Executive Summary of the PhD thesis entitled

"Association of Amphiphilic Molecules in Various Solvent Systems"

To be submitted to

The Maharaja Sayajirao University of Baroda

For the Degree of

Doctor of Philosophy

In

Applied Chemistry

By

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❖ Introduction:

Amphiphiles are organic compounds with hydrophilic (water-attracting) and lipophilic (oil-attracting) properties [1]. These molecules are composed of a hydrophilic head and a hydrophobic tail that are linked together by a covalent bond. The distinct molecular configuration of amphiphiles allows them to develop into a wide range of structures, such as micelles, vesicles, and bilayers [2,3]. These structures play a crucial role in biological membranes and cellular physiology. Lipid bilayers have vital roles in delineating the structural boundaries of cells and organelles [4]. This class of substances includes surfactants, lipids, fatty acids, and polymers, each playing unique roles in scientific research and industrial sectors [5].

Surfactants, also known as surface-active agents, are molecules that have both a polar head group and a long hydrocarbon tail. The hydrophobic tail typically contains 8-18 carbon atoms, whereas the hydrophilic head can be either ionic or polar, with different properties [1]. Surfactants are categorized according to the charge of their head group as anionic (negatively charged), cationic (positively charged), non-ionic (no charge), and zwitterionic (both negatively and positively charged) [1]. Gemini surfactants consist of two amphiphilic units connected by a spacer. The features of these surfactants can be modified based on the characteristics of the spacer, such as its length, rigidity, and polarity [6]. Surfactants of many forms have important functions in both industrial applications and scientific research, making substantial contributions to fields such as detergent formulation, biomedicine, and materials science [7,8]. **Figure 1** represents structures of examples of different types of surfactants.

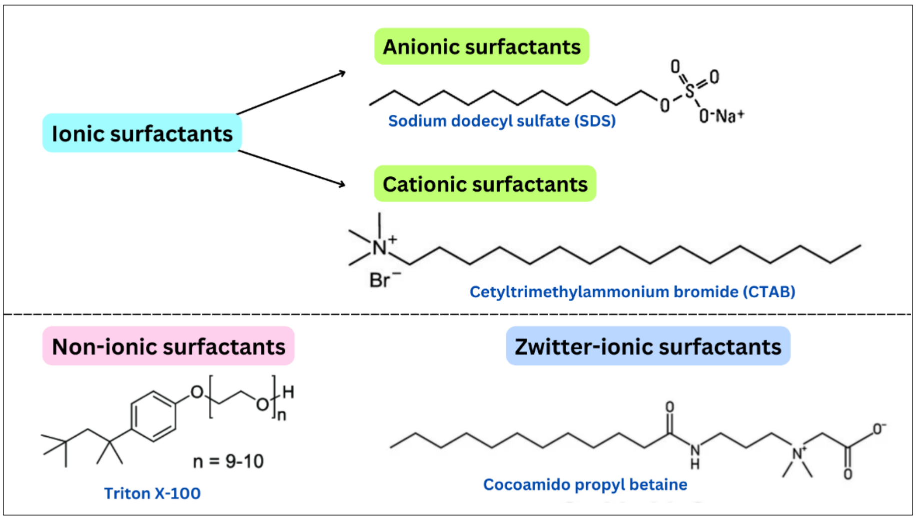

Figure 1: Structure of examples of different types of surfactants.

Surfactant solutions exhibit a range of phenomena, such as micellization, clouding, and solubilization, which have significance for applications in biological studies and industrial processes. Surfactants exhibit an ability to form aggregates known as micelles, which are governed by factors such as the length of the hydrophobic chain and the characteristics of the head group. The critical micelle concentration (CMC) is the minimum concentration at which micelles are formed due to the combined effects of hydrophobic interactions and electrostatic forces [1,9]. Micelles, which are usually spherical when in water, can assume other forms under particular conditions, such as changes in temperature or the presence of electrolytes. Supramolecular assemblies have a wide range of uses in various disciplines such as pollution removal, metal ion extraction, and liquid-liquid extraction. This demonstrates their versatility and significance in scientific and industrial settings [10–12].

Clouding in surfactant solutions refers to the phenomenon of liquid-liquid phase separation (LLPS) that occurs when the solution is heated. This effect is particularly apparent in non-ionic surfactants that have specific cloud points (CP) [13]. Mechanisms include the process of removing water from hydrophilic heads and the formation of micellar aggregates. These mechanisms have an impact on the phase behaviour and suitability of cloud point extraction (CPE) for pre-concentrating environmental and biological samples [14,15]. Micellar solubilization increases the solubility of hydrophobic compounds in water by forming micelles. This process can be controlled by additives or temperature provides ecologically acceptable approaches for enhancing drug solubility and allows for the inclusion of different molecules within surfactant micelles, depending on their polarity and size [16].

The environmental factors that affect micellization, such as the polarity of the solvent, the strength of ions present, and the surface tension, have a significant impact on the surfactant self-assembly, prompting extensive research into micellization behaviours in aqueous and non-aqueous solvents, including deep eutectic solvents (DES) analogous to ionic liquids (ILs). Abbot et al. [17] carried out pioneering research on eutectic solvents (Ess) by mixing quaternary salts ($[Y(CH_2)_2N(CH_3)_3]Cl$, Y = OH or Cl) with $ZnCl_2$ or $SnCl_2$. Subsequently, it was found that the melting point of the combination lowered drastically, resulting in the formation of a DES called 'reline'. This occurred when a hydrogen bond acceptor (HBA), such as choline chloride (ChCl), and a hydrogen bond donor (HBD), such as urea, were combined in a eutectic ratio [18]. Recent studies have proposed that specific mole ratios of aqueous solutions of ChCl can also function as DESs [19–21]. One example is the “water-in-salt (WiS)” DES called “aquoline,” which consists of a mixture of ChCl and water in a ratio of 1:3.33. In the context of DESs, the term "deep" refers to a significant reduction in the melting point of the eutectic mixture that occurs when the two components (HBD and HBA) combine. However, DESs have challenges as a result of their elevated viscosity, which restricts their practicality. **Figure 2** represents the phase diagram of DESs.

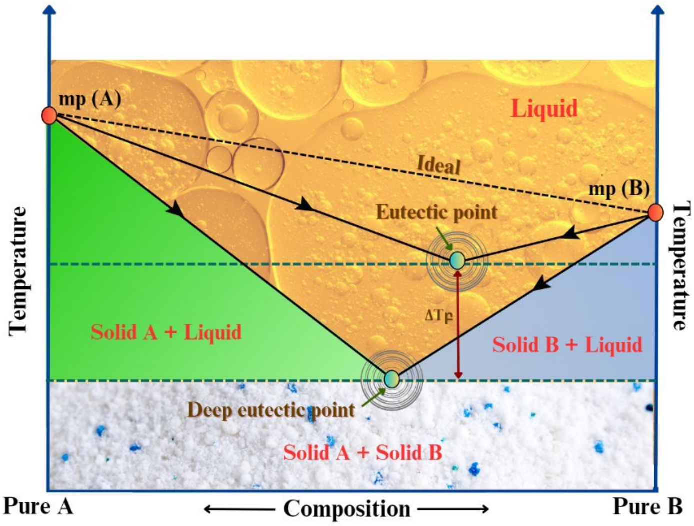

Figure 2: Different phases with a composition of A and B in a typical eutectic mixture.

In recent decades, there has been an increase in studies focused on understanding the process of surfactant aggregation in ILs and DESs. Surfactants like sodium dodecyl sulfate (SDS) and Cetyl trimethyl ammonium bromide (CTAB) have been demonstrated to form micellar structures in DESs like reline and glyceline, which impact their shape and CMC. Techniques such as SANS (Small-Angle Neutron Scattering), X-ray reflectivity, and fluorescence probes provide evidence that different micellar forms are formed in DESs.

❖ Brief Research Methodology:

Surfactants, consisting of hydrophilic and hydrophobic components, have a significant impact on self-aggregation processes, such as the formation of micelles and various morphological formations. Different types of aggregated structures can be formed in surfactant solutions, depending on the characteristics, concentration, and chemical composition. Micellization plays an important role in various applications, including drug delivery systems and increased oil recovery. DESs can be synthesized by combining and heating their components in a eutectic ratio, or by dissolving each component in a suitable solvent and subsequently allowing the solvent to evaporate [22]. DESs can be produced efficiently by utilizing cost-effective quaternary ammonium chloride (ChCl), phosphonium, or sulfonium cation salts (HBA) and HBDs through simple synthesis methods, without requiring additional purification. The nano-structure of DES, with or without water, can influence the aggregation behaviour of surfactants. DESs exhibit a unique morphology of micellar aggregates, which are spherical in water but adopt an ellipsoidal to rod-shaped structure in DESs. Micellar solutions have been employed in several applications such as drug solubilization and delivery, extraction, reaction medium, and increased oil recovery, among others.

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.

Chapter 1 provides a general introduction, covering the literature on surfactants, micellization/solubilization in different solvents, and the classification and properties of DESs. This chapter includes a thorough examination of amphiphilic compounds, with a specific emphasis on surfactants and their diverse range of uses. The chapter also explores the processes related to surfactant solutions, such as micellization, which occurs when surfactant molecules gather into micelles at a specific concentration value. The difference between current demand and available research has been recognized, and the conducted experiments are also introduced in this chapter.

Chapter 2 is devoted entirely to the materials and methodologies that were employed in the research. The chapter includes a list of the sources of material used in the study, structures of material used for the study, and preparation of samples, followed by a description of the experimental technique applied. These techniques include Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (^{1}H NMR), UV-visible absorption spectroscopy (UV-Vis), fluorescence measurement, rheological measurements to determine viscosity, electrical conductivity measurements to assess ion mobility, pH measurements, surface tension measurements using the Du Nouy ring method, density measurements, contact angle measurement, and polarizing optical microscopy (POM).

Chapter 3 outlines the methodologies for preparing, characterizing, and analyzing the physical properties of various DESs. It encompasses the methods used to prepare type-III DESs, water-based DESs, hydrophobic DESs, and ternary DESs. The synthesis methodology generally utilizes the thermal method, which involves heating and stirring the components to generate a uniform mixture, followed by vacuum drying to remove moisture. Various types of DES, including reline, ethaline, glyceline, and aquolines, were prepared by combining

ChCl with certain HBDs in specific molar ratios. The chapter emphasizes the synthesis of hydrophobic DESs (HDES) and ternary DESs (TDES) using specific eutectic-forming components. This chapter also includes the characterization methods (1H NMR and IR spectroscopic) used for DES characterization. In addition, the study assessed the physicochemical characteristics of the DESs, such as viscosity, surface tension, conductivity, density, and refractive index. The analysis highlights the significance of these characteristics in assessing the suitability of DESs for particular applications, therefore contributing to the preservation of materials and energy in industrial processes.

In **Chapter 4**, the main emphasis is on the micellization of different surfactants in DESs. The study examines the mechanisms of these processes in diverse DES environments, including reline-water mixtures and aquolines. The chapter emphasizes the critical role of surfactant micellization. The study examines the CMC of conventional and gemini surfactants using fluorescence techniques. It shows the impact of DESs, specifically aquolines, on micellization compared to pure water. The results indicate that the micellization process is affected by the polarity of the solvent and the interaction between surfactant molecules and the solvent environment. This chapter also includes the impact of different salts on the process of micellization in aquolines, focusing on the influence of potassium and sodium salts on dodecyl trimethyl ammonium bromide (DTAB). The findings reveal that the addition of these salts might cause considerable changes in micellization behaviour.

In **Chapter 5**, the phenomenon of clouding in the presence of the anionic surfactant SDS + tetra-n-butylammonium bromide (TBAB) in DESs and their combinations with water were investigated. It also includes the impact of varying concentrations of SDS and TBAB on the CP. The findings indicate that higher concentrations of SDS increase CP, whereas higher concentrations of TBAB result in a decrease in CP. In this chapter, the CP values in both aqueous solutions and DES mixture were studied, finding that DESs typically lead to greater CPs as a result of their impact on micellar structures. The chapter also explores the impact of metal salts, namely $ZnCl_2$ and $CdCl_2$, on the CP behaviour of the SDS + TBAB system in reline-water combinations. The results determine that $CdCl_2$ enhances the CP, while $ZnCl_2$ decreases it, as a result of the distinct interactions among metal ions, TBA^+, and the DES-water network. The study determines that the clouding phenomenon in these systems is intricate and affected by various elements, such as the concentration of surfactants, the composition of DES, and the existence of metal ions.

Chapter 6 focuses on the solubility and photophysical properties of curcumin (CCM) in different DESs, such as reline, glyceline, ternary DESs, and aquolines. The study also examines the effects of surfactants and salts on CCM solubility and photophysical behaviour. The study employs UV-visible and fluorescence spectroscopies to investigate these interactions. This chapter emphasizes the potential of DESs to increase the solubility of CCM, hence expanding its practical uses. The study shows that DES can significantly improve the solubility of CCM, both with and without the addition of surfactants and salts. This chapter also highlights the significance of comprehending the solubilization mechanisms of CCM in different solvent systems, which will facilitate future research in enhancing curcumin-based formulations for medicinal and pharmacological purposes.

The study covers the synthesis and characterization of DESs, micellization, clouding phenomena, and solubilization processes of surfactants and CCM. **Chapter 7** describes the overall conclusion of this thesis. It provides a comprehensive summary of the research.

❖ Key Findings:

The thesis presents a comprehensive study of the association behavior of surfactants in various solvent systems (focusing on DESs). DESs are effectively used for micellization of conventional and some gemini surfactants. Factors such as DES composition, counterion binding, and micellar architecture influence the clouding phenomenon. The DES-surfactant system was employed for solubilizing water-insoluble substances (CCM), and the system is also optimized for future applications. The potential of DESs, surfactants, and salts in enhancing the solubility and fluorescence properties of CCM, with implications for its extraction, formulation, and analysis was highlighted. This study reflects the unique features and interactions of DESs, which may be tailored depending on specific purposes. Consequently, DESs hold great potential for improving solubility and improving a wide range of industrial and pharmaceutical processes.

❖ Conclusion:

The study involved the synthesis and characterization of different DESs, studying their physicochemical properties, and evaluating their potential as alternative solvents. Various spectroscopic and physicochemical methods, including FTIR, NMR, UV-vis spectroscopy, rheology, conductance, and contact angle measurements, were used to analyze DESs and explore their interactions with surfactants and additives. The study of micellization revealed the impact of DESs, reline-water mixtures, and aquolines on the behaviour of surfactants, emphasizing the significance of water and salts in influencing the CMC and the properties of micelles. The clouding phenomenon of SDS in the presence of TBAB was explored, showing the effect of solvent composition, counterion binding, and micellar structure on clouding behavior. In addition, the solubility and fluorescence behaviour of CCM in DESs (reline, glyceline, ternary DESs, and aquolines) was studied using UV-visible and fluorescence spectroscopy. The outcomes concluded that surfactants and salts can enhance the solubility of CCM, with cationic surfactants being particularly effective.

❖ Recommendations and Suggestions:

To improve the understanding and application of DESs, additional studies should be performed to examine their physicochemical characteristics, optimize surfactant systems, and explore drug solubilization efficiency. DES-surfactant systems have been shown to increase the aqueous solubility of insoluble drugs in water. It is suggested to emphasize the application of green chemistry, adopt a multidisciplinary approach, and establish standards for the preparation and characterization of DES. Furthermore, conducting long-term stability research is essential to assuring reliability. By prioritizing these areas, researchers can use the potential of DESs and surfactant systems, resulting in progress in basic research and practical implementations, while reducing the environmental impact of chemical processes.

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