Department of Pharmacy GP (Uttawar)

PHARMACEUTICAL EMULSIONS

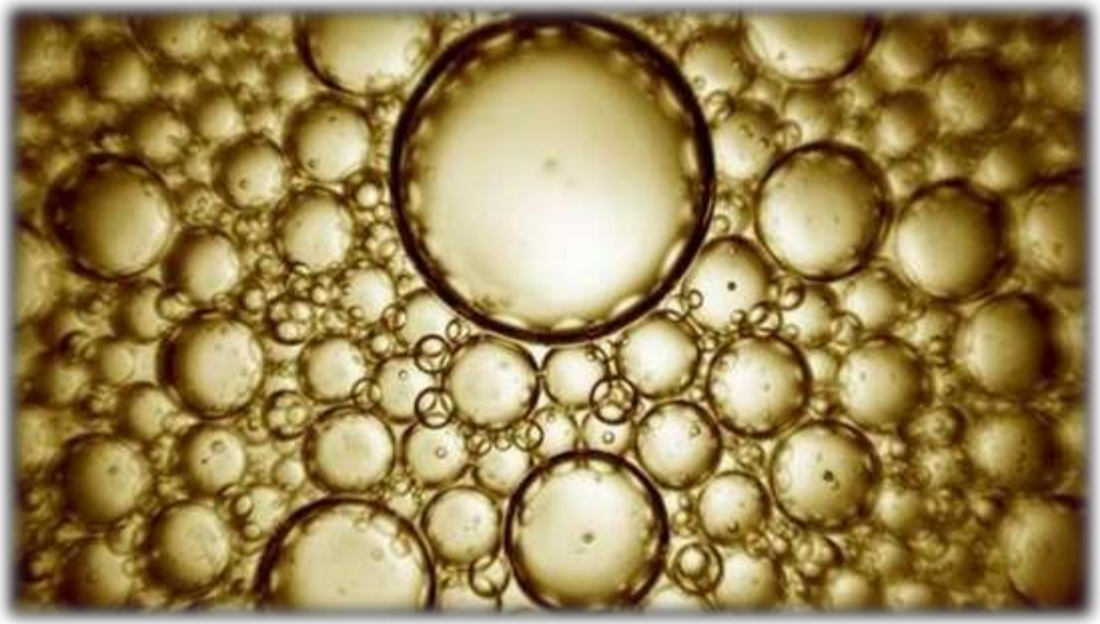
(Pharmaceutics II)
Unit 6 (b)

Topics to be Covered …

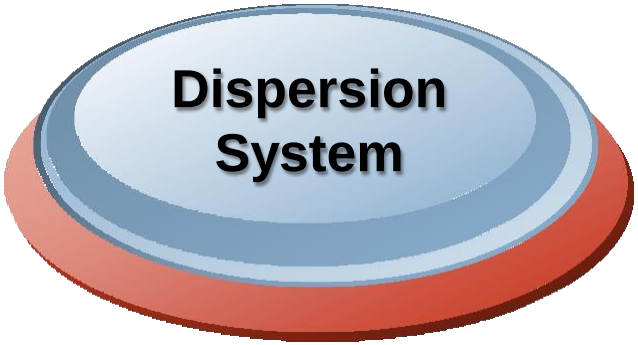
1. Emulsions - Basic Intro
2. Stability of Emulsions
3. Manufacturing of Emulsions
4. Tests for Emulsion Type
5. Pharmaceutical Application

EMULSION- BASIC INTRO

- **Section contains:**
- ✓ Introduction
- ✓ Types of emulsions
- ✓ Classification of Emulsions
- ✓ Theories of emulsification
- ✓ Additives for formulation of emulsion



What are Emulsions?



Emulsion
is a dispersion in which the dispersed phase is composed of small globules of a liquid distributed throughout a vehicle in which it is immiscible

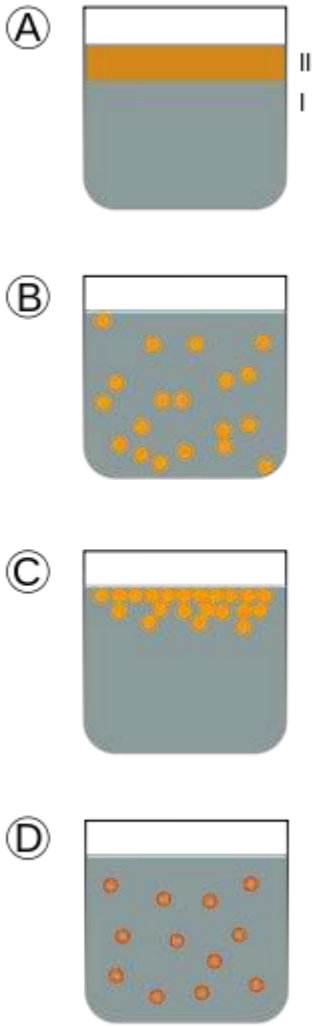
Suspension
is a two phased system in which a finely divided solid is dispersed in a continuous phase of solid, liquid, or gas.

Emulsions (Definition)

- *An emulsion is a **thermodynamically** unstable system consisting of at least two immiscible liquid phases one of which is dispersed as globules in the other liquid phase stabilized by a third substance called emulsifying agent.*

-OR-

- *An emulsion is a dispersion in which the dispersed phase is composed of **small globules** of a liquid distributed throughout a vehicle in which it is immiscible.*



A.: Two immiscible liquids not emulsified

B.An emulsion of phase B dispersed in Phase A

C. Unstable emulsion slowly separates.

D. The emulsifying agent

(black film) places it self on the interface between phase A and phase B and stabilizes the emulsion.

Internal Phase or External Phase in Emulsions

- *The dispersed liquid is known as the **Internal or Discontinuous phase.***

The droplet phase is called the dispersed phase or internal phase

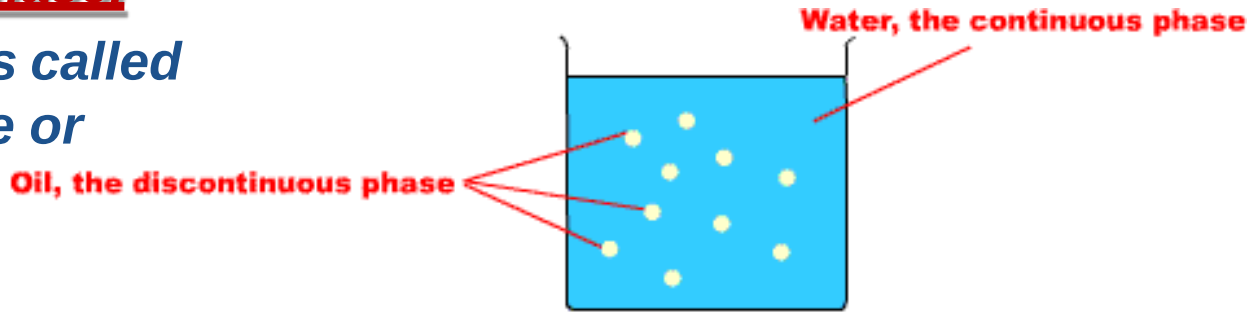


Figure 1a: O/W emulsion

- *whereas the dispersion medium is known as the **External or Continuous phase***

The liquid in which droplets are dispersed is called the external or continuous phase.

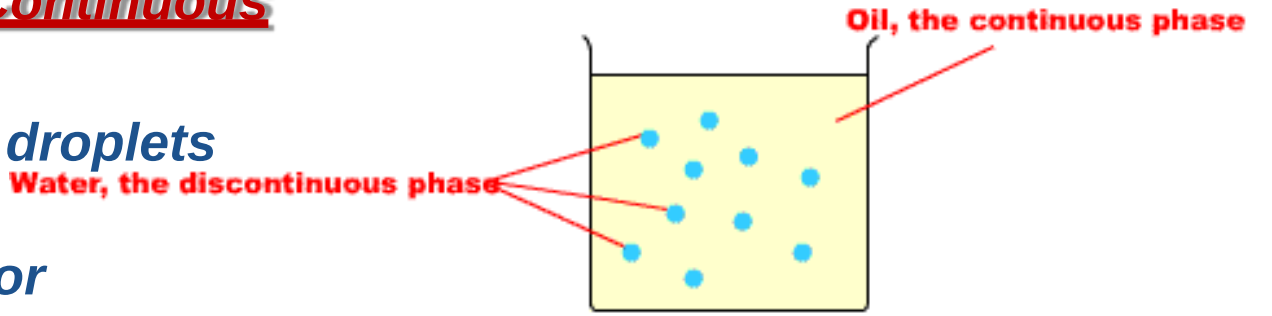
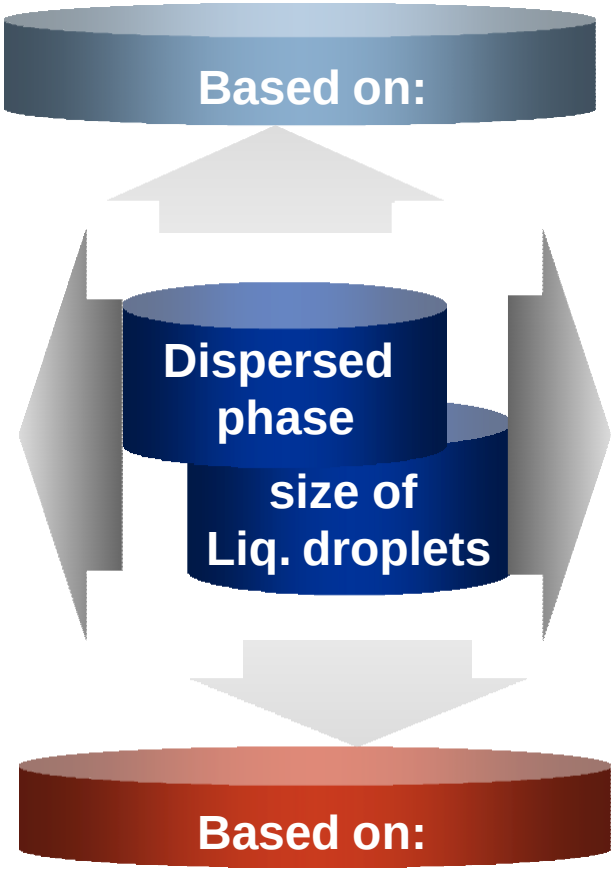


Figure 1b: W/O emulsion

Classification of Emulsion



Oil in Water (O/W): *Oil droplets dispersed in water*

Water in Oil (W/O): *Water droplets dispersed in oil*

0.2 – 50 mm Macro emulsions ***(Kinetically Stable)***

0.01 – 0.2 mm Micro emulsions ***(Thermody-namically Stable)***

Types of Emuslion

Simple emulsions

(Macro emulsions)

Oil-in-water (O/W)
Water-in-oil (W/O)

- diameter greater than 0.1 µm

Multiple emulsions

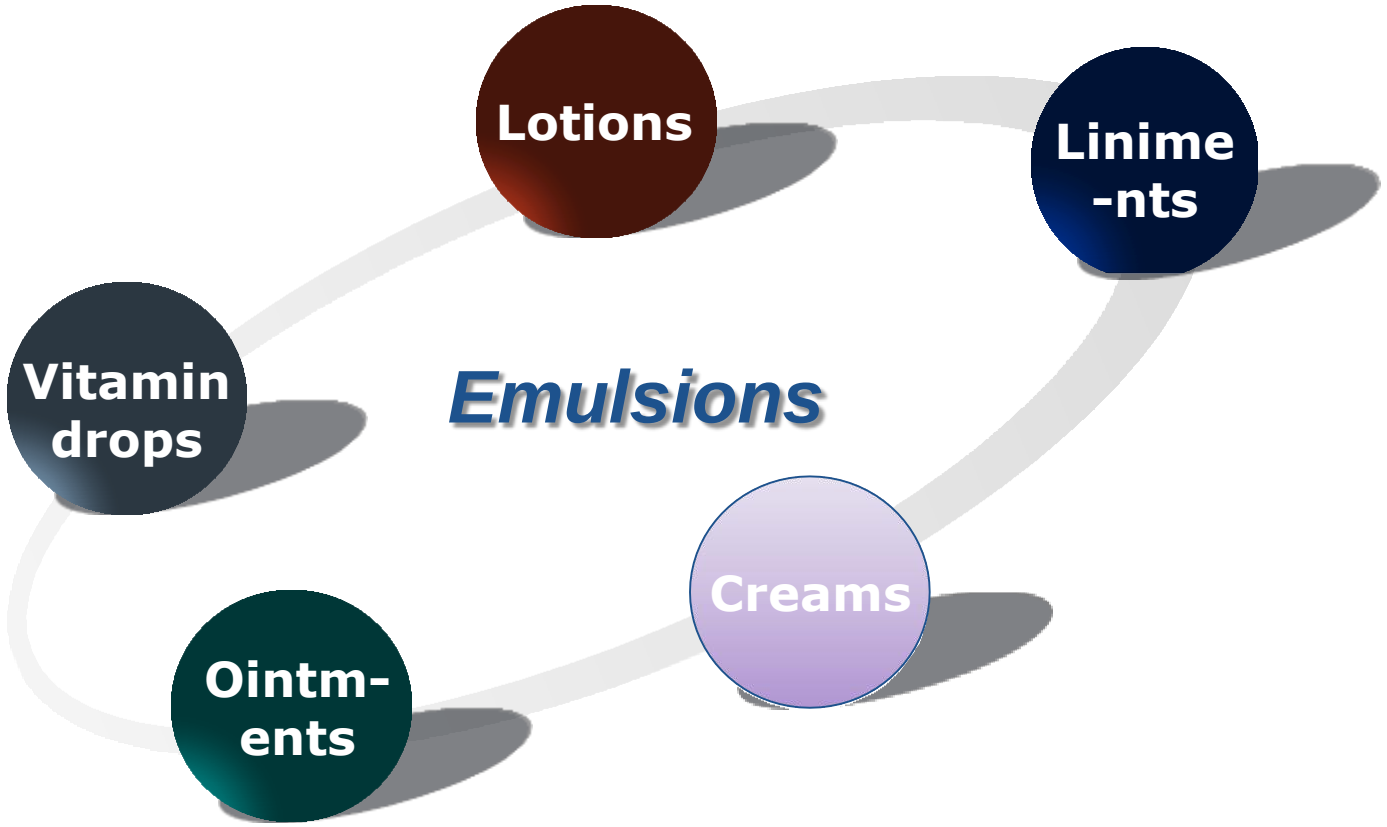
Oil-in-water-in-oil (O/W/O)
Water-in-oil-in-water (W/O/W)

Micro emulsions

Nano emulsions

- thermodynamically stable optically transparent , mixtures of a biphasic oil –water system stabilized with surfactants

General Types of Pharmaceutical Emulsions



Theories of Emulsification

Surface Tension Theory

by lowering of interfacial tension

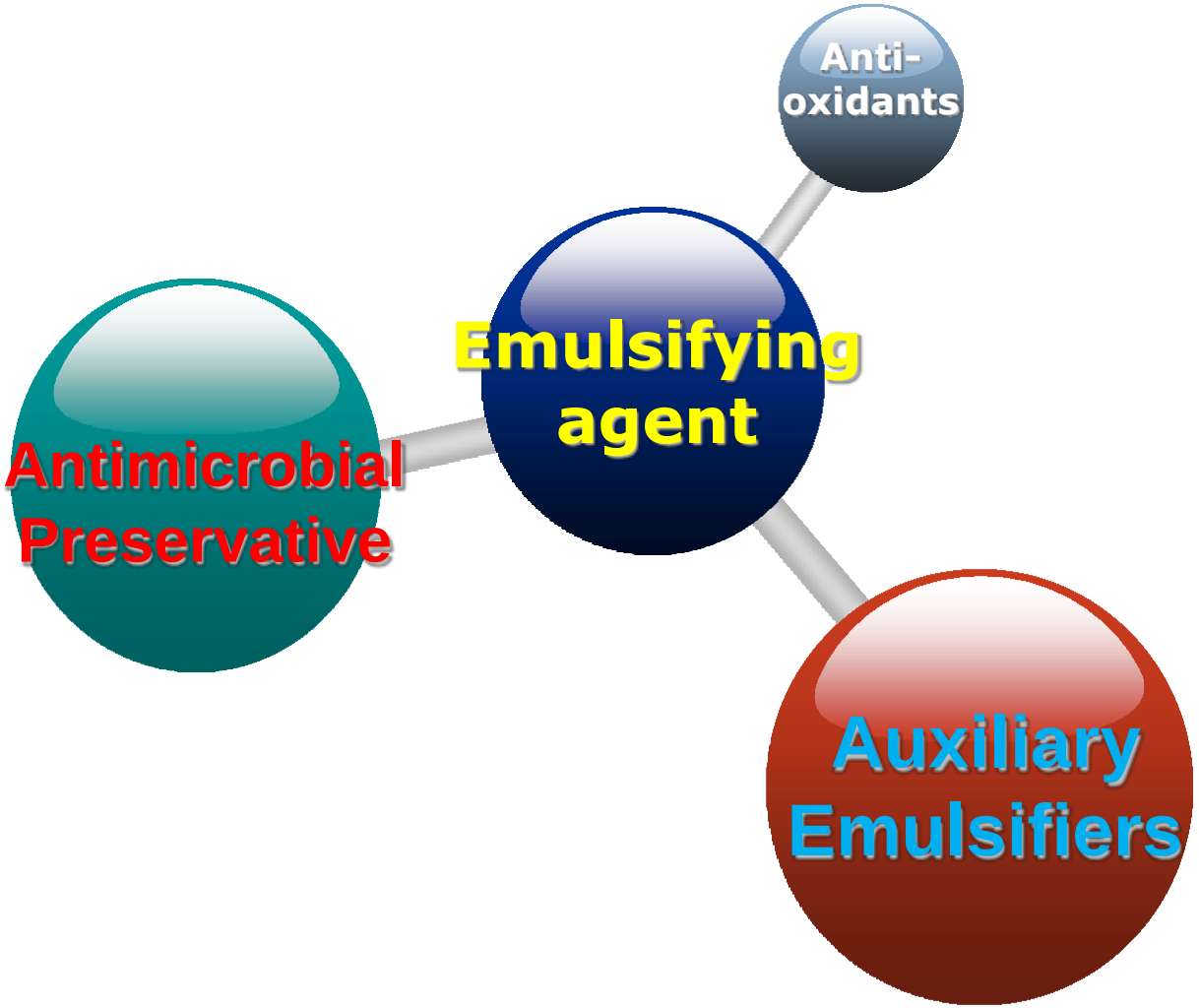
Oriented-Wedge Theory

mono molecular layers of emulsifying agents are curved around a droplet of the internal phase of the emulsion

Interfacial Film theory

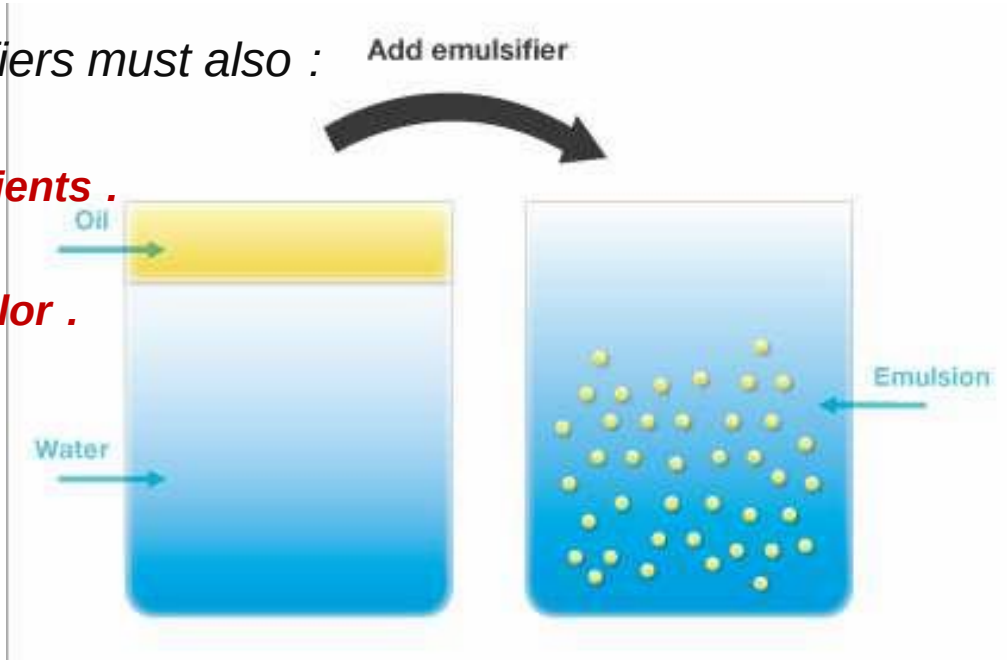
A film of emulsifying agent prevents the contact and coalescing of the dispersed phase.

Additives For Formulation Of Emulsion



Emulsifying Agents

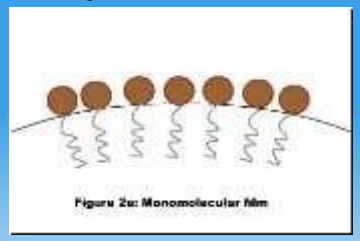
- *They are the substances added to an emulsion to prevent the coalescence of the globules of the dispersed phase. They are also known as emulgents or emulsifiers.*
- *They help in formation of emulsion by three mechanisms.*
  - *Reduction in interfacial tension – thermodynamic stabilization*
  - *Formation of a rigid interfacial film – mechanical barrier to coalescence*
  - *Formation of an electrical double layer – electrical barrier to approach of particles.*
- *Pharmaceutically acceptable emulsifiers must also :*
  - ***Be stable .***
  - ***Be compatible with other ingredients .***
  - ***Be non – toxic .***
  - ***Possess little odor , taste , or color .***
  - ***Not interfere with the stability of efficacy of the active agent .***



Classification of Emulsifiers

1

Synthetic Surface active agents (Monomolecular films)



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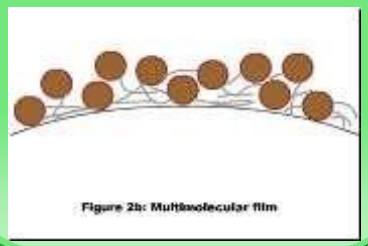
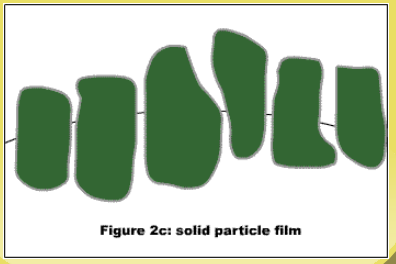
Semi synthetic and natural Hydrophilic colloids (Multi-molecular films)



3

Finely divided solid particles (Particulate film)



1. Synthetic surface active agents

- ***Reduce interfacial tension and make the emulsion thermodynamically more stable.***
- ***To reduce the interfacial tension Oil droplets are surrounded by a coherent monolayer of the surfactant which prevents coalescence. If the emulsifier is ionized, the presence of strong charge may lead to repulsion in droplets and hence increasing stability. Adsorbed at oil/water interface to form.***
- ***Form protective monomolecular film***
- ***Micelle formation***

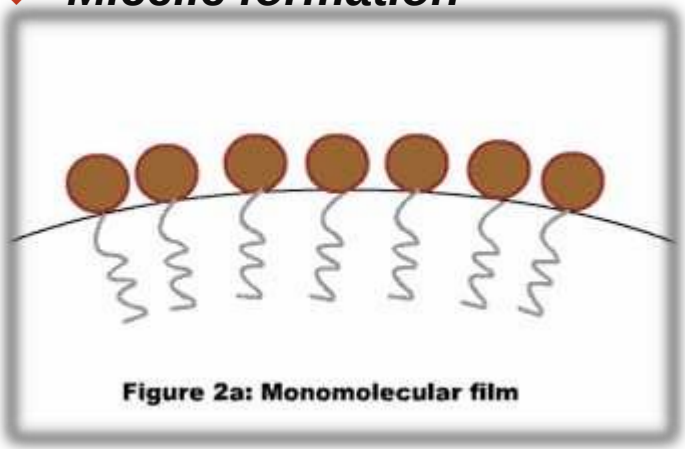
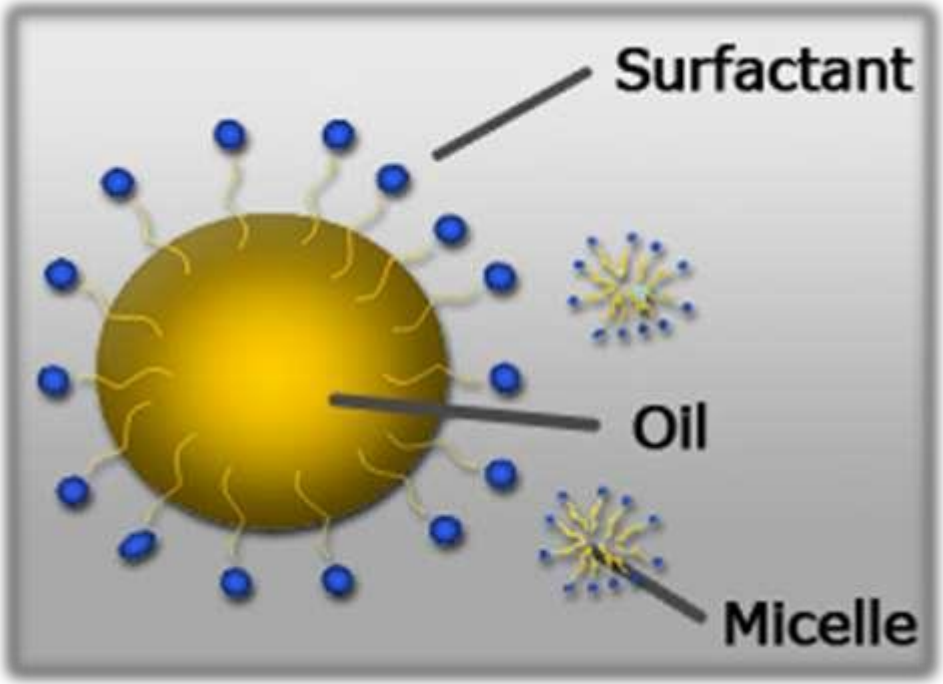


Figure 2a: Monomolecular film



Classification of Surfactants

- ***Cationic***
  - *Quaternary ammonium compounds*
- ***Nonionic***
  - *Polyoxy ethylene fatty alcohol ethers*
    $C_{12}H_{25}(OCH_2CH_2)nOH$
  - *Sorbitan fatty acid esters*
  - *Polyoxyethylene sorbitan fatty acid esters*
  - *Polyoxyethylene polyoxypopylene block copolymers*
  - *Lanolin alcohols and ethoxylated lanolin alcohols*
- ***Anionic***
  - *Soaps*
    -Mono valent
    -Polyvalent
    -Organic
  - *Sulphates*
  - *Sulphonates (CH3(CH2)n CH2SO3 – Na+)*

2. Semi synthetic and natural surface active agents

- *Also known as Hydrocolloid Emulsifying agents*
- *Provide a protective sheath (Multi-molecular films)around the droplets*
- *Impart a charge to the dispersed droplets (so that they repel each other*
- *Swell to increase the viscosity of the system (so that droplets are less likely to change.)*

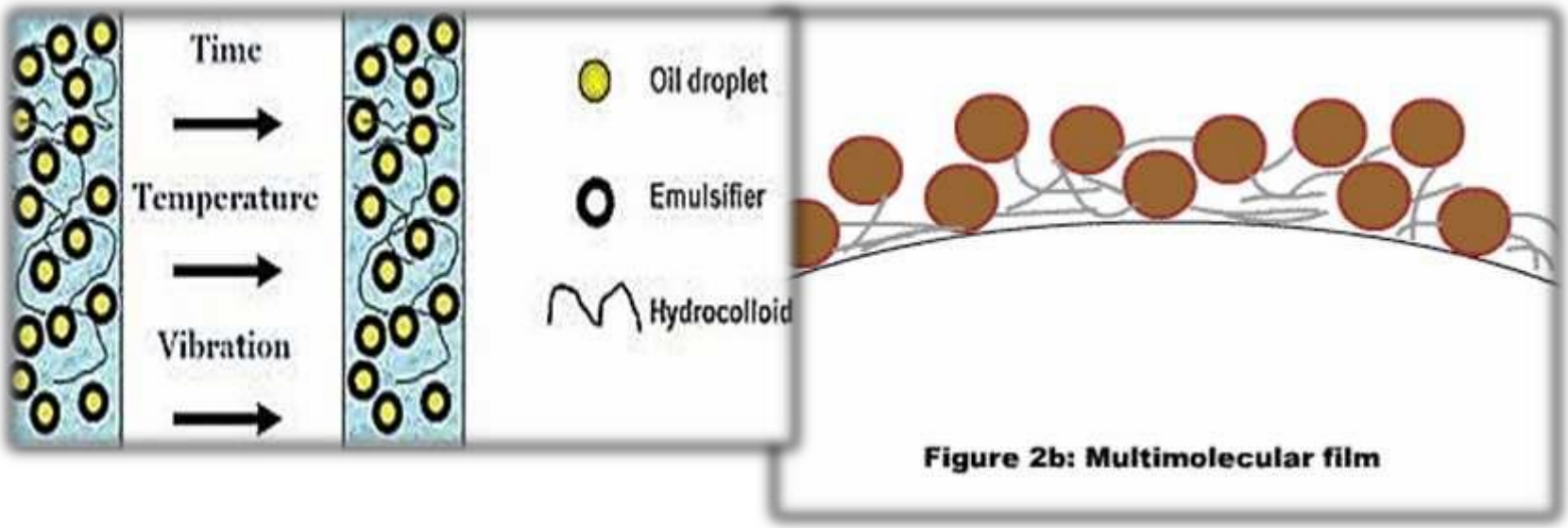


Figure 2b: Multimolecular film

Classification of Hydrocolloidals

- ***Semisynthetic***

Includes mainly cellulose derivatives like sodium carboxymethyl cellulose, hydroxyl propyl cellulose and methyl cellulose. They are used for formulating o/w type of emulsions. They primarily act by increasing the viscosity of the system. e.g., methyl cellulose, hydroxypropyl cellulose and sodium carboxy methyl cellulose.

- ***Natural***

-Plant origin

Polysaccharides

(Acacia, tragacanth, agar, pectin, lecithin)

-Animal origin

Proteins (Gelatin)

Lecithin

Cholesterol

Wool fat

Egg yolk

3. Finely divided solid particles

- *Also known as Particulate films*
- *Form a particulate "film“ around dispersed particles.*
- *These particles rely on adsorption to interfaces and like the hydrophilic colloids, function by forming a physical barrier to coalescence.*
- *Finely divided solid particles that are wetted to some degree by both oil and water act as emulsifying agents. This results from their being concentrated at interface, where they produce a particulate film around the dispersed droplets to prevent coalescence.*

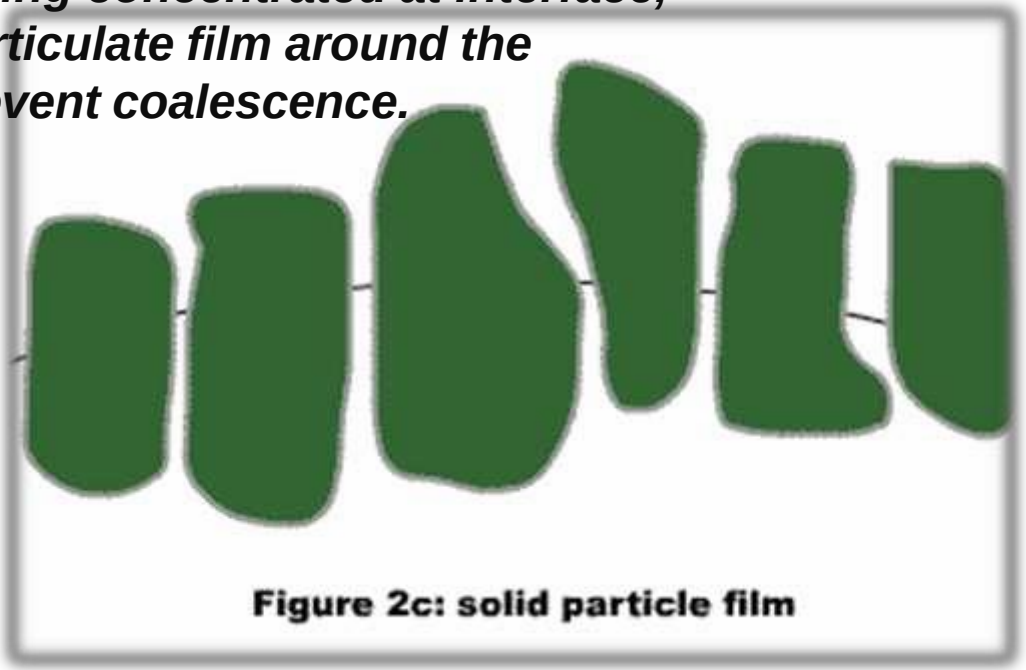


Figure 2c: solid particle film

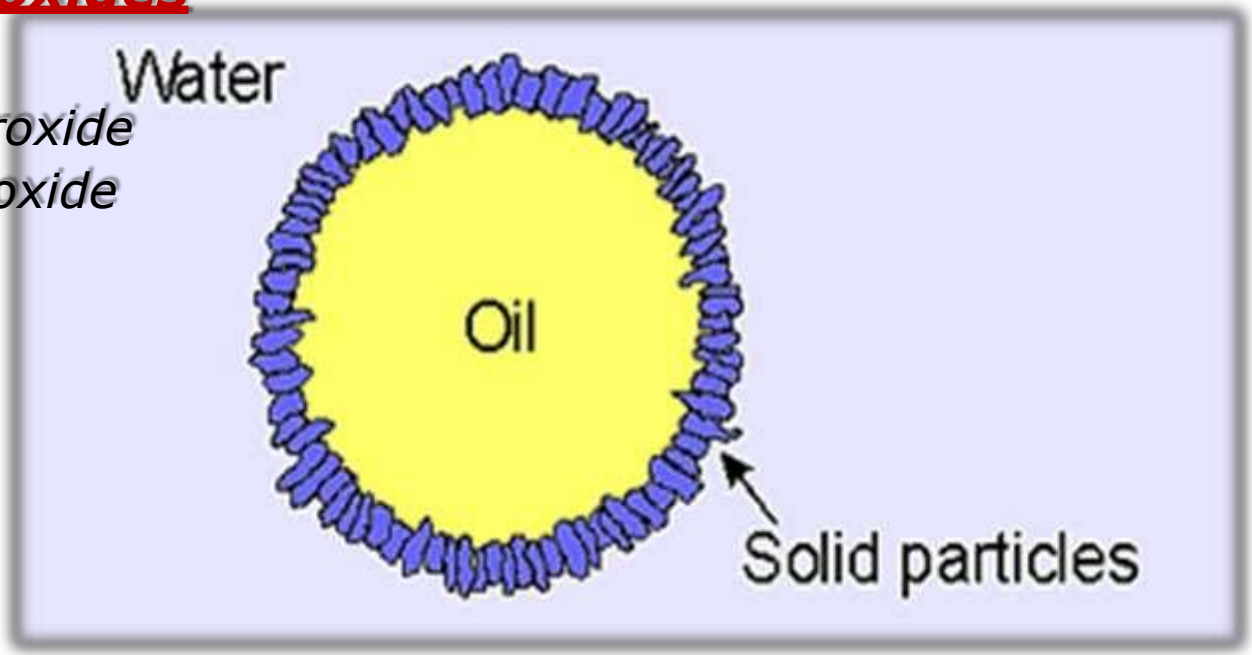
Classification of Particulate films

- ***Colloidal Clays***

- *Bentonite,(Al2O3.4SiO2.H2O),*
- *Veegum (Magnesium Aluminium silicate)*
- *Magnesium trisilicate*

- ***Metallic hydroxides***

- *Magnesium hydroxide*
- *Aluminium hydroxide*



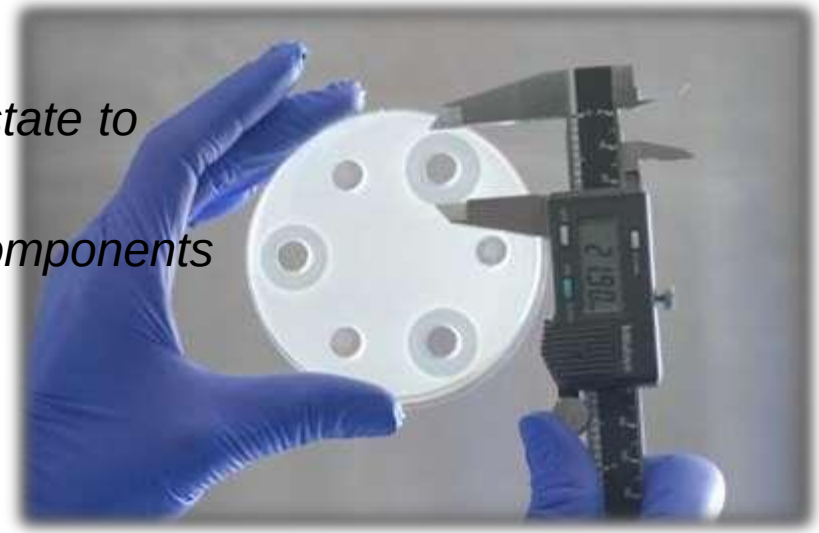
Auxiliary Emulsifiers

- ***Auxiliary (Secondary) emulsifying agents include those compounds that are normally incapable themselves of forming stable emulsion. Their main value lies in their ability to function as thickening agents and thereby help stabilize the emulsion.***

Product	Source and composition	Use
Cetyl alcohol		Lipophilic thickening agent and stabiliser for o/w lotions and ointments.
Glyceryl mono stearate		Lipophilic thickening agent and stabiliser for o/w lotions and ointments.
Methyl cellulose	Series of methyl esters of cellulose	Hydrophilic thickening agent and stabiliser for o/w emulsions , weak w/o emulsions.
Sodium carboxcymethyl cellulose	Sodium salt of the carboxy methyl esters of cellulose	Hydrophilic thickening agent and stabiliser for o/w emulsions ,
Stearic acid	A mixture of solid acids from fats, chiefly stearic and palmitic	Lipophilic thickening agent and stabiliser for o/w lotions and ointments. Forms a true emulsifier when reacted with alkali.

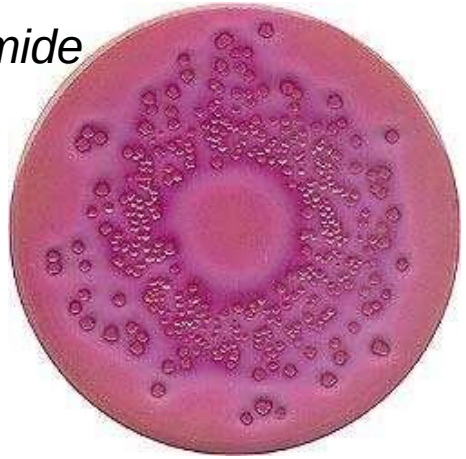
Antimicrobial Preservatives

- *The preservative must be :*
- *Less toxic*
- *Stable to heat and storage*
- *Chemically compatible*
- *Reasonable cost*
- *Acceptable taste, odor and color.*
- *Effective against fungus, yeast, bacteria.*
- *Available in oil and aqueous phase at effective level concentration.*
- *Preservative should be in unionized state to penetrate the bacteria.*
- *Preservative must no bind to other components of the emulsion*



- Examples of Antimicrobial agents

- ***Acids and acid derivatives*** – *Benzoic acid* – **Antifungal agent**
- ***Aldehydes*** – *Formaldehyde* – **Broad spectrum**
- ***Phenolics*** – *Phenol* – **Broad spectrum**
  Cresol
  Propyl p-hydroxy benzoate
- ***Quaternaries*** –*Chlorhexidine and salts* – **Broad spectrum**
  Benzalkonium chloride
  sCetyl trimethyl ammonium bromide
- ***Mercurials*** -*Phenyl mercuric acetate* - **Broad spectrum**

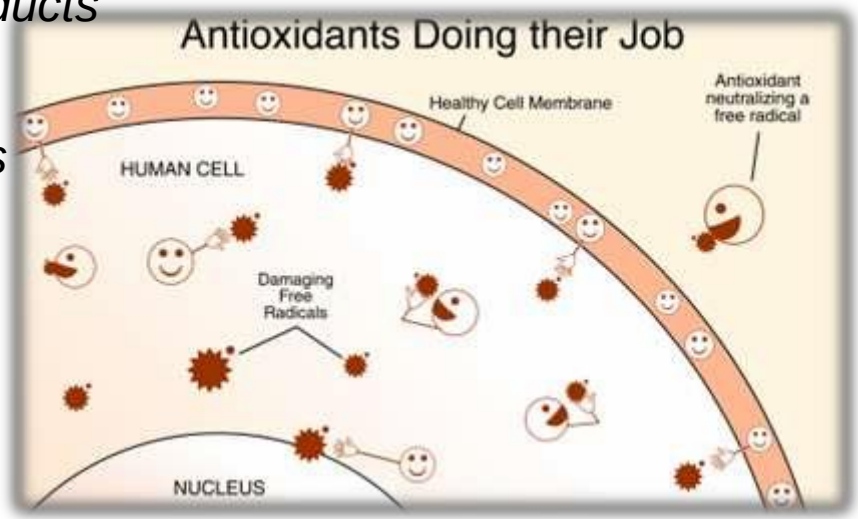


Antioxidants

- *Autoxidation occurs by free radical reaction*
- *Can be prevented by*
- ✓ *absence of oxygen,*
- ✓ *a free radical chain breaker*
- ✓ *by reducing agent*

Examples:

- *Gallic acid, Propyl gallate - pharmaceuticals and cosmetics - Bitter taste*
- *Ascorbic acid – Suitable for oral use products*
- *Sulphites - Suitable for oral use products*
- *L-tocopherol - pharmaceuticals and cosmetics -Suitable for oral preparations e.g. those containing vitamin A*

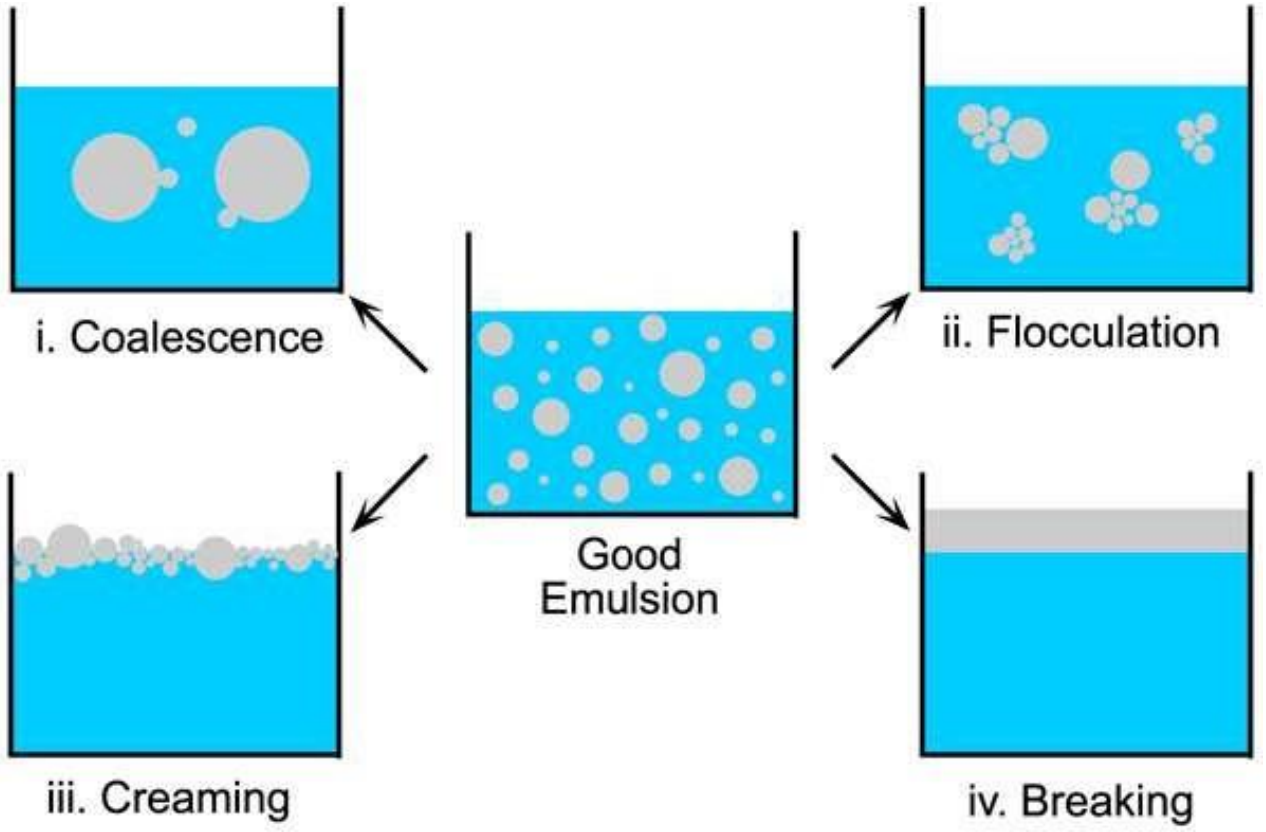


STABILITY OF EMULSION

❖ **Section contains:**

✓ **Physical Instability**

Creaming
Flocculation
Phase Inversion



Emulsions are Kinetically Stable!

INSTABILITY OF EMULSION

- Emulsification is not a spontaneous process and hence emulsions have minimal stability.

- Reasons for instability can be understood from the nature of immiscible phases and their interfacial properties.

When two immiscible liquids are agitated together

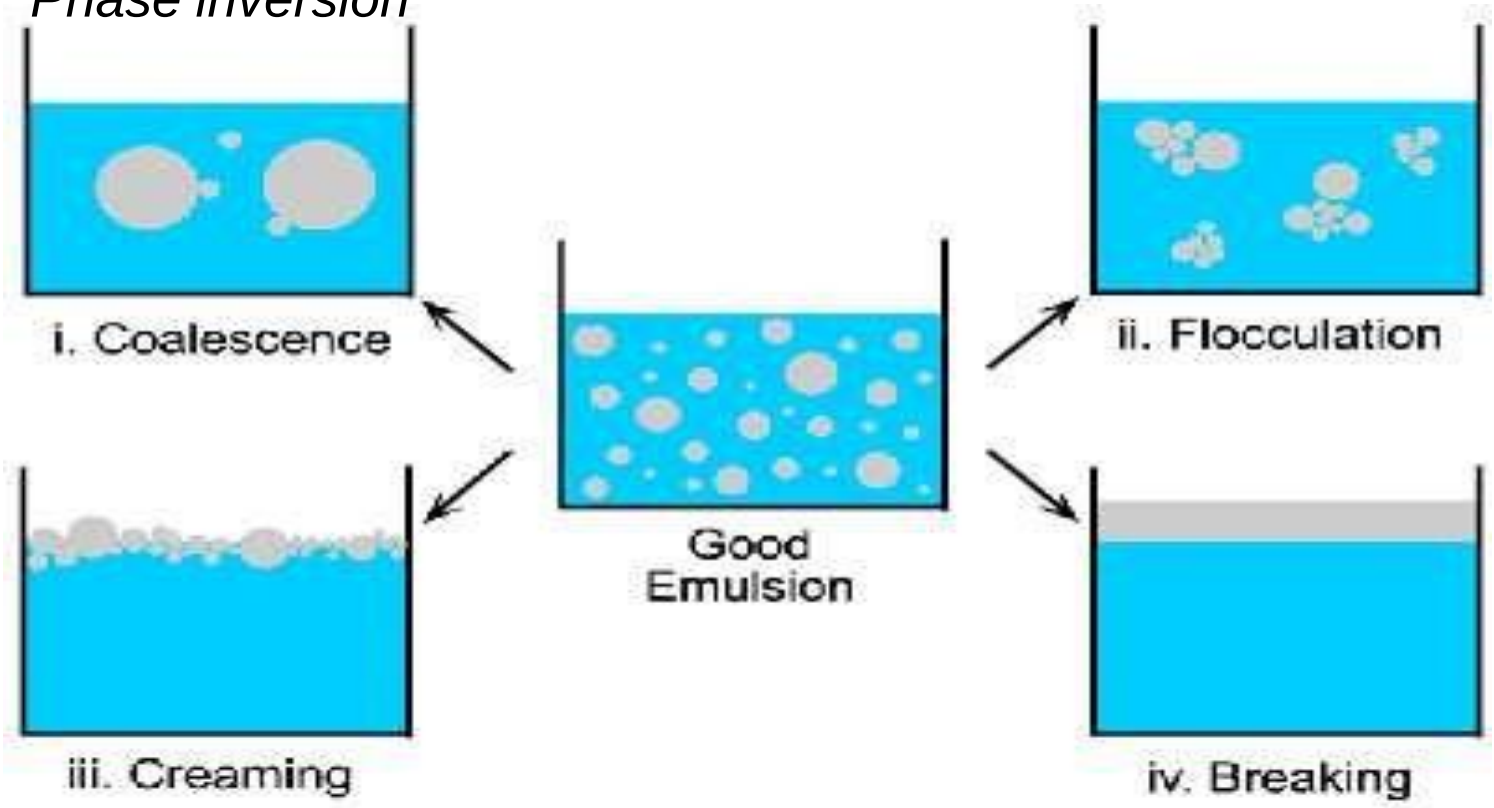
polar (aqueous) and non polar (oil) liquids are mixed together

one of the liquids forms small droplets and gets dispersed in the other liquid

forms an emulsion.

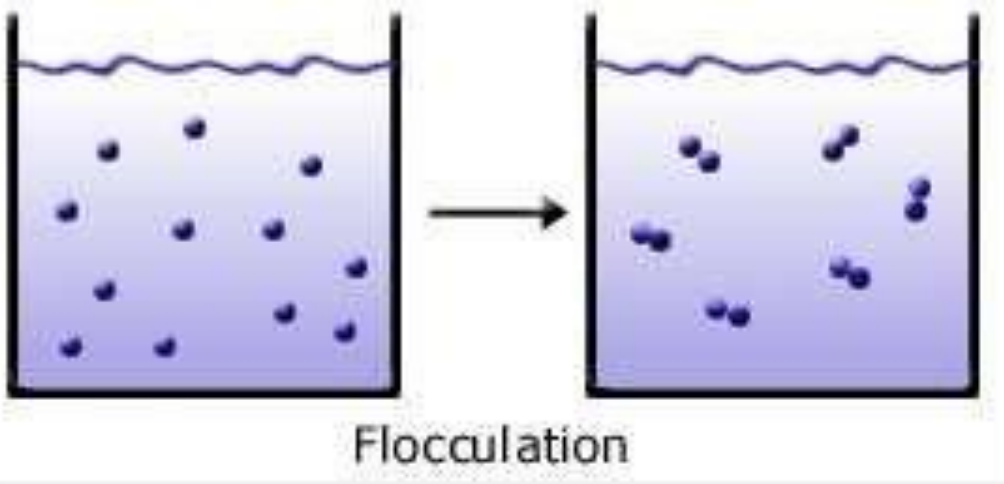
Types - Physical Instability

- ***Types of Physical instability are:***
- ✓ *Flocculation*
- ✓ *Creaming or sedimentation*
- ✓ *Aggregation or coalescence*
- ✓ *Phase inversion*



I - Flocculation

- *Neighboring globules come closer to each other and form colonies in the continuous phase. This aggregation of globules is not clearly visible.*
- *This is the initial stage that leads to instability.*
- *Flocculation of the dispersed phase may take place before, during or after creaming.*



- *The reversibility of flocculation depends upon strength of interaction between particles as determined by:*

a the chemical nature of emulsifier,

b the phase volume ratio,

c. the concentration of dissolved substances, specially electrolytes and ionic emulsifiers.

- The extent of flocculation of globules depends on

  (a) globule **size distribution**.

  (b) **charge** on the globule surface.

  (c) **viscosity** of the external medium.

(a) Globule size distribution

- Uniform sized globules prevent flocculation.
- This can be achieved by proper size reduction process.

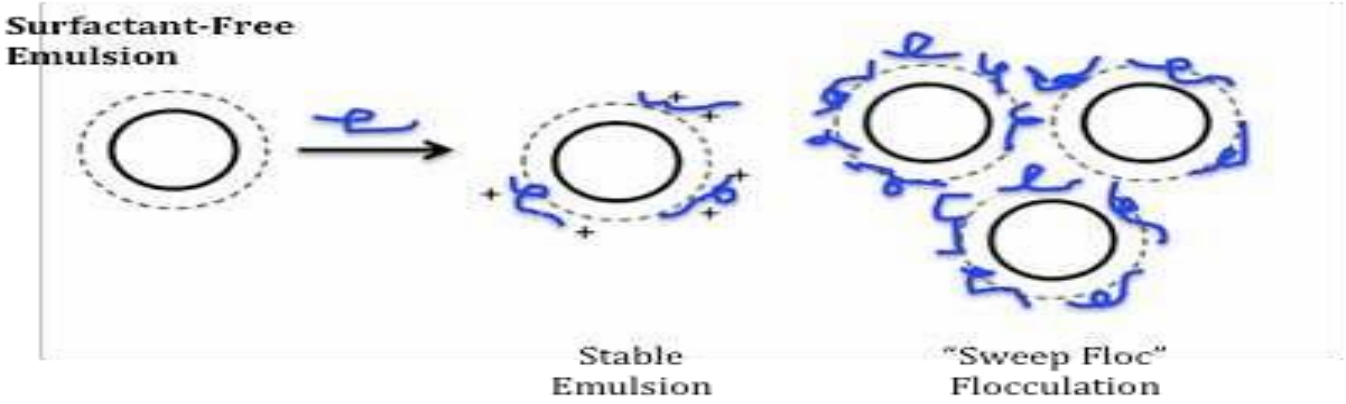
(b) Charge on the globule surface

- A charge on the globules exert repulsive forces with the neighboring globules.
- This can be achieved by using ionic emulsifying agent, electrolytes etc.

(c) Viscosity of the external medium.

- If the viscosity of the external medium is increased, the globules become relatively immobile and flocculation can be prevented.

- This can be obtained by adding viscosity improving agents (bodying agents or thickening agents) such as hydrocolloids or waxes.
- Flocs slowly move either upward or downward leading to creaming.
- Flocculation is due to the interaction of attractive and repulsive forces, whereas creaming is due to density differences in the two phases.

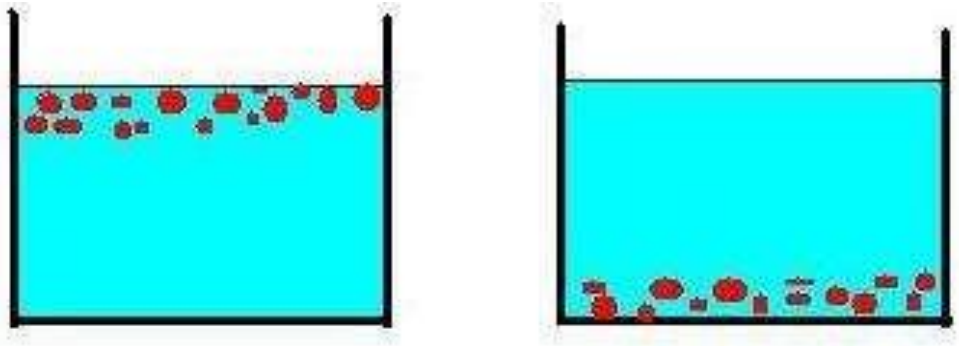


II - Creaming

- *Creaming is the upward movement of dispersed droplets of emulsion relative to the continuous phase (due to the density difference between two phases).*
- *Creaming is the concentration of globules at the top or bottom of the emulsion.*
- *Droplets larger than 1 mm may settle preferentially to the top or the bottom under gravitational forces.*
- *Creaming may also be observed on account of the difference of individual globules (movement rather than flocs).*
- *It can be observed by a difference in color shade of the layers.*
- *It is a reversible process, i.e., cream can be re-dispersed easily by agitation, this is possible because the oil globules are still surrounded by the protective sheath of the emulsifier.*

- *Creaming results in a lack of uniformity of drug distribution. This leads to variable dosage. Therefore, the emulsion should be shaken thoroughly before use.*

- *Creaming is of two types, upward creaming and downward creaming*



- *Upward creaming, is due to the dispersed phase is less dense than the continuous phase. This is normally observed in o/w emulsions. The velocity of sedimentation becomes negative.*

- *Downward creaming occurs if the dispersed phase is heavier than the continuous phase. Due to gravitational pull, the globules settle down. This is normally observed in w/o emulsions.*

- *Since creaming involves the movement of globules in an emulsion, Stokes' law can be applied.*

- ***Creaming is influenced by,***

  - *Globule size*
  - *Viscosity of the dispersion medium*
  - *Difference in the densities of dispersed phase and dispersion medium.*

- ***Creaming can be reduced or prevented by:***

1.Reducing the particle size by homogenization. Doubling the diameter of oil globules increases the creaming rate by a factor of four.

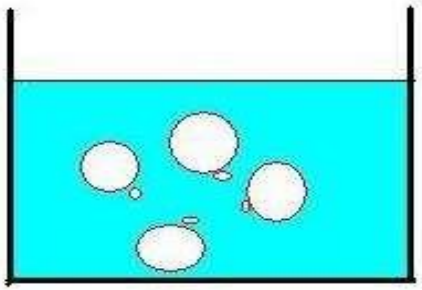
2.Increasing the viscosity of the external phase by adding the thickening agents such as methyl cellulose tragacanth or sodium alginate.

3.Reducing the difference in the densities between the dispersed phase and dispersion medium.

III- Coalescence

Aggregation, Coalescence, Breaking

- ***Aggregation*** *: Dispersed particles come together but do not fuse.*
- ***Coalescence*** *is the process by which emulsified particles merge with each to form large particles.*



- *This type of closed packing induces greater cohesion which leads to coalescence.*
- *In this process, the emulsifier film around the globules is destroyed to a certain extent. This step can be recognized by increased globule size and reduced number of globules.*

- ***Coalescence is observed due to:***

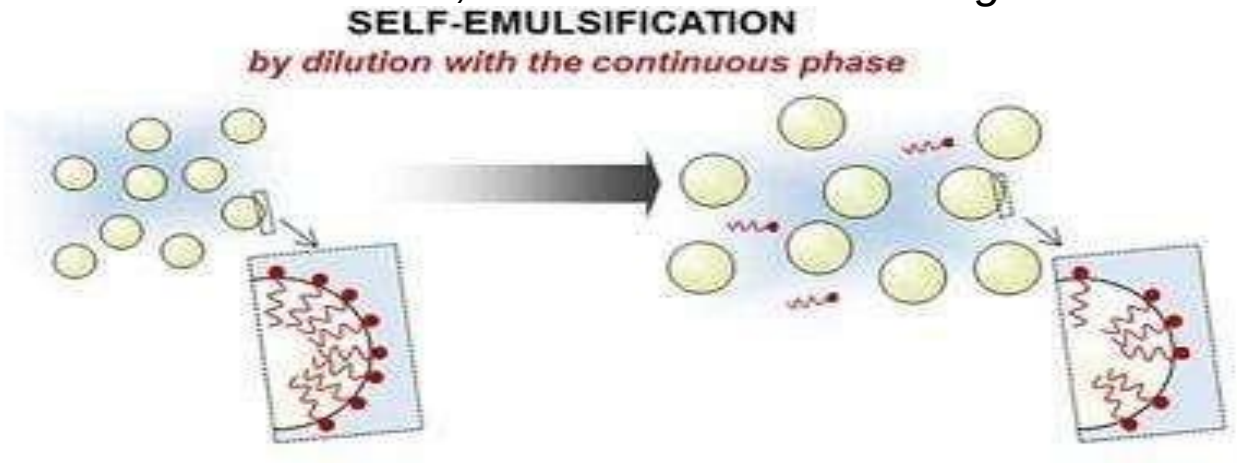
✓ *Insufficient amount of the emulsifying agent.*
✓ *Altered partitioning of the emulsifying agent.*
✓ *Incompatibilities between emulsifying agents.*

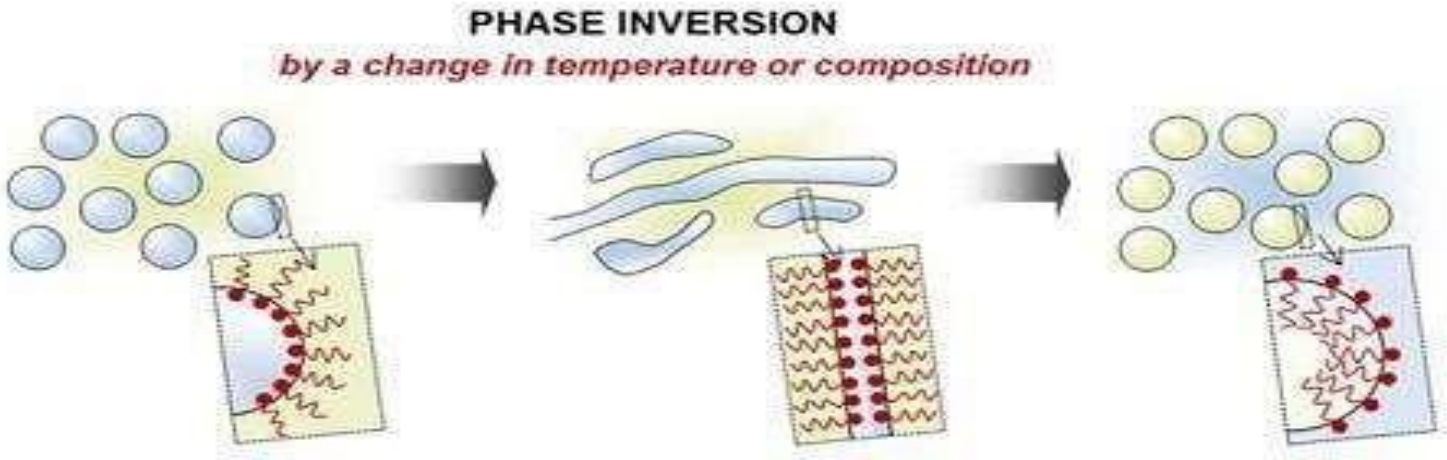
- *Phase volume ratio of an emulsion has a secondary influence on the stability of the product and represents the relative volume of water to oil in emulsion.*
- *The major factor to prevent coalescence is the mechanical strength of the interfacial film.*

- ***Breaking:***
- *Breaking is the destroying of the film surrounding the particles.*
- *Separation of the internal phase from the external phase is called breaking of the emulsion.*
- *This is indicated by complete separation of oil and aqueous phases, is an irreversible process, i.e., simple mixing fails. It is to re-suspend the globules into an uniform emulsion.*
- *In breaking, the protective sheath around the globules is completely destroyed and oil tends to coalesce.*

IV- Phase Inversion

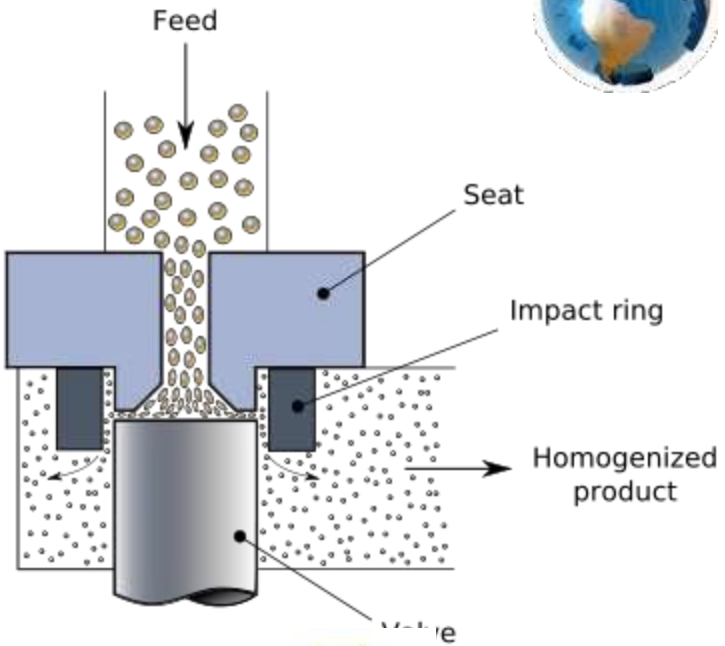
- *This involves the change of emulsion type from o/w to w/o or vice versa.*
- *When we intend to prepare one type of emulsion say o/w, and if the final emulsion turns out to be w/o, it can be termed as a sign of instability.*

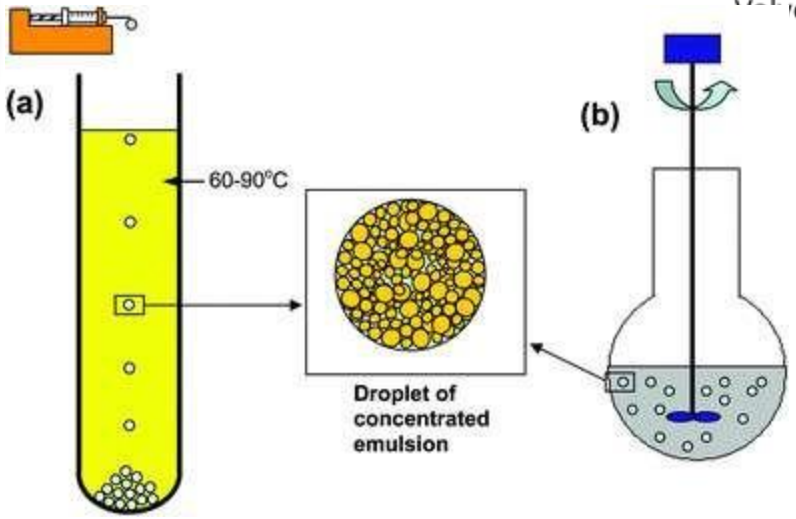




MANUFACTURING OF EMULSION

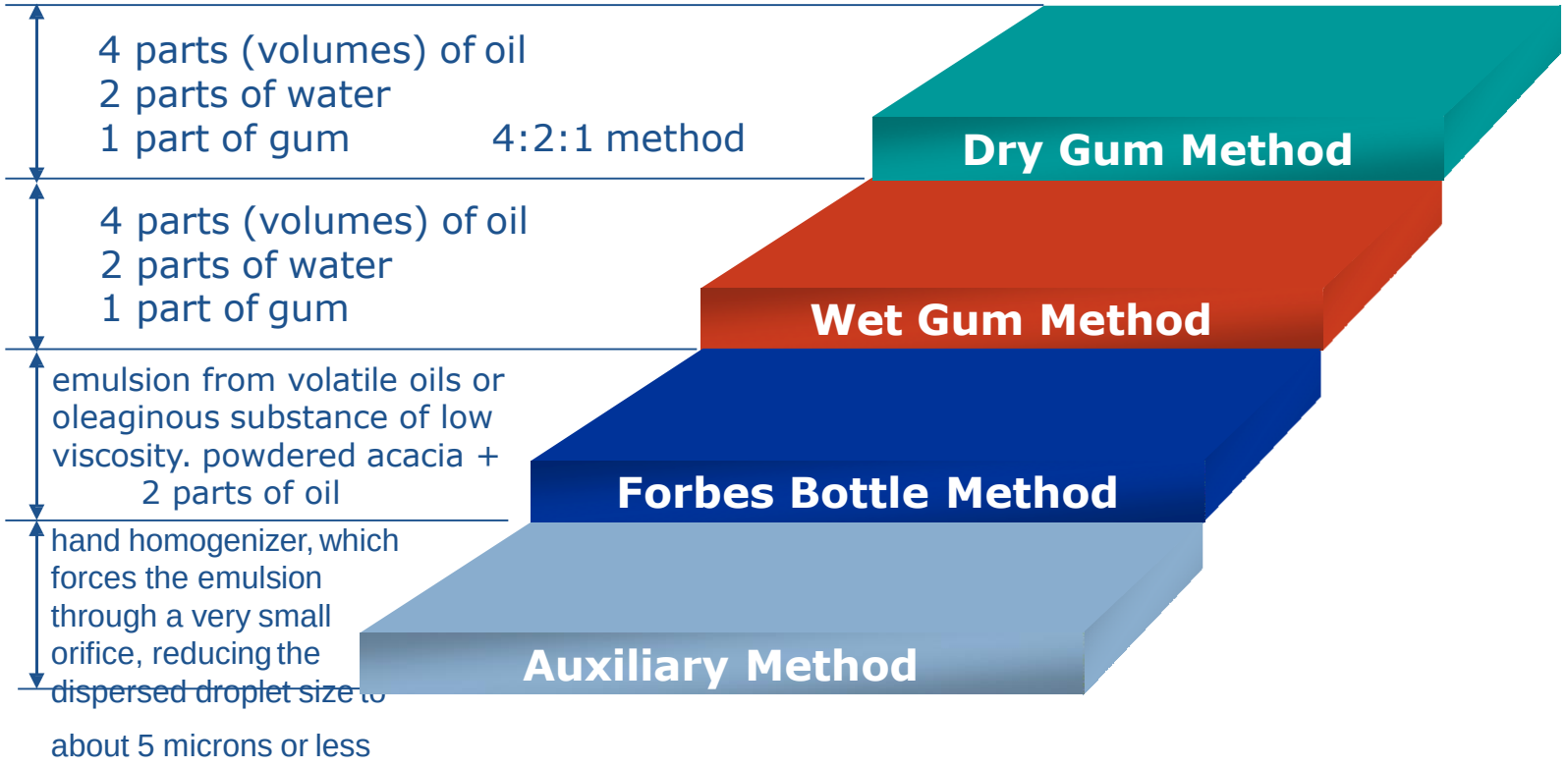
- **Section contains:**
- ✓ Extemporaneous Methods
- ✓ Large Scale Methods





Extemporaneous Methods

Emulsification process can be carried out by four methods mainly:



Large Scale Methods

Physical parameters affecting the droplet size distribution , viscosity, and stability of emulsion:

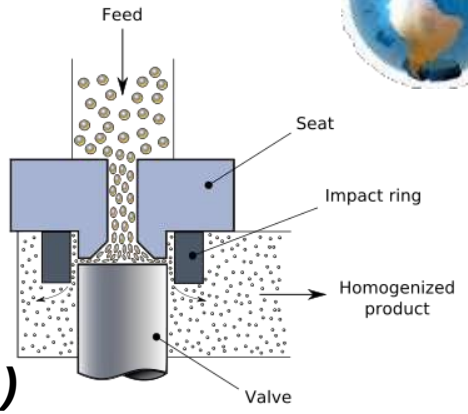
- Location of the emulsifier,
- method of incorporation of the phases,
- the rates of addition ,
- the temperature of each phase and
- the rate of cooling after mixing of the phases considerably

Energy may be supplied in the form of:

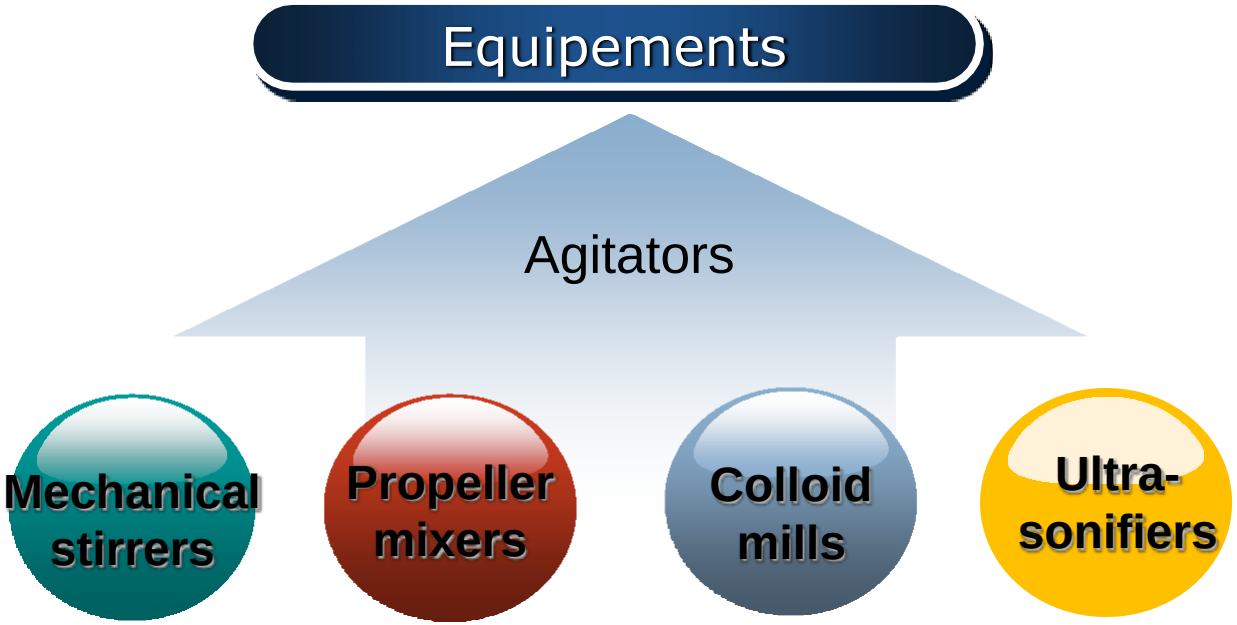
- Heat
- Homogenization
- Agitation

Heat :

- Emulsification by vaporization
- Emulsification by phase inversion
- Low energy emulsification



Mechanical equipment for emulsification (Agitation)



Mechanical Stirrers

- *An emulsion may be stirred by means of various impellers mounted on shafts, which are placed directly into the system to be emulsified.*

- *This is used for mixing, suspending, milling, dispersing, disintegrating solids etc. & reduces batch time. It consists of stator and rotor assembly. The rotor rotates inside the stator assembly which is fixed with three tie rods to the motor.*

Propeller Mixers

- *Simple top entering propeller mixers are adequate for routine development work in the laboratory and production.*

- *The degree of agitation is controlled by propeller rotation but the pattern of liquid flow and resultant efficiency of mixing are controlled by the type of impeller, its position in the container, the presence of baffles, and the general shape of the container. These stirrers can not be used when :*

  vigorous agitation is needed,

  extremely small droplets are needed.

- *Foaming at high shear rates must be avoided.*

- *These mixers may have paddle blades, counter rotating blades or planetary blades .*

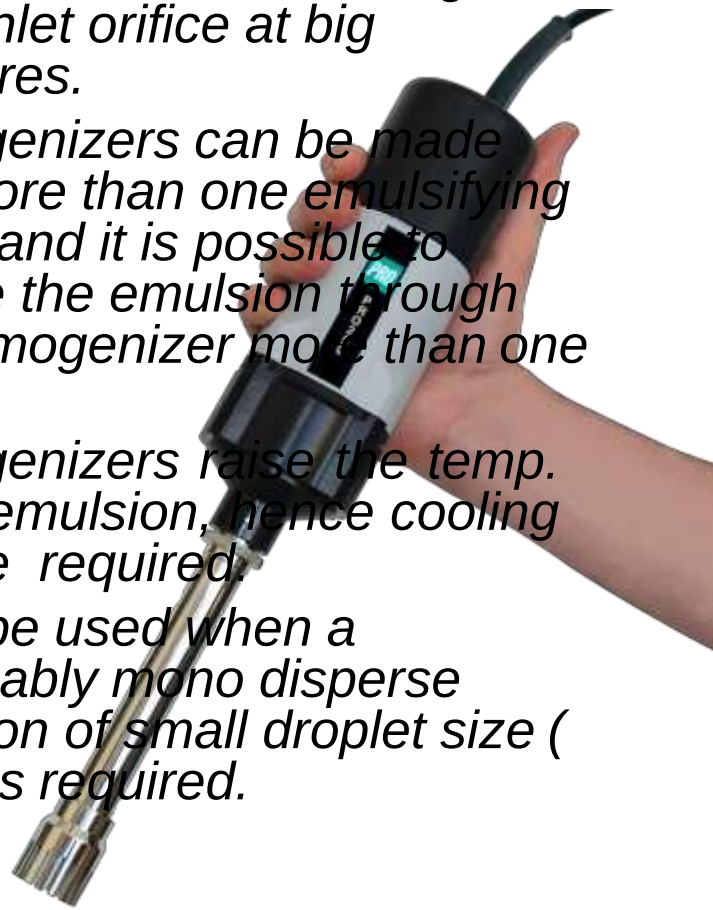
Major Types…

Turbine Type Mixers

- *If more vigorous agitation is required or viscosity is more , turbine type mixers can be used.*

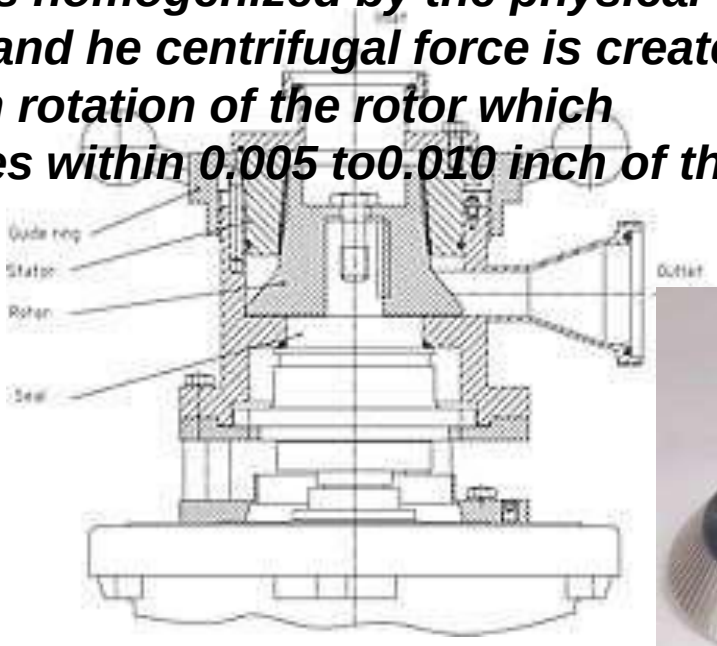
Homogenizers

- *In homogenizers the dispersion of two liquids is achieved by forcing their mixture through a small inlet orifice at big pressures.*
- *Homogenizers can be made with more than one emulsifying stage, and it is possible to recycle the emulsion through the homogenizer more than one time.*
- *Homogenizers raise the temp. of the emulsion, hence cooling may be required.*
- *It can be used when a reasonably mono disperse emulsion of small droplet size (1 nm) is required.*



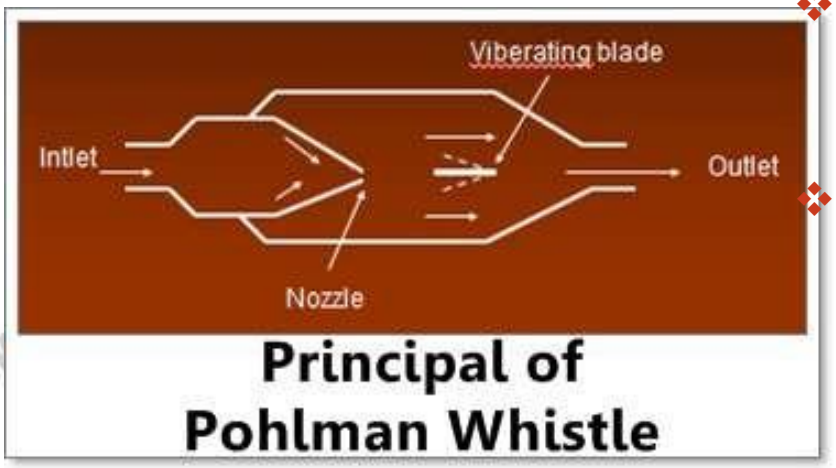
Colloid Mills

- *They operate on principle of high shear which is normally generated between rotor and stator of the mill.*
- *Colloid mill consists of a fixed stator plate and a high speed rotating rotator plea.*
- *Material drawn or pumped through an adjustable gap set between the rotor and stator is homogenized by the physical action and he centrifugal force is created by high rotation of the rotor which operates within 0.005 to0.010 inch of the stator.*



ROTOR AND STATOR

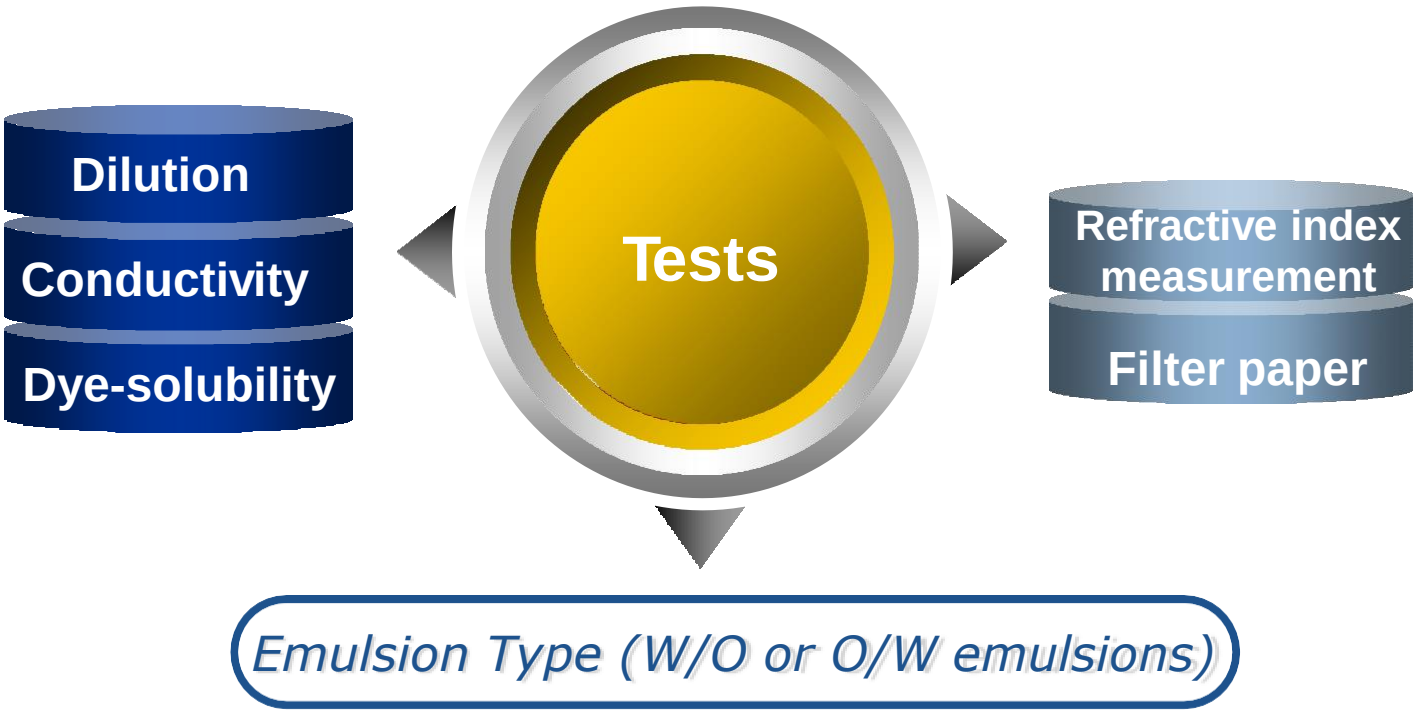
Ultrasonifiers



- *Ultrasonic energy s used to produce pharmaceutical emulsions.*
- *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.*
- *Commercial equipment is based n principle of Pohlmn liquid whistle. The dispersion is forced through an orifice at modest pressure and is allowed to impinge on a blade. The pressure range is from 150-350 psi . This pressure causes blade to vibrate rapidly to produce an ultrasonic note. When the system reaches a steady state, a cavitational field is generated at the leading edge of the blade and the pressure fluctuations of approx. 60 tones psi can be achieved in commercial equipment.*

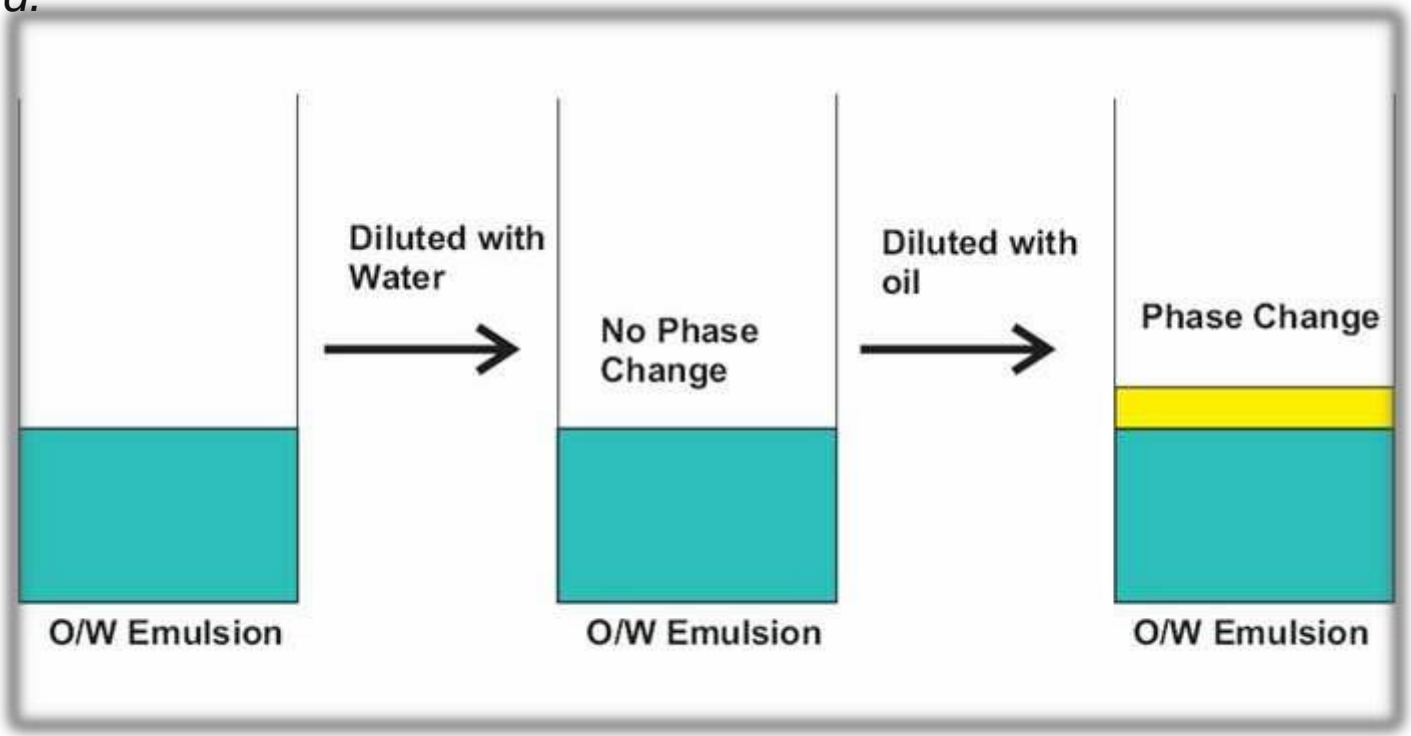
TESTS FOR EMULSION TYPE

Emulsion Type and Means of Detection



Dilution Test

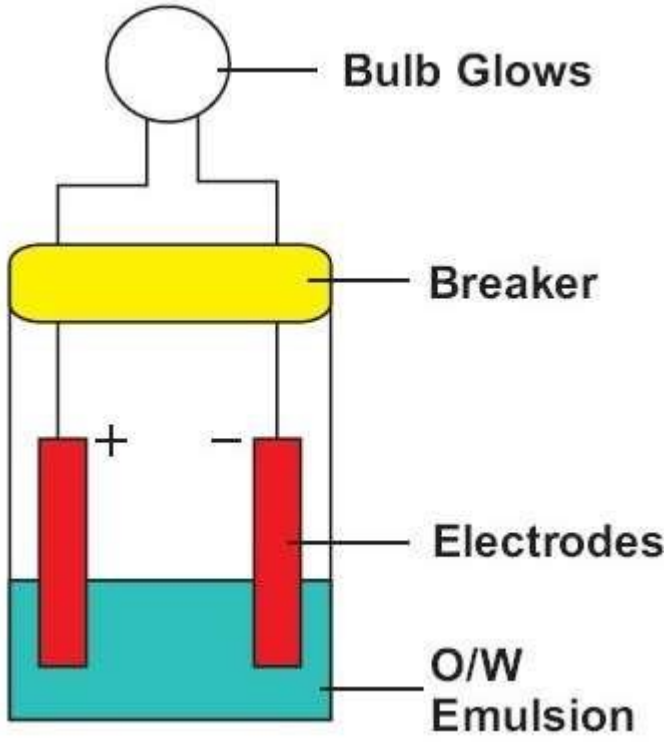
- *In this test the emulsion is diluted either with oil or water. If the emulsion is o/w type and it is diluted with water, it will remain stable as water is the dispersion medium" but if it is diluted with oil, the emulsion will break as oil and water are not miscible with each other. Oil in water emulsion can easily be diluted with an aqueous solvent whereas water in oil emulsion can be diluted with a oily liquid.*



Conductivity Test

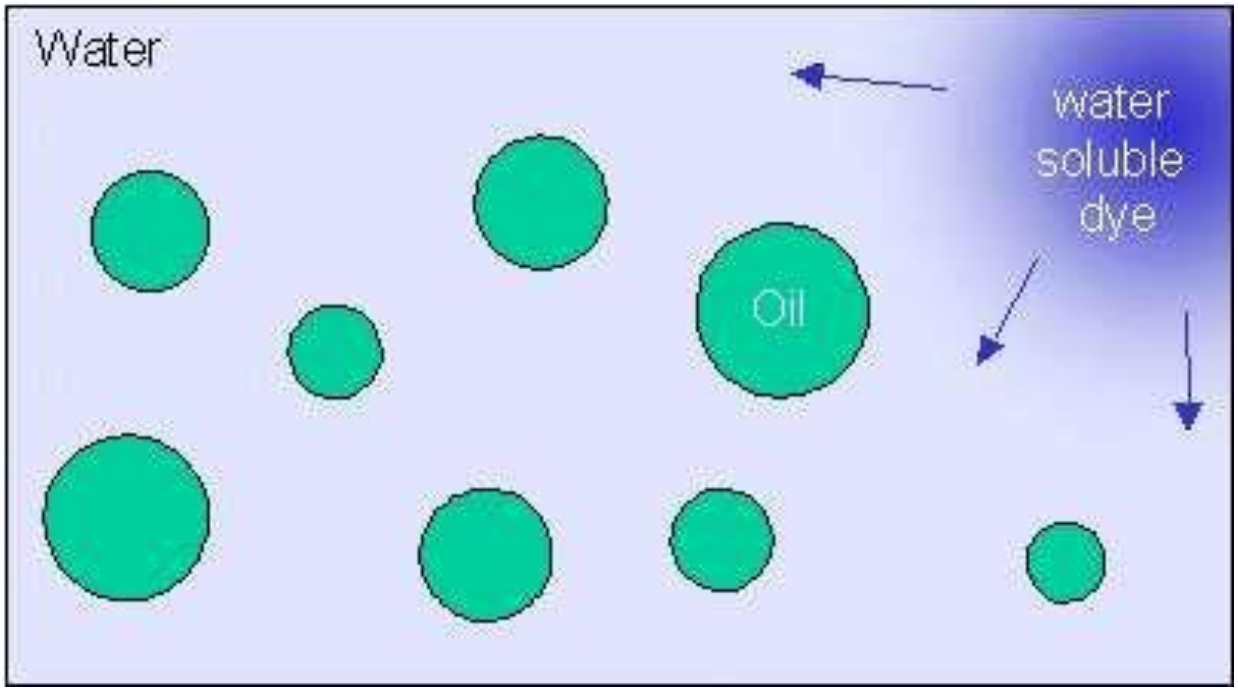
- *The basic principle of this test is that water is a good conductor of electricity. Therefore in case of o/w emulsion, this test will be positive as water is the external phase.*

'In this test, an assembly is used in which a pair of electrodes connected to an electric bulb is dipped into an emulsion. If the emulsion is o/w type, the electric bulb glows.'



Dye-Solubility Test

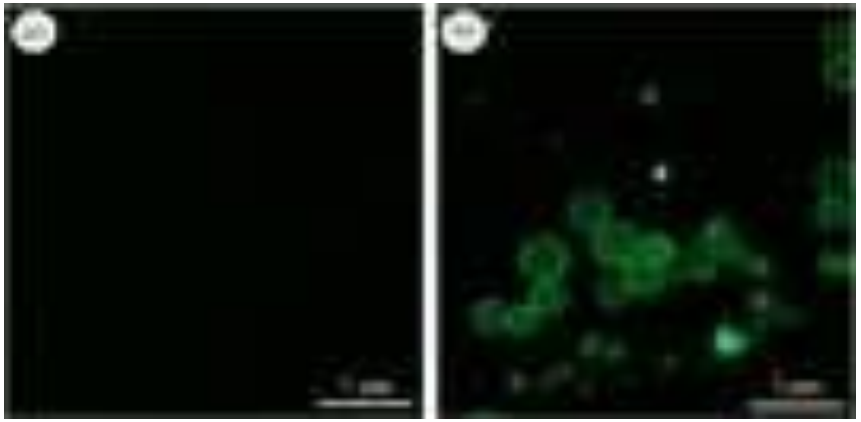
- *In this test an emulsion is mixed with a water soluble dye (amaranth) and observed under the microscope. If the continuous phase appears red, it means that the emulsion is o/w type as water is in the external phase and the dye will dissolve in it to give color. If the scattered globules appear red and continuous phase colorless, then it is w/o type. Similarly if an oil soluble dye (Scarlet red C or Sudan III) is added to an emulsion and the continuous phase appears red, then it is w/o emulsion.*



Ref. Index & Filter paper Test

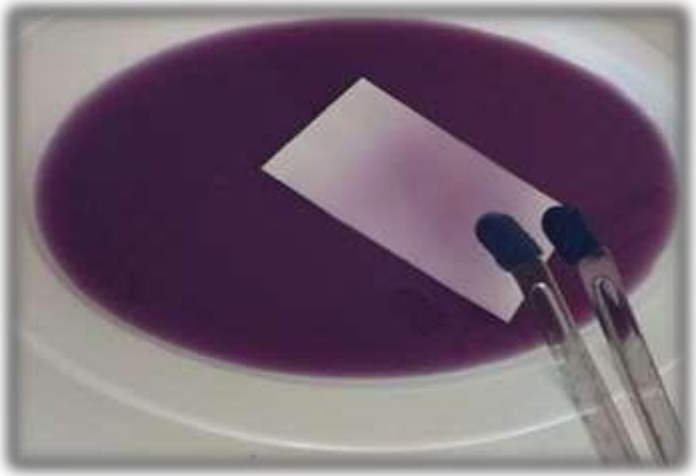
Fluorescence Test:

- *If an emulsion on exposure to ultra-violet radiations shows continuous fluorescence under microscope, then it is w/o type and if it shows only spotty fluorescence, then it is o/w type.*



Cobalt Chloride Test:

- *When a filter paper soaked in cobalt chloride solution is dipped in to an emulsion and dried, it turns from blue to pink, indicating that the emulsion is o/w type.*



PHARMACEUTICAL APPLICATIONS

Emulsions can be used for following dosage forms:

Oil Products

Emulsions are used for administering drugs orally due to following reasons :

***a.More palatable** : Objectionable taste or texture of medicinal agents gets masked.*

***b.Better absorption** : Due to small globule size, the medicinal agent gets absorbed faster.*

O/W Parenteral

a. I/V route :

Lipid nutrients are emulsified and given to patients by i/v rout. Such emulsions have particle size less than 100 nm.

b. Depot injections :

W/o emulsions are used to disperse water soluble antigenic materials in mineral oil for i/m depot injection.

Topical Products

O/W emulsions are more acceptable as water washable drug bases for cosmetic purposes.

W/O emulsions are used for treatment of dry skin.

Emulsions have following advantages when used for topical purpose:

a. ***Patient acceptance***
b. ***washable character,***
c. ***Acceptable viscosity,***
d. ***Less greasiness.***