shell (V) mixer
with agitator bar

Tumbling blenders disadvantages:

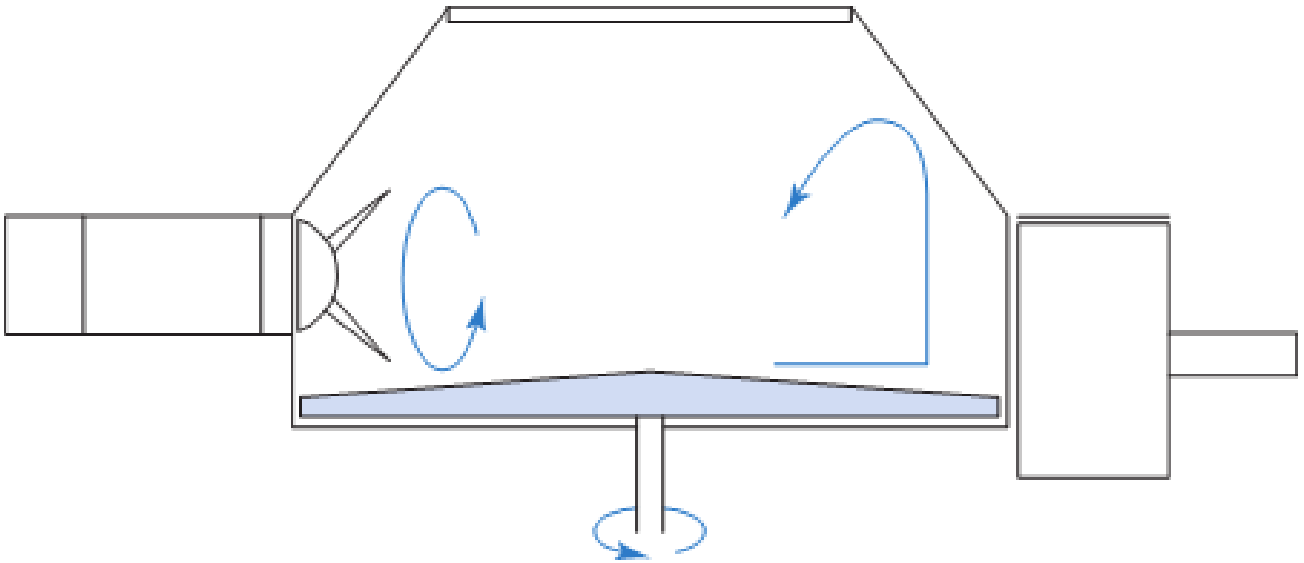
- Less effective for cohesive/ poorly flowing powders because the shear forces generated are usually insufficient to break up any aggregates.

- Care also needs to be taken if there are significant differences in particle size present since segregation is likely to occur

2. High-speed mixer-granulators:

Mixing and granulating

Mixing done by high shear forces (arising from the high velocity) and the expansion in bed volume which allows diffusive mixing.



High-speed mixer-granulators disadvantages

- Because of the high-speed movement within a mixer-granulator, care needs to be taken if the material being mixed fractures easily.
- Problems associated with overmixing of lubricants, means that this type of mixer is not normally used for blending lubricants.

3. Fluidized-bed mixers:

The main use of fluidized-bed equipment is in the drying of granules or the coating of multiparticulates.

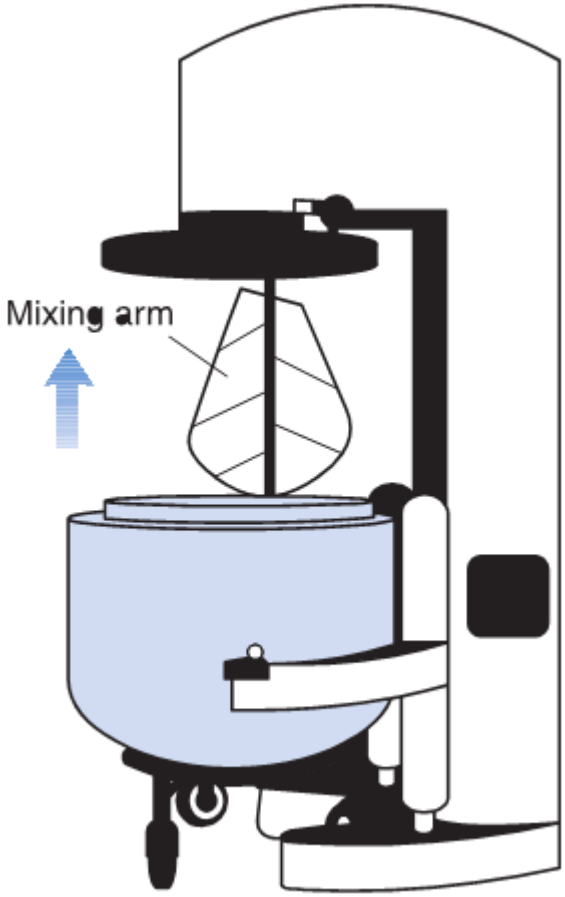
Fluidized-bed equipment can, however, be used to mix powders prior to granulation in the same bowl.

4. Agitator mixers:

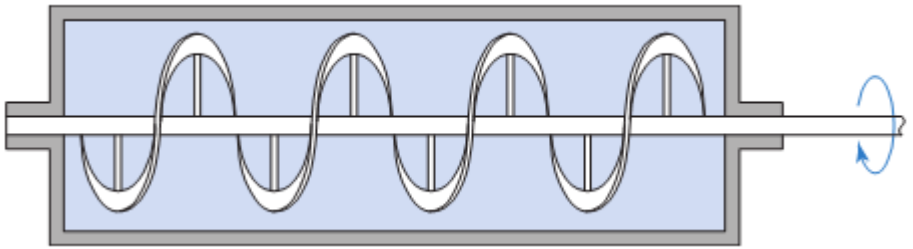
Depends on the motion of a blade or paddle through the product, and hence the main mixing mechanism is convection.

Ribbon mixer and the planetary mixer.

Agitator mixers:



Planetary mixer



Ribbon agitator powder mixer.

The end

Powder flow

Pharmaceutical technology

Dr. Basheer Al-kasmi

Lecture 5

Benefit of producing free-flowing powders:

- Uniform flow = particle packing in a constant volume-to-mass ratio = tablet weight uniformity.

- Uneven powder flow = entrapped air within powders = may promote capping or lamination.

Powder flowability relate to :

- Particle properties
- Particle size
- Particle shape
- Particle density (true density)

Particle properties

Cohesion occurs between like surfaces, such as the same component particles in a bulk solid.
Adhesion occurs between two different objects, for example between two different particles, or between a particle and a hopper wall.

Adhesive and cohesive forces acting between particles in a powder bed are composed mainly from: van der Waals forces which increase as particle size decreases and vary with changes in relative humidity

Particle size effects

In general, fine particles with very high surface-to-mass ratios are more adhesive/ cohesive than coarser particles which are influenced more by gravitational forces.

Particles larger than 250 µm are usually relatively free flowing but as the size falls below 100 µm, powders become more adhesive/cohesive and flow problems are likely to occur.

Powders having a particle size less than 10 µm are usually extremely adhesive/ cohesive and resist flow under gravity. exception to this reduction in flowability is ordered mixing.

Particle shape

Powders with similar particle sizes but dissimilar shapes can have markedly different flow properties owing to differences in inter particulate contact areas

Spheres has minimum inter particulate contact and generally optimal flow properties

Irregular shaped particles may experience mechanical interlocking in addition to adhesional and cohesional forces

Particle density (true density)

Powders normally flow under the influence of gravity, higher density particles are generally less adhesive/ cohesive than less dense particles of the same size and shape.

Driving and drag forces

at equilibrium:

$$\Sigma f(\text{driving forces}) = \Sigma f(\text{drag forces})$$

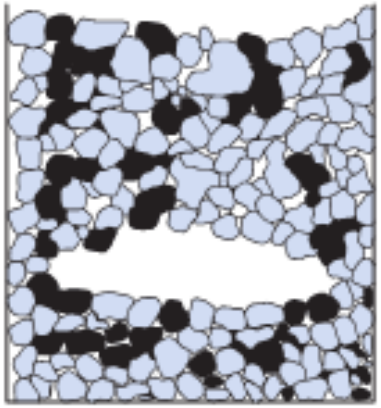
$$\Sigma f(\text{gravitational force, particle mass, angle of inclination of powder bed, static head of powder, mechanical force} \ldots) = \Sigma f(\text{adhesive forces, cohesive forces, other surface forces, mechanical interlocking} \ldots)$$

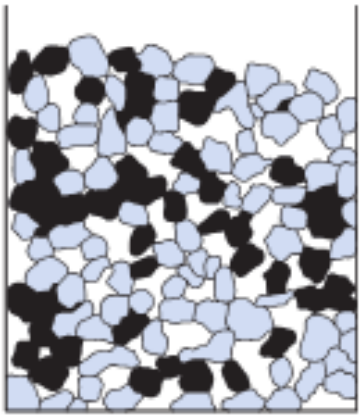
Packing geometry

$$k = \frac{\text{bulk density}}{\text{true density}}$$

$$\rho_B = \frac{M}{V} \text{kg m}^{-3}$$

$$1 - k = e$$

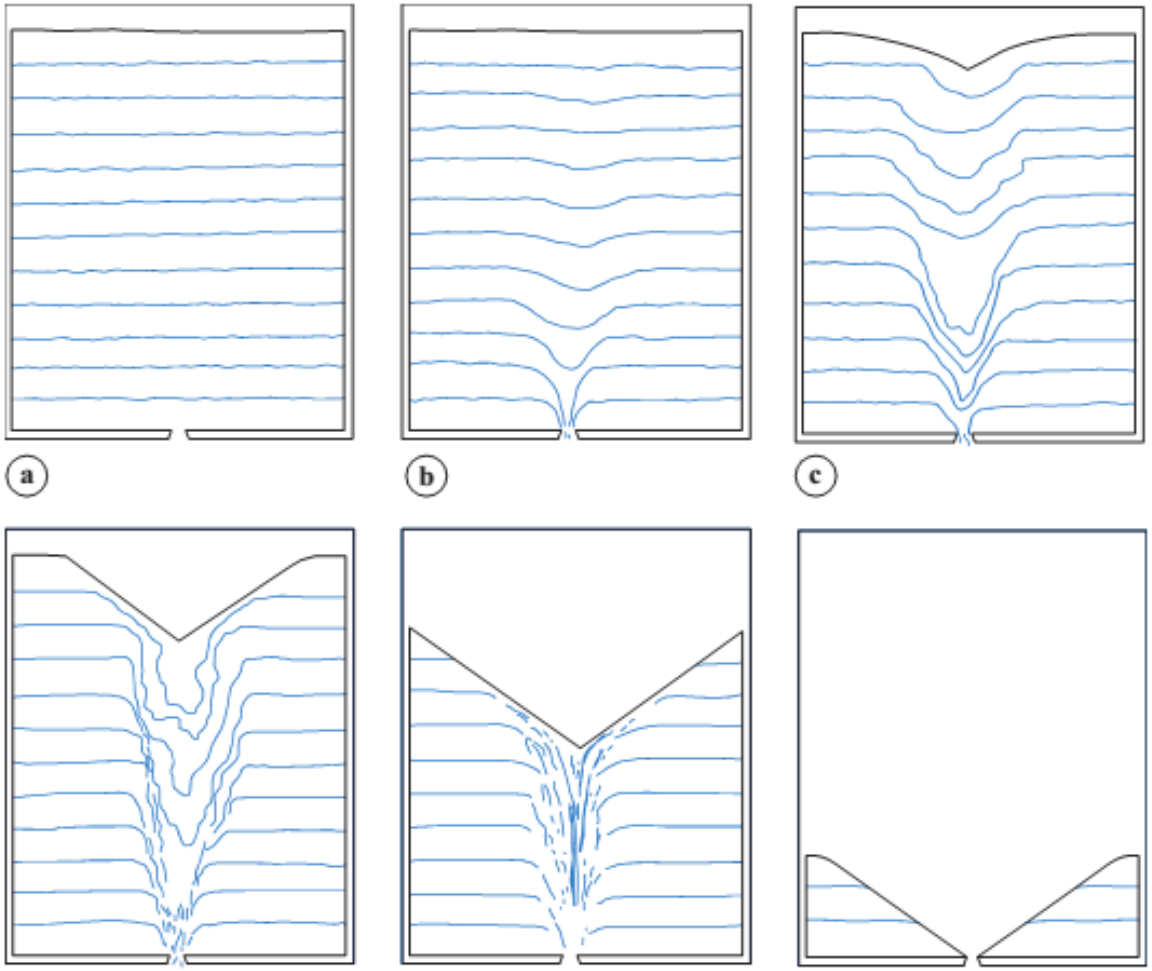


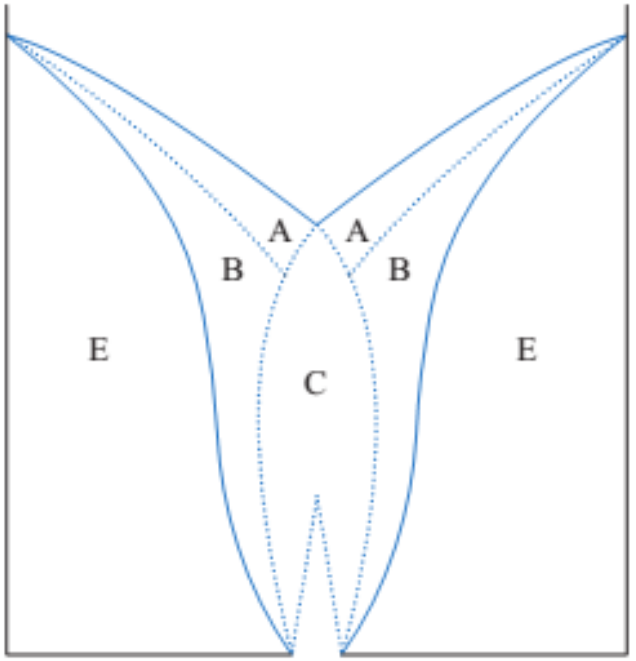


K: fractional solids content (percentage)
e: porosity (percentage)

The measurement of packing geometry by an assessment of percentage compressibility and changes in bulk density have proved to be useful indirect methods to estimate powder flow.

Flow through an orifice (free- flowing powder)





Factors affecting flow rates through orifices

1. Orifice diameter
2. Hopper width
3. Height of powder in the hopper
4. Hopper wall angle

Characterization of powder flow

No single, simple test will truly characterize the flow properties during large-scale manufacture but, with careful control, the tests can give a good estimate.

1. Indirect methods
2. Direct methods

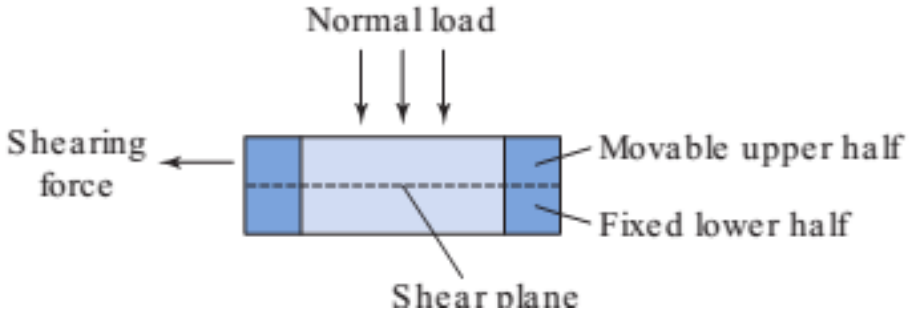
Indirect methods

1. Measurement of cohesive/adhesive properties
2. Angle of repose
3. Bulk density
4. Critical orifice diameter

Shear strength (sliding tension)

The stress (force per unit area) necessary to shear a powder bed under conditions of zero normal load.

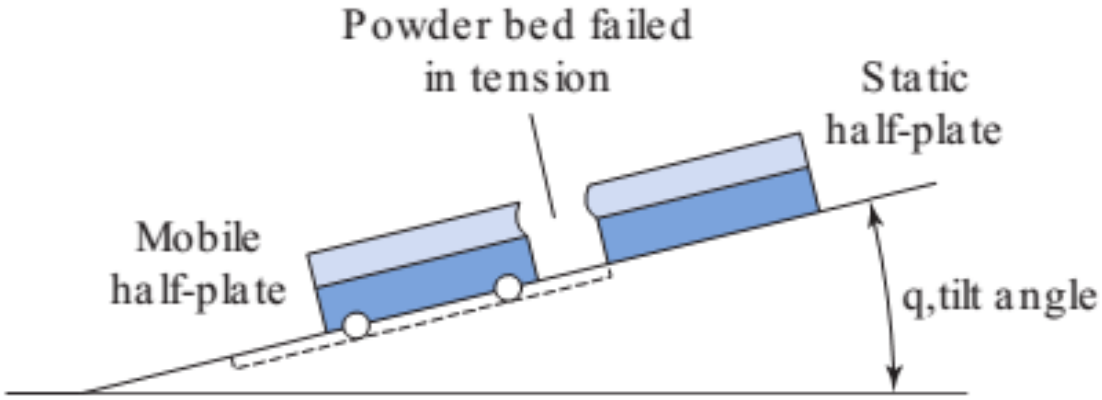
To calculate it:



Shear stress is plotted against normal stress and extrapolated back to zero normal stress, as the shear stress at zero normal stress is, by definition, equal to the cohesion of the powder.

Tensile strength (splitting tension)

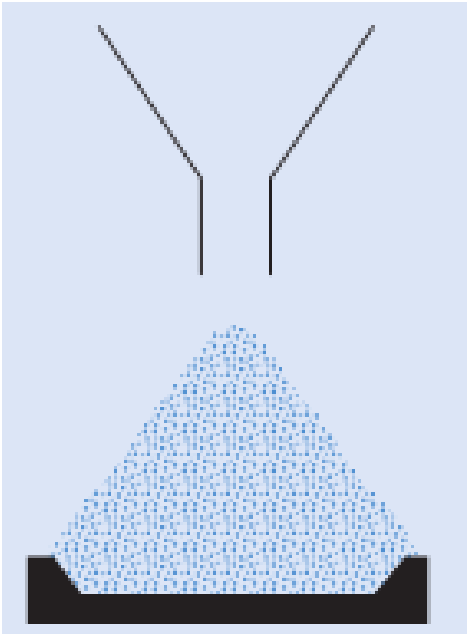
$$\sigma_t = \frac{Mg\sin\theta}{A}$$



σ t: tensile strength
M: the mass of the mobile half-plate plus powder
θ: angle of the tilted table
A: cross-sectional area of the powder bed

Angle of repose:

For very poor flowing material: using different concentrations of it with a non-adhesive/ cohesive powder. The angles of repose are plotted against mixture concentration and extrapolated to 100% of the very poor flowing material



Angle of repose (degrees)	Type of flow
25–30	Excellent
31–35	Good
36–40	Fair (flow aid not needed)
41–45	Passable (may hang up, flow aid might be needed)
46–55	Poor (agitation or vibration needed)
56–65	Very poor
Over 66	Very, very poor

Determinations based on bulk density

A consolidated powder is likely to have a greater arch strength than a less consolidated one and may therefore be more resistant to powder flow.

The volume decreases from its original state (V_o) to a final state (V_f) i.e. unchanging arrangement.

$$\text{Bulk density} = m/V_o$$

$$\text{Tapped density} = m/V_f$$

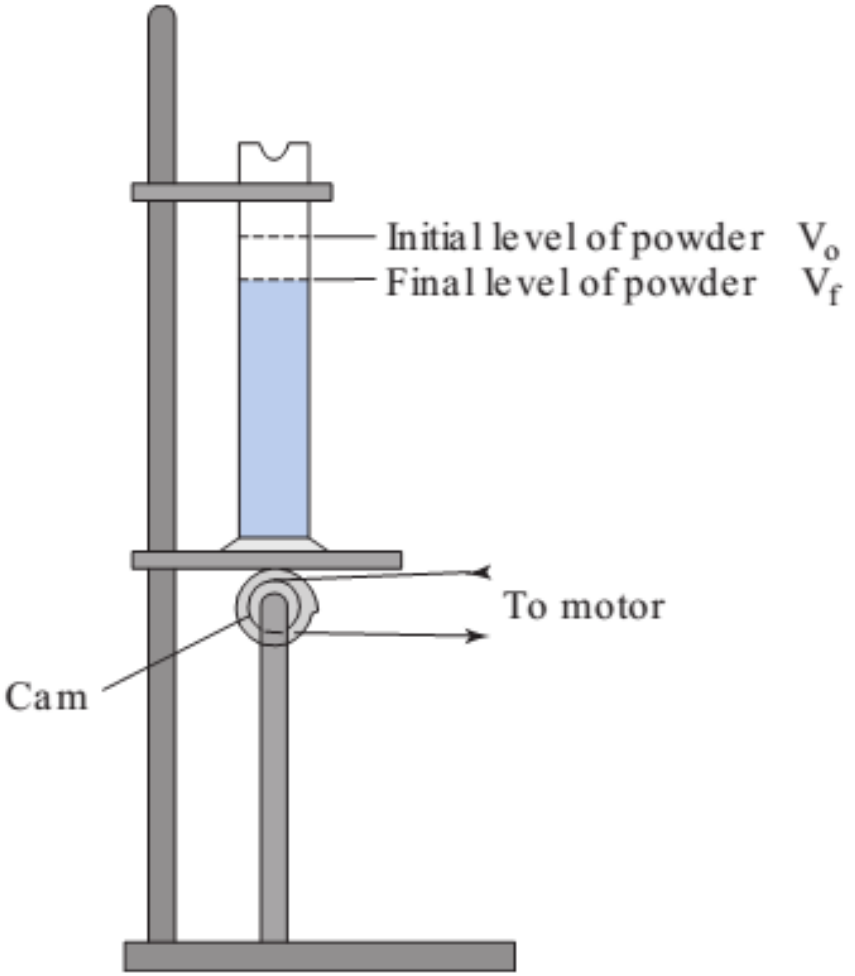
Determinations based on bulk density

Bulk density = m/V_o

Tapped density = m/V_f

$$\text{Hausner ratio} = \frac{\text{Tapped density } (\rho_{Bmax})}{\text{Poured density } (\rho_{Bmin})}$$

$$\text{\% compressibility} = \text{Carr's index} = \frac{\rho_{Bmax} - \rho_{Bmin}}{\rho_{Bmax}} \times 100$$



Compressibility index (%) (Carr's index)	Type of f ow	Hausner ratio
1–10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Critical orifice diameter

The critical orifice diameter is the size of the smallest hole through which powder discharges when the tray is lifted or the shutter removed

can be used as a simple standard to specify materials for use in filling given capsule sizes, sachets or producing particular tablet sizes at a specified rate.

Direct measurements of flow

1. Hopper flow rate:

Mass flow rate: By dividing the discharged powder mass by this time.

2. Recording flow meter:

powder is discharged from a hopper onto a balance

Improvement of powder flowability

1. Alteration of particle size and size distribution:

coarse (largest) particles are generally less cohesive than fine (smaller) particles.

Particle size can be increased by granulation

Improvement of powder flowability

2. Alteration of particle shape or texture:

More spherical particles have better flow properties than more irregular particles.

Spray-drying can be used to produce near-spherical excipients (spray-dried lactose)

Texture: particles with very rough surfaces will have a greater tendency to interlock than smooth-surfaced particles.

Crystallization conditions effect on particle shape or texture

Improvement of powder flowability

3. Alteration of surface forces
Reduction of electrostatic charges can improve powder flowability (electrostatic charges are prevented by efficient earth connections).

The moisture content of particles is also of importance to powder flowability, as adsorbed surface moisture films tend to increase bulk density and reduce porosity.

Improvement of powder flowability

4. Formulation additives: flow activators

Glidants: improve the flowability of powders by:

- Reducing adhesion and cohesion (Colloidal silicon dioxide).
- Disrupt the continuous film of adsorbed water surrounding the moist particles (magnesium oxide).

Improvement of powder flowability

5. Alteration of process conditions

- Use of vibration-assisted hoppers.
- Use of force feeders

The end

Granulation

Pharmaceutical technology

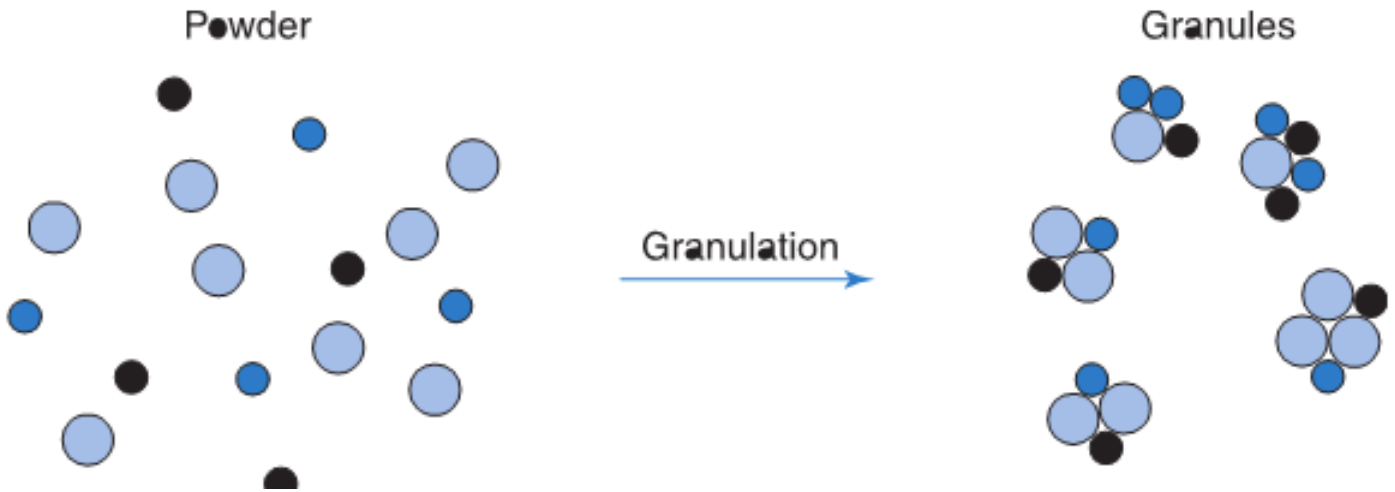
Dr. Basheer Al-kasmi

Lecture 6

Defination

Granulation is the process in which dry primary powder particles are processed to adhere to form larger multiparticle entities called granules.

Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm



Reasons for granulation

1. Prevent segregation of the constituents of the powder mix
2. Improve the flow properties of the mix.
3. Improve the compaction characteristics of the mix
4. The granulation of powdered toxic materials will reduce the hazard associated with the generation of toxic dust that may arise during handling
5. Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder. Granulation may reduce this hazard as the granules will be able to absorb some moisture and yet retain their flowability because of their size.
6. Granules, having a greater bulk denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment

Pharmaceutical granulation processes

1. Dry granulation

Powder particles are aggregated at high pressure.

Either by large tablet (known as a ‘slug‘) or the powder is squeezed between two rollers to produce a sheet or flakes of material (roller compaction) then milling

Used for drugs which do not compress well after wet granulation or those which are sensitive to moisture.

Pharmaceutical granulation processes

2. Wet granulating by Granulating fluid:

The granulating fluid contains a solvent that must be volatile, is non-toxic, and may contain dissolved adhesive (binder).

Water:

(+) economic, ecological reasons, non- flammable (safety)

(-) drug stability, longer drying time than organic solvents.

Organic solvent (ethanol or isopropanol):

When water sensitive drugs are processed, or when a rapid drying time is required

Particle bonding mechanisms

1. adhesion and cohesion forces in the immobile liquid films between individual primary powder particles
2. interfacial forces in mobile liquid films within the granules
3. the formation of solid bridges after solvent evaporation
4. attractive forces between solid particles
5. mechanical interlocking.

Particle bonding mechanisms

1. adhesion and cohesion forces (immobile liquid films):

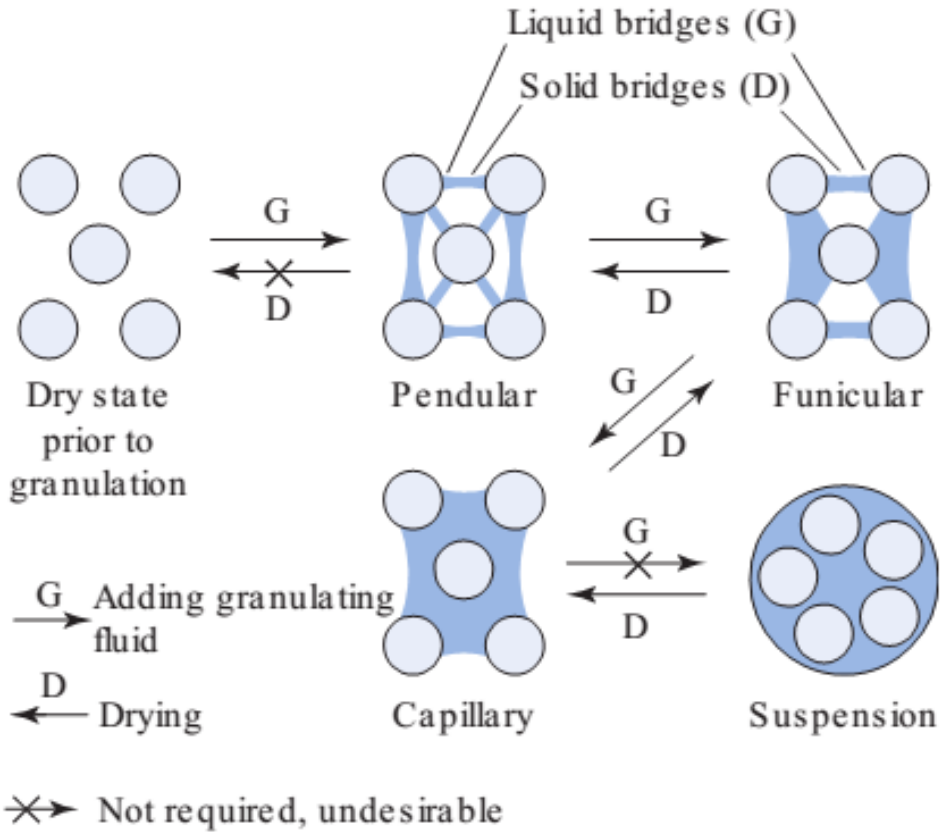
Granulation liquid form a very thin, immobile layer, there will be an effective decrease in interparticulate distance and an increase in contact area between the particles.

This situation will arise with adsorbed moisture.

Particle bonding mechanisms

2. Interfacial forces in mobile liquid films

Add more granulation liquid or/and more Kneading time.



Particle bonding mechanisms

3. Solid bridges: formed by
- partial melting
- hardening binders
- crystallization of dissolved substances.

Dry granulation

During compression: melting of low melting point materials When the pressure is relieved, crystallization will take place, binding the particles together.

Wet granulation

the adhesive in liquid bridges will harden or crystallize on drying to form solid bridges to bind the particles

Mechanisms of granule formation

1. Nucleation

Granulation starts with particle–particle contact and adhesion due to liquid bridges.

A number of particles will join to form the pendular state.

Further agitation densifies the pendular bodies to form the capillary state and these bodies act as nuclei for further granule growth.

Mechanisms of granule formation

2. Transition

Nuclei can grow by two possible mechanisms: either single particles can be added to the nuclei by pendular bridges or two or more nuclei may combine.

In this stage: Presence of a large number of small granules with a fairly wide size distribution.

This represents a suitable uniform tablet die or capsule fill.

Mechanisms of granule formation

3. Ball.growth

granule growth produces large, spherical granules and the mean particle size of the granulating
system will increase with time.

If agitation is continued, granule coalescence will continue and produce an unusable, over-massed system

Pharmaceutical granulation equipment

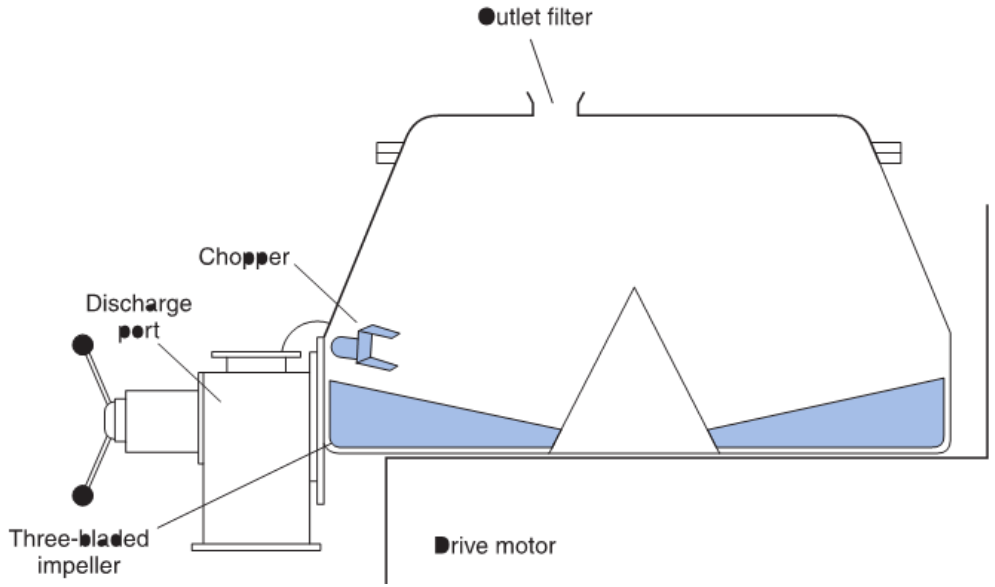
1. Shear granulators (planetary):

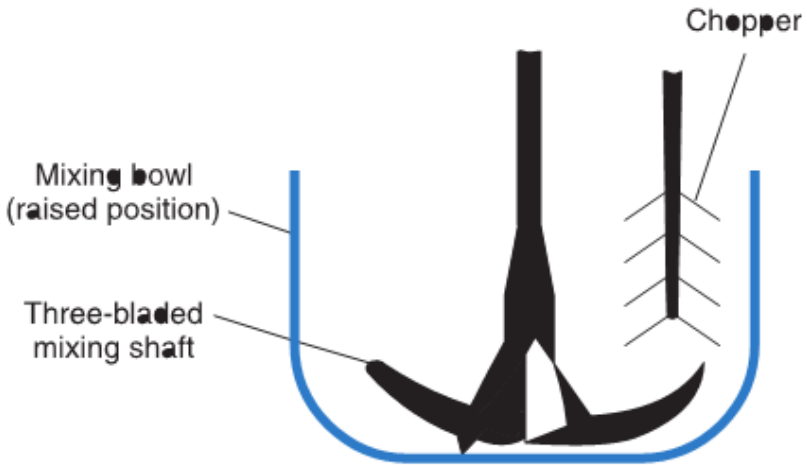
dry-powder blending usually has to be performed as a separate initial operation using different powder-mixing equipment

disadvantages: its long duration, the need for several pieces of equipment and the high material losses which can be incurred because of the transfer stages between the different equipment

Pharmaceutical granulation equipment

2. High-speed.mixer/granulators:





Pharmaceutical granulation equipment

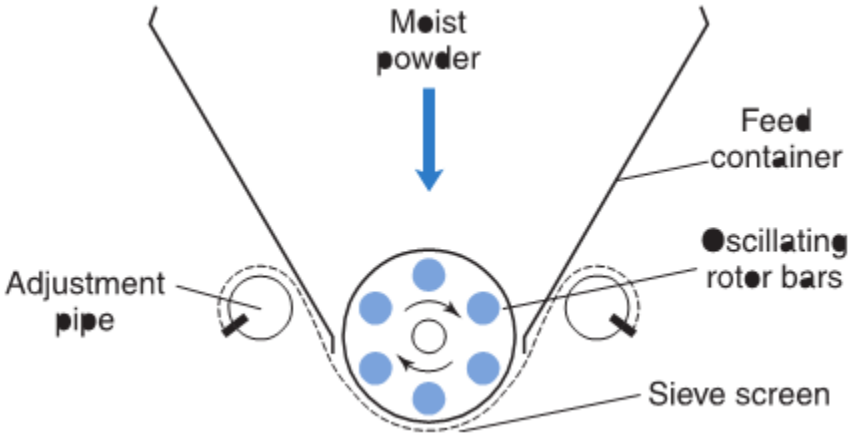
2. High-speed mixer/granulators:

The advantage of the process is that powder blending, wet massing and granulation are all performed in a few minutes in the same piece of equipment. The process needs to be controlled with care as the granulation progresses so rapidly that a usable granule can be transformed very quickly into an unusable, over massed system.

Pharmaceutical granulation equipment

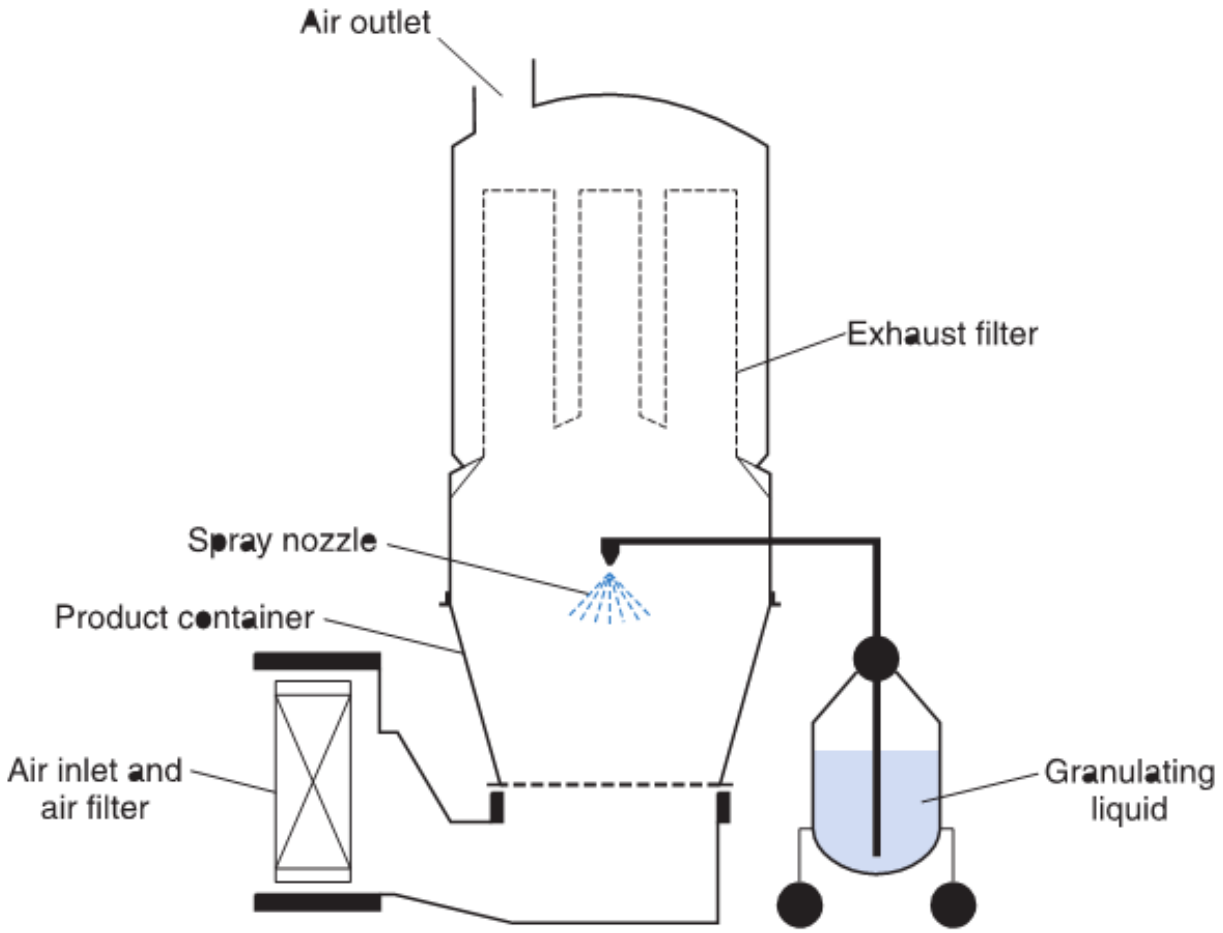
3. oscillating granulator:

If excess liquid is added at the wet massing stage, strings of material will be formed and if the mix is too dry, the mass will be sieved to a powder, and granules will not be formed



Pharmaceutical granulation equipment

4. Fluidized-bed granulators



Pharmaceutical granulation equipment

4. Fluidized-bed granulators advantages:

- All granulation processes are performed in one unit
- saving labour costs, transfer losses and time
- automation of the process.

Disadvantages:

- expensive equipment
- optimization of process needs extensive development work

Pharmaceutical granulation equipment

5. Spray driers:

These differ from the method discussed above in that a dry, granular product is made from a solution or a suspension rather than from dry primary powder particles. The solution or suspension may be of drug alone, a single excipient or a complete formulation.

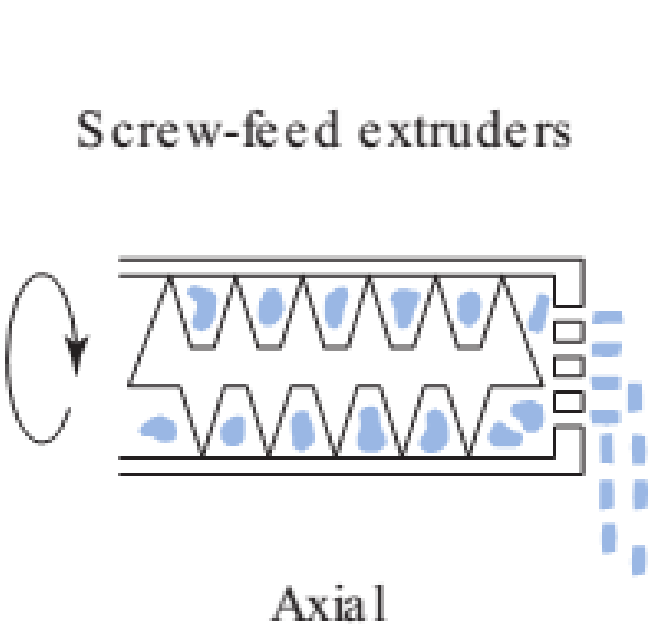
Pharmaceutical granulation equipment

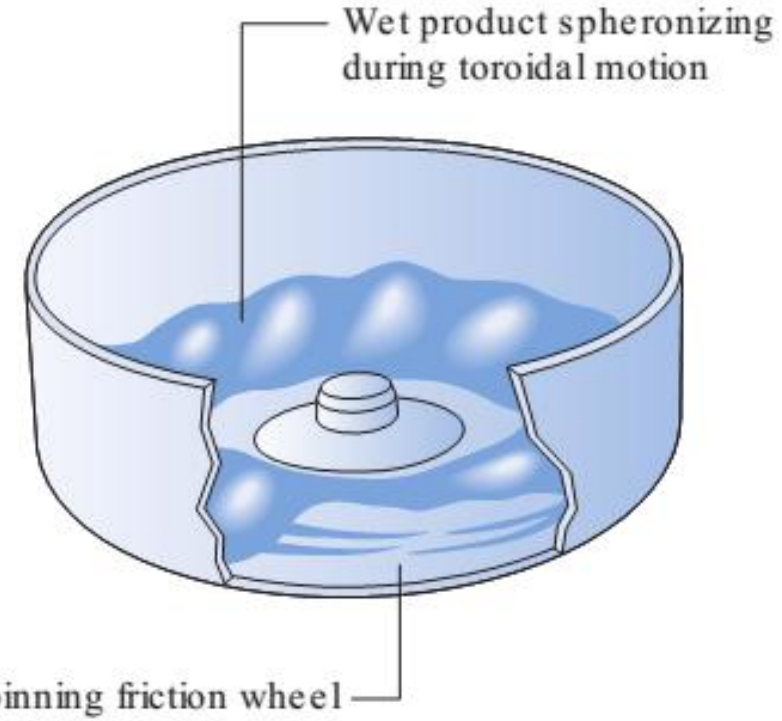
5. Spheronizers /pelletizers (pellets):

The main steps of the process are:

- dry mixing of ingredients to achieve a homogeneous powder dispersion
- wet massing to produce a sufficiently plastic wet mass
- extrusion to form rod-shaped particles of uniform diameter
- spheronization to round off these rods into spherical particles
- drying to achieve the desired final moisture content
- screening (optional) to achieve the desired narrow size distribution.

Applications of extrusion/spheronization





Applications of extrusion/spheronization

1.Controlled drug release:

Both immediate-release and controlled-release pellets can be formed. these pellets can either be filled into hard gelatin capsule shells or compacted with suitable excipients into tablets

Pellets can contain two or more ingredients in the same individual unit or incompatible ingredients can be manufactured in separate pellets.

Pellets can be coated in sub-batches to give, say, rapid-, intermediate- and prolonged-release pellets in the same capsule shell. Dense multiparticulates disperse evenly within the gastrointestinal tract and have less variable gastric emptying and intestinal transit times than single units, such as coated monolithic tablets.

Applications of extrusion/spheronization

2. Processing:

The process of extrusion/spheronization
can be used to increase the bulk density, improve flow properties and reduce the problems of dust

Applications of extrusion/spheronization

Advantages:

- uniform spherical shape
- uniform size
- good ow properties
- reproducible packing (into hard gelatin capsules)
- high strength
- low friability
- low dust
- smooth surface
- ease of coating

6. Melt granulation

Melt granulation is a size enlargement process in which a thermosetting material (hot-melt binder) is used to bind the primary powder particles into granules.

It is a water-free alternative to wet granulation.
The binder/ granulating agent is a semi-solid or solid hydrophilic polymer or a hydrophobic wax

6. Melt granulation

Technique:

- the hot-melt binder is added as a solid powder to the drug-excipient powder mix at room temperature and mixed while the temperature of the mix is raised to above the melting point of the binder
- the hot-melt binder is heated and melted then sprayed on to the powder in a fluidized bed granulator or high-speed mixer granulator

6. Melt granulation

Hot-melt binders:
hydrophilic water-soluble binders: polyethylene glycols (PEG s). PEG 3000 being well suited (melting point 48–54 °C).

Hydrophobic water-insoluble binders: carnauba wax, hydrogenated castor oil, hydrogenated cottonseed oil, stearic acid

6. Melt granulation

Advantages:

use of water is avoided and so damage to hydrolytic drug molecules is minimized.

avoids the use of organic solvents.

Disadvantages:

thermal degradation can still be a problem.

7. Dry granulators

Dry granulation converts primary powder particles into granules using the application of pressure without the intermediate use of a liquid.

It therefore avoids heat/ temperature combinations which may degrade the product.

7. Dry granulators

Dry granulation converts primary powder particles into granules using the application of pressure without the intermediate use of a liquid.

It therefore avoids heat/ temperature combinations which may degrade the product.

Two pieces of equipment are necessary for dry granulation:

1. machine for compressing the dry powders into compacts or flakes
2. Mill for breaking up these intermediate products into granules

7. Dry granulators

Slugging
Slug: typically 25 mm diameter by about 10–15 mm thick.

Hammer mill is suitable for breaking the slugs.

Disadvantages:
work hardening which results in poor recompaction of these already compacted granules.

7. Dry granulators

Roller compaction

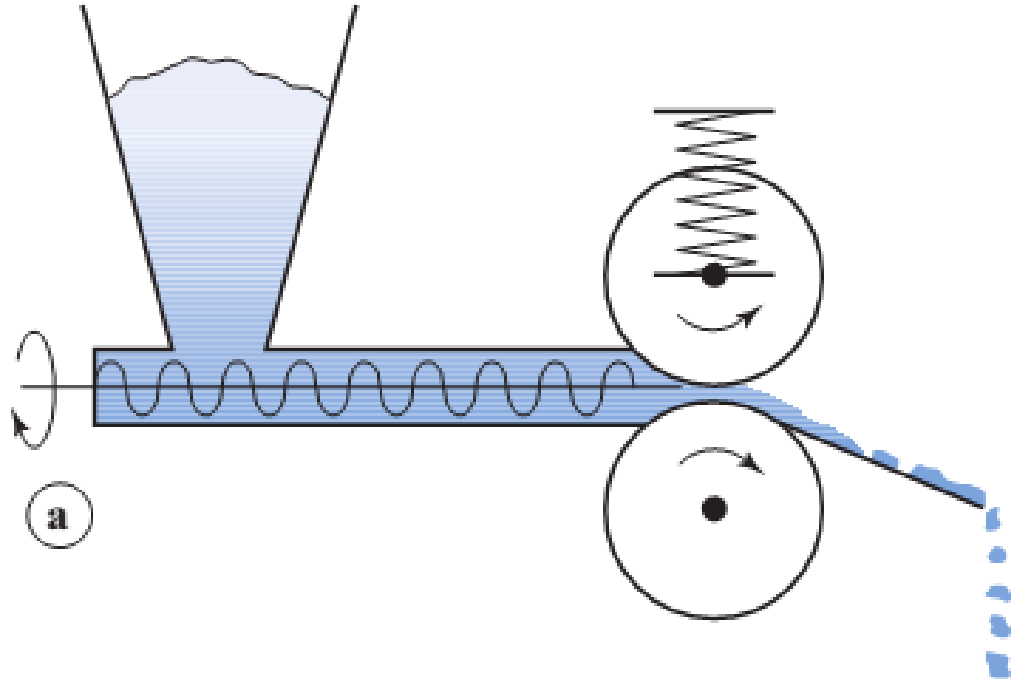
Roller compaction is an alternative gentler method, the powder mix being squeezed between two counter-rotating rollers to form a compressed sheet

The sheet so formed is normally weak and brittle and breaks immediately into flakes (as corn flakes).

Flask convert to granules by just screening or using oscillating granulator

7. Dry granulators

Roller compactor



7. Dry granulators

Advantages of the roller compaction

1. The process is economical
2. It can cope with a wide range of materials, particle size, bulk density and flowability.
3. The process is easily scaled up
4. The product has uniform properties with respect to its mechanical strength
5. No work-hardening problems encountered with slugging.

7. Dry granulators

Disadvantages of the roller compaction:

Not all materials respond to roller compaction as they do not possess suitable deformation or cohesion properties.

The end

Drying

Pharmaceutical technology

Dr. Basheer Al-kasmi

Lecture 6

Definition:

Moisture content of wet solids: kg of moisture associated with 1 kg of the moisture free or 'bone-dry' solid

Total moisture content of a solid is equal to its free moisture content (unbound water) plus its equilibrium moisture content (bound water).

Definition:

Unbound water: The unbound water associated with a wet solid exists as a liquid and it exerts its full vapour pressure. It can be removed readily by evaporation

Bound water: Part of the moisture present in a wet solid may be adsorbed on surfaces of the solid or be absorbed within its structure to such an extent that it is prevented from developing its full vapour pressure and therefore from being easily removed by evaporation

Definition:

The moisture content of air is expressed as kg of water per kg of 'bone-dry' (water-free) dry air.

Relative Humidity (RH) of air:

$$\frac{\text{Mass of water vapour present per kg of dry air}}{\text{Mass of water vapour required to saturate 1 kg of dry air at the same temperature}} \times 100$$

RH of air is dependent on the amount of moisture in the air and its temperature (saturation degree).

During a drying process:

The temperature and moisture content could change for:

1. uptake into the drying air of evaporated water vapour from the drying solid

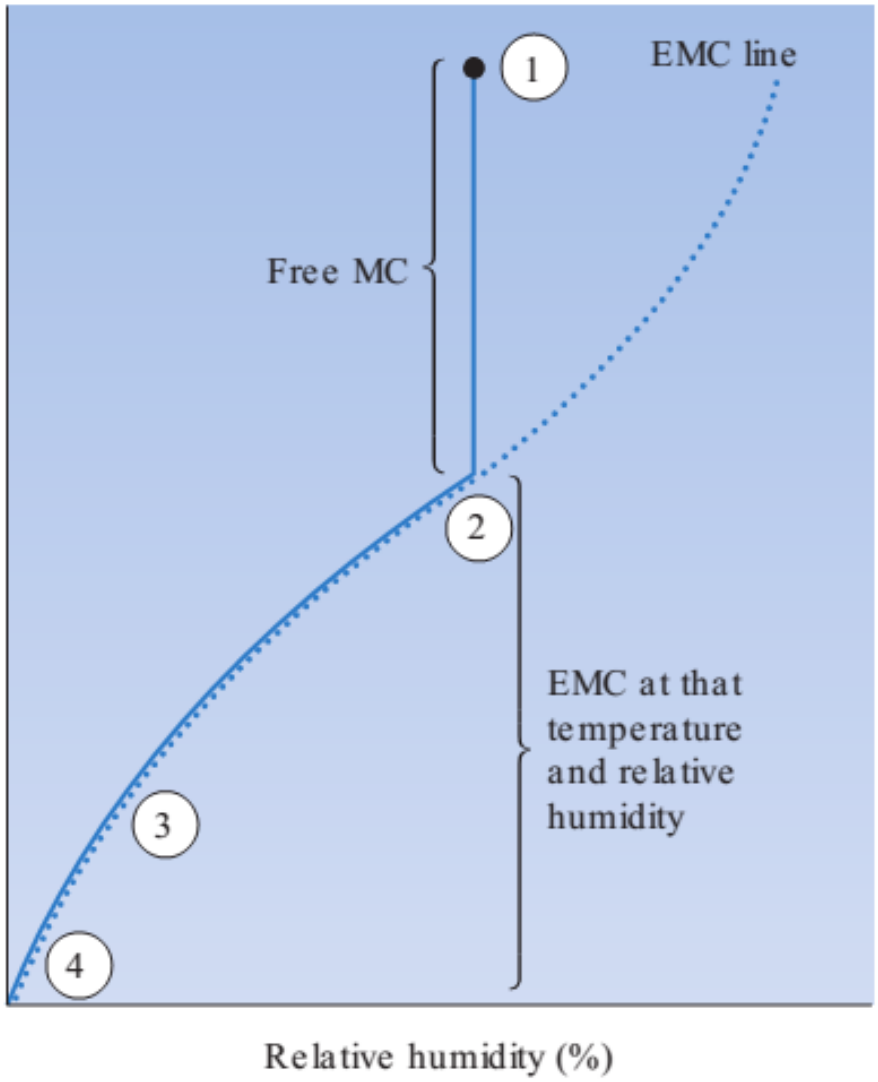
If evaporation is high and vapour removal inefficient, the drying efficiency will rapidly fall

2. evaporative cooling: air transfers latent heat to the wet solid

If the cooling is excessive the temperature of the air may fall to a value known as the dew point

Loss of water from wet solids:

Loss of water from a drying solid. The wet solid prior to drying is at condition (1). It can lose water by evaporation to position (2), its equilibrium moisture content (EMC) at that RH. The only way the solid can lose more water is to reduce the RH of the atmosphere, to (3) with silica gel or to (4) with phosphorus pentoxide



Types of pharmaceutical dryers:

According to the heat transfer method:

1. Convection
2. Conduction
3. Radiation.

Convective drying of wet solids: Dynamic convective dryers

Fluidized-bed dryer: Advantages:

1. Efficient heat and mass transfer give high drying rates, so that drying times are short.
2. Most of the drying will occur at a constant rate
3. The temperature of a fluidized bed is uniform through out and can be controlled precisely.
4. The turbulence in a fluidized bed causes some attrition to the surface of the granule. This produces a more spherical free- owing product.
5. The free movement of individual particles reduces the risk of soluble materials migrating during drying.

Convective drying of wet solids: Dynamic convective dryers

Fluidized-bed dryer: Advantages:

6. Keeping the granules separate during drying also reduces the problems of aggregation and reduces the need for a sieving stage after drying.

7. The fluidization containers can be mobile, making handling and movement around the production area simple, thus reducing labour costs.

8. Short drying times mean that the unit has a high product output from a small floor space.

Convective drying of wet solids: Dynamic convective dryers

Fluidized-bed dryer: disadvantages:

1. The turbulence may cause damage to some granules and the production of too much dust.

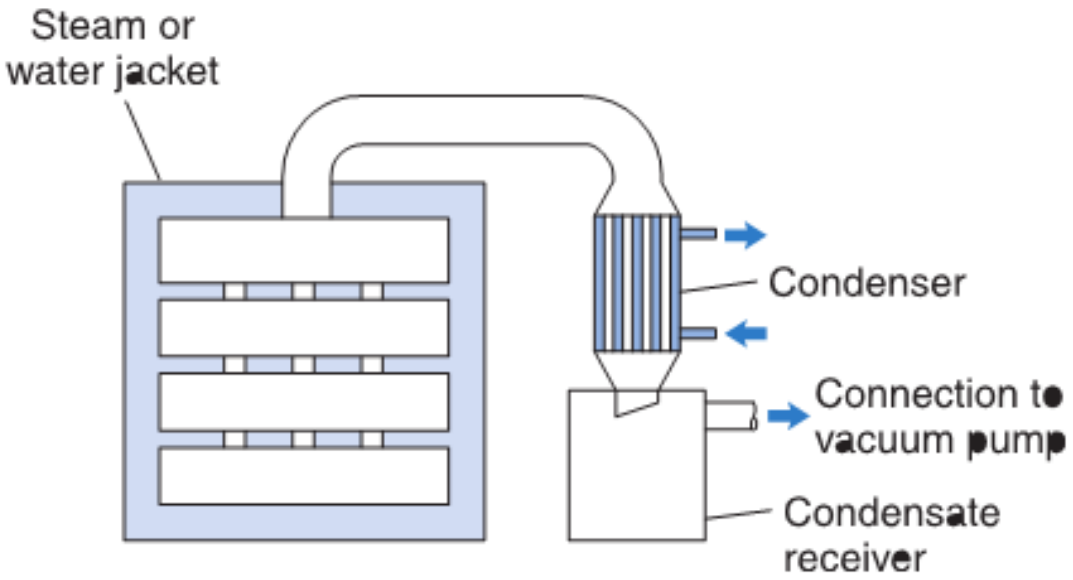
2. Fine particles collect by bag filters so care must be taken to avoid segregation and loss of fines.

3. The vigorous movement of particles in hot dry air can lead to the generation of charges of static electricity which may cause explosion especially if organic solvent used in granulation (Adequate electrical earthing is essential)

Conductive drying of we t solids:

Vacuum oven:

Operating pressure can be as low as 0.03–0.06 bar, at which water boils at 25–35 °C



Conductive drying of we t solids:

Vacuum oven:

The main advantage of a vacuum oven is that drying takes place at a low temperature, and since there is little air present, there is minimal risk of oxidation

Vacuum ovens are rarely used nowadays for production but are still worthy of mention as they may be the only method available to dry particularly thermolabile or oxygen-sensitive materials

Radiation drying of wet solids:
Radiant heat transmission:

Heat transmission by radiation differs from heat transfer by conduction or convection in that no transfer medium (solid, liquid or gaseous) needs be present. Heat energy in the form of radiation can cross empty space or travel through the atmosphere virtually without loss. If it falls on a body capable of absorbing it, then it appears as heat although a proportion may be reflected or transmitted

Radiation drying of wet solids: microwave radiation:

Microwave radiation in the wavelength range 10 mm to 1 m has been found to be an efficient heating and drying method

Disadvantages of microwave drying:

1. The batch size of microwave dryers is smaller than the batch sizes available for fluidized-bed drying.
2. Care must be taken to shield operators from the microwave radiation, which can cause damage to organs such as the eyes.

Radiation drying of wet solids: microwave radiation:

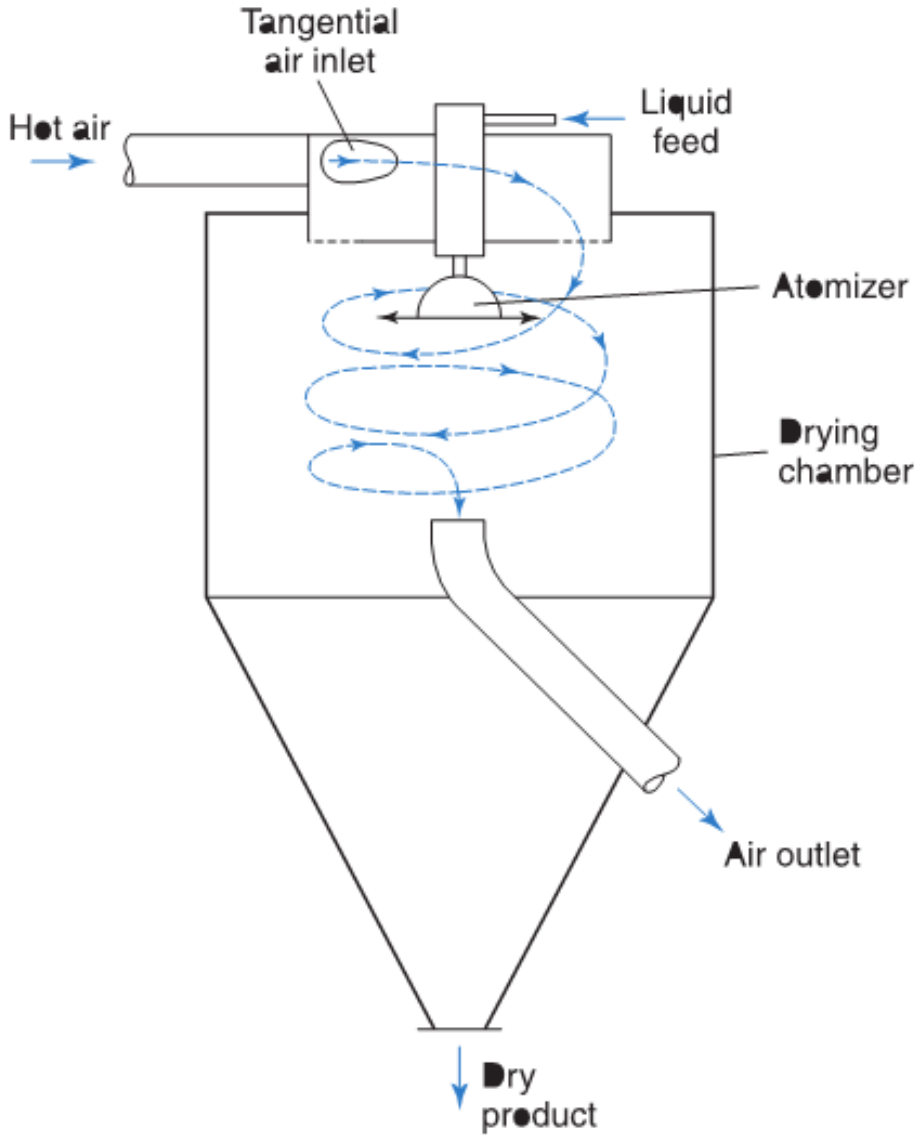
Advantages of microwave drying:

1. It provides rapid drying at fairly low temperatures
2. The thermal efficiency is high since Most of the microwave energy is absorbed by the liquid in the wet material
3. The bed is stationary, avoiding problems of dust and attrition
4. Solute migration is reduced as there is uniform heating of the wet mass
5. All the requirements of product and operator safety have been incorporated into machines without detracting from GMP considerations
6. Granulation endpoint detection is possible by measuring the residual microwave energy (as this rises sharply within the dryer when there is little solvent left to evaporate)

Dryers for solutions and suspensions:

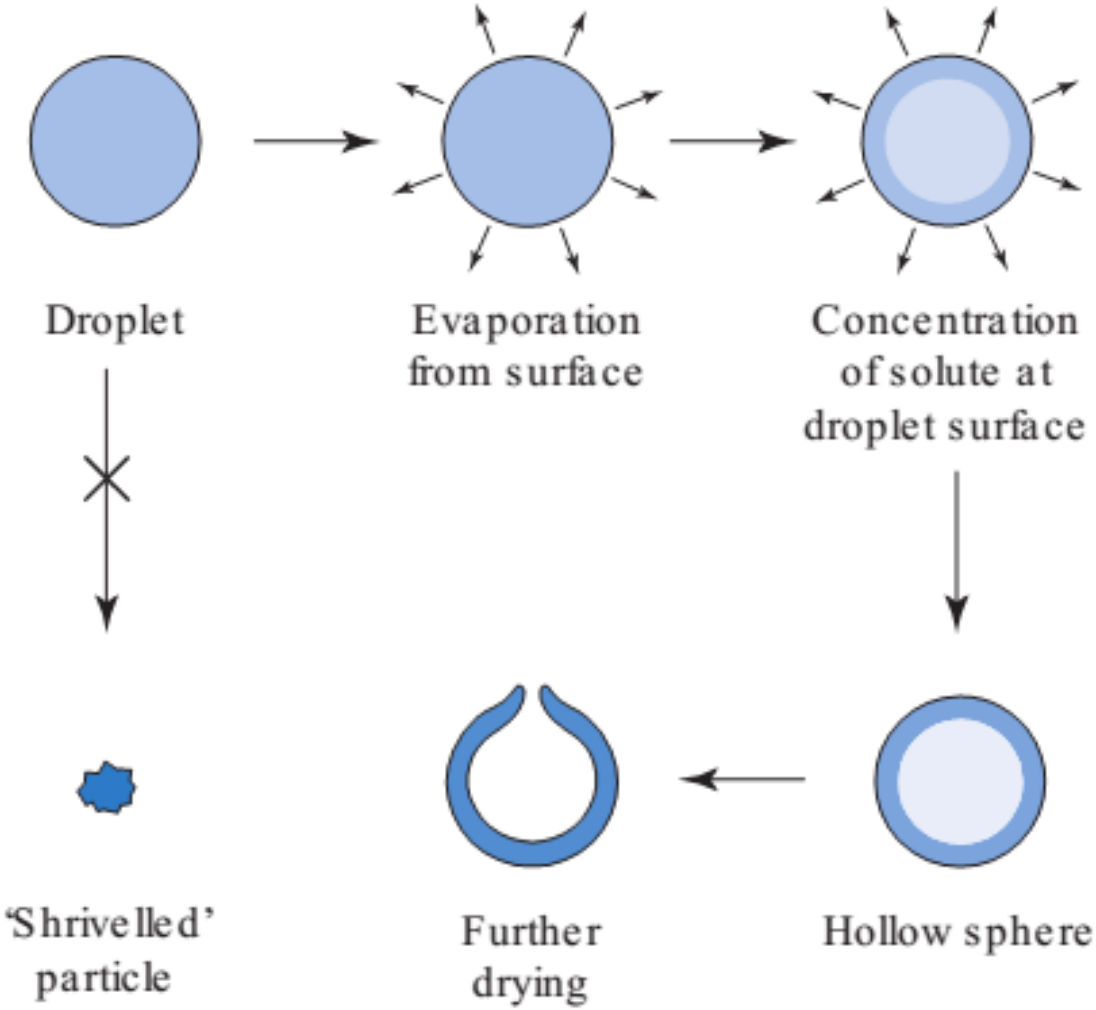
Spray dryer:

Liquid is atomized into small droplets. Then are sprayed into a stream of circulating hot air, so that each droplet dries to an individual solid particle. Thus, particle formation and drying occur in the one process.



Dryers for solutions and suspensions:

Spray dryer:



Dryers for solutions and suspensions:

Spray dryer (Advantages):

1. The actual drying time of a droplet is only a fraction of a second, and the overall time in the dryer only a few seconds
2. Because evaporation is very rapid, the temperature of the particles is kept low by evaporative cooling.
3. High bulk density and rapid dissolution
4. Uniform and controllable particle size
5. Product has excellent flow and compaction properties
6. It can be used as a continuous process if required.

Dryers for solutions and suspensions: Spray dryer (Disadvantages):

1. The equipment is very bulky and expensive.
2. The overall thermal efficiency is rather low since the air must still be hot enough when it leaves the dryer to avoid condensation of moisture. Also, large volumes of heated air pass through the chamber without contacting a particle and thus not contributing directly to the drying process

Dryers for solutions and suspensions:

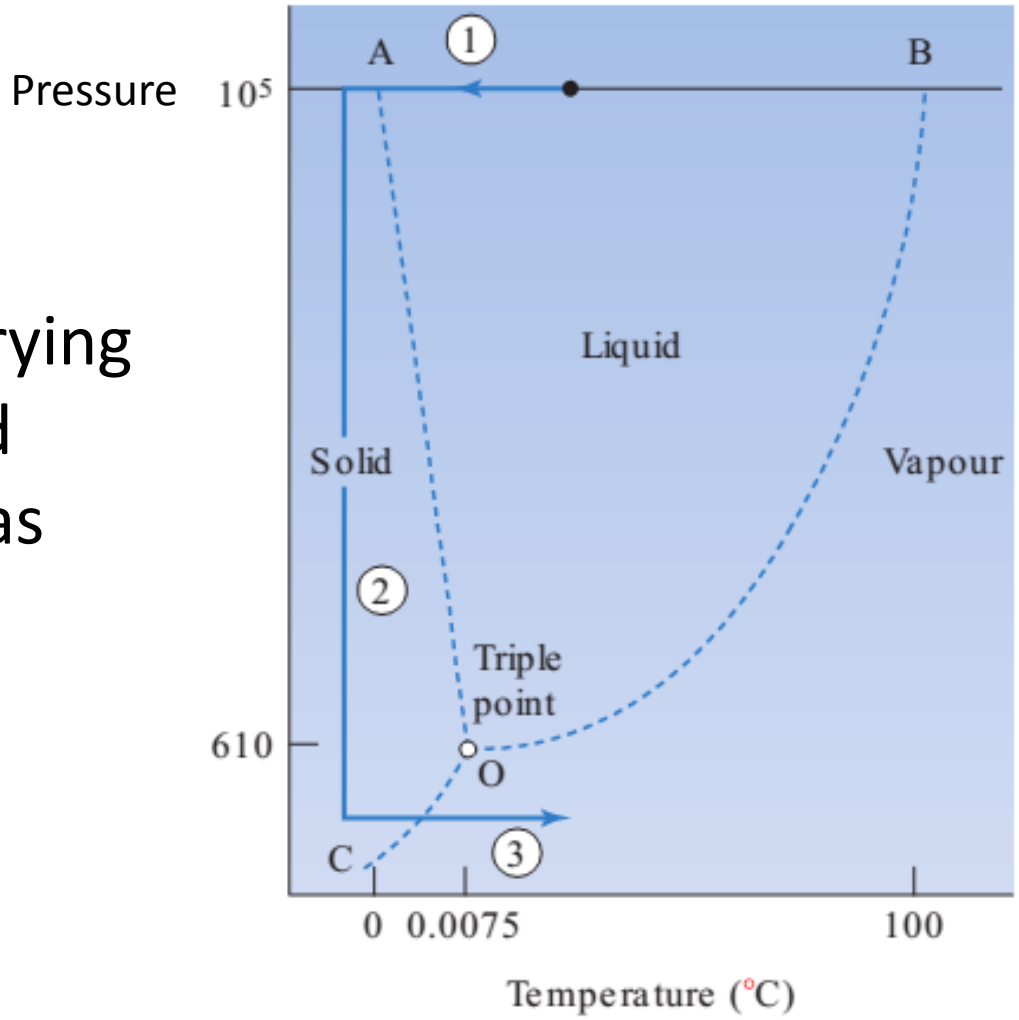
Freeze drying:

Freeze drying is a process used to dry extremely heat-sensitive materials. It can allow the drying, without excessive damage, of proteins, blood products and even microorganisms which retain a small but significant viability

Dryers for solutions and suspensions:

The phase diagram for water:

To ensure freeze drying the vapour evolved must be removed as fast as it is formed.



Dryers for solutions and suspensions:

Freeze drying (Process):

1. freezing the solution
2. reducing the atmospheric pressure above the ice to below that of the triple point of the product
3. adding heat to the system to raise the temperature to the sublimation curve (CO in phase diagram)

Dryers for solutions and suspensions:

Freeze drying (Advantages):

1. Drying takes place at very low temperatures
2. The solution is frozen such that the final dry product is a network of solid occupying the same volume as the original solution. Thus the product is light and porous
3. The porous form of the product gives ready solubility of the freeze-dried product.

Dryers for solutions and suspensions:

Freeze drying (Advantages):

4. There is no concentration of the solution prior to drying. Hence, salts do not concentrate in the wet state and denature proteins, as occurs with other drying methods.
5. Since the process takes place under high vacuum, there is little contact with air and oxidation is minimized

Dryers for solutions and suspensions:

Freeze drying (disadvantages):

1. The porosity, ready solubility and complete dryness of the product result in one with a very hygroscopic nature. Unless dried in the final container and sealed in situ, packaging requires special consideration.
2. The process is very slow and uses complicated plant that is very expensive. It is not a general method of drying, therefore, but is limited to certain types of valuable products that, because of their heat sensitivity, cannot be dried by any other means.

Solute migration during drying:

1. Intergranular migration (between granules) as in the surface of granules in oven.

2. Intragranular migration (within individual granules) as in FBD

The end

Compaction

Pharmaceutical technology

Dr. Basheer Al-kasmi

Lecture 8

Tablets Definition:

Solid preparations each containing a single dose of one or more active substances obtained by compressing uniform volumes of particles

Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated.

Tablets are used mainly for systemic or local drug delivery

Tablets are popular for several reasons:

- The oral route represents a convenient and safe way of drug administration.
- Compared to liquid dosage forms, tablets have general advantages in terms of the chemical, physical and microbiological stability of the dosage form
- The preparation procedure enables accurate dosing of the drug.
- Tablets are convenient to handle and can be prepared in a versatile way with respect to their use and the delivery of the drug.
- Finally, tablets can be relatively cheaply mass produced, with robust and quality-controlled production procedures giving an elegant preparation of consistent quality.

Tablets disadvantages :

- the problem of poor bioavailability of drugs due to unfavourable drug properties, e.g. poor solubility, poor absorption properties
- instability in the gastrointestinal tract.
- some drugs may cause local irritant effects or otherwise cause harm to the gastrointestinal mucosa.

Stages in tablet formation:

1. Die filling:

This is normally accomplished by gravitational flow of the powder from a hopper via the die table into the die (although presses based on centrifugal die filling are also used). The die is closed at its lower end by the lower punch.

Stages in tablet formation:

2. Tablet formation:

The upper punch descends and enters the die and the powder is compressed until a tablet is formed. During the compression phase, the lower punch can be stationary or can move upwards in the die. After the maximum applied force is reached, the upper punch leaves the powder, i.e. the decompression phase

Stages in tablet formation:

3. Tablet ejection

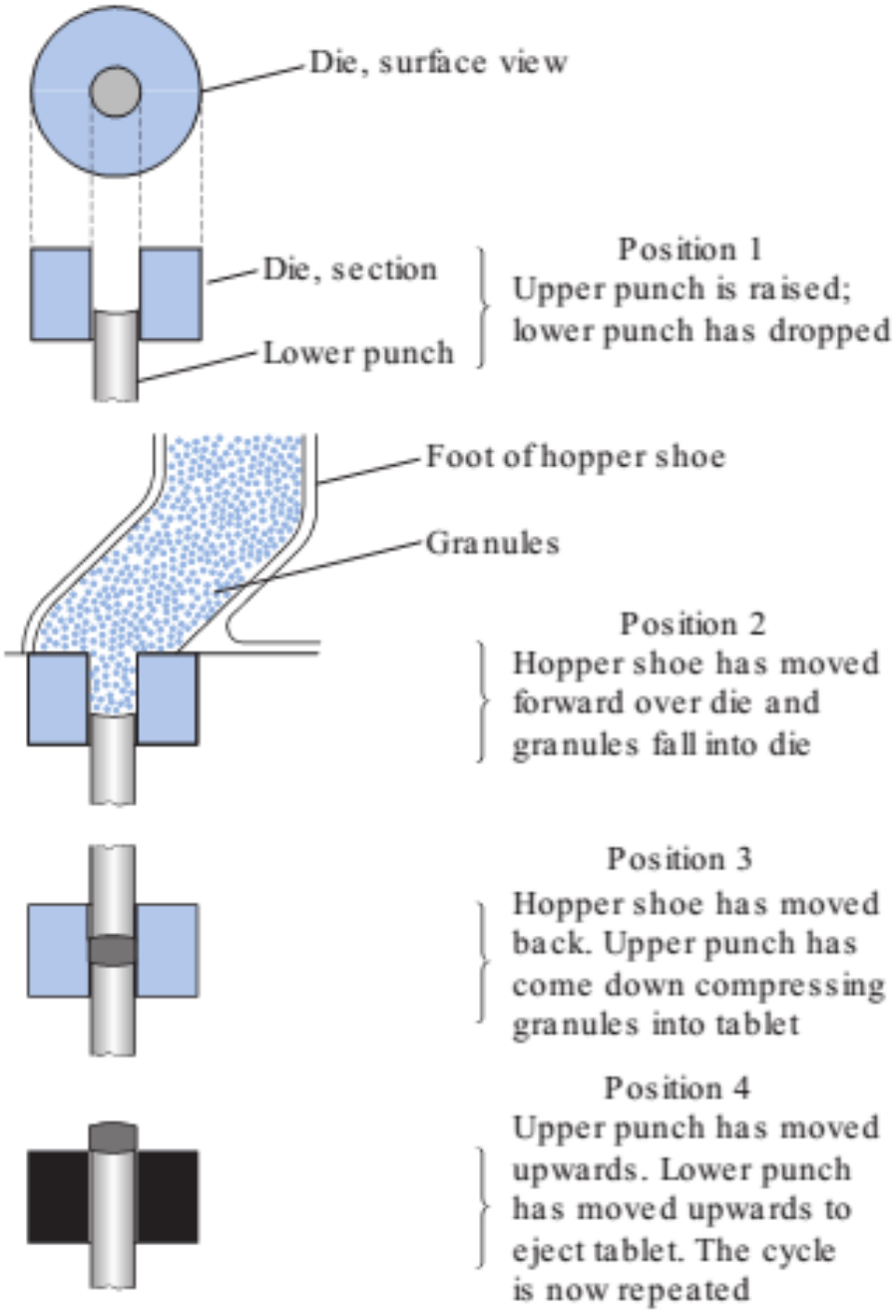
During this phase the lower punch rises until its tip reaches the level of the top of the die. The tablet is subsequently removed from the die table by a pushing device.

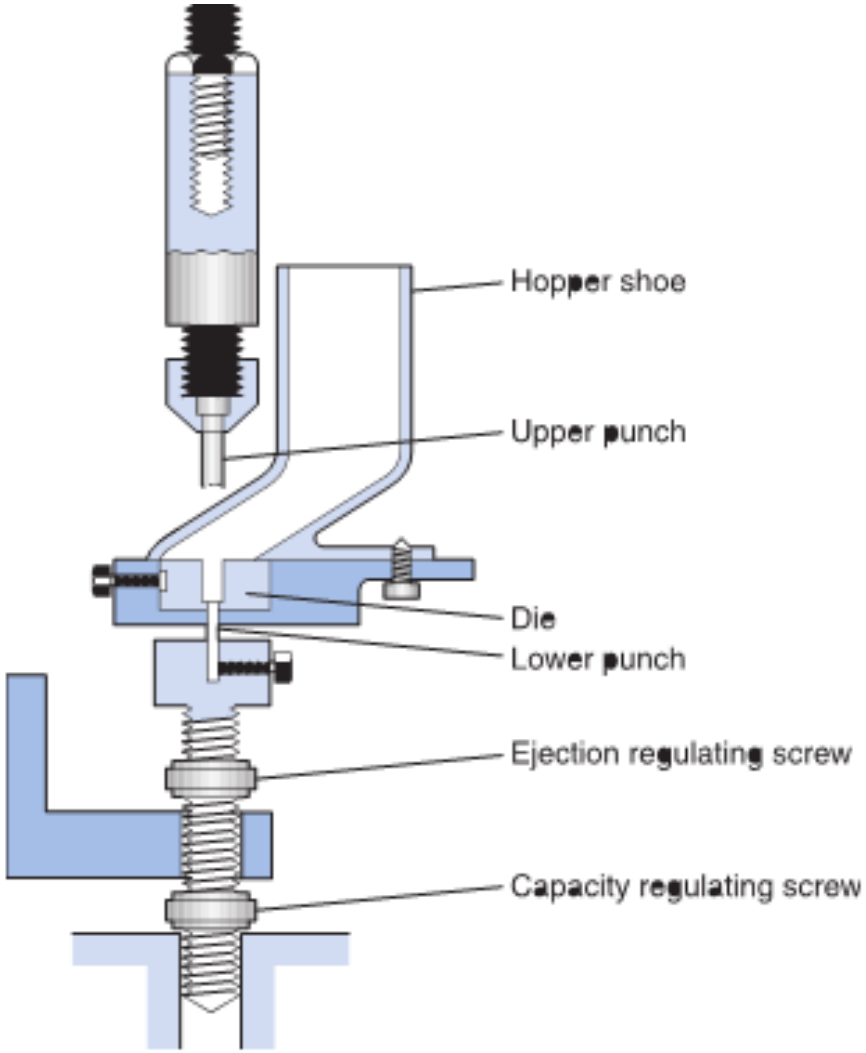
Tablet presses:

1. Single-punch press:

The output of tablets from a single-punch press is up to about 200 tablets per minute.

It is used in formulation development and production of tablets for clinical trials.


Die, surface view
Die, section
Lower punch
Position 1
Upper punch is raised;
lower punch has dropped
Foot of hopper shoe
Granules
Position 2
Hopper shoe has moved
forward over die and
granules fall into die
Position 3
Hopper shoe has moved
back. Upper punch has
come down compressing
granules into tablet
Position 4
Upper punch has moved
upwards. Lower punch
has moved upwards to
eject tablet. The cycle
is now repeated


Hopper shoe
Upper punch
Die
Lower punch
Ejection regulating screw
Capacity regulating screw

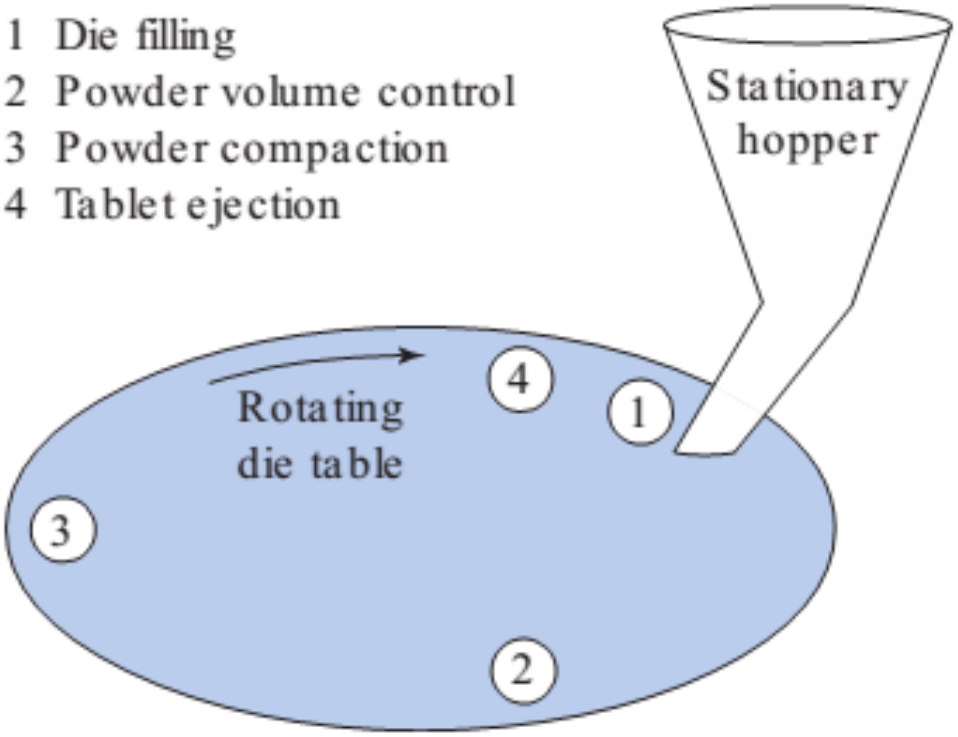
Tablet presses:

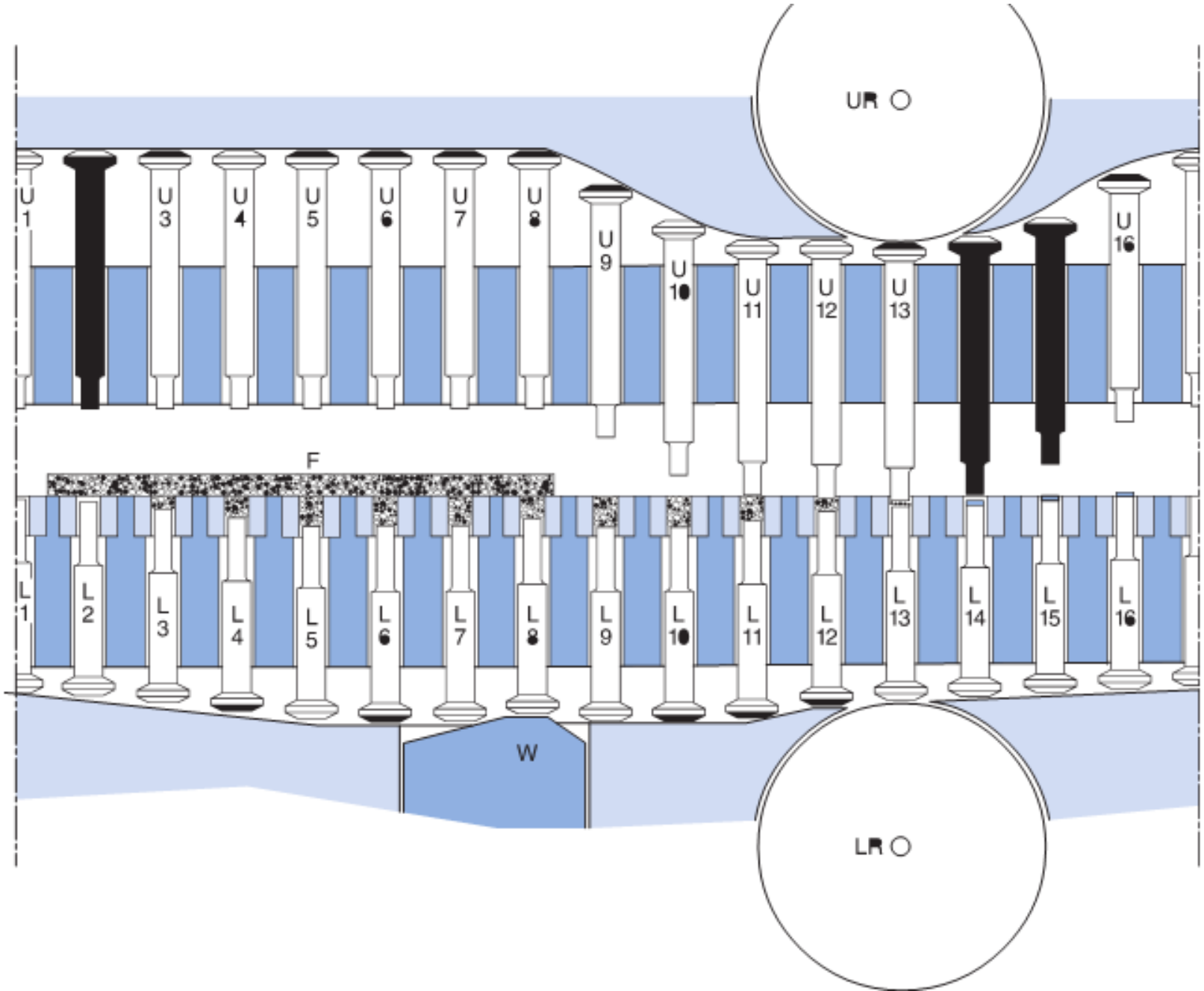
2. Rotary press:

Outputs of over 10 000 tablets per minute.

It is used in production.

Punches number: from 3 to up to 60 or more.

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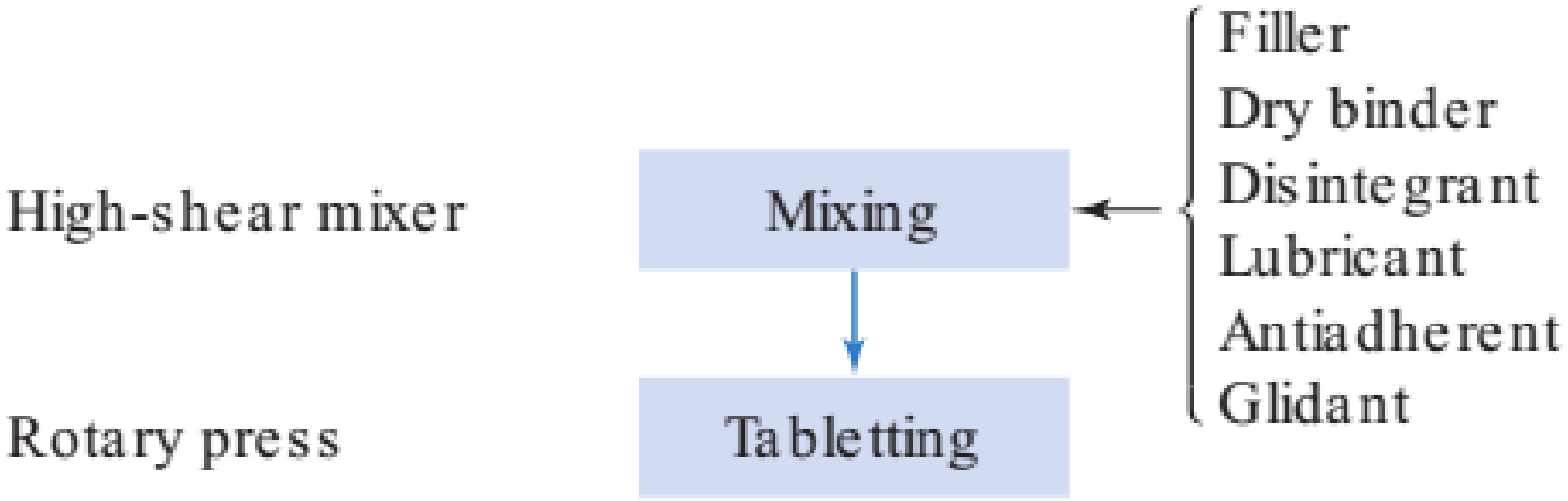
LR

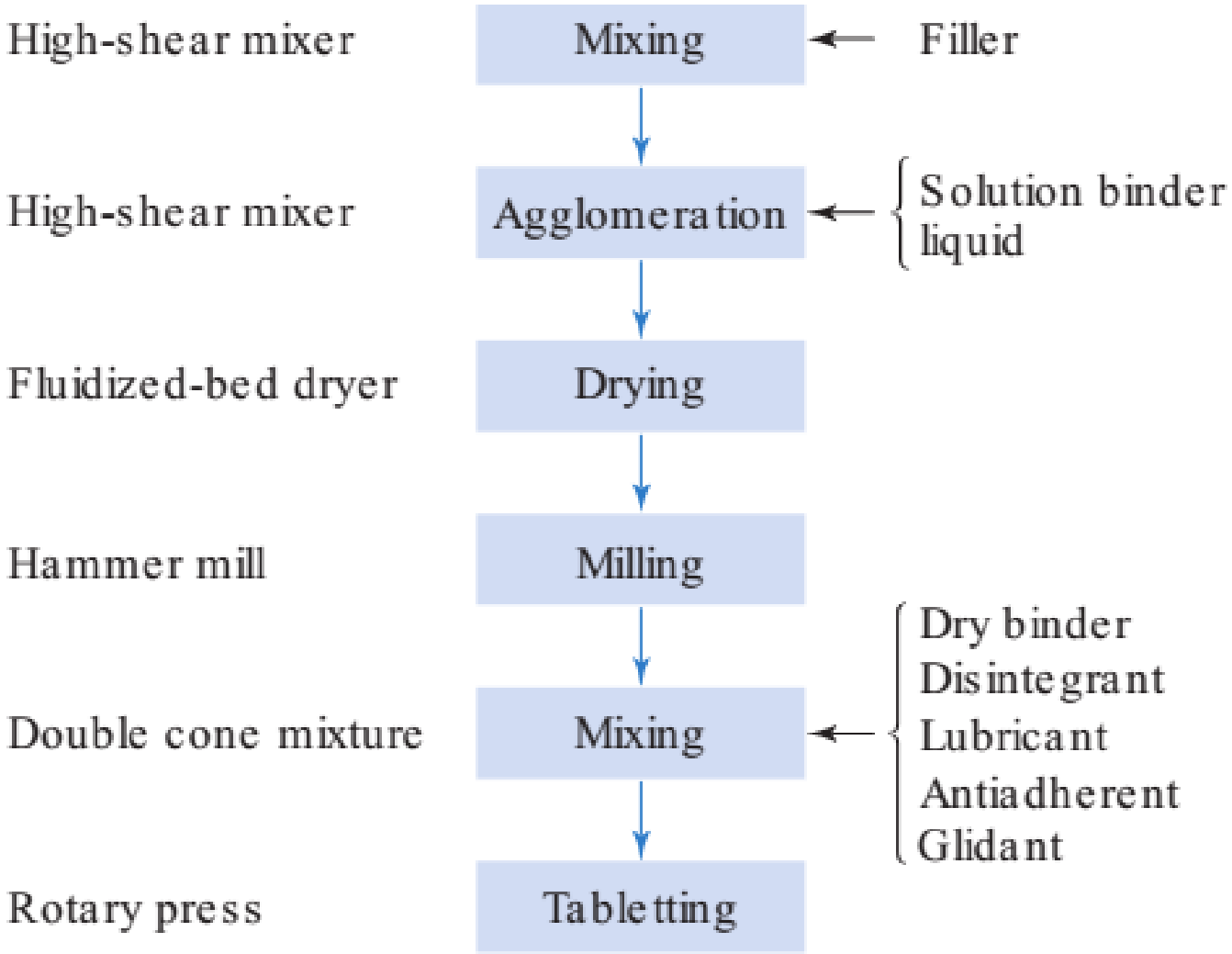
Rationale for granulating powders prior to tableting:

- increase the bulk density of the powder mixture and thus ensure that the required volume of powder can be filled into the die
- improve the flowability of the powder in order to ensure that tablets with a low and acceptable tablet weight variation can be prepared
- improve mixing homogeneity and reduce segregation by mixing small particles which subsequently adhere to each other
- improve the compactability of the powder by adding a solution binder, which is effectively distributed on the particle surfaces
- ensure a homogeneous colour in a tablet by adding the colour in a manner that ensures its effective distribution over the particle surfaces
- affect the dissolution process for hydrophobic, poorly soluble particles by using a fine particulate drug which is thoroughly mixed with a hydrophilic filler and a hydrophilic binder

Tablet excipients (DC):



Tablet excipients (wet granulation):



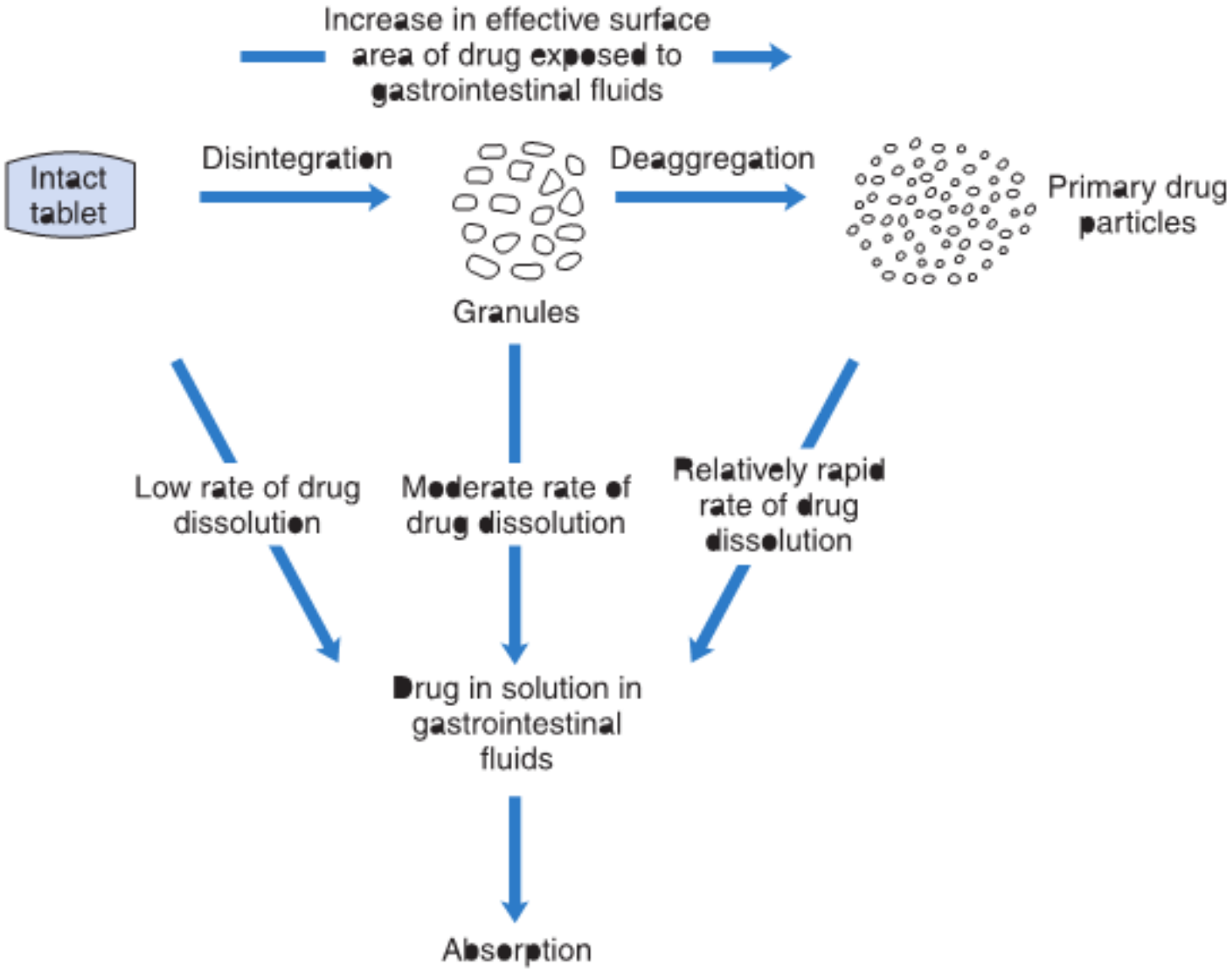
Filler (or diluent):

Tablets normally weigh at least 50 mg. Therefore, a low dose of a potent drug requires the incorporation of a substance into the formulation to increase the bulk volume of the powder and hence the size of the tablet

Requirements: chemically inert, non-hygroscopic, biocompatible, good biopharmaceutical properties, good technical properties, acceptable taste, cheap

Ex.: Lactose (crystalline or amorphous), Microcrystalline cellulose, Dicalcium phosphate dihydrate.

Disintegrant:



Disintegrant (types):

1. Disintegrants that facilitate water uptake.

These disintegrants act by facilitating the transport of liquids into the pores of the tablet, with the consequence that the tablet may break into fragments.

2. Disintegrants that will rupture the tablet.

Rupturing of tablets can be caused by swelling of the disintegrant particles during sorption of water

3. Producing gas, normally carbon dioxide,

when in contact with water. Such disintegrants are used in effervescent tablets and normally not in tablets that should be swallowed as a solid

Disintegrant (examples):

1. Starch up to 10%
2. Superdisintegrant (1 – 5%):

- Crosslinked polyvinyl pyrrolidone
- Sodium starch glycolate
- Sodium carboxymethyl cellulose

Disintegrants can be mixed with intragranular addition and extragranular addition

Binder (adhesive):

Binders can be added to a powder in different ways

- As a dry powder which is mixed with the other ingredients before wet agglomeration (2-10%).
- As a solution which is used as agglomeration liquid during wet agglomeration (2-10%).
- As a dry powder which is mixed with the other ingredients before compaction (slugging or tableting). The binder is here often referred to as a dry binder (10-80%)

Binder (example):

Solution binder:

Gelatin, Polyvinyl pyrrolidone (PVP), Cellulose derivatives (e.g. hydroxypropylmethyl cellulose HPMC), Polyethylene glycol (PEG), Sucrose, Starch

Dry binder:

Microcrystalline cellulose MCC (Avicel), Methyl cellulose, Polyvinyl pyrrolidone, Polyethylene glycol

Dissolution enhancer:

For drugs of low aqueous solubility, the dissolution of the drug may be the rate-limiting step in the overall drug release and absorption processes.

wetting agent (like sodium lauryl sulphate SLS or Polysorbate) is used to improve solubility of drug.

Glidant:

Improve the flowability of the powder.

- Talc (1-2 %)
- colloidal silicone dioxide (erosil): (about 0.2%)
- Silica particles are very small they adhere to the particle surfaces of the other ingredients and improve flow by reducing interparticulate friction
- Magnesium stearate, normally used as a lubricant, can also use as glidant (<1%)

Lubricant:

ensure that tablet formation and ejection can occur with low friction between the solid and the die wall.

Lubrication is achieved mainly by two mechanisms:

1. fluid lubrication (liquid paraffin):

a layer of fluid is located between and separates the moving surfaces of the solids from each other and thus reduces the friction (seldom used)

Lubricant:

2. Boundary lubrication: the sliding surfaces are separated by only a very thin film of lubricant.

Lubrication effected by mixing time and intensity

(-): many lubricants are hydrophobic, tablet mechanical strength, disintegration and dissolution are often retarded by the addition of a lubricant

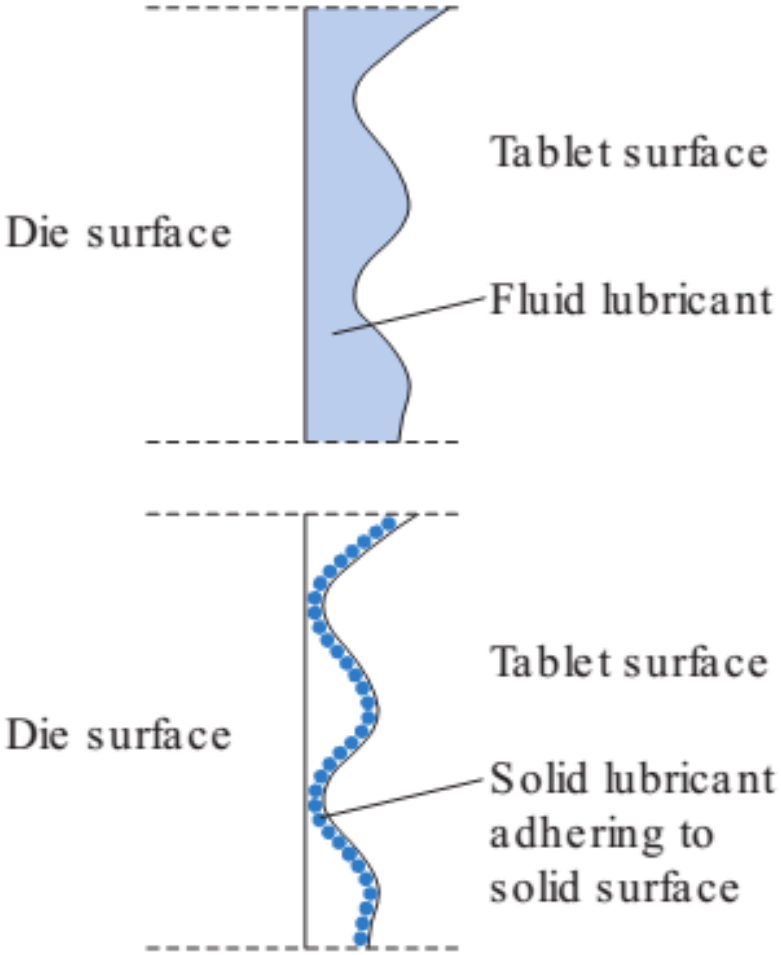
Lubricant:

Hydrophobic lubricants:

stearic acid or Magnesium stearate (0.5 – 2%)

Hydrophilic lubricants:

surface-active agents and polyethylene glycol



Antiadherent:

reduce adhesion between the powder and the punch faces and thus prevent particles sticking to the punches.

Many lubricants, such as magnesium stearate, also have antiadherent properties. However, other substances with limited ability to reduce friction can also act as antiadherents, such as talc and starch

Other excipients:

Sorbent: capable of sorbing some quantities of fluids in an apparently dry state as Microcrystalline cellulose and silica.

Flavour: to give the tablet a more pleasant taste or to mask an unpleasant one. Flavouring agents are often thermolabile and so cannot be added prior to an operation involving heat.

Colourant: to aid identification and patient compliance. can be added as an insoluble powder or dissolved in the granulation liquid

The end

Compaction

Pharmaceutical technology

Dr. Basheer Al-kasmi

Lecture 9

Tablet types:

Immediate-release tablets:

The drug is intended to be released rapidly after administration, or the tablet is dissolved in liquid before intake and thus administered as a solution.

Immediate-release tablets are the most common type of tablet and include disintegrating, chewable, effervescent, sublingual and buccal tablets

Tablet types:

Modified-release tablets:

prolonged release, pulsatile release and delayed release

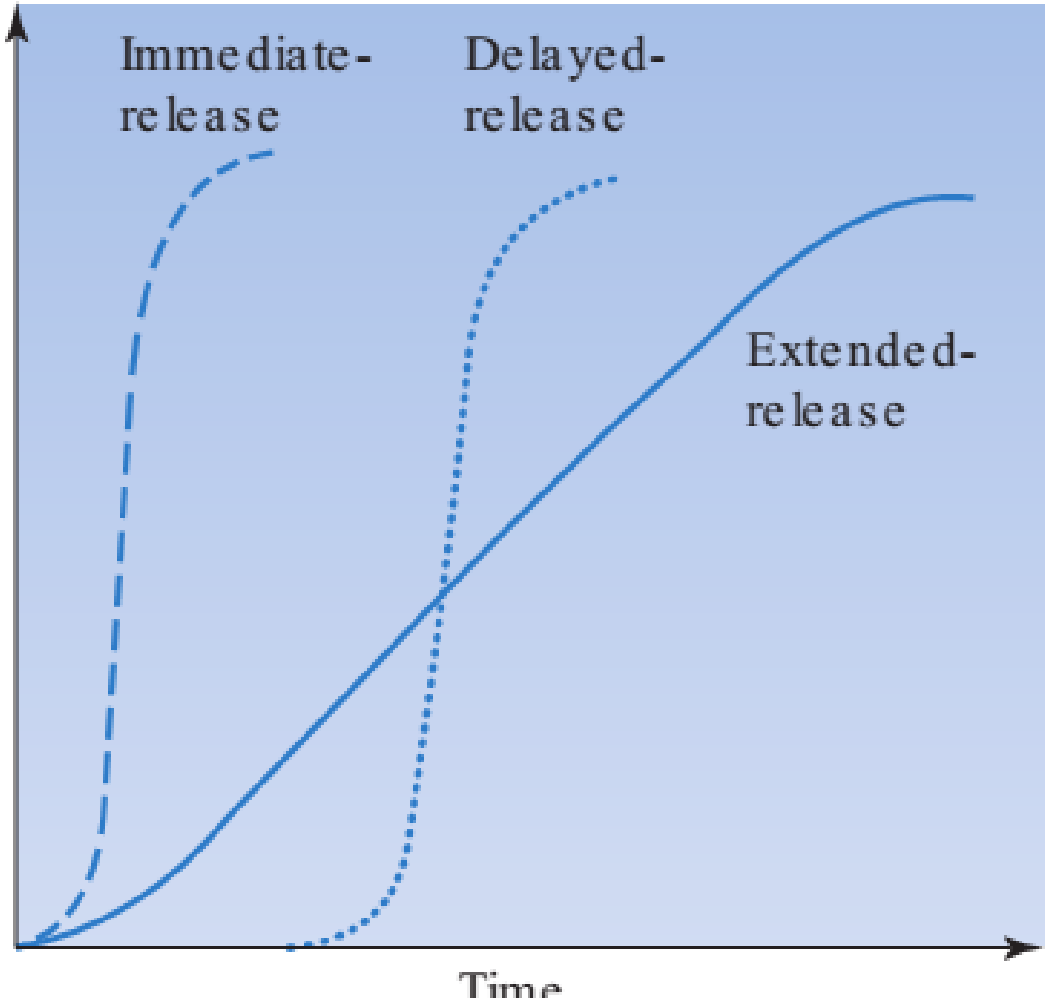
Prolonged-release tablet is used to indicate that the drug is released slowly at a nearly constant rate. If the rate of release is constant during a substantial period of time, a zero-order type of release is obtained, i.e. M = kt (where M is the cumulative amount of drug released and t is the release time). This is sometimes described as an ideal type of prolonged-release preparation

Tablet types:

Pulsatile release is another means to increase the time period for drug absorption after a single administration and is accomplished by releasing the drug in two or more pulses.

Delayed-release tablets the drug is liberated from the tablet some time after administration. After this period has elapsed, the release is normally rapid (enteric coating).

Table t types:



Tablet types:

Disintegrating tablets: The most common type of tablet is intended to be swallowed and to release the drug in a relatively short time.

excipients: Filler, disintegrant, binder, glidant, lubricant and antiadherent

Multilayer tablets are prepared by repeated compression of powders and are made primarily to separate incompatible drugs from each other

Tablet types:

Chewable tablets are chewed and thus are mechanically disintegrated in the mouth (antacid tablets). For rapid drug effect – or to facilitate the administration of the tablet

Chewable tablets are similar in composition to conventional tablets except that a disintegrant is normally not included in the composition.

Flavouring and colouring agents are common and sorbitol and mannitol are common examples of fillers

Tablet types:

Effervescent tablets

the effervescent carbon dioxide is created by a reaction in water between a carbonate or bicarbonate and a weak acid such as citric or tartaric acids. obtain rapid drug action(analgesic drugs).

buffered water solution will be obtained which increases the pH of the stomach. The result is a rapid emptying of the stomach and the residence time of the drug in the stomach will thus be short. That will fast drug absorption as most drug absorbed from small intestine also drug-induced gastric irritation can be avoided.

Excipient: flavour, colourant and water-soluble lubricant

Moisture must be avoided during preparation and stored.

Tablet types:

Compressed lozenges

Compressed lozenges are tablets that dissolve slowly in the mouth and so release the drug dissolved in the saliva. Disintegrants are not used, The filler (glucose, sorbitol and mannitol)and binder (gelatin) should be water soluble and have a good taste.

Lozenges are normally prepared by compaction at high applied pressures in order to obtain a tablet of high mechanical strength and low porosity which can dissolve slowly in the mouth.

Tablet types:

Sublingual tablets and buccal tablets:

Sublingual tablets and buccal tablets are used for drug release in the mouth followed by systemic uptake of the drug. A rapid systemic drug effect can thus be obtained without first-pass liver metabolism

Sublingual and buccal tablets are often small and porous, the latter facilitating fast disintegration and drug release. Other designs, comprising high molecular weight hydrophilic polymers and/ or gums, adhere in place by forming a gel. They remain in position, releasing drug, for 1–2 hours

Controlled release mechanisms:

The most common means used to achieve a slow, controlled release of the drug from tablets:

- drug transport control by diffusion
- dissolution control (changing drug solubility)
- erosion control
- drug transport control by convective flow (osmotic pumping)
- ion exchange control.

Diffusion-controlled release systems:

In diffusion-controlled prolonged-release systems, the transport by diffusion of dissolved drugs in pores filled with gastric or intestinal juice is the release-controlling process

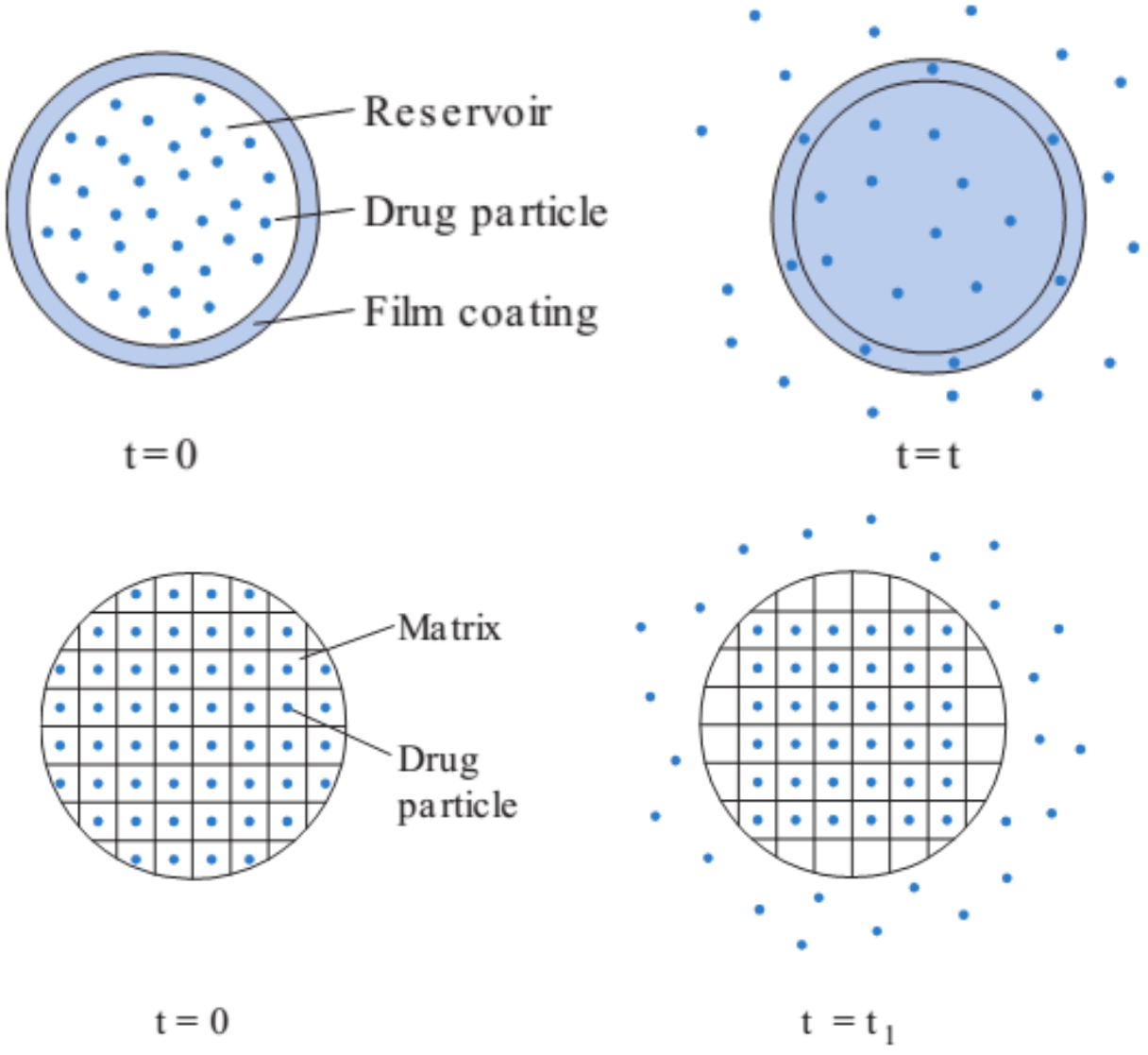
Diffusion controlled release systems are divided into:

1. Matrix systems: Diffusion occurs in pores located within the bulk of the release unit.
2. Reservoir systems: diffusion takes place in a thin water-insoluble lm or membrane, often about 5–20 µm thick, which surrounds the release unit.

Diffusion-controlled release systems:

Drug is released from a diffusion-controlled release unit in two steps:

1. The liquid that surrounds the dosage form penetrates the release unit and dissolves the drug.
2. The dissolved drug will diffuse in the pores of the release unit or the surrounding membrane and thus be released

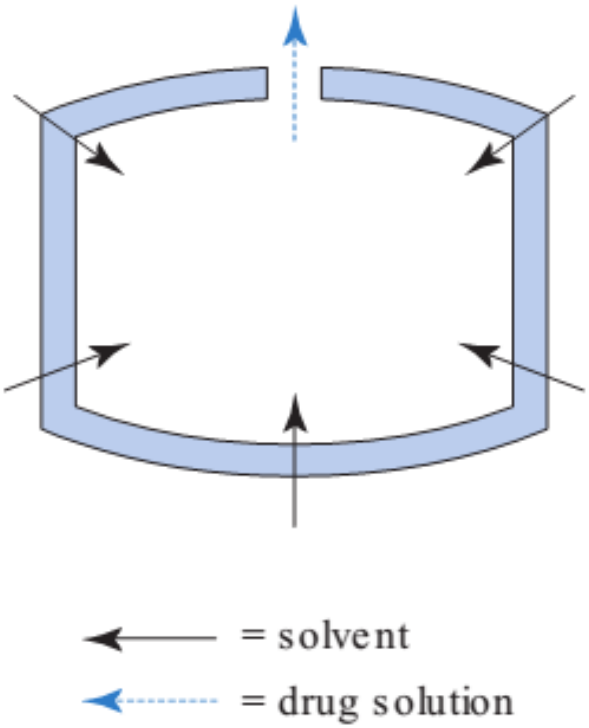

Reservoir
Drug particle
Film coating
t=0
t=t
Matrix
Drug particle
t = 0
t = t1

Osmosis-controlled release systems:

Osmosis can be defined as the flow of a solvent from a compartment with a low concentration of solute to a compartment with a high concentration. The two compartments are separated by a semi-permeable membrane, which allows flow of solvent but not of solute

Osmosis-controlled release systems:

- Release process:
  Osmotic transport of liquid into the release unit.
- Dissolution of drug within the release unit.
- Convective transport of a saturated drug solution by pumping of the solution through a single orifice



Tablet testing:

Uniformity of content of active ingredient:

1. Uniformity of weight (mass)
2. Uniformity of active ingredient

- drug substance forms the greater part of the tablet mass
- excipients form the greater part of the tablet weight

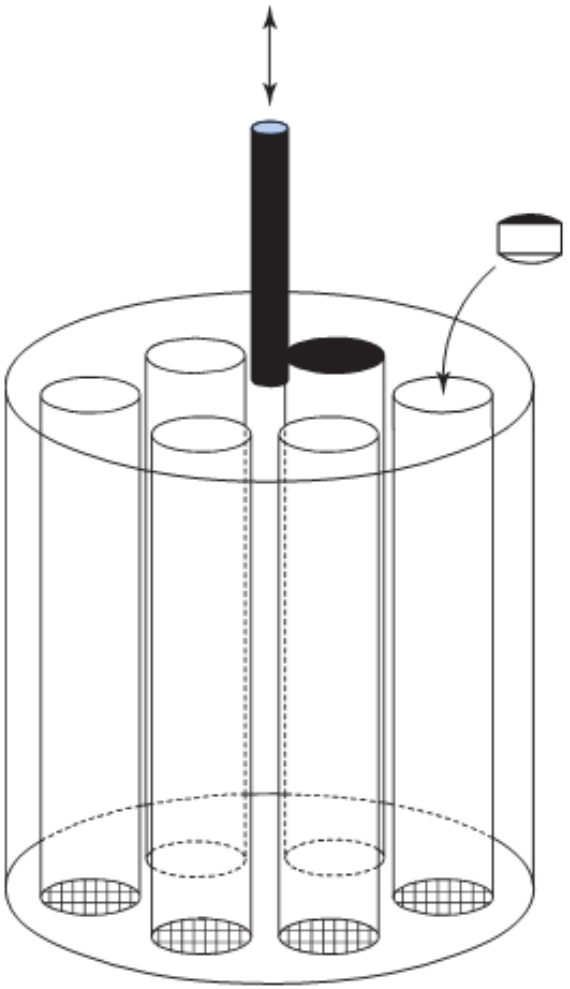
Tablet testing:

Disintegration:

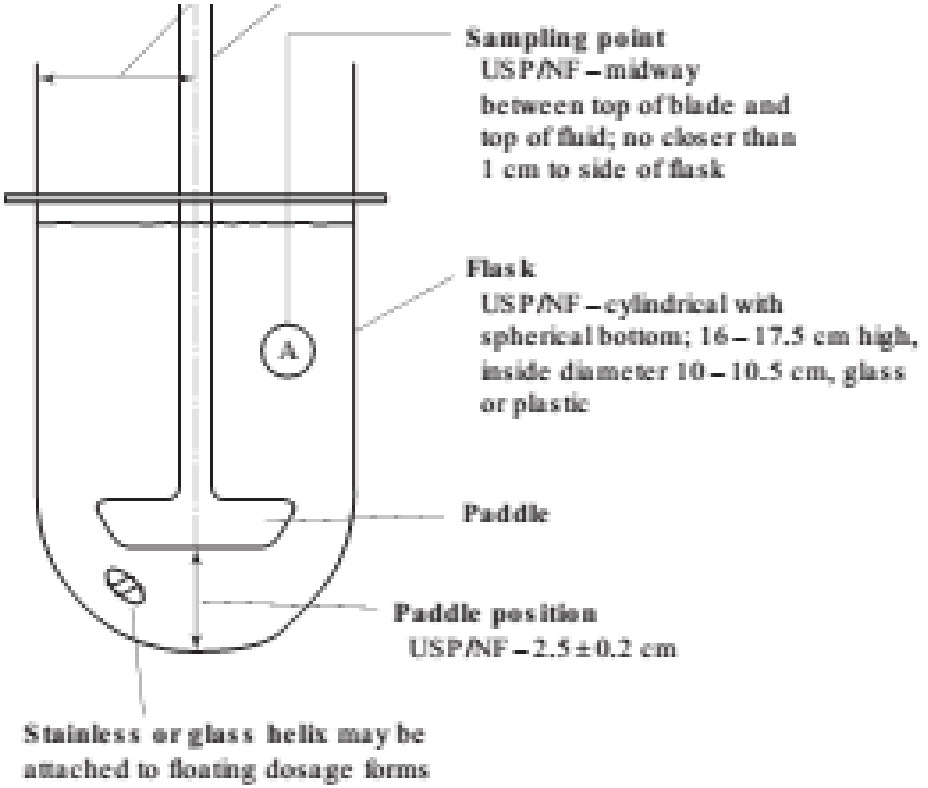
Temperature: 37 ± 2° C

Time: NMT 15 min for immediate release tablet

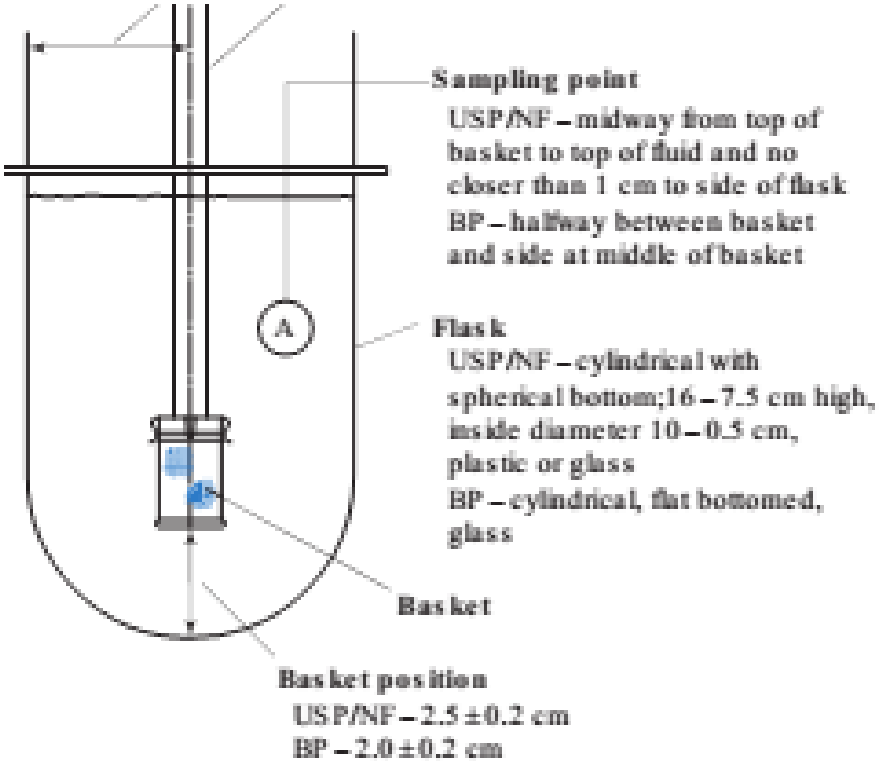
Tests for disintegration do not normally seek to establish a correlation with in vivo behaviour



Dissolution:



Apparatus 2



Apparatus 1

Tablet testing:

Dissolution:

Dissolution testing is the most important tool to assess bioavailability

Parameters:

- Temperature: 37 ± 0.5° C
- Apparatus : 1, 2, 3, or 4
- Medium
- Speed
- Tolerance: NLT Q% of the labeled amount of API is dissolved

Tablet testing:

Mechanical strength:

An acceptable tablet must remain intact during handling at all stages, i.e. during production, packaging, warehousing, distribution, dispensing and administration by the patient.

Testing can be subcategorized into two main groups:

- Attrition resistance methods (friability tests)
- Fracture resistance methods

Attrition resistance methods (friability test)

Time: 4 min, Speed 25 rpm

Friability (weight loss): NLT 1% also tablets should not show capping or cracking during such testing

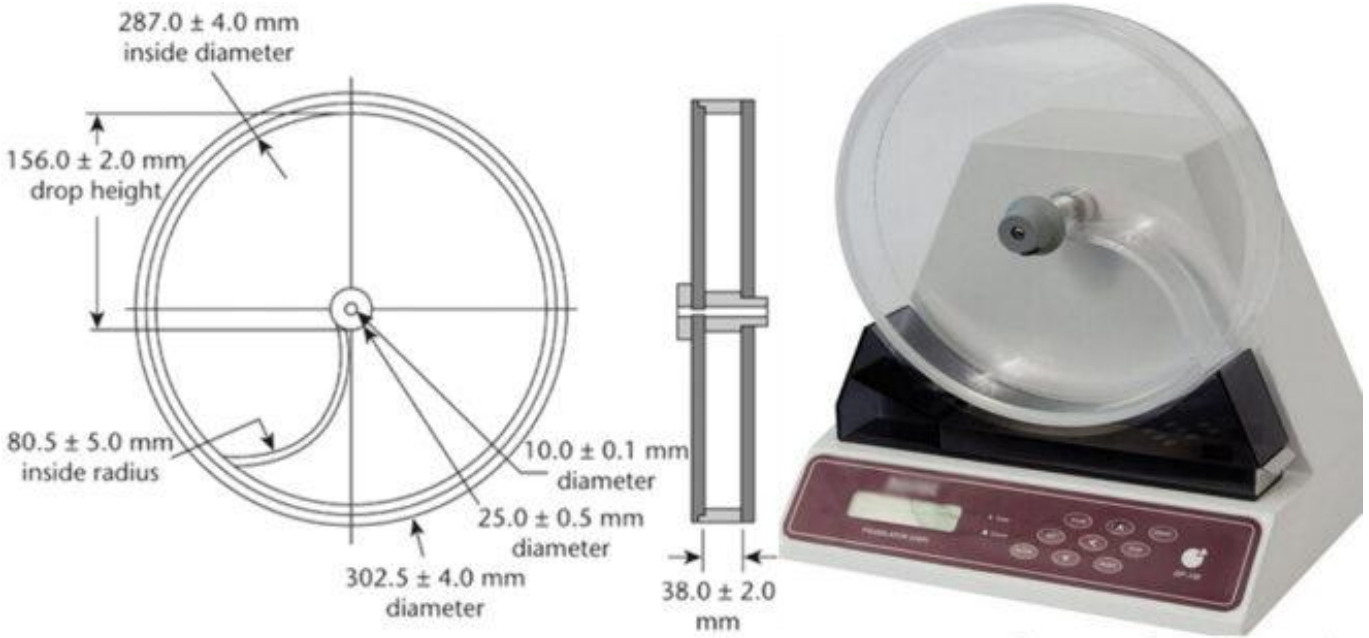
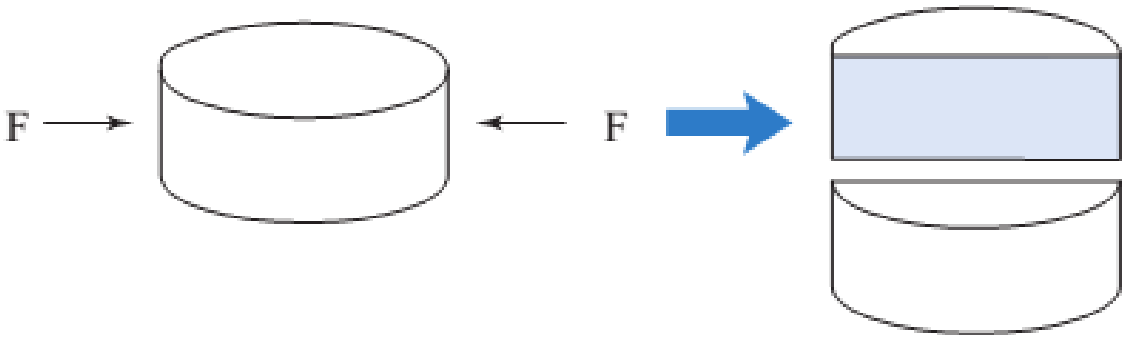


Fig: Roche Friabilator For Uncoated Tablets

Fracture resistance methods:

Analysis of the fracture resistance of tablets involves the application of a load on the tablet and the determination of the force needed to fracture or break the specimen along its diameter or other axis.



Tableting problem:

Problem	Cause
Weight variation	Powder flowability
Capping or Lamination	air is entrapped in the tablet too much elastic energy is stored Inadequate binding over-dried granules excessive lubricant sticking of the compact
Sticking or Picking	raw material properties as well as temperatures inside the press Insufficient or a limited extent of lubrication. Surface roughness of the tooling. Slight dampness of the granulation.
Chipping	Too dry granules. Worn out punches and die. take-off plate being set too high.
Low tensile strength	Too high an initial level of the lubricant, Excessive shear during the lubrication stage, Excessive lubrication time

The end

Modified-release oral drug delivery

Pharmaceutical technology

Dr. Basheer Al-kasmi

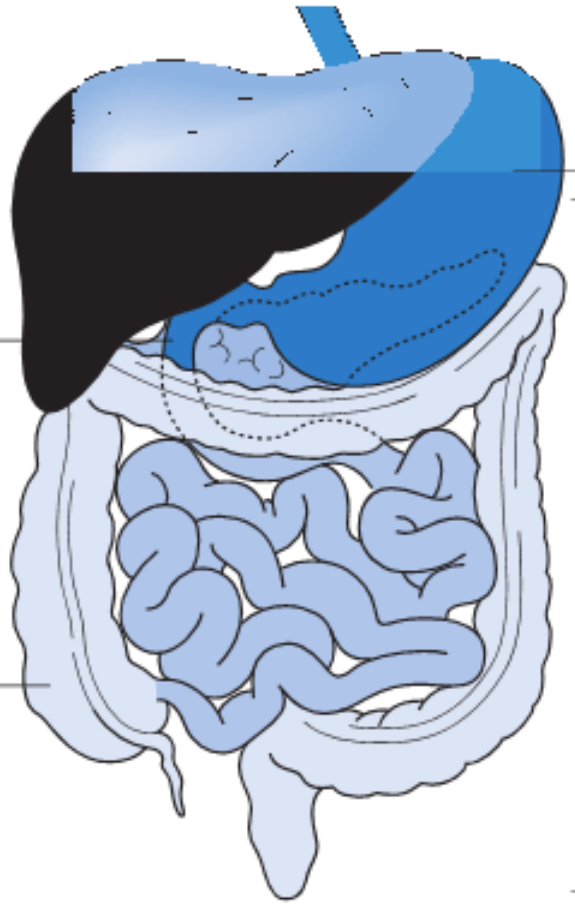
Lecture 10

Modified-release drug delivery:

refers to the manipulation or modification of drug release from a dosage form (e.g. tablet, pellet, capsule) with the specific aim of delivering active pharmaceutical ingredients (API) at:

1. desired rates
2. pre-defined time points, or
3. specific sites in the gastrointestinal tract

The site of action for various oral modifed drug delivery systems:



Small intestinal targeted (enteric) systems can release their drug load in the small intestine

Colonic systems release their drug here and may be able to extend release throughout the large intestine

Gastroretentive systems are retained in the stomach and should release drug in the stomach and small intestine

Extended release systems can theoretically release drug all through the gastrointestinal tract

Modified-release drug delivery benefits:

1. Keeping drug in the therapeutic range for long time
2. Mainta ining drug levels overnight
3. Reducing side effects.
4. Improving compliance (once-daily dosing)
5. Treatment of local area s in the gastrointestinal tract. Some conditions such as inflammatory bowel disease require topical treatment (e.g. with steroids) at the inflamed intestinal surface. Site-specific drug targeting (e.g. to the colon) can deliver the drug directly to its site of action

Sites of action:

1. **Gastrointestinal tract**
   (1) drug release from the dosage form, (2) dissolution of the drug, (3) absorption of drug molecules
2. **pH**
   Stomach: 1 – 3, Small intestine: 4.8 – 6.8, Colon: 7
3. **Transit time**
   in the fasted state, the stomach will empty a non-disintegrating (i.e. nonimmediate release) dosage form within 1 – 2 hours. Ingestion of food delays this mechanism,
   Small intestine 0.5 – 9 hours, Colon 1 – 72 hours
4. **Fluid**
   stomach around 100 mL of total fluid. In the small intestine there is around 50–100 mL of free fluid (i.e. that not bound up with digested material). The colonic contents can be very viscous with only around 10 mL of free fluid actually available.

Formulation, factors to consider:

1. Single-unit or multiple-unit:

single-entity (usually a tablet): monolithic dosage forms. They do not disintegrate in the stomach, the dosage form could become trapped in the stomach for a long time (with food)

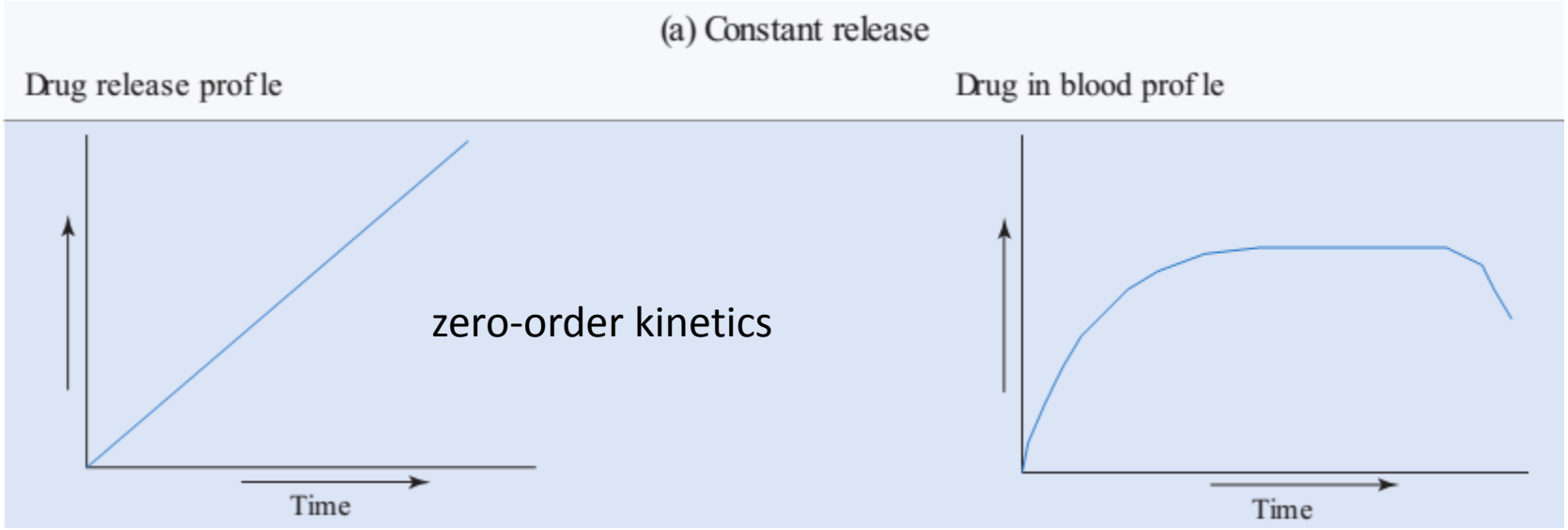
Multiple-unit systems (e.g. pellets or granules filled into a hard capsule shell. (more difficult to manufacture and to scale-up).

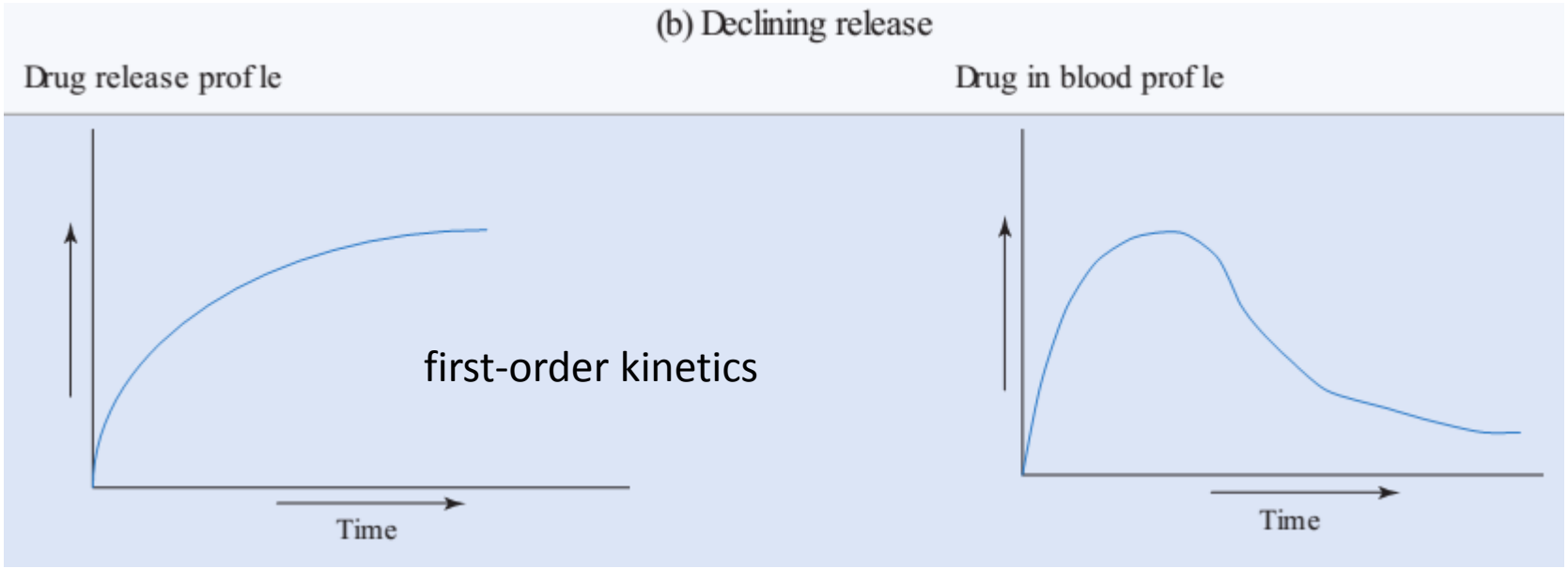
2. Matrix formulation or coated formulation

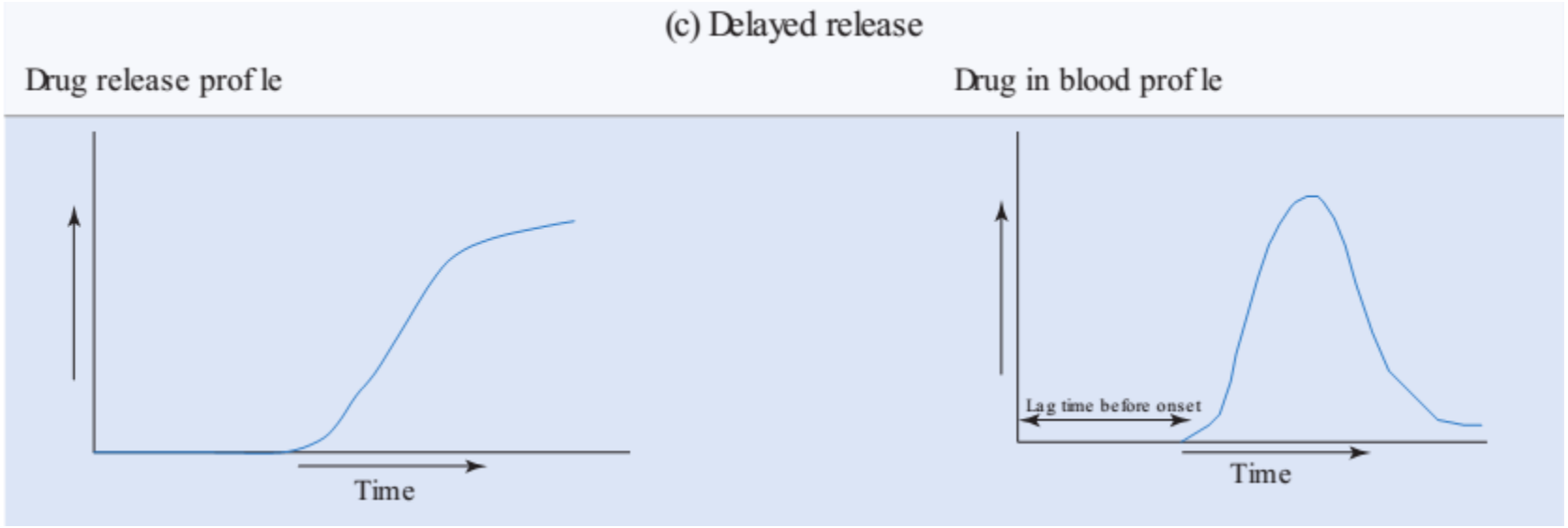
Formulation, factors to consider:

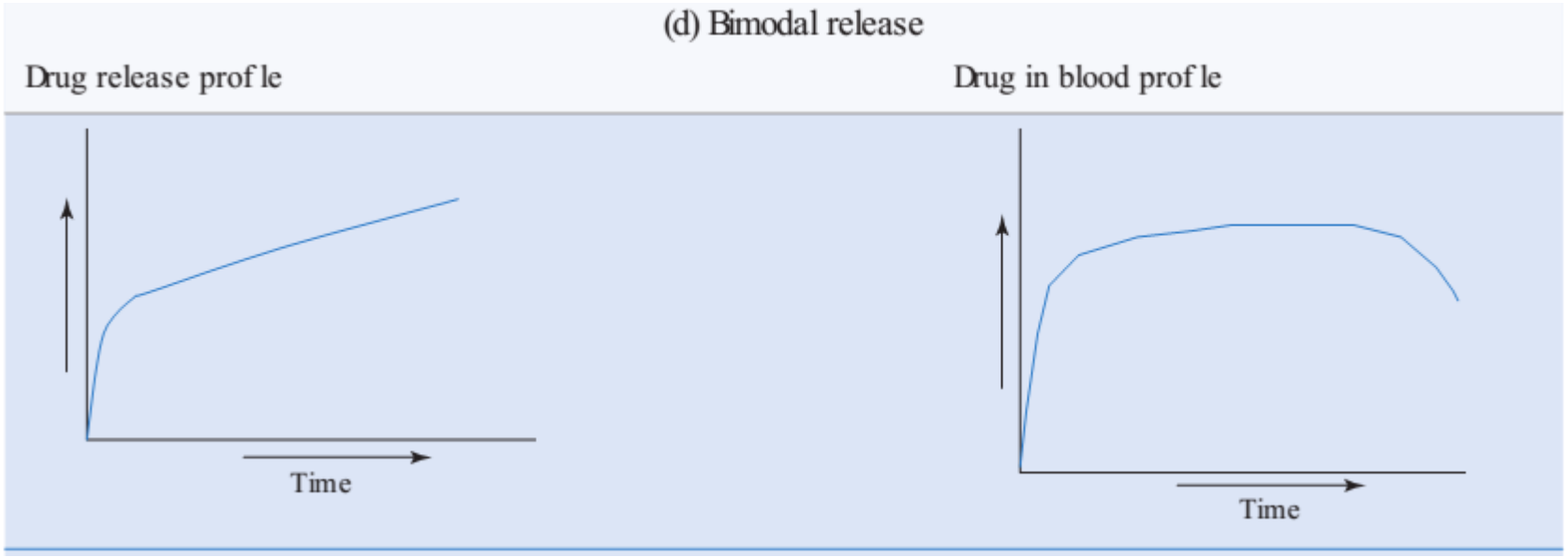
3. Type of release rate:

Two basic mechanisms can control the rate and extent of drug release. These are (1) dissolution of the active drug component and (2) diffusion of dissolved species


(a) Constant release
Drug release profile
Drug in blood profile
zero-order kinetics
Time
Time


(b) Declining release
Drug release profile
Drug in blood profile
first-order kinetics
Time
Time


(c) Delayed release
Drug release profile
Drug in blood profile
Time
Lag time before onset
Time


(d) Bimodal release
Drug release profile
Drug in blood profile
Time
Time

Formulation, factors to consider:

4. Biopharmaceutics classification System of drugs :

Type I: high solubility, high permeability (most suitable for ER)
Type II: low solubility, high permeability (inherent ER)
Type III: high solubility, low permeability (inherent ER)
Type IV: low solubility, low permeability (most challenging)

Formulation: factors to consider:

5. Eliminated rate:

The most suitable drugs may have relatively short half lives ($t_{1/2}$ = 4–6 hours).

Drugs with long half-lives may achieve pseudo-sustained release blood levels despite being formulated as immediate release, whereas shorter half-lives may need very high doses to maintain blood levels

6. Dose: Up to 1000 mg potency tablets are available

Hydrophilic matrix systems:

Drug is mixed with a water-swellable, hydrophilic polymer (high MW) with other excipient and compressed into a tablet

On exposure to fluid, the polymer material in the tablet starts to swell, producing a gel matrix. The drug releases by diffusion through the gel layer and erosion of the gel and release the drug particles trapped within it

Often polymer type and concentration are used to control drug release, which can be tailored (faster and slower) as required

Ex.: hydroxypropyl methylcellulose (HPMC)or polyethylene oxide (PEO)

Insoluble polymer matrix:

Less commonly used
They consist of an inert matrix system in which drug is embedded in an inert polymer. Their structure has been likened to that of a sponge.
stay intact throughout the gastrointestinal tract.

Drug release rate from insoluble polymer matrices is controlled by the pore size and number of pores, and tortuosity of the matrix

The drug release does not follow zero-order kinetics; drug release decreases with time due to the increasing distance drug molecules have to travel to reach the surface of the device

Membrane-controlled systems:

The rate-controlling part of the system is a membrane through which the drug must diffuse.

Drug release through a membrane is controlled by the thickness and the porosity of the membrane, as well as the solubility of the drug in the gastrointestinal fluids.

Membrane-controlled drug delivery systems may be more likely to be in the form of pellets than in monolithic systems (tablet).

Ex.: Eudragit RL, Eudragit RS

Eudragit RL films are more permeable than those of Eudragit RSand films of varying permeability can be obtained by mixing the two types together.

Gastroretention:

Gastroretention is the mechanism by which a dosage form is retained in the stomach, generally for the purposes of improving drug delivery.

It is used for local action in the stomach (e.g. to treat H. pylori), drugs have a narrow absorption window in the small intestine and drugs which are degraded in the colon.

Gastroretention system types:

1. Mucoadhesion: Chitosan, Carbopol, polycarbophil
2. Floating: Gas generating agents like bicarbonate
3. Size increasing systems: Swellable polymers such as hydroxypropyl methyl cellulose, polyethylene oxide, and xanthan gum

Delayed release:

Gastro-resistant coatings:

Gastro-resistant coatings are polymer coatings which are insoluble at low pH, but are soluble at higher pH (5–7).

Purpose: to protect the stomach from the drug or to protect acid-sensitive drugs from the stomach environment.

Ex.: Hypromellose phthalate, Polymethacrylates (Eudragit): Eudragit L (pH> 6); Eudragit S (pH > 7)

Delayed release:

It is difficult to direct the drug to **colon** by using pH dependent coating (dissolve at pH 7) for dosage unit may stay in in the region of highest pH for a short time (i.e. it does not disintegrate and is passed intact in the stools, consequently, not releasing the drug).

A coating is prepared from a material which is insoluble in the gastrointestinal fluids (e.g. ethylcellulose), but it will also contain a component that can be digested only by colonic bacteria (not by pancreatic enzymes). An example of a material that can be used is the polysaccharide known as ‘resistant starch’. This type of starch can only be broken down by bacterial enzymes in the colon. When the dosage form reaches the colon, the starch component of the coat is digested and dissolves, leaving pores through which drug can be released.

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Delayed release:

However, there may be some patient populations in which gastrointestinal microorganism (microbiota) levels are affected by disease, and the effect on such modified-release drug delivery systems is not fully known.

New system have also been proposed which combine both Eudragit S (pH 7) as the polymer and resistant starch to give a dual release mechanism.

The end

Coating

Pharmaceutical technology

Dr. Basheer Al-kasmi

Lecture 11

Definition of coating:

Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits that broadly range from facilitating product identification to modifying drug release from the dosage form

Reasons for coating:

1. Protecting API from the environment.
2. Masking the taste o drug substances
3. Improving the ease of swallowing large dosage forms
4. Masking any batch differences in the appearance of raw material
5. Providing a means of improving product appearance and aiding in brand identification
6. Easily handled on high-speed automatic filling and packaging equipment by improving product flow, increasing the mechanical strength of the product and reducing the risk o cross contamination by minimizing ‘dusting’ problems
7. Imparting modified-release characteristics

Types of coating processes:

1. film coating
2. sugar coating
3. compression coating

Film coating:

Film-coating (solution or suspension) formulations typically comprise:

- polymer
- plasticizer
- colourants
- solvent/ vehicle

Ideal characteristics of a film-coating polymer:

Solubility: important for:

- It determines the behaviour of the coated product in the gastrointestinal tract
- It determines the solubility of the coating in a chosen solvent system

Viscosity: is very much a limiting actor with regard to the ease with which a film coating can be applied.

Prefer under 500 mPa s.

Permeability: is of significant importance when the film coating is intended to:

- mask the unpleasant taste of the active ingredient.
- improve stability of the dosage
- modify the rate of active ingredient will be released.

Ideal characteristics of a film-coating polymer:

Mechanical properties:

- film strength, which greatly a effects the ability of the coating to resist the mechanical stresses to which it will be exposed during the coating process and during subsequent handling of the coated product
- film flexibility, minimizes film cracking during handling or subsequent storage
- film adhesion, which is necessary to ensure that the coating remains adherent to the surface of the dosage form

Immediate-release coatings:

Cellulose derivatives:

HPMC: It is readily soluble in aqueous media and forms films that have suitable mechanical properties, and coatings that are relatively easy to apply

Vinyl derivatives:

polyvinyl pyrrolidone (**PVP**): limited use in film coating because of its inherent tackiness.

polyvinyl alcohol (**PVA**): can be used to produce film coatings that have suitable mechanical properties and are highly adherent to pharmaceutical tablets.PVA exhibits good barrier properties to environmental gases and water vapour.

Aminoalkyl methacrylate copolymers (Eudragit E):

readily soluble in aqueous media at low pH only, It is used for taste masking.

Modified-release coatings:

Use as solutions in organic solvents or aqueous dispersions
Cellulose derivatives:

the level of substitution in this case is usually much higher, thus rendering the polymer insoluble in water

EC, cellulose acetate (CA).

Methylmethacrylate copolymers:

Eudragit (L, S, RL or RS)

Phthalate esters:

Delayed-release application. hydroxypropylmethylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), and polyvinyl acetate phthalate (PVAP).

Plasticizers:

increased film flexibility
reduced residual stresses within the coating as it shrinks around the core during drying.

Examples of commonly used plasticizers are:

- polyols, such as polyethylene glycols and propylene glycol
- organic esters, such as diethyl phthalate and triethyl citrate
- oils/ glycerides, such as fractionated coconut oil.

Colourants:

Dyes: water-soluble, Pigments: water-insoluble.

The insoluble form is preferred:

- pigments tend to be more chemically stable towards light, provide better opacity and covering power
- provide a means of optimizing the permeability properties of the applied film coating.
- water-insoluble pigments will not suffer of mottling caused by solute migration.

Examples: iron oxide pigments, titanium dioxide, aluminium lakes (a pigment formed by bonding water-soluble colourants to approved substrata, such as fine alumina hydrate particles).

Solvents:

Organic solvents possess many disadvantages:

1. Environmental issues
2. Safety issues
3. Financial issues
4. Solvent residue issues

aqueous coating formulations is better so it is used as: solution or dispersion

Film-coating defects:

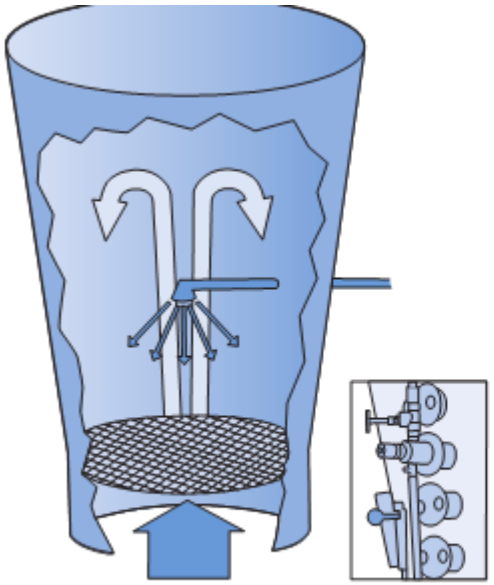
Processing issues:

these are typically associated with an imbalance between the rate of delivery of the coating liquid and the rate of evaporation during the drying process. This imbalance results in either over wetting (tablets stuck together) or over drying, when surface erosion of the tablets, as well as chipping of the tablet edges may result

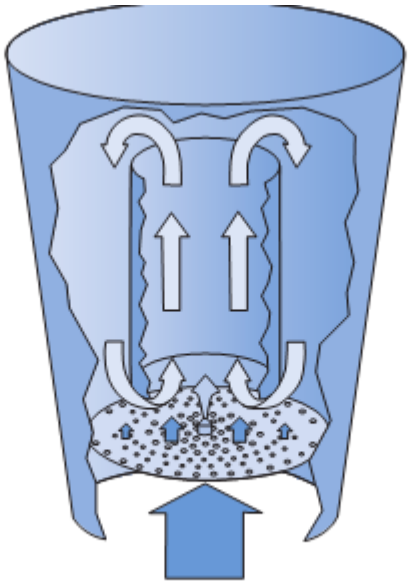
Film-coating defects:

Formulation issues:

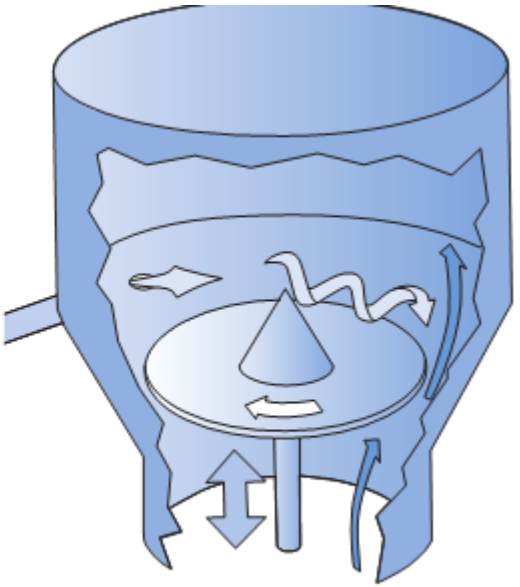
these are usually associated with some defficiency in the core or the coating. Core formulation issues often result in mechanical defects, so that the core is not able to withstand the attritional effects o the coating
process, leading to tablet breakage and erosion. Coating formulation issues often result in a film of inadequate mechanical strength, leading to film cracking and chipping, or inadequate film adhesion, resulting in film peeling and logo bridging.



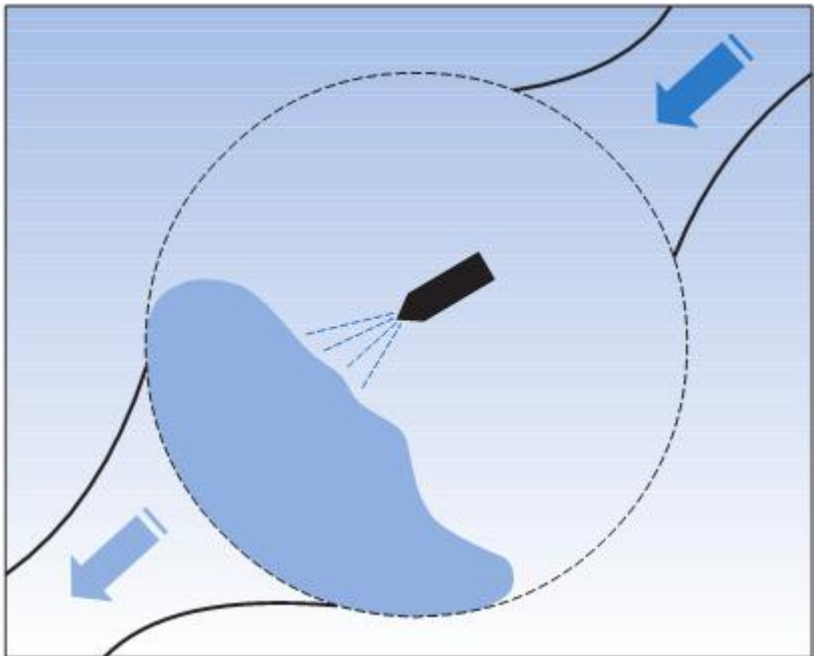
1. Top spray



2. Bottom spray



3. Tangential



Sugar coating:

It involves the successive application of sucrose-based coating formulations to tablet cores in suitable coating equipment. Conventional panning equipment with manual application of syrup has been extensively used.

Sugar coatings are composed of ingredients that are readily soluble, or disintegrate rapidly, in water.

Process equipment:

1. Sealing of the tablet cores
2. Subcoating
3. Smoothing
4. Colouring
5. Polishing
6. Printing

Sealing:

Sugar coatings are aqueous formulations that are, quite literally, poured directly onto the tumbling tablets. Hence, water has an opportunity to penetrate directly into the tablet cores, potentially affecting product stability and possibly causing premature tablet disintegration.

To prevent these problems, the cores are usually sealed initially with a water-proofing or sealing coat. Traditionally, alcoholic solutions of shellac were used or this purpose although the use of synthetic polymers, such as cellulose acetate phthalate or polyvinyl acetate phthalate, is now favored.

the amount of sealing coat applied has to be carefully calculated so that there is no negative influence on drug release

Subcoating:

Sugar coatings are usually applied in quite substantial quantities to the tablet core (typically increasing the weight by as much as 50–100%) in order to round of the tablet edges. Much of this material build-up occurs during the subcoating stage and is achieved by adding bulking agents such as calcium carbonate to the sucrose solutions. In addition, antiadherents such as talc may be used to prevent tablets sticking together, and polysaccharide gums, such as gum acacia, may also be added as a binder in order to reduce brittleness

Smoothing:

The subcoating stage is producing a surface finish that is somewhat rough. To facilitate the application of the colouring layer (which requires a smooth surface), subcoated tablets are usually smoothed out by applying a sucrose coating that is often coloured with titanium dioxide to achieve the desired level of whiteness

Colouring:

Colour coatings usually consist of sucrose syrups containing the requisite colouring materials.
As with film coating colours, sugar-coating colourants may be subdivided into either water-soluble dyes or water-insoluble pigments.

Polishing :

Once the colour coating layers have been applied and dried, the tablet surface tends to be smooth but somewhat dull in appearance. To achieve the glossy finish that typifes sugar-coated products, a final stage involving the application of waxes is employed. Suitable waxes include beeswax, carnauba wax or candelilla wax applied as finely ground powders or as suspensions/ solutions in an appropriate organic solvent.

Printing

It is common practice to identify all oral solid dosage forms with a manufacturer's logo, product name, dosage strength or other appropriate code. For sugar-coated products such identification can only be achieved by means of a printing process by edible inks.

Features	Sugar coating	Film coating
Tablets		
Appearance	Rounded with high degree of polish	Retains contour of original core Usually not as shiny as sugar coat types
Weight increase due to coating materials	30–50%	2–3%
Logo or 'breaklines'	Not possible	Possible
Other solid dosage forms	Coating possible but little industrial importance	Coating of multiparticulates very important in modified-release forms
Process		
Stages	Multistage process	Usually single stage
Typical batch coating time	8 hours, but easily longer	1.5–2 hours
Functional coatings	Not usually possible apart from gastro-resistant (enteric) coating	Easily adaptable for controlled release

The end