

# تفريغ حساب وتركيب الأشكال الصيدلانية



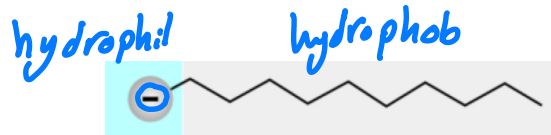
بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

اسم الموضوع: Emulsion 21-55

إعداد الصيدلاني /  
ياسمين خليل



لجان الرفعات



## Emulsifying agents

### Surfactants

يعني تروا في surfactant دون تحديد إذا ابتلوا أو يزيدوا

#### Anionic surfactants:

- These are organic salts which, in water, have a surface-active anion.
- Some examples include:
- Alkali metal and ammonium soaps (salts of long chain fatty acids) such as sodium stearate and potassium oleate (o/w).
- Soaps of divalent and trivalent metals such as calcium oleate (w/o).
- Amine and ammonium soaps such as triethanolamine oleate (o/w).
- Alkyl sulphates such as sodium lauryl sulphate (SLS) (o/w).

#### Disadvantages: → Sensitive to cations such as cetrinide

- Incompatible with some organic and inorganic cations and with large organic cations such as cetrinide.
- They are irritant internally so widely used in external preparations as o/w emulsifying agents. *Their use only*
- pH sensitivity: They must be in their ionized form to be effective and emulsions made with anionic surfactants are generally stable at more alkaline pH.

## Anionic Surfactants: Soaps

Lipophilic Hydrophilic

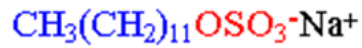


Alkali Soaps (sodium palmitate)

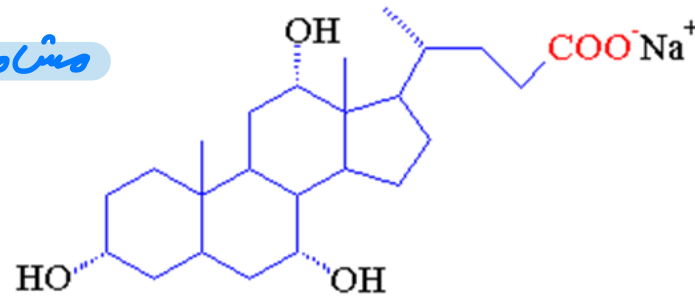
Amine Soaps (triethanolamine oleate)

الاسم مهم

من المطلوب structure

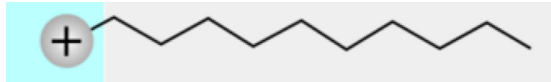


Alkylsulfates (sodium laurylsulfate)



Bile Salts (sodium cholate)

اللهم صلِّ وسلم وباركْ  
على محمدٍ وآلِ محمدٍ وعليه وسلم



# Emulsifying agents

## Surfactants

### Cationic surfactants:

- These are usually quaternary ammonium compounds which have a surface-active cation.
- Examples include cetrimide and benzalkonium chloride.
- They are used in the preparation of o/w emulsions for external use and must be in their ionized form to be effective. *مشتق مع أنيون*
- The cationic surfactants also have antimicrobial (bactericidal) activity.

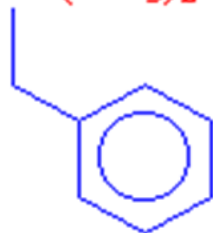
### Disadvantages:

- They are sensitive to anionic surfactants and drugs.
- Emulsions formed by a cationic surfactant are generally stable at acidic pH.
- They are more toxic than other surfactants.

*لأنه السبب استخدامه قليل*

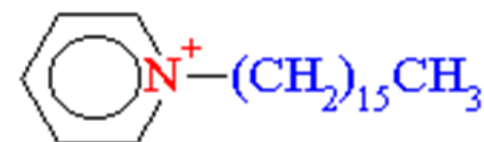
# Cationic Surfactants: Inverted Soaps

Lipophilic    Hydrophilic

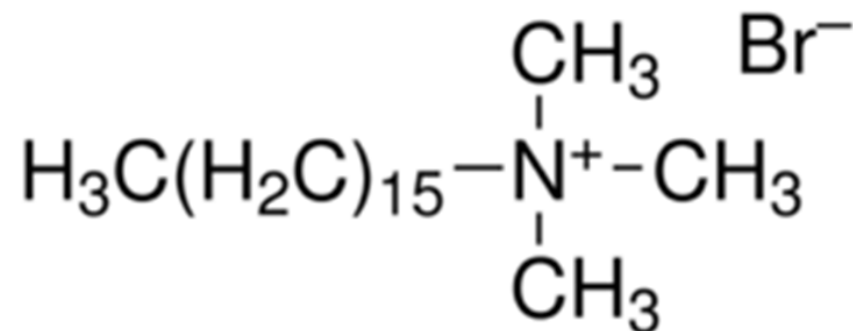


**Quaternary Ammonium Salts**  
(lauryldimethylbenzylammonium chloride)

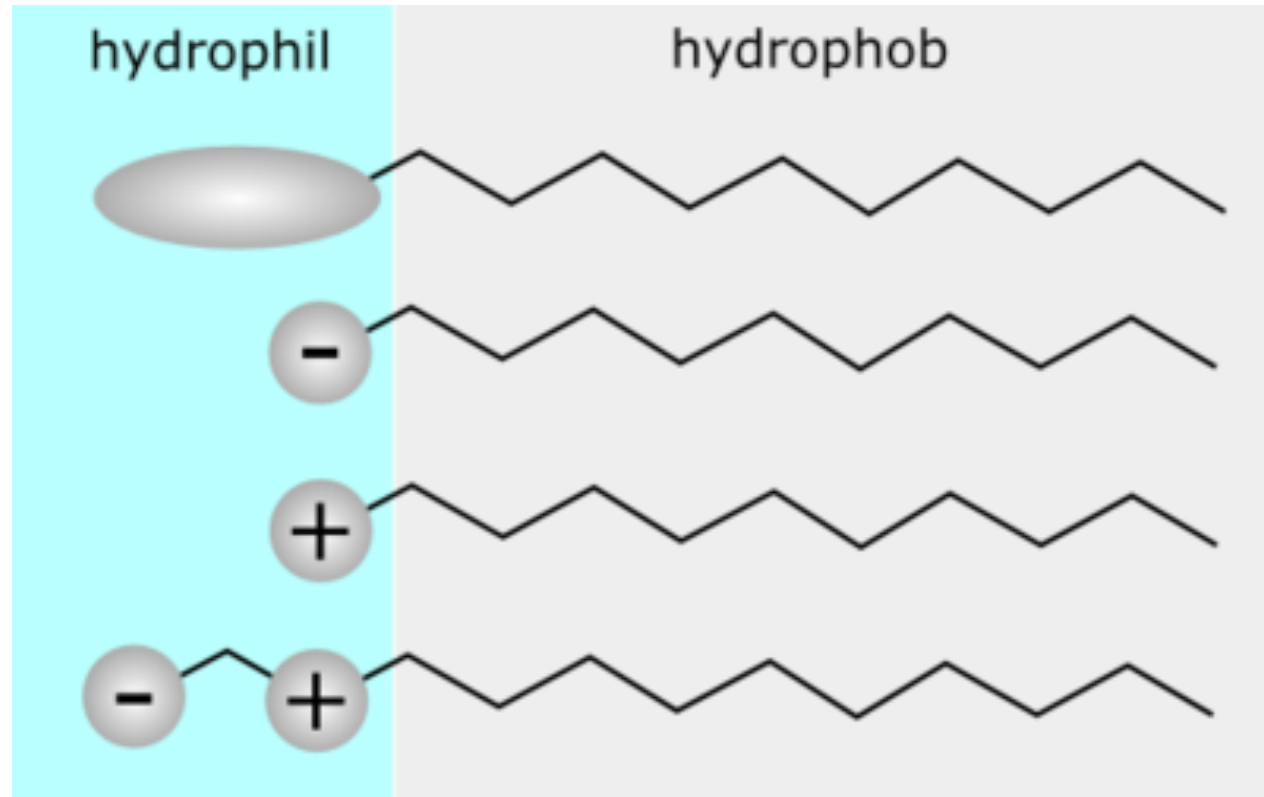
$\text{Br}^-$



**Pyridinium Salts**  
(Cetylpyridinium bromide)



**Cetrimide (cetyltrimethylammonium bromide)**  
o/w emulsifier, but also preservative



سبحان الله وبحمده  
سبحان الله العظيم

# Emulsifying agents

## Surfactants

### Non-Ionic surfactants

- They are synthetic materials and make up the largest group of surfactants.
- The non-ionic surfactants are compatible with both anionic and cationic substances and are highly resistant to pH change.
- They are used to produce either o/w or w/o emulsions for both external and internal use.
- The type of emulsion formed depends on the balance between hydrophilic and lipophilic groups which is given by the HLB (hydrophilic-lipophilic balance) number.
- Examples of the main types include:
- Esters: such as glycol esters, glycerol esters, macrogol esters, sorbitan esters (spans) and polysorbates (tweens).
- Amides: such as alknolamides.
- Ethers: such as macrogol ethers and poloxamers.

Spans

fatty acid chain

w/o

tweens

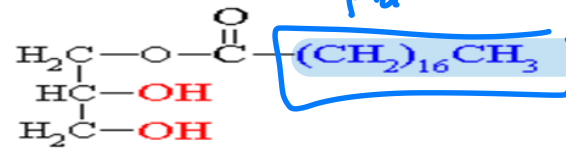
hydrophilic side

o/w and w/o

# Nonionic Surfactants

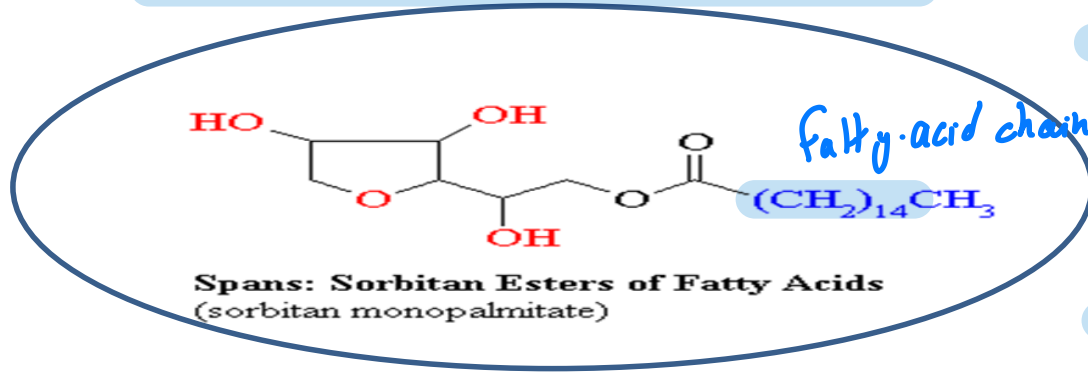
**Lipophilic Hydrophilic**  
 $\text{CH}_3(\text{CH}_2)_n\text{OH}$

د. اسراء حكت  
 الارقام بهاد السلاية  
 مغنا



**Partial Fatty Acid Esters of Multivalent Alcohols**  
 (glycerol monostearate)

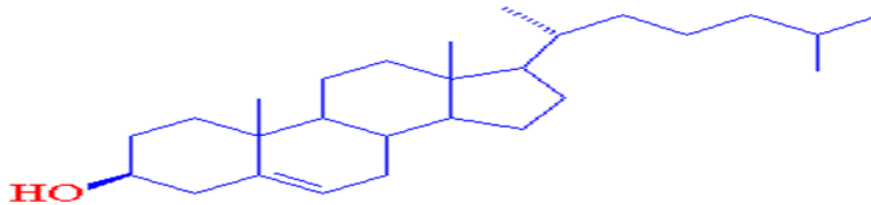
**Fatty Alcohols**  
 (n=11, lauryl; n=15, cetyl; n=17, stearyl alcohol)



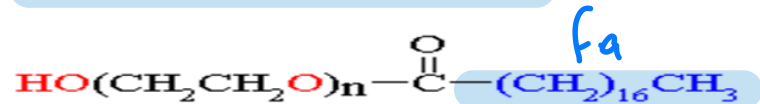
**Spans: Sorbitan Esters of Fatty Acids**  
 (sorbitan monopalmitate)



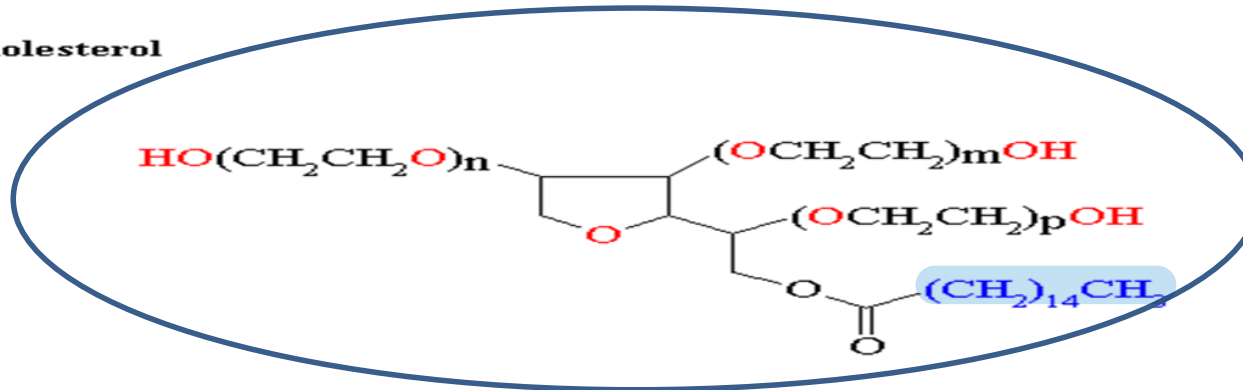
**Brij: Polyethyleneglycol (PEG) Ether**  
 (PEG-200 lauryl ether, Brij 30)



**Cholesterol**



**Cremophor: Polyethyleneglycol (PEG) Fatty Acid Ester**  
 (PEG-400 stearate)

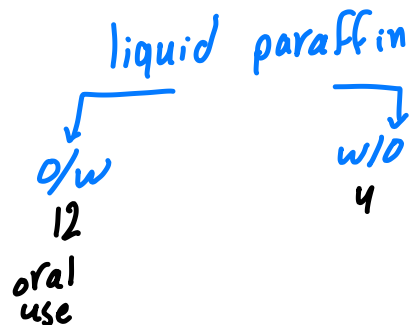


**Polysorbates, Tweens: PEG-Sorbitan Fatty Acids Esters**  
 (PEG-200-sorbitan monostearate, Polysorbate 60)

# Emulsifying agents

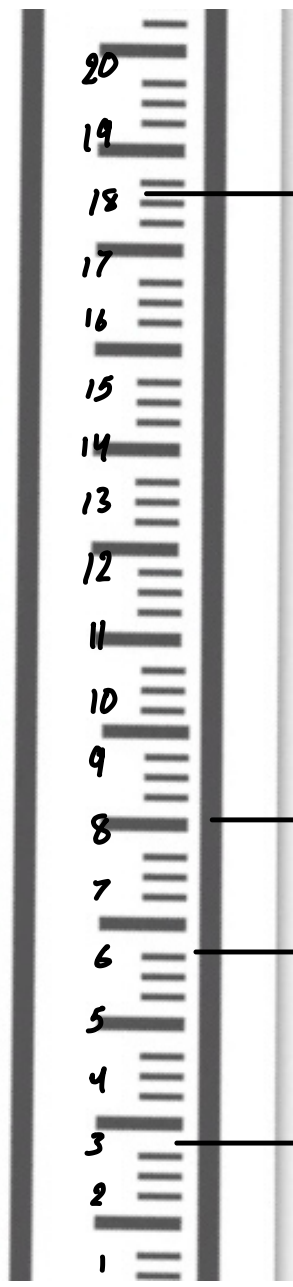
## The HLB (Hydrophilic lipophilic balance system):

- An HLB number (1-20) represents the relative proportions of the lipophilic and hydrophilic parts of the molecule.
- High numbers (8-18) indicate a hydrophilic molecule, and produce an o/w emulsion.
- Low numbers (3-6) indicate a lipophilic molecule and produce a w/o emulsion.
- Oils and waxy materials have a 'required HLB number' which helps in the selection of appropriate emulsifying agents when formulating emulsions.
- Liquid paraffin, for example, has a required HLB value of 4 to obtain a w/o emulsion and 12 for an o/w emulsion.



Hydrophil

lipophil



O/W emulsifiers [8-18]

w/o emulsifiers [3-6]

# HLB and Use of Surfactants

*hydrophobic + hydrophilic*

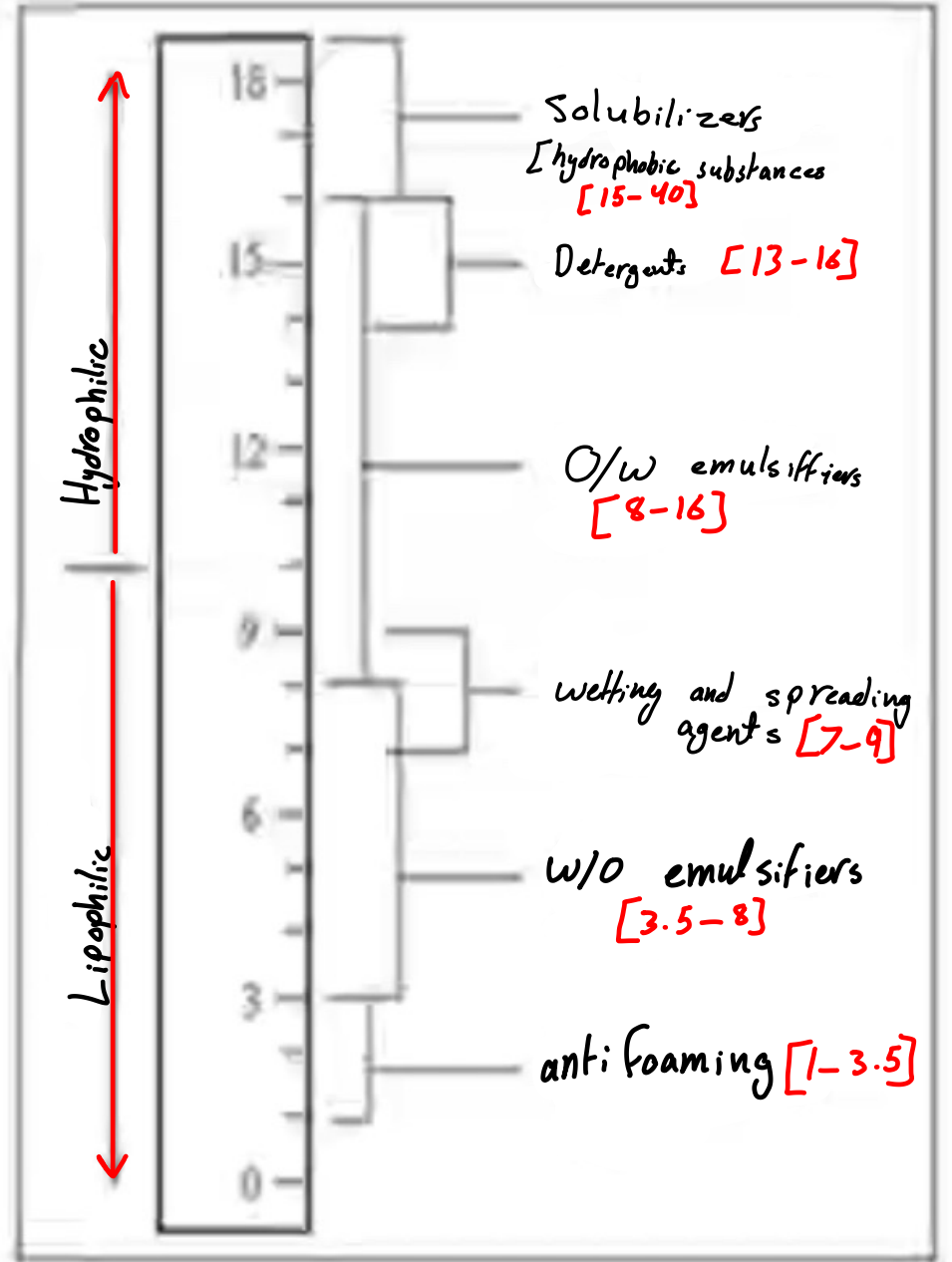
Amphiphilic surfactants are characterized by the hydrophilic-lipophilic balance (HLB): a relative ratio of polar and non-polar groups in the surfactant

- HLB ca. 3.5 to 8: Water-in-Oil Emulsifiers *lipophil*
- HLB ca. 1 to 3.5: Antifoams *lipophil*
- HLB ca. 7 to 9: Wetting and spreading agents *lipophil*
- HLB ca. 8 to 16: Oil-in-Water Emulsifiers *hydrophil*
- HLB ca. 13 to 16: Detergents *hydrophil*
- HLB ca. 15 to 40: Solubilizers *hydrophil*



كلما قلنا فيه 10 تزيد hydrophilic وكل ما نزلنا

أكثر تزيد hydrophobic / lipophilic



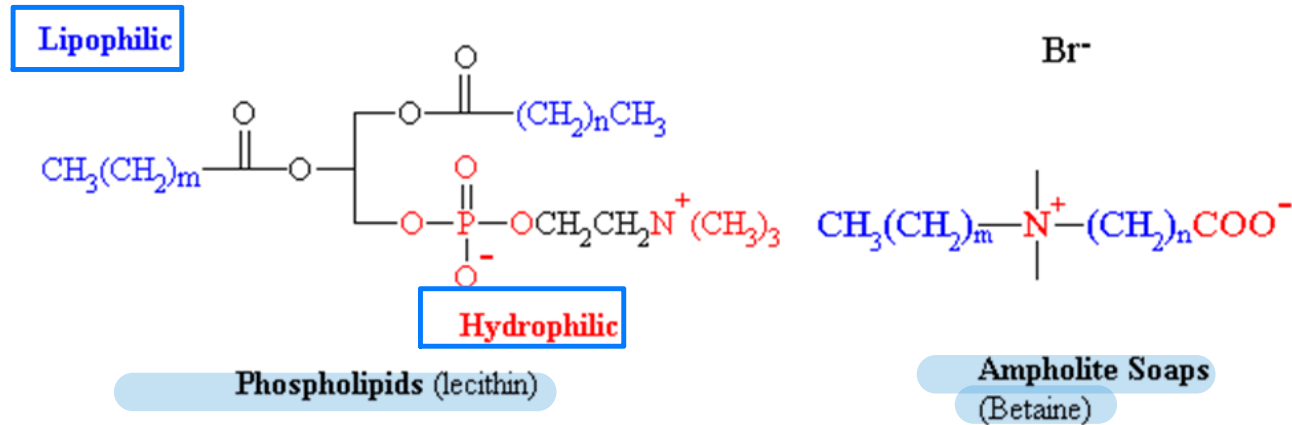
اللهم انصر اخواننا المستضعفين

في بلاد المسلمين

*Cation + anion*

# Amphoteric (Zwitterionic) Surfactants

## Amphoteric Surfactants

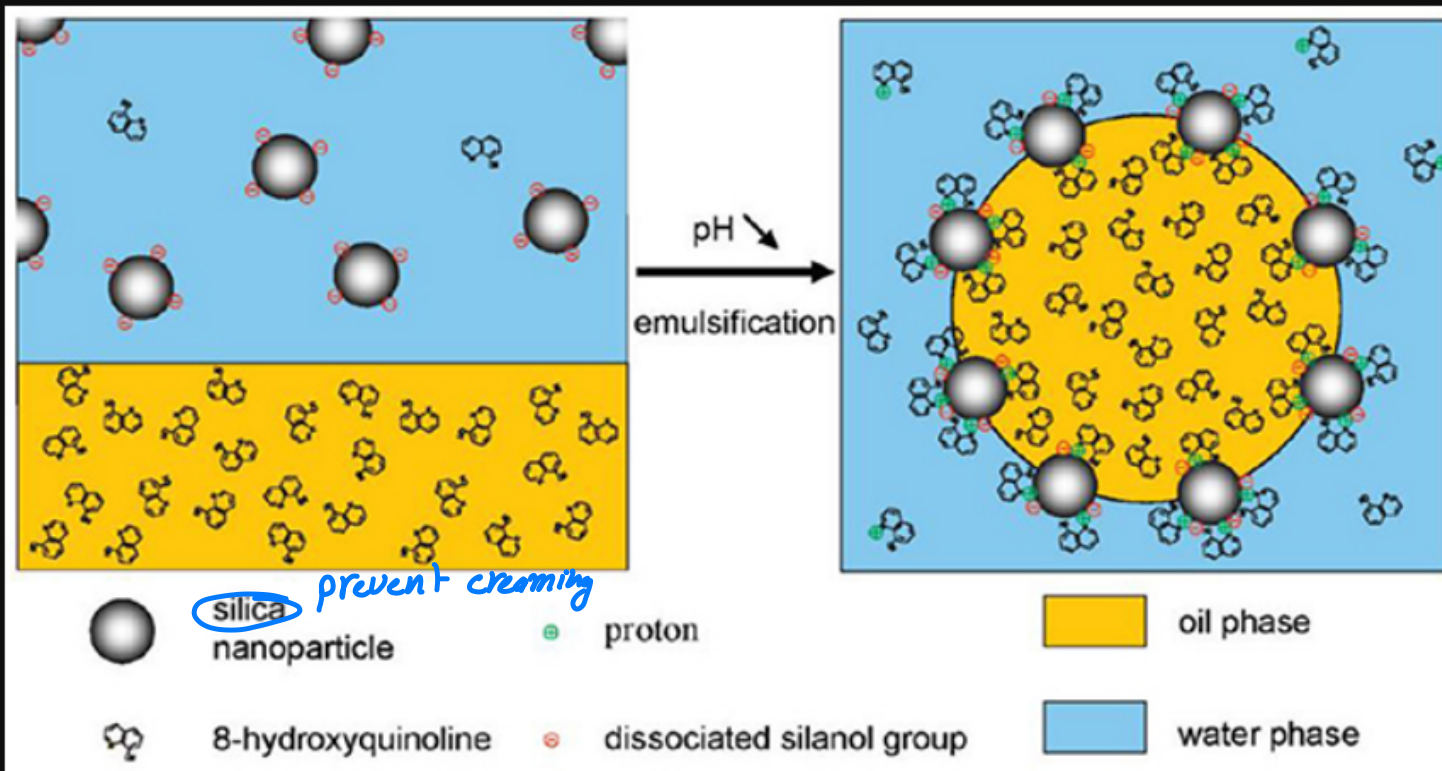


**Proteins (gelatin, casein)**

last emulsifying agent

## ← Finely divided solids

- Finely divided solids can be adsorbed at the oil-water interface to form a coherent film that prevents coalescence of the dispersed globules.
- Additionally, most of them swell in the dispersing medium resulting in an enhanced viscosity. *to decrease sedimentation*
- 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 prone to microbial contamination than those formed with other naturally derived agents. *قابلية عالية*  
*المواد كما يكون صامرا من الطبيعة يكون سهل ينمو فيها microbes*
- Examples:
- *طبي* Natural clays as bentonite and aluminium magnesium silicate.
- Synthetic materials as colloidal silicon dioxide (Aerosil®).
- Colloidal aluminium and magnesium hydroxides are used for internal preparations. *→ antiacids. ←*



# Auxiliary emulsifying agents

عوامل استحلاب إضافية مع الرئيسية

## Sterol-containing substances:

hydrophobic

- These agents act as water-in-oil emulsifying agents.
- Examples include beeswax, wool fat and wool alcohols

شمع النحل

# Choosing an emulsifying agent

emul. agent على أساس اختيار

- The **active ingredients** and the **intended use** of the product will determine the choice of emulsifying agent.
- Natural polysaccharides (acacia) and non-ionic emulsifying agents are useful for internal emulsions. *oral*
- The taste should be bland and palatable, again suggesting the natural polysaccharides. **Polysorbates** have a disagreeable taste, therefore flavouring ingredients are necessary. ← *طعم غير مرغوب والحل صلين*
- **Soap emulsions** *→ internally* irritate the gastrointestinal tract and have a laxative effect.
- A wider range of emulsifying agents can be used externally, although the polysaccharides are normally considered too sticky. *مقن للمريض الذي ما بقدر يأخذ مثل صرين ال coma*
- Only certain **non-ionic** emulsifying agents are suitable for parenteral use including lecithin, polysorbate 80, methylcellulose, gelatin and serum albumin.

# Antioxidants (Stabilizers)

نهيغه كونه الزيت صمكنا (بترنخ) وتعين خمها دمه

- 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.

نادرا

• Color is rarely needed in an emulsion

• emulsion for oral use will usually contain some flavouring agents.



# Antimicrobial preservatives

- Contamination may be introduced from a variety of sources including:
  - Water, if not properly stored.
  - Natural emulsifying agents, e.g. starch and acacia *Cause it contains microbes*
  - Carelessly cleaned equipment.
  - Poor closures on containers.
- مكتابه ميل نستخدم مواد مافطة Microbes produce unpleasant odours, colour changes and gases. Additionally, they may affect the emulsifying agents, possibly causing the breakdown of the emulsion.  
*= cracking*

# Antimicrobial preservatives

Antimicrobial preservatives :

- Should be free from toxic effects, odour, taste (for <sup>oral</sup> internal use) and colour.
- Should be bactericidal rather than bacteriostatic.  
*يُضَعِّقُ نَعْوَالِ الْبِكْتِيرِيَا* *قَاتِلٌ بِكْتِيرِيَا*
- Have a rapid action and wide antibacterial spectrum over a range of temperatures and pH.  
*مُتَنَكِّدٌ*
- Additionally emulsion ingredients should not affect their activity and they should be resistant to attack by microorganisms.
- The effect of the partition coefficient is also important: A preservative with a low oil/water partition coefficient will have a higher concentration in the aqueous phase and hence better antimicrobial activity. A combination of preservatives may give the best preservative cover for an emulsion system.  
*تَعْكُضُ تَوَضُّعِ الْمَادَّةِ الْمَحَاطَّةِ بَيْنَ طَبَقَةِ الْزَيْتِ وَالْمَاءِ*  
*لِيُعْنَى تَدْرُجُ فِي الْبُجْزِ الْمَائِي*

# Antimicrobial preservatives

Some preservatives in use are listed below:

1. Benzoic acid: effective at a concentration of 0.1% at a pH below 5
2. Esters of parahydroxybenzoic acid such as methyl paraben (0.01-0.3%)
3. Chloroform, as chloroform water (0.25% v/v)
4. Chlorocresol (0.05--0.2%)
5. Phenoxyethanol (0.5-1.0%)
6. Benzyl alcohol (0.1-3%)
7. Quaternary ammonium compounds, e.g. cetrimide, which can be used as a primary emulsifying agent but can also be used as a preservative
8. Organic mercurial compounds such as phenyl mercuric nitrate and acetate (0.001--0.002%).

# 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.

# Emulsions for oral use

- **Acacia gum** is usually used when making extemporaneous o/w emulsions for oral use, unless otherwise specified.

هو الجزء الاول من emulsion بعد ان ينضيف عليه رابحة فان لا فري

- If using acacia, a primary emulsion should be prepared first. This is a thick stable emulsion prepared using optimal proportions of the ingredients. These vary with the nature of the oil.

primary emulsion :

اذا تربط في كل الخطوات من بعد بقر بها  
اذا صار بها فلا ما توقف عند لانه الى بعد صار تربط

Method of compounding emulsions

Dry gum method

wet gum method

Bottle method

Beater method

Auxiliary method

4:2:1  
oil water gum

firstly: oil + gum  
then water.

[water adding at once]

→ trituration until 1° emulsion

formed [creamy white + cracking sound]

4:2:1  
oil water gum

water + gum →  
then oil adding with trituration

trituration until emulsion is formed

4:2:1  
oil water gum

volatile oil, low viscosity

gum placed in dry bottle + oil then shake it add water at once

صحت لازم نعل شيل لوقت طويل

4:2:1  
oil water gum

For non-gum emulsifier

اول أي نعمل مكونات الزيتية في beaker كالم  
وفي beaker ثاني نستخدم المكونات المائية بعد بنسب beaker  
الزيت في حرارة 70  
والحمار أعل بيتوي، آف اي  
نغزيم ونعل نعل لحد  
صانول حرارة الغرفة

4:2:1  
oil water gum

use other method such as: homogenizer

The formulation is improved in stability and appearance

# Methods of compounding emulsions:

## 1. Continental (Dry gum or 4:2:1) Method

فيها طريقة جافة، ذويب الماء اخر اشي

oil water agent (gum)

- 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. ملاحظة-

Firstly, oil + gum  
then water

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 trituated until the primary emulsion formed is creamy white and produces a "cracking" sound as it is trituated (usually 3-4 minutes). زققة

+ mixing طحن وضمغ الماء نحصل صبر البرسيمات المهزما يمكن

# 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 trituated 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

هو إضافة الماء و gum أولاً بعد ذلك oil

# Methods of compounding emulsions:

## 3. Bottle (Forbes) Method

أنتج الـ ايل متطابق

gum + oil  
then water

النسبة ثابتة لكل الطرم  
1. oil 2. water  
1. gum

- 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**.

first step

# 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.

# 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



# Methods of compounding emulsions:

## In Situ Soap Method <sup>هو ما يتكون</sup> <sup>الـ emulsifying agent دافل التركيبة</sup>

- Self emulsifying emulsions
- The two types of soaps developed by this method are calcium soaps and soft soaps (olive oil soap).
- Calcium soaps are w/o emulsions that contain certain vegetable oils, such as oleic acid, in combination with limewater (synonym: Calcium Hydroxide Solution, USP).
- They are prepared simply by mixing equal volumes of the oil and limewater. The emulsifying agent in this instance is the calcium salt of the free fatty acid formed from the combination of the two entities.
- In the case of olive oil, the free fatty acid is oleic acid and the resultant emulsifying agent is calcium oleate.

# Methods of compounding emulsions: In Situ Soap Method

- A typical example of this emulsion is calamine liniment:
  - Calamine
  - Zinc oxide
  - Olive oil
  - Calcium hydroxide solution
  - qs ad 1000.0 mL

# Adding ingredients to a primary emulsion:

الإضافات على primary emulsion

- Solid substances (active ingredients, preservatives, colors) are dissolved and added as a solution to the primary emulsion
- Volatile ingredients (flavors, odors, or active drugs) should be added once the product has cooled if heat was used
- Small amounts of oil soluble substances may be incorporated directly into the primary emulsion

عشان مثلا  
صايفصل  
عندي الطبقتين  
عن بعض

- Any substance might reduce the physical stability of the emulsion (i.e. alcohol) should be added to the near end of the process

# Adding ingredients to a primary emulsion:

- *↗ for external phase*  
Viscosity enhancers can be added to a primary emulsion to increase stability of the formulation
- The enhancers should be miscible in the external phase of the emulsion
- o/w → hydrocolloids *miscible with water (hydrophilic)*
- w/o → viscous oils, fatty alcohols, or fatty acids *(lipophilic)  
miscible with oil*

# Adding ingredients to a primary 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.

اللهم اغفر لي ولوالدي والمسلمين  
والمسلمات والمؤمنين والمؤمنات  
الأحياء منهم والأَمْوات

# Adding ingredients to a commercially prepared emulsion

- With w/o <sup>external</sup> emulsions:
  - Oils and insoluble powders can be incorporated directly into the external phase using a tile and spatula <sup>تدمج</sup>
  - If a large amount of insoluble powder is being added a levigating agent (i.e. mineral oil) may be necessary that should be miscible with oil phase

زِي مَا مَعْلَنَا  
بالاب المعجون  
باستخدام  
البلاطة

# Adding ingredients to a commercially prepared emulsion

- With w/o emulsions (cont.):
  - If an aqueous soluble material to be added, excess emulsifier must be present
  - For those w/o emulsion that do not have <sup>on w/o</sup> excess emulsifier, additional emulsifier may have to be added
  - An aqueous solution may be added using a pill tile and spatula, but some may require heat

# Adding ingredients to a commercially prepared emulsion

- With o/w emulsions:
  - Levigating agents for aqueous insoluble substances should be water miscible as glycerin, propylene glycol, polyethylene glycol, or alcohol
  - If heat is used to incorporate → work quickly → be careful not to evaporate water from the product → stiff
  - In many commercial o/w emulsions, sufficient emulsifying agents is already present in the preparation to accommodate the added oils or powders

*to prevent water evaporation* ↓

# Flavoring emulsions

- Select it based on the external phase
- Flavoring oil can be mixed with emulsifier or with a water miscible solvents as glycerin or ethanol