

MODULE 2:
Lecture 10



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The logo of Galgotias University is a stylized, circular emblem. It features a central white swirl that transitions into a blue swirl, which then transitions into a yellow swirl, and finally into a red swirl. The entire emblem is set against a light pinkish-red circular background.

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Emulsions



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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 .
- At least 2 phases:
 - ✓ Disperse or internal phase
 - ✓ Continuous or external phase.

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Emulsion types

- o/w emulsions.
- w/o emulsions.
- Multiple emulsions (e.g. w/o/w emulsions).



Identification of emulsion type

- **Miscibility test:** An emulsion will only mix with a liquid that is miscible with its continuous phase. Therefore an o/w emulsion is miscible with water. a w/o emulsion with an oil.
- **Conductivity measurement:** Systems with an aqueous continuous phase will conduct electricity, whilst systems with an oily continuous phase will not.
- **Staining test:** A dry filter paper impregnated with cobalt chloride turns from blue to pink on exposure to stable o/w emulsions.
- **Dye test:** If an oil-soluble dye is used, o/w emulsions are paler in colour than w/o emulsions and vice versa. If examined microscopically. an o/w emulsion will appear as coloured globules on a colourless background whilst a w/o emulsion will appear as colourless globules against a coloured background.

Pharmaceutical application of emulsions

Why emulsions?

Oral route:

- Oral administration of oil-soluble drugs (o/w emulsions).
- ✓ To enhance palatability of oils when given orally by disguising both taste and oiliness.
- ✓ Increasing absorption of oils and oil-soluble drugs through intestinal walls. An example is griseofulvin suspended in oil in an oil-in-water emulsion.

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.

Pharmaceutical application of emulsions

Why emulsions?

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.

Topical applications

Transdermal route

Rectal route

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Formulation of emulsions

Stability problems

1. Sedimentation and creaming.
2. Thermodynamic instability (coalescence or cracking).
3. Phase inversion.

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

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

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

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
 - ✓ it is inelegant and inaccurate dosing is possible if shaking is not thorough.
 - ✓ Additionally, creaming increases the likelihood of coalescence of globules and therefore break down of the emulsion due to cracking.

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Stability of emulsions

Cracking or coalescence:

- Emulsions are thermodynamically unstable systems; there is positive interfacial free energy (IFE) between the two phases.

$$\text{IFE} = \text{Interfacial tension} * \text{surface area}$$

- To enhance their stability, the dispersed droplets come closer to each other and fuse in an attempt to decrease the exposed surface area.
- Coalescence is the fusion of two or more droplets of the disperse phase forming one droplet.
- 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.

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.

Stability of emulsions

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

- **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.
 - ❖ Higher percentages of oil phase (o/w).
 - ❖ Decreasing the particle size of the internal phase.
 - ❖ 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)?

- **Using emulsifying agents (hydrocolloids, surfactants and other) :**
 - ✓ Forming interfacial film mechanical barrier which decreases the potential for coalescence (more important).
 - ✓ Surfactants may reduce the interfacial tension between the two phases (less important).
 - ✓ 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).

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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.
- ✓ 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.

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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 colourless, odourless, tasteless, non-toxic, non-irritant and able to produce stable emulsions at low concentrations.
- Emulsifying agents are either:
 - ✓ Hydrocolloids.
 - ✓ Surface active agents (SAA) (surfactants).
 - ✓ Finely divided solids.
 - ✓ Auxiliary emulsifiers.

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)

Synthetic hydrocolloids:

- ✓ Carbopol
- ✓ Polyvinyl alcohol (PVA).
- ✓ Polyvinyl pyrrolidone (PVP)

Emulsifying agents

Surfactants

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:

- Incompatible with some organic and inorganic cations and with large organic cations such as cetrimide.
- They are irritant internally so widely used in **external** preparations as o/w emulsifying agents.
- 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



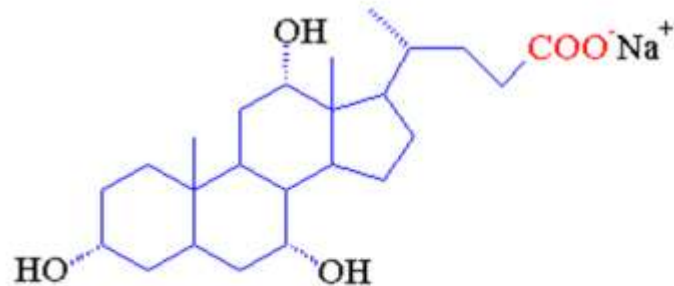
Alkali Soaps (sodium palmitate)



Amine Soaps (triethanoleamine oleate)



Alkylsulfates (sodium laurylsulfate)



Bile Salts (sodium cholate)

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Emulsifying agents

Surfactants

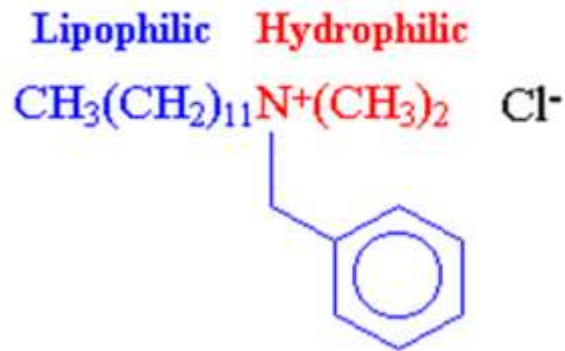
Cationic surfactants:

- 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.
- The cationic surfactants also have antimicrobial activity.

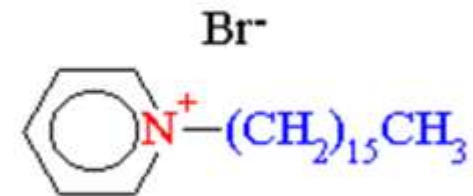
Disadvantages:

- 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.

Cationic Surfactants: Inverted Soaps



Quaternary Ammonium Salts
(lauryldimethylbenzylammonium chloride)



Pyridinium Salts
(Cetylpyridinium bromide)

Emulsifying agents

Surfactants

Non-ionic surfactants

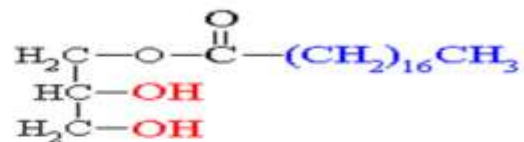
- They are synthetic materials and make up the largest group of surfactants.
- The non-ionic surfactants are compatible with both anionic and cationic substances and are highly resistant to pH change.
- They are used to produce either o/w or w/o emulsions for both external and internal use.
- The type 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.

Nonionic Surfactants

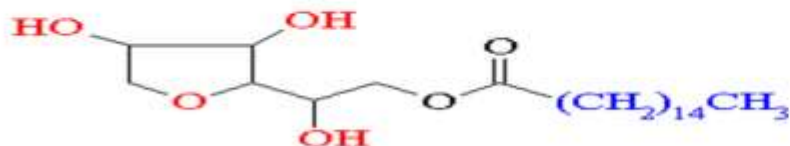
Lipophilic **Hydrophilic**
 $\text{CH}_3(\text{CH}_2)_n\text{OH}$

Fatty Alcohols

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



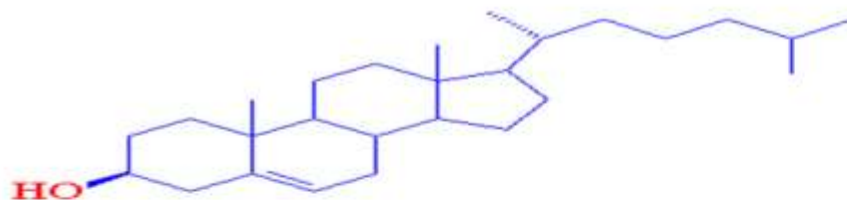
Partial Fatty Acid Esters of Multivalent Alcohols
 (glycerol monostearate)



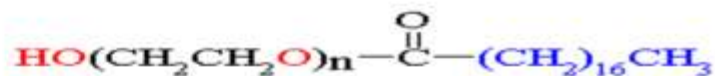
Spans: Sorbitan Esters of Fatty Acids
 (sorbitan monopalmitate)



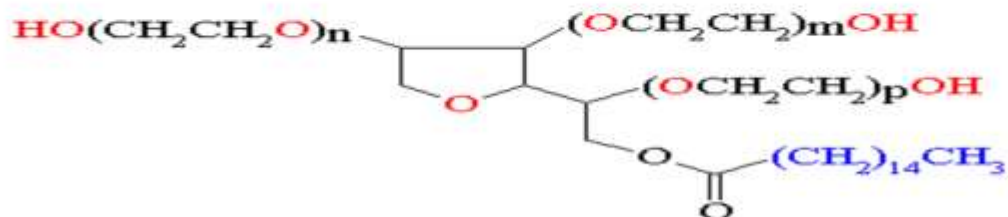
Brij: Polyethyleneglycol (PEG) Ether
 (PEG-200 lauryl ether, Brij 30)



Cholesterol

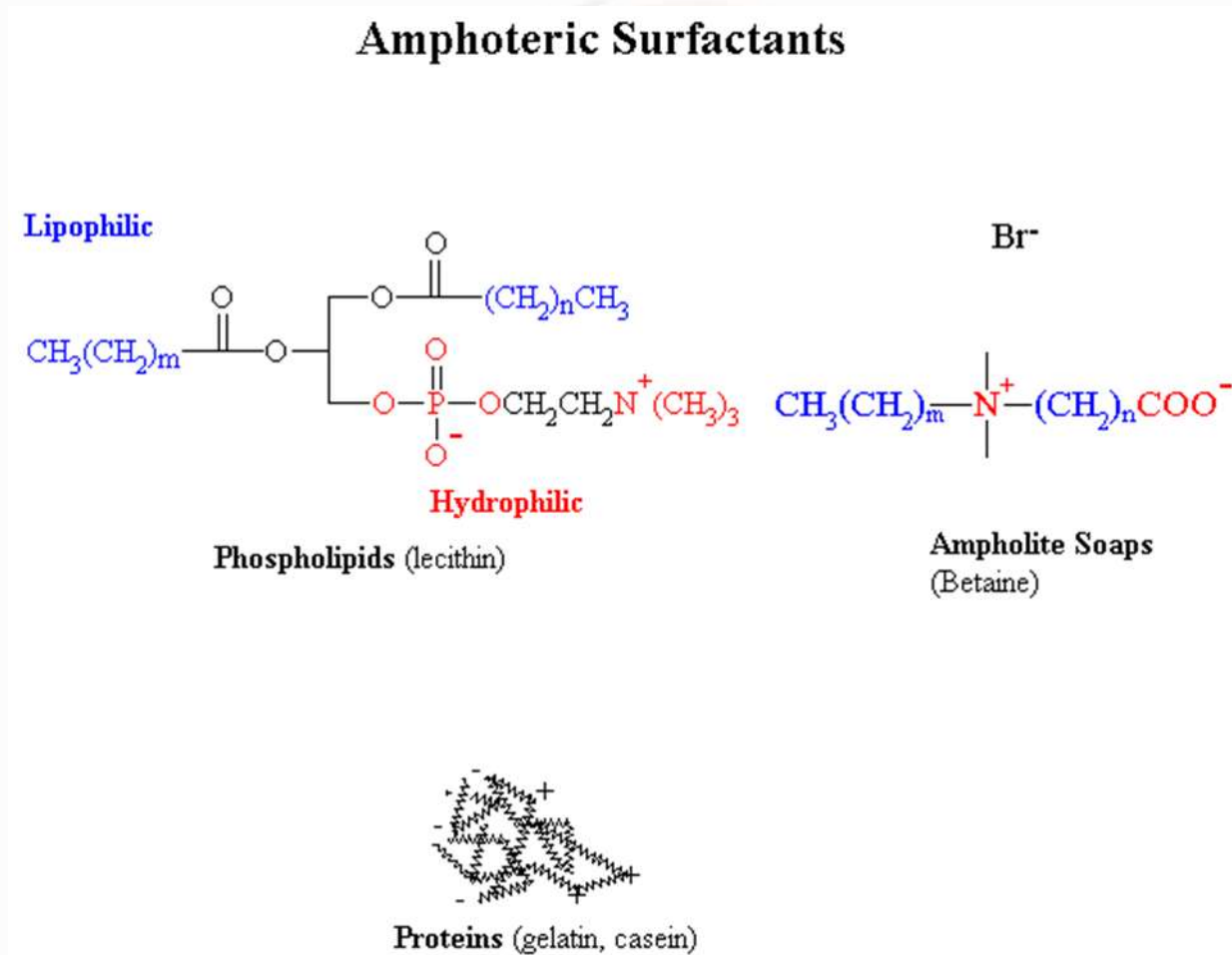


Cremophor: Polyethyleneglycol (PEG) Fatty Acid Ester
 (PEG-400 stearate)



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

Amphoteric (Zwitterionic) Surfactants



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.
- 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.
- Examples:
 - ✓ 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.

Auxiliary emulsifying agents

Sterol-containing substances:

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

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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.

HLB and Use of Surfactants

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

Choosing an emulsifying agent

- 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.
- The taste should be bland and palatable, again suggesting the natural polysaccharides. Polysorbates have a disagreeable taste, therefore flavouring ingredients are necessary.
- Soap emulsions 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.
- Only certain non-ionic emulsifying agents are suitable for parenteral use including lecithin, polysorbate 80, methylcellulose, gelatin and serum albumin.

Antioxidants (Stabilizers)

- 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.



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
 - ✓ Carelessly cleaned equipment.
 - ✓ Poor closures on containers.
- Microbes produce unpleasant odours, colour changes and gases. Additionally, they may affect the emulsifying agents, possibly causing the breakdown of the emulsion.

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Antimicrobial preservatives

Antimicrobial preservatives :

- Should be free from toxic effects, odour, taste (for internal use) and colour.
- Should be bactericidal rather than bacteriostatic.
- Have a rapid action and wide antibacterial spectrum over a range of temperatures and pH.
- 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.

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.

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Emulsions for oral use

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

Emulsions for oral use

Quantities for primary emulsions

Type of oil	examples	Oil	water	Gum (acacia)
		Parts by volume (ml)		Parts by weight (g)
fixed	Almond, arachis, cod liver, castor	4	2	1
Mineral (hydrocarbon)	Liquid paraffin	3	2	1
volatile	Turpentine, cinnamon, peppermint	2	2	1
Oleo-resin	Male fern extract	1	2	1

Emulsions for oral use

Quantities for primary emulsions

- **Example: Calculate the quantities for a primary emulsion for the following:**

Cod liver oil	30 ml
Water	to 100 ml

- **Answer: Primary emulsion quantities:**

Cod liver oil is a fixed oil, therefore the primary emulsion proportions are 4 : 2 : 1 .Hence:

- | | | |
|-----------------------|-------|---|
| • Cod liver oil | 30 ml | 4 |
| • Water | 15 ml | 2 |
| • Powdered acacia gum | 7.5g | 1 |

Emulsions for oral use

Variations to primary emulsion calculations

- If the proportion of oil is too small, modifications must be made.
- Acacia emulsions containing less than 20% oil tend to cream readily. A bland, inert oil, such as arachis, sesame, cottonseed or maize oil, should be added to increase the amount of oil and so prevent this from happening.
- Care should be taken in selection of the bulking oil because of the increasing incidence of nut allergy. It is often, therefore, advisable to avoid oils such as arachis, especially for children.

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Emulsions for oral use

Variations to primary emulsion calculations

- Example: Rx Calciferol solution, 0.15 ml per 5 ml dose.
- Answer: The percentage of oil in each dose is 3%. The oil content must be made up to at least 20% to produce a stable emulsion.
Since 20% of 5 ml = 1 ml the volume of bland oil required is $1 - 0.15 = 0.85$ ml

Formula for primary emulsion (for 50 mL)

- | | | |
|-----------------------|--------|---|
| • Calciferol solution | 1.5 ml | 4 |
| • Cottonseed oil | 8.5 ml | |
| • Water | 5 ml | 2 |
| • Acacia | 2.5g | 1 |

Emulsions for oral use

Methods of preparation of extemporaneous emulsions

- Dry gum method.
- Wet gum method.

Refer back to the textbook for full details.

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Emulsions for oral use

Problems when producing the primary emulsion

The primary emulsion may not form and a thin oily liquid is formed instead. Possible causes are:

- Phase inversion has occurred
- Incorrect quantities of oil or water were used
- Cross-contamination of water and oil
- A wet mortar was used
- The mortar was too small and curved or the pestle was too round giving insufficient shear
- Excessive mixing of oil and gum before adding water (dry gum method)
- Diluting the primary emulsion too soon or too rapid dilution of primary emulsion
- Poor-quality acacia

Emulsions for oral use

Shelf life, storage, containers

- Emulsions should be stored at room temperature and will either be recently or freshly prepared. Some official preparations will have specific expiry dates. They should not be frozen.
- A plain amber medicine bottle is used for internal use with an airtight child-resistant closures.
- Containers with a wide mouth are useful for very viscous preparations.

Emulsions for oral use

- Prepare 200ml cod liver oil emulsion to the following formula:
- Cod liver oil 60 ml
- Chloroform 0.4ml
- Cinnamon water to 200ml

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Emulsions for oral use

- 100ml Liquid Paraffin Oral Emulsion BP 1968.
- Liquid paraffin 50ml
- Vanillin 50mg
- Chloroform 0.25ml
- Benzoic acid solution 2ml
- Methylcellulose 20 2g
- Saccharin sodium 5mg
- Water to 100ml

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Emulsions for external use

- Liquid or semi-liquid emulsions may be used as applications, liniments and lotions .
- The extemporaneous preparation of emulsions for external use does not require the preparation of a primary emulsion.
- Soaps are commonly used as the emulsifying agent and some are prepared 'in situ' by mixing the oily phase containing a fatty acid and the aqueous phase containing the alkali.
- Alternatively the emulsifying agent can be dissolved in the oily or aqueous phase and the disperse phase added to the continuous phase, either gradually or in one portion.
- Creams are semisolid emulsions which may be o/w (e.g. aqueous cream) or w/o (e.g. oily cream).

Emulsions for external use

- Applications: solutions or emulsions that frequently contain parasiticides.
- Liniments: alcoholic or oily solutions or emulsions designed to be rubbed into the skin. The medicament is usually a rubefacient.
- Lotions : aqueous solutions, suspensions or emulsions that cool inflamed skin and deposit a protective layer of solid.
- Creams are semisolid emulsions which may be o/w (e.g. aqueous cream) or w/o (e.g. oily cream).

Emulsions for external use

Shelf life, storage, containers

- Emulsions should be stored at room temperature and will either be recently or freshly prepared. Some official preparations will have specific expiry dates. They should not be frozen.
- A ribbed amber bottle is used for external use, with an airtight child-resistant closures.

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Emulsions for external use

Liquid emulsions

Rx 100ml Oily Calamine Lotion 1980

- Calamine 5g
- Wool fat 1g
- Oleic acid 0.5ml
- Arachis oil 50ml
- Calcium hydroxide solution to 100ml

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