Mechanism of mixing of solids

1. Convective mixing/Macro mixing:

Inversion of the powder bed using blades or paddles or screw element, in which large mass of material moves from one place to another.

2. Shear mixing:

In this type, forces of attraction are broken down so that each particle moves on its own between regions of different components and parallel to their surface.

3. Diffusion mixing/Micro mixing:

Involves the random motion of particle within the powder bed, thereby particles change their position relative to one another.

Mixing process - steps

- In the solid-solid mixing operations , four steps are involves. These are:

1. Expansion of the bed of solids
2. Application of 3-dimensional shear forces to the powder bed.
3. Mix long enough to permit true randomization of particles.
4. Maintain randomization.

The law of mixing appears to follow first order,

$$M = A\,(1 - e^{-kt})$$

Where M = degree of mixing after time t,

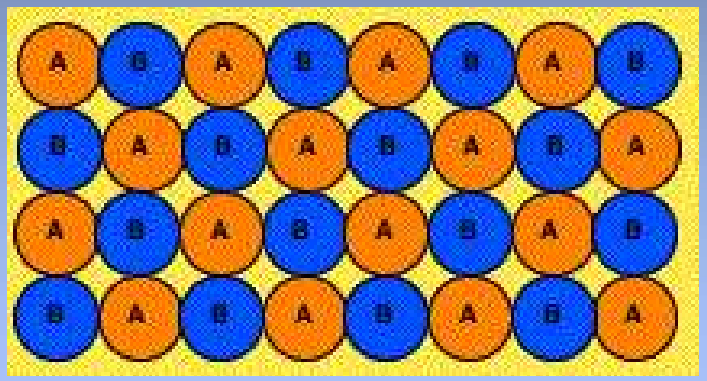
T = time

A and k = constants

- A and k depends on the
  - ✓ Mixer geometry
  - ✓ Physical characteristics of the powders and
  - ✓ Proportion of the material being mixed.

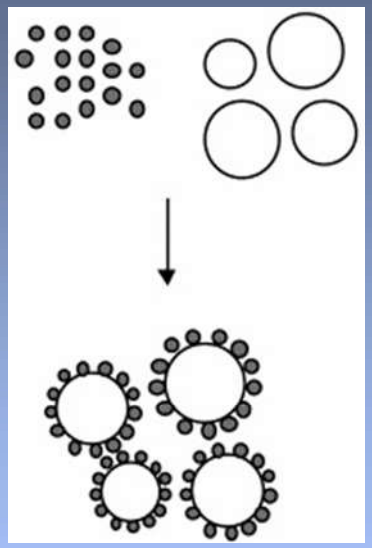
Degree of mixing

- Ideal mixing or perfect mixing:



- Acceptable mixing:
  1. Random mixing
  2. Ordered mixing
     - Mechanical means of ordered mixing
     - Adhesion means of ordered mixing
     - Coating means of ordered mixing

Adhesion means of ordered mixing:



Coating means of ordered mixing:

Statistical parameters

Arithmetic mean:

Size distribution is calculated

$$\text{Arithmetic mean } \bar{y} = \sum_i^n \frac{y_i}{n}$$

Standard deviation:

Used to know the spread of dispersion.

$$\text{Standard deviation } \sigma = \sqrt{\frac{\sum_i^n (y_i - \bar{y})^2}{(n-1)}}$$

- Mixing should be continued until the amount of the active drug that is required is with in ± 3 SD units that of found by assay in a representative number of sample dose.

Relative standard deviation:

- It replace the S.D as a measure of sample uniformity.
- Useful for comparing the efficiency of two or more mixing operations or different sample size or different composition.

$$percent\ relative\ S.D = \frac{standard\ deviation(\sigma)}{mean(\bar{y})}\ X\ 100$$

Mixing indices

- Involves the comparison of SD of sample of a mixture under study with the estimated standard deviation of a completely random mixture.
- It can be expressed in two ways:-

$$M = \frac{\sigma_R}{\sigma} \quad \text{or} \quad M = \frac{\sigma_o - \sigma}{\sigma_o - \sigma_R}$$

Where,

M = *mixing index*

σ_R = *standard deviation of the random blend*

σ = *standard deviation of the sample blend*

σ_o = *standard deviation of the unmixed powder*

Statistical evaluation

Objectives:

- To compare the efficiency of two or more mixing operations.
- To compare the efficiency of two or more equipment.
- To follow the mixing process with time.
- To optimize processing parameters
- To investigate the mechanism of mixing in a given piece of equipment.

Sample size:

- Approximately a unit dose of the final product.

Number of samples:

- Required – 30
- Ideal – 100
- Economical sampling – 20

Sample collection:

- At different intervals when the blend is in motion.
- After blending is completed

Sample utilization:

- Scooping sampling
- Thief probing

Sampling methods:

- Non destructive
- destructive

Factors influencing mixing

- Nature of the surface
- Density of the particles
- Particle size
- Particle shape
- Particle charge
- Proportion of materials

EQUIPMENT

Criteria:

1. Powder bed should not be filled for more than 60%
2. Particles should be subjected to movement in three directions
3. Shearing force should be sufficient to prevent aggregation.
4. There should be no centrifugal effect
5. Forces should not cause breakage of the particles.
6. The mixing process should be stopped abruptly.

Classification of equipment for solid mixing

- Based on **flow properties**:
  1. Free flowing solids:
     e.g.: V cone blend , Double cone blender
  2. Cohesive solids:
     e.g.: Sigma blender, Planetary mixer
- Based on **scale of mixing**:
  1. Batch type(small scale):
     e.g.: Mortar and pestle, V cone blender, Double cone blender, Ribbon blender, Sigma blender, Planetary paddle, Fluidized mixer
  2. Continuous type(large scale):
     e.g.: barrel type, zigzag type

S.no.	Nature of mixer	Examples	Mechanism of mixing
1	Batch type	Mortar pestle	Trituration
2	Tumbling mixers or cylindrical mixers with no mixing blade	Double cone blender V cone blender	Tumbling action
3	Tumbling mixer with a mixing blade	V cone blender double cone blender	Tumbling action as well as shearing with blade
4	Static mixers	Ribbon blender Sigma blender Planetary paddle	Stationary shell and rotating blade
5	Air mixers or fluidized mixers	Fluidized mixer	Air supported blending
6	Continuous type	Barrel type Zigzag type	Rotating shell with rotating blade

Tumblers or cylindrical blenders with no mixing blade

- Meant for dry powders
- Equipment consists of a container of any geometric form.
- Container is mounted on special roller so that it can be rotated about any axis.
- Edge of 27 degrees is good for mixing.
- Efficiency of a tumbler mixer highly depends on the speed of rotation. It should be critical and optimum.
- Slow rotation- no intense tumbling, No cascade motion, Not enough shear rates are applied.
- Rapid rotation-sufficient centrifugal action to the powder to the side of the mixer, more dusting and segregation of fines is possible.
- Rate of rotation depends upon size , shape of the tumbler and nature of the material to be mixed. Common range is 30-100rpm.
- Mixing is done by tumbling motion, which is accentuated by virtue of the shape of the container.

Twin shell blender or V cone blender

- It is V shaped and made up of stainless steel or transparent plastic.
- Material is loaded through shell hatches and emptying is normally done through and apex port.
- The material is loaded approximately 50-60% of the total volume.
- Small models – 20 kg , rotate at 35rpm
- Large models – 1 ton, rotate at 15rpm
- As the blender rotates , the material undergoes tumbling motion.
- When V is inverted, the material splits into two portions. This process of dividing and recombining continuously yields ordered mixing by mechanical means.

Double cone blender

- It consists of double cone on rotating shaft.
- It is usually used for small amount of powders.
- It is efficient for mixing powders of different densities.
- Material is loaded and emptying is done through the same port.
- The rate of rotation should be optimum depending upon the size, shape of the tumbler and nature of the material to be mixed.
- The rate of rotation commonly ranges from 30-100rpm.
- Mixing occurs due to tumbling motion.

Double cone blender

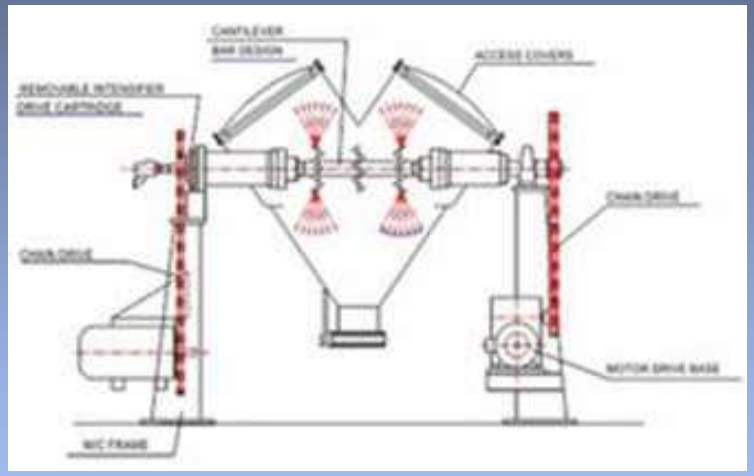
Advantages of V cone blender and double cone blenders:

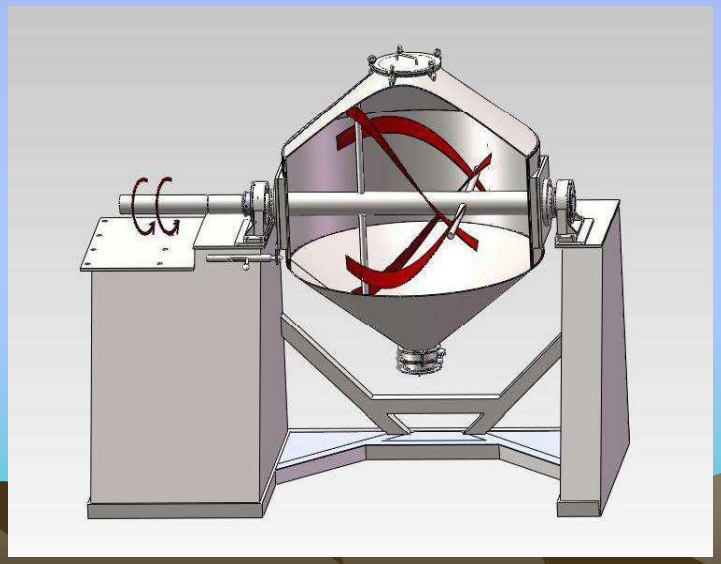
- If fragile granules are to be blended, twin shell blender is suitable because of minimum attrition.
- They handle large capacities.
- Easy to clean , load, and unload.
- This equipment requires minimum maintenance.

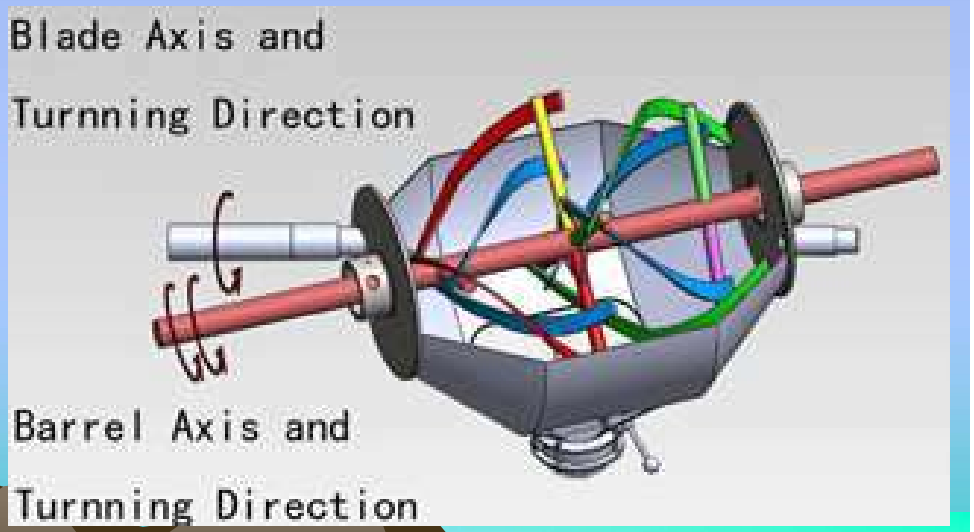
Disadvantages of V cone blender and double cone blenders:

- Twin shell blender needs high headspace for installation.
- It is not suitable for fine particulate system or ingredients of large differences in the particle size distribution, because not enough shear is applied.
- If powders are free flowing, serial dilution is required for the addition of low dose active ingredients.

Tumbling blenders with agitator mixing blades







Advantages of tumblers with blades:

- Baffles are useful for both wet and dry mixing.
- Wide range of shearing force can be applied with agitator bars permitting the intimate mixing of very fine as well as coarse powders.
- Serial dilution is not needed when incorporating low-dose active ingredients.

Disadvantages of tumblers with blades:

- Attrition is large, size reduction of friable particles results.
- Scale-up can prove a problem, because general principles of scale-up do not work
- Cleaning may be a problem, because agitator assembly must be removed and the packing should be replaced for a product changeover
- Potential packing (sealing) problems occur.

Ribbon blender

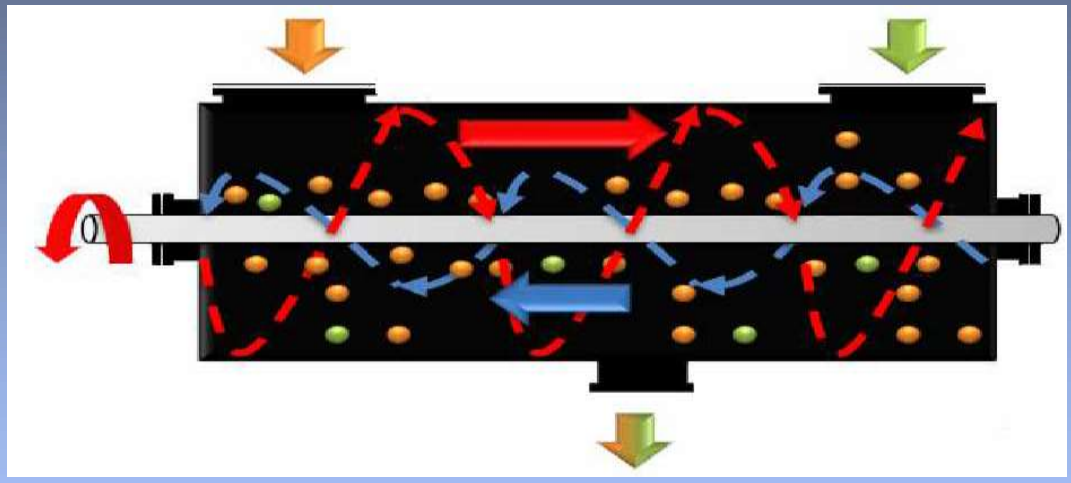
Principle:

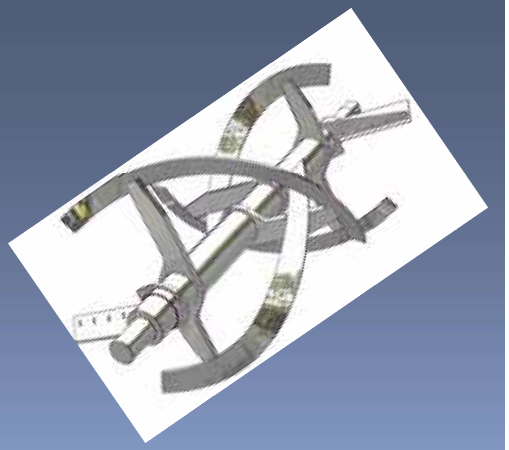
Mechanism of mixing is shear. Shear is transferred by moving blades. High shear rates are effective in breaking lumps and aggregates. Convective mixing also occurs as the powder bed is lifted and allowed to cascade to the bottom of the container. An equilibrium state of mixing can be achieved.

Construction:

- Consists of horizontal cylindrical trough usually open at the top. It is fitted with two helical blades, which are mounted on the same shaft through the long axis of the trough.
- Blades have both right and left hand twists.
- Blades are connected to fixed speed drive.
- It can be loaded by top loading and emptying is done through bottom port.

Working:





Uses:

- Used for mixing of finely divided solids, wet solid mass, and plastic solids.
- Uniform size and density materials can be easily mixed.
- Used for solid – solid and liquid – solid mixing.

Advantages of ribbon blender:

- High shear can be applied by using perforated baffles, which bring about a rubbing and breakdown aggregates.
- Headroom requires less space.

Disadvantages of ribbon blender:

- It is a poor mixer, because movement of particles is two dimensional..
- Shearing action is less than in planetary mixer.
- Dead spots are observed in the mixer, though they are minimum.
- It has fixed speed drive.

Sigma blade mixer

Principle – shear. Inter meshing of sigma blades creates high shear and kneading action.

Construction and working:

- It consists of double tough shaped stationary bowl.
- Two sigma shaped blades are fitted horizontally in each tough of the bowl.
- These blades are connected to a fixed speed drive.
- Mixer is loaded from top and unloaded by tilting the entire bowl.
- The blades move at different speeds , one about twice than the other, which allows movement of powder from sides to centers.
- The material also moves top to downwards and gets sheared between the blades and the wall of the tough resulting cascading action.
- Perforated blades can be used to break lumps and aggregates which creates high shear forces.
- The final stage of mix represents an equilibrium state.

Sigma blade mixer

Uses of sigma blade mixer:

- Used in the wet granulation process in the manufacture of tablets, pill masses and ointments,
- It is primarily used for liquid – solid mixing, although it can be used for solid – solid mixing.

Advantages of sigma blade mixer:

- Sigma blade mixer creates a minimum dead space during mixing.
- It has close tolerances between the blades and the sidewalls as well as bottom of the mixer shell.

Disadvantages of sigma blade mixer:

- Sigma blade mixer works at a fixed speed.

Planetary mixer

Principle:

Mechanism of mixing is shear. Shear is applied between moving blade and stationary wall. Mixing arm moves around its own axis and around the central axis so that it reaches every spot of the vessel. The plates in the blades are sloped so that powder makes an upward movement to achieve tumbling action also.

Construction:

- Consists of vertical cylinder shell which can be removed.
- The blade is mounted from the top of the bowl.
- Mixing shaft is driven by planetary gear and it is normally built with variable speed drive.

Uses :

- Break down agglomerates rapidly.
- Low speeds are used for dry blending and fast for wet granulation.

Advantages:

- Speed of rotation can be varied at will.
- More useful for wet granulation process.

Disadvantages:

- Mechanical heat is buildup within the powder mix.
- It requires high power.
- It has limited size and is useful for batch work only.

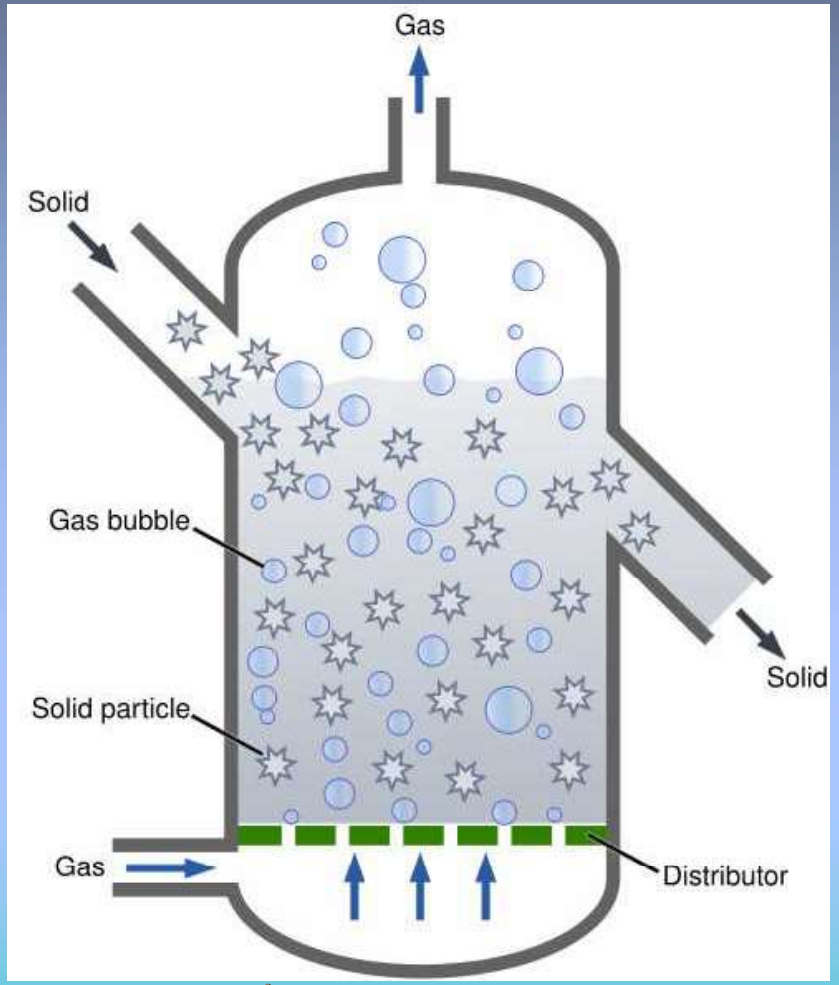
Air mixer or Fluidized mixer

Principle:

The air movement is used for mixing powders. Air is admitted at its base at an angle which gives tumbling action and spiral movements to the powder. Thus mixing is achieved.

Construction:

- It consists of stationary vessel which may be horizontal or vertical which is made up of stainless steel.
- A wire mesh is placed at the bottom of the vessel which acts as support for placing the materials.
- Air is allowed from beneath the mesh and circulated by using a fan.



Advantages of fluidized mixer:

- Reduced mixing time.
- Mixing is intimate and efficient
- Useful for drying and wet massing.
- Also useful for coating with some modifications.

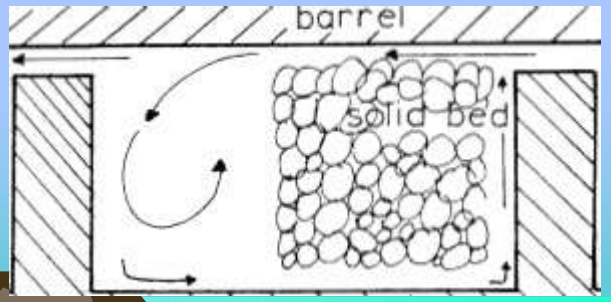
Barrel type continuous mixer

Principle:

Rotating shell keeps the material under tumbling motion. When the material approach the mid-point of the shell, another set of baffles causes part of the material to move towards the direction of inlet end allowing the remaining part to move forward. This process continuous up to discharge end, while another set of baffles guide the material to the discharge port.

Construction:

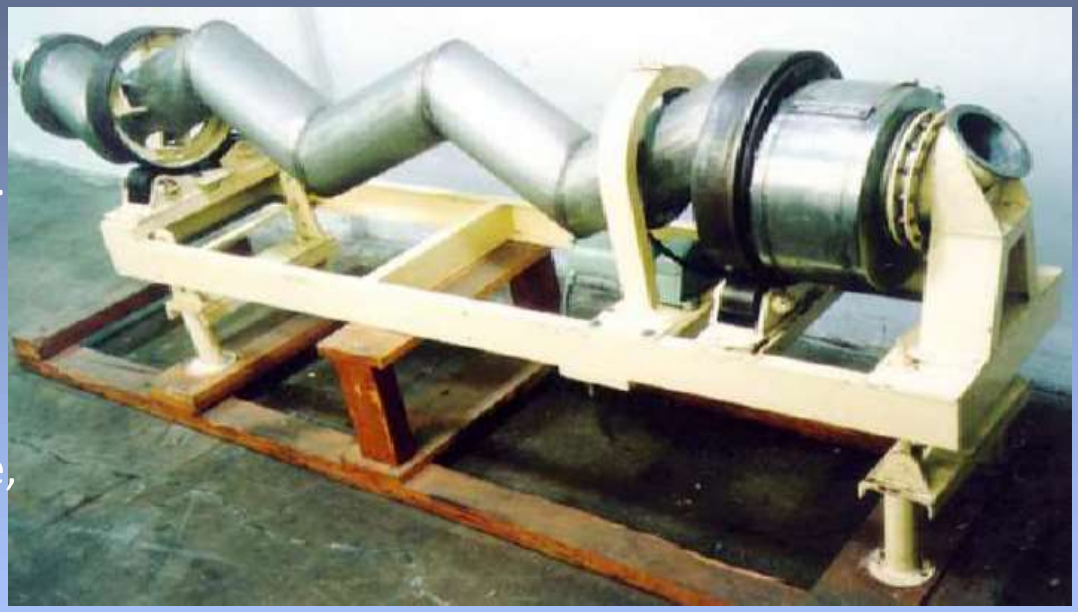
Resembles large cement mixer.
Baffles are fitted to the inner surface of the shell.
Shell is fixed to a shaft, which is allowed to rotate using electrical power.
Side openings are provided on each side for charging and discharging of the material.



Zigzag continuous blender

Principle :

•Material undergoes tumbling motion.
•It is rotating shell type having several V shaped blenders connected in series.
•When V section is inverted the material splits into two portions ; one half moves backward while another half moves forward.
•As the first V section clears the charge, a fresh feed enters, hence used for continuous blending.



Zigzag continuous blender

Construction :

•It consists of a long shell, which takes the shape of several V shaped blenders connected in series.
•At one end of the shell a chamber for feeding is attached.
•The other end allows the discharge of material
•The shell is inclined towards to discharge end.

Applications of solid mixing

- Involved in the preparation of many types of formulations.
- It is also an intermediate stage in the production of several dosage forms.
  - Wet mixing in the granulation step in the production of tablets and capsules.
  - Dry mixing of several ingredients ready for direct compression as in tablets.
  - Dry blending of powders in capsules, dry syrups and compound powders.
  - Production of pellets for capsules.