/ /

*Emulsion:- is a dispersion in which the dispersed phase is composed of small globules of a liquid distributed throughout a vehicle in which it's immiscible.

بالإعتماد على مكوناتها

* Viscosity of emulsion can vary greatly debending on their constituents.

* pharmaceutical emulsions maybe prepared as liquids or semisolids.

* Emulsions include certain lotions, liniments, creams, ointments

* Two immiscible components formulated by:
1- Emulsifying agents 2- Energy & to make the three ingredients: water, oil, emulsifying agents.

* The dispersed liquid: internal, discontinous phase.
* The dispersion medium: external, continous phase.

*Rule of Bancroft: the phase in which it's more soluble being the continous phas (monomolecular adsorption)

Introduction

- Energy can be supplied by:

1. Triturating the ingredients in a mortar with a pestle
2. Heating the ingredients
3. Shaking the ingredients in a bottle
4. Extruding the ingredients through a small orifice of an homogenizer
5. Mechanically blending the ingredients with a high speed mixer or blender

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Introduction

Oil-in-water (o/w) emulsion

- Oils, petrolatum hydrocarbons, or waxes are the dispersed phase
- Aqueous solution is the continuous phase
- Aqueous phase constitutes > 45% of the total weight
- Hydrophilic emulsifier
- Miscible with water
- Water washable
- Non occlusive
- Non greasy

Water-in-oil (w/o) emulsion

- Water or aqueous solutions are the dispersed phase
- Oleaginous solution is the continuous phase
- Aqueous phase constitutes < 45% of the total weight
- Lipophilic emulsifier
- Not water washable
- Occlusive
- Greasy

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Emulsions

1. Orally (o/w) emulsion:
   - Mask the taste of a bitter drug
   - May enhance bioavailability of a drug

2. Topically: Lotions and creams:
   - Creams are thick emulsions
   - Lotions are fluid emulsions (some lotions actually are suspensions rather than emulsions)

3. Parenteral nutrition

/ /

* Three levels of instability:

1- Creaming ⇒ dispersed oil droplets merge (تندمج) and rise to the top (O/W) or settle to the bottom (W/O)

* the emulsion here can be easily redispersed by shaking.

2- Coalescence (الالتحام): (fusion), Viscosity adjustment (تعديل اللزوجة), using optimum phase.

* Volume ratio may minimize coalescence.

3- phase inversion ⇒ changing from W/O to O/W (or Vice Versa (والعكس))

* Good Emulsion: 1- coalescence 2- Flocculation
3- Creaming 4- Breaking (irreversable)

* Emulsions are formed by: - adding an emulsifier or - adding emulsifying agents

* liquid is in content (احتواء) with second liquid (insoluble, immiscible) ⇒ The force causing each liq resist (مقاومة) breaking up into smaller particle is called: interfacial tension

* المواد اللي بتقلل هاي المقاومة بتشجع السائل انه يتكسر لجزيئات أو قطرات (substances that reduce this resistance encourage a liq to break up) أصغر into smaller drops or particles

Increasing the stability of an emulsion:

1. Use the optimum phase:volume ratio (i.e. the ratio of the internal volume to the total volume of the product)
2. Reduce the globule size of the internal phase
3. Increase the viscosity of the external aqueous phase
4. Adjust the densities of both the internal phase and the external phase so the densities are the same

الكثافة

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Emulsifying agent classification:

1. **Chemical structure:**
   - Synthetic
   - Natural
   - Finely dispersed solids
   - Auxiliary agents

2. **Mechanism of action:**
   - Surface active agents (adsorb at the oil/water interface forming a monomolecular layer)
   - Hydrophilic colloids (form multimolecular layers at the interface)
   - Finely divided solid particles (adsorb at the interface and form a layer of particles around the droplets

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Synthetic emulsifying agents

- Have both a hydrophilic part (e.g. carboxyl, hydroxyl, amino groups) and a lipophilic part (e.g. alkyl chain)
- Classified based on the properties of the hydrophilic part as:
  - Anionic
  - Cationic
  - Nonionic
  - Amphoteric

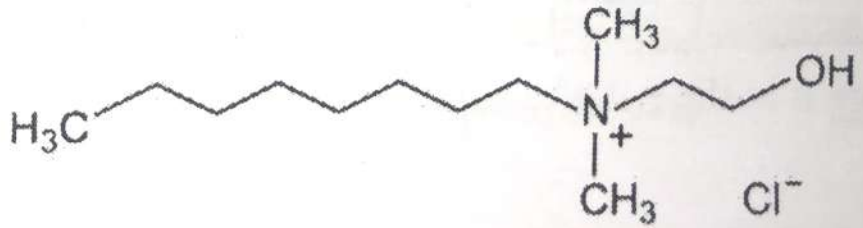
Synthetic emulsifying agents:
Cationic surfactants

نادر و انستخدمه

- Are used as bactericidal agents
- Long chain amino and quaternary ammonium salts
- Are used in topical o/w emulsions
- Cationic agents (quarternary ammonium salts) are incompatible with organic anions and are infrequently used as emulsifiers

غير متوافق

- cationic surfactants are effective over pH range of 3 to 7



an alkyl quaternary system

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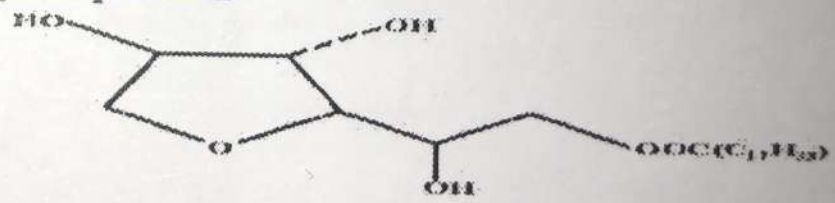
Synthetic emulsifying agents:
Nonionic surfactants

- Most frequently used of all the surfactants
- Have a neutral pH and resist the addition of acids and electrolytes
- Nonionic surfactants are effective over pH range of 3 to 10;
- They are superior in compatibility, stability, and lack of toxicity
- Divided into:

1. Those that are more hydrophobic
2. Those that are more hydrophilic



SPAN 80

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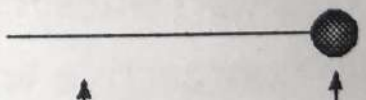
Synthetic emulsifying agents:

Anionic Surfactants

- Contain, carboxylate, sulfate, and sulfonate groups
- Are soaps and detergents
- Carboxylate surfactants have the tendency to undergo hydrolysis and decompose
- The long alkyl sulfates typically are used as surfactants of which sodium lauryl sulfate is the best known
- Anionic surfactants require a pH greater than 8
- Are used in topical o/w emulsion

nonpolar tail — water soluble head

Sodium Lauryl Sulfate



nonpolar tail — water soluble head

Lazy chemist's representation of Sodium Lauryl Sulfate

Natural Emulsifying Agents:

- are natural products derived from plant or animal tissue.
- Most of them form hydrated lyophilic colloids (called **hydrocolloids**) that form multimolecular layers around emulsion droplets.
- Lyophilic: (of a colloid) readily dispersed by a solvent and not easily precipitated.
- Hydrocolloid type emulsifiers have little or no effect on interfacial tension
- They exert a protective colloid effect, reducing the potential for coalescence, by:

- providing a protective sheath around the droplets
- imparting a charge to the dispersed droplets (so that they repel each other)
- swelling to increase the viscosity of the system (so that droplets are less likely to merge)

Natural Emulsifying Agents:

Hydrocolloid emulsifiers may be classified as:

1. Vegetable derivatives, e.g., acacia, tragacanth, agar, pectin, carrageenan
2. Animal derivatives, e.g., gelatin, lanolin, cholesterol, lecithin
3. Semi-synthetic agents, e.g., methylcellulose, carboxymethylcellulose (من سيليلوز)
4. Synthetic agents, e.g., Carbopols®

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Natural Emulsifying Agents: Vegetable hydrocolloids

- have the advantages of being inexpensive, easy to handle, and nontoxic.
- Their disadvantages are that they require relatively large quantities to be effective as emulsifiers, and they are subject to microbial growth and thus their formulations require a preservative.
- Vegetable derivatives are generally limited to use as o/w emulsifiers.
- Form multimolecular film around the droplets

مواد حافظة

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Natural Emulsifying Agents:

Animal derivatives

- Lecithin and cholesterol form a monomolecular layer around the emulsion droplet instead of the typically multimolecular layers.
- Cholesterol is a major constituent of wool alcohols and it gives lanolin the capacity to absorb water and form a w/o emulsion.
- Lecithin (a phospholipid derived from egg yolk) produces o/w emulsions because of its strong hydrophilic character.
- Animal derivatives are more likely to cause allergic reactions and are subject to microbial growth and rancidity.
- Their advantage is in their ability to support formation of w/o emulsions.

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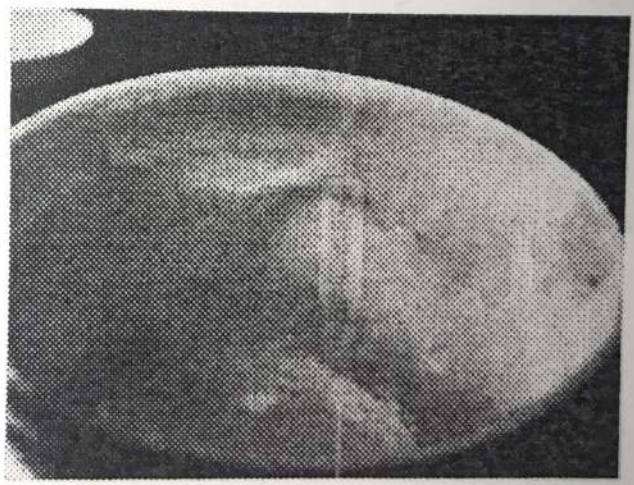
Natural Emulsifying Agents: Animal derivatives

- **Wool alcohols** are the principle component of **lanolin**
- **Lanolin** is a natural product obtained from the fleece of sheep.
- Sebum is extracted from the **wool**, cleaned and refined to produce anhydrous **lanolin**.



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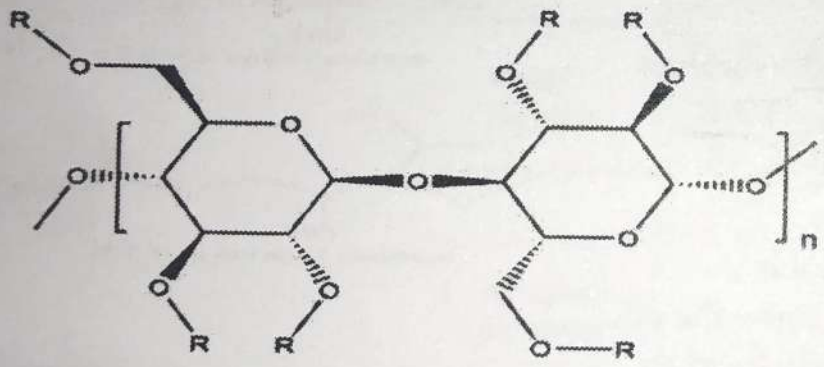
Natural Emulsifying Agents:
Semi-synthetic agents

- Semi-synthetic agents are stronger emulsifiers
- are nontoxic,
- and are less subject to microbial growth



Cellulose: R = H
Methyl cellulose: R = CH_3 (40-90%) or H

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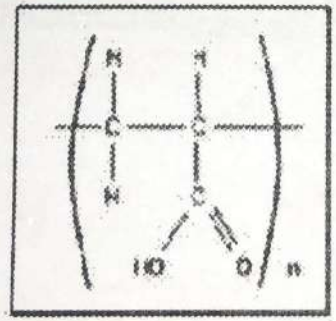
* الـ synthetic أبدًا ما بتدعم نمو البايكروبات (microbial growth)

* بس الـ semi-synthetic بتدعم بس بشكل قليل (less subject to microbial growth)

Natural Emulsifying Agents:
Synthetic hydrocolloids

- Are the strongest emulsifiers,
- are nontoxic,
- and do not support microbial growth.
- However, their cost may be prohibitive.
- These synthetic agents are generally limited to use as o/w emulsifiers.



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General structure of carbopol polymer

General structure of carbopol polymer

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Finely divided or dispersed solid particle emulsifiers:

- These agents form a particulate layer around dispersed particles.
- Most will swell in the dispersion medium to increase viscosity and reduce the interaction between dispersed droplets.
- Most commonly they support the formation of o/w emulsions, but some may support w/o emulsions.
- These agents include bentonite, veegum, hectorite, magnesium hydroxide, aluminum hydroxide and magnesium trisilicate.

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Auxiliary emulsifying agents

- A variety of fatty acids (e.g., stearic acid), fatty alcohols (e.g., stearyl or cetyl alcohol), and fatty esters (e.g., glyceryl monostearate)
- Serve to stabilize emulsions through their ability to thicken the emulsion.
- Because these agents have only weak emulsifying properties, they are always use in combination with other emulsifiers.

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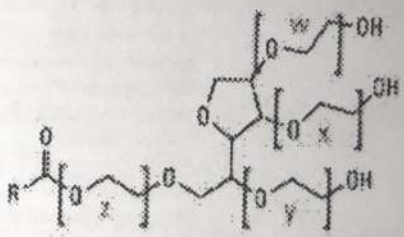
The Hydrophile-Lipophile balance (HLB) System

- A system was developed to assist in making systemic decisions about the amounts and types of surfactants needed in stable products.
- The system is called the HLB (hydrophile-lipophile balance) system and has an arbitrary scale of 1 - 20.
- HLB numbers are experimentally determined for the different emulsifiers

HLB الى ∞ طريق ج hydrophilic groups

The Hydrophile-Lipophile balance (HLB) System

- The higher HLB number would indicate that the emulsifier has a large number of hydrophilic groups on the molecule and therefore should be more hydrophilic in character.
- The Tweens® (polyoxyethylene derivatives of sorbitan esters) have higher HLB numbers and they are also water soluble.
- Because of their water soluble character, Tweens® will cause the water phase to predominate and form an o/w emulsion.

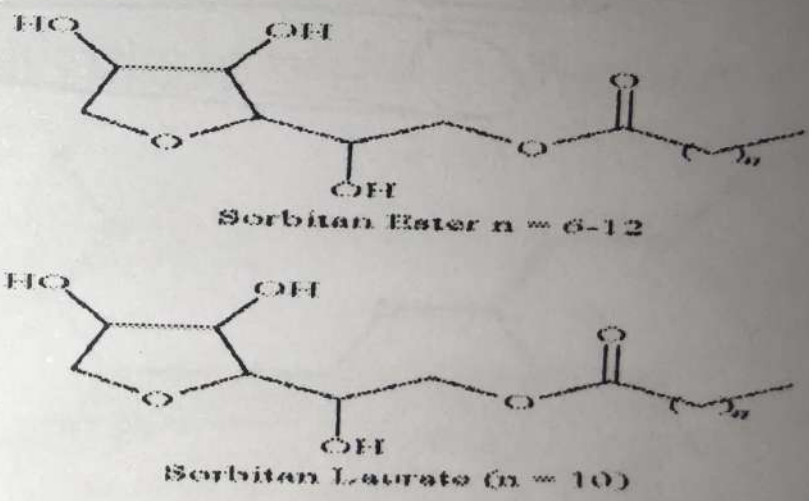


Tween® 20 Detergent

MW 1228

The Hydrophile-Lipophile balance (HLB) System

- If an emulsifier has a low HLB number, there is a low number of hydrophilic groups on the molecule and it will have more of a lipophilic character.
- For example, the Spans® (sorbitan esters) generally have low HLB numbers and they are also oil soluble.
- Because of their oil soluble character, Spans® will cause the oil phase to predominate and form an w/o emulsion.



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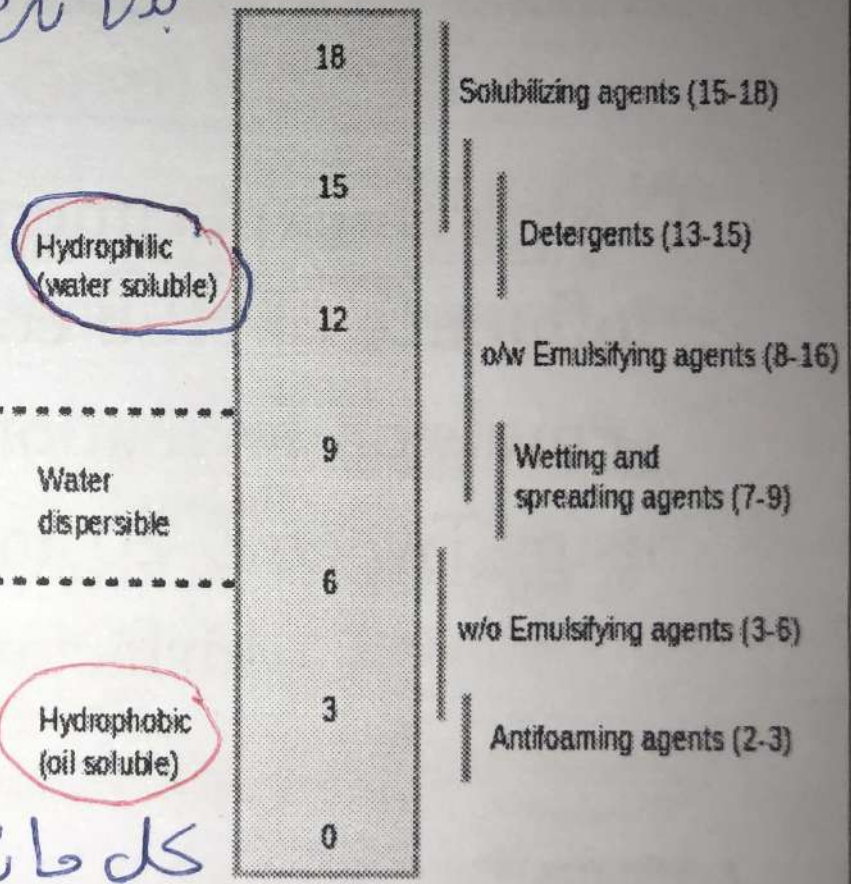
بدنا نعرف كل ما طلعنا لفوق بصير hydrophilic

- the phase in which the emulsifying agent is more soluble will become the continuous or external phase



كل ما نزلنا لتحت hydrophobic

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The Hydrophile-Lipophile balance (HLB) System

Combinations of emulsifiers can produce more stable emulsions than using a single emulsifier with the same HLB number. The HLB value of a combination of emulsifiers can be calculated as follows:

$$HLB = \frac{(Quantity\ of\ surfactant\ 1)(HLB\ surfactant\ 1) + (quantity\ of\ surfactant\ 2)(HLB\ surfactant\ 2)}{quantity\ of\ surfactant\ 1 + quantity\ of\ surfactant\ 2}$$

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كل ما كان عنا مزيج من ال emulsions كان يكون أكثر استقرار

(quantity of surfactant(1))(HLB surfactant1) + (qu / // // (2))(// // 2)

quantity(1) + quantity(2)

* These tension-lowering substances are surface active (surfactan

* Surfactant (polar head, non polar tail)

* Wetting agents (are surfactants) with HLB Value ⇒ 7-9
particles (liquids, solid) إلى contact

* Emulsifying agents (surfactants) HLB: 4 to 6 (w/o) or 8 to 18 (o/w)

① reduce interfacial tension between oil and water
② minimizing surface energy through the formation of globules.

* Detergent (surfactants) HLB: 13 to 15
① reduce the surface tension
② aid in wetting the surface and the dirt

So the soil will be emulsified and foaming occurs ⇒
التربة — رغوة

(washing away from dirt)

* Solubilizing agents: HLB → 15 to 20

Methods of compounding emulsions:

1. Continental (Dry gum or 4:2:1) 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 oil, 2 parts water, and 1 part emulsifier.
- In a mortar, the 1 part gum is levigated with the 4 parts oil until the powder is thoroughly wetted; then the 2 parts water are added all at once, and the mixture is vigorously and continually triturated until the primary emulsion formed is creamy white and produces a "cracking" sound as it is triturated (usually 3-4 minutes).

Methods of compounding emulsions:

creamy white and produces a "cracking" sound as it is triturated (usually 3-4 minutes).

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Methods of compounding emulsions:
2. English (Wet Gum) Method

- In this method the order and techniques of mixing are different.
- The 1 part gum is triturated with 2 parts water to form a mucilage; then the 4 parts oil is added slowly, in portions, while triturating.
- After all the oil is added, the mixture is triturated for several minutes to form the primary emulsion.
- Generally speaking, the English method is more difficult to perform successfully, especially with more viscous oils, but may result in a more stable emulsion.
- The ratio of oil: water: emulsifier depend on oil and emulsifier being used

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Methods of compounding emulsions:
3. Bottle (Forbes) Method

زيوت متطايرة

- This method may be used to prepare emulsions of volatile oils, or oleaginous substances of very low viscosities. It is not suitable for very viscous oils since they cannot be sufficiently agitated in a bottle.
- This method is a variation of the dry gum method.
- One part powdered acacia (or other gum) is placed in a dry bottle and four parts 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 forms.
- It is important to minimize the initial amount of time the gum and oil are mixed. The gum will tend to imbibe the oil, and will become more waterproof.

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and oil are mixed. The gum will tend to imbibe the oil, and will become more waterproof.

51

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Methods of compounding emulsions: 4. Beaker Method

- When synthetic or non-gum emulsifiers are used, the previous methods become meaningless.
- The most appropriate method for preparing emulsions from surfactants or other non-gum emulsifiers is to begin by dividing components into water soluble and oil soluble components.
- All oil soluble components are dissolved in the oily phase in one beaker and all water soluble components are dissolved in the water in a separate beaker.
- Both phases (i.e. beakers) are heated to approximately 70°C over a water bath (the aqueous phase should be heated to a few degree higher).
- The internal phase is then added to the external phase with stirring until the product reaches room temperature.
- The mixing of such emulsions can be carried out in a beaker, mortar, or blender.

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Methods of compounding emulsions: 5. Auxiliary Methods

- Instead of, or in addition to, any of the preceding methods, the pharmacist can usually prepare an excellent emulsion using an electric mixer or blender.
- An emulsion prepared by other methods can also usually 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.
- The formulation usually is improved in both stability (because droplet size is reduced) and appearance

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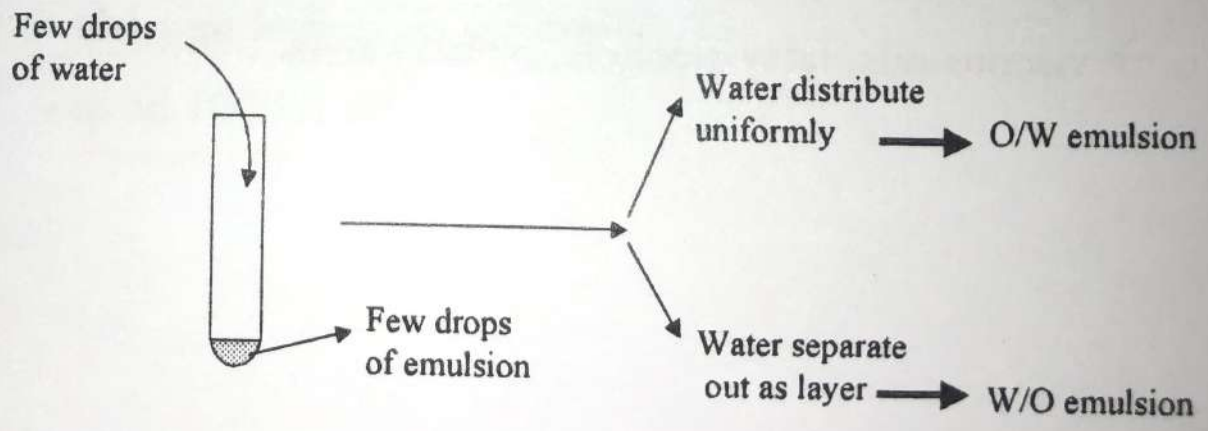
Determining type of emulsion:
1. Dilution test

- based on the solubility of external phase:

- o/w emulsion can be diluted with water.

- w/o emulsion can be diluted with oil.



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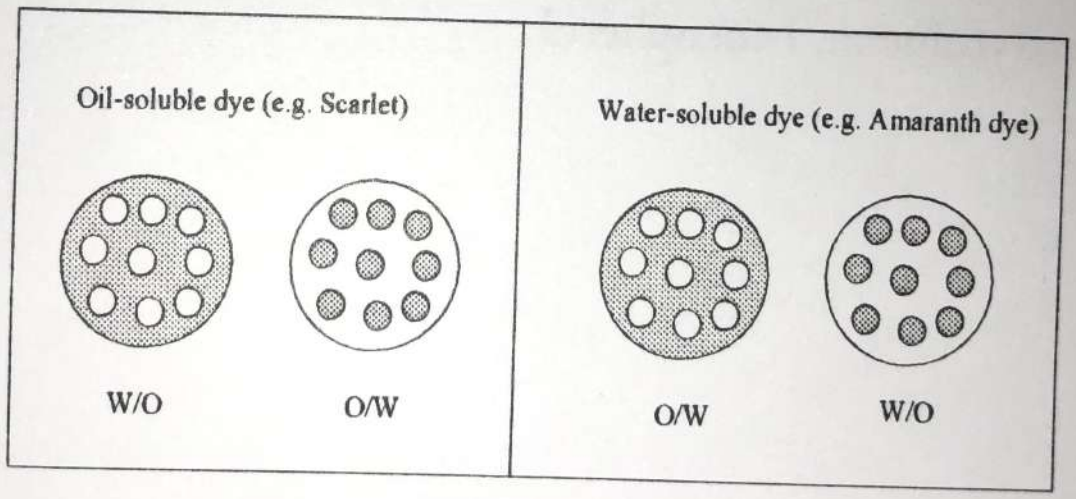
Determining type of emulsion:
2. Dye test:

- Water-soluble dye will dissolve in the aqueous phase.
- Oil-soluble dye will dissolve in the oil phase.



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Determining type of emulsion:
3. Drop test:

- Put a drop of the formulation on the surface of water
- If the drop spreads out, the emulsion is an o/w emulsion because the external phase is miscible with water
- If the drop stays as a drop or "balls up", it is a w/o emulsion

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Packaging

- Tight containers to avoid loss of water
- Tubes, pumps, squeeze bottles, jars
- If it is liquid:
  - → enough room for shaking
  - → Large opening bottle for easy pouring

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Observing formulations for evidence of instability:

- Breaking (i.e. separation of an oil phase that is not easily dispersed)
- Crystal growth
- Shrinkage due to water evaporation
- Microbial contamination