Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

Emulsions

INTRODUCTION

Emulsification is the process of preparing emulsions, which are heterogenous systems consisting of at least one immiscible liquid intimately dispersed in another in the form of droplets, whose diameters generally exceed 0.1μ. Emulsions are also defined as thermodynamically unstable mixtures of two essentially immiscible liquids and are characterized by a third phase, an emulsifying agent.

The extemporaneous preparation of an emulsion depends on a number of considerations by the pharmacist. These include the purpose of the drug, internal or external use, concentration of the active drug, liquid vehicle, physicochemical stability of the drug, preservation, buffers, solubilizers, emulsifying agents, viscosity enhancers, colors and flavors.

DEFINITIONS AND CHARACTERISTICS

In emulsions, one phase is dispersed throughout the second phase as "globules". An emulsion consists, then, of a dispersed phase (internal phase, discontinuous phase), a dispersion medium (external phase, continuous phase) and a third component known as an emulsifying agent. There are different types of emulsifying agents as will be discussed later. The diameter of the dispersed phase globules is generally in the range of about 0.1 to 10μ, though some as small as 0.01μ and as large as 100μ are not uncommon.

Emulsions are used when two immiscible liquids must be dispensed in the same preparation for some

designated reason. Ordinarily, this means there is a polar and a nonpolar component, each of which is a liquid. When the dispersed phase is nonpolar (oil) and the external phase is polar (water), the emulsion is known as an oil-in-water emulsion. When the dispersed phase is water and the dispersion medium is oil, the emulsion is of the water-in-oil kind. Ordinarily, but not always, emulsions for internal use are of the oil-in-water type and emulsions for external use are of either type.

Water-in-oil emulsions are insoluble in water, not water-washable, will absorb water, are occlusive, and may be "greasy". Oil-in-water emulsions are miscible with water, are water washable, will absorb water, are nonocclusive, and are nongreasy.

USES AND APPLICATIONS

Emulsions are widely used in the form of topical creams and lotions. *Creams* are opaque, soft solids or thick liquids intended for external application, consisting of medicaments dissolved or suspended in water removable (vanishing cream) or emollient bases. They are of the water-in-oil or oil-in-water type. The term "cream" is most frequently applied to soft, o/w, cosmetically acceptable types of preparations. These usually are applied to moist, weeping lesions as they have somewhat of a "drying" effect in that the fluids will be miscible with the aqueous external phase of the creams. *Lotions* are fluid emulsions or suspensions for external application. They generally are applied to intertriginous areas, *i.e.*, where skin rubbing occurs as between fingers, thighs, under the arms, etc., as they have a lubricating effect.

Emulsions are used internally to dispense oil and water drugs together, mask the taste of poorly tasting oily drugs and sometimes to enhance the absorption

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The extemporaneous preparation of an emulsion depends on a number of considerations by the pharmacist.

Emulsions are used internally to dispense oil and water drugs together, mask the taste of poorly tasting oily drugs and sometimes to enhance the absorption of selected drugs.

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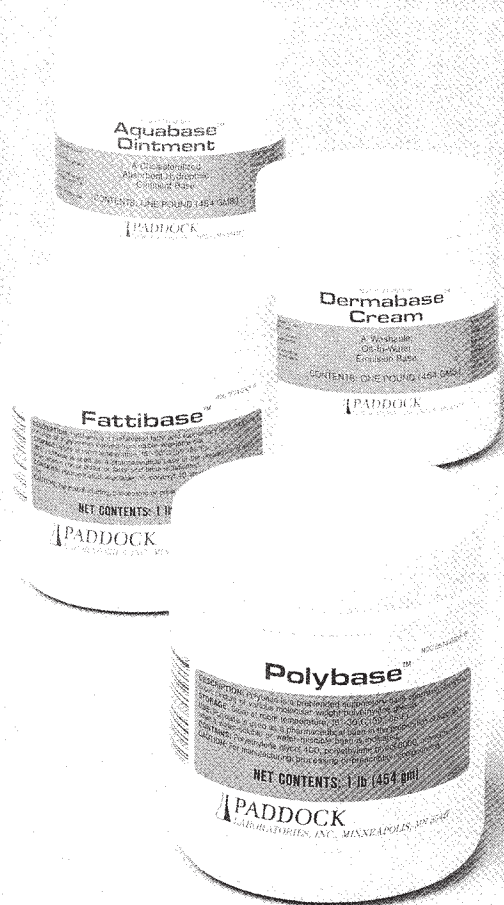
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of selected drugs. Intravenously-administered emulsions are widely used to administer high calorie oil to severely debilitated patients.

COMPOSITION

Generally, emulsions contain three components: a lipid phase, an aqueous phase and the emulsifier. Of these, the compounding pharmacist generally has greatest flexibility in the choice of the emulsifier. Emulsifiers that can be used are shown in Table 1.

TABLE 1	
Emulsifiers and Stabilizers for Emulsions	
Carbohydrates	Surfactants
Acacia	Anionic
Agar	Cationic
Chondrus	Nonionic
Pectin	Solids
Tragacanth	Aluminum hydroxide
Proteins	Bentonite
Casein	Magnesium hydroxide
Egg yolk	
Gelatin	
High Molecular Weight Alcohols	
Cetyl alcohol	
Glyceryl monostearate	
Stearyl alcohol	

DETERMINATION OF TYPE OF EMULSIONS

It is important to know whether an emulsion is o/w or w/o in the event additional ingredients must be added. The type of emulsion can be determined by some simple tests, including the drop dilution test, dye solubility test, electrical conductivity test, and the filter paper test. The drop dilution test is based on the principle that an emulsion is miscible with its external phase and is simply performed by dropping a small quantity of the emulsion onto a surface of water. If the drop is miscible with the water, it will spread, indicating that water is the external phase (an o/w emulsion). The dye solubility test is based on the principle that a dye disperses uniformly throughout an emulsion if it is soluble in the external phase and is conducted by adding a small quantity of a water soluble dye (powder or solution) to the emulsion. If it diffuses uniformly throughout the emulsion, water is the external phase (an o/w emulsion). The electrical conductivity test is based on the principle that water conducts an electric current while oils do not. Generally, o/w emulsions have a tendency to conduct electricity better than w/o emulsions, if the required equipment is available. The filter paper test involves putting a drop of emulsion onto a clean piece of filter paper. If the drop spreads rapidly into the filter paper, it is an o/w emulsion as water (the external phase) tends to spread more rapidly throughout the filter paper than does oil.

Multiple emulsions can be prepared by emulsifying an emulsion to add another external phase. An example would be the combination of a w/o emulsifier (sorbitan monooleate) with liquid petrolatum, addition to an aqueous phase to form a w/o emulsion, followed by dispersion in an aqueous solution of an o/w emulsifying agent (Tween 80) to form a final w/o/w emulsion. Similarly, an o/w/o emulsion can be prepared. Numerous applications suggested include detoxification, drug targeting/localization, prolonged acting dosage forms and potential application in cosmetics.

If two immiscible liquids are in contact with each other, they will tend to maintain as small an interface as possible. Consequently, it is very difficult to mix the two liquids. When they are shaken together, spherical droplets will form, as the liquids tend to maintain as small a surface area as possible and an interfacial tension will be maintained between the two liquids. When a "surface-active" ingredient is added, its molecules will tend to be oriented between the two faces with the

polar ends in the polar phase and the nonpolar ends in the nonpolar phase, which will lower interfacial tension. This will result in miscibility of the two liquids.

There are three different general methods whereby emulsifying agents aid in the formation of emulsions. These include (1) reduction of interfacial tension, (2) formation of a rigid interfacial film, and (3) formation of an electrical double layer. If the emulsifier concentration is sufficiently high, a rigid film can be formed between the immiscible phases which can act as a mechanical barrier to coalescence of the globules. An electrical double layer results in repulsive electrical forces between approaching droplets to minimize coalescence.

PREPARATION METHODS/ TECHNIQUES OF EMULSIONS

Emulsions do not form spontaneously when liquids are mixed, but rather require energy input to break up the liquids, resulting in an increased surface area of the internal phase. This energy input can be in the form of mechanical agitation, ultrasonic vibration or heat.

Emulsions generally can be prepared by manual and mechanical methods. Commonly used techniques involve the use of a mortar and pestle, electric mixer, hand homogenizer, shaking, sonifiers, and beakers.

A mortar and pestle can be used with both the English and Continental methods described below. For best results, the mortar should have rough surfaces to aid in shearing the liquid into small globules.

The ENGLISH METHOD, also called the Wet Gum Method, relies on the use of mucilages or dissolved gums and generally involves the use of a mortar and pestle. The ratio of oil:water:emulsifier often ranges from 3-4:2:1 for forming the primary emulsion. The mucilage is made first by adding a small quantity of water to the hydrocolloid, e.g. acacia, with trituration until uniform. The oil is added in small quantities with rapid trituration. The mixture will become thick and viscous. Additional water is added very slowly with rapid trituration until complete.

The CONTINENTAL METHOD, also called the Dry Gum Method, also generally uses the mortar and pestle. The ratio of oil:water:emulsifier for preparing the primary emulsion is generally approximately 4:2:1. The dry gum method involves mixing the hydrocolloid with the oil with rapid mixing for only a very short time, followed by the addition of all the water at once with very rapid trituration until a snapping sound is heard, This indicates that the primary emulsion is formed. The required amount of additional water is added slowly with rapid trituration until complete.

The bottle method (shaking) can be used in the preparation of emulsions containing volatile oils and other non-viscous oils. It avoids the splashing problem sometimes encountered using the mortar and pestle. The bottle method is a variation of the dry gum method and involves mixing the powder (emulsifier) and oil in a bottle followed by rapid shaking with short strokes. The required quantity of water is added all at once and the mixture shaken rapidly to form the primary emulsion (4:2:1 ratio). The additional water, if required, is added in small quantities with shaking after each addition. It is very important NOT to allow the oil and the gum to be in contact too long as the gum may imbibe the oil and cause the powder to become somewhat waterproof.

The beaker method is often used with synthetic emulsifying agents. The prescription ingredients generally are divided into two separate phases: oil and water. The two phases are heated individually to about 60-70°C, if needed. The internal phase is then added to the external phase with stirring. The product is removed from the heat and gently and periodically stirred, until cooled (congealed).

A mechanical stirrer using various impellers may be employed by placing the unit's propeller directly into the system to be emulsified. A number of mixers are available commercially and may be found in department stores and gourmet cook shops.

Hand homogenizers are available and function by forcing the mixture of liquids through a small inlet orifice at a high pressure, resulting in a breakup of the globules.

Incorporating materials into a water-in-oil emulsion:

Oils and insoluble powders can be incorporated directly using a pill tile and spatula or mortar and pestle. If large amounts of insoluble powders are required, it may be necessary to use a levigating agent. In many water-in-oil emulsions, there is sufficient agent to emulsify an additional reasonable quantity of an aqueous solution of a drug which can be incorporated on a pill tile with a spatula, mortar and pestle, or by gentle heat using a water bath. If heat is used, the preparation should not be held at a high temperature very long as loss of some water may occur, resulting in a change in volume of the product. The addition of oily ingredients usually poses no problem. Some crystalline drugs may need to be dissolved in oil first, if possible. It may be necessary to use the base form and not the salt form of a drug in this case. It is difficult to add water to these emulsions unless an excess quantity of the emulsifier is present.

Incorporating materials into an oil-in-water emulsion:

Insoluble powders and aqueous solutions can be incorporated using a pill tile and spatula or mortar and pestle. It may be advisable to use a levigating agent such as glycerin or propylene glycol to aid mixing of the insoluble powder with the emulsion. Crystalline materials should be dissolved in a small quantity of water prior to adding to the emulsion. Water-soluble materials can be added by dissolving the powder in a small quantity of water and incorporating the solution into the base. A small quantity of an oil may be incorporated directly into the base as there is usually an excess of emulsifying agent, but if larger amounts of an oil must be added, it may be necessary to add a small quantity of an oil-in-water surfactant to assist in uniform dispersion of the oil in the vehicle. It generally is easy to add water-soluble ingredients.

If heat is used while incorporating an ingredient into an oil-in-water vehicle, it is important to work quickly as water may be lost rather rapidly from the product. If this occurs, the product will change in volume and, if a semisolid, may tend to become stiff and "waxy".

EMULSIFYING AGENTS

The purpose of an emulsifying agent is to minimize the tendency of the globules to coalesce, or join together to form larger globules, with eventual separation of the two liquids. The stability of an emulsion is dependent upon the properties of the emulsifier and the film it forms at the interface between the two phases. The film at the interface must be both tough and elastic and should be rapidly formed during the preparation, or emulsification, process.

Emulsifying agents can be divided into three different categories: (1) surface-active agents, (2) hydrophilic colloids and (3) finely divided solid particles. Surface-active agents are adsorbed at oil:water interfaces to form monomolecular films, resulting in a decrease in interfacial tension. Hydrophilic colloids form multi-molecular films about the dispersed particles. Finely divided solid particles are adsorbed at the interface between the two liquid phases of the globules and form a film of particles around the dispersed globules. Common to each of these three categories is the formation of a "film".

HLB

The HLB (Hydrophile-Lipophile Balance) system is used for describing the characteristics of a surface-active agent. It consists of an arbitrary scale to which HLB values are experimentally determined and assigned. If the HLB value is low, there is a low number of hydrophilic groups on the surfactant and it is more lipophilic (oil soluble) than hydrophilic (water soluble). For example, Span 80 has an

HLB value of 4.3, from Table 2, and is oil soluble. If the HLB value is high, there is a large number of hydrophilic groups on the surfactant and it is more hydrophilic (water soluble) than oil soluble. For example, Tween 20 has an HLB value of 16.7 and is water soluble. Some general applications of materials with various HLB values are as follows:

Low	1-3	Antifoaming agents	
	3-6	Emulsifying agents	(w/o emulsions)
	7-9	Wetting agents	
	8-18	Emulsifying agents	(o/w emulsions)
	13-16	Detergents	
	16-18	Solubilizing agents	

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 resulting in 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, foaming may occur, and the dirt will wash away. Solubilizing agents have HLB values of 16 to 18.

An HLB of 10 or greater is primarily hydrophilic and less than 10 would be lipophilic. Spans have HLB values ranging from 1.8 to 8.6, indicative of oil-soluble or oil-dispersible molecules. Consequently, the oil phase will predominate and the emulsion formed will be water-in-oil. Tweens have HLB values between 9.6 to 16.7, characteristic of water-soluble or water-dispersible molecules. Therefore, the water phase will predominate and oil-in-water emulsions will be formed.

BLENDING OF SURFACTANTS

Often a blend of emulsifiers produces a more stable emulsion than the use of a single emulsifier with the correct, calculated HLB. Since the HLB numbers are additive, the HLB value of a blend can be calculated.

For example if 20 mL of an HLB of 9.65 are required, then two surfactants (with HLB values of 8.6 and 12.8) can be blended in a

TABLE 2
HLB Values of Emulsifiers

Commercial Name	Chemical Name	HLB Value
Acacia	Acacia	12.0
Glyceryl monostearate	Glyceryl monostearate	3.8
Methocel 15 cps	Methylcellulose	10.5
PEG 400 Monoleate	Polyoxyethylene monooleate	11.4
PEG 400 Monostearate	Polyoxyethylene monostearate	11.6
PEG 400 Monolaurate	Polyoxyethylene monolaurate	13.1
Parmagel B	Gelatin	9.8
Potassium oleate	Potassium oleate	20.0
Sodium lauryl sulfate	Sodium lauryl sulfate	40
Sodium oleate	Sodium oleate	18
Span 20	Sorbitan monolaurate	8.6
Span 40	Sorbitan monopalmitate	6.7
Span 60	Sorbitan monostearate	4.7
Span 65	Sorbitan tristearate	2.1
Span 80	Sorbitan monooleate	4.3
Span 85	Sorbitan trioleate	1.8
Tragacanth	Tragacanth	13.2
Triethanolamine oleate	Triethanolamine oleate	12
Tween 20	Polyoxyethylene sorbitan monolaurate	16.7
Tween 21	Polyoxyethylene sorbitan monolaurate	13.3
Tween 40	Polyoxyethylene sorbitan monopalmitate	15.6
Tween 60	Polyoxyethylene sorbitan monostearate	14.9
Tween 61	Polyoxyethylene sorbitan monostearate	9.6
Tween 65	Polyoxyethylene sorbitan tristearate	10.5
Tween 80	Polyoxyethylene sorbitan monooleate	15.0
Tween 81	Polyoxyethylene sorbitan monooleate	10.0
Tween 85	Polyoxyethylene sorbitan trioleate	11.0

3:1 ratio. The following quantities of each will be required:

$$\frac{3}{4} \times 8.6 = 6.45 \ (15 \ mL)$$
$$\frac{1}{4} \times 12.8 = 3.20 \ (5 \ mL)$$
$$TOTAL \ HLB = 9.65 \ (20 \ mL)$$

PRESERVATION OF EMULSIONS

Emulsions will support microbiological growth. Contamination of the products can occur during the preparation of the emulsion as well as during its use. To minimize contamination, the work area and equipment should be clean and every attempt made to produce a "clean" product. However, if the product is to be stored for any length of time, consideration must be given to the addition of a preservative.

TABLE 3	
Required HLB Values for Some Common Lipid Material to Prepare o/w Emulsions	
Material	**Required HLB**
Beeswax	12
Cetyl alcohol	15
Cottonseed oil	10
Lanolin, anhydrous	10
Mineral oil, light/heavy	12
Paraffin wax	11
Petrolatum	12
Stearic acid	15
Stearyl alcohol	14

TABLE 4	
Preservatives Used for Emulsions	
Alcohol	15%
Benzoic acid, sodium benzoate (pH $\leq$ 4)	0.05-0.10%
Benzyl alcohol (pH $\triangleright$ 5)	1-4%
Chlorobutanol*	0.5%
Imidazolidinyl Urea (Imidurea)	0.05-0.5%
Mercurials	0.005%
Organic Mercurials	
Phenylmercuric Nitrate	0.002-0.004%
Phenylmercuric Acetate	0.002-0.004%
Thimerosal	0.005-0.02%
Parabens**	
Methylparaben	0.05-0.3%
Propylparaben	0.02-0.2%
Butylparaben	0.02-0.2%
Quaternary Ammonium Compounds	
Benzalkonium Chloride	0.002-0.1%
Sorbic acid (pH $\triangleleft$ 6)	0.1-0.2%

*Chlorbutanol needs a Ph $\triangleleft$ 5, It will also sorb to plastic.
**Usually used in pairs. Low water solubility. Poor taste. May degrade at a pH $\triangleright$ 8. Use at pH 4-8.

A preservative must be nontoxic, stable, compatible, inexpensive, and have an acceptable taste, odor and color. It should also be effective against a wide variety of bacteria, fungi and yeasts.

Preservatives may partition into the oil phase and lose their effectiveness. Bacterial growth normally will occur in the acqueous phase. Consequently, the preservative should be concentrated in the acqueous phase. Additionally, since the un-ionized form of the preservative will be more effective against bacteria, the majority of the preservative should be present in the non-ionized state. The preservative must neither be bound nor adsorbed to any agent in the emulsion or the container in order to be effective. In summary, only the preservative in the aqueous phase in the free, unbound, unadsorbed, un-ionized state will be effective in emulsions. Example preservatives often used in emulsions are shown in Table 4. The parabens (methylparaben, propylparaben, butylparaben) are among the most satisfactory preservatives for emulsions.

ANTIOXIDANTS FOR EMULSIONS
Oils and fats are subject to rancidification resulting in a product exhibiting an unpleasant odor, appearance and taste. In order to minimize this, antioxidants can be added to the preparation. Example antioxidants are listed in Table 5.

FLAVORING EMULSIONS
The selection of an appropriate flavoring agent must be made with consideration of the external phase of the emulsion. For example, if a flavoring oil is used and the majority partitions into the internal phase, the flavor strength will be reduced. Oils can be incorporated using small quantities of surfactants (usually surfactants with HLB values of 15-18 are used, often in conjunction with a surfactant with an HLB value in the range of 8 to 12). As a general rule, from three to five times as much surfactant as oil is required to insure solubilization. In order to accomplish this with best results, the oil should be mixed with the surfactants prior to addition into the aqueous phase. Since there is a loss of some of the potency of the flavor using this technique, an alternative is to use a cosolvent system rather than a surfactant system to incorporate the flavor. The use of ethanol, glycerin or some appropriate solvent often provides acceptable results.

EMULSION STABILITY
Emulsion stability can be enhanced by (1) decreasing the globule size of the internal phase, (2) obtaining an optimum ratio of oil to water, and (3) increasing the viscosity of the system. Since the oil-to-water ratio is frequently determined by the referring physician (concentration of active ingredient: oil), the compounding pharmacist can work with the first and third items listed above to enhance the emulsion's stability.

TABLE 5

Antioxidants for Emulsions
Ascorbic acid
Ascorbyl palmitate
Butylated hydroxyanisole
Butylated hydroxytoluene
Gallic acid
4-Hydroxymethyl-2, 6, -di-tert-buylphenol
Propyl gallate
Sulfites
L-Tocopherol

If the globule size is reduced to less than 5 microns, the stability and dispersion of the emulsion will increase. This can be accomplished with the shearing action of a mortar/pestle and an homogenizer.

The optimum phase volume ratio generally is obtained when the internal phase is about 40-60% of the total quantity of the product. As the percentage of the internal phase increases, the viscosity of the product also increases.

Enhancement of viscosity of the external phase also will tend to enhance the stability of the emulsion. This is accomplished by the addition of a substance which is soluble in or miscible with the external phase of the emulsion. For o/w emulsions, hydrocolloids can be used. For w/o emulsions,waxes and viscous oils as well as fatty alcohols and fatty acids can be used.

Of obvious concern in the preparation of emulsions is their physical stability. This is characterized by an absence of creaming and coalescence and the maintenance of the original appearance, odor, color and other physical properties.

Creaming occurs when the globules flocculate and concentrate in one specific part of the emulsion. This results in a lack of uniformity of drug distribution and unsightly product. Creaming is most often characterized in o/w emulsions by the oil globules gathering and rising to the top. This is due to a the fact that the oil generally is less dense than the water phase. Creaming is easily reversible and the product can be evenly redistributed by shaking. It is reversible because the dispersed globules still have the protective film around them. Two methods of minimizing creaming include enhancing the viscosity of the external aqueous phase and reducing the globule size to a very fine state with an homogenizer. Another approach would be to adjust the densities of both the internal and external phase so that the densities are the same, which would result in no tendency for either phase to rise to the top or settle to the bottom.

Coalescence, or breaking, is an irreversible process since the film surrounding the individual globules has been destroyed. Viscosity alterations may help to stabilize these and minimize a tendency to coalescence. An optimum viscosity can be experimentally determined. Another factor is the phase volume ratio, or the ratio of the internal volume to the total volume of the product. A maximum phase volume ratio that can be achieved, assuming perfectly spherical particles, is 74%. In general, a phase-volume ratio of about 50%, which approximates loose packing of spherical particles (*i.e.*, a porosity of 48% of the total bulk volume of a powder), results in a reasonably stable emulsion.

PHASE INVERSION

Phase inversion can be viewed as both good and bad. It occurs when an emulsion inverts from one form to another, that is, o/w to w/o or w/o to o/w. Phase inversion **can** result in the formation of a better emulsion and is the basis for the Continental method of emulsion preparation. Monovalent cations tend to form o/w emulsions and divalent tend to form w/o emulsions. If sodium stearate is used initially to form an o/w emulsion, followed by the addition of a calcium salt to form calcium stearate, then the emulsion inverts from an o/w into a w/o emulsion. The Continental method of emulsion preparation involves the use of a small proportion of water in the presence of a large proportion of oil. The initial emulsion nucleus that is formed is of the w/o type. Further addition of water, in small quantities, eventually results in an inversion into an o/w emulsion.

General Comments on Emulsions
- The viscosity of emulsions generally increases upon aging.
- The greater the volume of the internal phase, the greater the apparent viscosity.
- There is a linear relationship between emulsion viscosity and the viscosity of the continuous phase.
- It has been said that, under a given set of conditions, an oil-in-water emulsion is more easily produced with glass equipment and a water-in-oil emulsion is more easily produced with water-repellent plastic equipment. This could be related to the "wettability" of the external phase in contact with the surface of the equipment.

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