Pharmaceutics- (Emulsions)

Dr. Sonia Alqadi

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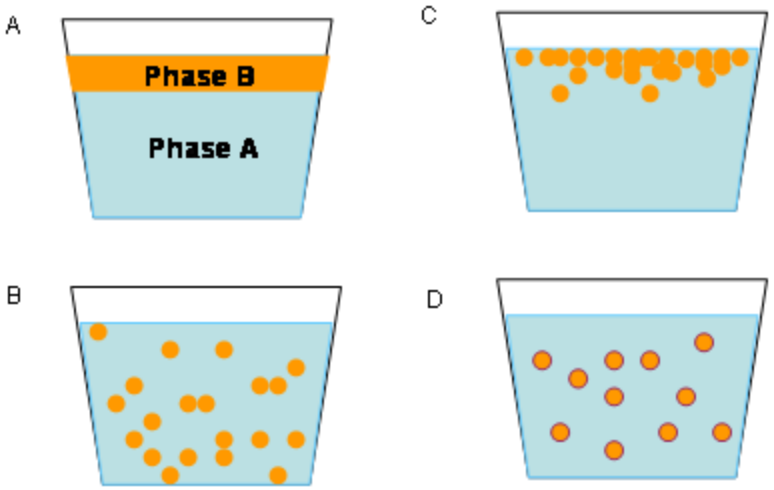
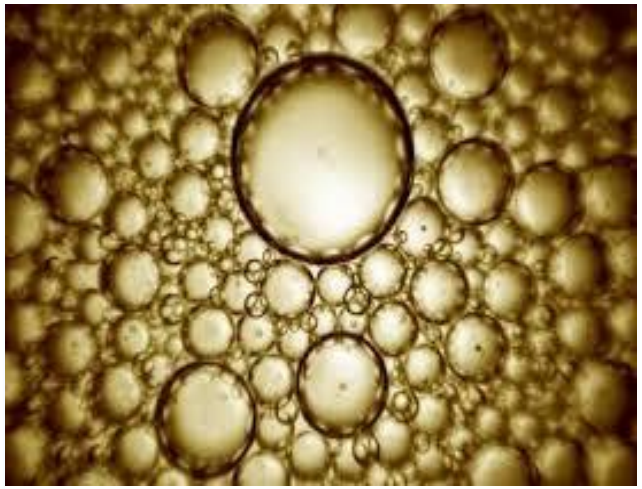
Emulsion

An emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases, one of which is dispersed as globules in the other liquid phase, stabilized by the presence of an emulsifying agent.



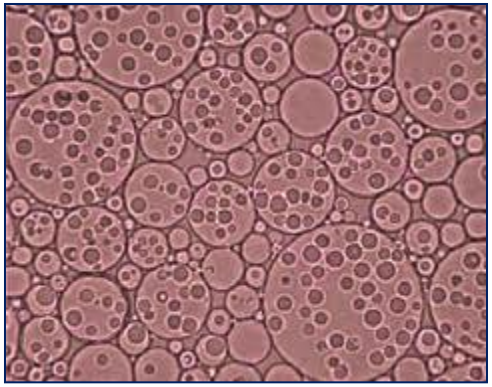


A: Two immisicble liquids, not emulsified; B: An emulsion of Phase B dispersed in Phase A; C: The unstable emulsion progressively separates; D: The (purple) surfactant positions itself on the interfaces between Phase A and Phase B, stabilizing the emulsion

Emulsion types

➢ **Types**

- Oil-in-water (o/w)
- Water-in-oil (w/o)
- Oil-in-water-in-oil (o/w/o)
- Water-in-oil-in-water (w/o/w)



➢ **Pharmaceutical emulsions an be divided according to droplet size:**

Microemulsions

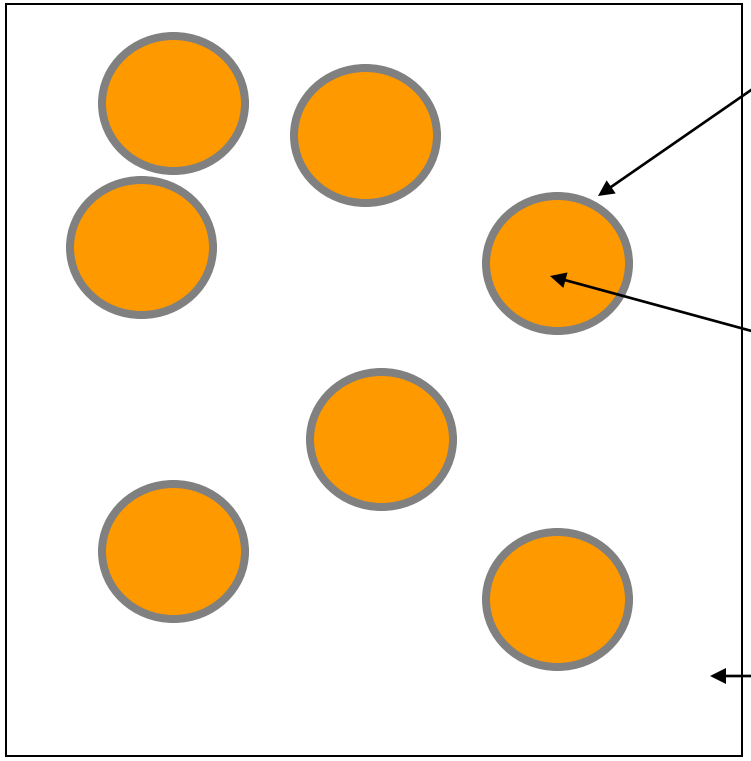
Nanoemulsions

➢ **Determination of o/w or w/o**

- Dye solubility test (e.g., methylene blue)
- Dilution of emulsions
- Conductivity measurement

Emulsion: Composition

Example: o/w emulsion



Interfacial layer (emulsifying agent). Essential to stabilizing the emulsion

Oil Phase (dispersed medium). Limited effects on the properties of the emulsion

Aqueous Phase (contineous medium). Aqueous chemical reactions affect the interface and hence emulsion stability

Pharmaceutical emulsions.

- Applications of emulsions:

- Oral emulsions: o/w (liquid)

- External emulsions: liniments, lotions (liquid)
  Creams (semi-solid)

- Parenteral emulsions: o/w (parenteral nutrition)
  o/w or w/o intramuscular.

Emulsions

The characteristics of an acceptable pharmceutical emulsion include:.

✓Physical stability (no phase separation).

✓The flow properties of the emulsion should enable the formulation to be easily removed from the container. Furthermore, if the formulation is designed for external application to the skin, for example, the formulation must be easily spread over the affected area.

✓The formulation must be aesthetically and texturally pleasing. If the emulsion is designed for oral administration, a suitable flavourant must be included, whereas if emulsions are to be externally applied, they must have the correct "feel" (termed texture).

Emulsions-Advantages

✓ Pharmaceutical emulsions may be used to deliver drugs with low aqueous solubility. For instance, in o/w emulsions, the therapeutic agent is dissolved in the internal oil phase. Following oral administration, the oil droplet containing the drug may be then absorbed using the normal absorption mechanisms of oils.

✓Emulsions may be used to mask the unpleasant taste of a therapeutic agent, by dissolving it in the internal phase of an o/w emulsion. The external phase (water) may be then formulated to contain the appropriate sweetening and flavoring agents.

✓Emulsions are employed for total parenteral nutrition.

Emulsions-Advantages

✓Pharmaceutical emulsions may be used to administer oils having a therapeutic effect. For example, the cathartic effect of oils (e.g., liquid paraffin) is enhanced following administration to the patient as droplets within an o/w emulsion. The taste of the oil may be masked using a sweetening and flavouring agent.

✓If the therapeutic agent is irritant when applied topically, irritancy may be reduced by formulating it within the internal phase of an o/w emulsion.

✓Pharmaceutical emulsions may be employed to deliver drugs to patients who have difficulty to swallow solid dosage forms.

Emulsions-Disadvantages

✓Pharmaceutical emulsions are thermodynamically unstable and, therefore must be correctly formulated to avoid the separation of the two phases (emulsion stabilization) .

✓Pharmaceutical emulsions are sometimes difficult to manufacture.

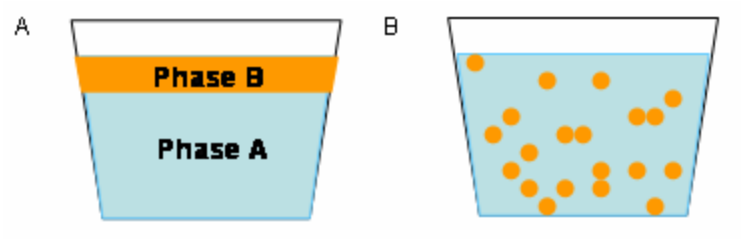
Emulsifier versus Emulsion

- An emulsion is a mixture of oil and water
- An emulsifier is a specific molecule able to bind the two ends so they 'stick together' (i.e. the oil and water bind) and, consequently stabilizes the emulsion.
- E.g. Lecithin is an emulsifier which binds the emulsion of water and oil

Pharmaceutically acceptable emulsifiers must also :

- be stable .
- be compatible with other ingredients .
- be non – toxic .
- possess little odor , taste , or color.
- not interfere with the stability of efficacy of the active agent .

Theory of emulsification



Change from A to B will significantly increase of the surface area of phase.

e.g., if 1 cm^3 of mineral oil is dispersed into globules having diameter of 0.01 mm in 1 cm^3 of water, how much will be the surface area increased.

The surface area will become 600 m^2 (greater than a basketball court); the surface free energy will increase by 8 calories. Therefore, emulsions are thermodynamically unstable, and the droplets have the tendency to **coalesce**.

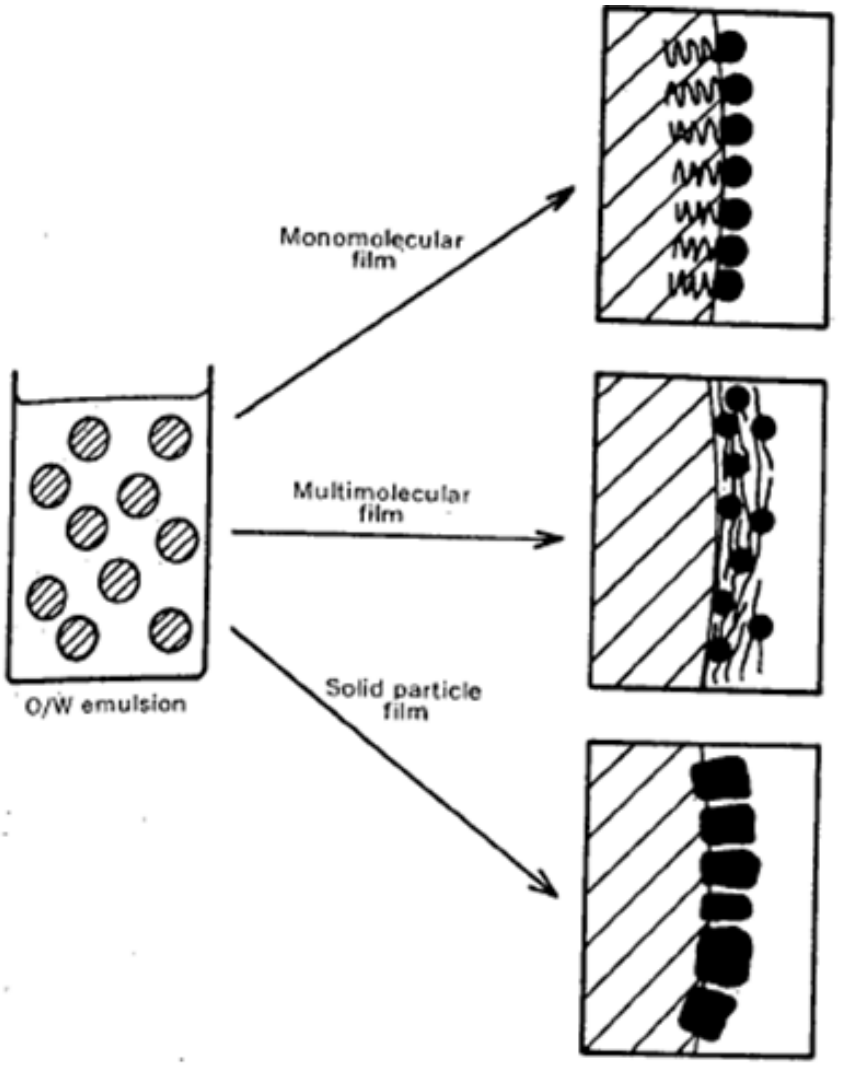
Emulsifying agents are needed to decrease the surface tension and to stabilize the droplets.

Classification of emulsifying agents

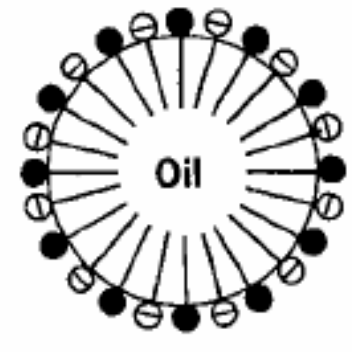
I. **Surface-active agents** (monomolecular film)

II. **Hydrophilic colloids** (multimolecular film)

III. **Finely divided solid** particles (Particulate film)



I. Surface-active agents: Monomolecular adsorption

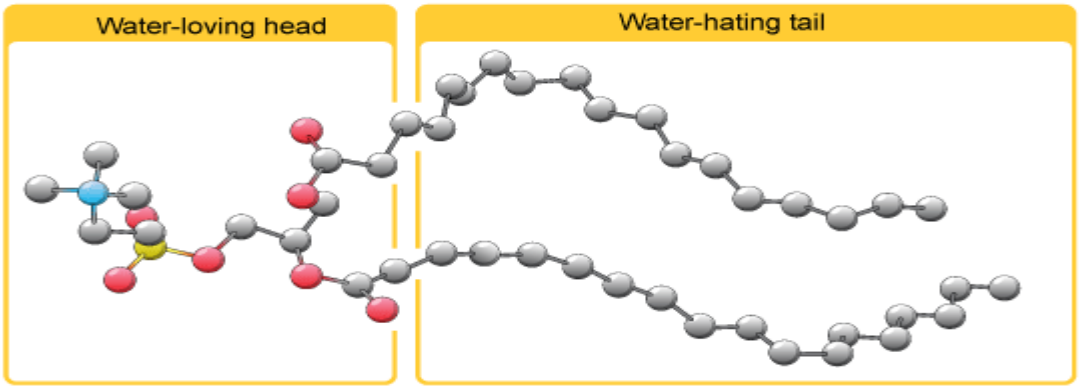


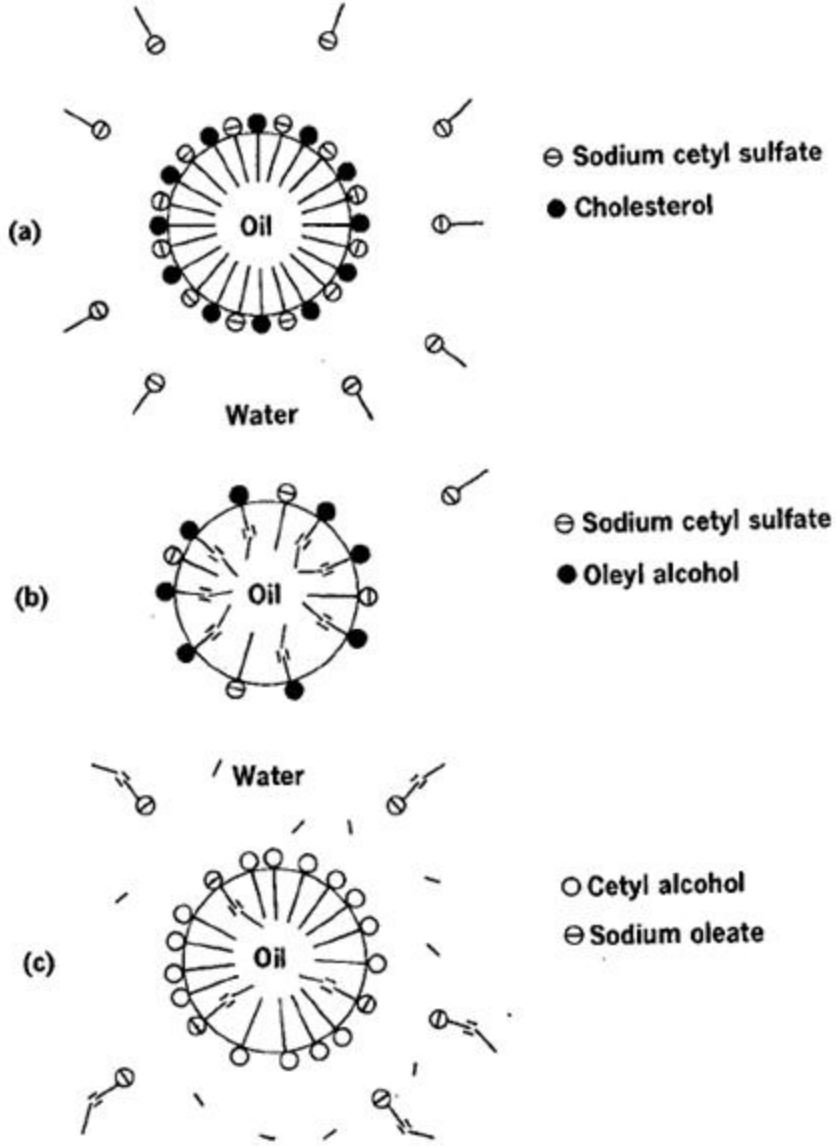
Interfacial film formation: The subdivision of the one of the phases (either the oil or water phase) into small droplets (globules) results in a large increase in the surface area and, hence interfacial free energy of the system. The system is thus thermodynamically unstable which means that the resulting spherical globules tend to coalesce, causing phase separation which represents the state of minimum surface free energy.

The adsorption of surface-active agents (surfactants) at the globule interface will lower the interfacial tension (air displacement). Ionic surfactants with charged heads (anionic or cationic) will create and an electrostatic barrier around globules (electrostatic repulsion that resist coalescence of globules), whilst non-ionic surfactants stabilize emulsions against globules coagulation by steric stabilization.

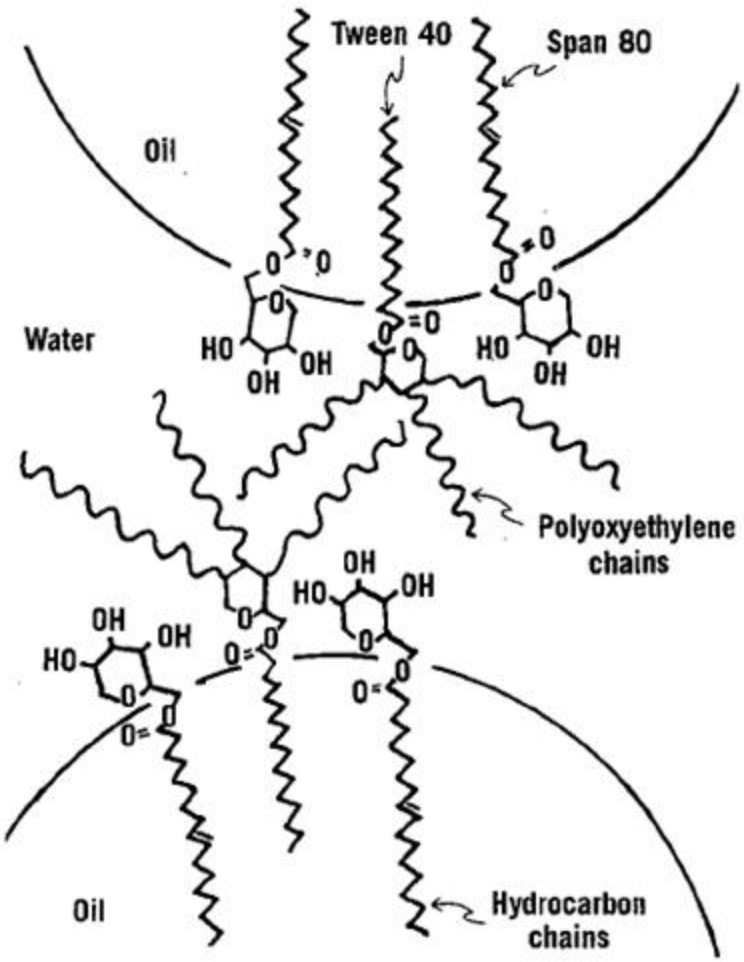
Surface-active agents (Surfactants)

- Surfactants are molecules that have two)different ends:
  - A hydrophilic end (water-loving) that forms chemical bonds with water but not with oils
  - A hydrophobic end (water-hating) that forms chemical bonds with oils but not with water.
- The hydrophilic 'head' dissolves in the water and the hydrophobic 'tail' dissolves in the oil
- In this way, the water and oil droplets become unable to separate out – the mixture formed is called an emulsion

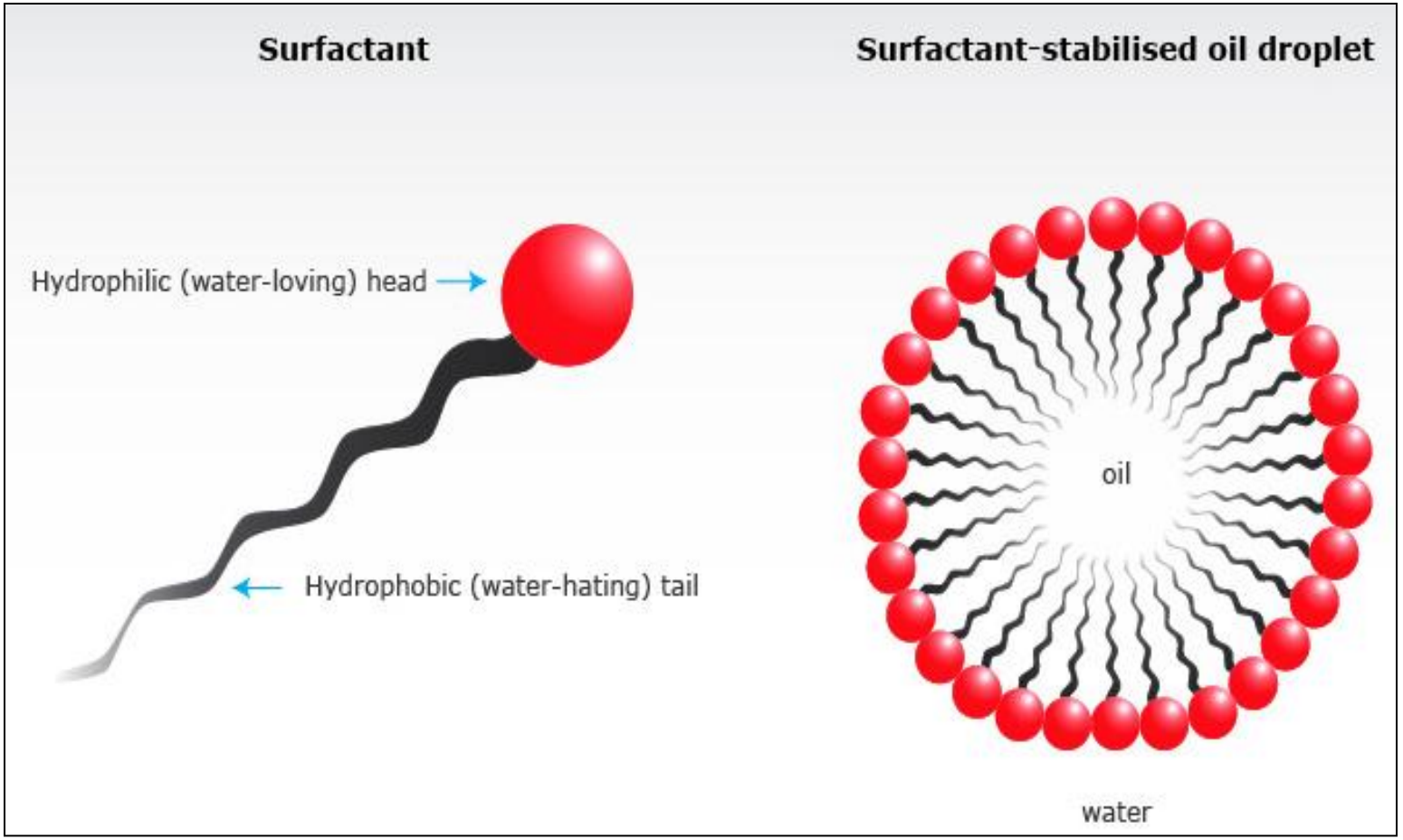


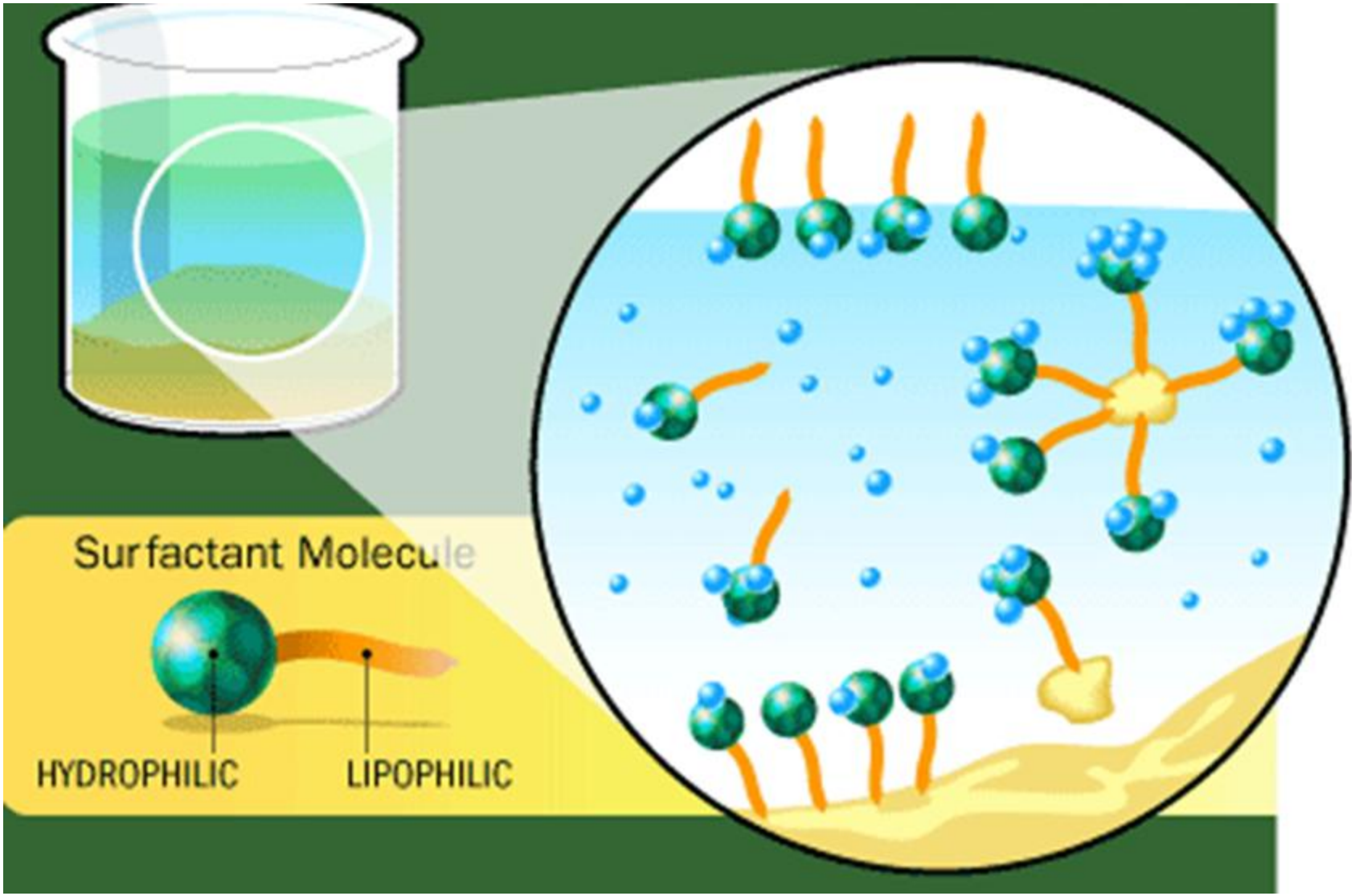


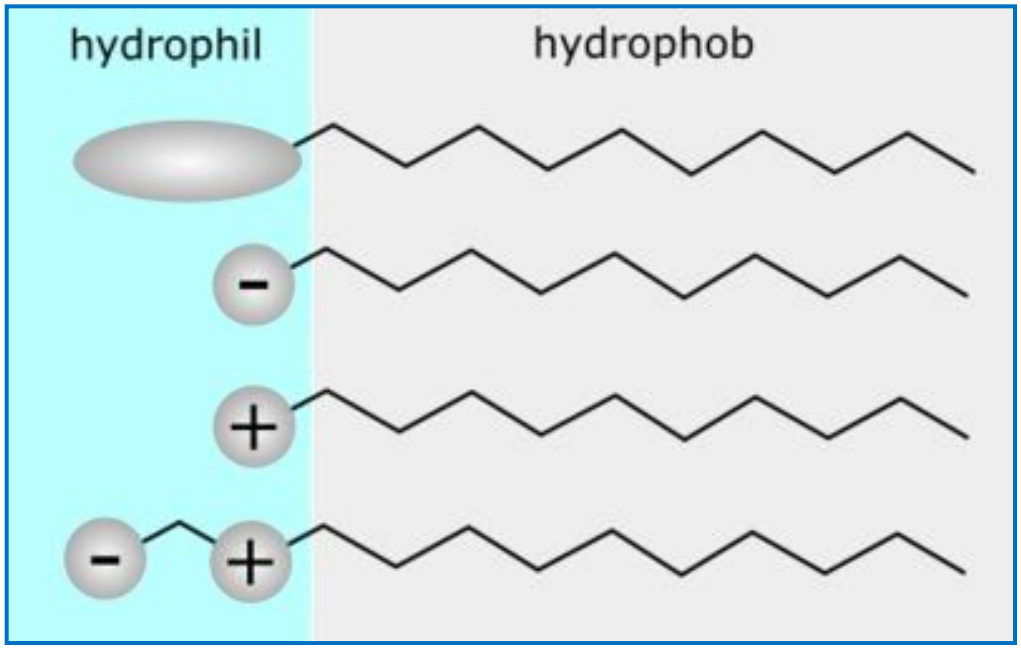
Representations of combinations of emulsifying agents at the oil–water interface of an emulsion.



Schematic of oil droplets in an oil–water emulsion, showing the orientation of a Tween and a Span molecule at the interface.

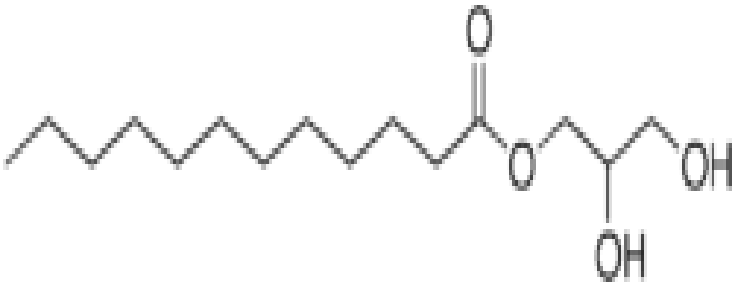

Surfactant
Surfactant-stabilised oil droplet
Hydrophilic (water-loving) head
Hydrophobic (water-hating) tail
oil
water


Surfactant Molecule
HYDROPHILIC
LIPOPHILIC

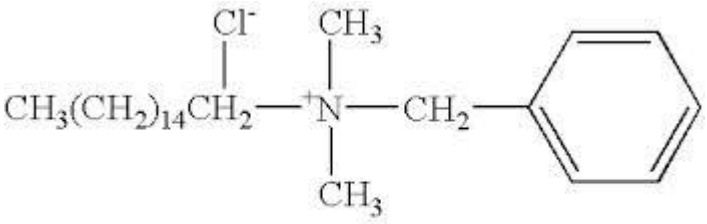


Types of surfactants

Sodium lauryl sulphate



glyceryl laurate



Benzalkonium Chloride

Surfactants

Polymeric surfactants

They are polyxamers (also known as **pluronics®)** which are a series of neutral synthetic polyoxyethylene-polyoxypropylene block co-polymers. E.g., poloxamer 188 (Pluronic ® F68).

Ionic surfactants are rritant & toxic to the mucous membranes

Anionic surfactants

cationic surfactants

They also have antimicrobial properties & are the most toxic and irritant, as compard with other surfactants e.g., cetrimide (cetyltrimethyl ammonium bromide)

Least toxic surfactants

Non-ionic surfactants

Based on:

- <u>A hydrophobic moiety</u> with 12-18 carbon atoms. The starting aterial may be a fatty acid or sorbitan.
- <u>A hydrophilic moiety</u> composed of an alcohol (-OH) and/or ethylene oxide groups linked together to form long polyoxyethylene chains.

Amphoteric surfactants

E.g., Glyceryl monostearate & glyceryl monooleate

Non-ionic surfactants

- Polyoxyethylene glycol ethers (**macrogols**): used as both o/w and w/o emulsifiers. Their water or oil solubility can be controlled by alterin both the length of the hydrocarbon chain and the length of the polyoxyethylene (POE) chain.

- Sorbitan esters (commerially known as **Spans®**): produced by esterifiation of one or more of the hydroxyl groups of sorbitan with a fatty acid. E.g., sorbitan monolaurate (Span 20), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60), sorbitan monooleate (Span 80).

- Polyoxyethylene sorbitan ester (polysorbates; also known as **Tweens®**): They are more hydrophilic polyoxyethylene derivatives of sorbitan esters. E.g., polyethylene 20 sorbitan monolaurate (polysorbate 20, Tween 20), polyethylene 20 sorbitan monopalmitate (polysorbate 40, tween 40), polyethylene 20 sorbitan monostearate (polysorbate 60, Tween 60), polyethylene 20 sorbitan monooleate (polysorbate 80, Tween 80).

Non-ionic surfactants

Table 27.4 HLB values for some pharmaceutical non-ionic surfactants

Commercial name	Pharmacopoeia name	HLB value
Span 85	Sorbitan trioleate	1.8
Span 80	Sorbitan oleate	4.3
Span 60	Sorbitan monostearate	4.7
Span 20	Sorbitan monolaurate	8.6
Brij 98	Polyoxyethylene 10 stearyl ether	12
Tween 60	Polysorbate 60 (polyoxyethylene 20 sorbitan monostearate)	14.9
Tween 80	Polysorbate 80 (polyoxyethylene 20 sorbitan oleate)	15
Cetomacrogol 1000	Macrogol cetostearyl ether	15.7
Tween 20	Polysorbate 20 (polyoxyethylene 20 sorbitan monolaurate)	16.7
	Potassium oleate	20
	Sodium dodecyl (lauryl) sulphate	40

Table 27.2 Synthetic surface active emulsifying agents

Class	Example	Structure	Emulsion type, route of administration
Anionic			
Alkyl sulphates	Sodium lauryl sulphate	$C_{12}H_{25}OSO_3^-Na^+$	o/w; topical
Monovalent salts of fatty acids	Sodium stearate	$C_{17}H_{35}COO^-Na^+$	o/w; topical
Divalent salts of fatty acid	Calcium oleate	$(C_{17}H_{35}COO^-)_2Ca^{++}$	w/o; topical
Cationic			
Quaternary ammonium compounds	Cetrimide	$C_{16}H_{33}N^+(CH_3)_3$	o/w; topical
Non-ionic			
Alcohol polyethylene glycol ethers	Cetomacrogol 1000	$CH_3(CH_2)_n(OCH_2CH_2)_mOH$ n = 15 or 17; m = 20-24	o/w; topical
Fatty acid polyethylene glycol esters	Polyethylene glycol 40 stearate	$CH_3(CH_2)_{16}CO(OCH_2CH_2)_{40}OH$	o/w; topical
Sorbitan fatty acid esters	Sorbitan monooleate (Span 80)	See text	w/o; topical
Polyoxyethylene sorbitan fatty acid esters	Polyoxyethylene sorbitan monooleate (Tween 80)	See text	o/w; topical, parenteral
Polymeric			
Polyoxyethylene/ polyoxypropylene block co-polymers	Poloxomers (Pluronic F-68)	$OH(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_a$	o/w; parenteral
Fatty amphiphiles			
Fatty alcohols	Cetyl alcohol	$C_{16}H_{33}O^-H^+$	w/o; topical
Fatty acids	Stearic acid	$C_{16}H_{33}COO^-H^+$	w/o; topical
Monoglycerides	Glyceryl monostearate		w/o; topical

II. Hydrocolloids: Multi-molecular adsorption and film formation

- Generally, they exhibit little surface activity.
- They adsorb at the oil/water interface, providing a protective sheath in the form of multilayers around the droplets. These multilayers are viscoelastic (gel-like) that resist rupture and, hence form mechanical barriers to coalescence.
- They also swell to increase the viscosity of the system (so that droplets are less likely to merge).
- Some of them (e.g., acacia, protein emulsifiers) have ionizable groups (e.g., amino & carboxylic acid groups) that impart a charge to the dispersed droplets, thus providing electrostatic repulsion as an additional barrier to coalescence.

II. Multi-molecular adsorption and film formation

➢ Classification of hydrocolloids

1. Polysaccharides

- Gums: acacia, tragacanth
- Alginate & cellulose derivatives

- They are susceptible to degradation e.g., depolymerization.
- Provide a good growth medium for microorganisms ➡ Preservatives must be used.
- They do not lower interfacial tension but stablize emulsions by the formation of thick multi-layered films.
- They also act as viscosity modifiers, increasing the consistency of the external phase ➡ Inhibit creaming & coalescence

II. Multi-molecular adsorption and film formation

➢ Classification of hydrocolloids

2. Phospholipids (lecithins)

- Animal: egg yolk
- Plant: soya bean oil.

- They are extensively used as o/w emulsifiers in parenteral an oral liquid emulsions.
- They are complex mixtures of neutral (e.g., phosphatidylcholine, phosphatidylethanolamine) and negatively charged phospholipids (e.g., phosphatidylserine, phosphatidylglycerol & phosphatidic acid).
- They stabilize emulsions by increasing the surface charge of droplets and formation of interfacial liquid crystalline phases.

II. Multi-molecular adsorption and film formation

➢ Classification of hydrocolloids

3. Steroidal emulsifiers

Animal: wool fat (lanolin), beewax & cholesterol.

- They are used as complex mixtures in dermatological emulsions (w/o) and for their emollient effect.
- They are prone to oxidation and hydrolysis ⇨ Anti-oxidants are needed in the emulsion.
- Some times they are modified to produce o/w emulsions e.g., a water soluble lanolin derivative (a product of lanolin reaction with ethylene oxide).

II. Multi-molecular adsorption and film formation

➢ Classification of hydrocolloids

4. Others

- Proteins: gelatin, casein
- Synthetic agents, e.g., carbomers (PEG and acrylic acid)

III. Solid particle adsorption

- **Description:** Finely divided solid particles that are wetted to some degree by both oil and water can act as emulsifying agents. This results from their being concentrated at the interface, where they produce a particulate film around the dispersed droplets to prevent coalescence.

- **Example of agents**:
- Bentonite ($Al_2O_3.4SiO_2.H_2O$), veegum (Magnesium Aluminum Silicate), hectorite, magnesium hydroxide, aluminum hydroxide and magnesium trisilicate: They are preferentially wetted by water and hence stabilize o/w emulsions.
- Carbon black and talc are preferentially wetted by oil and thus stabilize w/o emulsions.

Table 27.3 Natural emulsifying agents

Class	Example	Emulsion type; route of administration
Polysaccharide	Acacia	o/w; oral
	Methylcellulose	o/w; oral
Phospholipid	Purified lecithins	o/w; oral, parenteral
Sterol	Wool fat	w/o; topical
	Cholesterol and its esters	w/o; topical
Finely divided solid	Bentonite	o/w and w/o; topical
	Aluminium hydroxide	o/w, oral

Emulsifier selection: Hydrophile-lipophile balance (HLB)

- ✓ The solubility characteristics of the emulsifier define the type of emulsion formed. Therefore, polymers and surfactants that are predominantly hydrophilic will form o/w emulsions, whereas predominantly hydrophobic surfactants will form w/o emulsions.
- ✓ Surfactants contain both hydrophilic and lipophilic groups and, therefore it is the relative contribution of such groups that determine wheather the surfactant is predominantly hydrophilic or lipophilic (hydrophobic).
- ✓ The contribution of these groups to the overall solubility is commonly referred to as the HLB.
- ✓ HLB: a ratio scale that assigns a number to a surfactant, based on the contribution of the individual groups of the surfactant molecule. This number can be then used when selecting surfactants for the formulation of o/w or w/o emulsions.

Emulsifier selection: Hydrophile-lipophile balance (HLB)

- ✓ So, HLB expresses the strength of the polar portion relative to the non-polar portion of the molecule. Accordingly, the higher the higher the HLB number, the more hydrophilic or water soluble the surfactant, and the lower number the more lipophilic (oil soluble) the surfactant.

- ✓ HLB value of a surfactant can be estimated by Griffin's method for as follows:

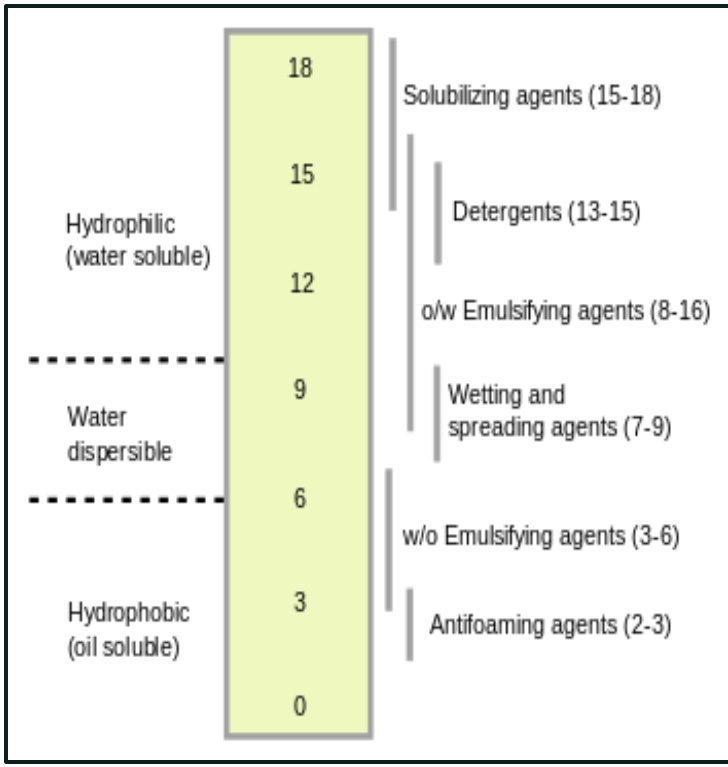
$$HLB = 20 * M_h/M$$

Where M_h is the molecular mass of the hydrophilic portion of the molecule, and M is the molecular mass of the whole molecule, giving a result on a scale of 0 to 50.

Emulsifier selection: Hydrophile-lipophile balance (HLB)

The HLB value can be used to predict the surfactant properties of a molecule:

- ✓ Surfactants exhibiting HLB values from 3-6 are used to produce w/o emulsions and are therefore termed w/o emulsifiers e.g., Span 80 (HLB 4.3).
- ✓ Surfactants exhibiting HLB from 8-16 are used to produce o/w emulsions and, thus termed o/w emulsifiers e.g., Tween 65 (HLB 10.5).
- ✓ HLB values of ionic surfactants are greater than 16 (up to 50).



Emulsifier selection: Hydrophile-lipophile balance (HLB)

- ✓ A mixture of surfactants give more stable emulsions than when singly used.
- ✓ The HLB value of the emulsifier blend giving a more stable emulsion is known as "the required HLB value" for that oil phase.
- ✓ The HLB of a mixture of surfactants, consisting of fraction x of emulsifier A and (1-x) of emulsifier B, can be calculated as follows:

$$HLB_{mix} = xHLB_A + (1-x)HLB_B$$

Emulsifier selection: Hydrophile-lipophile balance (HLB)

Table 27.5 The 'required' HLB values for oils and oil phase ingredients

Oil	O/W emulsion	W/O emulsion
Petrolatum	7-8	4
Liquid paraffin	10.5	4
Mineral oil, light	12	4
Castor oil	14	–
Lanolin, anhydrous	12	8
Beeswax	9	5
Cottonseed oil	6	–
Pine oil	16	–

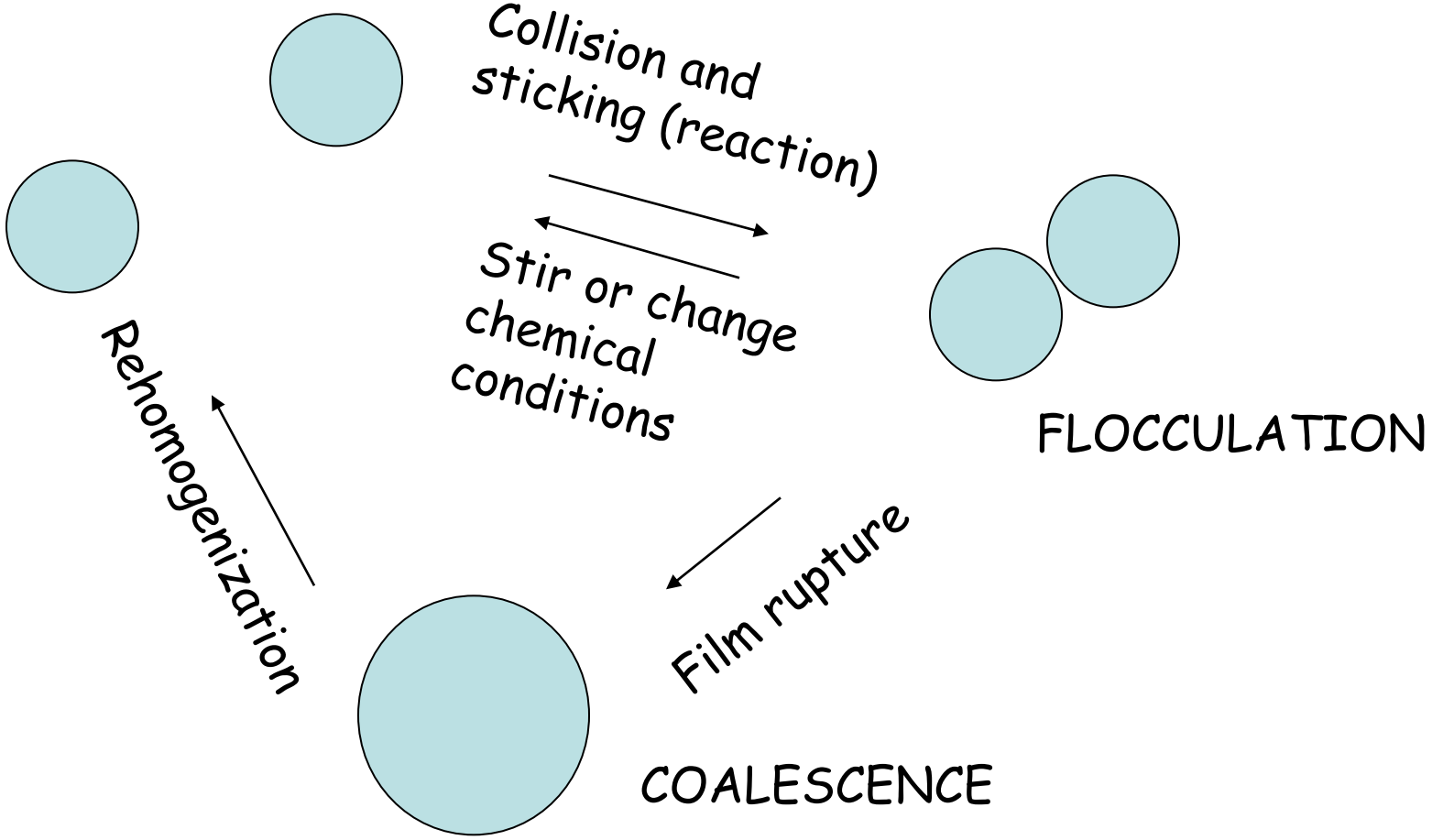
❑ Stability of emulsions:

A stable emulsion may be defined as a system in which globues retain their initial character (retain their diameter) and remain uniformly distributed throughout the contineous phase.

1.1. Flocculation: On standing, neighbouring globules of the dispersed phase come closer to each other and form colonies in the contineous phase (due to the interaction of attracrive and repulsive forces). However, the droplets may be redispersed by shaking and may lead to coalescence.

✓ The extent of flocculation depends on:
- Globules size distribution
- Charge on globules surface
- Viscosity of external medium (contineous phase)

Flocculation and Coalescence



❑ Stability of emulsions:

1.2. Creaming:

- On standing, creaming is the concentration of globules at the top or bottom of emulsion (due to density differencs between the two phases).
- Globules move either upwards (o/w emulsion) or sink downwards (w/o emulsion) leading to creaming.
- It can be observed by a differnce in color shade of both layers, and in both cases, emulsion can be easily redispersed by shaking.
- As in flocculation, droplets do not coalesce and can be redispersed by gentle shaking.

- Creaming is however undesirable pharmaceutically beacuse:

1. Increased possibility of coalescence of droplets
2. Creamed emulsion is inelegant
3. Risk of incorrect dose if not skaken enough.

❑ Stability of emulsions:

1.2. Creaming:

- ✓ Factors affecting creaming are best described by Stoke's law.

- ✓ Creaming can be reduced by:

1. Reducing globule size by homogenization
2. Increasing viscosity of dispersion medium
3. Reducing the difference in density.

❑ Stability of emulsions:

1.3. Coalescence:

The major fact preventing coalescence is the mechanical strength of the interfacial film.

- Is followed by the creaming stage wherein droplets merge froming larger droplets (irreversible process). This process continues until the emulsion breaks (cracks).
- In this process, the emulsifier film around globules is destroyed to a certain extent.
- This step is recongized by increased size but reduced number of globules.

- Coalescence is observed due to:
  - Insufficient amount of the emulsifying agent.
  - Altered partitioning of the emulsifier.
  - Incompatibilities between emulsifiers.

❑ Stability of emulsions:

1.4. Cracking (breaking):

- It is indicated by complete separation of oil and the aqueous phase.
- It is an irreversible process that simple mixing fails to resuspend globules into a uniform emulsion.
- In breaking, the protective sheath around globules is completely destroyed.

❑ Stability of emulsions:

1.4. Cracking (breaking)

Factors that cause emulsion cracking:

- The addition of a chemical that is incompatible with the emulsifier e.g., addition of a cationic surfactant to an emulsion stabilized with an anionic surfactant; addition of electrolytes to emulsion stabilized with opposite ionic surfactants.
- Bacterial growth: Protein and polysaccharide emulsifiers are excellent media for bacterial growth.
- Temperature fluctuations: Protein emulsfifiers may be denatured and the solubility of non-ionic surfactants change with a rise in temperature (heating above 70C destroys most emulsifiers). Freezing will also crack emulsion because the ice crystals formd distrup the interfacial film around droplets.

❑ Stability of emulsions:

1.5. Phase inversion:

- This involves the change of emulsion type from o/w to w/o and viceversa.
- When we intend to prepare an o/w emulsion and if the final emulsion turns out to be w/o, it can be termed as a sign of instability.

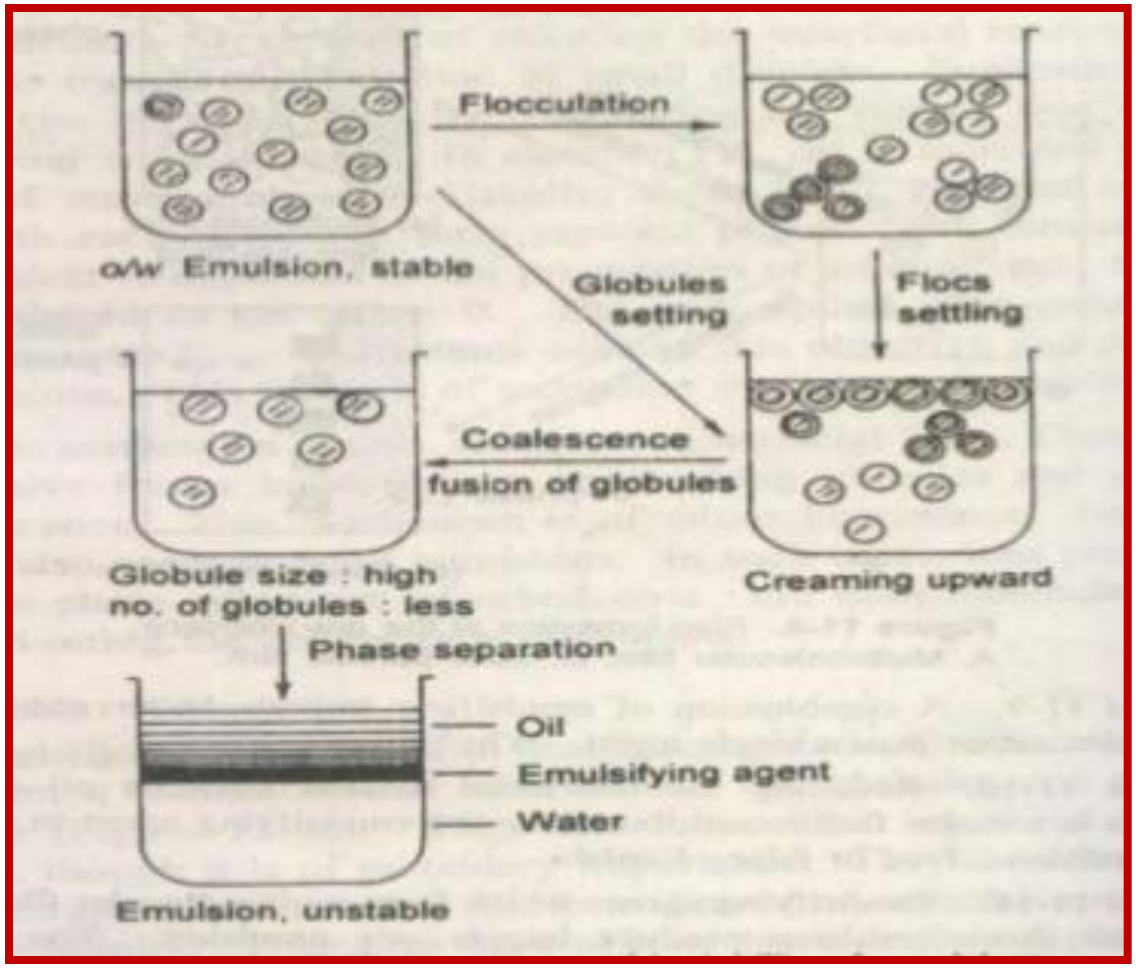
❑ Stability of emulsions:

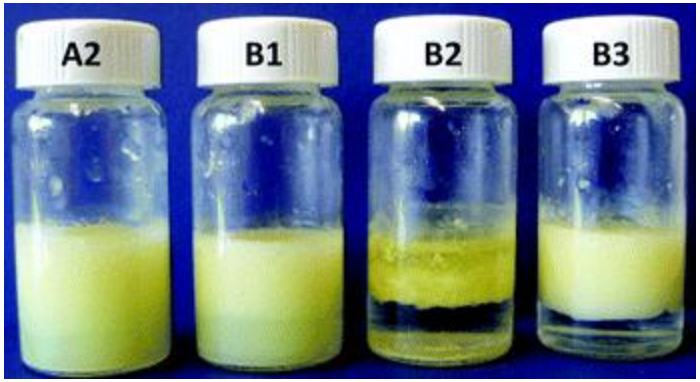
1.5. Phase inversion

Reasons of phase inversion:

- Increasing the dispersed phase concentration above the accepted value: the most suitable range of dispersed phase concentration is 30-60% (o/w 74%, w/o 40%).
- Adding substances that alter the solubility of the emulsifier (e.g., precipitation of hydrophilic colloids in the presence of alcohol).
- Suppression of ionization for ionic surfactants by adding subbstances with opposite charges (e.g., addition of $CaCl_2$ into o/w emulsion formed by sodium stearate can be inverted to w/o).
- Phase volume ratio.
- Temperature of the system: ↑Temperature of o/w makes the emulsifier more hydrophobic and the emulsion may invert to w/o (e.g., temperature-induced breakage of H-bonds of polysorbates, which are responsible for hydrophilicity, will lower HLB value).

❑ Physical instability of emulsions:





❑ Physical instability of emulsions:

Rate of coalescence, which is a measure of emulsion stability, depends on:

(a) **Physical nature of the interfacial surfactant film**

(b) **Electrical or steric barrier**

(c) **Viscosity of the continuous phase**

Viscosity may be increased by adding natural or synthetic thickening agents

(d) **Phase volume ratio**

As volume of dispersed phase ↑, stability of emulsion ↓

(eventually phase inversion can occur)

(e) Size distribution of droplets

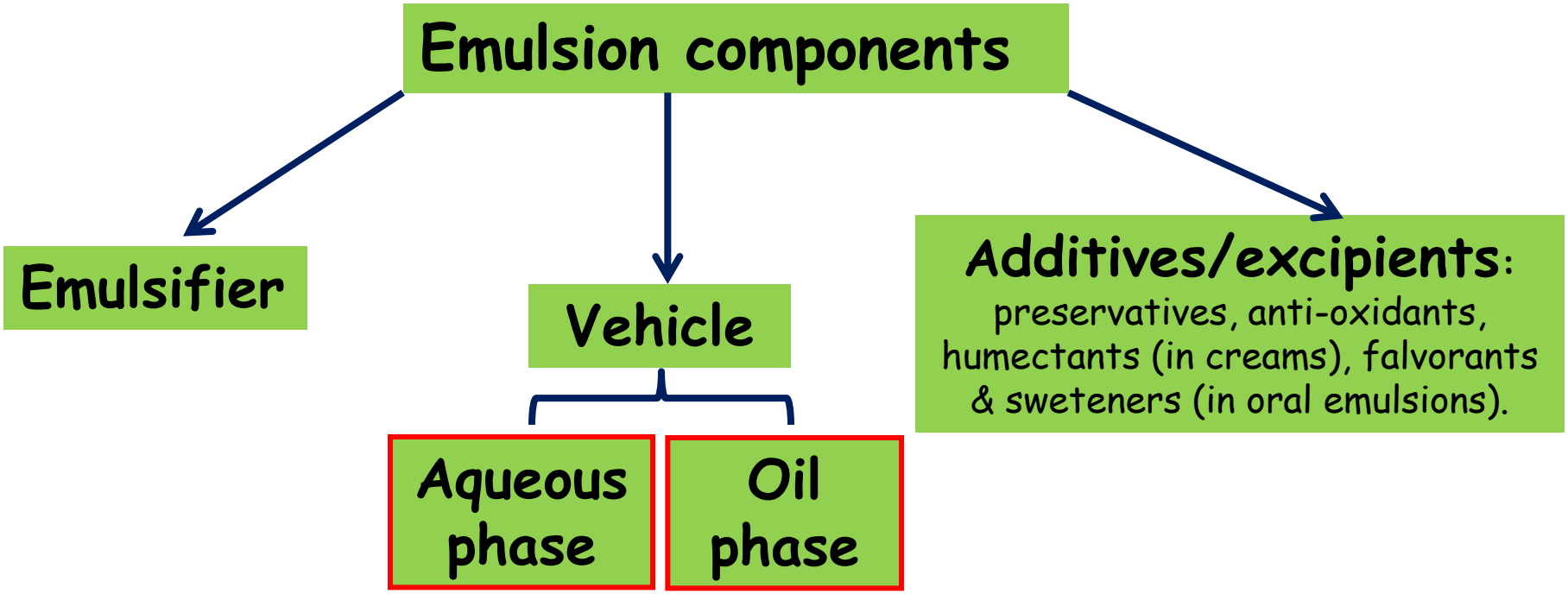
Emulsion with a fairly uniform size distribution is more stable. On the other hand, controlling droplet size of emulsions is very important especially when emulsions are intended for parenteral administration so that the formation of emboli can be avoided.

(f) Temperature

- ✓ Temperature ↑, usually emulsion stability ↓
- ✓ Temperature affects interfacial tension, solubility of surfactant and viscosity of liquid.

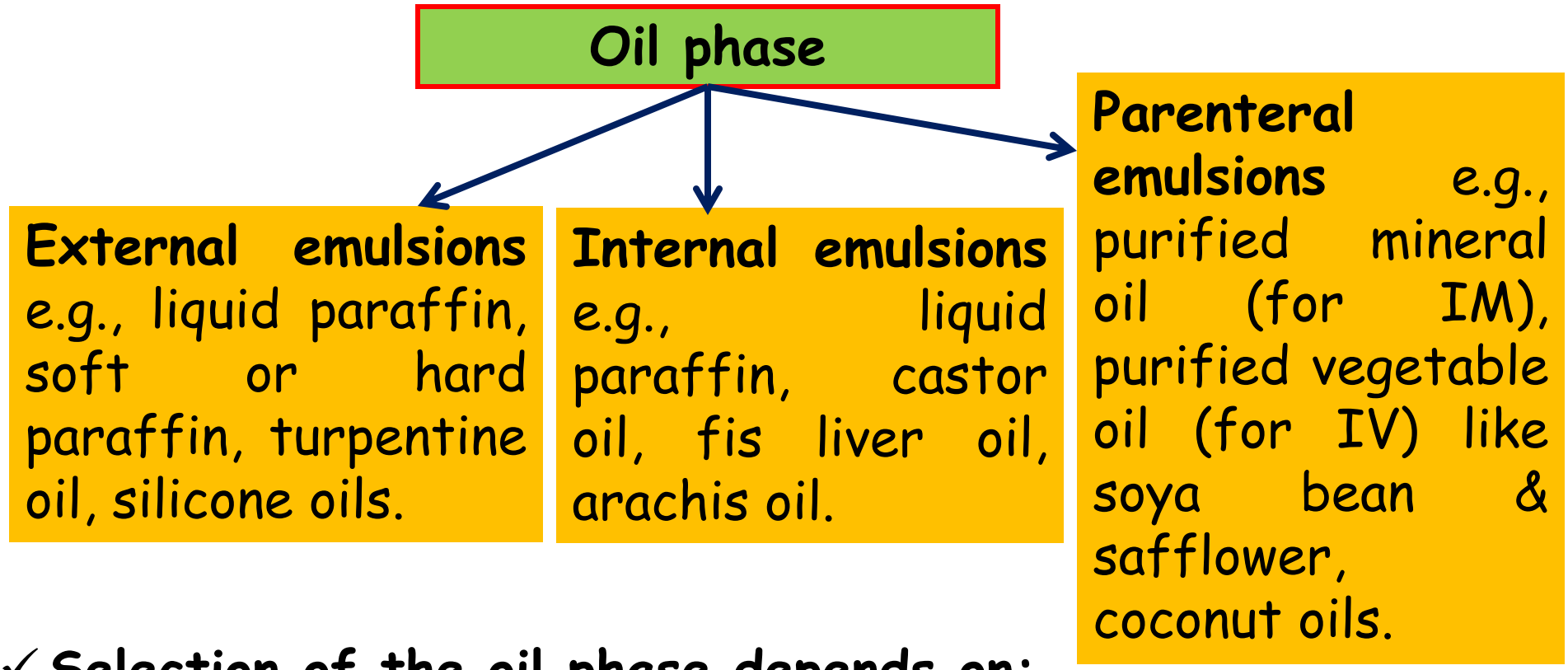
Formulation of emulsions

- ✓ When formulating a pharmaceutical emulsion, the choice of oil, emulsifier, and emulsion type (w/o, o/w, or multiple emulsions) will depend on the route of administration and ultimate therapeutic use.



Aqueous and oil phases are formulated separately

Formulation of emulsions



✓ **Selection of the oil phase depends on:**

- The desired physical properties of the emulsion
- The miscibility of the oil and aqueous phase.
- The solubility of drug (if present in the oil phase)
- The desired consistency of the final emulsion.

Formulation of emulsions

✓ Prolems with oils used in emulsions:

- Some of them, particularly unsaturated oils of vegetable origin, are liable to auto-oxidation and become rancid.

Additives/excipients

Humectants: often added to dermatological emulsions e.g., glycerol, propylene glycol, sorbitol (up to 5%).

Preservatives e.g., phenoxyethanol, benzoic acid, parabenzoates.

- Preservatives should be in aqueous phase.
- They must not bind to other components of the emulsion.

Anti-oxidants: added to prevent oxidation of oil, emulsifier and probably the drug during storage e.g., Butylated hydroxyanisole, butylated hydroxytoluene (up to 0.2%), alkyl gallates (0.001-0.1%), alpha tocopherol.

Important message:

The type of emulsifiers used dictate the stability and type of emulsion produced.