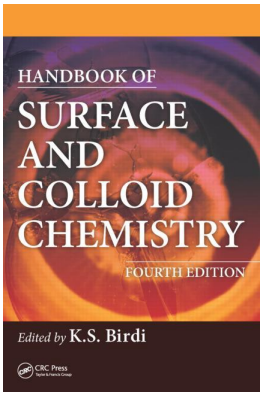

Handbook of Surface and Colloid Chemistry Fourth Edition

K.S. Birdi

Microemulsions and Their Applications in Drug Delivery

Publication details
https://www.routledgehandbooks.com/doi/10.1201/b18633-11
Wang Ziheng, Pal Rajinder
Published online on: 25 Jun 2015

10 Microemulsions and Their Applications in Drug Delivery

Ziheng Wang and Rajinder Pal

CONTENTS

10.1 INTRODUCTION

Microemulsions are being increasingly used as vehicles for lipophilic drugs. They can be used for parenteral drug delivery systems (Date and Nagarsenker 2010) or could be encapsulated into softgel capsules as a convenient solid dosage form (Gullapalli 2010). In contrast to conventional emulsions, microemulsions are small droplet size (typically between 20 and 200 nm) (Talegaonkar et al. 2008) and exhibit long-term stability (McClements 2012). They have been proven to promote the gastric-intestinal (GI) absorption of lipophilic drugs and consequently enhance the bioavailability of some active pharmaceutical ingredients (API) (Lawrence and Rees 2000). Food and Drug Administration in the United States (U.S. FDA) has classified APIs into four groups based on the Biopharmaceutical Classification System (BCS). APIs in class II (high permeability, low solubility) and class IV (low permeability, low solubility) are ideal candidates for microemulsion-based drug delivery systems due to their poor solubility in the aqueous phase. Table 10.1 gives examples of drugs that have been successfully delivered in microemulsion form.

Microemulsions are isotropic, thermodynamically stable systems. They appear to be transparent (or translucent) (Lawrence and Rees 2000). They can be easily prepared and identified in different ways. For example, when 7 mL of a household liquid detergent, 14 mL of white spirit,

TABLE 10.1
Examples of Drugs Delivered in Microemulsion Form

Drug Name	Usage	References
Paclitaxel	Anticancer	Gao et al. (2003)
Fenofibrate	Antihyperlipidemic	Liang et al. (2006)
Cholesterol ester transfer protein (CETP) inhibitors		Gumkowski et al. (2005)
Atorvastatin		Shen and Zhong (2006)
Fluvastatin		Benameur et al. (2003)
Rapamycin	Immunosuppressive drug	Fricker et al. (2006)
Cyclosporine		Ward and Cotter (1987)
Felodipine	Antihypertensive drug	Von Corswant (2003)
Nifedipine		Rudnic et al. (1999)
Indomethacin	Analgesic drug	Farah and Denis (2000)
Ibuprofen		Bauer et al. (2002)
Naproxen		Mulye (2002)
Tipranavir	Anti-HIV drug	Chen and Gunn (2003)
Progesterone	Hormone	Gao and Morozowich (2003)
Testosterone		Gao and Morozowich (2003)
Fish oil	Nutrition supplement	Mishra et al. (2001)
Acyclovir	Antiviral drug	Burnside et al. (1999)
Melatonin	Immunomodulator	Eugster et al. (1996)

and 4 mL of *n*-pentanol (amyl alcohol) or *n*-butanol are gently mixed, a two-phase system is produced at equilibrium (Makoto 1998) where the upper oil phase of the system exhibiting a strong Tyndall effect is identified as the microemulsion phase (Makoto 1998). Microemulsion-based drugs normally exhibit long shelf-life due to the high stability of microemulsions. Other advantages of using microemulsion as a lipophilic drug carrier include the enhanced bioavailability (due to small droplet size) and the ease of formation (due to low interfacial tension) (Lawrence and Rees 2000; Talegaonkar et al. 2008). The small droplet size of microemulsion also facilitates the permeability of the drug passing through the mucous membrane. Microemulsion-based drugs can be delivered through different routes such as oral delivery as softgel capsules (Kovarik et al. 1994), topical or transdermal delivery as lotions (Gupta et al. 2005), and parenteral delivery as intramuscular and intravenous injections (Von Corswant et al. 1998).

Microemulsions are ternary systems containing oil, water, and surfactant. The terms "oil" and "water" in a microemulsion system normally refer to "oil phase (oil and oil soluble components such as cyclosporine)" and "aqueous phase (water and water soluble components such as sodium chloride)," respectively. The phase behavior of water–oil–surfactant mixtures was extensively studied by Winsor (1948). Based on his experimental observations, Winsor classified equilibrium mixtures of water–oil–surfactant into four systems: (1) type I (Winsor I) system where water continuous or oil-in-water (O/W) type microemulsion coexists with the oil phase. In these systems, the aqueous phase is surfactant-rich; (2) type II (Winsor II) system where oil continuous or water-in-oil (W/O) type microemulsion coexists with the aqueous phase. In these systems, the oil phase is surfactant-rich; (3) type III (Winsor III) system where bicontinuous type microemulsion (also referred to as surfactant-rich middle-phase) coexists with excess oil at the top and excess water at the bottom; and (4) type IV (Winsor IV) system where only a single-phase (microemulsion) exists. The surfactant concentration in type IV microemulsion is generally greater than 30 wt%. Type IV microemulsion could be water continuous, bicontinuous, or oil continuous depending on the chemical composition. The phase behavior of microemulsions is often described as a *fish* diagram shown in Figure 10.1 (Komesvarakul et al. 2006).

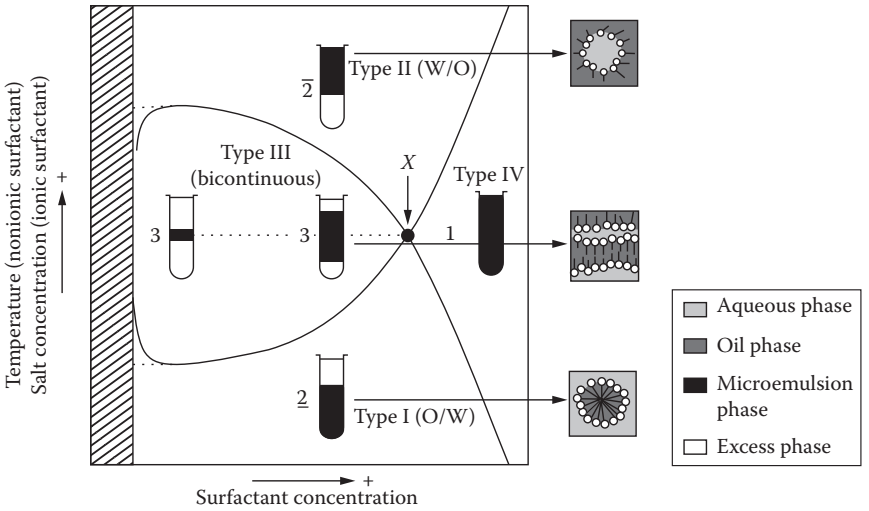

FIGURE 10.1 *Fish* diagram: 1—single-phase region; 2—two-phase region (upper bar: microemulsion phase at the top; lower bar: microemulsion phase at the bottom); and 3—three-phase region. *X*: tri-critical point. This diagram assumes that the density of the aqueous phase is greater than that of the oil phase. (Adapted from Komesvarakul, N. et al., *J. Cosmet. Sci*., 55, 309, 2006.)

10.1.1 Continuous and Dispersed Phases

The fluid phase of a microemulsion in which oil or water is distributed as droplets is called continuous phase. Oil or water droplets dispersed in the continuous phase are collectively called dispersed phase. In type I microemulsion, the dispersed phase is oil and the continuous phase is water. Type II microemulsions have a reverse arrangement in that the dispersed phase is water and the continuous phase is oil. There is no dispersed phase in type III microemulsion as type III microemulsion is bicontinuous in nature. Likewise the bicontinuous form of type IV microemulsion has no dispersed or continuous phase. The concept of dispersed and continuous phases is important in quantifying the droplet size of microemulsion. The droplet size distribution can be obtained for different types of microemulsions using dynamic light scattering (DLS). However, one should keep in mind that the droplet size distribution is meaningless for type III or type IV bicontinuous microemulsion due to its bicontinuous nature.

10.1.2 Surfactants

Surfactants are amphiphilic molecules composed of both hydrophilic part (e.g., ethylene oxide group) and hydrophobic part (e.g., alkyl chain). There are three types of surfactants: ionic (anionic and cationic), nonionic, and zwitterionic. The hydrophilic part of surfactant bears either negative charge (anionic) or positive charge (cationic) in the case of ionic surfactant, no charge in the case of nonionic surfactant, and both negative and positive charges in the case of zwitterionic surfactant. At a very low concentration of surfactant, the surfactant molecules exist as monomers in the base liquid. The surfactant molecules also adsorb onto the interface between two immiscible phases (oil–water or gas–liquid interfaces). With the increase in surfactant concentration, the surfactant molecules begin to aggregate. As an example, consider the addition of surfactant to water. The surfactant molecules initially disperse in water as monomers and also adsorb on to the air–water interface till they reach surface saturation. Then monomers in water begin to aggregate as clusters with their hydrophobic groups toward the interior of clusters and their hydrophilic groups toward water. These clusters are called *micelles* and the concentration where micelles

begin to form is called the *critical micelle concentration* (cmc) of the surfactant (Rosen 2004). The cmc of a surfactant makes it unique from other amphiphilic molecules. For example, the molecules of a co-surfactant are also amphiphilic but co-surfactants generally have no cmc. With continuous addition of surfactant to water above cmc, changes in the microstructure of surfactant/water system occur as shown in Figure 10.2a from spherical micelle solution to cylindrical micelle solution to hexagonal liquid crystal (LC) to cubic liquid crystal and to lamellar liquid crystal. Note that liquid crystal (LC) is a material in semisolid state that has both organized structure (like solid) and disordered structure (like liquid) at a molecular level. The changes in the microstructure summarized in Figure 10.2a are normally accompanied by changes in the viscosity of the system. For example, the viscosity of LC is much higher than that of micellar solutions; hexagonal LC has the highest viscosity among the three types of liquid crystals (Rosen 2004). It should be noted that the lamellar structure could be either flat or curved depending on the surfactant structure (Kik et al. 2005).

When surfactant is added to oil, the surfactant molecules form micelles as usual at surfactant concentrations above cmc but the micelles formed in oil are called *reverse micelles* as they have a reverse arrangement of surfactant molecules as compared with the arrangement of surfactant molecules in micelles formed in aqueous systems. In reverse micelles, the hydrophilic heads of the

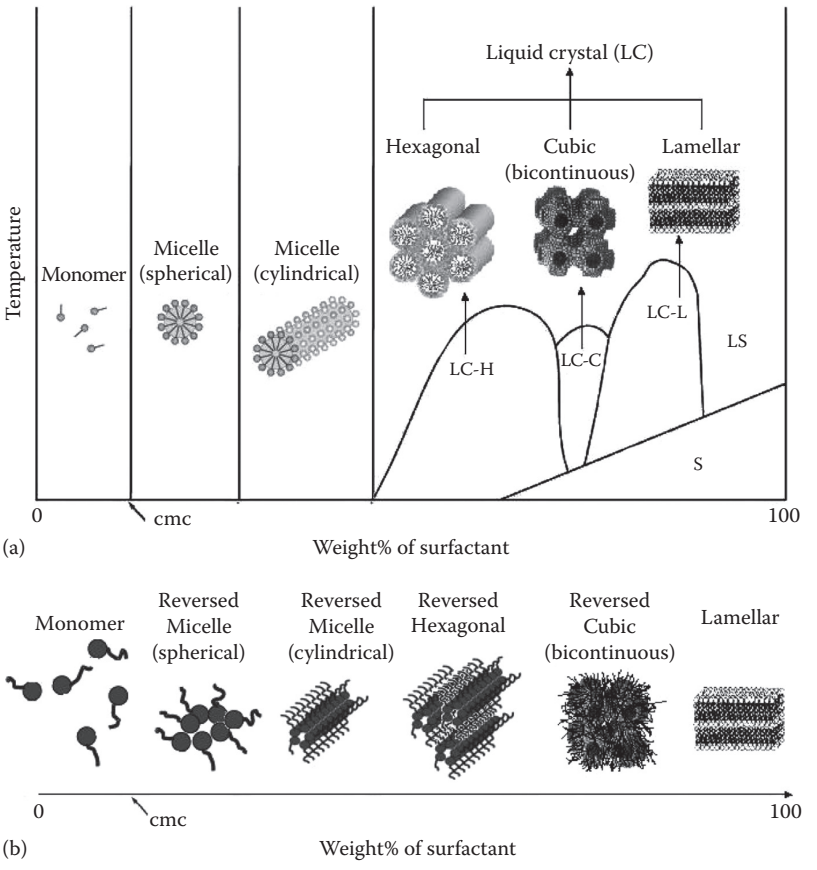

FIGURE 10.2 (a) Phase diagram of surfactant–water system. LC-H, liquid crystal-hexagonal region; LC-C, liquid crystal-cubic region; LC-L, liquid crystal-lamellar region; LS, liquid surfactant region (water in surfactant); and S, solid region. (b) Microstructural changes in surfactant–oil system with the increase in surfactant concentration. (Adapted from Rosen, M.J., *Surfactants and Interfacial Phenomena*, 3rd edn., John Wiley & Sons, Inc., New York, 2004, pp. 1–33, 110–113, 208–234.)

surfactant molecules are inside the micelles and the hydrophobic tails of the surfactant molecules extend away from the core of the micelles to the oil phase. Figure 10.2b shows the microstructural changes that occur upon continuous addition of surfactant to oil (Rosen 2004).

The adsorption of surfactant at the interface alters the interfacial free energy. The interfacial free energy is defined as the minimum work required to create the interface (Rosen 2004). Interfacial tension (γ), which is the interfacial free energy normalized by area, is the minimum work required to create the interface of unit area. Physically, interfacial tension is a measure of the strength of interaction between two phases. The higher the interfacial tension, the weaker is the interaction between the two phases. For example, pure trichloroethylene (TCE) and water are immiscible phases with $\gamma = 39.6$ mJ/m^2 at 25°C (Ma et al. 2008). To create interfacial contact area between the two phases, that is, to formulate TCE–water emulsions, energy input exceeding 39.6 mJ/m^2 is required. With the addition of certain amounts of anionic surfactant sodium oleate (SO) and cationic surfactant benzethonium chloride (BC), γ can be lowered to as low as 3.7 ± 0.4 mJ/m^2 (Wang and Acosta 2013). This reduction in interfacial tension occurs because the surfactant partitions between TCE and water phases, and as a result, an increase in interaction between TCE and water phases is observed. Due to a decrease in the interfacial tension, less energy input is required to create new interfacial contact area. It should be noted that γ should be very low (as low as 1 mJ/m^2 or lower) in order to formulate microemulsions (Upadhyaya et al. 2006). Due to a very low interfacial tension, microemulsions are normally formed under gentle agitation with ultralow energy input (e.g., stomach agitation in vivo is sufficient). To achieve ultralow values of interfacial tension, it is often necessary to add a co-surfactant to the system. Thus, microemulsions are usually formulated using a combination of surfactant and co-surfactant.

In the pharmaceutical field, nonionic surfactants are widely used as they are less irritative than ionic surfactants (Mason et al. 2006). Before the design and formulation of any microemulsion-based drug delivery system, it is important to consult the inactive ingredient guide (IIG) published by FDA on their website to check the limits for different surfactants.

10.1.3 Co-Surfactant and Linker

Co-surfactant is a small amphiphilic molecule. It has smaller head and tail groups as compared with a surfactant molecule. The most common types of co-surfactants are C_3–C_6 alcohols, such as *sec*-butanol (Salager et al. 2005). The co-surfactant adsorbs at the oil–water interface and modifies the formulation requirements. For example, it modifies the hydrophilic–lipophilic balance (*HLB*) requirement of the surfactant. Co-surfactants with short chain lengths (C_3–C_5) tend to be more hydrophilic whereas co-surfactants with long chain lengths (C_5 or higher) tend to be more lipophilic. Therefore, a less hydrophilic surfactant is required in the formulation when co-surfactants with short chain lengths (C_3–C_5) are used, whereas a less lipophilic surfactant is required when co-surfactants with long chain lengths (C_5 or higher) are used (Bavière et al. 1981). The co-surfactants also interfere in the surfactant–surfactant interactions by pushing the surfactant molecules apart, disrupting the LC structure, and reducing the viscosity of the mixture (Jones and Dreher 1976). The weight ratio of surfactant to co-surfactant can vary from 1:0.5 (w/w) to 1:3 (w/w), depending on the stability of the system (Kang et al. 2004; Wang and Pal 2014).

As already noted, the addition of co-surfactant to a microemulsion modifies the *HLB* requirement of the surfactant. The addition of co-surfactant also replaces a certain amount of surfactant at the oil–water interface. These effects need to be compensated for in the formulation design in order to obtain a microemulsion that has the same phase behavior as that of one without the presence of a co-surfactant. For example, the contribution of ethanol as a co-surfactant is hydrophilic. Therefore, the surfactant needs to be less hydrophilic, which can be achieved by reducing the number of ethylene oxide groups in the surfactant structure. However, a higher surfactant concentration is required in the formulation since ethanol as a co-surfactant replaces some of the surfactant from oil–water interface (Salager et al. 2005). In practice, *sec*-butanol or a mixture of propanol and

butanol (1:1 in weight ratio) is often selected as a co-surfactant in order to disrupt the order of the LC structure while maintaining the original phase behavior (Salager et al. 2005).

With the increase in alkyl chain length of a co-surfactant, the mixture of surfactant and co-surfactant becomes more lipophilic. However, the adsorption of co-surfactant at the interface becomes less significant. This is because a long-chain alcohol has more affinity for the oil phase. Therefore, instead of replacing surfactant at the oil–water interface by pushing the head groups of surfactant molecules apart at oil–water interface, a long chain co-surfactant preferentially stays with the hydrophobic part of the surfactant (e.g., tail group). This type of co-surfactant with long alkyl chain length ($>C_{10}$) is called a lipophilic *linker* (Salager et al. 2005). A linker is different from co-surfactant in that the linker is either hydrophilic or lipophilic enough to co-adsorb at only one side of the oil–water interface whereas co-surfactant interacts with both oil and water phases and replaces the surfactant at the oil–water interface. Due to the co-adsorption effect, microemulsions formulated using linkers may exhibit larger solubilization capacity than the ones without a linker (Acosta et al. 2005). Typical linkers include hexyl glucoside (hydrophilic linker), sorbitan monooleate (lipophilic linker), and long chain ($>C_{10}$) alcohols (lipophilic linker) (Acosta et al. 2005).

10.1.4 Microemulsion and Nanoemulsion: Their Similarities and Differences

Microemulsion is a self-assembling nano-scale emulsion whereas nanoemulsion is a nano-scale emulsion formed under intense mechanical shear (McClements 2012). Microemulsion is an isotropic solution of oil and water, prepared using a high surfactant concentration of around 40 wt% under gentle stirring or shaking. The usage of a large concentration of surfactant ensures ultralow oil–water interfacial tension and spontaneous formation of microemulsion without any mechanical shear. The preparation of nanoemulsions requires very high shear in order to rupture large droplets into nano-scale droplets. The mechanical shear should be intensive enough to overcome the large interfacial tension (McClements 2011).

Thermodynamically, the change in free energy to formulate either a microemulsion or a nanoemulsion from two separate phases (i.e., $\Delta G_{\text{formation}}$) can be expressed as follows (McClements 2012):

$$\Delta G_{\text{formation}} = \Delta G_I + (-T\Delta S) \tag{10.1}$$

where

ΔG_I (J/mol) is the change in interfacial free energy
$-T\Delta S$ (J/mol) is the entropic contribution to free energy of formation

The entropic contribution is due to the change in configuration from two stratified phases to an emulsion with a large number of droplets. The change in the interfacial free energy ΔG_I is given as follows:

$$\Delta G_I = \gamma \Delta A \tag{10.2}$$

where

γ is the interfacial tension
ΔA is the increase in the interfacial contact area between the phases due to the formation of a microemulsion or a nanoemulsion

The change in interfacial free energy ΔG_I is always positive in the formation of a microemulsion or a nanoemulsion as both γ and ΔA are positive; positive ΔA is due to an increase in the interfacial area between oil and water when droplets are formed. The entropy contribution $-T\Delta S$ is always negative as both T and ΔS are positive; positive ΔS is due to an increase in the disorder of the

system when droplets are formed. Therefore, $\Delta G_{\text{formation}}$ can be either positive or negative depending on the balance between ΔG_I and $-T\Delta S$. In the case of microemulsions, $\Delta G_{\text{formation}}$ is negative and therefore microemulsions are formed spontaneously and are thermodynamically stable systems. The $\Delta G_{\text{formation}}$ is negative in microemulsions due to an ultralow value of interfacial tension between oil and water. Unlike microemulsions, nanoemulsions are thermodynamically unstable systems as $\Delta G_{\text{formation}}$ is positive due to high interfacial tension between the oil and water phases. Although nanoemulsions are thermodynamically unstable systems, they can be made kinetically stable due to steric stabilization of the droplets.

Kinetically, the rate of separation of nanoemulsion into two separate phases can be described by the Arrhenius equation (Missen et al. 1999):

$$k = Ae^{-E_a/RT} \tag{10.3}$$

where

k is the rate constant
A is the pre-exponential factor
E_a is the activation energy
R is the universal gas constant
T is the absolute temperature (in K)

At constant temperature, the rate of separation of nanoemulsion into separate phases depends on the activation energy.

10.2 CHARACTERIZATION OF MICROEMULSIONS

10.2.1 Types of Microemulsions

As shown in Figure 10.1, four types of microemulsion systems can be formulated. In type I to type III microemulsion systems, two or more phases are present in equilibrium with each other. Only in the case of type IV (Winsor IV) microemulsion, a single phase is present. However, type IV microemulsion could be either water continuous, bicontinuous, or oil continuous. Several techniques could be used to identify different types of microemulsions. For example, the Tyndall effect can be observed in the lower phase of type I, middle phase of type III, and upper phase of type II microemulsion by simply pointing a laser pointer toward the sample as shown in Figure 10.3.

The change in electrical conductivity can be used to differentiate different types of microemulsions. For example, type II or type IV oil continuous microemulsions have a very low electrical conductivity (say less than 1 μS/cm); type III or type IV bicontinuous microemulsions have a medium electrical conductivity (say in between 1 and 10 μS/cm); and type I or type IV water continuous

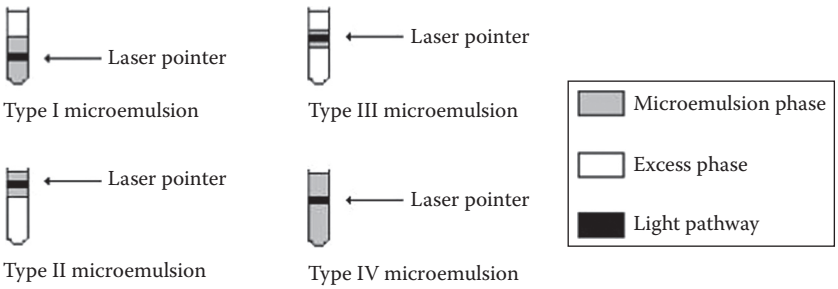

FIGURE 10.3 Tyndall effect in type I, II, III, and IV microemulsions. These observations assume that the density of the oil phase is smaller than that of the water phase.

microemulsions have a high conductivity (say greater than 10 μS/cm) due to water as the continuous phase (Krauel et al. 2005).

The phase transition from type IV oil continuous microemulsion to type IV water continuous microemulsion could be captured by observing changes in the viscosity (Watanabe et al. 2004). For example, the viscosity of type IV oil continuous (W/O) microemulsion rises slowly initially with the increase in water concentration. With further addition of water the viscosity begins to increase sharply. The increase in viscosity is mainly due to the transition from type IV oil continuous (W/O) microemulsion to type IV bicontinuous microemulsion. The viscosity reaches a maximum value at some water concentration. Upon further increase in water concentration, the transition of type IV bicontinuous microemulsion to type IV water continuous (O/W) microemulsion occurs resulting in a sharp decrease in viscosity. The viscosity of type IV water continuous (O/W) microemulsion continues to decrease with further increase in aqueous fraction (Watanabe et al. 2004).

Other methods such as dying (Ho et al. 1996) and cryo-field emission scanning electron microscopy (Cryo-FESEM) (Krauel et al. 2005) could also be used to identify the types of microemulsions.

The droplet size distribution of microemulsions can be determined using the dynamic light scattering (DLS) technique. The average droplet size of about 80–120 nm is an acceptable level for microemulsion-based drug delivery systems (Wang and Pal 2014).

10.2.2 Hydrophilic Lipophilic Difference Method to Prepare Microemulsions

Generally speaking, hydrophilic surfactant is used to formulate water continuous microemulsions and lipophilic surfactant is used to formulate oil continuous microemulsions. The hydrophilicity of surfactant can be measured in terms of the *HLB* (Pasquali et al. 2008). The *HLB* value of a surfactant is defined as follows based on Griffin's method:

$$HLB = 20 \times \frac{M_h}{M} \tag{10.4}$$

where

M_h is the molecular weight of the hydrophilic part of the surfactant

M is the molecular weight of the whole surfactant molecule

According to Equation 10.4, the *HLB* scale ranges from 0 to 20. The surfactant with *HLB* value between 12 and 16 is considered to be suitable for the formulation of O/W (oil in water) microemulsions. Surfactants with *HLB* values between 7 and 11 are more suitable for the preparation of W/O (water in oil) microemulsions. The *HLB* concept is simple to use and the database is available for a large number of surfactants. However, the main disadvantage of the *HLB* concept is that it does not consider the impact of other factors on microemulsion formulation, such as temperature, aqueous phase salinity, oil-chain length, and co-surfactant. For example, water continuous microemulsion could be formulated using Cremophor EL (*HLB* = 13.5) at room temperature (20°C –25°C) (Wang and Pal 2014). However, one may end up with bicontinuous type microemulsion using the same formulation at 37°C in vivo due to the change in temperature. In summary, the impact of factors such as co-surfactant, chemical nature of oil, temperature, salinity of aqueous phase, etc., on microemulsion type are not captured in the *HLB* concept.

To overcome the limitations of the *HLB* method to formulate microemulsions, a different approach called *hydrophilic–lipophilic difference* (HLD) was developed by Salager et al. (1983, 2000). The *HLD* approach captures the impact of various factors on microemulsion type. The *HLD* value for nonionic and ionic surfactants can be calculated as follows (Acosta and Bhakta 2009):

Nonionic surfactants:

$$HLD = b(S) - K \times N_{CO} - \phi(A) + c_T \Delta T + CC \tag{10.5}$$

Ionic surfactants:

$$HLD = \ln(S) - K \times N_{CO} - f(A) - \alpha_T \Delta T + CC \tag{10.6}$$

where

S is the salinity (g/100 mL) of aqueous phase
b is an empirical constant equal to 0.13 for NaCl and 0.1 for $CaCl_2$ (Acosta and Bhakta 2009)
K is a constant that ranges from 0.1 to 0.2 (normally is around 0.17)
N_{CO} is the alkane carbon number (ACN) of oil, which is a measure of hydrophobicity of the oil phase (Ontiveros et al. 2013)

The more hydrophobic (e.g., long chain length) the oil phase, the higher is the N_{CO} value. In the case of non-alkane oils, an equivalent alkane carbon number (EACN) is used (Acosta and Bhakta 2009); $\phi(A)$ or $f(A)$ is a factor that takes into account the influence of co-surfactant. It is related to the partitioning of co-surfactant in the two phases. If there is no partitioning of co-surfactant observed in the formulation (e.g., using *sec*-butanol as noted earlier) or no co-surfactant is present in the system, $\phi(A)$ or $f(A)$ is zero (Salager et al. 2005; Acosta and Bhakta 2009); c_T and α_T are temperature factors, equal to 0.06 and 0.01 K^{-1}, respectively; ΔT is temperature difference from 25°C; and *CC* is called *characteristic curvature* of the surfactant. Like *HLB*, *CC* is also a measure of the hydrophilicity of surfactant. However, the *CC* scale is different from that of *HLB* (Acosta et al. 2008). The smaller the *CC* value, the more hydrophilic is the surfactant (e.g., the *CC* value of sodium oleate is −1.7 whereas oleic acid has a *CC* value of 0) (Acosta et al. 2008).

The *HLD* criteria for the formulation of different types of microemulsions are as follows: for type I microemulsion, $HLD < 0$; for type III microemulsion, $HLD \approx 0$; and for type II microemulsion, $HLD > 0$ (Salager et al. 2000; Mason et al. 2006; Ontiveros et al. 2013). According to Equations 10.5 and 10.6, oil with a long-chain structure (high alkane carbon number) is preferred for the formulation of type I microemulsion, if other factors such as temperature, surfactant, co-surfactant, and electrolyte concentration are kept the same. In the case of nonionic surfactant, the temperature effect is more pronounced than the electrolyte concentration effect. The hydrophilic parts of nonionic surfactants are more sensitive to temperature changes than to electrolyte concentration changes. The breakage of hydrogen bonds at high temperature makes nonionic surfactant more lipophilic (Nilsson and Lindman 1983). On the contrary, ionic surfactant is more sensitive to changes in electrolyte concentration than to temperature changes. A high electrolyte concentration can compress the electrical double layer of the hydrophilic part and make the ionic surfactant more lipophilic (Srinivasan and Blankschtein 2003).

Although the *HLD* method has a limited database (*CC* value is known only for a limited number of surfactants; likewise the N_{CO} value is known for a limited number of oils) as compared with the *HLB* method, this concept can play an important role in the formulation design.

10.2.3 Self-Microemulsifying Drug Delivery System

The self-microemulsifying drug delivery system (SMEDDS) is a very promising drug delivery system for oil-soluble drugs. It is only a pre-mixture of oil-soluble drug, oil, surfactants, and co-surfactants and is able to form a microemulsion spontaneously under gentle agitation in vivo (Kang et al. 2004). During the in vitro tests, temperature is usually maintained at 37°C since this is the actual temperature at which microemulsion would be formed in vivo. No water is loaded in SMEDDS as water comes from the aqueous phase present in vivo. The system with zero water loading can be stored in capsules as reverse micelles. The amount of drug solubilized in the reverse micelles of SMEDDS is a very important factor to evaluate the system. The drug solubilization ability of the system dictates the selection of various ingredients.

Drugs are known to solubilize at the interface of microemulsion droplets or micelles. Research work by Spernath et al. (2003) has demonstrated that reverse micelles have a higher drug solubilization capacity than that of the individual components. They entrapped lycopene (model drug) in the reverse micelles of *R*-(+)-limonene (model oil) and surfactant polysorbate 60 (Tween 60). The drug capacity reached 1500 ppm as compared with 700 ppm in *R*-(+)-limonene alone (Spernath et al. 2002). The reason for the increased capacity of drug solubilization is that the drug can now distribute at the surface of the reverse micelles rather than occupy the core. However, drug solubilization at the surface of reverse micelles is highly dependent on the physical properties of surfactant, co-surfactant, and drug. The interactions between the drug and surfactant, and the hydrophobicity of surfactant are also important. Different components can result in different solubilization capacity of drugs (Narang et al. 2007). It should also be noted that drug solubilization may reduce after oral administration of SMEDDS due to aqueous phase dilution and structural changes in vivo from reverse micelles to O/W microemulsion.

10.3 FORMULATION DEVELOPMENTS

10.3.1 Interaction between the Two Phases

Molecules at the interface between two immiscible liquids have a higher potential energy as compared with the molecules in the bulk phase (Rosen 2004). Figure 10.4 shows a schematic representation of the interface between two phases. The increase in the potential energy of molecules "*a*" per unit area is equal to the interaction energy of molecules in the bulk (γ_{aa}) minus the interaction energy at the interface (γ_{ab}) (Rosen 2004). Likewise, the increase in potential energy of molecules "*b*" is $\gamma_{bb} - \gamma_{ab}$. Therefore, the interfacial free energy per unit area or the interfacial tension (γ_I) can be expressed as follows (Rosen 2004):

$$\gamma_I = \left(\gamma_{aa} - \gamma_{ab}\right) + \left(\gamma_{bb} - \gamma_{ab}\right) = \gamma_{aa} + \gamma_{bb} - 2\gamma_{ab} \tag{10.7}$$

It should be noted that the interaction energy between the like molecules (i.e., γ_{aa} or γ_{bb}) is always greater than the interaction energy between the unlike molecules (γ_{ab}). When the phase consisting of "*a*" molecules is a gas phase, $\gamma_{aa} \approx 0$ and $\gamma_{ab} \approx 0$, and therefore γ_I is the surface tension of phase "*b*" given as γ_{bb}. Likewise, γ_{aa} is the surface tension of phase "*a*" (Rosen 2004). According to Equation 10.7, the interfacial tension γ_I increases with the decrease in γ_{ab} as the surface tensions γ_{aa}

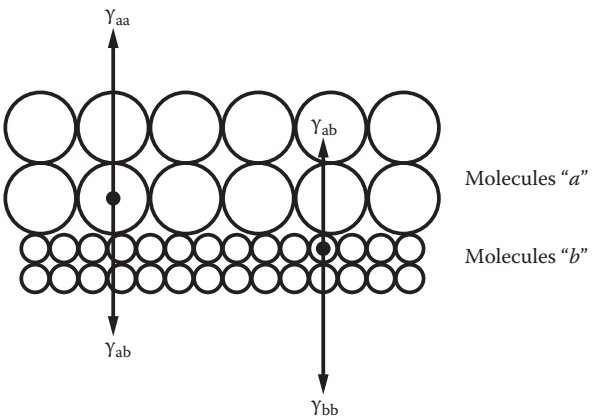

FIGURE 10.4 Interaction between two immiscible liquids. (Adapted from Rosen, M.J., *Surfactants and Interfacial Phenomena*, 3rd edn., John Wiley & Sons, Inc., New York, 2004, pp. 1–33, 110–113, 208–234.)

and γ_{bb} are fixed values. Therefore, interfacial tension (γ_I) is a measure of interaction between the two phases. The higher the γ_I, the weaker is the interaction between the two phases.

To formulate a microemulsion, the interfacial tension (γ_I) should be ultralow (<1 mJ/m^2) (Upadhyaya et al. 2006) and the interaction between the two phases (γ_{ab}) must be high. Therefore, a certain amount of surfactant is needed to increase the interaction between the two phases to a level where a microemulsion is formed spontaneously. This concentration is called critical microemulsion concentration (cμc), which is the minimum surfactant concentration required to formulate a microemulsion (Aveyard et al. 1989).

10.3.2 Phase Scan

The purpose of a phase scan is to determine the temperature (in case of nonionic surfactants) or salinity (in case of ionic surfactants) that can produce a microemulsion of desired type (O/W, W/O, or bicontinuous) and properties (such as solubilization). Figure 10.5 shows a typical phase scan (Rosen 2004). Phase scan is normally run from type I (Winsor I) system to type II (Winsor II) system by increasing the temperature (in case of nonionic surfactant) or salinity (in case of ionic surfactant). As shown in Figure 10.5, oil solubilization increases from sample 1 to 2 with the increase in temperature or salinity. With the increase in temperature/salinity, the surfactant becomes more lipophilic due to the increased dehydration. Consequently, the interaction between oil and water phase (γ_{ab}) increases and the interfacial tension (γ_{OW}) decreases. As surfactant becomes continuously more lipophilic with the increase in temperature/salinity, a B_M phase (bicontinuous or middle phase) begins to separate from W_M phase (water continuous O/W microemulsion phase). At the start of the separation (sample 3), the interfacial tension between oil and B_M phase (γ_{OB}) is still high and the interfacial tension between B_M and water phase (γ_{BW}) is zero (B_M and water are miscible).

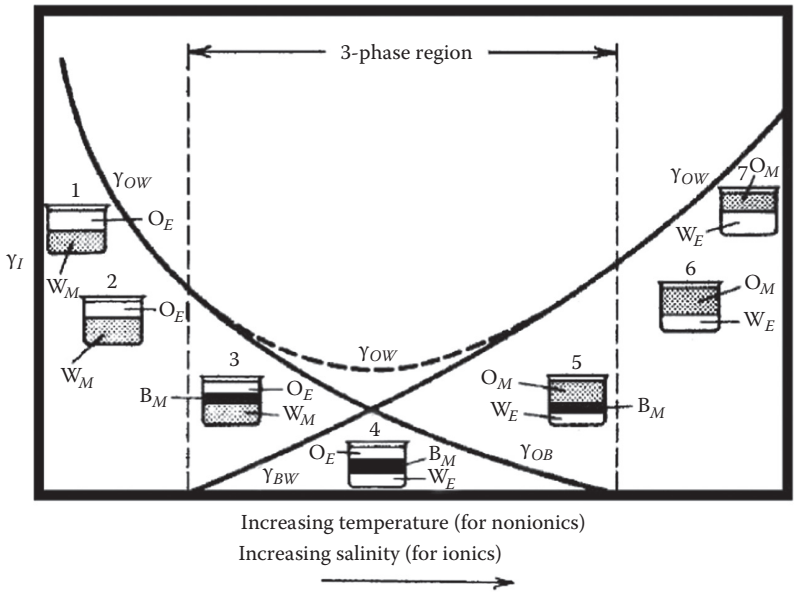

FIGURE 10.5 Phase scan with temperature (for nonionic surfactant) or salinity (for ionic surfactant). O_E, excess oil phase; O_M, microemulsion (W/O) phase; W_E, excess water phase; W_M, microemulsion (O/W) phase; B_M, microemulsion (bicontinuous) phase; γ_{OW}, interfacial tension between oil and water phase; γ_{BW}, interfacial tension between bicontinuous and water phase; and γ_{OB}, interfacial tension between oil and bicontinuous phase. (Adapted from Rosen, M.J., *Surfactants and Interfacial Phenomena*, 3rd edn., John Wiley & Sons, Inc., New York, 2004, pp. 1–33, 110–113, 208–234.)

The apparent interfacial tension between oil and water (γ_{OW}) in the three-phase region, with a middle phase present between oil and water phases, can be calculated as follows (Rosen 2004):

$$\gamma_{OW} = \gamma_{OB} + \gamma_{BW} \tag{10.8}$$

The apparent interfacial tension in the three-phase region is shown as a dashed line in Figure 10.5. When the temperature/salinity is increased to a certain level (sample 4 in Figure 10.5), most of the surfactants from W_M migrate to the middle phase resulting in two excess phases (O_E and W_E) and minimum apparent γ_{OW}. This Winsor III formulation shown as sample 4 in Figure 10.5 is the optimal formulation. The temperature corresponding to the optimal formulation is the phase-inversion temperature (PIT) and the corresponding salinity is the optimum salinity (Rosen 2004).

With further increase in temperature/salinity from sample 4 to 5, the surfactant starts migrating from the middle phase (B_M phase) to the oil phase (O_E phase) and type II microemulsion (O_M phase) begins to form. As surfactant becomes more lipophilic, the middle phase (B_M phase) disappears. Water solubilization decreases and γ_{OW} increases with further increase in temperature/salinity from sample 6 to 7. These changes are due to the transfer of surfactant to the oil phase and the reduction in the interaction between oil and water phases.

As already pointed out, the purpose of the phase scan is to determine the optimal temperature/salinity that can produce microemulsion of desired type and properties. Once the optimal temperature/salinity is established, one can further investigate the effects of composition on phase behavior using the ternary phase diagram.

10.3.3 Pseudo-Ternary Phase Diagram

A pseudo-ternary phase diagram of drug, oil, surfactant, co-surfactant, and water can be very helpful in formulating a suitable composition of self-microemulsifying drug delivery system (Prajapati et al. 2012). In general, three types of phases are encountered in a pseudo-ternary phase diagram: microemulsion (ME), liquid crystal (LC), and coarse emulsion (EM). The microemulsion (ME) region is a single-phase region (Salager et al. 2005) and is the region of main interest in the formulation of SMEDDS. A large microemulsion region can offer more flexibility in the selection of the optimal dosage composition (Wang and Pal 2014). Formulations in this region result in type IV microemulsions (Winsor IV) at equilibrium state and can be identified with their clear and transparent appearance. They also exhibit Tyndall effect. Liquid crystal (LC) could be of three types: hexagonal, cubic, and lamellar LC. Hexagonal and lamellar LCs are anisotropic and exhibit oil streaks or angular and striated textures under crossed polarized microscope (Cistola et al. 1986). Figure 10.6 shows the pictures of liquid crystal samples under crossed polarized microscope. The lamellar LC exhibits oil streaks as shown in Figure 10.6a and the hexagonal LC exhibits angular and striated textures as shown in Figure 10.6b. Cubic LC is an isotropic structure and cannot be observed under crossed polarized microscope. Coarse emulsion (EM) is the traditional thermodynamically unstable emulsion; it appears as milky white during the preparation and ends up into two or three phases at equilibrium (Salager et al. 2005). The droplet size of coarse emulsion can range anywhere from sub-microns to microns (Li et al. 2005). Formulations in the EM region are only kinetically stable. At equilibrium they end up into either two separate phases, or type I microemulsion with excess oil phase, or type II microemulsion with excess water phase, or type III microemulsion with both excess oil and water phase. The boundary lines between the two emulsion regions (ME/EM) are drawn out according to the emulsion appearance and droplet size.

Figure 10.7 shows a ternary diagram without the specification of different phase regions and boundaries. The ternary diagram represents a three-component system (oil, water, and surfactant in the present case). If the surfactant phase is a mixture of surfactant and co-surfactant, the ternary

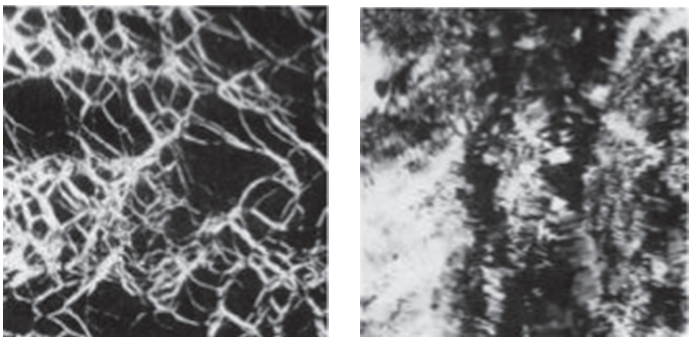

FIGURE 10.6 Liquid crystal structure under crossed polarized microscope. (a) Oil streaks-lamellar LC and (b) angular and striated textures-hexagonal LC. (Adapted from Cistola, D.P. et al., *Biochemistry*, 25(10), 2804, 1986.)

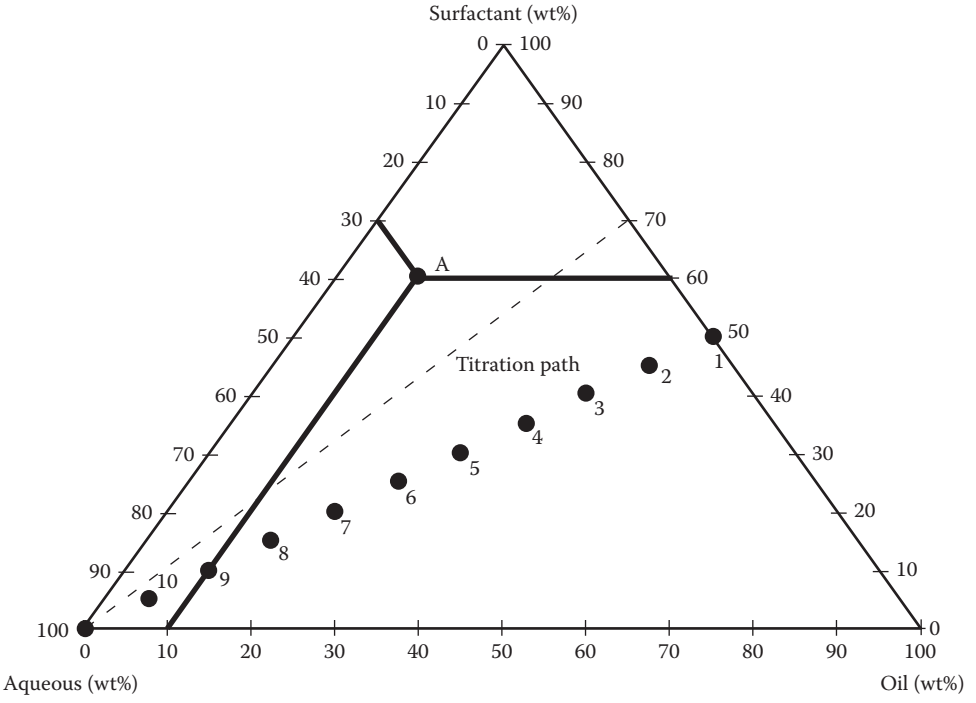

FIGURE 10.7 Ternary diagram. Point A represents 30 wt% of aqueous phase, 10 wt% of oil phase, and 60 wt% of surfactant phase.

diagram is referred to as a *pseudo-ternary* diagram. The ternary diagram can be read following the solid lines shown in the figure. For example, point A corresponds to a composition of 30% water phase, 60% surfactant phase, and 10% oil phase. The phase region to which point A belongs depends on the particle size and the appearance of the sample. In order to mark different phase regions and boundaries on the ternary diagram, a titration technique is employed (Wang and Pal 2014). The titration begins by fixing two components and varying the third component. For example, the dashed line shown in Figure 10.7 is followed with the addition of water. The titration procedure begins with zero loading of aqueous phase and ends up at a point of 100% aqueous phase loading.

TABLE 10.2
An Example of Titrating Water to Surfactant + Oil System (Points Are Shown in Figure 10.7 as Black Dots)

#	Surfactant (wt%)	Oil (wt%)	Water (wt%)
1	50	50	0
2	45	45	10
3	40	40	20
4	35	35	30
5	30	30	40
6	25	25	50
7	20	20	60
8	15	15	70
9	10	10	80
10	5	5	90

The titration procedure is repeated for different ratios of surfactant phase to the oil phase. As an example, Table 10.2 gives the compositions of mixtures for one set of titration experiments represented by black dots shown in Figure 10.7.

Figure 10.8 shows the typical ternary phase diagram with phase regions and boundaries. The phase diagram is developed using the titration method (Prajapati et al. 2012). Three different regions (ME, LC, and EM) are identified on the phase diagram. Titration begins at different surfactant/oil ratios with zero aqueous phase loading. At the start of the titration, type IV oil-continuous microemulsion (W/O) is formed. With continuous addition of water, phase transitions from W/O

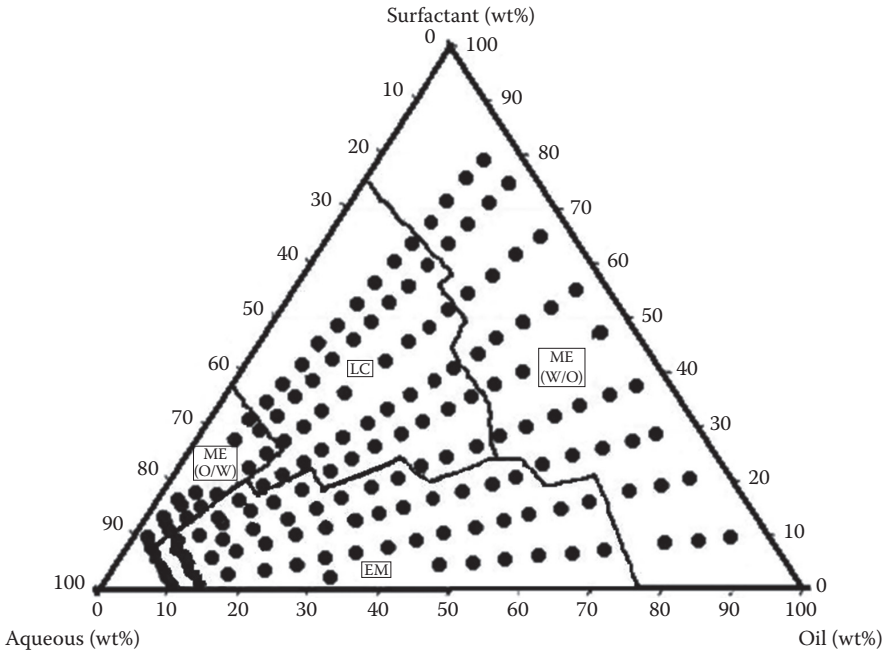

FIGURE 10.8 Ternary phase diagram of water (aqueous phase), PEG-35 castor oil (Cremophor EL, surfactant phase), and mixture of glycerol monocaprylocaprate and caprylic/capric triglycerides (1:3) (oil phase) at 37°C. (Adapted from Prajapati, H.N. et al., *Pharm. Res.*, 29(1), 285, 2012.)

microemulsion to LC and from LC to O/W microemulsion are observed provided that the surfactant/oil ratio is high at the start of the titration (e.g., 80 wt% of surfactant/20 wt% of oil). The continuous addition of water changes the spontaneous curvature of surfactant in oil phase and induces phase inversion from W/O to O/W microemulsion (Fernandez et al. 2004). Note that at a certain water wt%, water and oil phases begin to merge and intertwine together to form LC. This point is called the emulsion inversion point (EIP) and the interfacial tension is minimum at this point (Forgiarini et al. 2001). The formulation ends up with type IV water-continuous microemulsion (O/W) with further addition of water. It should be noted that at low to medium surfactant concentrations (<40 wt% of surfactant at the start of the titration), the formulation may end up in the coarse emulsion (EM) region. Thus, as noted earlier, a certain amount of surfactant (critical microemulsion concentration) is always required to formulate a microemulsion.

10.4 CHALLENGES OF MICROEMULSION-BASED DRUG DELIVERY SYSTEM

10.4.1 Toxicity and Safety of SMEDDS

As a large amount of surfactant is required to form microemulsions, the toxicity of surfactants should be considered in the design and formulation of SMEDDS (Swenson and Curatolo 1992). The presence of a large amount of surfactant can cause irritation or tissue damage as surfactant can disrupt the lipid bilayer of the epithelial cell membrane and interact with the mucosa. For the repeated administration of SMEDDS, a large dosage of surfactant may be given with serious toxicological impact on humans and must be carefully evaluated (Swenson and Curatolo 1992).

Toxicity studies can be divided into two parts: acute oral toxicity and chronic oral toxicity. Swenson et al. (1994) studied the effect of different surfactants on a single pass rat intestinal perfusion system. They uncovered the enhancement ability of drug absorption for different surfactants (Tween 80, bile salts, and sodium dodecyl sulfate) and studied the damage on the intestinal wall resulting from surfactants (Swenson et al. 1994). The studies have shown that the epithelial cells can repair damage upon termination of drug administration. However, long-term effects for repeated drug administration cannot be ignored. A study of chronic oral toxicity is necessary for all the surfactant-containing microemulsion drugs. The study can be executed on a proper animal model using gelatin capsules. The results will reveal relations between the therapeutic effects and the toxicity of a specific surfactant (Constantinides 1995). Extensive research is also needed to reduce the usage of surfactants in drug formulations and maintain the drugs absorption rate at the same time.

10.4.2 Scale-Up and Manufacturing

Compared to the challenge of reducing the drug toxicity, scale-up and manufacturing of SMEDDS is easier. Two important characteristics of SMEDDS, that is, spontaneous formation and thermodynamic stability, are helpful in the scale-up and manufacturing processes. Burskirk et al. (1994) have discussed the general issues related to the SMEDDS manufacturing. Because of the advantages of SMEDDS, the manufacturing process requires only very basic mixing equipment to provide mild agitation to form micelles. The preparation does not require careful in-process control needed in the manufacturing of other drugs (Burskirk et al. 1994). In batch-by-batch manufacturing, the degree of the purity and the chemical instabilities should be monitored carefully. The selection of capsules (soft or hard gelatin capsules), the selection of oil that can maximize drug solubility, and the hygroscopicity of the contents that can either dehydrate or dissolve the gelatin shell are important considerations in the manufacturing of pharmaceuticals (Constantinides 1995). The manufacturing conditions are highly dependent on the nature of the drug. Thus, different drugs should be considered separately to obtain the optimum conditions. Furthermore, the dynamic changes of the drug should be investigated thoroughly before manufacturing the drug.

REFERENCES

Acosta, E.J., A.S. Bhakta. 2009. The HLD-NAC model for mixtures of ionic and non-ionic surfactants. *J Surfactants Deterg* 12(1): 7–19.

Acosta, E.J., T. Nguyen, A. Witthayapanyanon, J.H. Harwell, D.A. Sabatini. 2005. Linker-based bio-compatible microemulsions. *Environ Sci Technol* 39(5): 1275–1282.

Acosta, E.J., J.S. Yuan, A.S. Bhakta. 2008. The characteristic curvature of ionic surfactants. *J Surfactants Deterg* 11: 145–158.

Aveyard, R., B.P. Binks, P.D.I. Fletcher. 1989. Interfacial tensions and aggregate structure in pentaethylene glycol monododecyl ether/oil/water microemulsion systems. *Langmuir* 5: 1210–1217.

Bauer, K., C. Neuber, A. Schmid, K.M. Volker. 2002. Oil in water microemulsion, US Patent 6426078-B1.

Bavière, M., R.S. Schechter, W.H. Wade. 1981. The influence of alcohol on microemulsion composition. *J Colloid Interface Sci*. 81: 266–279.

Benameur, H., V. Jannin, D. Roulot. 2003. Method and formulation for decreasing statin metabolism, US Patent 6652865-B2.

Burnside, B.A., C.E. Mattes, C.M. McGuinness, E.M. Rudnic, G.W. Belendiuk. 1999. Oral acyclovir delivery, US Patent 5883103-A.

Burskirk, G.A., V.P. Shah, D. Adair. 1994. Workshop III report: Scale-up of liquid and semisolid disperse systems. *Eur J Pharm Biopharm* 40: 251–254.

Chen, S., J.A. Gunn. 2003. Oral dosage self-emulsifying formulations of pyranone protease inhibitors, US Patent 6555558-B2.

Cistola, D.P., D. Atkinson, J.A. Hamilton, D.M. Small. 1986. Phase behavior and bilayer properties of fatty acids: Hydrated 1:1 acid-soaps. *Biochemistry* 25(10): 2804–2812.

Constantinides, P.P. 1995. Lipid microemulsions for improving drug dissolution and oral absorption: Physical and biopharmaceutical aspects. *Pharm Res* 12: 1561–1572.

Date, A.A., M.S. Nagarsenker. 2010. Design and evaluation of microemulsions for improved parenteral delivery of propofol. *AAPS PharmSciTech* 9(1): 138–145.

Eugster, C., C.H. Eugster, W. Haldemann, G. Rivara. 1996. Spontaneously dispersible concentrates and aqueous microemulsions with steryl retinates having anti-tumor activity, US Patent 5496813-A.

Farah, N., J. Denis. 2000. Orally administrable composition capable of providing enhanced bioavailability when ingested, US Patent 6054136-A.

Fernandez, P., V. André, J. Rieger, A. Kühnle. 2004. Nano-emulsion formation by emulsion phase inversion. *Colloids Surf A* 251(1): 53–58.

Forgiarini, A., J. Esquena, C. Gonzalez, C. Solans. 2001. Formation of nano-emulsions by low-energy emulsification methods at constant temperature. *Langmuir* 17: 2076–2083.

Fricker, G., B. Haeberlin, A. Meinzer, J. Vonderscher. 2006. Galenical formulations, US Patent 7025975-B2.

Gao, P., W. Morozowich. 2003. Self-emulsifying formulation for lipophilic compounds, US Patent 6531139-B1.

Gao, P., B.D. Rush, W.P. Pfund et al. 2003. Development of a supersaturable SEDDS (S-SEDDS) formulation of paclitaxel with improved oral bioavailability. *J Pharm Sci* 92(12): 2386–2398.

Gullapalli, R.P. 2010. Review-soft gelatin capsules (softgels). *J Pharm Sci* 99: 4107–4148.

Gumkowski, M.J., L. Franco, S.B. Murdande, M.E. Perlman. 2005. Self-emulsifying formulations of cholesteryl ester transfer protein inhibitors, US Patent 6962931-B2.

Gupta, R.R., S.K. Jain, M. Varshney. 2005. AOT water-in-oil microemulsions as a penetration enhancer in transdermal drug delivery of 5-fluorouracil. *Colloids Surf B* 41: 25–32.

Ho, H.O., C.C. Hsiao, M.T. Sheu. 1996. Preparation of microemulsions using polyglycerol fatty acid esters as surfactant for the delivery of protein drugs. *J Pharm Sci* 85(2): 138–143.

Jones, S.C., K.D. Dreher. 1976. Co-surfactant in micellar systems used for tertiary oil recovery. *Soc Petrol Eng J* 16: 161–167.

Kang, B.K., J.S. Lee, S.K. Chon et al. 2004. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. *Int J Pharm* 274: 65–73.

Kik, R.A., J.M. Kleijn, F.A.M. Leermakers. 2005. Bending moduli and spontaneous curvature of the monolayer in a surfactant bilayer. *J Phys Chem B* 109: 14251–14256.

Komesvarakul, N., M.D. Sanders, E. Szekeres et al. 2006. Microemulsions of triglyceride-based oils: The effect of co-oil and salinity on phase diagrams. *J Cosmet Sci* 55: 309–325.

Kovarik, J.M., E.A. Mueller, J.B. Van Bree, W. Tetzloff, K. Kutz. 1994. Reduced inter and intra intraindividual variability in cyclosporine pharmacokinetics from a microemulsion formulation. *J Pharm Sci* 83: 444–446.

Krauel, K., N.M. Davies, S. Hook, T. Rades. 2005. Using different structure types of microemulsions for the preparation of poly(alkylcyanoacrylate) nanoparticles by interfacial polymerization. *J Control Release* 106(1–2): 76–87.

Lawrence, M.J., G.D. Rees. 2000. Microemulsion-based media as novel drug delivery systems. *Adv Drug Deliv Rev* 45: 89–121.

Li, P., A. Ghosh, R.F. Wagner, S. Krill, Y.M. Joshi, A.T.M. Serajuddin. 2005. Effect of combined use of nonionic surfactant on formation of oil-in-water microemulsions. *Int J Pharm* 288: 27–34.

Liang, L., A.H. Shojaei, S.A. Ibrahim, B.A. Burnside. 2006. Self-emulsifying formulations of fenofibrate and/or fenofibrate derivatives with improved oral bioavailability and/or reduced food effect, US Patent 7022337-B2.

Ma, H., M. Luo, L.L. Dai. 2008. Influences of surfactant and nanoparticle assembly on effective interfacial tensions. *Phys Chem Chem Phys* 10: 2207–2213.

Makoto, T. (ed.). 1998. *Disperse Systems*. Wiley-VCH, Weinheim, Germany, pp. 244–245, ISBN: 3-527-29458-9.

Mason, T.G., J.N. Wilking, K. Meleson, C.B. Chang, S.M. Graves. 2006. Nanoemulsions: Formation, structure, and physical properties. *J Phys Condens Matter* 18: 635–666.

McClements, D.J. 2011. Edible nanoemulsions: Fabrication, properties, and functional performance. *Soft Matter* 7(6): 2297–2316.

McClements, D.J. 2012. Nanoemulsions versus microemulsions: Terminology, differences, and similarities. *Soft Matter* 8: 1719–1729.

Mishra, A., I. Moussa, Z. Ramtoola, N. Clarke. 2001. Pharmaceutical compositions containing an omega-3 fatty acid oil, US Patent 6284268-B1.

Missen, R.W., C.A. Mims, B.A. Saville. 1999. *Introduction to Chemical Reaction Engineering and Kinetics*. John Wiley & Sons, Inc., New York, p. 44.

Mulye, N. 2002. Self-emulsifying compositions for drugs poorly soluble in water, US Patent 6436430-B1.

Narang, A.S., D. Delmarre, D. Gao. 2007. Stable drug encapsulation in micelles and microemulsions. *Int J Pharm* 345: 9–25.

Nilsson, P.G., B. Lindman. 1983. Water self-diffusion in nonionic surfactant solutions. Hydration and obstruction effects. *J Phys Chem* 87(23): 4756–4761.

Ontiveros, J.F., C. Pierlot, M. Catté et al. 2013. Classification of ester oils according to their equivalent alkane carbon number (EACN) and asymmetry of fish diagrams of C10E4/ester oil/water systems. *J Colloid Interface Sci* 403: 67–76.

Pasquali, R.C., M.P. Taurozzi, C. Bregni. 2008. Some considerations about the hydrophilic-lipophilic balance system. *Int J Pharm* 356(1): 44–51.

Prajapati, H.N., D.M. Dalrymple, A.T. Serajuddin. 2012. A comparative evaluation of mono-, di-and triglyceride of medium chain fatty acids by lipid/surfactant/water phase diagram, solubility determination and dispersion testing for application in pharmaceutical dosage form development. *Pharm Res* 29(1): 285–305.

Rosen, M.J. 2004. *Surfactants and Interfacial Phenomena*, 3rd edn. John Wiley & Sons, Inc., New York, pp. 1–33, 110–113, 208–234.

Rudnic, E., J. McCarty, B. Burnside, C. McGuinness, G. Belenduik. 1999. Emulsified drug delivery systems, US Patent 5952004-A.

Salager, J.L., R.E. Antón, D.A. Sabatini, J.H. Harwell, E.J. Acosta, L.I. Tolosa. 2005. Enhancing solubilization in microemulsions-state of the art and current trends. *J Surfactants Deterg* 8(1): 3–21.

Salager, J.L., N. Marquez, A. Graciaa, J. Lachaise. 2000. Partitioning of ethoxylated octylphenol surfactants in microemulsion-oil-water systems: Influence of temperature and relation between partitioning coefficient and physicochemical formulation. *Langmuir* 16(13): 5534–5539.

Salager, J.L., M. Minana-Perez, M. Perez-Sanchez, C.I. Rojas. 1983. Surfactant-oil-water systems near the affinity inversion part III: The two kinds of emulsion inversion. *J Disp Sci Technol* 4(3): 313–329.

Shen, H., M. Zhong. 2006. Preparation and evaluation of self-microemulsifying drug delivery systems (SMEDDS) containing atorvastatin. *J Pharm Pharmacol* 58(9): 1183–1191.

Spernath, A., A. Yaghmur, A. Aserin, R.E. Hoffman, N. Garti. 2002. Food-grade microemulsions based on nonionic emulsifiers: Media to enhance lycopene solubilization. *J Agric Food Chem* 50: 6917–6922.

Spernath, A., A. Yaghmur, A. Aserin, R.E. Hoffman, N. Garti. 2003. Self-diffusion nuclear magnetic resonance, microstructure transitions, and solubilization capacity of phytosterols and cholesterol in Winsor IV food-grade microemulsions. *J Agric Food Chem* 51: 2359–2364.

Srinivasan, V., D. Blankschtein. 2003. Effect of counterion binding on micellar solution behavior: 2. Prediction of micellar solution properties of ionic surfactant-electrolyte systems. *Langmuir* 19(23): 9946–9961.

Swenson, E.S., W.J. Curatolo. 1992. Means to enhance penetration: (2) Intestinal permeability enhancement for proteins, peptides and other polar drugs: Mechanisms and potential toxicity. *Adv Drug Deliv Rev* 8: 39–92.

Swenson, E.S., W.B. Milisen, W. Curatolo. 1994. Intestinal permeability enhancement: Efficacy, acute local toxicity and reversibility. *Pharm Res* 11: 1132–1142.

Talegaonkar, S., A. Azeem, F.J. Ahmad et al. 2008. Microemulsions: A novel approach to enhanced drug delivery. *Recent Pat Drug Deliv Formul* 2: 238–257.

Upadhyaya, A., E.J. Acosta, J.F. Scamehorn, D.A. Sabatini. 2006. Microemulsion phase behavior of anionic-cationic surfactant mixtures: Effect of tail branching. *J Surfactants Deterg* 9(2): 169–179.

Von Corswant, C. 2003. Microemulsions for use as vehicles for administration of active compounds, US Patent 6602511-B2.

Von Corswant, C., P. Thoren, S. Engstrom. 1998. Triglyceride based microemulsion for intravenous administration of sparingly soluble substances. *J Pharm Sci* 87: 200–208.

Wang, Z., E. Acosta. 2013. Formulation design for target delivery of iron nanoparticles to TCE zones. *J Contam Hydrol* 155: 9–19.

Wang, Z., R. Pal. 2014. Enlargement of nanoemulsion region in pseudo-ternary mixing diagrams for a drug delivery system. *J Surfactants Deterg* 17: 49–58.

Ward, M.V., R. Cotter. 1987. Rapid acting intravenous emulsions of omega-3 fatty acid esters, US Patent 4678808-A.

Watanabe, K., A. Noda, M. Masuda, T. Kimura, K. Komatsu, K. Nakamura. 2004. Bicontinuous microemulsion type cleansing containing silicone oil. II. Characterization of the solution and its application to cleansing agent. *J Oleo Sci* 53(11): 547–555.

Winsor, P.A. 1948. Hydrotropy, solubilisation and related emulsification processes. *Trans Faraday Soc* 44: 376–398.