CHAPTER 2

Surfactants, Lipids, and Surface Chemistry

Contents

2.1 INTRODUCTION

This chapter presents an introduction to surface chemistry and surfactants in pharmaceutical formulations. The choice and quantity of surfactants are essential factors in the formation of stable and efficacious emulsions as pharmaceutical dosage forms (including oral, topical, and injectable/infusible dosage forms). Understanding the physical chemistry of surfactant molecules in aqueous systems and at the air–water or liquid–liquid interface is fundamental to designing drug delivery systems. Important parameters include surface tension, contact angle, and critical micelle concentration.

Surfactants are "amphiphilic" molecules (or "amphiphiles"), containing both hydrophilic and hydrophobic portions on the same molecule. They have been termed "surface active agents" due to their activity at the air–water or water–oil interfaces, reducing surface tension and improving miscibility. They are also

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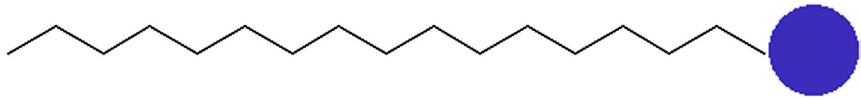

Figure 2.1 Schematic representation of a surfactant molecule. The circle represents the hydrophilic part of the molecule (also known as the head group or polar group), and the long acyl chain represents the hydrophobic (lipophilic) part of the molecule.

considered as chemicals that form "new surfaces" (micelles, liposomes, etc.) in the presence of water [1]. Surfactants are a class of chemicals that has ubiquitous applications in industries; almost all industries need to use surfactants, including engineering, food, petrochemical, pharmaceutical, and consumer products.

2.2 TYPES OF SURFACTANTS

A schematic representation of a surfactant molecule is shown in Figure 2.1; the hydrophilic ("water loving") end of the surfactant molecule is referred to as the "head group" or polar group, and the hydrophobic ("water hating") portion is referred to as the "tail" (or lipophilic, oil-soluble end). Depending on the charge of the polar group, surfactants are generally classified as cationic, anionic, nonionic, or zwitterionic (amphoteric) surfactants. Surfactants can be water soluble or insoluble, natural or synthetic in origin, and their chemical structures could be simple or large molecules or polymeric. Surfactants that have polar groups at each end of a long acyl chain are sometimes known as "bolaamphiphiles" [2].

When mixed in water, surfactants reduce the surface tension of the water. As the concentration of the surfactant is increased, the surface tension continues to drop. Above a certain concentration, the surfactant molecules spontaneously form micelles. When these micelles start forming, further additions of surfactant have no further effect on the surface tension of the water. This concentration, at which the surface tension remains constant, is called the Critical Micelle Concentration (CMC). A typical representation of surface tension versus surfactant concentration is shown in Figure 2.2.

2.2.1 Surfactant Micelles

Micelles are self-assembled microstructures formed by surfactants in aqueous systems. They can trap hydrophobic molecules in their hydrophobic core and thereby act as wetting agents or solubilizing agents. This behavior enables them to be effective cleansing agents. Depending on the structure of the surfactant molecules, micelles of different shapes (including spherical, cylindrical, hexagonal, cubic lamellar, inverted cylindrical, and inverted spherical) can be formed.

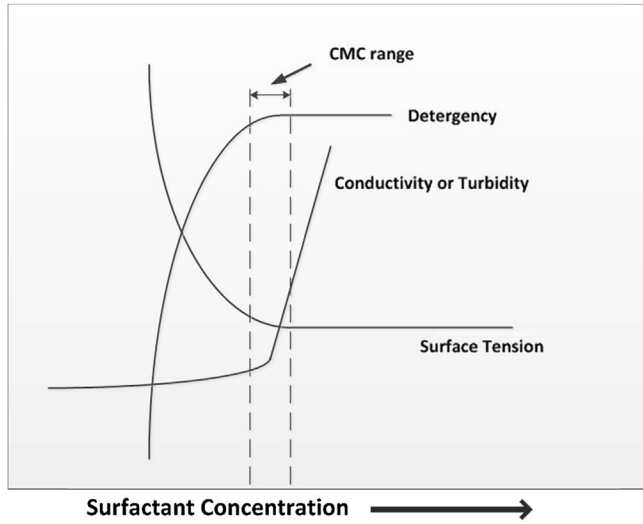

Figure 2.2 A schematic representation of trend lines for surfactant physical properties such as surface tension, conductivity, turbidity, and detergency as a function of surfactant concentration. A change in trend is observed after Critical Micelle Concentration (CMC) is reached. *Adapted from Barnes, G. and Gentle, I., Interfacial Science An Introduction, Oxford University Press, 2005.*

The size of a micelle is related to the number of monomers per micelle (commonly called the aggregation number) or the molecular weight of the micelle.

Factors affecting the formation of micelles include:

- Chain length of the surfactant molecule: molecules with longer chain lengths are less soluble, and will form micelles at lower concentrations.
- The CMC of ionic surfactants is greatly affected by the presence of dissolved salts in the solution. The CMC is lowered as the concentration of salts is increased [3,4] (see Table 2.1).
- When alcohol is added to the water, the CMC increases considerably. It has been shown that, within a series of alcohols ranging from methanol to butanol (at 10% concentration in water), there was no uniform trend observed for the change in CMC for polysorbate 20 [5].
- Increase in temperature increases the CMC.
- If two or more surfactants are present in a solution, the surfactant with higher CMC acts like an electrolyte, and the overall CMC of the mixture will depend on the nature of the individual surfactants (i.e., ionic or nonionic).

2.2.2 Anionic Surfactants

Surfactants with a negative charge on the head group are called "anionic." Common examples are sodium salts of fatty acids and fatty sulfates, including

Table 2.1 Change in critical micelle concentration (CMC) and aggregation number (N) with salt concentration for ionic surfactants

Surfactant	Medium	CMC (mM)	N
Sodium dodecylsulfate	Water	8.1	58
	0.1 M NaCl	1.4	91
	0.2 M NaCl	0.83	105
	0.4 M NaCl	0.52	129
Dodecyltrimethylammonium bromide	Water	14.8	43
	0.0175 M NaBr	10.4	71
	0.05 M NaBr	7.0	76
	0.1 M NaBr	4.65	78

Data from Ref. [3].

sodium lauryl sulfate. Typically, sodium, potassium, or ammonium salts of fatty sulfonates with C8–C14 acyl chains tend to possess foaming and cleansing properties, and are suitable for use in shampoo-type applications. Anionic surfactants also assist in the dissolution or absorption of drugs. Bile salts in the stomach are anionic surfactants and play a critical role in food digestion [6,7].

2.2.3 Cationic Surfactants

Surfactants with a positive charge on their head group are called "cationic." Examples of cationic surfactants include long-chain quaternary ammonium compounds (e.g., Dimethyldioctadecylammonium chloride). Some long-chain quaternary surfactants show antimicrobial properties, and are used as preservatives in pharmaceutical formulations.

2.2.4 Nonionic Surfactants

These do not ionize in the presence of water, and generally have a low irritancy potential compared to ionic surfactants. The hydrophilic portion of the nonionic surfactant molecule could be an alcohol, polyol derivative, or esters of fatty molecules (waxes). Nonionic surfactants are widely used in pharmaceutical formulations.

The structure of some of the synthetic surfactants are shown in Figure 2.3.

2.3 NATURAL SURFACTANTS

Surfactants are abundant in nature, and are present in both plants and animals. Some proteins behave like surfactants and play critical roles in various biological processes. An important group of protein surfactants

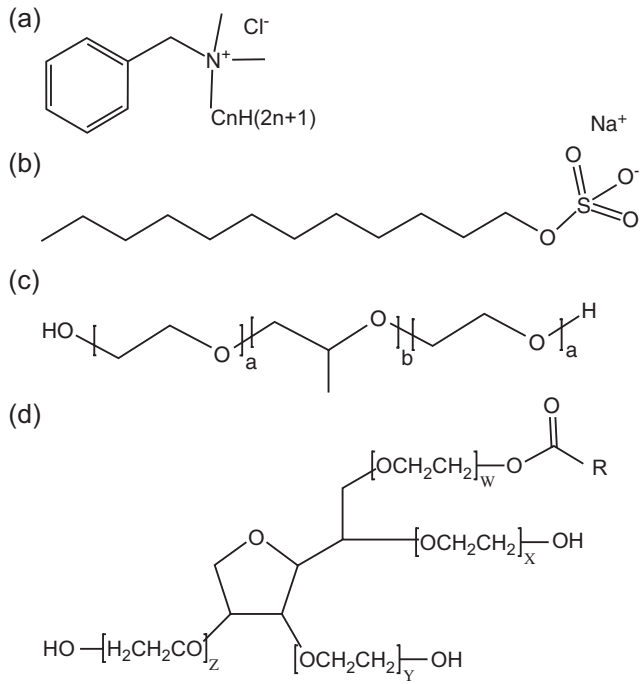

Figure 2.3 (a) Benzalkonium chloride where n = C_8 to C_{18}. (b) Sodium lauryl sulfate (sodium dodecyl sulfate). (c) Poloxamer (for Poloxamer 124, a = 12 and b = 20; Poloxamer 188, a = 80 and b = 27; Poloxamer 237, a = 64 and b = 37; Poloxamer 338, a = 141 and b = 44; Poloxamer 407, a = 101 and b = 56). (d) Polysorbates (W + X + Y + Z = 20); For Polysorbates 20, 40, 60, and 80, R = laurate, palmitate, stearate, and oleate, respectively.

from a therapeutic point of view are "lung surfactants" (or "pulmonary surfacants") [8]. In humans, lung surfactants are composed of approximately 90% lipids (phospholipids, cholesterol, and other lipids) and four types of pulmonary surfactant proteins (SP-A, SP-B, SP-C, and SP-D). The lung surfactants facilitate gas exchange in the lungs and prevent them from collapsing. The deficiency of lung surfactants can be caused by several reasons, including: premature birth, lung injury, or genetic mutations that inhibit surfactant production or function. Patients with lung surfactant deficiency are in risk of respiratory failure (e.g., Respiratory Distress Syndrome or Acute Respiratory Distress Syndrome) and the condition needs to be treated using lung surfactant supplements. Examples of medications include Survanta® and Surfaxin® (visit http://reference.medscape.com/drugs/lung-surfactants for additional information). Other examples of natural surfactants are bile salts [6,7,9].

2.3.1 Lipids

Lipids are a subset of a large domain of natural surfactants and are extremely important in pharmaceutical formulations as excipients. The word "lipid" (or "lipide" in French) implies organic compounds originating from animal or plant grease/fat. Typically, lipids are water insoluble and their natural physical state is oily or waxy. Included under the general category of "lipids" are simple long-chain fatty acids, fatty alcohols, esters, amines, plant- or animal-derived oils (triglycerides), phospholipids (also known as lecithin), and cholesterols. There are several other lipid classes within the general group of "phospholipids." Although lipids of natural origin are water insoluble, they can be synthesized to meet specific head group or acyl chain requirements for commercial applications. The chemical structures of some lipids are shown in Figure 2.4. The critical micelle concentration (CMC) of lipids is typically very low and as the chain length of the lipids increase, the CMC decreases considerably. Table 2.2 shows that phospholipids with acyl chains of more than nine carbon atoms have a CMC of the order of 10^{-3} mM or less. Consequently, for all practical purposes, phospholipids with long fatty acyl chains do not form micelles when suspended in water. At very low concentrations they form monomolecular films at the air–water interface. When in excess, they self-assemble into bilayers that are the building blocks of cell membranes.

Lipids play a very significant role in pharmaceutical formulations of parenteral, topical, transdermal, and oral dosage forms [10]. The lipids not only form drug delivery systems for both water-soluble and water-insoluble drugs, they also enhance drug penetration through the skin and drug absorption through intestinal mucosal membranes for oral dosages. Lipid analysis of human skin has been extensively investigated, and it is well established that a variety of lipids including fatty acids, phospholipids, ceramides, and many other types are present [11,12]. Topical or transdermal formulations containing lipids are considered to be well tolerated/less irritating to human skin [13,14].

Lipid-based formulations (LBS) of oral dosages, in particular liquid formulations in soft-gel capsules, have shown improved efficacy by enhancing the bioavailability of the drug. Digestion and dispersion are critical factors that affect the performance of oral dosages of lipid-based formulations. This is because during intestinal processing, physicochemical properties may change and impact performance by causing drug

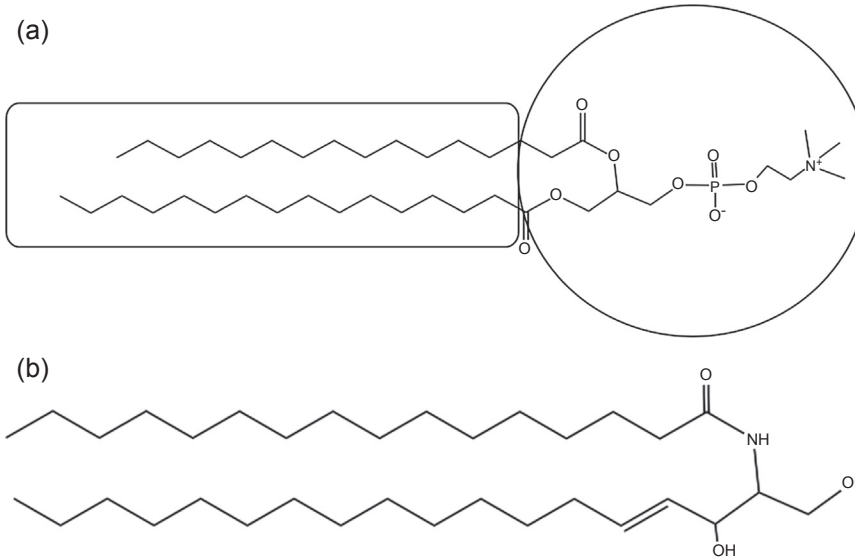

Figure 2.4 (a) Structure of dipalmitoyl phosphatidyl choline (DPPC), a typical phospholipid. *(From Kulkarni VS, Liposomes in personal care products. Delivery system handbook for personal care and cosmetic products. In: Meyer R. Rosen, editor. Technology, applications and formulations; in print 2005).* (b) A type of sphingo lipid known as ceramide; several different types of ceramides (variations in N-acyl chain length) are present in stratum corneum of human skin.

Table 2.2 Critical micelle concentrations for lecithins with increasing acyl chain lengths

Lipids	CMC (mM)
Dibutanoyl lecithn	80
Dihexanoyl lecithin	14.6
Dioctanoyl lecithin	0.265
Dinonanoyllecithin	2.87×10^{-3}
Dipalmitoyl phosphatidyl choline	2×10^{-8}

Compiled from Refs [31].

precipitation before the drug is absorbed. In order to aid formulation development and assess which factors affect performance, standardized in vitro methods have been developed along with a system for classifying LBS formulations [15–17]. This classification is based on formulation components and their dependence on digestion to facilitate dispersion.

Five categories have been proposed; Type-I: drug mixed in triglyceride or glyceride formulations; Type-II: formulations additionally having lipophilic surfactants; Type-IIIA: fine emulsion–self-emulsifying formulations with hydrophilic surfactants and cosolvents; Type-IIIB: those that form microemulsions with surfactants and cosolvents; and Type-IV: formulations composed of surfactants and cosolvents.

Some of the lipid-based oral drugs in the marketplace are listed in Table 2.3 along with the surfactants or lipids used in their formulations.

2.4 THE ROLE OF SURFACTANTS IN PHARMACEUTICAL FORMULATIONS

Surfactants, by the virtue of their intrinsic property of reducing the surface tension of water and being amphiphilic in nature, have found various roles in pharmaceutical formulations and have been used in all dosage forms. Some of the surfactants used in different dosage forms as listed in FDA's (U.S. Food Drug Administration) "Inactive Ingredient Guide" (IIG) database are shown in Table 2.4.

2.4.1 Skin Penetration Enhancers

The primary function of the skin is to protect the internal organs from external invasion by forming a strong barrier between the outside environment and the body. However, for topical dosage formulations such as transdermals, penetration of the drug into the skin is essential. Therefore, transdermal/topical formulations need to act against the natural function of the skin [18]. Although the skin acts as a barrier, it is not completely impermeable. Chemical penetration enhancers and certain surfactants can be incorporated into topical/transdermal formulations to help facilitate penetration of the drug into the skin [19]. Fatty acids (e.g., oleic acid), fatty alcohols (e.g., myristyl or oleoyl alcohols), fatty esters (e.g., isopropyl myristate), lipids, anionic and nonionic surfactants are commonly used as chemical penetration enhancers. Although the use of surfactants can enhance penetration of the drug into the skin, they increase the risk of skin irritation. Consequently, skin irritation potential becomes a critical factor to be considered when formulating products for use on compromised skin. Formulations targeted for mucosal membranes (such as nasal, buccal cavity, vaginal, or suppositories) generally use nonionic surfactants as they are less irritating than ionic surfactants.

Table 2.3 Lipids and surfactants used in some drug products in the marketplace

Trade names	Drug	Therapeutic use	Lipids/surfactants
Agenerases	Amprenavir	HIV antiviral	Tocopherol PEG succinate, and PEG 400
Rocaltrols	Calcitriol	Calcium regulator	Medium-chain triglycerides
Sandimmune	Cyclosporin	Immunosuppressant	Corn oil, and linoleoyl macrogolglyceride
Neorals	Cyclosporin A/I	Immunosuppressant	Corn oil monodiglycerides, and polyoxyl 40 hydrogenated castor oil
Gengrafs	CyclosporinA/III	Immunosuppressant	Polyoxyl 35 castor oil, polysorbate 80, and sorbitan monooleate
Accutanes	Isotretinoin	Anti-comedogenic	Hydrogenated soybean oil flakes, hydrogenated vegetable oils, and soybean oil
Kaletras	Lopinavir and ritonavir	HIV antiviral	Oleic acid, and polyoxyl 35 castor oil
Norvirs	Ritonavir	HIV antiviral	Oleic acid, and polyoxyl 35 castor oil
Lamprene	Clofazamine	Treatment of leprosy	Rapeseed oil, soybean lecithin, hydrogenated soybean oil, and partially hydrogenated vegetable oils
Sustivas	Efavirenz	HIV antiviral	Sodium lauryl sulfate, and sodium starch glycolate
Lofibra	Finofibrate	Lipid-regulating	Sodium lauryl sulfate
Restandol	Testosteroneundecanoate	Hormone replacement therapy	Castor oil, and propylene glycol laurate
Prometrium	Progesterone	Hyperplasia	Peanut oil, and lecithin
Rapamune	Sirolimus	Immunosuppressant	Phosphatidylcholine, and polysorbate 80
Vesanoid	Tretinoin	Acute promyelocytic leukemia	Hydrogenated soybean oil flakes, hydrogenated vegetable oils, and soybean oil

Compiled from Refs [15,16].

Table 2.4 Some of the surfactants listed in FDA's Inactive ingredient guide with the reported use in different dosage forms

Type of surfactant	Surfactant	Dosage form
Anionics	Ammonium lauryl sulfate	Topical aerosol, emulsions
	Sodium lauryl sulfate	Topical creams, gels, oral capsule, drops, tablets
	Alkyl aryl sodium sulfonate	Topical suspension
	Sodium cholestryl sulfate	IV (infusion), injection suspensions
Catatonics	Polyquaternium 10	Topical
	Quaternium-15 and -52	Topical emulsion, aerosol foams
	Benzalkonium chloride	Topical, nasal, ophthalmic, injectables
	Cetrimonium chloride	Topical
	Cetylpyridinium chloride	Inhalation aerosol, capsules
Nonionics	Polysorbate X (X = 20 or 40 or 60 or 65 or 80)	Injection, IV infusion, nasal sprays, ophthalmic suspensions, topical creams
	Sorbitan monolaurate (or sorbitan monostearate)	Topical lotions, emulsions ointments
	Glyceryl oleate (monostearate or dibehenate)	Topical, oral
	Glyceryl trioleate	Injection suspensions
	PEG 5 oleate	Topical, vaginal
	Poloxamers (e.g., 124, 188, 407)	Oral, topical, I.V. injection, subcutaneous, and ophthalmic
	Polyglyceryl-3-oleate	Oral capsules
Zwitterionics	Dioleoyl glycerophosphocholines	Injections, liposomal
	Egg phospholipids	Intravenous, injection
	Lecithin (soy lecithin)	Liposomal, injection, oral, nasal, inhalation aerosol
	Coco betaine	Topical

Compiled from http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

2.4.2 Emulsifying Agents

Oil and water are immiscible with each other because of the very high interfacial tension at the oil-water interface. In the presence of surfactants, however, this oil-water interfacial tension can be reduced to such an extent that the two immiscible phases can be made miscible. Many topical/transdermal

dosages are creams that are emulsions of oil and water phases. Other emulsion dosage forms including injectables, nasal sprays, and ophthalmic drops are available commercially. The selection of the surfactants to use and their concentration in the formulation are critical to making stable emulsions. A study of the oil-water interfacial tension as a function of surfactant concentration helps to determine the critical concentration of surfactant needed to achieve emulsification.

2.4.2.1 Hydrophile–Lipophile Balance (HLB) System

Surfactants are used to produce emulsions of oil droplets dispersed in water (oil-in-water) or water droplets dispersed in oil (water-in-oil). Consequently, emulsions have a large technological application, including in pharmaceutical dosages. An empirical but very useful numerical rating system was introduced by Griffin and is known as the Hydrophile–Lipophile Balance or HLB number [20]. In general, highly water-soluble surfactants have high HLB values and highly oil-soluble surfactants have low HLB values. HLB number ranges based on the solubility or dispersability of the surfactants are shown in Table 2.5.

Generally, surfactants with an HLB in the range of 4–6 are water-in-oil emulsifiers and 8–18 are oil-in-water emulsifiers. HLB values can also be determined experimentally as $HLB = 20(1 - S/A)$ in which S = saponification number of the ester and A = acid value of recovered acid.

HLB numbers for some common surfactants are shown in Table 2.6.

2.4.3 Aerosol Formulations

Surfactants have been used extensively in aerosol formulations. Surfactants reduce the surface tension of water and thereby facilitate atomization of the formulation. For nasal spray formulations, the formation of uniform plumes depends not only on the device but also on the formulation. The use of surfactants in nasal sprays is common to achieve the effective delivered dose (proper droplet size and plume) [22]. The use of surfactants in topical aerosols (wound healing sprays or pain relief sprays) or foam formulations is also common.

2.4.4 Surfactant Gels

The formation of gels by small amphiphilic molecules (surfactants) is well documented [23–25]. Gel formation by surfactants is considered a process similar to micellization rather than crystallization. Poloxamers™ are polymeric nonionic surfactants of ethylene oxide and propylene oxide, and several varieties of Poloxamers™ are listed in the FDA IIG database for use in pharmaceutical

Table 2.5 Surfactant water solubility and HLB ranges

Water solubility	HLB range
No dispersibility in water	1–4
Poor dispersion	3–6
Milky dispersion after vigorous shaking	6–8
Stable milky dispersion	8–10
Translucent to clear dispersion	10–13
Clear solution	13+

Table 2.6 HLB values for some common surfactants

Surfactant	HLB
Sorbitan tristearate	2.1
Sucrose distearate	3
Glyceryl monooleate	3.4
Glyceryl monostearate	3.8
Span 80 (sorbitan monooleate)	4.3
Glyceryl monolaurate	5.2
Sorbitan monopalmitate	6.7
Soy lecithin	8
Sorbitan monolaurate	8.6
Tween 81	10
Tween 80	15
Sodium stearoyl-2-lactylate	12
Sodium oleate	18
Ammonium lauryl sulfate	31

Some of the values are from Ref. [21].

formulations. Two of the Poloxamers™, Poloxamer 188 and Poloxamer 407, exhibit thermo-sensitive properties—that is, they are soluble in water at low temperature and gel at higher temperature.

2.5 SURFACE CHEMISTRY FOR PHARMACEUTICAL FORMULATIONS

2.5.1 Surface and Interfacial Tension

Physical properties including surface tension, osmotic pressure, conductivity, and detergency will change (either increase or decrease) as the concentration of surfactant increases. There are several methods,

including Du Nouy ring, Wilhelmy plate, maximum bubble pressure, drop volume, pendant drop, sessile drop, spinning drop, and capillary rise available to measure surface and interfacial tension [26]. Du Nouy ring and Wilhelmy plate can be used for both air–liquid and liquid–liquid interfacial tension measurements, and these are the most commonly used methods. American Society for Testing and Materials method number D1331-14 describes the test methods for "Surface and Interfacial Tension of Solutions of Paints, Solvents, Solutions of Surface-Active Agents, and Related Materials." Measurements of interfacial tension between oil and water in the presence of a surfactant provide information on the amount of surfactants required to reduce the interfacial tension to a level at which an emulsion can be formed. Pecora et al. [27] have pointed out that drug formulations used in dental treatments typically have a low surface tension so that the drug formulation penetrates through the tiny cavities to the site of the wound.

2.5.2 Contact Angle

The contact angle between a liquid and a solid is the angle within the body of the liquid formed at the gas–liquid–solid interface. This is geometrically determined by drawing a tangent from the contact point along the gas–liquid interface, as shown in Figure 2.5.

If the contact angle between a liquid and a solid is $<90°$, the liquid will wet the surface and spread over it. If the contact angle is $\geq 90°$, the liquid will stay on the surface as a bead. Therefore, the contact angle between a liquid and a solid is dependent on the nature of the liquid as well as the surface characteristics of the solid. Both of these factors are critical when formulating nasal or ophthalmic drop dosages. The drop size and drop weight delivered from the bottles are dependent on the geometry of the orifice and the surface characteristics of the material used for the primary container, as well as the surface tension of the formulation. Van Santvliet et al. [28–30] have studied the influence of the formulation surface tension and the dropper tip angle for ophthalmic dosages. Their data suggested that the drop weight, which equates the dose weight, is dependent on the dropper angle, capillary orifice, and surface tension of the formulation. The material used for making the dropper (glass vs plastic) is also suspected to play a role in the dose weight of liquid dosages to be delivered via capillary droppers.

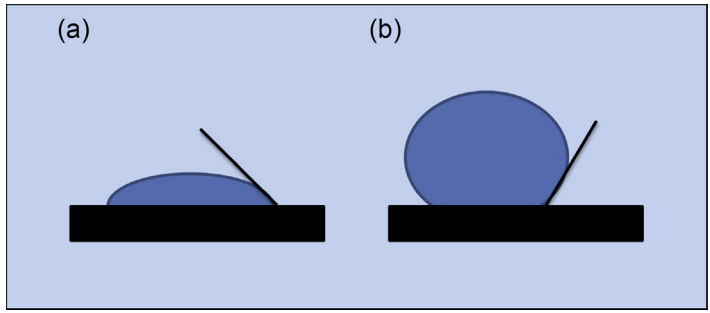

Figure 2.5 Contact angle of a water drop with a solid surface; <90° indicates wetting (a) and ≥90° indicates nonwetting (b).

2.6 CONCLUSION

Surfactants are ubiquitous in nature. Both natural and synthetic surfactants are used in pharmaceutical formulations. The FDA-IIG database lists numerous surfactants, indicating that surfactants are important excipients in all dosage forms. Surface phenomena including surface tension and contact angle studies play a critical role in formulation development, as well as in the design or selection of container closure systems for liquid dosages.

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