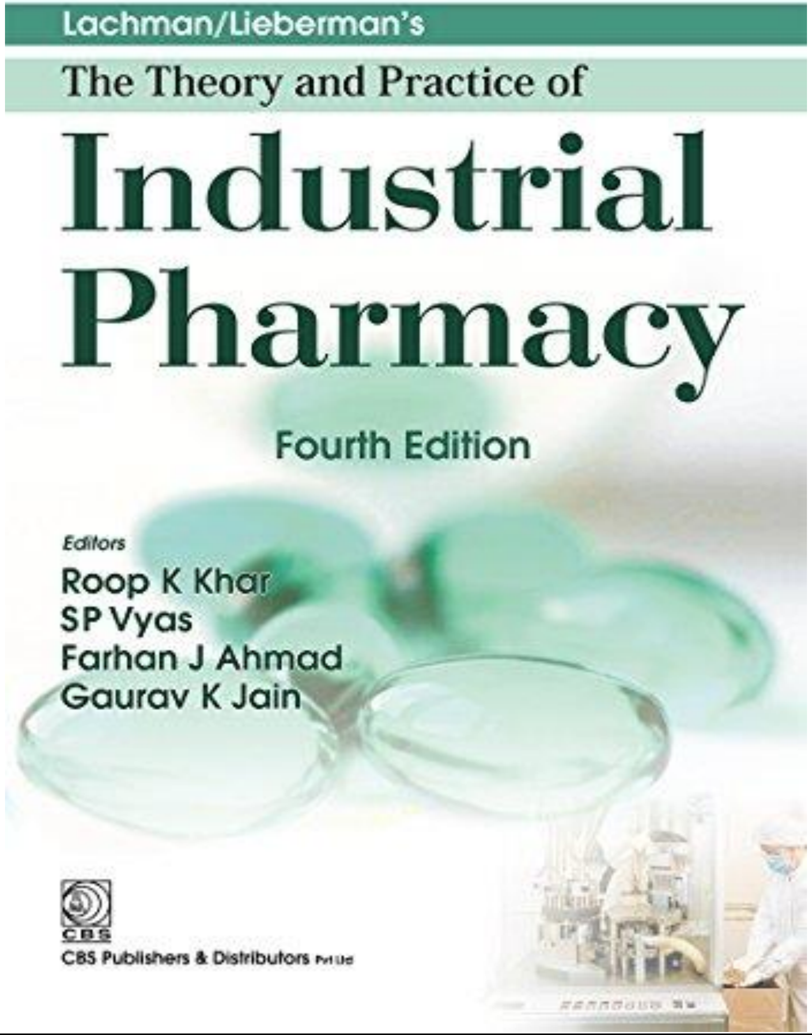
Syllabus

- **Required Textbook**
- **Course meet** Thursdays at 8:30 am – 11:30am // room EC103
- **Course evaluation**: Mid term 20%

  Atten. + Activities 5%

  Lab work: 25%

  Final exam 50%

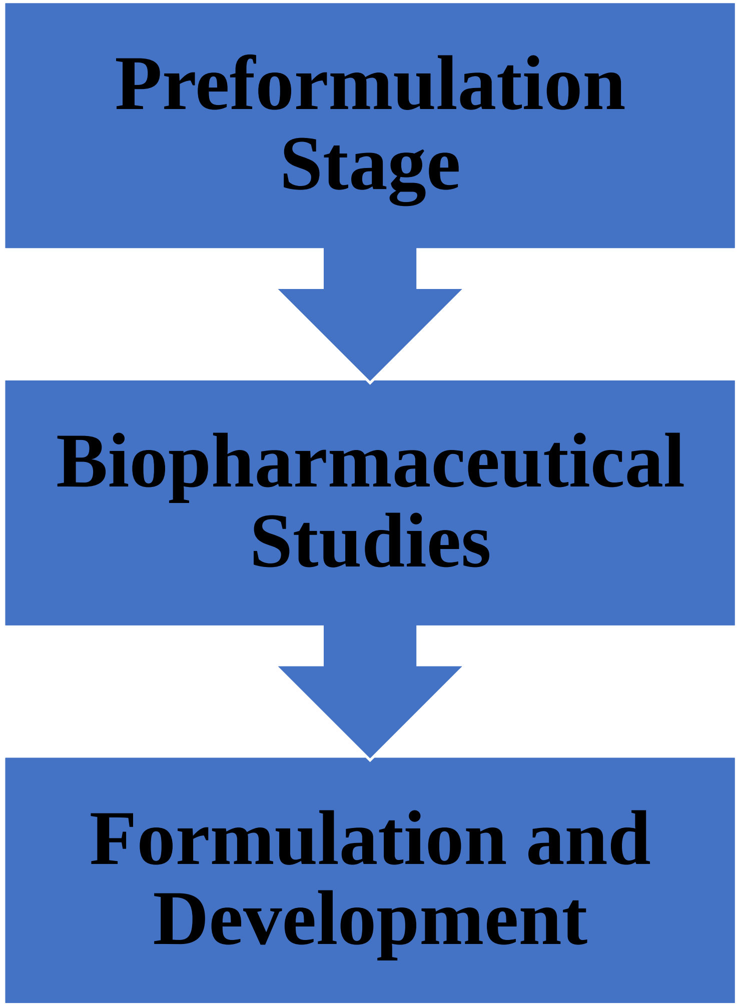


- **Course Goals**:
- Aim to teach pharmacy students the steps in the process of preformulation of pharmaceutical dosage forms .
- This course provides the required principles to integrate knowledge of Pharmaceutical Technology in preformulation of a perfect dosage form.
- It includes milling, mixing, drying and filtration, besides sterilization to achieve a proper processing of dosage forms.

Industrial Pharmacy
Stages in Manufacturing of a Product

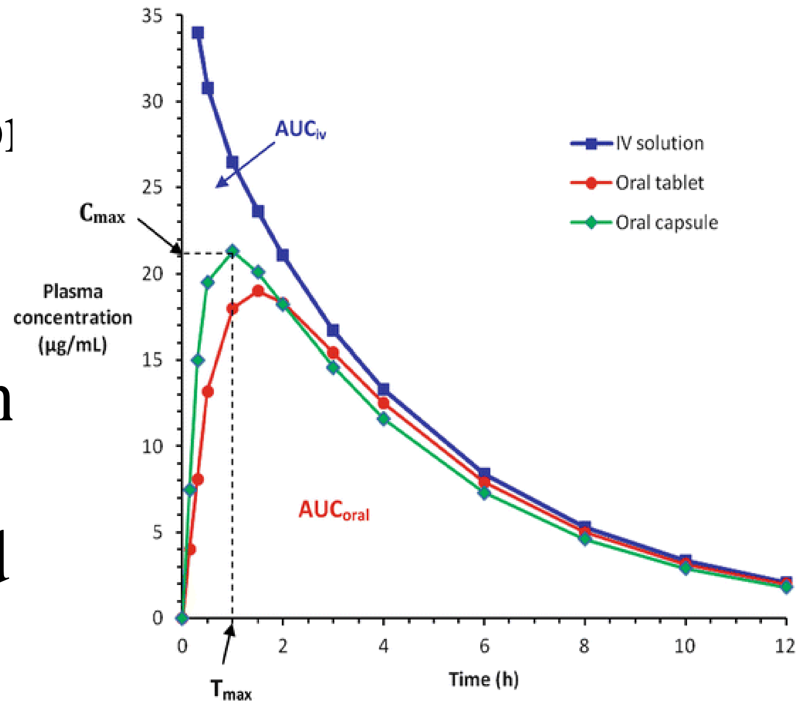
- Industrial pharmacy deals with all processes related to drugs and dosage from starting after drug discovery until the drug expiry date.
- This includes drug development, evaluation, testing, manufacturing, packaging, marketing.
- **Stages in Manufacturing:**
- **A- Pre-formulation stage**: preliminary studies to identify

1. Physical and chemical properties of the medicinal substance will indicate the efficacy and bioavailability of the candidate dosage form.
2. Evaluation of particle size, solubility, stability, excipient compatibility, and crystal/surface properties.



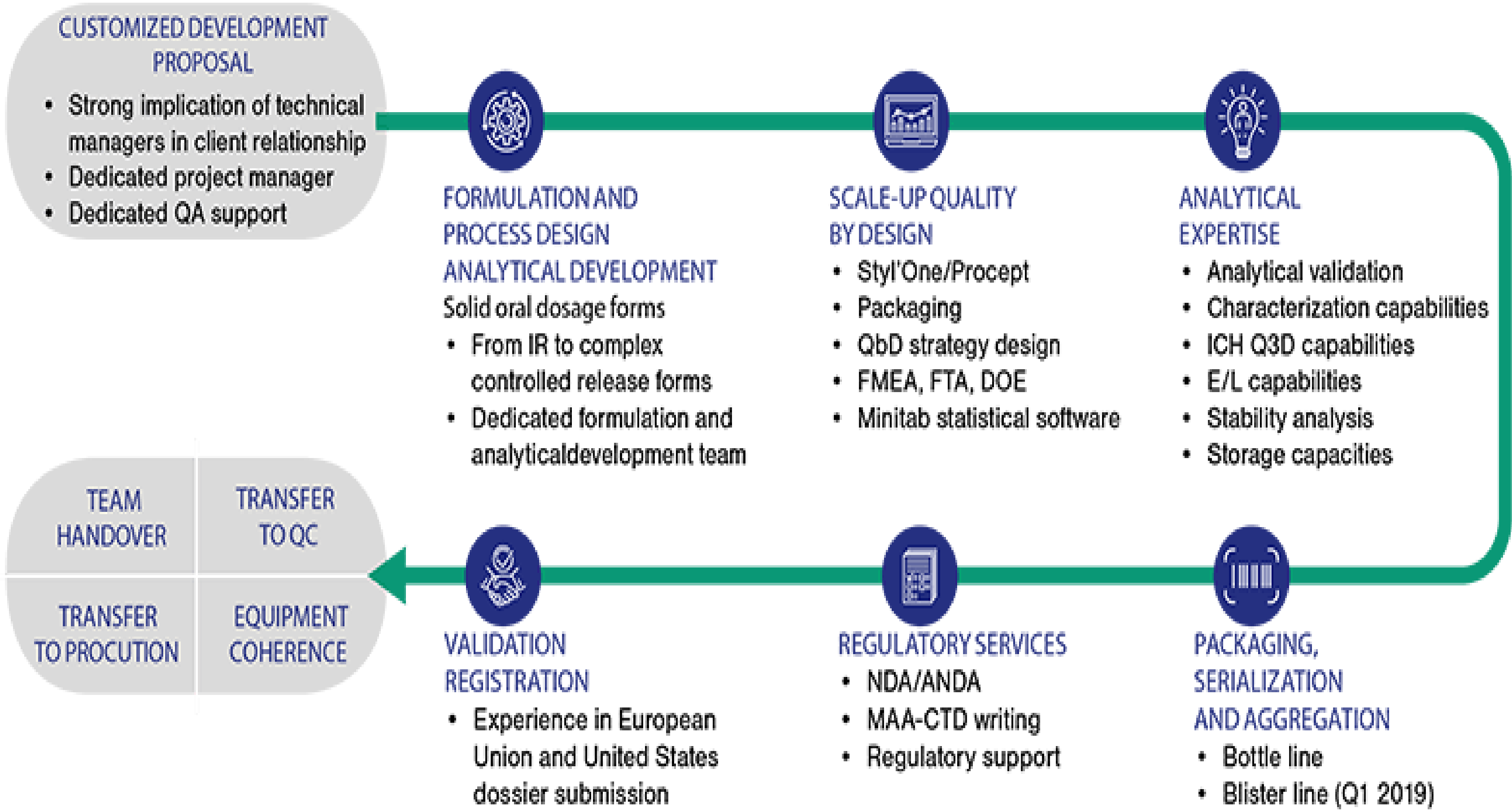
B- Biopharmaceutical studies: to discover the rate and extent to which candidate drug will be available at the site of action, this includes:

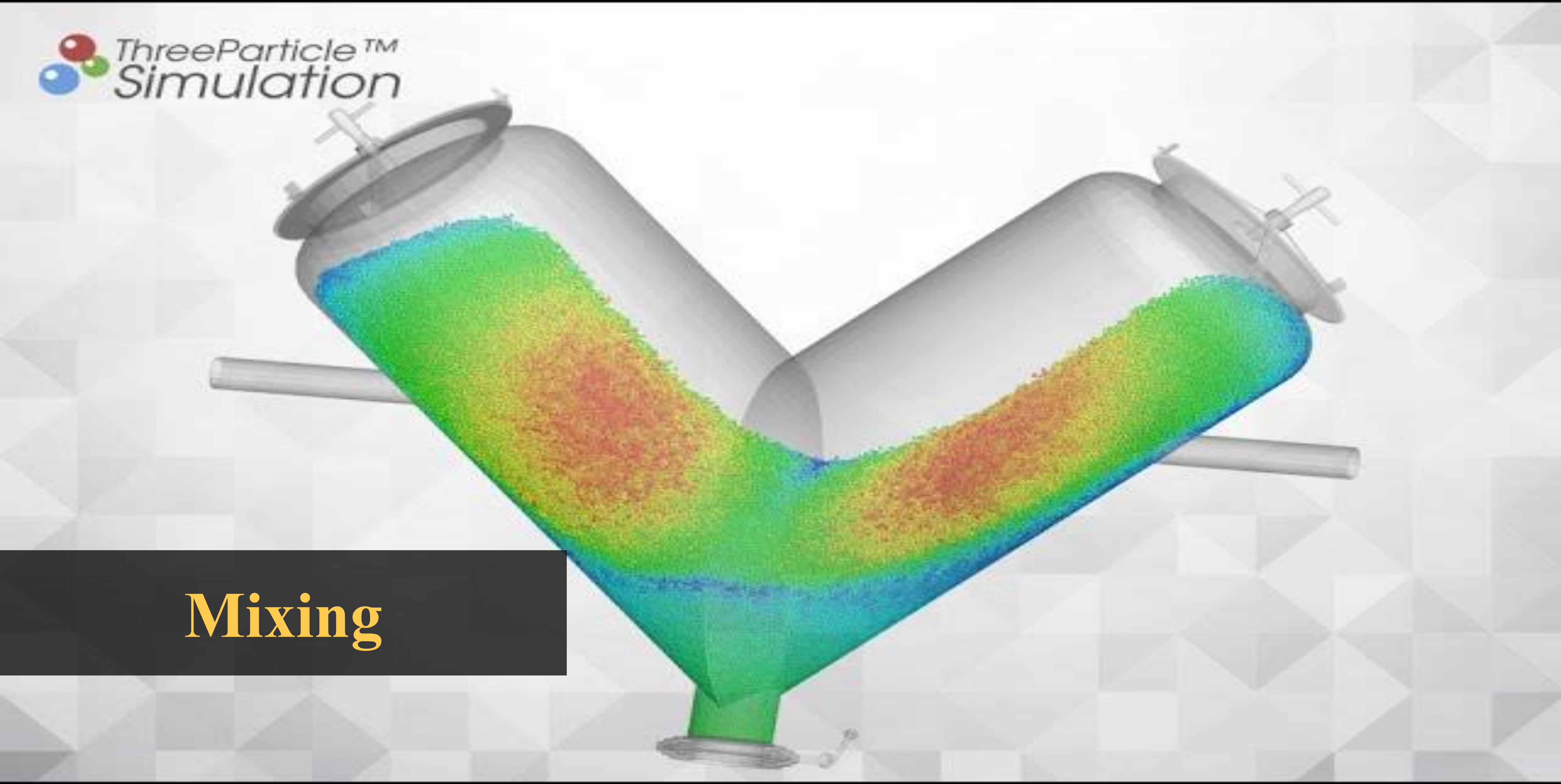
1. **Pharmacodynamic studies**: or the effect of the drug on the body which studies therapeutic effect, toxic effect, and adverse drug reaction.
2. **Product analysis**: make several candidate dosage form and test bioavailability, pharmacokinetic (effect of the body on the drug), preferred dosage form, and required dose.
3. **Other studies**: includes patient compliance, cost of manufacturing, and stability of the final dosage form.



Stages in Manufacturing of a Product

- **C- Formulation and development**: involve the actual formulation of the desired dosage form
- In this course, we will go over some of these processes but we will talk mainly about the science behind the basic processes that we use in all manufacturing procedures such as mixing, milling, drying.

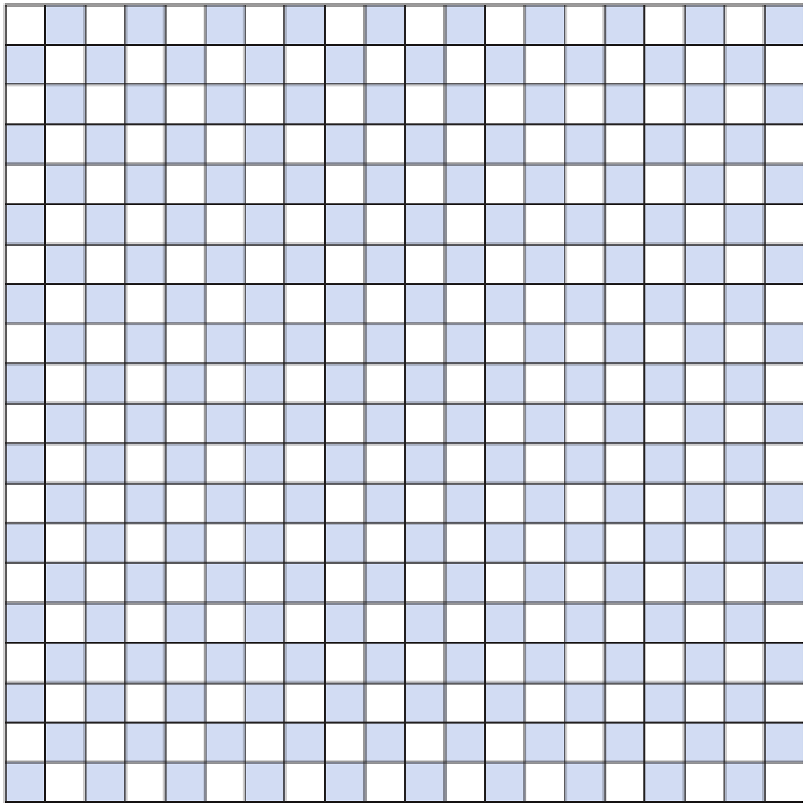




Mixing

Mixing

- A crucial step in the formulation of pharmaceutical dosage form.
- Most pharmaceutical products contain more than one component so they do need mixing.
- Mixing can be **defined** as a process in which two or more ingredients in separate or roughly mixed conditions are retreated so that each particle of any one ingredient is as nearly as possible adjacent to a particle of each other ingredients.
- Good mixing in needed in all pharmaceutical products but it is of special importance in some conditions such as drugs with narrow therapeutic index.



Mixing

Mixing is a fundamental step in most process sequences and is normally carried out for:

1. Ensure **even appearance** of the final dosage form.
2. Ensure **even distribution** of the active ingredients.
3. **Promote** physical and chemical reaction such as dissolution.

Mixing

- **Types of mixture**:
- **Positive mixtures**: such as gases and miscible liquid, where irreversible mixing is happened and no energy is needed to keep mixing state. This type of materials will cause no problem during manufacturing.
- **Negative mixtures**: where mixed component tends to separate out and if that happens quickly, so energy input is required to keep mixing state. For example, suspension dosage form requires regular shaking (energy input) to keep uniformly mixed dosage form.
- **Neutral mixtures**: type of material that will not mix spontaneously but when mixed will not segregate spontaneously such as powders, paste and ointments.

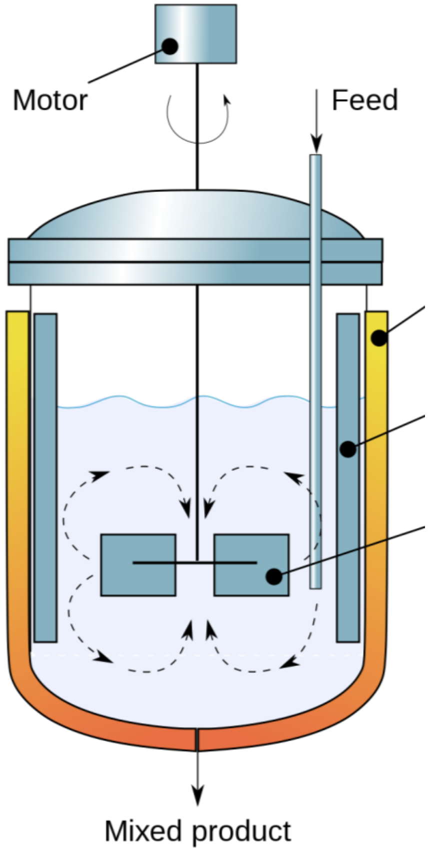
Dosage Form Classification

- Dosage forms can be classified based on their physical form into four types:

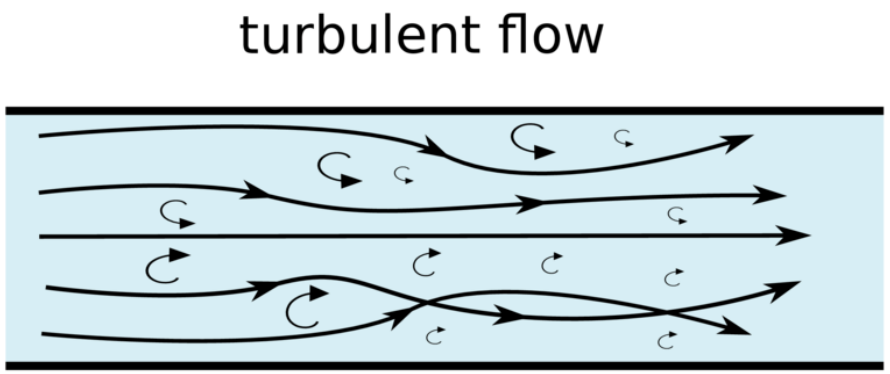
1. Gaseous
2. Liquids
3. Semisolids
4. Solids

Liquid Mixing

- **Mixing Mechanisms:** can be divided into four mechanisms and usually more than one of them occur in mixing of liquid:
- **First: Bulk transport**
- Movement of **large portion** of liquid to be mixed from one location to another.
- This can be achieved by for example paddle mixer.
- For efficient mixing the movement should be adequate and in **different direction**.
- However, this mechanism leaves part of liquid within the moving material unmixed.

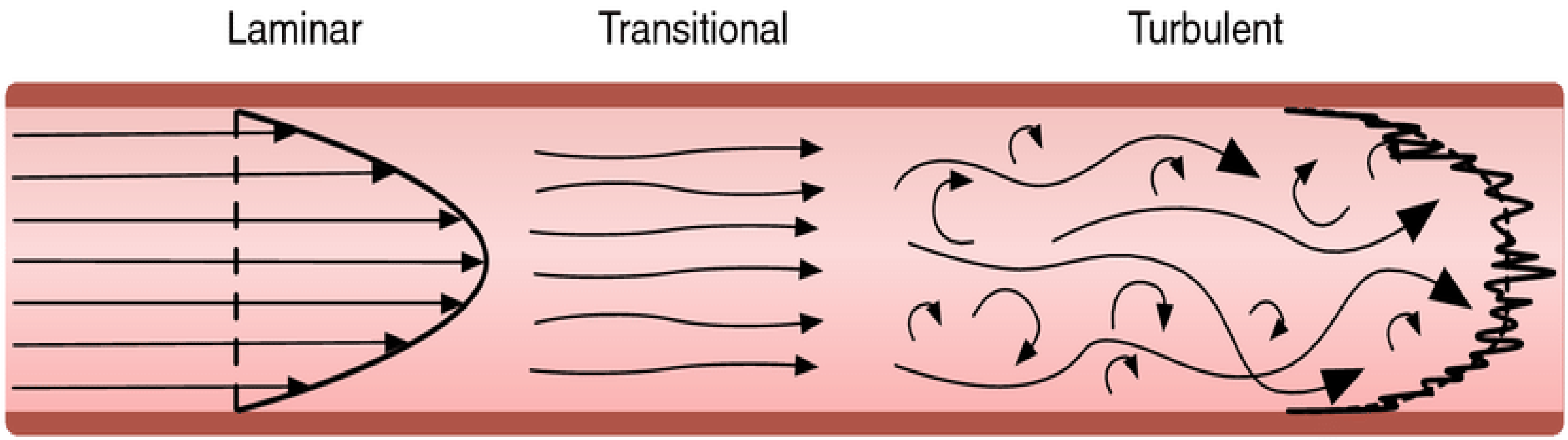


- **Second: Turbulent flow**
- Resulted from turbulent fluid flow which characterized by random fluctuation of fluid velocities at any given point within the system.
- In this mechanism, fluid movement (mixing) can be visualized as a movement of **portions of various sizes (eddies)** that moves together.
- The mixing here **depends on size of eddies** and **velocity** by which it moves.
- This mechanism also leaves part of eddies unmixed within each eddies and **near the liquid surface.**



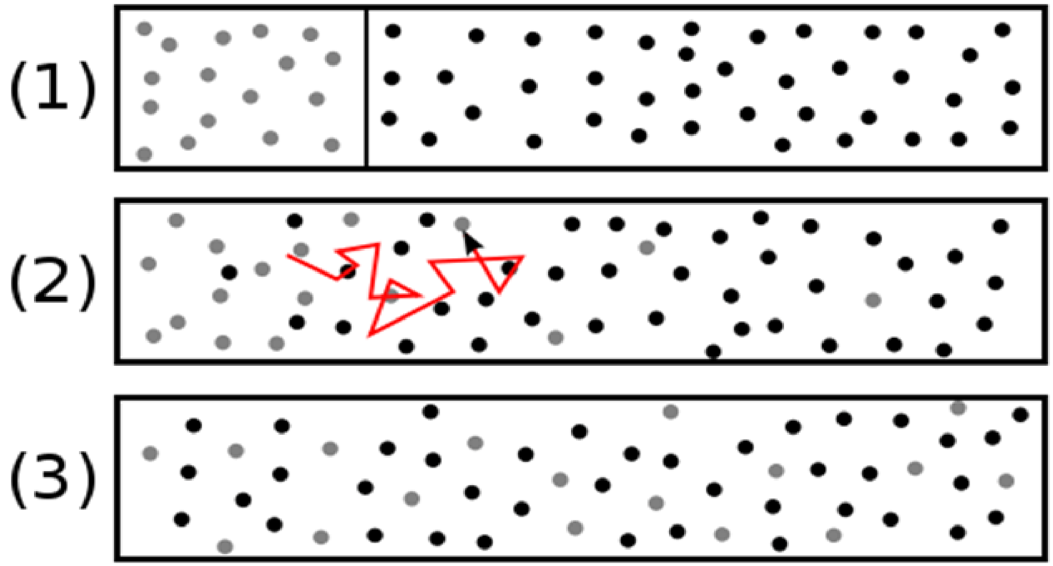
Liquid Mixing

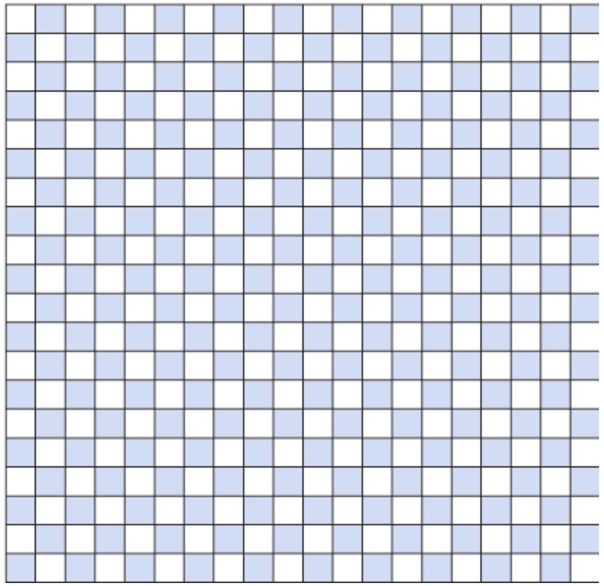
- **Third: Laminar flow**
- This type of flow is happening when mixing **high viscous fluids**.
- This can be described by layers of the fluid is moving into another fluid.
- This kind of mixing is **slow and need longer time** for complete mixing without interference of other mechanisms.



Liquid Mixing

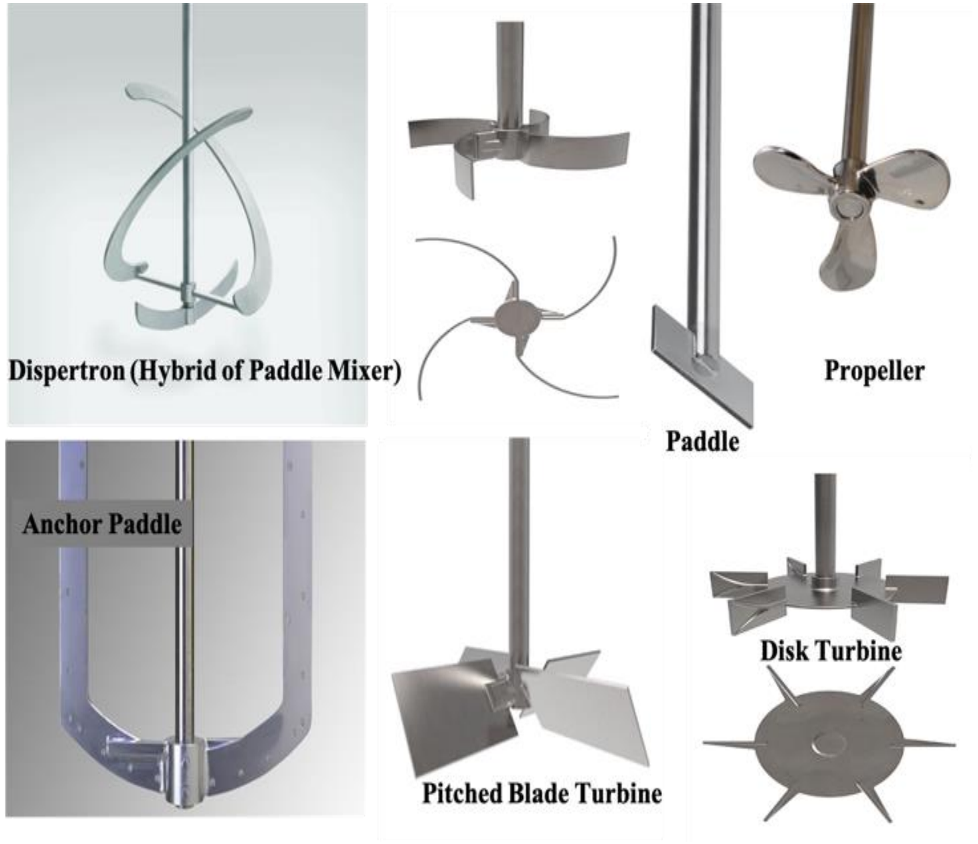
- **Fourth: Molecular diffusion.**
- Mixing of **molecules** of one fluid through another by random molecular motion.
- This is the primary mechanism **responsible for mixing at the molecular level**.
- In this mechanism, molecules move according to the **concentration gradients** until result in complete mixing.





Equipment for Fluid Mixing

- Generally fluid mixers consist of a tank or a container and a suitable **energy transfer tool** such as impeller, liquid jet or air stream.
- **Impellers**: these are the main mixing unit in fluid mixers. It can be either propellers, turbines or paddle. These impellers cause turbulence and prevent the formation of a dead zones.
- **Jet Mixers:**
- **Air Jets**: stream of air or other gasses is used to mix the fluids. Fluids should be of low viscosity, nonfoaming, nonreactive with the gas (or air) and reasonably nonvolatile.
- **Fluid jet**: liquid is pumped at high pressure into the tank.
- https://youtu.be/kobc3DdaofE



Semisolid Mixing

- **Semisolids include**: ointments, paste, creams, gels etc.

1. **Kneaders**:

A. **Sigma-blade Mixer**: contains counter rotating heavy arms that rotate in 2:1 speed ratio (one move faster than the other).

B. **Planetary Mixer**: Provided planetary mixing action where the mixing arm rotates around itself and around the circumference of the container.

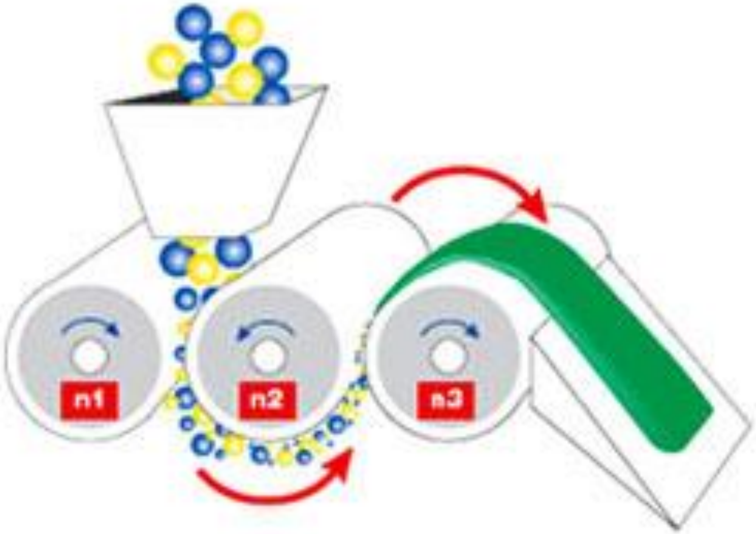
- This two-rotation movement reduces or prevent the formation of **dead zones of mixing.**

Semisolid Mixing

2. Mills

A. **Roller Mills**: Consists of one or more rollers.

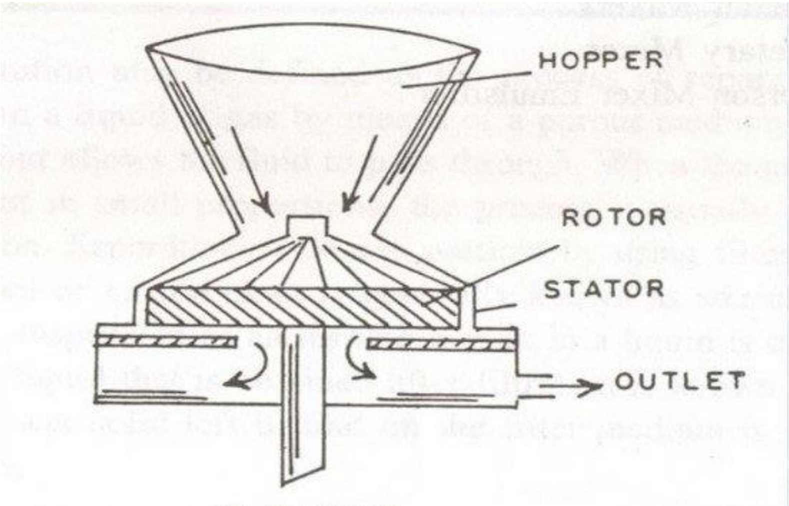
- Usually, **triple roller** system is used.
- Roller is made of **hard abrasion resistance** materials and arranged to come into close proximity to each other and rotated at different rates.
- The **gap** between the rolls **help in particle size** reduction to get smooth and grit free product.
- This type of mixer is applied for **heavy work** like working with **pastes**.



Semisolid Mixing

B. Colloid mills: consist of high-speed rotor and a stator with conical milling surfaces.

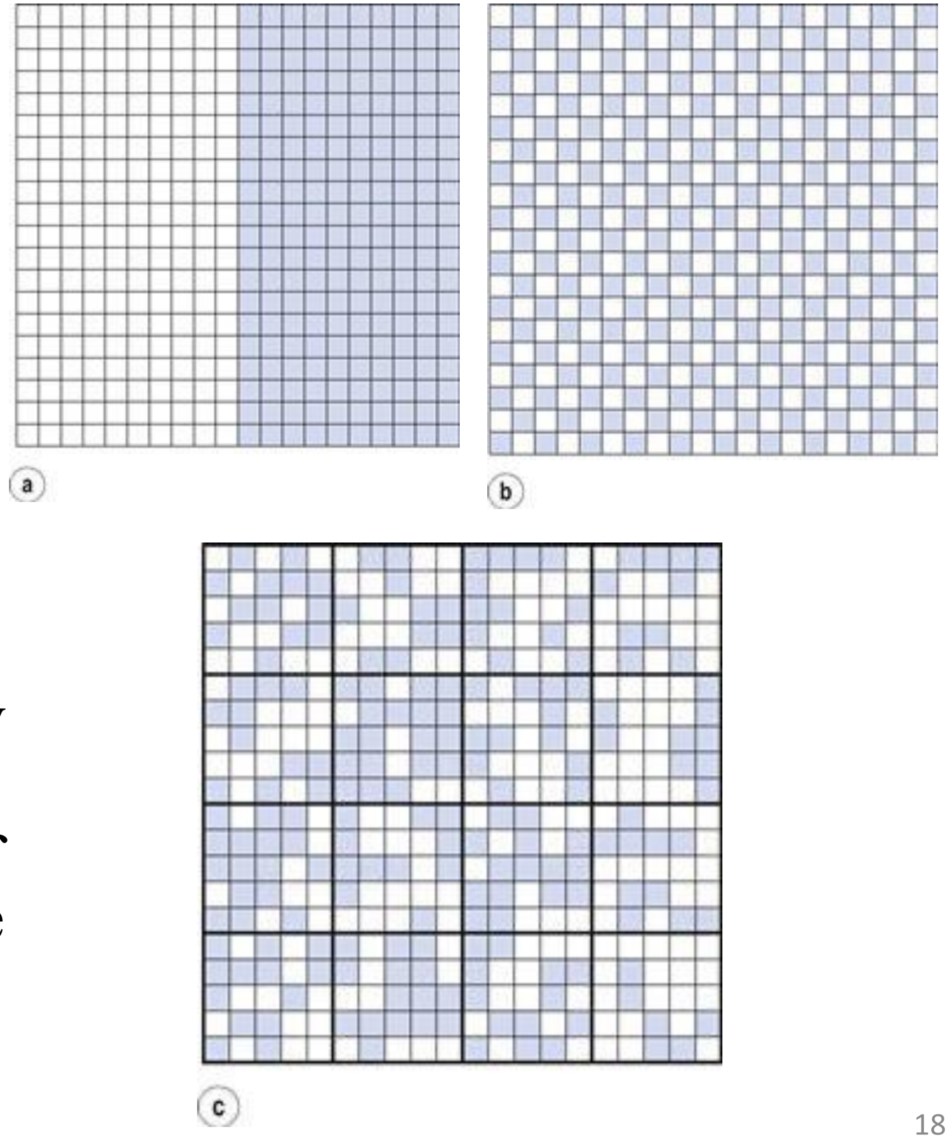
- The distance between these surfaces can be adjusted to the required size range.



Colloid Mill.

Solid Mixing

- Solid mixing is similar to liquid mixing.
- However, it shows some **differences** mainly comes from that solid mixture after mixing is subjected to **demixing or segregation**.
- Solid mixing can be represented with the following model where
- **(A)** is the complete segregation state.
- **(B)** is the **Ideal mixing** state.
- **(C)** is **Random Mixing**.
- However, **B** is virtually impossible to get in practice by any mixing equipment.
- The best powder mixing process will result in a case of random mix where the **probability of finding** one type of particle at any point in the mixture is equal to its proportion in the mixture.



Mechanism of Mixing

1. **Convective Mixing**: resemble 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 of by inverting the whole container such as in V-shape mixer.

2. **Shear mixing**: occur when layer of powder particle moves relative to other layers and this will help in reducing the scale of segregation of powder mixture.
3. **Diffusive mixing**: occurs when single particle (not bulk of powder) starts changing their location relative to one another.

- This is an important mechanism in powder mixing and can be induced by modifying the mixer such as adding baffles.

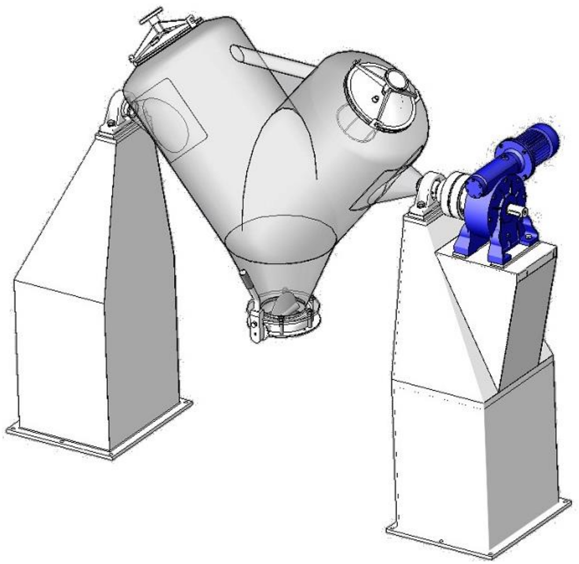
Equipment

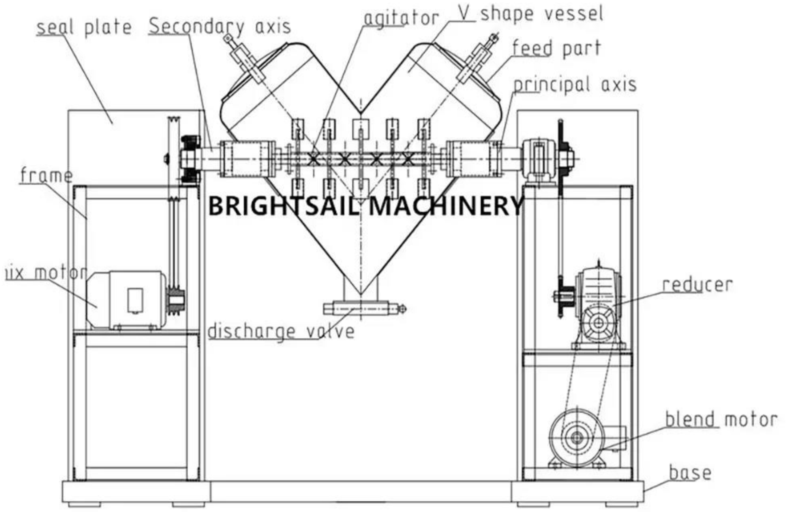
A. Tumbler mixers: consist of a container of different geometrical shape and rotated around its axis and cause movement of materials in all planes.

- It can be in different shapes such as twin shell, double cone, cube, drum and tetrahedral blenders.
- Of these types the twin shape mixer (**V-shape mixer)** is the most preferred once which results in a satisfactory mixing in a reasonable time.

Tumbler Mixers
V-Shape Mixer (Twin Shell Mixer)

- It consists of two cylinders connected to each other in 45° angle.
- When rotates, material is collected to the bottom and then splits into two halves when rotate to the other direction.
- This is very effective because of the **convective, shear** mechanisms involved.
- A bar containing blades is added inside which rotates in opposite direction to increase mixing efficiency. This will **add diffusive mixing mechanism**
- Rotation speed should be adjusted depending on the size of the mixer and the amount of material exist.
- **Too slow** rotation result in **no mixing** and **too fast** result in **centrifugal action** that hold the material to one side of the mixer and result in no mixing.
- https://youtu.be/SOoOmhrPLdQ

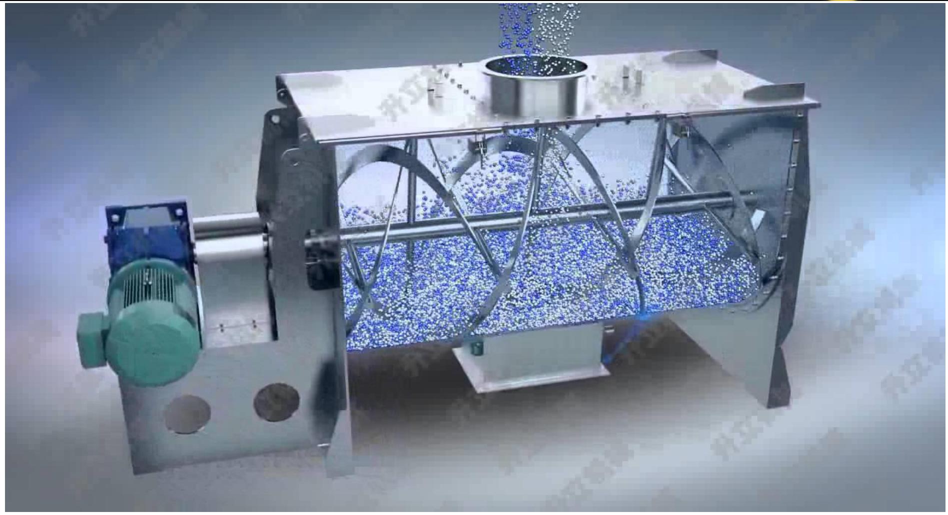




Agitator Mixers

B. **Agitator mixers**: consist of a **fixed container** that contains a moving screw or a paddle to mix the powder materials.

- These types of mixers are **more effective** in mixing **wet powders** that do not mix well using tumbler mixers. There are **three** types of agitato mixers:



1. **Ribbon mixers**: consist of a horizontal cylindrical tank usually opening at the top and fitted with helical blades or ribbons.
2. **Nauta mixers**: it's a vertical screw mixer which **impart 3D** mixing. A screw assembly is mounted inside a conical chamber, the screw is revolving around itself and around the cone for better mixing.

https://youtu.be/7JPSLKW5T_8
https://youtu.be/Mmrk3ZgHCWw

Agitator Mixers

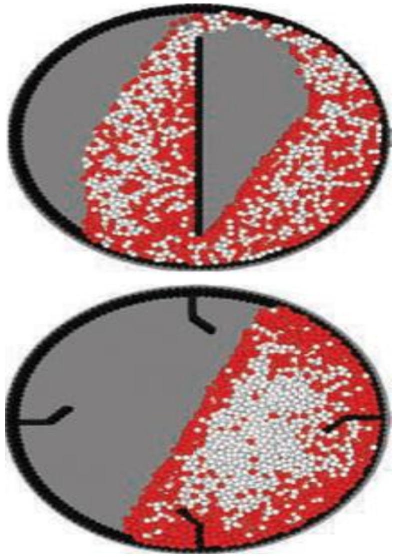
C.Rapid mixer granulator:

- Newer models that can perform **both** wet and dry mixing efficiently in lesser time.
- This means it can perform dual action like mixing and tablet granulation which is an important process in tablet formulation (more on that in Lab).
- Example of these mixers is **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

Consideration in Working with Powder Mixing Segregation

1. **Segregation of demixing**: powder can segregate during **mixing** and/or during **handling** and processing after mixing. The factors that affect demixing include:

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

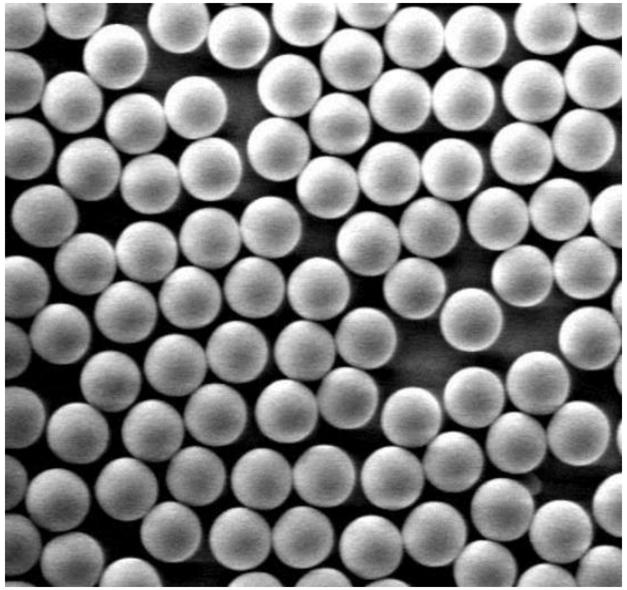


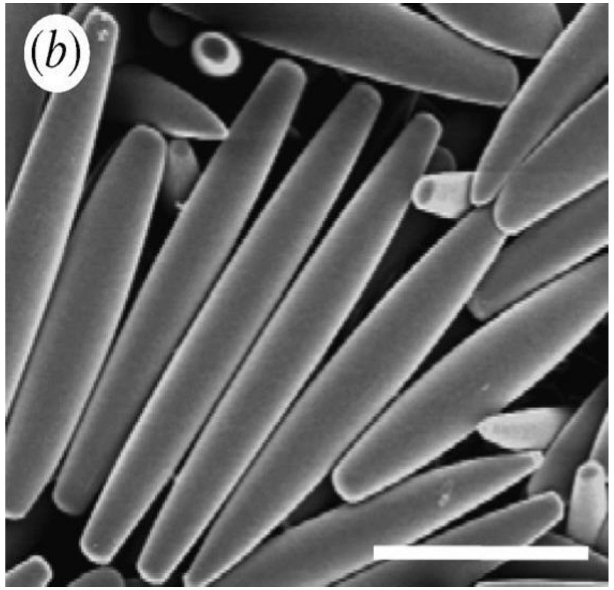
- **Small** particle tends to fill the gaps between larger particles and move towards the **bottom** of the mass.
- **Larger** particle will have higher kinetic energy and will move to a larger distance compared to small particles.
- This segregation problem can be decreased by:

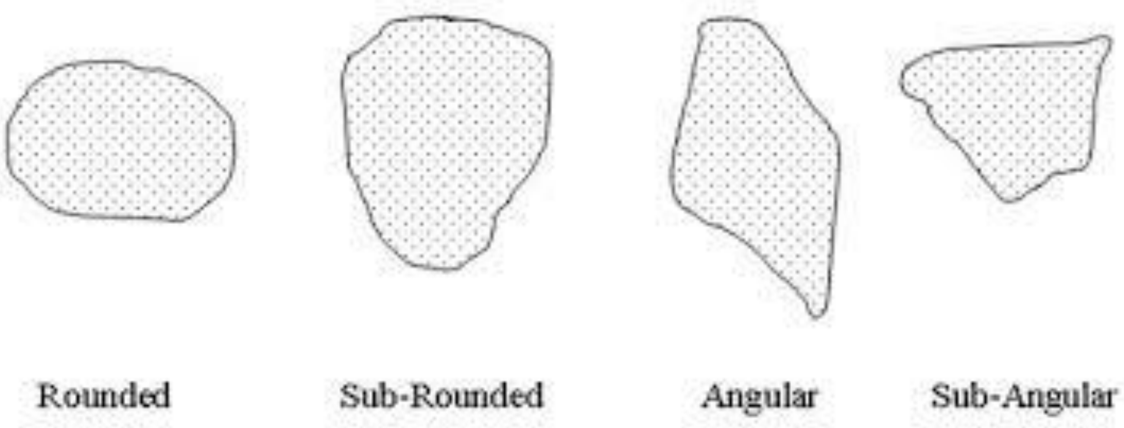
1. Selection of a particle with a **close size** range and this can be achieved by sieving.
2. Milling of the component before mixing to get homogenous particle size.
3. Granulation of the powder mix (enlarging the particle size),

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.
- **Needle shape** particles may become interlocked decreasing the tendency to segregate once mixed has occurred.







Consideration in Working with Powder Mixing Segregation

B. Particle charge:

- Surface charge can be **generated during** mixing and may become a reason for segregation.
- This can be **prevented** by adding small amount of **surfactant** or mixing under condition of **increased humidity** (above 40%) to increase powder conductivity to discharge the generated charge.

C. Particle density:

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

Consideration in Working with Powder Mixing
Mixing Small Drug Quantities

- If we are dealing with very potent drug (which contains very low amount of active ingredient):
- The **lower** the particle size of the mixture the **higher** the chance to get a random mixture that contain even drug amount in each sample.
- But this benefit of particle size reduction is working to a certain limit because **very fine** particle may agglomerate and may **have poor flow properties**.

Mixing Evaluation

- It is important to examine each mixture during mixing process to ensure that we have enough mixing (i.e. random mixing). There are few terms to be considered here:

A. Scale of scrutiny:

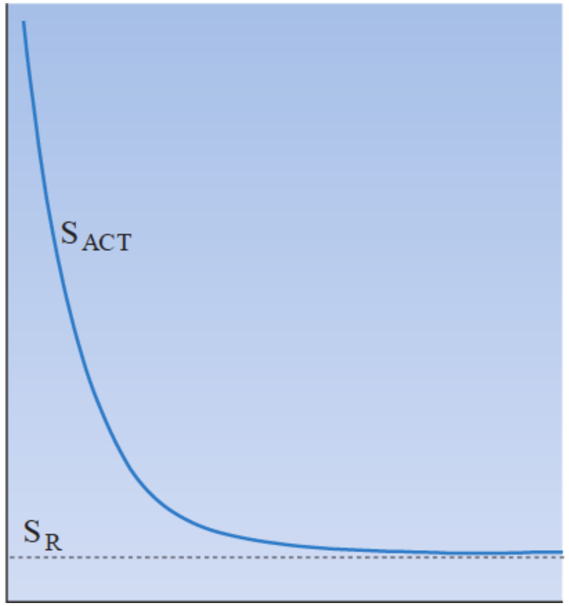
- It's done by examining an amount of mixture equal to the desired dosage form.
- **It is the amount of material within which the quality of mixing is important**.
- For example, if the average final tablet weight will be 200 mg so the amount to be examined from the mixture is 200 mg.
- **This 200 mg is called scale of scrutiny**.
- If we examined less of more of that amount the result will not reflect the actual mixing status and may lead to incorrect results.
- For liquid dosage form we will examine the final dose volume (for most drugs the final dose is 5 ml)

Mixing Evaluation
Mixing Index

- One evaluation method involves the generation of a **mixing index.**
- This index compares the **content standard deviation** of samples taken from a mix under investigation (S_{ACT}) with the content standard deviation of **samples from a fully random mix** (S_R).
- Comparison with a random mix is made since this is theoretically likely to be the best mix that is practically achievable. The simplest form of a mixing index (M) can be calculated as:

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

- At the start of the mixing process the value of S_{ACT} will be **high so** that **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 and M = 1**.



Sampling Technique

- Sampling is very important to test the mixing efficiency.
- Without good sampling, different calculations regarding the mixing quality may be worthless.
- Samples may be withdrawn **periodically** during discharge of the mixture or may be taken directly from the mixer by a **sampling "thief"**.
- This tool is composed of two concentric tubes, one enclosing the other and can be used for free-flowing powders.
- The outer tube is pointed, with holes cut in corresponding positions in inner and outer tubes.
- The holes are opened or closed through the rotation of the inner tube to capture the material.

Mixer selection

- **Selection will depend on**:

1. **Physical properties** of the materials to be mixed, such as density, viscosity and miscibility.
2. **Economic considerations** regarding processing for example the **time required** for mixing and power expenditure necessary.
3. **Cost and maintenance** of the equipment.

- However, in fluid and semisolid (or in we granulation)of these factors the **viscosity** is the main factor to be taken in consideration when selecting the mixer, where at:
- **Low viscosity systems**: such as monophasic fluids of low viscosity there is **little problems** during mixing and turbulence mixer is enough such as air jet, fluid jet and high-speed propellers is enough for adequate mixing.

Mixer Selection

- **Intermediate viscosity systems**: such as **emulsions** (immiscible liquids) or suspensions (fine particle in liquid). These system needs the subdivision or degradation on one phase and subsequent dispersion (mixing) into the other phase. In this case turbine mixer (such as colloidal mill, micro-pulverizers) can be considered the best mixer for such systems.
- **High viscosity systems**: such as ointments which requires a **shearing action** between two surfaces that are close to each other and moving in different velocities, so mixers such as paddled mixers (kneaders) or mills can be used.