Operation of mixing

University of Pécs

Institute of Pharmaceutical Technology and Biopharmacy

Operation of Mixing

Definition of mixing

Mixing may be defined as a **unit operation** that aims to **homogenize two or more components**.

During mixing two or more substances get into **homogeneous distribution** in each other.

Theory of Mixing

Theory of Mixing

In pharmaceutical practice can be:

- **Self-mixing** materials (mixing occurs due to heat movements of molecules, generally a slow process. Such materials are gases and liquids with low viscosity.)
- **Non-self-mixing** materials :
  1. *Structures **retaining mixture state***
     - powders,
     - liquid with high viscosity,
     - stabile disperse structures.

  2. *Structures **non-retaining mixture state***
     - suspension,
     - emulsion, which are separating into phaseses.

Theory of Mixing

Aims

- homogenization,
- dispersion (emulsifying, suspending),
- heating,
- cooling,
- wetting,
- drying,
- crystallization,
- disintegration,
- granulation,
- preparation of ointment and suppositories,
- microencapsulation,
- preparation of micropellets,
- preparation of nano medicines,
- chemical reaction,
- biochemical reaction, fermentation
- biopharmacy examination (e.g. dissolution, membrane permeability),
- coating.

Theory of Mixing

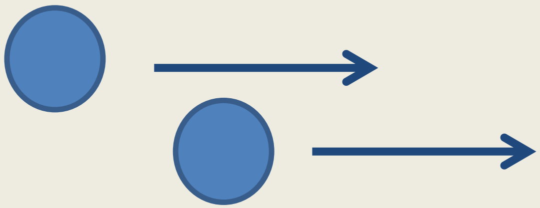
During the operation of mixing, several processes, phenomena can be regarded:

- *increase in particle size* (e.g. at granulation),
- *decrease in particle size* (e.g. at emulsifying),
- *deformation* (e.g. at disintegration),
- *flowing property of material.*

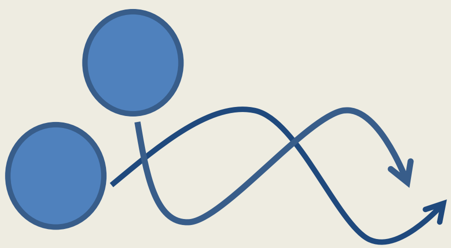
Theory of Mixing

Flow of material can be laminar and turbulent:

- At ***laminar flow***, vector of speed of particles is parallel along flow line (parallel with axle tube).
  Particles move orderly next to each other without any mixing.



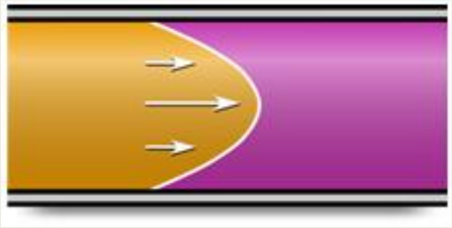
- At ***turbulent flow***, movement of particles shows only overall the flow line. Due to the swirling, whirling movement of the particles, the layers next to each other are blended.



Theory of Mixing

Flow of material can be laminar and turbulent:

Laminar flow or streamline flow in pipes (or tubes) occurs when a fluid flows **in parallel layers, with no disruption** between the layers.
At low velocities, the fluid tends to flow without lateral mixing. There are no cross-currents perpendicular to the direction of flow, nor eddies or swirls of fluids.
In laminar flow, the motion of the particles of the fluid is very orderly with all particles moving in straight lines parallel to the pipe walls.



Turbulent flow is a flow regime characterized by **chaotic property changes**. This includes rapid variation of pressure and flow velocity in space and time.
In contrast to laminar flow the fluid no longer travels in layers and mixing across the tube is highly efficient.

Theory of Mixing

Euler number *(Eu)* is a specific <u>non-dimensional</u> number to flow occurring at mixing:

$$Eu = \frac{P}{d^5 n^3 \rho}$$

P = performance of stirrer
d = diameter of stirrer
n = rotational speed of stirrer
ρ = density of mixed material

Theory of Mixing

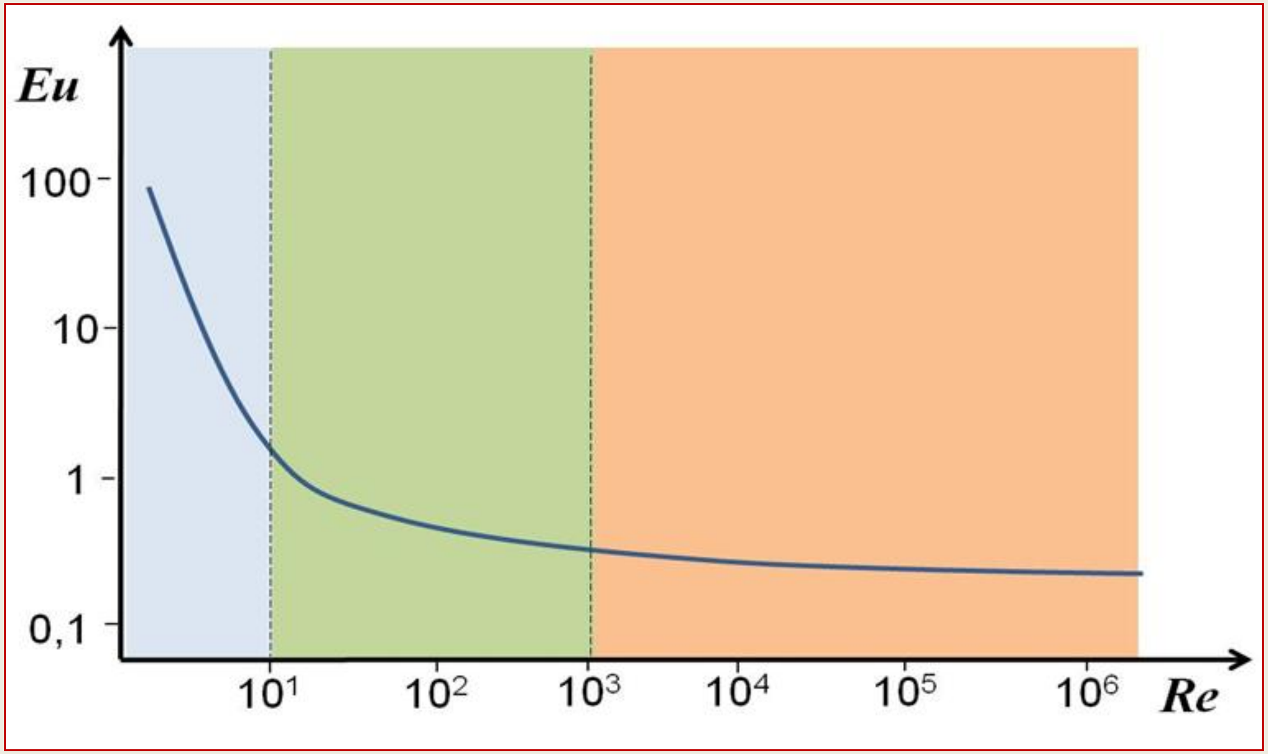
Reynolds number (*Re*) is also a specific <u>non-dimensional</u> number for mixing.
The value of *Re* in laminar interval is from 10 to 60, in turbulent interval is $>10^3$

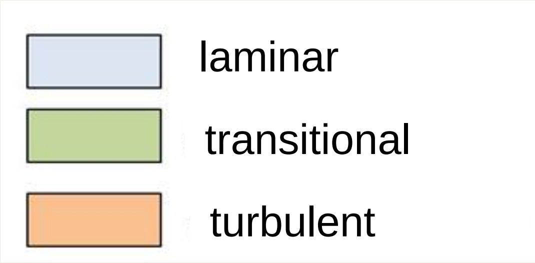
$$\mathrm{Re} = \frac{d^2 n \rho}{\mu}$$

μ = dynamic viscosity of the fluid
d = diameter of stirrer
n = rotational speed of stirrer
ρ = density of mixed material

Theory of Mixing

Euler-Reynolds diagram

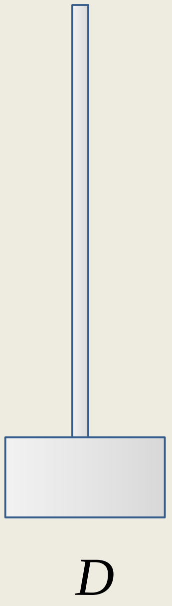




Theory of Mixing

The **performance** required for mixing can be characterized by the following expression:

$$P = N_e \cdot \rho \cdot n^3 \cdot D^5$$



N_e = Newton-number (resistance factor) [number without dimension]

ρ = density of material

n = speed of stirrer

D = diameter of stirrer

Theory of Mixing

Degree of mixing *(M)* can be calculated from relative standard deviation and can be characterized by the following **first-order kinetic formula**:

$$M = RSD_{\infty} + (RSD_{o} - RSD_{\infty})e^{-kt}$$

RSD_o = relative standard deviation in initial stage

RSD_∞ = relative standard deviation at the measured degree of mixing

k = rate constant

t = time

Practice of mixing

Theory of Mixing

What type of mixer should be chosen?

What should be stirred?

- liquid's mixture,
- dissolution (dissolution of solid substances),
- suspension,
- emulsion,

} liquid

- ointment,
- paste

} semi-solid

- powder
- granules
- dragée formation

} solid

Theory of Mixing

Speed of mixing:

- **slow** stirring speed **< 100 rpm**

  to avoid sedimentation, for crystallization

- **medium** stirring speed **100 - 1000 rpm**

  for viscous substances, syrups, ointments

- **fast** stirring speed **> 1000 rpm**

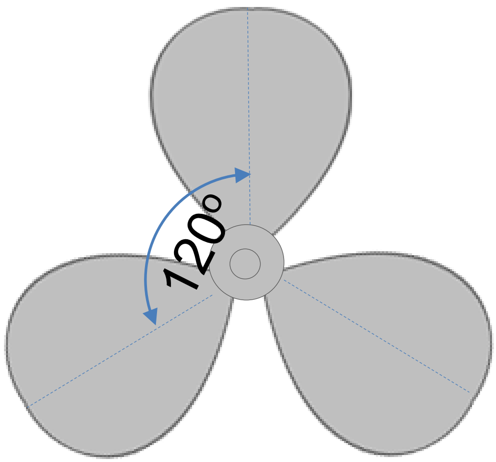
  to dissolve of solid substances,

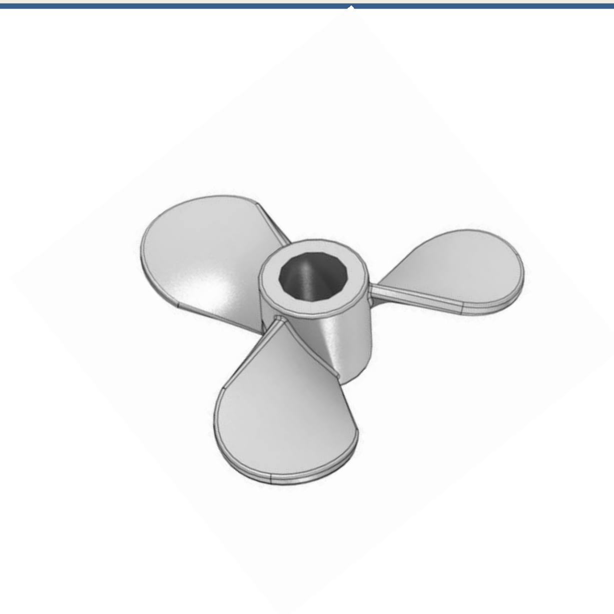
  for preparation of liquid mixtures

Mixing of liquids

Mixing of liquids

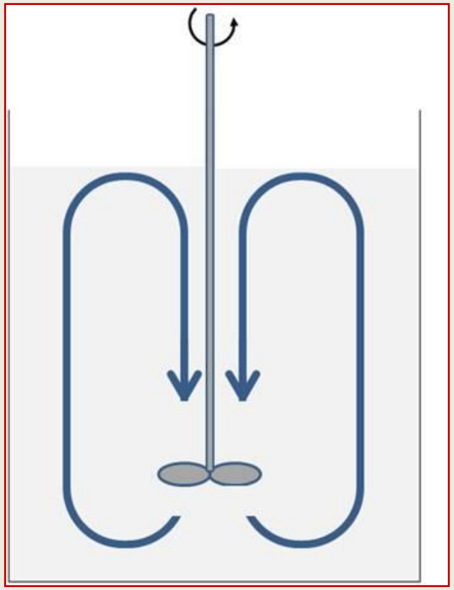
Propellers

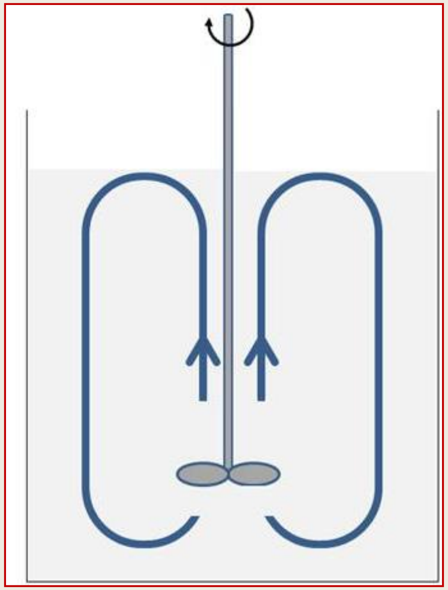


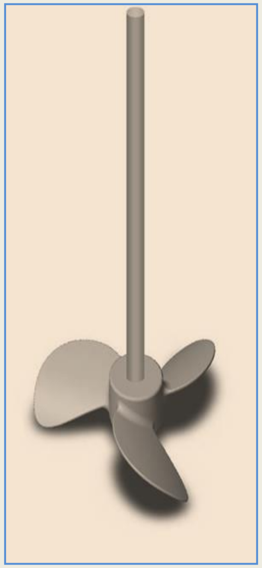


Mixing of liquids

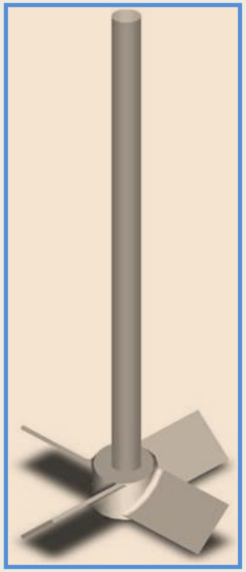
Axial flow







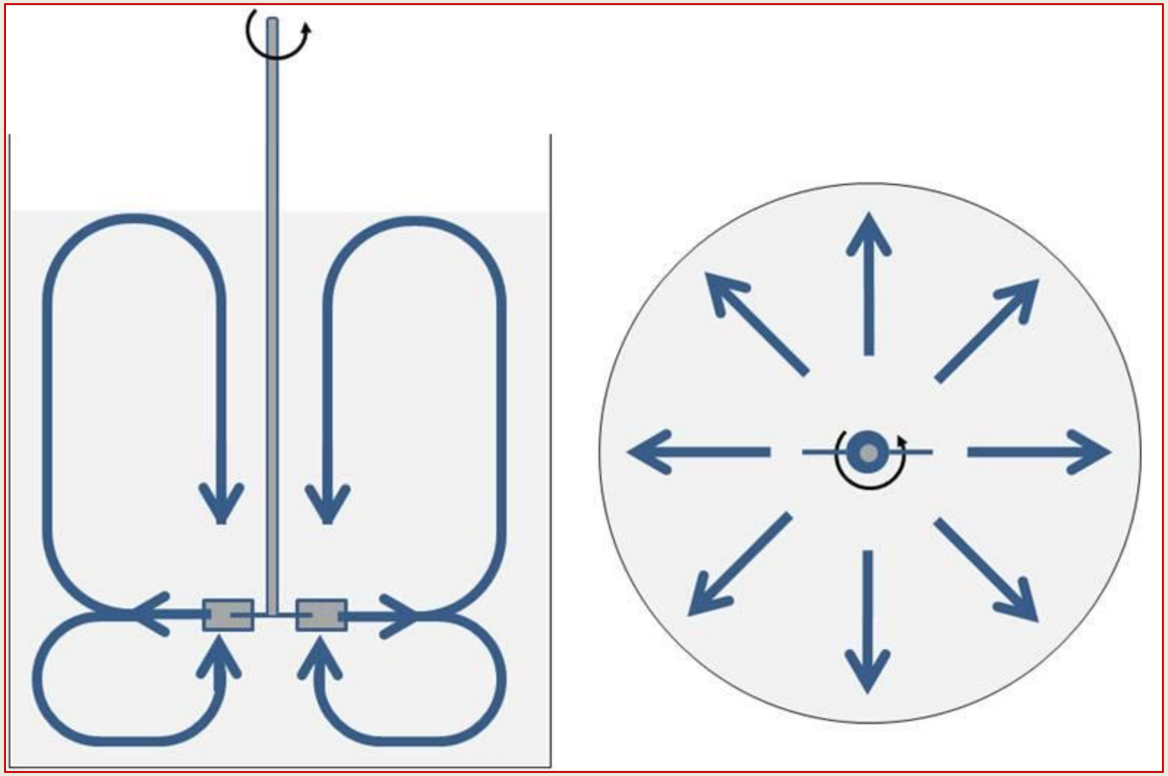
Tree blade
popeller stirrer



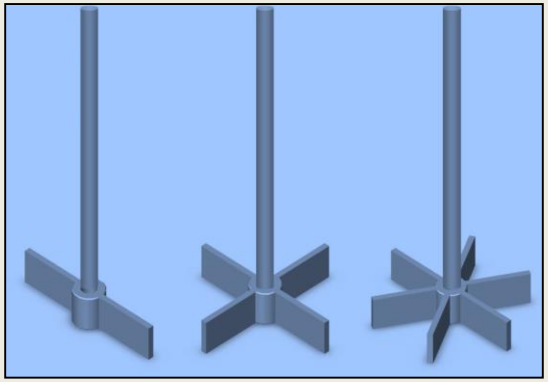
Four blade
oblique stirrer

Mixing of liquids

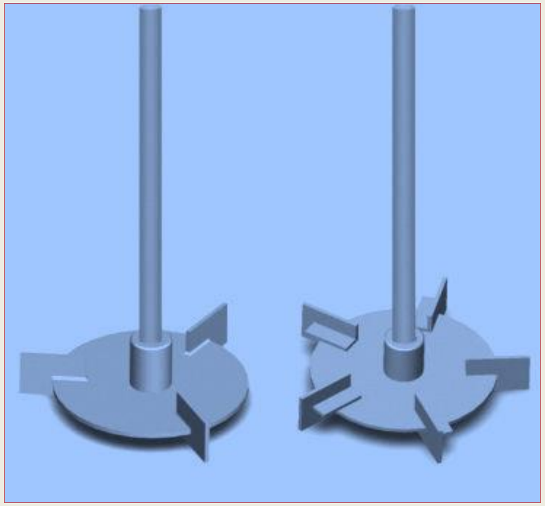
Radial flow



Opened turbine stirrer

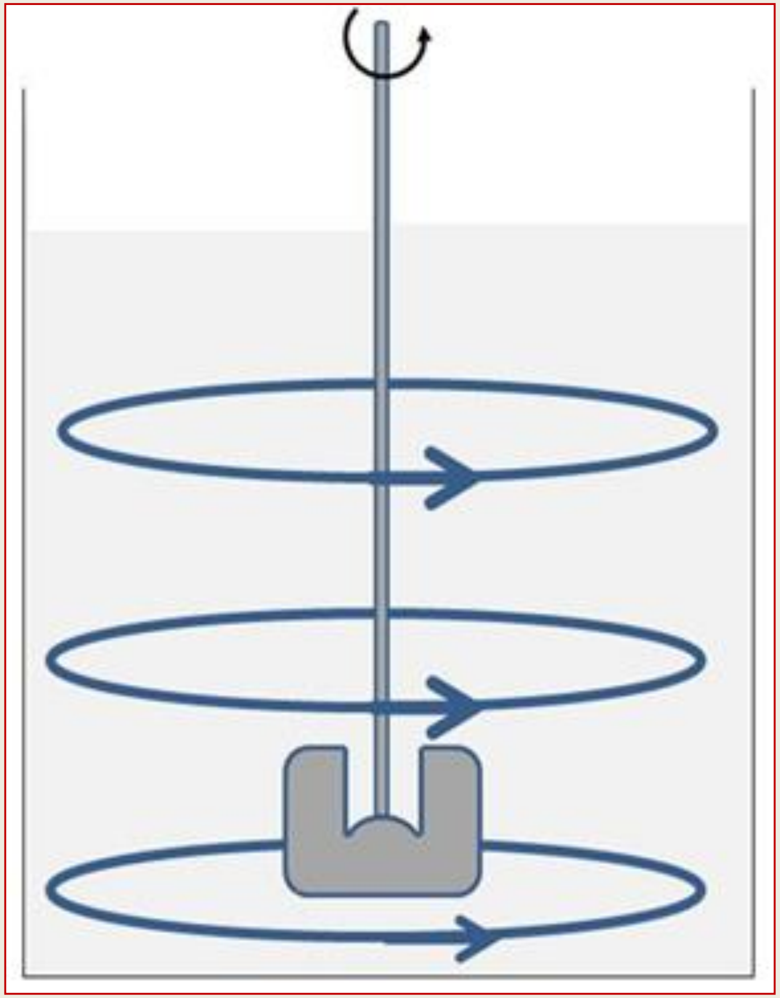


Disc turbine stirrer



Mixing of liquids

Tangential flow



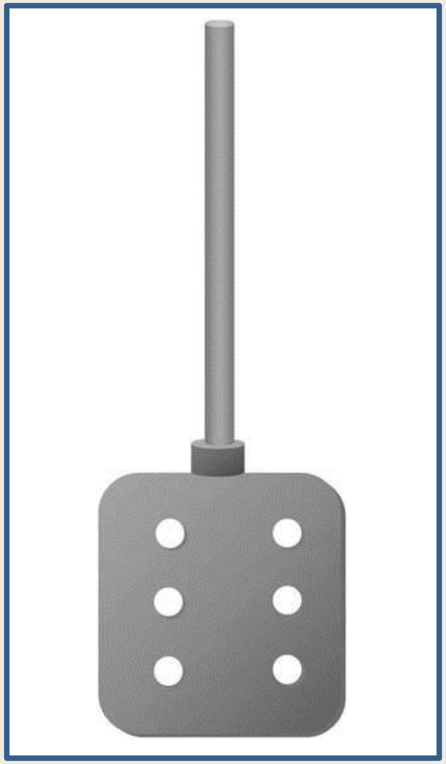


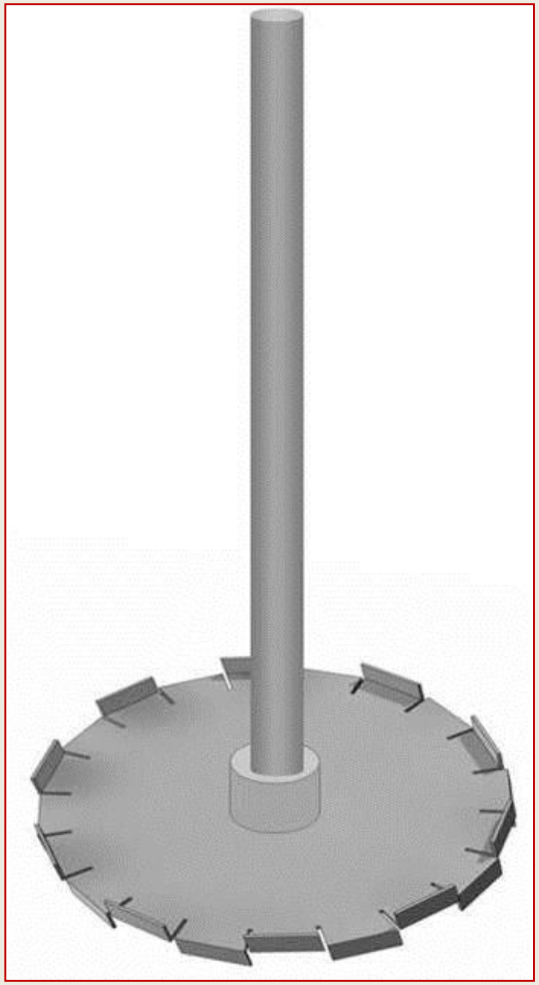
Plate stirrer

Mixing of liquids

Tangential flow

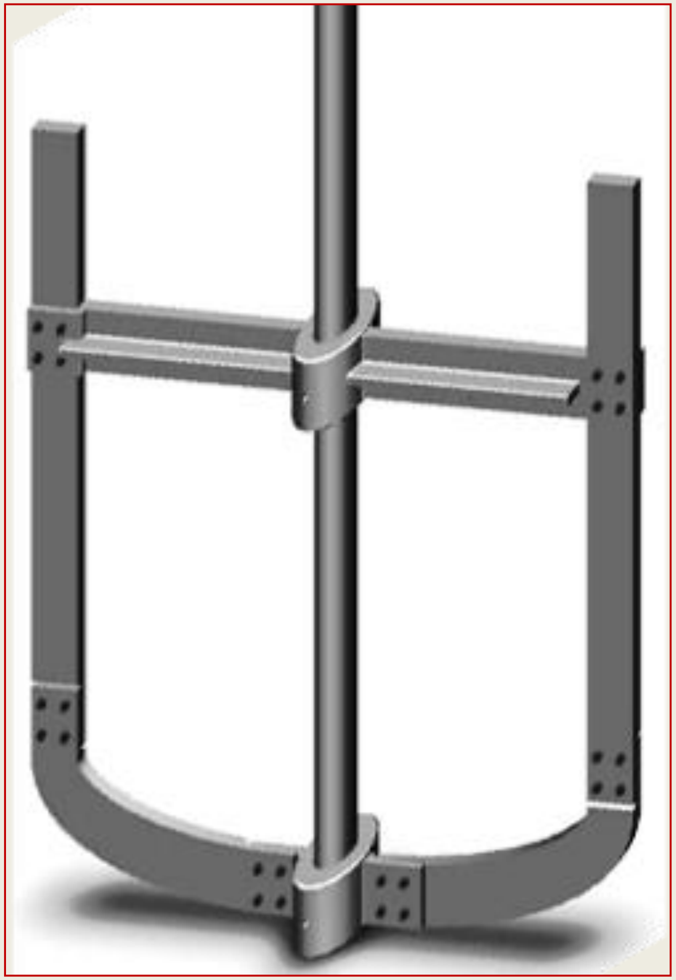
Mixing of liquids

Blade mixer



Mixing of liquids

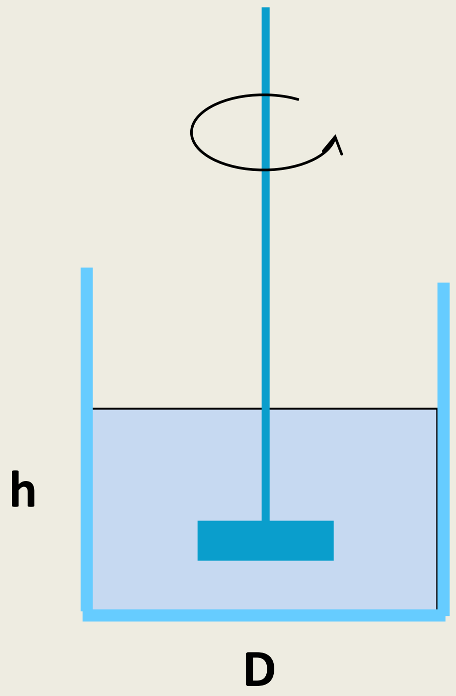
Anchor mixer



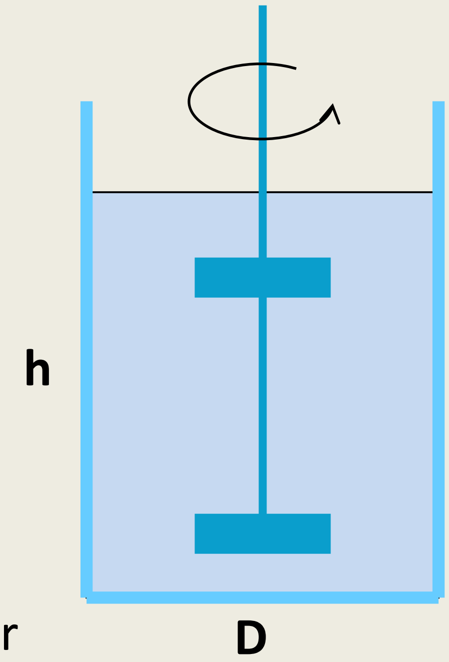
Mixing of liquids

Kneading stirrer

Mixing of liquids



h = height
D = stirrer diameter



good wettable materials

poor wettable materials

$$k = \frac{h}{D} \leq 1$$

$$k = \frac{h}{D} \geq 1{,}5$$

Mixing of liquids

magnetic stirrer

Mixing of liquids

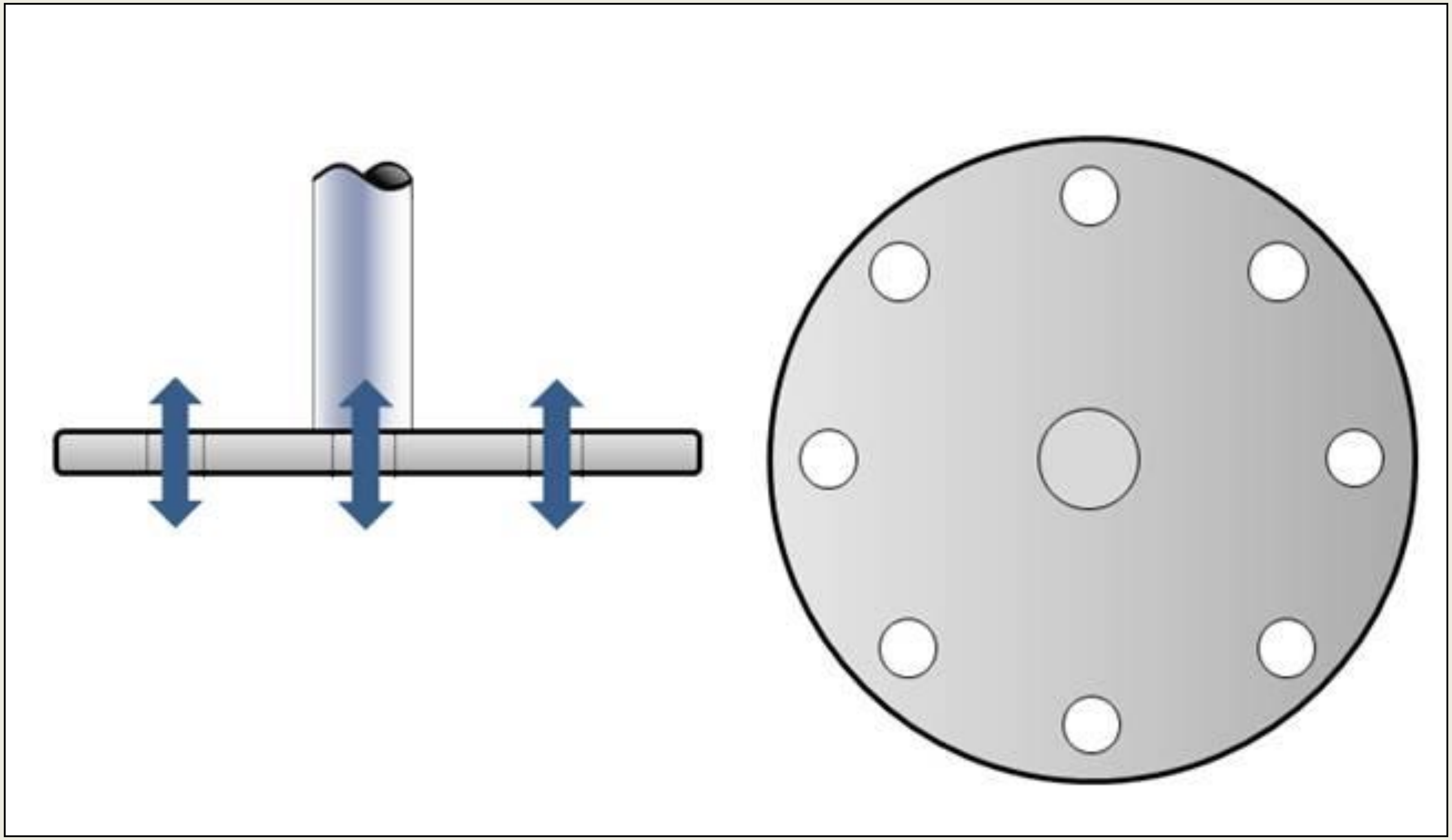
Vortex stirrer

Mixing of liquids

Ultrasonic stirrer

Mixing of liquids

Vibration stirer



Mixing of liquids

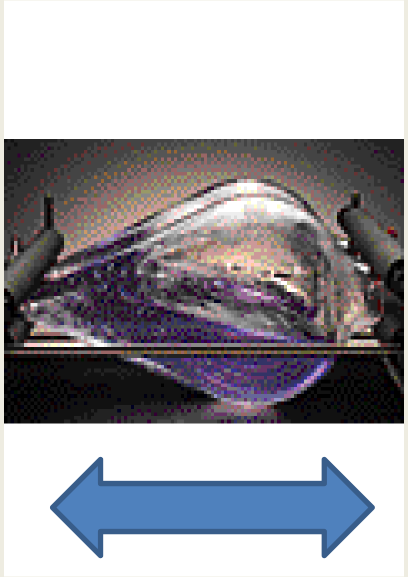
Rapid mixer

Mixing of liquids

shaker

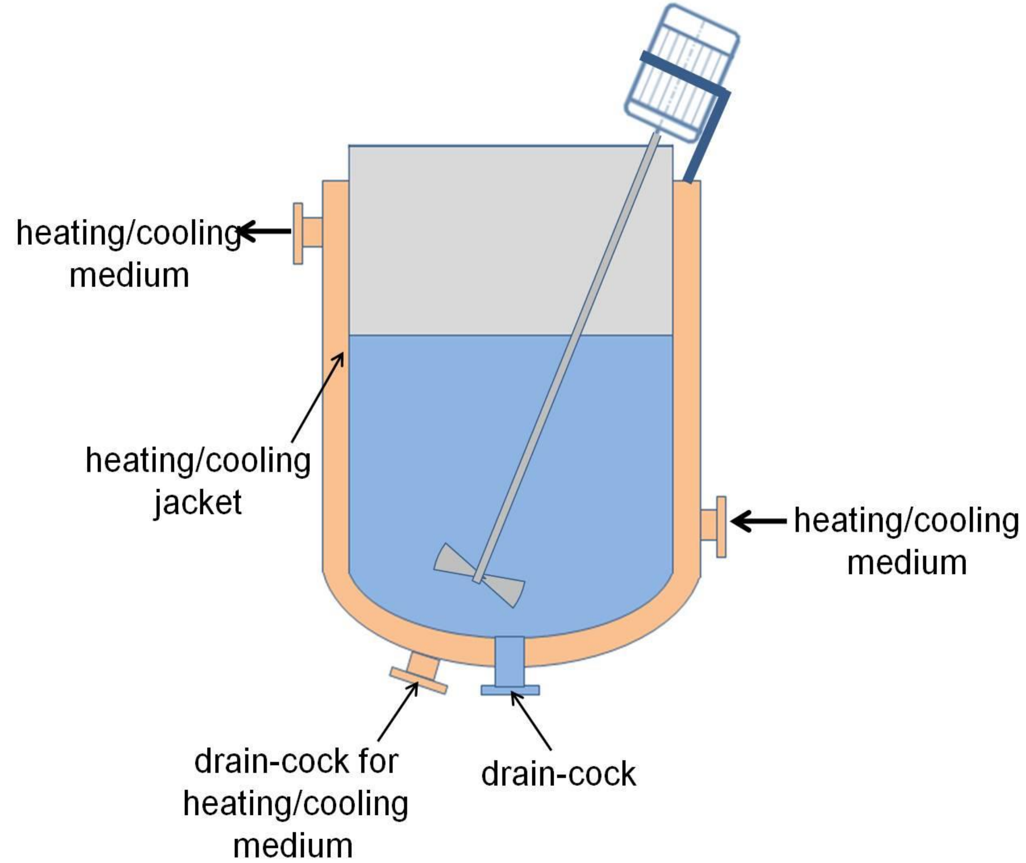
Mixing of liquids

shaker



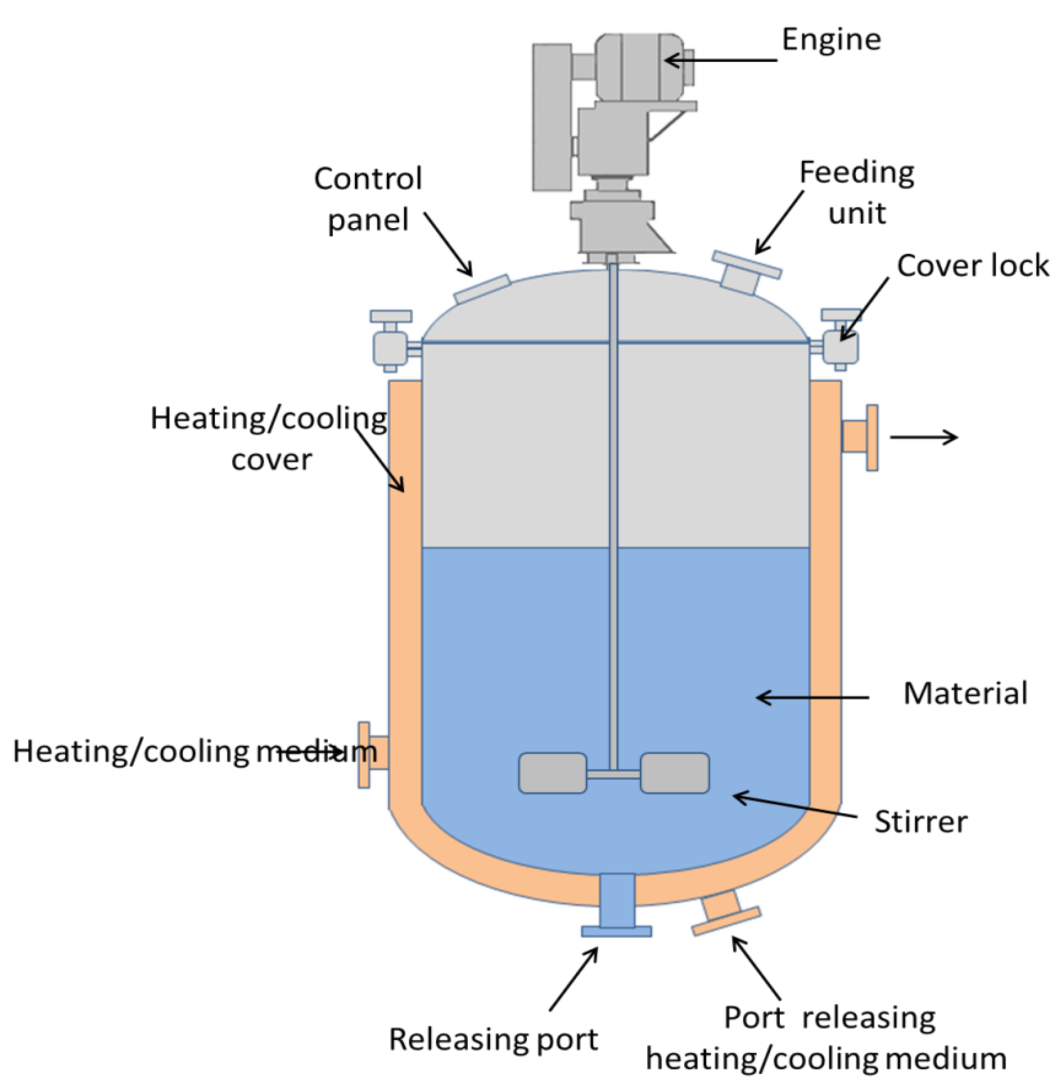
Mixing of liquids

industrial
opened duplicator with
oblique stirrer



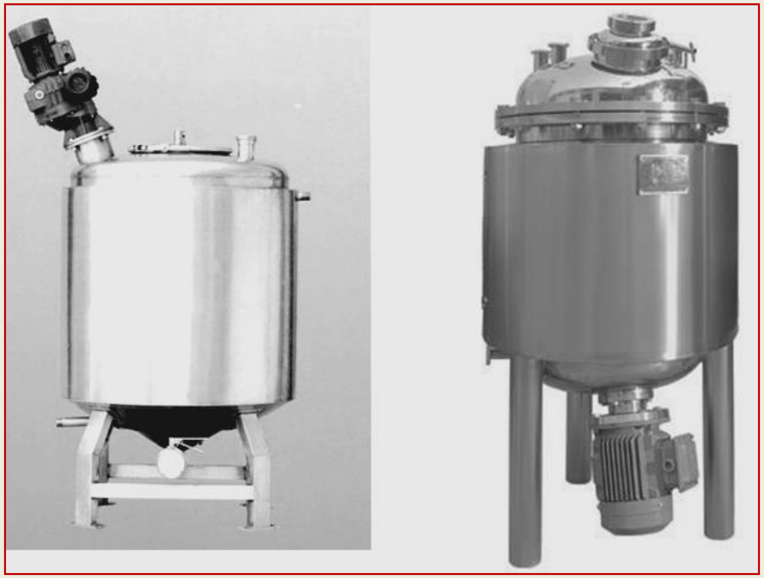
Mixing of liquids

industrial
closed duplicator with
stirrer



Mixing of liquids

industrial closed duplicator with stirrer

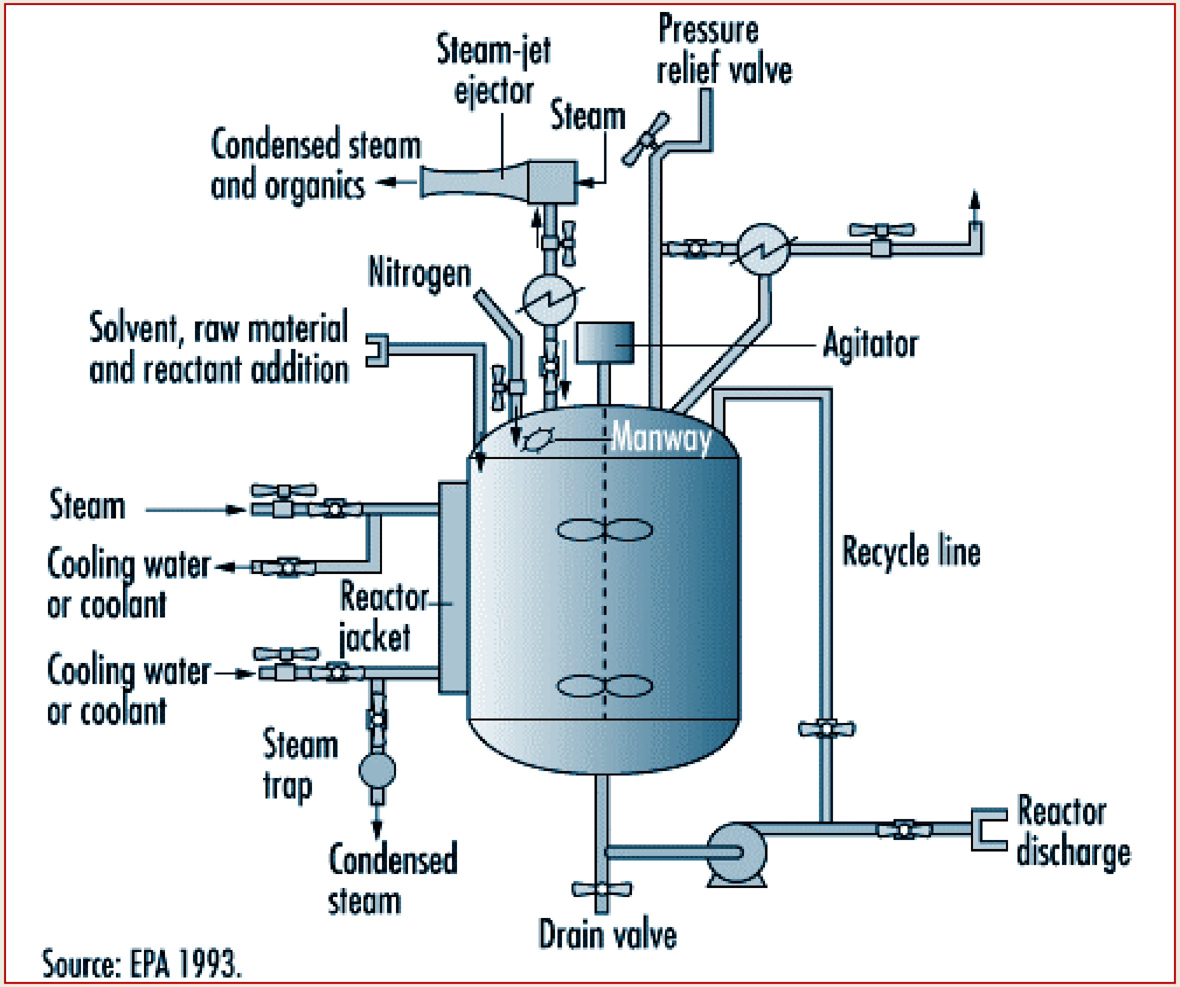


Upper and lower powered industrial duplicators with oblique stirrer

Duplicator apparatus with propeller stirrer

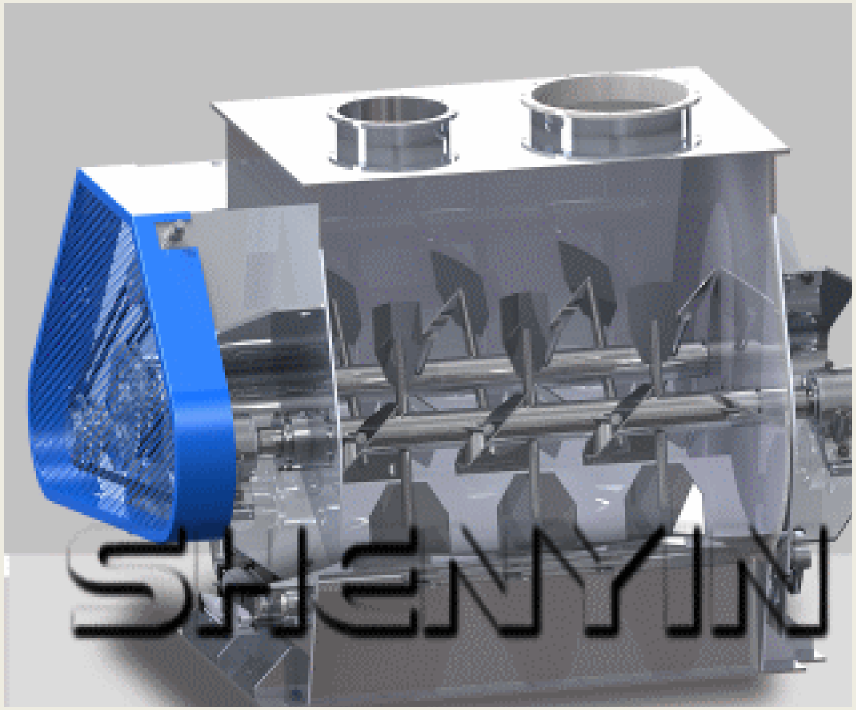
Mixing of liquids

Reractors for chemical (organic synthesis), fermentors duplicartors crytallization and equipments for biotechnological operations



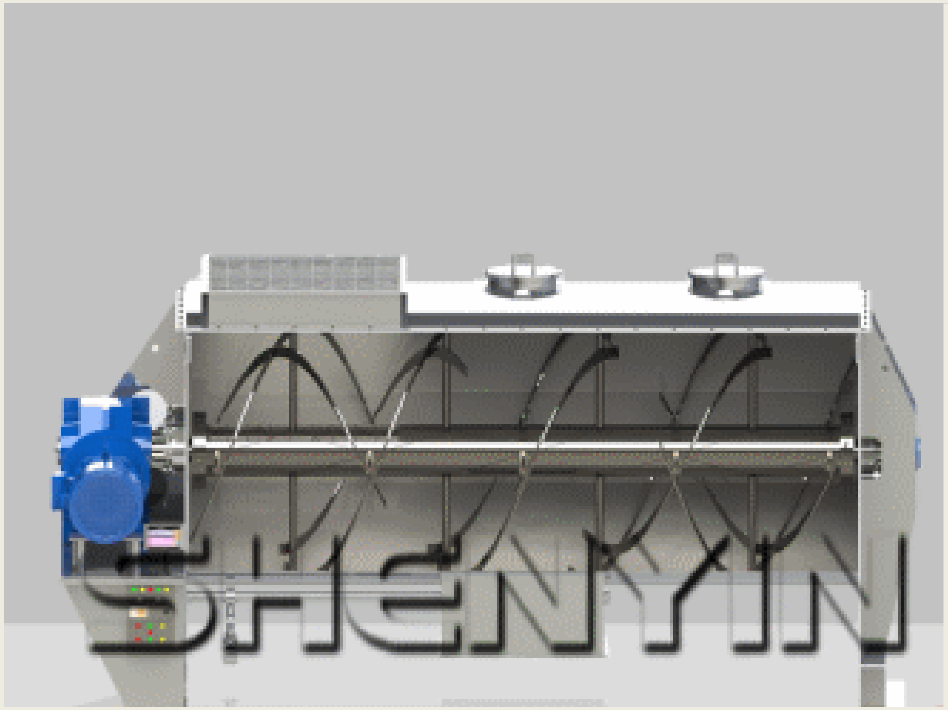
Mixing of liquids

Double Shafts Paddle Mixer



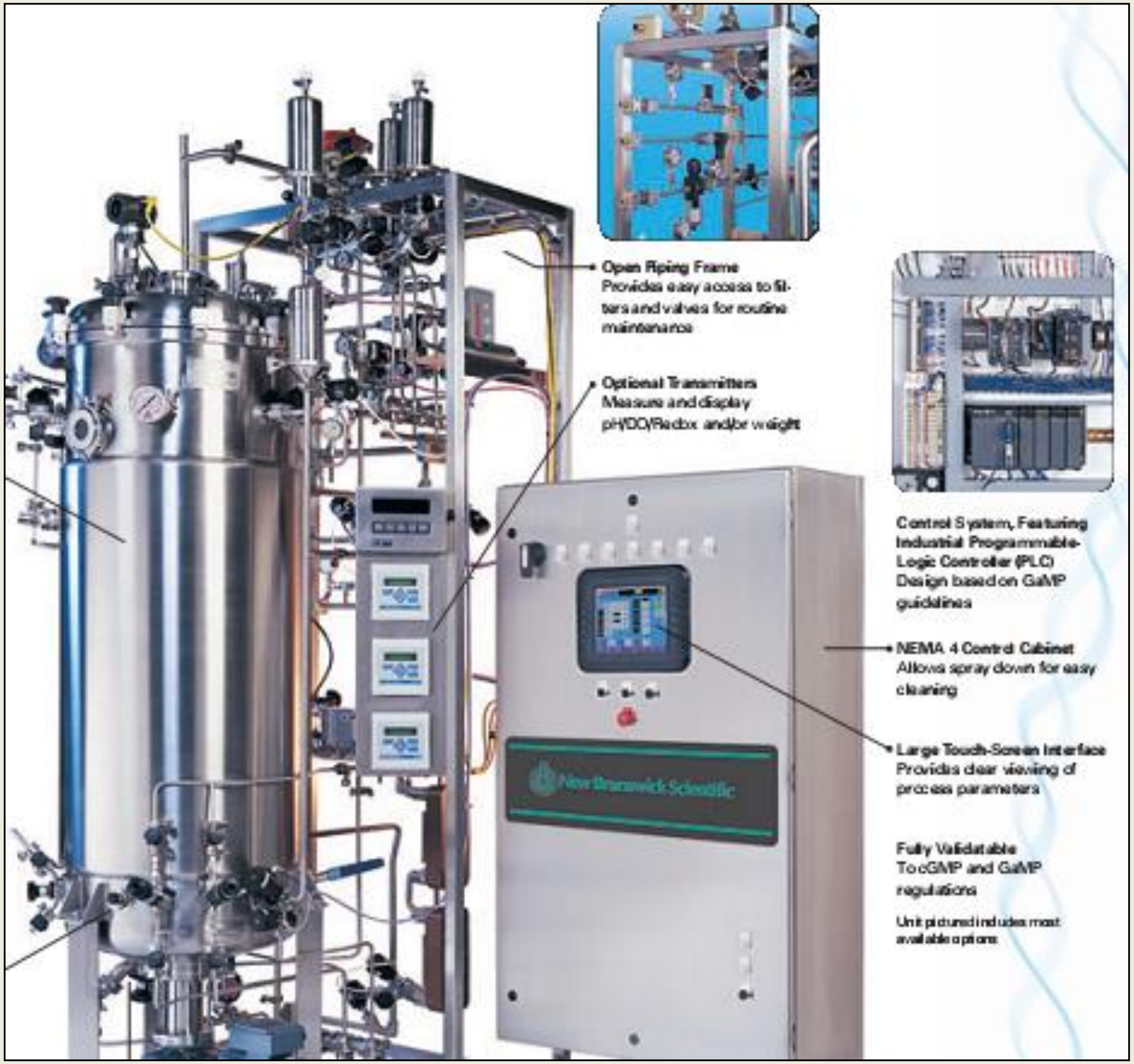
Mixing of liquids

Horizontal ribbon Mixer



Mixing of liquids

Fermenters



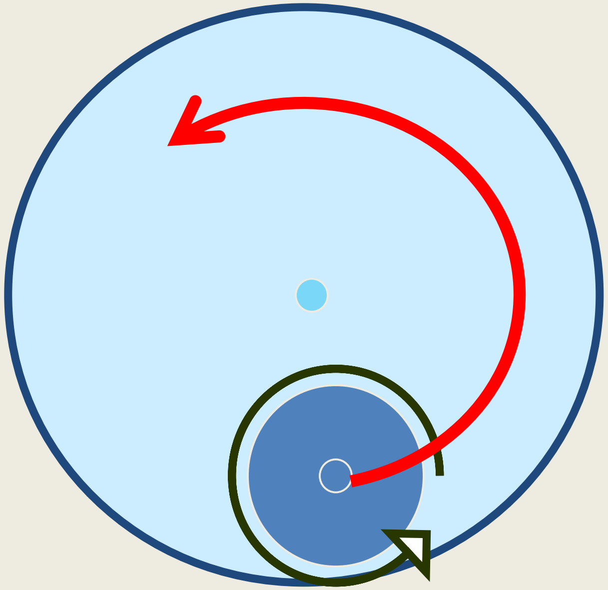
Mixing of liquids

Biotechnology

Mixing of semisolids

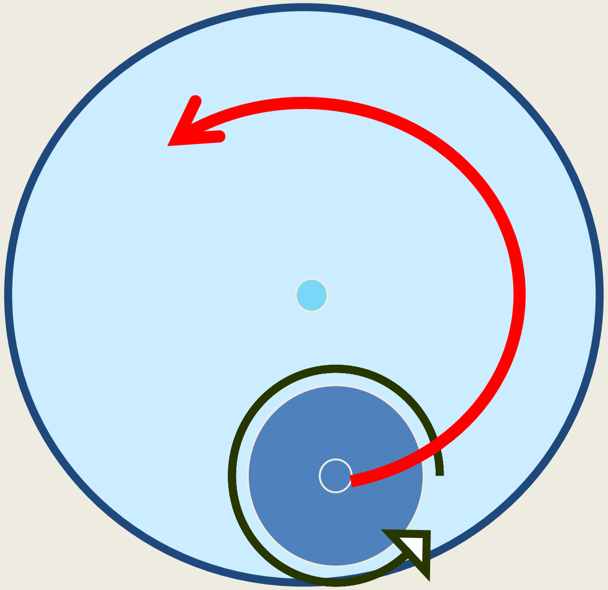
Mixing of semisolids

Planetary mixer



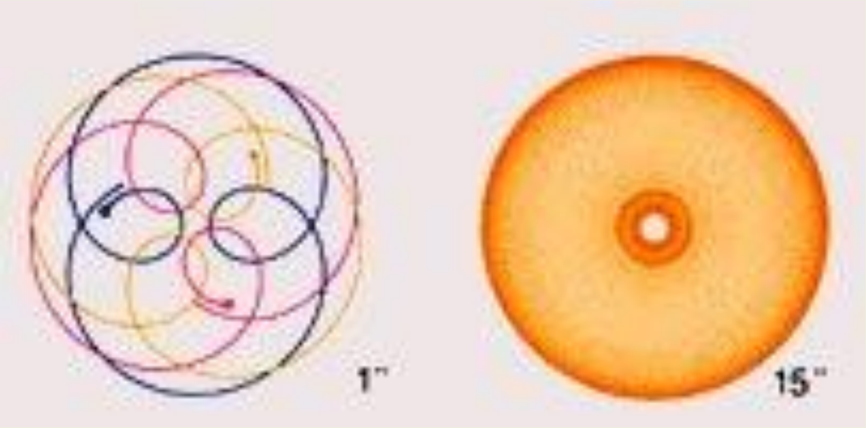
Mixing of semisolids

Planetary mixer



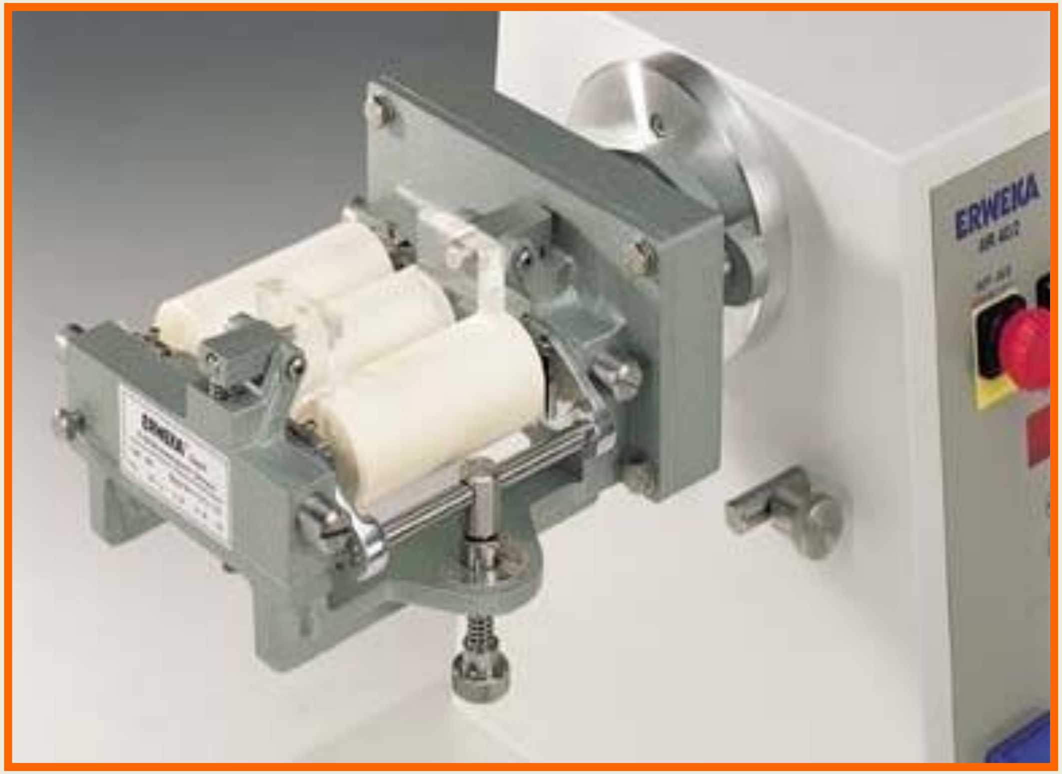
Mixing of semisolids

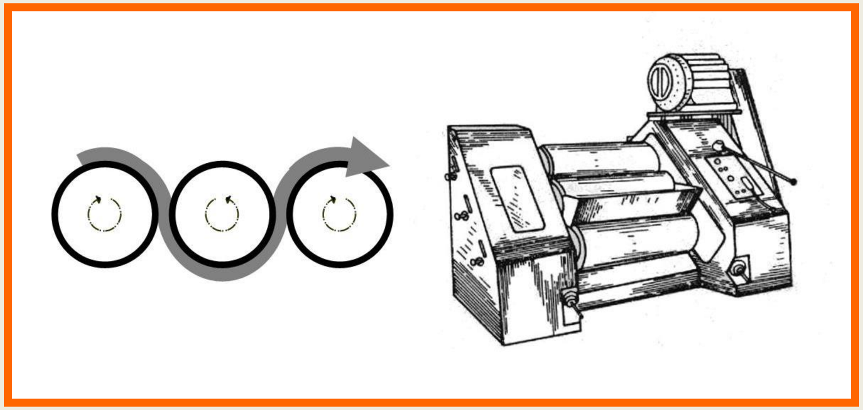
Planetary mixer



Mixing of semisolids

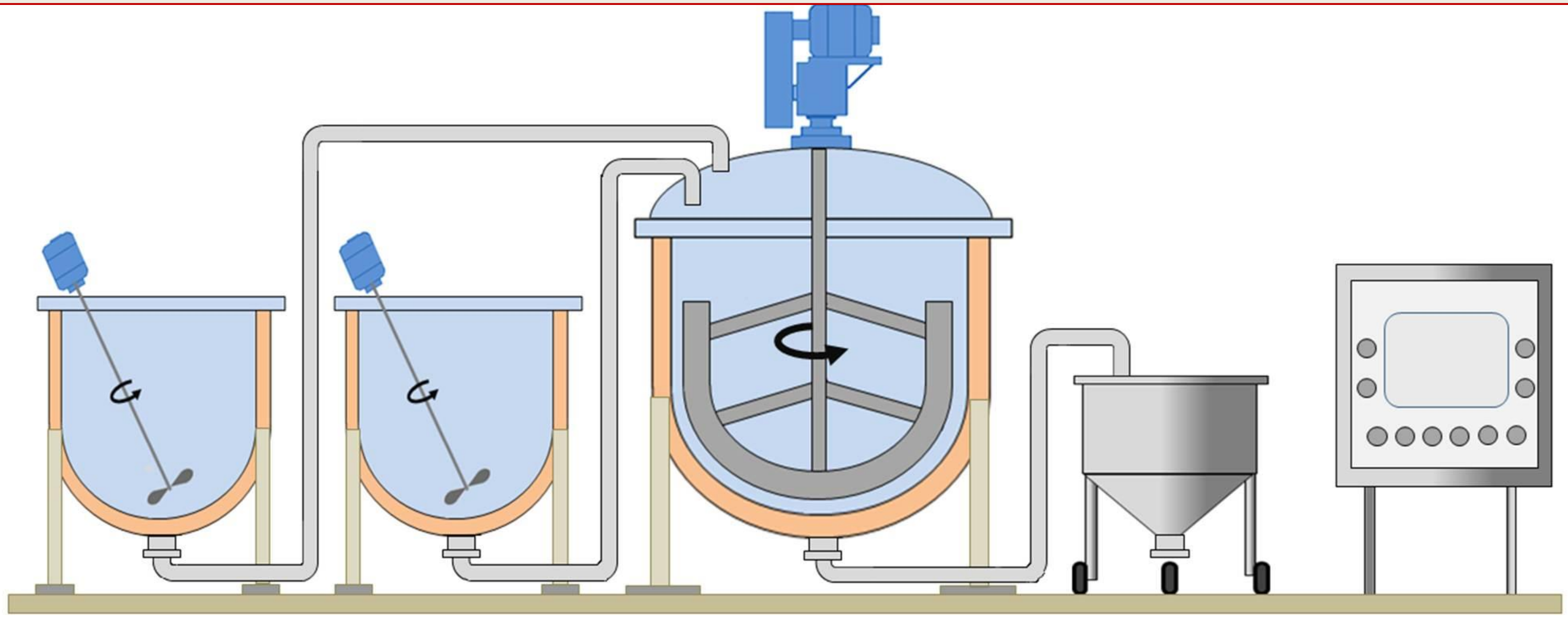
Triple-roll-mill





Mixing of melted semisolids

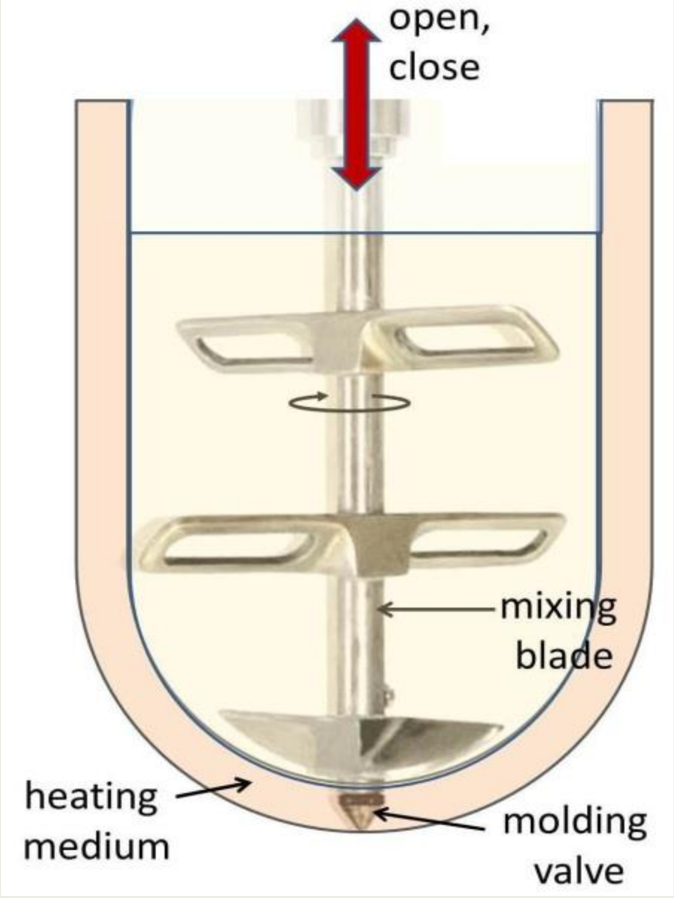
Preparation of cosmetics



Automated production line for making ointments and creams

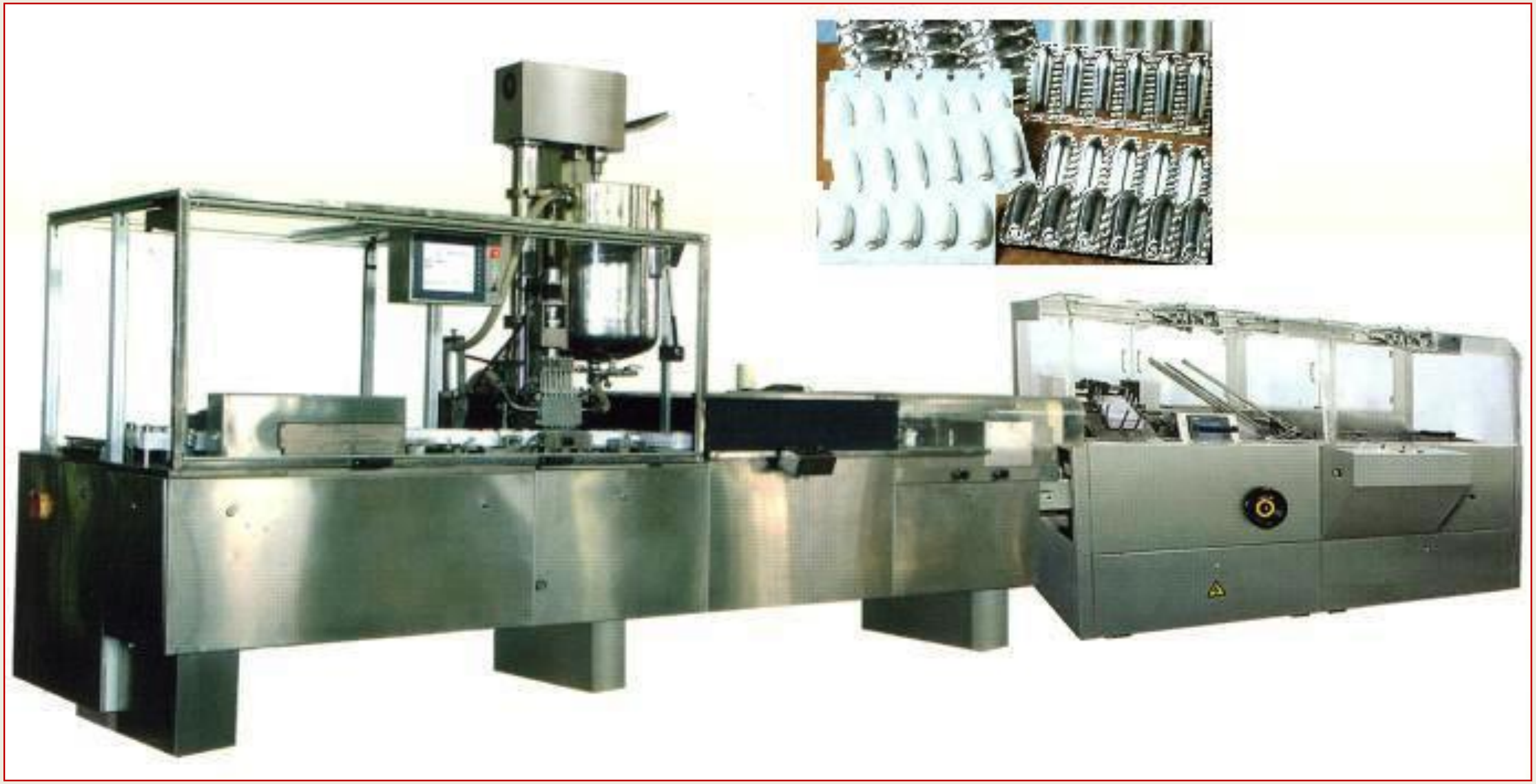
Mixing of melted semisolids

Preparation of suppositories



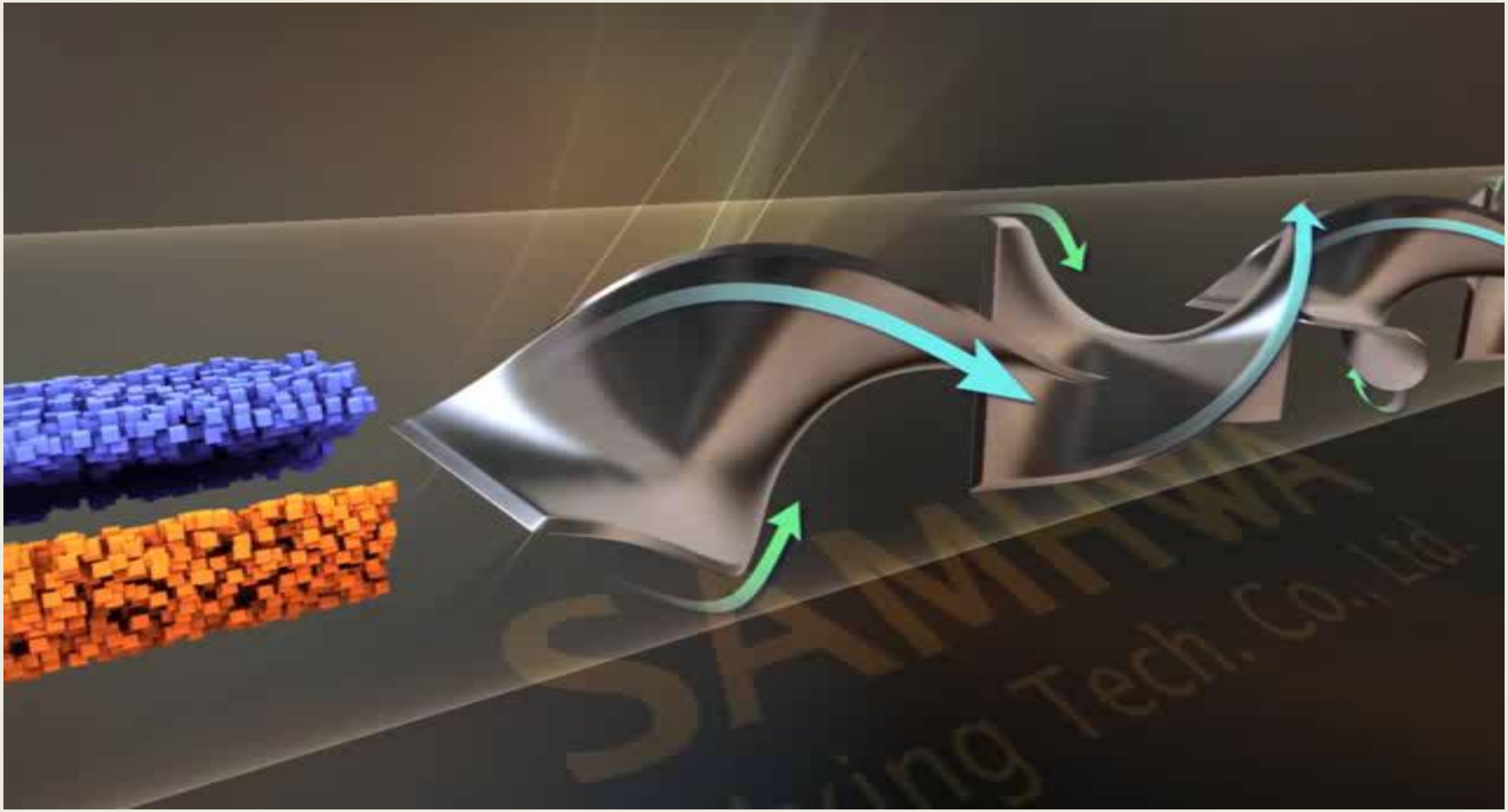
Mixing of melted semisolids

Preparation of suppositories



Mixing of melted semisolids

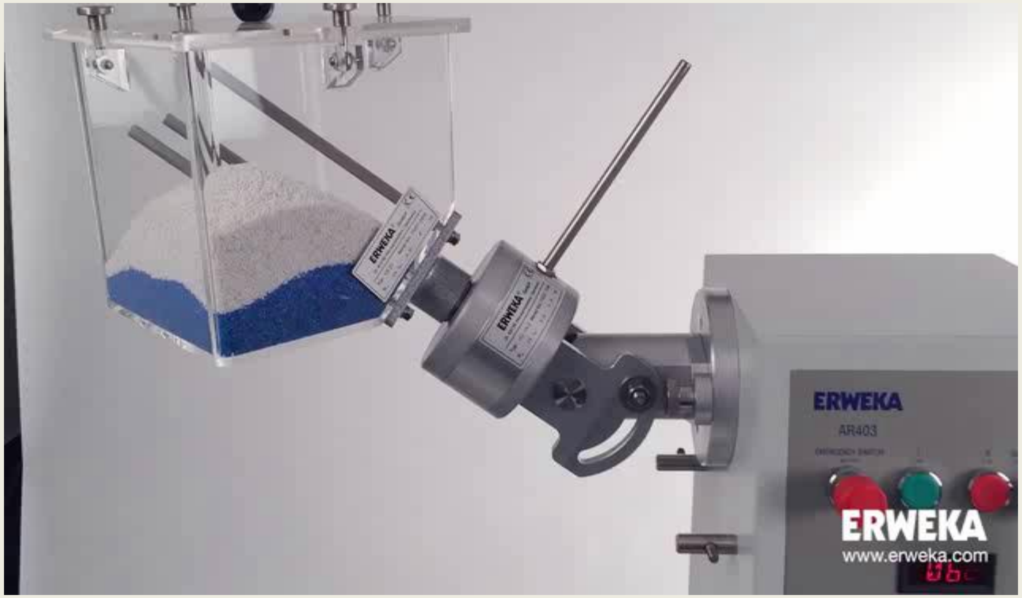
Static mixer

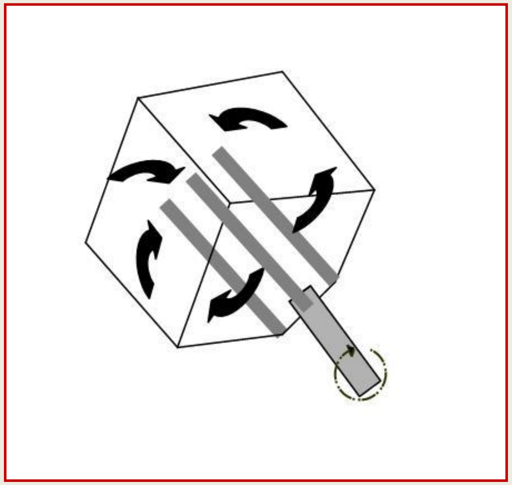


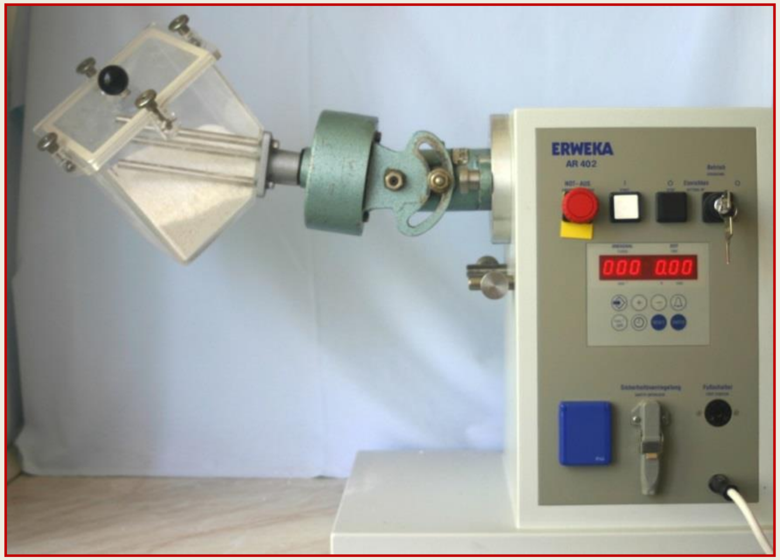
Mixing of solids

Mixing of solids

Rotating cube mixer



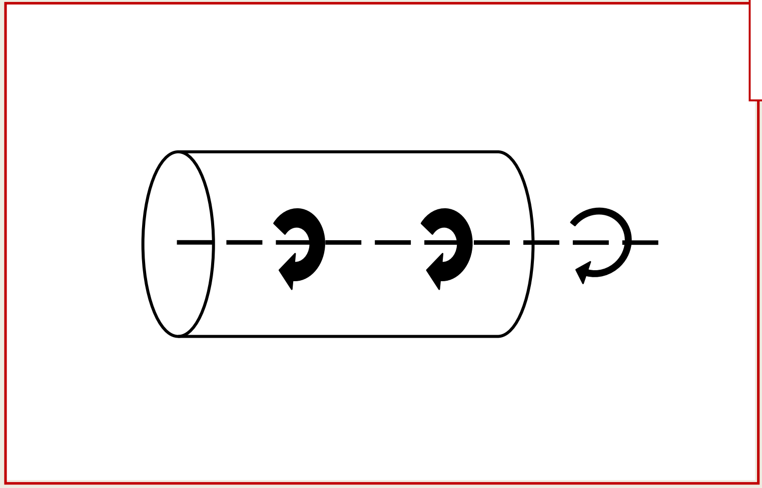


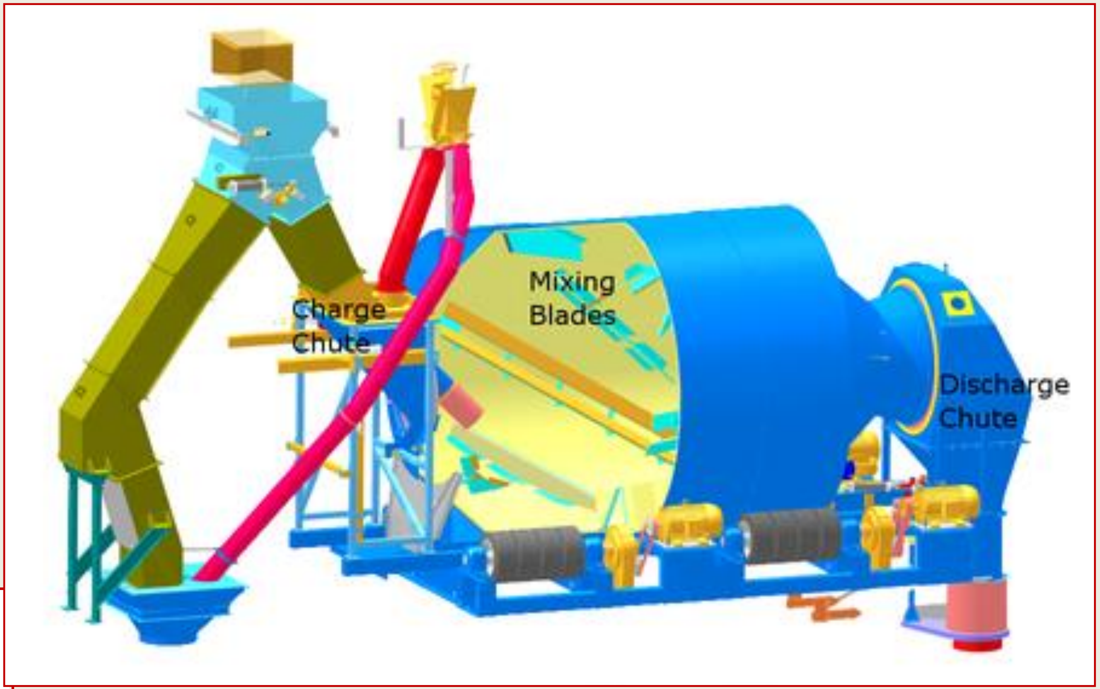


Mixing of solids

Drum mixer

same direction of axis

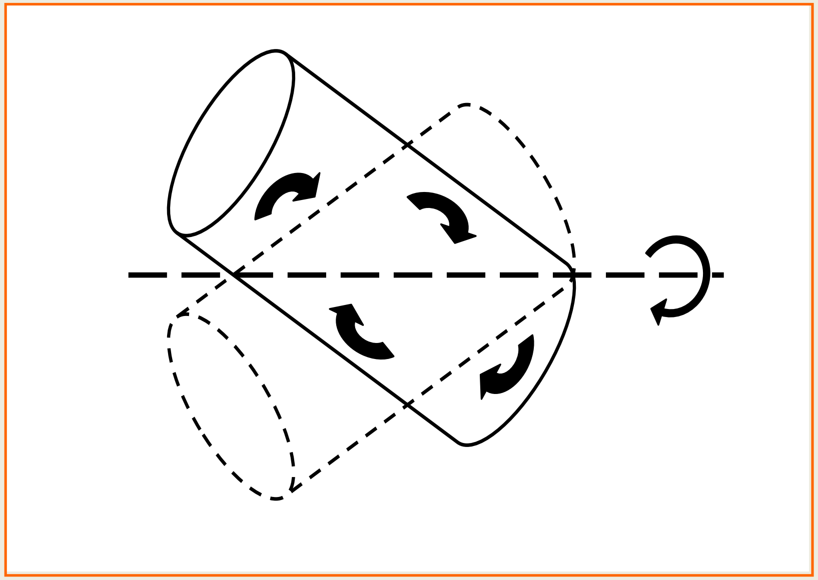




Mixing of solids

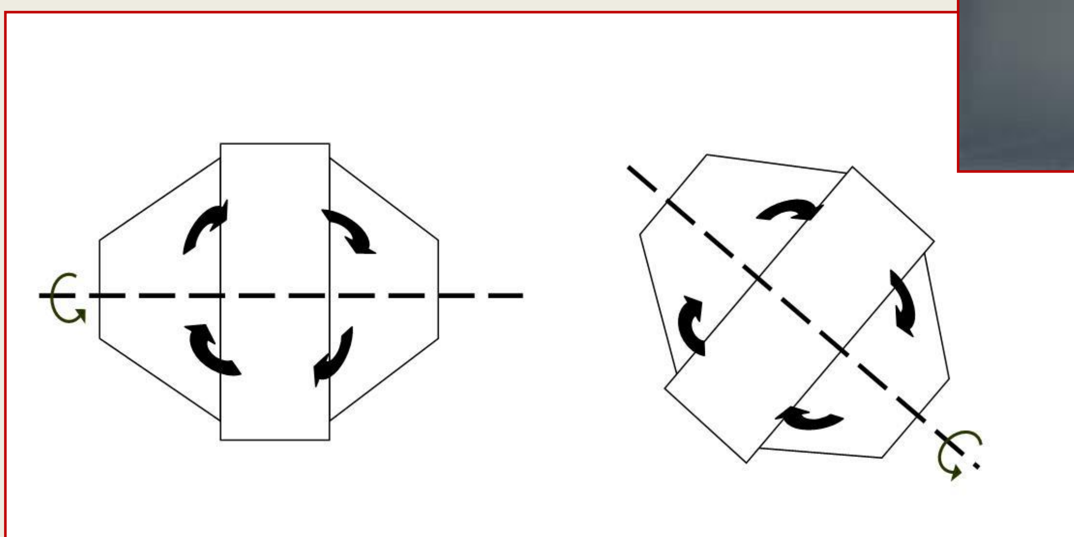
Drum mixer

alternate direction of axis



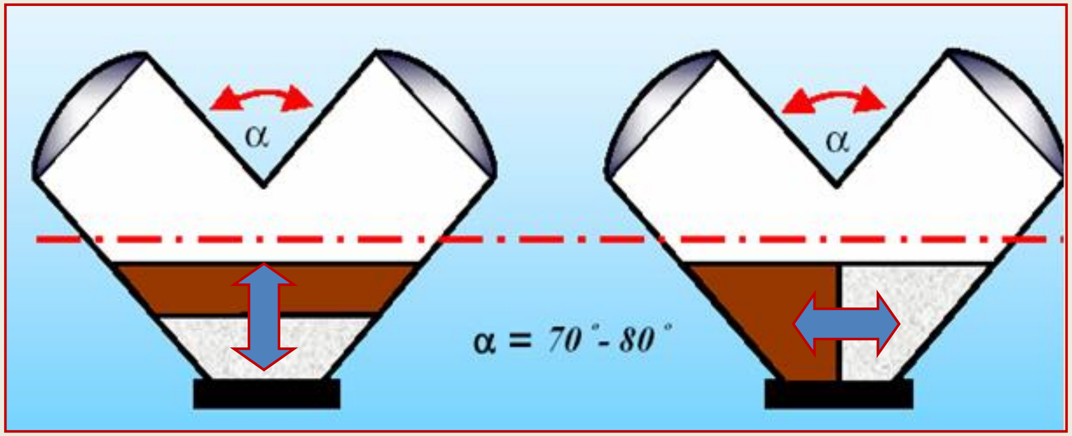
Mixing of solids

Double cone mixer



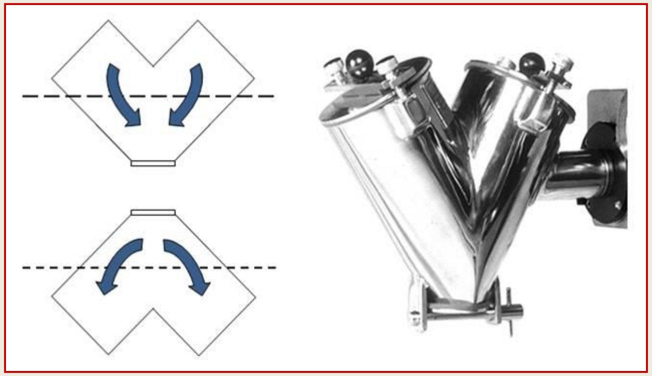
Mixing of solids

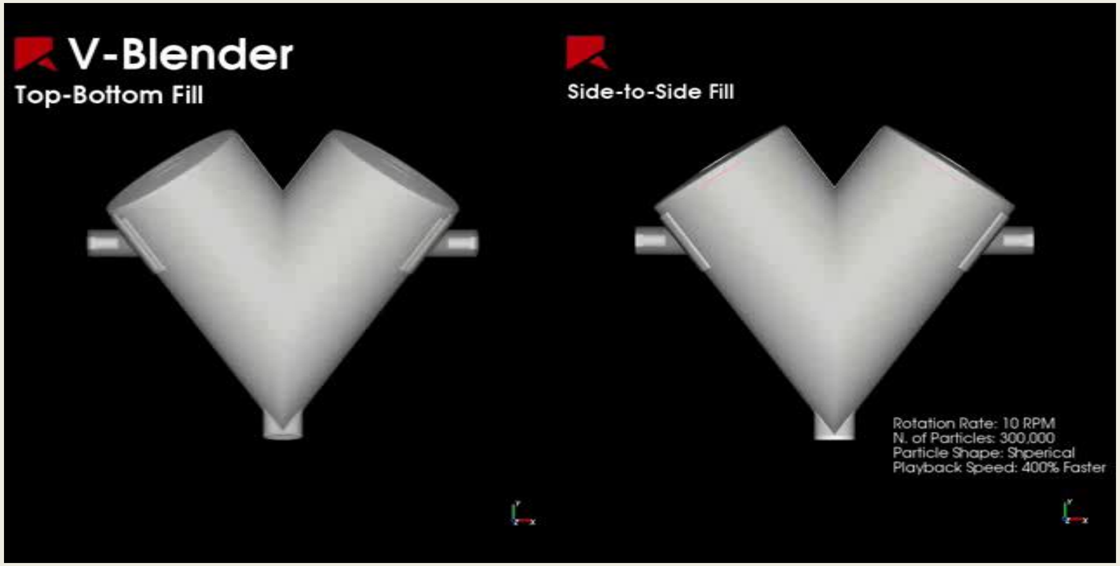
V-mixer



a./
The horizontal layers
are mixed
by each side.

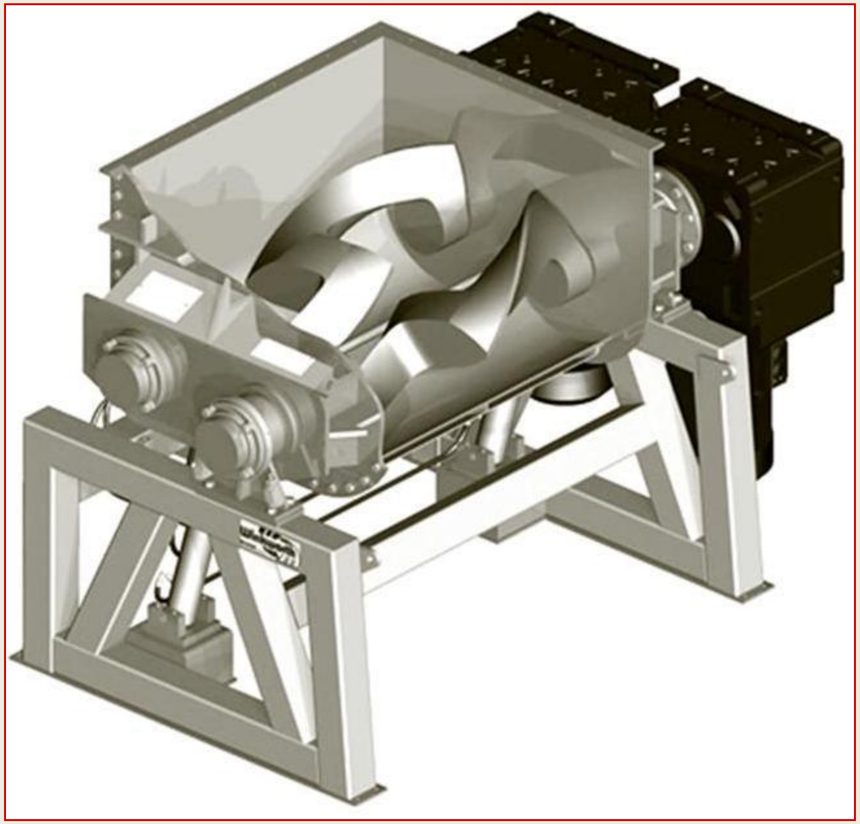
b./
The vertical layers
are mixed
from one side to other.

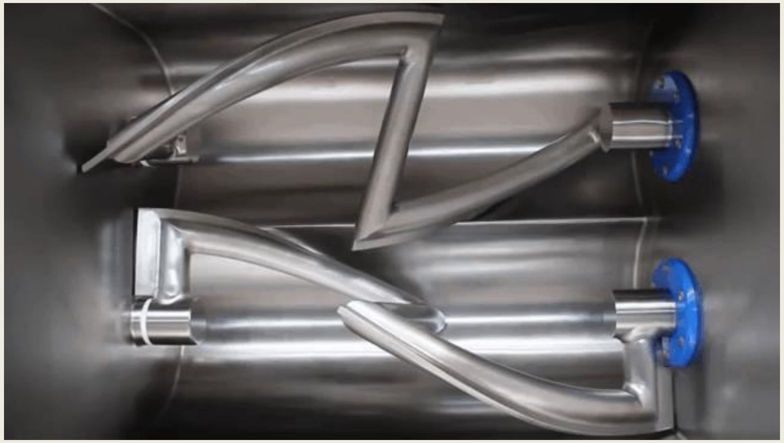




Mixing of solids

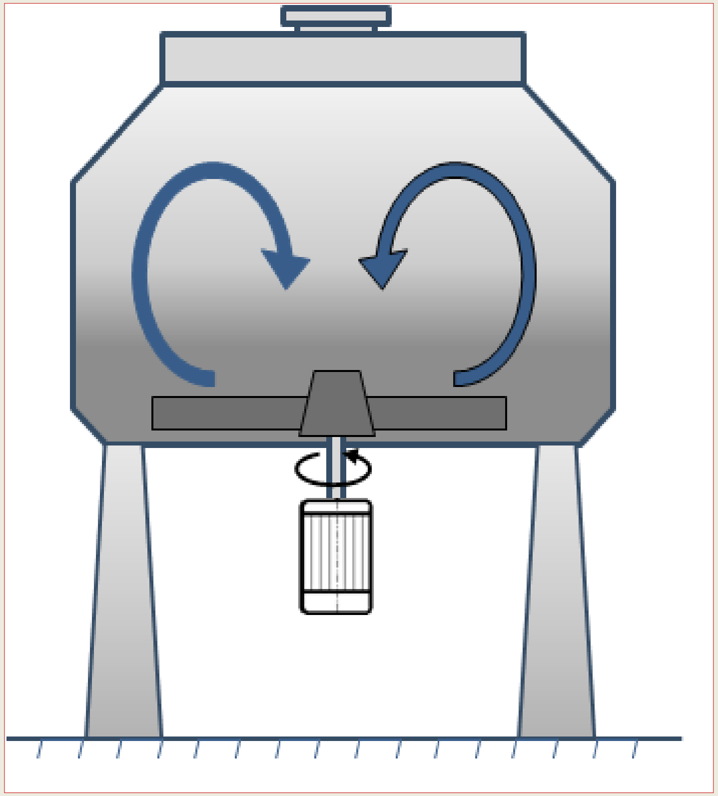
Z-arm mixer (Sigma blade mixer)





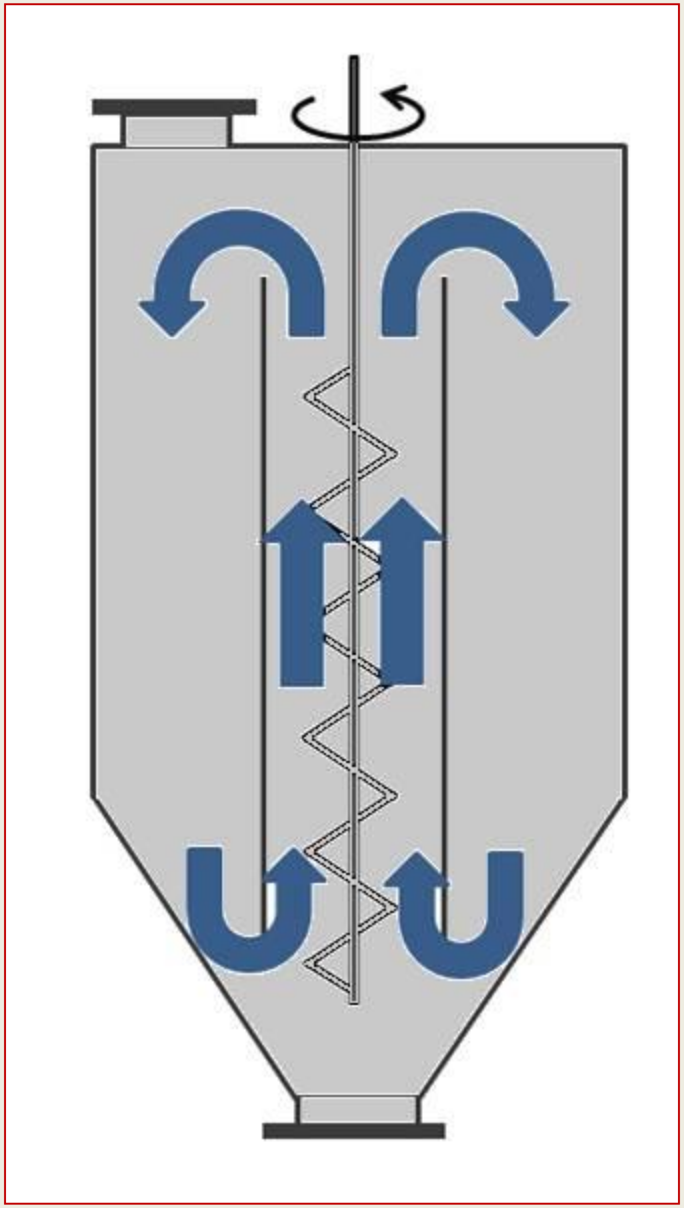
Mixing of solids

High shear mixer



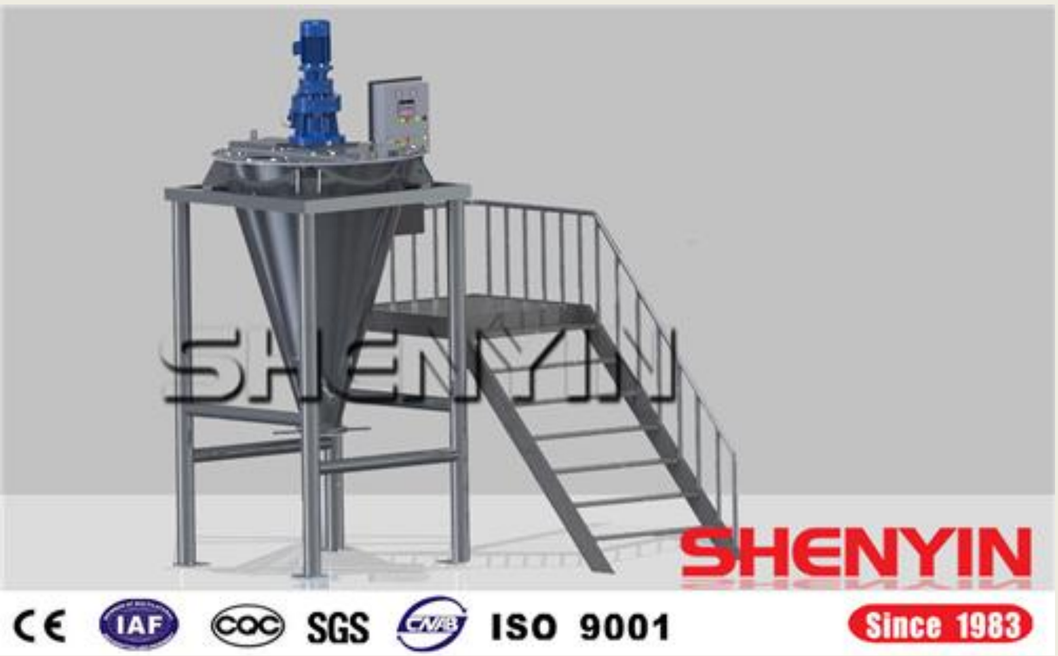
Mixing of solids

Vertical screw mixer



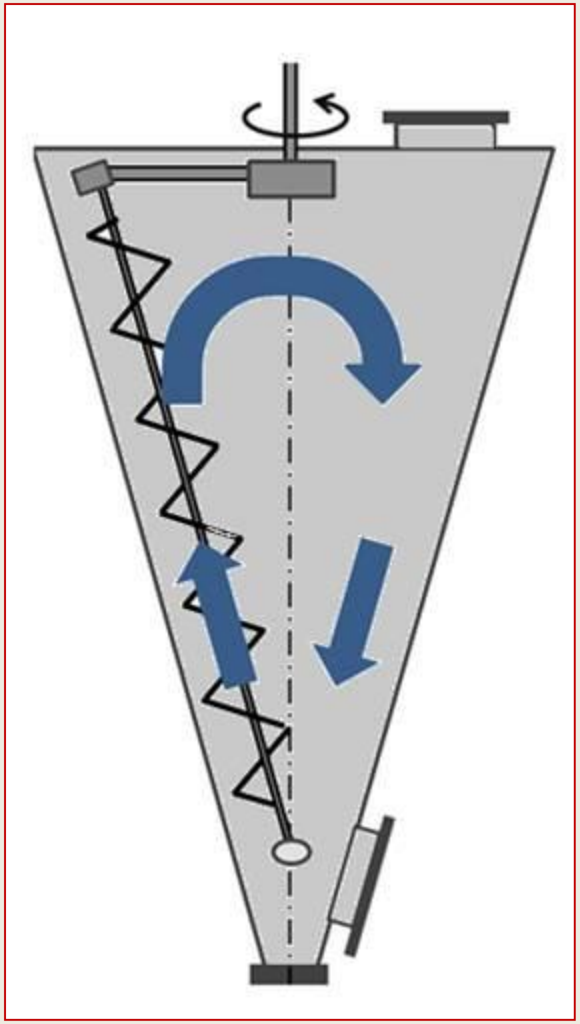
Mixing of solids

Conical vertical screw mixer



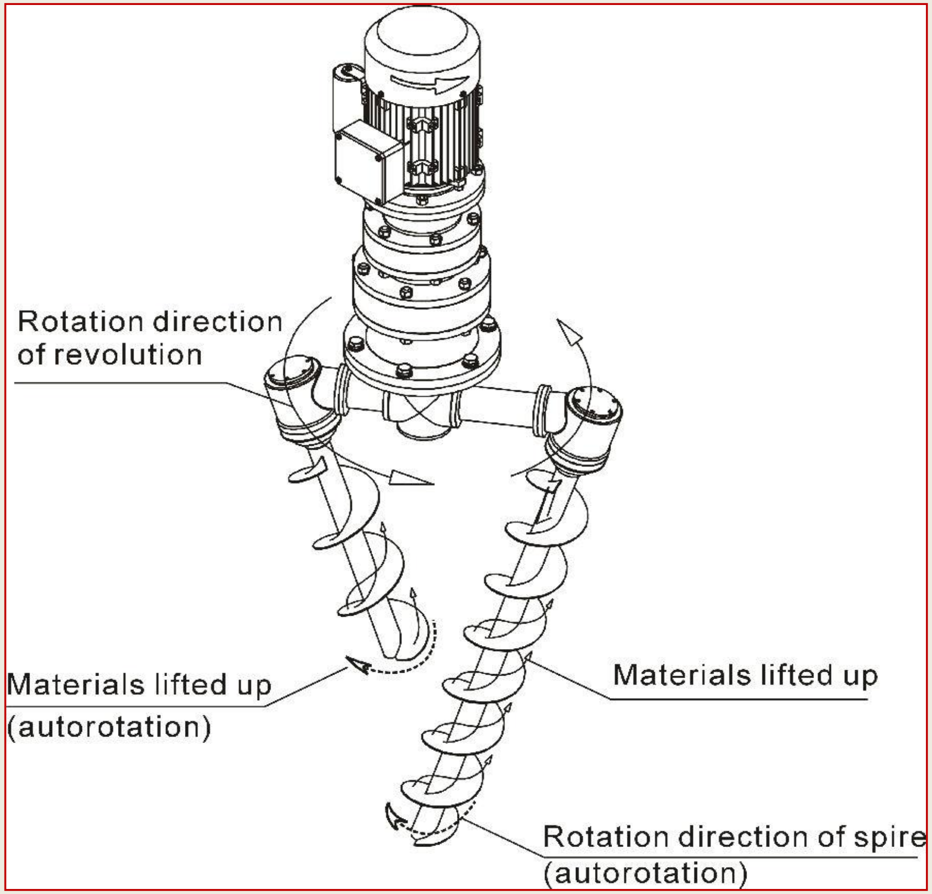
Mixing of solids

Conical oblique screw mixer



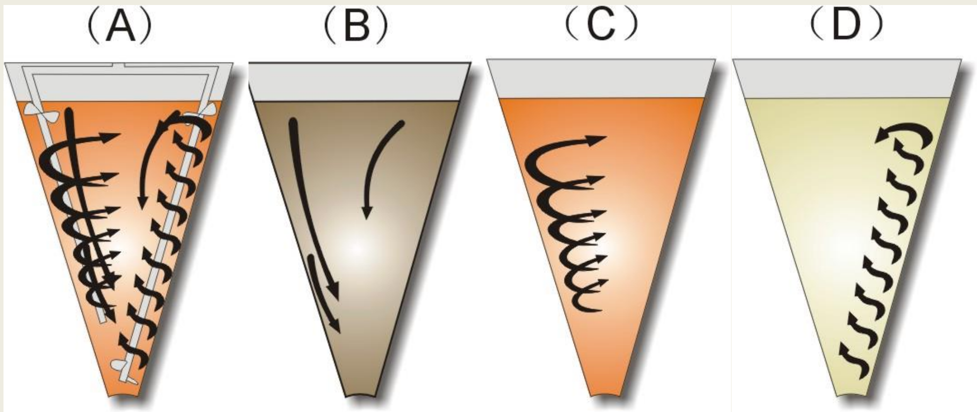
Mixing of solids

Conical oblique double screw mixer



Mixing of solids

Conical oblique double screw mixer



Mixing of solids

Drum mixer

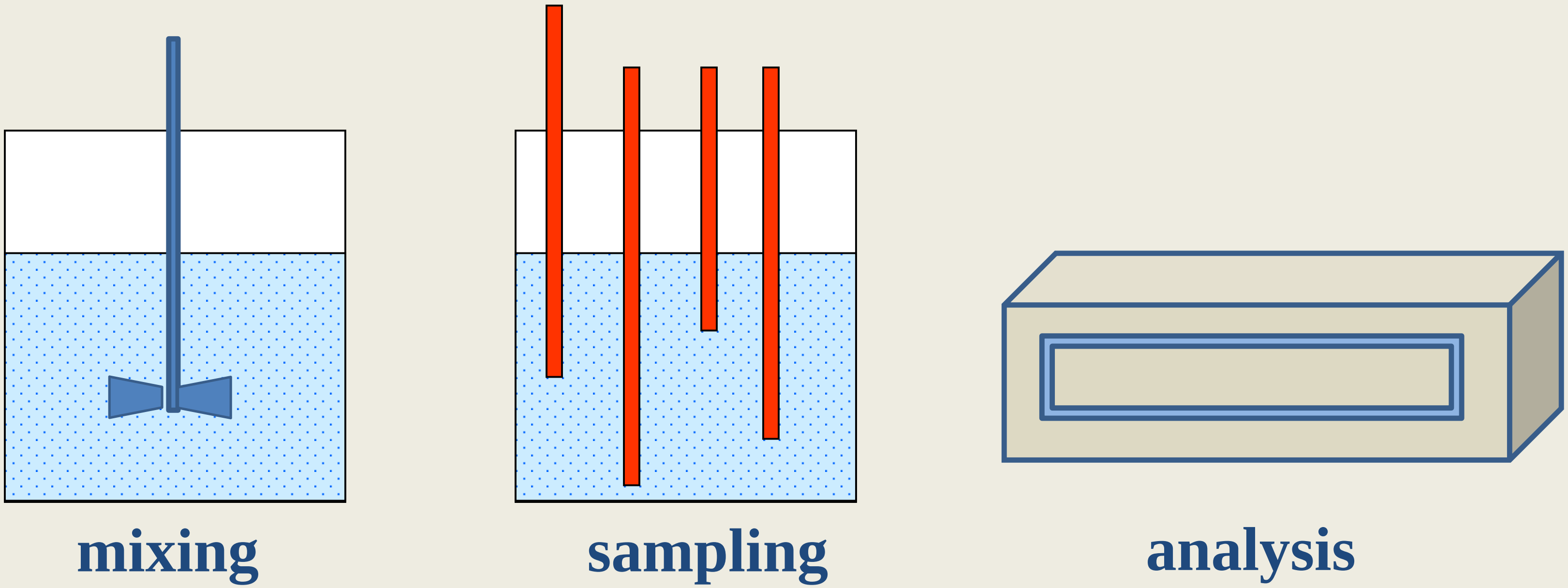
Controlling and optimization of mixing

Controlling and optimization of mixing

Examination of homogeneity

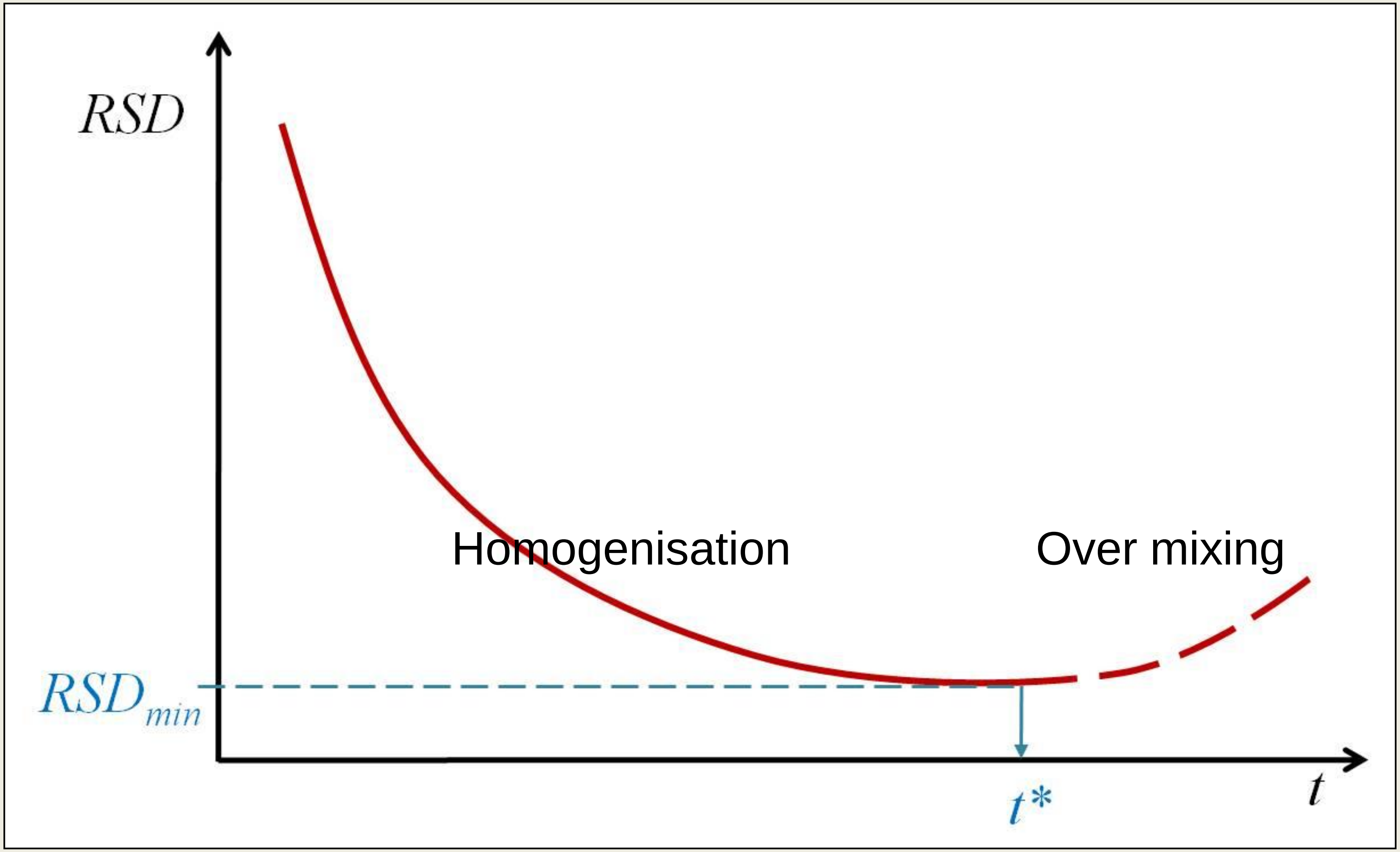
The proper number of samples are taken from different places of the system (liquid)

- determination of API content
- mean, standard deviation, boundary value analysis



Controlling and optimization of mixing

Examination of homogeneity



Thank you
for your attention!!!