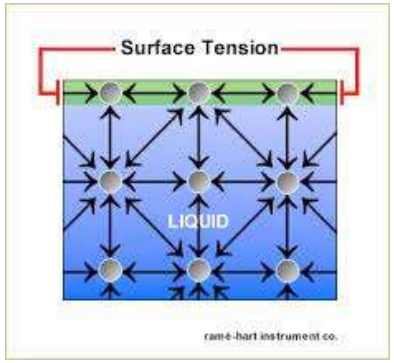
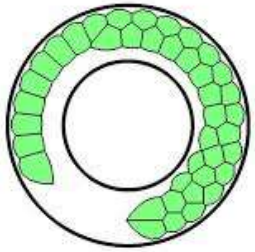
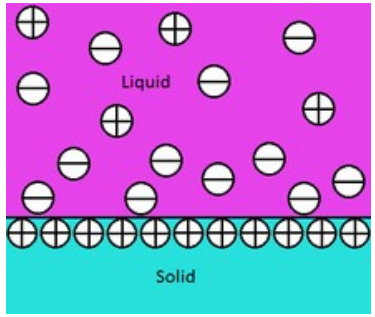
• Emulsifying agents:

- The functions of surface active agents to provide stability to dispersed droplets are as following:
  i. **Reduction of the interfacial tension**.
  ii. **Form coherent monolayer to prevent the coalescence** of two droplet when they approach each other.
  iii. Provide **surface charge which cause repulsion** between adjust particles.

- Combination of surface-active agents is used most frequently. The combination should **form film that closely packed and condensed.**







Emulsifying agents:

- If the emulsifying agent is more soluble in water i.e. **Hydrophilic**, then water will be the continuous phase and an

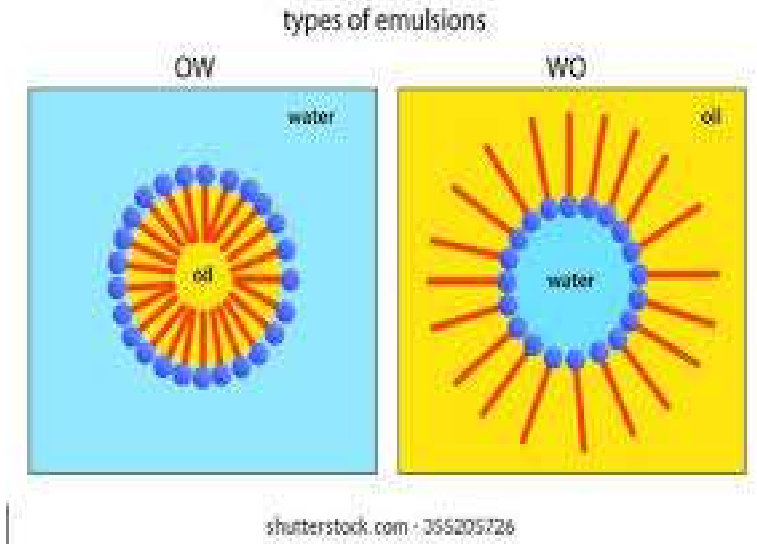
o/w emulsion will be formed.

- If the emulsifying agent is more soluble

in oil, i.e. **lipophilic**, then oil will be the

continuous phase and a **w/o** emulsion will

be formed.



- The **o/w** emulsion requires hydrophilic emulsifiers with **HLB 8 -18**.
- The **w/o** emulsion requires lipophilic Emulsifiers with **HLB 3 - 6**.

Gibbs free energy in an emulsion

$$\Delta G = \Delta A \gamma$$

- **A** is the total surface area of dispersed particles,
- **γ** is the interfacial tension,
- **G** is the surface free energy.

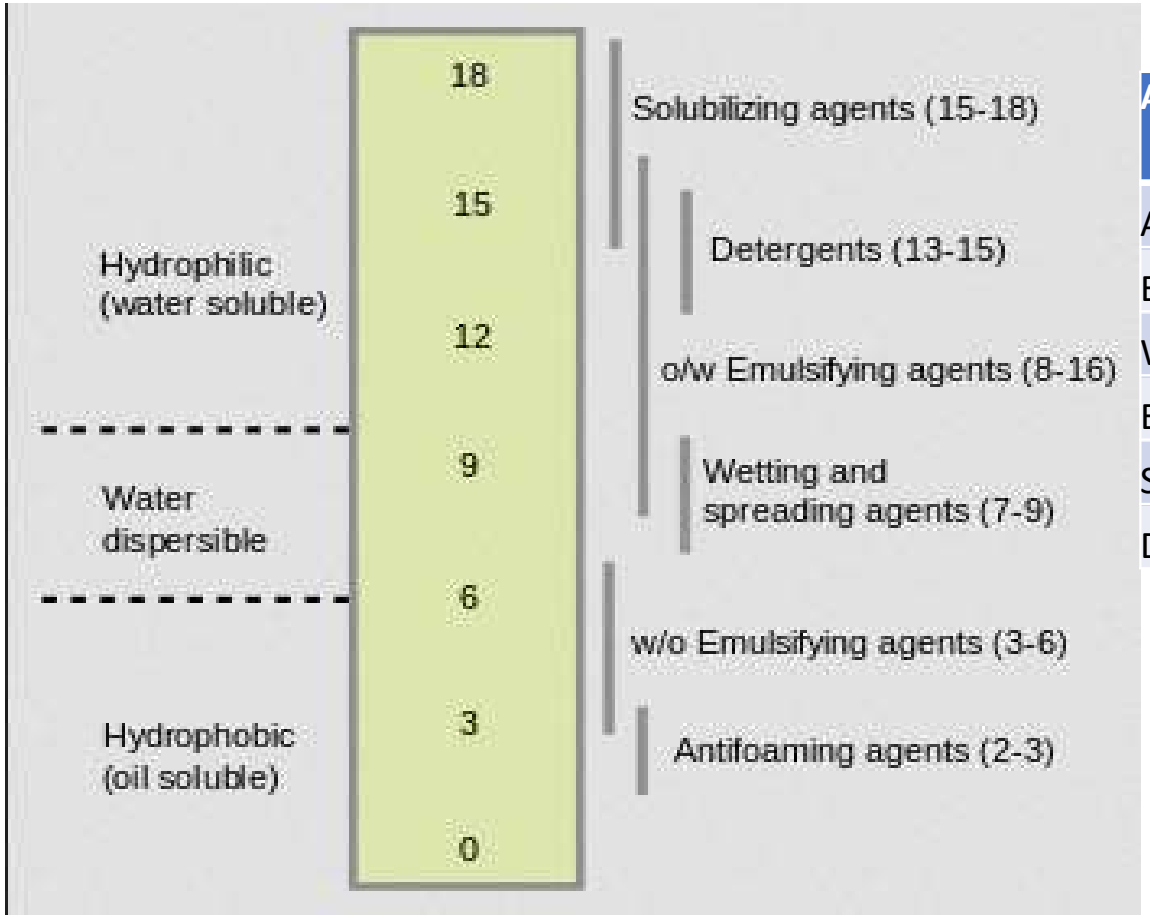
- Stable emulsions must have **a large "A"** and **a small "G"** concurrently for consistent and uniform dosing. This is done by **decreasing "γ",** which will decrease "G," which will decrease self-attraction of dispersed phase particles.

- In emulsion, the surface area is high to maintain the dispersion of the droplets. Thus, based on the above equation surface free energy becomes high consequently. The only way to keep it low is to reduce the interfacial tension.

General principles of emulsifying agents

1. EA must be compatible with the other formula ingredients.
2. Not interfere with the stability and efficacy of the drug.
3. Non toxic.
4. Little odor, taste, or color.
5. Maintain the stability of the emulsion for the intended shelf life of the product.
6. Select EA having the same HLB or close HLB as the oil depending on the type of emulsion desired.

HLB values of surfactants



ACTIVITY	ASSIGNED HLB
Antifoaming	1-3
Emulsifiers (w/o)	3-6
Wetting agents	7-9
Emulsifiers (o/w)	8-18
Solubilizers	15-20
Detergents	13-16

Substance	HLB	Substance	HLB
Oleic acid	1	Methyl cellulose (Methocel 15 cps)	10.5
Polyoxyethylene sorbitol beeswax derivative	2	Polyoxyethylene lauryl ether	10.8
Sorbitan tristearate	2.1	Polyoxyethylene monostearate (Myrj 45)	11.1
Glyceryl monostearate	3.8	Triethanolamine oleate	12
Sorbitan monooleate (Span 80)	4.3	Polyoxyethylene alkyl phenol	12.8
Diethylene glycol monostearate	4.7	Polyethylene glycol 400 monolaurate	13.1
Glyceryl monostearate, self-emulsifying (Tegin)	5.5	Polyoxyethylene sorbitan monooleate(Tween 80)	15
Diethylene glycol monolaurate	6.1	Polyoxyethylene sorbitan monolaurate(Tween 20)	16.7
Sorbitan monolaurate (Span 20)	8.6	Polyoxyethylene lauryl ether (Brij 35)	16.9
Polyethylene lauryl ether (Brij 30)	9.5	Sodium oleate	18
Gelatin (Pharmagel B)	9.8	Potassium oleate	20
		Sodium lauryl sulfate	40

Classification of emulsifying agents

A- o/w emulsifying agents:

- 1- **Monovalent soaps** such as sodium oleate. it has HLB value of **18**.
- 2- **Polyoxyethylene sorbitan mono-oleate (polysorbate 80 or Tween 80).** It is hydrophilic nonionic surface-active agent has HLB value of **15**.
- 3- **Acacia** (salts of d-glucuronic acid).It is hydrophilic colloid has HLB value of **8**.
- 4- **Tragacanth** (polysaccharide).It has HLB value of **13.2**.
- 5- **Gelatin** (polypeptide and amino acids). It is hydrophilic colloid with HLB value of **9.8**.
- 6- **Triethanolamineoleate** .It is anionic surface active agent has HLB value of **12**.
- 7- **lecithin** (phospholipid). It is the chief emulsifier In egg yolk.
- 8- **Bentonite** (hydrated aluminum silicate). It is solid particles.

B- w/o emulsifying agent:

- 1- **Polyvalent soaps** such as calcium plamitate. .
- 2- **Span 80**. It is lipophilic nonionic surface active agent has HLB value of 4.3.
- 3- **Cholesterol**.
- 4- **Woolfat**.

Classification of emulsifying agents:

- Emulsifying agents can be classed into three groups:
  - Naturally occurring.
  - Surfactants.
  - finely divided solids.

A-Naturally occurring emulsifying agents:

1- Polysaccharides:

- **Acacia**
  - used to prepared **oral** emulsions.
  - Not used externally as it is **too sticky**.
- **Tragacanth**
  - is used to increase the viscosity of an emulsion and prevent creaming.
- **Other polysaccharides**, such as **starch** and **pectin** are use to stabilize an emulsion.

2- Semi-synthetic polysaccharides;

- Low viscosity grades of **methylcellulose** and **carboxymethylcellulose** will form o/w emulsions.

3- Sterol-containing substances:

- E.g., **beeswax, woolfat and wool alcohols**, produce w/o emulsions.

4- Proteins:

- E.g., **gelatin,** which produces o/w emulsions. ,

5- Phospholipids :

- E.g., **lecithin**, which produces o/w emulsions.

B- Surfactants:

- These agents contain both hydrophilic and lipophilic regions in the molecule. They are classified according to their **ionic characteristics** as anionic, cationic and nonionic. The latter are used as detergents and soaps but are not widely used in pharmacy.

1- Anionic surfactants:

- In water (ionized) have a surface active anion.
- They are sensitive to cationic surfactants such as cetrimide.
- Used in preparations of o/w emulsion for external use.
- Emulsions made with anionic surfactants are generally stable at alkaline pH. Some examples include:
  - Soaps of divalent and trivalent metals such as **calcium oleate** (w/o).
  - Alkyl sulphates such as **sodium lauryl sulphate** (o/w).

2- Cationic surfactants:

- In water (ionized) have a surface active cation.
- They are sensitive to anionic surfactants such as the soaps.
- Used in preparations of o/w emulsion for external use.
- Emulsions formed by a cationic surfactant are generally stable at acidic pH. The cationic surfactants also, have anti-microbialactivity.
  - These are usually **quaternary ammonium compounds.**

  - Examples include **cetrimide** and **bezalkoniumchloride**.

3- Non-ionic surfactants:

- They are used to **produce either o/w or w/o emulsions** for both **external** and **internal** use. The non-ionic surfactants are **compatible** with both anionic and cationic substances and are **highly resistant to pH change**.
- The type of emulsion formed depends on the balance between hydrophilic and lipophilic groups which is given by the HLB (hydrophilic lipophilic balance) number.
  - High HLB numbers (8-18) indicate a hydrophilic molecule, and produce an o/w emulsion.
  - Low HLB numbers (3-6) indicate a lipophilic molecule and produce a w/o emulsion.
  - Examples include;

  - **Tween 80**, has HLB number of 15 and is more soluble in water to give o/w emulsion and

  - **Span 80**, has HLB number of 4.3 and is more soluble in oil to give w/o emulsion.

C- Finely divided solids:

- They can be **adsorbed** at the oil-water interface to form a coherent film that prevents coalescence of the dispersed globules.
- If the particles are preferentially wetted by oil, a w/o emulsion is formed. Conversely, if the particles are preferentially wetted by water, an o/w emulsion is formed.
- They form emulsions with good stability, which are less liable to microbial contamination than those formed with other naturally derived agents.
- Examples are
  - **Bentonite, aluminium magnesium silicate** are used for **external** preparations.
  - **Colloidal aluminium and magnesium hydroxides** are used for **internal** preparations.

Formulation additives:

1- Antioxidants.

2- Preservatives.

3- Humectants.

4- Colors and flavorings.

1- Antioxidants:

- Some oils are liable to degradation by oxidation and therefore antioxidants may be added to the formulation. They should be preferentially soluble in the oily phase. Antioxidants used in oral emulsions which are odorless and tasteless include **ascorbic acid, citric acid, sodium metabisulphite and sodium sulphite**.
- Antioxidant is commonly used at concentrations ranging from **0.001 to 0.1%.**

2- Preservatives:

- **Emulsions contain water**, which will support microbial growth. Microbes produce unpleasant odors, color changes and gases, pH change and breakdown of the emulsion.
- Microbial growth normally occurs in the **aqueous phase of an emulsion**, therefore it is important that a sufficient concentration of preservative is, present in the aqueous phase.

- **Some preservatives in use are listed below:**
  - **Methylparahydroxybenzoate** in 0.2% & **Propyl parahydroxybezoate** in 0.02%. ,They are suitable for both external and internal use.
  - **Benzoic acid**, which is effective at a concentration of 0.1% at pH below 5.
  - **Chloroform**, as chloroform water (0.25% v/v).
  - **Chlorocresol** (0.1 %).

3- Humectants:

- To reduce the evaporation of the water either from the packaged product when the closure is removed or from the surface of the skin after application.
- E.g., **Propylene glycol, glycerol and sorbitol** at a concentration around 5%.

4-Colours and flavourings:

- Colour is rarely needed in an emulsion, as most have an elegant white colour and thick texture.
- Emulsions for oral use will usually contain some flavouring agent.

Example of emulsion formulations

R/

- Code liver oil 30 ml
- Chloroform 0.2 ml
- Cinnamon water to 100 ml
  - Prepare 100 ml cod liver oil emulsion (o/w emulsion for internal use)

- **Formulation**
  - Cod liver oil is a **fixed oil** that requires the addition of acacia gum as an o/w emulsifying agent.
  - Preparation of primary emulsion
  - 0 w G
  - 4 2 1
  - 30 ml 15ml 7.5 g
  - Therefore 30 ml cod liver oil, 15 ml of cinnamon water and 7.5 g of acacia gum will be used to prepare the primary emulsion. Cinnamon water acts as a flavouring agent and vehicle. .chloroform is dense only slowly soluble and act as a preservative.