Chapter

1

General Introduction

Contents

A concise overview of surfactants, deep eutectic solvents, and the solution behaviour of surfactants is provided in this chapter as part of the scope and rationale of a thesis.

1.1 Introduction

Amphiphiles are organic molecules that have an affinity for both water (hydrophilic) as well as for oil (lipophilic). The term amphiphile is derived from the Greek words amphis (meaning "both") and philia (meaning "attraction") [1]. They consist of a hydrophilic "head" portion and a hydrophobic "tail" part linked by a covalent bond. The head group might be ionic, polar, or hydrogen-bonding, which makes them water-soluble. Lipophilic components are often long hydrocarbon chains [2]. Amphiphiles can be classified as surfactants, lipid molecules, simple fatty acids, and polymers having covalently bonded and structurally separated hydrophilic and hydrophobic chemical moieties [3]. Amphiphilic molecules are efficient natural substances that are frequently employed in a variety of applications. The amphiphilic behaviour of these compounds contributes to their participation in significant processes in biology, most notably the generation and stabilization of the membranes of cells [4].

Amphiphiles with various structural characteristics exhibit various self-assembly behaviour in solutions and at interfaces. They can self-assemble into a broad range of structures such as micelles, vesicles, nanotubes, nanofibers, and lamellae [5]. One example of a self-driven aggregation process is amphiphile self-assembly. The lipophilic-hydrophobic interaction is one of the most essential forces for the development of self-assemblies of amphiphilic molecules, and it is considered to be the natural force with the highest level of significance. (*e.g.,* association colloids or micelles, bilayers or vesicles, biological membranes, and living cells) [6,7].

The lipid bilayers that cover cellular and organelles in cells are made up of amphiphilic phospholipids [8], exhibiting the importance of amphiphiles in establishing the structural restrictions of biology. Apart from biology, amphiphiles have a wide range of commercial uses, including detergency, emulsification, and nanoparticle production, due to their ability to disperse insoluble materials [9]. One of the examples of amphiphiles is soap, which is made up of sodium or potassium salts of fatty acids. The dual nature of soap allows them to emulsify and remove oils and dirt from surfaces. Another example of an amphiphilic molecule is cholesterol (an essential component of animal cell membranes) [10] which contains a hydrophilic hydroxyl moiety and a hydrophobic steroid ring, which helps in membrane fluidity

management. Furthermore, lipoproteins, which are made of lipids and proteins and transport lipids across water, are an example of amphiphiles [9]. A bile salts [11], which are created by the liver and stored in the gallbladder, have both hydrophilic and hydrophobic parts and are essential in the digestion and absorption of dietary lipids in the gut. Other examples include saponins, polymer amphiphiles, bio amphiphiles, supraamphiles, hybrid amphiphiles, Janus amphiphiles, polygonal oligomeric silescoyoxanes, or polyoxometates [12]. Surfactant is one of the simplest amphiphilic structures, which will be used in this study.

1.2 Surfactants

The term "surfactant" derives from the word "surface-active agent" [13]. Surfactants, also known as detergents, are amphiphilic molecules that are organic or organometallic. These molecules contain a polar head group that is attached to a long non-polar hydrocarbon tail, which gives different hydrophobic and hydrophilic functionalities [1]. The hydrophobic component usually consists of a linear hydrocarbon chain with 8-18 carbon atoms, whereas the hydrophilic component is characterized by its ionic or polar properties. The hydrophobic region exhibits solubility in oil and other non-polar solvents while showing limited solubility in water and other polar solvents. This hydrophobic region is covalently linked to the polar functional area, commonly referred to as the hydrophilic head. The water at the interface between hydrophobic and hydrophilic surfaces is important in numerous self-assembly phenomena [14,15]. **Figure 1.1** illustrates the typical representation of a surfactant molecule.

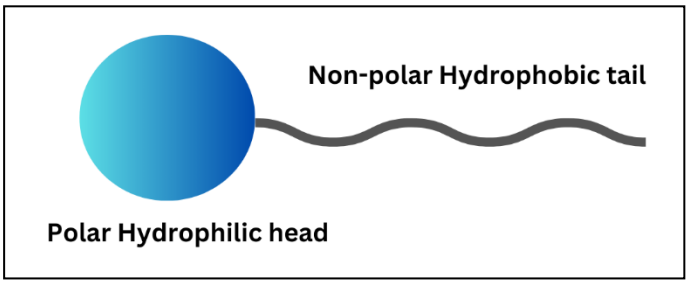

Figure 1.1: Representative structure of a typical surfactant molecule.

1.3 Classification of surfactants

Amphiphilic surfactants can be distinguished in several ways. The hydrophilic component may be an ionic group or an extremely polar group. The primary way to categorize surfactants is based on the nature of their electrical charge, which can be either positive or negative, and on the hydrophilic polar head group. There is no charge on the head group of a

non-ionic surfactant. Surfactants can be classified into four categories: anionic, cationic, non-ionic, and zwitterionic.

1.3.1 Anionic surfactants

If the head group of a surfactant in an aqueous solution carries a negative charge, it is categorized as an anionic surfactant. Sulfonic acid salts, alcohol sulfates, alkyl benzene sulfonates, phosphoric acid, esters, and carboxylic acid salts are all examples of anionic surfactant groups. These surfactants belong to the oldest category and continue to be utilized [16]. These surfactants are commonly utilized in industrial applications [17,18] because they are relatively affordable to manufacture. Anionics are commonly utilized in the majority of detergent formulations, with the greatest effective cleaning ability achieved through the usage of alkyl and alkyl aryl chains within the C_{12}–C_{18} range. Anionic surfactants exhibit excellent solubilizing properties and are generally considered to be relatively non-toxic. A common example of an anionic surfactant is SDS (**Figure 1.2**).

1.3.2 Cationic surfactants

A surfactant is cationic when it possesses a head group with a positive charge (which makes it cationic) and a counter-ion with a negative charge in a solution. Quaternary ammonium, imidazolium, pyridinium, esterified quaternary, etc. are examples of positively charged head groups. Quaternary ammonium surfactants are one of the head groups that are effective in neutral, alkaline, and acidic environments [19]. Cationic surfactants are primarily utilized for their affinity to adhere to surfaces that carry a negative charge. This makes them suitable for various applications such as protecting steel against corrosion, collecting minerals during flotation, dispersing inorganic pigments, reducing static electricity on surfaces, softening fabrics, preventing clumping in fertilizers, and acting as bactericides [19–21]. CTAB is a recognized example of a cationic surfactant (**Figure 1.2**).

1.3.3 Non-ionic surfactants

If the head group of a surfactant has no charge or is neutral in a solution, it is referred to as a non-ionic surfactant. Alcohol ethoxylates, phenol ethoxylates, alkanol amides, alkane diols, and mono- and disaccharides are examples of non-ionic head groups. The hydrophobic portion consists of either saturated or unsaturated fatty acids or fatty alcohols, which are in the form of a hydrogenated or fluorinated chain. These surfactants possess exceptional properties

for removing grease and oil and are less affected by the hardness of water [22]. Triton X-100 is an example of non-ionic surfactant (**Figure 1.2**).

1.3.4 Zwitter-ionic Surfactants:

If a surfactant contains both positive and negative functionalities on the same molecule, it is classified as a zwitterionic (amphoteric) surfactant. These surfactants can be described as a mixture of anionic and cationic surfactants, with the positive charge group typically being ammonium, while the source of the negative charge can vary, including carboxylate, sulfates, or sulfonates. The behaviour of these surfactants is significantly influenced by the pH of the solution [23]. These surfactants have also been utilized as a co-surfactant with other surfactants in bio-medicinal applications [24]. Cocoamido propyl betaine is a common example of this category of surfactants (**Figure 1.2**).

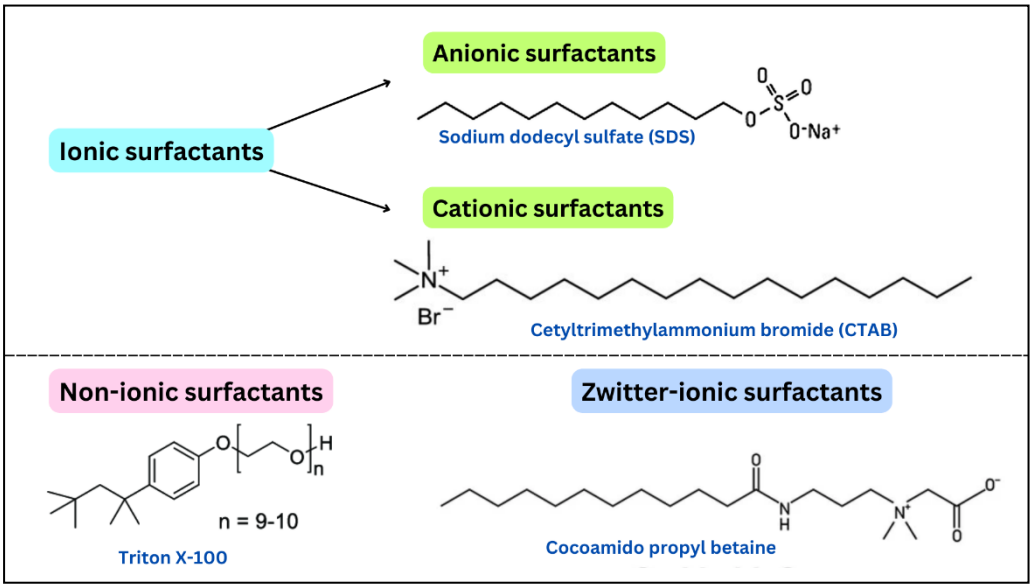

Figure 1.2: Structure of examples of different types of surfactants.

1.3.5 Gemini Surfactant

Gemini surfactants consist of two amphiphilic monomers connected at the polar head group of each monomer through a spacer [17,25–27]. The properties in the gemini solution are influenced by the distance between the polar heads, which is determined by nature, as well as the length of the spacer [28]. The cationic bis (alkyl dimethylammonium) alkane dibromide type of gemini surfactants, denoted as m-s-m (where m represents the number of carbon atoms in the alkyl chain and s represents the number of carbon atoms in the spacer), has garnered significant interest. The polar group can have a positive charge (ammonium), negative charge (phosphate or carboxylate), or no charge (polyether or sugar). Structure variations can be

observed in the spacer's characteristics, including length, rigidity, flexibility, polarity, cleavability, and non-cleavability [29]. The impact of spacer hydrophobicity on the morphology of aqueous aggregates has been reported [26]. The schematic representation of a gemini surfactant is given in **Figure 1.3**.

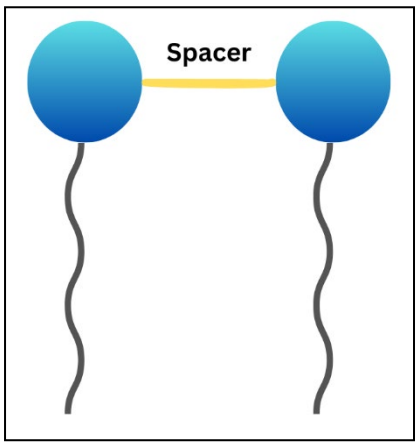

Figure 1.3: Schematic representation of a gemini surfactant.

Gemini surfactants were initially synthesized and examined due to their excellent catalytic capabilities in organic reactions [30]. The distinctive characteristics of dimeric surfactants, commonly known as "gemini" surfactants, have garnered significant interest, exceeding the properties of traditional "monomeric surfactants." Gemini surfactants have enhanced surface activity and a reduced CMC, resulting in noticeable changes in viscosity with a concentration of the surfactant. They exhibit greater efficacy in decreasing surface tension, enhanced ability in wetting and solubilizing, and possess unconventional micellar structures [29,31–33]. Due to their distinctive properties, Gemini surfactants are utilized in several industries including biochemistry [34], pharmaceuticals [35], petroleum [36], gene therapy [37], corrosion protection [38], and catalysis [39]. Gemini surfactants in aqueous environments form micelles with rod or worm-like shapes, liquid crystalline phases, and various complex structures at different concentrations.

1.4 Various phenomena in surfactant solution

An aqueous solution of surfactant shows several phenomena and characteristics, such as micellization, clouding, adsorption, spreading, wetting, solubilization, and emulsification (**Figure 1.4**). They can serve as samples for biological investigations, as well as electrochemical detectors and various other applications. Furthermore, surfactant solutions are frequently subjected to many distinct characteristics, such as the hydrophilic-lipophilic balance (HLB), the aggregation number (N_{agg}), phase inversion temperature (PIT), and kraft

temperature. In addition to the phenomena mentioned above, the present study focused primarily on the processes of micellization, clouding phenomena, and solubilization in various solvent systems with and without additives. Information on various phenomena can be found in literature through published papers, monographs, or textbooks [1,40–42].

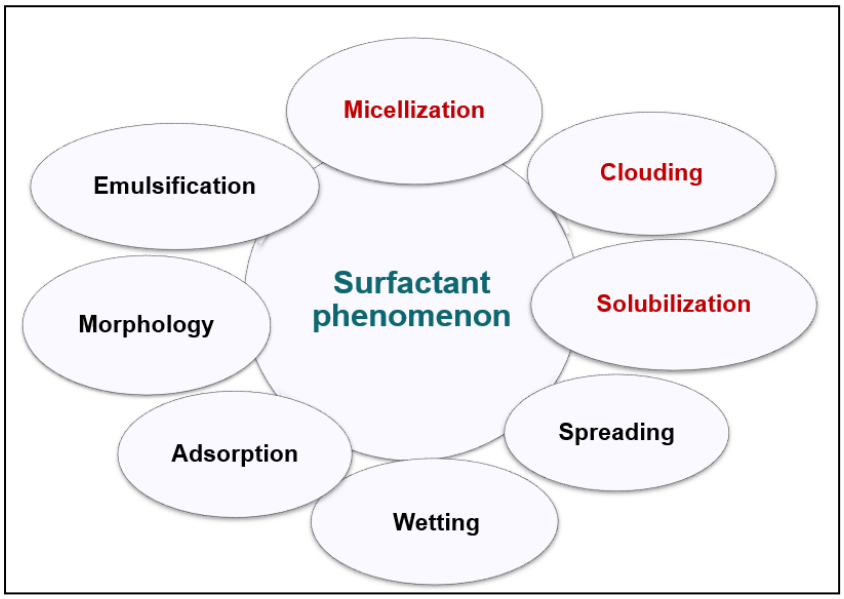

Figure 1.4: Representation of various phenomena of aqueous surfactant solution.

1.4.1 Micellization/aggregation behaviour

The primary phenomenon associated with surfactants is their tendency to aggregate. On the addition of surfactant molecules to water, they tend to partition themselves among the interfaces, and the bulk solution formed between the solid-liquid and gas-liquid phases. As the concentration of surfactant in solution increases, surfactant molecules saturate the surface. In this case, the surfactant molecules aggregate in the bulk phase more efficiently from a thermodynamic aspect where the hydrophobic tails of the surfactant interact with each other, while the hydrophilic head groups interact with water. Two opposing forces are generated as the concentration of the surfactant increases: the hydrocarbon-water interactions, specifically the hydrophobic forces supporting aggregation, and the electrostatic repulsions between the head groups for ionic surfactants. These forces compel the hydrocarbon tails to interact at the center of the micelle to minimize repulsion from the hydrophilic group. This results in the formation of a micelle, as depicted in **Figure 1.5**.

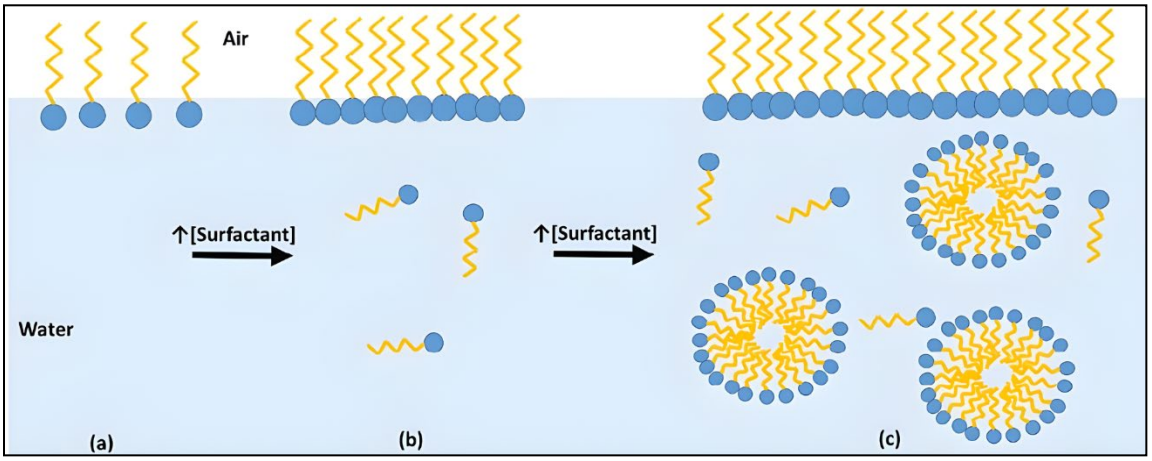

Figure 1.5: Schematic diagram for formation of micelles in aqueous solution [43].

The critical micelle concentration (CMC) refers to the lowest concentration of surfactant required for the process of aggregation (micelle formation) to take place at a given temperature [1,44]. At CMC, these aggregates exist in a state of dynamic equilibrium with the monomers. The micelle formation occurs when the length of the hydrophobic alkyl chain is greater than C_{10}, from a structural perspective. Generally, the CMC decreases as the chain length increases, but it increases with an increase in several head groups. Micelles are referred to as 'association colloids' in surface and colloid science because of their size range. However, surfactant molecules remain in their monomeric state below the CMC. The CMC can be determined using various physico-chemical methods that exhibit a specific range characterized by a sharp inflected curve as illustrated in Preston's [45] classical graph (**Figure 1.6**).

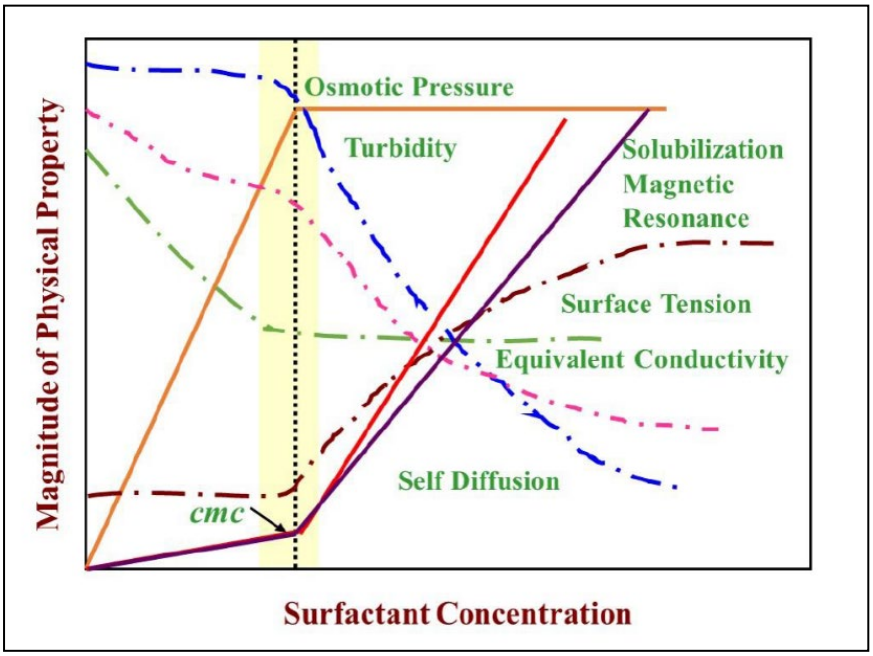

Figure 1.6: Various physicochemical methods for determination of CMC [45].

The CMC in aqueous solutions is influenced by several factors, including (i) the amphiphile's structure, (ii) the inclusion of different additives in the solution, and (iii) experimental conditions such as temperature, pH, pressure, solvent, and others.

Surfactant aggregation is influenced by several forces, such as hydrogen bonding, hydrophobic effect, electrostatic interaction, and van der Waal's forces. However, hydrogen bonding and the hydrophobic effect serve as the primary driving forces for surfactants to form supramolecular structures. Nonpolar molecules are widely recognized for their ability to disrupt the arrangement of water molecules in a solution, causing hydrophobic moieties (methylene groups) to come together. This occurs because methylene groups cannot establish hydrogen bonds or dipole bonds with water. The presence of surfactants causes water molecules to align and form a more organized structure, resulting in an increase in the number of bonds with nearby solvent molecules. Consequently, this leads to an increase in the local order or a reduction in entropy, and subsequently an increase in the free energy of the solvent molecules in the surrounding environment compared to those in the larger solution. The hydrophobic effect plays a crucial role in prompting the self-aggregation of the hydrophobic portion of the surfactant. The N_{agg} refers to the number of surfactant monomers that combine to form a micelle. The micelles that spontaneously form above the CMC may consist of several surfactant monomers (about 40-200) whose configuration and size are determined by multiple factors. The monomers and micelles exist in a state of equilibrium, although they quickly assemble and disassemble in an aqueous solution, making it difficult to accurately quantify their specific size, shape, or aggregation number. This phenomenon occurs as a result of a competition between the adsorption and complete mixing of the surfactant molecules, leading to a reduction in surface tension. The concept of 'micelle' is highly intriguing to both organic chemists, due to its ability to catalyze organic processes in unconventional ways [46], and biochemists, where it serves as a model system for studying biological membranes or globular proteins [47–49] due to its simpler structure and easy modifiability.

The charge on micelle can vary depending on the chemical structure of the surfactant, and it can be anionic, cationic, non-ionic, or amphoteric. Typically, micelles exhibit a spherical shape, but under specific physicochemical conditions such as temperature variations and the presence of electrolytes, they can adopt alternative forms like cylindrical, worm-like, double layers, or disk-like structures [50]. Although the precise structure of micelles remains somewhat debatable, **Figure 1.7** provides a basic schematic illustrating the primary forms that micelles can form. Surfactants have the special capability to create micellar structures, which

results in surfactant solutions being considered as micro-heterogeneous media. Despite appearing homogeneous on a macroscopic scale, a microscopic view reveals inherent heterogeneity in these solutions [51].

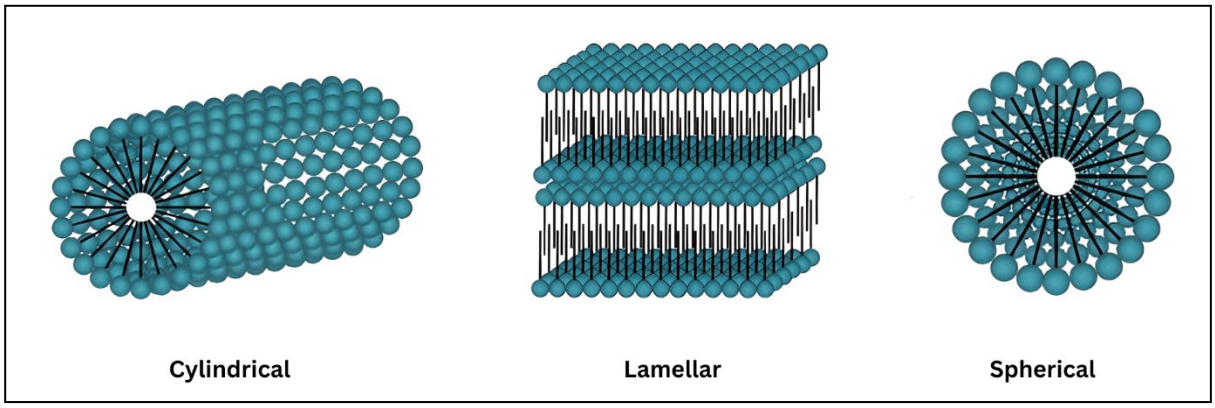

Figure 1.7: Schematic diagram of micelle configurations [52].

Normal micelles are formed in aqueous media whereas reverse micelles are aggregations of surfactant molecules in an organic solvent (**Figure 1.8**). The core of these clusters consists of a polar phase formed by the hydrophilic head groups of the surfactant, while the hydrophobic tails are immersed in the organic solvent. The core constitutes a nano-sized water droplet, stabilized within the organic solvent through the action of the surfactant. These substances are commonly referred to as water-in-oil microemulsions.

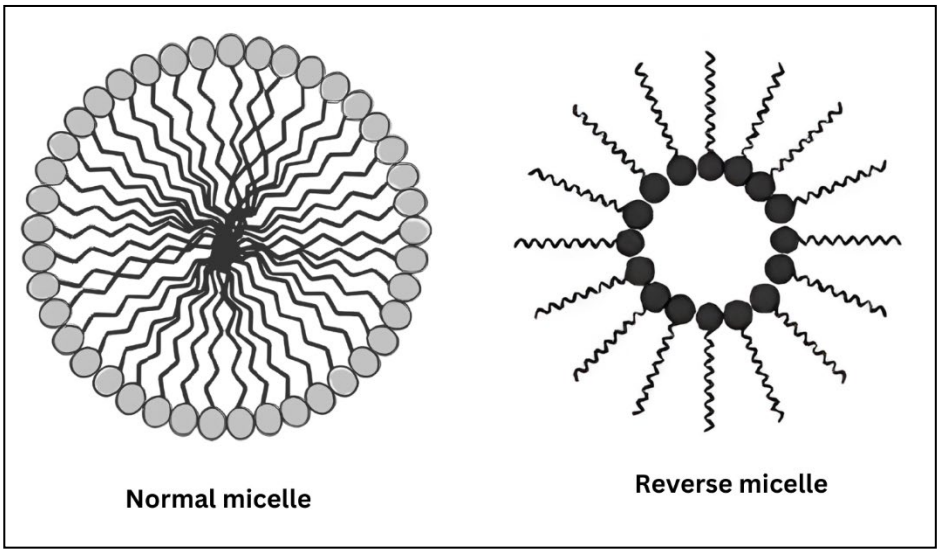

Figure 1.8: Structure of normal and reverse micelle [52].

Micellar solution has a variety of applications including removal of pollutants from water [53], separation and removal of metal ions from dilute solutions using micellar-enhanced ultra-filtration [54], oil recovery [55], polymerization [56], drug delivery [57], as well as for electrochemical applications [58]. Micellar systems are also utilized for liquid-liquid extraction [59], which is a significant application. This extraction method is commonly employed for extracting bioactive molecules from an aqueous phase into reverse micelles within the organic phase [60]. Subsequently, the biomolecules are transported and concentrated back into the aqueous phase. Utilizing reverse micelles in liquid-liquid extraction is an optimal technique for the purification of medicines, including amoxicillin [61].

1.4.2 Clouding

Clouding, also known as liquid-liquid phase separation, is a physical transformation that takes place in surfactant solutions when they are heated. In general, the behaviour of two types of surfactants (ionic and non-ionic) differs significantly in terms of their response to temperature. Non-ionic surfactant solutions, exemplified by the CiEj type (where i and j represent the number of carbon atoms in the tail and the number of oxyethylene groups, respectively), are unable to tolerate high temperatures. As a result, they experience clouding and subsequently separate into two isotropic liquids: a phase with a low concentration of surfactant and a phase with a high concentration of surfactant. This separation occurs at a specific temperature known as the cloud point (CP) [62]. Clouding, often referred to as lower consolute behaviour or coacervate phase behaviour, is a phenomenon that occurs. CP can refer to either the lower consolute solution temperature (LCST), which is the temperature at which the two phases become apparent, or the upper consolute solution temperature (UCST), which is the temperature below which the two-phase region is present (**Figure 1.9**).

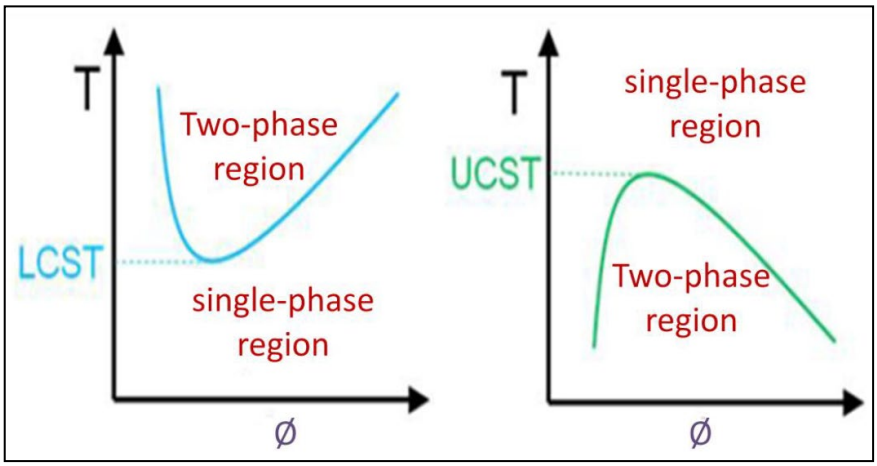

Figure 1.9: Temperature v/s Surfactant Volume Fraction (ϕ).

The CP phenomenon has been observed in various applications across diverse fields [63–65]. However, the underlying mechanism of this phenomenon remains unclear and is a subject of controversy between different groups [66]. The occurrence of the phenomenon is believed to be a result of the effective dehydration of the hydrophilic portion of micelles upon heating. According to the Langer-Schwartz theory [67], the nucleated phase could exist either as a cluster of tiny droplets that gradually increase in size above the critical droplet size or as a single droplet that rapidly expands to a significant size. This theory draws an analogy to a surfactant solution, wherein liquid-liquid immiscibility occurs above the LCST or CP. In this case, micelles are attracted to each other, forming clusters as the CP is approached [68]. Previously, the separation of phases was ascribed to the generation of micelles, the coacervation of micelles, or variations in the structure of poly (oxyethylene) chains due to temperature. The ongoing debate centers around the roles of oscillation in critical concentration and micellar growth as potential mechanisms for the clouding phenomenon. Another group suggested that the clouding phenomena are caused by interaction between micelles of non-ionic surfactants through an attractive potential, which becomes stronger as the temperature increases [69]. Additionally, according to lattice gas theory, it has been shown that the CP results from a sudden enhancement in rotational entropy, brought about by the rapid disruption of hydrogen bonds between water and surfactant heads [70]. Recent investigations suggest that the clouding phenomena may be caused by the establishment of a connected micellar network or by significant orientation-based interactions among water and micellar head groups [71].

The value of CP is determined by the composition and concentration of the surfactant, as well as its resulting hydrophobic properties when additives are present. Numerous studies focus on examining mixed micelle systems and exploring the impact of additives on the solution behaviour of non-ionic surfactants. The introduction of salt to a nonionic surfactant solution induces a gradual dehydration process, leading to a reduction in the effective headgroup area and subsequently lowering the CP. A change in micelle morphology accompanies this process. Furthermore, it is widely recognized that the use of an ionic surfactant enhances the CP of non-ionic counterparts. It has been reported that the increase in CP by considering the surface charge per micelle, contributes to electrostatic repulsion between the micelles [72]. It has been suggested that clouding and phase separation cannot be observed in aqueous solutions of ionic surfactants because of the electrostatic repulsion between the charged headgroups or micelles. In ionic surfactant solutions, the interactions between water and headgroups are strengthened by ion-dipole interactions, making it difficult for hydrogen

bonds to break upon heating— which is the primary cause of clouding in non-ionic surfactant solutions. Interestingly, the occurrence of a cloud point was initially reported by Yu and Xu [73] in the case of an aqueous solution containing tetrabutylammonium tetradecyl sulphate (TBATS), an anionic surfactant. It has been noted that the cloud point decreases with an increase in the concentration of TBATS.

The clouding phenomena are extensively utilized for the extraction and pre-concentration of diverse analytes. The use of this strategy was initially proposed by Watanabe *et al.* [74]. In the past twenty years, cloud point extraction (CPE) has become significantly more common than conventional extraction techniques (such as solvent extraction) for separating environmental [75,76] and biological samples [77,78] of interest. Subsequently, the approach was widely utilized as a key process for separating and purifying proteins. Paleologos *et al.* [79] provided a comprehensive overview encompassing the fundamentals, methodology, and applications of the CPE technique. Until now, CPE has been predominantly employed for the pre-concentration of analytes, utilizing non-ionic surfactant systems [80]. However, the effectiveness of CPE in extracting thermally sensitive substances is often constrained, particularly when the surfactant solution exhibits a high CP, or when a significantly elevated temperature, surpassing the CP, needs to be sustained for an extended period to facilitate optimal extraction [81,82]. This challenge can be addressed by employing surfactants with CP values close to ambient temperature. Regrettably, the practical application of ionic supramolecular assembly-based separations has encountered difficulties, as the occurrence of the clouding phenomenon is rare in charged surfactant systems. Theoretical and practical perspectives find conditions that cause clouding in ionic supramolecular systems interesting. A recent study conducted a thorough examination of the application of supramolecular solvents for extracting organic compounds [83]. Cloud point extraction methodology (CPEM) refers to the approaches used for extracting compounds by using the cloud point phenomenon. CPE shows potential as an alternative to hazardous solvent-based extraction techniques, making it beneficial in the context of green chemistry principles.

1.4.3 Solubilization

Micellar solubilization is an interesting property of surfactants, involving the increased solubility of hydrophobic substances in water due to the production of micelles (as seen in **Figure 1.10**). This property has been widely employed in environmentally friendly methods for solubilizing specific quantities of organic compounds or drugs over the past few

decades [84]. The number of organic components can be increased by increasing the dehydration of micelles through the application of various stimuli (such as additives or temperature), leading to a more hydrophobic environment [46].

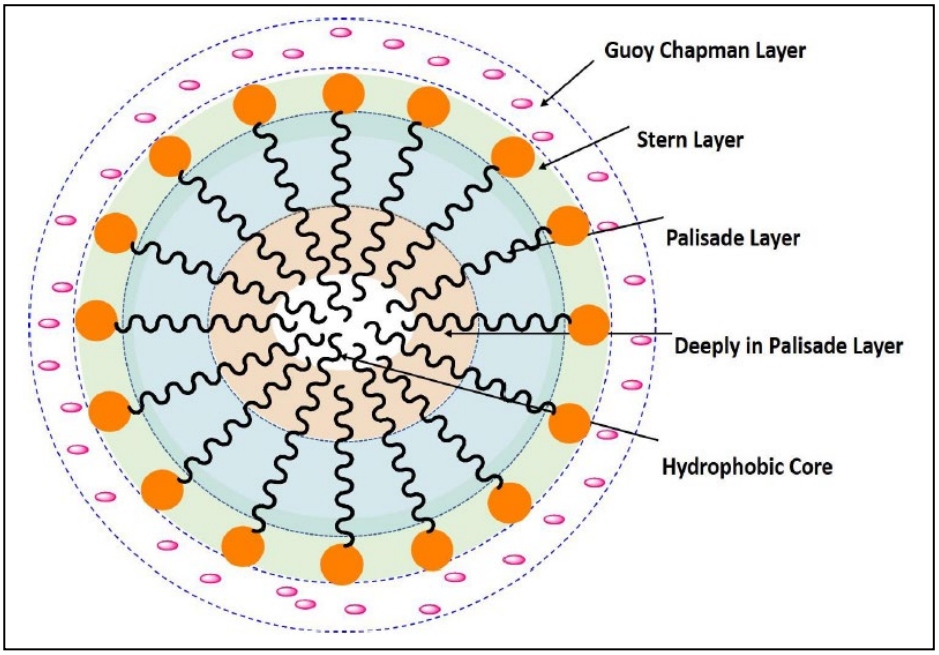

Figure 1.10: Various solubilization sites of the normal micelle.

Numerous research has been performed to find the specific location of a solubilizate within a micelle at various sites. The location of additive solubilization may vary depending on its polarity or charge, and potential sites include the following:

- Small polar molecules or hydrophobic species with opposing charges are located near the surface within the palisade layer or attach to the interface between the micelle and water.
- Short-chain phenols that are solubilized in nonionic surfactants are situated between the polyoxyethylene chains.
- Dyestuffs, which are large polar molecules, are present in the palisade layer.
- Saturated aliphatic and cyclic hydrocarbons are located in the inner core of the micelle.
- Higher alkyl chain length aliphatic hydrocarbons are solubilized within the interior of the micelle.

However, the extent to which the solubilizate molecule can penetrate the palisade layer is determined by the ratio of polar to non-polar structures in the molecule. Compounds with longer chains and lower polarity have greater penetration depth compared to those with shorter chains and higher polarity. Additionally, the solubilizate molecule, along with its quantity, can

influence the ultimate micellar shape, size, and surface-active (physiological) characteristics [84]. Surfactant solutions have been investigated as efficient systems to improve the aqueous solubility and stability of drugs [85].

1.5 Solvents as a media for micellization

The process of micellization is greatly affected by the surrounding environment, and understanding how the environment influences self-assembly is a significant area of study. The physicochemical characteristics of the continuous medium, including polarity, ionic strength, and surface tension, play a crucial role in driving the process of micellization. A comprehensive understanding of these factors enables a more precise prediction of the morphology of the aggregates formed [86]. Extensive research has been conducted on the association behaviour of surfactants in aqueous environments, with a growing focus on exploring micellization in non-aqueous solvents. The study of amphiphile behaviour in organic polar solvents, advancements in technologies involving supercritical fluids, and the micellization of surfactants in unconventional environments have garnered scientific and technological interest. Various solvents, including glycerol, ethylene glycol, formamide, alcohols, and supercritical CO_2, have been investigated as media for the micellization of surfactants [87–89]. The objective of the present study is to explore the association behaviour of surfactants in different solvent systems including ionic environments, with a specific emphasis on deep eutectic solvents (DES), which are an analog of ionic liquid. Providing a comprehensive overview of ionic liquids (ILs) is essential, with a specific focus on DESs.

1.6 Ionic liquids (ILs)

In recent years, researchers and industrialists have been exploring alternatives to replace conventional hazardous, toxic, and flammable organic solvents. Ionic liquids (ILs) have garnered significant interest as environmentally friendly substitutes for conventional organic solvents. Their versatile applications span various fields, including catalysis, electrochemical devices, chemical synthesis, oil recovery, and pharmaceutical applications [89–91].

Salts generally possess a significantly elevated melting point as a result of their high lattice energies. Although molten salts have high melting points, often exceeding 500 °C, they are frequently employed in metal processing. The lattice energy of salts decreases with an increase in the radius of either the cation or anion. In cases when significantly large non-symmetric organic cations and anions are employed, the melting point of the salts may drop within the range of room temperature, and frequently even lower. Walden is widely

acknowledged for his role in synthesizing the first ionic liquid, ethylammonium nitrate [EtNH3]-[NO3], in 1914. This compound has a specific melting point of 12°C [92]. Ionic liquids are organic compounds that consist exclusively of ions and have melting points lower than 100ºC. This classification is subjective and has been extended throughout time to encompass mostly ionic systems, i.e. they may have molecular components but the properties of the liquids are mainly controlled by electrostatic interactions. The characteristics of an ionic liquid can be adjusted by altering the ionic constituents. This implies that the characteristics of the solvent can be controlled based on the specific requirements of a specific application. Hence, ILs have been described as designer solvents [93]. ILs often exhibit reduced volatility and enhanced thermal stability in comparison to molecular solvents. Generally, ILs are non-flammable and exhibit favorable solubility for both organic and inorganic compounds. They typically possess broad electrochemical windows, increased conductivity, and higher viscosities in comparison to conventional molecular solvents.

There are less expensive and less harmful alternatives available, however, it is important to note that these alternatives are generally less stable to heat and have a little higher tendency to evaporate, but still lower than conventional solvents. There is no universally ideal solvent for all purposes, but ionic liquids are becoming known for their ability to produce typical solvents designed for particular uses. Another category of alternative liquids gaining attention is referred to as Deep Eutectic Solvents [94].

1.7 Deep eutectic solvents (DESs)

Ionic liquids (ILs) and Eutectic solvents (ESs) have been mentioned in scientific literature for over a century [92,95]. However, their practical application gained significance much later, around the turn of the 21st century for ILs [91,96–98], and in the early 2000s for ESs [92,99]. Abbot *et al.* [99] conducted groundbreaking research on ESs by combining quaternary salts ([$Y(CH_2)_2N(CH_3)_3$] Cl, Y = OH or Cl) with $ZnCl_2$ or $SnCl_2$. They later discovered that the mixture's melting point significantly decreased (creating a deep eutectic solvent, known as 'reline') when a hydrogen bond acceptor (HBA, such as choline chloride, ChCl) and a hydrogen bond donor (HBD, such as urea) were judiciously mixed [100]. Since then, the research on DESs with a wide range of HBAs (amino acids, alditols, aromatic/aliphatic acids, etc.) has been combined with quaternary salts. Over time, DESs have been developed using hydrated transition metal halides/nitrates and organic ligands as HBDs. Recently, DESs have been created solely through hydrogen bond exchange between non-ionic

HBAs and HBDs, such as terpenoids. The progression of DES inventions is illustrated in **Figure 1.11**. One noteworthy advantage of DESs is their ability to be tailored to specific properties based on their constituents or composition, making them suitable for various scientific fields. Currently, ILs and DESs are distinct classes of materials with unique characteristics and can be considered alternatives to volatile organic compounds (VOCs). Researchers worldwide are actively working at an accelerated pace to fully explore the potential of DESs.

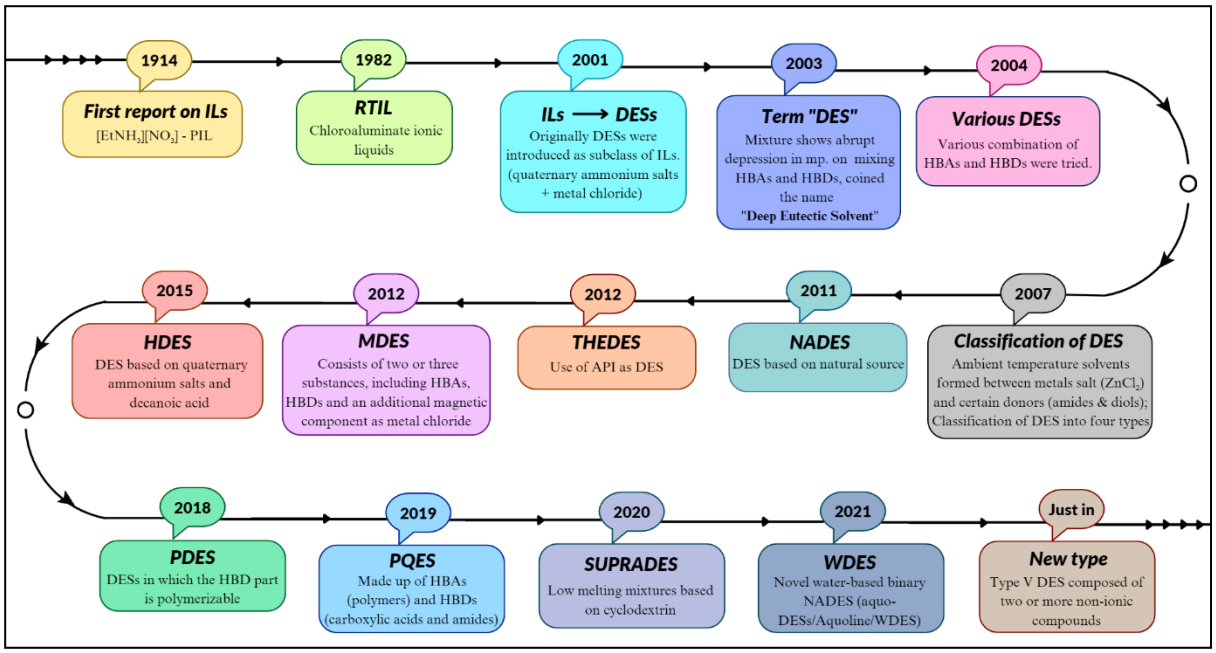

Figure 1.11: Landmarks and milestones in DES research [101].

1.7.1 Classification of DESs

The term DES was coined to describe the liquid state that forms when polar components (solids or liquids) mix through hydrogen bonding at ambient temperature. Various combinations of constituents, sources, and physicochemical properties have been explored and categorized into different classes [102–104]. In 2007, Abbott proposed a common formula for DES, RN+X-zY, where RN+ represents ammonium, phosphonium, or sulphonium cation, X is typically a halide anion (Lewis's base), and Y is a Lewis or Bronsted acid (z represents the number of Y molecules interacting with the halide anion) [105]. Based on the types of acids and bases used, DES can be classified into five types as shown in **Figure 1.12**. Type I consists of quaternary ammonium halides (HBAs) and anhydrous metal chlorides (HBDs) with low melting points. If hydrated metal halides are used instead of anhydrous ones, it is referred to as Type II DES, which has an even lower melting point due to the presence of water of hydration.

Type II DES is preferred in industrial operations due to its better economy and moisture resistance compared to Type I.

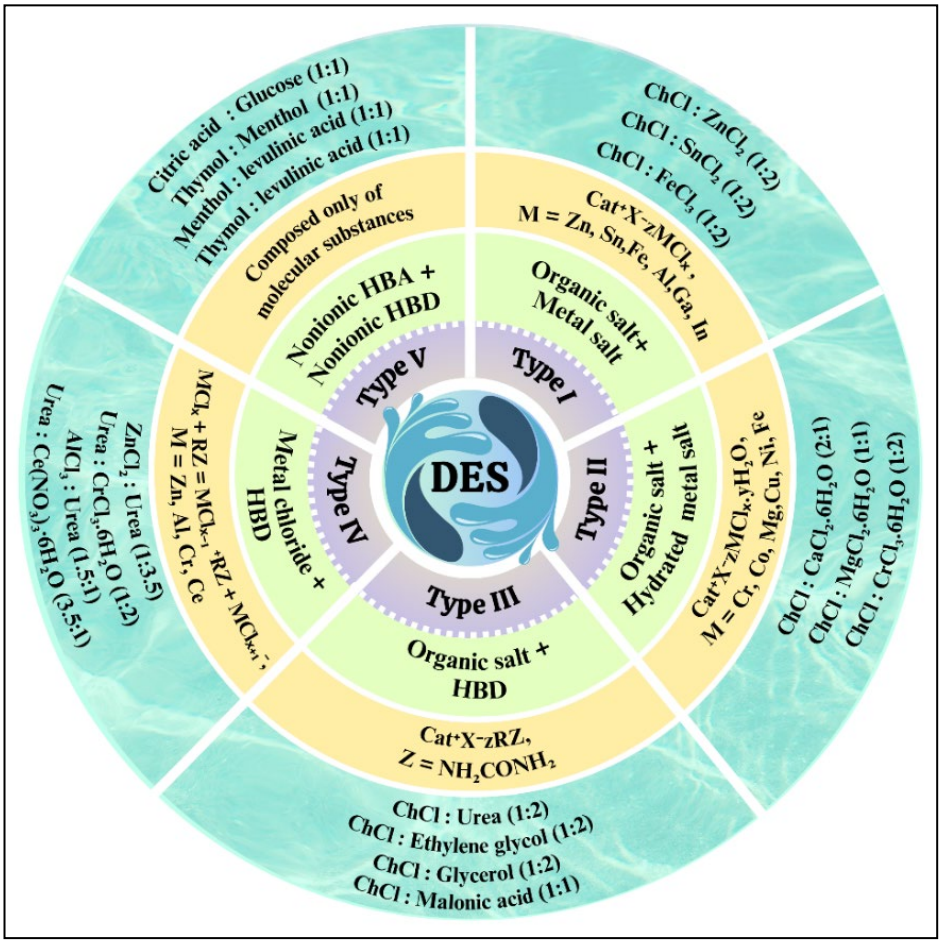

Figure 1.12: Types of DESs with some relevant examples [101].

Type III DES is a combination of HBAs and HBDs and offers readily available, affordable, and often biodegradable options. **Figure 1.13** shows a library of HBAs and HBDs used for synthesis of DESs. This class of DESs is versatile due to the availability of various HBDs [104,106,107]. Type IV DES includes eutectics of transition metal/lanthanide halides with organic ligands, which can withstand ambient temperature and possess properties such as higher surface tension, density, and lower viscosity [108–110]. A new class of DES called Type V DESs has been introduced based on non-ionic components (HBD and HBA), where a substantial hydrogen bonding network generates DES properties [111–113].

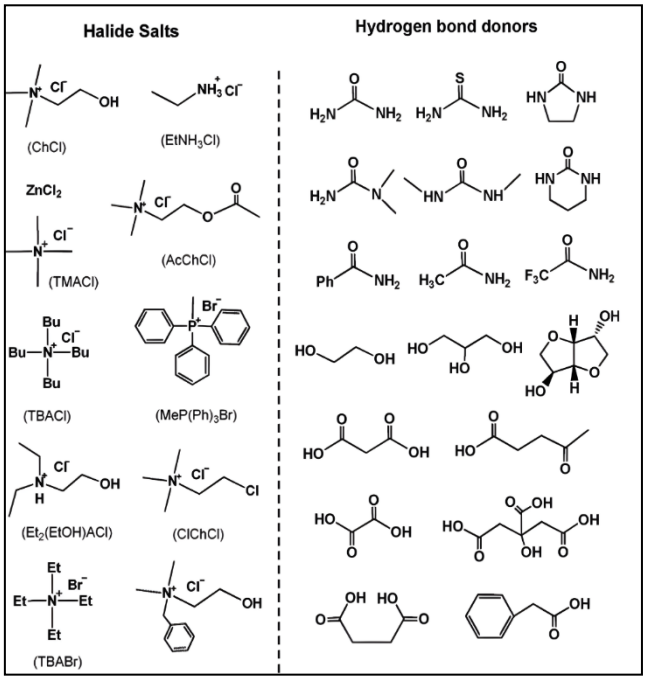

Figure 1.13: Library of HBAs and HBDs used for synthesis of DESs [104].

In addition to the above classification, other categorizations found in the literature include natural or synthetic, acidic or alkaline, ionic or nonionic, lyophobic or lyophilic (hydrophobic/hydrophilic when water is used as a solvent), therapeutic, poly-quasi, polymeric, or water-based DES. In the present work, we have used mainly type-III (reline, with and without water; water-based DES) for the micellization of conventional and gemini surfactants.

1.7.2 Natural deep eutectic solvents (NADESs)

In 2011, Choi *et al.* [114] made an important discovery regarding a special type of DES called Natural Deep Eutectic Solvents (NADES). These NADES are composed of choline chloride (ChCl) along with natural carboxylic acids and various sugars, with or without water in smaller amounts. Unlike other DESs, NADES have the advantage of being more environmentally friendly and having lower toxicity risks since they consist of naturally occurring components [114–117]. As a result, there has been a significant increase in research on NADES due to these favorable characteristics [118–121]. NADESs utilize HBD and HBA derived from plant metabolism or eukaryotic cellular systems [122]. NADESs have been proposed as potential solvents found in living cells, which could explain the higher concentrations of compounds that are typically insoluble in water [114]. One of the benefits of NADESs is that they create liquid micro-environments, thereby reducing the physicochemical limitations of metabolite transport and cellular processes [123]. The most commonly used NADESs are ChCl and betaine, mainly due to their affordability, lack of

toxicity, and biodegradability [124,125]. However, other eco-friendly and biocompatible molecules such as proline, glycine, alanine, histidine, lidocaine, acetylcholine chloride, and nicotinic acid are also utilized [126]. These DESs offer several advantages such as low melting points, low volatility, non-flammability, low vapor pressure, polarity, thermal and chemical stability, and miscibility [102,104,127–129]. Furthermore, they have a minimal environmental impact, promote efficient use of atoms, and are cost-effective with high yields. Since NADESs are formed through intermolecular hydrogen bond interactions rather than chemical reactions, they do not produce secondary compounds, resulting in reduced requirements for additional purification steps and minimizing waste generation [104,129–131].

1.7.3 Hydrophilic and hydrophobic deep eutectic solvents (HDESs)

Hydrophilic deep eutectic solvents (HPLDES) and hydrophobic deep eutectic solvents (HPBDES or HDES) are two types of DESs categorized based on their interaction with water. When DESs contain hydrophilic functional groups like hydroxyl, carboxyl, or amino groups, they fall under the HPLDES category. However, HPBDESs are unstable when in contact with water, which limits their practical applications. On the other hand, HPLDESs offer significant advantages in extracting hydrophilic substances from non-aqueous materials. Van Osch *et al.* [132] introduced the first HPBDES, which consisted of decanoic acid and long-chain quaternary ammonium salt. This development aimed to expand the applicability of DESs for handling aqueous samples. Subsequently, various HPBDES were created using different fatty alcohols, long-chain fatty acids, and long-alkyl-chain quaternary ammonium salts [132]. Another type of HPBDES, proposed by Ribeiro *et al.* [133] incorporated DL-menthol, a natural monoterpene, as the HBA, and several short-chain acids (such as acetic, lactic, and pyruvic acids) as the HBD. Other terpenes like thymol [134], camphor [135], and lidocaine [136] can also be used to formulate HPBDES. However, the presence of hydrophilic components can reduce their stability. These HPBDES have demonstrated their ability to extract various substances such as curcumin from turmeric [137], artemisinin from leaves [138], cannabinoids from raw cannabis plants [139], pesticides [140], antibiotics from water [141], drugs from human urine [142], and endocrine disruptor compounds from water [143].

1.7.4 Water-based deep eutectic solvents (WDESs)

Research studies have primarily focused on investigating the role of water in DESs through the combination of ChCl with well-known HBDs such as lactic acid [144,145],

urea [107,146–148], glycols [107,144,149–151], and sugars [144]. However, recent studies have proposed that specific mole ratios of aqueous solutions of ChCl can also function as DESs [152–154]. One example is the "water-in-salt (WiS)" non-aqueous DES (NaDES) called "aquoline," which consists of a mixture of ChCl and water in a ratio of 1:3.33 [153]. However, the solid–liquid phase diagram (SLPD) of the ChCl-water mixture has not been adequately considered in this case. Other studies have explored mixtures composed solely of water as the HBD and ChCl as the HBA. Various techniques such as Differential Scanning Calorimetry (DSC), 1H Nuclear Magnetic Resonance (NMR), and Brillouin spectroscopy have been employed to investigate these mixtures [154]. It was found that the dilution of ChCl/2H_2O with approximately 80 wt% ChCl/2H_2O content results in a eutectic mixture. Furthermore, the use of water-based DESs, such as aquoline, has been explored in the context of micellization behaviour of ionic and gemini surfactants in combination with ChCl, where water acts as the HBD [155]. Studies have also examined binary mixtures of water with other compounds such as glycolic acid (GA) and trimethylglycine (TMG) at specific molar ratios [156]. The solubility of amino acids, phenols, and carboxylic acids was measured in these DESs, and in 45 % w/w water 8 solution of GA/TMG DES. Additionally, the phase behaviour of pure ChCl and binary mixtures of ChCl and water has been investigated using calorimetric and analytical techniques by Ferreira *et al*. [157]. Thus, the major focus has been on investigating the role of water in DESs, including its potential as a DES component and its effects on phase behaviour and solubility in various DES systems.

1.8 Properties of DESs

DESs offer a safer and more environmentally friendly alternative to ILs and commonly used solution media, as they find applications in various fields [158–161]. They have a wide liquid state range, allowing them to be used at temperatures below the freezing point or above the boiling point of water. These DESs are created by blending specific constituents, known as HBAs and HBDs, in a specific mixing ratio (**Figure 1.14**). The term "deep" in DESs refers to the significant decrease in the melting point of the eutectic mixture when the two components (HBD and HBA) are combined. However, DESs face challenges due to their high viscosity, which limits their usability. The extensive hydrogen bond network formed between the components of DESs restricts the mobility of free species within the solvent, leading to increased viscosity. Additionally, DESs often have small void volumes and large ions, further contributing to their high viscosity.

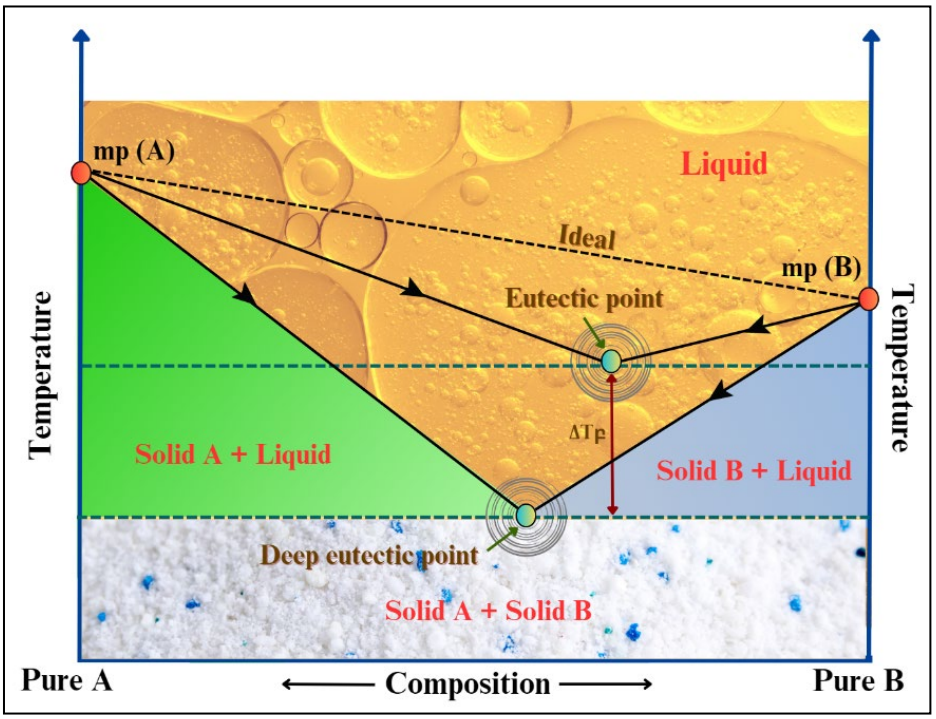

Figure 1.14: Different phases with a composition of A and B in a typical eutectic mixture [101].

Factors such as composition, molar ratio, temperature, and water content influence the physical properties of DESs. To address this issue, researchers have explored the use of water as an additional HBD in DESs. Water has been utilized to modify the properties, particularly viscosity, of DESs without affecting their structural requirements. By incorporating water into DESs or DESs mixed with water, studies have been conducted to investigate various physicochemical properties such as density, refractive index, conductivity, surface tension, etc., as well as the interactions between the components and how they change with the addition of water [146,153,154,162–164]. **Figure 1.15** illustrates the diverse properties exhibited by DESs.

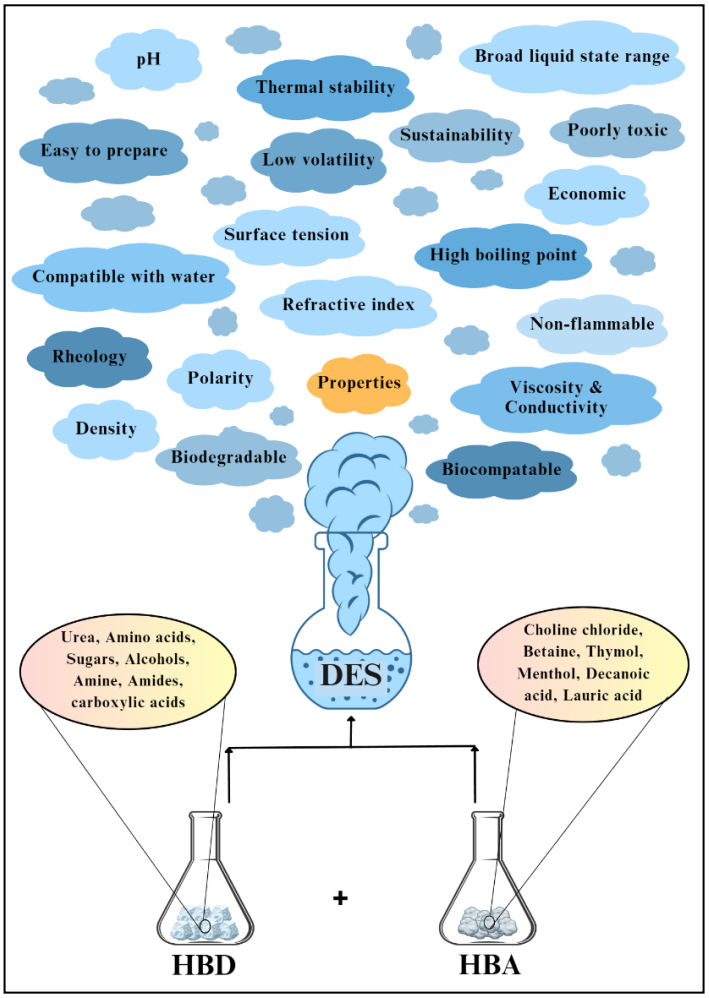

Figure 1.15: Properties and characteristics of DESs [101].

1.9 Application of DESs

DESs possess several useful solvent properties that make them suitable for dissolving various substances such as carbon dioxide, metal oxides, drugs (both natural and synthetic), and dyes [165–168]. The versatility of DES is demonstrated in **Figure 1.16**, which showcases its wide range of applications in diverse fields. Due to its high polarity, DES can act as an extractant for glycerol in the purification of biodiesel [169,170]. It can also serve as a medium for acid, base, transition metal-catalyzed, and bio-catalyzed reactions. This is significant because volatile organic solvents (VOSs) are commonly used in organic syntheses, but DES has the potential to partially or completely replace VOSs, offering a more environmentally friendly and sustainable alternative [159,171]. DES exhibits similarities to ILs, allowing it to be utilized in electrochemistry as electrolytes, solvents, or metal dissolution [172–174]. Furthermore, DES can find applications in dye-sensitized solar cells [175].

Figure 1.16: Potential applications of DES in different fields [101].

In recent times, DES has been employed as a solvent medium for the synthesis of various materials, including metal phosphates, porous materials, nanoparticles, and carbon materials. Moreover, DES has also been explored in uncharted territories, such as its role in association and clouding phenomena in surfactant systems [176–179]. Ionic surfactants are involved in the advanced oxidation processes using various oxidizing agents with or without metallic nanoparticles [180,181]. Notably, DES holds potential as a significantly less toxic and biocompatible medium, giving rise to new possibilities for the delivery of APIs. This concept is inspired by the existence of DESs naturally formed in living organisms.

1.10 Association behaviour of surfactants in DES

Over the past two decades, there has been a growing focus on studying the self-aggregation and behaviour of surfactants in polar solvents other than water. While micelles can form in both aqueous solutions and non-polar aqueous solvents, there is significantly more research focused on micelle formation in water compared to other solvents [182]. The exploration of non-aqueous media was started by Evans and his coworkers, who demonstrated the micellization of surfactants in various solvents [183]. Researchers have conducted studies on the ability of surfactants to develop amphiphilic structures including micelles, vesicles, and liquid crystalline phases in ionic liquids. The self-aggregation of surfactant in ILs occurs due to the solvophobic interaction between the tails of the surfactant and ILs. This interaction is influenced by the anionic species present in the ILs [182].

DESs as a medium for surfactant aggregation have received relatively little attention. However, in the past four years, there has been an increase in early investigations on this topic. In the first investigation by Pal *et al.* [176], utilizing fluorescence probes, electrical conductivity, and surface tension experiments, it was observed that assemblies of SDS were present in reline containing varying amounts of water, whereas this was not the case in pure reline. Furthermore, it has been reported that SDS can dissolve hydrophobic cyclohexane and create microemulsions. Various techniques such as surface tension measurements, dynamic light scattering, and small-angle X-ray scattering were employed to confirm the microstructure. The same research group later reported that cationic surfactants from the n-alkyl trimethylammonium family exhibited self-aggregation in glyceline (ChCl: glycerol; 1:2), as evidenced by fluorescence probe, electrical conductivity, surface tension, small-angle X-ray, dynamic light scattering, and transmission electron microscopy experiments. Arnold *et al.* [184] employed X-ray reflectivity (XRR) and small angle neutron scattering (SANS) to provide evidence for the belief that SDS forms self-aggregates in pure DESs, specifically reline. Furthermore, they observed that the behaviour of SDS aggregates in reline is notably distinct from that in water.

In a study conducted by Sanchez-Fernandez *et al.* [185], the morphology of SDS aggregates in reline was examined using SANS. The results again verified that the SDS molecules form cylindrical aggregates in this medium. In their subsequent investigation, Sanchez-Fernandez *et al.* [186] examined the behaviour of cationic CTAB surfactants in glyceline. The researchers utilized surface tension, X-ray, neutron reflectivity, and SANS techniques to observe the formation of globular micelles with ellipsoidal forms by these surfactants. Furthermore, the CMC values were similar to those reported in water. Additionally, a study was conducted on the influence of various counter ions on the process of micellization of SDS in DESs (reline and glyceline) [187]. The counter ion was found to have an impact on both the CMC and the morphology of micelles, similar to what is observed in aqueous solutions. The nature of HBD in the DES influences the morphology of micelles and it has been observed that more elongated aggregates are formed in reline than in glyceline.

DESs have been studied as solvents for the self-assembly of various amphiphilic substances, such as lipids [188], proteins [189], and polymers [190]. The study indicated that reline can enhance the process of phospholipid self-assembly into vesicles. Additional research has demonstrated that lysozyme and bovine serum albumin can form organized structures when placed in DES and when mixed with water [189]. The configuration of poly (ethylene oxide)

(PEO) was examined in DESs containing ethyl or butyl ammonium bromide and a molecular HBD, such as glycerol or ethylene glycol [190].

As can be seen from the previous sections of this chapter, surfactants and DESs are two important classes of materials that have various potential applications in chemical sciences, pharmaceutical sciences, and material sciences together with future cutting-edge technologies [101,173,191,192]. looking into this subject, it is desirable to conduct a systematic study on the association behaviour of surfactants in DESs to unravel the potential of the resultant hybrid system. Such systems can be applied to change the solution behaviour, solvent efficacy, and strategies for designing new media for sustainability and greener future technologies.

1.11 Aim and objective of the work

The main objective of this work is to examine and understand the behaviour of amphiphilic molecules (surfactants) in various solvent systems. Surfactants, which include both hydrophilic and hydrophobic parts, play an important role in the process of self-aggregation, such as micelles formation and different morphological structures. The primary goal is to acquire the physicochemical properties of DES as a unique class of solvents and an understanding of the interactions and organization of surfactant molecules in this solvent other than conventional aqueous systems. Understanding the fundamental properties of DES, such as their viscosity, polarity, pH, surface tension, conductivity, refractive index, etc., is crucial for explaining their potential as alternatives to conventional solvents.

The focus of the research is to study the micellization phenomena of surfactants in DES and DES-water mixture. Micellization plays an essential role in numerous applications, from drug delivery systems to enhanced oil recovery. The aim is to study the factors affecting micelle formation in a solvent, with a particular emphasis on the unique environment provided by DES. The study aims to identify how the micelle size, stability, and critical micelle concentration are affected by the properties of DESs.

Clouding phenomena in surfactants are another significant aspect of the thesis. The aim is to investigate the clouding behaviour of surfactants in DES and DES-water mixture. Clouding, marked by the transition of a clear solution to a cloudy state due to surfactant aggregation, is influenced by factors such as temperature, surfactant concentration, and the nature of the solvent. Understanding the phenomenon of clouding in DES explains the

thermodynamic stability of amphiphilic assemblies in these solvents, providing useful insights for potential applications in separation procedures or drug formulations.

In addition, the thesis aims to investigate the solubilization of the drug (curcumin) in DES. The objective is to investigate the capability of amphiphilic molecules in DES to solubilize hydrophobic drugs, a crucial aspect of pharmaceutical applications. By studying the solubilization behaviour, the research aims to identify optimal conditions for maximizing drug solubility in DES, considering factors such as surfactant type, concentration, and the specific DES composition. This investigation has implications for the development of novel drug delivery systems with improved bioavailability and therapeutic efficacy.

To summarize, the objective of the thesis is to enhance the understanding of the behaviour of amphiphilic molecules in different solvent systems, particularly focusing on the unique properties and potential applications of deep eutectic solvents. The research aims to investigate the physicochemical properties of DESs, explore micellization processes and the clouding behaviour of surfactants, and examine the solubilization of drugs in DES and DES-surfactant systems. The purpose of this comprehensive method is to offer a significant understanding of the interaction of amphiphilic molecules with various solvents (DESs), which will facilitate progress in a wide range of scientific and technical fields.

1.12 Constitution of the thesis

The thesis entitled "Association of Amphiphilic Molecules in Various Solvent Systems" consists of seven chapters including: **Chapter 1:** General Introduction; **Chapter 2:** Materials and Methodologies; **Chapter 3:** Preparation, Characterization, and Physical Properties of Deep Eutectic Solvents; **Chapter 4:** Micellization of Various Surfactants in Deep Eutectic Solvents; **Chapter 5:** Clouding Phenomenon of Ionic Surfactant (+TBAB) in Deep Eutectic Solvents; **Chapter 6:** Solubilization of Curcumin with and without Additives in Deep Eutectic Solvents; **Chapter 7:** Overall Conclusion.

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