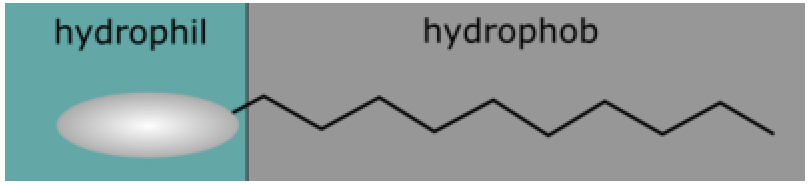
The HLB System

The hydrophilic-lipophilic balance (HLB) of the molecule determines the type of activity which may be expected of the agent. The compound will serve as a wetting agent, a detergent, a solubilising agent, an o/w or w/o emulsifying agent depending on the HLB.

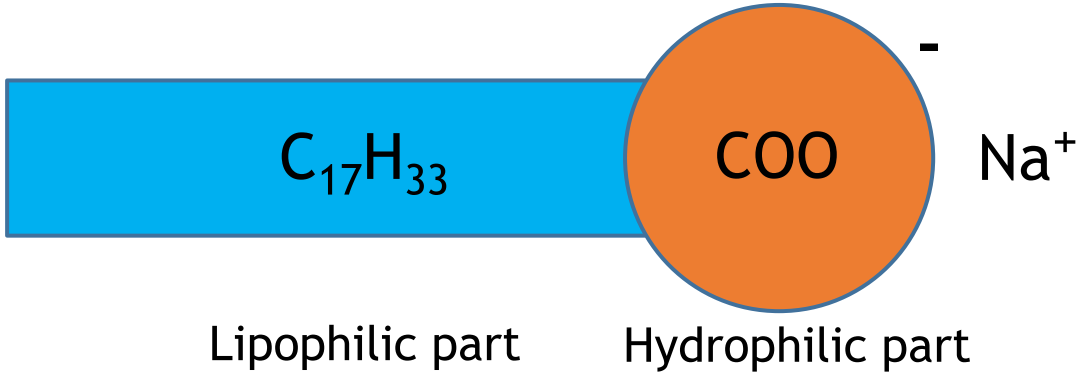
Each EA contains a water-attracting (hydrophilic part) and an oil-attracting (lipophilic part).



If the agent is too hydrophilic it dissolves completely in the aqueous phase and exerts no effect at the interface. If it is too lipophilic it dissolves completely in the oil phase and does not concentrate at the interface.

The molecule of a well-balanced emulsifying agent when dispersed initially in the oil or the aqueous phase, it will migrate to and concentrate predominantly at the interface, where it is oriented with the hydrophilic portion in the water and the lipophilic portion in the oil. An EA which displays these properties is said to have the proper HLB.

If an EA is hydrophilic it will tend to form an o/w emulsion, if it is lipophilic it will favour the formation of a w/o emulsion. Sodium oleate has a good o/w EA characteristics since it possesses a hydrophilic carboxyl group (COO^-) that predominates over the lipophilic hydrocarbon group ($C_{17}H_{33}$).


$C_{17}H_{33}$

COO^-

Na^+

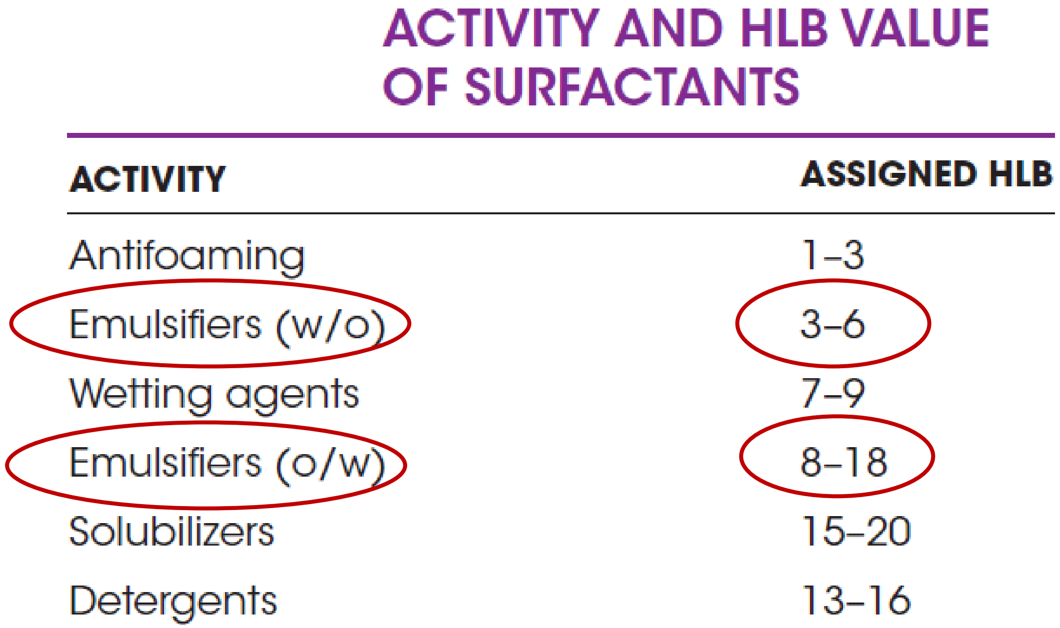
Lipophilic part

Hydrophilic part

On the other hand, calcium oleate and other polyvalent soaps are predominantly lipophilic and form w/o emulsions.

The hydrophilic-lipophilic balance of surface active agents has been expressed in terms of a numerical scale that extends from 1-50 but the usual range is between 1-20.

An agent with a low HLB is lipophilic, while a surfactant a surfactant having a higher HLB is hydrophilic. For the preparation of a w/o emulsion, the EA should have an HLB value of about (3-6). An o/w emulsion on the other hand is favoured by an EA with HLB value of about (8-18).



ACTIVITY AND HLB VALUE OF SURFACTANTS

ACTIVITY	ASSIGNED HLB
Antifoaming	1–3
Emulsifiers (w/o)	3–6
Wetting agents	7–9
Emulsifiers (o/w)	8–18
Solubilizers	15–20
Detergents	13–16

In practice, Spans and Tweens are usually mixed to provide an emulsifier combination that has the HLB necessary to produce a stable emulsion of the desired type.

By knowing the required HLB of the oil phase, one may calculate the quantities of any Span and Tween that are necessary to produce the proper balance for a stable emulsion.

Each oil requires an EA of a specific HLB value for the formation of an o/w emulsion and another value for the formation of a w/o product. These are known as the “required HLB” values of the oil.

In the HLB system, in addition to assigning values to the EAs values are also assigned to oils. In using the HLB concept in the preparation of an emulsion, one selects EAs having the same or nearly the same HLB value as the oil phase of the intended emulsion.

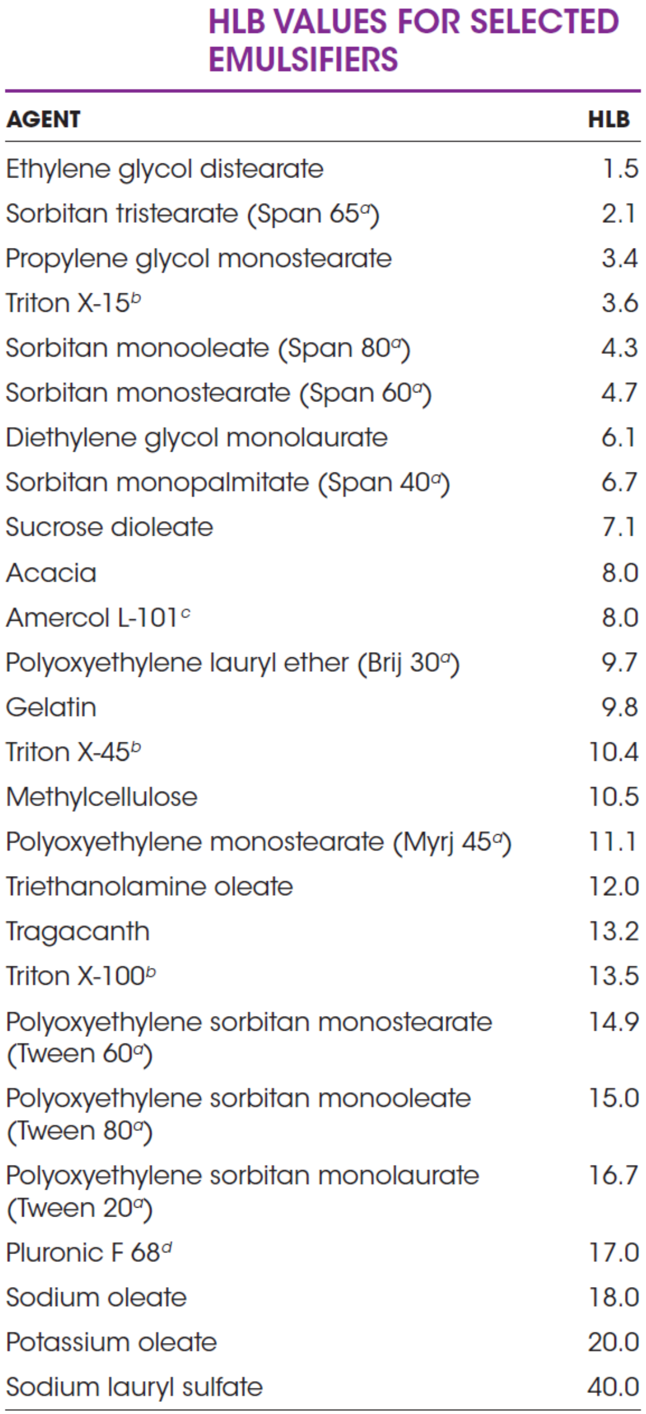
For example, mineral oil has an HLB value of 4 if a w/o emulsion is desired and a value of 10.5 if an o/w emulsion is to be prepared. Therefore, to prepare a stable emulsion the EA should have an HLB value similar to the one of mineral oil depending on the type of emulsion required. When needed two or more EAs may be combined to achieve the proper HLB value.

Mixed EAs or a blend of emulsifiers is more efficient to give a stable emulsion than either each agent alone. The mixture contributes one or several actions:

1. It provides the proper hydrophilic-lipophilic nature.
2. It establishes a stable film at the interface.
3. It supplies the desired consistency to the product.

Mixed EAs tend to form interfacial complexes at the surface of the globules, for example the o/w emulsifying action of sodium oleate is improved by combination with cetyl alcohol or cholesterol through the tendency of the molecules to form a complex.

Tragacanth or agar are frequently combined with acacia to thicken the external phase of an o/w emulsion and reduce the rate of creaming. Pectin, alginates and cellulose esters are used as well for this purpose.



HLB VALUES FOR SELECTED EMULSIFIERS

AGENT	HLB
Ethylene glycol distearate	1.5
Sorbitan tristearate (Span 65[a])	2.1
Propylene glycol monostearate	3.4
Triton X-15[b]	3.6
Sorbitan monooleate (Span 80[a])	4.3
Sorbitan monostearate (Span 60[a])	4.7
Diethylene glycol monolaurate	6.1
Sorbitan monopalmitate (Span 40[a])	6.7
Sucrose dioleate	7.1
Acacia	8.0
Amercol L-101[c]	8.0
Polyoxyethylene lauryl ether (Brij 30[a])	9.7
Gelatin	9.8
Triton X-45[b]	10.4
Methylcellulose	10.5
Polyoxyethylene monostearate (Myrj 45[a])	11.1
Triethanolamine oleate	12.0
Tragacanth	13.2
Triton X-100[b]	13.5
Polyoxyethylene sorbitan monostearate (Tween 60[a])	14.9
Polyoxyethylene sorbitan monooleate (Tween 80[a])	15.0
Polyoxyethylene sorbitan monolaurate (Tween 20[a])	16.7
Pluronic F 68[d]	17.0
Sodium oleate	18.0
Potassium oleate	20.0
Sodium lauryl sulfate	40.0

Rx

Mineral oil		8 g
E.A. (Span 80 + Tween 80)		2 g
Purified water	q.s.	100 mL

The required HLB for the mineral oil = 10.5, the HLB for Span 80 = 4.3 and the HLB for Tween 80 = 15.

How much Span 80 and Tween 80 are required to produce a stable emulsion?

$$\mathbf{F_S * HLB\ s + F_T * HLB_T = \text{Required HLB of the oil}}$$

Let the fraction of Span = X

Let the fraction of Tween = 1-X

$X*4.3 + (1-X)*15 = 10.5$

$10.7\ X = 4.5$

X= 0.42 fraction of Span

Amount of Span = 2 * 0.42 = 0.84 g

1-X = 1- 0.42 = 0.58 fraction of Tween

Amount of Tween = 2 * 0.58 = 1.16 g

Let the fraction of Tween = X

Let the fraction of Span = 1-X

$(1-X)*4.3 + X*15 = 10.5$

$10.7\ X = 6.2$

X= 0.58 fraction of Tween

Amount of Tween = 2 * 0.58 = 1.16 g

1-X = 1- 0.58 = 0.42 fraction of Span

Amount of Span = 2 * 0.42 = 0.84 g

Types of Emulsifying Agents

1. **Carbohydrate materials**, such as acacia, tragacanth, agar and pectin. These materials form hydrophilic colloids when added to water and generally produce o/w emulsions.
2. **Protein substances**, such as gelatine, egg yolk. These substances produce o/w emulsion.
3. **High molecular weight alcohols**, such as stearyl alcohol, cetyl alcohol and glyceryl monostearate. These substances are employed primarily as thickening agents and stabilisers for o/w emulsions used externally. Cholesterol and cholesterol derivatives may also employed in externally used emulsions to promote w/o emulsions.
4. **Wetting agents**, which may be anionic, cationic or non-ionic. The non-ionic surfactants are effective over pH range (3-10), cationic surfactants are effective over pH range (3-7) and anionic surfactants require a pH greater than 8.

5. **Finely divided solids**, such as colloidal clays including bentonite, magnesium hydroxide and aluminium hydroxide. These substances can form either o/w or w/o emulsions depending on the order of mixing.

Examples of oral emulsions

1. Castor oil Emulsion (o/w): This emulsion is utilised as a laxative. Castor oil works directly on the small intestine to promote bowel movement.
2. Simethicone Emulsion (o/w): used as a defoaming agent for the relief of painful symptoms of excess gas in the GIT. Available in drop form for infants.

- Sterile vitamin K Emulsion (o/w) for I.V. administration.

Deterioration and preservation of Emulsions

One of the most important properties of emulsions is the stability of the finished product.

A stable emulsion is characterised by:

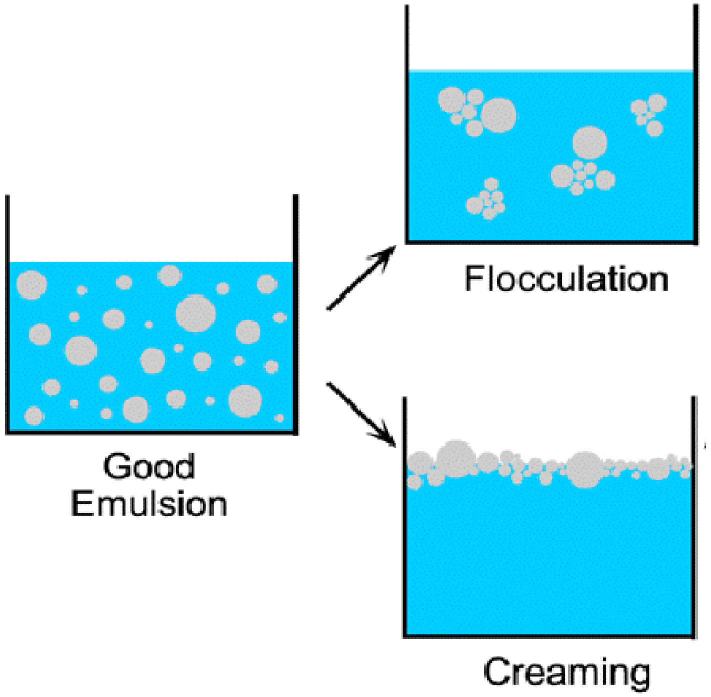
1. The absence of flocculation and creaming.
2. The absence of coalescence of globules and the separation of the internal phase from the emulsion.
3. The absence of deterioration by microorganisms.
4. Maintenance of elegance with respect to general appearance, odour, colour and consistency.

1. Flocculation and creaming

Flocculation is the joining together of globules to form large clumps of floccules, which rise or settle in the emulsion more rapidly than do the individual particles.

The passage of an emulsion through an orifice at a high pressure sometimes results in flocculation.

Creaming is the rising (upward creaming) or settling (downward creaming) of floccules to form a concentrated layer at the surface or at the bottom of the emulsion.



Creaming is regarded as a mark of instability in pharmaceutical emulsions. Creaming results in a lack of uniformity of the product and unless the container is agitated thoroughly before each dose, it may lead to variations in the amount of drug which is administered. Furthermore, the appearance of the emulsion is affected by creaming.

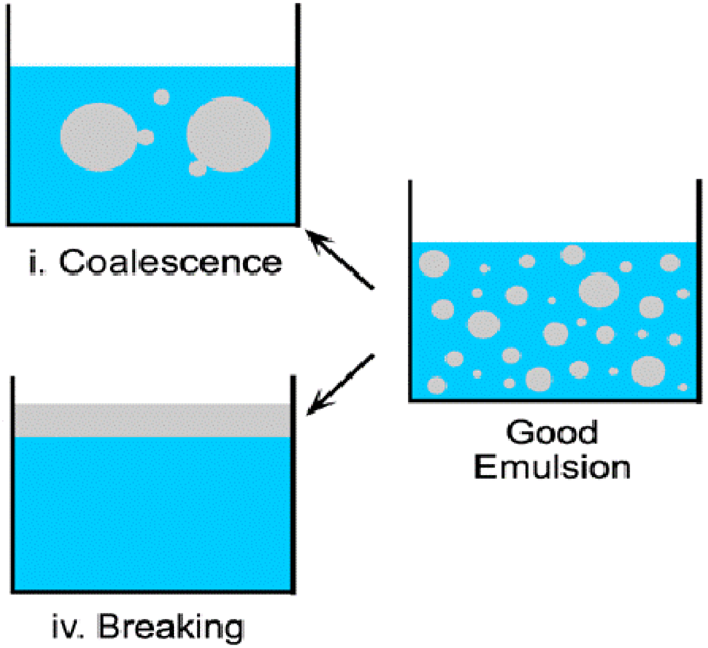
Reducing the particle size by passing the emulsion through a homogeniser decreases the velocity of creaming but homogenisation under high pressure sometimes leads to flocculation and the large clumps which are formed may cream rapidly than individual globules in the unhomogenised emulsion.

2. Coalescence and breaking

Unlike creaming, the coalescence of globules and the subsequent breaking of an emulsion are irreversible processes.

Under the conditions of creaming, the globules are still surrounded by a protective sheath of EA and may redispersed simply by agitating the product.

However, in an emulsion which has broken (i.e.) in which the phases have separated as distinct layers, simple mixing fails to re-establish the stable emulsion.



The emulsion may be reconstituted only by incorporating more emulsifying agent and passing the product through the proper emulsifying machinery.

The globules coalesce slowly or rapidly depending on the strength of the emulsifier film, until the product is completely cracked (broken).

Although many properties such as low interfacial tension and increased viscosity have been suggested as stabilising factors, its generally agreed today that the most significant element in stabilising an emulsion against breaking is the emulsifier film surrounding the dispersed particles.

If the EA is adsorbed and oriented at the interface in a manner such as to form a tough, coherent barrier, the film will withstand the tendency of the globules to coalesce and the emulsion will remain stable for the desired period of time.

3. Deterioration by microorganisms

Moulds, yeasts and bacteria may bring about the decomposition of the emulsifying agents, contaminate the aqueous phase and produce rancidity of the oil phase.

A preservative should be a powerful fungistatic rather than bacteriostatic agent, since it is more likely that fungi (moulds and yeasts) may contaminate emulsions.

The presence of certain drugs such as benzoic and salicylic acid or high concentration of alcoholic solutions may provide adequate protection against microorganisms. However, it is usually desirable to add an agent which will act specifically as a preservative.

Combination of parahydroxybenzoates of methyl ester (0.1-0.2%) and (0.02- 0.05%) of propyl ester are frequently used. This combination is effective against moulds, yeasts and bacteria, as long as the EA and other formulation ingredients do not complex with preservatives to nullify their actions.

4. Miscellaneous physical and chemical changes

Care must be taken to protect emulsions against deterioration by light, extreme temperature, oxidative and hydrolytic rancidity of the oil.

Freezing and thawing result in a coarsening of globules and sometimes breaking of emulsions. High temperatures produce the same effects as well.

Light and rancidity influence the colour and odour of oils and may destroy their vitamin activity.

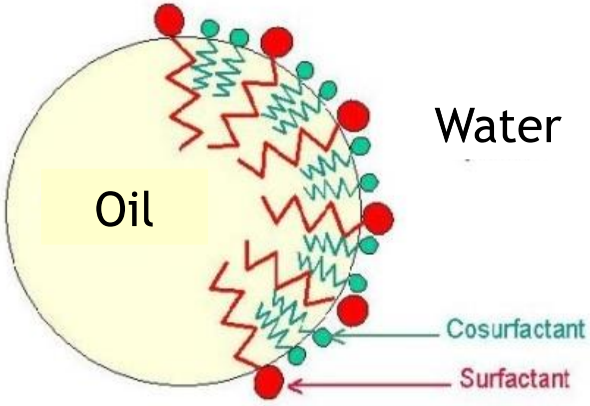
Emulsions should be kept in tight containers and stored at moderate temperature and if they affected by light they should be stored in dark containers.

Microemulsions

Microemulsions are optically transparent, thermodynamically stable, isotropic mixture of a biphasic system (oil and water) stabilised with surfactants and co-surfactants.

Microemulsion

Emulsion



Surfactant forms the interfacial film

Co-surfactant ensures flexibility of the interfacial layer which reduces the interfacial tension to a great extent

The diameter of droplets in a microemulsion may be in the range of 10-100 nm, whereas in a macroemulsion the droplet may be 0.5 μm in diameter.

Property	Emulsions	Microemulsions
Droplet size	0.2-10 μm	<100 nm
Appearance	cloudy	transparent
Preparation	requires energy input	spontaneous formation
Interfacial energy	high	very low

Both o/w or w/o microemulsions may be formed spontaneously by mixing the oil and water phases with carefully selected surfactants and co-surfactants. The type of emulsion produced depends on the proportion of each phase and the properties of the surfactants.

Hydrophilic surfactants in the HLB range of (15-18) can produce transparent o/w microemulsions of many oils including flavouring oils and vitamin oils such as A, D and E.

Microemulsions are dispersions of oil, not true solutions. However, because of the appearance of the product, the surfactant mixture is commonly said to solubilise the oil.

Examples of surfactants commonly used in the preparation of microemulsions are Tween 60 and Tween 80. Co-surfactants such as ethanol and propylene glycol.

Advantages of Microemulsions

1. More rapid and efficient oral absorption of drugs.
2. Enhanced transdermal drug delivery through increased drug diffusion through the skin
3. Application of microemulsions in the targeting of cytotoxic drugs to cancer cells.

Lotions

Lotions are liquid preparations containing material for topical application. Some pharmaceutical lotions belong in the class of true solutions but most of them are suspensions or emulsions.

Medicinal lotions are used as antiseptics in the treatment of skin diseases or as cooling and mild anaesthetic preparation for skin irritation.

Since lotions may contain a suspended matter and are applied topically, they usually carry on their labels the statement “Shake well before use” in addition to “for external use only”.

Properties of good lotions

1. A lotion should pour freely from the bottle.
2. It should Applied evenly over the affected area which dries quickly and provides a protective film on the skin.

3. Lotions should also have an acceptable colour and odour.
4. They must remain physically and chemically stable and free of mould growth during storage.

Note: lotions may be sometimes preferred over semisolid preparations such as ointments and creams due to their non-greasy character and their increased spreadability over large areas of the skin.

Examples:

Benzyl Benzoate Lotion: It is an emulsion of benzyl benzoate in water (o/w) which is stabilised by the EA (triethanolamine oleate). It is used as a non-staining water washable product for the treatment of scabies and lice.

Calamine Lotion: It is a suspension of calamine in calcium hydroxide (used as a vehicle) in the presence of bentonite as the suspending agent. It is used as a mild astringent and protective coating for the treatment of skin irritation and itching such as in chicken pox.

Liniments

Liniments are oily or alcoholic liquids and semisolids for external application, usually applied with friction. This class of pharmaceuticals sometimes is referred to as embrocations because of the method of application.

Liniments can be divided into:

1. Alcoholic solutions
2. Oily solutions
3. Emulsions and suspensions

- **Alcoholic solutions:** alcohol and hydroalcoholic mixtures are used widely as vehicles for liniments, not only because alcohol is a good solvent for many drugs but also because it can penetrate the skin and it is in itself a mild rubefacient, counterirritant and astringent. Frequently soaps and oils are added to alcoholic liniments to make them slippery and thus facilitate the rubbing action involved in their application. The official liniments that fall into this class should be clear solutions.

e.g.

- **camphor and soap liniments** (soap liniment or camphorated tincture of soap): prepared by making a solution of camphor, rosemary oil and green soap in hydroalcoholic solvent.

This liniment makes an excellent base for other liniments (i.e. it can be used as a solvent for many substances). The percentage of alcohol present (62-66%) aiding in this respect. The small amount of camphor present gives only a mild rubefacient action.

- **Chloroform liniments:** are made by mixing chloroform with camphor and soap liniment, the addition of chloroform makes these liniments strong, quick acting rubefacient and counterirritants.

- **Oily solutions:** solutions of medicinal agents in fixed or volatile oils are used as liniments. Fixed oils are good solvents for some rubefacient drugs and also they give the necessary lubricant action for the rubbing of a liniment.

Their ability to penetrate the skin is not as great as that of alcoholic liniments, consequently their action is milder.

Cotton seed, olive, almond and other oils such as methyl salicylate and turpentine oil are rubefacient and counterirritant in themselves. They may be used alone or as solvents for other drugs. Like liniments of class one, they should be free from insoluble materials.

e.g. Camphor liniments (camphorated oil) is 20% solution of camphor in cotton seed oil. Cotton seed oil is preferred for making this liniment because of its lower cost. Camphorated oil is very popular counterirritant for minor sprains and also for chest colds.

- **Emulsions and suspensions:** liniments may contain insoluble materials or they may consist of mixtures of immiscible liquids, when such condition exist it is best that an emulsion be formed to prevent rapid separation of the ingredients and to improve the appearance of the product.

Emulsification of liniments usually is accomplished by the formation of a soap which acts as the EA.

In addition to the usual label (for external use only), liniments which are emulsions or suspensions should bear the label (shake well) to ensure equal distribution of all constituents.

e.g. Ammonia liniments and calamine liniments