Mixing

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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.

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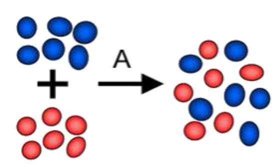

This may be:

1) Mixing of Powdered materials (e.g. tablets, capsules, dry powder inhalers).

2) Mixing of miscible liquids (e.g. solutions) or immiscible (e.g. emulsions).

3) Mixing of insoluble solid and liquid (e.g. Suspensions).

4) Mixing of semisolids or dispersion of particles in semisolids (e.g. pastes and ointments).

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Mixing

- Types of mixtures:

1) ***Positive mixtures***: Mixtures that form spontaneously (do not need energy) and irreversibly (when formed do not tend to separate).

    (e.g. gases and miscible liquids)

2) ***Negative mixtures***: Mixtures that need energy input (work) to form and keep. Once the energy input is stopped they tend to separate.

    (e.g. Suspensions, emulsions and creams)

3) ***Neutral mixtures***: Mixtures that do not form spontaneously (i.e they need energy input) but once formed they do not tend to separate.

    (e.g. Powder mixtures, pastes and ointments)

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The mixing Process

Perfect mixture: The situation in which particles of one component lay as closely as possible in contact with particles of other component.

- It is an ideal situation which is practically impossible.

Random mixture: A mixture where the probability of sampling a particular type of of particle is the same at all positions and is proportional to the number of such particle on the total mix.

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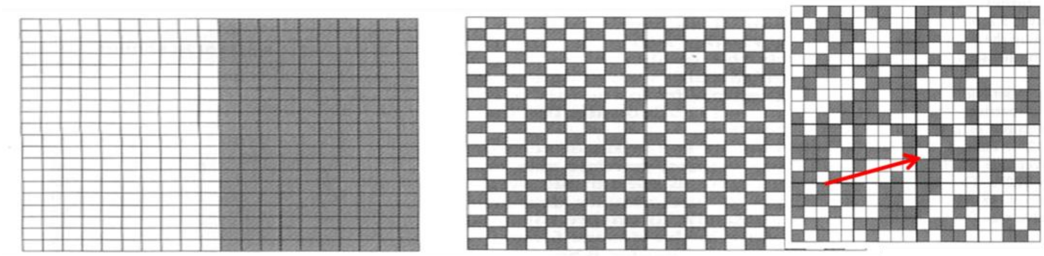
The mixing process



Unmixed system
Complete segregation

Mixed Ordered system
Perfect (ideal) mix

Mixed random system

•**Ordered system**: particles are arranged in **iterative** rule (**repetitive pattern**) (not random)

•We can consider mixing as vector quantity (spatial orientation and translational velocity of the particles)

The mixing Process

- It is the weight/volume of the dosage unit that dictates how closely the mix must be examined/analyzed to ensure it contains the correct dose/concentration.

- This weight/volume is known as the scale of scrutiny and it is the amount of material within which the quality of mixing is important.

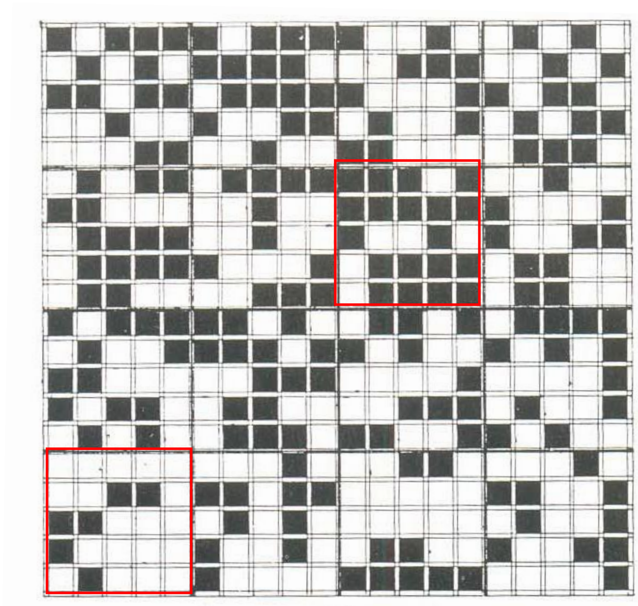
The mixing Process

- For example, if the unit dose of tablets is 200 mg (containing 100 mg active drug) then 200 mg sample from the mix needs to be analyzed.

- The number of particles in scale of scrutiny depends on sample weight, particle size and particle density.

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	**10 000**	**100 000**
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
Mean	0.9	9.9	99.6
Standard deviation	0.78	3.38	11.18
% CV	86.86	34.17	11.23
Deviation from theoretical content	±100%	±50%	±16%



Theoretical percentage of white particles is 50 %

In the total 400 particles (20 * 20) the percentage of white is 51 % (= 102 % of theoretical)

If divided to 16 blocks of 25 particles (5 * 5) the percentage of white is 24-76 % (= 48 – 152 % of theoretical)

24%*200

48%*200

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The mixing Process

- Another factor to consider in mixing is the proportion of the active component in the dosage form/scale of scrutiny.

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Fig. 32.2 Computer generated mixtures of nominal 50% active ingredient. The numbers in parentheses refer to the number of

Ratio: 50 %

Total number = 400

Theoretical number of white particles = 200

194/200=97%

202/200=101%

198/200=99%

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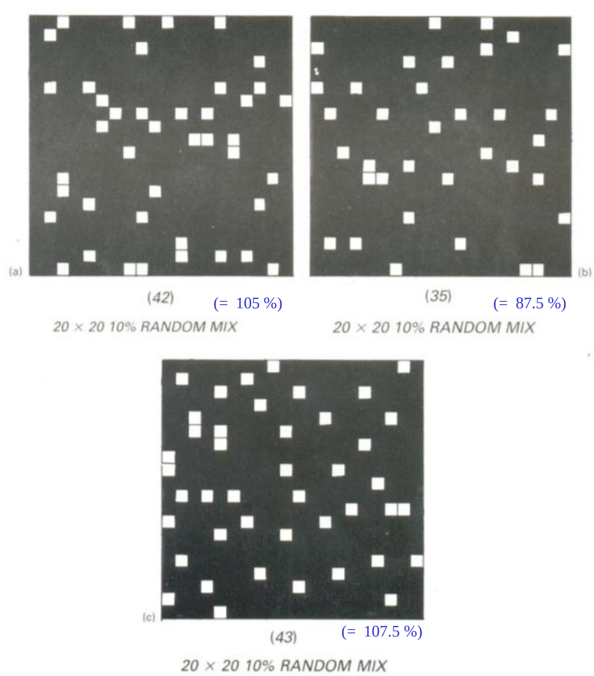

Fig. 32.3 Computer generated mixtures of nominal 10% active ingredient. The numbers in parentheses refer to the number of 'white' particles in each mix, theoretically 40

Ratio: 10 %

Total number = 400

Theoretical number of white particles = 40

42/40=105%

35/40=87.5%

43/40=107.5

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The mixing Process

- The variation in component percentage between different samples taken from a mixture increases:

1. as the amount (number of particles) in scale of scrutiny decreases.
2. as the proportion of a component in mixture decreases.

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The mixing Process

- This indicates that:
  - the lower the percentage of active ingredient (potent drug) in mixture, the more difficult it is to achieve an acceptably low deviation in active content.
  - The more particles are present in dose (scale of scrutiny) the lower the deviation of content → The number of particles can be increased by decreasing particle size (This can be done by milling).

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Mathematical treatment of mixing process

- There will be always some variation in the composition of samples taken from random mixtures.
- The aim during formulation and processing is to minimize this variation to acceptable levels by selecting appropriate :
  - scale of scrutiny
  - particle size
  - mixing procedure

Mathematical treatment of mixing process

- For random mix, if we consider that particles are all of same size, shape and density then:

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

- P is the proportion of a component in total mix
- As p increases, %CV decrease

Example:

n = 100 000, p = 0.5 $\Rightarrow$ SD = 1.58×10^{-3}, %CV = 0.32%

n = 100 000, p = 0.001 $\Rightarrow$ SD = 9.99×10^{-5}, %CV =10 %

- The scale of scrutiny can be increased by increasing the amount of additives in the mixture but this will lead to a decrease in *p*.

Evaluation of degree of mixing

Needs for monitoring of mixing:

- To follow a mixing process:
  - To indicate the degree of mixing
  - To indicate when sufficient mixing has occurred and determine the suitable mixing time
- To assess the efficiency of a mixer

Sampling

- Scoop sampling
- Thief sampling

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Unit dose thief sampler

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Evaluation of degree of mixing

Mixing Index (M)

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

S_R : Content standard deviation of random mixture

S_{ACT} : Content standard deviation of mixture under investigation.

- In some cases, it is possible to achieve an acceptable variation in content before obtaining a random mix

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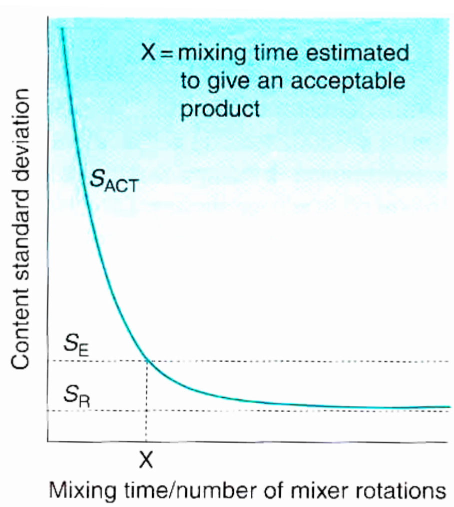

Fig. 12.4 The reduction in mixing time possible if a random mix is not required. S_{ACT} represents the content standard deviation of samples taken from the mix, S_E the estimated acceptable standard deviation and S_R the standard deviation expected from a random mix.

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Mechanisms of mixing

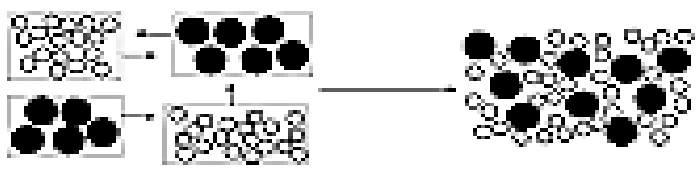
Powders

There are three main mechanisms for powder mixing:

a) ***<u>Convection</u>*** (the transfer of large amount of particles from one part of the powder bed to another).

This may occur when a mixer blade or paddle moves through the mix.

This mechanism contributes mainly to macroscopic mixing of powders, but mixing does not occur within the group of particles moving together.



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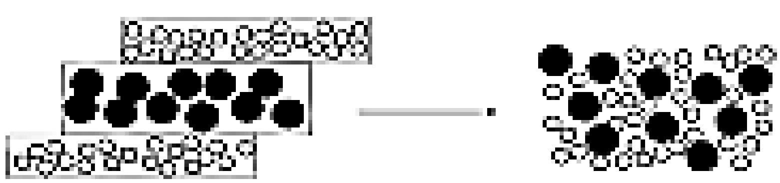
Mechanisms of mixing

Powders

b) ***<u>Shear</u>*** (Layer of powder flows over another layer)

This may occur when some of the material is removed (e.g. by convective mixing) causing powder bed to collapse.



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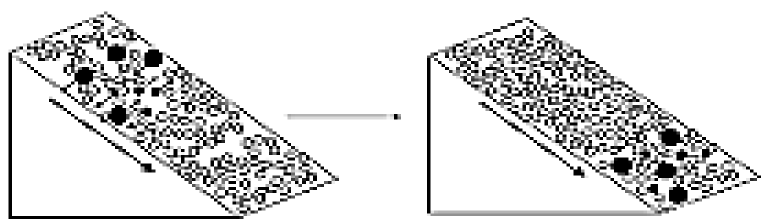
Mechanisms of mixing

Powders

c) ***Diffusion*** (mixing of individual particles)

This mechanism is necessary to form true random mixture.

When a powder bed is forced to move or flow it will dilate (the particles become less tightly packed and the voids between them increase). This allows particles to fall under gravity trough the voids created.



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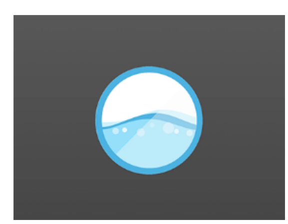
Mechanisms of mixing

Liquids

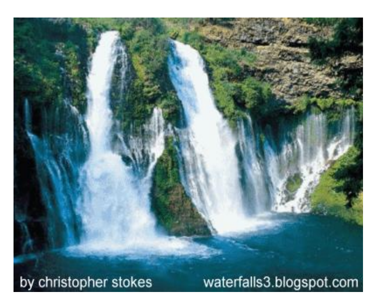


a) Bulk transport

- The movement of a large portion of the material being mixed from one position in the system to another.

b) Turbulent mixing

- The haphazard movement of molecules when forced to move in turbulent manner, which means random fluctuation of the fluid speed and movement direction, so that the fluid has different instantaneous velocities at different locations at the same time.



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Mechanisms of mixing

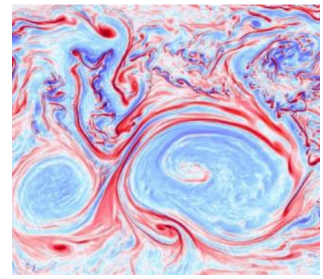
Liquids

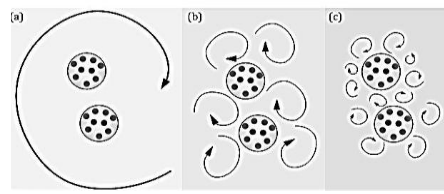
b) Turbulent mixing

- It can be seen as a composite of different eddies (small portions of fluid moving as a unit) of various sizes.

The large ones tend to break into smaller and smaller sizes until they are no longer distinguishable.

- Turbulence is a highly effective mechanism for mixing.





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Mechanisms of mixing

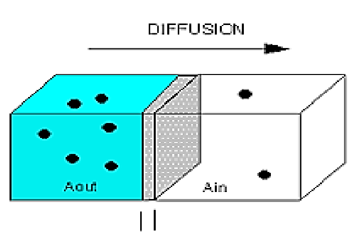
Liquids

c) Molecular diffusion

- The molecular diffusion is the primary mechanism responsible for mixing at the molecular level.

- This mechanism produces well mixed liquids if there is sufficient time.

- Considerable time is needed if this is the only mixing mechanism.



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Powder segregation (demixing)

- Segregation is the opposite effect to mixing, i.e. components tend to separate out (S_{ACT} increases).
- It may cause a random mixture to change to non-random or may be responsible that a random mixture never occurs.
- Segregation is more likely to occur if powder bed is subjected to <u>vibration</u> and when the particles have <u>greater flowability.</u>

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Segregation can be due to difference in :

1. Particle charge
2. Particle density
3. Particle shape
4. Particle size and size distribution

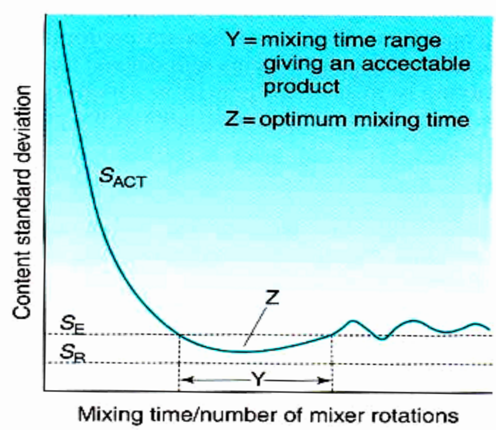

Fig. 12.5 Possible effect of extended mixing time on the content standard deviation of samples taken from a mix prone to segregation. S_{ACT} represents the content standard deviation of samples taken from the mix. S_E the estimated acceptable standard deviation and S_R the standard deviation expected from a random mix.

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Powder segregation (demixing)

Factors affecting segregation:

1. Particle size

Percolation segregation

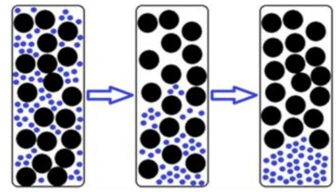
(small particles tend to fall through voids between large particles)

Trajectory segregation

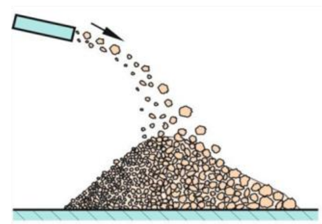
(large particles tend to have greater kinetic energy)

Elutriation segregation (dusting out)

(Air-blown small particles sediment and form a layer over coarse particles



Percolation segregation:



Trajectory segregation

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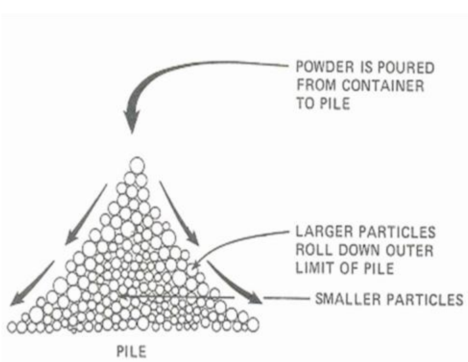
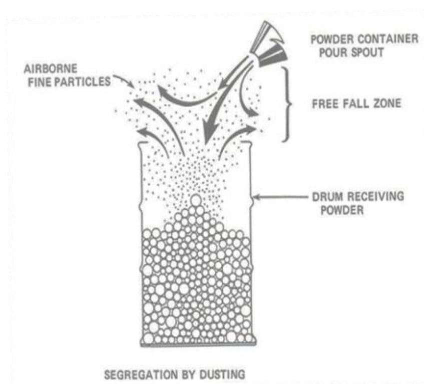
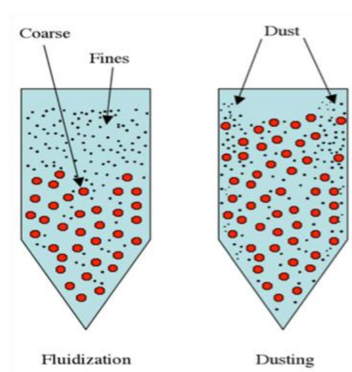


Trajectory segregation



(Elutriation)



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Powder segregation (demixing)

Factors affecting segregation:

2. Particle density

Segregation occurs due to density differences.

3. Particle shape

Spherical particles are easier to be mixed but also to segregate than irregular or needle shaped particles.

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Approaches to solve the problem of segregation

1. Selection of particular size fractions to achieve drug and excipients of the same particle size range.

2. Milling of the components so that there size becomes small and same.

3. Controlled crystallization during production of drug or excipient to give particles of particular size or shape.

4. Selection of excipients which have similar density to the drug.

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Approaches to solve the problem of segregation

- 5. Granulation of powder mixture.

- 6. Reduce the extent to which the powder mass is subjected to vibration or movement after mixing.

- 7. Using equipments where several processes can be carried out without transferring the mix.

- 8. Production of an ordered mix.

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Ordered mixing

- It is termed also adhesive or interactive mixing.
- In this case, very small particles may become adsorbed onto the active sites of large particles.

- This minimizes the segregation between small (adsorbed) particles and large (carrier) particles.

- Ordered mixing is most likely to occur when the adsorbed particles are very small so that the adsorption force is higher than the gravitational force trying to separate the components.

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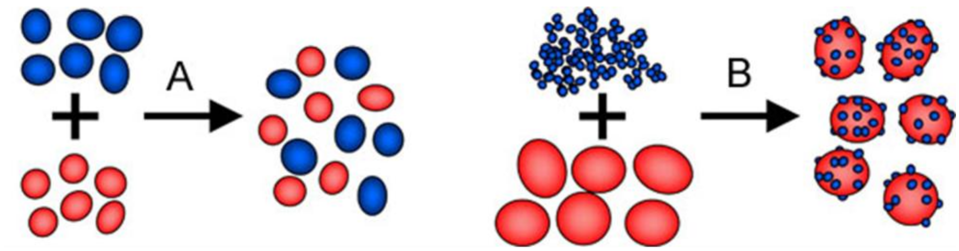

Random mixture

Interactive mixture

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Application of ordered mixing

1. Dry antibiotic formulations (fine antibiotic powder is blended with and adsorbed onto the surface of large sucrose or sorbitol particles.
2. Dry powder inhaler formulations
3. Direct compression formulations
4. Formulation of potent drugs

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Segregation in ordered mixes

Ordered unit segregation

- The carrier particles vary in size.

- In this case segregation occurs within the carrier particles according to size.
- The small particles <u>have higher specific surface</u> area than the large and so higher content of adsorbed material.

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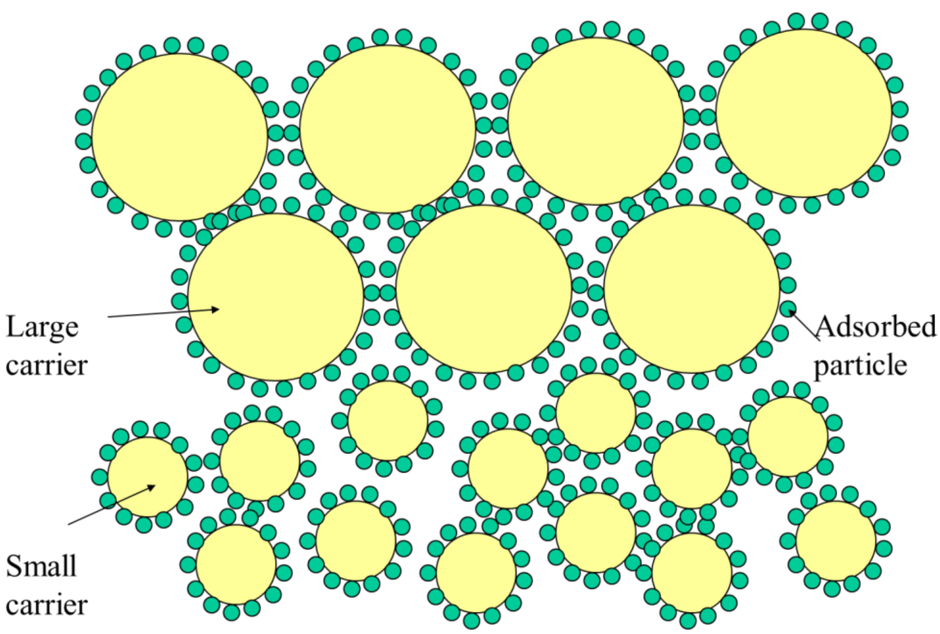

Ordered-unit segregation

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Segregation in ordered mixes

Displacement segregation

- There is competition for the active sites on the carrier.
- This occurs when a component is added to an ordered mixture that competes with the adsorbed material for the site on the carrier and displaces it

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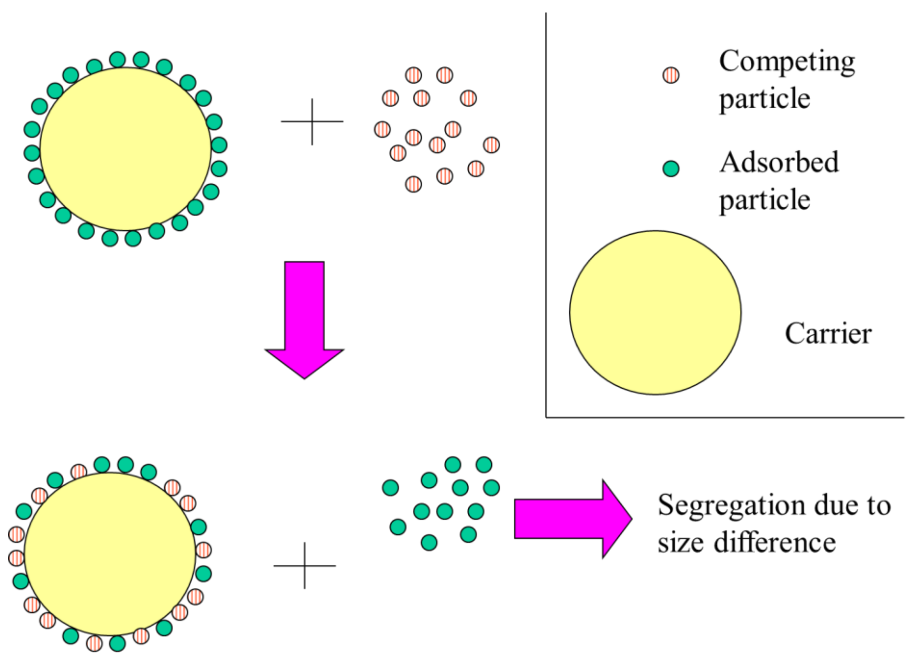

Displacement segregation

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Segregation in ordered mixes

Saturation segregation

- There are insufficient carrier particles

- If the added amount of small-sized material is higher than the capacity of the carrier particles then the excess amount will be free (not adsorbed) and it segregate due to size difference.

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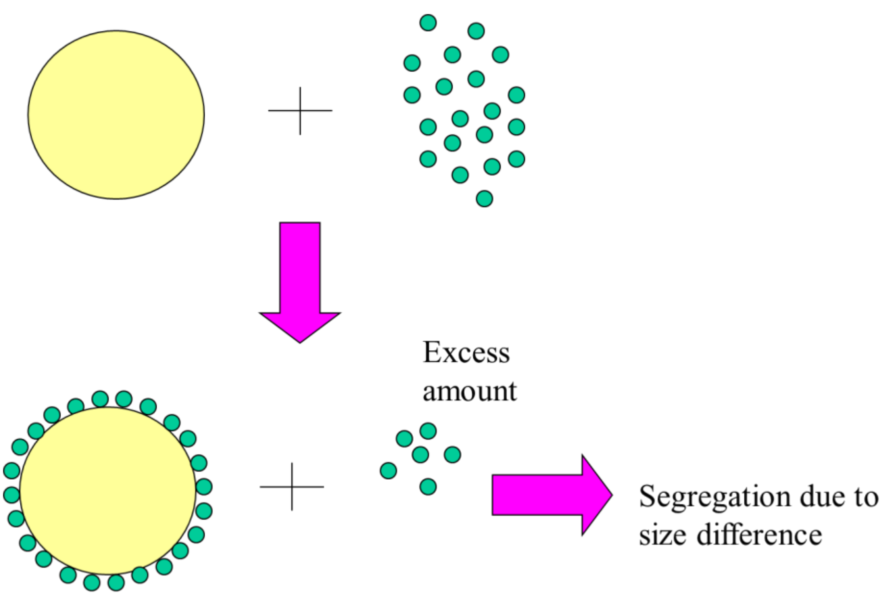

Saturation segregation

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Practical considerations in Powder mixing

- When mixing formulations where the proportion of active drug is low, a more even distribution may be obtained by building up the amount of material in the mixture sequentially (geometric dilution).

- The volume of powder mixture in the mixer should be appropriate. Both overfilling and underfilling may reduce mixing efficiency.

- The mixer should produce the mixing mechanism appropriate for the formulation:
  - Potent drugs: diffusion is necessary
  - Cohesive material: shear mixing

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Practical considerations in Powder mixing

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

2. Static charges may be generated during mixing that result in reduction in diffusive mixing.

3. This is enhanced by low humidity in atmosphere. The mixer should be suitably earthed to dissipate the static charge.

4. Vibrations may cause segregation in normal mixes and dislodging of adsorbed particles in ordered mixes.

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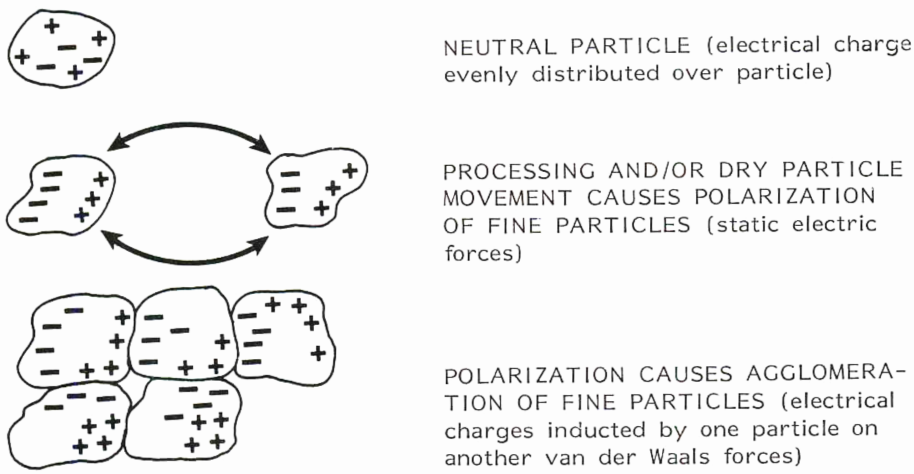

Figure 22 Effect of electrical forces on fine particles.

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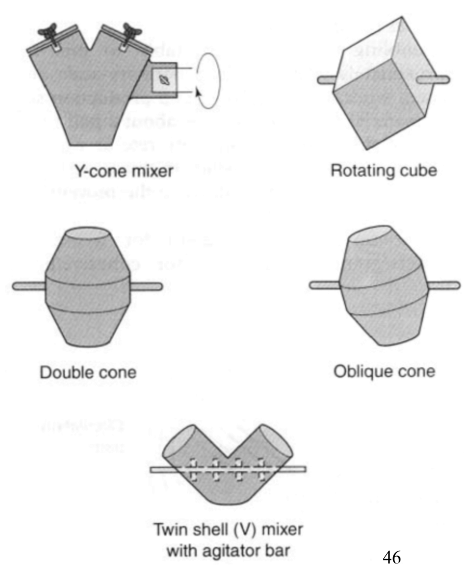
Powder mixing equipment

Tumbling mixers

- Mixing containers are mounted so that they can rotate about an axis.
- Commonly used for mixing of free flowing powders and are not suitable for cohesive powders.

- Commonly used for mixing granules with lubricant, glidant and external disintegrant.



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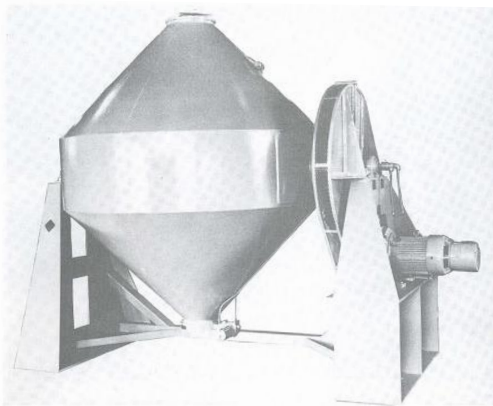

Figure 28 Double-cone blender. (Courtesy of Patterson-Kelley Company, Division of HARSCO Corporation, East Stroudsburg, Pennsylvania.)

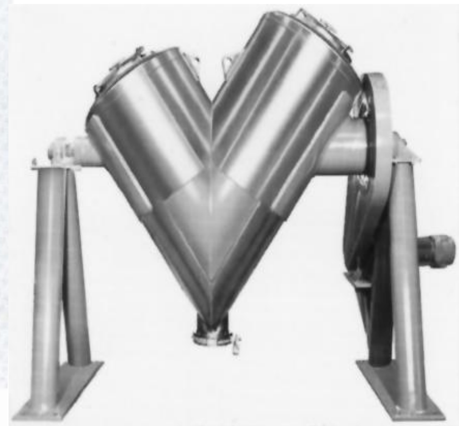

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Figure 29 Slant double-cone mixer. (Courtesy Gemc Jersey.)

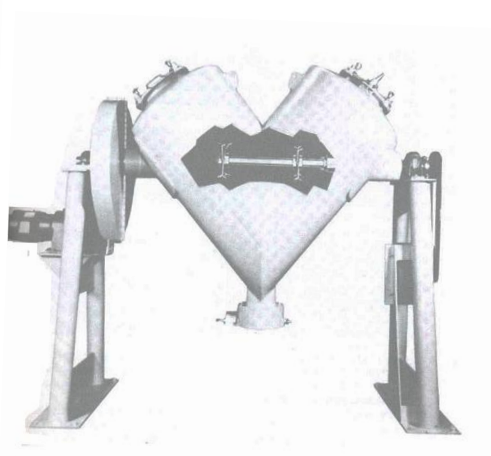

Figure 31 V-shaped blender with agitator mixing assembly. (Courtesy of Gemco, Middlesex, New Jersey.)

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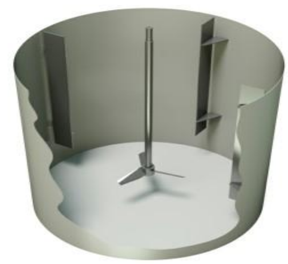
Powder mixing equipment

Tumbling mixers

- The shear mechanism occurs because of velocity gradient produced while diffusion occur through voids produced during powder flow.
- The addition of prongs, baffles or rotating bars helps convective mixing.
- Care about segregation is necessary.





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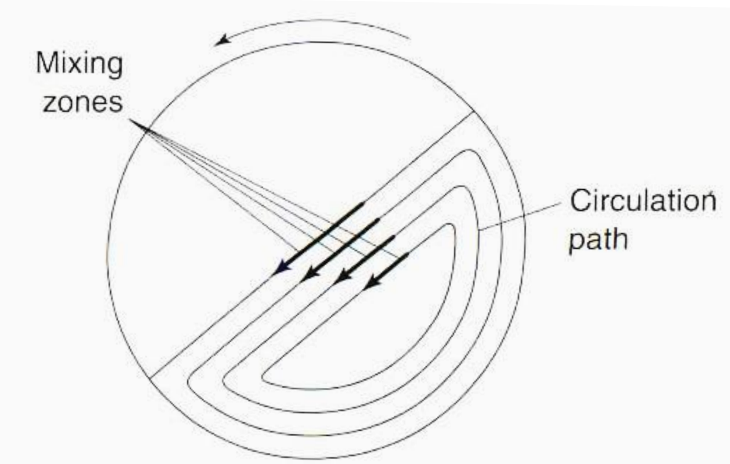

Fig. 13.8 Movement of the powder bed in a tumbling mixer.

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Powder mixing equipment

Tumbling mixers

- Capacity ranges from 50 g to 100 kg.
- The material typically occupies 1/2 to 2/3 of the mixer volume.
- The mixing efficiency depends on speed of rotation. Speed of rotation should be suitable:
  - Very high speed will cause the powder to be held on the mixer walls by centrifugal force.
  - Very low speed will generate insufficient bed expansion and little shear mixing.

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Table 9 Effect of Powder Fill on Blending Time of Double-Cone Blenders[a]

Volume percent of blender filled with powder charge	Approximate blend time (minutes) in production-size blenders
50	10
65	14
70	18
75	24
80[b]	40[b]

[a]Blending done in double-cone blenders and times measured to obtain comparable blends.

[b]Uniform blend not attainable with this fill level.

Source: Sweitzer, G. R., Blending and Drying Efficiency Double Cone vs. V-Shape, GEMCO, Newark, New Jersey.

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Powder mixing equipment

Tumbling mixers

- ***Intermediate bulk containers (IBCs)*** are containers used both as mixing bowl and to either feed the hopper of a tablet or capsule machine or as the hopper itself.

- ***The Turbula shaker mixer (WAB, Switzerland)*** is a more sophisticated form of tumbling mixer that uses inversional motion in addition to the rotational motion leading to more efficient mixing.

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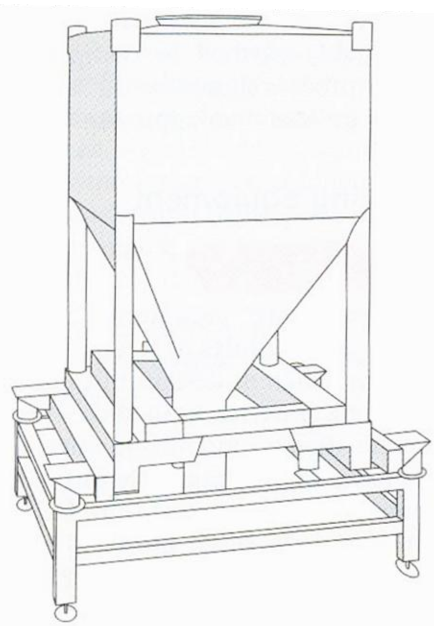

Fig. 13.7 Typical intermediate bulk container.

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Powder mixing equipment

High speed mixer granulators

- They are used both for mixing and granulation.
- It contains centrally mounted impeller blade that rotate at high speed throwing the material towards the mixing bowl.
- The side-mounted chopper blade helps in granulation.
- Care if material fractures easily.
- Not normally used for blending lubricants.

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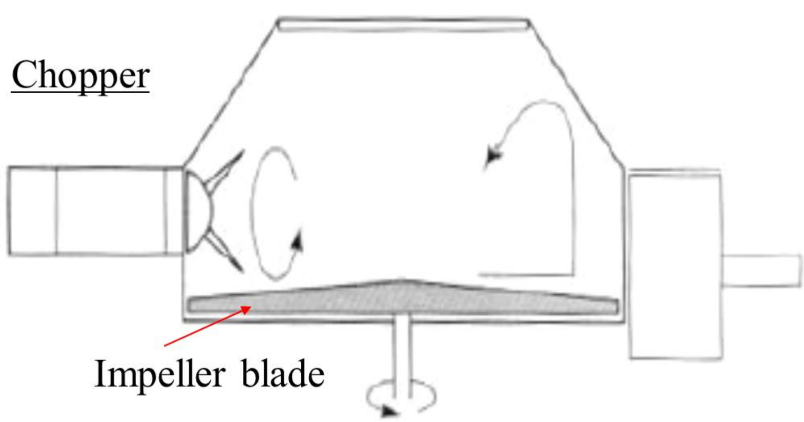

Fig. 13.9 Diagrammatic representation of a high-speed mixer–granulator.

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Powder mixing equipment

Agitator mixers

- These types of mixers depend on the motion of a blade or paddle though the product, and hence the main mixing mechanism is convection.

- There are three main designs of agitator mixers:
  - Ribbon mixer
  - Planetary (Orbital) mixer
  - Nautamixer

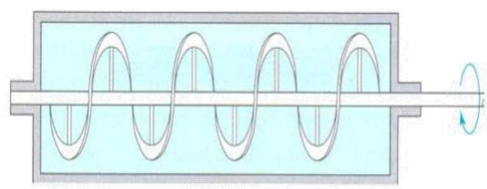

Fig. 12.10 Ribbon agitator powder mixer.

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Powder mixing equipment

Ribbon mixers

- Mixing is achieved by the rotation of helical blades in a cylindrical tank.

Advantages

- Suitable for mixing of poorly flowing materials.
- Segregation is less likely to occur than in tumbling mixer

Disadvantages

- Dead spots are difficult to eliminate.
- The shearing action caused by movement of the blades may be insufficient to break up drug aggregates.

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Powder mixing equipment

planetary mixers

- The rotational path of paddle is similar to that of a planet.
- It is used:
  - for mixing powders and semisolids
  - Wet massing (granulation)

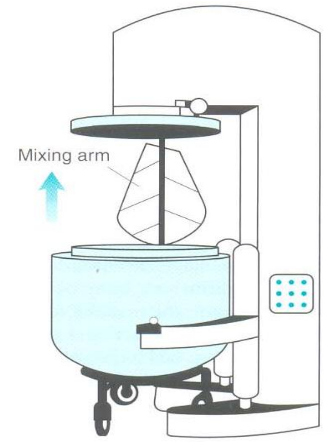

Fig. 12.11 Planetary mixer for powders and semi-solids.

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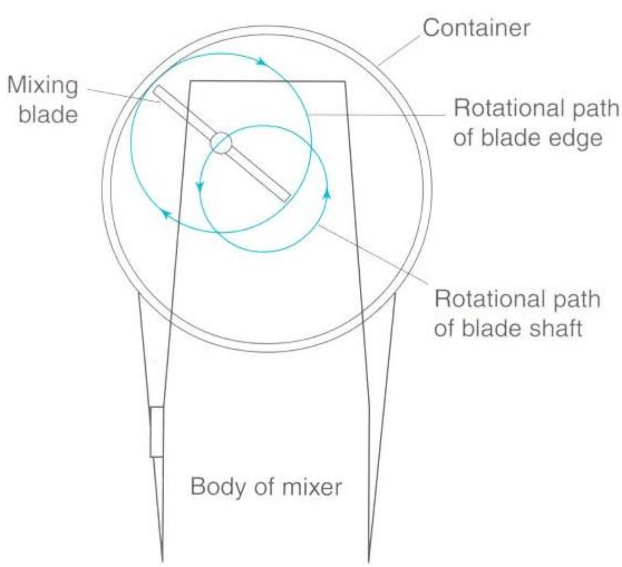

Fig. 12.12 Planetary mixer – top view, showing path of paddle.

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Powder mixing equipment

Nautamixer

- It consists of a conical vessel that contains inside a helical conveyor that conveys the material up to near the top where it cascades back into the mass.
- This mixer combines convective, shear and diffusion mixing

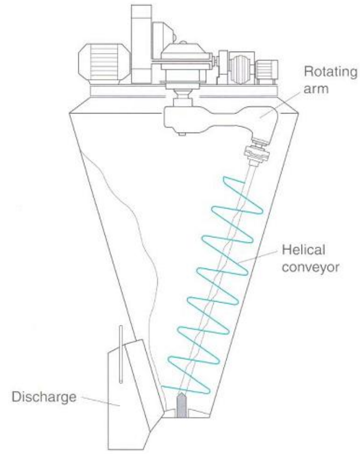

Fig. 12.13 Nautamixer (courtesy of Nautamixer Ltd).

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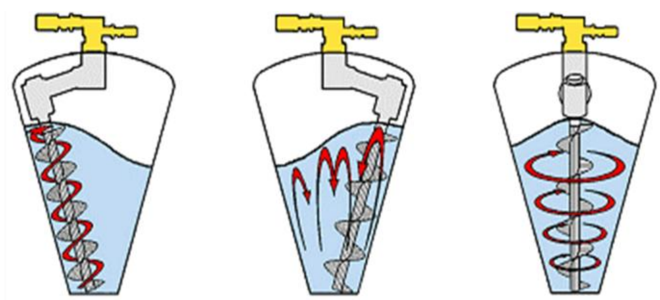
Nautamixer



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Powder mixing equipment

Fluidized bed mixers

- The fluidized bed equipment is used mainly in:
  - Drying
  - Granulation
  - Coating
- However it can be used for mixing of powders before granulation.
- Blown air fluidized and mixes the powder.
- Fluidization is very efficient mixing process.
- Diffusion of particles occur.

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Fluidized bed mixers

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Powder mixing equipment

Continuous mixers

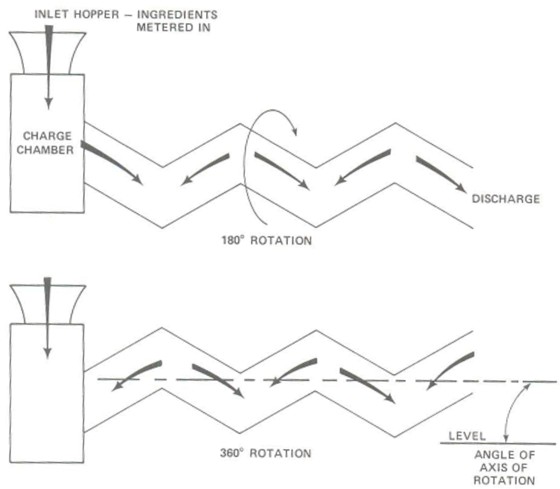

Figure 41 Schematic of "Zig Zag" continuous blender. (Courtesy of Patterson-Kelley Company, Division of HARSCO Corporation, East Stroudsburg, Pennsylvania.)

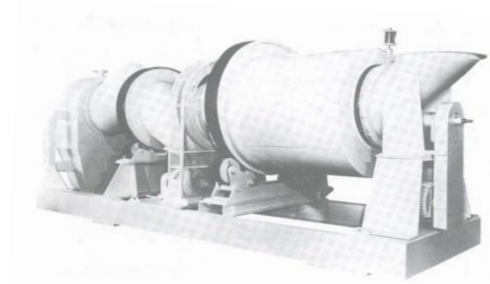

Figure 42 The "Zig Zag" continuous blender. (Courtesy of Patterson-Kelley Company, Division of HARSCO Corporation, East Stroudsburg, Pennsylvania.)

Scale-up of powder mixing

- The extent of mixing achieved at a small laboratory scale during development work may not necessarily be mirrored when the same formulation is mixed at a full production scale, even if the same mixer design is used for both.
- Often, mixing efficiency and the extent of mixing is improved on scale-up owing to increased shear forces.
- This is likely to be beneficial in most cases, although when blending lubricants care is needed to avoid overlubrication.

Scale-up of powder mixing

- The optimum mixing time and conditions should therefore be established and validated at a production scale, so that the appropriate degree of mixing is obtained without segregation, overlubrication or damage to component particles.
- Minimum and maximum mixing times that give a satisfactory product should be determined if appropriate, so that the 'robustness' of the mixing process is established.

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Types of mixers used for liquids and suspensions

Propeller (Impeller) mixers

- Three basic types of flow may be produced: radial, axial and tangential.
- Angled blades cause fluid to circulate in both an axial and a radial direction.
- The ratio of the diameter of propeller to that of the vessel is 1:10 - 1:20 and it typically rotates at speeds of 1 - 20 rps.

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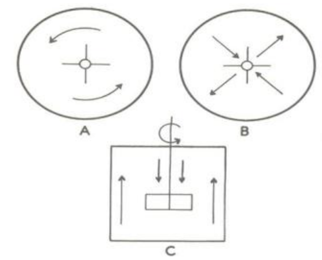
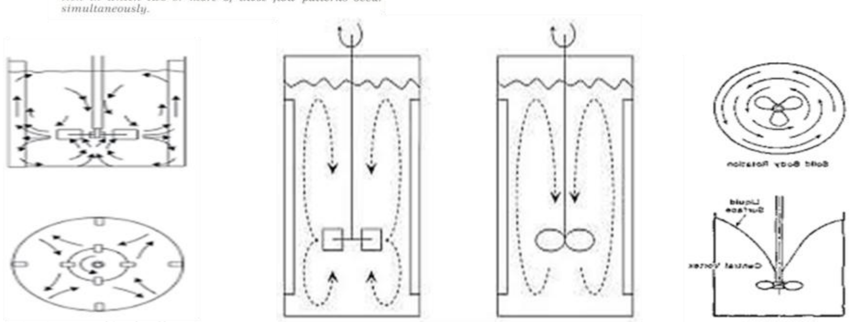


FIG. 1-2. A and B, Diagrammatic representation of cylindric tanks in which tangential and radial flow occur, respectively. C, Side view of a similar tank in which axial flow occurs. These diagrams represent systems in which only one type of flow occurs, in contrast to the usual situation in which two or more of these flow patterns occur simultaneously.



(A)Radial flow (B) axial (C)tangential flow 69

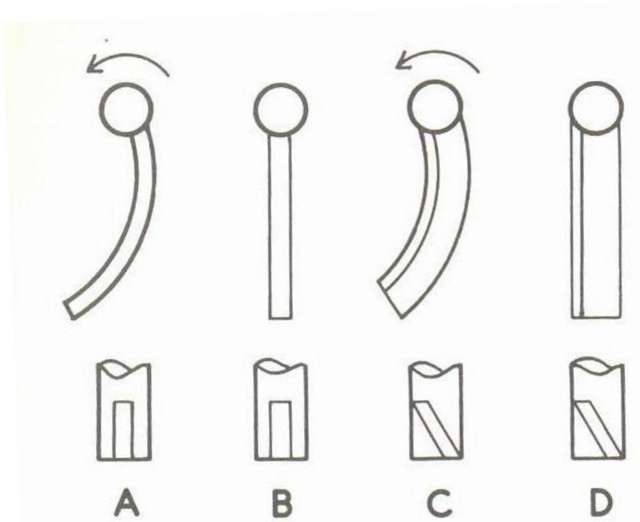


FIG. 1-3. Impeller blade types (only one blade shown), top and side views. A and B, Radial flow design: C and D, mixed radial-axial flow design. For axial pumping, the blade must be set at an incline to the axis of the shaft.

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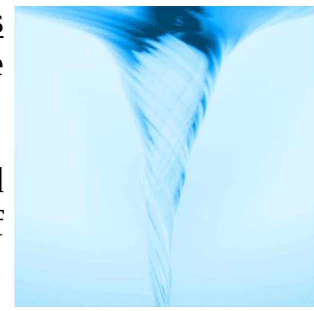
Types of mixers used for liquids and suspensions

Propeller (Impeller) mixers

- A vortex forms when the centrifugal force imparted to the liquid by the propeller blades causes it to back up around the sides of vessel and create a depression at the shaft.
- An off-center mounting of propeller and vertical baffles discourage the formation of vortex.
- Propellers are more efficient when they run at high speed in liquids with low viscosity.



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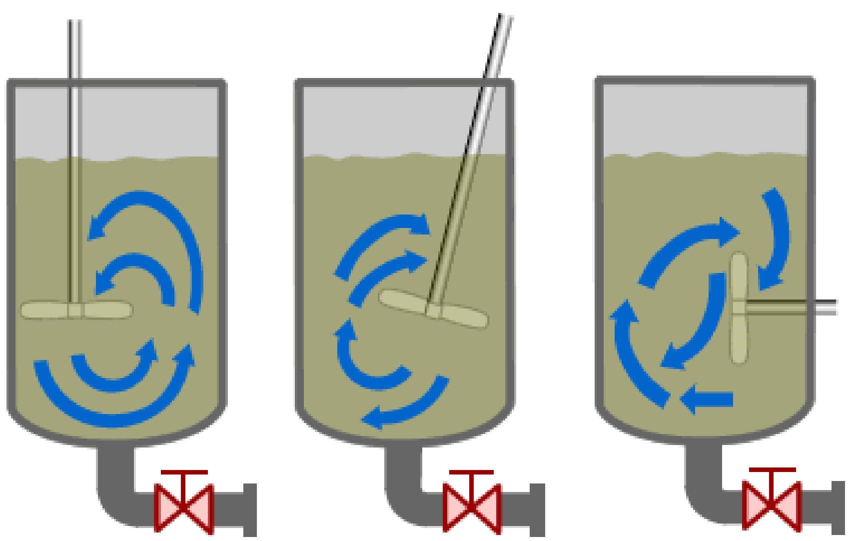

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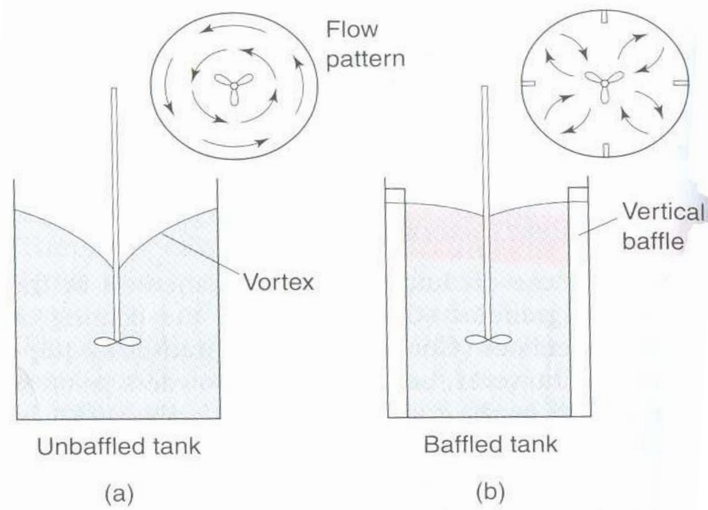

Fig. 13.13 Propeller mixer with (a) unbaffled tank and (b) baffled tank.

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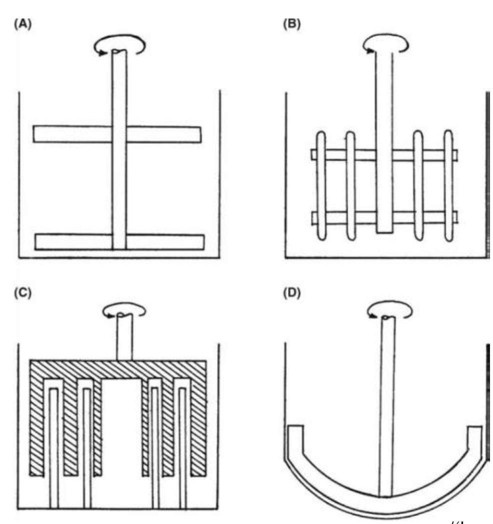
Types of mixers used for liquids and suspensions

Paddle mixers

- The mixing element is large in relation to the vessel and rotates at low speeds (10–100 rpm).



Paddle mixers

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Types of mixers used for liquids and suspensions

Turbine mixers

- Turbine mixers may be used for more viscous liquids than those mixed by propeller.

- The impeller has four flat blades surrounded by perforated inner and outer diffuser ring.

- The rotating impeller draws the liquid into the mixer head and forces the liquids through the perforations

- They can produce stable emulsions.

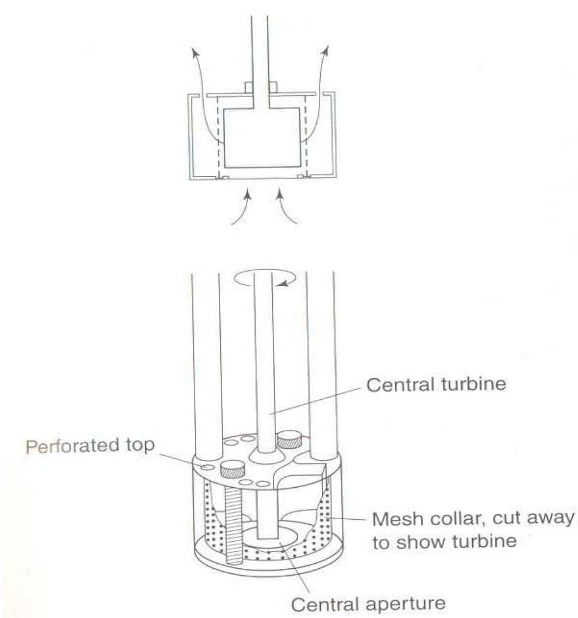
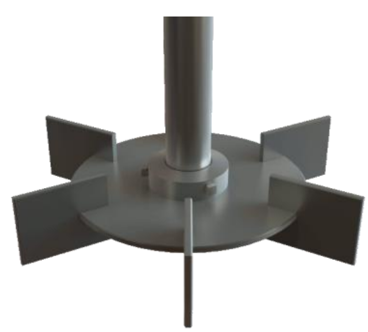


Fig. 13.14 Turbine mixer.



Types of mixers used for liquids and suspensions

Air jet mixers

- These mixers utilize jets of air or some other gases.
- The liquid must be of low viscosity, non-foaming, unreactive with the gas employed and reasonably nonvolatile.

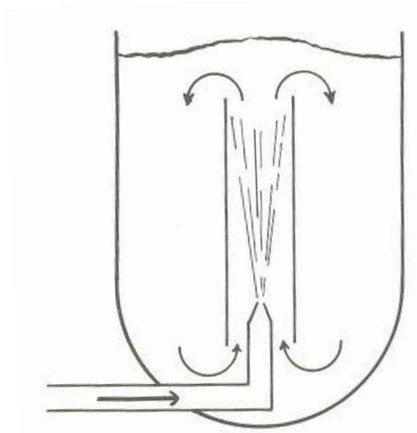
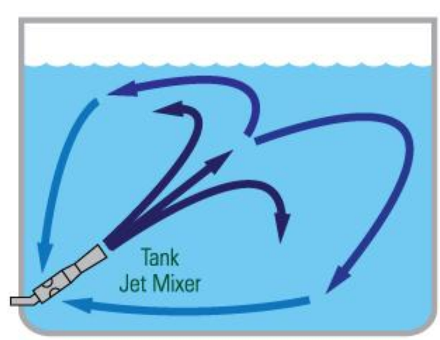


FIG. 1-4. *Vertical tank with centrally located air jet and draft tube. Bubbles confined within the draft tube rise, inducing an upward fluid flow in the tube. This flow tends to circulate fluid in the tank, bringing it into the turbulent region in the vicinity of the jet.*

Types of mixers used for liquids and suspensions

Fluid jet mixers

- When liquids are to be pumped into a tank for mixing, the power required for pumping is often used to accomplish the mixing.
- The fluids are pumped through a nozzle arranged to permit good circulation of the material through the tank.
- It is also possible to pump the liquid from the tank through the jet into the tank.



Types of mixers used for liquids and suspensions

Inline mixers (Continuous mixing)

- In this case, mobile, miscible components are fed through an inline mixer designed to create turbulence in a flowing fluid stream.
- It can be accomplished essentially in two ways: in a tube (pipe) through which the fluids flow,or in a chamber in which a considerable amount of hold up and recirculation occur.
- Controlling the feeding rate of raw materials is necessary to ensure uniform mixtures.

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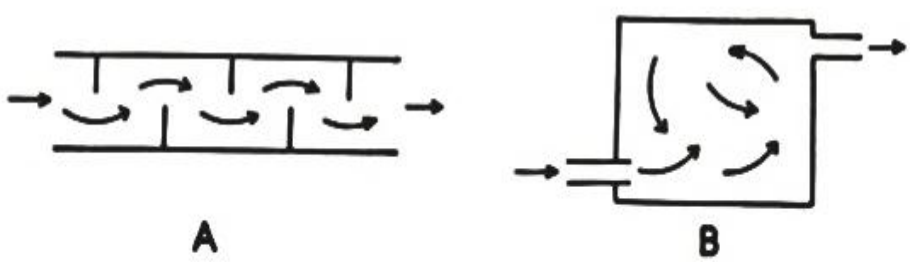

FIG. 1-5. *Continuous fluids mixing devices. A, Baffled pipe mixer; B, mixing chamber with flow induced recirculation.*

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Types of mixers used for liquids and suspensions

•On an industrial scale, solutions are prepared in large mixing vessels with ports for mechanical stirrers.

•When heat is desired, thermostatically controlled mixing tanks may be used.

FIGURE 13.1 Large-scale pharmaceutical mixing vessels. (Courtesy of Schering Laboratories.)

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Mixing of semisolids

- Semisolids, unlike liquids and powders, do not flow easily.
- The suitable mixers must have rotating elements with narrow clearances between them selves and the mixing vessel to avoid dead spots

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Types of mixers for semisolids

1) Planetary mixers
2) Sigma blade mixer
3) Vessels (tanks) with counter-rotating mixing bars

- 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 <u>roller mill or colloid mill</u>, so as to 'rub out' these particles by the intense shear generated by rollers or cones set with a very small clearance between them.

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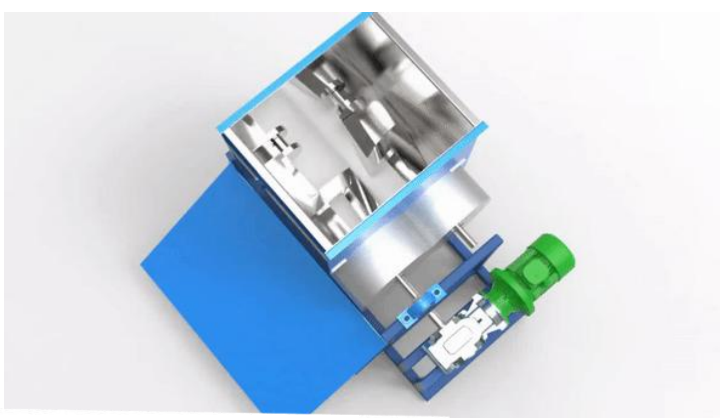

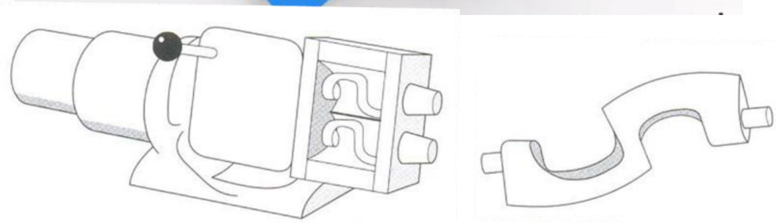

Fig. 13.15 Sigma blade mixer.

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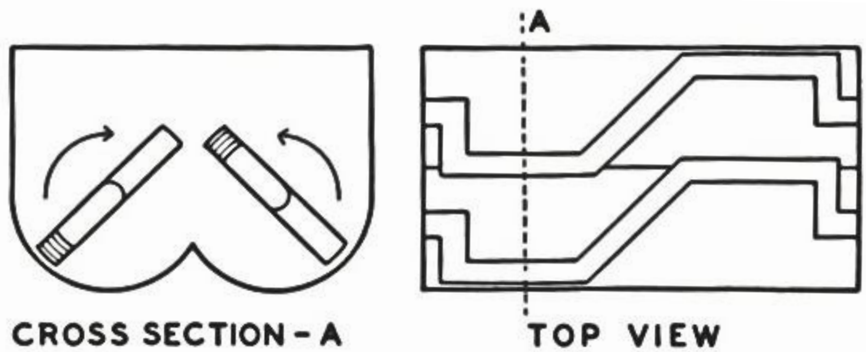

FIG. 1-8. *Schematic drawing of a top-loading sigma-blade mixer with overlapping blades. The top view shows the relationship of the counter rotating blades to the overall geometry of the mixer.*

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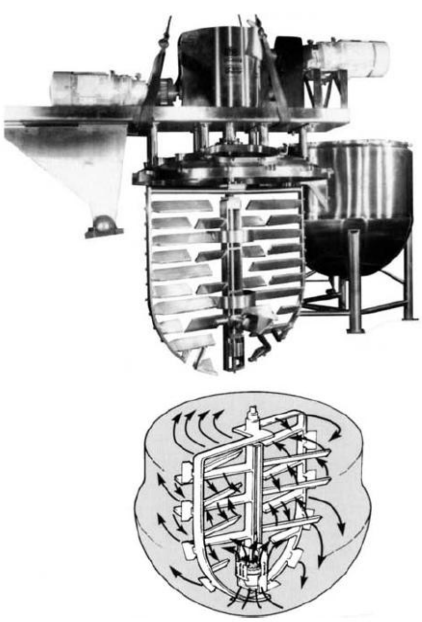

Fig. 5 Large-scale manufacturing unit (Tri-mix Turboshear) with counter-rotating mixing bars. (Courtesy of Lee Industries, Inc., Philipsburg, Pennsylvania.)

Stainless steel tank, which
has counter sweep agitation and a
built-in homogenizer.

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