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Thermo-acoustical analysis of sodium dodecyl sulfate: Fluconazole (antifungal drug) based micellar system in hydro-ethanol solutions for potential drug topical application

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ABSTRACT

Micellar systems hold excellent drug delivery applications due to their capability to solubilize a large number of hydrophobic and hydrophilic molecules. In this present work, the mixed micelle formation between the anionic surfactant sodium dodecyl sulfate (SDS) and the 'Azole' derivative antifungal drug fluconazole (FLZ) have been studied at four temperatures in different hydro-ethanolic solutions. The critical micelle concentration (CMC) was determined by specific conductance techniques and the experimental data was used to calculate several useful thermodynamic parameters, like standard free energy, enthalpy and entropy of micelle formation. Early micellization was found with critical micelle concentration shifting towards lower concentration (CMC) than the standard concentration of SDS in water at 25 °C suggesting that drug and the solvent system facilitates the micellization process. In addition, the transport properties were examined by employing controlled approaches likely, apparent molar volume (ϕ_v), apparent molar adiabatic compression (ϕ_k), and isentropic compression (κ_s) of SDS in presence of FLZ. These parameters revealed the existence of intermolecular interactions within the molecules. Therefore, this study would cast light on utilizing surfactant immobilized FLZ system for better topical biological action.

1. Introduction

An increased number of serious fungal infections caused by opportunistic and pathogenic fungi were reported in early 1990s [1]. However to date, fungal infection poses a continuous and serious threat to human health and life. Healthy individuals are susceptible to a host of superficial, cutaneous, subcutaneous and in certain instances, systemic infections that cause a variety of conditions ranging from foot and nail infections to severe life threatening disseminated diseases [2]. Antifungal drugs are employed worldwide and lend to one fourth of all prescriptions that account for half of the allocated drug budget in infirmaries. Out of the available antifungal drugs for treatment of fungal infections especially caused by *Candida species*, the azoles, and particularly fluconazole (FLZ), has been most commonly utilized drug candidate [3]. Fluconazole exhibit activity against a wide range of yeasts, moulds, rusts and mushrooms such as *Blastomyces dermatitidis, Candida species, Coccidioides immitis, Epidermophyton species, Histoplasma capsulatum, Microsporum species*, and *Trichophyton species etc.* [4]. Rationally, FLZ inhibits the ergosterol which is the main component of fungal cell membrane. It inhibits 14 α-demethylase resulting in a decreased ergosterol synthesis and causes the accumulation of 14 methylated sterols, thus, prevents the 14-α demethylation of lanosterol into ergosterol in the ergosterol synthetic pathway [5]. Unfortunately, the widespread use of FLZ has led to the appearance of resistance among various fungal species, importantly *Candida species* and also exhibits a decrease susceptibility to other drugs (*e.g.* Itraconazole) [6]. The hydrophobic nature of FLZ poses problems in a suitable topical dosage form for topical delivery. Hence, for the solubilization of FLZ, micellar system could appear to be an alternative approach.

The interactions of drug which could occur throughout formulation, storage and pharmacological actions are commonly categorized as physico–chemical interactions. The colloidal properties

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of such drugs are mostly determined by the nature of aromatic ring system of their hydrophobic moieties. Such drugs are considered as practicable for examining the relationship between molecular architecture and physico–chemical properties. It is believed that the behavior of these drugs can be modified in solutions due to the presence of substituent's on the hydrophobic core or variations in the hydrocarbon chain length [7]. In this context, the understanding the mechanism of interaction of drug with surfactant micelles are believed as significant in designing a drug formulation or delivery system.

Micellar delivery systems have gained great attention for delivery of hydrophobic agents for systemic and local treatment [8,9]. A similar kind of literature [10–13], reveals the importance of micellar interactions. On the other hand, micellization process is a result of a delicate balance of intermolecular forces, including hydrophobic, steric, electrostatic, hydrogen bonding and van der Waals interactions. Since, both the surface activity and micellization have implications on the biological efficacy of many drugs, many pharmaceutical formulations consume surfactants for water insoluble drugs or as solubilizers in the micelles for desired applications as micelles which can incorporate or intact the other molecular species, such as drugs in their micellar structure [14].

Therefore, in the present study, an anionic surfactant, *i.e.* sodium dodecyl sulfate (SDS), an organosulfate comprising of a 12 carbon tail attached to a sulfate group, having amphiphilic properties was selected. Biologically, it also possesses its use as pre-operative skin cleanser with antimicrobial profile, as well as, in medicated shampoos and tooth paste. In recent time, micelle formation in hydro-ethanol solutions is an area of attention for investigators. Hydro-ethanol systems have been considered because of their functional high rate of diffusion through skin membrane (epidermis or dermis) and widely utilized in cosmetic and pharmaceutical topical products [15]. Therefore, three hydro-ethanol compositions (10, 20 and 30)% v/v were taken into consideration in order to understand the effect of ethanolic hydrocarbon chain.

Keeping in view the advantageous behavior of micellar system, the aim of this work was to evaluate micellar behavior and the interactions present between SDS and FLZ, along with temperature dependence and SDS concentration on the micellar system in hydro-ethanolic system. In particular, we employed (i) specific conductance to attain critical micelle concentration (CMC), thermodynamic parameters were calculated using CMC values, and (ii) density and speed of sound studies with volumetric and compressibility parameters. This study would therefore be valuable to tune the SDS micellar properties with regard to concentration and hydro-ethanol composition in order to design surfactant immobilized/aided drug's topical applications.

2. Experimental

2.1. Material and method

Fluconazole was obtained as a gift sample from Meridian Pvt. Ltd (Solan, Himachal Pradesh, India). An anionic surfactant; sodium dodecyl sulfate (SDS) of AR grade, and ethanol absolute was supplied by Merck Chemicals India and used as such without any purification. See table 1. Freshly prepared doubly distilled water [double distillation unit (HARCO)] was employed to carry out the entire study and was having specific conductance and pH in the range $\approx$ (1 to 4) 10^{-7} S · cm^{-1} and (6.5 to 7.0) at 25 °C, respectively.

2.1.1. Conductivity study

Specific conductance was measured as a function of SDS concentration in the presence of FLZ (3.3 mmol · kg^{-1}) using digital conductivity meter Cyber Scan CON-510. The conductivity cell was calibrated by 0.01 mol · kg^{-1} KCl sample solution supplied by Merck chemicals. The reproducibility of the conductance measurement was well within ±0.3%. The entire experiment was limited to four temperatures *viz.* (25, 30, 35 and 40) °C pertaining to minimum standard temperature and pressure *i.e.* 25 °C and relevance to body temperature which remains near to 37 °C. Circulating water from thermostat through a double walled vessel containing the solution was employed to maintain the temperature constant at ±0.1 °C.

The provenance and mass fraction purity are provided in table 1.

2.1.2. Density and speed of sound measurement

The density (ρ) and speed of sound (u) data were calculated using density and sound analyser (DSA-5000), Anton Paar, a digital high precision instrument. In general, the sample is introduced into a U-shaped glass tube that is being excited to vibrate at its characteristic frequency electronically. The characteristic frequency changes depending on the density of sample. The calibration of the instrument was carried with deionised water obtained from a Millipore-Elix system having conductivity, κ = (6.8 to 7.0) 10^{-7} S · cm^{-1} at pH 1–2. The reproducibility of the speed of sound and density measurements was ±0.2 m · s^{-1} and ±2 · 10^{-6} g · cm^{-3}, respectively. Further various parameters such as compressibility coefficient (κ_s), apparent molar volume (ϕ_v) and apparent molar compressibility (ϕ_k) were calculated by utilizing the density and speed of sound data.

3. Results and discussion

3.1. Conductometric study

Conductivity measurement is considered to be one of the best methods for determining the critical micelle concentration (CMC) of surfactant-additive system [16,17]. Specific conductance data are provided as supplementary files (S1–S3). Here, the value of CMC of SDS was obtained from the plots of the specific conductance (κ) *vs.* concentration of SDS (1.00 to 14.08) mmol · kg^{-1} containing FLZ (3.3 mmol · kg^{-1}) in hydro-ethanol solutions (10%, 20% and 30% v/v) as a solvent medium. The plot between the specific conductance (κ) and SDS concentration resulted reverse sigmoidal curves having the two straight lines, corresponding to the monomeric SDS and SDS aggregation zones, respectively; intersection of these two lines usually coincides to get critical micelle concentration (CMC) as shown in figure 1. The experimentally determined CMC values of SDS in the presence of FLZ were found to lie within the range of (6.0 to 9.8) mmol · kg^{-1}. The influence of temperature and nature of solvent (ethanol) on the degree of micellization of SDS was also evaluated and is given in table 1. It is well observed that in presence of drug at 10% and 20% v/v hydro-ethanol solution,

TABLE 1
Provenance and mass fraction purity of chemical samples studied.

Chemical name	Source	Initial mole fraction purity	Purification method	Final mass fraction purity
Fluconazole (FLZ)	Meridian	0.98	None	0.98[a]
Sodium dodecyl sulfate (SDS)	Merck	0.99	None	0.99[a]
Ethanol	Merck	0.99	None	0.99[a]

[a] Declared by supplier.