تفريغ حساب وتركيب الأشكال الصيدلانية

اسم الموضوع: Emulsions

Part (1)

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لجان الدُّفعات

عبارة عن زيت
+ ماء

Emulsions

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* الـ colloid and gel عبارة عن solid in liquid

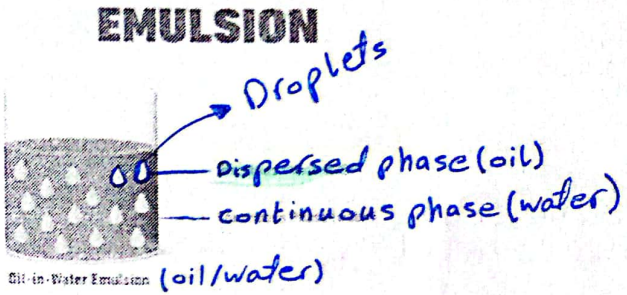
* الـ Emulsion عبارة عن two immiscible liquid

water Oil

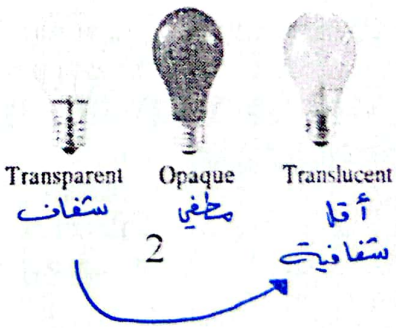
Emulsions

- An emulsion consists of two immiscible liquids, one of which is uniformly dispersed throughout the other as fine droplets normally of diameter 0.1-100 µm.

oil / water



- At least 2 phases:
  - ✓ **Disperse** or internal phase (داخلي)
  - ✓ **Continuous** or external phase (خارجي). ← Media / Vehicle أو
  - ✓ Emulsions can be transparent (شفاف) or translucent (نصف شفاف) for emulsion composed of droplets approximately < 200 nm to milky white and opaque (معتم) for emulsion containing larger droplets



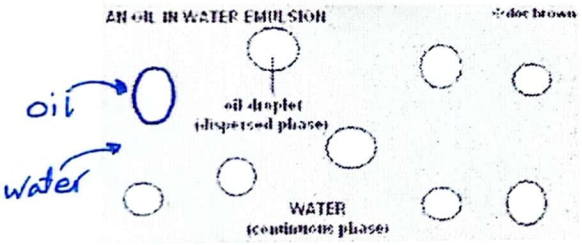
* Transparent and Translucent ⇒ droplets < 200 nm ⇒ small droplets (شفاف)

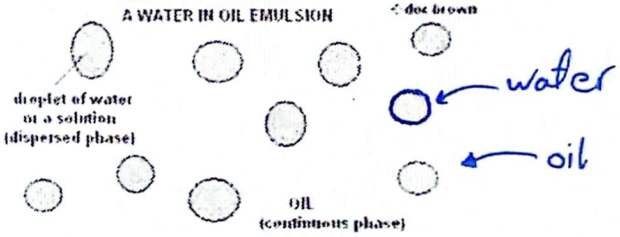
* Opaque ⇒ larger droplets (معتم)

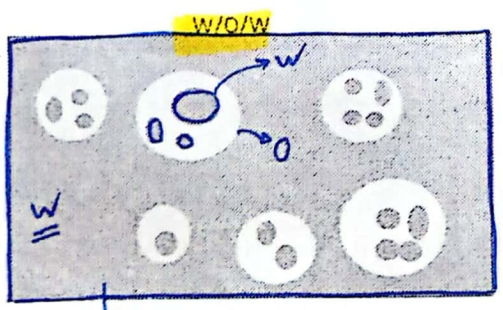
* كلما زادت أحجام الـ droplets قلت شفافية الـ emulsion ← واتجه إلى Opaque .

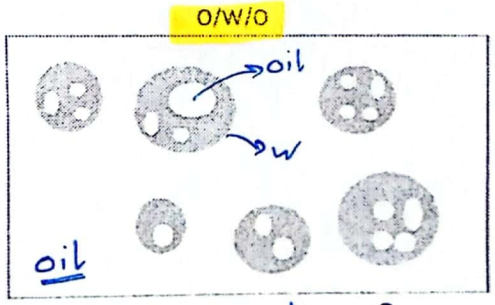
Emulsion types

- O/W emulsions.
- W/O emulsions.
- Multiple emulsions (e.g. W/O/W emulsions for delayed action drug delivery).









Pharmaceutical application of emulsions

Why emulsions?

Oral route:

- Oral administration of oils or oil-soluble drugs (o/w emulsions).

✓ To enhance palatability of oils when given orally by disguising both taste and oiliness (*Taste, odor and oiliness typical of oils are suppressed when administered in the internal phase of an emulsion*).

✓ Increasing absorption of oils and oil-soluble drugs through intestinal walls. An example is griseofulvin suspended in oil in an oil-in-water emulsion.

✓ Formulation of oil- and water-soluble drugs together.

Note: Medicinal oils for the local effect of constipation and oral food supplements oil such as fish liver oil +oral delivery of drugs and vitamins of low aqueous solubility small droplets >> large surface area available for contact at the absorption site

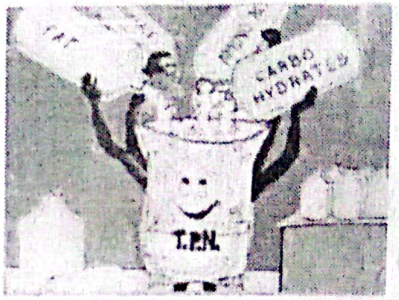
- w/o emulsions can be used to prolong the delivery of **water soluble antigens** as The vaccine must first diffuse from the aqueous droplets through the oily external phase before it reaches the tissue.

Pharmaceutical application of emulsions

Why emulsions?

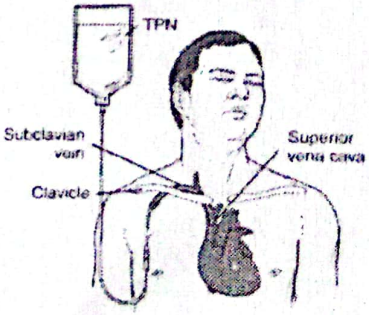
IM route:

- IM depot therapy: Intramuscular injections of some water-soluble vaccines (w/o emulsions) provide slow release and therefore a greater antibody response and longer-Lasting immunity.



A. IV route:

- IV (o/w) emulsions for hydrophobic drugs.
- Total parenteral nutrition (TPN) makes use of a sterile oil-in water emulsion to deliver oily nutrients intravenously to patients, using non-toxic emulsifying agents, such as lecithin.



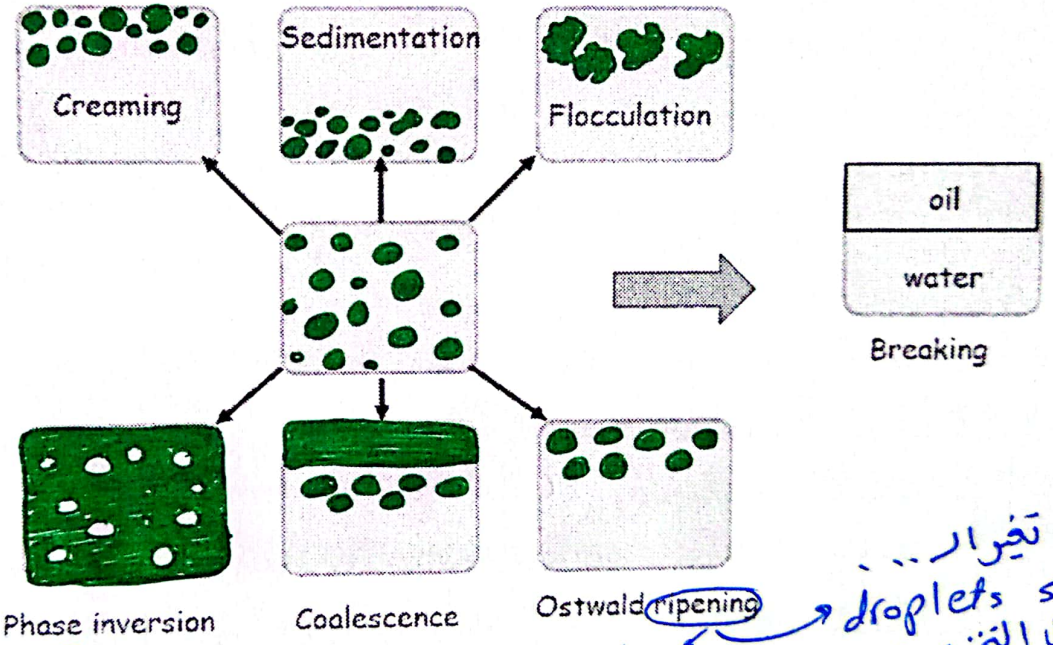
B. Topical applications (both o/w and w/o emulsions)

C. Rectal route

Formulation of emulsions

Stability problems

1. Sedimentation and creaming.
2. Coalescence or cracking.
3. Phase inversion.



واحد من الـ phases بيفضل لأسفل (sedimentation) أو للأعلى (creaming).

بتبدأ فيها الـ droplets مع بعض وبيصير Fussion وبكبر حجمها. واذا زاد الموضوع بتوصل لـ cracking (بيفصل الزيت عن الماء) two layers.

بتبدأ بـ (o/w) وبصير (w/o)

تغير الـ droplets size خلال التخزين.

الصغيرة تكبر والكبيرة تصغر.

* الحركة حتكون حسب الـ density.

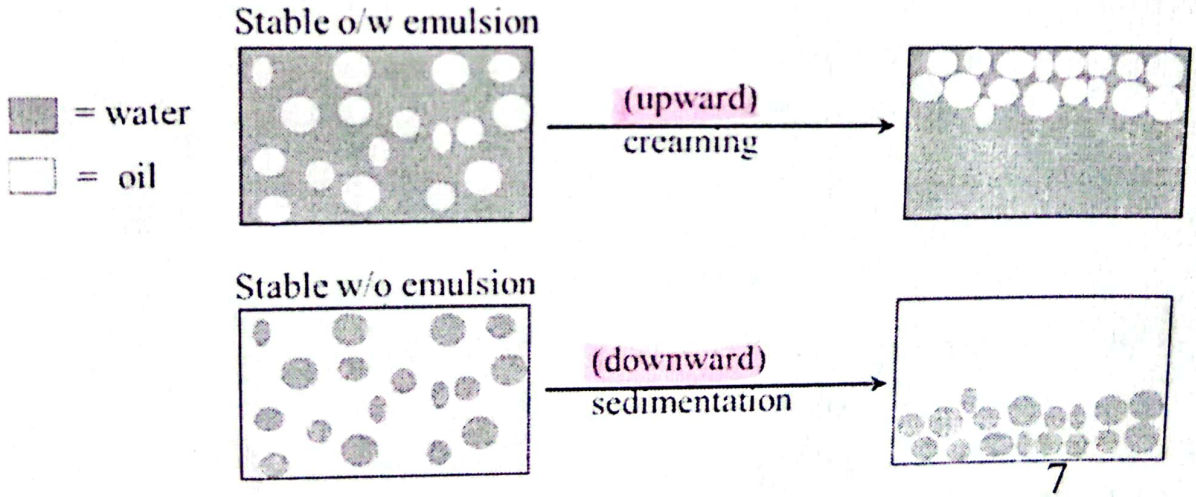
Stability of emulsions

Creaming and sedimentation:

- As the dispersed droplets are subjected to gravity force, they tend to move upward (creaming) or downward (sedimentation) but not both.
- Creaming usually happens in o/w emulsions.
- Sedimentation usually happens in w/o emulsion.

In most cases oil is less dense than water, hence generally:

بشكل عام المواد الزيتية أو الدهنية كثافتها أقل فتطفو للأعلى .



Stability of emulsions

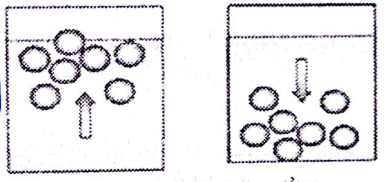
Creaming and sedimentation:

- The rate of sedimentation or creaming is described by **Stoke's law.**

density (globule) — density (media)

velocity ← $v = \frac{2r^2(\sigma - \rho)g}{9\eta}$ → gravity

radius — viscosity



(a) (b)

$(\sigma - \rho)$

negative (−) → creaming

positive (+) → sedimentation

- Where v= velocity of sedimentation or creaming of a dispersed droplet or globule of radius r, and density σ, in a liquid of density ρ, and viscosity ŋ, and where g is the acceleration due to gravity.

- A theoretical consideration of this equation shows that the rate of creaming will be reduced by:

✓ Reduction in the globules size. ↓r

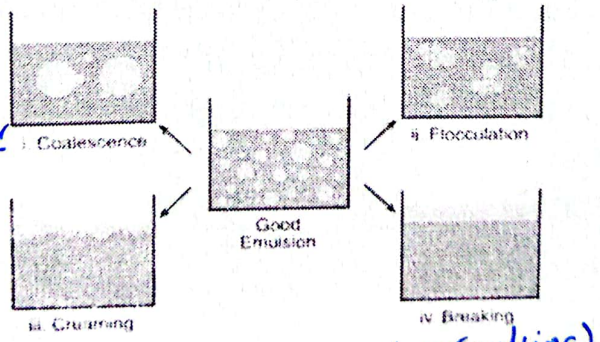
✓ A decrease in density difference between the two phases. ↓$(\sigma - \rho)$

✓ An increase in the viscosity of the continuous phases ↑ŋ

Stability of emulsions

Creaming and sedimentation:

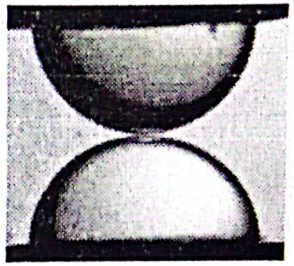
- The process is **reversible** and gentle shaking redistributes the droplets throughout the continuous phase.
- However, creaming is undesirable because:
  - if shaking is not thorough, it is inelegant and inaccurate dosing is possible
  - Additionally, creaming increases the likelihood of coalescence of globules and therefore break down of the emulsion due to cracking



Stability of emulsions

Cracking or coalescence:

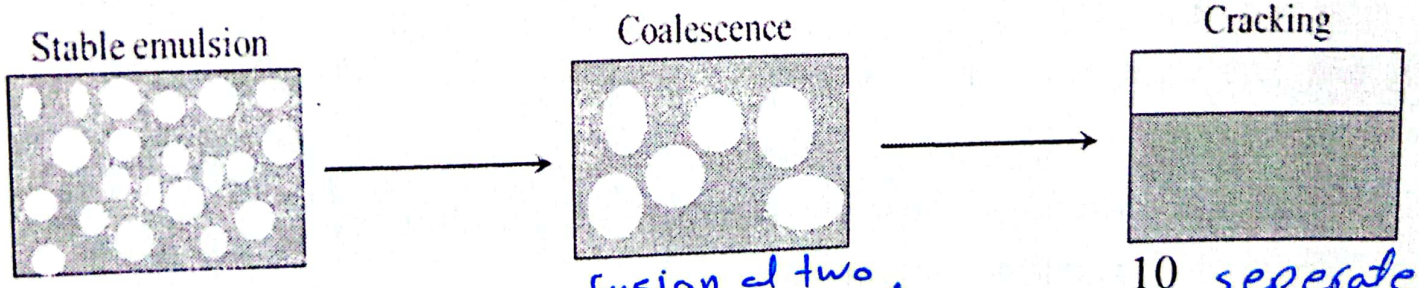
- Coalescence is the fusion of two or more droplets of the disperse phase forming one droplet.



Breaking (cracking)

- This ends up to the separation of the disperse phase as a separate layer (phase separation).

- Coalescence is an **irreversible** process and redispersion cannot be achieved by shaking.



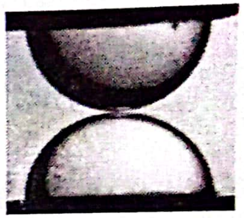
Good emulsion

Fusion of two or more droplets to form one droplet.

10 seperate layer.

*irreversible process.
*Coalescence: Fusion of two or more droplets to form larger droplet.
*Cracking: Complete seperate of layer between water and oil phase.

Coalescence

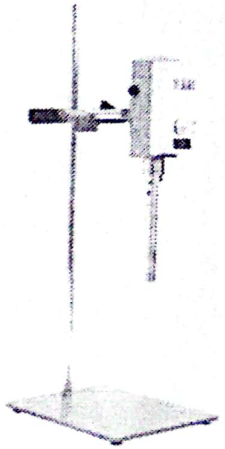


- Coalescence describes the irreversible process in which dispersed phase droplets merge to from a larger droplet.
- The process will continue until cracking; in this case, there is complete separation of oil and water phases.
- Coalescence and cracking occur because emulsions are thermodynamically unstable systems hence to enhance their stability, the dispersed droplets come closer to each other and fuse in an attempt to decrease the exposed surface area.
- Coalescence and cracking are irreversible processes and re-dispersion cannot be achieved by shaking.

خلال التخزين..
بشكل عام لما تكون الـ droplets
صغيرة بتكون surface energy
عالية، وهاد الاشي ما بيزبط
فبادروا الـ droplets يقللوا اهاي
الطاقة (surface energy) من خلال
زيادة الـ size لالهم فبتقل الـ
surface area.

Stability of emulsions

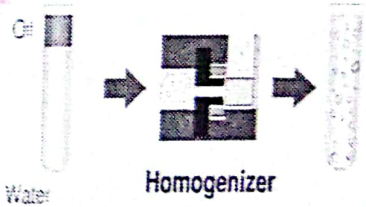
How to enhance stability (to prevent creaming and cracking)?



- **Globule size:**

✓ Smaller particles have slower creaming or sedimentation than larger particles (Stoke's law).

- Stable emulsions require a maximal number of small sized (1-3 µm) globules and as few as possible larger (>15 µm) diameter globules.



- A **homogenizer** will efficiently reduce droplet size by forcing the emulsion through a small aperture to reduce the size of the globules.

✓ Additionally, reducing droplet size may additionally increase the viscosity if more than 30% of disperse phase is present.

القطرات الصغيرة من مرتبط sedimentation/ creaming للـ تكون اقل من القطرات الأكبر .

لازم يكون عبارة عن :
* small sized (1-3 µm)
* Few of larger . (اقل ما يمكن)

homogenizer يعمل mixing بسرعة عالية جدًا فينقل حجم droplets

إذا كان الـ emulsion يحتوي على أكثر من 30% من dispersed phase ، بتزيد الـ viscosity و بتقل droplets size .

How to enhance stability (to prevent creaming and cracking)?

dispersal نسبة عالية من يعني لزوجة أعلى يعني droplets حركة أقل لل Fusion بالتالي فرصة creaming أقل فارق يصير دا عيزه .

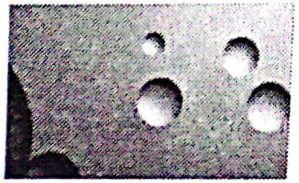
By keeping the concentration of dispersed phase > 20%.

Emulsions containing > 20% disperse phase result in hindrance of movements of the droplets → Therefore there will be reduction in the rate of creaming compared to emulsions where the dispersed phase is < 20%.

Higher percentages of oil phase (o/w).

Higher amounts of solid fats in the oily phase (i.e. high ratios of solid fat to liquid fats).

Stability of emulsions



How to enhance stability (to prevent creaming and cracking)?

↑ Viscosity
↳ ↓ rate of velocity
↳ ↓ movement of globules
↳ ↓ creaming and others.

❑ **Viscosity of the continuous phase:**

✓ Increasing the viscosity of the continuous phase will reduce the potential for globule creaming and hence **coalescence** as this reduces the movement of globules.

✓ How to increase viscosity?

➢ **Viscosity enhancing agents**, which increase the viscosity of the continuous phase, may be used in o/w emulsions. e.g tragacanth, sodium alginate and methylcellulose.

➢ **Decreasing the droplet size** of the internal phase.

ممكن نستعمل
Homogenizer

Stability of emulsions

How to enhance stability (to prevent cracking)?

- ❑ **Using emulsifying agents (hydrocolloids, surfactants and other) :**
  - Forming interfacial film mechanical barrier which decreases the potential for coalescence.
  - Surfactants may reduce the interfacial tension between the two phases.
  - Hydrocolloids enhance the viscosity of the medium.

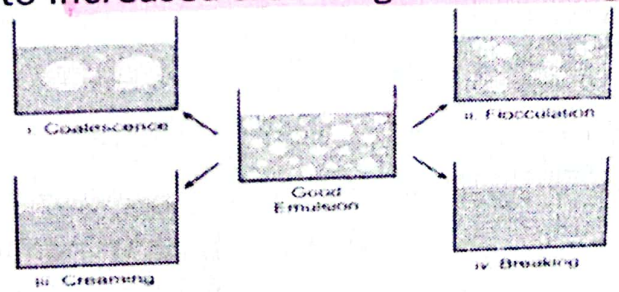
Note: Care should be taken for any effects that could affect the interfacial film (chemical, physical or biological effects).

Stability of emulsions

Stability of emulsions

How to enhance stability (to prevent creaming and cracking)?

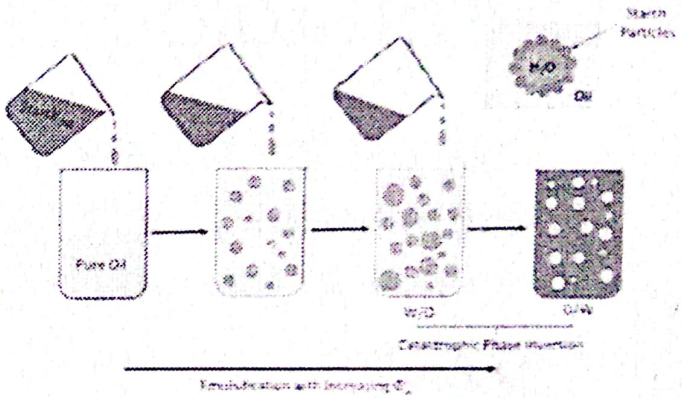
- ***Storage temperature:***
  - Extremes of temperature can lead to an emulsion cracking.
  - When water freezes it expands, so undue pressure is exerted on dispersed globules and the emulsifying agent film, which may lead to cracking. probably because the ice formation disrupts the interfacial film around the droplets.
  - Conversely, an increased temperature decreases the viscosity of the continuous phase and disrupts the integrity of the interfacial film.
  - An increasing number of collisions between droplets will also occur, leading to increased creaming and cracking.



Stability of emulsions

Phase inversion

- Emulsion type is determined by:
  - The oil to water ratio (amounts).
  - The solubility of the emulsifying agent



- Phase inversion is the process in which an emulsion changes from one type to another, say o/w to w/o.
- The most stable range of disperse phase concentration is 30-60%. If the amount of disperse phase approaches or exceeds a theoretical maximum of 74% of the total volume, then phase inversion may occur.
- Addition of substances which alter the solubility of an emulsifying agent may also cause phase inversion.
- The process is **irreversible**.

Formulation of emulsions

Emulsifying agents (emulsifiers):

- An emulsifying agent is any material that enhances the stability of an emulsion (i.e. Prevention of coalescence and reducing creaming).
- **The ideal emulsifying agent is**
  1. colourless, odourless, tasteless,
  2. non-toxic,
  3. non-irritant
  4. able to produce stable emulsions at low concentrations.
- **<u>Emulsifying agents are either:</u>**
  a) Hydrocolloids.
  b) Surface active agents (SAA) (surfactants).
  c) Finely divided solids.
  d) Auxiliary emulsifiers.

Dermatological emulsions

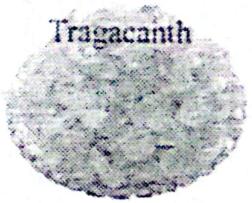
- They are the largest class of emulsions used in pharmacy and range in consistency from fluids lotions and liniments to semisolids (creams).
- A w/o emulsion can usually be applied more evenly, because the skin is covered with a thin film of sebum, and this surface is more readily wetted by oil than by water.
- A w/o emulsion is also more softening to the skin, because it resists drying and removal by contact with water.
- Dermatological emulsions can facilitate drug permeation into and through the skin by occlusion

Emulsifying agents

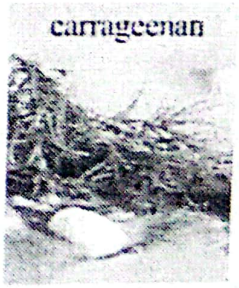
Hydrocolloids

Natural Polysaccharides:

- The main problem with these agents is their natural variability between batches and microbial contamination.
- These materials should not be used externally as they leave a sticky feel on the skin.



- *Acacia is the best emulsifying agent for extemporaneously prepared oral emulsions* as it forms a thick film at the oil-water interface to act as a barrier to coalescence. It is too sticky for external use.



- Tragacanth is used to increase the viscosity of an emulsion and prevent creaming.
- Other polysaccharides, such as starch, pectin and carrageenan, are used to stabilize an emulsion.

Emulsifying agents

Hydrocolloids

Semi-synthetic polysaccharides:

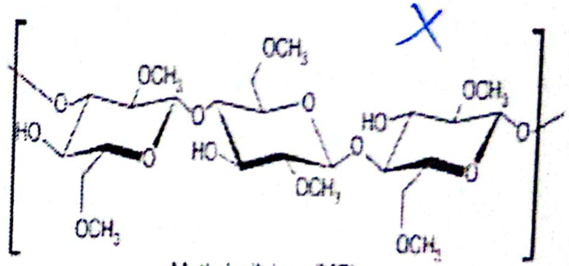
- These are derived from the naturally occurring polysaccharide cellulose and generally form o/w emulsions.
- **Examples include low-viscosity grades of**

✓ Methylcellulose (MC)

✓ Carboxymethylcellulose (CMC)

✓ Hydroxypropylmethylcellulose (HPMC)

بيتص جزوا الماء ، بعمل له swelling بكبر حجمه ، وبتزيد viscosity.



Methylcellulose (MC)

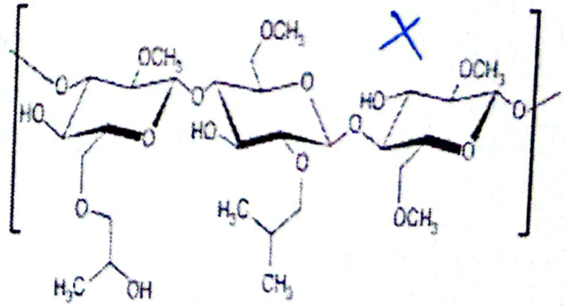
Synthetic hydrocolloids:

✓ Carbopol

✓ Polyvinyl alcohol (PVA).

✓ Polyvinyl pyrolidone (PVP)

قليل استعماله orally عكس العين أو skin



Hydroxypropyl methylcellulose (HPMC)