Emulsions

An emulsion is a dispersion in which the dispersed phase is composed of small globules of a liquid distributed throughout a vehicle in which it is immiscible. In emulsion terminology, the dispersed phase is the *internal phase*, and the dispersion medium is the *external* or *continuous phase*.

Emulsions with an oleaginous internal phase and an aqueous external phase are *oil-in-water* (o/w) emulsions. Conversely, emulsions having an aqueous internal phase and an oleaginous external phase are termed *water-in-oil (w/o) emulsions. Since the external phase of an emulsion is continuous, an o/w emulsion may be diluted or extended with water or an aqueous preparation and a w/o emulsion, with an oleaginous or oil-miscible liquid.*

Generally, to prepare a stable emulsion, a third phase, an emulsifying agent, is necessary. Depending on their constituents, the viscosity of emulsions can vary greatly and pharmaceutical emulsions may be prepared as liquids or semisolids. Based on the constituents and the intended application, liquid emulsions may be employed orally, topically, or parenterally; semisolid emulsions, topically.

Many pharmaceutical preparations that are actually emulsions are not classified as such because they fit some other pharmaceutical category more appropriately. For instance, emulsions include certain lotions, liniments, creams, ointments, and commercial vitamin drops that are discussed in this book under these various designations.

ADVANTAGES OF EMULSIFICATION

1- It enables the pharmacist to prepare relatively stable and homogeneous mixtures of two immiscible liquids.

2- It permits administration of a liquid drug in the form of minute globules rather than in bulk.

3- For orally administered emulsions, the o/w type permits palatable administration of an otherwise distasteful oil by dispersing it in a sweetened, flavored aqueous vehicle & the reduced particle size of the oil globules may render the oil more digestible and more readily absorbed

5- Emulsions to be applied to the skin medicinal agents that irritate the skin generally are less irritating in the internal phase of an emulsified topical preparation than in the external phase.

6- A w/o emulsion can usually be applied more evenly to the skin because the skin is covered with a thin film of sebum, and this surface is more readily wetted by oil than by water. A w/o emulsion is also more softening to the skin, because it resists drying and removal by contact with water.

THEORIES OF EMULSIFICATION

Many theories have been advanced in an attempt to explain how emulsifying agents promote emulsification and maintain the stability of the emulsion. They may be viewed in a general way to describe the manner in which emulsions may be produced and stabilized. Among the most prevalent theories are the surface tension theory, the oriented-wedge theory, and the plastic or interfacial film theory.

All liquids have a tendency to assume a shape having the minimal surface area exposed. For a drop of a liquid, that shape is the sphere. A liquid drop has the shape of a sphere. It possesses internal forces that tend to promote association of the molecules to resist distortion of the sphere. If two or more drops of the same liquid come into contact with one another, the tendency is for them to join or to coalesce, making one larger drop having a smaller surface area than the total surface area of the individual drops. This tendency of liquids may be measured quantitatively, and when the surrounding of the liquid is air, it is referred to as the liquid's **surface tension**. When the liquid is in contact with a second liquid in which it is insoluble and immiscible, the force causing each liquid to resist breaking up into smaller particles is called **interfacial tension**. Substances that reduce this resistance encourage a liquid to break up into smaller drops or particles. These tension-lowering substances are surface active (surfactant) or wetting agents. According to the **surface tension theory** of emulsification, the use of these substances as emulsifiers and stabilizers lowers the interfacial tension of the two immiscible liquids, reducing the repellent force between the liquids and diminishing each liquid's attraction for its own molecules. Thus, the surface-active agents facilitate the breaking up of large globules into smaller ones, which then have a lesser tendency to reunite or coalesce.

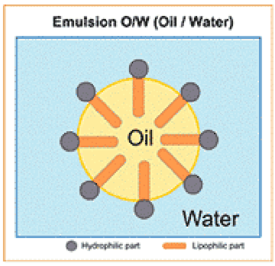
The **oriented-wedge theory** assumes monomolecular layers of emulsifying agent curved around a droplet of the internal phase of the emulsion. The theory is based on the presumption that certain emulsifying agents orient themselves about and within a liquid in a manner reflective of their solubility in that particular liquid. In a system containing two immiscible liquids, presumably the emulsifying agent is preferentially soluble in one of the phases and is embedded more deeply and tenaciously in that phase than the other. Because many molecules of substances upon which this theory is based (e.g., soaps) have a hydrophilic or water-loving portion and a hydrophobic or water-hating portion (but usually lipophilic or oil loving), the molecules position or orient themselves into each phase. Depending on the shape and size of the molecules, their solubility characteristics, and thus their orientation, the wedge shape envisioned for the molecules causes either oil globules or water globules to be surrounded. **Generally, an emulsifying agent having a greater hydrophilic than hydrophobic character will promote an o/w emulsion, and a w/o emulsion results from use of an emulsifying agent that is more hydrophobic than hydrophilic**. Putting it another way, the phase in which the emulsifying agent is more soluble will become the continuous or external phase of the emulsion. Although this theory may not represent a totally accurate depiction of the molecular arrangement of the emulsifier molecules, the concept that water-soluble emulsifiers generally do form o/w emulsions is important and is frequently encountered in practice.

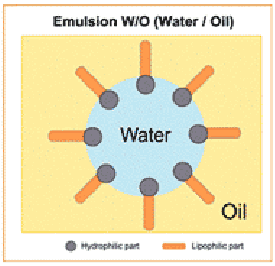
The plastic or interfacial film theory places the emulsifying agent at the interface between the oil and water, surrounding the droplets of the internal phase as a thin layer of film adsorbed on the surface of the drops. The film prevents contact and coalescing of the dispersed phase; the tougher and more pliable the film, the greater the stability of the emulsion. Naturally, enough of the film-forming material must be available to coat the entire surface of each drop of the internal phase. Here again, the formation of an o/w or a w/o emulsion depends on the degree of solubility of the agent in the two phases, with water-soluble agents encouraging o/w emulsions and oil-soluble emulsifiers the reverse.

In actuality, it is unlikely that a single theory of emulsification can explain the means by which the many and varied emulsifiers promote emulsion formation and stability. It is more than likely that even within a given emulsion system, more than one of the aforementioned theories play a part. For instance, lowering of the interfacial tension is important in the initial formation of an emulsion, but the formation of a protective wedge of molecules or film of emulsifier is important for continued stability. No doubt certain emulsifiers are capable of both tasks.

Emulsifying Agents

The initial step in preparation of an emulsion is selection of the emulsifier. To be useful in a pharmaceutical preparation, the emulsifying agent must be compatible with the other formulative ingredients and must not interfere with the stability or efficacy of the therapeutic agent. It should be stable and not deteriorate in the preparation. The emulsifier should be nontoxic with respect to its intended use and the amount to be consumed by the patient. Also, it should possess little odor, taste, or color. Of primary importance is **the capability of the emulsifying agent to promote emulsification and to maintain the stability of the emulsion for the intended shelf life of the product.**





Various types of materials have been used in pharmacy as emulsifying agents:

1. Carbohydrate materials, such as the naturally occurring agents acacia, tragacanth, agar, chondrus, and pectin. These materials form hydrophilic colloids which when added to water and generally produce o/w emulsions. Acacia is frequently used in the preparation of extemporaneous emulsions. Microcrystalline cellulose is employed in a number of commercial suspensions and emulsions as a viscosity regulator to retard particle settling and provide dispersion stability.

2. Protein substances, such as gelatin, egg yolk, and casein. These substances produce o/w emulsions.

3. High–molecular-weight alcohols, such as stearyl alcohol, cetyl alcohol, and glyceryl monostearate. These are employed primarily as thickening agents and stabilizers for o/w emulsions of certain lotions and ointments used externally. Cholesterol and cholesterol derivatives may also be employed in externally used emulsions to promote w/o emulsions.

4. Wetting agents, which may be anionic, cationic, or nonionic. These agents contain both hydrophilic and lipophilic groups, with the lipophilic protein of the molecule generally accounting for the surface activity of the molecule. In anionic agents, this lipophilic portion is negatively charged, but in the cationic agent, it is positively charged. Owing to their opposing ionic charges, anionic and cationic agents tend to neutralize each other and are thus considered incompatible . Nonionic emulsifiers show no inclination to ionize. Depending on their individual nature, certain of the members of these groups form o/w emulsions and others, w/o emulsions.

Anionic emulsifiers include various monovalent, polyvalent, and organic soaps, such as triethanolamine oleate, and sulfonates, such as sodium lauryl sulfate. Benzalkonium chloride, known primarily for its bactericidal properties, may be employed as a cationic emulsifier. Agents of the nonionic type include the sorbitan esters and the polyoxyethylene derivatives

The ionic nature of a surfactant is a prime consideration. Nonionic surfactants are effective over pH range of 3 to 10; cationic surfactants are effective over pH range of 3 to 7; and, anionic surfactants require a pH greater than 8.

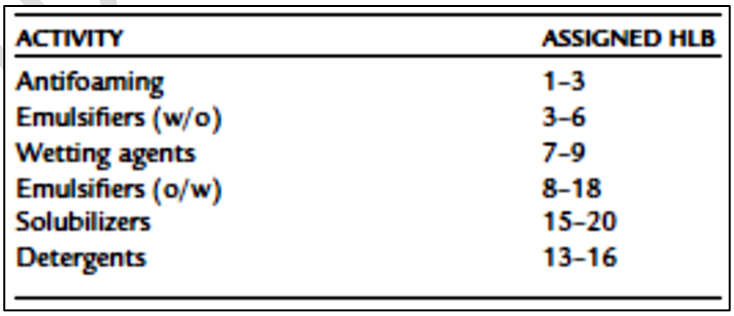
5. Finely divided solids such as colloidal clays, including bentonite, magnesium hydroxide, and aluminum hydroxide. Generally, these form o/w emulsions when the insoluble material is added to the aqueous phase if there is a greater volume of the aqueous phase than of the oleaginous phase. However, if the powdered solid is added to the oil and the oleaginous phase volume predominates, a substance such as bentonite is capable of forming a w/o emulsion.

The relative volume of internal and external phases of an emulsion is important, regardless of the type of emulsifier used. As the internal concentration of an emulsion increases, so does the viscosity of the emulsion to a certain point, after which the viscosity decreases sharply. At this point, the emulsion has undergone **inversion**; that is, it has changed from an o/w emulsion to a w/o, or vice versa. In practice, emulsions may be prepared without inversion with as much as about 75% of the volume of the product being internal phase.

The HLB System Generally

Each emulsifying agent has a hydrophilic portion and a lipophilic portion, with one or the other being more or less predominant and determines the type of emulsion. A method has been devised whereby emulsifying or surface-active agents may be categorized on the basis of their chemical makeup as to their hydrophil–lipophil balance, or HLB. By this method, each agent is assigned an HLB value or number indicating the substance's polarity. The usual range is between 1-20. Materials that are highly polar or hydrophilic have been assigned higher numbers than materials that are less polar and more lipophilic. Generally, surface active agents having an assigned HLB value of 3-6 are greatly lipophilic and produce w/o emulsions, and agents with HLB values of about 8-18 produce o/w emulsions.

In the HLB system, in addition to the emulsifying agents, values are assigned to oils and oil-like substances. One selects emulsifying agents having the same or nearly the same HLB value as the oleaginous phase of the intended emulsion. For example, mineral oil has an assigned 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. To prepare a stable emulsion, the emulsifying agent should have an HLB value similar to the one for mineral oil, depending on the type of emulsion desired. When needed, two or more emulsifiers may be combined to achieve the proper HLB value.



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

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Blending of Surfactants

Wetting agents are surfactants with HLB values of **7** to **9**. Wetting agents aid in attaining intimate contact between solid particles and liquids.

Emulsifying agents are surfactants with HLB values of **3** to **6** or **8** to **18**. Emulsifying agents reduce interfacial tension between oil and water, minimizing surface energy through the formation of globules.

Detergents are surfactants with HLB values of **13** to **16**. Detergents will reduce the surface tension and aid in wetting the surface and the dirt. The soil will be emulsified, and foaming generally occurs, and a washing away of the dirt.

Solubilizing agents have HLB values of **15** to **20**. HLB values are additive, and often surfactants are blended. For example, if 20 mL of an HLB of 9.0 is required, two surfactants (with HLB values of 8.0 and 12.0) can be blended in a 3:1 ratio. The following quantities of each will be required:

$0.75 \times 8.0 = 6.0$

$0.25 \times 12.0 = 3.0$

Total HLB = 9.0

Methods of Emulsion Preparation

Emulsions may be prepared by several methods, depending upon the nature of the components and the equipment. On a small scale, as in the laboratory or pharmacy, emulsions may be prepared using a dry Wedgwood or porcelain mortar and pestle or a mechanical blender or mixer. On a large scale, large mixing tanks may be used to form the emulsion through the action of a high-speed impeller.

In the small-scale extemporaneous preparation of emulsions, three methods may be used. They are the Continental or dry gum method, the English or wet gum method, and the bottle or Forbes bottle method. In the first method, the emulsifying agent (usually acacia) is mixed with the oil before the addition of water, that is, dry gum. In the second method, the emulsifying agent is added to the water (in which it is soluble) to form mucilage, and then the oil is slowly incorporated to form the emulsion, that is, wet gum. The bottle method is reserved for volatile oils or less viscous oils and is a variation of the dry gum method.

Continental or Dry Gum Method

The continental method is also referred to as the 4:2:1 method because for every 4 parts by volume of oil, 2 parts of water and 1 part of gum are added in preparing the initial or primary emulsion. In this method, the acacia or other o/w emulsifier is triturated with the oil in a perfectly dry Wedgwood or porcelain mortar until thoroughly mixed. A mortar with a rough rather than smooth inner surface must be used to ensure proper grinding action and reduction of the globule size. After the oil and gum have been mixed, the two parts of water are added all at once, and the mixture is triturated immediately, rapidly, and continuously until the primary emulsion is creamy white and produces a crackling sound to the movement of the pestle.

Provided the dispersion of the acacia in the oil is adequate, the dry gum method can almost be guaranteed to produce an acceptable emulsion. Sometimes, however, the amount of acacia must be adjusted upward to ensure that an emulsion can be produced. For example, volatile oils, liquid petrolatum (mineral oil), and linseed oil usually require a 3:2:1 or 2:2:1 ratio for adequate preparation.

English or Wet Gum Method

By this method, the same proportions of oil, water, and gum are used as in the continental or dry gum method, but the order of mixing is different, and the proportion of ingredients may be varied during the preparation of the primary emulsion as is deemed necessary by the operator. Generally, a mucilage of the gum is prepared by triturating in a mortar granular acacia with twice its weight of water. The oil is then added slowly in portions, and the mixture is triturated to emulsify the oil.

Bottle or Forbes Bottle Method

The bottle method is useful for the extemporaneous preparation of emulsions from volatile oils or oleaginous substances of low viscosities. Powdered acacia is placed in a dry bottle, two parts of oil are added, and the mixture is thoroughly shaken in the capped container. A volume of water approximately equal to that of the oil is then added in portions and the mixture thoroughly shaken after each addition. When all of the water has been added, the primary emulsion thus formed may be diluted to the proper volume with water. This method is not suited for viscous oils because they cannot be thoroughly agitated in the bottle when mixed with the emulsifying agent.

In Situ Soap Method

The two types of soaps developed by this method are calcium soaps and soft soaps. Calcium soaps are w/o emulsions that contain certain vegetable oils, such as oleic acid, in combination with limewater (synonym: Calcium Hydroxide Solution, USP). They are prepared simply by mixing equal volumes of the oil and limewater. The emulsifying agent in this instance is the calcium salt of the free fatty acid formed from the combination of the two entities. In the case of olive oil, the free fatty acid is oleic acid and the resultant emulsifying agent is calcium oleate.

A difficulty that sometimes arises when preparing this self-emulsifying product is that the amount of free fatty acids in the oil may be insufficient on a 1:1 basis with calcium hydroxide. Typically, to make up for this deficiency a little excess of the olive oil, or even a small amount of oleic acid, is needed to ensure a nice, homogeneous emulsion. Otherwise, tiny droplets of water form on the surface of the preparation. Because the oil phase is the external phase, this formulation is ideal where occlusion and skin softening are desired, such as for itchy, dry skin or sunburned skin.

STABILITY OF EMULSIONS

Generally speaking, an emulsion is considered to be physically unstable if (a) the internal or dispersed phase upon standing tends to form aggregates of globules, (b) large globules or aggregates of globules rise to the top or fall to the bottom of the emulsion to form a concentrated layer of the internal phase, and (c) if all or part of the liquid of the internal phase separates and forms a distinct layer on the top or bottom of the emulsion as a result of the coalescing of the globules of the internal phase.

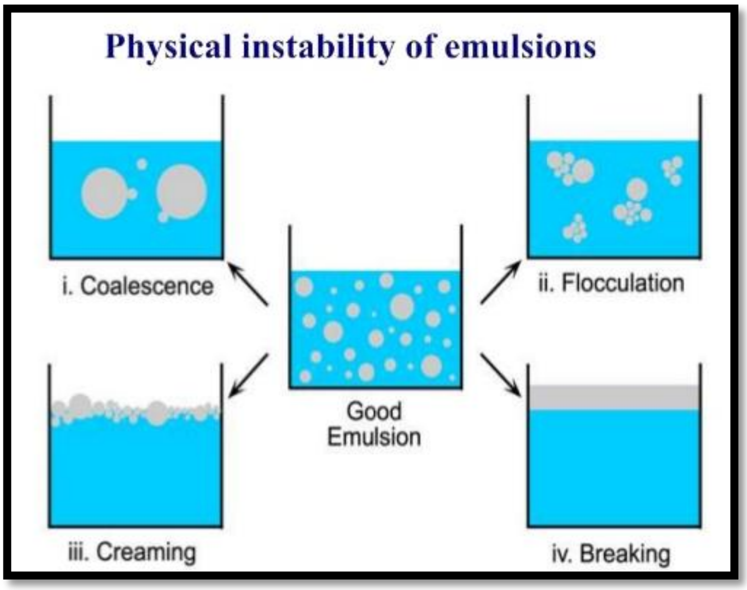
In addition, an emulsion may be adversely affected by microbial contamination and growth and by other chemical and physical alterations.

Aggregation & Creaming: Aggregates of globules of the internal phase have a greater tendency than do individual particles to rise to the top of the emulsion or fall to the bottom. Such a preparation of the globules is termed the **creaming** of the emulsion, and provided coalescence is absent, it is a reversible process.

The creamed portion of an emulsion may be redistributed rather homogeneously upon shaking, but if the aggregates are difficult to disassemble or if insufficient shaking is employed before each dose, improper dosage of the internal phase substance may result. Furthermore, a creamed emulsion is not esthetically acceptable to the pharmacist or appealing to the consumer. More important, it increases the risk that the globules will coalesce.

According to Stokes' equation, the rate of separation of the dispersed phase of an emulsion may be related to such factors as the particle size of the dispersed phase, the difference in density between the phases, and the viscosity of the external phase. It is important to recall that the rate of separation is increased by increased particle size of the internal phase, larger density difference between the two phases, and decreased viscosity of the external phase. Therefore, to increase the stability of an emulsion, the globule or particle size should be reduced as fine as is practically possible, the density difference between the internal and external phases should be minimal, and the viscosity of the external phase should be reasonably high. Thickeners such as tragacanth and microcrystalline cellulose are frequently added to emulsions to increase the viscosity of the external phase. Upward creaming takes place in unstable emulsions of the o/w in which the internal phase has a lesser density than the external phase. Downward creaming takes place in unstable emulsions in which the opposite is true.

More destructive to an emulsion than creaming is **coalescence** of the globules of the internal phase and separation of that phase into a layer. Separation of the internal phase from the emulsion is called breaking, and the emulsion is described as being cracked or broken. This is irreversible, because the protective sheath about the globules of the internal phase no longer exists. Attempts to reestablish the emulsion by agitation of the two separate layers are generally unsuccessful. Additional emulsifying agent and reprocessing through appropriate machinery are usually necessary to reproduce an emulsion.



Generally, care must be taken to protect emulsions against extremes of cold and heat. Freezing and thawing coarsen an emulsion and sometimes break it. Excessive heat has the same effect. Because emulsion products may be transported to and used in locations with climates of extremely high or low temperature, manufacturers must know their emulsions' stability before they may be shipped.

For most emulsions, the industry performs tests at 5°C, 40°C, and 50°C (41°F, 104°F, and 122°F) to determine the product's stability. Stability at both 5°C and 40°C for 3 months is considered minimal. Shorter exposure periods at 50°C may be used as an alternative test.

Because other environmental conditions, such as the presence of light, air, and contaminating microorganisms can adversely affect the stability of an emulsion, appropriate formulative and packaging steps are usually taken to minimize such hazards to stability. For light-sensitive emulsions, light-resistant containers are used. For emulsions susceptible to oxidative decomposition, antioxidants may be included in the formulation and adequate label warning provided to ensure that the container is tightly closed to air after each use. Many molds, yeasts, and bacteria can decompose the emulsifying agent, disrupting the system. Even if the emulsify er is not affected by the microbes, the product can be rendered unsightly by their presence and growth and will of course not be efficacious from a pharmaceutical or therapeutic standpoint. Because fungi (molds and yeasts) are more likely to contaminate emulsions than are bacteria, fungistatic preservatives, commonly combinations of methylparaben and propylparaben, are generally included in the aqueous phase of an o/w emulsion. Alcohol in the amount of 12% to 15% based on the external phase volume is frequently added to oral o/w emulsions for preservation.