

Industrial Pharmacy

Mixing

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The importance of mixing

- In the vast majority of pharmaceutical products several ingredients are needed.
- Whenever a product contains more than one component, a mixing or blending stage will be required in the manufacturing process.
- The unit operation of mixing is therefore involved at some stage in the production of practically every pharmaceutical preparation.

Definition and objectives of mixing

- Mixing may be defined as a 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.

- If this is achieved it produces a theoretical 'ideal' situation, i.e. a ***perfect mix.***
- this situation is not normally practicable.
- How closely it is attempted to approach the 'ideal' situation depends on the product being manufactured and the objective of the mixing operation.

- For example, if a small amount of a potent drug is being mixed in a powder then the degree of mixing must be of a high order to ensure a consistent dose.

- In the case of mixing lubricants during tablet production, however, there is a danger of overmixing and the subsequent production of a weak tablet with an increased disintegration time

Types of mixtures

- *Positive mixtures*
  - formed from materials such as gases or miscible liquids which mix ***spontaneously* and *irreversibly*** by diffusion, and tend to approach a perfect mix.
  - There is no input of energy required if the time available for mixing is unlimited, although it will shorten the time required to obtain the desired degree of mixing.
  - In general materials that mix by positive mixing present no problems during product manufacture

- *Negative mixtures*
- more difficult to form and maintain and require a higher degree of mixing efficiency than do positive mixtures.

- the components will tend to separate out.

- If this occurs quickly, then energy must be continuously input to keep the components adequately dispersed,
- e.g. with a suspension formulation, such as calamine lotion, where there is a dispersion of solids in a liquid of low viscosity.

- With other negative mixtures the components tend to separate very slowly,
- e.g. emulsions, creams and viscous suspensions.

- *Neutral mixtures*
- static in behavior, i.e. the components have no tendency to mix spontaneously or segregate spontaneously once work has been input to mix them.

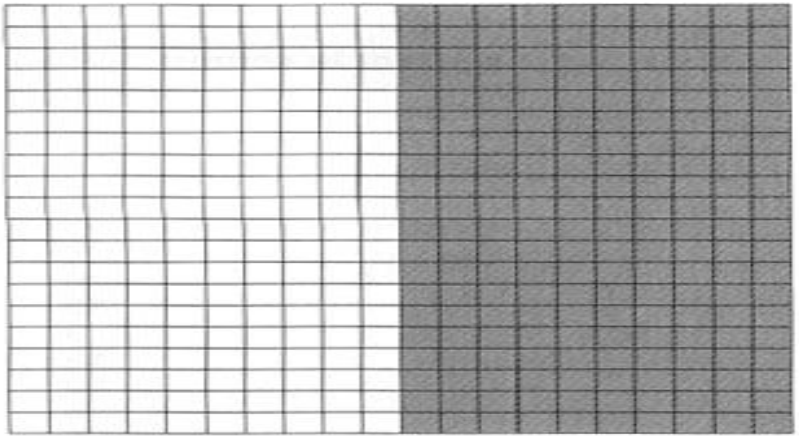
- Examples: mixed powders, pastes and ointments.

- **The mixing process**

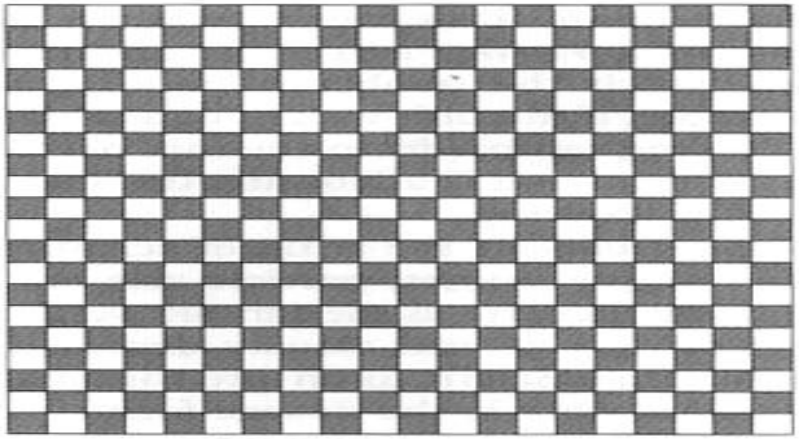
- the ideal situation or '*perfect mix*' would be produced when each particle lay adjacent to a particle of the other component (i.e. each particle lies as closely as possible in contact with a particle of the other component).Figure (b),

- If this mix were viewed in three dimensions then behind and in front of each grey particle would be a white particle, and vice versa.

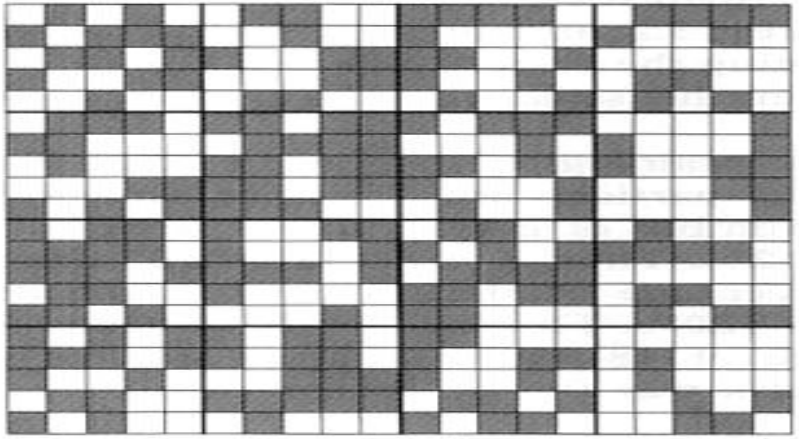
- Powder mixing, however, is a 'chance' process, and the situation shown in Figure (b) can be considered impossible.
- In practice, the best type of mix likely to be obtained will have the components under consideration distributed as in Figure (c).
- This is referred to as a ***random mix,*** which is defined as 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.



(a)



(b)



(c)

Scale of scrutiny

- It is the amount of material within which the quality of mixing is important.
- For example, if the unit weight of a tablet is 200 mg then a 200 mg sample from the mix needs to be analyzed to see if mixing is adequate; the scale of scrutiny is therefore 200 mg.

Mathematical treatment of the mixing process

- there will always be some variation in the composition of samples taken from a random mix.
- The aim during formulation and processing is to minimize this variation to acceptable levels by selecting an appropriate scale of scrutiny, particle size and mixing procedure (choice of mixer, rotation speed etc).

- The variation in the proportion of a component in samples taken from the random mix can be calculated from:

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

- where SD is the standard deviation in the proportion of the component in the samples (content sample deviation).
- p is the proportion of the component in the total mix.
- n is the total number of particles in the sample

- A more useful parameter to determine is the percentage coefficient of variation (%CV), which indicates the average deviation as a percentage of the mean amount of active component in the samples.

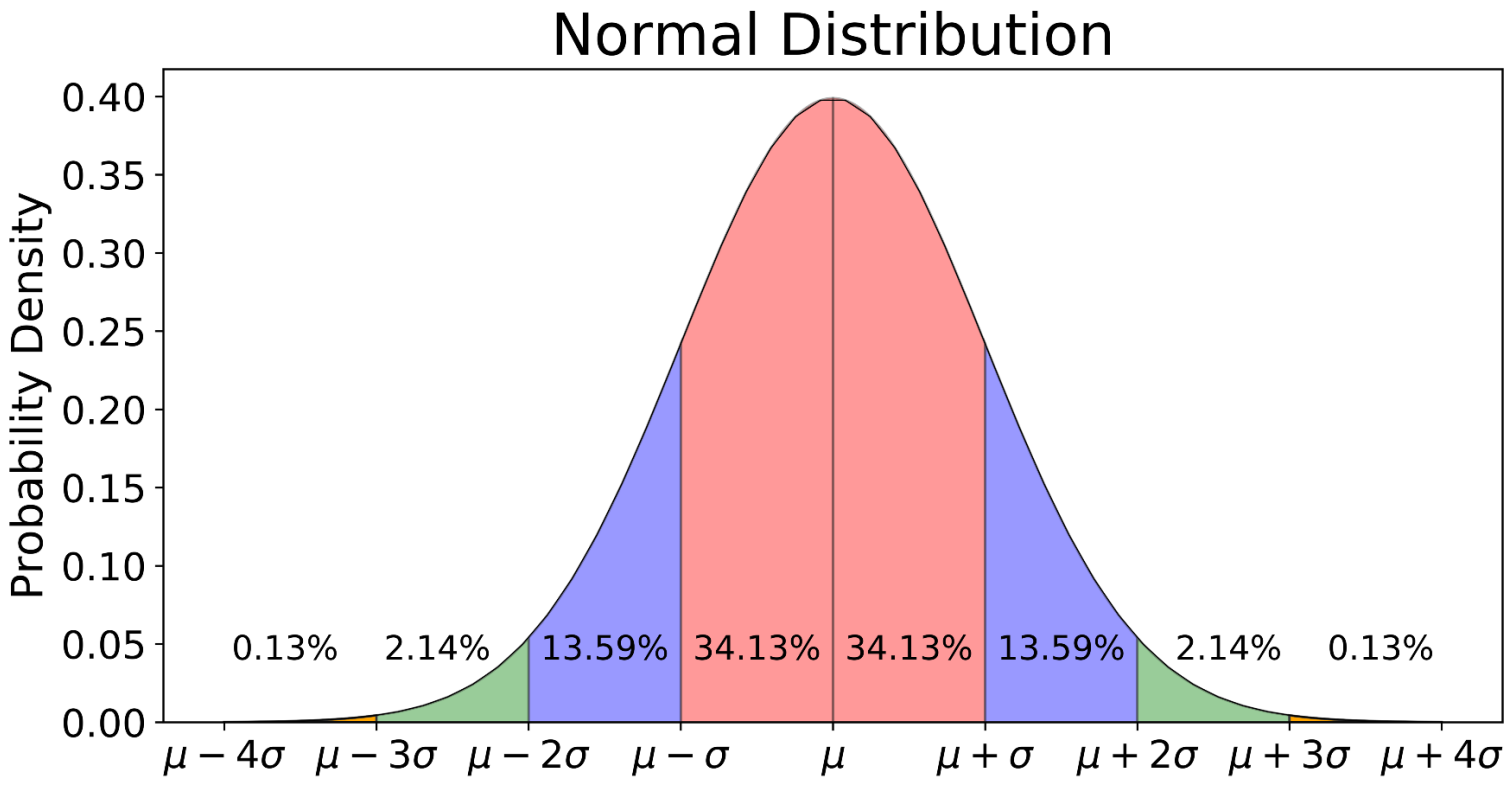
- %CV = (content standard deviation/mean content) x 100.

- Consider the situation where n = 100 000 and p = 0.5.
- SD = 1.58×10^{-3}
- %CV = $(1.58 \times 10^{-3} / 0.5) \times 100 = 0.32\%$.

- if p is reduced to 0.001 and n remains at
- 100 000 there is a reduction in SD to 9.99×10^{-5}, but the %CV = $(9.99 \times 10^{-5} / 0.001) \times 100 = 10\%$.

- In a true random mix the content of samples taken from the mix will follow a normal distribution.

- With a normal distribution, 68.3% of samples will be within ±1 SD of the overall proportion of the component (p).
- 95.5% will be within ±2 SD of *p*.
- 99.7% of samples will be within ±3 SD *of p*.


Normal Distribution
Probability Density
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0.13%
2.14%
13.59%
34.13%
34.13%
13.59%
2.14%
0.13%
$\mu - 4\sigma$
$\mu - 3\sigma$
$\mu - 2\sigma$
$\mu - \sigma$
μ
$\mu + \sigma$
$\mu + 2\sigma$
$\mu + 3\sigma$
$\mu + 4\sigma$

- For example, if p = 0.5 and the standard deviation in content is 0.02, then for 99.7% of samples the proportion of the component will be between 0.44 and 0.56.

- if 1000 samples were analysed, 997 would contain between 44% and 56% of drug (mean = 50%).

❖ Evaluation of the degree of mixing

- ✓ Manufacturers require some means of monitoring a mixing process for a variety of reasons:

- ✓ To indicate the degree/extent of mixing
- ✓ To follow a mixing process
- ✓ To indicate when sufficient mixing has occurred
- ✓ To assess the efficiency of a mixer
- ✓ To determine the mixing time required for a
- ✓ particular process.

- ***mixing index (M):***

$$M = \frac{S_R}{S_{ACT}}$$

- compares the content standard deviation of samples taken from a mix under investigation (S_{ACT}) with that of samples from a fully random mix (S_R).

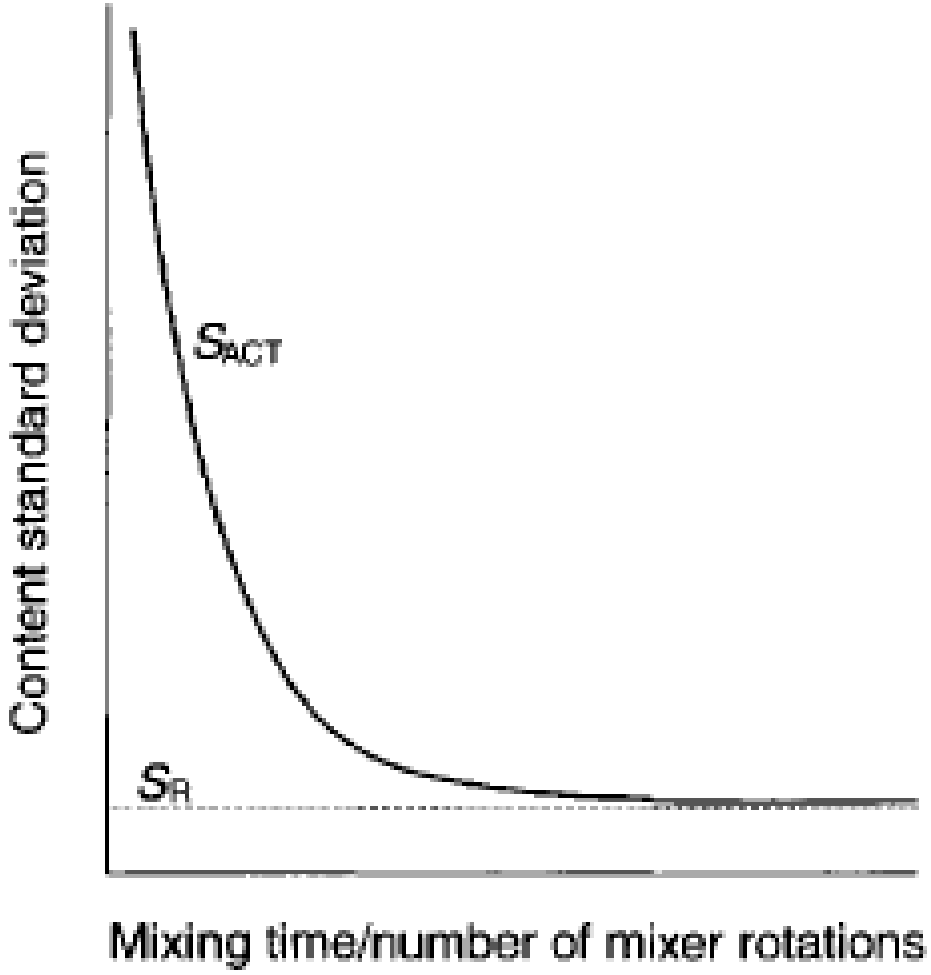
- Comparison with a random mix is made because this is theoretically likely to be the best mix that is practically achievable.

- At the start of the mixing process the value of S_{ACT} will be high and that for *M* will be low.

- As mixing proceeds S_{ACT} will tend to decrease as the mix approaches a random mix.

- If the mix becomes random:
- $S_{ACT} = S_R$
- $M = 1$.

- There is typically an exponential decrease in S_{ACT} as the mixing time or number of mixer rotations increases.


Content standard deviation
S_{ACT}
S_R
Mixing time/number of mixer rotations

- In order to evaluate a mixing process in this way there are two basic requirements:

1. a sufficient number of samples which are representative of the mix as a whole must be removed and analysed.
   - A minimum of 10 samples is usually taken, these being removed from different depths into the mixer and from the middle and sides

- Samples are often taken with a 'sampling thief', which is a device that can be inserted into the mix and samples withdrawn with minimum disruption to the powder bed.

2. a suitable analytical technique must be available so that the value of S_{ACT} is a true reflection of the variation in content in the samples and not due to variation arising from the method of analysis.

- When mixing formulations where the proportion of active component is high it is possible to achieve an acceptably low variation in content without obtaining a random mix.

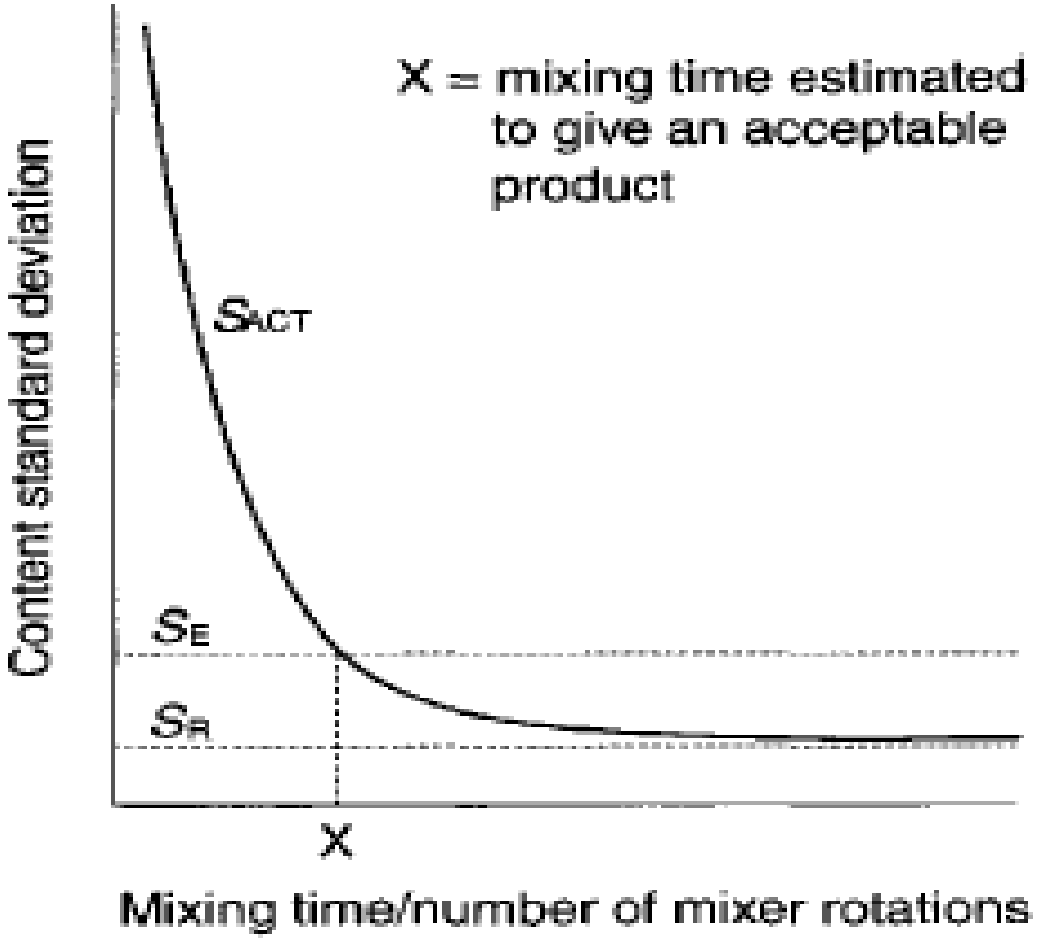
- Thus it may be possible to stop the mixing process before a random mix is achieved and thereby reduce manufacturing costs.

- estimated acceptable standard deviation value *(S_E)* will allow the product to meets its specification.

- For example, if the proportion of active component present in the formulation is 0.5 and the acceptable variation from the mean content is ±5% for 99.7% of samples.

- 3 x SD = *p* x (% acceptable deviation/100)

$$S_E = \frac{0.5 \times (5/100)}{3} = 8.3 \times 10^{-3}$$


X = mixing time estimated to give an acceptable product
Content standard deviation
S_{ACT}
S_E
S_R
X
Mixing time/number of mixer rotations

➢ MECHANISMS OF MIXING *(Powders)*

1. ***Convection.***
2. ***Shear.***
3. ***diffusion.***

- Convective mixing:
- arises when there is the transfer of relatively large groups of particles from one part of the powder bed to another.

- Occurs when a mixer blade or paddle moves through the mix.

- Contributes mainly to the macroscopic mixing of powder mixtures.

- tends to produce a large degree of mixing fairly quickly (as evidenced by a rapid drop in S_{ACT}).
- Mixing does not, however, occur ***within*** the group of particles moving together as a unit.
- in order to achieve a random mix an extended mixing time is required.

- Shear mixing:
- occurs when a 'layer' of material moves/flows over another 'layer'.
- This might be due to the removal of a mass by convective mixing creating an unstable shear/slip plane, which causes the powder bed to collapse.

- It may also occur in high shear mixers or tumbling mixers, where the action of the mixer induces velocity gradients within the powder bed and hence 'shearing' of one layer over another.

- diffusive mixing:

- Movement of individual particles (In order to achieve a true random mix).

- When a powder bed is forced to move or flow it will 'dilate', i.e. the volume occupied by the bed will increase.
- This is because the powder particles will become less tightly packed and there is an increase in the air spaces or voids between them.

- Under these circumstances there is the potential for the particles to fall under gravity, through the voids created.
- produces a random mix.
- results in a low rate of mixing.

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

- Which one predominates and the extent to which each occurs will depend on:

1. The mixer type.
2. mixing process conditions (mixer load, speed etc.)
3. the flowability of the powder components.

MECHANISMS OF MIXING

(Liquids)

- ***bulk transport.***
- ***turbulent mixing.***
- ***molecular diffusion.***

- Bulk transport :
- analogous to the convective mixing of powders.

- involves the movement of a relatively large amount of material from one position in the mix to another, e.g. due to a mixer paddle.

- It too tends to produce a large degree of mixing fairly quickly, but leaves the liquid within the moving material unmixed.

- Turbulent mixing:
- arises from the haphazard movement of molecules when forced to move in a turbulent manner.

- The constant changes in speed and direction of movement means that induced turbulence is a highly effective mechanism for mixing.

- Within a turbulent fluid there are, however, small groups of molecules moving together as a unit, referred to as eddies.

- These eddies tend to reduce in size and eventually break up, being replaced by new eddies.

- Turbulent mixing alone may therefore leave small unmixed areas within the eddies and in areas near the container surface which will exhibit streamlined flow.

- molecular diffusion:

- Analogous to diffusive mixing in powders.
- Mixing of individual molecules in eddies and in areas near the container surface.
- This will occur with miscible fluids wherever a concentration gradient exists and will eventually produce a well-mixed product,
- considerable time may be required if this is the only mixing mechanism.

- In most mixers all three mechanisms will occur, bulk transport and turbulence arising from the movement of a stirrer or mixer paddle set at a suitable speed.

Powder segregation (demixing)

- Segregation is the opposite effect to mixing, i.e. components tend to separate out.
- Care must be taken to avoid segregation during handling after powders have been mixed, e.g. during transfer to filling machines, or in the hopper of tablet/capsule/sachet-filling machine.

- Segregation will cause an increase in content variation in samples taken from the mix and may cause a batch to fail a uniformity of content test.

- If segregation of granules occurs in the hopper of a filling machine an unacceptable variation in weight may result.

- Segregation arises because powder mixes encountered practically are not composed of mono-sized spherical particles, but contain particles that differ in size, shape and density.
- These variations mean that particles will tend to behave differently when forced to move and hence, tend to separate.
- Particles exhibiting similar properties tend to congregate together, giving regions in the powder bed which have a higher concentration of a particular component.

- Segregation is more likely to occur, or may occur to a greater extent:

  - if the powder bed is subjected to vibration
  - when the particles have greater flowability.

Particle-size effects

- ***percolation segregation.***
- ***trajectory segregation.***
- ***elutriation segregation***

- ***percolation segregation.***

- A difference in the particle sizes of components of a formulation is the main cause of segregation in powder mixes in practice.

- Smaller particles tend to fall through the voids between larger ones and so move to the bottom of the mass.

- It may occur in static powder beds if the percolating particles are so small that they can fall into the void spaces between larger particles,

- occurs to a greater extent as the bed 'dilates' on being disturbed. e.g. during vibration, stirring or pouring.

- ***trajectory segregation***

- During mixing, larger particles will tend to have greater kinetic energy imparted to them (owing to their larger mass) and therefore move greater distances than smaller particles before they come to rest.

- This may result in the separation of particles of different size.
- This effect, along with percolation segregation, accounts for the occurrence of the larger particles at the edge of a powder heap when it is poured from a container.

- ***elutriation segregation***

- During mixing, or when a material is discharged from a container, 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.

- also referred to as '***dusting out***'

Particle-density effects

- If components are of different density, the more dense material will have a tendency to move downwards even if the particle sizes are similar.
- Trajectory segregation may also occur with particles of the same size but different densities, owing to their difference in mass.
- The effect of density on percolation segregation may be potentiated if the more dense particles are also smaller.

- Alternatively, size and density effects may cancel each other out if the larger particles are more dense.
- Often materials used in pharmaceutical formulations have similar density values and density effects are not generally too important.
- An exception to this is in fluidized beds, where density differences are often more serious than particle size differences.

- *Particle-shape effects*

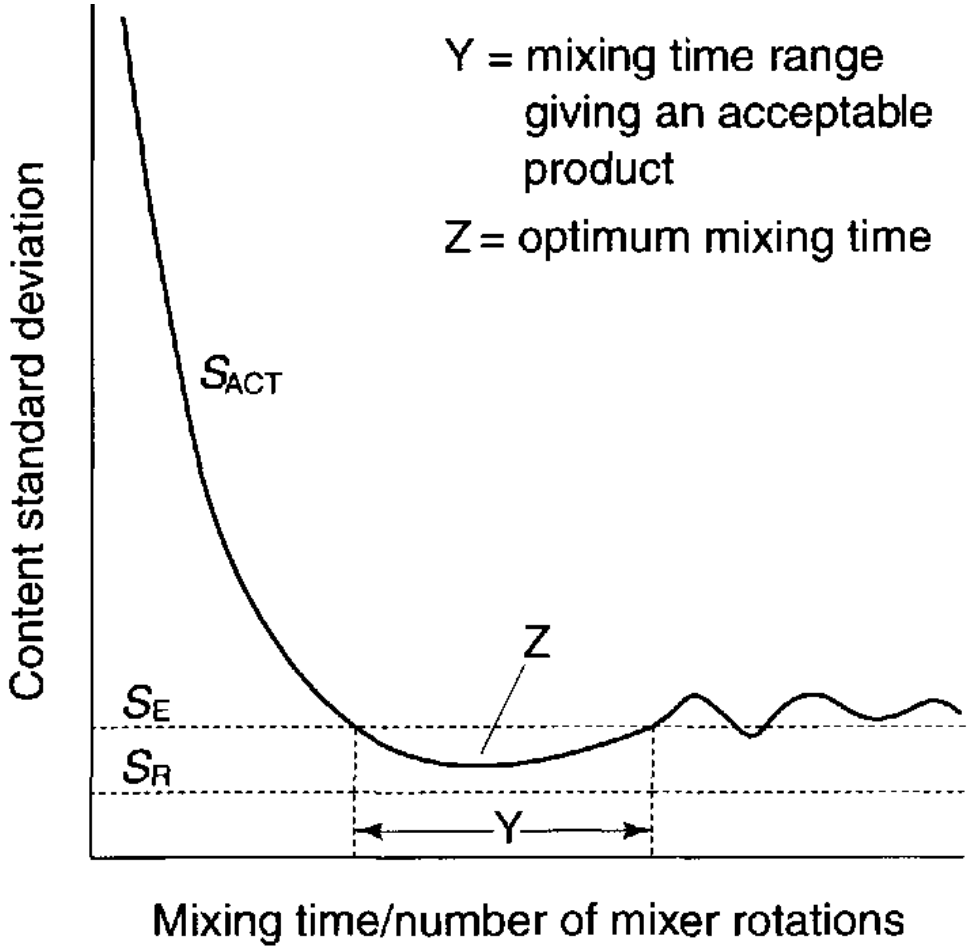
- Spherical particles exhibit the greatest flowability and are therefore more easily mixed, but they also segregate more easily than non-spherical particles.

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

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

- *Mixing- time effect*
- Non-segregating mixes will improve with continued increases in mixing time.
- This may not, however, occur for segregating mixes, where there is often an optimum mixing time.
- This is because the factors causing segregation generally require longer to take effect than the time needed to produce a reasonable degree of mixing.

- During the initial stages of the process the rate of mixing is greater than the rate of demixing.
- After a period of time, the rate of demixing may predominate until eventually an equilibrium situation will be reached where the two effects are balanced.


Y = mixing time range giving an acceptable product
Z = optimum mixing time
Content standard deviation
S_{ACT}
Z
S_E
S_R
Y
Mixing time/number of mixer rotations

- If segregation is a problem with a formulation there are a number of approaches that may be attempted to rectify the situation. These include:

- ✓ Selection of particular size fractions (e.g. by sieving to remove fines or lumps) to achieve drug and excipients of the same narrow particle size range.

- ✓ Milling of components (size reduction) either to reduce the particle size range (this may need to be followed by a sieving stage to remove fines) or to ensure that all particles are below approximately 30 μm - at which size segregation does not tend to cause serious problems (but may give rise to aggregation);

- ✓ Controlled crystallization during production of the drug/excipients to give components of a particular crystal shape or size range.
- ✓ Selection of excipients which have a density similar to the active component.
- ✓ Granulation of the powder mix (size enlargement) so that large numbers of different particles are evenly distributed in each segregating 'unit'/granule.

- ✓ Reduce the extent to which the powder mass is subjected to vibration or movement after mixing.
- ✓ Use filling machine hoppers designed so that powder residence time is minimized.
- ✓ Use equipment where several operations can be carried out without transferring the mix, e.g. a fluidized-bed drier or a high-speed mixer/ granulator for mixing and granulating.
- ✓ adhesive or interactive mixing: Production of an 'ordered' mix.

- **Ordered mixing**

- if one powder is sufficiently small (micronized) it may become adsorbed on to the 'active sites' on the surface of a larger 'carrier' particle and exhibit great resistance to being dislodged.

- This has the effect of minimizing segregation while maintaining good flow properties.

- If a carrier particle is removed then some of the adsorbed smaller particles will automatically be removed with it.

- Ordered mixing has been used in the production of:

1. dry antibiotic formulations to which water is added before use to form a liquid or syrup product.

- the antibiotic in fine powder form is blended with, and adsorbed on to, the surface of larger sucrose or sorbitol particles

2. Dry powder inhaler formulations.

- By adsorbing the drug on to larger carrier particles (usually lactose)

- With an ordered mix it may be possible to achieve a degree of mixing which is superior to that of a random mix, which may be beneficial for potent drugs.

- Pharmaceutical mixes are likely to be partly ordered and partly random.

❖ *Segregation in ordered mixes*

- Although ordered mixes can reduce or prevent segregation, it may still occur if:

1. ***The carrier particles vary in size.***

- Different sized particles will have different surface area to weight ratios and will contain different amounts of adsorbed material per unit mass.
- If the different-sized carrier particles separate (e.g. by percolation segregation), drug-rich areas where the smaller carrier particles congregate may result.
- This is referred to as ***ordered unit segregation.***

2. ***There is competition for the active sites on the carrier particle.***

- If another component competes for sites on the carrier it may displace the original adsorbed material, which may then segregate owing to its small size.

- This is known as ***displacement segregation,*** and has been shown to occur with the addition of the lubricant magnesium stearate to tablet formulations.

3. ***There are insufficient carrier particles.***

- Each carrier particle can only accommodate a certain amount of adsorbed material on its surface.
- If there is any excess small-sized material that is not adsorbed on to the carrier particles this may quickly separate.
- This is referred to as ***saturation segregation,***
- may limit the proportion of the active component that can be used in the formulation.

MIXING OF POWDERS

- **Practical considerations:**

1. When mixing formulations where there is a relatively low proportion of active ingredient(s) a more even distribution may be obtained by building up the amount of material in the mixer sequentially.

- This may be achieved by initially mixing the active component(s) with an approximately equal volume of diluent (s).

- Further amounts of diluents, equal to the amount of material in the mixer, can then be added and mixed, the process being continued until all material has been added.

- It may be more appropriate to pre-blend the active component with a diluent in a smaller mixer prior to transferring it to the main mixer in cases where the amount of active ingredient is very small.

2. Care must be taken to ensure that the volume of powder in the mixer is appropriate, as both over and underfilling may significantly reduce mixing efficiency.

- In overfilling, sufficient bed dilation may not take place for diffusive mixing to occur to the required extent, or the material may not be able to flow in a way that enables shear mixing to occur satisfactorily.

- under filling may mean the powder bed does not move in the required manner in the mixer, or that an increased number of mixing operations may be needed for a batch of material.

3. The mixer used should produce the mixing mechanisms appropriate for the formulation.

- diffusive mixing is generally preferable for potent drugs, and high shear is needed to break up aggregates of cohesive materials and ensure mixing at a particulate level.

- The impact or attrition forces generated if too-high shear forces are used may, however, damage fragile material and so produce fines.

4. The mixer design should be such that it is dust-tight, can be easily cleaned, and the product can be fully discharged.

- These reduce the risk of cross contamination between batches and protect the operator from the product.

5. In order to determine the appropriate mixing time, the process should be checked by removing and analyzing representative samples after different mixing intervals.

- This may also indicate whether segregation is occurring in the mixer, and whether problems occur if the mixing time is extended.

6. When particles rub past each other as they move within the mixer, static charges will be produced.

- These tend to result in 'clumping' and a reduction in diffusive mixing, and cause material to adhere to machine or container surfaces.

- To avoid this, mixers should be suitably earthed to dissipate the static charge and the process should be carried out at a relative humidity greater than approximately 40%.

- **Powder mixing equipment**

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

- *Tumbling mixers/blenders*

  - are commonly used for the mixing/blending of granules or free-flowing powders.

  - different designs of tumbling mixer, e.g. double-cone mixers, twin-shell mixers, cube mixers, Y-cone mixers and drum mixers.

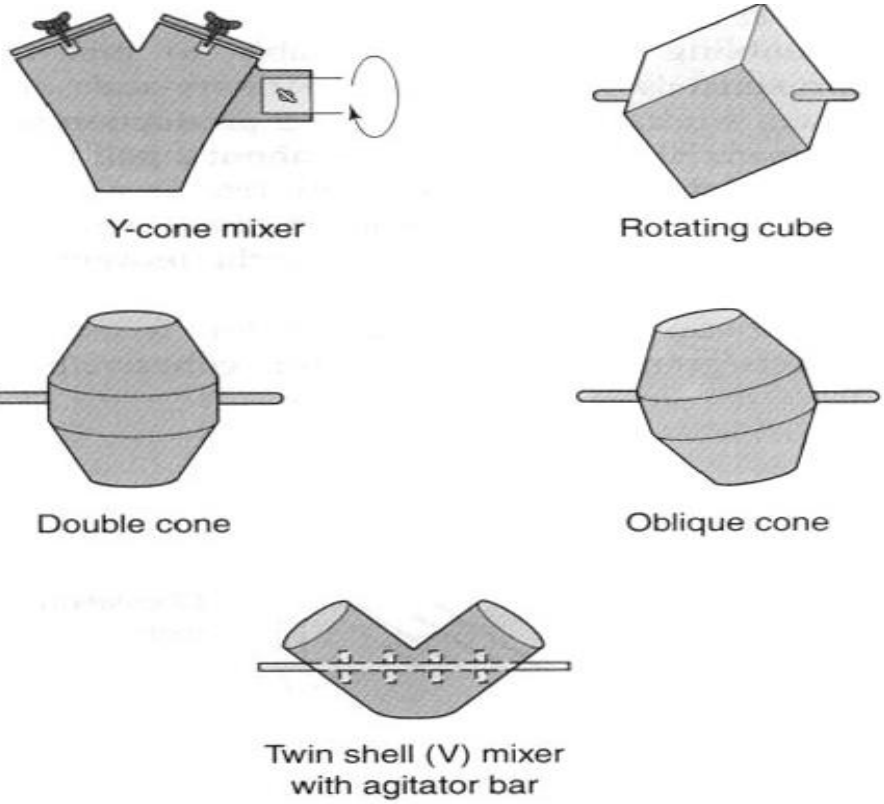
  - It is now common to use ***intermediate bulk containers*** (IBCs) both as the mixer bowl and to either feed the hopper of a tablet or capsule machine or as the hopper itself.

- Mixing containers are generally mounted so that they can be rotated about an axis. When operated at the correct speed, the tumbling action is achieved.

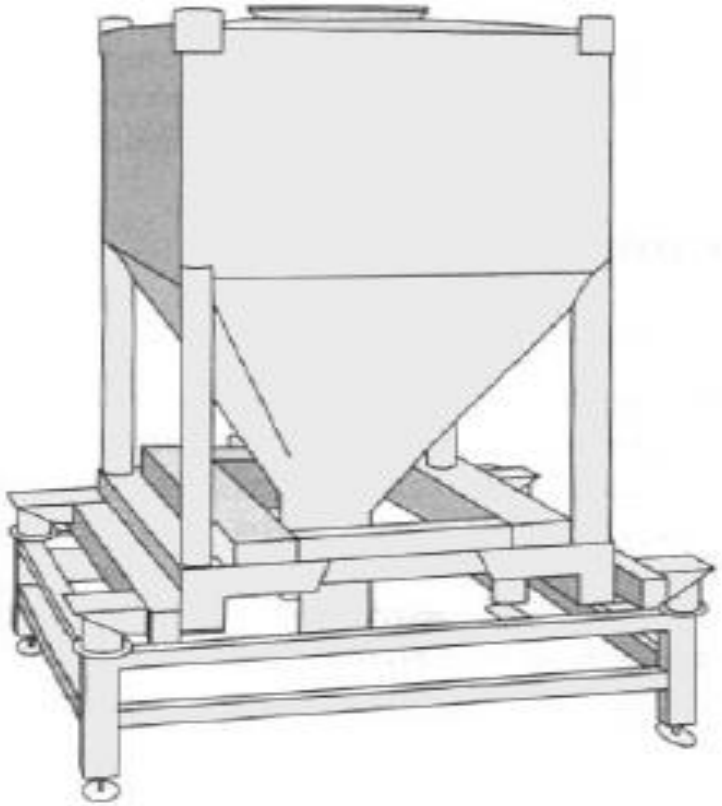
- Shear mixing will occur as a velocity gradient is produced, the top layer moving with the greatest velocity and the velocity decreasing as the distance from the surface increases.

- When the bed tumbles it dilates, allowing particles to move downwards under gravity, and so diffusive mixing occurs.
- Too high a rotation speed will cause the material to be held on the mixer walls by centrifugal force, and too low a speed will generate insufficient bed expansion and little shear mixing.
- The addition of 'prongs', baffles or rotating bars will also cause convective mixing.

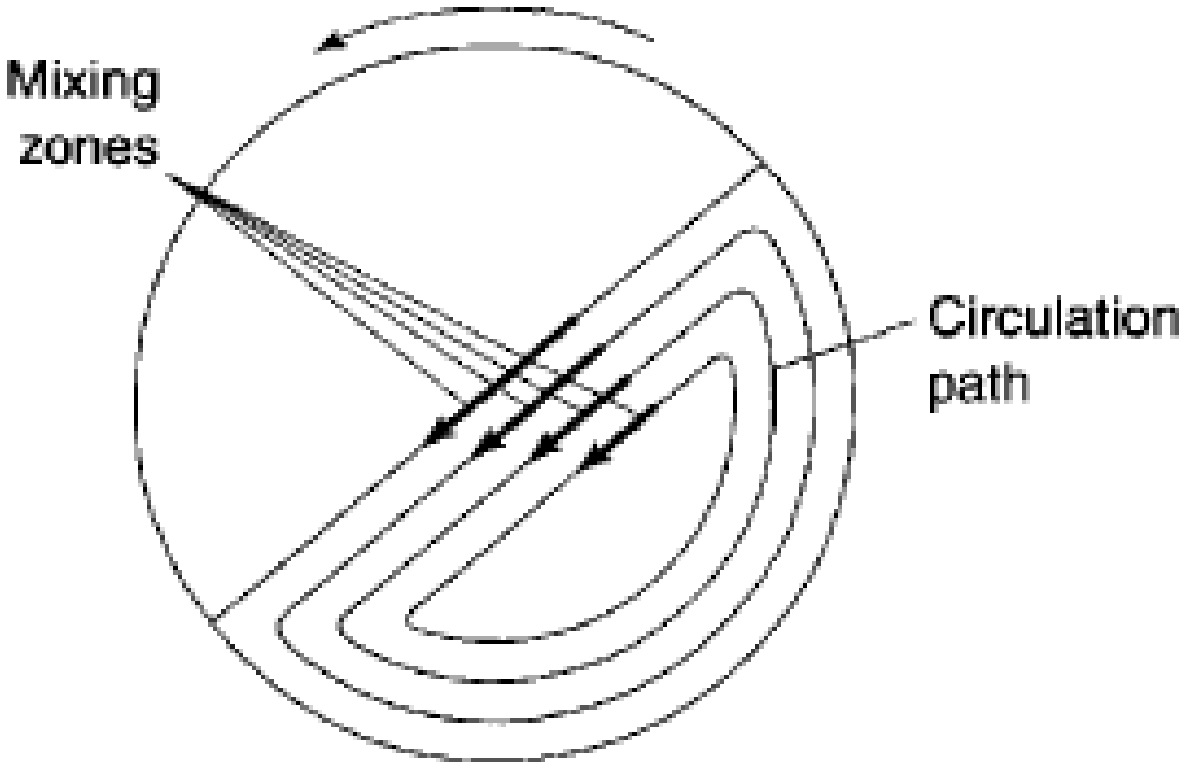
- Different designs of the tumbling mixers



- Typical intermediate bulk container



- Movement of the powder bed in a tumbling mixer



- Tumbling mixers are available to mix from approximately 50 g, e.g. for laboratory-scale development work, to over 100 kg at a production scale.
- The material typically occupies about a half to two thirds of the mixer volume.
- The rate at which the product is mixed will depend on mixer design and rotation speed, as these influence the movement of the material in the mixer.

- Tumbling mixers are good for free-flowing powders/granules but poor for cohesive/poorly flowing powders, because the shear forces generated are usually insufficient to break up any aggregates.

- Care must also be taken if there are significant differences in particle size present, as segregation is likely to occur.

- Common uses of tumbling mixers:

1. the blending of lubricants, glidants or external disintegrants with granules prior to tableting.

2. to produce ordered mixes, although the process is often slow because of the cohesiveness of the adsorbing particles.

- The Turbula shaker-mixer (WAB, Switzerland) is a more sophisticated form of tumbling mixer that uses inversional motion in addition to the rotational and translational motion of traditional tumbling mixers.

- This leads to more efficient mixing and makes it less likely that materials of different sizes and densities will segregate.

- *High-speed mixer-granulators*

- In pharmaceutical product manufacture it is often preferable to use one piece of equipment to carry out more than one function.

- a mixer-granulator can both mix and granulate a product, thereby removing the need to transfer the product between pieces of equipment and so reducing the opportunity for segregation to occur.

- The centrally mounted impeller blade at the bottom of the mixer rotates at high speed, throwing the material towards the mixer bowl wall by centrifugal force.

- The material is then forced upwards before dropping back down towards the centre of the mixer.

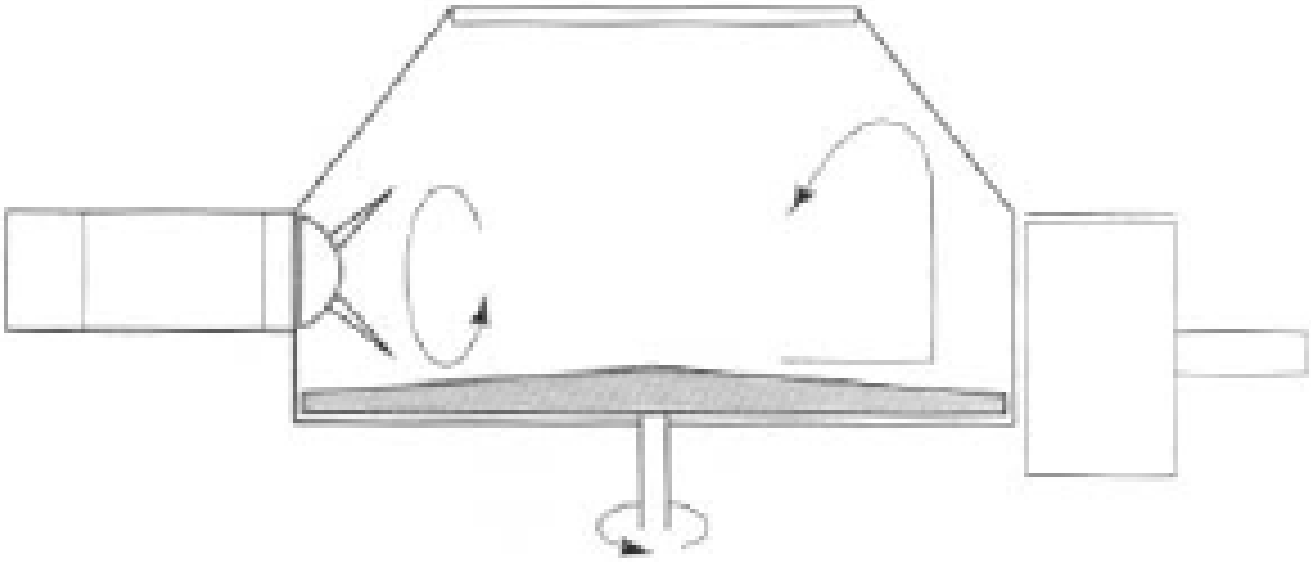
- The particulate movement within the bowl tends to mix the components quickly owing to high shear forces (arising from the high velocity) and the expansion in bed volume that allows diffusive mixing.

- Once mixed, granulating agent can be added and granules formed in situ using a slower impeller speed and the action of the side-mounted chopper blade.

- Because of the high-speed movement within a mixer-granulator:

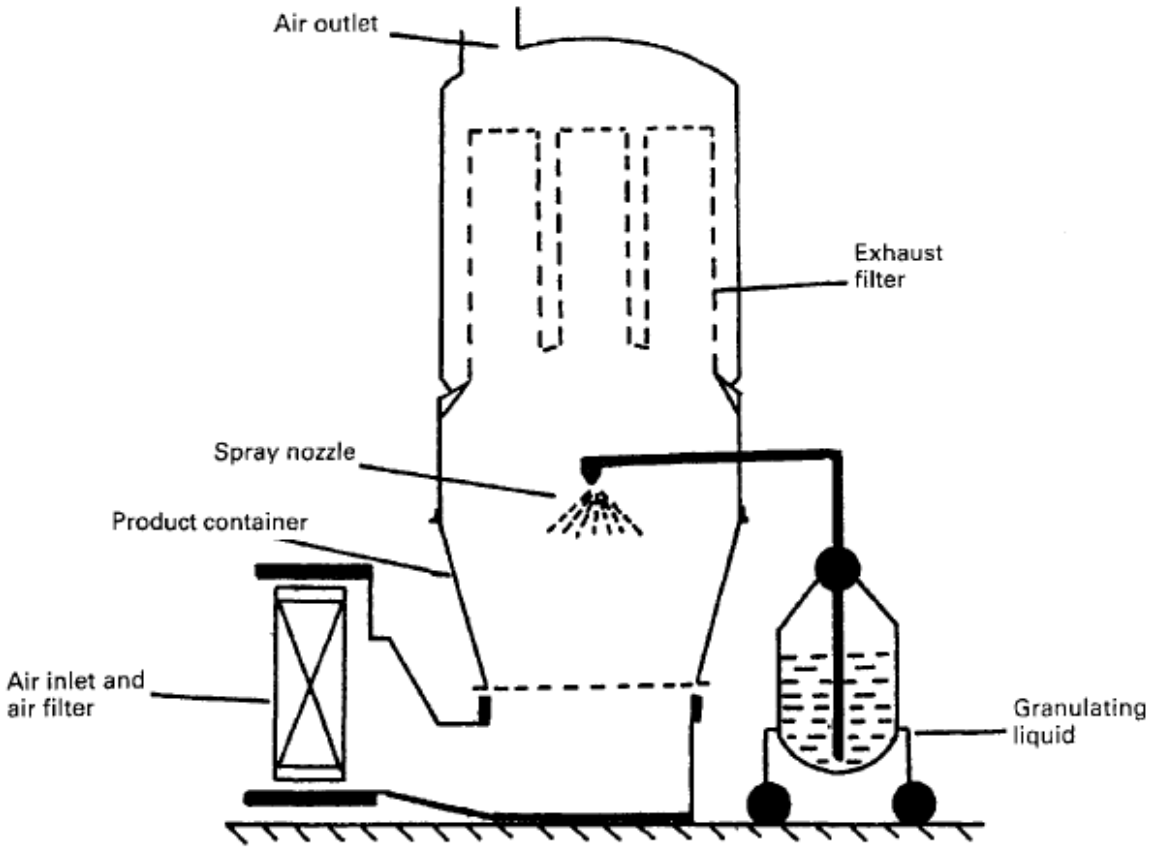
1. care must be taken if material fractures easily.
2. the problems associated with overmixing of lubricants, means that this type of mixer is not normally used for blending lubricants.

- Diagrammatic representation of a high-speed mixer-granulator



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.


Air outlet
Exhaust filter
Spray nozzle
Product container
Air inlet and air filter
Granulating liquid

- *Agitator mixers*
  - This type of mixer depends on the motion of a blade or paddle through the product, and hence the main mixing mechanism is convection.

  - Examples include:

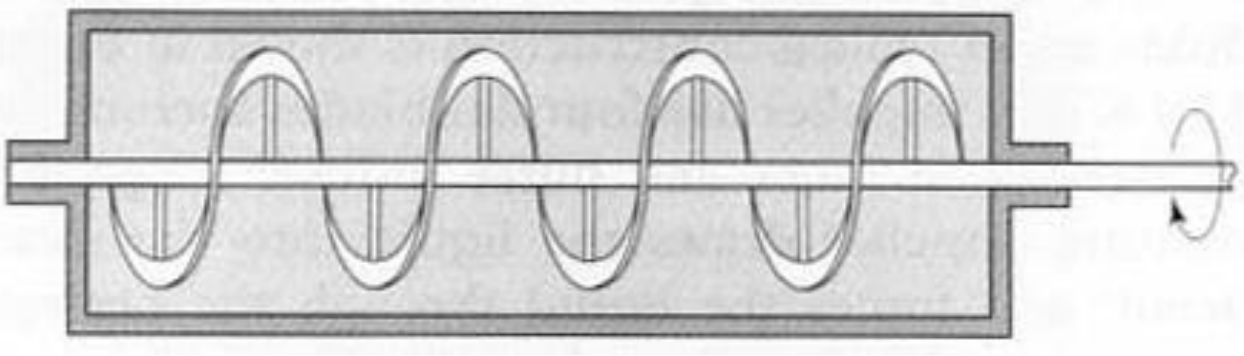
1. the ribbon mixer
2. the planetary mixer
3. the Nautamixer

- the ribbon mixer:
- mixing is achieved by the rotation of helical blades in a hemispherical trough.

- 'Dead spots' are difficult to eliminate in this type of mixer and the shearing action caused by the movement of the blades may be insufficient to break up drug aggregates.

- The mixer mix poorly flowing material and is less likely to cause segregation than a tumbling mixer.

- Ribbon agitator powder mixer

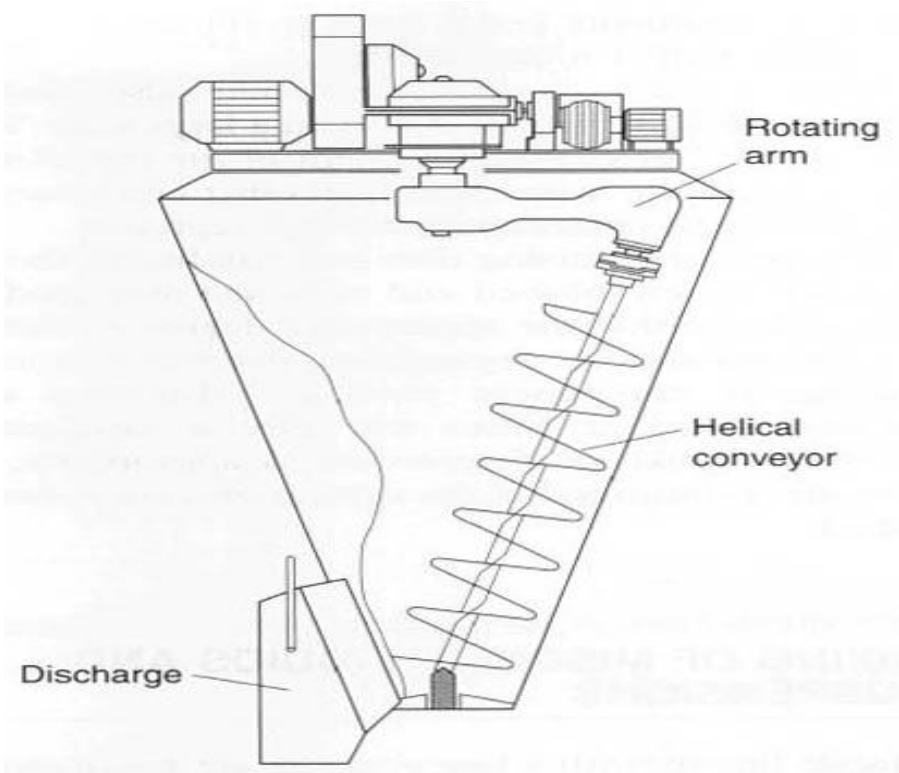


- The Nautamixer:
- consists of a conical vessel fitted at the base with a rotating screw, which is fastened to the end of a rotating arm at the upper end.

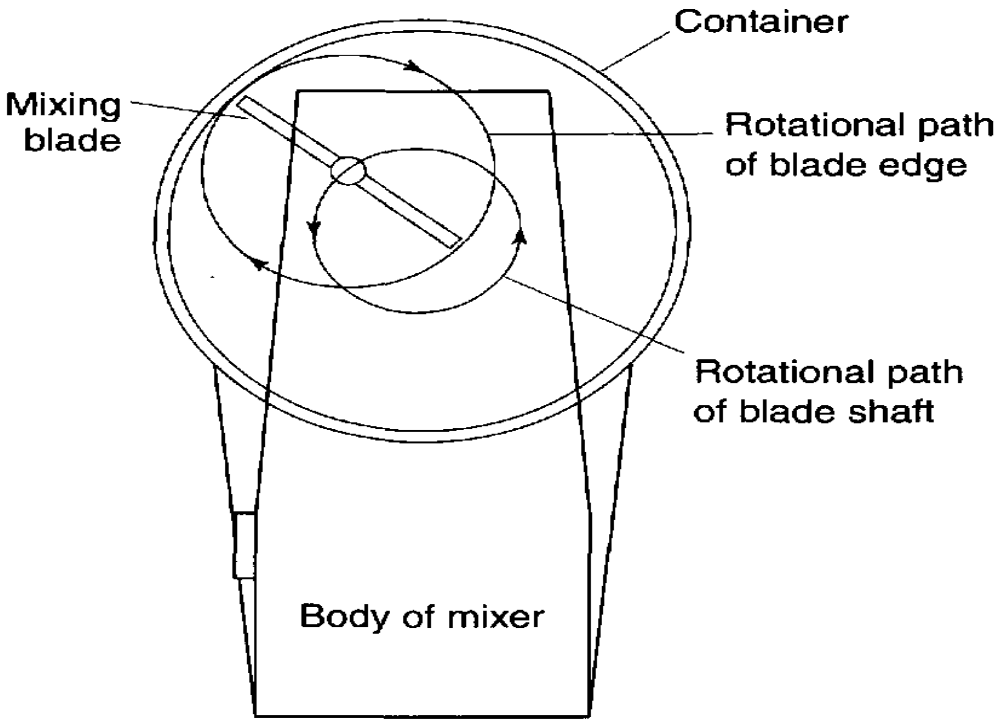
- The screw conveys the material to near the top, where it cascades back into the mass.

- The mixer thus combines convective mixing (as the material is raised by the helical conveyor) and shear and diffusive mixing (as the material cascades downwards).

- Nautamixer



- Planetary mixer – top view, showing path of paddle



MIXING OF MISCIBLE LIQUIDS AND SUSPENSIONS

- Mobile liquids with a low viscosity are easily mixed with each other. solid particles are readily suspended in mobile liquids, although the particles are likely to settle rapidly when mixing is discontinued.

- Viscous liquids are more difficult to stir and mix, but they reduce the sedimentation rate of suspended particles.

1. *Propeller mixers.*
2. *Turbine mixers.*
3. *Inline mixers.*

- *Propeller mixers*
  - for medium-scale fluid mixing.
  - a propeller-type stirrer may be clamped to the edge of a vessel.
  - A propeller has angled blades, which cause the fluid to circulate in both an axial and a radial direction.
  - An off-centre mounting discourages the formation of a vortex, which may occur when the stirrer is mounted centrally.

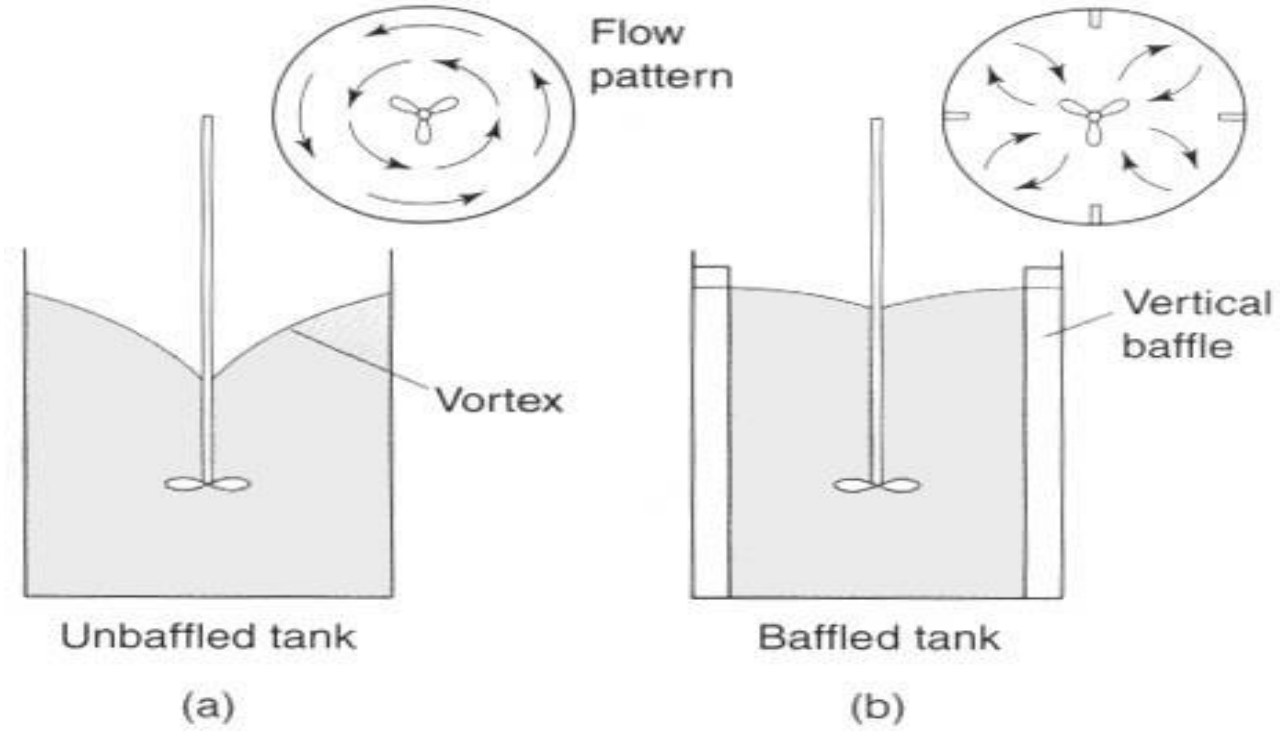
- A vortex forms when the centrifugal force imparted to the liquid by the propeller blades causes it to back up around the sides of the vessel and create a depression at the shaft.

- As the speed of rotation is increased air may be sucked into the fluid by the formation of a vortex; this can cause frothing and possible oxidation (Figure (a)).

- Another method of suppressing a vortex is to fit vertical baffles into the vessel.
- These divert the rotating fluid from its circular path into the centre of the vessel, where the vortex would otherwise form (Figure (b)).

- The ratio of the diameter of a propeller stirrer to that of the vessel is commonly 1:10-1:20, and it typically operates at speeds of 1-20 rps.
- The propeller stirrer depends for its action on a satisfactory axial and radial flow pattern, which will not occur if the fluid is sufficiently viscous.
- There must be a fast flow of fluid towards the propeller, which can only occur if the fluid is mobile.

- Propeller mixer with (a) unbaffled tank and (b)baffled tank



- *Turbine mixers*

- used for more viscous fluids.
- The impeller has four flat blades surrounded by perforated inner and outer diffuser rings.
- The rotating impeller draws the liquid into the mixer 'head' and forces the liquid through the perforations with considerable radial velocity, sufficient to overcome the viscous drag of the bulk of the fluid.

- Drawback: the absence of an axial component, but a different head with the perforations pointing upwards can be fitted if this is desired.

- As the liquid is forced through the small orifices of the diffuser rings at high velocity large shear forces are produced.

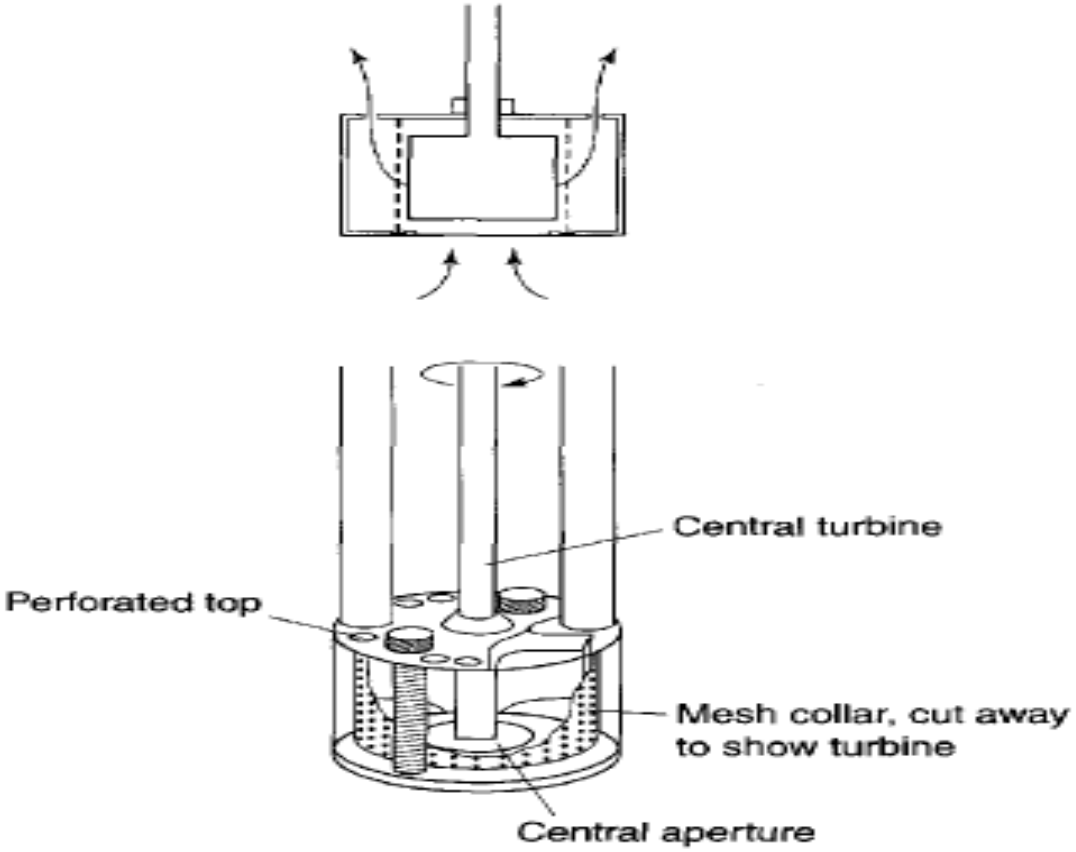
- When mixing immiscible liquids, if the orifices are sufficiently small and velocity sufficiently high, the shear forces produced enable the generation of droplets of the dispersed phase which are small enough to produce stable dispersions (water-in-oil or oil-in-water).

- Turbine mixers of this type are therefore often fitted to vessels used for the large-scale production of emulsions and creams

- Turbine-type mixes will not cope with liquids of very high viscosity, as the material will not be drawn into the mixer head.

- These liquids are best treated as semisolids and handled in the same equipment as used for such materials.

- Turbine mixer



- *Inline mixers*
- As an alternative to mixing fluids in batches in vessels, mobile miscible components may be fed through an 'inline' mixer designed to create turbulence in a flowing fluid stream.

- In this case a continuous mixing process is possible.

MIXING OF SEMISOLIDS

- The problems that arise during the mixing of semisolids (ointments and pastes) stem from the fact that, unlike powders and liquids, semisolids will not flow easily.

- Material that finds its way to 'dead' spots will remain there.

- For this reason, suitable mixers must:

1. have rotating elements with narrow clearances between themselves and the mixing vessel wall

2. produce a high degree of shear mixing, as diffusion and convection cannot occur.

- **Mixers for semisolids:**

1. *Planetary mixers.*
2. *Sigma-blade mixer.*

- *Planetary mixers*
- commonly found in the domestic kitchen (e.g. Kenwood-type mixers) and larger used in industry.
- The mixing blade is set off-centre and is carried on a rotating arm.
- It therefore travels round the circumference of the mixing bowl while simultaneously rotating around its own axis.
- This is therefore a double rotation similar to that of a spinning planet rotating around the sun.

- A small clearance between the vessel and the paddle gives shear, but 'scraping down' several times is necessary to mix the contents well as some materials are forced to the top of the bowl.

- Planetary mixers are also sometimes used to mix powders, particularly if a wet mass for granulation is required.

- *Sigma-blade mixer*

- This robust mixer will deal with stiff pastes and ointments and depends for its action on the close intermeshing of the two blades which resemble the Greek letter ∑ in shape.

- The clearance between the blades and the mixing trough is kept small by the shape

- It is very difficult using primary mixers to completely disperse powder particles in a semisolid base so that they are invisible to the eye.
- The mix is usually subjected to the further action of a roller mill or colloid mill, so as to 'rub out' these particles by the intense shear generated by rollers or cones set with a very small clearance between them.

- Sigma blade mixer.

