EMULSIONS-I

Description Emulsification

- Emulsification is the breakdown of large fat globules into smaller, uniformly distributed particles.
- It is accomplished mainly by bile acids in the small intestine (preparation of fat for chemical digestion by specific enzymes)
- It is the most important phenomenon caused by the adsorption of surfactantat liquid-liquid interfaces.

Description-Emulsion Pharmaceutical technology

Emulsions are heterogeneous systems with homogeneous appearance, formed by dispersing at least two unmixable liquid phases in droplets by using an **emulsifying agent**.

The globular phase is called the dispersed or inner phase or

discontinous phase

The other phase is the dispersion medium or external phase

or contionus phase

Pharmaceutical emulsions are in the colloidal state, i.e. the disperse phase sizes range from nanometres to the visible (several micrometres).

Appearance of Emulsions

Droplet size	Appearance
1 µm <	White
0.1-1 µm	Blue-White
50-100 nm	Semitransparent
50 nm >	Transparent

Emulsion components

Oil phase (resins, waxes, hydrocarbon, etc.)

Water phase (aqueous solutions of salts and organic or colloidal substances)

Emulsifier

Advantages of Emulsions

- Mask the bad taste and smells of the ingredients
- Improve the absorption of active agents;
- Improve the chemical stability of active agents

- They form a thin layer on skin after topical application and can be easily washed
- Rapid penetration through skin
- IV emulsion forms are used as lipid nutrient
- Multiple emulsions are used for extended drug release and im reservoir systems
- Radiopaque emulsions are used for diagnostic purposes

Emulsion types
1- Classical Emulsions- Macro Emulsions

- Oil in water type (o/w): Oil droplets are dispersed within aqueous phase. Commonly used for oral and topical applications

- Water in oil type (w/o): Water droplets are dispersed within oil phase. Commonly used for topical applications

Bancroft's rule

Bancroft's rule states that the phase in which the emulsifying agent is more soluble will be the external phase.

In O/W emulsions – emulsifying agents are more soluble in water than in oil.

In W/O emulsions – emulsifying agents are more soluble in oil than in water.

O/W emulsions

- Fats or oils for oral administration, either as medicaments in their own right, or as vehicles for oil soluble drugs, are always formulated as oil in water (O/W) emulsions.
- They are non greasy and are easily removable from the skin surface
- They are used externally to provide cooling effect
- They are used internally to also mask the bitter taste of oil.
- Water soluble drugs are more quickly released from O/W emulsion.

W/O emulsions

- They have an occlusive effect by hydrating the stratum corneum and inhibiting evaporation of eccrine secretions.
- It has an effect on the absorption of drugs from W/O emulsions.
- W/O emulsion is also useful for cleansing the skin of oil soluble dirt, although its greasy texture is not always cosmetically acceptable.
- They are greasy and not water washable and are used externally to prevent evaporation of the moisture from the surface of skin e.g. cold cream.
- Oil soluble drugs are more quickly released from W/O emulsion.
- They are preferred for formulation meant for external use like cream

Identification of emulsion type

Properties	O/W	W/O
Color	Generally milky white	Depends on the color of the oil phase
Feel	Lighter feel	Oily
Dilution	Can be diluted with water	Can be diluted with oil
Electrical conductivity	Conductive	Very little conductor or none
Dye penetration • Lipid soluble dyes • Water soluble dyes	 Globules are stained External phase is stained	 External phase is stained Globules are stained
Diffusion through filter paper	+	-
Under UV light	Does not emit UV light	Emits UV light

Emulsion types
2- Multiple Emulsions

These type of emulsions contain two type of emulsion within one system. They are also defined as «the emulsion of emulsion».
W/O/W-O/W/O

Multiple Emulsions-
pharmaceutical applications / advantages/disadvantages

Pharmaceutical applications /Advantages

- 🙂taste masking
- 🙂adjuvant vaccines
- 🙂immobilization of enzymes
- 🙂sorbent reservoir of overdose treatments
- 🙂augmentation of external skin or dermal absorption
- 🙂formulated as cosmetics, such as skin moisturizer.
- 🙂obtaining prolonged release
- 🙂protection of the loaded drugs
- 🙂the possibilities of incorporating several actives ingredient in the different compartments

Disadvantages

- ☹multiple emulsions have limitations because of thermodynamic instability and their complex structure

Emulsion types
3- Microemulsions

- Microemulsions are homogeneous transparent systems of low viscosity which contain a high percentage of both oil and water and high concentrations (15–25%) of emulsifier mixture.
- Microemulsions form spontaneously when the components are mixed in the appropriate ratios and are thermodynamically stable..
- W/O-O/W
- Contains a second amphiphile (the cosurfactant) such as a short-chain alcohol in the formulation.

LIPIMIX ™

Rx:

Glycerin 98%

Distile water

Disodium edetate

Alpha tocopherol

Medium chain triglycerides

Soy oil

Emulsion types
4- Nanoemulsions

- Nanoemulsions are emulsions with droplet size on the order of 100 nm.
- A typical nanoemulsion contains oil, water and an emulsifier.
- The emulsifier plays a role in stabilizing nanoemulsions through repulsive electrostatic interactions and steric hindrance.

Emulsion types
5a- Dry Emulsions

- They are prepared using water soluble or insoluble carriers.
- Obtained by drying o/w emulsions containing powder carriers.
- They are in powder form
- Form o/w emulsions in in-vivo conditions
- Commonly used water soluble carriers : lactose, mannitol, HPMC, MC
- Water insoluble carrier: colloidal silica

Emulsion Types
5b- Dry adsorbed emulsions

These are the solid emulsion systems with particle size of 100-1000 μm prepared from w/o emulsions.

Absorbent powder with appropriate polarity is added to each phase of the emulsion. These type of emulsions can be compressed as tablets or filled in hard gelatin capsules.

Hydrophilic adsorbent: silica, pectin, chitosan
Hydrophobic adsorbent: silica with bonded alkyl group

Advantages:

1) Better stability
2) Appropriate to formulate active agents that should be protected from light and oxidation and have low aqueous solubility
3) Provide controlled drug release

Applications of dry emulsions:

1. Oral drug delivery

2. Transdermal drug delivery

3. Parentral drug delivery

4. In the formulation of antifoams.

5. In cosmetic formulations

6. In household care wipes, in skin care wipes, in baby care wipes and in makeup removing wipes.

7. In bath salt formulations.

8. In surface coating formulations for e.g.: in paints

Emulsion Types
6- Perfluorocarbon emulsions

- It is used as a blood substitute and used in treatments that require oxygen transport

- The ability of perfluorocarbons to dissolve gases such as oxygen and carbon dioxide is high

- They are chemically and biologically compatible and inert

Emulsion Types
7- Lipid submicron emulsions

These are colloidal carrier systems used in recent years to improve the bioavailability and pharmacological properties of active agent which demonstrate low bioavailability and short half life.

Administration Routes of Emulsions

Oral emulsions:

- Purpose: To mask bad taste
- Improve the absorption and bioavailability of some active agents. Poorly water soluble drugs can be formulated by dissolving in oil phase, thus improve their bioavailability.
- They are o/w type emulsions. Laxatives such as liquid paraffin, oil soluble vitamins, oily nutrition preparations
- Non-ionic surfactants are commonly used as emulsifiers.

RICILAKS ™

Rx:

Castor oil	40g
Sodium benzoate	
Poceau 4R	
Saccharin sodium	
Raspberry essence	
Polysorbate 80	
BHT (Butyl hydroxy Toluene)	
Deionized water	
Citric acid monohydrate	

Administration Routes of Emulsions

Topical emulsions

Lotions and liniments.

Most of them are cosmetic preparations

Both o/w (local) and w/o (oclusives, skin cleanser) types are used

Their usefulness depends on their ability to penetrate.

Administration Routes of Emulsions

Parenteral Emulsions

The oil-soluble active agent is dissolved in a suitable carrier and the mixture is emulsified.

The droplet diameter should be <1µm.

-IV emulsions of Vitamins A and K, Hormones,antineoplastic agents are prepared

IV emulsions;

- contain 10-20% fat
- Diameter 0.1-0.5µm
- pHs are 5.5-8.0
- o / w type

Lecithin and poloxamers are used as emulsifiers

IM emulsions are w/o type (reservior effect)

Administration Routes of Emulsions

Ocular Emulsions

RESTASİS® ophthalmic emulsion

Cyclosporine………………… 0.5mg (%0.05)
Glycerol 2.0mg
Castor 12.5mg
Polysorbate 80 .... 10.0 mg
Carbomer 1342 ....0.5 mg
Sodium hydroxide………..q.s.

THEORIES OF EMULSIFICATION

The demixing of the liquids is due to the fact that the cohesive force between each separated liquid molecule is greater than the adhesive force between the two liquids.

Cohesive force $>$ Adhesive force

THEORIES OF EMULSIFICATION

According to the classical emulsion theory, surfactants reduce the interface tension and provide emulsion formation by acting as a barrier in the coalescence of the droplets as an adsorbent at the interface. The emulsifier's emulsifying mechanism has three theory.

THEORIES OF EMULSIFICATION

1) Reduction of the interface tension and providing thermodynamic stabilization

2) Formation of an interface film and providing mechanical barrier against coalescence

3. Formation an electrical double layer and providing electrical barrier

THEORIES OF EMULSIFICATION

1) Reduction of the interface tension and providing thermodynamic stabilization

By lowering the interface tension, the free surface energy at the interface of the dispersion also decrease. Emulsifiers play an important role as interface barriers and provide emulsion stability.

THEORIES OF EMULSIFICATION

2) Formation of an interface film and providing mechanical barrier against coalescence

A film is formed by the emulsifier on the surface of water and oil droplets.

Emulsifiers are adsorbed by forming a monomolecular film at the water-oil interface.

The use of emulsifiers at high concentrations creates a solid film between the phases that do not mix and this film acts as a mechanical barrier against both adhesion and coalescence of the emulsion droplets.

THEORIES OF EMULSIFICATION

3. Formation an electrical double layer and providing electrical barrier

As the droplets come close to each other electrical impulse forces become effective.

The electrostatic repulsion is due to the increase of the electrically charged groups on the surface of the emulsifying globules and the electrical double layer.

Figure shows a schematic representation of the electrical double layer at the O / W interface.

The tail of the hydrocarbon chain dissolves in the oil droplet, while the ionic head faces the continuous aqueous phase

Emulsifier selection

The most important factor in the development of a successful emulsion formulation is the selection of a suitable emulsifier. The choice of emulsifier depends on the desired properties of the emulsifier, the shelf life of the emulsion, the type of emulsion and the cost of the emulsifier. The properties of ideal emulsifiers are:

- They must be surface active and can reduce surface tension to less than 10 dyn / cm
- Must be adsorbed around dispersed droplets, forming film at the interface and preventing coalescence
- Increase the viscosity of the emulsion,
- Must be emulsifier even at low concentrations
- Should have hydrophilic and lipophilic parts
- Not to be toxic (especially for oral emulsions)

The emulsifiers do not have these properties at the same time.

An emulsifier should provide adsorption and accumulation of small particles at the interface as monolayer around dispersed droplets.

EMULSIFIERS
Classification of emulsifiers according to their structure

- Synthetic
  - Anionic emulsifiers
  - Cationic
  - Nonionic
  - Amphoteric
- Natural
- Fine ground powders

Anionic emulsifiers

Active groups are anionic and carry negative charge. They are used in topical preparations due to their toxicity.

Na, NH3, Ca, Al, Zn salts of long hydrocarbon chain carboxylic acids (such as lauric and oleic acid) or K, Na and NH3 salts of sulfonated or sulphated compounds of these acids.

They also form in situ emulsifier. With the reaction of oleic acid and ammonium a soap forms and this soap stabilize the white liniment by emulsifying effect.

They are incompatible with multivalent cations. For this reason, deionized water should be used in formulations.

- Potassium laurate
- Sodium stearate

Cationic emulsifiers

- Active groups are cationic and positively charged.
- They are disinfectant and protective.
- They form emulsions with a pH of 4-6.
- Emulsion formation abilities are poor.
- They are not compatible with anionics.
  - • Quaternary ammonium compounds.
    - Benzalkonium chloride
    - Cetyl trimethylammonium bromide (Cetrimide)

Nonionic emulsifiers

- esters of long chain fatty acids with polyhydric alcohols and their esters and ethers with ethylene oxide (polyol esters)
- Stabilizes both o / w and w / o type emulsions.
- Toxicity and irritant properties are low.
- Some may be used in oral and parenteral preparations.
- Less susceptible to pH changes and electrolytes.
- They are more expensive.

Amphoteric emulsifiers

- Contains both anionic and cationic groups within the same molecule.
- They exhibit anionic or cationic properties depending on the pH of the medium.
- Cationic at low pH, anionic at high pH.
  - • Sodium N alkyl amino propionate
  - • Lecithin

Natural emulsifiers

- They are of vegetable or animal origin.
- Generally form o / w type emulsions
- May cause microorganism proliferation

  - • Arabian gum
  - • Gelatin
  - • Agar
  - • Tragacanth gum
  - • Cholesterol

Fine ground powders

- Consist of very small solid particles
- They form a solid particulate film around the globules which can be wetted by both phases.
- Form w / o and o / w type emulsions.
  - • Bentonite (Aluminum silicate) (externally)
  - • Veegum (Magnesium aluminum silicate) (externally)
  - • Hektorite
  - • Kaolin (internal)

OTHER EXCIPIENTS

Several other excipients are used to adjust viscosity and to provide physical stability.

Eg. Cetyl alcohol, glyceryl monostearate, methyl cellulose, hydroxypropyl cellulose, stearic acid, alginates, polyacrylic acid (Carbomer).

These are mostly used in lotions and creams.

PREPARATION OF EMULSIONS -HLB system

- The hydrophilic–lipophilic balance (HLB) number is a measure of the balance between hydrophobic and hydrophilic portions of a surfactant.
- The HLB of a surfactant is expressed using an arbitrary scale which for non-ionic surfactants ranges from 0 to 20.
- At the higher end of the scale, the surfactants are hydrophilic and act as solubilizing agents, detergents and oil-in-water emulsifiers.
- Oil-soluble surfactants with a low HLB act as water-in-oil emulsifiers.

HLB values can be calculated according to empirical but useful formulae:

For simple alkyl ethers in which the hydrophile consists only of ethylene oxide,

$$HLB = \frac{\%wt\ hidrofil}{5}$$

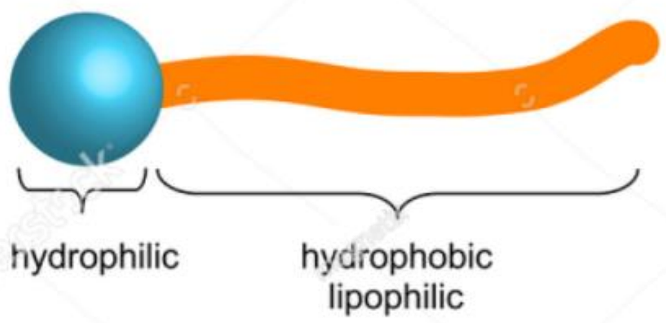
BRIJ 98: Polyoxyethylene(20) oleyl ether

The HLB of polyhydric alcohol fatty acid esters such as glyceryl monostearate may be obtained from the equation:

$$HLB = 20\left(1 - \frac{S}{A}\right)$$

where *S* is the saponification number of the ester and *A* is the acid number of the fatty acid.

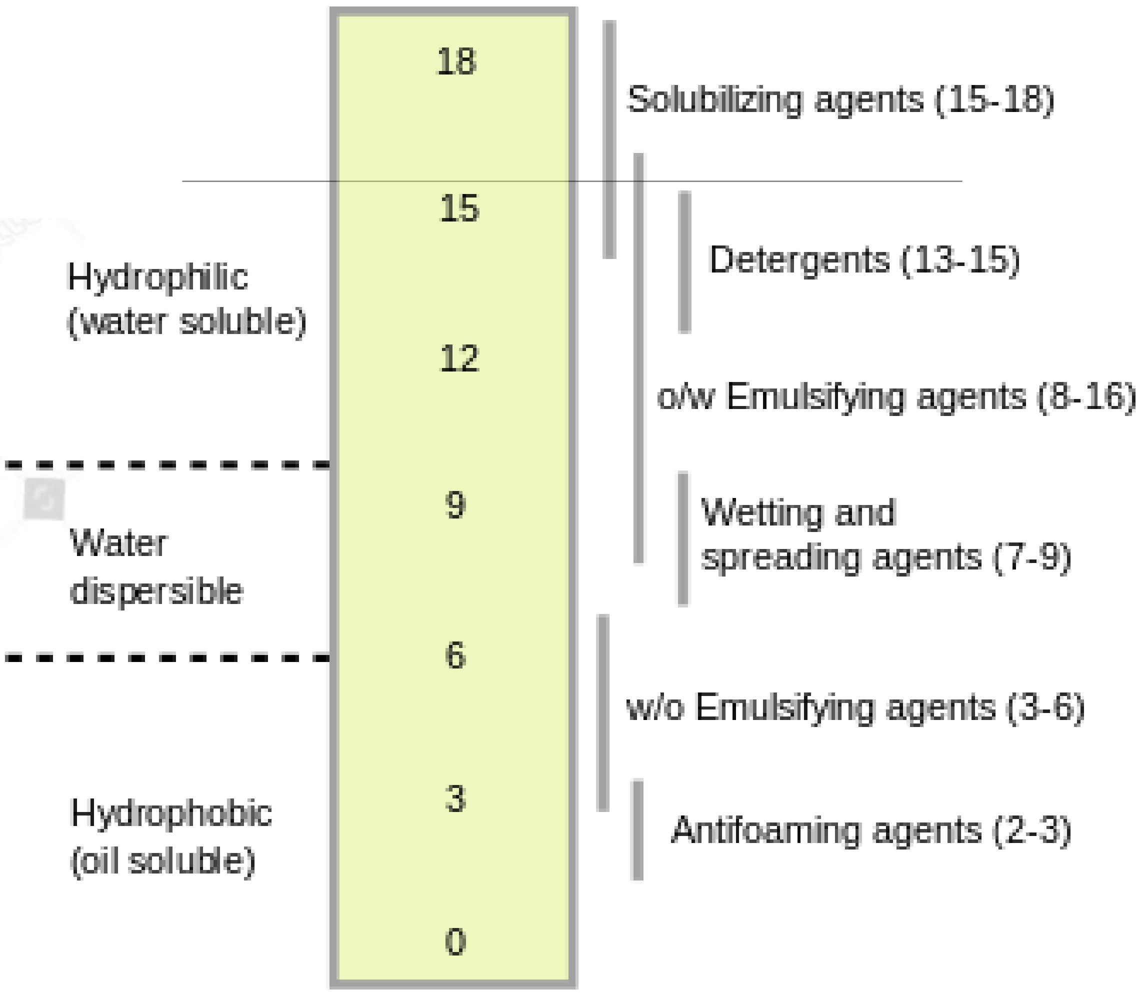
Hydrophilic - Lipophilic - Balance



HLB = 0 to 9 emulsifier is predominantly soluble in oil

HLB = 11 to 20 emulsifier is predominantly soluble in water

HLB = 10 same solubility in water and oil



- Spans are sorbitan fatty acid esters having low HLB values ranging from 1.8 to 8.6.
- Tweens are polyoxyethylene derivatives of spans. So, they are more hydrophilic having higher HLB values ranging from 9.6 to 16.7.

RHLB-required HLB

Through long experience in using the HLB System, technologists have found that all oils, waxes and other materials likely to be incorporated into emulsions have an individual «Required HLB».

From these values, you can calculate required HLB values for blends of these oils and waxes, each component contributing its share to the whole.

For the same oil, the required HLB value for O/W emulsion is higher than the required HLB value for W/O emulsion.

Table 2A — Required HLB for O/W Emulsions of a Variety of Emulsion Ingredients (Approx. ± 1)

Acetophenone	14	Carbon Tetrachloride	16	Isopropyl Myristate	11-12	toluamide	7-8
Acid, Dimer	14	Carnauba Wax	15	Isopropyl Lanolate	14	Nonyl Phenol	14
Acid, Isostearic	15-16	Castor Oil	14	Isopropyl Palmitate	11-12	Orthodichlorobenzene	13
Acid, Lauric	16	Ceresine Wax	8	Jojoba Oil	6-7	Palm Oil	10
Acid, Linoleic	16	Chlorinated Paraffin	12-14	Kerosene	12	Paraffin Wax	10
Acid, Oleic	17	Chlorobenzene	13	Lanolin, Anhydrous	9	Petrolatum	7-8

Calculation of the required HLB for a mixture of oils, fats or waxes

1. Multiply the required HLB of each ingredient by its fraction from the total oily phase.

2. Add the obtained values to get the total required HLB for the whole oily phase.

Example:

Rx

Liquid paraffin		35%
Wool fat		1 %
Cetyl alcohol		1%
Emulsifier system	q.s	7%
Water to		100%

Solution

The total percentage of the oily phase is 37

and the proportion of each is:

Liquid paraffin 35/37 x 100 = 94.6%

Wool fat 1/37 x 100 = 2.7%

Cetyl alcohol 1/37 x 100 = 2.7%

The total required HLB number is obtained as follows:
Liquid paraffin (RHLB 10.5) 94.6/100 X 10.5 = 9.93
Wool fat (RHLB 10) 2.7/100 x 10 = 0.3
Cetyl alcohol (RHLB 15) 2.7/100 X 15 = 0.4
Total RHLB = 10.63

Thereafter, two emulsifiers with HLB values below and one above the HLB value for the emulsion (HLB = 10.6 in this example) are selected. As an example, we can choose Tween 80 with an HLB value of 15 and Span 80 with an HLB value of 4.3.

% Tween 80 = (RHLB-HLB low) / (HLB high-HLB low)

% Tween 80 = (10.6 - 4.3) / (15.0 - 4.3) = 0.59

OR
Tween 80=x
Span80=1-x

10.6= 15x+ 4.3 (1-x)
X=0.59-------59 % (Percent of Tween 80)

For a 100 g emulsion Emulsifier system was 7g.

7 x 0.59 = 4.13 g Tween 80 should be taken and the remaining 2.87 g should be completed with Span 80.

Choice of emulsifier or emulsifier mixture

The appropriate choice of emulsifer or emulsifier mixture can be made by preparing a series of emulsions with a range of surfactants of varying HLB.

Mixtures of surfactants with high HLB and low HLB give more stable emulsions than do single surfactants.

The solubility of surfactant components in both the disperse and the continuous phase maintains the stability of the surfactant film at the interface from the reservoir created in each phase.

Choice of emulsifier or emulsifier mixture

In the experimental determination of optimum HLB the system with the minimum creaming or separation of phases is deemed to have an optimal HLB. It is therefore possible to determine optimum HLB numbers required to produce stable emulsions of a variety of oils.

At the optimum HLB the mean particle size of the emulsion is at a minimum, which explains the increased stability.