DRUG-SURFACTANT INTERACTIONS:

A PHYSICO-CHEMICAL APPROACH

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CERTIFICATE

This is to certify that the work titled “Drug-Surfactant interactions: A Physico-Chemical Approach” submitted by “ Amrita Budhiraja” in the partial fulfillment for the award of degree of B. Tech (Biotech.) at Jaypee University of Information Technology, Waknaghat has been carried out under my supervision. This work has not been submitted partially or wholly to any other University or Institute for the award of this or any other degree or diploma.

Signature of Supervisor ……..

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Date

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ABSTRACT

In the present study, sodium dodecyl sulfate (SDS) which is an anionic surfactant and antifungal drug Terbinafine HCl which is a derivative of 'Azole' family were used to study the thermodynamic parameters and acoustical parameters through thermo-acoustic methods. The critical micelle concentrations were studied at different concentrations of SDS (1 mmol dm^{-3}- 14 mmol dm^{-3}) at different temperatures (25°C- 40°C) with the difference of 5°C in various ethanol solutions- 10%, 20% and 30%. Comparative studies were also incorporated with the addition of turmeric as excipient and marketed formulation ($THCl_m$). Further thermodynamic parameters $\Delta H°_m$, $\Delta G°_m$ and $\Delta S°_m$, viscosity coefficients A and B coefficients and the acoustical studies which involve density and sound velocity analysis using DSA (500) were also measured for all the systems to evaluate physico- chemical analysis of drug- surfactant interaction.

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Signature of Student Signature of Supervisor

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Date Date

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List of Symbols and Acronyms

SDS	Sodium dodecyl sulfate
API	Active Pharmaceutical Ingredient
THCl	Terbinafine Hydrochloride
$THCl_m$	Marketed formulation of Terbinafine Hydrochloride
β	Compressibility Coefficient
Φ_v	Apparent Molar Volume
Φ_k	Apparent Molar Compressibility
$\Delta H°_m$	Standard Enthalpy Change
$\Delta S°_m$	Standard Entropy Change

1. INTRODUCTION

1.1. General introduction

Nature always stands as golden mark to represent the exceptional phenomenon of symbiosis. She has provided a complete store house of remedies to cure all ailments of mankind. The history of plant being used for medicinal purpose is probably as old as history of mankind. These medicinal plants consider as a rich resources of ingredients which can be used in drug development, synthesis and formulation [1]. Moreover, considering that the changing patterns of infectious diseases and the emergence of microbial strains resistant to current antibiotics, there is an urgent need to find out new potent natural antimicrobial agents as adjuvants to antibiotic therapy.

Drugs are basically amphiphilic molecules as they consist of both polar (hydrophilic) and non-polar (hydrophobic) groups which contribute to the therapeutic properties of the respective drugs [2]. As a part of long term objective, present study involves a physico-chemical approach of drug-surfactant interactions involving antifungal drug Terbinafine HCl and anionic surfactant- Sodium dodecyl sulfate in presence of Turmeric in order to improve the biological profile.

1.2. Drug-surfactant interactions

Drug–surfactant interactions have received an increased attention in the recent past because of widespread applications of surfactants in pharmaceutical field [3, 4]. The physico- chemical interactions of drugs with surfactant micelles can be visualized as an approximation for their interactions with biological membranes. An important and fundamental event in the interaction of drugs with biological tissues at the molecular level is their ability to bind to membranes resulting into drug action. As many biological processes occur at the ionisable surface of membranes or along their hydrophobic region, a comparative study of the drug interaction with cationic, zwiterionic, anionic and neutral surfactants is suggested to provide useful information on the nature of drug–membrane interactions [5, 6].

Micellar systems can solubilize poorly soluble drugs, increasing their bioavailability, and therefore, may be used as drug carriers by encapsulation of the drugs, in order to ensure the transport to specific sites of action, to minimize drug degradation and loss, to prevent harmful side effects, thus improving the treatment efficacy. Chemically, the drug combines with its respective receptor which leads to the formation of a Drug Receptor Complex (DR) which generates a specific response. There are two classes of the interactions between drug and body [7]: Pharmacodynamic process and Pharmacokinetic process.

Pharmacodynamic process describes action of drug on the body and Pharmacokinetic describes action of the body on the drug. These above mentioned classes are the main reasons of Physico-chemical interactions between drug and surfactants and are also important molecules in the living organisms.

1.3. Micellization

When surfactant molecules are added to water, they have tendency to dissolve and exist in solution in their monomeric state. The further increase in the surfactant concentration, the surfactant molecules aggregates to form an organized assembly of colloidal clusters known as micelle. This phenomenon of aggregation is known as micellization. This micellization is result of the delicate balance between various repulsive and attractive forces present in their solutions [8]. The polar head of the surfactant in the micelle entity are hydrophilic in nature and are oriented towards and in contact with water molecules and the hydrocarbon tails which are hydrophobic in nature are oriented away from the water phase and in contact with one another thus forming a hydrocarbon core region.

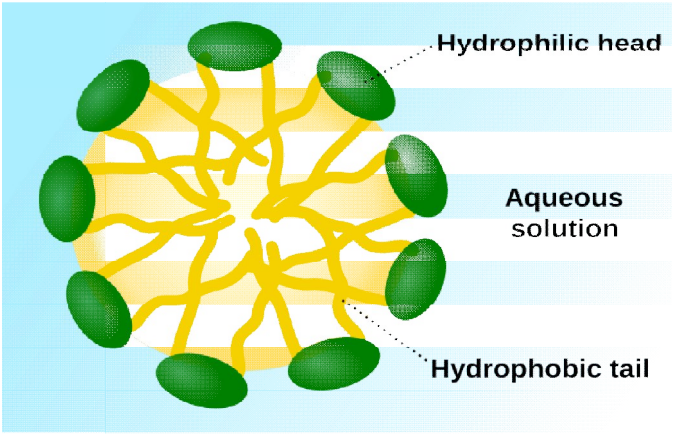

Figure 1.Structural representation of Micelle.

In order to form micelles in solution, the surfactant concentration must exceed a certain minimum surfactant concentration that is reffered to as the critical micelle (CMC). The critical micelle concentration (CMC) is the minimum concentration of surfactant required for micelles to form [9].

CMC of a surfactant is very important in determining various characteristic properties and parameters of micelles and can be utilized in formulating a pharmaceutical product for targeted drug delivery.

1.4. Fungal infections

In the past time fungi has been considered as the major source of pathogen which infect humans in systemic and superficial way. The word Fungus is taken directly from the Latin word "*fungus"* (mushroom), which in turn is derived from the Greek word "*sphongos"* which means macroscopic structures having the morphology of molds and mushrooms. The fungi are now considered as a separate kingdom and are not included in both plants and animals, from which they differentiated around one billion years ago [10]. The fungal infections are caused by microscopic organisms that invade the epithelial tissue. Fungi reproduce by spreading the microspores which can be inhaled from the air or which can come in contact with the skin directly which results in the infection. Mycosis is an infection of animals and humans caused by fungal infections. This happens due to inhalation of fungal spores or localized colonization of spores in the skin. Therefore, mycosis often starts in lungs or skin [11].

1.5. Terbinafine HCl (antifungal drug)

It is a synthetic allylamine antifungal drug, highly hydrophobic in nature. It is a white crystalline powder which is freely soluble in methanol and ethanol and insoluble in water. It is mainly used for curing skin diseases like – jock itch, athlete's foot and other type of ringworm. Basically, this drug inhibits the formation of ergosterol in fungi cell wall by inhibiting the enzyme squalene epoxidase which is responsible for cell wall synthesis and production of ergosterol. So, this leads to change in permeability of fungi's cell wall which ultimately results in cell lysis.

This is prescribed for the treatment of skin infections or fungal nail infections mainly by a dermatophyte or *Candida* species.

Terbinafine first became available in Europe and in United states in 1991 and in 1996, respectively.

On September 28, 2007, Food and Drug Administration [FDA] stated that Lamisil (terbinafine hydrochloride, by Novartis) is a new treatment approved for use by children age four and up. There are many side effects of Terbinafine HCl which are reported like- diarrhea, constipation, abdominal pain, headache etc [12].

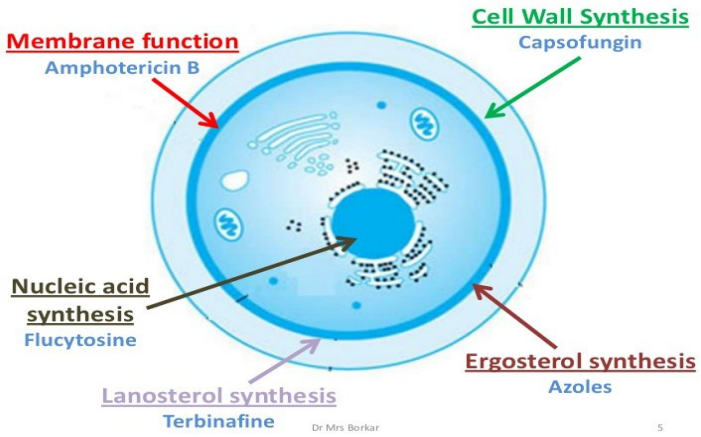

Figure2. Mechanism action of Terbinafine inhibits the Ergosterol synthesis which is an important component of cell wall synthesis.

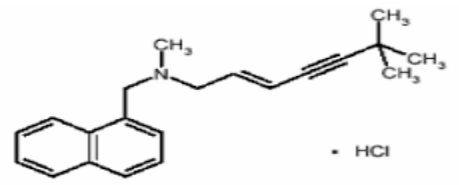

Figure3. Structural representation of drug. (N-(6,6-Dimethyl-2-hepten-4-ynyl)-N- methyl-1-naphthalene methanamine)

1.6. Surfactant: Sodium Dodecyl Sulfate (SDS)

Surfactants are amphiphilic molecules consisting of polar and non-polar parts that are hydrophilic and hydrophobic respectively which are responsible to undergo aggregation [13] which is known as micellization. This micellization or the aggregation phenomenon is the result of a delicate balance between various repulsive and attractive forces present in the solution.

These surfactants have many properties like- they act as wetting agents, solubilizing agents or emulsifying agents.

SDS is an anionic surfactant which is known commonly and is studied extensively with respect to micellization. It is mainly used as detergent in laundry and for many other cleaning purposes [14]. It is a highly effective surfactant and is used to remove the oil stains efficiently. It is found in toothpaste, shampoos, shaving cream and formulations.

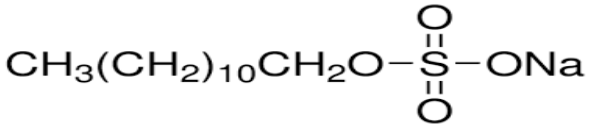

Figure4. The structure of SDS ($CH_3(CH_2)_{11}OSO_3Na$)

1.7. Turmeric

Turmeric can be defined as a spice that comes from the root *Curcuma longa*, a member of the ginger family, Zingaberaceae. In Ayurveda, it has been used for its medicinal properties. It is used to heal many health disorders like liver problems, digestive disorders, and treatment for skin diseases, wound healing and has anti-inflammatory since past [15]. Curcumin is the active ingredient in turmeric which has a wide range of therapeutic effects.

Figure 5: Turmeric plant (*Curcuma longa*)

2. Review of literature

2.1. The relevant studies related to Physico-chemical studies are presented in this section. The interest in studying drug surfactant systems starts from the increasing possibilities of their applications in a large number of formulations and associated processes [16]. A great deal of attempts is reported in literature to explore interactions between drugs with different additives including surfactants [17].

Khossravi [18] studied the Physico-chemical interactions in three modal drugs with different types of surfactants by measuring apparent permeability coefficients of drugs in the presence as well as absence of surfactants in vitro. The extent of interaction between the modal drugs and the surfactants can be best described by the hydrophobic interactions and the electrostatic interactions. For drugs that do not possess a significant hydrophobic surface area (timolol and cefoxitn), their interactios can be best described by electrostatic effect. This interaction is strong with oppositely charged surfactants. The interaction of L-692 585 with appreciable hydrophobic surface area in the presence of surfactant is due to hydrophobic effect, with the electrostatic effect playing a little secondary role. The apparent permeability coefficient of timolol as a function of the amount of surfactant in solution is modeled in light of miceller formation and entrapment or interaction of free drug with this miceller structure. Briefly, the extent of interaction as a function of amount of added surfactant for timolol indicates that initially as surfactant is added, the activity of drug for transport decreases significantly till a breaking point is achieved, after which the drug activity available for transport remains constant even upon addition of more surfactants.

An important property of micelles in pharmacy is that they have ability to increase the solubility of poorly soluble or insoluble drugs in water, hence increasing their bioavailability. In this regard, Carlota et al. [19] studied the solubilization of ibuprofen(IBU) in micellar solutions of three surfactants having the same hydrocarbon tail but different hydrophilic head groups, namely sodium dodecyl sulpahate (SDS), dodecyltrimethylammonium bromide (DTAB), and n-dodecyl octa(ethylene oxide)(C12E08). The results showed that, irrespective of the surfactant type, the solubility of IBU increased linearly with increasing surfactant concentration, due to the association between the drug and the micelles. However, due to the stronger tendency of the nonionic surfactant forming miceller solution, at the same surfactant concentration, the same solubility of IBU in both DTAB and C12E08 has been obtained. In other study, the same author studied the miceller solubalization of hydrophobic drugs in aqueous environment. In this work, the application of micelles in drug delivery, in order to minimize drug degradation and loss,

to prevent its harmful side effects, and to increase its bioavailability, is also shown. They also discussed the importance of surfactants and micelles as biological system models as well as their application in miceller catalysis and their use in pharmacy for many applications.

Taboada et al [20] studied the apparent molar volumes and adiabatic compressibilities of aqueous solutions of the amphiphilic antideppressents like- amitriptyline, notriptyline, and desipramine from density and ultrasound velocity measurements. Positive deviations of the apparent molar volume of nortriptyline from the Debye-huckel limiting law in dilute solution illustrated the premicellar association. The behavior of calculated isentropic apparent molar adiabatic compressibilities was similar to those of typical surfactants, indicating a decrease of hydrophobic hydration in association of the monomers of these drugs.

Tiwary et al [22] studied the micellization, aggregation behavior and thermodynamics of a cationic surfactant viz. cetyltrimethylammonium bromide (CTAB) in absence and in presence of tyrosine-hydantoin (TH) drug using conductivity, surface tension, UV-visible and fluorescence spectroscopic methods. The critical micelle concentration, aggregation number and standard free energy changes of aggregation of the surfactant (CTAB) in absence and in presence of TH in water have been evaluated at different temperatures (294,303 and 318K). The fluorescence spectroscopic method had been used to calculate the aggregation number. Thermodynamic parameters (the standard Gibbs energy), $\Delta G°_m$, the standard enthalpy change, $\Delta H°_m$, the standard entropy, $\Delta S°_m$, the standard Gibbs (transfer) energy, $(\Delta G°_m)tr$, and the excess free energy change of micellization, (ΔGex) have been evaluated. The negative value of standard Gibbs energy change indicated spontaneous micellization.

Schreier et al [23] studied the self –aggregation properties of drugs, as well as their interaction with membranes. It was seen that drug-membrane interactions were analogous to the interactions between membranes and classical detergents. The phenomenon such as shape change, vesiculation, membrane disruption, and solubalization seemed to be modulated by lipid flip-flop and formation of non-bilayer phases. The mechanism of drug solubilization by surfactants reviewed physco-chemical interactions with respect to drug intake and drug absorption by the organism.

Mehta et al and coworkers [24] studied the micellar properties of cationic surfactants (S) viz. dodecyltrimethyl ammoinium bromide (DDAB) and dodecyltrimethylammonium chloride(DTAC) in aqueous medium in the presence of diclofecnac sodium (D) by spectroscopic studies and conductivity measurements. The critical micelle concentration (CMC) and degree of counter ion binding (β) of the

micelles were determined at different temperatures from conductivity studies. A comparison of cmc and other thermodynamic parameters of S/W with those of S/D/W showed a considerable change in the nature of micellar media due to presence of surfactant. Thermodynamic parameters ($\Delta G°_m$, $\Delta H°_m$ and $\Delta S°_m$) for the micelle system were also estimated. At lower temperatures, the micellization was found to be entropy-driven while at higher temperatures it was enthalpy driven.

Ahmed et al [25] investigated the effects of different surfactants on crystal properties and dissolution behaviour of aspirin. Aspirin was crystallized by methanol in the presence of three surfactants namely cetrimide (cationic), sodium lauryl sulfate(anionic) and Tween 80 (non-ionic) in various concentrations ranging from 0.0001M to 0.1M. After characterising, the crystals using infra red spectroscopy, dissolution profile of aspirin tablets prepared with surfactant was compared to the control aspirin tablets. The concentration and charge of surfactants brought modifications in the crystal habit of aspirin, which subsequently affected the crystal properties such as density and equilibrium solubility. IR spectroscopic studies revealed that the internal lattice structure of aspirin was not altered in presence of the surfactants in all of the concentrations. However, presence of surfactants considerably modified crystal habit and other crystal properties. Such changes apparently appeared to be responsible for altered equilibrium solubility. Presence of surfactant (0.1 M SLS) in aspirin tablets enhanced the dissolution of aspirin significantly as compared to control aspirin tablets ($P<0.05$). From these results, it can be concluded that the choice of selection of surfactants and optimization of its concentration is an important factor in manufacturing dosage forms with aspirin.

Gokturn et al [26] studied the interaction of the cationic drug rivanol (RIV) with three types of surfactants namely [cationic (cetyltrimethylammonium bromide; CTAB), anionic (sodium dodecyl sulphate; SDS), and non-ionic (t-octylphenoxypolyethoxyethanol, TX-100)] spectrophotometrically as a function of surfactant concentration from the region of pre micelle to the region of post micelle. A comparison of the binding constants calculated from Benesi-Hildebrand equation indicated that the binding tendency of RIV with TX-100 micelles is higher than that with SDS micelles. The binding constants of RIV to both SDS and TX-100 micelles decrease in the presence of NaCl (0.225% wt./vol.), ethanol (5% vol./vol.), propylene glycol (5%vol./vol.). The addition of the additives to the medium had a pronounced effect on the association of RIV with micelles. They all tend to decrease the binding of RIV to micelles. The inhibitory effect of alcohols followed the order: water>glycerine>propylene glycol>ethanol.

The effects of types of surfactants on the solubalization and dissolution of poorly soluble acidic drugs were compared to identify the most suitable surfactant for conducting an acidic drug dissolution test by Park et al [27]. Cetyltrimethylammonium bromide (CTAB) as a cationic surfactant, sodium lauryl sulphate (SLS) as an anionic surfactant, and polysorbate 80 as a non-ionic surfactant were used in study. And, mefenamic acid, nimesulide, and ibuprofen were selected as model drugs. The dissolution rates of these acidic drugs were substantially increased in medium containing CTAB. Electrostatic interactions between acidic drugs and cationic surfactants were also confirmed by measuring UV spectra of each drug. Solubility of these drugs in various media and their partition coefficients into micelles were formed to depend on drug characteristics. For acidic drugs, the medium which contained a cationic surfactant discriminated the rate of dissolution of acidic drugs much more as compared to the medium containing other surfactant types.

The drug delievry system across the cell membrane is a complex biological process and is often difficult to understand because of its dynamic nature. In this regard, model lipid membranes, which mimic many aspects of cell-membrane lipids, have been very useful in determining the role of lipids in cellular interactions. Peetla et al [28] studied drug-lipid interactions to predict pharmacokinetic properties of drugs, such as their transport, biodistribution, accumulation and hence increase their efficacy.

Enache et al [29] studied the interaction of anti cancerous drug- mitoxantrone with anionic surfactant sodium dodecyl sulphate (SDS) in physiological conditions (phosphate buffer, ph 7.4) by using spectral (UV-vis absorption) and electrochemical (cyclic and linear voltammetry) methods. The partition coefficient of mitoxantrone between aqueous phase and SDS micelles was calculated, and the results illustrated that it is strongly dependent on the concentration of drug. Both absorption and cyclic voltammetry results have outlined two different processes depending on the surfactant concentration (i) in premicellar range, assigned to the interaction of the drug with the surfactant molecules, when electrostatic forces play an important role in the micellar range, when the surfactant micelles are formed and the drug is encapsulated in micelles in monomer form. The results of spectroscopy indicated that the drug is located in the micelle surface layer, both electrostatic and polar interactions playing important role in the binding of drug to SDS micelles.

Akhtar et al [30] studied the interaction of a cephalosporin antibiotic drug, cefadroxyl monohydrate (CFM) with hexadecyltrimethyl ammonium bromide (CTAB), a cationic surfactant, and sodium dodecyl sulphate (SDS), an anionic surfactant in aqueous medium by conductivity measurements over

a range of temperatures and salt concentrations. Values of critical micelle concentration (c*), degree of micelle ionization (a), and thermodynamic parameters were determined for both the systems in pure water as well as in aqueous NaCl solution. For both (CFM+CTAB) and (CFM+SDS) systems, $\Delta G°m$ values were negative which indicated that the drug mediated ionic micelle formation processes are thermodynamically spontaneous. For (CFM+CTAB) system, the micellization was entropy controlled at lower temperatures whereas at higher temperatures it became both entropy and enthalpy controlled, whereas for (CFM+SDS) systems, it was entropy controlled over the range of the temperature studied. In the presence of NaCl, enhancement of hydrophobic interaction was observed for both the systems at lower temperatures. A significant decrease of c* values in the presence of NaCl for both the surfactant system indicated that CFM supported ionic micelle formation was much favoured in NaCl as compared to that in pure water.

Chauhan et al [31] studied sound velocity and density measurements of aqueous solutions of the anionic surfactant SDS (sodium dodecyl sulfate) and the cationic surfactant CTAB (cetyltrimethylammonium bromide) with the drug furosemide (0.002 and 0.02 mol.dm-3) in the temperature range 20-40°C. From these measurements, the compressibility coefficient (β), apparent molar volume (Φ_v) and molar compressibility (Φ_k) were computed. From electrical conductivity measurements, the critical micelle concentrations (CMCs) of SDS and CTAB were determined in the above mentioned aqueous furosemide solutions. From the CMC values as a function of temperature, various thermodynamic parameters were evaluated: the standard enthalpy change ($\Delta H°_m$), standard entropy change ($\Delta S°_m$), and Gibbs energy change ($\Delta G°_m$) for micellization. This work also included viscosity studies of aqueous solutions of SDS and CTAB with the drug in order to determine its relative viscosity (η_r). UV-Vis studies were carried for the ternary drug/surfactant/water system having SDS in the concentration range 0.002-0.004 mol.dm^{-3}. All of these parameters were discussed in terms of drug-drug, drug-solvent and drug-surfactant interactions resulting from various electrostatic and hydrophobic interactions.

Sharma et al [32] studied partial molar volumes of the drugs Parvon Spas, Parvon Forte, Tramacip and Parvodex in aqueous mixtures of methanol (MeOH), ethanol (EtOH), and propan-1-ol (1-PrOH). The data was evaluated using the Masson equation. The parameters like- apparent molar volumes (Φ_v), partial molar volume ($\Phi°_v$), and S_v values (experimental slopes) were interpreted in terms of solute-solvent interactions. In addition, these studies were also extended to determine the effect of these drugs on the solution behaviour of an electrolyte (sodium chloride), a surfactant (sodium dodecyl sulfate),

and a non-electrolyte (sucrose). It can be inferred from these studies that all drug cations can be regarded as structures markers/promoters due to hydrophobic hydration. Furthermore, the results are correlated to understand the solution behaviour of drugs in aqueous-alcoholic systems, as a function of the nature of the alcohol and solutes.

Bhardwaj et al [33] studied the micellization behaviour of surfactant (SDS) in presence of synthetic antioxidants i.e., butylated hydroxyanisole/butylated hydroxytoluene (BHA/BHT) in various aqueous-alcoholic (methanol, ethanol and 1-propanol) solutions. Conductivity measurements were determined for above mentioned solutions at three different temperatures (25°C, 30°C and 35°C) as a function of SDS concentration ranging from 1-14 mmol dm^{-3}. However the concentration of BHA and BHT was fixed at 0.03 mol $dm^{-3}$and 0.02 $moldm^3$ respectively. The CMC values were determined from the plots of specific conductance versus concentration of SDS. The CMC values of SDS increases with increase in temperature as well as with increase of alcohol chain length. By using CMC data various thermodynamic parameters as; standard enthalpy change ($\Delta H°_m$), standard entropy change ($\Delta S°_m$) and standard Gibbs energy change ($\Delta G°_m$) have also been evaluated. The results of desired parameters have been discussed as a function of solvent mixtures, concentration of SDS and nature of alcohol. In particular, the investigation provided a significant information regarding effect of temperature and water-alcohol mixtures with respect to presence of essential functional moieties on BHA and BHT. The calculated thermodynamic parameter $|T\Delta S°_m|$ was larger than $|\Delta H°_m|$ which indicated that the micellization is entropy driven moreover, negative $\Delta H°_m$ and $\Delta G°_m$ values suggested feasibility of system which was found to be exothermic in nature.

Bhardwaj et al [34] studied the conductance, FTR as well as HNMR analysis for well known synthetic antioxidant; butylated hydroxyanisole (BHA) and anionic surfactant; sodium dodecyl sulphate (SDS). From the cmc and Xcmc values as a function of temperature, various thermodynamic parameters have been evaluated viz: (a) the standard enthalpy change ($\Delta H°_m$), (b) standard entropy change ($\Delta S°_m$), and (c) standard Gibbs energy change ($\Delta G°_m$). Utilizing the spectroscopic analysis, chemical shift/frequency was accounted in different conditions indicative of SDS molecule binding to BHA. Furthermore, the acoustic properties in three different compositions of ethanol containing water i.e., 100% (pure ethanol), 70% v/v (ethanol rich), and 30% v/v (water rich) solutions were also determined at three different temperatures at an interval of 5°C (25°C, 30°C, 35°C) . Specifically, the density (ρ), ultrasonic velocity (μ) and viscosity (η) as function of SDS containing BHA have been determined and the resulting data was used to estimate various acoustical parameters; the

compressibility coefficient (β), apparent molar volumes (Φ_v) and apparent molar compressibility (Φ_k). These calculated parameters were found to be sensitive toward the interactions prevailing in BHA-SDS-solvent system and interactions in different water-ethanol compositions. Convincingly existence of a good qualitative correlation is observed with regard to SDS-BHA interactions obtained from the measurements.

Saharty et al [35] studied a binary mixture of terbinafine hydrochloride and triamcinolone acetonide by three different methods. The first one concerned with determination of both drugs using first derivative (D_1) spectrophotometric technique at 297 and 274 nm over concentration ranges of 5–30 and 4–24 μg ml^{-1}, with mean percentage accuracies 99.90±0.67 and 100.25±0.49, respectively. The second method depends on ratio-spectra 1st derivative (RSD_1) spectrophotometry at 298 and 248 nm over the same concentration ranges with mean percentage accuracies 100.22±0.51 and 99.93±0.56, respectively. The spectrodensitometric analysis provided a rapid and precise method for the separation and quantitation of both terbinafine hydrochloride and triamcinolone acetonide. The method depends on the quantitative densitometric evaluation of thin layer chromatogram of terbinafine hydrochloride and triamcinolone acetonide at 283 and 238 nm over concentration ranges of 5–25 and 2.5–22.5 μg $spot^{-1}$, with mean percentage accuracies 100.66±0.51 and 100.27±0.73, respectively. The three methods retained their accuracy and precision when applying the standard addition technique. The results obtained by applying the proposed methods were statistically analysed and compared with those obtained by a reported method.

Prasad et al [36] made an attempt to standardize the aqueous extract of Curcuma longa (turmeric) in particular to Curcumin, Germplasm of Duggirala, and Guntur district of Coastal Andhra Pradesh, a traditional turmeric belt, subjected for Standardization parameters viz. Physico–Chemical, Organoleptic and Chromatographic Analytical techniques. Analysis of the extract shows values of particle size through 40 mesh 100%, Loss on Drying 6.08%, pH 6.35, Water Soluble Extractive 87.04%, Alcoholic soluble Extractive 35.68%, Total ash 31.45%, Acid insoluble ash 3.08%, Bulk Density (gm/ml) 0.69 and Trapped density (gm/ml) 0.90. Heavy metal and Microbial values are also within the prescribed limits of Ayurveda Pharmacopeia of India. HPTLC graph shows peak value of the total height 381.5 and total area 4991.8. Rf (Retention fraction) value of Curcumin was 0.32. Estimation of Value of Marker Compound shows Curcumoids by Spectrometric Method and Gallic acid By HPLC method were 0.30% on d/b and 9.19% respectively. The HPTLC method was a simple, precise, specific, sensitive and accurate, used for routine quality control of mono herbal extract as well as a formulation.

In another study by Surwase et al [37] turmerone was isolated from turmeric oil. Then it was further purified with activated charcoal or preparative TLC. Turmerone shows violet spot at R_f of 0.72 with vanillin-sulfuric acid on heating. A UV spectrum of the isolated compound shows two peaks of almost same intensity at 233.5 nm and 236 nm. IR spectra values in cm-1 were found to be 2988.7 and 2936.8 (for aromatic C=C stretching), 1735.4 and 1446.2 (for C=O Stretching), 939.0, 847.4 (for –CH bending). GC spectra of isolated compound shows the first peaks at retention time of 7.227 min. with area 99.2% and second peak at retention time of 9.667 min. with area 0.8%. GC-MS spectra of the isolated compound in positive ionization mode showed molecular ion peaks at m/z: 217.2 and 219.2 which correspond to molecular weight of ar-turmerone and turmerone.

An investigation was carried out by Dash et al [38] to study the physico-chemical characteristics of 10 selected turmeric germplasm of South Western region of Bangladesh. The physico-chemical characters of 10 germplasam of turmeric species were studied. There was significant variation among the germplasms in relation to rhizome characteristics and organoleptic evaluation. Better performance of turmeric was found in germplasm No.1 in respect of total rhizome weight, rhizome length, rhizome width, rhizome height, pulp weight, pulp thickness, skin weight, skin thickness and percents of edible part. Turmeric germplasm No. 5 and germplasm No. 4 gave better performance in respect of pH.

2.2. Aim of Present work

The aim of the present work is to investigate the physico-chemical properties of drug-surfactant interactions. Various thermodynamic and acoustical parameters were calculated in order to correlate the solute-solute and solute-solvent interactions. First of all critical micelle concentration (CMC) and various thermodynamic parameters as $\Delta G°_m$, $\Delta H°_m$, $\Delta S°_m$, were calculated to gain insight about the nature of process whether it is exothermic or endothermic. Further the drug-surfactant interactions were related to entropy driven or enthalpy driven processes. Then to obtain A and B coefficients, viscosity studies were included to understand the solution behavior of drugs in aqueous ethanolic systems as a function of the nature of ethanol. All these studies are further supported by performing Density and Sound velocity studies in order to calculate various acoustical parameters at different temperatures 25, 30, 35, 40°C in 10%, 20% and 30% v/v ethanol solutions. Further emphasis is laid on the comparative analysis of pure form of drug (Pure API), the marketed formulation of drug ($THCl_m$) and in presence of Turmeric (having antimicrobial activities) in order to increase the biological profile by changing its pharmacokinetics with the addition of turmeric.

3. Methodology

3.1. Chemicals and Reagents

3.1.1 Water: Water being one of the major solvent in the study which is also employed in calibration of instruments or apparatus was obtained by double distillation process. By volume, 1000 ml of pure water was collected from the double distillation unit (Harco & Co.) which was further subjected to distillation on acidified $KMnO_4$ over a 750 mm long fractionating column. Different fractions of distilled water were collected having specific conductivity and pH, κ(S cm^{-1}), $\approx$ 1-2 $\times$ 10^{-7}S cm^{-1} and 6.75 - 6.95, respectively.

3.1.2 Solvents: Absolute alcohol i.e. ethanol was obtained from Merck Chemicals with purity $\geq$ 99.9%. Other solvents in experimental and lab processes such as acetone, sulfuric acid and hydrochloric acid etc. for complete cleansing of glassware were also obtained from Merck Chemicals. Physico-chemical study of surfactant in presence of Terbinafine HCl was carried out in three different solvent compositions of alcohols i.e. 10, 20, 30% v/v ethanol.

3.1.3 Pharmaceutical Ingredients: Terbinafine HCl (THCl) was received as a gift sample from Health Blessings Pvt. Ltd. (Solan). Anionic surfactant; sodium dodecyl sulfate (SDS) was obtained from Merck Chemicals. Surfactant used in the study was of AR grade and purity > 99.0%. Marketed formulation of Terbinafine HCl ($THCl_m$) was purchased from Cipla Ltd. (Central Mumbai).Turmeric was purchased as an organic powder from Patanjali Ayurved Ltd.

3.2. Thermostat and temperature control

All the measurements were carried out in an automatic digital temperature controller high precision water thermostat (HARCO) having a temperature control of accuracy ± 0.05°C.

3.3. Conductance measurements

Conductance measurements were carried out with a calibrated digital conductivity meter (Cyber Scan CON 510 supplied by Merck). Specific conductance (κ) have been measured at four different temperature i.e. 25°C, 30°C, 35°C and 40°C by varying the concentration of SDS (1mM dm^{-3} to 14mM dm^{-3}) at 0.03 mol.dm^{-3} concentrations of Terbinafine Hcl (Pure API). From the graphs of κ vs concentration of SDS, CMC were evaluated and different thermodynamic parameters standard enthalpy change ($\Delta H°_m$), standard entropy change ($\Delta S°_m$), and standard Gibbs energy change ($\Delta G°_m$) were also

calculated. Further studies were also carried out at fixed concentration of Turmeric (0.01 mol.dm^{-3}) as well as marketed formulation of Terbinafine HCl ($THCl_m$) (0.003 mol.dm^{-3})

3.4. Viscosity measurements

Viscosity measurements were carried out with a calibrated jacketed Ubbelhode Viscometer. The precision achieved in viscosity measurement was ±0.1%. Density measurements were carried out with the help of specific gravity bottle. The viscosities and densities of aqueous solutions of (Pure API and SDS), (turmeric and SDS) and ($THCl_m$ and SDS) were measured at different temperatures i.e. 25°C, 30°C, 35°C and 40°C. From viscosity data A and B coefficients were calculated with the help of Jones Dole equation which are interpreted in terms of solute-solute and solute-solvent interactions.

3.5. Ultrasonic Sound Velocity

Ultrasonic velocities were measured by using Ultrasonic Interferometer (Mittal M-81) for the same concentration range of SDS in presence of fixed concentration of THCl (API). Various acoustical parameters were calculated such as the compressibility coefficient (β), apparent molar volume (Φ_v) and apparent molar compressibility (Φ_k). Propagation of Ultrasonic waves being sensitive to the nature of solvent medium, contributes to understand different kind of interactions that drug/surfactant molecules undergo in solution.

4. Results and Discussions

4.1 Conductivity Studies:

The micelle forming property of SDS has been studied for drug-surfactant interaction. This showed that κ (specific conductance) depends on the concentration of the surfactants (SDS) in aqueous media containing Pure API, turmeric and $THCl_m$ which is presented in figure 6 (a, b and c). The break points were obtained quite significantly, which favored the evaluation of CMC (Critical Micelle Concentration) properly and are reported in table 1, 2 and 3. The CMC values of SDS were found to be in range of (5.3 $mM.dm^{-3}$- 6.8 $mM.dm^{-3}$) for API, (6.2 $mM.dm^{-3}$- 7.0 $mM.dm^{-3}$) for $THCl_m$ and (4.2-5.9 $mM.dm^{-3}$) for Turmeric which are lower than its standard value (i.e. 8$mM.dm^{-3}$). This indicates that presence of bulkier moiety as *t*- dimethyl substitution and amine group which played significant role for interaction in case of Pure API and Marketed formulation. Thus, these substitutions contribute to better interactions leading to micellization much earlier. This is also due to lowering of repulsion between surfactant head group and also hydrophobic nature of drug which provides surface for micellization of SDS. Hence, the extra hydrophobicity offered by Terbinafine HCl seems to reduce the CMC values. However in case of turmeric extra hydrophobicity is offered by parahydroxyl and keto groups.

Table1. Values of CMC, $\Delta H°_m$, $\Delta G°_m$ and $\Delta S°_m$ at different concentration of SDS in 0.03$mol.dm^{-3}$ of API from 25-40°C temperature range:

Ethanol percentage	Concentration ($Mol.dm^{-3}$)	Temp. (°C)	CMC ($Mol.dm^{-3}$)	$\Delta H°_m$ (KJ/mol)	$\Delta G°_m$ (KJ/mol)	$\Delta S°_m$ ($Jmol^{-1}\ K^{-1}$)
10 %	0.03	25	0.053	-33.11	-122.63	300.40
10%	0.03	30	0.06	-33.84	-125.99	304.12
10%	0.03	35	0.042	-34.45	-128.44	305.16
10%	0.03	40	0.032	-35.04	-130.75	305.78
20%	0.03	25	0.068	-34.68	-134.55	335.13
20%	0.03	30	0.068	-35.76	-140.71	346.36
20%	0.03	35	0.064	-36.69	-145.72	353.99
20%	0.03	40	0.065	-37.87	-152.75	367.02
30%	0.03	25	0.025	-33.44	-122.36	298.38
30%	0.03	30	0.035	-33.75	-124.38	299.10
30%	0.03	35	0.045	-34.75	-128.67	304.93
30%	0.03	40	0.04	-35.87	-134.88	319.52

Table2. Values of CMC, ΔH°_m and ΔS°_m at different concentration of SDS in 0.03mol.dm^{-3} of $THCl_m$ from 25-40°C temperature range:

Ethanol percentage	Concentration (Mol.dm^{-3})	Temp (°C)	CMC (Mol.dm^{-3})	ΔH°_m (KJ/mol)	ΔG°_m (KJ/mol)	ΔS°_m (Jmol^{-1} K^{-1})
10%	0.03	25	0.007	-35.12	-122.02	310.60
10%	0.03	30	0.065	-36.07	-126.13	312.11
10%	0.03	35	0.064	-38.19	-129.44	315.07
10%	0.03	40	0.065	-39.40	-131.26	316.03
20%	0.03	25	0.065	-37.39	-135.61	325.40
20%	0.03	30	0.065	-39.42	-138.19	339.52
20%	0.03	35	0.065	-41.04	-139.63	341.10
20%	0.03	40	0.062	-43.40	-141.40	349.18
30%	0.03	25	0.065	-41.05	-141.59	333.11
30%	0.03	30	0.065	-43.17	-148.71	341.26
30%	0.03	35	0.065	-44.15	-150.03	345.07
30%	0.03	40	0.062	-46.19	-151.08	348.12

Table3. Values of CMC, ΔH°_m and ΔS°_m at different concentration of SDS in 0.03mol.dm^{-3} of turmeric from 25-40°C temperature range

Ethanol percentage	Concentration (Mol.dm^{-3})	Temp (°C)	CMC (Mol.dm^{-3})	ΔH°_m (KJ/mol)	ΔG°_m (KJ/mol)	ΔS°_m (Jmol^{-1} K^{-1})
10%	0.03	25	0.042	-38.30	-128.17	315.60
10%	0.03	30	0.053	-39.51	-131.01	317.81
10%	0.03	35	0.042	-42.16	-133.61	319.02
10%	0.03	40	0.042	-43.14	-134.58	320.01
20%	0.03	25	0.042	-40.14	-131.32	320.61
20%	0.03	30	0.045	-41.25	-133.51	325.19
20%	0.03	35	0.046	-43.08	-135.09	339.40
20%	0.03	40	0.042	-45.16	-137.06	340.18
30%	0.03	25	0.059	-42.18	-135.16	330.12
30%	0.03	30	0.053	-45.61	-138.19	332.19
30%	0.03	35	0.050	-46.77	-139.41	334.20
30%	0.03	40	0.050	-48.12	-140.41	341.21

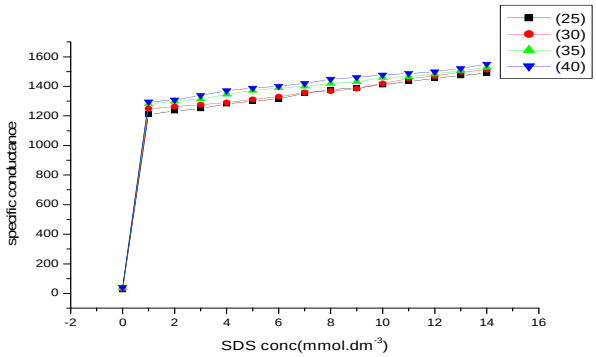

Figure 6(a). Variation of specific conductance (κ) with concentration of SDS at different temperatures in 0.03 mol.dm^{-3} of API in 10% ethanol system.

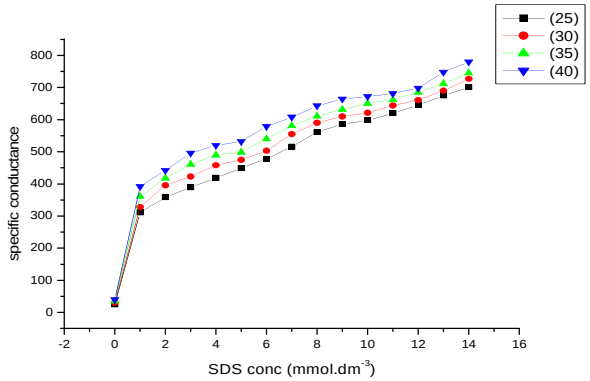

Figure 6(b). Variation of specific conductance (κ) with concentration of SDS at different temperatures in 0.03mol.dm^{-3} of $THCl_m$ in 10% ethanol system.

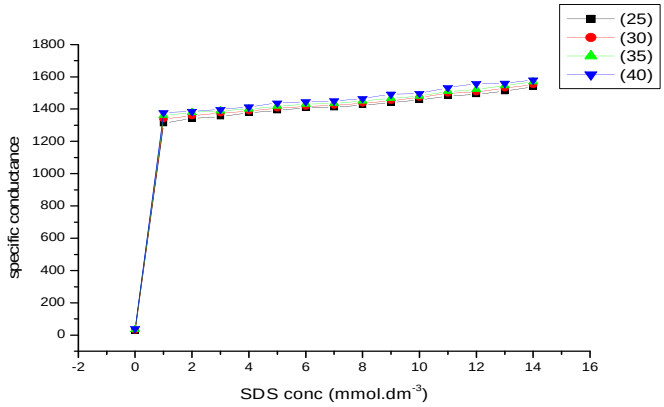

Figure 6(c). Variation of specific conductance (κ) with concentration of SDS at different temperatures in 0.01mol.dm^{-3} of turmeric in 10% ethanol system.

From the above mentioned graphs, it is clear that the CMC value decreases in 0.003 mol.dm^{-3} of API due to early micelle formation and further decreases in (0.01 mol.dm^{-3}) of turmeric.

$$CMC\ (THCl_m) > CMC\ (Pure\ API) > CMC\ (Turmeric)$$

5.1.1 Thermodynamics of Micellization of SDS in aqueous solutions of Terbinafine HCl

The thermodynamic parameters are used to derive further information about the drug-surfactant interactions from the experimental data obtained and are reported in Table 1, 2 and 3.The standard Gibbs free energy [39] change for micellization is given by:

$$\Delta G°_m = RT \ln (X_{CMC})$$

where, X_{cmc} = {CMC of surfactant/ (CMC of surfactant + concentration of drug+55.6)} with concentrations in units of mol.dm^{-3}, R is the gas constant, and T is temperature in Kelvin. The standard enthalpy change for micellization, $\Delta H°_m$ is obtained through a classical Van't Hoff equation [40]:

$$\Delta H°_m = -RT^2 [d \ln (X_{CMC})/dT]$$

where d ln (X_{CMC})/dT is the slope of the straight line obtained by plotting ln X_{CMC} against T.
The standard entropy changes for micellization $\Delta S°_m$ for SDS were determined as-

$$\Delta G°_m = \Delta H°_m - T\Delta S°_m$$

The negative values of $\Delta H°_m$ and $\Delta G°_m$ and positive value of $\Delta S°_m$ (Table 1, 2 and 3) indicates the drug-surfactant interactions. Figure 6(a), (b) and (c) illustrates that these thermodynamic parameters depends on the temperature. However, the increase in concentration of SDS did not show much variability in the parameters and hence, these parameters almost remain same (Table 1, 2 and 3). The decrease in the values with the successive increase in the temperature illustrates that the hydrophilic hydration of the surfactant head group as well as the hydrophilic part of Terbinafine HCl is decreasing, which results in hydrophobic interaction with the surfactant thus leading towards micellization.

The negative values of $\Delta H°_m$ illustrated that the drug is fully solublized in the SDS solution and this process of solubilization is an exothermic process.

The positive values of $\Delta S°_m$ (Figure 7d-f) illustrates the disruption of structure of water [41] at the hydrocarbon part of the additive molecules as they transfer from aqueous bulk phase to other parts of micellar aggregates. At the same time, there is breakage of water bonds which results in the increase of randomness of the hydrocarbon chains in the micellar core [42, 43]. Positive value of $\Delta S°_m$ indicates that the entire system is entropy driven which is the result of re-organization of water and ethanol molecules.

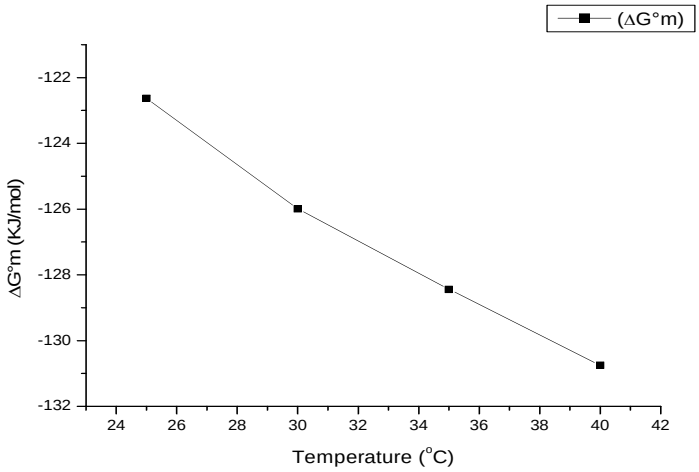

Figure 7(a). Variation of thermodynamic parameters $\Delta G°_m$ of SDS as a function of temperature in 0.03 mol.dm^{-3}of API in 10% of ethanol solution.

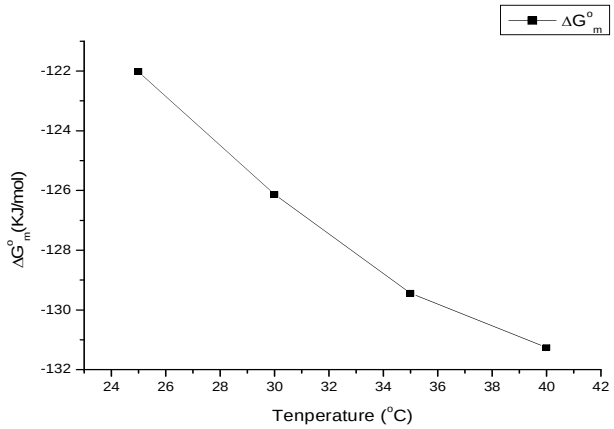

Figure 7(b). Variation of thermodynamic parameters $\Delta G°_m$ of SDS as a function of temperature in 0.03 mol.dm^{-3}of $THCl_m$ in 10% of ethanol solution.

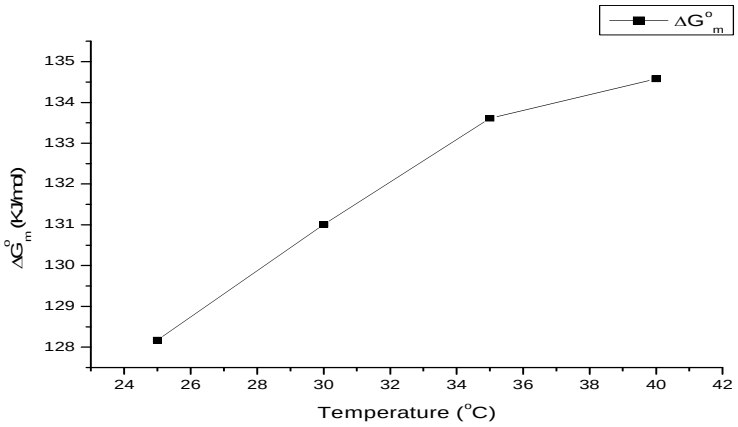

Figure 7(c). Variation of thermodynamic parameters $\Delta G°_m$ of SDS as a function of temperature in 0.01 mol.dm^{-3} of turmeric in 10% of ethanol solution.

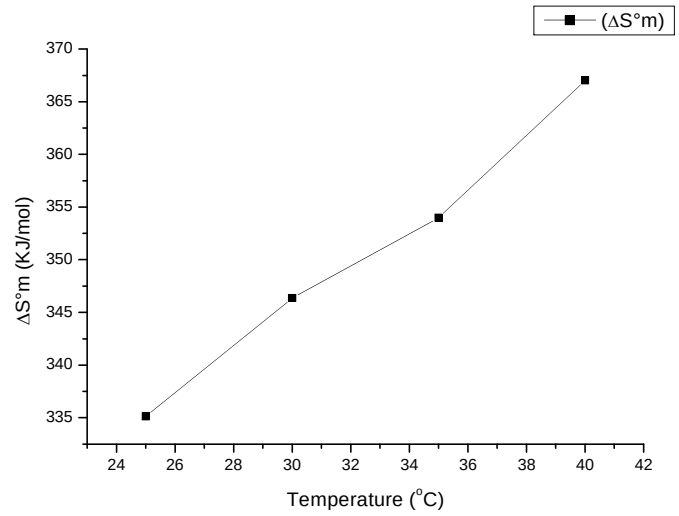

Figure 7(d). Variation of thermodynamic parameters $\Delta S°_m$ of SDS as a function of temperature in 0.03 mol.dm^{-3}of API in 20% of ethanol solution.

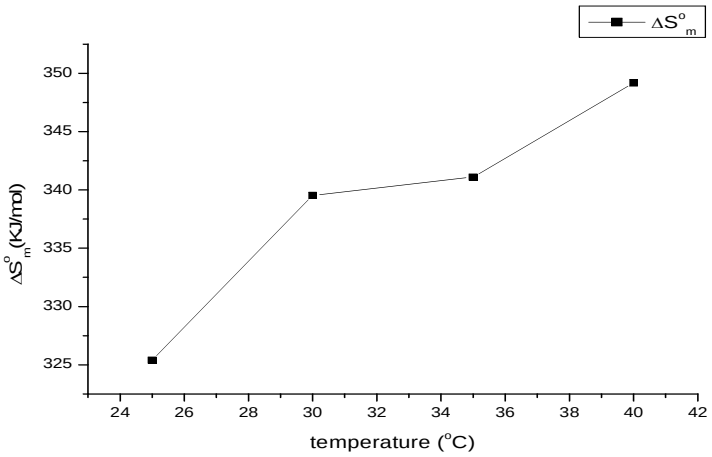

Figure 7(e). Variation of thermodynamic parameters $\Delta S°_m$ of SDS as a function of temperature in 0.03mol.dm^{-3} of $THCl_m$ in 20% of ethanol solution.

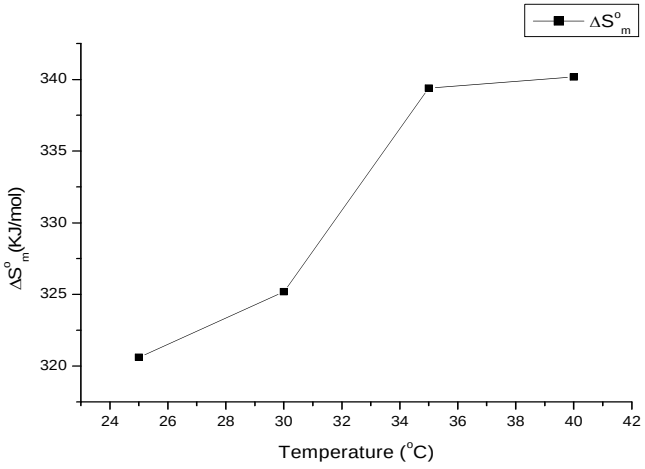

Figure 7(f). Variation of thermodynamic parameters $\Delta S°_m$ of SDS as a function of temperature in 0.01 mol.dm^{-3} of turmeric in 20% of ethanol solution

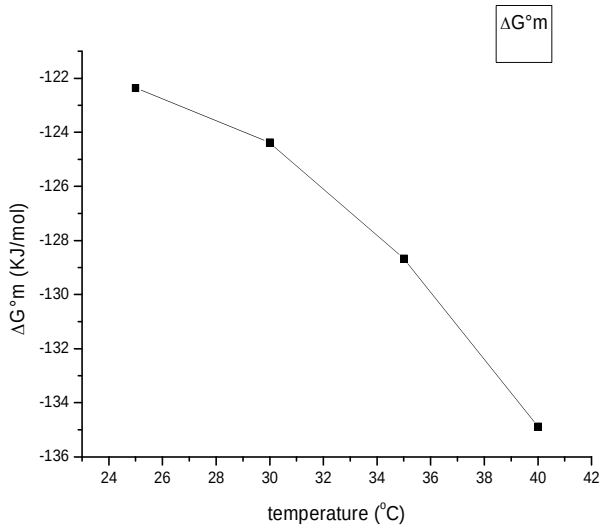

Figure7(g). Variation of thermodynamic parameters $\Delta H°_m$ of SDS as a function of temperature in 0.03 mol.dm^{-3} of API in 30% ethanol solution.

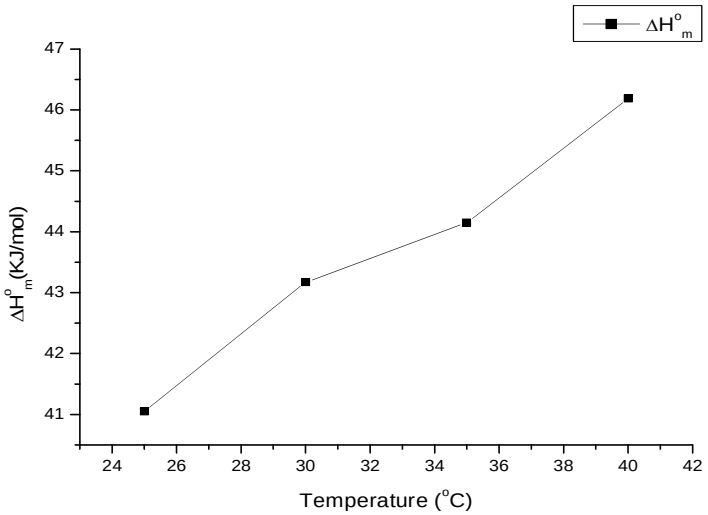

Figure7(h). Variation of thermodynamic parameters $\Delta H°_m$ of SDS as a function of temperature in 0.03 mol.dm^{-3} of $THCl_m$ in 30% ethanol solution.

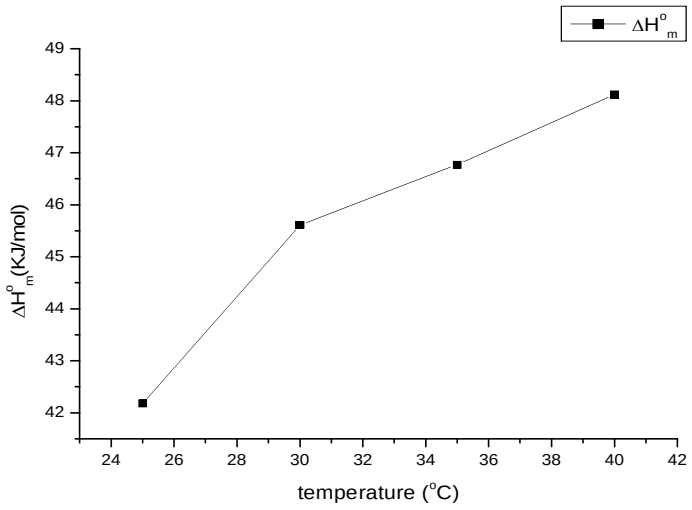

Figure7(i). Variation of thermodynamic parameters $\Delta H°_m$ of SDS as a function of temperature in 0.01 mol.dm^{-3} of turmeric in 30% ethanol solution.

This shows that the $\Delta H°_m$ values increases with increase in temperature (Figure7 g-i) and alcohol concentration and also it decreases in the aqueous solution of API and further increases in aqueous solution of $THCl_m$ and Turmeric. This illustrates that the micelle formation is highly exothermic in aqueous solution of Turmeric as compared to API.

$$\Delta H°_m\,(\text{Turmeric}) > \Delta H°_m\,(THCl_m) > \Delta H°_m\,(\text{API})$$

Similarly, an increase in values of $\Delta G°_m$ was also seen in the aqueous solution of Turmeric as compared to aqueous solution of $THCl_m$ and API. This illustrates that the micelle formation is spontaneous and feasible in aqueous solution of turmeric as compared to API.

$$\Delta G°_m\,(\text{Turmeric}) > \Delta G°_m\,(THCl_m) > \Delta G°_m\,(\text{API})$$

4.2 **Viscosity studies:**

The main property of the drug is to get solublized in its formulation and on reaching to its specific receptors it should get released out of its formulation for the drug- targeted delivery. So in this process the transport properties of the drug play a key role and viscosity is therefore an important transportation property of the drug which determines the solution behavior of drug molecules.

Basically, the change in viscosity of the solution is contributed by the regions of modified solvent system which surrounds the drug molecule. In present study, the effect of viscosity on the SDS concentration is studied which shows that there is a gradual increase in the viscosity with respect to the increase in concentration of SDS and temperature as shown in Figure (8a, 8b, 8c), in Figure (9a, 9b, 9c) and Figure (10a, 10b, 10c). The viscosity studies are examined in different aqueous ethanol solutions ranging from 10%- 30%.

Further A and B coefficients [44] were calculated from the viscosity data with the help of Jones Dole equation and are reported in Table 4:

$$\eta_r = \eta/\eta_o = 1 + AC^{1/2} + BC \text{ or}$$

$$(\eta_r - 1)/ C^{1/2} = \Psi = A + BC^{1/2}$$

where $\eta_r = (\eta/\eta_o)$, and η and η_o are viscosities of solution and solvent system respectively, C is the molar concentration. In the above mentioned equation, A accounts solute-solute interaction. However, B accounts for contribution arising from the size of solute, molar volume of the solvent and contribution due to solute-solvent interactions and estimates the order or disorder as a result of addition of solute into solvent.

The values of both A and B were found to be positive and are given in Table 4, 5 and 6 for API, $THCl_m$ and Turmeric respectively. Since A is a measure of ionic interaction, it is evident that there is a strong solute- solute interaction. B coefficient illustrates the solute-solvent interaction and directly depends upon size, shape and charge of the solute molecules. Therefore, B values describe the net structural effects of the drug and solvent molecules. The positive values of B-coefficient illustrates that there is a strong solute-solvent interaction and temperature dependent changes.

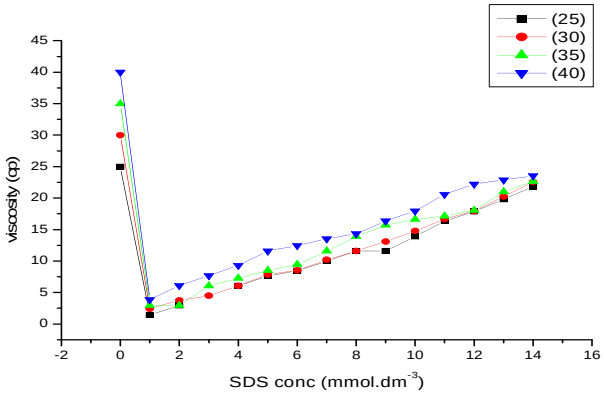

Figure 8(a). Viscosity coefficient (η) as a function of SDS in 0.03mol.dm^{-3} of API at different temperatures in 10% ethanol solution.

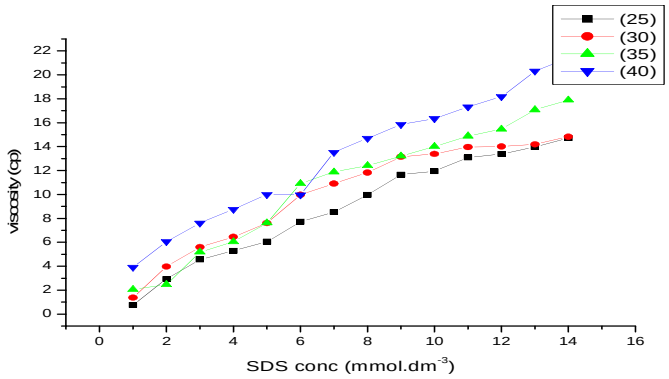

Figure 8(b). Viscosity coefficient (η) as a function of SDS in 0.03mol.dm^{-3} of API at different temperatures in 20% ethanol solution.

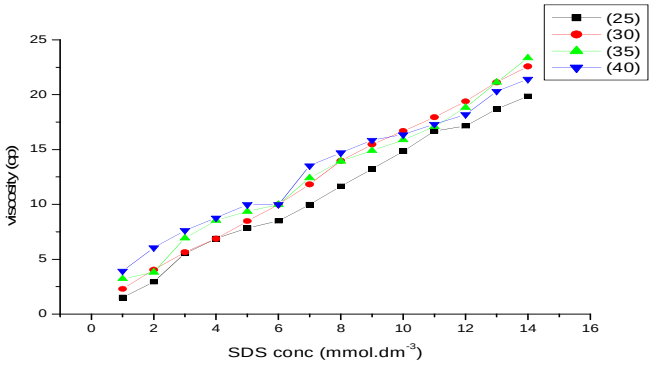

Figure 8(c). Viscosity coefficient (η) as a function of SDS in 0.03mol.dm^{-3} of API at different temperatures in 30% ethanol solution.

Table4. A and B coefficients in 0.03mol.dm^{-3} of API at different temperatures in 10%, 20% and 30% of ethanol solutions.

Ethanol percentage	Temperature 25°C	Temperature 30°C	Temperature 35°C	Temperature 40°C
10%	A=0.25, B=1.509	A=0.0962, B=1.51	A=0.98, B=1.52	A=0.008, B=1.52
20%	A=1.004, B=1.05	A=0.998, B=2.59	A=1.25, B=1.56	A=1.28, B=1.58
30%	A=0.607, B=1.39	A=0.85, B=1.56	A=1.41, B=1.80	A= 1.29, B=2.30

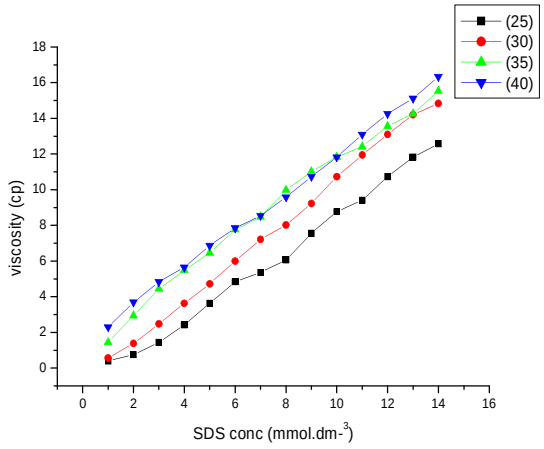

Figure 9(a). Viscosity coefficient (η) as a function of SDS in 0.03mol.dm^{-3} of $THCl_m$ at different temperatures in 10% ethanol solution.

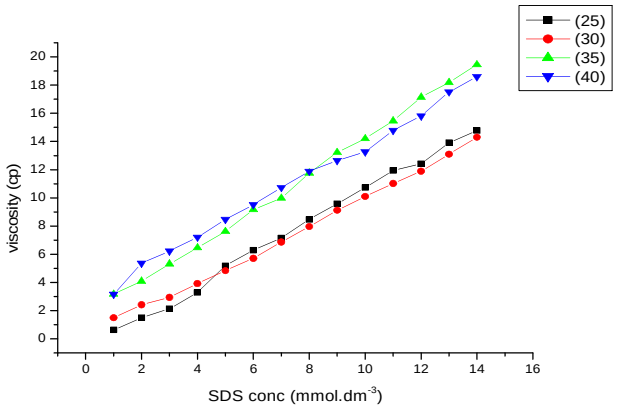

Figure 9(b). Viscosity coefficient (η) as a function of SDS in 0.03mol.dm^{-3} $THCl_m$ at different temperatures in 20% ethanol solution.

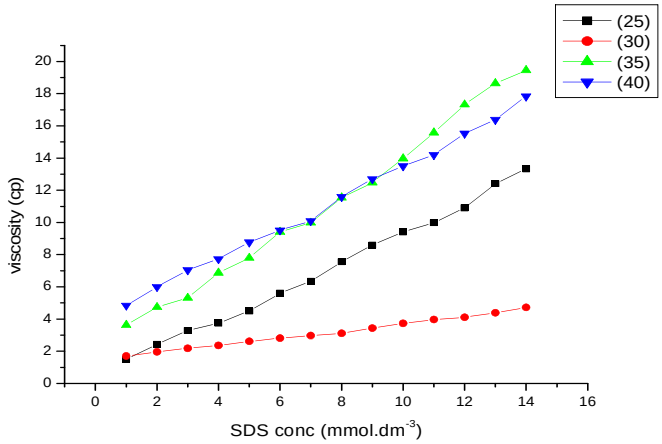

Figure 9(c). Viscosity coefficient (η) as a function of SDS in 0.03mol.dm^{-3} $THCl_m$ at different temperatures in 30% ethanol solution.

Table5. A and B coefficients 0.03mol.dm^{-3} aqueous solution of $THCl_m$ at different temperatures in 10%, 20% and 30% of ethanol solutions

Ethanol percentage	Temperature 25°C	Temperature 30°C	Temperature 35°C	Temperature 40°C
10%	A= 1.3, B= 0.98	A=0.86,B= 1.14	A= 1.10,B= 1.04	A= 1.4, B= 1.05
20%	A= 0.73,B=1.12	A=0.1, B=0.99	A=1.4, B=1.28	A=2.8, B=1.09
30%	A= 0.34,B=0.90	A=1.29, B=1.08	A=1.80,B=1.25	A=3.8,B=0.9

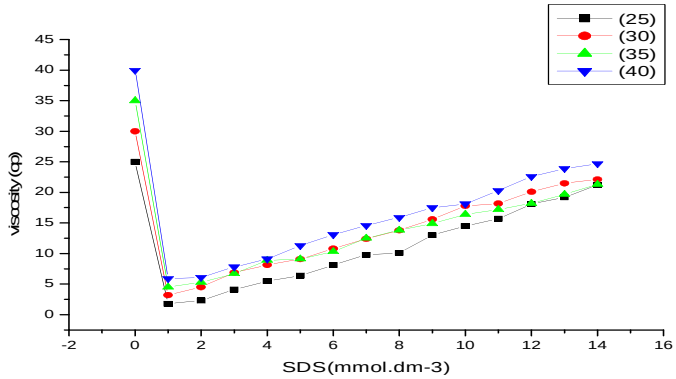

Figure 10(a). Viscosity coefficient (η) as a function of SDS in 0.01mol.dm^{-3} Turmeric at different temperatures in 10% ethanol solution.

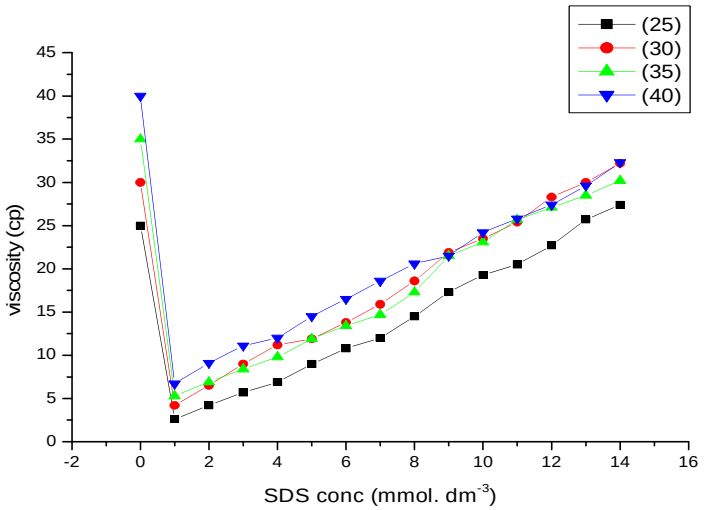

Figure 10(b). Viscosity coefficient (η) as a function of SDS in 0.01mol.dm^{-3} Turmeric at different temperatures in 20% ethanol solution.

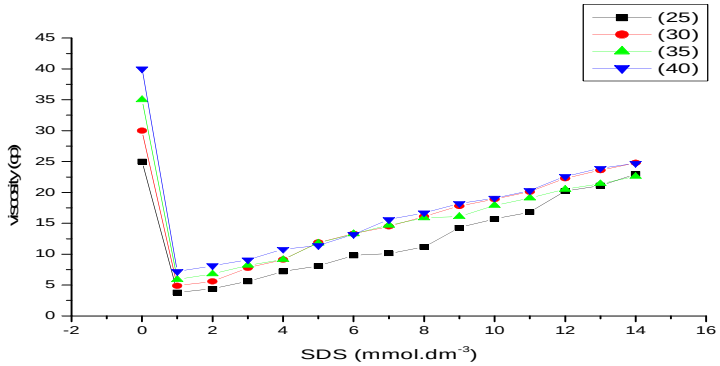

Figure 10(c). Viscosity coefficient (η) as a function of SDS in 0.01mol.dm^{-3} Turmeric at different temperatures in 30% ethanol solution.

Table6. A and B coefficients 0.01mol.dm^{-3} aqueous solution of Turmeric at different temperatures in 20% ethanol solution.

Ethanol percentage	Temperature 25°C	Temperature 30°C	Temperature 35°C	Temperature 40°C
10%	A=0.12,B=1.51	A=1.2,B=1.9	A=1.8,B=2.10	A=2.11,B=2.5
20%	A=0.32,B= 1.93	A=1.86,B= 2.15	A= 2.03,B= 2.18	A=2.19, B= 2.98
30%	A=0.56,B=2.1	A=1.9,B=2.7	A=2.2,B=3.0	A=2.6,B=3.3

4.3 Ultrasonic Sound Velocity Studies:

The ultrasonic velocity along with the density and viscosity illustrates the information about contributions that are arising due to different kinds of interactions due to the behavior of the solute spaces in the solution. Different parameters such as the apparent molar volume (Φ_v), apparent molar compressibility (Φ_k) and compressibility (β) were evaluated using the following relations [45-46] from density and sound velocity analysis and are reported in Tables 7, 8 and 9:

• Compressibility coefficient (β) :- $\beta = 1/dv^2$ Where, d is density and v is ultrasonic velocity of solution.
• Apparent molar volume Φ_v ($m^3\ mol^{-1}$):- $\Phi_v = 1000(d_o\text{-}d) / mdd_o + M / d$ Where, m is molality, d_o density of pure solvent, d is the density of the solution and M is the relative molar mass.
• Apparent molar compressibility:- $\Phi_k = 1000(\beta - \beta_o) / md_o + \Phi_v\beta$ Where, $\beta = 1/dv^2$ and $\beta o = 1/dv_o v^2_o$ refer to the adiabatic compressibility coefficients of solution and solvent respectively.

Consistent increase in β values was found with incease in temperature ranging from 25-40°C with interval of 5°C in all the three ethanol solutions respectively. However, with the increase in concentration of ethanol, a decrease in β values were noticed (10%, 20%, 30%) as shown in figure 11(a, b and c). Decrease in the β values indicates that there are more interactions with more efforts to compress the system. Significant interactions were accounted with interactive API and SDS due to extra hydrophobic hydration which is found to be temperature dependent.

Further, overlook into the nature and level of interaction of surfactant in the presence of drug in different ethanol + water solutions was obtained from the behavior of apparent molar volume, ϕ_v, and apparent molar adiabatic compression, ϕ_κ. The data could not be analyzed in terms of limiting apparent molar volume, (ϕ_v^o) and slope (S_v^*) values of the Masson's equation ($\phi_v = \phi_v^o + S_v^* C^{1/2}$), for the reason that ϕ_v dependence on SDS concentration is found to be non – linear which is not a characteristic feature of electrolytic solutions [34]. However, the values for ϕ_v and ϕ_κ were found to be

positive (Table 7, 8 and 9) and (Figure 12a,b and c) at all temperatures and at all compositions. As shown in Figure (12a,b and c), the ϕ_v values decreases sharply at lower concentration ~ 0 – 2 mmol Kg^{-1}, thereafter, the increase from 2-4 $mmolkg^{-1}$ and the variation is almost linear. This change in trend at ~ 5 mmol Kg^{-1} can be considered as the region of micellization or proper micelle formation. Since, THCl is lipophilic organic molecules, it seems that initially at lower concentration of SDS, the binding seems to be governed by electrostatic forces whereas with subsequent addition of surfactant, the pattern indicated the dominance of hydrophobic interactions. Hydrophobic, electrostatic interaction and favorable conditions for micellization were also found for SDS because of its anionic nature. Therefore linear consistence at higher surfactant concentration can be attributed to strong hydrophobic interactions. Moreover, at higher SDS concentration, the interchange in level of interactions among these molecules increases causing formation of SDS micelles. Moreover, higher ϕ_v and ϕ_κ values in alcohol are in good support of previous studies [33].

Table7. Apparent molar volume Φ_v (m^3/mol), Compressibility coefficient β(atm^{-1}) and apparent molar compressibility Φ_k (m^3 mol^{-1}atm), of SDS in 0.03mol.dm^{-3} aqueous solution of Pure API at different temperatures in 10% ethanol system.

[SDS]	25°C			30 °C			35°C			40°C		
Mol dm^{-3}	Φ_v	β	Φ_k	Φv	β	Φk	Φ_v	β	Φ_k	Φ_v	β	Φ_k
0.002	0.82	4.15	03.43	0.85	4.23	03.62	1.13	4.31	04.91	1.55	4.40	06.83
0.004	4.43	4.17	18.52	4.56	4.25	19.40	4.84	4.33	20.99	5.11	4.42	22.64
0.006	5.10	4.17	21.31	5.16	4.25	21.99	5.31	4.34	23.09	5.50	4.42	24.35
0.008	4.98	4.18	20.83	5.05	4.26	21.55	5.19	4.34	22.55	5.36	4.43	23.76
0.01	4.78	4.19	20.07	4.85	4.27	20.73	4.96	4.35	21.64	5.09	4.44	22.63
0.012	4.58	4.20	19.28	4.65	4.28	19.91	4.85	4.36	21.18	4.87	4.45	21.69
0.014	4.74	4.18	19.87	4.82	4.26	20.59	4.96	4.35	21.62	5.03	4.45	22.41

Table8. Apparent molar volume Φ_v (m^3/mol), Compressibility coefficient β(atm^{-1}) and apparent molar compressibility Φ_k (m^3 mol^{-1} atm), of SDS in 0.03 mol.dm^{-3} aqueous solution of Pure API at different temperatures in 20% ethanol solution.

[SDS]	25°C			30 °C			35°C			40°C		
Mol dm^{-3}	Φ_v	β	Φ_k	Φv	β	Φk	Φ_v	β	Φ_k	Φ_v	β	Φ_k
0.002	0.48	4.027	01.93	1.46	4.044	05.92	2.82	4.061	11.49	3.90	4.081	15.92
0.004	5.69	4.032	22.95	6.09	4.049	24.69	6.48	4.064	26.34	6.52	4.083	26.64
0.006	6.65	4.036	26.85	7.24	4.054	29.35	7.25	4.068	29.52	7.70	4.087	31.49
0.008	7.17	4.04	29.00	7.66	4.058	31.09	7.68	4.073	31.30	8.05	4.091	32.97
0.01	6.99	4.042	28.26	7.26	4.060	31.08	7.62	4.076	31.08	7.92	4.094	32.43
0.012	6.88	4.044	27.84	7.33	4.063	30.19	7.40	4.078	30.19	8.048	4.099	32.99
0.014	6.93	4.046	27.64	6.80	4.063	28.41	6.96	4.077	28.41	7.31	4.098	29.98

Table 9. Apparent molar volume Φ_v (m^3/mol), Compressibility coefficient β(atm^{-1}) and apparent molar compressibility Φ_k (m^3 mol^{-1} atm), of SDS in 0.003mol.dm^{-3} aqueous solution of Pure API at different temperatures in 30% ethanol solution.

[SDS]	25°C			30 °C			35°C			40°C		
Mol dm^{-3}	Φ_v	β	Φ_k	Φv	β	Φk	Φ_v	β	Φ_k	Φ_v	β	Φ_k
0.002	0.83	3.97	03.31	0.72	4.029	02.91	1.62	4.12	06.20	2.33	4.21	09.85
0.004	4.35	3.97	17.29	5.01	4.034	20.22	5.56	4.13	22.98	6.07	4.22	25.63
0.006	5.66	3.97	22.52	6.12	4.034	24.70	6.88	4.13	28.479	7.18	4.22	30.37
0.008	6.81	3.98	27.16	7.23	4.039	29.21	7.51	4.13	31.09	8.49	4.22	31.71
0.01	6.92	3.98	27.63	7.24	4.043	29.29	7.75	4.14	32.12	7.78	4.23	32.95
0.012	7.01	3.99	27.99	7.28	4.046	29.48	7.72	4.14	32.01	7.95	4.24	33.72
0.014	6.72	3.99	26.84	7.09	4.047	28.70	7.44	4.14	30.87	7.44	4.23	31.55

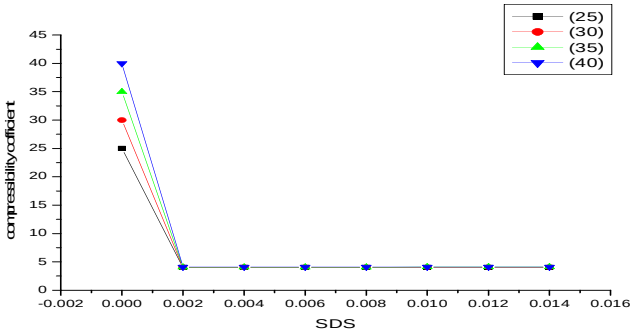

Figure 11(a). Adiabatic compressibility (β, atm^{-1}) co-efficient as a function of SDS in 0.03mol.dm^{-3} of API at different temperatures in 10% ethanol solution.

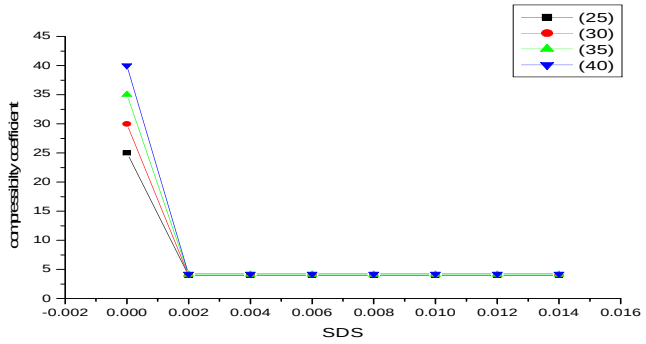

Figure11(b). Adiabatic compressibility (β, atm^{-1}) co-efficient as a function of SDS in 0.003mol.dm^{-3} of API at different temperatures in 20% ethanol solution.

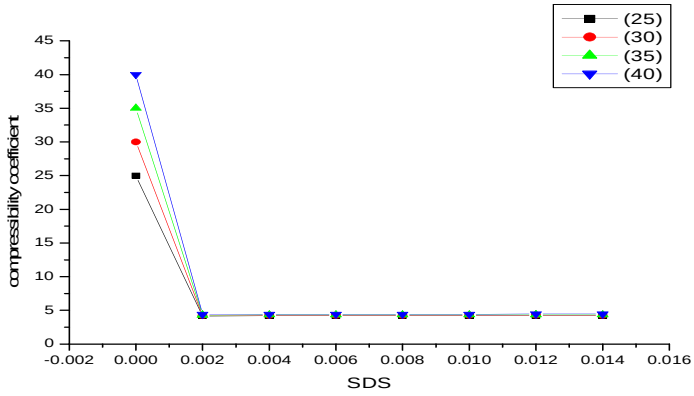

Figure 11(c). Adiabatic compressibility (β, atm^{-1}) co-efficient as a function of SDS in 0.03mol.dm^{-3} of API at different temperatures in 30% ethanol solution.

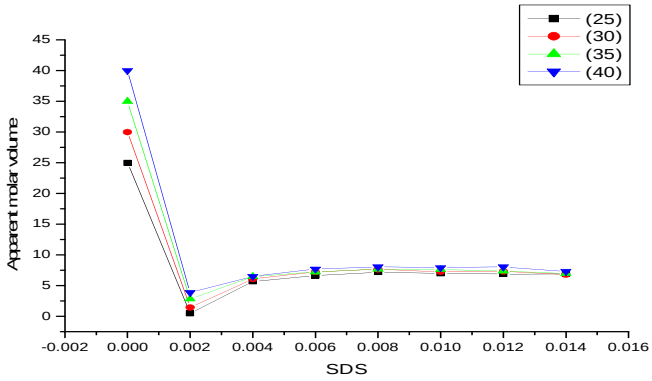

Figure 12(a). Apparent molar volume (Φ_v) as a function of SDS in 0.03mol.dm^{-3} of API at different temperatures in 10% ethanol solution.

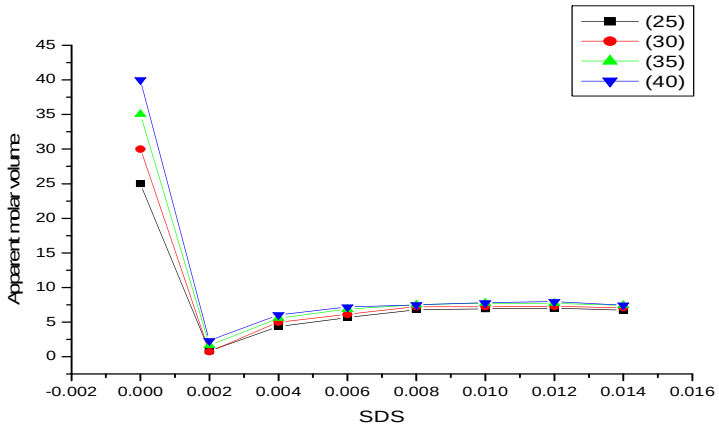

Figure 12(b). Apparent molar volume (Φ_v) as a function of SDS in 0.03mol.dm^{-3} of API at different temperatures in 20% ethanol solution.

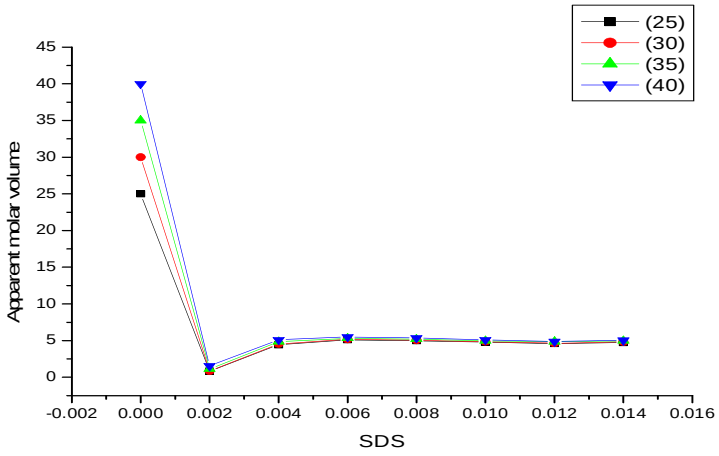

Figure 12(c). Apparent molar volume (Φ_v) as a function of SDS in 0.03mol.dm^{-3} of API at different temperatures in 30% ethanol solution.

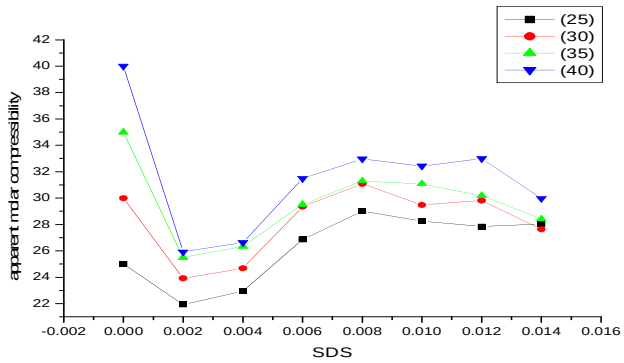

Figure 13(a). Apparent molar compressibility (Φ_k, m^3 mol^{-1}) as a function of SDS in 0.03mol.$dm^{-3}$of API at different temperatures in 10% ethanol solution.

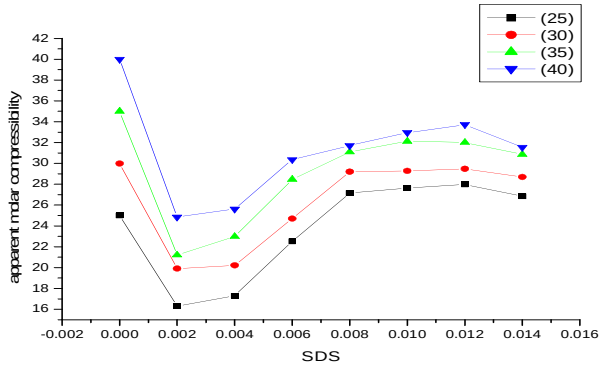

Figure 13(b). Apparent molar compressibility (Φ_k, m^3 mol^{-1}) as a function of SDS in 0.03mol.dm^{-3} of API at different temperatures in 20% ethanol solution.

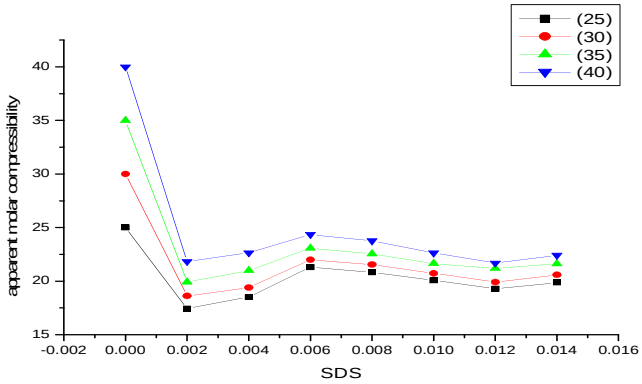

Figure 13(c). Apparent molar compressibility (Φ_k, m^3 mol^{-1}) as a function of SDS in 0.03mol.$dm^{-3}$of API at different temperatures in 30% ethanol solution.

5. Conclusions

Thermodynamic parameters and acoustical parameters have been reported experimentally in this dissertation. Conductivity, viscosity and ultrasonic velocity of Pure API and SDS, $THCl_m$ and SDS, turmeric and SDS in pure aqueous solution have been reported at different temperatures i.e. from 25-40°C at intervals of 5°C. The CMC values of turmeric's system were found to be least among all the aqueous solutions, indicating an early micellization due to the presence of excipient (turmeric). Thereafter, CMC from electrical conductivity measurements was used to calculate the thermodynamic parameters. A significant change in $\Delta H°_m$, $\Delta G°_m$, $\Delta S°_m$ was observed with increase in concentration of Terbinafine Hcl and temperature. The total Entropy change $|T\Delta S°_m|$ was found to be larger than the enthalpy change ($\Delta H°_m$) indicating the micelle formation is entropy ($\Delta S°_m$) driven whereas enthalpy change ($\Delta H°m$) and Gibb's free energy ($\Delta G°m$) values suggested that the system is feasible and exothermic in nature and this feasibility is more spontaneous in presence of Turmeric. Similarly, viscosity study was also found to be temperature dependent and positive viscosity B-coefficients are indicative of strong solute-solvent interactions. Further inference drawn from density and sound velocity studies is also supporting the previous measurements. Since, THCl is lipophilic organic molecules, it seems that initially at lower concentration of SDS, the binding seems to be governed by electrostatic forces whereas with subsequent addition of surfactant, the pattern indicated the dominance of hydrophobic interactions. These interactions are more favored in presence of Turmeric as compared to marketed formulation.

So, Turmeric can be used as excipients in improving the pharmacokinetics of Terbinafine HCl.

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