**Surfactants**

In daily life every person regularly comes into contact with surface active agents, or so-called surfactants. In food stuff, naturally occurring surfactants act as emulsifiers, such as casein in milk and other milk made products. In domestic, man-made surfactants are active components in detergents, personal care products, and pharmaceuticals. In industrial areas, surfactants are used in oil recovery, in pulp and paper manufacturing, in flotation where various reserves are separated from each other and a host of other applications. Over the years, both the type and uses of surfactants have changed. The previous evidence of surfactant invention has been found in clay cylinders originating from prehistoric Babylon, dating back to about 2800 B.C. A soapy substance was found in the cylinders and the inscriptions declare that fats were boiled with ashes, a known soap-making method, but the purpose of the soap was unknown. In the early 19th century, development in the chemical industry made large-scale commercial production of surfactants possible, being still based on fats and ashes. After sometime, the surfactants were utilized for cleaning clothes, and their increased use led to the improvement of effective surface active agents.

![HYDROPHILIC HEAD](<image_url>)  
**HYDROPHOBIC TAIL**

**Fig. 1.1:** Schematic representation of a surfactant.

Surfactants (Fig. 1.1) are chemicals that reveal amphiphilic behavior towards a solvent. Generally, surfactant molecules consisting of one water
compatible part, hydrophilic, and other oil compatible or water fearing part, referred to as hydrophobic or lipophilic, are called amphiphiles or amphipathic. The term originated from two Greek words, first *amphi*, meaning double and second term *philos*, meaning affinity. This combination makes the surfactant ambivalent; the hydrophilic head group is attracted to polar environments, for example water, while the hydrophobic tail is attracted to nonpolar environments, for example oil. Consequently, the surfactants can dissolve either in water or oil and have the capacity to solubilise water in oil and vice versa, thus creating homogeneous systems.

A hydrophilic molecule or portion of a molecule is one that is typically charge-polarized and capable of hydrogen bonding, enabling it to dissolve more readily in water than in oil or other hydrophobic solvents. However, surfactants tend to self-assemble or aggregate when dissolved in either polar or nonpolar environments. The so-called hydrophobic effect is the driving force for this aggregation in water, caused by the hydrophobic tail avoiding contact with the solvent i.e., the water. Hydrophilic and hydrophobic parts of molecules are also known as polar and nonpolar, respectively. This duality of the surfactants makes them accumulate at interfaces, thereby decreasing the surface tension, enabling emulsification, adsorption and desorption.

In aqueous solution low concentrations of surfactant work much as common electrolytes, but at higher concentrations very different behavior results. This behavior is described in terms of the formation of well organized aggregates, which are formed by numerous numbers of molecules, called micelles, in which the hydrophobic parts of the surfactants combine in the core of the aggregate leaving hydrophilic parts towards the aqueous medium. The formation of aggregates in aqueous solution is usually viewed as a settlement between the tendency for alkyl chains to resist actively unfavorable contacts with water, and
the desire for the polar head groups to remain in contact with the aqueous environment.

Water and hydrocarbons are immiscible in nature; the limited miscibility of hydrocarbons in water can be ascribed to the hydrophobic effect. This effect spontaneously reduces the undesirable hydrocarbon-water contact and increases the entropy of the system. However, the hydrocarbon chains come closer to reduce water contact, the polar head groups of the same charge tend to stay away from each other as a result of electrostatic repulsion and extensive group hydration. Therefore, in a micellar aggregate, the equilibrium gap between the polar heads is maintained as a result of settlement between the two divergent tendencies. However, micellization is not only considered to aqueous solution; it is also noticed in other polar solvents such as ethylene glycol and non-polar solvents such as hexane (in the second case giving rise to reverse structures) [1]. The amphiphiles with more or less equilibrated hydrophilic and hydrophobic tendencies are likely to move around to the surface or interface. It doesn’t occur if the amphiphilic molecule is too hydrophilic or too hydrophobic, in which case it stays in one of the phases. Because of its dual tendency, an amphiphilic molecule doesn’t feel comfort in any solvent. This is why amphiphilic molecules reveal a very strong tendency to migrate to interfaces or surfaces and to orient so that the polar group is towards the water and the non-polar or apolar is placed out of it.

Amphiphiles play a key role in the existence of the life and widely used in the industry, medicine, pharmacology, etc. [2, 3]. The single feature of amphiphiles that gives rise to broad utility is their ability to coexist with and function as an interface between polar and non-polar phases. This ability is determined by a balance between ionic and dipolar interactions with polar media and dispersion interactions with non-polar media.
Introduction

On the basis of the chemical structure, the hydrophobic self-association of solute may be categorized into following four classes: (1) flexible chain compounds (surfactants, etc.), (2) aromatic or heterocyclic ring or fused ring structures (drugs, dyes, etc.), (3) alicyclic fused ring compounds (bile salts, etc.), and (4) macromolecular solutes (proteins, etc.) [4]. The self-association behavior depends upon the chemical structure of solutes. The easiest form of association, viz., dimerization, can take place in all the self-associating systems. The formation of higher multimers may overshadow it, however, more or less completely [4].

Classification of surfactants

The term surfactant is a combination of surface active agent [5]. Surfactants are generally organic compounds that are amphiphilic, meaning they contain both hydrophobic groups (their tails) and hydrophilic groups (their heads).

First surface-active product was prepared commercially by C. Schollar in Germany in 1930 [6]. Surfactants have found a wide range of applications in both academic and industry. The most common surfactant application is detergency. The ability of surfactants to aid in the mixing of hydrophobic and hydrophilic molecules is used extensively in the chemical industry in applications such as removal of oily materials from a substrate, which is known as detergency. Surfactants have impact on almost all aspects of our daily life, either directly in household detergents and personal care products or indirectly in the production and processing of materials which surround us [3, 5-8]. In environmental applications, surfactant micelles can be used to solubilize and separate toxic ingredients in waste water for water purification [9, 10]. Surfactants have even been the subject of investigation into the origin of life; meteorites containing lipid-like compounds and may be an interstellar prebiotic earth source of cell membrane materials [11]. Moreover, surfactants play a major role in the oil industry, for example in enhanced and tertiary oil recovery. Surfactants are also involved in the
production of many common food items and can be found in the extraction of cholesterol, solubilization of oil, emulsification, prevention of component separation and solubilization of essential nutrients. Some surfactants are known to be toxic to animals, ecosystems and humans, and can increase the diffusion of other environmental contaminants [12-14].

Surfactants can be classified according to their physical properties or functionalities. The most common classification is based on the nature of the hydrophilic group [15-18]. A non-ionic surfactant has no charge groups in its head. The head of an ionic surfactant carries a net charge. If the charge is negative, the surfactant is more specifically called anionic; if the charge is positive, it is called cationic. If a surfactant contains a head with two oppositely charged groups, it is termed zwitterionic.

(i) Cationic surfactants

The surface-active portion of the molecules bears a cationic charge. Some common cationic surfactant head groups includes amines and quaternary ammonium ions (amines only function as a surfactant in the protonated state, and hence cannot be used at high pH). Cationic surfactants, with a utilization of approximately seventy lakh tons per year, have a wide variety of applications, such as fabric softeners, corrosion inhibitors, tarmac additives, biocides, fabric auxiliaries, etc [10, 17]. Cationic surfactants containing quaternary ammonium groups are important because of their positive charge which does not depend on solution pH. The prime use of cationic surfactants is their tendency to adsorb at negatively charged surfaces, e.g., anticorrosive agents for steel, flotation collectors for mineral ores, dispersants for inorganic pigments, antistatic agents for plastics, other antistatic agents and fabric softeners, hair conditioners, anticaking agent for fertilizers and as bactericides. However, these surfactants have higher aquatic toxicity than other surfactants. They are more toxic for aquatic organism including
microorganisms as they cause cellular breakdown, protein denaturation, membrane disruption and change other enzymatic behavior. They are more irritating to the skin and eyes. The toxicity of these surfactants is believed to stem from their affinity to interact strongly with negatively charged surfaces, as well as the lipid membranes of biological cells [19, 20]. Cationic head groups also increase the disinfecting properties of household cleaners.

*Examples:* Cetyltrimethyl ammonium bromide: $\text{C}_{16}\text{H}_{33}\text{N}^+(\text{CH}_3)_3\text{Br}^-$

Dodecyldimethyl ethyl ammonium bromide: $\text{C}_{12}\text{H}_{25}\text{N}^+(\text{CH}_3)_2(\text{C}_2\text{H}_5)\text{Br}^-$

**(ii) Anionic surfactants**

Anionic surfactants have negatively charged head groups. Some of the more commonly used anionic head groups are sulfates, sulfonates and ethoxylates. The counterions most frequently involve are sodium, potassium, ammonium, calcium and various protonated alkyl amines. Sodium and potassium impart water solubility, whereas calcium and magnesium promote oil solubility. Anionics are used in greater volume than any other surfactant class (approx 60%). These are the most widely used class of surfactants in industrial applications [21, 22] due to their relatively low cost of manufacture. Anionics are commonly used in cleaning products, such as shampoos, laundry detergents and soaps, because of their ability to remove dirt from soft mediums such as fabrics.

*Examples:* Sodium dodecyl benzene sulfonate: $\text{C}_{12}\text{H}_{25}(\text{C}_6\text{H}_4)\text{SO}_3^-\text{Na}^+$

Sodium dodecyl sulfate: $\text{C}_{12}\text{H}_{25}\text{SO}_4^-\text{Na}^+$

**(iii) Zwitterionic surfactants**

Zwitterionic surfactants have both the charges on polar head group. While the positive charge is almost invariably ammonium, the source of negative charge may vary, although carboxylate is the most common one. Zwitterionics are often
referred to as ‘amphoteric’. Zwitterionic surfactants have excellent dermatological properties. They are frequently used in shampoos and other cosmetic products, and also in hand washing liquids because of their high foaming properties. Amphoteric surfactant is one that changes from net cationic via zwitterionics to net anionic on going from low to high pH. Neither the acidic nor the basic site is permanently charged, i.e., the compound is only zwitterionic over a certain pH range. The change in the charge with pH of the truly amphoteric surfactants naturally affects properties such as foaming, wetting, detergency, etc. All these properties strongly depend on the solution pH. Zwitterionic surfactants are generally quite expensive, and consequently, their use is limited to very special applications such as cosmetics where their high biological compatibility and low toxicity is of primary importance. Surfactants containing perfluorinated hydrophobic moieties are used in a wide variety of applications, ranging from fire extinguishing media to electroplating additives and water-repellent fiber coatings [23].

*Examples:* Lauryl-N-methylsarcosine: $\text{C}_{12}\text{H}_{25}\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{COO}^-$

Cocamidopropyl betaine: $\text{C}_{11}\text{H}_{23}(\text{CO})\text{N}(\text{CH}_3)\text{C}_3\text{H}_7\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{COO}^-$

**(iv) Polymeric surfactants**

There has been considerable recent interest in polymeric surfactants due to their wide application as stabilizers for suspensions and emulsions. These are formed by association of one or several macromolecular structures exhibiting hydrophilic and lipophilic characters. They are now very commonly used in formulating products as different as cosmetics, paints, foodstuffs, and petroleum production additives.

*Example:* Poly(ethylene glycol)-poly(propylene glycol)-poly(ethylene glycol):

$\text{HO(CH}_2\text{CH}_2\text{O})_{20}(\text{CH}_2\text{CH(\text{CH}_3})\text{O})_{70}(\text{CH}_2\text{CH}_2\text{O})_{20}\text{H}$

Polyethylene glycol nonylphenyl ether: $\text{C}_{9}\text{H}_{19}(\text{C}_6\text{H}_4)(\text{CH}_2\text{CO})_2\text{OH}$
(vi) Non-ionic surfactants

Non-ionic surfactants are composed of uncharged polar head groups. The most common nonionic surfactants are those based on polyethylene oxide, referred to as ethoxylated surfactants. Non-ionic surfactants come as a close second with about 45% of the overall industrial production. They do not ionize in aqueous solution, because their hydrophilic group is of a nondissociable type, such as alcohol, phenol, ether, ester, or amide. In the majority of non-ionics, the polar group is a polyether consisting of oxyethylene units, prepared by the polymerization of ethylene oxide. Strictly speaking, the prefix ‘poly’ is a misnomer. The typical number of oxyethylene units in the polar chain is five to ten, although some surfactants, e.g., dispersants, often have much longer oxyethylene chains. Nonionic surfactants function very well as grease removers and used in detergents, soaps and household cleaners.

Example: Polyoxyethylene [4] lauryl ether: C_{12}H_{25}(CH_{2}CO)_{4}OH

(vi) Gemini surfactants

Search for a newer surfactant with greater surface activity gave birth to bis-surfactants, which were later termed as “Gemini” surfactants. Menger et al. [24-26] assigned the term “gemini” to the bis-surfactants containing a rigid spacer such as benzene or stilbene. The term was then extended to other bis or double tailed surfactants, irrespective of the nature of the spacer. Geminis are significantly more surface active than conventional monomeric surfactants. All geminis possess at least two hydrophobic chains and two ionic or polar head groups and spacers with different nature [27] such as short or long flexible chains of methylene groups, rigid (stilbene, polyether) and non-polar (aliphatic, aromatic) groups. A schematic representation of a gemini surfactant is shown in Fig. 1.2.
Geminis were known long before to Bunton et al. [28], who studied catalysis of nucleophilic substitutions by “dicationic detergents” and to Devinsky et al. [29] who reported the surface activity and micelle formation of some new “bisquaternary ammonium salts”. Then Okahara [30] prepared and examined amphiphatic compounds with two sulphate groups and two lipophilic alkyl chains.

![Schematic representation of a gemini surfactant.](image)

**Fig. 1.2:** Schematic representation of a gemini surfactant.

Most geminis are composed of two identical halves, but unsymmetrical gemini surfactants have also been synthesized, either having different hydrophobic tail lengths, or different types of polar groups (heterogemini surfactants), or both.

The gemini surfactants with their unusual and exceptional chemical structures have been found to possess properties which are superior to conventional surfactants (single head/single tail). These include low critical micelle concentration (cmc) values and unusually high surface activity, better solubilization and multiplicity of aggregation [31], as a result of which many
manufacturers and researchers have shown keen interest in gemini surfactants. Significantly among the gemini surfactants, the cationic alkanediyl-α, ω-bis(alkyldimethylammonium bromide) type, designated as \( C_m-C_S-C_m \), where ‘\( C_m \)’ refers to the length of the alkyl tails and ‘\( C_S \)’ is the number of methylene units that make up the alkyl spacer, has established more consideration. The three structural basics—hydrophilic head group, a hydrophobic tail group, and their linkage—may be varied to change the properties of the gemini surfactants. They recently have achieved greater attention in academic areas and among scientists at surfactant manufacturing companies for the following causes:

(a) Gemini surfactants have at least one order of magnitude lower cmc value than their conventional analogs (monomeric) surfactants, on a weight % basis.

(b) They are 10–100 times more capable at reducing the surface tension of water and the interfacial tension at an oil/water interface than conventional surfactants.

(c) They show better solubilizing, foaming, wetting, and lime-soap dispersing ability than the conventional surfactants. Some anionic gemini surfactants have low Krafft temperatures, which make them applicable in cold water as well as cationic gemini surfactants contain remarkable biological properties.

(d) The aqueous solutions of some gemini surfactants with a short spacer can have unusual rheological properties (viscoelasticity, shear-thickening) at comparatively low concentration.

(e) The micelles present in solutions of some gemini surfactants can hold special shapes as, for example, ring-like or elongated with several branches.

(f) Gemini surfactants can be synthesized with a vast variety of structures. In standard, it is likely to join any two identical or different surfactants among the available ones by a spacer group that can be hydrophilic or hydrophobic, flexible or rigid, heteroatomic, aromatic, etc. This is only limited by the talent of the
organic synthetic chemist. Therefore, the structures and properties of gemini surfactants can be more finely adjusted for a given application than for conventional surfactants.

Much attempt is also being dedicated to develop the particular geometry of gemini surfactants to form structures of distinct geometry. Gemini surfactants form vesicles and liquid crystalline phase over broad concentration ranges, a property that can be taken advantage of for a variety of applications. One example of such work is the preparation of mesoporous molecular sieves. A number of patents and papers have appeared in scientific literature [31-34]. All charge types of gemini surfactants, cationic [35, 36], anionic [37], non-ionic [38] and zwitterionic [39] and a variety of structural types; alkylglucoside based [40], sugar based [41], with unsaturated linkages [42, 43, 44] and almost all types with flexible, rigid, and heterotype spacers have been synthesized.

Another class of gemini surfactants is counterion coupled gemini surfactants or cocogems. In cocogems two surfactant tails are bound via a geometrically well-defined functional counterion [45, 46]. The search for the synthesis of new novel types of gemini surfactants is increasing from their application point of view [47, 48].

Example: Hexanediyl-1, 6-bis(hexadecyldimethylammonium bromide):

\[ \text{C}_{16}\text{H}_{33}\text{N}^+(\text{CH}_3)_2\text{C}_6\text{H}_{12}(\text{CH}_3)_2\text{N}^+\text{C}_{16}\text{H}_{33} 2\text{Br}^- \]

(vii) Bolaform surfactants

Bolaform surfactants or bolaamphiphiles (also known as bolaphiles or alpha-omega-type surfactants) are amphiphilic molecules which consist of two hydrophilic head groups, connected by a long, linear polymethylene chain (Fig. 1.3).
Their self-association ability is less, compared to conventional ionic surfactants. However, they show biological activity [49, 50] and some special bolaforms are able giving rise to organized assemblies of peculiar structure [51].

*Example:* Hexadecanediyl-1, 16-bis(trimethylammonium bromide):

\[(\text{CH}_3)_3\text{N}^+(\text{CH}_2)_{16}\text{N}^+(\text{CH}_3)_3 \, 2\text{Br}^-\]

**Micelle formation and critical micelle concentration**

At low surfactant concentrations in water, surfactants occur as monomers in the solution as well as at the interface. The distribution of monomers between the solution and the interface is in equilibrium. As the surfactant concentration is increased the monomers start to interact, self-assemble, and aggregation starts when the surfactant concentration exceeds a certain value, the critical micelle concentration or cmc. Surface tension measurements can be used to determine the cmc value since the surfactant monomers disrupt the hydrogen bonding between water molecules at the surface and thus lower the surface tension. At the cmc the water/air interface is saturated with surfactant monomers and the reduction of the surface tension strongly diminishes. The magnitude of the cmc value is specific for each surfactant.
The main reason for micelle formation is the attainment of a minimum free energy state. The main driving force for the formation of micelles is the increase of entropy that occurs when the hydrophobic regions of the surfactant are removed from water and the ordered structure of the water molecules around this region of the molecule is lost.

![Diagram showing micelle formation](image)

**Fig. 1.4:** Surfactant existence in different phases, dependent on surfactant concentration.

Micellization is an important phenomenon not only because a number of important interfacial phenomena, such as detergency and solubilization, depend on the existence of micelles in solutions, but also because it affects other interfacial phenomena, such as surface or interfacial tension reduction, that do not directly involve micelles. Two principal factors govern such organization: (1) tail-tail interactions, in which the hydrophobic effect causes the nonpolar entities to coalesce; (2) head-head and head-water interactions which oppose the total separation of surfactant into a nonpolar phase. The interplay of these two factors determines the concentration onset of micelle formation, the micelle size
distribution, and subsequent physical and chemical properties. The length of the hydrocarbon tail, size of the head group, and interaction of the hydrocarbon tails, with one another and with the aqueous solution establish the size and shape of the micelle, the cmc, and the aggregation number. Shapes of micelles can differ from rough spheres to prolate ellipsoids, and the diameter of micelles usually ranges from 3 to 6 nm \[52\].

The cmc is a significant property of the surfactants which reveals its micellization ability. Below the cmc value, the physico-chemical properties of ionic surfactants are similar to those of strong electrolytes and, above the cmc, these properties change dramatically, representing a highly cooperative association. This is illustrated by Preston’s classic graph \[53\] in Fig. 1.5. Just above the cmc, micellar structure is considered to be roughly globular or spherical \[54, 55\].

**Fig. 1.5:** Preston’s classic graph showing variation in physical properties of surfactant solutions below and above the cmc value of sodium dodecyl sulphate.
The common method of obtaining the cmc value of a surfactant micelle is to plot a suitable physico-chemical property vs. the surfactant concentration and detect the break point in the plot. The most general methods to obtain cmc are IR spectroscopy, UV/visible, NMR spectroscopy, fluorescence, scattering techniques, voltammetry, calorimetry, surface tension, conductivity and foaming. For many of the techniques applied appears [56] that the uncertainties in the experimental cmc determinations increase with increasing temperature because at the same time the surfactant aggregation number decreases and the aggregation distribution increases. However, Mukerjee and Mysels, [57] in their huge compilation of cmc values, have noted that the majority of values for a single surfactant are in good agreement and the outlying values are simply related for. The cmc values are essential in all of the process industry surfactant applications, from mineral processing to formulation of personal care products, foods to drug delivery systems, and to new surfactant remediation technologies. In these processes, surfactant must usually be present at a concentration higher than the cmc because the best result of the surfactants, whether in interfacial tension lowering, emulsification, suspension stabilization, as a delivery vehicle, or in promoting foam stability, is achieved when a significant concentration of micelles is present.

Types of micelles

Micelle! The small, intangible, self-assembled systems are the flagship of colloid chemistry. Ever since McBain proposed the occurrence of molecular aggregates in soap solutions on the basis of the strange alteration in electrical conductivity observed with changing soap concentration [58], the structure of micellar aggregates has been a subject of discussion. Hartley proposed that micelles are spherical with the charged groups located at the micellar surface [59], whereas McBain recommended that lamellar and spherical forms coexist [60]. X-ray studies by Harkins et al. [61, 62] then suggested the sandwich or lamellar model. Later, Debye and Anacker [63] proposed that micelles are rod-shaped
rather than spherical or disk-like. In 1956, Hartley’s spherical model was established by Reich [64] from the point of view of entropy, and the spherical form is now generally accepted as resembling the actual structure.

There are three types of micelles formed in surfactant solutions. Micelles formed in polar solvents are called normal micelles and those formed in nonpolar solvents are called reverse micelles. Another type is mixed micelle which is formed upon mixing of two or more surfactants. All the three are briefly discussed below.

![Schematic presentation of normal (A), reverse (B) and mixed micelles (C). In (C), and indicate different surfactant monomers.](image)

**Fig. 1.6:** Schematic presentation of normal (A), reverse (B) and mixed micelles (C). In (C), and indicate different surfactant monomers.

(i) Normal micelle

The structure of normal micelle just above the cmc can be considered as roughly spherical (Fig. 1.6) [65, 66]. When the hydrophobic portion of the surfactant is a hydrocarbon chain, the micelle will consist of liquid-like hydrocarbon core. The radius of this core is roughly equal to the length of fully extended hydrocarbon chain (~12-30 Å).

The micellar surface appears to be an amphipathic structure which is supported by the binding of both hydrophobic organic molecules and hydrophilic
ions with micelles. The amphipathicity is a property shared with the surfaces of proteins and membranes [67, 68]. Menger has proposed that water can penetrate inside the micelle up to a certain level [69, 70], the idea got support from fluorescence and $^1$H NMR measurements. Partial molar volume determinations specify that the alkyl chains in the core are more stretched than those in the normal liquid state [71].

![Schematic representation of the regions of spherical micelle.](image)

**Fig. 1.7:** Schematic representation of the regions of spherical micelle.

A normal ionic micelle consists of three regions (Fig. 1.7):

(i) **Core region:** A liquid-like hydrocarbon core (as the interior part consists of the hydrophobic hydrocarbon chains of the surfactant molecules). The
radius of this core is roughly equal to the length of fully stretched hydrocarbon chain (~12-30 Å).

(ii) Stern layer: Surrounding the core is an aqueous layer known as the Stern layer. The Stern layer constitutes the inner part of the electrical double layer. It contains the regularly spaced charged head groups and 60-90% of the counterions (the bound counterions). The head groups are hydrated by a number of water molecules. One or more methylene groups attached to the head group may be wet. The core and the Stern layer form the kinetic micelle.

(iii) Guoy-Chapman layer: An outer layer which extends in to further aqueous phase, is called Guoy-Chapman layer. This layer consists of the remaining counterions. The thickness of this layer is determined by the effective ionic strength of the solution.

Micellization of ionic surfactants are ascribed to be a balance between hydrocarbon chain attraction and ionic repulsion. For nonionic surfactants, however, the hydrocarbon chain attraction is opposed by the requirements of hydrophilic groups for hydration and space. Therefore, the micellar structure is determined by equilibrium between the repulsive forces among hydrophilic groups and the short-range attractive forces among hydrophobic groups. In other words, the chemical structure of a given surfactant determines the size and shape of its micelles.

(ii) Reverse micelle

Micellization can also happen when amphiphiles are dissolved in nonpolar organic solvents. In a reverse micelle, head groups of surfactant molecules locate inside to form a polar core and hydrocarbon tails are directed towards the bulk solvent to form the outside shell of the micelle [72-75]. At a very low concentration of surfactant, the reverse micelles are very close to spherical in
which water molecules occupy the central part of the sphere, thus forming a so-called micro water-pool. These water molecules are in contact with head groups of reverse micelle-forming surfactant molecules. The tails of these surfactant molecules are extended toward bulk nonpolar solvent phase (Fig. 1.6(B)). The most often used reverse micellar system is the Aerosol OT (AOT)/H₂O/iso-octane system. AOT has a negatively charged polar head and two nonpolar tails (AOT, sodium bis (2-ethylhexyl) sulfosuccinate).

Reverse micelle is more complex than normal but can be used to solubilize polar solutes in nonpolar solvents. Dipole-dipole [76, 77] interactions hold the hydrophilic head groups together in the core. The water molecules are strongly linked with the head groups of surfactant. The aggregation properties of surfactants in nonpolar media are often altered markedly by the presence of traces of water or additives. The size and properties of reverse micelles vary with amount of water present [78-81]. Water in reverse micelles is predicted to behave very differently from ordinary water because of extensive binding and orientation effects induced by polar heads forming the water core [82]. The core of reverse micelles has been compared with active site of enzymes [80, 81]. Enzymes have been encapsulated inside the water pool of reverse micelles without affecting their activity. In recent years, the field of reverse micelles has witnessed a significant growth of interest, partly due to the finding that proteins, other biopolymers, and even bacterial cell can be solubilized in the reverse micellar system: in fact, this has permitted the extension of area of interest to new domain, i.e., biocatalysis and chemical biotechnology.

(iii) Mixed micelle

Mixing of two and more surfactants in an aqueous solution leads to the formation of mixed micelles. A mixed micelle is an aggregate of surfactant molecules composed of different types of surfactants present in aqueous solution.
However, the mixed micelle means a micelle composed of amphiphiles capable themselves of forming micelles. Thus, mixed micellization is a special case of solubilization. The physico-chemical properties of mixed micelles are quite different from those of pure micelles of individual components. From the application viewpoint, mixed micelles are of great importance in biological, technological, pharmaceutical and medicinal formulation, enhanced oil recovery process for the purpose of solubilization, suspension, dispersion, etc. [83].

Mixed micelles may also form when low molecular weight solutes are solubilized by micelles of amphiphiles containing a relatively larger nonpolar side chain. The solubilized substances, also called as the penetrating additives [84], may be located in both the hydrocarbon core [85] and in the hydrophilic layer [86-88].

The cmc of mixed micelles fall within the highest and lowest individual cmc values of components as shown for binary and ternary mixtures [89]. In aqueous solutions of binary surfactant mixtures, synergetic (attractive) interactions between the two surfactant species result in cmc’s which can be substantially lower than those in solutions containing the constituent single surfactants. On the other hand, antagonistic interactions, in mixtures of hydrocarbon-based and fluorocarbon-based surfactants in aqueous solution, result in mixture cmc’s that can be considerably higher than the cmc’s of the constituent single surfactants [90, 91].

**Factors affecting the value of critical micelle concentration**

As the properties of surfactant solutions change noticeably when micelle formation begins, many investigations have been concerned with determining values of the cmc in various systems. A great deal of work has been done on explaining the various factors that determine the cmc at which micelle formation
becomes significant, especially in aqueous media. A compilation of cmc data for many surfactants over a large variety of conditions have been published [57].

Among the factors known to effect the cmc markedly in aqueous solutions are:

(i) Structure of amphiphiles

(ii) Presence of various additives in the solution

(iii) Experimental conditions such as temperature, pressure, solvent, etc.

\textit{(i) Structure of amphiphiles}

(a) The hydrophobic group: The cmc in aqueous media decreases as the hydrophobic character of the surfactant increases. The large majority of amphiphiles, whether ionic or nonionic have hydrophobic regions composed of hydrocarbon chains. For nonionics and zwitterionics the decrease in cmc with increase in the hydrophobic group is somewhat larger, an increase by two methylene units reducing the cmc to about one-tenths its previous value (compared to one-quarter in ionics). As a general rule for ionic surfactants, the cmc is halved when the length of the straight hydrocarbon chain is increased by one methylene group, while in case of nonionic surfactants, the addition of one methylene group causes the cmc to decrease to approximately $\frac{1}{3}$ of its original value [92]. The presence of branched chains or double bond hinders micelle formation and thus increases the cmc. When the number of carbon atoms in a straight-chain hydrophobic group exceeds 16, however, the cmc no longer decreases so rapidly with increase in the length of the chain and when the chain exceeds 18 carbon atoms it may remain substantially unchanged with further increase in the chain length. This may be due to the coiling of these long chains in water [10]. When the hydrophobic group is branched, the carbon atoms on the branches appear to have about one-half the effect of carbon atoms on a straight chain [93].
(b) The hydrophilic group: Effect of nature of hydrophilic group of ionic surfactants on the micellar properties has been reported by Anacker and coworkers and they concluded that an important factor controlling the micellar size was mean distance of closest approach of a counterion to the charge center of the surfactant [94]. Thus, for example, decylammonium bromide forms very much larger micelles than decyltrimethylammonium bromide because the Br\(^-\) counterions are able to approach more closely to the charged nitrogen atom of decylammonium thus effectively shielding the repulsive electrical forces and permitting larger micelle to form. Cationics typically have slightly higher cmc’s than anionics. The cmc’s of nonionics are much lower than for ionics. For some nonionics, there is a moderate increase of the cmc as the polar head becomes larger. The more charged groups in the surfactants, the higher the cmc due to increased electrical work required to form micelles [95, 96]. As the hydrophilic group is moved from the terminal position to a more central position, however, the cmc increases. It is because the hydrophobic group seems to act as if it had become branched at the position of the hydrophilic group.

(ii) Presence of various additives in the solution

(a) Effect of electrolytes: Adding an indifferent electrolyte to a surfactant solution has a pronounced effect on the cmc, especially for ionic ones. For nonionic surfactants, the effect is smaller but still significant and the difference between the two is dramatically demonstrated by the difference in the functional dependence of cmc on salt concentration.

The following empirical equation relating the concentration of the electrolyte on the cmc of ionics has been used [97]

\[
\log \text{cmc} = -a\log C_e + b \tag{1.1}
\]
where $a$ and $b$ are constants for a particular ionic group and $C_c$ denotes the total counterion concentration.

The equation (1.1) does not hold for nonionics and zwitterionics. Instead, the effect is given by [98]

$$\log \text{cmc} = -K C_s + \text{constant} \quad (C_s < 1)$$

(1.2)

where $K$ is a constant for a particular surfactant, electrolyte, and temperature and $C_s$ is the concentration of electrolyte in moles per liter.

For the ionic surfactants, the principal effect of the salt is to partially screen the electrostatic repulsion between the head groups and so lower the cmc. The effect of salts of the same valence type are usually discussed in terms of the lyotropic series. For the nonionic ones the concentrations of salts required to produce significant effects are much higher and the discussion of such behavior introduces the notion of ‘salting-in’ and ‘salting-out’ of nonelectrolytes by the electrolyte [98].

Salting-out electrolytes are capable to reduce the cmc of nonionic surfactants while salting-in electrolytes enhance the cmc. Salting-in or salting-out by an ion depends upon whether the ion is a water structure breaker or a water structure maker. Ions with a large ionic charge/radius ratio are highly hydrated and are water structure makers, e.g., $F^-$, they salt-out the hydrophobic group of the monomeric form of the surfactant and decrease the cmc while ions with the small ionic charge/radius ratio are water structure breakers, e.g., $\text{CNS}^-$, they salt in the hydrophobic group of the monomeric form of the surfactant and increase the cmc.

(b) \textit{Effect of organic additives}: Addition of organic compounds affect the cmc either by penetrating into the micellar region, or by modifying solvent-micelle or solvent-monomer interactions.
Introduction

The type-1 compounds are molecules (like alcohols with moderate to long hydrocarbon chains) that appear to adsorb in the outer region of the micelles, forming a palisade (i.e., fence like) structure with the amphiphilic molecules. This lowers the free energy of micelle formation to more negative values, so reduce the cmc; such molecules can also influence the micelle shape. Water soluble compounds in type-1 may operate as members of type-1 while at high bulk phase concentration as members of type-2.

(iii) Effect of experimental conditions

(a) Temperature: The cmc value at a particular temperature is affected by two different ways: (i) dehydration of hydrophilic group and (ii) disruption of structured water around the hydrophobic group. Temperature increase favors micellization due to decreased hydration of the hydrophilic part. However, temperature increase also causes disruption of the structured water surrounding the hydrophobic group, an effect that disfavors micellization. The relative magnitude of these two opposing effects, therefore, determines whether the cmc increases or decreases over a particular temperature range. For ionic systems, cmc first decreases to a minimum value with temperature and then increases showing a U-shaped behavior [99, 100]. However, in some cases continuous increase in cmc is observed with increasing temperature [101, 102]. For nonionic systems, cmc decreases continuously with an increase in temperature due to an increase in the hydrophobicity caused by destruction of hydrogen bonds between water molecules and hydrophilic group [103]. From the data available, the minimum in the cmc-temperature curve appears to be around 25 °C for ionics [99] and around 50 °C for non-ionics [104, 105]. Data on the effect of temperature on zwitterionics are limited. They appear to indicate a steady decrease in the cmc of alkylbetains with increase in the temperature in the range of 6–60 °C [106, 107].
(b) Effect of pressure: Numerous reports have found on the effect of pressure on micellization of ionic [108-113] and nonionic amphiphiles [114]. With pressure, cmc of ionic surfactants increases up to 1000 atm followed by a decrease above this pressure [115-120]. Such behavior has been rationalized in terms of solidification of the micellar interior, increased dielectric constant of water [116] and other aspects related to water structure [117]. For nonionic amphiphiles, the cmc value increases monotonously and then levels off with increasing pressure. La Mesa [118] has also discussed the effect of pressure on the cmc.

(c) Effect of pH: In surfactants bearing ionizable group such as –NH₂, –(CH₃)₂N–O and –COOH, the degree of dissociation of the polar group will be pH dependent [121]. In general, the cmc will be high at pH values where the group is charged (low pH forms –NH₂, and –(CH₃)₂N–O and high pH forms –COOH) and low when uncharged. Some zwitterionic surfactants become cationic at low pH, a change that can be accompanied by a rapid rise in the cmc [122], or a more modest rise [123] depending on the structure and hence hydrophilicity of the zwitterionic form.

(d) Polar nonaqueous solvent: For micelle formation in polar nonaqueous solvents, the term “solvophobic interaction” has been coined, in analogy with “hydrophobic interactions” which causes micelles formation in aqueous medium [124].

Aggregation number

Micelle aggregation number, which is the number of monomers making up the micelle, is a basic parameter concerning the micelle. It gives an idea about the size of the micelle and is vital in determining the stability and practical applications of the investigated systems [20, 125]. It depends on different factors such as concentration of surfactant [126–129], temperature [125,130–132],
concentration of added electrolyte [128, 133–139], organic additives [140-142], etc. Various experimental techniques like dynamic light scattering (DLS), small-angle neutron scattering (SANS), steady-state fluorescence quenching (SSFQ), and time-resolved fluorescence quenching (TRFQ), etc. may be used for the determination of aggregation number [126-128,143-152].

Usually, in aqueous medium greater the dissimilarity between amphiphile and solvent, the greater the aggregation number. Hence, aggregation number appears to increase with increase in hydrophobic nature of the amphiphile. An increase in the temperature appears to cause a small decrease in the aggregation number in aqueous medium of ions. For nonionic surfactants, it increases markedly [103, 153, 154]. Micellar aggregation number decreases continuously with increase in pressure for nonionic surfactants [155, 156], although the number for ionic surfactants passes through a minimum at around 1000 atm. Aggregation number of ionic micelles is reported to increase [133, 157-160] by the addition of electrolytes.

**Molecular shape**

Amphiphilic molecules can associate into a variety of structures in aqueous solutions. These structures can transform from one to another when solution conditions are changed, for example, the electrolyte concentration, temperature, pressure or pH. Possible structures are restricted by the forces acting to keep amphiphiles’ polar and nonpolar parts in favorable environments. The shapes of the micelles produced in aqueous media are of importance in determining various properties of the surfactant solution, such as its viscosity, its capacity to solubilize water-insoluble materials, and its cloud point. It is known that the shape of micelles depends strongly upon the actual packing parameters in the micellar assembly [158, 161]. Israelachvili [132] has established an equation related to the geometry or packing properties of the surfactant. He showed that many surfactants
can be generalized into certain shape categories, which are likely to produce specific secondary aggregates in aqueous solution. The packing parameter \((p)\) determines which aggregate the surfactant is most likely to form [162]. It is calculated by dividing the volume of hydrocarbon chains \((v)\) (Table 1.1) by the cross-sectional surface area \((a_o)\) of the head groups and length of the alkyl chain \((l_c)\), so that the non-dimensional packing parameter \((p)\) is

\[
p = \frac{v}{a_o l_c} \tag{1.3}
\]

where the tail and volume of the hydrocarbon chain of \(n_c\) carbon atoms can be approximated by correlations of experimental data as:

\[
l_c = 1.54 + 1.265n_c \text{ (Å)} \tag{1.4}
\]

\[
v = 27.4 + 26.9n_c \text{ (Å)} \tag{1.5}
\]

As shown in Table 1.1, spherical micelles are formed when \(p\) is lower than 1/3; wormlike micelles are formed when \(p\) has a value in between \(1/3\) to \(1/2\); vesicles or bilayers are formed when \(1/2 < p < 1\). When the volume of the hydrocarbon part is large relative to the head group area \((p > 1)\), reverse micelles are formed.

The result of various parameters such as the length and branching of the surfactant alkyl chain, the size of the head group, the nature of the counterion, the ionic strength, etc., on the shape of micelles of conventional surfactants can be explained in terms of \(a_o\).
Table 1.1: Aggregate structures with their corresponding packing parameters

<table>
<thead>
<tr>
<th>Effective shape of the surfactant molecule</th>
<th>Packing parameter ($\rho$)</th>
<th>Type of aggregation</th>
</tr>
</thead>
<tbody>
<tr>
<td>cone</td>
<td>&lt;1/3</td>
<td>spherical micelles</td>
</tr>
<tr>
<td>truncated cone</td>
<td>1/3–1/2</td>
<td>wormlike micelles</td>
</tr>
<tr>
<td>cylinder</td>
<td>1/2–1</td>
<td>vesicles</td>
</tr>
<tr>
<td>inverted cone</td>
<td>&gt;1</td>
<td>bilayers</td>
</tr>
</tbody>
</table>

Thermodynamics of self-assembly of surfactants

The understanding of the thermodynamics of micelle formation is of much theoretical and practical importance. Several thorough discussions of the way to
calculate changes in thermodynamic properties that accompany micelle formation from experimental data have been described [3, 17, 159].

Thermodynamics of micellar process gives an explanation of both electrostatic and hydrophobic involvement to overall Gibbs energy of the system. Like all physical processes, self-assembly of surfactants is subject to the laws and limitations of thermodynamics. The micellization process is one of the most important characteristics of surfactant solution and hence it is essential to understand its mechanism and the driving forces of micellization. This requires an analysis of the dynamics of the process as well as the equilibrium aspects whereby the laws of thermodynamics may be applied to obtain the free energy, enthalpy, and entropy of micellization. Two general approaches have been employed to tackle micellization problems.

**(i) Phase Separation Model** [163-165]: this approach treats micelles as a separate but soluble phase, which begins to form at the cmc. This model also implies that at the cmc there are discontinuous changes in the properties of the micellar solution.

**(ii) Mass Action Model** [166-168]: this approach is consistent with the fact that the properties of the micellar solution change continuously at cmc. Micelles and singly dispersed surfactant molecules are considered to be in an association-dissociation equilibrium.

**(i) The phase separation model**

Phase--separation model has been shown to account for, at least semi-quantitatively, the observed concentration dependence of apparent molar properties and has been useful in deriving thermodynamic functions of micellization using both apparent and partial molar properties. In this model, micelles and counterions are treated as separate phase. However, the micelles do
Introduction

not constitute a “phase” according to the true definition of this concept since they are not homogeneous and uniform throughout. Similarly, there are problems associated with the application of the phase rule [169] while considering micelles as separate phase.

(a) Application of the phase separation model to non-ionic surfactants

To understand the thermodynamic process during micellization a primary requisite is to define the standard state. The hypothetical standard state for the surfactant in the aqueous phase is taken to be the solvated monomer at unit mole fraction with the properties of the infinitely dilute solution. For the surfactant in the micellar state, the micellar state itself is regarded as to be the standard state.

If $\mu_s$ and $\mu_m$ are the chemical potentials per mole of the unassociated surfactant in the aqueous phase and associated surfactant in the micellar phase, respectively, since these two phases are in equilibrium at and above the cmc

$$\mu_s = \mu_m$$ (1.6)

For non–ionized surfactant, suppose the concentration of free surfactant monomers to be low, we may write

$$\mu_s = \mu_s^o + RT \ln a_s$$ (1.7)

where $\mu_s^o$ is the chemical potential at standard state. Since the micellar phase is considered as a separate phase, the mole fraction of the associated surfactant in this phase is equal to one and therefore

$$\mu_m = \mu_s^o$$ (1.8)

At low concentration of free monomers, the activity $a_s$ is replaced by mole fraction $x_s$.  

30
If the $\Delta G_m^o$ is the standard free energy for the transfer of one mole of surfactant from the solution to micellar phase, then

$$\Delta G_m^o = \mu_m^o - \mu_s^o = \mu_m - (\mu_s - RT \ln x_s) = RT \ln x_s$$  \hspace{1cm} (1.9)

As the free surfactant concentration in the presence of micelles is supposed to be constant and equal to the cmc value in mole fraction scale, i.e., $x_{cmc}$, equation (1.9) changes to

$$\Delta G_m^o = RT \ln x_{cmc}$$  \hspace{1cm} (1.10)

$$x_{cmc} = \frac{n_s}{n_s + n_{H_2O}}$$  \hspace{1cm} (1.11)

Since the number of moles of free surfactant, $n_s$, is small compared to number of moles of water, $n_{H_2O}$, equation (1.11) can be written as

$$x_{cmc} = \frac{n_s}{n_{H_2O}}$$  \hspace{1cm} (1.12)

Substituting the value of equation (1.12) into the equation (1.10) and applying logarithm we found

$$\Delta G_m^o = 2.303RT (\log_{cmc} - \log w)$$  \hspace{1cm} (1.13)

where $w$ is the number of moles of water (55.56 mol dm$^{-3}$ at 25 °C).

Application of Gibbs –Helmholtz equation (1.10) to gives

$$\frac{\partial}{\partial T} \left( \frac{\Delta G_m^o}{T} \right)_p = -R \left( \frac{\partial \ln x_{cmc}}{\partial T} \right)_p = \frac{\Delta H_m^o}{T^2}$$  \hspace{1cm} (1.14)

Therefore, the standard enthalpy of micellization per mole of monomer, $\Delta H_m^o$, is
\[ \Delta H_m^o = -RT^2 \left( \frac{\partial \ln \chi_{mc}}{\partial T} \right)_P = R \left( \frac{\partial \ln \chi_{mc}}{\partial (1/T)} \right)_P \] (1.15)

Also, standard entropy of micellization per mole of monomer, \( \Delta S_m^o \), is given by

\[ \Delta S_m^o = \left( \frac{\Delta H_m^o - \Delta G_m^o}{T} \right) \] (1.16)

(b) Application of phase separation model to ionic surfactants

To calculate \( \Delta G_m^o \), it is necessary to consider the transfer of \((1-g)\) moles of counterions (where \(g\) is the degree of counterion dissociation) from its standard state to micellar state in addition to transfer of surfactant molecules from the aqueous phase. Therefore, equation (1.9) can be written as

\[ \Delta G_m^o = RT \ln x_s + (1-g)RT \ln x_X \] (1.17)

where \(x_s\) and \(x_X\) are the mole fractions of surfactant ions and counterions, respectively.

The related equations (1.10) and (1.13) for an ionic surfactant in the absence of added electrolyte are

\[ \Delta G_m^o = (2-g)RT \ln \chi_{mc} \] (1.18)

\[ \Delta G_m^o = (2-g)2.303RT (\log \chi_{mc} - \log \omega) \] (1.19)

It is supposed that micellar phase is composed of the charged aggregates together with an equivalent number of counterions, and equations (1.18) and (1.19) are approximated to

\[ \Delta G_m^o = 2RT \ln \chi_{mc} \] (1.20)
\[ \Delta G_m^o = 4.606RT(\log \text{cmc} - \log w) \]  \hspace{1cm} (1.21)

The enthalpy of micellization, \( \Delta H_m^o \), for ionic surfactants is given by

\[ \Delta H_m^o = -2RT^2 \left( \frac{\partial \ln x_m}{\partial T} \right)_P \]  \hspace{1cm} (1.22)

The phase separation model has been questioned for two main reasons. Firstly, according to this model a clear discontinuity in the physical property of a surfactant solution, such as surface tension, turbidity, etc. should be observed at the cmc. This is not always found experimentally and the cmc is not a sharp break point. Secondly, if two phases actually exist at the cmc, then equating the chemical potential of the surfactant molecule in the two phases would involve that the activity of the surfactant in the aqueous phase would be constant above the cmc. If this was the case, the surface tension of a surfactant solution should remain constant above the cmc. However, careful measurements have shown that the surface tension of a surfactant solution decreases slowly above the cmc, particularly when using purified surfactants.

**(ii) The mass-action model**

The mass action approach seems to give a more realistic description of the micelle formation from both thermodynamic and kinetic aspects. In this model, it is assumed that associated and unassociated surfactant ions are in association-dissociation equilibrium and micellization is considered as a reversible process. The mass action model was originally applied to ionic surfactants but latter it was applied to nonionic surfactants also. Micelles form spontaneously under the right conditions, which one may refer to as a process of self-assembly. To understand how the micelle formation took place and to apply the mass action law, the thermodynamic description of the aggregation behavior of surfactant molecules are given:
(a) Application of the mass-action model to non-ionic surfactants

Micelles, $M$, are considered to be formed by a single step reaction from $n$ monomers, $S$, according to

$$ nS \xrightleftharpoons{K_m} M $$

where $K_m$ is the equilibrium constant, and is given by

$$ K_m = \frac{[M]}{[S]^n} = \frac{a_m}{\langle a_i \rangle^n} \quad (1.23) $$

Assuming ideality, we can write

$$ K_m = \frac{x_m}{\langle x_i \rangle^n} \quad (1.24) $$

The free energy of micellization at the cmc is given by

$$ \Delta G_m^o = RT \left[ \left( 1 - \frac{1}{n} \right) \ln x_{cm} + f(n) \right] \quad (1.25) $$

where

$$ f(n) = \frac{1}{n} \left[ \ln n^2 \left( \frac{2n-1}{n-2} \right) + (n-1) \ln \frac{n(2n-1)}{2(n^2-1)} \right] \quad (1.26) $$

If $n$ is large, equation (1.25) reduces to

$$ \Delta G_m^o = RT \ln x_{cm} \quad (1.27) $$

Application of Gibbs–Helmholtz equation (1.27) to gives

$$ \Delta H_m^o = -RT^2 \left( \frac{\partial \ln x_{cm}}{\partial T} \right)_P = R \left( \frac{\partial \ln x_{cm}}{\partial (1/T)} \right)_P \quad (1.28) $$
(b) Application of mass-action model to ionic surfactants

The ionic micelle \( M^{p+} \) is considered to be formed by the association of \( n \) surfactant ions, \( S^+ \), and \((n - p)\) firmly bound counterions, \( X^- \)

\[
nS^+ + (n - p)X^- \leftrightarrow M^{p+}
\]

The equilibrium constant for micelle formation, assuming ideality, may be written as

\[
K_m = \frac{x_m}{(x_s)^n (x_c)^{n-p}}
\]  \hspace{1cm} (1.29)

where \( x_s \) is the mole fraction of counterion.

The standard free energy of micellization per mole of monomeric surfactant is given by

\[
\Delta G_m^o = -\frac{RT}{n} \ln K_m = -\frac{RT}{n} \ln \frac{x_m}{(x_s)^n (x_c)^{n-p}}
\]  \hspace{1cm} (1.30)

At cmc, the above equation reduces to (assuming \( n \) is large)

\[
\Delta G_m^o = \left(2 - \frac{g}{n}\right)RT \ln x_{\text{cmc}}
\]  \hspace{1cm} (1.31)

Since \( g = \frac{P}{n} \), the above equation is same as equation (1.18) obtained from phase separation model.

The standard enthalpy of micellization (per mole of monomer) may be written as

\[
\Delta H_m^o = -RT^2 (2 - g) \left( \frac{\partial \ln x_{\text{cmc}}}{\partial T} \right)_p
\]  \hspace{1cm} (1.32)
The mass action model is more reliable model than the phase separation model in describing the variation of monomer concentration with total concentration above cmc. However, it suffers a serious limitation in that it considers monodispersity of micelle size inspite of polydispersity. The phase separation model assumes constant surfactant activity and hence surface tension above cmc, although neither of them remains constant. If aggregation number $n$ is infinite then mass action and phase separation models are equivalent.

Both the mass action and phase separation models, despite their limitations, are useful representations of the micellar process and may be used to derive equations relating the cmc to the various factors that determine it. Neither mass action nor phase separation models are enough to explain the thermodynamics during micelle formation completely. From the practical point of view a complete approach was developed, known as multiple equilibrium model [170], which corrects the flaws of mass action model. The thermodynamic parameters are determined either by calorimetry or by measuring cmc at different temperatures but the results don’t agree well. So it is clear from the above discussion that more reliable data are necessary to overcome the present difficulties in the quantitative interpretation of micellization and also should be aware of limitations and analyze findings in terms of appropriate models.

(iii) Other thermodynamic models

The thermodynamics of small systems proposed by Hill [171] has been applied to nonionized, noninteracting surfactant systems by Hall and Pethica [172]. In this approach, aggregation number is treated as thermodynamic variable, thereby enabling variations in the thermodynamic functions of micelle formation with the mean aggregation number, $<n>$, to be examined. The thermodynamic functions of micellization assuming solution ideality are as under
\[ \Delta G_m^o = RT[\ln x_s - (\ln x_m^n / < n >)] \] (1.33)

\[ \Delta H_m^o = -RT^2[(\ln x_s/dT)_p - 1/ < n > (\ln x_m/dT)_p] \] (1.34)

\[ \Delta S_m^o = -RT(\ln x_s/dT)_p + RT/ < n > (\ln x_m/dT)_p + R\ln x_s + (R/ < n >)\ln x_m \] (1.35)

For systems with large \(<n>\) and changes slightly with temperature, equations (1.33) and (1.35) are reduced to the corresponding equations of mass action or phase separation models.

Another approach for that of small systems was developed by Corkill and coworkers and useful to systems of nonionic surfactants [173-175]. This multiple equilibrium model considers equilibria between all micellar solutions present in solution rather than with single micellar species as was considered by mass action theory.

Micellization takes place by the aggregation of monomeric surfactant molecules dispersed in a solvent. Aggregation is opposed by both an increase in electrostatic energy (for ionic surfactants) and a decrease in entropy due to aggregation.

Hence from the above discussion it is supposed that molecules containing the hydrophobic groups when dissolved in water, disrupt the structure of water and increase the free energy of the system. The micellization occurs only above a certain concentration, depends on the balance between the factors promoting the micelle formation and those opposing it. Micellization process is primarily governed by entropy gain associated with it by the transfer of lyophobic group from the solvent environment to the interior of the micelle. This entropy increase upon micelle formation happens by two ways, (1) by the increased freedom of the hydrophobic chain in the nonpolar core environment of the micelle compared to aqueous medium [176], and (2) structuring of the water molecules surrounding the
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hydrocarbon chains in aqueous medium, and subsequent transfer of these chains from the aqueous medium to the interior of the micelle by ‘hydrophobic bonding’ followed by the disruption of this structured structure [175]. Any structural or environmental factor that affects solvent–lyophobic group interactions or interactions between lyophobic groups in the interior of the micelle will, therefore, affect free energy of micellization ($\Delta G_m^\circ$) and hence the value of cmc. The negative values of $\Delta G_m^\circ$ are mainly due to the large positive entropy values ($\Delta S_m^\circ$), and $\Delta H_m^\circ$ values are often positive, and, even when negative, are much smaller than the values of $T\Delta S_m^\circ$.

Theories of Mixed Micellization

When two or more surfactants are mixed, either mixed micelles are formed, or the surfactants micellize separately. Interest in mixed micelles has largely been driven by industry, in search of properties that may improve the performance of surfactant systems. Such a synergistic effect greatly improves many technological applications in areas such as emulsion formulations, interfacial tension reduction, cosmetic products, pharmaceuticals, and petroleum recovery, etc. A synergistic interaction display between the components of a mixture makes its physico-chemical properties better than individual formulation. Many theoretical models have been put forward for dealing with the mixed binary system to evaluate the composition and interaction parameter among the components at the air/water interface and in the micellar phase.

The first model, given by Lange [177] and used by Clint [178, 179], is a phase separation model which relates the mole fraction and the critical micellar concentration of the $i$th components ($i = 1, 2$) in an ideal mixture, which is successfully applicable to systems of mixed surfactants of similar structure, but hardly applicable to combinations with dissimilar structures. This model is an idealization which neglects the interaction among different surfactants in the
aggregated state. Rubingh’s model is the first model developed for nonideal mixed system [180]. It is based on a regular solution approach for the treatment of nonideal mixing, and due to its simplicity, it has been mostly used, even after the development of more complex models. Gu and Rosen [181] have extended the nonideal solution treatment of Rubingh for mixed micelle formation by binary surfactant systems to estimate, from surface tension data, the surfactant molecular interactions and also the composition in the adsorbed mixed monolayer at air/water interface. Though these theories are satisfactory but are questioned on thermodynamic grounds [182-184]. Motomura [185] considered the mixed micelles as a macroscopic bulk phase and proposed his thermodynamic model to describe the mixed micellar properties as a function of excess thermodynamic quantities, defined with reference to the spherical dividing surface. This model is independent of nature of surfactants and their counterions and is suitable for prediction of micellar composition. Maeda [186] introduced a term, $G_{\text{mic}}$, as a measure of stability of mixed systems. Maeda suggested that besides regular solution interaction parameter, there could be another parameter that actually contributes to the stability of mixed micelles and put forward an equation to calculate the thermodynamic stability of ionic-nonionic mixed micelle through free energy of micellization function of micellar mole fraction of ionic components in the mixed micelles. By the introduction of values of interaction parameter and micellar mole fraction from different models, thermodynamic stability of mixed micelles can be evaluated. Attempts by other workers [187-190] have been made to predict the properties of and interactions in binary surfactant systems, particularly remarkable in this respect are the efforts recently carried out by the Blankschtein’s group [188, 191-194], who proposed a molecular-thermodynamic approach as a valuable tool to predict solution properties of mixed surfactant systems. This is based on the cmc, chemical structure of hydrophobic and hydrophilic moieties of individual components, surfactant concentration, temperature, salt effect, etc. This theory helps to find out the cmc of binary
surfactant mixtures, size and shape of the micelles and phase behavior of solutions.

Georgiev’s model is based on Markov’s chain model [195] for polymerization process of mixed micelles, and has introduced two molecular parameters instead of one as in RST.

Molecular thermodynamic theory has a quantitative basis than RST, and can be extended to multicomponent systems, expected to work better to know exact information on a mixed surfactant system [191].

**Drugs**

The word ‘drug’ is defined by the World Health Organization as ‘any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient’ [196]. The term medication and medicine usually refer to the drug mixed in a formulation with other ingredients to improve the stability, taste or physical form, in order to allow appropriate administration of the active drug.

Medication also have the potential to cause harm, as indicated by the fact that the Greek word ‘pharmakeia’ used for drug was also the word for poison. If the effect helps the body, the drug is a medicine. However, if a drug causes a harmful effect on the body, the drug is a poison. The same chemical can be a medicine and a poison depending on conditions of use and the person using it. To administer a drug safely, one must know the usual dose, frequency and route of administration, indication and contraindications, significant adverse reactions, major interactions, dietary implications (if applicable) and appropriate monitoring techniques and interventions.
Drug is a chemical having useful action on living tissue, hence, many substances could be classed as drugs: even oxygen, sugar, salt and water affect the body but can be toxic in overdose. Drugs usually have other important attributes:

**Potency:** The amount of chemical required to produce an effect; it is an inverse relationship—the more potent the drug, the lower the dose required.

**Selectivity:** The narrowness of a drug’s range of actions on particular receptors, cellular processes or tissues. The antidepressant drugs known as selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, have fewer adverse effects than older antidepressants because they are more selective in inhibiting the transport of the neurotransmitters serotonin into cells.

**Specificity:** Specificity may be used loosely like ‘selectivity’ to refer to the narrowness of the range of actions of a drug.

In designing a new drug, a research pharmacologist might aim for it to be: easily administered (preferable orally) and fully absorbed from the gastrointestinal tract, not highly protein-bound in the blood plasma, potent, highly specific, selective, with rapid onset and useful duration of action, of high therapeutic index (no adverse drug reactions, no interference with body functions), unlikely to interact with any other drugs or foodstuffs, spontaneously eliminated, stable chemically and microbiologically, readily formulated into an easily taken form and inexpensive. Sadly, not even pharmacologists live in an ideal world, and so we must admit that there is no ideal drug, whether natural product or synthetic. It has been well said that any substance powerful enough to be useful is also powerful to do harm.
Sources of drugs

Drugs and biological products have been identified or derived from several main sources:

(i) **Microorganisms:** e.g., fungi used as sources of antibiotics and bacteria and yeasts genetically engineered to produce drugs such as human insulin.

(ii) **Plants:** e.g., *Atropa beliadonna, Cannubis sativa, Coffea arabica.*

(iii) **Humans and other animals:** e.g., adrenaline, bovine insulin, human chorionic gonadotrophin and erythropoletin were or are obtained, sometimes by recombinant techniques.

(iv) **Minerals or mineral products:** e.g., iron, iodine and Epsom salts.

(v) **Laboratories:** substances are synthesized, such as sulfonamides, β-blockers and antidepressants. Drugs may also be classed as semi-synthetic when the starting material is a natural product, such as a plant steroid or microbial metabolite, which is then chemically altered to produce the desired drug molecule.

Classification of drugs

So far, the complex nature of medicines has escaped a unique, generally accepted drug classification system. The origin of the drugs (natural or synthetic), their chemical structure (betalactams, steroids, etc.), the mode of action (enzyme inhibitors, antihistaminics, etc.) or the nature of the disease (anticancer drugs, antihypertensive drugs, etc.) has been at the base of some classification systems. Drugs are regarded as biologically active chemical compounds mostly with a therapeutic purpose which can be broadly classified according to various criteria including chemical structure or pharmacological action into:
(i) **By pharmacological effect:** drugs are grouped depending on the biological effect they have, e.g., analgesics, antipsychotics, antihypertensives, antiasthmatics, antibiotics, etc.

(ii) **By chemical structure:** many drugs which have a common skeleton are grouped together, e.g., penicillin, barbiturates, opiates, steroids, catecholamines, etc.

(iii) **By target system:** these are compounds which are classed according to whether they affect a certain target system in the body—usually involving a neurotransmitter, e.g., antihistamines, cholinergics, etc.

(iv) **By site of action:** these are compounds which are grouped according to the enzyme or receptor with which they interact. For example, anticholinesterases are a group of drugs which act through inhibition of the enzyme acetylcholinesterase.

A large range of drugs are, in fact, known to be surface active in nature [197-204]. This activity does not appear to be a fortuitous concurrence. In a number of cases admirable correlations between surface activity and biological effects have been confirmed [205-212]. These drugs may undergo various types of associations and whose site of action in the organism commonly is the plasma membrane. Even if their target is intracellular, the interaction with this first barrier plays an essential role [213].

Category of amphiphilic drugs include phenothiazines [214-220] and benzodiazepines [221], tranquilizers [222-224], analgesics [224], peptide [225] and nonpeptide [226, 227], antibiotics [227, 228], tricyclic antidepressants [229-232], antihistamines [233], anticholinergics [234], ß-blockers [235], local anesthetics [236-239], non-steroidal anti-inflammatory drugs [240], anticancer drugs [241], etc. Many of these drugs have one or more (condensed or not) aromatic nuclei, while others are of peptide nature. A great deal of data on the
surface active properties of the amphiphilic drugs can be found in the book by Attwood and Florence [242] and other reviews [243-245].

**Theories of drug action**

There are three theories related to drug action namely, occupancy theory, rate theory and inactivation theory.

*(i) Occupancy theory*

Biological responses to drugs are, as a rule, evaluated; they can be measured on a continuous scale and, there is a systematic relationship between the dose of a drug and the extent of the response. Application of the law of mass action to the dose-response relationship was largely done by Clark [246, 247]. An observed biological effect was assumed to be a suggestion of the combination of drug molecules with receptors. The extent of a response was proposed to be directly proportional to the occupancy of receptors by drug molecules. The maximal response is assumed to be acquired when all the receptors are occupied.

*(ii) Rate theory*

The fundamental thought in this theory is dissimilar from that in the occupancy theory. Instead of attributing excitation to the occupation of receptors by drug molecules, it is ascribed to the process of occupation—each association between a drug molecule and a receptor providing one quantum of excitation. The extent of biological response is comparative to the rate at which drug molecules associate with receptor sites. This rate depends on the concentration of free drug, the concentration of free receptor sites and the rate constants for association of drug molecules with receptor [248-250].

*(iii) Inactivation theory*

Receptor inactivation theory is based on the two state model firstly proposed by Katz and Thesleff for ion channels [251]. Kenakin in his work on
the Torpedo nicotinic receptor reported that the multimeric receptor presents in active and inactive states with ligand binding varying the equilibrium between these two states. Receptor inactivation theory reveals a synthesis of both occupancy theory and rate theory providing another concern for the study of the receptor ligand interaction. Inactivation theory assumes that RL complex is an intermediate “active state” that gives rise to an inactive form of the receptor, R, which is part of a RL complex, termed R’L [252].

\[
\begin{align*}
[R] + [L] & \xleftrightarrow{k_1} [RL] \\
& \xrightarrow{k_2} [R'] \\
& \xrightarrow{k_3} [R'L]
\end{align*}
\]

where R stands for receptor and L for ligand, \( k_1, k_2, k_3 \) are corresponding rate constants.

Arrangement of cell membranes and place of receptor proteins in lipid bilayers is a result of surface activity. It is, therefore, logical to suppose that the drugs acting by changing the permeability cell membranes after interacting with them are likely to be surface active in nature. This is because the lipid bilayers, with receptors in them, represent the interface and the drugs interacting with them will not reach the interface unless they are surface active in nature.

Surface activity is omnipresent in living systems. Take any body fluid or cell soup, its surface tension is always less than that of water. Most of the biomolecules, proteins, lipids, etc. are surface active in nature. Molecules of surface active nature are essential to living matter and its organization. Surface activity in living systems is a matter of evolution, i.e., it is need-based and therefore should have a fundamental role to play in biological action.
**Mode of drug action**

It is essential to differentiate between actions of drugs and their effects. Actions of drugs are the biochemical physiological mechanisms by which the chemical produces a response in living organisms. The effect is the noticeable consequence of a drug action. For example, the action of penicillin is to interfere with cell wall synthesis in bacteria and the effect is the death of the bacteria.

The most important problem of pharmacology is that no drug produces a single effect or ideal behavior. The primary effect is the desired therapeutic effect. Secondary effects are all other undesirable effects which may be either beneficial or harmful. Drugs are chosen to develop differences between normal metabolic processes and any abnormalities which may be present. Since the differences may not be very great, drugs may be nonspecific in action and alter normal functions as well as the undesirable ones. This leads to undesirable side effects.

The biological effects noticed after a drug has been administered are the result of an interaction between that chemical and some part of the organism. Mechanisms of drug action can be viewed from different perspectives, namely, the site of action and the general nature of the drug-cell interaction.

**Sites of drug action**

(i) *Enzyme inhibition*

Drugs act within the cell by modifying normal biochemical reactions. Enzyme inhibition may be reversible or non-reversible; competitive or non-competitive. Antimetabolites may be used which mimic natural metabolites. Gene functions may be suppressed.
(ii) **Drug-receptor interaction**

Drugs act on the cell membrane by physical and/or chemical interactions. This is usually through specific drug receptor sites known to be located on the membrane. A receptor is the specific chemical constituent of the cell with which a drug interacts to produce its pharmacological effects. Some receptor sites have been identified with specific parts of proteins and nucleic acids. In most cases, the chemical nature of the receptor site remains obscure.

(iii) **Non-specific interactions**

Drugs act exclusively by physical means outside of cells. These sites include external surfaces of skin and gastrointestinal tract. Drugs also act outside of cell membranes by chemical interactions. Neutralization of stomach acid by antacids is a good example.

**Relevance of the Research Problem**

Synthetic organic chemistry and surface chemistry are two different areas within the field of chemistry, the former dealing with preparation of carbon-containing compounds from small simple building blocks, and the latter describing the physical chemistry at interfaces. Nevertheless, we have tried to merge these two fields, by synthesizing compounds with a preference to adsorb at interfaces, i.e., surfactants. Surfactant synthesis offers a challenge to a synthetic organic chemist for several reasons. Most commercial surfactants are obtained as regioisomeric mixtures, and together with unreacted starting material. The synthesis of pure and well-characterized surfactant systems therefore requires other synthetic pathways than those utilized for commercial production. The synthetic plan might also be obstructed by the different polarities of the components building the surfactant, and the final product carries properties making purification and handling difficult. Surfactants used in bio-medical
applications, on the other hand, have to be pure. The production of such compounds may need several synthetic steps and careful purification. Several structural types of gemini surfactants are included in this thesis. Common building blocks have been used in most of the compounds in order to give the potentially most viable commercial surfactants.

The overall theme of this thesis is to make physico-chemical study of interactions between some novel gemini surfactants and drugs. Beside active drug substances most drug formulations contain mixtures of excipients of different type and function. The physico-chemical behavior of drug-surfactant systems is important to understand both in the formulation, e.g. for stability reasons, and as the formulation enters and dissolves in the body fluids.

Nowadays surfactant micelles have acquired rising scientific interest as an alternative potential drug delivery vehicle to conventional liposomes. The self-association of surfactants is governed by hydrophobic interactions between the nonpolar alkyl chains and the electrostatic interactions of the polar or ionic head groups. A clear understanding of the self-aggregation mechanism of amphiphilic drugs and their interactions with surfactants in aqueous solution is of great importance in the reasonable formulation of more efficient drug delivery systems [253]. The surfactant micelles have numerous importance than the phospholipid-based vesicles, such as higher micellar stability, lesser care in handling and storage and lower in price. These qualities make surfactant micelles more commercial and useful than phospholipids for industrial area both in the field of pharmaceutical and cosmetics [254–258]. Furthermore, surfactant micelles, like liposomes, are proficient of encapsulating both hydrophilic and hydrophobic drugs [259, 260]. The encapsulation of drugs in micelles can minimize drug degradation and inactivation after administration, prevent undesirable side effects, and increase drug bioavailability and targeting to the pathological area.
Micellar solubilization is the most convenient method to increase the solubility of drugs. A mixed amphiphile system can exhibit surface and colloidal properties different from those of the pure individual components. Nonideal mixing of amphiphilic components often causes synergism in the properties of the mixtures that may be exploited in their applications.

Gemini surfactants, as a focus of this research aimed at developing drug delivery vehicle, have a general structure that presents an unlimited versatility in their design and synthesis. This gives a significant opportunity in the search for clinically efficient gemini surfactant molecules for routine drug delivery applications. For gemini surfactants to pass a test of optimal utility in drug delivery, the surfactant molecules must meet important requirements; these include the ability to efficiently mediate drug delivery and to exert minimal or no toxic effects on their biological hosts. Understanding the physico-chemical properties of gemini surfactant-amphiphilic drug systems would improve their interaction behavior with amphiphilic drugs and lead to efficient excipient or drug carrier.

We have had three main interests during this research:

- To design and synthesize ecologically compatible compounds that can be used as surfactant.
- These surfactants can be used as drug carrier and enhance drug delivery with reducing their side effects.
- To evaluate the physico-chemical behavior of drug-surfactant systems.

Keeping the above in view and the fact that surfactant micelles, like many other amphiphilic substances, are potentially important encapsulating/solubilizing agents, we have synthesized gemini surfactant and performed tensiometric studies of their interactions with amphiphilic drugs.
Layout of the Thesis

This thesis consists of four chapters including this one which is concerned mainly with the general introduction of amphiphiles. Experimental details, synthesis and characterization of different ionic gemini surfactants are provided in Chapter II.

Chapter III presents the systematic and detailed study of interactions of two antidepressant drugs with the synthesized zwitterionic gemini surfactants in aqueous media.

Chapter IV is divided in two parts. First part deals with the interaction of drugs and counterion coupled gemini surfactants and second part describes the physico-chemical aspects of amphiphilic drugs and anionic gemini mixed systems.
References:


Introduction


