International Journal of Biotechnology and Biomedical Sciences
p-ISSN 2454-4582, e-ISSN 2454-7808, Volume 4, Issue 2; July-December, 2018 pp. 108-113

http://www.krishisanskriti.org/Publication.html

Elucidation of Binding Interactions between Sulfamethazine and Surfactants to Facilitate Drug Delivery via Drug-Micelle Aggregate Formation

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Abstract—*Surfactant systems with amphiphilic character are interesting vehicles for effective drug delivery and their ability to solubilize hydrophobic drugs in water medium is studied through complex formation of SMZ (sulfamethazine, a well-known antibiotic drug) with Sodium-dodecyl-sulfate (SDS) and Cetyl-tri-methyl-ammonium-bromide (CTAB), two well-known anionic and cationic surfactants respectively. Different bio-physical techniques like spectroscopy, microscopy and calorimetry have been used to monitor the said complex formation quantitatively. The results obtained from UV−vis spectroscopy showed the stepwise interaction between SMZ and the surfactants in the free form and under the micellar condition. Successful and stable micelle formation was supported by microscopic images. Thermodynamics of the two-step interaction was clearly revealed by calorimetric results. The former being exothermic in nature which is spontaneous and enthalpy-driven but the latter is endothermic, spontaneous and entropy-driven.*

Introduction

In recent years, great progress has been achieved for drug's targeted and controlled release via surfactant system.[1] Surfactants are amphiphilic molecules with polar head groups, which may be anionic, cationic, nonionic and zwitter-ionic. The hydrophobic tails of such surfactant molecules may be hydrogenated or fluorinated, linear or branched. It is well known that they are associated into micelles above the critical micelle concentration (CMC).[2] Surfactant systems with amphiphilic character are interesting vehicles for effective drug delivery and their ability to solubilize hydrophobic drugs in water medium is also well known. Carrying a drug to a specific target region and selective and efficient release are important from the pharmacological standpoint. A detailed understanding of the mechanism of molecular interaction between drugs and surfactants is thus an important aspect in the formulation of a new drug molecule and its effective delivery to specific targets. [3-6] Depending on the hydrophobic nature and electrical charge on the drug molecule, it can be solubilized in the inner core of the micelle, on the surface, or at an intermediate location in the palisade layer.[7-11] Surfactants also aide in the passage of active ingredients across various membranes, that must be traversed in order for the active ingredient to reach the target site. Therefore, micellar solubilization works as a smart solution for the bioavailability of sparingly soluble drug molecules. [12]

Sulfamethazine (SMZ), is a commonly used sulfonamide drug in veterinary medicine as an antibacterial compound. It has also been used in animal feeds to promote growth. SMZ drug can hinder the synthesis of folic acid in micro-organisms and eventually inhibits the increase in bacteria but do not actively kill them.[13-14] But the problem of SMZ as a pharmaceutical drug is its poor solubility to aqueous media. To solve these problems, attempts have been made through micellization of the drug with surfactants (Fig. 1). Here, we have studied the complex formation of SMZ with Sodium-dodecyl-sulfate (SDS) and Cetyl-tri-methyl-ammonium-bromide (CTAB), two well-known anionic and cationic surfactants respectively. Different bio-physical techniques like spectroscopy (UV-Vis, Infra-red), microscopy (High Resolution Optical Microscope) and calorimetry have been used to monitor the said complex formation quantitatively.

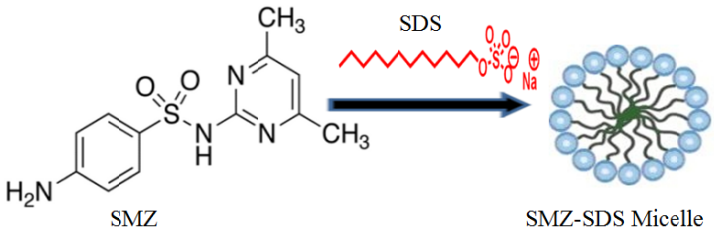

Fig. 1: Chemical structure of SMZ, sodium dodecyl sulfate (SDS) monomer and schematic representation of SMZ-SDS micelle formation.

Materials and Methods

Materials

Sulfamethazine (SMZ), Sodium-dodecyl-sulfate (SDS) and Cetyl-tri-methyl-ammonium-bromide (CTAB) were procured from Sigma-Aldrich Corporation. Samples preparation and reactions were carried out in Millipore water. All other chemicals and reagents used in this study were of analytical grade obtained from Sigma-Aldrich.

Methods

UV-Vis Absorption Spectroscopy

An Agilent, Cary 100 series UV-Vis spectrophotometer in standard quartz cuvettes of 3.5 ml with 10 mm optical path length was used to analyze the absorption spectral studies at (25±0.5) °C (298 K) . For the drug-surfactant study before recording the absorbance values, the solution was properly mixed and permitted to change state after each fraction of the surfactant to the drug solution.

FT-IR Spectrometry

The FT-IR spectra of SMZ in the presence and absence of surfactant at 298 K were recorded on an Agilent Cary 630 FTIR spectrometer in the range of 500–4000 cm^{-1}. The concentrations of SMZ was 5 µM and SDS 50 µM, CTAB 50 µM in Millipore water.

High Resolution Optical Microscopy

High Resolution Optical Microscopy, Leica DM2700 M, is a microscopy method that gives highly magnified image of a surface. The samples for High Resolution Optical Microscopy for SMZ-CTAB and SMZ-SDS were prepared by adding 5 µM of the SMZ solution to 50 µM SDS and 50 µM CTAB solution separately.

Results and Discussion

Absorption Spectral Study

Ultraviolet- visible (UV-Vis) spectroscopy is one of the most useful instrumental techniques that can investigate the macromolecular structure.[15] The UV-Vis absorption spectroscopic experiments were performed to monitor the interaction between SMZ drug and Surfactants (SDS, CTAB) and the spectral data are depicted in Fig.2.

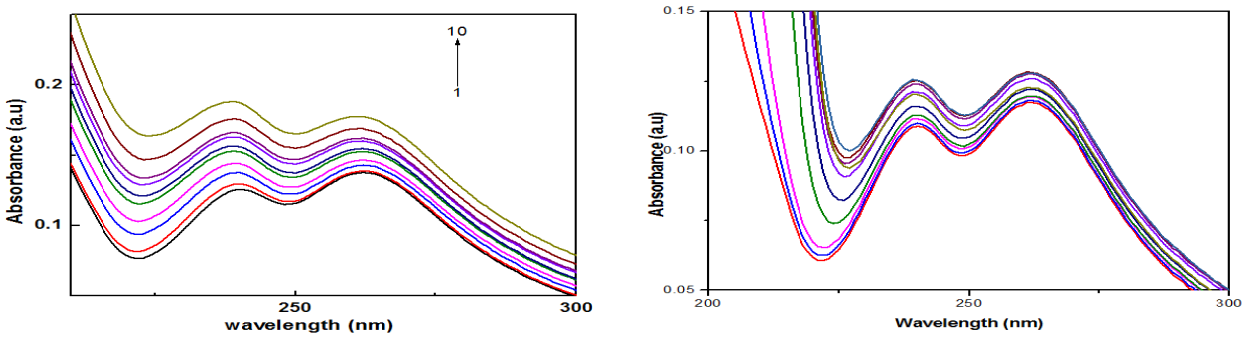

Figure 2: Absorption spectral changes of SMZ in the presence of increasing concentrations of SDS and CTAB. Curve 1-10 denotes addition of 2, 4, 6, 8, 10, 12,14, 16, 18, 20µl of (a) 10.4 mM of SDS and (b) 8.4 mM of CTAB concentrations respectively. [SMZ] = 50 µM. Temp = 298 K

The absorption spectral changes of SMZ aliquot are monitored at 260 nm (which is the λ_{max} of sulfamethazine). With increasing concentration of SDS, the absorption spectra of SMZ–SDS complex (Fig. 2a) showed a hyperchromic effect without a noticeable shift in the band position upto the critical micelle concentration (CMC). For CTAB addition, the spectral changes (Fig. 2b) were similar *i.e* it shows hyperchromic effect but there was no noticeable shift in the band position upto the critical micelle concentration at 260 nm. Increase in absorbance values indicate towards increase in solubility of the drug upon binding of drug to surfactant molecules. From the above stepwise spectral changes, we can observe the increasing solubility of SMZ with the interaction of SDS and CTAB through micelle formation.[12] Thus through significant increase in solubility of the drug via micelle formation will increase the bio-availability of the drug molecules to the target cells.

IR Spectroscopy

IR spectroscopy is an effective technique to show the changes in vibrational frequencies of the adsorbed molecule bound to a free molecule; thus it has become an integral part of biological/biomedical and pharmacological research.[16] The micelle/complex formation of SMZ-SDS and SMZ-CTAB were studied by IR spectroscopy. The IR spectra of free drug and complexes of SMZ-SDS and SMZ-CTAB is shown in Fig. 3.

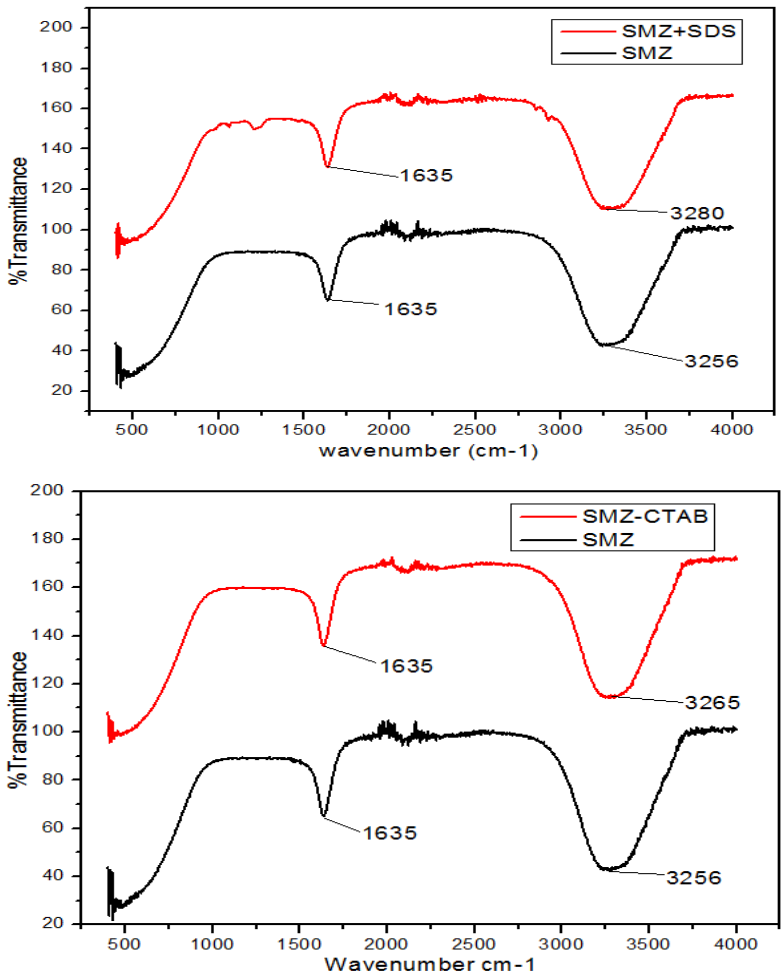

Figure 3: IR spectra of SMZ in the absence and presence of (a) SDS. (b) CTAB.

The spectra of free SMZ shows absorption band at 1635 cm^{-1} for the C=C and C=N bond, absorption band at 3256 cm^{-1} is due to N-H and C-H bond.[17] On interaction of free drug with SDS and CTAB, the complex formation of SMZ-SDS was confirmed by the shifting of N-H and C-H peak from 3256 to 3280 cm^{-1}, similarly for SMZ-CTAB complex, shifting of band N-H and C-H from 3256 cm^{-1} to 3265 cm^{-1} is observed which indicates the complex formation between the free drug and the surfactant molecule via hydrogen bonding.

High Resolution Optical Microscopic Study

Different kind of microscopic techniques including High Resolution Optical Microscopy are very effective techniques to visualize aggregate formation and to understand the shape, size, etc. of the aggregates in detail.[18-20] Here, the drug (SMZ) induced SDS and CTAB micelle formation from free surfactant and drug molecules mixture has been reported which can benefit drug delivery systems. To visualize the micelle structures the high resolution microscopic data has been used here. Figure 4 shows the interaction of SMZ with the surfactant as a representative case at room temperature. From the images at a scale of 20 μm, the SMZ-surfactant aggregated structures with a micelle shape are clearly visible. Thus the microscopic images are good evidence of SMZ-surfactant micelle complex formation. The sizes of micelles are varying between 10-20 μm range.

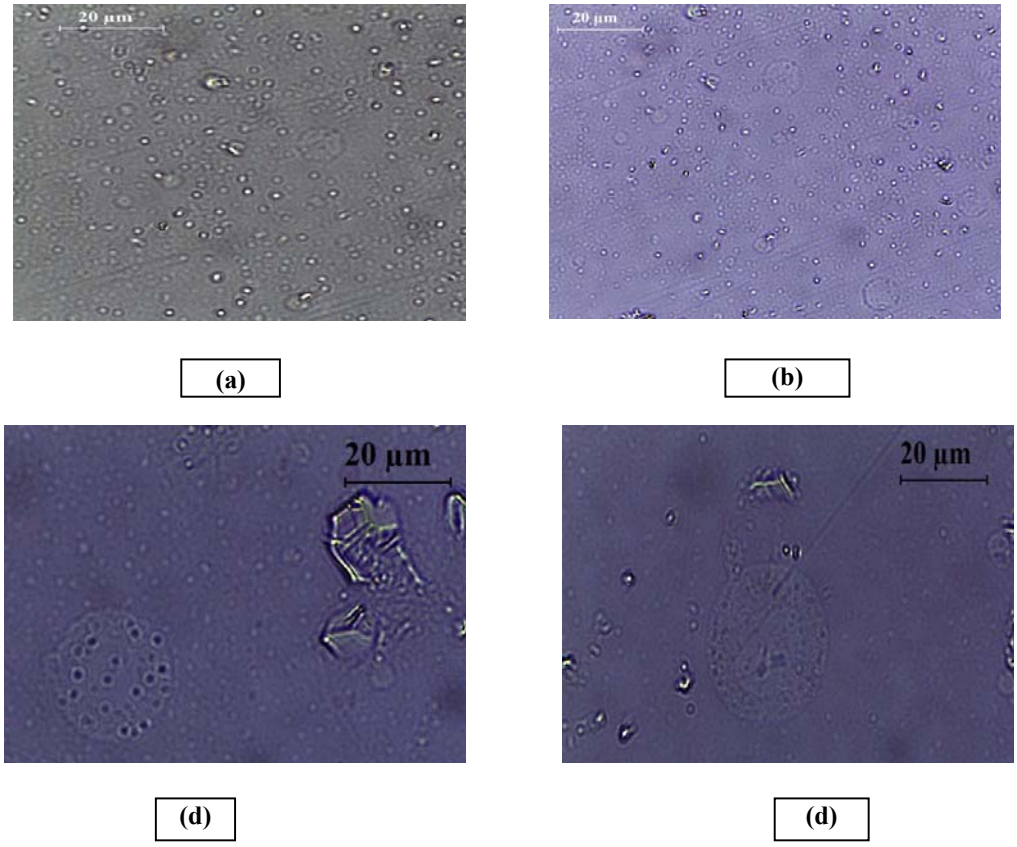

Fig. 4: High Resolution Optical Microscope, Leica DM2700 M of (a) and (b) SMZ-SDS (c) and (d) SMZ-CTAB.

Calorimetry

The energitics/thermodynamic profile of drug binding towards surfactants and micelle formation has been estimated via calorimetric studies (data not shown). Results suggested an exothermic enthalpy-driven initial electrostatic binding followed by an endothermic entropy-driven binding in the micellar core, both are spontaneous in nature. Generally the driving force for micellization is the transfer of hydrocarbon chains from water into the oil-like interior of the micelle which influences the entropy of the system. This entropic effect can be described as hydrophobic effect. The increase in entropy of the surrounding water molecules due to hydrophobic interaction is relatively less as the water molecules are usually arranged in an ordered fashion around the hydrocarbon chain.[12, 21-25] The aggregation between the SMZ and the surfactant (SDS and CTAB) molecules was mainly characterized by two steps of binding. At first, the interaction was initiated by electrostatic forces where free drug and surfactants interact and beyond the CMC, the surfactant molecules form micelles, and then the interaction is predominantly between the drug and the micelles. These data are in accordance with the UV-Vis experimental results where the anionic surfactant SDS behaves differently than the cationic surfactant CTAB. The results obtained from UV-Vis spectroscopy presented stepwise spectral change for the binding interaction between the SMZ molecules and surfactants in free form and under the micellar condition.

Conclusion

In this work we have tried to see the interaction of SMZ with two surfactant SDS and CTAB an anionic and cationic surfactant. The results obtained from UV− vis spectroscopy showed the interaction between SMZ and the surfactants (SDS and CTAB) under the free and micellar conditions. This confirmed the increase in solubility of SMZ through micelle formation which increases the bioavailability leading to effective drug delivery. The UV- Vis spectroscopy data was supported by the IR- spectral studies. The IR spectra of free SMZ gives a sharp peak at 1635 cm^{-1} for the C=C, C=N bond, Peak at 3256 cm^{-1} for the N-H, C-H bond. Upon interaction/binding with SDS and CTAB , the SMZ-SDS and SMZ-CTAB complex, shifting of N-H and C-H peak to 3280 and 3265 cm^{-1} indicates the development of hydrogen bonded structure during the course of micellization. Thermodynamics interaction was revealed by calorimetric data. The reaction is exothermic, spontaneous and enthalpy-driven. The overall process is highly spontaneous and energetically favorable. High Resolution Optical Microscope, Leica DM2700 M of SMZ-CTAB and SMZ-SDS results clearly visualized the shape of micelle formation. Therefore, the main limitation for SMZ as a pharmaceutical drug (poor solubility in water, low bioavailability & medium selectivity to target cells) can be resolved through this kind of micelle formation as drug carriers.

Acknowledgement

This work was supported from the research project CRS-M-266 funded by UGC-DAE, Mumbai Center, BARC, Mumbai. Project fellowship to AM from the same scheme is acknowledged. Gratitude to Prof. G, Suresh Kumar, Ex-Chief Scientist, Chemistry Division, CSIR-Indian Institute of Chemical Biology (IICB), Kolkata and Dr. S. Chatterjee, PDF, LSUHSC, New Orleans, USA (former SRF, CSIR-IICB), for their help and support.

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