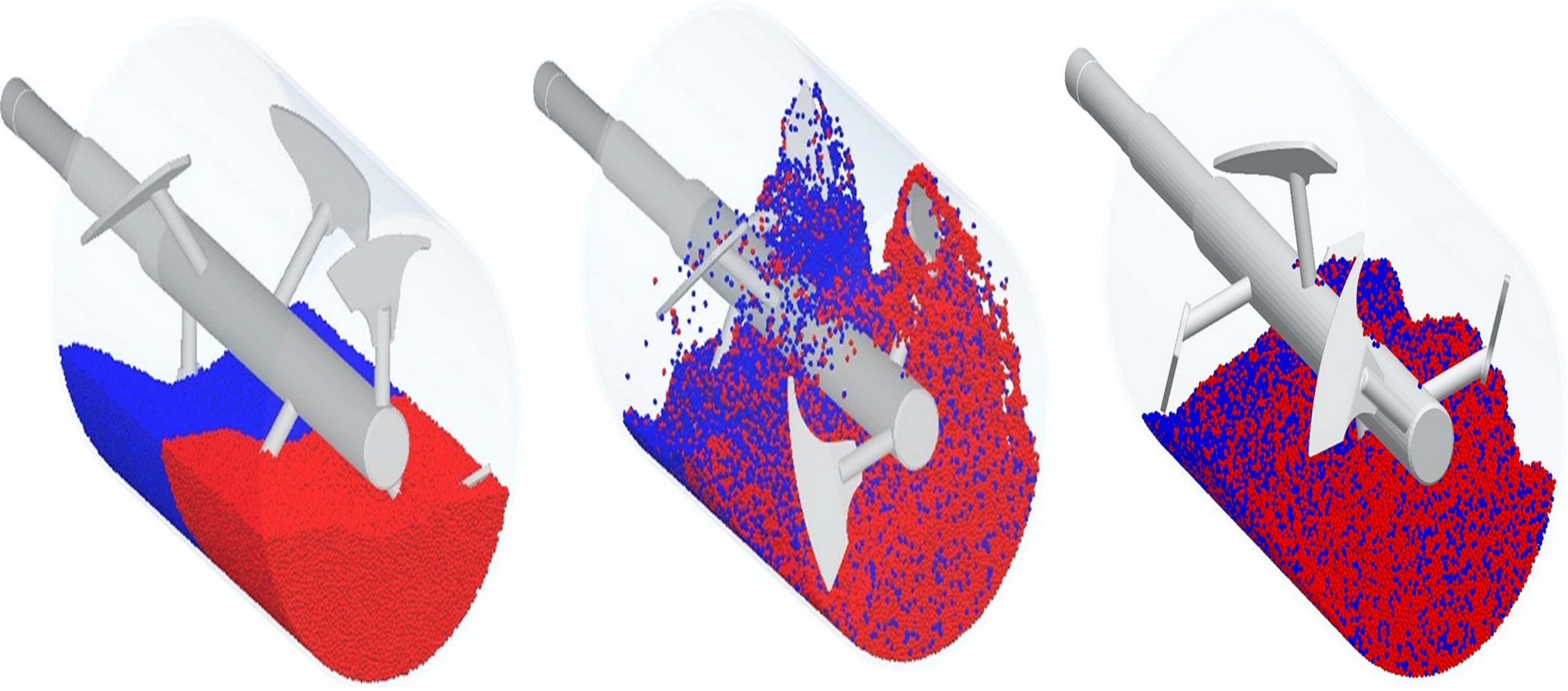
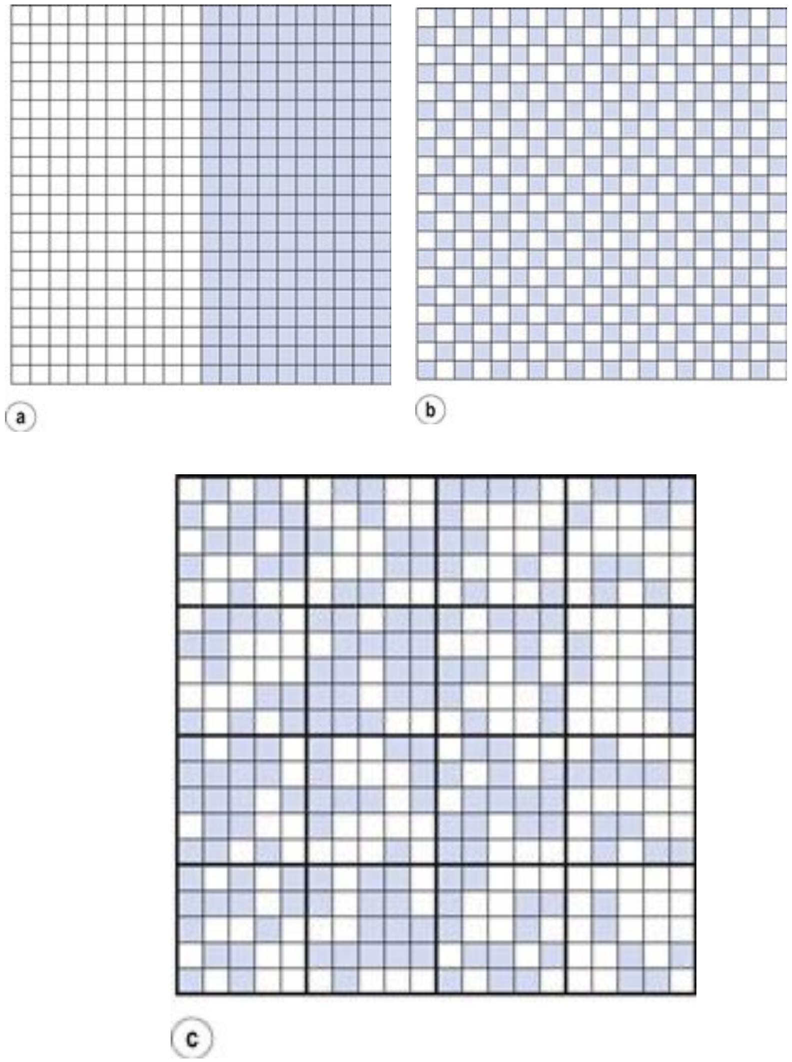


Solids Mixing

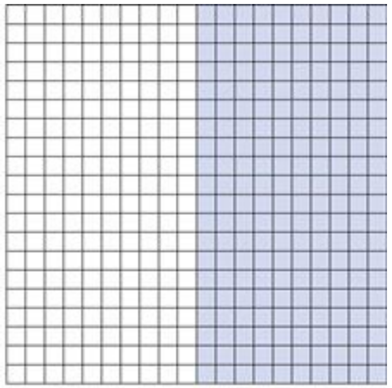
Solid Mixing

- Mixing is considered a critical factor, especially in the **case of potent drugs and low-dose** drugs where high amounts of adjuvants are added.
- Solid mixing is similar to liquid mixing.
- However, it shows some **differences** mainly come from that solid mixture after mixing (and sometimes during mixing) is subjected to **demixing or segregation**.
- The diverse characteristics of particles such **as size, shape, volume, surface area, density, porosity, and flow charge** contribute to the solid mixing.

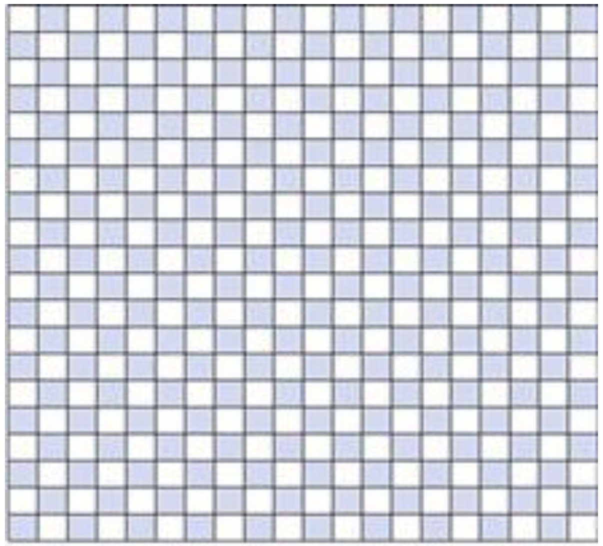


Solid Mixing

- Solid mixing can be represented with the following model where
- **(A)** is a complete segregation state.
- **(B)** is the **Ideal mixing** state (**perfect mix**).
- **(C)** is **Random Mixing**.

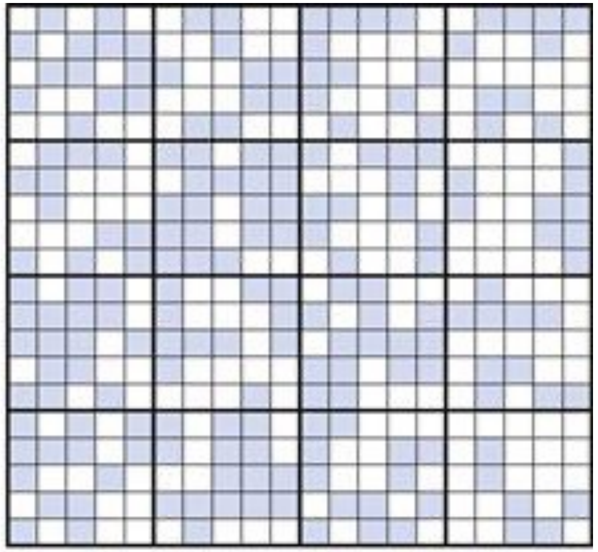


a



b

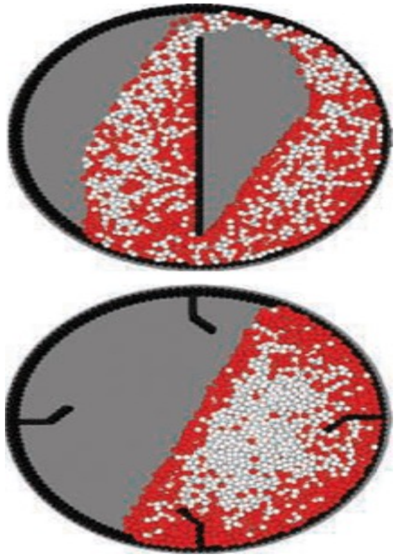
- However, **B (perfect mix)** is virtually **impossible** to get in practice with **any mixing equipment**.
- The best powder mixing process will result in a case of the random mix where the **probability (chance) of finding** one type of particle at any point in the mixture **is equal** to its proportion in the mixture.



c

Practical Consideration in Working with Powder Mixing

- **Segregation or demixing:**
- Segregation is the central problem associated with the mixing and handling of the solid particles,
- The powder can segregate **1-** during **mixing** and/or **2-** during **handling** and **3-** processing after mixing.
- **Causes**: Solids tend to segregate by virtue of differences in the particle **size**, **density**, **shape**, and other properties of the particles of which they are composed.
- **The second requirement for segregation** can be met by the Earth's gravitational field, or by a centrifugal, electrical, or magnetic field **generated in the course of processing**



Factors Affecting Demixing

A. **Particle size and size distribution**: The difference in particle size between the components is the **main cause** of segregation in powder mixes.

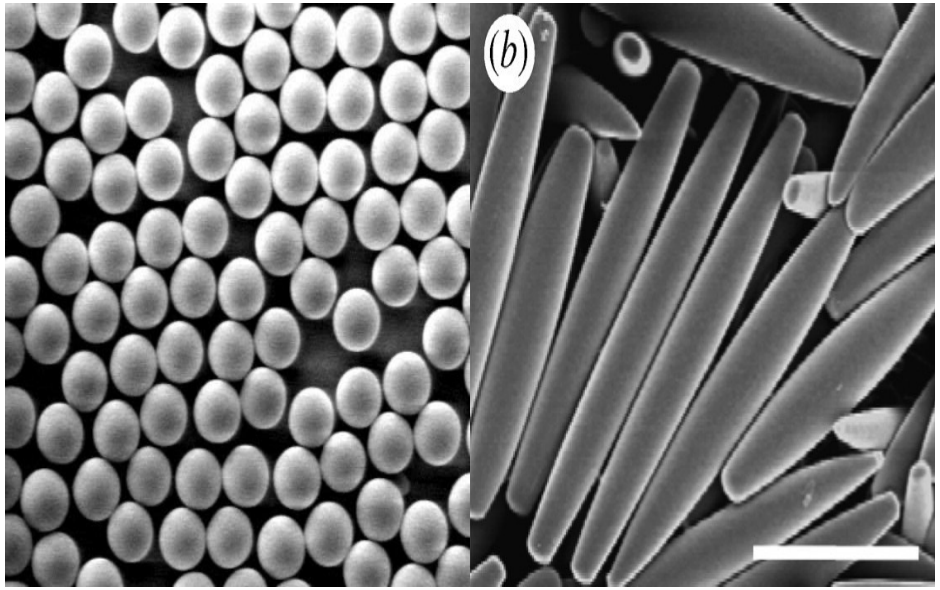
- **Small** particle tends to fill the gaps (void) between larger particles and move toward the **bottom** of the mass.
- **The larger** particle will have higher kinetic energy and will move to a larger distance compared to small particles.
- This segregation problem can be decreased by:

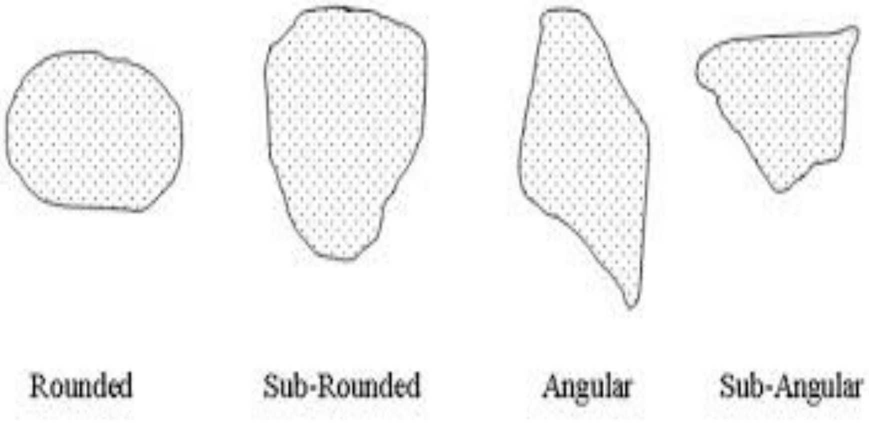
1. Selection of a particle with a **close size** range that can be achieved by sieving (to remove fine or lumps).
2. Milling of the component before mixing to get a homogenous particle size below 30µm, at which size segregation does **not** tend to cause serious problems
3. **Granulation** of the powder mix (enlarging the particle size).

Factors Affecting Demixing

B. Particle shape:

- Particle shape is important because as the shape of a particle **deviates** more significantly from a spherical form, → the free movement it experiences along its major axis also **decreases**.
  - **Spherical** particles exhibit the greatest flowability and are therefore **more easily** mixed **but** they also segregate more easily than non-spherical particles.
  - **Irregular or Needle shaped** particles may become interlocked decreasing the tendency to segregate once mixing has occurred.
- Controlled crystallization during production of the drug/excipients to give components of a particular crystal shape or size range **reduces the tendency** to segregate.





Factors Affecting Demixing

C. Particle charge:

- The mixing of particles whose surfaces are non-conducting (electrically) often results in the **generation of surface charges**, as evidenced by a tendency of the powder to **clump** following a period of agitation.
- Surface charging of particles during mixing is undesirable, for it tends to **decrease** the process of inter-particulate "diffusion."

D. Particle density: (minor problem)

- If components are of different densities, the **denser particles** will have a tendency to **move downward** regardless of their particle size.
- **Most** materials used in the pharmaceutical industry are of close densities and this problem is **not common in powder mixing.**

Mechanism of Mixing (For Solids)

1. **Convective Mixing**: resembles **bulk transport** in fluid mixing.
   - It includes moving a large bulk of solid at once.
   - This can occur by inversion of the powder bed by blades, paddle, a revolving screw, or by inverting the whole container such as in a V-shape mixer.
2. **Shear mixing**: As a result of forces within the particulate mass, slip planes are set up and this gives rise to **laminar flow**.
   - When shear occurs between regions of different compositions & parallel to their interface, it reduces the scale of segregation by thinning the dissimilar layers.
3. **Diffusive mixing:** When a random motion of particles within a powder bed causes them to change position relative to one another. Such an exchange of positions by single particles results in a reduction of the intensity of segregation.
   - Diffusive mixing occurs at the interfaces of dissimilar regions that are undergoing shear and **therefore** results from **shear mixing**.

Equipment

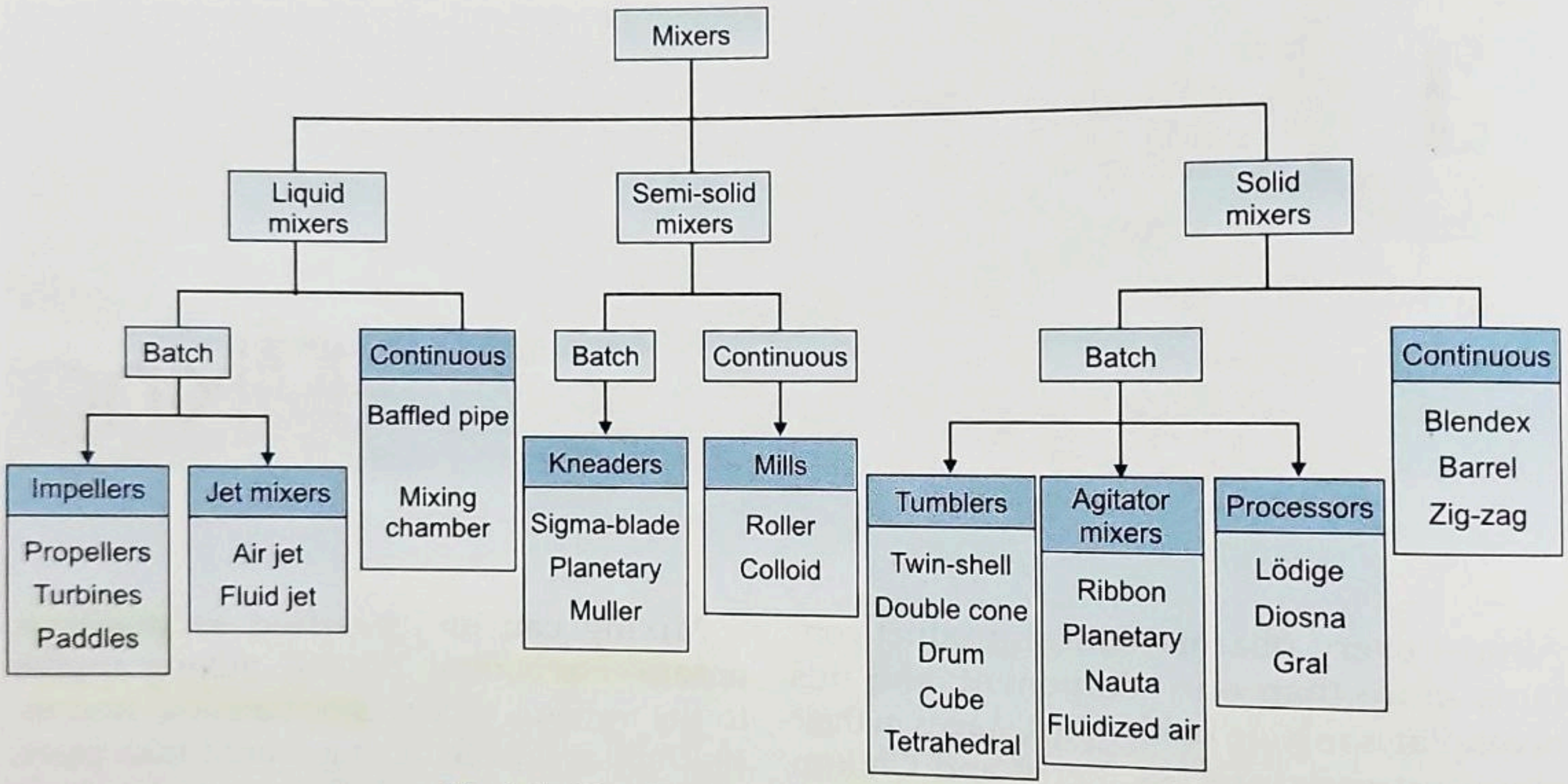


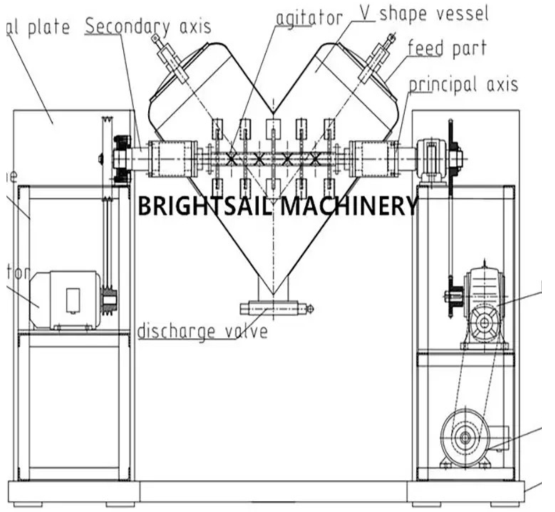
Fig. 1.1: Classification tree of mixing equipments

- **Tumbler/blenders**: consist of a container of different geometrical shapes **rotated** around its axis and cause movement of materials in all planes.
  - The resulting tumbling motion **is accentuated through baffles**, lifter blades, or simply by the shape of the container.
- It can be in different shapes such as **twin shells**, **double cones**, **cubes, drums, and tetrahedral** blenders are commercially available.
- Of these types, the **twin-shape mixer (V-shape** mixer) is the most preferred one, resulting in **satisfactory mixing in a reasonable time**.
- These types of solid mixers are:
  - Efficient, **not** aggressive (good for friable powders),
  - And **preferable** when mixing powders that have different particle sizes

V-Shape Mixer (Twin Shell Mixer)

- It consists of **two cylinders** connected at a 45° angle.
- When rotates, the material is collected to the bottom and then splits into two halves when rotated in the other direction.
    - This is quite effective **because** the bulk transport (convective) and shear, which occur in tumbling mixers, generally are accentuated by this design.
- The rotation speed should be adjusted depending on **1-** the size of the mixer and **2-** the amount of material existing.

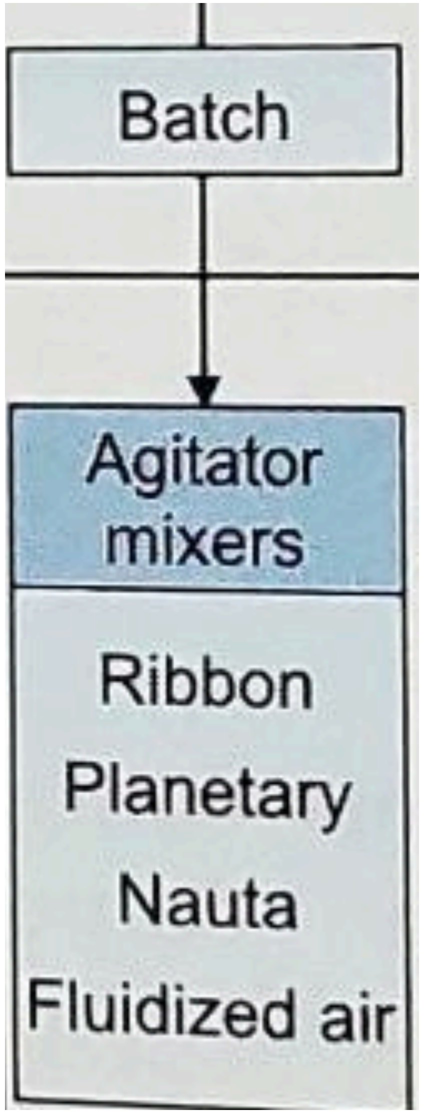
1. **Too slow** rotation results in **no mixing** (insufficient tumbling and does not generate rapid shear rates).
2. **Too fast** results in **centrifugal action** that holds the material to one side of the mixer and results in **no mixing**.



- https://youtu.be/SOoOmhrPLdQ

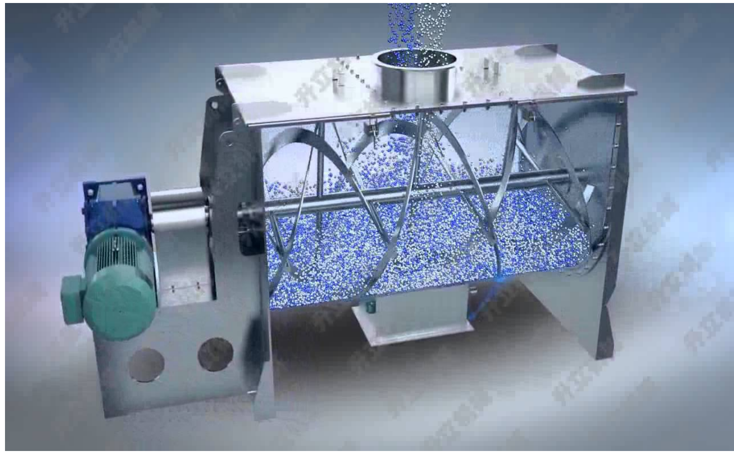
2- Agitator Mixers (batch mixers)

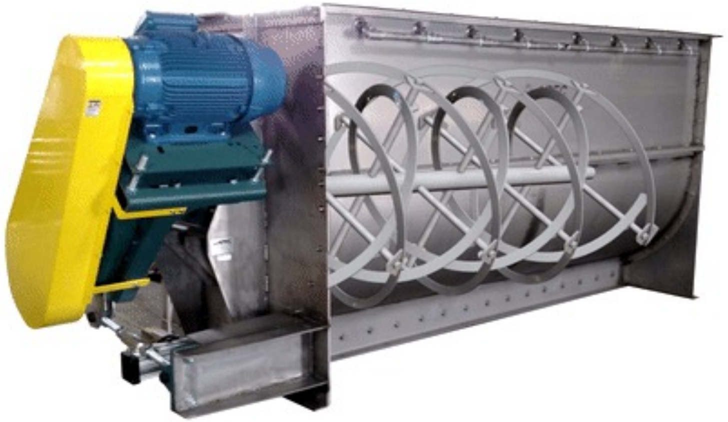
- **Agitator mixers**: consist of a **fixed container** that contains a moving screw, a paddle, or a plate to mix the powder materials.
- These types of mixers are **more effective** in mixing **wet powders** that do not mix well using tumbler mixers. This is because these mixers **do not depend entirely on gravity**.
- The **high shear** forces that are set up are effective in breaking up lumps or aggregates.
- There are **three** types of agitato mixers:



A- Ribbon mixer/blender

- **Design**: Consists of a horizontal cylindrical tank usually opening at the top and fitted with helical blades or ribbons.
- **Operation**: The blades are mounted on the horizontal axle by struts and are rotated to circulate the material to be mixed
- The helical blades are **wound (turned)** (in most cases) in opposite directions to **provide for the movement of material in both directions** along the axis of the tank.
- Although little axial mixing in the vicinity of the shaft occurs, mixtures with high homogeneity can be produced by **prolonged mixing** even when the components differ in particle size, shape, or density, or there is some tendency to aggregate.





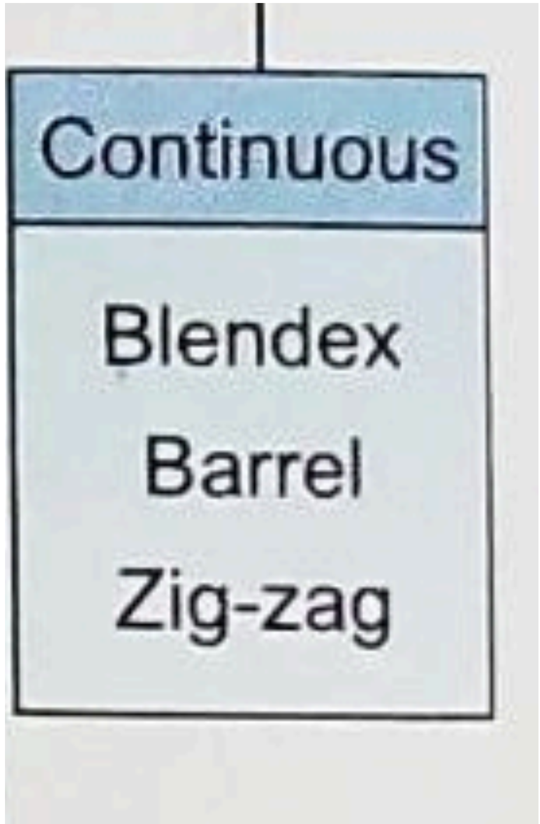
https://youtu.be/7JPSLKW5T_8

3- Rapid Mixer Granulator (batch mixers)

- **Rapid mixer granulator**:
- **Newer models** that can perform **both** wet and dry mixing efficiently in lesser time.
- This means it can perform **dual actions** like **1-** mixing and **2-** tablet granulation which is an important process in tablet formulation.
- An example of these mixers is the **Lödige mixer**.
  - It's a **high-shear** mixer that consists of a horizontal cylindrical shell equipped with a series of **plow-shaped** mixing tools and one or more high-speed **blending chopper** assemblies mounted at the **rear of the mixer**.
- https://youtu.be/I-33cIrn8vc

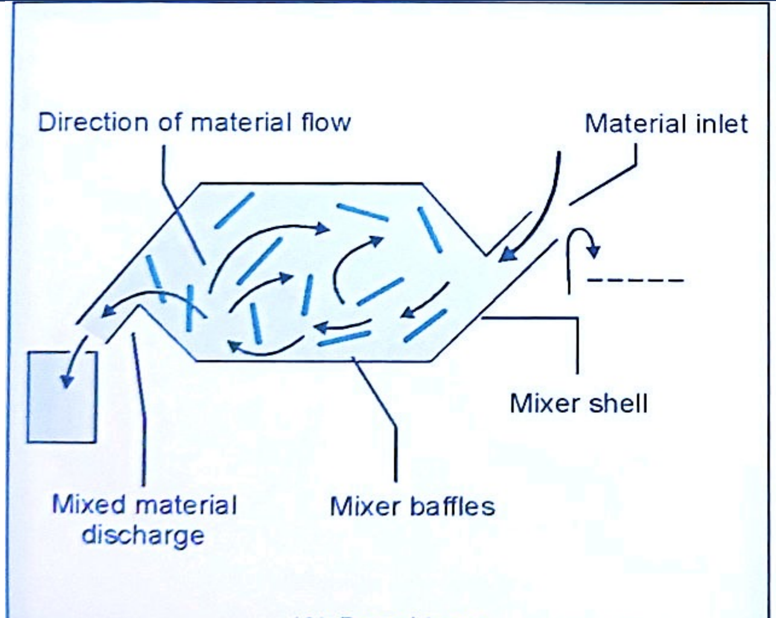
Continuous mixers

- A characteristic of solids mixing equipment is that all else being equal, **but:**
- Mixtures produced by **large mixers** have greater variations in composition than those produced by **small mixers**.
- This is an important consideration when relatively small portions of the mixture are required to fall consistently within a narrow composition range. ➔ it is recommended to use batch mixers for small quantities.
- Continuous mixing processes are somewhat analogous to those discussed under fluid mixing.
- **Metered quantities** of the powders or granules are passed through a device that **reduces both the scale and intensity of segregation**, usually by impact or shearing action.

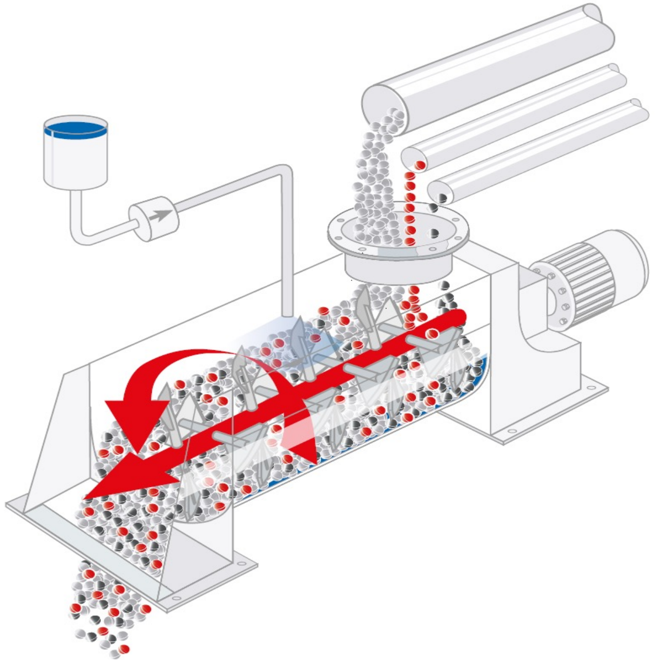


Barrel Type Continuous Mixer

- In this mixer, the material is mixed under a **tumbling motion**.
- The presence of **baffles** further enhances the mixing.
- **Operation**: When the material approaches the midpoint of the shell, a set of baffles causes a part of the material to move **backward**.
- Such a mechanism provides an intense mixing of ingredients

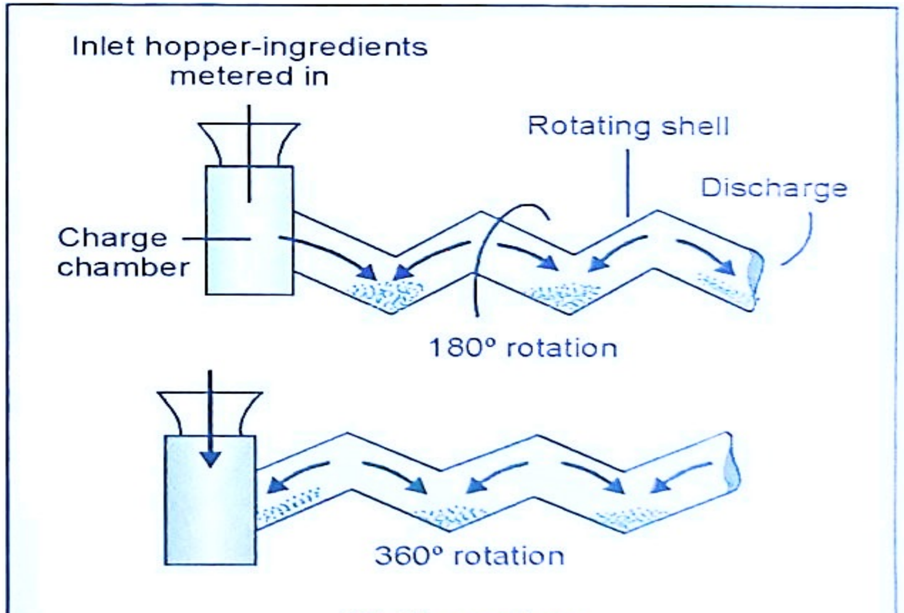


(A) Barrel type



Zig-zag Continuous Blender

- **Design**: It consists of several "V"-shaped blenders connected in series.
- **Operation**: When the blender is inverted, the material splits into two portions, one-half of the material moves **backward**, while the other moves **forward**.
    - In each rotation, a part of the material moves toward the discharge end.

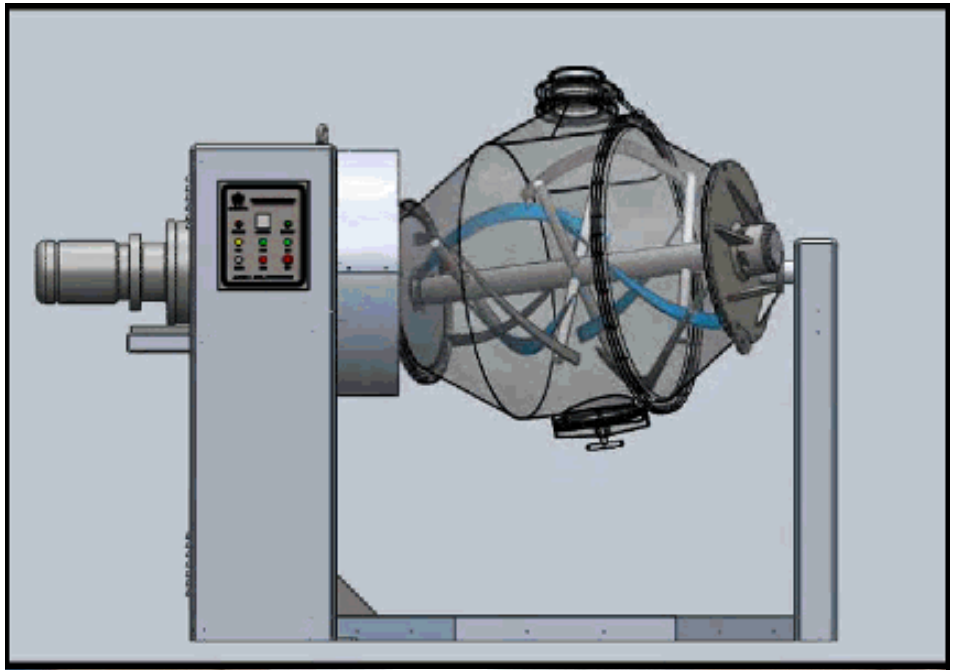


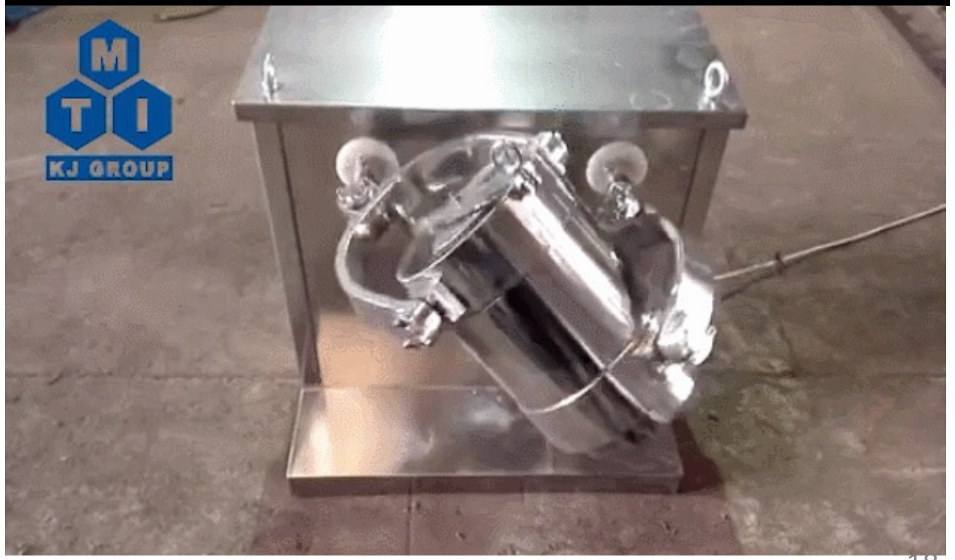
(B) Zig-zag type

Mixer Selection

- **Mixer Properties:**
- An **ideal mixer** should produce a complete blend rapidly with as **gentle (**slow speed**)** mixing action as possible to **avoid product damage**.
- It should be:

1. Dust-tight,
2. Cleaned easily,
3. Discharged easily, and
4. Requires low maintenance and low power consumption.





- **Tumbler Mixers:**

1. Rotating shell mixers suffer from poor cross-flow along the axis. ➔
   - The addition of **baffles or inclining the drum** on the axis increases cross-flow and improves the mixing action.
2. In **cubical and polyhedron-shaped blenders**, due to their flat surfaces, the powder is subjected more to **sliding** than a rolling action, a motion that **is not** conducive to efficient mixing.
3. In double-cone blenders, the mixing pattern provides a **good cross-flow with a rolling rather than sliding motion.**
4. The uneven length of each shell in a **twin-shell** blender provides **additional** mixing action when the powder bed recombines during each revolution of the blender. Twin-shell and double-cone blenders are recommended for precision blending.

Mixer Selection Mixer Properties:

- **Agitator Mixers:**

1. The **shearing action** that develops between moving blades and troughs (the tank) in agitator mixers serves to **break down powder agglomerates**.
2. **Ribbon mixers** are **not precision** blenders and also suffer from the disadvantage of being **1-** more **difficult to clean** than tumblers and **2-** having a higher power requirement.
3. The **1-** mechanical **heat build-up** and **2-** the relatively higher power requirement are the **drawbacks** also associated with **Sigma blades** and **planetary mixers**.
   - However, the shorter time interval necessary to achieve a satisfactory blend may offset these factors.
4. Blendex provides efficient batch and continuous mixing for a wide variety of solids without particle size reduction and heat generation.

Mixer Selection: Material Property

- Powders that are **1- not** free-flowing or **2**- that exhibit high forces of cohesion or adhesion between particles of similar or dissimilar composition are often **difficult** to mix owing to agglomeration.
- The clumps of particles can be broken down in such cases by the use of mixers that generate high shear forces or that subject the powder to impact.
- The use of agitators preferably **planetary** and **sigma blade mixers** is recommended for such powders.
- For **strongly cohesive materials**, it is typically necessary to fragment agglomerates through the introduction of high shear, "intensification," devices such **as agitators or mills** that energetically deform grains on the finest scale.