EMULSIONS

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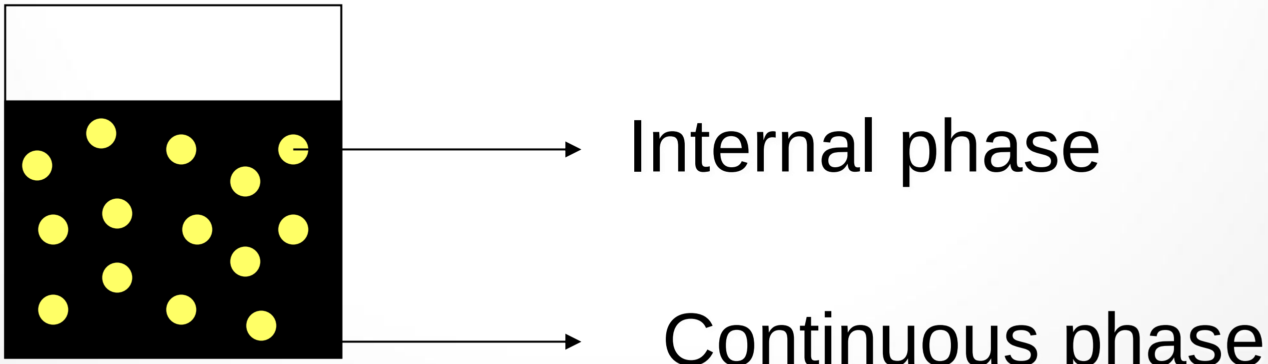
EMULSION

Definition

- An emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases, one of which is finely subdivided and uniformly distributed as globules (the dispersed phase) throughout the other liquid phase (the continuous phase), stabilized by the presence of an emulsifying agent.

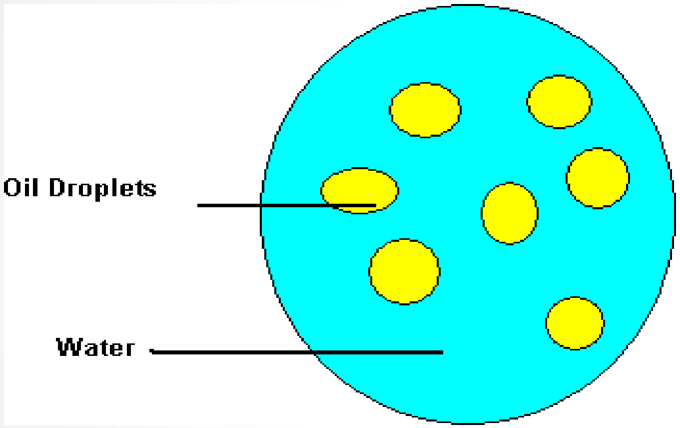
- *Internal phase* = the dispersed phase, (size ~ 0.5 and 25 μm)
- *External phase* or *dispersion medium* = continuous phase.

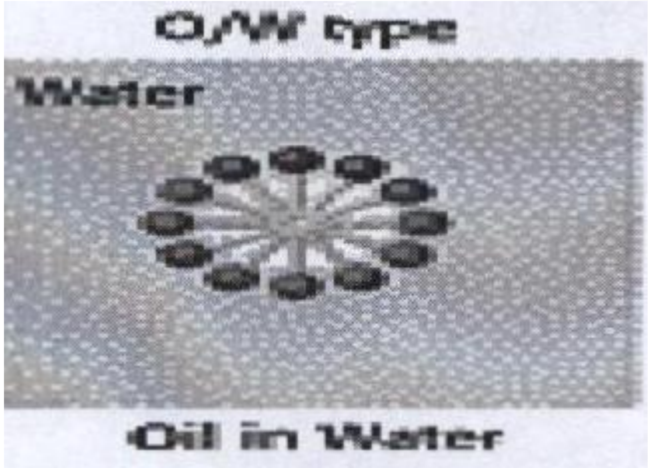


Types of emulsions

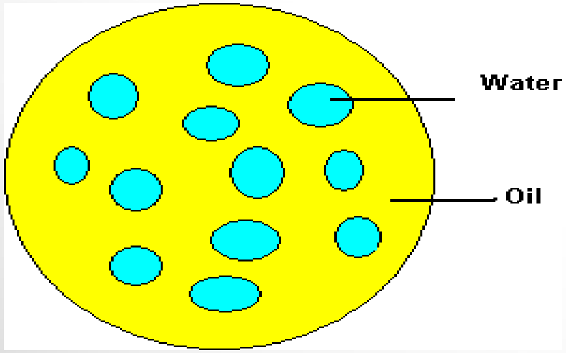
According to the nature of external and internal phases there are

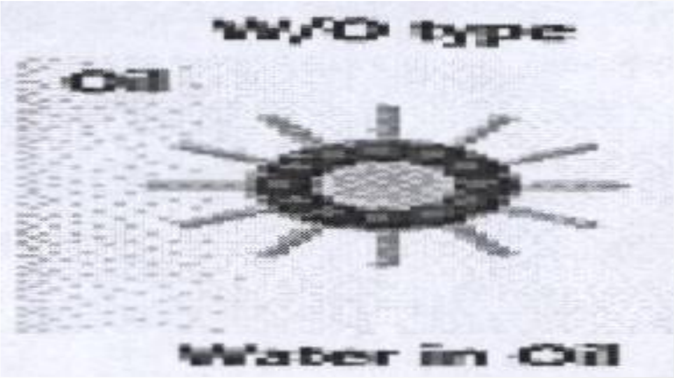
1. **o/w (oil in water)** → the internal phase is oil, - the external phase is water.





2. **w/o (water in oil)** → the internal phase is water, - the external phase is oil.





Types of emulsions

According to the nature of external and internal phases there are

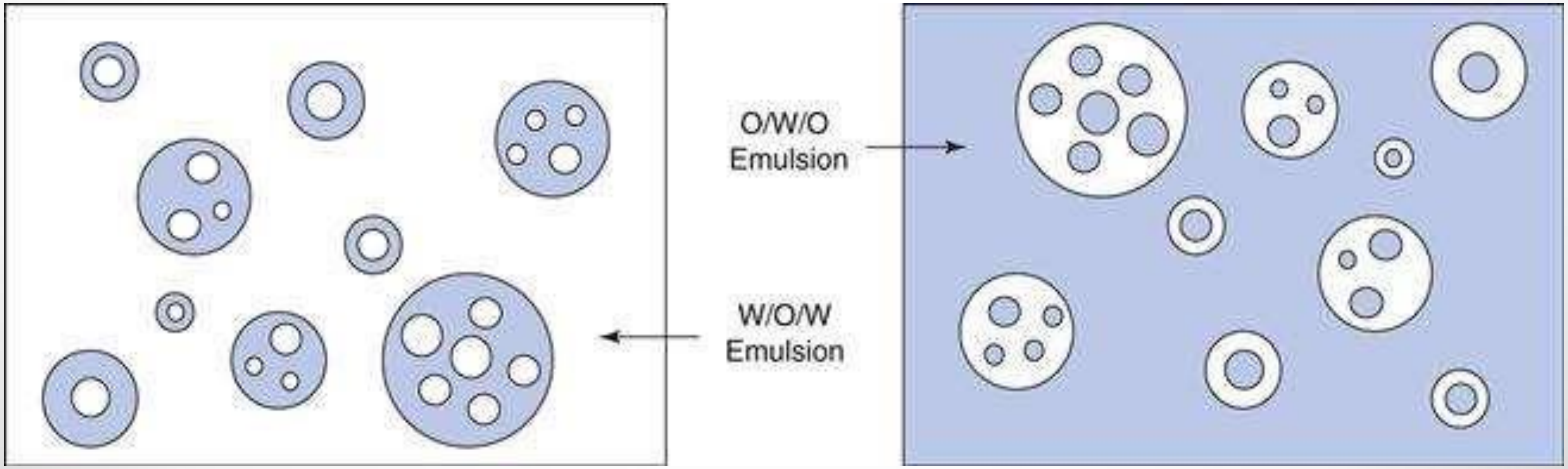
3. Multiple emulsion systems

a). w/o/w   water in oil in water

- Small water droplets are enclosed within larger oil droplets which are themselves then dispersed in water.

b). o/w/o   oil in water in oil

- Small droplets of oil are enclosed within larger droplets of water which are themselves then dispersed in oil.

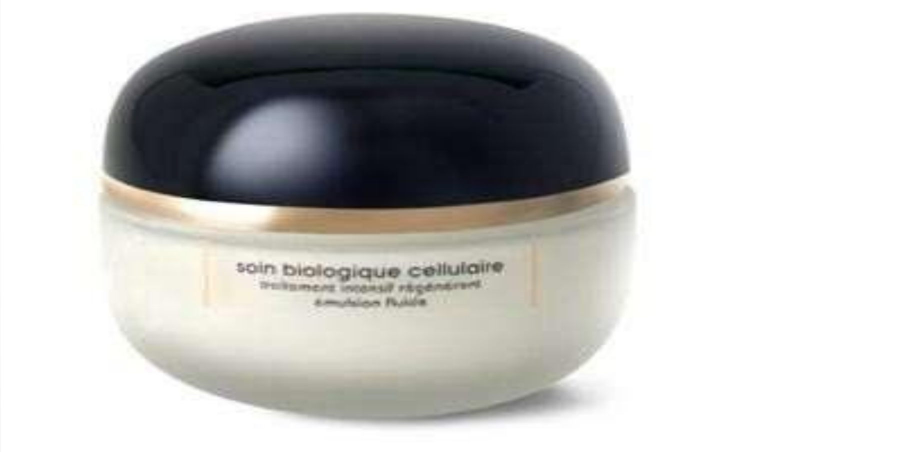


Types of emulsions

<u>**Based on size of liquid droplets**</u>

- 0.2 – 50 mm Macroemulsions
- 0.01 – 0.2 mm Microemulsions
- 50 – 1000 nm Nanoemulsions

PHARMACEUTICAL EMULSIONS



DIFFERENCE BETWEEN O/W AND W/O EMULSIONS

Oil in water emulsion (o/w)	Water in oil emulsion (w/o)
Water is the dispersion medium and oil is the dispersed phase.	Oil is the dispersion medium and water is the dispersed phase.
Water soluble drugs are quickly released from o/w emulsions	Oil soluble drugs are more quickly released from w/o emulsions .
They are preferred for formulations meant for internal use as bitter taste of oils can be masked.	They are preferred for formulations meant for external use like creams.
They are non greasy and easily removable from the skin surface.	They are greasy and not water washable.
They are used externally to provide cooling effect e.g. vanishing cream	They are used externally to prevent evaporation of moisture from the surface of skin e.g. Cold cream.
O/W emulsions give a positive conductivity test as water is the external phase which is a good conductor of electricity.	W/O emulsions go not give a positive conductivity test as oil is the external phase which is a poor conductor of electricity.

Phase-volume ratio:

- Phase-volume ratio is the relative volume of the internal phase compared with that of the external phase.
- The most stable emulsions have an internal phase occupying between 40 to 60 % of the emulsion (loose packing of globules.).
- The upper limit: the internal phase can occupy no more than 74% of the total volume of an emulsion.
- **Critical point** is defined as the concentration of internal phase above which the emulsifying agent cannot produce a stable emulsion of the desired type.

Pharmaceutical applications of emulsions:

1. Oral, rectal and topical administration of oils and oil-soluble drugs.
2. The unpleasant taste or odor can be masked by emulsification. To enhance palatability, an o/w emulsion is a convenient means of orally administering water-insoluble liquids.
3. The absorption and penetration of oil-soluble compounds through intestinal walls are enhanced by emulsification, e.g.; vitamins, are absorbed more completely when emulsified than when administered orally as an oily solution.
4. Patient acceptance is important in topically applied emulsions. Medicinal agents that are irritating to the skin are less irritating if present in the internal phase of emulsion.
5. Intramuscular injections: w/o emulsions have been employed to disperse water-soluble drugs or vaccine in mineral oil to provide slow release.

Pharmaceutical applications of emulsions:

6. The use of sterile stable i.v emulsion containing fats, carbohydrates and vitamins as a potential nutrition.
7. multiple emulsion system as (w/o/w) emulsion can also be used for the prolonged release of drugs that are incorporated into the internal aqueous phase.

N.B

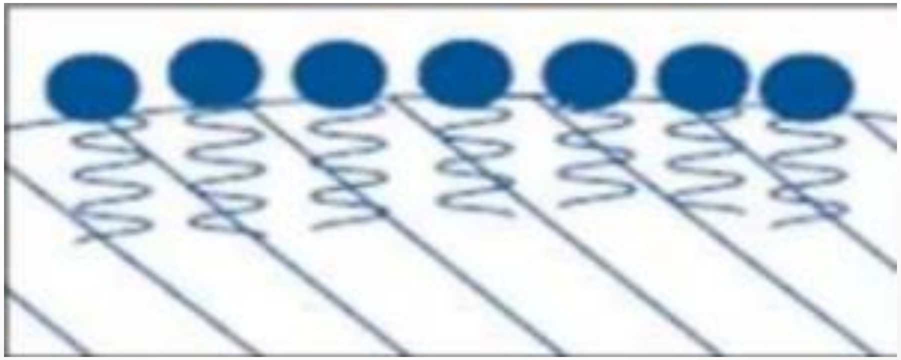
a) I.M, → may be O/W or W/O, but w/o is prefer for depot action.
b) I.V, → must be O/W and the globule size must be kept below 1 μm to avoid the formation of emboli.
c) Oral → O/W emulsion
d) External use, → O/W or W/O, but O/W emulsions are more cosmetically acceptable than W/O because it less greasy, easily washed off the skin and have an emollient effect, which hydrates upper layers of skin.

Theory of Emulsification:

- Film theory or adsorption theory
- Viscosity theory
- Wedge theory
- Interfacial tension theory

Film theory or adsorption theory

- As per this theory, the added emulsifying agent forms a mechanical monomolecular film by getting adsorption at the oil-water interface of the liquid→ ↓ interfacial tension and offers stability to the emulsion.
- However, this theory could not explain the formation of type of emulsion.



Theory of Emulsification:

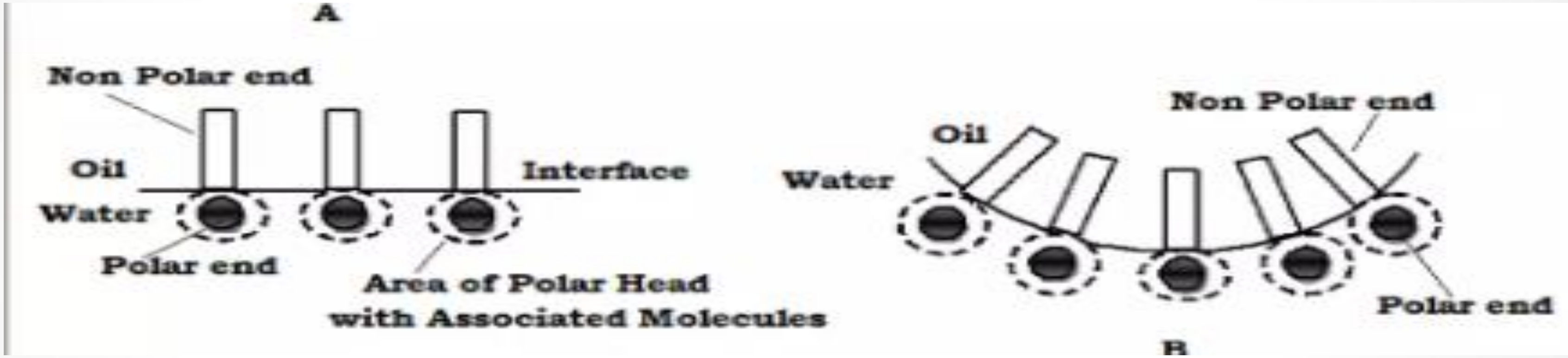
Viscosity theory

- As per this theory, an increase in viscosity of an emulsion → will lead to an increase in stability.
- This theory failed to explain about the milk which shows considerable stability even though its viscosity is less.
- This theory is holds good for emulsions prepared with gums as emulsifying agents, but it collapse or no explanation of emulsions made which comparatively low viscosity and great stability.

Theory of Emulsification:

❑ **Wedge theory**

▪ This theory deals with formation of monomolecular layers of emulsifying agent curved around a droplet of the internal phase of the emulsion.



A. Emulsifier molecules oriented at interface. Dotted lines indicate the large volume occupied by polar head due to formation of hydrated complex.

B. Shows that close packing of molecules ‘ fits’ this curvature.

▪ Example: In a system containing two immiscible liquids, emulsifying agents would be preferentially soluble in one of the phases and would be embedded تضمينها in that phase.

Theory of Emulsification:

Interfacial tension theory

- When two immiscible liquids come in contact, the force causing each liquid to resist breakage is known as interfacial tension. When a high interfacial tension existed between two liquids → emulsification is difficult, and if the tension could be reduced → emulsification facilitated.
- In accordance with this theory the added emulsifying agent reduces the interfacial tension between the oil and water phases and → thus a stable emulsion is formed. This theory could not explain the formation of type of emulsion.

The explanation

- in oil in water dispersion, the interfacial tension is so great that when two globules of dispersed phase approach each other it withdraws the liquid from between them, with the result they coalesce.
- When the interfacial tension is greatly reduced by the addition of emulsifier the globules remain separate.

Stability of Emulsions

I. Physical Instability

A. Creaming

- The upward or downward movement of dispersed droplets globules to form a thick layer at the surface of emulsion relative to the continuous phase.
- This is the separation of an emulsion into two regions, → one of which is richer in the disperse phase than the other

❑ creaming is not a serious instability problem as a uniform dispersion can be re-obtained simply by mild shaking or stirring to get again a homogenous emulsion.

❑ Creaming is influenced by

a) globule size
b) viscosity of the dispersion medium
c) differences in the densities of dispersed phase and dispersion medium

Stability of Emulsions

I. Physical Instability

B. Breaking (Cracking)

- Cracking is the coalescence of dispersed globules and complete separation of the disperse phase as a separate layer.
- It is an irreversible process difficult to redisperse by simple shaking.
- Cracking may occur due to following reasons:-

1. By addition of emulsifying agent of opposite type
2. Bacterial growth: protein materials and non-ionic surface-active agents are excellent media for bacterial growth.
3. Change in temperature: protein emulsifying agents may be denaturated and the solubility characteristics of non-ionic emulsifying agent change with a rise in temperature, heating > 70°C

- Freezing will also crack an emulsion; this may be due to the ice formed disrupting the interfacial film around the droplets.

Stability of Emulsions

I. Physical Instability

C. Phase inversion:

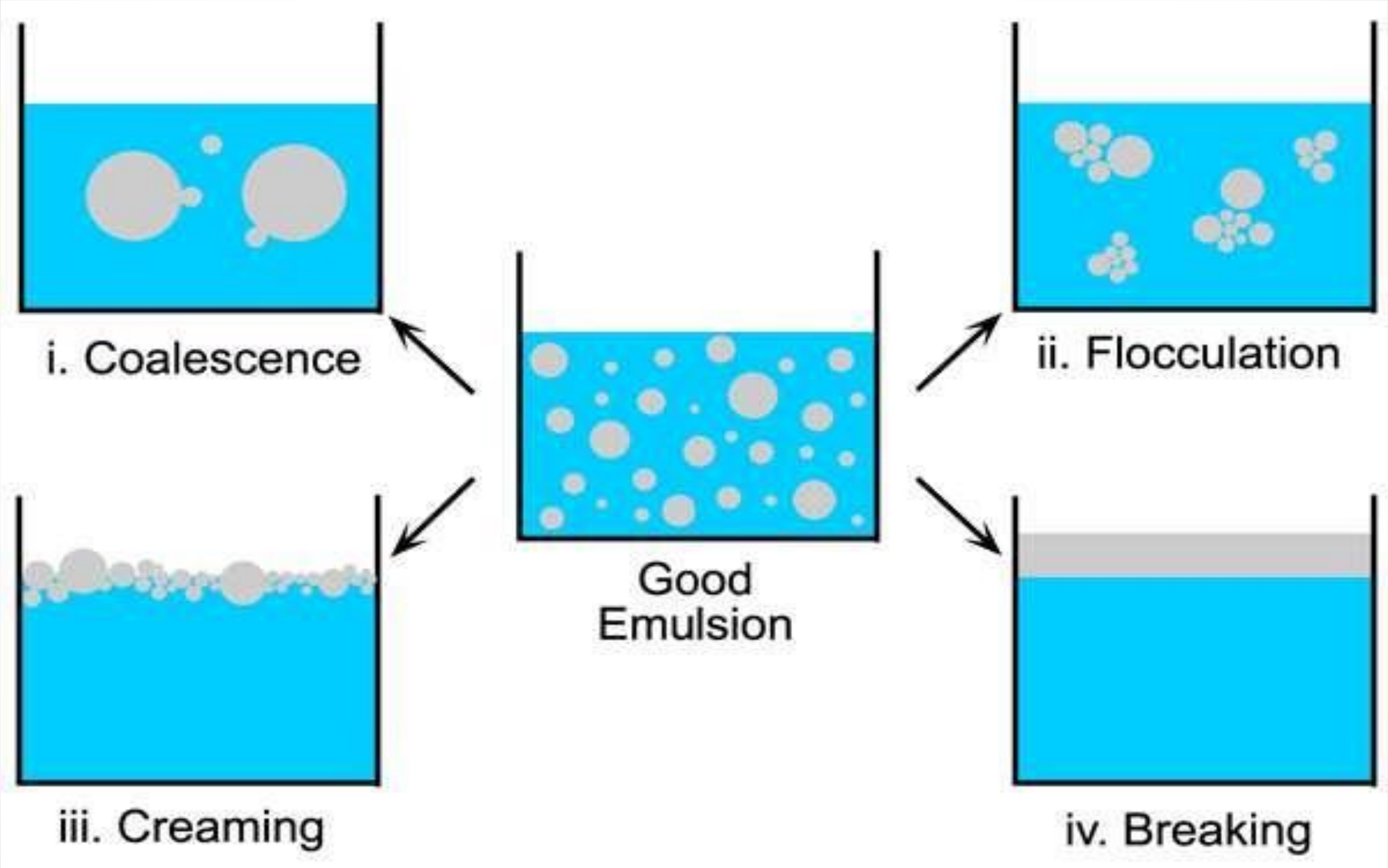
- This involves the change of emulsion type from o/w to w/o or vice versa.
- Soaps of divalent metals produce w/o emulsions while soaps of monovalent metals (and ammonium soaps) produce o/w emulsions.

→ Emulsion type is determined by the solubility of the emulsifying agent; if it is more soluble in water than in oil the former will be the continuous phase, and vice versa

Due to the following reason, phase inversion can take place

1. By the addition of an electrolyte
2. By changing the phase-volume ratio
3. By temperature change
4. By changing the emulsifying agent : An o/w emulsion stabilized with sodium stearate can be inverted to the w/o type by adding calcium chloride to form calcium stearate.

Stability of Emulsions



Methods of Emulsion Preparation

On a small scale, emulsions may be prepared using:

- A dry porcelain mortar and pestle.
- A mechanical blender or mixer.
- A simple prescription bottle.

On a large scale

- High speed impeller in large volume mixing tanks may be used to form the coarse emulsion then the colloid mill is used to produce fine emulsions.
- By passage through a large homogenizer, in which the liquid is forced under a great pressure through a small valve opening.

Mechanical Equipment for Emulsification:

- Almost all methods used for breaking up the internal phase into droplets require some sort of agitation.
- Various types of equipment are available to effect droplet break-up and emulsification either in the laboratory or in production.

❑ Regardless of size and minor variations, such equipment can be divided into four broad categories:

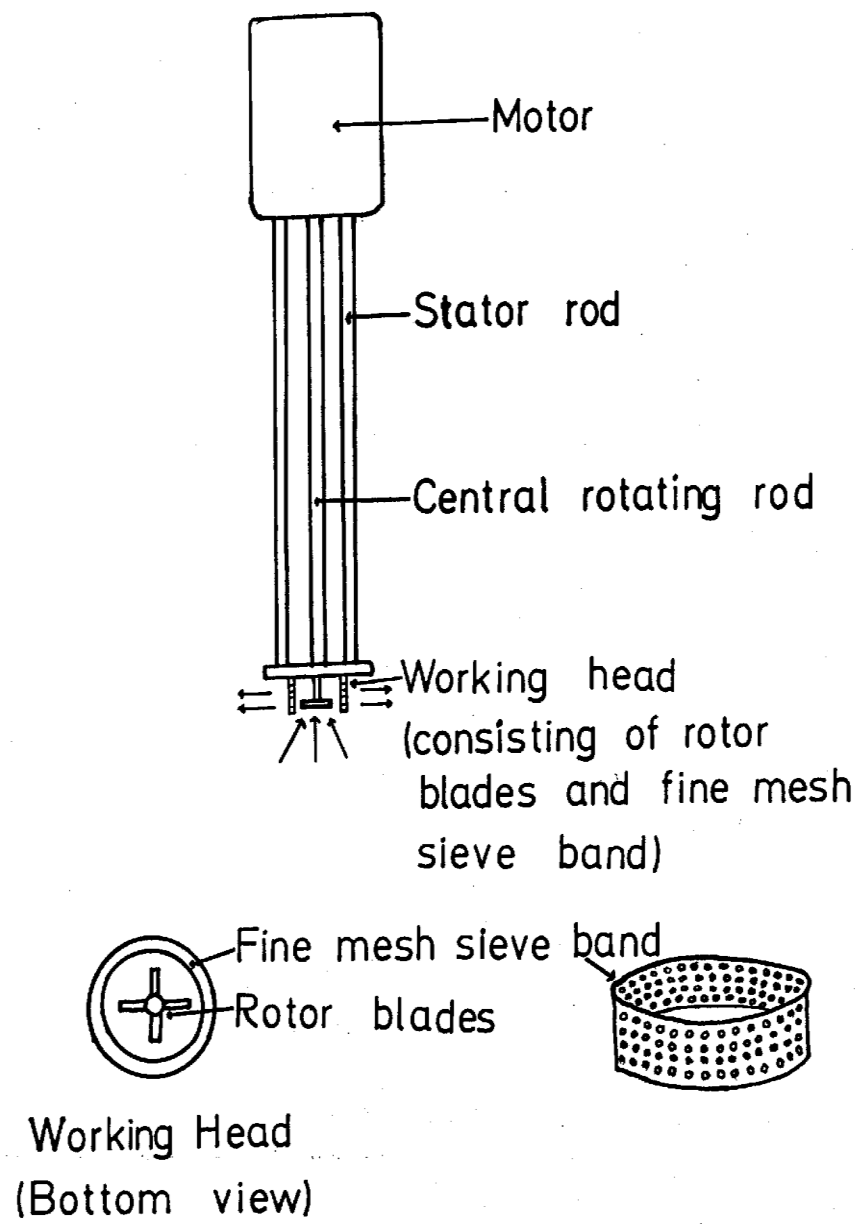
1. Mechanical stirrers.
2. Homogenizers.
3. Colloid mills.
4. Ultrasonifiers.

1. Mechanical stirrers.

I. Silverson mixer -Emulsifier

Construction

- It consists of long supporting columns and a central portion.
- Central portion consists of a shaft which is connected to motor at one end and other to the stainless-steel working head.
- Head carries turbine blades, that are surrounded by a mesh sieve band, which is further enclosed by a cover having openings.



1. Mechanical stirrers.

I. Silverson mixer -Emulsifier

Principle:

- It produces intense **shearing forces and turbulence** by use of high-speed rotors.
- Circulation of material takes place through the head by the suction produced in the inlet at the bottom of the head.
- Circulation of the material ensures rapid breakdown of the dispersed liquid into smaller globules.

❑ **Uses:** Used for the preparation of emulsions and creams of fine particle size.

❑ **Advantages:**

1. Silver son mixer is available in different sizes to handle the liquids ranging from a few milli liters to several thousand liters.
2. Can be used for batch operations as well as for continuous operations by incorporating into a pipeline, through which the immiscible liquids flow.

❑ **Disadvantages**:

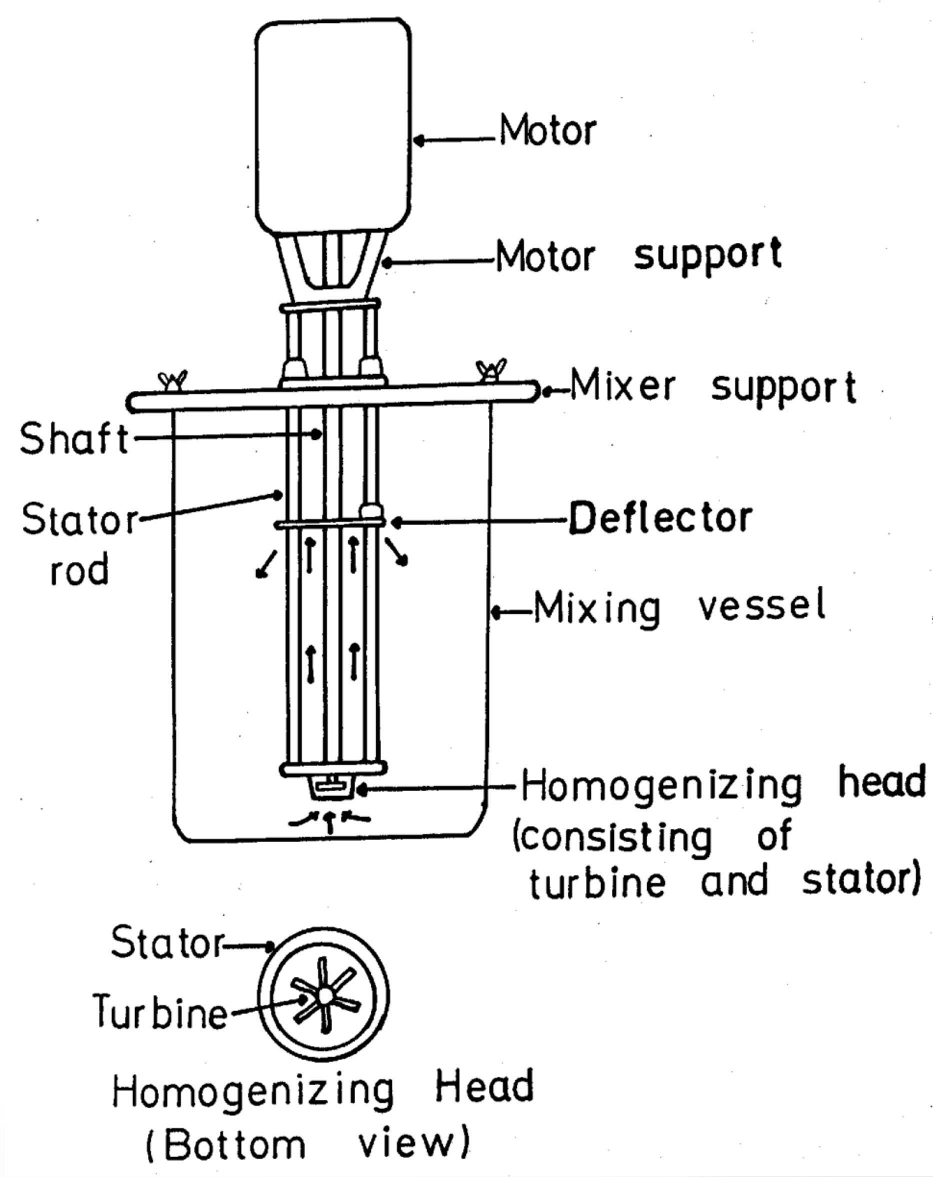
- Occasionally, there is a chance is clogging of pores of the mesh.

1. Mechanical stirrers.

II. Eppenbach Homo-Mirer

Construction

- This consists of a motor mounted above the homogenizing head,
- Head consists of a turbine impeller and a stator (الثابت).
- The clearance between the turbine and stator is fixed and the head is stabilized by means of guide rods extending from the motor support to the stator.



1. Mechanical stirrers.

II. Eppenbach Homo-Mirer

Principle:

- Homogenization is carried out by immersing the homogenizing head in the tank or mixing vessel containing the material to be treated.
- The turbine rotates at speed from *3500 to 10000 r.p.m.,* creating a → pressure differential between the bottom of the turbine and the surface of the material being processed.

→ As a result, the material is continuously drawn from the bottom of the vessel and forced to pass through the restricted openings between the rotor (turbine) and stator in the homogenizing head, where it is subjected to intense forces of hydraulic shear and impact, → thus broken up to small particles.

→ The material is discharged in an upward direction after it has passed through the homogenizing zone → **An adjustable baffle حاجز** then deflects this rising current toward the sides of the tank, which in turn direct the material back down into the mixing zone where the cycle is repeated.

1. Mechanical stirrers.

II. Eppenbach Homo-Mirer

❑ Advantages of the Homo-Mixer:

1. Homogeneous dispersions of solids or pigments and emulsions of different types can be obtained in a short period of time.
2. Little or no vortex is formed because of the presence of the deflector and the fact that the mixer draws material from the bottom of the vessel.→ Therefore, a minimum amount of air is incorporated into the processed material.

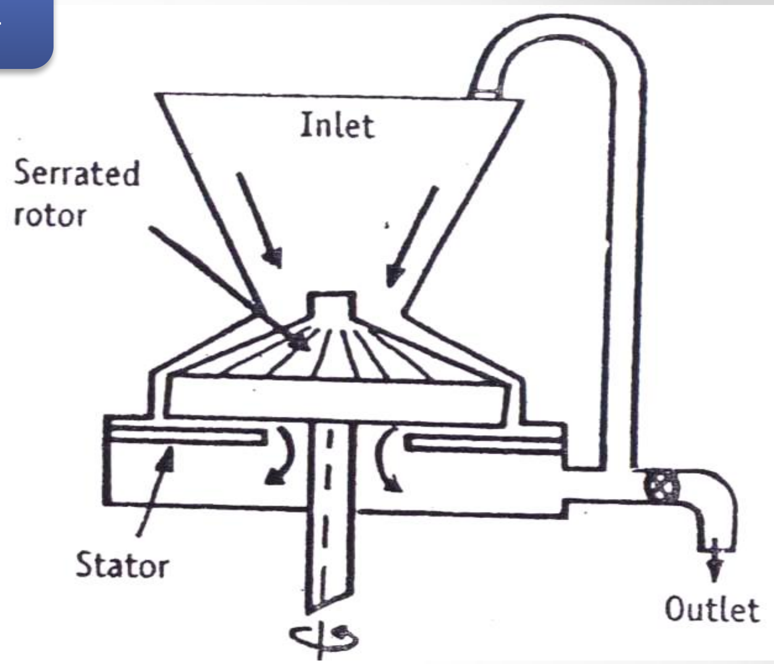
2. Colloid mill

❑**Principle**: shearing (Hydraulic shear)

- They operate on principle of high shear which is normally generated between rotor and stator of the mill.

❑**Construction**:

- It consists of two steel discs; fixed stator plate & high-speed rotating rotor plate with conical milling surface in between (adjustable clearance) which can be adjusted from 0.002 to 0.03 inches.
- Rotors & the stator may be smooth or rough surfaced.

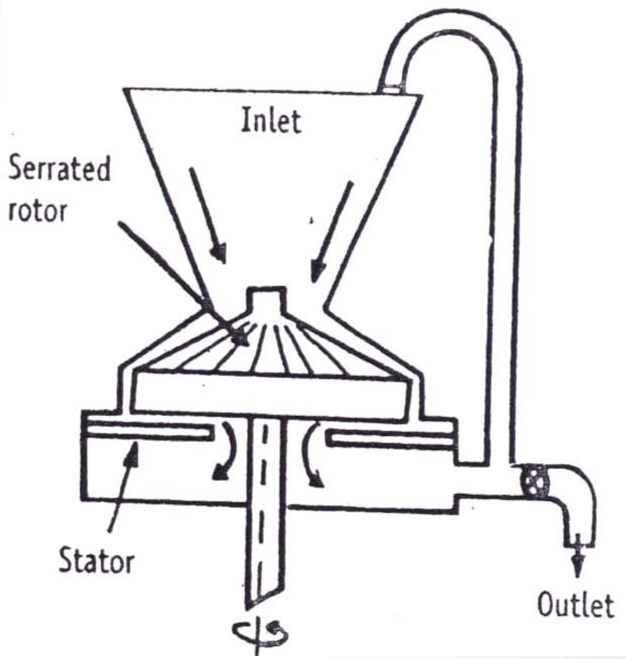


2. Colloid mill

Working:

- Solids should be premilled as fine as possible then mixed with liquid vehicle before introduced into the colloid mill to prevent mill damage.

- The rotor rotates at 3000 – 20000 rpm/min, → When the material is passed through these discs, they get sheared → coarse particles are broken down in small particles due to shear.



2. Colloid mill

❑Uses:

1. Preparing colloidal dispersions, Suspensions, emulsions with particle size < 1 micron.
2. Obtain high degree of dispersion of solid or liquid in liquid

❑Advantages:

1. High capacity with minimal space requirements.
2. Rapid handling and easy cleaning .
3. It can be used in the production of sterile products.
4. Suitable for products of high viscosity range.
5. Infinitely adjustable gap settings between rotor/ stator for control particle size reduction.

❑Disadvantages

1. High power required for running the mill.
2. Consumes more energy.
3. Its not use for dry milling (Wet materials needed for grinding).
4. Due to shear→ heat is generated, thus not suitable for thermolabile material.

COLLOID MILL

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3. Ultrasonifiers

- The use of ultrasonic energy are useful for the **laboratory** preparation of fluid emulsions of **moderate viscosity** and **extremely low particle size.**
- Depending upon the source and method being used to generate the *ultrasonic waves*→ Ultrasonic equipment may be divided into three basic types of units.

A. Piezoelectric generators.

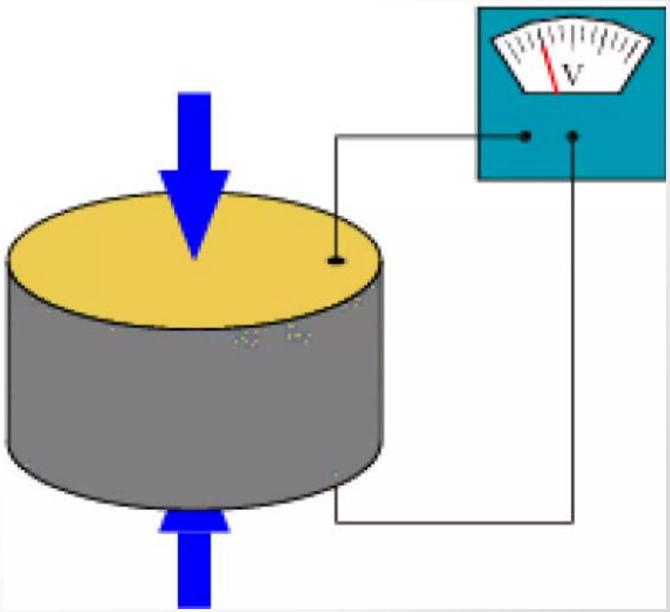
B. Magnetostriction generators, and

C. Hydrodynamic generators.

3. Ultrasonifiers

A. Piezoelectric generators.

- Piezoelectricity is the ability of certain crystals (piezoelectric materials) to develop an electrical potential on their surfaces (became electrically polarized) when subjected to mechanical stress.
- The degree of polarization was proportional to the applied strain
- Piezoelectric materials also show the ***opposite effect***, where application of an electrical field creates mechanical stress (size modification) in the crystal.
- Such as those of Rochelle salt and quartz.
- These transduced piezoelectric devices have limited output and are expensive
- They are useful for laboratory preparation of emulsions of moderate viscosity and extremely low particle size



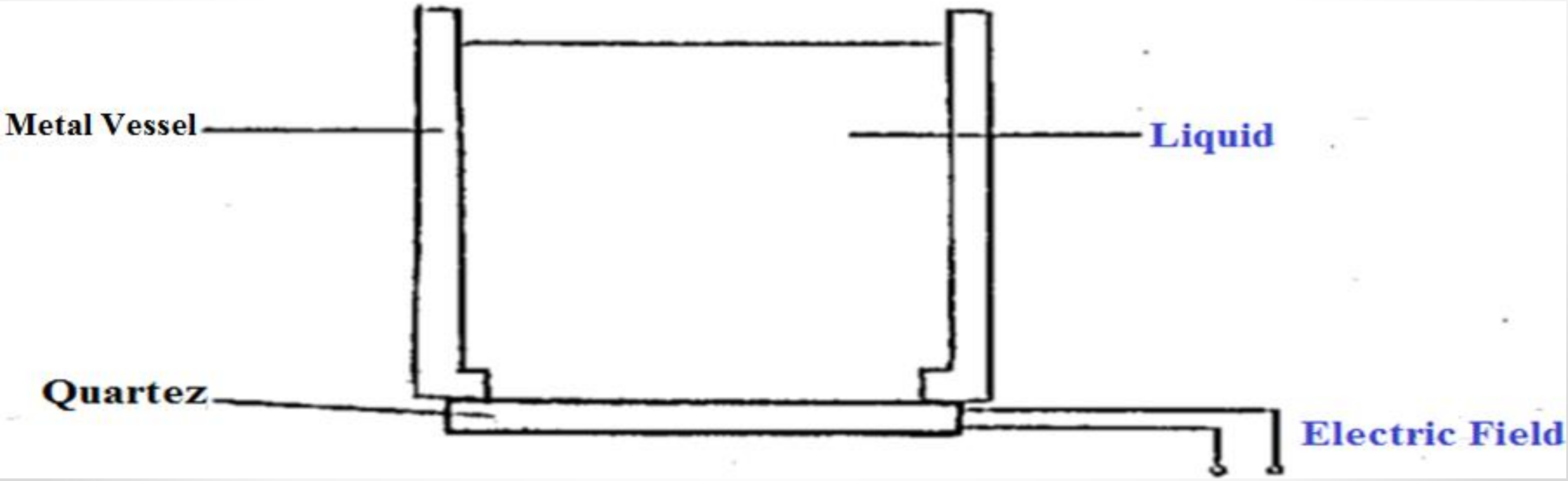
N.B: Rochelle salt, is a **Potassium sodium tartrate tetrahydrate**,

3. Ultrasonifiers

A. Piezoelectric generators.

Procedure:

- A quartz piezo crystal is immersed in an oil or water bath.
- An alternating source of electric potential of suitable frequency is applied → the crystal is set into vibrations producing stationary waves in the liquid which is thus violently agitated.
- The material to be treated may be placed in a suitable container and dipped in the bath → The energy is then transferred from the liquid in the bath through the wall of the container into the material.



3. Ultrasonifiers

A. Piezoelectric generators.

Advantages

- **Ultrasonic frequencies as high as 500 MHz can be obtained.**
- **Output of this oscillator is very high.**
- **Not affected by temperature and humidity.**

Disadvantages

- **Cost of piezo electric quartz is very high.**
- **Cutting and shaping of quartz crystal are very complex.**

3. Ultrasonifiers

B. Magnetostriction Generators.

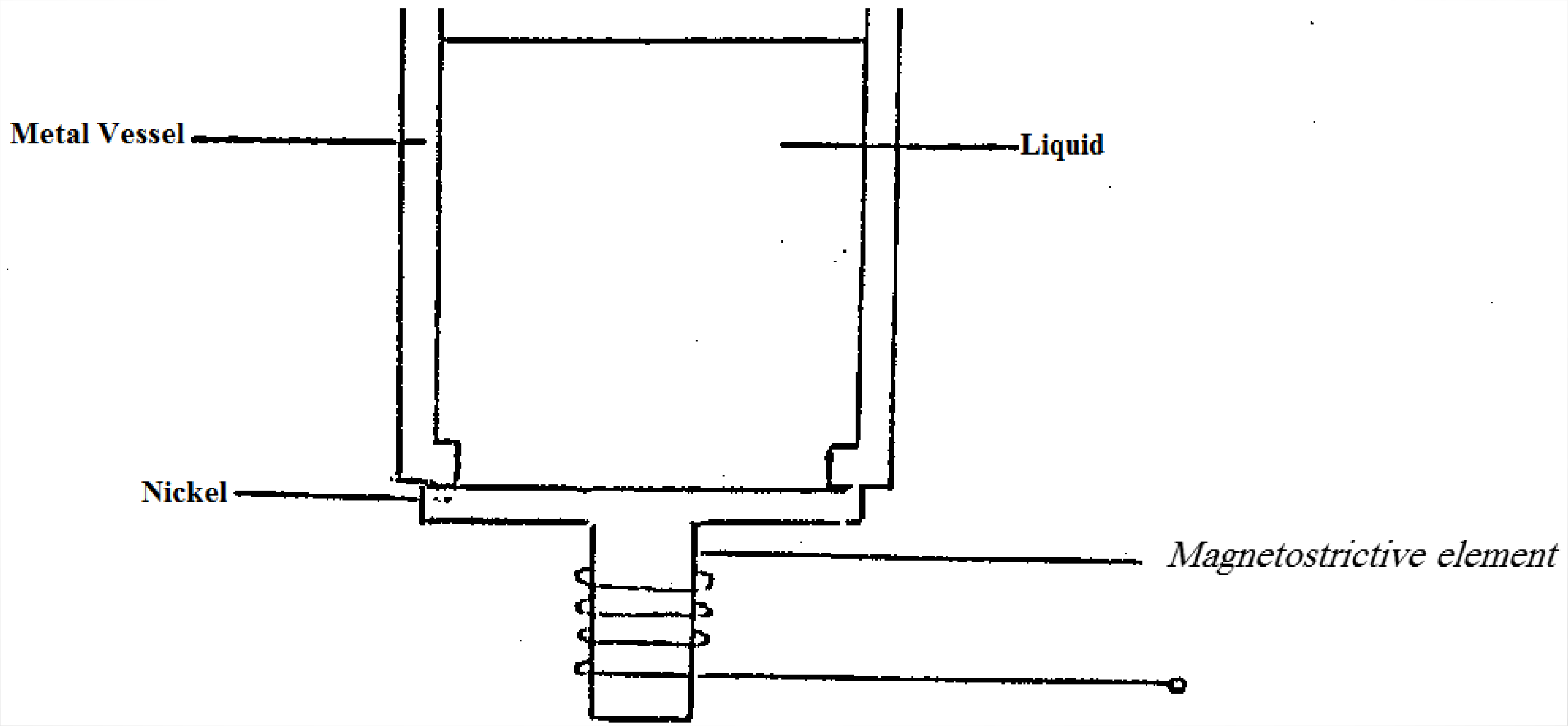
Principle:

- When certain crystals such as nickel and its alloys وسبائكه is placed in an alternating magnetic field parallel or perpendicular to its length, → the rod experiences a small change in its length (will be periodically elongated and contracted), → thus setting up vibrations.
- The change in length (increase or decrease) produced in the rod depends upon
  a. the strength of the magnetic field,
  b. the nature of the materials
  c. independent of the direction of the magnetic field applied.

3. Ultrasonifiers

B. Magnetostriction Generators.

- The alternating magnetic field is adjusted to the natural frequency of the vibrating metal rod, which may be placed directly in the liquid to be treated as shown in figure below.
- This avoids any energy loss due to absorption or reflection by the treatment container.



3. Ultrasonifiers

B. Magnetostriction Generators.

Advantages

- very simple design
- production cost is low
- large power output without the damage of the oscillatory circuit.

Disadvantages

- Cannot generate ultrasonic frequency above 3000 kHz.
- frequency of oscillations depends on temperature.
- Energy loss due to hysteresis and eddy current. التباطؤ و التيار الدوامة.

3. Ultrasonifiers

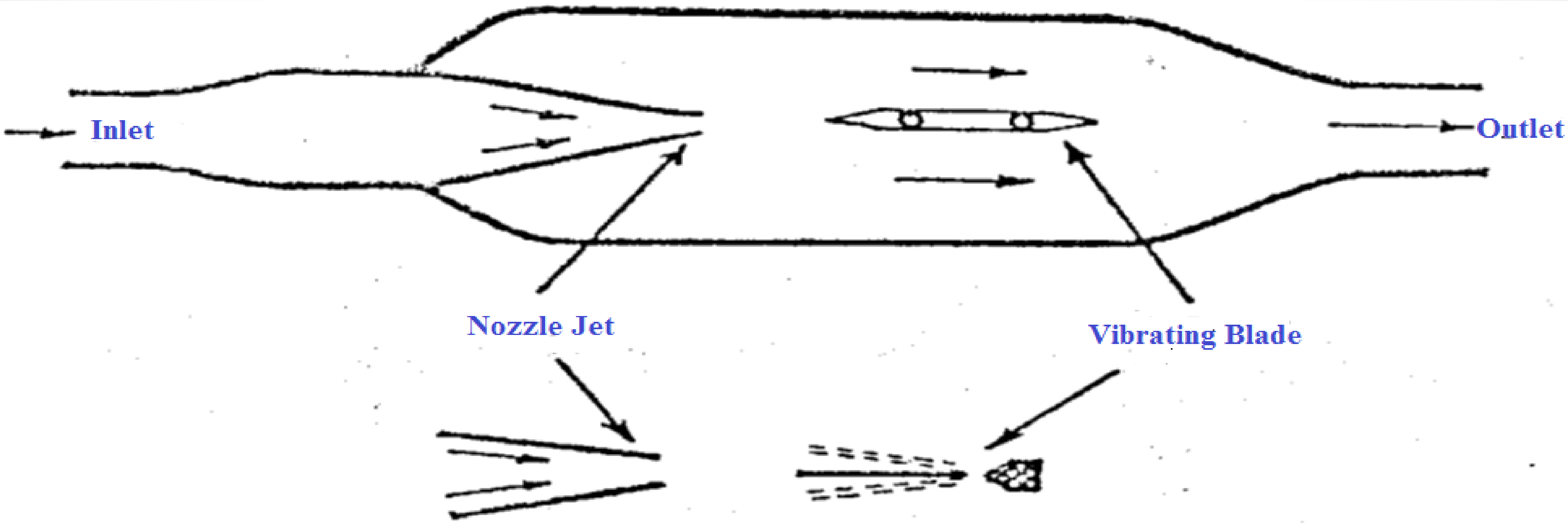
C. Hydrodynamic Generators.

“lquid whistle ويسل" or "sonolator".

Principle: (Pohlman)

→ The dispersion is forced through an orifice at modest pressure (150 - 350 psi) and is allowed to impinge الاصطدام upon a blade edge →

→ This pressure cause the blade to vibrate very rapidly to produce an ultrasonic note. → . This ultrasonic energy is sufficient to cause emulsification or dispersion.



3. Ultrasonifiers

C. Hydrodynamic Generators.

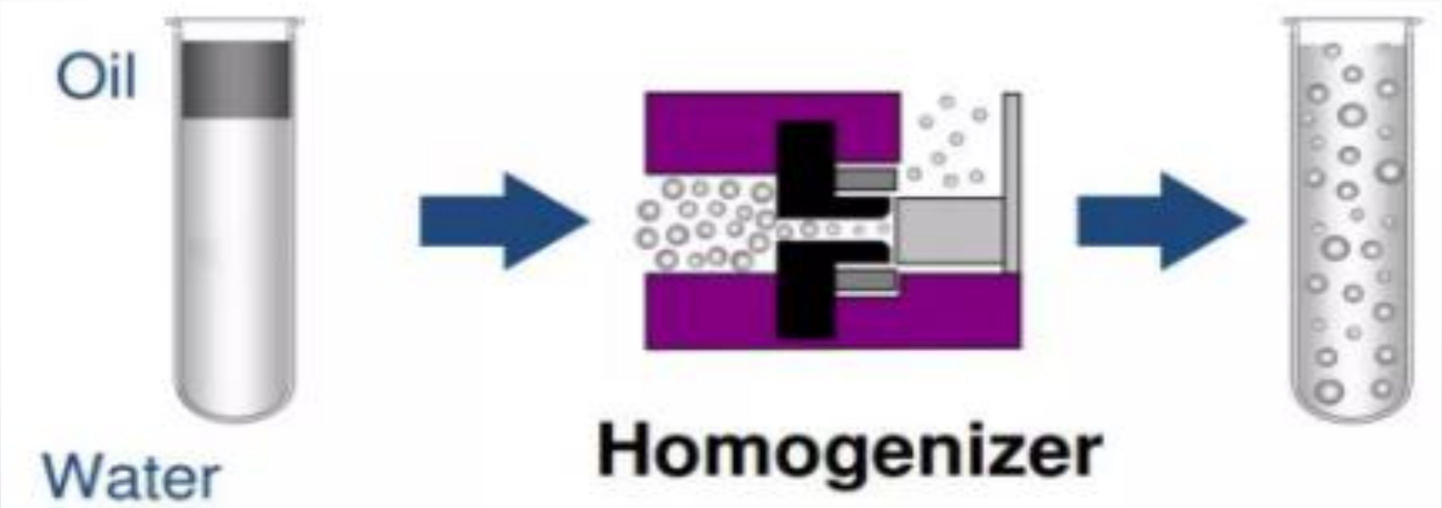
- The hydrodynamic generator is the most suitable for production use since the piezoelectric and the magnetostrictive generators suffer from the difficulties (disadvantage) of :

– obtaining large enough piezo crystals for processing large volumes of liquids and

– transmitting the whole ultrasonic energy to the material being treated.

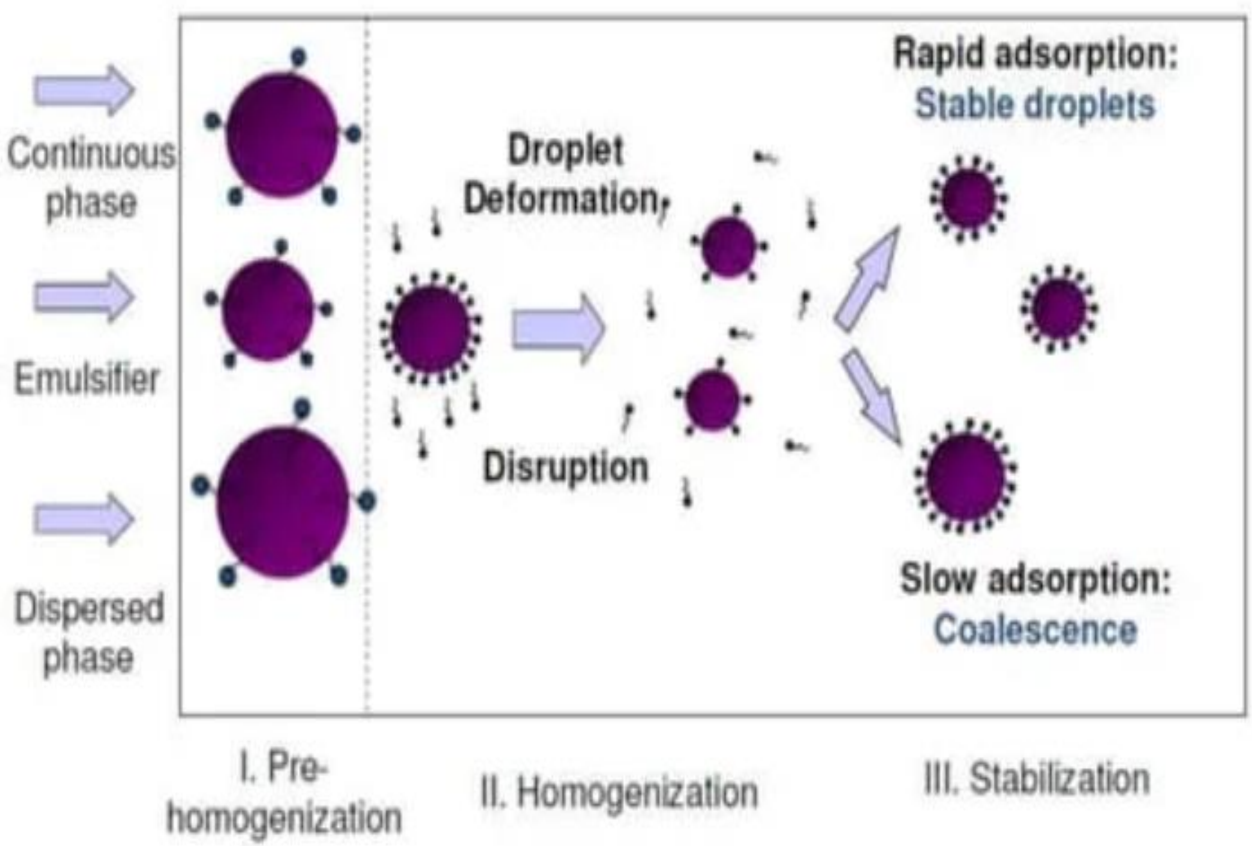
4. Homogenizers

- **Homogenization**: It is a process in which coarse globules in emulsion are converted into smaller globules of uniform composition, so that each measured dose has the same composition.
- The process of homogenization was invented and patented by Auguste Gaulin جولين in 1899 when he described a process for homogenizing milk.
- **Principle**: It is based on the principle that when large globules in coarse emulsion are passed under high pressure through a narrow orifice are broken into smaller globules having a greater degree of uniformity and stability.



4. Homogenizers

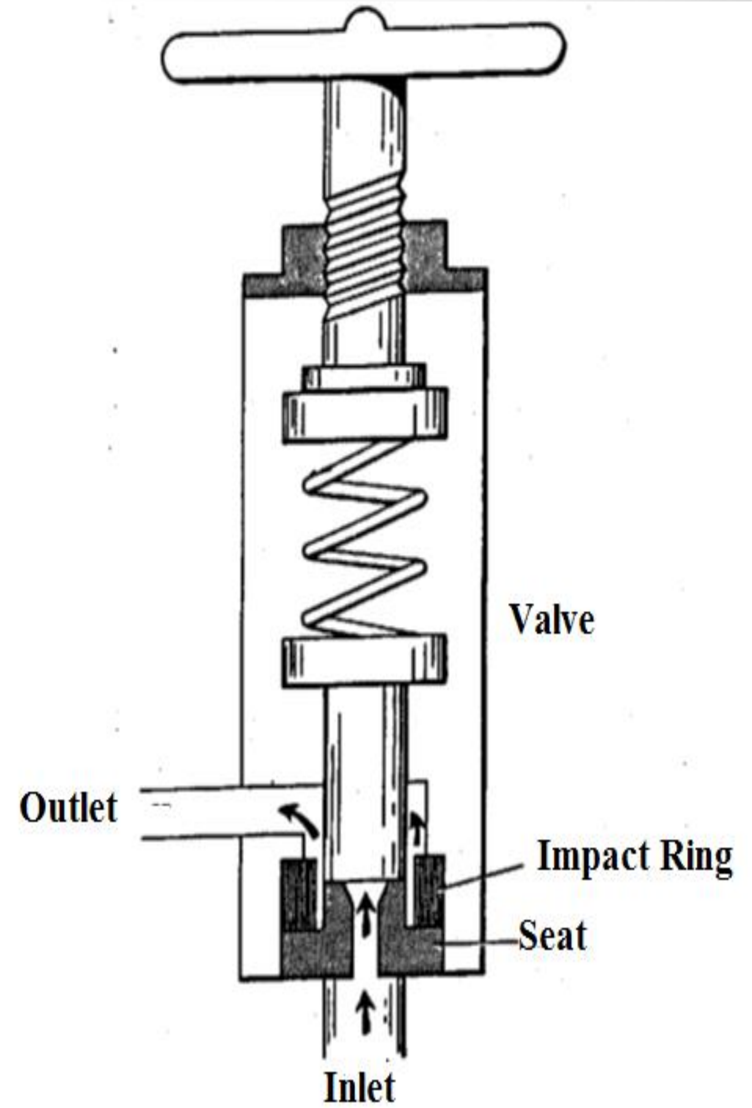
Physicochemical Process Occurring during Homogenization



4. Homogenizers

Gaulin Homogenizer

1. It consists of a high-pressure pump and a spring-seated homogenizing with an adjustable clearance between the valve head and seat (having a small orifice) through which the coarse emulsion strikes upon the homogenizing valve.
2. pump that rises the pressure of the dispersion to a range of 500-5000 psi.
3. The pressure exerted by the spring can be varied by a hand wheel which also adjusts the clearance between the valve and seat to only a few thousandth of an inch, (0.025 - 0.5 of a millimeter).

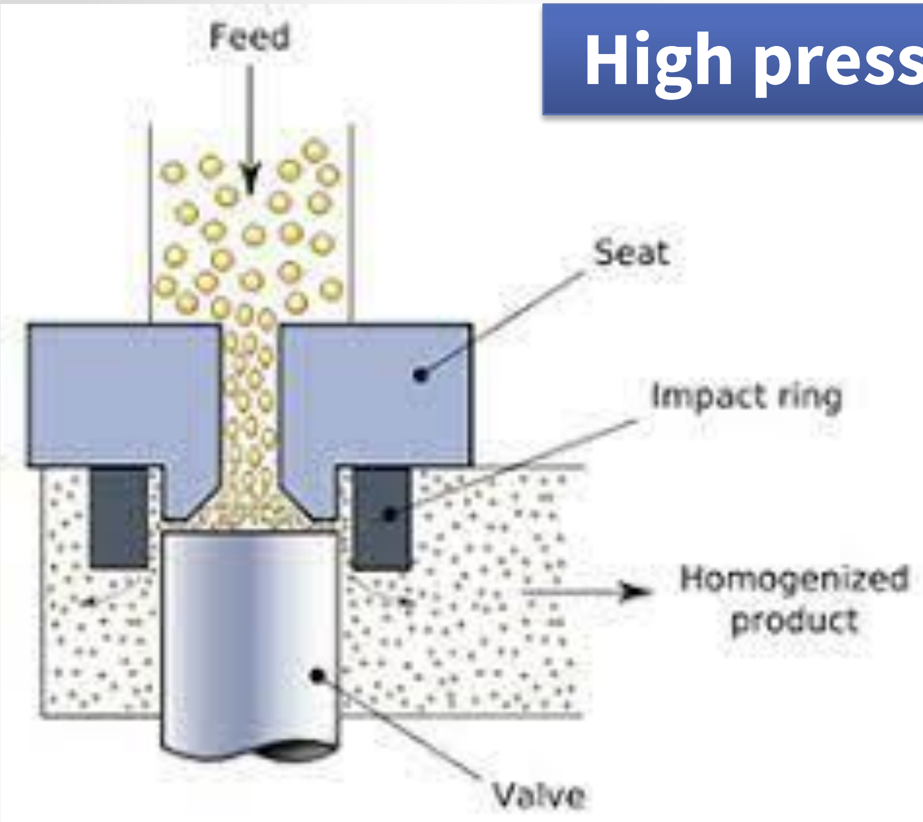


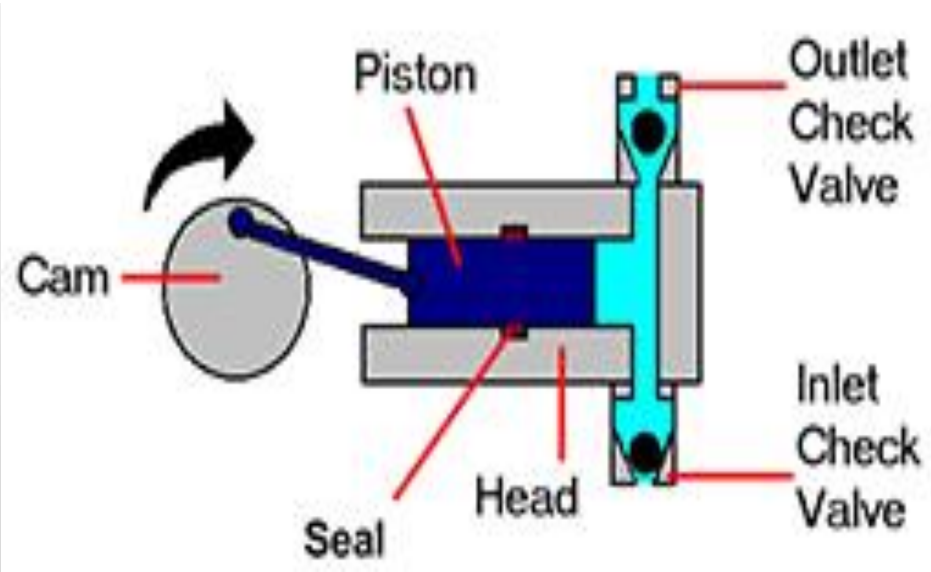
4. Homogenizers

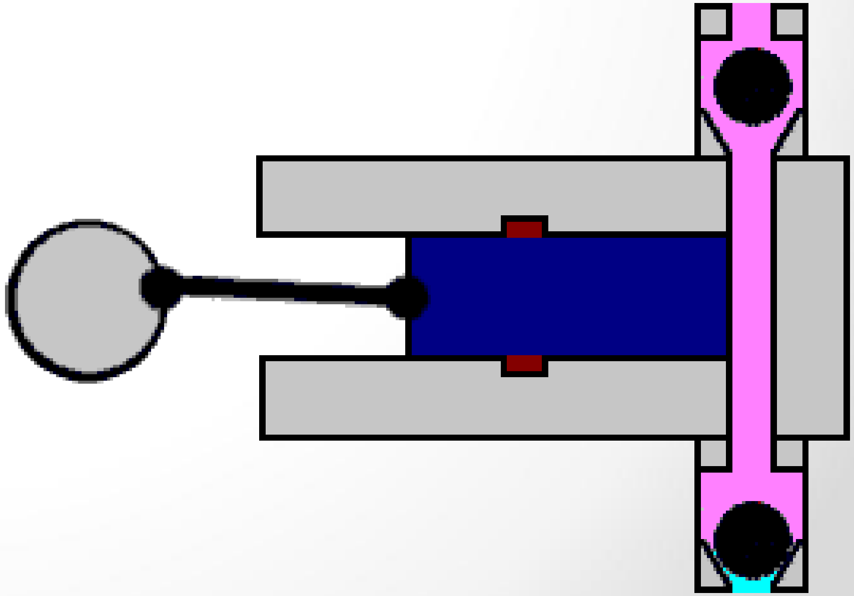
Gaulin Homogenizer

- In this homogenizer, the material at high pressure (500 to 5 000 psi) enters the homogenizing valve assembly through the homogenizing valve seat and passes through the clearance between the lapped ملفوفة faces of the valve and seat.
- At this point, the high pressure is instantaneously changed to high velocity. → The material impinges against the impact ring and shatter into particles as small as 0.02 μ.
- All this action occurs in as short period of time as 9 microseconds.
- Initial homogenization may produce the desired size reduction, but subsequent agglomeration often occurs.
- A second homogenization at a lower pressure will break up these agglomerates.
- Two- and three-stage homogenizers are often used in processing pharmaceutical polyphasic systems.

High pressure homogenization







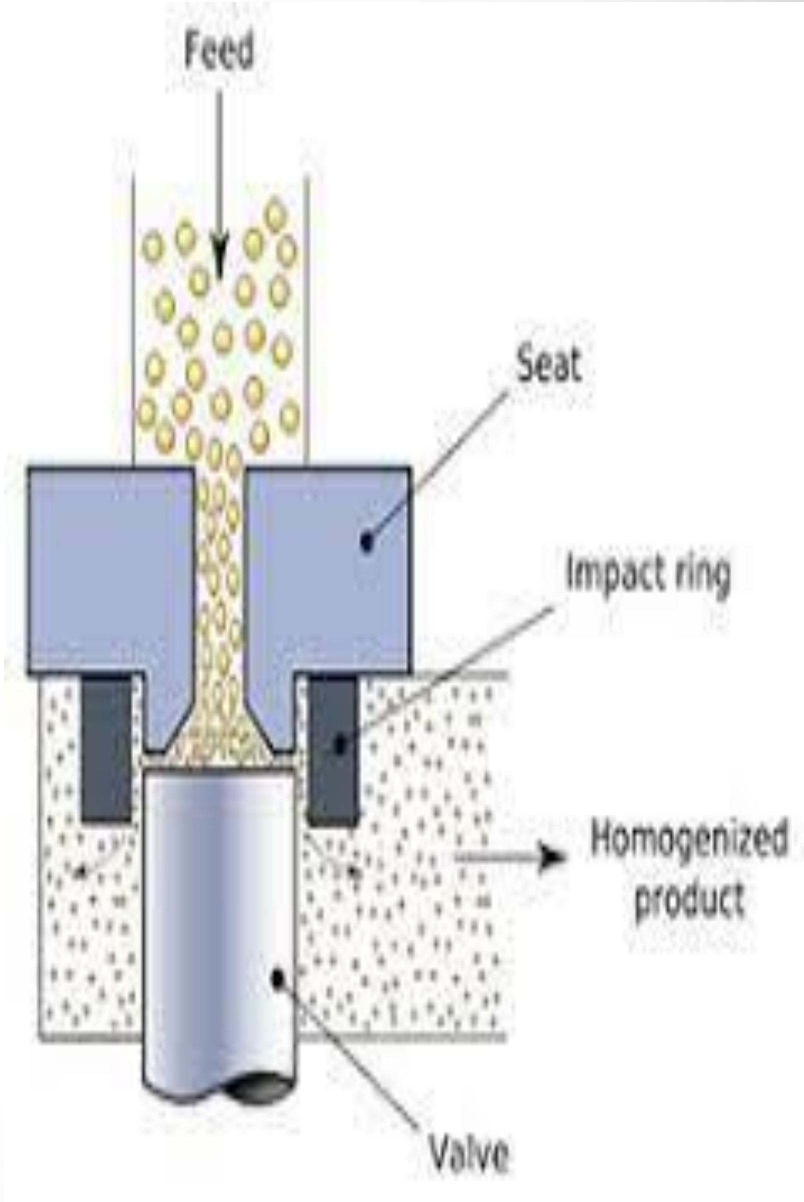
High pressure homogenization

- In a high-pressure homogenizer, the dispersion of two liquids (oily phase and aqueous phase) or finely divided solids in liquid is achieved by forcing their mixture through a small inlet orifice at very high pressure (500 to 5000 psi), which subjects the product to intense turbulence and hydraulic shear resulting in extremely fine particles of emulsion/ suspension.

High pressure homogenization

It is most widely used method for preparing nanosuspensions of many poorly aqueous soluble drugs. It involves three steps.

- ❑ Firstly: drug powders are dispersed in stabilizer solution to form pre-suspensions.
- ❑ Secondly: the pre-suspension is homogenized in high pressure homogenizer at a low pressure for premilling.
- ❑ Finally: homogenized at high pressure for 10 to 25 cycles until the nano-suspensions of desired size are formed. High Pressure Homogenization



High pressure homogenization

Advantages

- **Low risk of product contamination.**
- **Allows aseptic production of nanosuspensions for parenteral administration.**
- **Particle size may reduce up to 1 nm. .**

Disadvantages

- **Prerequisite of micronized drug particles.**
- **Prerequisite of suspension formation using high-speed mixers before subjecting it to homogenization.**

IPQC tests for emulsions

1. Appearance.
2. Clarity testing.
3. pH value.
4. Viscosity Rheology.
5. Drug content uniformity.
6. Particle size distribution.
7. Densities of phases

IPQC tests for emulsions

1. Appearance.

- With visual inspection, the ingredients and the final products are carefully examined for purity and for appearance.
- For patient adherence and compliance is critical so it should be: Good looking Elegant in appearance.

2. Viscosity

- As the viscosity increases,→ flocculation of globules will be reduced → simultaneously the Brownian movement of globules will also be hindered → leading to creaming.
- Due to this antagonistic effect an optimum viscosity is desirable for good stability.
- Viscosity can be measured by

a) cup and bob viscometer

b) cone and plate viscometer

IPQC tests for emulsions

3. Particle size .

- As the globule size is reduced, they tend to exhibit Brownian movement.
- According to stokes law, the diameter of the globule is considered as a major factor in creaming of emulsion.
- The rate of creaming decreases four folds when the globule diameter is halved. → So it is necessary to choose the optimum globule size for maximum stability.

4. Particle size distribution

- Globules of uniform size, impart maximum stability.
- In such emulsions globules pack loosely and globule to globule contact is less.
- Globule distribution is affected by viscosity, phase volume ratio, density of phases etc.
- An optimum degree of size distribution range should be chosen to achieve maximum physical stability.

Microemulsions

Comparison between microemulsions and conventional emulsions.	
Microemulsions	Emulsions
Droplet size with a mean diameter range 60 to 1000 Å (0.006 to 0.1 μ)	0.5 to 25 μ
Transparent or translucent.	Most emulsions are opaque.
Need surfactants and cosurfactants in large amounts.	Need only surfactants (emulsifying agent) in small amounts.
1. Thermodynamically stable, 2. formed spontaneously when oil, / water surfactants & cosurfactants are mixed together.	Unstable, therefore required input of considerable mechanical energy for their preparation which may supplied by colloid mills, homogenizers or ultrasonic generators.
On the borderline between lyophobic and lyophilic colloids.	Lypophobic.