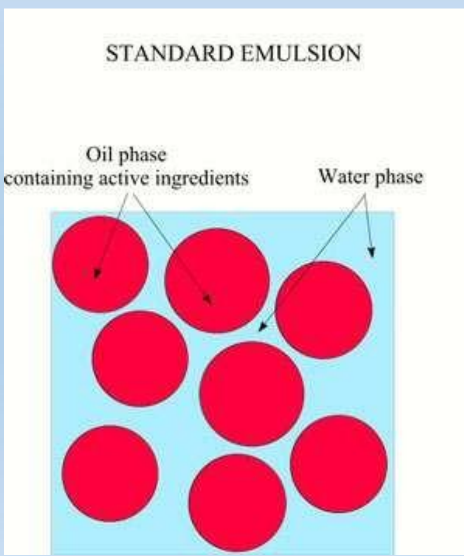
EMULSION

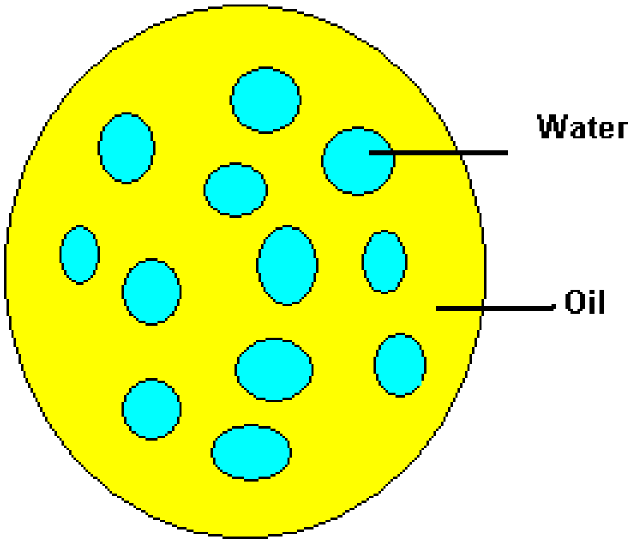
PHARMACEUTICAL EMULSIONS

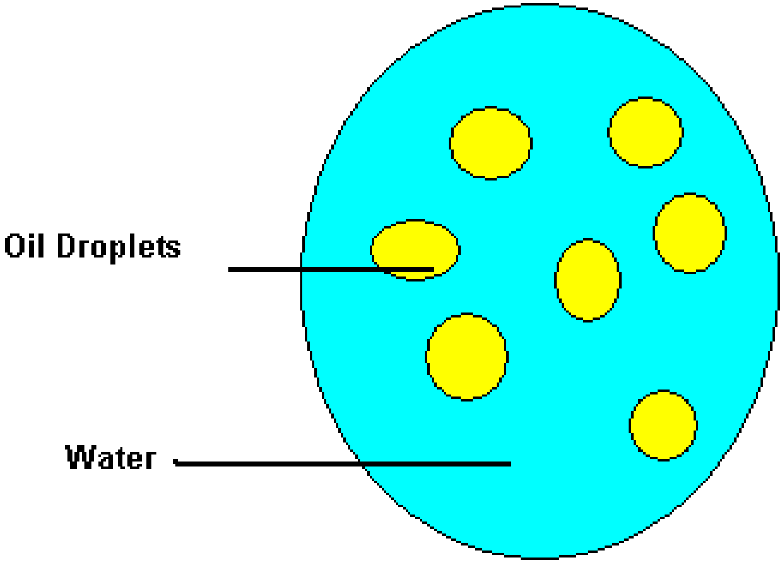


Emulsion

An emulsion consists of two immiscible liquids one of which is uniformly dispersed through the other as droplets of diameter greater than 0.1 μm.

The system is stabilized by the presence of emulsifying agent. The particle diameter of the disperse phase extends from 0.1 to 100 μm.


Water
Oil


Oil Droplets
Water

Pharmaceutical application of emulsions:

- ➢- Oral, rectal and topical administration of oils and oil-soluble drugs.
- ➢- The unpleasant taste or odor can be masked by emulsification
- ➢- The absorption and penetration of medicament are enhanced by emulsification
- ➢- Intramuscular injections of water-soluble drugs or vaccine to provide slow release.
- ➢- The use of sterile stable i.v emulsion containing fats, carbohydrates and vitamins as a potential nutrition

- Examples:
- Oral use:

Cod-liver, Liquid paraffin, castor oil emulsions

- External use

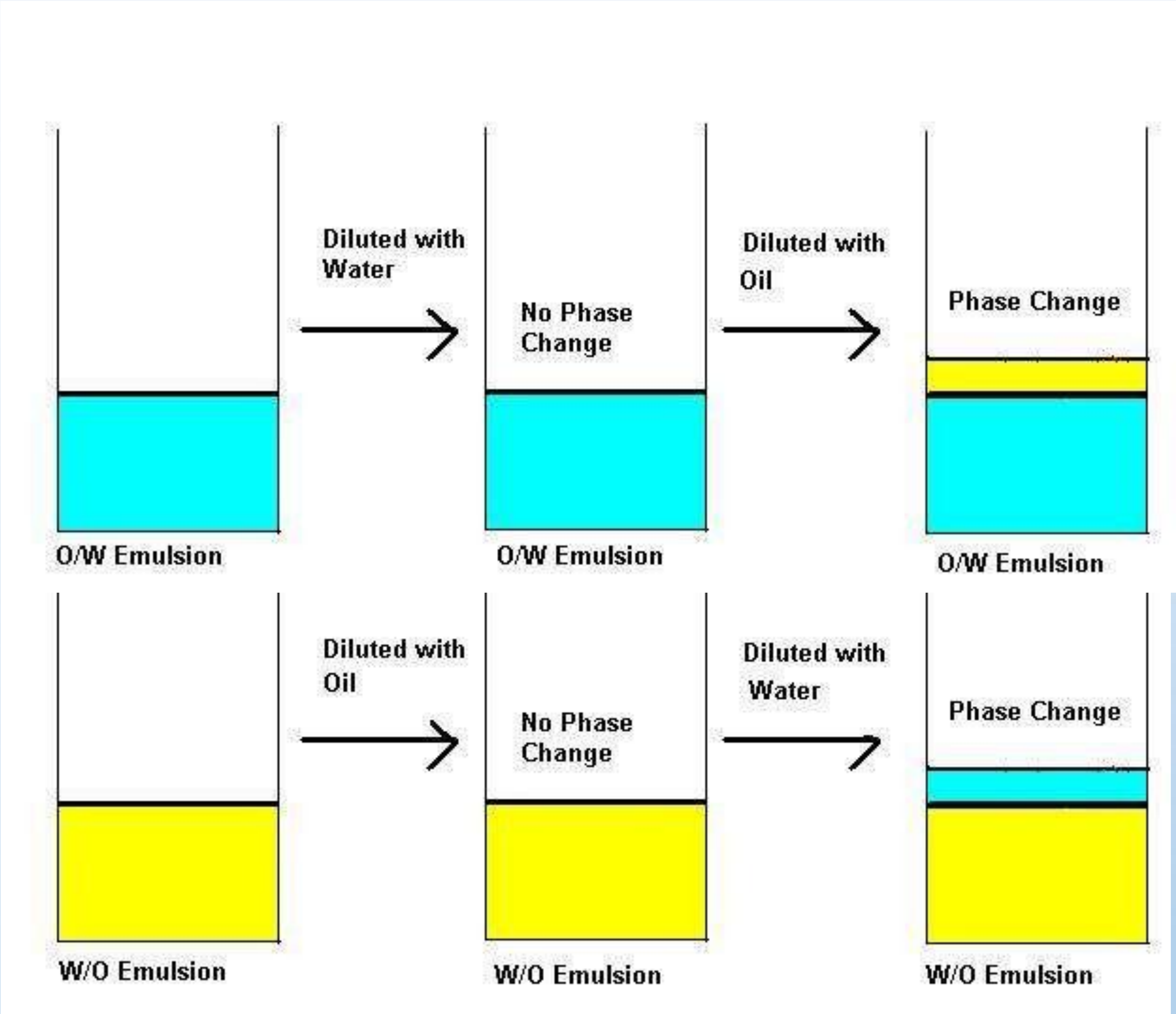
Turpentine Liniment BP, Oily calamine lotion BP.

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
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
Water soluble drugs are more 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.
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.

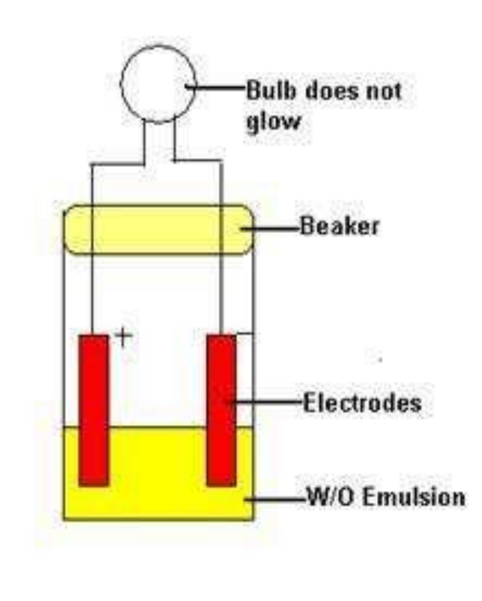
Test for identification of emulsion type:

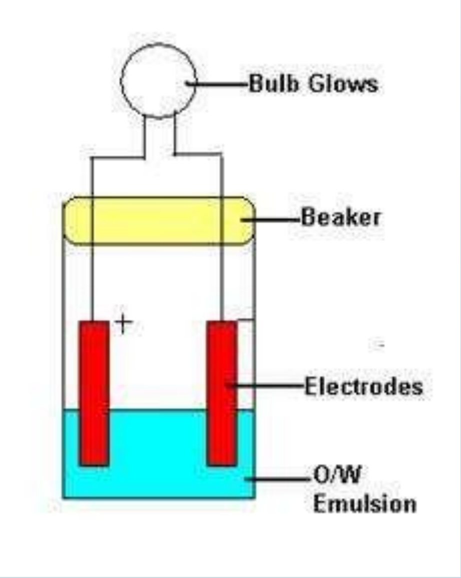
- Dilution test (miscibility test)
- Staining test (dye solubility test)
- Conductivity measurement
- $CoCl_2$ Filter test
- Fluorescence test


Diluted with Water
No Phase Change
Diluted with Oil
Phase Change
O/W Emulsion
O/W Emulsion
O/W Emulsion
Diluted with Oil
No Phase Change
Diluted with Water
Phase Change
W/O Emulsion
W/O Emulsion
W/O Emulsion

Conductivity Test

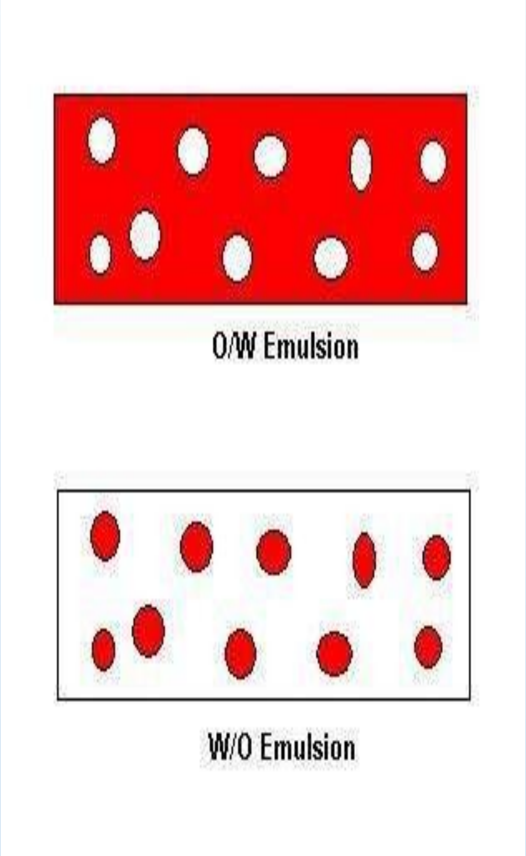
This test is based on the basic principle that water is a good conductor of electricity. Therefore in case of o/w emulsion , this test will be positive as water is the external phase. In this test. An assembly consisting of a pair of electrodes connected to a lamp is dipped into an emulsion. If the emulsion is o/w type, the lamp glows.





Dye Solubility Test

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



Fluorescence test

- Many oils exhibit Fluorescence when exposed to UV light.
- When a w/o emulsion exposed to fluorescent light under microscope , the entire field fluorescence.
- If the fluorescence is spotty ,the emulsion of o/w –type .
- However, all oils do not exhibit fluorescence under UV light and thus the method does not have universal application.

Theory of emulsification

Droplets can be stabilized by three methods

By reducing interfacial tension

- By preventing the coalescence of droplets.
  a. By formation of rigid interfacial film
  b. By forming electrical double layer.
- Viscosity theory.
- Film theory or adsorption theory.
- Wedge theory.

By lowering the interfacial tension (Reduction in interfacial tension thermodynamic stabilization)

- The increased surface energy associated with formation of droplets, and hence surface area in an emulsion can be reduced by lowering of interfacial tension. Assuming the droplets to be spherical

$$\Delta F = 6 \gamma V/d$$

where, ΔF = energy in put required

γ = interfacial tension

V = volume of dispersed phase in ml

d = mean diameter of particles

By preventing the coalescence of droplets

- Coalescence of droplets can be prevented by two methods

  (a) By formation of rigid film

  (b) By formation of electrical double layer.

Film theory (or) Adsorption theory

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

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.

Wedge theory

- According to this theory, monovalent soap like sodium stearate give o/w type emulsion and divalent soap like calcium stearate give w/o type emulsion. This was explained by successful accommodation of the soap molecules to give the type of emulsion

Instabilities In Emulsions

- An emulsion is a thermodynamically unstable preparation so care has to be taken that the chemical as well as the physical stability of the preparation remains intact throughout the shelf life.
- There should be no appreciable change in the mean particle size or the size distribution of the droplets of the dispersed phase and secondly droplets of the dispersed phase should remain uniformly distributed throughout the system.

Creaming

An emulsion is said to cream when the oil or fat rises to the surface, but remains in the form of globules, which may be redistributed throughout the dispersion medium by shaking. An oil of low viscosity tends to cream more readily than one of high viscosity.

Increasing the viscosity of the medium decreases the tendency to cream.

Creaming is a reversible phenomenon which can be corrected by mild shaking.

The factors affecting creaming are best described by Stoke's law:

$$V = 2r^2 (d_1 - d_2)\, g/9\eta$$

Where V= rate of creaming

r=radius of globules

d_1= density of dispersed phase

d_2= density of dispersion medium

g= gravitational constant

η = viscosity of the dispersion medium

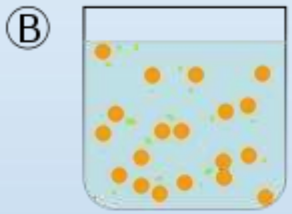
The following approaches can be used for decreasing Creaming

- Reduction of globule size: According to stoke’š™ law, rate of creaming is directly proportional to the size of globules. Bigger is the size of the globules, more will be the creaming. Therefore in order to minimize creaming, globule size should be reduced by homogenization.
- Increasing the viscosity of the continuous phase: Rate of creaming is inversely proportional to the viscosity of the continuous phase i.e. more the viscosity of the continuous phase, less will the problem of creaming. Therefore to avoid creaming in emulsions, the viscosity of the continuous phase should be increased by adding suitable viscosity enhancers like gum acacia, tragacanth etc.

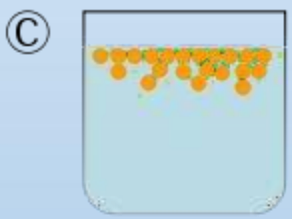
Cracking

- Occasionally, it happens that an emulsion cracks during preparation, i.e., the primary emulsion does not become white but acquires an oily translucent appearance.
- In such a case, it is impossible to dilute the emulsion nucleus with water and the oil separates out (irreversible process)
- Cracking of emulsion can be due to:
- Addition of an incompatible emulsifying agent,
- Chemical or microbial decomposition of emulsifying agent,
- Addition of electrolytes,
- Exposure to increased or reduced temperature or change in pH.

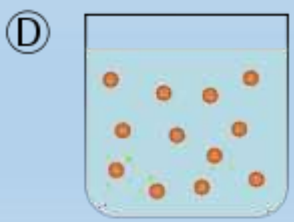
A. Two immiscible liquids, not yet emulsified.



B. An emulsion of Phase II dispersed in Phase I.



C. The unstable emulsion progressively separates.



D. The surfactant positions itself on the interfaces between Phase II and Phase I, stabilizing the emulsion

Phase Inversion

- In phase inversion o/w type emulsion changes into w/o type and vice versa.
- It is a physical instability.
- It may be brought about by the addition of an electrolyte or
  by changing the phase volume ratio or
- by temperature changes.
- Phase inversion can be minimized by using the proper emulsifying agent in adequate concentration,
- keeping the concentration of dispersed phase between 30 to 60 percent and by storing the emulsion in a cool place.

Points to be considered during formulations of emulsions

- Stability of the active ingredient
- Stability of the excipients
- Visual appearance
- Color
- Odor (development of pungent odor/loss of fragrance)
- Viscosity, extrudability
- Loss of water and other volatile vehicle components
- Concentration of emulsifier
- Order of addition of ingredients
- Particle size distribution of dispersed phases

- pH
- Temperature of emulsification
- Type of equipment
- Method and rate of cooling
- Texture, feel upon application (stiffness, grittiness, greasiness, tackiness, spreadibility)
- Microbial contamination/sterility (in the unopened container and under conditions of use)
- Release/bioavailability (percutaneous absorption)
- Phase distribution, Phase Inversion (homogeneity/phase separation, bleeding

Packaging, Labeling and Storage of Emulsions

- Depending on the use, emulsions should be packed in suitable containers. Emulsions meant for oral use are usually packed in well filled bottles having an air tight closure.
- Light sensitive products are packed in amber coloured bottles.
- For viscous emulsions, wide mouth bottles should be used. The label on the emulsion should mention that these products have to be shaken thoroughly before use.
- External use products should clearly mention on their label that they are meant for external use only.
- Emulsions should be stored in a cool place but refrigeration should be avoided as this low temperature can adversely effect the stability of preparation.

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 stream .

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

- Examples of antimicrobial preservatives used to preserve emulsified systems include
- parahydroxybenzoate esters such as methyl, propyl and butyl parabens,
- organic acids such as ascorbic acid and benzoic acid,
- organic mercurials such as phenylmercuric acetate and phenylmercuric nitrate,
- quarternary ammonium compounds such as cetrimide,
- cresol derivatives such as chlorocresol
- and miscellaneous agents such as sodium benzoate, chloroform and phenoxyethano

- The ideal antioxidant should be:

- nontoxic, nonirritant,
- effective at low concentration under the expected conditions of storage and use,
- soluble in the medium and stable.
- Antioxidants for use in oral preparation should also be odorless and tasteless.

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

Preparation of Emulsions

- Preparation Of Emulsions
- Preparation of emulsions depends on the scale at which it is produced.
- On small scale mortar and pestle can be used but its efficiency is limited. To overcome these drawback small electric mixers can be used although care must be exercised to avoid excessive entrapment of air.
- For large scale production mechanical stirrers are used

  to provide controlled agitation and shearing stress

  to produce stable emulsions.

- The methods commonly used to prepare emulsions can be divided into two categories:

A- *Trituration Method*

This method consists of dry gum method and wet gum method.

1- Dry Gum Method

In this method the oil is first triturated with gum with a little amount of water to form the primary emulsion. The trituration is continued till a characteristic ‘clicking’ sound is heard and a thick white cream is formed. Once the primary emulsion is formed, the remaining quantity of water is slowly added to form the final emulsion.

2- Wet Gum Method

As the name implies, in this method first gum and water are triturated together to form a mucilage. The required quantity of oil is then added gradually in small proportions with thorough trituration to form the primary emulsion.

Once the primary emulsion has been formed remaining quantity of water is added to make the final emulsion.

B- Bottle Method

This method is employed for preparing emulsions containing volatile and other non-viscous oils. Both dry gum and wet gum methods can be employed for the preparation.

- As volatile oils have a low viscosity as compared to fixed oils, they require comparatively large quantity of gum for emulsification.

In this method, oil or water is first shaken thoroughly and vigorously with the calculated amount of gum. Once this has emulsified completely, the second liquid (either oil or water) is then added all at once and the bottle is again shaken vigorously to form the primary emulsion. More of water is added in small portions with constant agitation after each addition to produce the final volume.

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

Colloidal mill

Homogeniser

Emulsifying Agents 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 act by reducing the interfacial tension between the two phases and forming a stable interfacial film.
- The choice of selection of emulsifying agent plays a very important role in the formulation of a stable emulsion.
- No single emulsifying agent possesses all the properties required for the formulation of a stable emulsion therefore sometimes blends of emulsifying agents have to be taken.

Criteria For The Selection of Emulsifying Agents

- An ideal emulsifying agent should posses the following characteristics:
- It should be able to reduce the interfacial tension between the two immiscible liquids.
- It should be physically and chemically stable , inert and compatible with the other ingredients of the formulation.
- It should be non irritant and non toxic in the conc., used.
- It should be organoleptically inert i.e. should not impart any color, odor or taste to the preparation.
- It should be able to produce and maintain the required viscosity of the preparation.
- It should be able to form a coherent film around the globules of the dispersed phase and should prevent the coalescence of the droplet of the dispersed phase.

1-Natural emulsifying agents from vegetable sources

- These consist of agents which are carbohydrates and include gums and mucilaginous substances. Since these substances are of variable chemical composition,
- Since carbohydrates acts a good medium for the growth of microorganism, therefore emulsions prepared using these emulsifying agents have to be suitable preserved in order to prevent microbial contamination.
- E.g. tragacanth, acacia, agar, pectin and starch.

2-Natural emulsifying agents from animal source

- The examples include gelatin, egg yolk and wool fat (anhydrous lanolin). Type A gelatin (Cationic) is generally used for preparing o/w emulsion while type B gelatin is used for o/w emulsions of pH 8 and above.
- Lecithin and cholesterol present in egg yolk also act as emulsifying agent. They show surface activity and are used for formulating o/w emulsions. .
- Wool fat is mainly used in w/o emulsions meant for external use. They absorb large quantities of water and form stable w/o emulsions with other oils and fats.

3- Semi-synthetic polysaccharides

- `Includes mainly cellulose derivatives like sodium carboxy methyl 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.

4- Synthetic emulsifying agents

- This group contains surface active agents which act by getting adsorbed at the oil water interface in such a way that the hydrophilic polar groups are oriented towards water and lipophillic non polar groups are oriented towards oil, thus forming a stable film.
- They are classified according to the ionic charge possessed by the molecules of the surfactant e.g., anionic, cationic, non-ionic and ampholytic.

4.1. Anionic Surfactants

- The long anion chain on dissociation imparts surface activity, while the cation is inactive.
- These agents are primarily used for external preparations and not for internal use as they have an unpleasant bitter taste and irritant action on the intestinal mucosa.
- e.g., alkali soaps, amine soaps, metallic soaps, alkyl sulphates and phosphates and alkyl sulphonates.

4.2. Cationic surfactants

- The positive charge cations produced on dissociation are responsible for emulsifying properties.
- They are mainly used in external preparations such as lotions and creams.
- Quaternary ammonium compounds such as cetrimide, benzalkonium chloride and benzethonium chloride are examples of important cationic surfactants.

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4.3. Non-ionic surfactants

- They are the class of surfactants widely used as emulsifying agents. .
- They also show low irritancy as compared to other surfactants.
- E.g. glyceryl esters such as glyceryl monostearate, propylene glycol monostearate, macrogol esters such as polyoxyl stearates and polyoxyl-castor oil derivatives, sorbitan fatty acid esters such as spans and their polyoxyethylene derivatives such as tweens (polysorbates).

4.4.- Finely divided Solids

- This group consist of finely divided solids having balanced hydrophilic lipophillic properties. .
- If the solid particles are preferentially wetted by oil, a w/o emulsion is formed while if wetting is done by water then o/w emulsion is seen.
- e.g., bentonite, aluminium magnesium stearate, attapulgite, colloidal anhydrous silica and hectorite. The emulsions formed using finely divided solids are stable and less prone to microbial contamination.

Quality control tests for Emulsions

The following are the quality control tests done for emulsions:

- 1. Determination of particle size and particle count: Determination of changes in the average particle size or the size distribution of droplets is an important parameter used for the evaluation of emulsions. It is performed by optical microscopy, sedimentation by using Andreasen apparatus and Coulter counter apparatus.
- 2. Determination of viscosity: Determination of viscosity is done to assess the changes that might take place during aging. Emulsions exhibit non-newtonian type of flow characterstics.
- The viscometers which should be used include cone and plate viscometers.

3. **Determination of phase separation:** This is another parameter used for assessing the stability of the formulation.

Phase separation may be observed visually or by measuring the volume of the separated phases.

4. **Determination of electrophoretic properties:** Determination of electrophoretic properties like zeta potential is useful for assessing flocculation since electrical charges on particles influence the rate of flocculation.

O/W emulsion having a fine particle size will exhibit low resistance but if the particle size increase, then it indicates a sign of oil droplet aggregation and instability.

Stability testing

Stability of emulsions is an important parameter for the formulator.

Stability testing of emulsions involves determining stability at long term storage conditions, accelerated storage conditions, freezing and thawing conditions. Stress conditions are applied in order to speed up the stability testing.

The stress conditions used for speeding up instability of emulsions include:

- Centrifugal force, Agitational force, Aging and temperature

- The following physical parameters are evaluated to assess the effect of any of the above stress conditions:

  Phase separation

  Viscosity

  Electrophoretic properties

  Particle size and particle count

Stress condition for study of emulsion stability

:1. 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:

2. 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.

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- Adam R. Abate,‡a Julian Thiele‡ab and David A. Weitz*a Received 23rd July 2010, Accepted 21st September 2010DOI: 10.1039/c0lc00236d

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Thank you…