EMULSIONS

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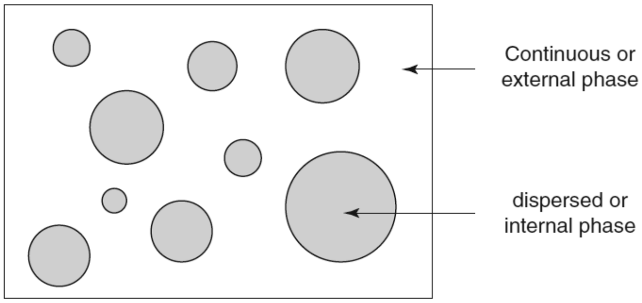
Introduction

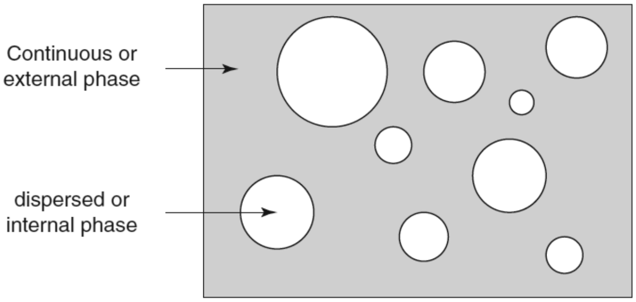
- An emulsion is a dispersion of two immiscible (or partially miscible) liquids, one of which is distributed uniformly in the form of fine droplets (the dispersed phase) throughout the other (the continuous phase).

Types of emulsion

- Oil-in-water emulsions (o/w): contain oil droplet dispersed in water

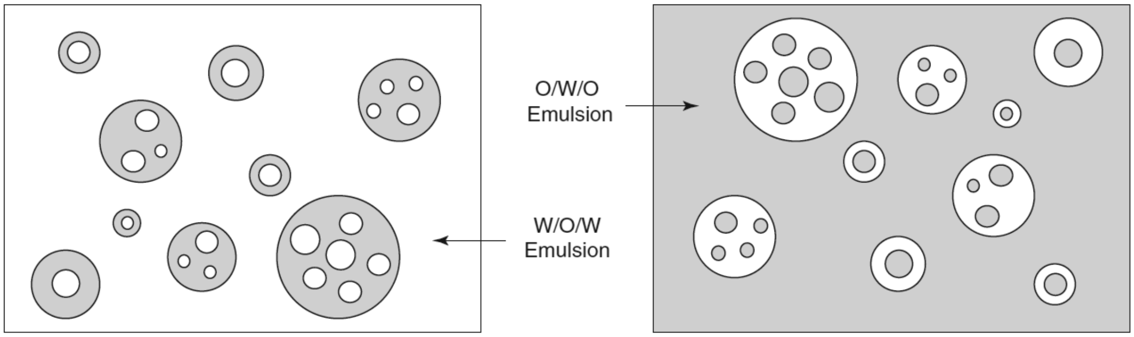


- Water-in-oil emulsions (w/o): contain water droplets dispersed in oil



Introduction

Multiple emulsions can also be formed from oil and water by the re-emulsification of an existing emulsion to form two disperse phases.
For example oil-in-water-in-oil (o/w/o) and (w/o/w).



Shaded area represents the oil.

Pharmaceutical emulsions

Oral o/w emulsion:

For the local treatment of constipation (e.g. mineral oil, castor oil) and as oral food supplements (e.g. fish liver oils and vegetable oils) in a more palatable and acceptable form.

For the oral delivery of drugs and vitamins of low aqueous solubility.

Sterile intravenous lipid o/w emulsions

- Used as a source of calories and essential fatty acids for debilitated patients (e.g Intralipid®)
- Used as drug carriers for drugs of limited water solubility; such as diazepam and vitamin K.

***Advantages**:* a higher drug payload, lower toxicity, less pain on injection and protection of labile drugs by the oily environment.

Pharmaceutical emulsions

SC or IM w/o emulsions:

Used to prolong the delivery of water-soluble drugs (e.g antigens), they are sometimes difficult to inject because of the high viscosity of the oily continuous phase.

(multiple w/o/w emulsions?.?). To reduce pain..

Dermatological w/o and w/o emulsions:

w/o emulsions tend to be greasy.

- w/o emulsions do not mix well with aqueous wound exudates and are also sometimes difficult to wash of the skin but they hydrate the skin by occlusion.
- o/w lotions and creams mix well with tissue exudates and are more easily removed by washing.

Emulsion formation

- When two *immiscible* liquids are placed together in a container, they will form layers with a minimum area of contact (interfacial area) between the two liquids, in this state, the surface free energy, *G*, is at a minimum

- On mixing or mechanical agitation, both liquids will form droplets of different sizes, increasing the interfacial area between the liquids with a corresponding increase in the surface free energy of the system.

- Emulsions are therefore *thermodynamically* ***unstable***.

Emulsion formation

Emulsification result of two competing processes that occur simultaneously:

1. The first process requires energy input to disrupt the bulk liquids and form fine droplets and increasing the free energy of the system.
2. The second process, which involves the coalescence of droplets, occurs spontaneously to reduce the interfacial area and minimize the free energy.

Since emulsions are thermodynamically unstable, they will revert back to separate oil and water unless kinetically stabilized by the addition of *emulsifying agents.*

Emulsion formation

The choice of oil, emulsifier and emulsion type (o/w, w/o or multiple emulsion) when formulating a pharmaceutical emulsion depends on:

1. The route of administration and its clinical use.
2. The emulsion stability and therapeutic response (by optimizing the droplet size distributions and rheology).
3. The potential toxicity of all the excipients.
4. The cost and possible chemical incompatibilities in the final formulation.

Selection of the oil phase

- The oil used in the preparation of pharmaceutical emulsions may be the drug itself or it may function as a carrier for a lipid-soluble drug.
- For externally applied emulsions: oils based on hydrocarbons are used (Liquid paraffin, either alone or combined with soft or hard paraffin) as a vehicle for the drug, and for the **occlusive** characteristics.
- Turpentine oil, benzyl benzoate and silicone oils are examples of other externally applied oils.
- In oral emulsions: the most widely used medicinal oils are castor oil and liquid paraffin, which are non-biodegradable and provide a local laxative effect in the gastrointestinal tract.
- Vegetable oils are also used as drug carriers as they are absorbed in the gastrointestinal tract.

Selection of the oil phase

- Emulsions for parenteral administration:

1. The choice of oil is limited by toxicity.
2. Purified mineral oil is used in some water-in-oil depot preparations or intramuscular injection, but it is too toxic to be used in the intravenous emulsions.
3. Purified vegetable oils used in lipid emulsions for parenteral nutrition and as intravenous carriers for drugs of limited aqueous solubility.

Selection of the oil phase

Vegetable oils used in parenteral products:

- Mixtures of long-chain triglycerides containing C12-C18 saturated and unsaturated fatty acid moieties, mainly oleic, linoleic, palmitic and stearic acids.
- Medium chain triglycerides which contain shorter fatty acid moieties (~ C6-C10) which provide a more rapidly available source of energy, as well as enhancing the solubilizing capacity for lipid soluble drugs.
- Mixtures containing both long and medium chain triglycerides.

Selection of the emulsifying agent (emulsifier)

- Emulsifiers are used to control emulsion stability during a shelf life that can vary from days to months or years.
- In practice, combinations of emulsifiers rather than single agents are generally used.
- The choice of emulsifier depends on:

1. The type of emulsion to be prepared,
2. Emulsifier toxicity (or irritancy if applied to the skin) and potential cost and availability,
3. The final clinical use of the emulsion (by their influence on droplet size distribution, and the charge and surface properties of the droplets).

Function of emulsifying agents

- Emulsifiers generally impart time-dependent stability by the formation of:
- a *mechanical* or *electrostatic barrier* at the droplet interface (an interfacial film) or in the external phase (a *rheological barrier*).
- The interfacial film may increase droplet-droplet repulsion by the introduction of electrostatic or steric repulsive forces to counteract the van der Waals forces of attraction.

Function of emulsifying agents

- The interfacial film may also provide a mechanical barrier to prevent droplet coalescence
- Surfactant emulsifiers lower the interfacial tension between the oil and water.
- Emulsifiers that thicken the external phase but do not form an interfacial film are described as *auxiliary emulsifiers.*

Emulsion type

- The type of emulsion that forms (whether o/w or w/o or multiple emulsion) and droplet size distribution depend on :
  - The **method** of preparation (energy input),
  - the relative **volumes** of the oil and water phases and the **chemical nature** o the emulsifying agent.
  - With the inclusion of an emulsifier, the type of emulsion that forms is no longer a function of phase volume alone, but also depends on the **relative solubility of the emulsifier in the oil and water phases**.
- In general, the phase in which the emulsifying agent is more soluble (or in the case of solids, more easily wetted by) will form the continuous phase. Thus, hydrophilic surfactants and polymers promote o/w emulsions and lipophilic emulsifiers (with low HLB, see ‘Emulsifier selection’ section below) promote w/o systems.
- In practice, pharmaceutical emulsions usually contain 10-30% disperse phase.

Classification of emulsifying agents

1. Synthetic or semi-synthetic surface active agents and polymers

2. Naturally occurring materials and their derivatives.

Surface active agents and polymers

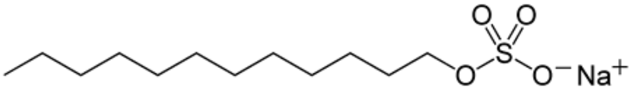
- Surface active agents are classified as ionic (i.e. anionic or cationic) or non-ionic according to their characteristics on dissociation.
- The majority of the synthetic surfactants are **toxic** and **irritant** to the skin and the mucous membranes of the gastrointestinal tract.
- In general, cationic surfactants are the most toxic and irritant and non-ionic surfactants the least.
- Ionic synthetic surfactants are used only in external **topical** preparations.

Anionic surfactants

- Anionic surfactants dissociate at high pH to form a long-chain anion with surface activity.
- Emulsifying properties are lost and emulsions are unstable in acid conditions and in the presence of cationic materials.

1. Alkyl sulphates. Sodium lauryl sulphate (SLS): is the most widely used surfactant in topical products.

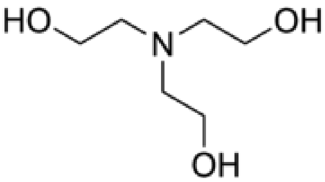
- It is a weak emulsifier of the o/w type, but forms a powerful o/w blend when it is used in conjunction with cetostearyl alcohol.



Anionic surfactants

2. Monovalent salts of fatty acids.

Consist of the alkali salts of long chain fatty acids, e.g. C17H35COO^{-} X^{+}, where X may be Na, K, NH4 or triethanolamine (TEA).



Triethanolamine (TEA)

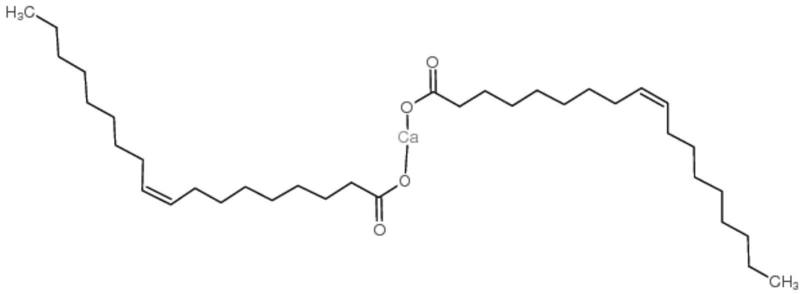
- Alone, these ‘soaps’ promote unstable, mobile o/w emulsions, but when combined with fatty acids they form powerful o/w emulsifying blends that stabilize The dermatological products.

Anionic surfactants

3. <u>Divalent salts of fatty acids.</u>

Calcium salts of fatty acids containing two hydrocarbon chains, form w/o emulsions due to their limited solubility in water.

e.g. calcium oleate in zinc cream is formed in situ from the interaction between oleic acid and calcium hydroxide.



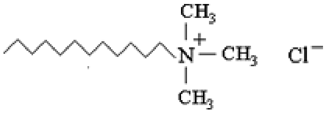
Cationic surfactants

Cationic surfactants dissociate at low pH to form a long-chain surface-active cation.

Emulsions containing cationic surfactant as emulsifier are unstable at high pH and in the presence of anionic materials including anionic surfactants and polymers.

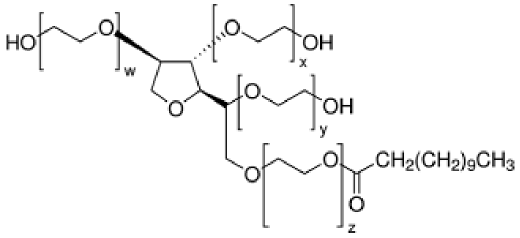
1. <u>Quaternary ammonium compounds</u>:

- They also have antimicrobial properties.
- Cetrimide (cetyltrimethyl ammonium bromide) is blended with cetostearyl alcohol to form cationic emulsifying wax which is the mixed emulsifier used in cetrimide cream.



Non-ionic surfactants

- Non-ionic surfactants are useful as emulsifiers because they are less toxic and irritant than ionic surfactants, and therefore a limited number (e.g. polysorbate 80; Tween® 80) are used in parenteral and oral products.
- Nonionic surfactants do not ionize to any extent and thus are more resistant than ionic surfactants to changes in pH and the presence of electrolytes and polyvalent ions.



Non-ionic surfactants

Most non-ionic surfactants are based on:

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

Non-ionic surfactants

1. Polyoxyethylene glycol ethers (macrogols).

- Condensation products of fatty alcohols with hydrocarbon chain lengths from C12-C18 and polyethylene glycol.
- They are used as both o/w and w/o emulsifiers as their oil and water solubility can be controlled by altering both the length of the hydrocarbon chain and the length of the polyoxyethylene (POE) chain.
- The most widely used emulsifier in this class is cetomacrogol 1000 which is used combined with cetostearyl alcohol to stabilize o/w lotions and creams

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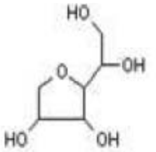
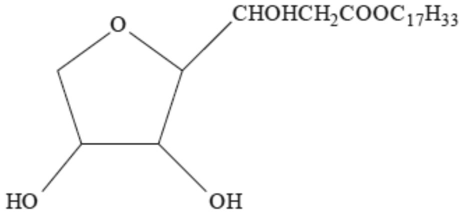
Non-ionic surfactants



Sorbitol

2. Sorbitan esters. (Spans®)

- Produced by the esterification of one or more of the hydroxyl groups of sorbitan with a fatty acid.
- Various fatty acids are combined resulting in a range of products, e.g. sorbitan monolaurate (Span 20), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60), sorbitan monooleate (Span 80).
- Sorbitan esters are hydrophobic in nature and by themselves produce w/o emulsions.

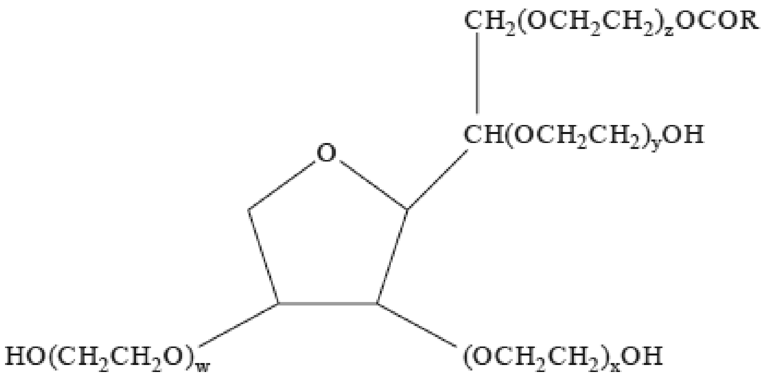


Non-ionic surfactants

3. Polyoxyethylene sorbitan esters (polysorbates), (Tweens®).

- The polysorbates are more hydrophilic polyoxyethylene derivatives of the sorbitan esters. e.g. polyethylene 20 sorbitan monolaurate (polysorbate 20).
- Range of polysorbate surfactants of differing oil and water solubility are available by controlling the fatty acid and the length of the polyethylene glycol chains in the molecule.
- Polysorbates are able to stabilize both w/o and o/w emulsions, depending on their HLB value.

Tween 80



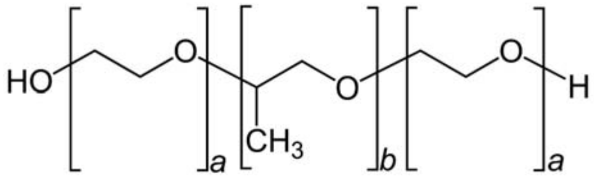
Fatty amphiphiles

1. Fatty alcohols and fatty acids.

When used alone, they are weak w/o emulsifiers, in the presence of ionic or non-ionic surfactants, they are very powerful o/w blends.

Polymeric surfactants

- The poloxamers (also known as Pluronics®) are a series of neutral synthetic polyoxyethylene-polyoxypropylene block co-polymers which are used either alone, or as auxiliary emulsifiers with lecithin in small-volume parenteral injections.
- Poloxamer 188 (1800 molecular mass of the **polyoxypropylene** core, 80% **polyoxyethylene** flankes) is resistant to breakdown during autoclave sterilization and its combination with lecithin may stabilize the emulsion.

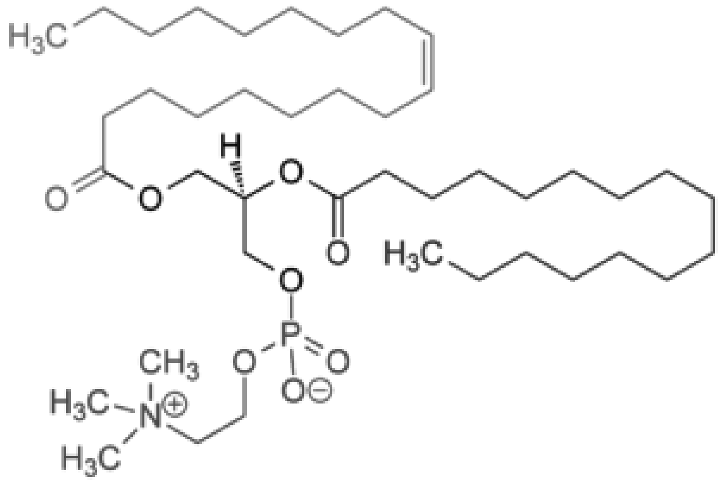


Natural macromolecular materials

1. Phospholipids

- Purified lecithins are natural surfactants derived from egg yolk or soya bean oil.
- They are used extensively as o/w emulsifiers in parenteral and oral lipid emulsions.
- Lecithins are composed of complex mixtures of neutral and negatively charged phospholipids of which the major components are phosphatidylcholine and phosphatidylethanolamine (~ 90%)
- The lecithins stabilize lipid emulsions by increasing the surface charge of the droplets.

- Licithin



Natural macromolecular materials

2. Hydrophilic colloids polysaccharides

- Polysaccharides, including gums, such as acacia and tragacanth, and alginate and cellulose derivatives are hydrophilic colloids that are used as emulsifying agents in oral preparations.
- They are susceptible to degradation, in particular by depolymerization.
- Polysaccharides needs preservation of emulsions containing them.
- Some polysaccharides including acacia and purified and semisynthetic derivatives of methylcellulose, stabilize o/w emulsions by the formation of thick multilayered films.

Natural macromolecular materials

3. Steroidal emulsifiers

- Wool fat (lanolin), wool alcohols (lanolin alcohols), beeswax and cholesterol.
- They are generally complex mixtures of cholesterol, long-chain alcohols and related sterols.
- Used in dermatological emulsions, such as creams, as w/o emulsifiers, and for their emollient properties.
- Non-ionic water soluble lanolin derivatives promote the formation of o/w emulsions.

Table 27.2 Synthetic surface-active emulsifying agents

Class	Example	Structure	Emulsion type	Route of administration
Anionic				
Alkyl sulfates	Sodium lauryl sulfate	$C_{12}H_{25}OSO_3^-Na^+$	Oil in water	Topical
Monovalent salts of fatty acids	Sodium stearate	$C_{17}H_{35}COO^-Na^+$	Oil in water	Topical
Divalent salts of fatty acid	Calcium oleate	$(C_{17}H_{35}COO^-)_2Ca^{2+}$	Water in oil	Topical
Cationic				
Quaternary ammonium compounds	Cetrimide	$C_{16}H_{33}N^+(CH_3)_3$	Oil in water	Topical
Nonionic				
Alcohol polyethylene glycol ethers	Cetomacrogol 1000	$CH_3(CH_2)_n(OCH_2CH_2)_mOH$ $n = 15$ or 17; $m = 20–24$	Oil in water	Topical
Fatty acid polyethylene glycol esters	Polyethylene glycol 40 stearate	$CH_3(CH_2)_{16}CO(OCH_2CH_2)_{40}OH$	Oil in water	Topical
Sorbitan fatty acid esters	Sorbitan monooleate (Span 80)	See the text	Water in oil	Topical
Polyoxyethylene sorbitan fatty acid esters	Polyoxyethylene sorbitan monooleate (Tween 80)	See the text	Oil in water	Topical, parenteral
Polymeric				
Polyoxyethylene–polyoxypropylene block copolymers	Poloxomers (Pluronic F-68)	$OH(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_a$	Oil in water	Parenteral
Fatty amphiphiles				
Fatty alcohols	Cetyl alcohol	$C_{16}H_{33}O^-H^+$	Water in oil	Topical
Fatty acids	Stearic acid	$C_{16}H_{33}COO^-H^+$	Water in oil	Topical
Monoglycerides	Glyceryl monostearate		Water in oil	Topical

3-Solid particles

- Finely divided solid particles stabilize emulsions if they are preferentially wetted by one phase and possess sufficient adhesion for one another such that they form a film around the dispersed droplets. So it give a mechanical barrier against droplet coalescence.
- If the particles are preferentially wetted by the aqueous phase, an o/w emulsion forms whereas if the solid is preferentially wetted by oil, a w/o emulsion is produced.
- Emulsions stabilized by solid particles are described as **pickering** emulsions or **surfactant- free** emulsions.

e.g. Magnesium hydroxide.

- Solid particles may also act as viscosity modifiers.

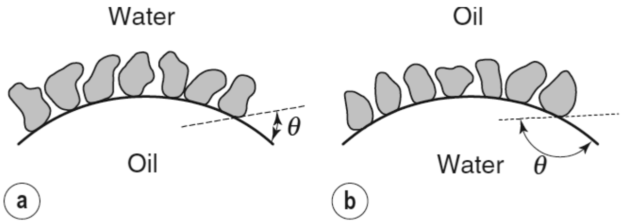


Fig. 5.15 • Emulsion stabilization by solid particles. **(a)** Preferential wetting of the solid by water, leading to an oil-in-water emulsion. **(b)** Preferential wetting of the solid by oil, leading to a water-in-oil emulsion.

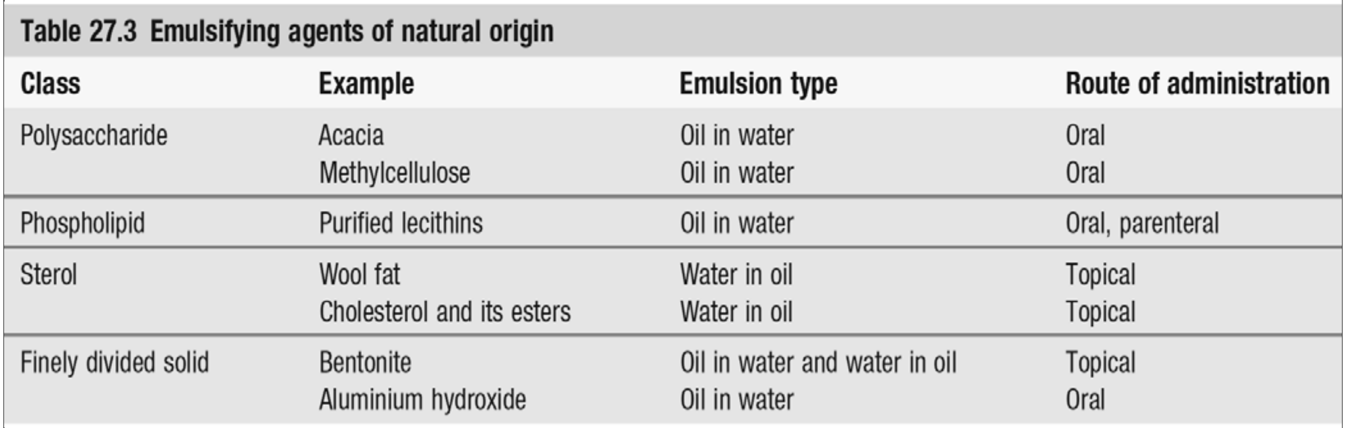


Table 27.3 Emulsifying agents of natural origin

Class	Example	Emulsion type	Route of administration
Polysaccharide	Acacia	Oil in water	Oral
	Methylcellulose	Oil in water	Oral
Phospholipid	Purified lecithins	Oil in water	Oral, parenteral
Sterol	Wool fat	Water in oil	Topical
	Cholesterol and its esters	Water in oil	Topical
Finely divided solid	Bentonite	Oil in water and water in oil	Topical
	Aluminium hydroxide	Oil in water	Oral

Emulsifier selection

The hydrophile -lipophile balance (HLB) method:

- Provides a systematic method of selecting mixtures of emulsifying agents to produce physically stable emulsions.
- Each surfactant is allocated an HLB number between 0 and 20 which expresses numerically the **size** and **strength** of the **polar portion** relative to the non-polar portion of the molecule.
- The higher the HLB number, the more hydrophilic the surfactant, and the lower the number, the more lipophilic the surfactant.
- The HLB values of ionic surfactants are much higher (up to 50) as they are based on ionization properties.

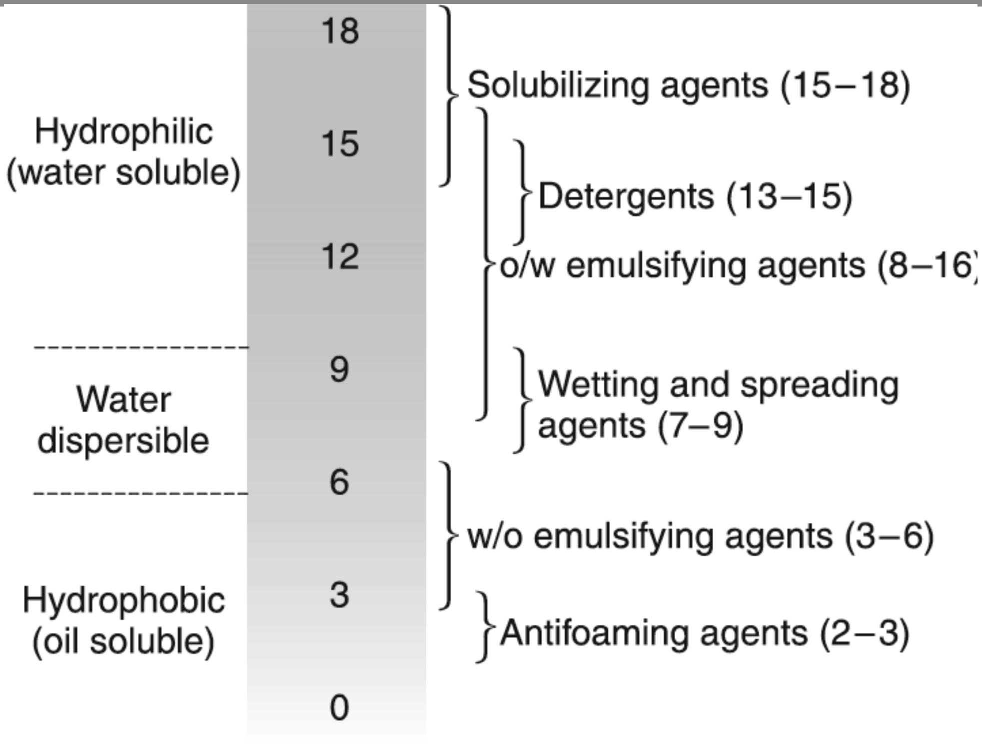


Fig. 5.16 • Hydrophile–lipophile balance scale showing classification of surfactant function. *o/w,* Water-in-oil; *w/o,* oil-in-water.

Determination of ‘required HLB’ value

- The HLB value of the emulsifier blend giving the most stable emulsion is known as the ‘required HLB value’ for that oil phase.
- The HLB value required to most effectively form an emulsion for a range of individual oils, fats and waxes may be obtained from the literature.
- If a mixed emulsifier system is used in a formulation and the HLB values of the individual components in an oily mixture are known, the required HLB can be calculated theoretically from the proportions of each component in the oil phase.

Determination of ‘required HLB’ value

Individual oils are given two ‘required’ HLB numbers – a high value to form an o/w emulsions and a low one to form w/o emulsions, respectively.

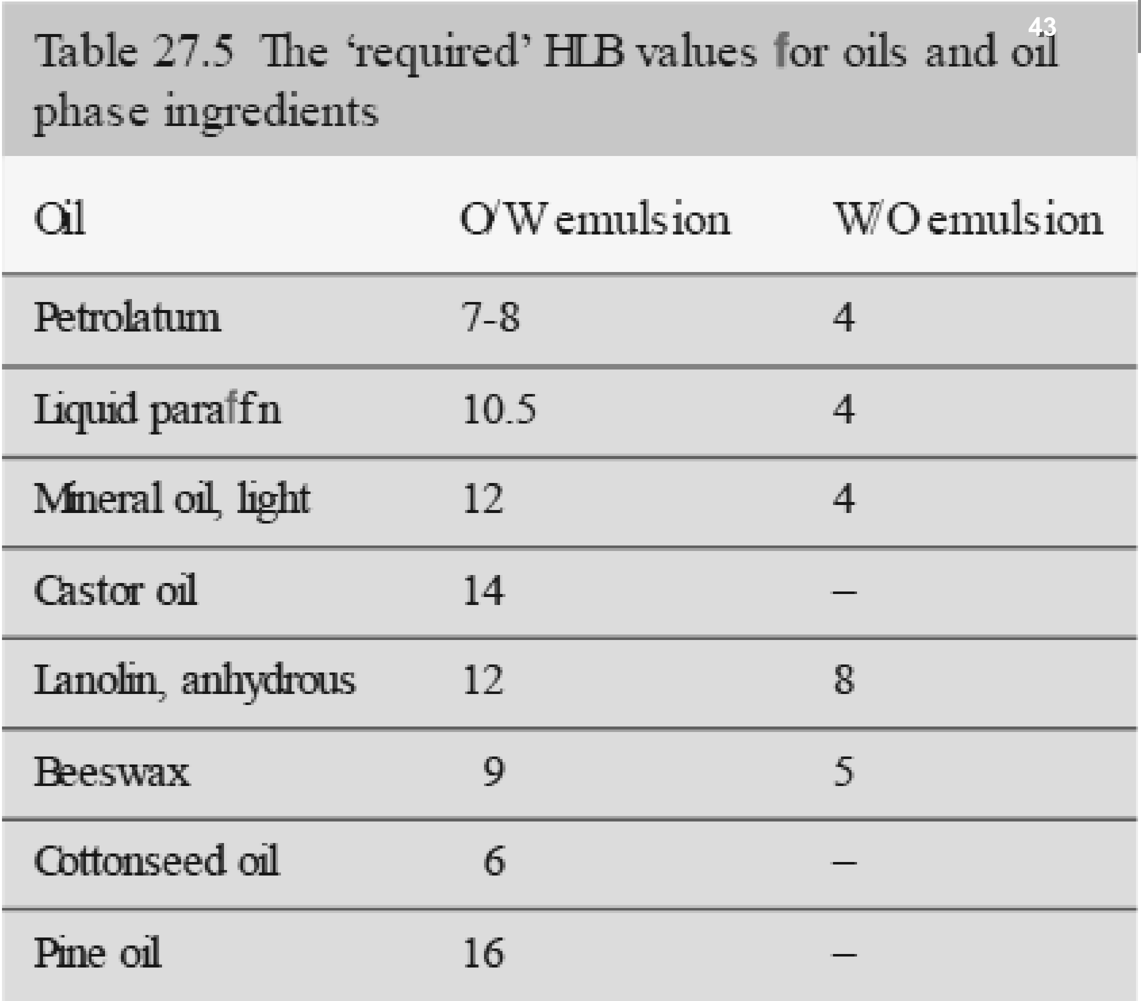


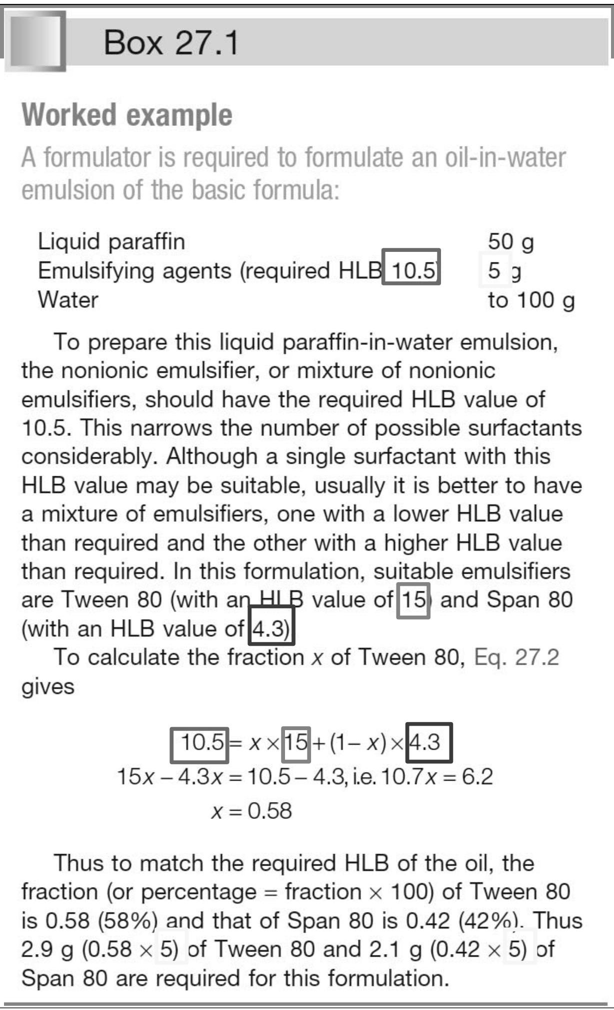
Table 27.5 The 'required' HLB values for oils and oil phase ingredients

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	–

Calculation of ratio of emulsifier to produce a particular required HLB value

- The HLB values are additive if the amount of each in a blend is taken into account.
- Thus, blends of high and low HLB surfactants can be used to obtain the required HLB of an oil.
- The HLB of the mixture of surfactants, consisting of fraction x of A and (1 − x) of B, is assumed to be the mean of the two HLB numbers, i.e.:

$$\mathbf{HLB_{mixture} = \mathit{x}HLB_A + (1 - \mathit{x})HLB_B}$$



Box 27.1

Worked example

A formulator is required to formulate an oil-in-water emulsion of the basic formula:

Liquid paraffin	50 g
Emulsifying agents (required HLB $\boxed{10.5}$	5 g
Water	to 100 g

To prepare this liquid paraffin-in-water emulsion, the nonionic emulsifier, or mixture of nonionic emulsifiers, should have the required HLB value of 10.5. This narrows the number of possible surfactants considerably. Although a single surfactant with this HLB value may be suitable, usually it is better to have a mixture of emulsifiers, one with a lower HLB value than required and the other with a higher HLB value than required. In this formulation, suitable emulsifiers are Tween 80 (with an HLB value of $\boxed{15}$) and Span 80 (with an HLB value of $\boxed{4.3}$)

To calculate the fraction x of Tween 80, Eq. 27.2 gives

$$\boxed{10.5} = x \times \boxed{15} + (1 - x) \times \boxed{4.3}$$
$$15x - 4.3x = 10.5 - 4.3, \text{ i.e. } 10.7x = 6.2$$
$$x = 0.58$$

Thus to match the required HLB of the oil, the fraction (or percentage = fraction × 100) of Tween 80 is 0.58 (58%) and that of Span 80 is 0.42 (42%). Thus 2.9 g (0.58 × 5) of Tween 80 and 2.1 g (0.42 × 5) of Span 80 are required for this formulation.

Other excipients

Preservatives

- The aqueous continuous phase of an oil-in-water emulsion can produce ideal conditions for the growth of bacteria, molds and fungi.
- Water-in-oil emulsions are less susceptible to contamination because the aqueous phase is enclosed and protected by the oil.
- An ideal preservative should exhibit a wide spectrum of activity against bacteria, yeasts and moulds and it should be free from toxic, irritant or sensitizing Activity.

Other excipients

Preservatives

- Phenoxyethanol, benzoic acid, and the parabenzoates are used as preservatives in oral and topical emulsions.

- The preservative will partition between the oil and aqueous phases, with the oil phase acting as a reservoir.

- Aqueous pH is an additional factor to be considered, as a sufficient concentration of the unionized form must be present to ensure proper preservation.

Antioxidants

- Antioxidants are added to some emulsions to prevent oxidative deterioration of the oil, emulsifier or the drug itself during storage.

e.g. butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) at concentrations up to 0.2%,

Humectants

Humectants, such as propylene glycol, glycerol and sorbitol at concentrations **up to 5%**, are added to dermatological preparations to reduce the evaporation of the water from the emulsion during storage and use.

However, high concentrations may also remove moisture from the skin, causing dryness.

Emulsion properties

1. <u>Identification of emulsion type:</u>

Water or oil miscibility:

- An emulsion will only mix freely with a liquid that is miscible with its continuous phase.
- Thus, a small quantity of water dropped onto the surface of an o/w emulsion will immediately mix with the external phase and disappear, whereas the water droplets will remain on the surface of a w/o emulsion.

Emulsion properties

- *Filter paper test*.

The test involves putting a few drops of emulsion onto filter paper. If the droplet spreads rapidly into the filter paper, it is an o/w emulsion.

- *Conductivity measurements*.

o/w emulsions have a much higher electrical conductivity than w/o emulsions.

- *Dye solubility tests.*

These tests involve blending either a water soluble dye or an oil soluble dye with the emulsion. If a water soluble dye is used, an o/w emulsion will be evenly colored, whereas a w/o emulsion will be much paler in appearance.

Emulsion properties

<u>2. Droplet size distribution:</u>

- Large droplets have a greater tendency to cream and coalesce, and a broad particle size distribution encourages an increase in droplet size by Ostwald ripening.
- Thus, the most physically stable pharmaceutical emulsions generally have **small droplets** and **narrow size distributions**.

- For **oral** emulsions, gastrointestinal absorption increases as droplet sizes decreases, this may give adverse clinical effects with laxative oils that are used for a local effect and are toxic if absorbed.

Cont.

- Negatively charged droplets are cleared more rapidly from the blood than neutral or positively charged ones.
- Emulsions stabilized by non-ionic polyoxyethylene (POE) surfactants are longer circulating in the blood and cationic emulsions are better for dermatological delivery.

Emulsion properties

3. Rheology:

- The consistency of the emulsion is similar to that of the continuous phase. Thus, w/o emulsions are generally thicker than o/w emulsions.
- The consistencies of o/w systems are further increased by the addition of emulsifiers such as gums and polymers.
- At rest, the high apparent viscosity inhibits the movement of droplets to maintain a physically stable emulsion.
- During use, higher shear rates are applied and apparent viscosities reduce (shear thinning) so the emulsion flows freely when injected, or poured from a container.

Formulation of Emulsions

- w/o emulsion: The disperse phase is added to the continuous phase during the initial mixing. The other ingredients are dissolved, prior to mixing in the phase in which they are soluble.
- o/w emulsion: made by phase inversion technique; in which the aqueous phase is slowly added to the oil phase during mixing. Initially a w/o emulsion is formed but as further aqueous phase is added, the emulsion inverts to form o/w emulsion of very low mean droplet size.

Emulsion stability

Chemical stability

- Pharmaceutical oils may be susceptible to oxidation by atmospheric oxygen or microbial contamination developing an unpleasant odor and taste.
- Antioxidants and preservatives may be incorporated into the emulsion to minimize these effects.
- Polymeric emulsifiers may undergo depolymerization by hydrolysis or microbial degradation, with loss of emulsification power and consistency.

Cont.

- Interactions between the emulsifying agent and other components: For example, polyoxyethylene non-ionic emulsifiers form hydrogen bonds with phenolic preservatives, leading to poor preservation as well as loss in emulsifying power.
- Ionic emulsifying agents are usually incompatible with materials of the opposite charge.
- The presence of high concentration of electrolytes may cause salting-out effect, that form hydrated layers and so cause precipitation
- Emulsifying agents may be precipitated by the addition of materials in which they are insoluble
- Changes in pH may lead to the breaking of emulsions

Emulsion stability

Physical stability

- Creaming, flocculation, coalescence and Ostwald ripening.
- Phase inversion: where a w/o emulsion inverts to an o/w emulsion or vice versa.

- Coalescence and Ostwald ripening are the most serious types of instability.

- Creaming and flocculation, on the other hand, are more subtle forms.

Emulsion stability

Physical stability

Creaming

- When the dispersed droplets separate under the influence of gravity to form a layer of more concentrated emulsion.
- Creaming occurs in emulsion containing relatively large droplets (~ 1 µm) if there is a density difference between the oil and water phases, the oil droplets in an o/w emulsion rise to the surface to form an upper layer of cream, whereas water droplets sediment to form a lower layer in w/ o emulsions.
- **Reversible**
- To reduce creaming, prepare emulsions with small droplet sizes, and to thicken the external phase.

Emulsion stability

Physical stability

Flocculation

- Is a weak, **reversible** association between emulsion droplets which are separated by trapped continuous phase.
- The tendency for flocculation can be reduced by the use of a suitable emulsifier.
- Flocculation is generally considered undesirable because floccules cream more rapidly under the effect of gravity.

Emulsion stability

Physical stability

Coalescence

- An **irreversible** process in which dispersed phase droplets merge to form larger droplets. The process will continue until the emulsion breaks (cracks).
- Coalescence occurs when the emulsion droplets are able to overcome the repulsive energy barrier.
- Coalescence begins with the drainage of liquid films of continuous phase and ends with the rupture of the film
- Rigid close-packed elastic films and thick multilayered films provided by many polymers protect droplets against coalescence.

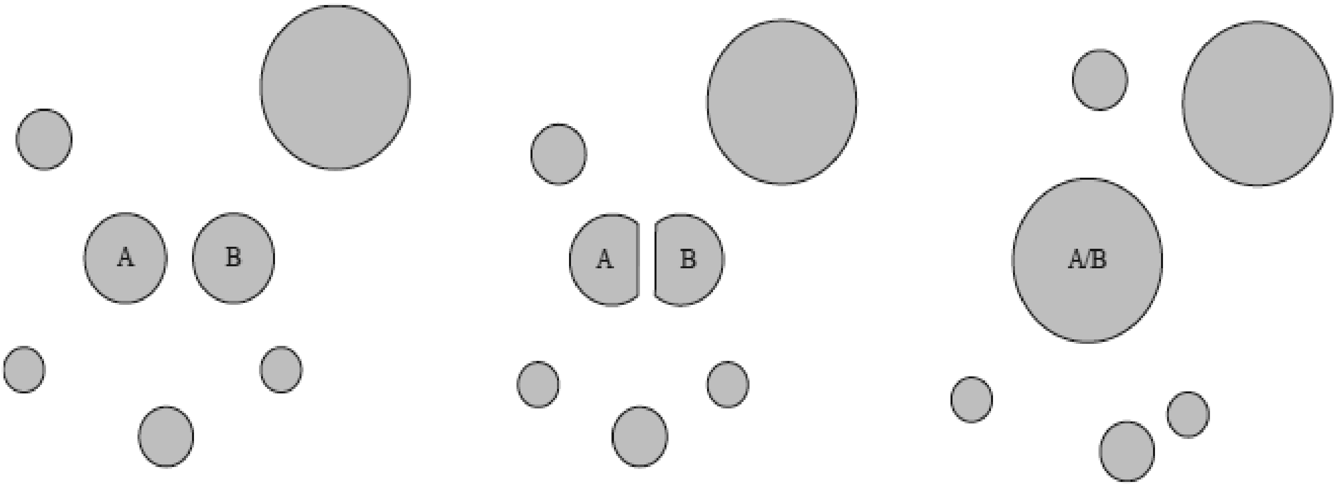


Fig. 27.8 • Schematic representation of flocculation and coalescence of dispersed droplets.

Emulsion stability

Physical stability

Ostwald ripening

- Is an **irreversible** process which involves the growth of large droplets at the expense of smaller ones.
- Ostwald ripening occurs in emulsions containing small droplets (less than ~ 600 nm), provided that the dispersed phase also has a significant solubility in the continuous phase.
- In order to reach the state of equilibrium, the small droplets dissolve and their molecules diffuse through the continuous phase and re-deposit onto larger droplets which grow bigger
- Ostwald ripening differs from coalescence in that it does not need any contact between the droplets.
- Ostwald ripening can be prevented by the addition of a small quantity of an immiscible second oil and by Pluronic F68® surfactant that is strongly adsorbed at the o/w interface.

Emulsion stability

Physical stability

Emulsion inversion

- A change in emulsifier solubility from water soluble at low temperature to oil soluble at high temperature causes phase inversion at a specific temperature from an o/w emulsion to a w/o emulsion.
- Emulsion inversion may also occur by specific interactions with other additives. For example, if a sodium salt is used to stabilize an o/w emulsion, the emulsion may invert to a w/o emulsion by the addition of divalent ions, such as Ca^{2+} ions, to form the calcium salt, which stabilizes a w/o emulsion.

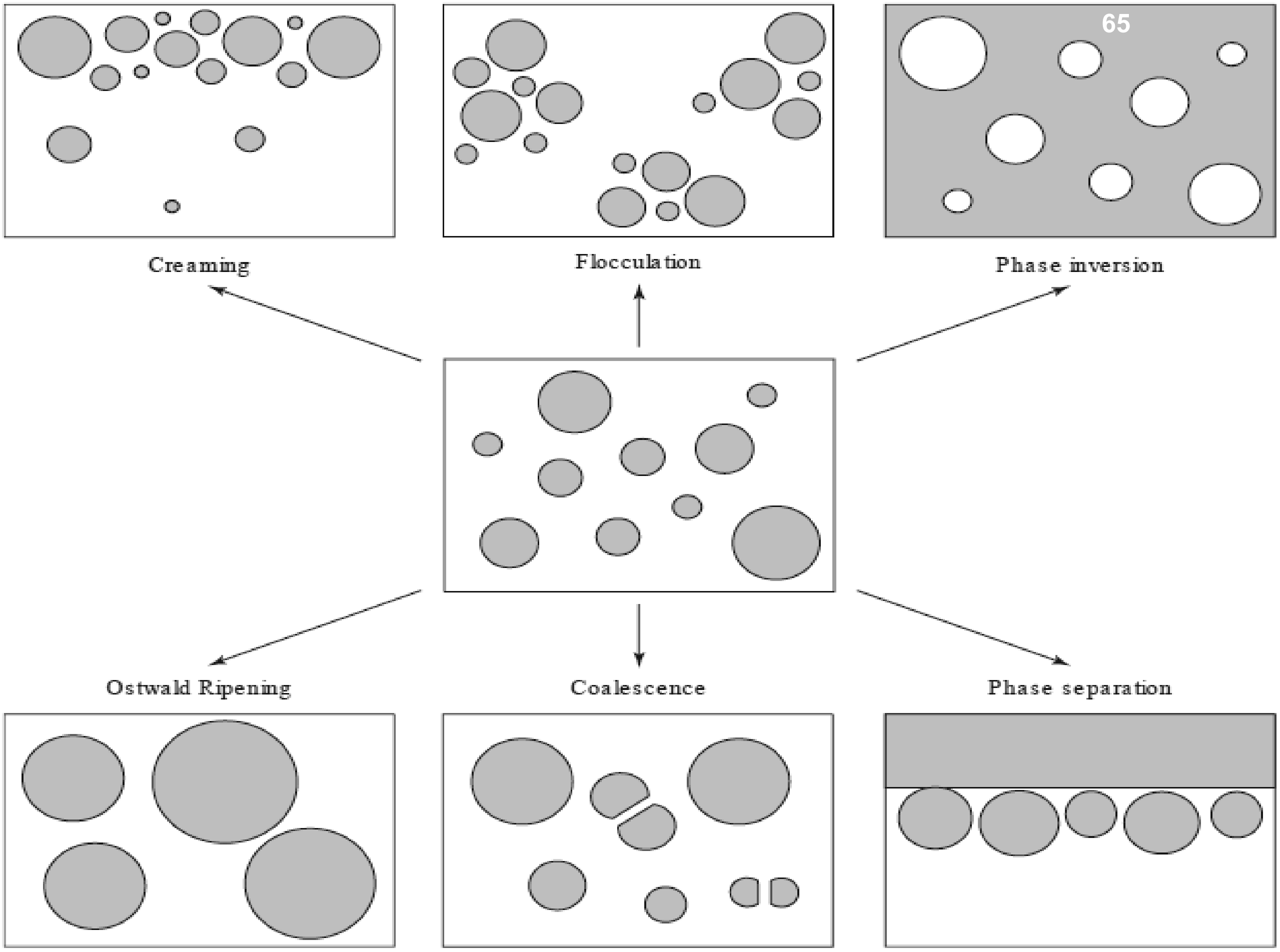


Fig. 27.7 • Schematic representation of the processes of emulsion breakdown.

Evaluation of emulsion stability

1. Appearance

A visible assessment of the extent of ‘creaming’ that occurs on storage.

2. Droplet size analysis

Optical microscopy: In emulsions containing droplets greater than 1 µm.

Laser light scattering techniques: for emulsions containing sub-micrometre droplets.

Evaluation of emulsion stability

3. Droplet charge, zeta potential

Useful for assessing instability due to flocculation.

For assessing the stability of fat emulsions and other emulsions containing charged droplets, where the presence of additives may result in changes in zeta Potential.

Evaluation of emulsion stability

6. Rheological measurements

- To evaluate emulsion stability over time.
- Changes in droplet size distributions, degree of flocculation and creaming, or phase behavior of the emulsifiers usually alter the rheological properties.
- Fluid emulsions generally exhibit shear thinning pseudoplastic or plastic behaviour, sometimes accompanied by thixotropy.

Nanoemulsion

- Nanoemulsions are clear or transluscent emulsions containing droplet sizes typically below ~ 200 nm (0.2 μm).
- Nanoemulsions are relatively stable physically, as the droplets do not collide as frequently as in ordinary emulsions and their small droplet sizes enable them to penetrate deep into the tissues through fine capillaries.
- May be used as drug carriers and target specific sites in the body including the liver and the brain.
- The surface properties of emulsions can be modified by controlling the charged nature of the interfacial film.

Nanoemulsion

- Negatively charged droplets are cleared more rapidly from the blood than neutral or positively charged ones.

- Positively charged (cationic) nanoemulsions have been shown to improve skin permeation of poorly soluble drugs.

- Water-in-oil nanoemulsion formulations are under investigation in cancer chemotherapy for prolonging drug release after intramuscular injection.