CHAPTER 10

NATURAL SURFACTANTS FOR PHARMACEUTICAL EMULSIONS

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Introduction

An emulsion is basically a mixture of at least two types of liquids that are immiscible and appears homogeneous. Most emulsions can be classified as either oil-in-water (o/w) emulsion, or water-in-oil (w/o) emulsion. In the first case, the continuous medium, or the dispersing medium is water, while in the latter, the continuous medium is oil. The dispersed phase consists of fine to coarse droplets of either water and oil, which are evenly distributed in the continuous medium. A common example is the commercialized cod liver oil emulsion.

Oil-in-water emulsions are commonly used in food preparation, pharmaceutics, hairstyling, personal hygiene and cosmetics. The type of emulsion used in pharmaceuticals depends very much on the route of administration, and thus will influence the formulation (Aulton, 2007). This includes the type and amount of oil, water content and the emulsifying system employed. Often, the emulsifying system dictates the type of emulsion formed: o/w or w/o. Other than the two types of emulsions mentioned above, there exists another type which is known as microemulsion. An example of its application is in vaccines using soybean oil with droplet size in the range of 400-600 nm (Troy et al., 2006).

An important applications of pharmaceutical emulsions is skin therapy. A good topical formulation should be one in which the dosage form has both physical and chemical stability and cosmetic acceptability and that also provides the optimal environment for the active ingredients to reach the skin (Block, 1996; Davis et al., 1985). Frequently, the extent of release of a drug or cosmetic ingredient from a topical product is dependent of emulsion type. Emulsion is an example of an effective formulation for the delivery of drugs and in the field of cosmetics (Magdassi & Touitou, 1999).

The interest in emulsion as topical drug delivery systems is related to their advantageous characteristics, frequently enhancing the bioavailability of the drug substance. Emulsions also offer potential in the design of systems capable of giving controlled rates of drug release and of affording protection to drugs susceptible to oxidation or hydrolysis due to the presence of hydrophilic and lipophilic domains (Junginger, 1994).

Emulsion Formation

Emulsions can be prepared easily by blending the immiscible liquids in the presence of a very important third component, which is a surfactant. When a surfactant is used in emulsification, it is widely known as an emulsifier. The degree of agitation required depends on the properties of the liquids, which will influence at least the resulting viscosity. This in turn, will somehow dictate the degree of intensity of mixing enabling the breaking of the oil into droplets. Agitation may come in the form of a simple kitchen blender, homogenizer or ultrasonic.

In most manufacturing industries, emulsification is achieved using the homogenizer. For straightforward preparation, Bancroft rule can be used in determining the type of emulsion: o/w or w/o. The rule proposes that the phase into which the emulsifier is dissolved will become the continuous one. Another useful guide is the hydrophile-lipophile balance (HLB). This is a value

ascribed to a surfactant based upon the chemical composition and its hydrophilicity. Emulsion behavior and stability are affected by the properties of the adsorbed layers that stabilize the oil-water interfaces. In this case the adsorbed layers consist of molecules of surfactants. Determination of the surface tension may give some ideas on the possibility of emulsification but insufficient to understand stability, phase separation or the rheological behavior.

In a not so straightforward emulsion such as petroleum emulsions, the oil is composed of surface-active molecules or surfactants contained in the crude. Examples are low molecular weight naphthenic acids and asphaltenes. These molecules, due to their structures, can adsorb at the oil/water interfaces. The rheology for asphaltene emulsion is very different and could have explained the differences between surfactant and asphaltene emulsions. The naturally occurring surface active compounds found in heavy oils are in large amount and would definitely influence emulsion characteristics (Mullins & Sheu, 1995).

The use of mineral oil such as paraffin oil, which is very different from the heavy oils described above, is very common in pharmaceuticals and in cosmetics. The reason is mainly due to its inert property. However, there is a growing trend in using non-mineral oil. Vegetable oil such as palm oil has many advantages over mineral oil. Vegetable oils and fats and their derivatives, are renewable, biodegradable and harmless to the environment. The major components of vegetable oils are triglycerides. Triglycerides are esters of glycerol with three fatty acid molecules. The minor components include fatty alcohol, phytosterols, vitamins and phospholipids. The oil uses depend mainly on the type and proportion of fatty acids which vary according to the species of plants. Oils such as almond oil, apricot oil, avocado oil, soybean oil, cocoa oil and palm oil have high content of unsaturated fatty acids such as oleic, linoleic and linolenic acid. These oils have emollient properties and are used in bar soaps, shampoos and hair

conditioners, creams and lotions, lip balms and suntan products. However, the oils with high content of polyunsaturated fatty acid such as walnut oil and safflower oil are less stable and therefore less suitable to be used in its original state into the formulation. Safflower oil which contains 75-80% of linoleic acid requires treatment to convert linoleic acid to oleic acid, to produce stable formulations. Highly saturated vegetable oils are also gaining interest in the cosmetic and pharmaceutical fields due to their fewer tendencies to produce free radicals from the oxidation process (Alias & Julianto, 2005). For instance, coconut oil is suitable for the preparation of cosmetic due to high composition of saturated fatty acids (lauric, 50% and myristic, 20%) and minor content of caprylic acid that exhibited antifungal activity (Alvarez & Rodriguez, 2000).

Emulsion type is an important consideration in the preparation of pharmaceutical emulsions and also in cosmetics. Emulsions of the oil-in-water type are washable and less oily than water-in-oil emulsions. Therefore oil-in-water types are more useful as water-washable bases for general cosmetic purposes. They spread easily and have the advantage that as the water evaporates they exert a cooling effect at the skin surface. The major disadvantage is that despite the fat content, they dry out. On application to the skin, much of the continuous phase evaporates and increases the concentration of a water-soluble drug in the adhering film (Magdassi & Touitou, 1999). The water-in-oil emulsions exist in a wide range of consistencies depending on the components in the oil and the aqueous phase. The amount of each phase and the properties of the various auxiliary agents have a marked effect (Idson, 1996).

Stable and Unstable Emulsion

Stable emulsion can be defined as an emulsion which will not separate into its components under the conditions for which it was made. As mentioned earlier, a stable emulsion consisting of two

pure liquids can only achieve stability after incorporating a third component. An emulsifying agent or emulsifier must be used. Emulsions are stabilized by these emulsifiers. The emulsifier molecules can form films at the droplets' surface and impart mechanical stability. Presence of the emulsifier molecules at the oil-water interface is accompanied by a decrease in the interfacial tension between the two phases (water and oil). There are many types of emulsifiers: anionic, cationic, amphoteric and non-ionic. This is a classification based on the charge that the surfactant molecule carries on its polar head or the hydrophilic part. The hydrophobic part of the surfactant molecule may consist of a paraffinic chain. Yet, even solid powders can have the ability to emulsify. The phase in which the powders are preferably wetted will be the continuous medium. Naturally occurring surfactants or emulsifiers can be any of these.

In fact, few natural emulsifiers are capable of giving good and stable emulsion, which at the same time exhibit good storage stability and good spreading power. Generally, protein and low molecular weight (LMW) surfactants have important roles in the stabilization of emulsions and foams. The stability of emulsions depend on the behavior of the adsorbed layer of surfactants at the interfaces (Bos & Van, 2001). When protein is involved, the solubility under varying conditions greatly influences emulsification (Kinsella, 1982). When adsorbed at the interface, they form a mechanical barrier that encapsulates the dispersed phase and hence preventing coalescence (Halling, 1981). The barrier formed is a result of intermolecular interactions between the adsorbed protein molecules. The rheological properties of the adsorbed layer, which is the barrier, immobilize the proteins. Presence of proteins is important in the stabilization of many naturally occurring emulsions, with milk being an important example. On the other hand, lipids that stabilize the dispersed droplet do so by forming a densely packed single molecular layer. This layer is stabilized by the Gibbs-Marangoni mechanisms (Fillery-Travis et al., 2000).

Oil-in-water emulsions can also be stabilized by water-soluble polymers. Thus, in commercial emulsions, often the surfactant system is not a single surfactant but consists of a mixture of small surfactants, proteins and water-soluble polymers. The composition of the surfactant system, thickness and viscoelasticity of the adsorbed layer stabilizing the oil-water interface, and the strength and nature of the interactions between adsorbed layers on different droplets affect the emulsion structure, stability and rheological properties (Dickinson, 1992). The strength of this interfacial film will prevent coalescence, which is the merging of the droplets when the interfacial film is broken.

There are a number of factors that have been shown to be important in determining emulsion stability. First, the nature of the oil phase: the most stable emulsions are formed with more polar compounds. This is attributed to its high polarity and ability to form water-like hydrogen bonded network. Second, the interfacial behavior of the surfactant employed: interfacial data for aqueous solutions in contact with hydrocarbon do not adequately describe surfactant performance and a much better guide is the hydrophilic-lipophilic balance (HLB) value of the surfactant (O'Hagan, 2000). Particle size is an important indication of emulsion stability. It depends not only on the oil/water/surfactant system types and concentrations but also on homogenization conditions. The temperature during homogenization, the pressure or the speed of the homogenizer and the duration would influence the particle size. In general, emulsion having smaller initial particle size appears more stable than that with bigger initial particle size (Chung et al., 2001; Solan et al., 2005). One of the reasons is that the emulsion containing lower number of big droplets creamed lesser than that containing higher number of big oil droplets (Ahmad et al., 1996). According to Stoke's law, a decrease in particle size is very important in reducing the rate of creaming; the rate of creaming being a square-root function of the particle

diameter. The creaming rate is also reduced by increasing viscosity of the medium. This explains the widely used water-soluble polymers in emulsification.

Surfactants

Surfactants are substances that are active at interfaces. Often, the molecule is made up of two parts: the hydrophilic part, or sometimes referred to as the head for the purpose of visualisation, and the lipophilic part, which is referred to as the head. Due to this special characteristic within a molecule, surfactant has an affinity for both organic solvents and water. Thus, surfactant molecules can adsorb at miscellaneous interfaces. At low concentration of surfactant, they adsorb at the interface forming a single layer. As the concentration of surfactant increases, they form clusters known as micelles and progressively transformed into more organised structures, such as a bilayer. These structures develop as a result of the orientation of the surfactant molecules: the hydrophilic part of the molecule will maintain contact with water, while the lipophilic part will move away from water. As they are within a molecule, this is possible only by reorientation of the surfactant molecules. Its solubility depends on the balance of its affinity to water and organic solvents. Presence of these surfactant molecules at the oil-water interface keeps the oil and water from separating into two distinguished layers.

Surfactants are used widely in various applications presented in many forms. Agricultural sprays, paints and ice-creams are some of the common examples. In biomedical, applications include artificial implants, gene transfection, biomembranes, ophthalmology, and pharmaceuticals (Abraham, 2003).

Naturally occurring surfactants such as biological surfactants, play an important role in the metabolic processes of living organisms. Sucrose is a factor causing dental cavities and higher caloric contents. To counter this, non-ionic sorbitol is introduced to replace sugar in some

food formulation. Other natural emulsifiers present in our body systems are phospholipid lecithin, bile salts, certain fatty acids and their derivatives. These emulsifiers reduce the surface tension at the fat globules-water interface. The fat globules are thus kept in the dispersed state in water and hence solubilized.

Natural and Synthetic Surfactants

Surfactants produced from oleochemicals such as palm oil are often called natural while those derived from petrochemicals are synthetic. Linear alkylbenzenesulfonate, a ubiquitous surfactant, is derived from crude oil. One of the differences between the natural and synthetic surfactants lies in the number of carbon chains. In natural surfactants, they are linear and even-numbered, but may be branched and having odd number of carbon atoms in synthetic. Biologically, linear chain is the healthy form of carbon chains (Stalmans, 2003). Numerous works involving natural substances in pharmaceuticals, cosmetics and drug delivery have been reported and many of these were later commercialized (Salager, 2000). Improvements in overall infant mortality had also been linked to the use of natural surfactant in food processing (Schwartz et al., 1994).

Synthetic surfactant can be prepared directly from chemical intermediates, for example, alkyl benzene from the condensation of paraffin derivatives and benzene for manufacturing sulfonates through sulfonation with sulfur trioxide (SO_3) in a falling-film reactor. These are mainly anionic surfactants, such as tetrapropylene benzene sulfonates causing some quality, environmental, or ecological problems (Gilbert, 1996). Also, some minor harmful products are known to occur during chemical synthesis of many of the petrochemical-based surfactants. For example, the cancer-promoting substance dioxane is formed during sulfonation of polyoxyethylenated alcohol to make alcohol ether sulphate, or sulfamine in the reaction of ethanolamine-like compounds with sulfoxidation (Ifendu & Xia, 2001). Due to these potential

environmental and biological problems associated with the synthetic surfactant, natural-based surfactants should be the preferred choice.

Natural rubber latex, human's milk, cow's milk and a variety of milk produced by mammals, are stabilized by proteins, and are examples of natural colloidal systems. In fact, milk casein has been for a long while isolated, to be later incorporated in manufactured products. Soybean oil and soy protein are also used as the starting materials for surfactants. Another popular use of natural surfactant is in the food and pharmaceutical industries (El-Nasri & El-Tinay, 2007).

Gum arabic is a natural emulsifier obtained from *Acacia Senegal.* It is an acidic polysaccharide with important applications in pharmaceutical formulations. The polysaccharide structure and hydrophilic nature enable gum arabic to be used as a suspending agent or viscosity modifier, emulsifying agent and also in pastilles, lozenges and as binder in tabletting (Bhardwaj et al., 2000).

Lecithins from soybean and egg yolk have been used as emulsifiers in pharmaceutical preparations such as intralipid total parenteral nutrition (Leong et al., 2004). Phospholipids in palm olein are natural emulsifiers (Marti-Mestres & Nielloud, 2000). With the presence of phospholipids, palm olein has the added advantage to be used as oil base in the formation of good quality emulsion (Sufian & Ahmad, 2006).

Topical applications in cosmetic and dermatology involve the use of vegetable phospholipids. They contain esterified essential fatty acids, especially linoleic acid. Presence of linoleic acid helps to decrease water loss within a short time after application (Radebaugh, 1996). Soya bean phospholipids or other vegetable phospholipids can form liposomes, which can not only transport linoleic acid (Magdassi & Touitou, 1999) but also other water-insoluble

substances into the skin. Generally, emulsion is one of the most widely used dosage form in pharmaceutical delivery system and is an attractive vehicle for the administration of poorly soluble drugs. Pharmaceutical and cosmetic form of emulsions can be prepared in the form of liquids or semisolids, based on intended application.

Interfacial Activity and Critical Micelle Concentration

Since surfactants are amphiphilic molecules containing both hydrophilic and hydrophobic parts, surface active molecules adsorb at the air/water interface and this reduces the interfacial tension or surface tension in this case. Water molecules interact very strongly due to hydrogen bonding and this gives the high surface tension. When surfactant molecules adsorbed at the air/water interface, the surfactant molecules disrupt the continuity of the interaction between the water molecules at the surface. Similarly, an increase in the temperature will also disturb the interaction between the water molecules due to lesser hydrogen bonding. Both situations will lower the surface tension of water. In an emulsion, adsorption of the surfactant molecules at the oil-water interface will reduce the interfacial tension. The adsorbed layer of surfactant molecules at the interface is said to behave as an elastic sheet (Taylor, 2003).

Molecular interactions at the interface of oil-in-water systems studied included the use of lecithin and sodium cholate as oil-soluble and water-soluble natural surfactants (Ogino et al., 1981). Lecithin is an important constituent of biological substances. It is described as being a natural multi functional surface active agent and as an excellent emulsifier. Lecithin as a typical surfactant greatly speeds up dispersion of fatty and aqueous components in many types of emulsion preparations. It also accelerates moisture distribution, making mixing easier and improving texture. It was reported that when hydroxypropyl cellulose was mixed with lecithin,

the oil-in-water surface rheological properties produced a more stable emulsion (Misenti et al., 1998).

As mentioned previously, when concentration of surfactant increases, after they have all occupied the interfaces, in water, the molecules will at first form micelles and gradually form well-arranged structures. The point at which the molecules have occupied the interfaces available and start forming micelles is known as the critical micelle concentration (CMC). CMC is guide in choosing potential surfactants for emulsification. The CMC varies for different surfactants and depend on various factors. This includes the length of the molecules and their internal rigidity (Bhattacharya & Mahanti, 2001).

Natural Surfactants from Medicinal Plants

Medicinal plants may contain a variety of components such as, carbohydrates, lipids, amino acids, peptides, proteins, enzymes, phenolics, acetates, terpenoids, steroids, alkaloids and saponins. Some of these may have surface activity due to their chemical structures and would be of great significance in the preparation of stable emulsion. The surface activity of a particular plant extract would be expected to correlate with the respective composition of the plant. Saponin for instance has surface activity which can be exploited for emulsion formation. Some medicinal plants that showed signs of antimicrobial activity and have the potential to be used as surfactants in the pharmaceutical industry is mentioned briefly in the following sections.

Fenugreek (*Trigonella foenum-graecum)*

Trigonella foenum-graecum is a medicinal plant belonging to the Leguminoseae or legume family. It can be found in South East Asia including Malaysia (Flammang et al., 2004). *T. foenum-graecum* seeds are rich in proteins and polysaccharides called galactomannans. The seeds contain a good proportion of carbohydrate fraction which includes mucilaginous fiber and

galactomannan), proteins in the range of 20-30% including tryptophan and lysine, pyridine-type alkaloids, flavonoids, saponins, glycosides, vitamins, minerals, and volatile oils (Zohary & Hopf, 2000). The reduction of cholesterol in the blood stream following consumption of ground fenugreek (Madar & Shomer, 1990), could also have been attributed by the solubilizing role of proteins present in the seeds. Anti-microbial and anti-bacterial properties of *T. foenum-graecum* were reported by Omoloso & Vagi (2001) and Pritee et al. (2007).

Galactomannans are the most important components that are found in *T. foenum-graecum* seeds. These compounds have high capacity to bind water and thus can form very viscous solutions at low concentration (Ana et al., 2001). Garti et al., (1997) reported that the purified galactomannans from *T. foenum-graecum* can reduce the surface tension more efficiently than guar gum, which is a galactomannan extracted from the guar bean. The interfacial activity was higher than other types of galactomannans. This led to the formation of superior emulsions having long-term stability consisting of small droplets in the range of 2-3 µm. The galactomannans of *T. foenum-graecum* adsorbed at the oil-water interface to form a thick interfacial film. Galactomannans are widely used in foods as emulsifier agents.

Beluru (*Entada spiralis*)

Entada spiralis grows widely in South East Asia and Australia. In Malaysia, *E. spiralis* which is known as beluru, is traditionally used as a hair cleaner and treatment for some kind of skin disease. It was reported that all species of *Entada* possess antimicrobial activity **(**Ramli et al., 2008). Phytochemical screening of *E. spiralis* showed the presence of saponins from all parts of the plant. Tannins and glycosides were found in some of the extracts (Okerulu & Chinwe, 2001). Saponins are natural surfactants. The hydrophilic part consists of glycoside moieties while the

lipophilic part is made up of derivatives of triterpene (Hostettmann & Marsden, 1995). The surface active saponins enable the application of *E. spiralis* as cleansers.

Clove (*Syzygium aromaticum*)

Syzygium aromaticum, from a tree in the family Myrtaceae, is a plant that has dry flower buds. Cloves are commodities in the Indian sub-continent including Malaysia. It has found enormous use in kitchens all over the world. The aroma is given by the compound eugenol. Eugenol ($C_{10}H_{12}O_2$, 4-allyl-2-methoxy-phenol) is the main component having 72-90% composition in the essential oil. Also present are other essential oils which include acetyl eugenol, beta-caryophylline and vanillin; crategolic acid; tannins, tannic acid, methyl salicylate; flavanoids, triterpenoids such as oleanolic acid, and sesquiterpenes (Chaieb et al., 2007).

The use of the essential oil to relieve pain is well known. It can also function as antimicrobial, antioxidant, antifungal and provide antiviral activity, anti-inflammatory and anesthetic properties (Chaieb et al., 2007). Recently, it was found that the ethanol/water (1:1) and the aqueous extracts of clove can emulsify palm olein and water at 10% concentration (Hadi, 2010). Four types of solvents were used but extracts obtained from ethanol/water (9:1) and isopropanol-choloroform showed poor emulsifying ability. The types of compounds extracted depend on the types of solvents used. The extracts showed anti-microbial activity although the effectiveness differs.

Conclusion

The above are only a few examples of extracts from plants that have been found to have emulsifying properties. There are more plants which may give extracts that have the same or even superior emulsifying properties and at the same time possess anti-microbial properties.

These extracts have the potential to replace surfactant systems currently used in pharmaceutical preparations in particular pharmaceutical emulsions, lotions or creams.

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