CHAPTER 1

General Introduction
Amphiphile is a term describing a chemical compound possessing both hydrophilic (water-loving) and lipophilic (fat-loving) properties. Such a compound is called amphiphilic or amphipathic. It is derived from Greek word *amphi*, meaning both, and terms relates to the facts that all surfactant molecules consist of at least two parts, one which is soluble in specific fluid (the lyophilic part) and one which is insoluble (the lyophobic part). When the fluid is water, one usually talks about the hydrophobic and hydrophilic parts, respectively. 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. Hydrophilic and hydrophobic parts of molecules are also known as polar and non-polar, respectively. Hydrophobic portion of molecules in water often cluster together forming micelles. Water on hydrophobic surfaces will exhibit a high contact angle.

Amphiphilic compounds bear an ionic (cationic, anionic, or zwitterionic) or non-ionic polar head group and a hydrophobic portion. In aqueous medium, they are able to organize themselves as micelles, bilayers, monolayers, hexagonal or cubic phases. Aggregation is not, however, just limited to aqueous solution; it is sometimes observed in non-aqueous polar solvents such as ethylene glycol and non-polar solvents such as hexane (in the latter case giving rise to inverse structures) [1]. The extent of the hydrophobic and hydrophilic portions determines the extent of partitioning. The spatial separation between the polar and non-polar moieties, as well as molecular shape [2] and hydrophilic and hydrophobic balance
determines their tendency to form the different structures, which eventually can be interconverted as a function of pH, temperature, ionic strength, and concentration. Alkyl chain-containing surfactants seem to associate according to phase separation model. Normally, these micelles exhibit aggregation numbers between 50 and 200 [4]. The amphiphile with more or less equilibrated hydrophilic and lipophilic tendencies are likely to migrate to surface or interface. It doesn’t happen if the amphiphilic molecule is too hydrophilic or too hydrophobic, in which case it stays in one of the phases. Because of its dual affinity, an amphiphilic molecule doesn’t feel ‘at ease’ in any solvent. This is why amphiphilic molecules exhibit a very strong tendency to migrate to interface or surfaces and to orientate so that the polar group lies in water and the non-polar or apolar is placed out of it. Amphiphiles often exhibit other properties besides lowering of surface tension.

Amphiphiles play a key role in the existence of the life and widely used in the industry, medicine, pharmacology, etc. [5, 6]. The single features of amphiphiles that give 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.

Solute showing hydrophobic self-association may be classified into four categories on the basis of chemical structure: (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.) [7]. The self-association behavior must relate to the chemical structure of solutes. The simplest type of association, viz., dimerization, may take place in all the self-associating systems being considered. The formation of higher multimers may overshadow it, however, more or less completely [7].

**Surfactants and Their Classification**

The term surfactant is a blend of surface active agent [8]. Surfactants are usually organic compounds that are amphiphilic, meaning they contain both hydrophobic groups (their tails) and hydrophilic groups (their heads). Therefore, they are soluble in both organic solvents and water. The term surfactant was coined by Antara products in 1950. In Index Medicus and the United States National Library of Medicine, surfactant is reserved for the meaning pulmonary surfactant. The tail part may consist of one or more hydrocarbon chains, usually with 6-22 carbon atoms. The chains may be linear or branched, may contain unsaturated portions or aromatic moieties, and may be partly or completely halogenated (as in fluorocarbon surfactants) while a charged or uncharged hydrophilic species (group) acts as the head part of the molecule. The hydrocarbon chain interacts weakly with the water molecules in an aqueous environment, whereas the polar or ionic head group interacts strongly with water molecules via
dipole or ion–dipole interactions. It is this strong interaction with the water molecules that renders the surfactant soluble in water.

Surfactants reduce the surface tension of water by adsorbing at the liquid-gas interface. They also reduce the interfacial tension between oil and water by adsorbing at the liquid-liquid interface. Many surfactants can also assemble in the bulk solution into aggregates. Examples of such aggregates are vesicles and micelles. Thermodynamics of the surfactant systems are of great importance, theoretically and practically [9]. This is because surfactant systems represent systems between ordered and disordered states of matter. Surfactant solutions may contain an ordered phase (micelles) and a disordered phase (free surfactant molecules and/or ions in the solution).

Surfactants have been widely used in both industrial and domestic fields since the first surface-active product was prepared commercially by C. Scholl in Germany in 1930 [10]. 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 [10-14]. 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 [15]. Moreover, surfactants play a major role in the oil industry, for example in enhanced and tertiary oil recovery. They are also occasionally used for environmental protection, e.g., in oil slick dispersants. Some surfactants are known to be toxic to animals, ecosystems and humans, and
can increase the diffusion of other environmental contaminants [16-18]. Despite this, they are routinely deposited in numerous ways on land and into water systems, whether as part of an intended process or as industrial and household waste. Some surfactants have proposed or voluntary restrictions on their use.

A surfactant can be classified by the presence of formally charged groups in its head. 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 vast majority of cationic surfactants are based on the nitrogen atom carrying positive charge. Both amine and quaternary ammonium-based products are common [19, 20]. A common class of cationics is the alkyl trimethyl ammonium chloride, where R contains 8–18 C atoms. Primary, secondary or tertiary amines of cationic surfactants are pH dependent. Primary amines become positively charged at pH < 10, secondary amines become charged at pH < 4. 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.
Examples: Dodecyltrimethylammonium bromide \( \text{CH}_3(\text{CH}_2)_{11}\text{N}^+(\text{CH}_3)\text{Br}^- \)

Dodecylamine hydrochloride \( \text{CH}_3(\text{CH}_2)_{11}\text{N}^+\text{H}_3\text{Cl}^- \)

(ii) Anionic Surfactants

The surface-active portion of the molecules bears a negative charge. Carboxylate \( (\text{C}_n\text{H}_{2n+1}\text{COO}^-\text{X}^+) \), sulfate \( (\text{C}_n\text{H}_{2n+1}\text{OSO}_3^-\text{X}^+) \), and sulfonate \( (\text{C}_n\text{H}_{2n+1}\text{SO}_3^-\text{X}^+) \), are the polar groups found in anionic surfactants. These are the most widely used class of surfactants in industrial applications [21, 22] due to their relatively low cost of manufacture. Anionics are used in most detergent formulations and the best detergency is obtained by alkyl and alkylaryle chains in the \( \text{C}_{12}^-\text{C}_{18} \) range. The counterions most commonly used are sodium, potassium, ammonium, calcium and various protonated alkyl amines.

Examples: Sodium laurate \( \text{CH}_3(\text{CH}_2)_{10}\text{COO}^-\text{Na}^+ \)

Sodium dodecylbenzene sulfonate \( \text{CH}_3(\text{CH}_2)_{11}\text{C}_6\text{H}_4\text{SO}_3^-\text{Na}^+ \)

(iii) Non-ionic surfactants

The surface-active portion of the molecules bears no apparent ionic charge. Non-ionic surfactants have either a polyether or a polyhydroxy unit as the polar group. In the vast majority of non-ions, the polar group is a polyether consisting of oxyethylene units, made by polymerization of ethylene oxide. Several classes can be distinguished: alcohol ethoxylates, alkyl phenol ethoxylates, fatty acid ethoxylates, monoalkanolamide ethoxylates, sorbitan ester ethoxylates, fatty amine
ethoxylates and ethylene oxide–propylene oxide copolymers (sometimes referred to as polymeric surfactants).

*Examples:* Polyoxyethylene monohexadecyl ether \( \text{CH}_3(\text{CH}_2)_{15}(\text{OCH}_2\text{CH}_2)_{21}\text{OH} \)

Polyoxyethylene octylphenylether \( \text{C}_{14}\text{H}_{22}\text{O(C}_2\text{H}_4\text{O)}_{9.5} \)

(iv) **Zwitterionic surfactants**

Zwitterionic surfactants contain two charged groups of different sign. Whereas the positive charge is almost invariably ammonium, the source of negative charge may vary, although corboxylate is by far the most common. Zwitterionics are often referred to as amphoteric. An amphoteric surfactant is one that changes from net cationic via zwitterionics to net anionic on going from low to high pH. Neither the acid nor the basic site is permanently charged, i.e., compound is only zwitterionic over a certain pH range.

The change in charge with pH of the truly amphoteric surfactants naturally affects properties such as foaming, wetting, detergency, etc. These will all depend strongly on solution pH. At the isoelectric point the physico-chemical behavior often resembles that of non-ionic surfactants. Zwitterionic as a group are characterized by having excellent dermatological properties. They also exhibit low eye irritation and are frequently used in shampoo and other cosmetic products. Common types of zwitterionic surfactants are N-alkyl derivatives of simple amino acid, such as glycine (NH\(_2\)CH\(_2\)COOH), betaine (CH\(_2\)_2NCH\(_2\)COOH) and amino propionoic acid (NH\(_2\)CH\(_2\)CH\(_2\)COOH).
Examples: 3-(Dimethyldodecylammonio)-propane-1-sulfonate

\[ \text{CH}_3(\text{CH}_2)_{11}\text{N}^+\text{(CH}_3)_2\text{(CH}_2)_3\text{SO}_3^{-} \]

\[ N\text{-Dodecyl-N,N-dimethyl betaine } \text{CH}_3(\text{CH}_2)_{11}\text{N}^+\text{(CH}_3)_2\text{CH}_2\text{COO}^{-} \]

(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.

Example: Polystyrene-block-poly(vinyl acetate)

(v) Gemini surfactants

A surfactant usually contains only one polar group. Recently, there has been considerable research interest in a new class of surfactants, the gemini surfactants [23-25] have generated interest in colloid chemistry due to their superior performance over conventional surfactants in various industrial applications. Gemini surfactants are also referred to as twin surfactants, dimeric surfactants [8, 26], or bis surfactants. The term ‘Gemini surfactant’, coined by Menger, has become accepted in the surfactant literature for describing dimeric surfactants, that is, surfactant molecules containing two hydrophobic groups and
two hydrophilic groups, connected by a linkage (spacer) close to hydrophilic groups. A schematic representation of a gemini surfactant is shown in Fig.1.1. 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 first reports on dimeric surfactants concerned bisquaternary ammonium halide surfactants which were used to catalyze chemical reactions [27].

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

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

Gemini surfactants are subject to much evaluation work at the present time and one may foresee that the attractive features of these surfactants, such as high efficiency, low cmc (at least one order of magnitude lower than for the corresponding conventional (monomeric) surfactants, on a weight percent basis) and surface tension values (10–100 times more efficient at reducing the surface tension of water and the interfacial tension at an oil/water interface than conventional surfactants), and a very steep rise in viscosity with concentration, will find practical use. The high surfactant efficiency and the low cmc values have triggered much effort into the potential use of gemini surfactants as solubilizers of various kinds. In model experiments, using hydrocarbons as the compound to be
solubilized, geminis have been found to be better than conventional surfactants, both on a molar and weight basis. Gemini is also of interest as lubricating agents as a result of their tight packing at the surfaces. Some anionic gemini surfactants have low Krafft temperatures, which make them applicable in cold water. Also, cationic gemini surfactants possess interesting biological properties.

Much effort is also being devoted to exploit the specific geometry of gemini surfactants to create structures of well-defined 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 [24, 25, 28, 29]. All charge types of gemini surfactants cationic [30, 31], anionic [32], non-ionic [33] and zwitterionic [34] and a variety of structural types; alkylglucoside based [35], sugar based [36], with unsaturated linkages [37] and almost all types with flexible, rigid, and heterotype spacers have been synthesized. The search for the synthesis of new novel types of gemini surfactants is increasing from their application point of view [38, 39].

(vi) Bolaform Surfactants

Connecting two surfactant moieties towards the end of their hydrophobic tail results in a so-called ‘bolaform surfactant’ (Fig.1.2) and the physico-chemical properties of such species are very different from those of conventional and gemini surfactants. Their self-association ability is less, compared to conventional
ionic surfactants. However, they show biological activity [40, 41] and some special bolaforms are capable of giving rise to organized assemblies of peculiar structure [42].

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

**Micelle formation and critical micelle concentration**

Micelle formation, or 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.

The characteristic property of amphiphilic molecules is their capacity to aggregate in solutions. The aggregation process depends on the amphiphilic species and the conditions of the system at which they are dissolved. The concentration at which this phenomenon occurs is called the critical micelle concentration (cmc) [43, 44]. Micelle formation is primarily controlled by three forces: the hydrophobic repulsion between the hydrocarbon chains and aqueous solution, the charge repulsion of ionic head groups, and the van der Waals attraction between the hydrocarbon tails [45, 46]. 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 determines the size and shape of the micelle, the cmc, and the aggregation number. Shapes of micelles can vary from rough spheres to prolate ellipsoids, and the diameter of micelles generally ranges from 3 to 6 nm [46]. This small diameter prevents micelles from being filtered from solution and form appreciably scattering light. The term cmc was established by Davis and Bury [47] defining it as a concentration range below which the surfactant molecules in the solution remain as monomers and above which practically all additional surfactants added to the solution form micelles. cmc is an important property of the surfactants which reflects its micellization ability. Below the cmc value, the physico-chemical properties of ionic surfactants resemble those of strong electrolytes and, above the cmc, these properties change dramatically, indicating a highly cooperative association is taking place. This is illustrated by Preston’s classic graph [43] in Fig.1.3. Just above the cmc, micellar structure is considered to be roughly globular or spherical [4, 48].
Fig.1.3: Preston’s classic graph showing variation in physical properties of surfactant solutions below and above the cmc value of sodium dodecyl sulphate.

The determination of the value of cmc can be made by use of many physical properties, but most commonly the breaks in electrical conductivity, surface tension, light scattering, or fluorescence spectroscopy–concentration curves have been used for this purpose. The cmcs also have very frequently been determined from change in spectral characteristics of some dyestuff added to surfactant solution when the cmc of the latter is reached. However, this method is open to the serious objection that the presence of dyestuff may affect the value of
cmc. An excellent critical evaluation of the methods determining cmc is included in a comprehensive compilation by Mukerjee and Mysels [44].

In a micellar solution, there is always a dynamic equilibrium between surfactants monomers, monolayers and micelles (Fig.1.4).

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

**Types of micelles**

**Normal micelle**

Normal micelle structure just above the cmc can be considered as roughly spherical [49-51]. In aqueous solution the hydrocarbon tails are oriented inward and head groups are positioned into the bulk solvent [52]. The micelles are always
in dynamic equilibrium. The interior of a micelle is viewed as being much like a liquid hydrocarbon droplet.

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 [53, 54]. Menger has proposed that water can penetrate inside the micelle up to a certain level [55, 56], the idea gets support from fluorescence and $^1$H–NMR measurements. Partial molar volume determinations indicate that the alkyl chains in the core are more expanded than those in the normal liquid state [57].

An ionic micelle formed in polar solvents such as water generally consists of three regions (Fig. 1.5): (i) The interior or core of the micelle which is hydrocarbon-like as it consists of hydrocarbon chains of the ionic surfactant molecules. (ii) 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) The outer layer is a diffuse layer and contains the remaining counterions and is called the Gouy-Chapman layer that extends further into aqueous phase. The thickness of this layer is determined by the (effective) ionic strength of the solution.
Counterions bind a considerable amount to ionic micelles, which can be evaluated by electrochemical measurement. They are bound to micelles primarily not only by strong electrical field created by head groups, but also by specific interactions that depend upon head group and counterion type [4, 51, 58]. A two-site model has been successfully applied to the distributions of counterions; i.e., they are assumed to be either “bound” to the micellar pseudophase or “free” in the aqueous phase [59-61]. The head group and counterion concentrations in the interfacial region of an ionic micelle are on the order of 3-5 M, which gives the micellar surface some of the properties of concentrated salt solutions [61-63]. Although the solution as a whole is electrically neutral, both the micellar and aqueous pseudophases carry a net charge because thermal forces distribute a fraction of the counterions radially into the aqueous phase [60, 61].
For non-ionic micelles the structure is essentially the same, except that the outer region contains no counterions. It arrests water molecules at the palisade layer (which includes the head groups and first few methylene groups) by hydrogen bonding of the water with polyethylene oxide groups [64]. Water may remain trapped in this region.

**Reverse micelle**

Aggregation of monomers can occur when amphiphiles are dissolved in non-polar organic solvents. In reversed micelles the hydrocarbon tails are oriented outward into the bulk solvent while the hydrophilic head groups are oriented inward. Reverse micelle is more complex than normal micelles but can be used to solubilize polar solutes in non-polar solvents. Dipole-dipole [65, 66] interactions hold the hydrophilic head groups together in the core. The water molecules are strongly associated with the head groups of surfactant. The aggregation properties of surfactants in non-polar 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 [67-70]. Water in reverse micelles is expected to behave very differently from ordinary water because of extensive binding and orientation effects induced by polar heads forming the water core [71]. The inner cavity of reverse micelles has been compared with active site of enzymes [69, 70]. 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 domains, i.e., biocatalysis and chemical biotechnology.

**Mixed micelle**

The formation of micelles from more than one chemical species gives rise to what are known as mixed micelles. As usually used, however, the mixed micelles means a micelle composed of amphiphiles capable themselves of forming micelles. Thus mixed micellization is a special case of solubilization. The physicochemical properties of mixed micelles are quite different from those of pure micelles of individual components. From the application point of view, 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. [72]. Clint [73] developed analytical description which contained both micelle composition and monomer concentration above the mixed cmc for mixtures of non-ionic surfactants. Clint’s treatment assumed ideal mixing in the micelle. The properties of mixtures of ionic and non-ionic amphiphiles [74-76] have been interpreted with the aid of the mixed micelle formation. It was pointed out that the cmc of mixed surfactants was lower than either of the single surfactants [73, 77].
Mixed micelles may also form when low molecular weight solutes are solubilized by micelles of amphiphiles containing a relatively larger non-polar side chain. The solubilized substances, also called as the penetrating additives [78], may be located in both the hydrocarbon core [79] and in the hydrophilic mantle [80-82].

**Aggregation number**

One of the most fundamental parameters defining a micelle is the aggregation number (N), which provides direct information about the general size and shape of aggregates formed by amphiphiles in the solution, and how these properties are related to the molecular structure of amphiphile. The average number of monomers in a micelle in a given population distribution or simply the numbers of monomers making up a micelles, is known as the aggregation number and is typically 30-200 in water. It is affected by the different factors such as nature of amphiphile, temperature [2, 83-85], type and concentration of added electrolyte [83, 86-88], organic additives [89-92], etc. Generally, 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 character of the amphiphile. An increase in the temperature appears to cause a small decrease in the aggregation number in aqueous medium of ionics. For non-ionic surfactants, it increases markedly [93-95].
Micellar aggregation number decreases continuously with increase in pressure for non-ionic surfactants [96, 97], although the number for ionic surfactants passes through a minimum at around 1000 atm. Aggregation number of ionic micelles is reported to increase [98-101] by the addition of electrolytes.

Various experimental techniques, like dynamic light scattering (DLS), small angle neutron scattering (SANS), steady-state fluorescence quenching (SSFQ), time-resolved fluorescence quenching (TRFQ), etc., have been used for determination of the aggregation number [102-109].

**Molecular shape**

The extent of interaction between water and amphiphilic molecules can be expressed by molecular shape and it is mainly determined by a balance between hydrophobic interactions of the hydrocarbon tails, electrostatic repulsion and hydration of head groups [14]. The shape of micelle produced in aqueous media determines various amphiphilic solution properties such as, viscosity, solubilization, and cloud point. Amphiphiles, which form spherical micelles in water, have a conical shape in this aggregate type. Cylindrically formed molecules have a polar region that is equal to non-polar, whereas wedge-shaped molecules have a large non-polar region thus forming, for example, reversed micelles. Substances with one hydrocarbon chain often belong to the conical group whereas substances with two chains or one chain with unsaturations, giving kinks, belong to cylinders and wedges.
A theory of micellar structure, based upon the geometry of various micellar shapes and space occupied by the hydrophilic and hydrophobic groups of the amphiphile molecules, has been developed by Israelachvili, Mitchell, and Ninham [110, 111]. The volume $V_H$ occupied by the hydrophobic groups in the micellar core, the length of hydrophobic group in the core $l_c$, and the cross-sectional area $a_0$ occupied by the hydrophilic group at the micelle-solution interface are used to calculate a packing parameter ($R_p$), which determines the shape of the micelle

$$R_p = \frac{V_H}{a_0 l_c}$$  \hspace{1cm} (1.1)

The optimal cross-sectional area per amphiphile molecule is observed experimentally by X-ray diffraction of bilayer systems while the volume and length of hydrocarbon tail may be calculated by Tanford [112] equations:

$$V_H = (27.4 + 26.9 \ n) \ \text{Å}^3$$  \hspace{1cm} (1.2)

$$l_c = (1.5 + 1.26 \ n) \ \text{Å}$$  \hspace{1cm} (1.3)

($n$ is the number of carbon atoms in the hydrocarbon chain).

As shown in Table 1.1, spherical micelles are formed when $R_p$ is lower than 1/3; wormlike micelles are formed when $R_p$ has a value in between 1/3 to 1/2; vesicles or bilayers are formed when $1/2 < R_p < 1$. When the volume of the hydrocarbon part is large relative to the head group area ($R_p > 1$), reverse micelles are formed.
Table 1.1: Aggregate structures with their corresponding packing parameters.

<table>
<thead>
<tr>
<th>Effective shape of the surfactant molecule</th>
<th>Packing parameter ($R_p$)</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>bilayers</td>
</tr>
<tr>
<td>inverted cone</td>
<td>&gt;1</td>
<td>reverse micelles</td>
</tr>
</tbody>
</table>
However, it is to be noted that the solution parameters such as concentration, pH, temperature and solvent polarity may heavily modify the specific structures formed.

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

Since the properties of solutions of amphiphiles change markedly when micelle formation commences, a great deal of work has been done on elucidating the various factors that determine the concentration at which micelle formation becomes significant (i.e., cmc), especially in aqueous media.

Among the factors known to affect 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, pH, solvent, etc.

**(i) Structure of amphiphiles**

**(a) The hydrophobic group:** The large majority of amphiphiles, whether ionic or non-ionic have hydrophobic regions composed of hydrocarbon chains. For ionic amphiphiles, increase in the number of carbon atoms in the unbranched hydrocarbon chains leads to a decrease in the cmc. A generally used rule for amphiphiles is that the cmc is halved by the addition of one methylene group to a straight chain hydrophobic group attached to a single terminal hydrophilic group. 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 [14]. A phenyl group that is a part of a hydrophobic group with terminal hydrophilic group is equivalent to about three and one-half methylene groups. The replacement of hydrocarbon-based hydrophobic group by a fluorocarbon-based one with the same number of carbon atoms appears to cause a decrease in cmc. This is explained in term of the enhanced hydrophobicity.

(b) *The hydrophilic group:* There is pronounced difference between the cmcs of ionic and non-ionic surfactants with identical hydrophobic moieties. The lower cmcs of non-ionic surfactants are a consequence of the lack of electrical work necessary in forming the micelles.

Effect of nature of polar 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 [113]. Thus, for example, decylammonium bromide forms very much larger micelles than decyltrimethylammonium bromide because the Br⁻ counterions are able to approach more closely the charged nitrogen atom of decylammonium thus effectively shielding the repulsive electrical forces and allowing larger micelle to form. The more charged groups in the surfactants, the higher the cmc due to increased electrical work required to form micelles [114, 115]. Zwitterionics
appear to have about the same cmc as ionics with the same number of carbon atoms in the hydrophobic group. 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: Addition of electrolyte causes a reduction in the thickness of the ionic atmosphere surrounding the polar head groups and a consequent decreased repulsion between head groups of ionic micelles. These effects are manifest as a reduction in cmc and an increase in aggregation number, the effect being more pronounced for anionic and cationic than for zwitterionic surfactants, and more pronounced for zwitterionics than for non-ionics. The effect of the concentration of electrolyte on the cmc of ionics is given by the following relation

\[ \log \text{cmc} = a \log c_1 + b \]  

(1.4)

where \(a\) and \(b\) are constants for a particular ionic group and \(c_1\) denotes the total counterion concentration in molar unit [116].

For non-ionics and zwitterionics, Eq. (1.4) does not hold. Instead, the effect is given by equation [117]

\[ \log \text{cmc} = -k c_1 + \text{constant} \quad (c_1 < 1) \]  

(1.5)

where \(k\) is the constant for a particular surfactant, electrolyte and temperature and \(c_1\) is concentration of electrolyte.
The size of counterion is also a determining factor for the cmc value. As the size of counterion increases, counterion binding also increases due to decrease in hydrated radius of ion, and hence decrease in cmc occurs [14]. This is the reason why \((\text{C}_3\text{H}_7)_4\text{N}^+\) is more efficient in reducing the cmc than \((\text{C}_2\text{H}_5)_4\text{N}^+\), which is more efficient than \((\text{CH}_3)_4\text{N}^+\).

There have been attempts to examine the salts effect on micelle formation in the light of Hofmeister (lyotropic) series [118, 119]. The series plays a notable role in a wide range of biological and physico-chemical phenomena. The change in cmc of non-ionic and zwitterionics on the addition of electrolyte has been attributed [120, 121] mainly to salting-out or salting-in (i.e., the effects of ion size and decrease in dielectric constant) of the hydrophobic groups in the aqueous solvent by the electrolyte, rather than to effect of the latter on the hydrophilic groups of the amphiphile. Electrolytes capable of salting-out reduce the cmc of non-ionic surfactants while salting-in electrolytes increase the cmc. The effect of anion and cation in the electrolyte is additive and appear to depend on the radius of the hydrated ion, that is, the lyotropic number; the smaller the radius of the hydrated ion, the greater the effect. A very recent study carried out by Moulik and coworkers [122] shows that, for a given anionic surfactant, the order of effectiveness in reducing the cmc decreases in the order: \(\text{Mg}^{2+} > \text{Cs}^+ > \text{K}^+ > \text{NH}_4^+ > \text{Na}^+ > \text{Li}^+\). For a given non-ionic surfactant, the effect of anions on the cmc follows the order: \(\text{F}^- > \text{Cl}^- > \text{SO}_4^{2-} > \text{Br}^- > \text{PO}_4^{3-} > \text{C}_3\text{H}_5\text{O(COO)}_3^{-} > \text{I}^-\).
SCN\(^-\), and the effect of cations follows the order: \(K^+ > Na^+ > Rb^+ > Li^+ > Ca^{2+} > Al^{3+}\) [123].

(b) Effect of organic additives: Organic materials may produce marked changes in the cmc in aqueous media, even if it is present in small amount. Since some of these materials may be present as impurities or byproducts of the amphiphiles, their presence may alter the properties of amphiphiles. A knowledge of the effects of organic materials on the cmc of amphiphiles is therefore of great importance for both theoretical and practical purposes. The main factor which causes a decrease in cmc is likely to be the reduction of the free energy of the micelle due to diluted surface charge density on micelle.

Organic compounds affect the cmc either by penetrating into the micellar region, or by modifying solvent-micelle or solvent-monomer interactions. Both increase and decrease of cmc are observed on addition of non-electrolytes like urea, amides, amino acids, esters, carbohydrates, alcohols, etc. [124-131]. Methanol and ethanol cause a cmc increase, the higher alcohols butanol and pentanol cause a decrease in this property. Propanol exhibits an intermediate effect, low concentrations causing a decrease in cmc, higher concentrations (\(> 1\) M) causing an increase. The cmc increasing effect of the lower alcohols has been attributed to a weakening of the hydrophobic bonding. The cmc decreasing effects are thought to be a consequence of the penetration of the alcohols into the palisade layer of micelle, forming a mixed micelle.
Compounds that affect the cmc by modifying solvent-micelle or solvent-surfactant interactions do so by modifying the structure of the water, its dielectric constant, or its solubility parameter (cohesive energy density). Water structure breakers like urea, formamide, and guinidinium salts are believed to increase the cmc of surfactants in aqueous solutions (the increase of cmc of ionics by urea is small), because of their disruption of water structure. Materials that promote water structure such as xylose or fructose decrease the cmc of surfactants [132].

(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. Dehydration of hydrophilic part favors the micellization while disruption of structured water around the hydrophobic part disfavors the micellization. The relative magnitude of these two opposing effects, therefore, determines whether the cmc increases or decreases over a particular temperature range.

The micellization of amphiphile (ionic or non-ionic) is affected by temperature due to change in interactions between hydrophobic tails and polar head groups. cmc vs. temperature studies have been performed to obtain information on these interactions [133]. For ionic systems, cmc first decreases to a minimum value with temperature and then increases showing a U-shaped behavior [134, 135]. However, in some cases continuous increase in cmc is observed with increasing temperature [136, 137]. For non-ionic 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 [94]. From the data available, the minimum in the cmc-temperature curve appears to be around 25 °C for ionics [134] and around 50 °C for non-ionics [138, 139]. 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 [140, 141].

(b) Effect of pressure: The effect of pressure on micelle formation of ionic [142] and non-ionic surfactants [143] has been studied. The cmc increases upto pressure of about 1000 atmosphere and decreases with further increase of pressure. It has been suggested that the surfactant molecules when present in the micelle are in a more expanded condition than when present as the monomer in solution, so that the initial effects of pressure tend to compress the micelle and mitigate against the increased freedom of the monomer in the micelle, thus giving a rise in cmc. The decrease in cmc on increasing the pressure above 1000 atmospheres may be due to an increase in the dielectric constant of water, making less electrical work necessary to bring the monomer into a micelle. For non-ionic amphiphiles, the cmc values increase monotonously and then level off with increasing pressure.

(c) Effect of pH: When amphiphile molecules contain ionizable groups such as –NH₂, –(CH₃)₂N→O and –COOH, the degree of dissociation of the polar group will be dependent on pH [144]. In general, the cmc will be high at pH values...
where the group is charged (low pH for $-\text{NH}_2$ and $-(\text{CH}_3)_2\text{N}\rightarrow\text{O}$, high pH for $-\text{COOH}$) 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 [145], or a more modest rise [146], depending on the structure and hence hydrophilicity of the zwitterionic form.

(d) Solvent medium: In ethylene glycol, the cmc of surfactants decrease as the length of the hydrophobic chain increases, but the change is much smaller than that in water [147]. For polyoxyethylenated non-ionic solutions in benzene and carbon tetrachloride, cmc decreases with increase in the length of the polyoxyethylene group at constant hydrophobic chain length.

The cmc in benzene for alkylammonium carboxylates increases with increase in the length of the alkyl chain of the anion but decreases with increase in the length of the alkyl chain of the cation; in carbon tetrachloride, there is no significant change in the value of the cmc with these structural changes. The cmc is lower in D$_2$O than H$_2$O for different amphiphiles [148, 149]. The hydrophobic bonds are expected to be stronger in D$_2$O than H$_2$O [150]. Also, micelles in D$_2$O are larger than H$_2$O [151].

**Thermodynamics of micellization**

The process of micellization is one of the most important characteristics of surfactant solution from theoretical as well as practical purposes and hence it is essential to understand its mechanism (the driving force for micelle formation).
This requires analysis of the dynamics of the process (i.e., the kinetic aspects) 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 micelle formation. The first and simplest approach treats micelles as a single phase, and is referred to as the phase separation model [152-154]. Here, micelle formation is considered as a phase separation phenomenon and the cmc is then the saturation concentration of the amphiphile in the monomeric state whereas the micelles constitute the separated pseudophase. Above the cmc, phase equilibrium exists with a constant activity of the surfactant in the micellar phase. The Krafft point is viewed as the temperature at which solid hydrated surfactant, micelles and a solution saturated with undissociated surfactant molecules are in equilibrium at a given pressure. In the second approach, micelles and single surfactant molecules or ions are considered to be in association–dissociation equilibrium. In its simplest form, a single equilibrium constant is used to treat the process. The cmc is merely a concentration range above which any added surfactant appears in solution in a micellar form. Since the solubility of the associated surfactant is much greater than that of the monomeric surfactant, the solubility of the surfactant as a whole will not increase markedly with temperature until it reaches the cmc region. Thus, in the mass action [155-157] approach, the Krafft point represents the temperature at which the surfactant solubility equals the cmc.
(1) **The phase separation model**

According to this model, micelles and counterions are treated as separate phase. However, the micelles do 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 [158] while considering micelles as separate phase.

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

To evaluate the thermodynamic parameters for the process of 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 considered 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, then since these two phases are in equilibrium

\[
\mu_s = \mu_m \quad (1.6)
\]

For non-ionized amphiphile,

\[
\mu_s = \mu^0_s + RT \ln a_s \quad (1.7)
\]

where \( \mu^0_s \) is the chemical potential of standard state.

Since the micellar state is in its standard state

\[
\mu_m = \mu^0_m \quad (1.8)
\]
At low concentration of free monomers, the activity $a_s$ is replaced by mole fraction $X_s$.

If the $\Delta G_m^0$ is the standard free energy for the transfer of one mole of amphiphile from the solution to micellar phase, then

$$\Delta G_m^0 = \mu_m^0 - \mu_s^0 = \mu_m - (\mu_s - RT \ln X_s) = RT \ln X_s$$  \hspace{1cm} (1.9)

Assuming that the concentration of free surfactant in the presence of micelle is constant and equal to the cmc value, $X_{cmc}$, then

$$\Delta G_m^0 = RT \ln X_{cmc}$$  \hspace{1cm} (1.10)

$X_{cmc}$ is the cmc expressed as a mole fraction, therefore,

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

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

$$X_{cmc} = n_s/n_{H_2O}$$  \hspace{1cm} (1.12)

Substituting Eq. (1.12) into Eq. (1.10) and applying logarithm we get

$$\Delta G_m^0 = 2.303RT (\log_{cmc} - \log_{w})$$  \hspace{1cm} (1.13)

where $w = 55.40$ M at 20 °C.

Application of Gibbs–Helmholtz equation to Eq. (1.10) gives

$$\partial / \partial T (\Delta G_m^0 / T)_p = -R(\partial \ln X_{cmc} / \partial T)_p = \Delta H_m^0 / T^2$$  \hspace{1cm} (1.14)

Hence the standard enthalpy of micellization per mole of monomer, $\Delta H_m^0$, is

$$\Delta H_m^0 = -RT^2 (\partial \ln X_{cmc} / \partial T)_p = R (\partial \ln X_{cmc} / \partial (1/T))_p$$  \hspace{1cm} (1.15)
Also, standard entropy of micellization per mole of monomer, $\Delta S_m^0$, is given by

$$\Delta S_m^0 = (\Delta H_m^0 - \Delta G_m^0) / T \tag{1.16}$$

**ii) Application of phase separation model to ionic surfactants**

Consider an anionic surfactant, in which $n$ surfactant anions, $S^-$, and $n$ counter ions $M^+$ associate to form a micelle, i.e.,

$$nS^- + nM^+ \Leftrightarrow S_n$$

The micelle is simply a charged aggregate of surfactant ions plus an equivalent number of counterions in the surrounding atmosphere and is treated as a separate phase.

In the calculation of $\Delta G_m^0$, it is necessary to consider the transfer of $(1 - g)$ moles of counterions from its standard state to micellar state in addition to transfer of surfactant molecules from the aqueous phase ($g$ is degree of dissociation). Therefore, Eq. (1.9) can be written as

$$\Delta G_m^0 = RT \ln X_s + (1 - g) RT \ln X_x \tag{1.17}$$

where $X_s$ and $X_x$ are the mole fractions of surfactant ions and counterions, respectively.

The analogous equations to Eqs. (1.10) and (1.13) for an ionic surfactant in the absence of added electrolyte are

$$\Delta G_m^0 = (2 - g) RT \ln X_{cmc} \tag{1.18}$$

$$\Delta G_m^0 = (2 - g) 2.303RT (\log c_{cmc} - \log w) \tag{1.19}$$
It is assumed that micellar phase is composed of the charged aggregates together with an equivalent number of counterions, and Eqs. (1.18) and (1.19) are approximated to

\[ \Delta G_m^0 = 2RT \ln X_{\text{cmc}} \]  

(1.20)

and

\[ \Delta G_m^0 = 4.606RT (\log \text{cmc} - \log w) \]  

(1.21)

The enthalpy of micellization, \( \Delta H_m^0 \), for ionic surfactants is given by

\[ \Delta H_m^0 = -2RT^2 (\partial \ln X_{\text{cmc}} / \partial T)_P \]  

(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 imply 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.
(2) The mass-action model

This model assumes dissociation-association equilibrium between surfactant monomers and micelles—thus equilibrium constant can be calculated. The mass-action model was originally applied to ionic surfactants but latter it was applied to non-ionic surfactants also.

(i) 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, D, according to

\[ nD \leftrightarrow M \]  \hspace{1cm} (1.23)

The equilibrium constant for micelle formation, \( K_m \), is then given by

\[ K_m = a_m / (a_s)^n \]  \hspace{1cm} (1.24)

Corkill et al. [159] have shown that at the cmc the standard free energy of micellization, \( \Delta G_m^0 \), is given by

\[ \Delta G_m^0 = RT [(1 − 1/n) \ln X_{cmc} + f(n)] \]  \hspace{1cm} (1.25)

where

\[ f(n) = 1/n [\ln n^2(2n−1/n−2) + (n−1) \ln n(2n−1)/2(n^2−1)] \]  \hspace{1cm} (1.26)

If \( n \) is large, Eq. (1.25) reduces to

\[ \Delta G_m^0 = RT \ln X_{cmc} \]  \hspace{1cm} (1.27)

Applying the Gibbs–Helmholtz equation and assuming the aggregation number, \( n \), to be large and independent of temperature

\[ \Delta H_m^0 = −RT^2 (\partial \ln X_{cmc} / \partial T)_p = R (\partial \ln X_{cmc} / \partial (1/T))_p \]  \hspace{1cm} (1.28)
The aggregation numbers of many non-ionic surfactants vary with temperature and in some cases a concentration dependence of \( n \) has been reported. In such cases Eq. (1.28) is not applicable.

(ii) Application of mass-action model to ionic surfactants

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

\[
nD^+ + (n - p) X^- \leftrightarrow M^{\mp}
\] (1.29)

The equilibrium constant for micelle formation assuming ideality, is thus,

\[
K_m = \frac{X_m}{(X_s)^n (X_x)^{n-p}}
\] (1.30)

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

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

\[
\Delta G_m^0 = -\frac{RT}{n} \ln K_m = -\frac{RT}{n} \ln X_m/(X_s)^n (X_x)^{n-p}
\] (1.31)

When \( n \) is large, and when data in the region of the cmc are considered, Eq. (1.31) becomes

\[
\Delta G_m^0 = (2 - p/n) \frac{RT}{n} \ln X_{\text{cmc}}
\] (1.32)

Eq. (1.32) is of the same form as Eq. (1.18) from the phase-separation model, since \( g = p/n \). The two equations differ slightly because of differences in the way in which the mole fractions are calculated. In the phase-separation model the total number of moles present at the cmc is equal to the sum of the moles of water and
surfactant whereas the total number of moles in the mass-action model is equal to the sum of the moles of water, surfactant ions, micelles, and free counterions. The standard enthalpy of micellization (per mole of monomer) is given by

\[ \Delta H_m^0 = -(2 - g) RT^2 (\partial \ln X_{\text{cmc}} / \partial T)_P \]

\[ = (2 - g) R [ (\partial \ln X_{\text{cmc}} / \partial (1/T))_P ] \tag{1.33} \]

The mass action model is more realistic 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 of micellization completely. From the practical point of view a comprehensive approach was developed, known as multiple equilibrium model [160], 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.

Nevertheless, because of the simplicity of its application, the pseudophase model is widely used to model thermodynamic data, particularly for long chain surfactants having low cmc values. The mass action model allows for modeling of thermodynamic properties over a broader concentration range, i.e., premicellar range as opposed to the pseudo-phase model, which is applicable only in the post-micellar range. As well, prediction of aggregation numbers can be made from the mass action model, and it has been more successfully applied to short chain surfactants.

(3) Other thermodynamic models

The thermodynamics of small systems developed by Hill [161] has been applied to non-ionized, non-interacting surfactant systems by Hall and Pethica [162]. 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

\[
\Delta G_m^0 = RT \left[ \ln X_s - \ln X_m / <n> \right] \tag{1.34}
\]

\[
\Delta H_m^0 = -RT^2 \left[ (d\ln X_s / dT)_P - 1 / <n>(d\ln X_m / dT)_P \right] \tag{1.35}
\]

\[
\Delta S_m^0 = -RT (d\ln X_s / dT)_P + R T / <n>(d\ln X_m / dT)_P - R \ln X_s + (R / <n>)\ln X_m \tag{1.36}
\]
For systems where $<n>$ is large and changes little with temperature, Eqs. (1.34) to (1.36) are reduced to the corresponding equations of mass-action or phase-separation models.

Another approach for that of small systems was formulated by Corkill and coworkers and applied to systems of non-ionic surfactants [163, 164]. This multiple equilibrium model considers equilibria between all micellar species present in solution rather than a single micellar species, as was considered by mass-action theory. The standard free energy and enthalpy of micellization are given by equations of similar form to equations (1.32) and (1.33) and are shown to approximate satisfactorily to the appropriate mass-action equations for systems in which the mean aggregation number exceeds 20.

An interesting model of micelle formation based on geometrical considerations of micelle shape has been proposed by Tanford [165]. Equations are presented which relate the micelle size and cmc to a size-dependent free energy of micellization. The calculations are based on the assumptions of an ellipsoidal shape. The hydrophobic component of the free energy is estimated in terms of the area of contact between the hydrophobic core and the solvent. The hydrophilic component of $\Delta G_m^0$, i.e., the free energy of repulsion between the head groups, is assumed to be inversely proportional to the surface area per head group. This approach has been further developed by Ruckenstein and Nagarajan [166] and used in the prediction of the properties of sodium octanoate micellar solutions [167].
Drugs and Their Classification

The term drug is derived from French word ‘Drogue’ which means a dry herb. A very broad definition of a drug would include ‘all chemicals other than food that affect living processes’. If the affect 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.

Another definition would be “medicinal agents used for diagnosis, prevention, treatment of symptoms, and cure of diseases”. Contraceptives would be outside of this definition unless pregnancy was considered a disease.

It is to be noted that drugs are to be used for the benefit of recipient and it is presumed that this refers to total benefit – physical, mental as well as economical.

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:

(A) Biological classification
(B) Chemical classification
(C) Classification of drugs according to commercial consideration
(D) Classification by the lay public

(A) Biological classification

Biological classification is based on pharmacotherapeutic and chemotherapeutic agent, i.e., this is as disease oriented classification of medicinal
agents used in various diseases and hence this classification is based on medicinal agents which are overall descriptive but not very accurate on scientific grounds. The broad classification based on gross overall biological effects is as follows:

(a) Drugs acting on central nervous system and peripheral nervous systems: The central nervous system (CNS) which consists of brain and spinal cord, and controls and regularizes the special functions like circulation, digestion and respiration and it also modifies the psychic reactions such as feeling, attitude, thoughts, and memory. It directs the functions of all tissues of the body. Chemical influences are capable of producing a myriad of effects on the activity and function of the central nervous system. Stimulants are drugs that exert their action through excitation of the central nervous system. Psychic stimulants include caffeine, cocaine, and various amphetamines. These drugs are used to enhance mental alertness and reduce drowsiness and fatigue. However, increasing the dosage of caffeine above 200 mg (about 2 cups of coffee) does not increase mental performance but may increase nervousness, irritability, tremors, and headache.

(b) Chemotherapeutic drugs: Chemotherapy, in its most general sense, is the treatment of disease by chemicals especially by killing micro-organisms or cancerous cells. Various drugs used in chemotherapy are known as chemotherapeutic drugs, which have important therapeutic use in the treatment of parasitic infections due to insects, worms, protozoa, viruses, bacteria, etc. These drugs destroy offending parasites or organisms without damaging the host tissues. First modern chemotherapeutic agent was Paul Ehrlich's arsphenamine, an arsenic
compound discovered in 1909 and used to treat syphilis. This was later followed by sulfonamides discovered by Domagk and penicillin discovered by Alexander Fleming. Most commonly, chemotherapy acts by killing cells that divide rapidly, one of the main properties of most cancer cells. This means that it also harms cells that divide rapidly under normal circumstances: cells in the bone marrow, digestive tract and hair follicles.

(c) **Pharmacodynamic agents**: These drugs affect the normal processes of the body like blood circulation, hemodynamic process, i.e., blood pressure, cardiac outputs, etc. Phamacodynamic agents include mainly the drugs which affect the heart and blood circulation. It also includes a wide variety of the drugs used in allergic and gastrointestinal diseases.

(d) **Metabolic diseases and endocrine function**: It includes variety of drugs which are not conveniently classified in the other groups, like:

(i) **Antirheumatic and autoimmuno disease drugs**: Diseases modifying antirheumatic drugs are the focus of treatment that addresses constant pain and inflammations of the lung, heart and eye and autoimmune diseases arise from an overactive immune response of the body against substances and tissues normally present in the body. In other words, the body actually attacks its own cells. The treatment of autoimmune diseases is typically with immunosuppression-medication which decreases the immune response.

(ii) **Dermatologicals**: Dermatology is the branch of medicine dealing with the skin and its diseases, a unique specialty with both medical and surgical
aspects. A dermatologist takes care of diseases, in the widest sense, and some cosmetic problems of the skin, scalp, hair, and nails.

   (iii) Anti-inflammatory drugs: Anti-inflammatory drugs are drugs with analgesic and antipyretic (fever-reducing) effects and which have, in higher doses, anti-inflammatory effects (reducing inflammation). The most prominent members of this group of drugs are aspirin, ibuprofen, and naproxen.

(B) Chemical classification

   Chemical classification is based on their chemical structure. According to this classification drugs may come under one or more of these categories such as quinines, semicarbazides, phenols, lactones, azo compounds, amides, alcohols, acetals, ketones, hydrocarbons, halogenated compounds, guanides, enols, esters, etc.

   The implication of this classification is that similar chemical structure should yield similar biological activities. Thus, structurally close analogous compounds are grouped together with some overall activity but sometimes this classification is not very accurate as a few compounds with similar structure lack the activity test. Chemical structural classification of drugs is of advantage for study of methodology and structure-activity relationship.

(C) Classification of drugs according to commercial consideration

   The manufacturers and distributors of therapeutic agents classify the drugs according to their operational expenses, research investment and profit margins.
Medicines for relatively rare diseases are called orphan drugs and such drugs lack patient protection as production costs are high and demand is less.

Another classification of commercial consideration depends on the way of administration of drug, i.e., drugs are given orally, parenterally (meaning introduced subcutaneously, intravenously or by any route other than by way of the digestive tract) by inhalation, sublingually, rectally, etc. On the whole, orally active drugs are preferred by physicians and patients.

(D) Classification by the lay public

The few broad public classification depends upon the action of the drug, for example, antiseptic and disinfectant, anthelmintics, expectorants, cough mixtures, laxative and purgative, analgesics, tonics, ointments for skin diseases, etc., but this classification is scientifically inadequate and public should be well informed about all aspects of chemistry, biological action and fate of medicinal agent by experimental biologists and medicinal chemists.

Many pharmacologically active compounds are amphiphilic or hydrophobic molecules, which may undergo different kinds of association, and whose site of action in the organism frequently is the plasma membrane. Even if their target is intracellular, the interaction with this first barrier plays a fundamental role [168].

Classes of amphiphilic drugs include phenothiazine [169-175] and benzodiazepine [176] tranquillizers [177-179], analgesics [179], peptide [180] and nonpeptide [182, 183], antibiotics [183, 184], tricyclic antidepressants [185-188], antihistamines [189], anticholinergics [190], β-blockers [191], local anesthetics
(LA) [192-195], non-steroidal anti-inflammatory drugs [196], anticancer drugs [197], etc. Many of these drugs contain one ore 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 [198] and other reviews [199-201].

Surface active drugs of quite different chemical structure are reported to self-associate and bind to membranes, causing disruption and solubilization, in a surfactant-like manner [168]. Depending on the kind of drug, the self-association of these drugs is classified into two modes: micellar and nonmicellar aggregations. Here the micellar aggregation means a single multimer (micelle) forms above the cmc, and nonmicellar (stepwise) aggregation means that i-mer is successively formed by aggregation of (i-1)-mer and monomer [198].

**Mode of drug action**

It is important to distinguish 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 observable 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.

One major problem of pharmacology is that no drug produces a single effect. The primary effect is the desired therapeutic effect. Secondary effects are all other effects beside the desired effect which may be either beneficial or
harmful. Drugs are chosen to exploit 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 observed 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.

**Theories of Mixed Micellization**

A mixed micelle consists of surfactant molecules of more than one type. 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 [77, 202] and used by Clint [73], is based on phase separation model that relates the mole fraction and the critical micellar concentration (cmc) of the component in an ideal mixture, which is applicable to systems of mixed surfactants of similar structure, but hardly applicable to
dissimilar combinations. This model is an idealization which neglects the interaction among different surfactants in the aggregated state. Rubingh [203] and Rosen [204, 205] have made an attempt to explain the composition and specific interaction parameters between two surfactants of nonideal mixture in the bulk and in the interface, on the basis of regular solution theory (RST). The Rubingh model treats the mixed micelles as a regular solution. Though these theories are satisfactory but are questioned on thermodynamic grounds [206-208]. Motomura [209] 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 [210] explained that a mixed ionic-nonionic surfactant system often has a lower cmc much lower than the cmc of the pure components. This can be attributed to the decrease in the ionic head group repulsion caused by the presence of non-ionic surfactant molecules between the head groups. 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.

Georgiev’s model is based on Markov’s chain model [211] for polymerization process of mixed micelles, and has introduced two molecular parameters instead of one as in RST. Blankschtein [212, 213] has thermodynamically formulated models for mixed-surfactant systems (nonideal mixtures) to evaluate various physico-chemical parameters. 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.

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 [213].

**Clouding Phenomenon in Aqueous Solutions**

The cloud point (CP) of a fluid is the temperature at which dissolved solids are no longer completely soluble, precipitating as a second phase giving the fluid a cloudy appearance [214]. This term is relevant to several applications with different consequences. Phase separation results from the competition between entropy, which favors miscibility of micelles in water, and enthalpy, which favors separation of micelles from water [215, 216]. Depending on the variation of these
two contributions with temperature, either a lower or an upper consolute point can result [215, 216].

Binary liquid mixtures that display partial miscibility exhibit critical solution temperatures (CST) or consolute temperatures. CST’s are of two kinds: upper critical solution temperature (UCST), above which the liquid pair is completely miscible and below which phase separation occurs, and lower critical solution temperature (LCST), below which the two components are completely miscible while above it the two components become partially miscible and form two separate phases. The appearance of LCST is a rather rare phenomenon for solutions of small molecules but is more frequent when at least one of the molecules is large. The importance of the entropy of mixing, which favors mixing, becomes relatively less important when the molecules get larger and the mixing process becomes more dominated by the enthalpy term, which may favor or disfavor mixing.

If the solution is cold, a temperature below which the amphiphile is not really very soluble (Fig.1.6) at all is reached, known as the Krafft temperature [217-220]. If, on the other hand, the temperature is raised, especially for non-ionic amphiphiles or those with some non-ionic polar groups, a two-phase region is encountered, above what is known as the CP [221-223] where two liquid (micellar) phases are in equilibrium. Finally, if we increase concentrations at ambient temperature, one starts to encounter, usually at amphiphile concentrations
above 40 % by weight, a series of mesomorphic phases sometimes called liquid crystalline phases.

![Diagram of phase behavior](image)

**Fig.1.6:** Schematic temperature (T)–concentration phase diagram illustrating the types of amphiphilic aggregates encountered by moving away from the micellar region.

One may find from the literature that there are two classes of surfactants and the temperature effect on the solution behaviors of each class are in sharp contrast. The first class is the non-ionic surfactants, the micellar size of which increases (or at least does not decrease) with increase in temperature. Such systems always have cloud point properties [19, 224-232]. This behavior has been attributed to dehydration of the hydrophilic group of the surfactant with increasing temperature [227]. The absence of long range electrostatic interactions between
aggregates and the decreasing hydration of non-ionic head groups with increasing temperature result in spontaneous phase separation.

The ionic surfactants belong to the second class in which the cloud point phenomenon is rarely observed [228]. Until recently it was thought that this type of behavior was not possible in binary ionic surfactant-water solutions due to large electrostatic repulsions between the aggregates.

The clouding behavior of amphiphiles is strongly affected by the presence of various additives in the solution either by changing the structural properties of the micelles by solubilization in the micellar aggregates or by dissolving in water phase and thus changing the environment of the micelles [229-234].

The mechanism of CP has not been exactly known and has been discussed from two view points. One is that the aggregation number of the micelles increases and intermicellar repulsions decrease with the increase in temperature [14, 235]. As the temperature increases, micellar growth and increased intermicellar attraction cause the formation of particles, e.g., rod like micelles that are so large that the solution becomes visibly turbid [236]. Turbidity measurements [224, 237-239] have been performed in order to determine the micellar size. However, this interpretation has been criticized [240, 241] because the turbidity must show a big increase owing to the presence of CP, a phenomenon that has nothing to do with an increase in the molecular weight of the micelles.

Other methods used to determine the micellar size [239, 242, 243], e.g. diffusion, viscosity and sedimentation measurements and osmometry, have, in
general, confirmed that the micelles are small at low temperatures but larger at higher ones. However, these methods are also subject to difficulties in distinguishing between molecular weight and intermicellar interactions.

Corti et al. [222] explained the behavior as critical fluctuation. The interpretation is that as the CP is approached the micelles come together, and above the CP they separate out as second phase. They were able to evaluate the critical exponents from the light scattering data. The existence of attractive interactions between poly(oxyethylene) alkyl ethers at elevated temperatures has been demonstrated convincingly by Claesson et al. [244]. Lindman [245] has advanced a model based on conformational changes in the poly(oxyethylene) chain with changing temperature, from which a change in the dipole moment of the hydrophilic chain arises. This, in turn, leads to a decrease in the polarity or hydrophilicity of the surfactant and, hence, to phase separation. Kjellender [246, 247] has argued persuasively that attractions between spherical micelles cannot give rise to the low observed critical concentrations but are a consequence of attraction between anisotropic micelles.

High concentration of salts can cause ionic surfactant solutions to separate into immiscible surfactant-rich and surfactant-poor phases [19]. This phenomenon has been investigated since the 1940s and was first observed for mixtures of the cationic surfactant Hyamine 1622 with salts such as potassium thiocynate (KSCN) and potassium chloride (KCl) [248, 249]. The phase separation is typically of the upper consolute type, i.e., it occurs on cooling below a characteristic temperature,
which, in turn, increases with salt content. Later on, few more studies on ionic surfactant-salt combinations were performed to show CP phenomenon (lower consolute type) [250, 251]. Appell and Porte [228] found cloud points at high concentrations of sodium chlorate (NaClO₃) in aqueous solutions of either cetyltrimethylammonium bromide (CTAB) or cetylpyridinium bromide (CPB). In a later study Warr et al. [250] showed that quaternary ammonium surfactants with tributyl head groups exhibit cloud points in binary aqueous solution. Adding salt to these surfactant solutions lowers the cloud point temperature. They [250] advanced a mechanism involving hydration shells to account for cloud points, whereas Appell and Porte [228] interpreted the clouding of CPB/NaClO₃ mixtures as being analogous to the phase separation of polymers in a poor solvent.

Recently, Raghavan et al. [252] has reported the clouding behavior in ionic amphiphiles in presence of salts with hydrophobic counterions. The plausible hypothesis given is that the binding of hydrophobic counterions promotes micellar branching. As free micellar ends are incorporated into a branched network, the viscosity of the solution drops, and the entropic attraction between junction eventually causes phase separation. Interest has been focussed on the possibility that upper or lower critical points could occur within ordered liquid crystal phases. An upper consolute loop within a lamellar phase has been reported for binary anionic [253] or cationic [254] surfactants in water. However, lower consolute loops are much rarer. Some ionic surfactants are reported [250] to undergo phase separation without the addition of electrolyte, and their micelles remain spherical
or near spherical throughout their region of stability. The parameters, which
govern the phase equilibria and particularly the lower consolute behavior of ionic
surfactant solutions, have been detailed [251].

According to Yu and Xu [255], there may be four factors responsible for
the CP phenomenon in ionic amphiphiles: van der Waals attraction, electrical
repulsion, solvation layer and hydrophobic interactions. They proposed a
mechanism for clouding in tetrabutyltetradecyl sulfate. They postulated that butyl
chains belonging to TBA$^+$ associated with one micelle could cross-link to another
micelle helping overcome the effects of electrostatic repulsion and an energetic
barrier due to oriented water near the surfaces of the two micelles. To be operative
g eo metrically, it appears that the two micelles would have to approach one another
intimately due to the limited extent of short butyl chains.

Zana et al. [256-259] opposed the mechanism for clouding in TBADS [or
SDS + TBA$^+$] which explains that reducing the water hydrating the micelles is
responsible for CP. The hypothesis is supported by the fact that alkylammonium
counterions are quite bulkyl and ought to expel water from the palisade layer in
the same way that bulky head groups do [260]. Measurements of the water content
of the palisade layer will be needed to confirm the expectation [261]. If indeed
clouding is induced somehow by dehydrating the micelle surface, then the
interpretation of the data will be further complicated by presence of Na$^+$ because
increasing the aggregation number of globular micelle leads to less water per
surfactant [259, 261]. This is a consequence of fact that the surface area of a
micelle grows more slowly than its volume, leading to a smaller volume per surfactant in which to fit the water [259, 261]. Adding Na\(^+\) increases the aggregation number of SDS. Therefore, there would be two competing mechanisms to dehydrate: one displacement of water by the counterions and another by the geometric constrictions due to micelle growth. Therefore, one would need to know the details of the micelle aggregation numbers in the presence of both TBA\(^+\) and Na\(^+\) to gain a clear understanding.

To the previously suggested mechanisms for clouding in ionic micelles, they suggested [256] that a second layer of TBA\(^+\) is loosely attached outside the polar shell of the TBADS micelle because steric restrictions did not appear to allow enough available volume to house a sufficient number of counterions. If this second layer is in fact available, the cross-linking between micelles could take place between butyl groups of the TBA\(^+\) ions in the second layer. This possibility is supported by the tendency of TBA\(^+\) ions to self-associate [262-265].

Recently, Kim and Shah [266-268] have observed the CP phenomenon in amphiphilic drug amitriptyline hydrochloride solutions and have explored the effect of additives. Also, Kabir-ud-Din and his group [269-271] have studied CP phenomenon in some amphiphilic drug solutions and examined the effects of different additives.
Relevance of the Research Problem

Although the pharmacological activity of the amphiphilic drugs appears at low concentration where aggregation is negligible [201], the accumulation of drug can occur at certain site of organism after long period of administration, giving rise to formation of aggregates that are unable to pass through membranes; decreasing transport rate and consequently leading to adverse effect on health. Thus, the study of physico-chemical properties of amphiphilic drugs is important from physical, chemical, biological and pharmaceutical point of view for their implication. As most of the drugs that we have so far considered form micelles at concentrations which they do not attain in vivo, it is most likely that it is their surface-active characteristics which are most important biologically, although the propensity of the molecules to form associations by hydrophobic bonding will manifest itself. The study of the properties of surface active drugs in solution provides an opportunity to investigate the influence of the structure of the hydrophobe on the mode of association of amphiphiles.

A most common challenge faced by pharmaceutical scientists as well as industry is to design and develop drugs with good aqueous solubility while simultaneously retaining potency and selectivity [272]. The absorption properties (which cause also bioavailability) of these compounds are influenced by their physico-chemical and biological properties. A number of methodologies have been adopted to improve the aqueous solubility (and hence bioavailability) of drugs. This problem can be overpowered by the use of mixed micelles of drug—
surfactant or surfactant–surfactant. Drug delivery systems which have attracted much attention for their potential to improve the pharmacological properties of the drug include nanocapsules [273], cell ghost [274], liposomes [275] and micelles [272, 276].

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. When a mixed amphiphile system shows lower critical micelle concentration (cmc) values than that of pure components, the system is said to be synergistic. As a result, mixed micelles are commonly used in pharmaceutical formulations, in industries, and in enhanced oil recovery processes [72, 277, 278].

Nowadays, gemini surfactants [26] are gaining wide attention due to their superior properties. These surfactants contain two hydrophobic tails and two hydrophilic heads joined with a spacer (of variable nature) at the level of head groups. These surfactants have cmc values 10–100 times lower than conventional surfactants.

Keeping the above in view and the fact that surfactant micelles, like many other amphiphilic substances, are potentially important encapsulating/solubilizing agents, we have performed conductometric measurements on some amphiphilic drug–surfactant mixed systems.
The solution properties of amphiphiles are sensitive to the presence of additives. The values of cmc are found to depend on the type and nature of additives. To optimize the applications of amphiphile mixtures, it is, therefore, important to understand the interplay of forces that govern the micellization behavior in the presence of additives. It was shown by Mouritsen and Jorgensen [279] and Tieleman et al. [280] that amphiphilic drugs insert into membranes as interstitial components and they affect the organization of lipids. As the electrolyte concentration in the membranes may vary, their presence and concentration may affect the micellization tendency of the drug. Therefore, it is important to have knowledge of drug’s association behavior with temperature and also when present with electrolytes.

In order to understand the effect of additives on the micellar properties of amphiphilic drugs, we have, therefore, determined the cmc in presence of inorganic salts and urea/thiourea as well as with the change in temperature by conductometric method.

The amphiphilic drugs, because of their surfactant-like nature, exhibit concentration, temperature and pH-dependent phase separation [254-256]. It was observed that cloud point (CP) can vary with additives. When using these drugs it should be kept in mind that normal body temperature is typically 12 degrees above ambient. Even if the CP of pure drug in buffer is above this temperature, it may decrease in presence of additives, especially surfactants which are used as drug-carrier. As clouding concentrates the drug in a small volume, it may affect the
activity of drugs and, therefore, it is important to have knowledge of clouding behavior of the drugs in designing more effective drug-carrier combinations. With this idea in mind, effects of various additives, viz., electrolytes, non-electrolytes, alcohols, surfactants, sugars, and amino acids have been examined on CP behavior of some amphiphilic drugs.

Layout of the Thesis

This thesis consists of five chapters including this one which is concerned mainly with the general introduction of amphiphiles. Experimental details are provided in Chapter II.

Chapter III presents a detailed and systematic study of micellar properties of two antidepressants (AMT and IMP) and a phenothiazine (PMT) drugs in presence of surfactants (conventional and gemini) in aqueous media. Surfactants are generally used as drug carriers in pharmaceuticals but presence of surfactants may alter the micellization tendency of a drug as surfactants form mixed micelles with the drug: this may affect the activity of the drug. Therefore, it is important to have knowledge of the effect of surfactants on micelle formation of drugs and the related energetics.

Chapter IV presents the effect of additives (salts and ureas) on the association behavior of the above mentioned drugs. Electrolytes and urea are found in the body and study of their effect on micellization will allow the better designing of effective therapeutic agents.
Studies on the effect of various additives on the CP values of the above mentioned drugs are described in Chapter V.
References:


