EMULSIONS

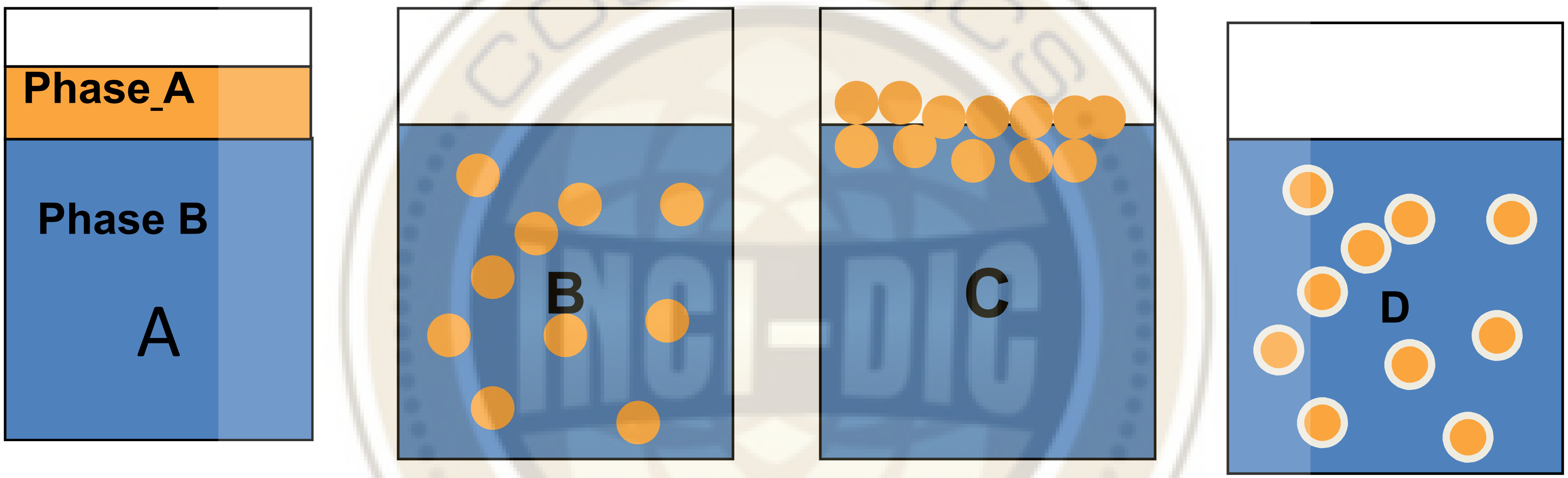
EMULSIONS

- Definition
- Classification
- Applications
- Theory of emulsification
- Additives for formulation of emulsion
- Formulation of emulsions
- Emulsification techniques
- Stability of emulsions
- Evaluation of emulsions

What is an emulsion ??

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.

Emulsions



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.

Types of emulsions

- Simple emulsions (Macro emulsions)
  - Oil-in-water (O/W)
  - Water-in-oil (W/O)
- Multiple emulsions
  - Oil-in-water-in-oil (O/W/O)
  - Water-in-oil-in-water (W/O/W)
- Micro emulsions

Factors affecting type of emulsion

- Type of emulsifying agent used
- Phase volume ratio
- Viscosity of each phase

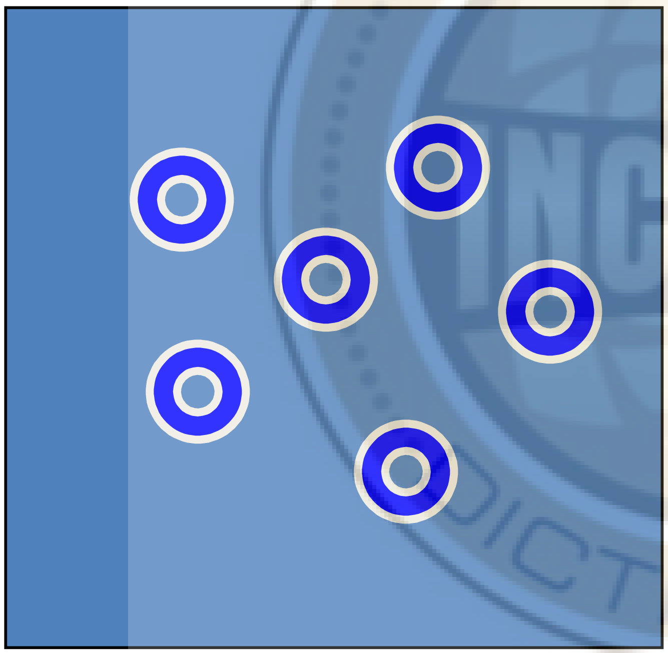
Determination of type of simple emulsion

- **Dilution test**
- **Dye solubility test**
- **Conductivity test**
- **CoCl2 filter test**
- **Fluorescence test**

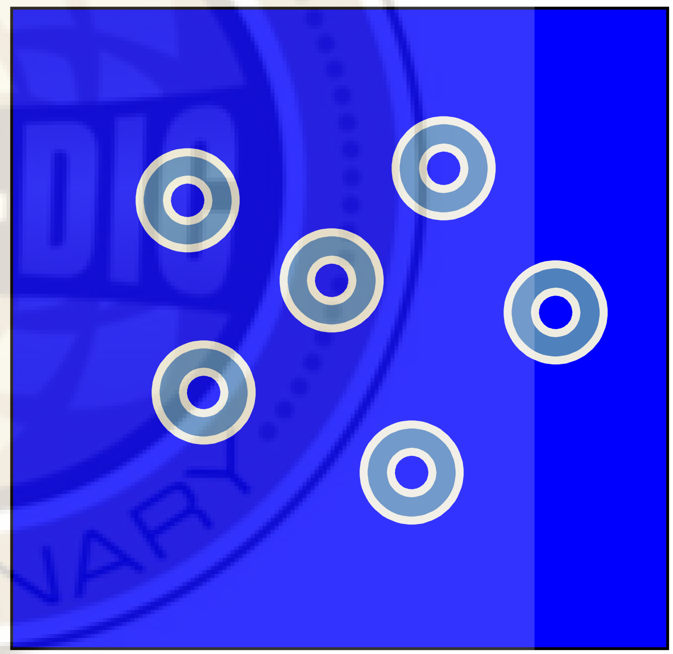
Types of emulsions

Multiple emulsions

w/o/w



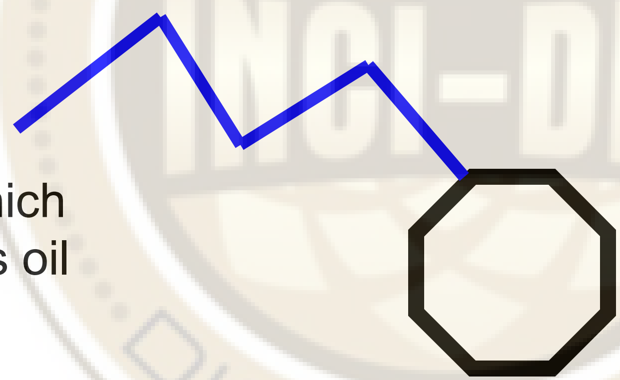
o/w/o



Microemulsions

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

	Microemulsion	Emulsion
Transparent	Yes	No
Size	10-120 nm	0.1 – 10 μ
Formation	Spontaneous	Require vigorous shaking
Type	o/w, w/o. cylinder	o/w, w/o, w/o/w, o/w/o
Stability	Thermodynamically stable	Thermodynamically unstable
Viscosity	Can accommodate 20 to 40% without increase in viscosity	More viscous


Tail which
prefers oil
Head which
prefers water

Pharmaceutical applications of microemulsions

- Increase bioavailability of drugs poorly soluble in water.
- Topical drug delivery systems
-

Pharmaceutical Applications of emulsions

- Oral products
  - It covers the unpleasant taste
  - Increases absorption rate

- O/W Parenteral use emulsion
  - i/v lipid nutrients
  - i/m – depot effect fr water soluble antigenic material

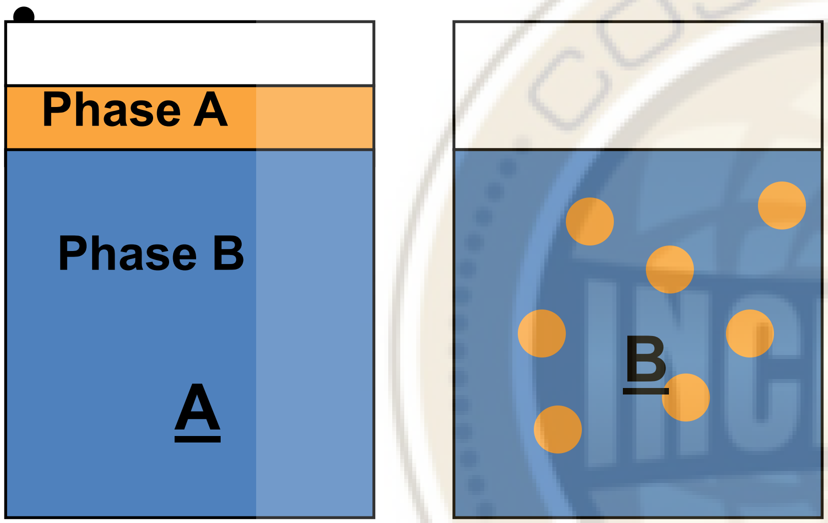
- Topical use :
  - Washable
  - Acceptable viscosity
  - Less greasy

Theory of emulsification

Droplets can be stabilized by three methods

i. By reducing interfacial tension
ii. By preventing the coalescence of droplets.
  a. By formation of rigid interfacial film
  b. By forming electrical double layer.

Theory of emulsification –reduction of interfacial tension



Change from A to B increases surface area of phase A, hence the Due to increased surface energy, the system is thermodynamically unstable.

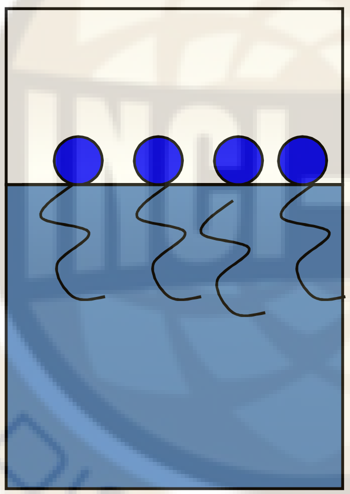
Emulsifying agents are needed to decrease the interfacial tension and to stabilize the emulsion.

Theory of emulsification – interfacial films

- Mono molecular
- Multimolecular
- Solid particle films

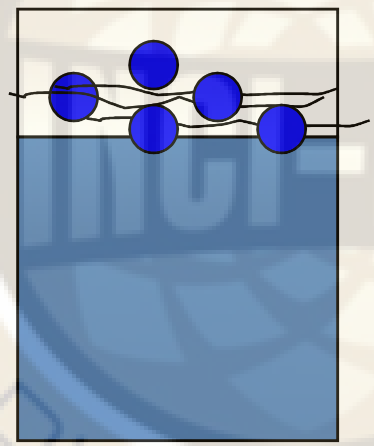
Interfacial films

- Monomolecular



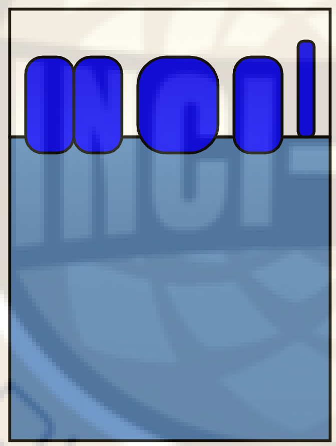
Interfacial films

- Multimolecular films

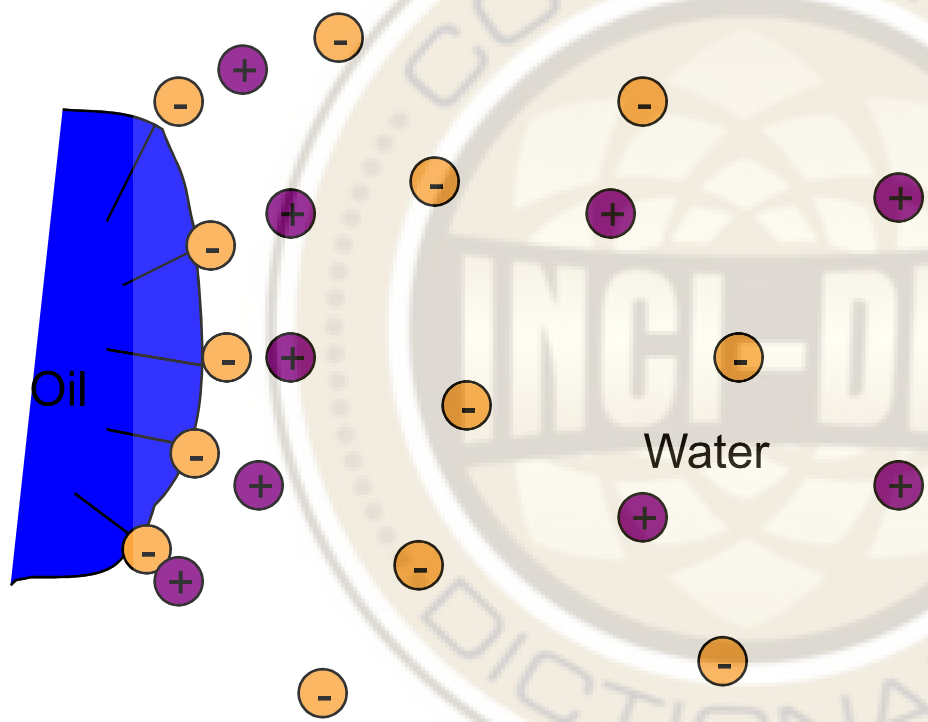


Interfacial films

- Solid particle film



Theory of emulsification -Formation of electrical double layer



Emulsion made with sodium soap.

Electrical double layer at oil-water interface

ADDITIVES FOR FORMULATION OF EMULSIONS

- 1. Emulsifying agents
- 2. Auxiliary emulsifiers.
- 3. Antimicrobial preservatives
- 4. Antioxidants

Emulsifying agents

- Added to an emulsion to prevent the coalescence of the globules of the dispersed phase .
- Help in emulsion formation by

➢ 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

Classification of emulsifying agents

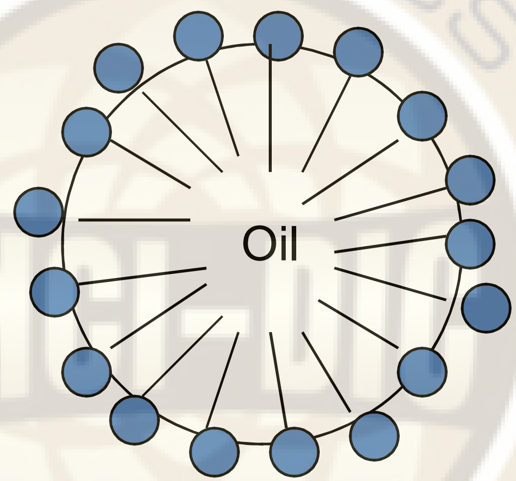
- Synthetic
- Surface active agents (Monomolecular films)
- Semi synthetic and natural
- Hydrophilic colloids (Multimolecular films)
- Finely divided solid particles (Particulate film)

Synthetic surface active agents

Description :

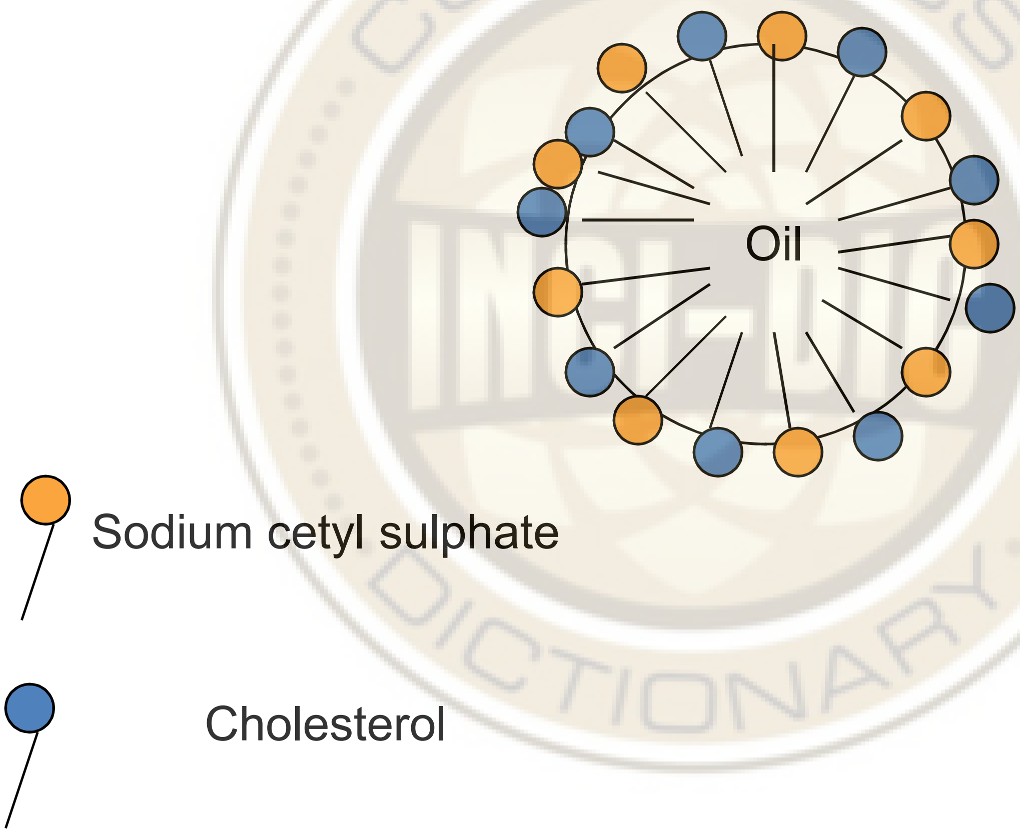
- Reduce interfacial tension and make the emulsion thermodynamically more stable.
- Form protective monomolecular film

Synthetic surface active agents
Monomolecular adsorption



Rule of Bancroft : Type of emulsion is a function of relative solubility of surfactant . The phase in which it is soluble becomes the continuous phase

Combination of emulsifying agents



Combination of emulsifying agents at the interface of oil and water.

Classification of Surfactant emulsifying agents

❖ Synthetic (Surfactants) (Monomolecular films)

➢ Anionic

- Soaps

  -Mono valent

  -Polyvalent

  -Organic

  Sulphates

  Sulphonates ($CH_3(CH_2)n\ CH_2SO_3 - Na^+$)

Classification of Surfactant emulsifying agents

- Synthetic (Surfactants) (Monomolecular films)
- Cationic
-
- 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

Hydrocolloid Emulsifying agents

Description

- Provide a protective sheath (Multimolecular 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.)

Classification of Hydrocolloid emulsifying agents

- ❖Semisynthetic
- ❖Natural
- Plant origin
- Animal origin

Classification of Hydrocolloid emulsifying agents

- Semi synthetic (Multi molecular films)

  Methyl cellulose

  Carboxy methyl cellulose

Classification of Hydrocolloid emulsifying agents

- Natural (Multimolecular films)
- From plant origin
  - Polysaccharides (Acacia, tragacanth, agar, pectin, lecithin)
- From animal origin

  Proteins (Gelatin)

  Lecithin

  Cholesterol

  Wool fat

  Egg yolk

Finely divided solids

- Description :

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.

Classification of Finely divided solid emulsifying agents

- Finely divided solids (Particulate film)
- Colloidal Clays
- Bentonite,($Al_2O_3.4SiO_2.H_2O$),
- Veegum (Magnesium Aluminium silicate) ,
- Magnesium trisilicate.
- Metallic hydroxides
- Magnesium hydroxide,
- Aluminium hydroxide,

Auxiliary emulsifying agents

- 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.

Auxiliary emulsifying agents

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.

Preservation of emulsions

- **Microbial contamination may occur due to:**
- contamination during development or production of emulsion or during its use.
- Usage of impure raw materials
- Poor sanitation conditions
- Invasion by an opportunistic microorganisms.
- Contamination by the consumer during use of the product..
- **Precautions to prevent microbial growth ;**
- Use of uncontaminated raw materials
- Careful cleaning of equipment with live straem .

Antimicrobial agents

- 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

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

  Cetyl 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

Antioxidants

- 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 vit A
- Butylated hydroxyl toluene - pharmaceuticals and cosmetics - Pronounced odor, to be used at low conc.
- Butylated hydroxylanisol - pharmaceuticals and cosmetics

Formulation of emulsions – Chemical factors

Factors affecting the choice of materials

- Purpose for which emulsion is to be used.
- Chemical stability
- Inertness
- Safety

Formulation of emulsions – Chemical factors

- Selection of liquid phase
- Phase ratio
- Selection of emulsifying agent
- Selection of preservative
- Selection of antioxidant

Selection of liquid phase:

- Choose from Lipids of natural or synthetic origin depends upon the release rate needed
- For topical pre[arations – feel of the product

Phase ratio

- Depends upon the solubility of the active ingredient
- Desired consistency

Selection of emulsifying agent

Properties of an ideal emulsifying agent

- reduce the interfacial tension between the two immiscible liquids.
- physically and chemically stable, inert and compatible with the other ingredients of the formulation.
- completely non irritant and non toxic in the concentrations used.
- organoleptically inert i.e. should not impart any colour, odour or taste to the preparation.
- form a coherent film around the globules of the dispersed phase and should prevent the coalescence of the droplets of the dispersed phase.
- produce and maintain the required viscosity of the preparation.

Selection of emulsifying agent

- Factors affecting choice of emulsifying agent :
  - Shelf life of the product
  - Type of emulsion desired
  - Cost of emulsifier.
  - Compatibility
  - Non toxicity
  - Taste
  - Chemical stability.

Method for Selection of emulsifying agent

- HLB method for selection of emulsifying agent

HLB blend = f x HLB (A) + (1-f) x HLB (B)

f = fraction of surfactant (A) in the blend

Specific considerations for formulation of emulsions

Consistency (viscosity)

- a consistency that provided the desired stability and yet has the appropriate flow characteristics must be attained.
- Can be changed by addition of auxiliary emulsifying agents.

Emulsification techniques

Two steps for emulsification :

i. Breaking of internal phase into droplets

   By putting energy into the system

ii. Stabilization of droplets

Emulsification techniques

- Laboratory scale preparation techniques
- Large scale preparation techniques

Extemporaneous (Laboratory scale) method of preparation

- Continental or dry gum method
- Wet gum method
- Bottle or Forbes bottle method
- Auxiliary method
- In situ soap method

Dry gum method (Continental method)

- The continental method is used to prepare the initial or primary emulsion from oil , water and a hydrocolloid or “gum” type emulsifier (usually acacia). The primary emulsion or emulsion nucleus is formed from 4 parts of oil, 2 parts of water and one part of gum. The 4 parts of oil and 1 part of gum represent their total amount for the fianl emulsion.
- In a mortar the 1 part of gum (acacia) is levigated with 4 parts of oil until the powder is thoroughly wetted; then the 2 parts water is added all at once and the mixture is vigorously and continuously trituarted until the primary emulsion formed is craemy white.
- Additional water or aqueous soltions may be incorporated after the primary emulsion is formed. Slid substances (e.g. active ingredients, preservatives , color,flavors) are generally dissolved and added as a solution to the primary emulsion ,oil soluble substancs in small amounts may be incorporated directly into the primary emulsion. Any substance which might reduce the physical stability of the emulsion, such as alcohohol (which may precipitate the gum) should be added as near to the end of the process as possible to avoid breaking th emulsion. When all agents have been incorporated , the emulsion sholud be transferred to a caliberated vessel, brought to fianl volume with water, then homogenised or blended to ensure unifrom distribution of ingredients.

Dry gum method (Continental method)

- used to prepare the initial or primary emulsion from oil , water and a hydrocolloid or “gum” type emulsifier (usually acacia).
- Ratio of oil :gum : water in primary emulsion

Fixed oil = 4:1:2

Mineral oil = 3:1:2

Volatile oil = 2:1;2

Oleo gum resin = 1:1:2

Dry gum method (Continental method)

- In a mortar gum (acacia) is levigated with oil until the powder is thoroughly wetted; Then water is added all at once and the mixture is vigorously and continuously triturated until the primary emulsion formed is creamy white.

- Additional water or aqueous solutions may be incorporated after the primary emulsion is formed.

- Solid substances (e.g. active ingredients, preservatives , color, flavors) are generally dissolved and added as a solution to the primary emulsion ,

Dry gum method (Continental method)

- oil soluble substances in small amounts may be incorporated directly into the primary emulsion.

- Any substance which might reduce the physical stability of the emulsion, such as alcohol (which may precipitate the gum) should be added as near to the end of the process as possible to avoid breaking the emulsion.

- When all agents have been incorporated , the emulsion should be transferred to a calibrated vessel, brought to final volume with water, then homogenized or blended to ensure uniform distribution of ingredients.

Preparing emulsion by dry gum method - example

Cod liver oil 50 ml

Acacia 12.5 gm

Syrup 10 ml

Flavor oil 0.4 ml

Purified oil up to 100 ml

- 1. Accurately weigh or measure each ingredient
- Place cod liver oil in dry mortar
- Add acacia and give it a very quick mix.
- Add 25 ml of water and immediately triturate to form thick white , homogenous primary emulsion.
- Add flaor and mix.
- Add syrup and mix.
- Add sufficient water to total 100 ml.

Wet gum method (English method)

- The proportion of oil and water and emulsifier (gum) are the same as in dry gum method , but the order and technique of mixing are different.
- The gum is triturated with water to form a mucilage;
- Then oil is slowly added in portions , while triturating.
- After all the oil is added , the mixture is triturated for several minutes to form the primary emulsion.
- Then other ingredients are added as in continental method.
- Generally speaking, the English method is more difficult to perform successfully , especially with more viscous oils, but may result in a more stable emulsion.

Bottle method

- Used to prepare emulsions of volatile oils, or oligeneous substances of vary low viscosities.
- Acacia (or other gum) is placed in a dry bottle and oil are added,
- The bottle is capped and thoroughly shaken.
- To this the required volume of water is added all at once and the mixture is shaken thoroughly until the primary emulsion is formed.
- It is important to minimise the initial amount of time the gum and oil are mxed. The gum will tend to imbibe the oil and will become water proof.

Auxiliary method

- An emulsion prepared by other methods can also be improved by passing it through a hand homogenizer, which forces the emulsion through a very small orifice, reducing the dispersed droplet size to about 5 microns or less.

In situ soap method

Calcium Soaps :

w/o emulsions contain oils such as oleic acid , in combination with lime water (calcium hydroxide solution, USP).

Prepared by mixing equal volumes of oil and lime water.

In situ soap method – Example Nascent soap

- Oil Phase : Olive oil / oleic acid ; olive oil may be replaces by other oils but oleic acid must be added.
- Lime water : $Ca(OH)2$ should be freshly prepared.
- The emulsin formed is w/o
- Method of preparation : Bottle method
- Mortar method : When the formulatio contains solid insoluble such as zinc oxide and calamine.

Emulsification techniques – large scale

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**

Preparation of emulsions- large scale

Energy may be supplied in the form of

- Heat
- Homogenization
- Agitation

Preparation of emulsions- large scale

Heat :

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

Preparation of emulsions

Mechanical equipment for emulsification (Agitation)

- Mechanical stirrers
- Propeller type mixers

  -Turbine mixers

  - Homogenizers
- Colloid mills
- Ultrasonifiers

Mechanical stirrers

Turbine stirrer

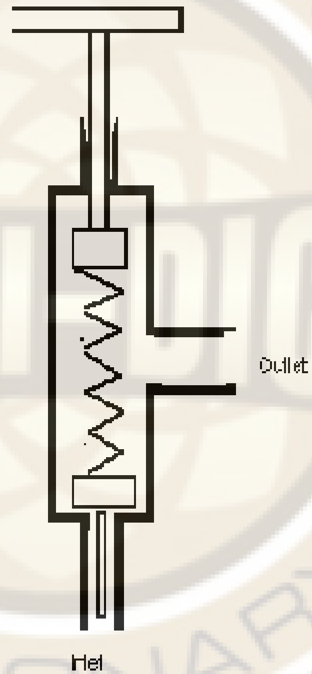
- For drawing the material to be mixed from above.
- Generates axial flow in the vessel.
-

Propeller stirrers

- **Standard stirring element. For drawing the material to be mixed from the top to the bottom.**
- **Local shearing forces.**
- **Generates axial flow in the vessel.**
- **Used at medium to high speeds.**

  .

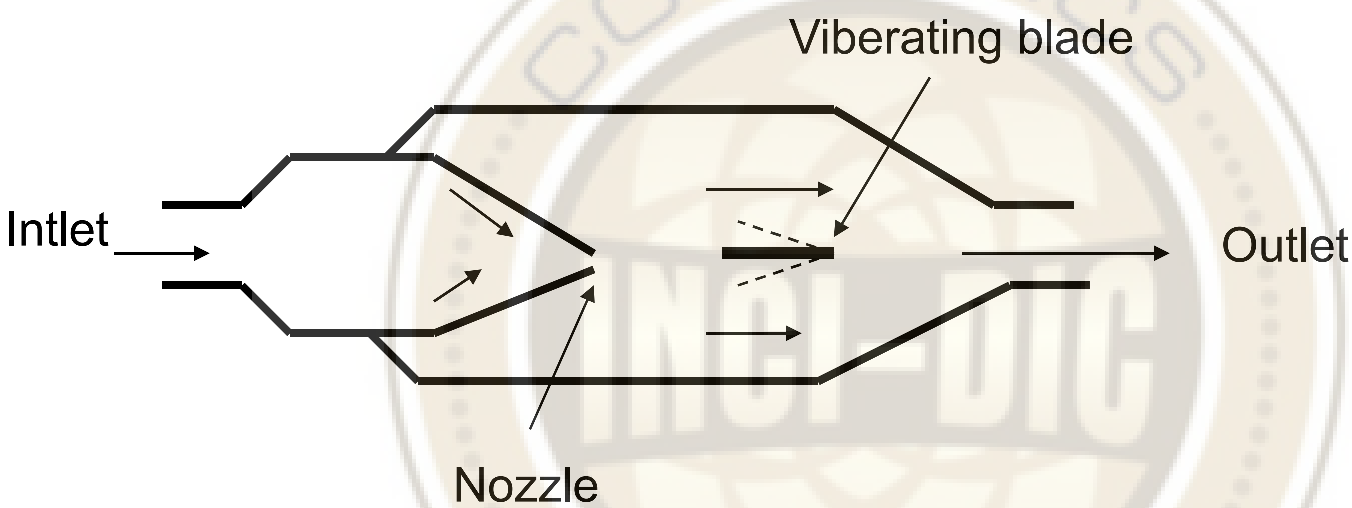
Preparation of emulsions - Homogeniser



Colloidal mill

Colloidal mill rotor and stator

Ultrasonifiers – Principle of Pohlman whistle



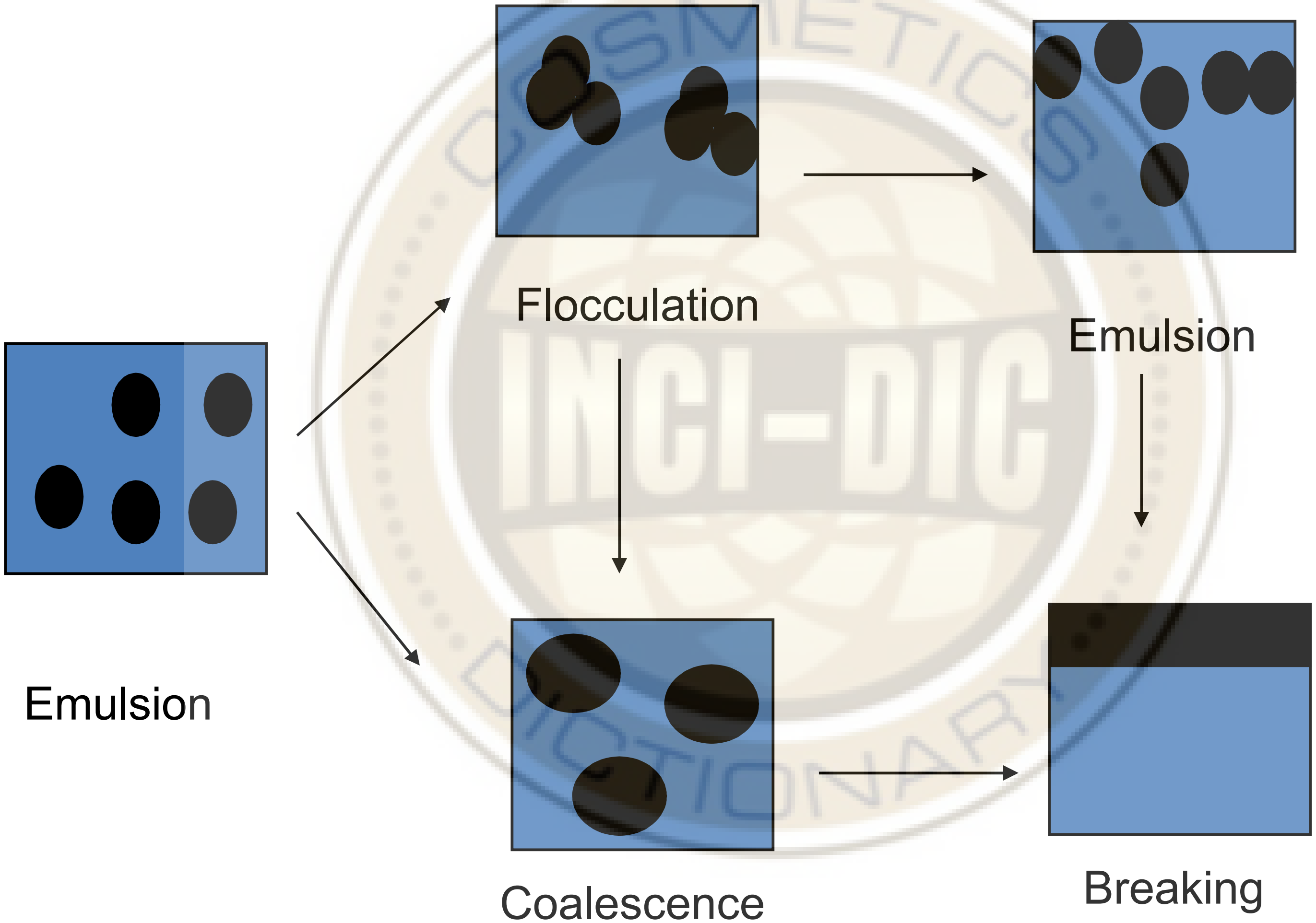
Incorporation of medicinal agents

- Addition of drug during emulsion formation
- Addition of drugs to a preformed emulsion
  1. Addition of materials into w/o emulsion
  2. Addition of oleaginous material to o/w emulsion
  3. Addition of water soluble materials to a w/o emulsion
  4. Addition of water soluble materials to an o/w emulsion

Emulsion stability (Instability) - Types

- Physical instability
- i. Flocculation
- Ii. Creaming or sedimentation
- iii. Aggregation or coalescence
- Iv. Phase inversion

Physical instability of emulsions



Emulsion stability (Instability) - Types

Flocculation :

- **Redispersible association of particle within an emulsion to form large aggregates.**
- **precursor to the irreversible coalescence.**
- **differs from coalescence mainly in that interfacial film and individual droplets remain intact.**
- **influenced by the charges on the surface of the emulsified globules.**

Emulsion stability (Instability) - Types

Flocculation :

- **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.**

Physical stability of emulsion

Creaming :

- Creaming is the upward movement of dispersed droplets of emulsion relative to the continuous phase (due to the density difference between two phases).
- Stoke's law : $dx / dt = d2 (\rho i- \rho e)g/18\eta$
- Dx/dt = rate of setting
- D = diameter of particles
- ρ_i and ρ_e density of internal nd external phase
- g = gravitational constant
- η =viscosity of medium

Physical stability of emulsion

- 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.
- Breaking is the destroying of the film surrounding the particles.
- The major factor to prevent coalescence is the mechanical strength of the interfacial film.

Physical stability of emulsion

Phase inversion

- An emulsion is said to invert when it changes from an o/w to w/o or vice versa.
- Addition of electrolyte :
- Addition of $CaCl_2$ into o/w emulsion by sodium soaps can be inverted to w/o.
- Changing the phase volume ratio :

Evaluation of emulsion stability

Final evaluation to be done in final container

As :

- The ingredients may interact with the container,
- Some material may leach out from the container
- Loss of water and volatile ingredients may occur through the container or closures.

Evaluation of emulsion stability

Stress condition for study of emulsion stability :

i. Thermal stress

- **Aging and temperature**
- **Phase inversion temperature**

ii. Gravitational stress

iii: Agitation

Evaluation of emulsion stability

Stress condition for study of emulsion stability :

i. Thermal stress

- **Aging and temperature**
- **Phase inversion temperature**

PIT is more , rate of coalescence will be less. So the emulsions must have a PIT as high as possible – always higher than the storage temp.

Evaluation of emulsion stability

Stress condition for study of emulsion stability :

ii. Gravitational stress

centrifugation at 3750 rpm in a 10 cm radius centrifuge for a period of 5 hrs is equivalent to the effect of gravity for about one year

iii: Agitation

Parameters for evaluation of emulsion stability (shelf life)

Physical parameters

- phase separation
- Viscosity
- Electrophoretic properties
- Zeta potential
- Electrical conductivity
- **Dielectric constant**
- Particle size number analysis
- Chemical parameters

Phase diagram