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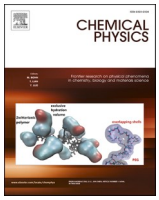

Thymoquinone-Micellar Interactions: A physico-chemical investigation at molecular level

Iram Nadeem [a,b,*], Farhat Yasmeen [a,*], Muhammad Sohail [c], Athar Yaseen Khan [d], Muhammad Nadeem Asghar [d]

[a] Department of Chemistry, University of Engineering and Technology, Lahore Campus, 54890 Lahore, Pakistan
[b] Department of Chemistry, COMSATS University Islamabad, Lahore Campus, 54000 Lahore, Pakistan
[c] Department of Chemistry, Government Islamia Graduate College, Civil Lines, Lahore 54000 Lahore, Pakistan
[d] Department of Chemistry, Forman Christian College (A Chartered University), 45600 Lahore, Pakistan

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ABSTRACT

Thymoquinone (TQ) is considered the most-active component of the well-known essential oil of the black cumin/seeds (*Nigella sativa* L.), also known for its wide-spectrum anticancer and other pharmacological potentials since ancient times. Apart from its thermo- and photo-sensitive nature, TQ has also been reported to demonstrate strong hydrophobicity and low bioavailability. These physico-chemicals, properties hinder the development of a successful oral dosage formulation. Interaction of the pharmacologically active molecule with biological membranes is crucial step to manifest health-related effects. However, further insight into the biophysical interactions of "active" natural chemotherapeutics with cellular membranes can play a vital role in designing and developing new anti-cancer regimens. In this context pseudo-membrane models comprising ionic and non-ionic micelles offer a useful way to explore *in vitro* drug-membrane interactions at the molecular level. The present study focuses on the physicochemical interactions of a thymoquinone (TQ) with micelles of ionic (dodecyl trimethylammonium bromide, DTAB; and sodium dodecyl sulfate, SDS) and non-ionic (tween-80 and TX-100) surfactants at the molecular level in aqueous medium. Volumetric and acoustic parameters (apparent molar volume ($\acute{E}_{,V}$), isentropic compressibility (K_s), apparent molar isentropic compressibility ($\acute{E}_{,k}$), specific acoustic impedance (Z), relative association (RA), intermolecular free length (L_f)) are calculated from experimental data of density and sound velocity and interpreted in terms of solute/solvent–solute/solvent interactions using the co-sphere overlap model and the electrostriction effect. Further, UV spectroscopy and conductivity studies are used to predict the locus of TQ in the micelles, binding constant (K_b), partition coefficient (K_c), and free energy changes of TQ-micelle systems in the presence of surfactants. The results show that the binding and partitioning of TQ is more significant with TX-100 as compared with other ionic and non-ionic surfactants used.

1. Introduction

Owing to their non-toxic, affordable, easily accessible and consistently available benefits, phytochemicals are playing a lead role in the development of anticancer drugs [1]. Approximately 70 % of the anti-cancer chemicals on the market today are derived from medicinal plants or their byproducts, making them the primary source for the creation of anti-cancer medications [2,3]. Presently quinones are one of the most active categories of bioactive phytochemicals against cancer. Thymoquinone (TQ), a member of the Quinone family, has drawn a lot of interest due to its wide-spectrum pharmacological characteristics and therapeutic potential [4]. It is the most abundant bioactive component of volatile oil of *Nigella sativa* L., a member of Ranunculaceae family. The seeds of *N. sativa* are faithfully used for dietary purposes in the Middle East countries and popularly known as *black cumin*. It is reported that the biological activity of *N. sativa* seeds are mainly due to its essential oil constituent that is TQ (30–48 %) which was first extracted by El–Dakhakhny [5]. The black seed oil is cataloged in the list of United States Food and Drug Administration as "Generally Recognized as Safe.".

The pharmaceutical development of TQ for wider use becomes a crucial and challenging assignment in the domain of drug discovery and development. TQ bears potent hydrophobicity or lipophilicity and is

* Corresponding authors at: Department of Chemistry, Faculty of Natural Sciences, Forman Christian College (A Chartered University), Lahore 54600, Pakistan.
E-mail addresses: iramzia@cuilahore.edu.pk (I. Nadeem), f.yasmeen@uet.edu.pk (F. Yasmeen).

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well-evidenced by the value of log $P = 2.54$. This presents a serious hindrance in the pharmaceutical development of TQ into the conventional dosage as tablet and capsule, which is further hindered due to its highly thermolabile nature.

In order to understand the structure, dynamics, and interaction of bio-membranes, several pseudo-membrane models have been proposed in literature [6]. These include micelles, bicelles, liposomes, lipid monolayers, and lipid bilayers, etc. Among these models, surfactant micelles are very simple systems due to their high curvature, small size, and approximately spherical shape [7]. Also, micelles have got important applications in pharmaceutical products as drug carriers. Their small size (~10–80 nm), narrow size distribution, and high solubilizing power for some poorly soluble drugs, make them an attractive choice compared to other alternatives such as liposomes and polymers. As drug-carrying vehicles, micelles are capable of encapsulating drugs, transporting them to the specific site of action, minimizing drug loss and degradation, preventing the harmful side effects, consequently enhancing the drug bioavailability [8]. However, in spite of these advantages, the existing literature shows only a limited number of reports focusing on improving the solubility and bioavailability of TQ using surfactants. Noteworthy studies include self-nanoemulsifying drug delivery system utilizing tween 80 [9], nanoproniosomal-based formulation using span 60 [10] and nanostructured lipid carrier-based system employing tween 80 and pluronic F27 [11]. Therefore, use of micellar solutions for drug solubilization can be considered as a potential drug delivery system to improve bioavailability, lessen toxicity and side effects, increase permeability across physiological barriers, and significantly alter drug distribution [12–15].

Small molecules like TQ, depending upon their spatial chemical structure and polarity, may be solubilized into the palisade layer and/or in the hydrophobic core of a particular micellar system. For a specific drug, the locus within the micelle mainly depends on hydrophobic effect, but the electrostatic and hydrophilic effects are also not irrelevant to be overlooked. The hydrophobic core of the micelles attracts non-polar moieties of the drug while polar head groups, having high charge density, cause electrostatic interaction between micellar surface and polar groups of the drug [16–19]. Micelles of sodium dodecyl sulphate (SDS) and dodecyltrimethylammonium bromide (DTAB), as well as nonionic surfactants such as *t*-octylphenoxypolyethoxyethanol (TX-100) and polyethylene glycol sorbitan monooleate (Tween-80) have frequently been employed as pseudo membrane models to study the intricate mechanisms governing drug interactions with the polar lipid components of the membranes [20–22]. While DTAB, a cationic surfactant, and SDS, an anionic surfactant, have been selected because of their comparable hydrophobic chain lengths with distinct head groups, Tween-80 and TX-100 have been chosen because of their similar polar groups but different chain lengths. This choice makes it easier to conduct a thorough and comparative investigation of how a medicine interacts with various micellar structures. A comparative analysis of the drug interaction with differently charged surfactants and varying alkyl chain lengths can shed light on the nature of the binding forces involved in the drug-membrane interaction, since many biological processes take place at the hydrophobic region or on the ionizable surface of membranes [20–23].

Present work reports physico-chemical interactions of a model drug TQ with ionic and non-ionic micelles in terms of different volumetric and compressibility (apparent molar volume, $\acute{E}_{,V}$; isentropic compressibility, κ_S; apparent molar compressibility $\acute{E}_{,\kappa}$; specific acoustic impedance, Z; relative association RA; intermolecular free length, Lf; and sound velocity number, U) spectroscopic (critical micelle concentration, CMC; partition coefficient, K_x; and binding constant, K_b; and the free energy changes of the interaction (ΔG)) and electrical conductivity (thermodynamic factors of micellization, ΔG^o, ΔH^o and ΔS^o) parameters in aqueous solutions at neutral pH and different temperatures. Figure S1 of Supporting Information (SI) shows the molecular structure of TQ, DTAB, SDS, TX-100 and Tween-80.

2. Material and methods

2.1. Reagents

Thymoquinone (2-Methyl-5-(propan-2-yl)cyclohexa-2,5-diene-1,4-dione; MW: 164.201 g.mol^{-1}, Purity ≥ 98 %, & CAS No. 490–91-5), sodium dodecyl sulphate (SDS, MW: 288.37 g.mol^{-1}, purity ≥ 99 %, & CAS No. 151–21-3), cationic surfactant, dodecyltrimethylammonium bromide (DTAB, MW: 308.34 g.mol^{-1}, purity ≥ 99 %, & CAS No. 1119–94-4), polyoxyethylene (20) sorbitan monooleate (tween 80, MW: 1310 g.mol^{-1}, & CAS No. 9005–65-6) and 2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy]ethanol (TX-100, MW: 625 g.mol^{-1}, & CAS No. 9036–19-5) were purchased from Sigma-Aldrich Co., (St. Louis, MO, USA) and were used as such without any further purification. Deionized water (specific conductivity (5–10) μS.cm^{-1}) was used throughout experimentation.

2.2. Procedures

A working solution of 2.0219×10^{-5} M of TQ was prepared by diluting an appropriate drug stock solution in the aqueous medium such that the solution adhered to the Beer-Lambert law limitation. This solution was used as diluent to prepare stock and working solutions of SDS, DTAB, Tween-80 and TX-100 solutions. To study the drug-micelle interaction at above and below the surfactant CMC, stock solutions of surfactants were diluted with drug solution to obtain concentrations in the pre- and post-micellar regions. The objective was to maintain the TQ concentration constant and gradually make up surfactant concentration from pre-micellar to post-micellar region. The drug-surfactant solution was taken in the sample cell while deionized water and the drug solution were placed in the reference cell, for recording normal and differential spectra, respectively.

2.2.1. Specific conductivity measurements

The specific conductivity measurements of TQ-Surfactant systems at various temperatures T = 298.15–313.15 (±0.05) K were performed to calculate thermodynamic parameters (ΔG^o, ΔH^o and ΔS^o) of micellization process. Pre- and post-micellar concentrations of the surfactants were made in the constant TQ concentration of 2.0219×10^{-5} M and subjected to specific conductivity measurement using benchtop conductivity meter InoLab® 7110 ((calibrated with a standard solution of 1413 μS.cm^{-1}) and a cell constant of 0.476 cm^{-1}) equipped with an MRC Labs Oil Bath (OBHR-3, UK) with a temperature stability within ± 1 K. The specific conductivity data obtained was used to calculate the thermodynamic parameters. All solutions were prepared using deionized water (~5–10) μS.cm^{-1}.

2.2.2. Density and sound velocity measurements

Density and sound velocity measurements of aqueous solutions of surfactant, DTAB, SDS, Tween-80 and TX-100, in the absence and presence of TQ (2.0219×10^{-5} M) were made at different temperatures [T = (298.15, 303.15, 308.15 and 313.15) ± 0.001 K] using a high-precision density and sound velocity meter (Anton Paar Gmbh, DSA 5000, Graz, Austria). The density and sound velocity data obtained is presented in the Tables S1-S8 of SI. In order to thoroughly evaluate the effect of temperature on different volumetric and electrochemical parameters, the temperature range [T = (298.15, 303.15, 308.15, and 313.15) K] was deliberately selected. Furthermore, this range encompasses the physiological temperature, which is very important for examining drug-membrane interactions [24,25]. The instrument uncertainty for the sound velocity and density measurements was ± 0.51 m/s and ± 0.16 kg/m-3, respectively.

2.2.3. Uv–visible spectroscopy

Shimadzu UV-1800 spectrophotometer was used for spectroscopic analysis of 2.0219 × 10^{-5} M TQ in aqueous medium in the absence and presence of surfactants. A quartz cuvette of 1 cm path length was used for measurement at temperature 298 K. All spectra were recorded in the wavelength (λ) range of 200–400 nm.

3. Results and discussion

3.1. Volumetric studies

Volumetric and acoustic investigations were performed to gain insight into the molecular interactions within the TQ-Surfactant-Water system. Several volumetric and compressibility parameters, such as the apparent molar volume ($\acute{E}_{,V}$), isentropic compressibility (κ_s), apparent molar compressibility ($\acute{E}_{,\kappa}$), specific acoustic impedance (Z), relative association (RA), intermolecular free length (L_f) and sound velocity number (U), were evaluated and interpreted at the molecular level. Equation (1) was used to calculate $\acute{E}_{,V}$ over the range of temperature and composition [26].

$$\acute{E}_{,V} = M/d + [d_o - d]/mdd_o \quad (1)$$

Where, m is the molality (mol. kg^{-1}) of the aqueous TQ-surfactant solution, M is the molar mass (kg.mol^{-1}) of surfactant, and d_o and d, are respectively the densities of the pure solvent and the solution. Molality (m) of TQ-surfactant aqueous solution was calculated using the formula: m = 1 / (d / C - M / 1000), where m is expressed in mol. kg^{-1}. Here, C stands for the molarity (mol. L^{-1}) of the surfactant solution, M for the surfactant's molar mass (kg.mol^{-1}), and d and d_o are densities of solutions and the pure solvent respectively. Tables S9-S12 of SI present the calculated ($\acute{E}_{,V}$) values for both ionic and non-ionic systems in the presence and absence of TQ. Masson's relationship cannot be used because of the estimated ($\acute{E}_{,V}$) *vs.* [S] graph's nonlinear behavior. This nonlinearity shows that the systems under study have electrostatic and hydrophobic interactions. Therefore, based on the established correlation of $\acute{E}_{,V}$ with [S], an attempt has been made to explain the drug-surfactant interactions.

The solute/solvent–solute/solvent interactions can be estimated quantitatively using volumetric parameters like $\acute{E}_{,V}$ and $\acute{E}_{,k}$. TQ is acidic in nature with a pK_a value of 5.1 [27], and in aqueous medium it may exist in both enol and keto-tautomeric forms, the latter of which is more stable (~90 %) [28]. The following interactions between drugs and surfactants may be anticipated at the molecular level by considering the chemical constitution of TQ-surfactant-water systems: (i) hydrophobe - hydrophobe interactions among the nonpolar moieties of TQ and the alkyl chains of surfactants; (ii) hydrophobe - hydrophile interactions between the alkyl chains of surfactants and hydrophilic groups (C═O, –OH) of TQ and, and between –OC_2H_5, –OH and –O– groups of non-ionic surfactants and hydrophobic moieties of TQ; (iii) hydrophobe-ion interactions between the nonpolar moieties of TQ and the ionic groups (Na^+ and $-OSO_3^-$ of SDS or Br– and $-N^+(CH_3)_3$ of DTAB) of surfactants; (iv) hydrophile-ion interactions between hydrophilic groups of TQ (>O =) and ionic groups (Na^+ and $-OSO_3^-$ of SDS or Br^- and $-N^+(CH_3)_3$ of DTAB) of surfactants; (v) hydrogen bonding among TQ, water, and surfactant molecules. The occurrence of such interactions has been reported in the literature, highlighting their significant role in shaping the physico-chemical properties of drug-surfactant systems [29–31]. The change in solution volume with respect to the pure solvent per mole of solute is known as the apparent molar volume ($\acute{E}_{,V}$) of a solute. When a solution is formed, solute and solvent molecules interact, changing the volume of the solution [32]. As shown in Fig. 1 and Fig. S2 of SI, we have plotted ($\acute{E}_{,V}$) *versus* the molality (m) of surfactants at various

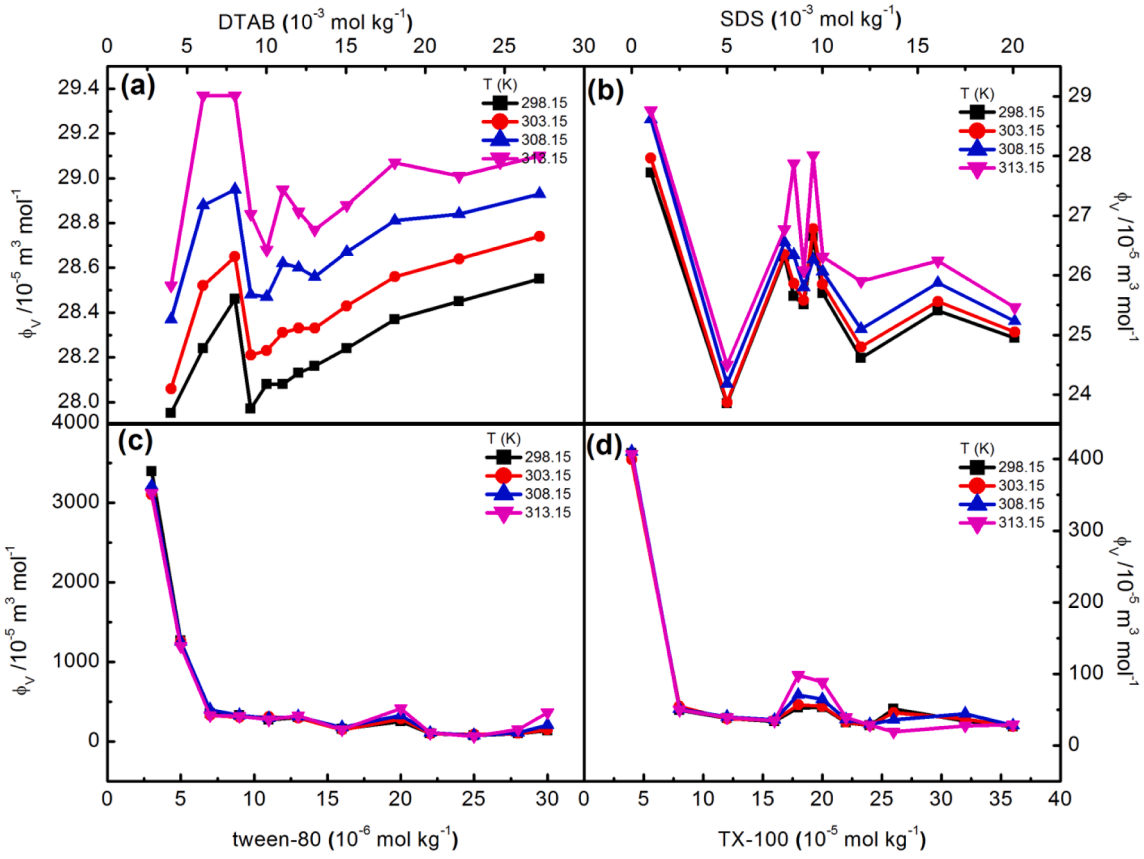

Fig. 1. Plot of $\acute{E}_{,V}$ *versus* m of (a) DTAB, (b) SDS, (c) tween-80 and (d) TX-100 in the presence of TQ (2.02107 × 10^{-5} mol.kg^{-1}) at different temperatures.

temperatures, both with and without TQ. In comparison to the bulk, the solution's physical and chemical characteristics around a solute molecule change significantly. A solute molecule in a solution typically has a hydrated structure called a co-sphere. The Co-sphere Overlap model put out by Gurney [33] and Evans [34] may be used to explain the fluctuation of ($\acute{E}_{,V}$) with [S] in aqueous solution and in solution of TQ. The model predicts that a positive volume transfer happens occurs when the cospheres of two ions or polar groups, or the ion and a hydrophilic group overlap. On the other hand, a negative volume transfer occurs when the cosphere of an ion or hydrophilic group overlaps with that of a hydrophobic group. Thus, all volume transfers, whether positive or negative, may be explained in terms of molecular cosphere overlaps. Thymoquinone is predominantly a hydrophobic molecule with hydrophobic regions (aromatic ring and isopropyl unit) and two hydrophilic > C═O groups, and thus the chemical nature of the cospheres around these groups is quite distinct. Moreover, the electrostriction effect, which causes the solvent to constrict around the solute, can also be used to explain the interactions between drugs and surfactants. The positive and negative values of $\acute{E}_{,V}$ are caused by a reduction and an increase in the volume of electrostriction in the vicinity of a solute molecule, respectively [35]. All studied surfactant systems displayed positive values of $\acute{E}_{,V}$ when TQ was present, indicating the presence of strong type (iv) and (v) electrostatic and hydrogen bonding forces between TQ's (>C═O) groups and the surfactant ions and hydrophilic regions. This reduced electrostriction in the area of these ions and led to the relaxation of the solvent molecules. Further, at any specific point in the $\acute{E}_{,V}$ *vs.* surfactant concentration [S] plot, temperature-dependent increase in $\acute{E}_{,V}$ may be attributed to a decrease in electrostriction near the hydrophilic/ionic centres of TQ and surfactants, which ultimately leads to stronger type (iv) & (v) electrostatic interactions [36].

In the absence of TQ, the $\acute{E}_{,V}$ values exhibit a sharp rise in the beginning with increasing [S] until they reach a steady state, which signifies the attainment of the Critical Micelle Concentration (CMC). It is well known that the hydrophobic interaction is the main driving force for micellization. The hydrophobic interaction most likely increases the molar volume as a function of the [S] (Fig. 1). The release of water from the area around the head groups/hydrophilic moieties is expected to contribute towards this rise. This water has a smaller molar volume than bulk water because it is electrostrictively restricted.

A closer examination of Fig. 1 reveals a general increasing trend in $\acute{E}_{,V}$ values for ionic surfactants in aqueous solutions reflecting the dominance of ionic and hydrophilic interactions of categories (iv) and (v) during the process of micellization. However, in the case of the DTAB system, the $\acute{E}_{,V}$ values initially increased until the concentration of DTAB approached 6.0 $mmol.kg^{-1}$. Subsequently, a rapid decline in $\acute{E}_{,V}$ was observed, signifying the attainment of the Critical Micelle Concentration (CMC) and the dominance of hydrophobic forces belonging to categories (i)-(iii). Nevertheless, upon crossing the CMC, a renewed upward trend in $\acute{E}_{,V}$ with a lower slope was noticed, followed by a transition to a steady state. This behavior suggests a gradual shift in dominance from forces of categories (i)-(iii) to forces of categories (iv) and (v). Overall the $\acute{E}_{,V}$ values tend to increase and become relatively positive with increasing [DTAB] and temperature, suggesting that the type (iv) and (v) interactions tend to dominate at higher temperatures. A similar trend was seen in the TQ-SDS system, but with one important exception: forces belonging to categories (i)–(iii) quickly become dominant, indicating the accomplishment of the Critical Micelle Concentration (CMC) at around [SDS] = 5.0. Hydrophilic-ion forces, however, gradually took control as the [SDS] concentration rose until a steady state condition was reached. In accordance with the cosphere overlap model, the mutual interactions of the cospheres of ionic and hydrophilic moieties of DTAB/SDS surfactant systems, TQ and water groups leads to a positive volume transfer due to relaxation of the electrostricted water molecules which were localized around ions and hydrophiles [37]. Conversely, the hydrophobe- (alkyl chains of surfactants and hydrophobic moieties of TQ) and polar water interactions contribute a negative volume transfer. These interactions operate simultaneously but counteractively; the overall change in $\acute{E}_{,V}$ is determined by the prevalence of one of these two counteracting interactions under the given conditions. Initially, the pre-micellar area of DTAB/SDS-water systems exhibits a dramatic shift in $\acute{E}_{,V}$ at a certain molality, indicating a transient dominance of electrostatic forces. However, with successive additions of [S], hydrophobic forces tend to become stronger, leading to a reduction in $\acute{E}_{,V}$. But when the CMC approaches, a significant jerk in $\acute{E}_{,V}$ is observed, which represents the rearrangement of surfactant monomers to form micelles, the remaking of the water structure, and the reestablishment of hydrophobic forces.

Conversely, an opposite trend is observed in the case of TX-100/Tween-80-TQ-water systems as compared to the DTAB/SDS-TQ-water systems. In the pre-micellar region, the electrostatic interactions of type (iii) and (iv) initially led to higher positive volume transfers, however, with further incremental increase in [S] a sharp decline in $\acute{E}_{,V}$ values is noticed until a plateau at CMC is reached. Here, with the addition of surfactant, the type (i)-(iii) hydrophobic forces significantly enhanced, resulting in early attainment of a steady state and a lower CMC values compared to literature-reported values. The relative higher hydrophilicity of Tween-80 is also indicated by the initially larger positive $\acute{E}_{,V}$ values for Tween-80 compared to TX-100.

The increase in $\acute{E}_{,V}$ with temperature may be ascribed to several factors including [38]:

(a) an enhanced dislocation of electrostricted water molecules from the cospheres of $(CH_3)_3N^+$–, $–OSO_3^-$ and hydrophilic moieties of TX-100/Tween-80 to bulk water and.

(b) a reduction in DTAB/SDS–water interactions and.

(c) a small negative volume change due to decreased H_2O-H_2O interactions as temperature rises.

Further, the drug-surfactant interactions can be explained on the basis of electrostriction effect (the contraction of solvent around the solute). The decrease and increase of the volume of electrostriction in the locality of a solute molecule results in the positive and negative values of $\acute{E}_{,V}$, respectively [39]. In the attendance of TQ, all the surfactant systems studied showed positive values of $\acute{E}_{,V}$, demonstrating the existence of strong type (iv) and (v) electrostatic and hydrogen bonding forces between (>C═O) groups of TQ and surfactant ions/hydrophilic regions resulting into reduction in the magnitude of electrostriction in the neighborhood of these ions and consequent relaxation of solvent molecules.

3.2. Acoustic studies

Isentropic compressibility (K) was calculated as:

$$\kappa_s = 1/u^2 d and \kappa_o = 1/u_o^2 d_o \quad (2)$$

Where κ_s and κ_o are respectively, the isentropic compressibility of aqueous solution of TQ and the solvent while u and u_o are, respectively, their sound velocities. The computed κ_s values for both ionic and non-ionic surfactants are tabulated in Table S13-S16 of SI.

Isentropic compressibility (κ_s) serves as a measure of inner pressure brought on by the compressed surrounding developed by molecular interactions between solute and solvent. The variation in κ_s of solutions after self-aggregation are strongly influenced by numerous factors: the release of water from hydrated alkyl chain in the hydrophobic core, the mutual electrostatic repulsion of head groups of surfactant molecules, and the release of hydrated water from the head groups as a result of counter ion binding [38].

The representative plots showing variation in κ_s as a function of [S] for ionic and non-ionic surfactants in the presence and absence of 2.02107×10^{-5} mol. kg^{-1} aqueous solution of TQ, have been graphed in

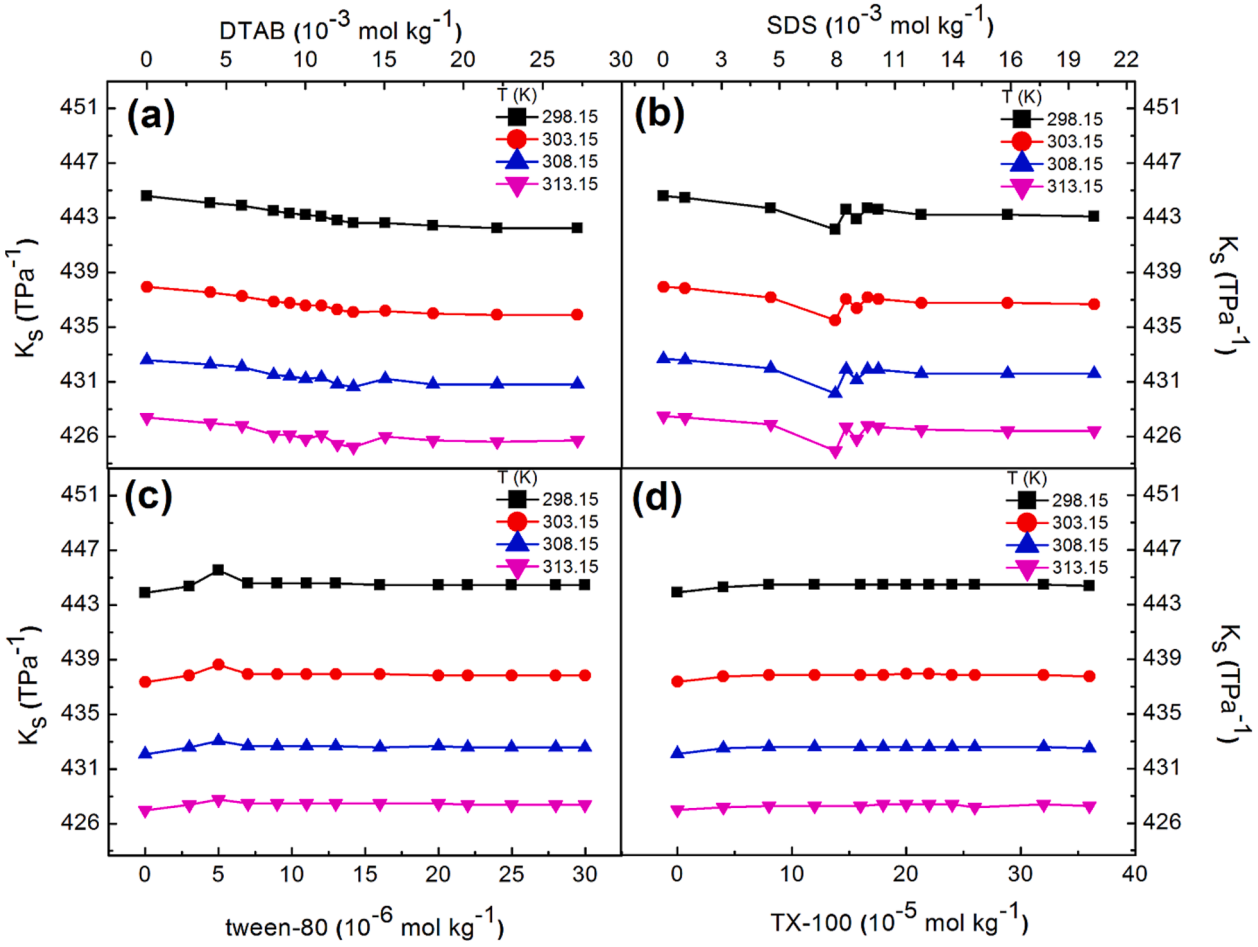

Fig. 2. Relation of K_s with m of surfactant (a) DTAB (b) SDS (c) tween-80 and (d) TX-100 in aqueous solution of 2.02107 × 10^{-5} mol. kg^{-1} TQ at different temperatures.

Fig. 2 and Fig. S3 of SI, respectively. The κ_s values are found to decrease with an increase in temperature for all the surfactants the temperatures studied which may be ascribed to thermal disintegration of water clusters, which produces smaller assemblies of water molecules and eventually leads to more densely packed clusters at high temperatures [39].

For ionic surfactants a decrease in κ_s with increase in [S] was seen, while an opposite trend was observed for non-ionic surfactants. In the pre-micellar region of ionic surfactants, the increase in [S] in the presence of TQ enhances the compactness of the system elicited by type (iv) and (v) interactions amongst the components of ternary mixture of TQ-surfactant-water that results in the reduction of κ_s [40]. At each examined temperature, as the [S] is increased, greater number of water molecules are electrostricted, leading to reduction in the volume of bulk water and a decrease in compression. In the micellar phase, the κ_s values are decreased as a function of [S] and temperature resulting from the water structure breaking effect around the hydrophobic moieties of surfactants (alkyl chains) and TQ (aromatic rings, alkyl residues) which in turn increase the intermolecular interactions.

It is also noteworthy that, though, κ_s values decrease with increasing [S] for ionic surfactants, and *vice-versa* for non-ionic surfactants, but they become almost constant above CMC. This behavior may be ascribed to the lower hydration tendency of the surfactant systems in micellar phase compared to monomeric form [41] and the establishment of almost maximum electrostrictive compactness of the existing system that was responsible for decrease in κ_s values [42].

In case of non-ionic surfactants, some very interesting results were found in κ_s patterns in the presence of TQ. In contrary to ionic surfactants, after CMC a slight increasing trend was observed in compressibility of the ternary systems. Generally, the decrease of κ_s values results from the combined effects of hydration of surfactant molecules and breaking of three dimensional network of water structure. According to Passynski [43], with the addition of solute the compressibility of water becomes strongly reduced compared to that of pure bulk water. At CMC, when the aggregate is formed, the released water molecules in the vicinity of the hydrophobic part of the molecule become part of bulk water. The water molecules around the hydrophobic part are highly structured, having a rather low compressibility compared to the bulk water. In case of tween-80/TX-100, when hydrophobic hydration involving the long alkyl chains and non-polar moieties of TQ, together with electrostricted water in the hydration shell around the oxyethylene groups of surfactants and > C═O groups of TQ, disappear at CMC, compressibility of the newly-formed micelles could not offset it, which leads to an increase in the Ks values in the post-micellar region.

Apparent molar compressibility ($\acute{E}_{,K}$), ~~is~~ the difference between the compressibility of the solution and that of the pure solvent per mole of solute, was computed by the following equation [44]:

$$\acute{E}_{,K} = \acute{E}_{,V}K_s + [K_s - K_o]/md_o \quad (3)$$

The representative plots in Fig. 3 and Fig. S4 of SI (Table S17-S20 of SI) show variation in $\acute{E}_{,K}$ values for both ionic and non-ionic surfactant systems as a function of m at various temperatures. Interesting conclusions may be drawn from comparing the $\acute{E}_{,K}$ *vs.* m plots for ionic surfactants (SDS/DTAB) in water and aqueous solutions of TQ. This finding implies that the presence of non-polar TQ close to the surfactant reduces

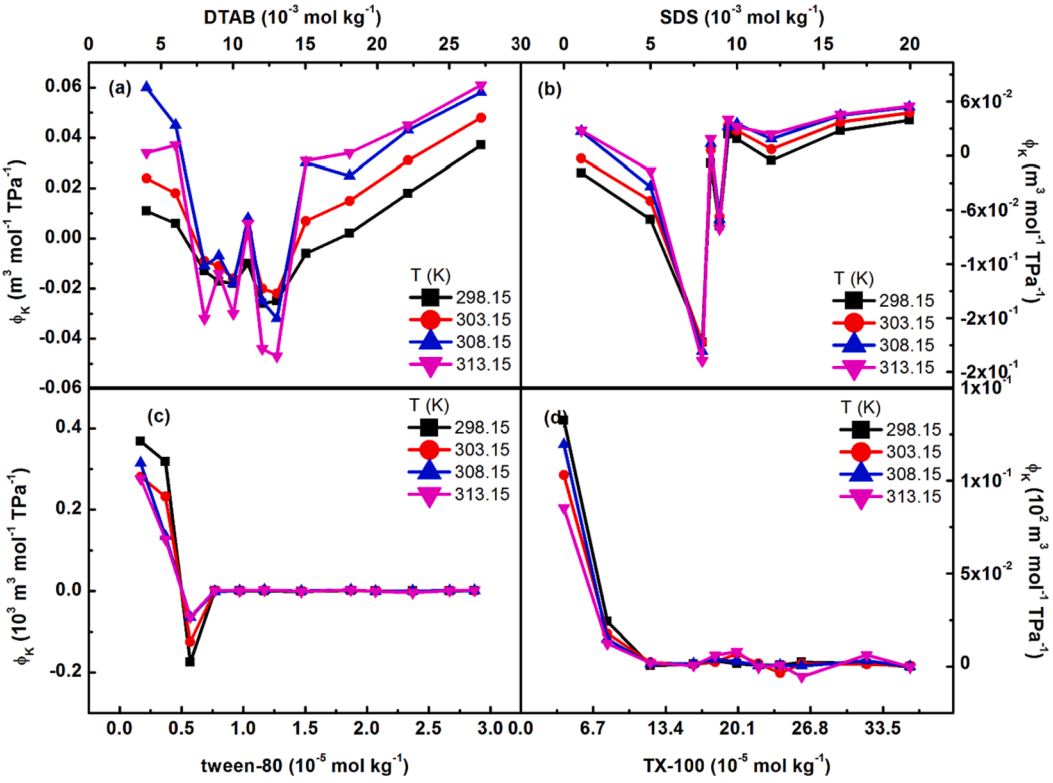

Fig. 3. Plot of $\acute{E}_{,K}$ *versus m* of ((a) DTAB (b) SDS, (c) Tween-80 and (d) TX-100 in the presence of 2.02107 × 10^{-5} mol. kg^{-1} TQ at different temperatures.

the electrostatic interactions that result from the hydration of amphiphilic head groups at low temperatures in the absence of TQ. The result is a more compressible solution.

The less negative $\acute{E}_{,K}$ or positive values for a surfactant at low concentrations in presence of TQ may be ascribed to binding of TQ to ionic surfactants through type (i)-(iii) interactions. Initially the $\acute{E}_{,K}$ values of TQ system decrease with increasing [S] indicating the increase in the hydration shells (electrostricted water) around the ionic head groups until the CMC is reached. Beyond the CMC, $\acute{E}_{,K}$ values become less negative suggesting the loss of hydrophobic hydration due to micellization of surfactant, which makes the micellar interior relatively compressible. A rise in $\acute{E}_{,K}$ values with respective surfactant concentrations depicts that the hydrophobic hydration structure of TQ-surfactant complex is lost due to the micellar solubilization of the TQ (Fig. 3a & 3b). However, the incremental rises of [DTAB/SDS] make the solutions more structured and less compressible. On the other hand, both the non-ionic systems at low [S] showed higher $\acute{E}_{,K}$ values in the presence of TQ suggesting that the water structure breaking effect of TQ in the direct locale of surfactant setting more and more electrostricted water free and thus making the solution more compressible. However, with the increase in the [tween-80] and [TX-100] the $\acute{E}_{,K}$ values decrease and hydrophobic interactions dominate till the attainment of CMC where the curve levels off. This indicates a transition from a more structured to a less compressible state.

Specific acoustic impedance (Z), relative association (RA), intermolecular free length (L_f) and sound velocity number (U) were computed by using Equations (4)-(7), respectively [38,44–47]:

$$z = ud \tag{4}$$

$$RA = (d/d_o)(u_o/u)^{1/3} \tag{5}$$

$$L_f = K/ud^{1/2} \tag{6}$$

$$U = u - u_o/u_o m \tag{7}$$

In Equation (6) K is a constant which is independent of the nature of liquid. Jacobson determined the value of K between 0 and 50 °C as (93.875 + 0.375) × 10^{-8} so L_f can also be calculated between 0 and 50 °C.

The values of Z, RA, L_f, and U calculated for both ionic and non-ionic systems are presented in Tables S21-S24 of SI. Z values indicate the impedance offered by the solution components to sound waves. The rise in Z values as a function of [S] of all the surfactant systems investigated, both in the absence and attendance of TQ, demonstrate the presence of strong interactions among different components of the solutions [35].

Acoustic impedance, Z, is the resistance offered to the propagation of sound waves by solution components. In the pre-micellar region, aqueous solutions of TQ exhibited relatively low values of Z with the variation in [S] as compared to the corresponding aqueous surfactant solutions, indicating the water structure breaking effect of TQ. Overall, a non-linear increase in Z values with rise in [S] was noticed implying that there exist strong intermolecular interactions among the solution components [48].

RA is a useful physical parameter that assesses the degree of association of components of medium i.e., a solution or a solvent. In general, RA values fall when the solvent structure is broken on introduction of solute, and rise when the solute ions are solvated, and *vice versa* [38,49]. In the case of an aqueous TQ solution, the progressive addition of DTAB/SDS causes a reduction in RA values in the pre-micellar region and then an increasing trend was observed after CMC. This could be attributed to TQ's first structure-breaking impact in the pre-micellar region and then hydration of the SDS head groups following CMC. In case of non-ionic surfactant systems (TX-100 or tween-80), no trend could be traversed demonstrating the ongoing battle between structural breakdown of solvent network and the solvent-ion developing interactions between the components.

Though in absolute terms, calculation of L_f values using Equation (6)

is not advisable for associated solvents like water, alcohols and organic acids etc., however, computation of L_f can help predict the general trends of intermolecular forces existing within the systems. A consistent [S]-dependent decrease in L_f values was observed in both ionic and non-ionic systems. This observation suggests a robust interaction between TQ and the surfactants. Furthermore, as the temperature increased, the L_f values also increased, indicating an expansion of the intermolecular distances among the components in the solution. This may be attributed to the disruption of the water network structure.

In order to further examine molecular interactions in the solution, the speed of sound (U) was computed. Sound speed normally rises with surfactant content, as seen in Table S21–S24 of SI. However, this increase is not linear and instead depends on the surfactant aggregate state (monomer or micelle). Particularly, below CMC, only the characteristics of the monomeric amphiphiles have an impact on the sound speed. Instead, above CMC, both surfactants in the micellar state (whose [S] = CMC) and those in the monomeric state have an impact on sound speed. As a result, below CMC, the increase in U is mostly reliant on [S] and is basically linear. Above CMC, the rise in sound speed is either slower or declines because the systems are more compressible as a result of the loss of water bound to the amphiphiles, during the micellization process. The intrinsic structure of the micellar aggregates affects the variance in sound speed above CMC. Strong molecular interactions between the various components of the solution may thus be inferred from the fluctuations in U values for ionic and non-ionic surfactants as well as with temperature [44,50].

3.3. Specific conductivity and micellization

3.3.1. Determination of CMC of DTAB and SDS in the presence of TQ

The aggregation behavior of ionic surfactants (DTAB and SDS) in aqueous medium in the presence of TQ is evaluated to have an insight into the thermodynamic mechanism of micellization in the presence of TQ molecules. Specific conductivity (κ) *vs.* [S] plots at different temperatures demonstrated a consistent dependence of κ on [S] (Fig. 4). A definite inflexion point in the slope of the κ *vs.* [S] plot is observed which was used to evaluate the CMC (Table 1). Using electrical conductivity method, the CMC value of SDS in the aqueous solution of TQ at 298.15 K was found to be higher than the standard literature value, while the CMC of DTAB under the same conditions was found to be less as compared to the standard value reported in literature, which are 8.0 $mM.dm^{-3}$ and 15.1 $mM.dm^{-3}$, respectively.

3.3.2. Thermodynamics of micellization

For ionic surfactants, the free energy of micellization may be calculated by following Equation (8) [51–53]:

$$\Delta G_m^o = (2-\beta)RTlnX_{CMC} \tag{8}$$

Where ΔG_m^o is the standard Gibbs free energy change of micellization, β is the degree of dissociation, the gas constant $R = 8.314$ $J.mol^{-1}.K^{-1}$, T is the absolute temperature, X_{CMC} is CMC in mole fraction (X_{CMC} = CMC/n_s, where n_s accounts for number of moles of solvent per litre at 298.15 K). The enthalpy of micellization (ΔH_m^o) can be determined by using the Gibbs–Helmholtz Equation (9) [52,54]:

$$\Delta H_m^o = -2.3(2-\beta)RT^2(\partial(logX_{CMC})/\partial T)_p \tag{9}$$

The term $(\partial log\ XCMC/\partial T)_P$ is calculated from the slope of the graph between log X_{CMC} and T. Finally, the standard entropy change during the micelle formation (ΔS_m^o) is calculated using following Equation (10):

$$\Delta S_m^o = (\Delta H_m^o - \Delta G_m^o)/T \tag{10}$$

The increase in CMC values can be ascribed to TQ's ability to modify the structure of water or the interactions involving water and surfactant monomers or micelles. TQ, owing to its non-polar nature, can disrupt the organization of water molecules, essentially acting as a water-structure breaker. This results in a relative increase in the degree of hydration of the hydrophilic groups, consequently raising the CMC. Moreover, the contribution of entropy effect may also be taken into account for reduction in the micellization process. When surfactant molecules dissolve in water, the hydration of hydrophobic alkyl chains produces a more ordered arrangement of water molecules around them, increasing the system's entropy during micellization process. However, the presence of TQ as a water-structure breaker in the system might interfere with this organized arrangement of water molecules around the alkyl chains, decreasing the entropy increase during micellization, and thus discouraging the overall micellization process. Moreover, the elevation of CMC can also be partly ascribed to a reduction in the dielectric

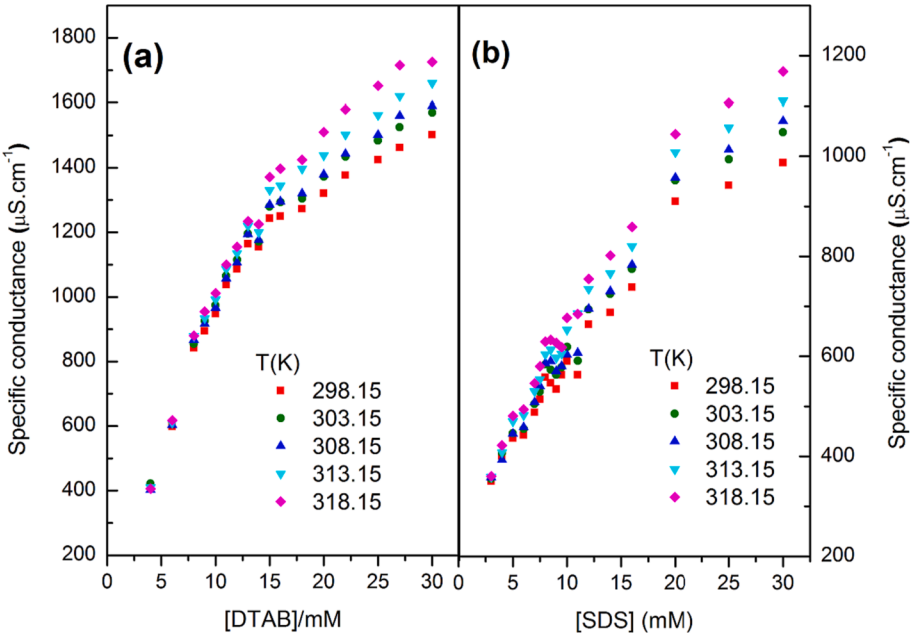

Fig. 4. Concentration-dependent variation in specific conductivity of aqueous solution of (a) DTAB and (b) SDS at different temperatures in the presence of constant concentration of TQ (2.0219×10^{-5} M).

Table 1
Thermodynamic parameters of aggregation process of TQ-DTAB/SDS systems at various temperatures.

System	Temp. Temp. (*K*)	CMC* (mmol/L)	**CMC***	*B*	$dlnX_{CMC}/dT$	ΔH_m^o (kJ.mol^{-1})	ΔG_m^o (kJ.mol^{-1})	ΔS_m^o (kJ.mol^{-1} K^{-1})	$T\,\Delta S_m^o$ (kJ.mol^{-1})
TQ-DTAB	298.15	13.8	15.03 [55]	0.285	0.0047	−5.96	−35.283	0.0984	29.32
	303.15	13.9	15.43 [55]	0.305	0.0047	−6.09	−35.405	0.0967	29.32
	308.15	14.0	15.62 [55]	0.338	0.0047	−6.17	−35.250	0.0944	29.08
	313.15	14.6	15.74 [55]	0.335	0.0047	−6.38	−35.699	0.0936	29.32
	318.15	15.0	15.03 [55]	0.372	0.0047	−6.44	−35.348	0.0909	28.91
TQ-SDS	298.15	8.6	7.90 [56]	0.397	0.0063	−7.47	−34.863	0.0919	27.40
	303.15	8.7	8.50 [56]	0.429	0.0063	−7.56	−34.687	0.0895	27.12
	308.15	9.0	9.00 [56]	0.450	0.0063	−7.71	−34.644	0.0874	26.93
	313.15	9.4	9.70 [56]	0.513	0.0063	−7.64	−33.596	0.0829	25.96
	318.15	9.6	9.80 [57,58]	0.441	0.0063	−8.27	−35.694	0.0862	27.45

Uncertainty involved in temperature is ± 0.01 K. The error limits of CMC, ΔH_m^o,ΔS_m^o *and* ΔG_m^o are ± 4, ±2, ±2 and ± 4 %, respectively.
* Literature values of aqueous DTAB and SDS using specific conductance[55–58].

constant of the aqueous medium surrounding the head group region, causing an increased mutual repulsion among the head group ions. On the other hand, the decrease in CMC of DTAB may be attributed to the increased hydrophilic dehydration and the greater hydrophobic interactions in the presence of aqueous TQ.

The negative values of ΔH_m^o and ΔG_m^o and positive values of ΔS_m^o as presented in Table 1 are suggestive of enthalpy–entropy-driven spontaneity of both the TQ–DTAB and TQ-SDS micellization processes. Negative values obtained of ΔH_m^o demonstrated that the overall process of micellization accompanying solubilization of TQ and its interaction with DTAB and SDS micelles is exothermic in nature. This is also indicative of the strong polar interactions between TQ and the two ionic surfactants used. Though both enthalpy and entropy may be considered as the driving forces in micellization phenomenon, however, the relatively higher ΔS_m^o values at different temperatures ($T\ \Delta S_m^o$) indicate entropy rise as the lead phenomenon responsible for micellization (Table 1). This can be justified as a re-organization of water molecules at CMC and partly by the solubilization of TQ at micellar surface. A temperature-dependent decrease in entropy may be ascribed to weakening of intermolecular bonds with temperature.

3.4. UV spectroscopy

The normal UV spectrum in aqueous medium is characterized by the presence of one distinct peak (λ_{max}) at 258 nm, as shown in Fig. 5. This peak is a characteristic peak of quinones and is thought to differentiate quinones from its analogue hydroquinone, which exhibits a peak at about 290 nm [59]. Fig. 6 shows the effect of variation in the [S] on absorption spectra of TQ in aqueous medium. The changes in absorbance and λ_{max} of TQ as a function of [S] are graphed in the insets of the respective figures.

Significant changes in the absorbance of 12.11 mM [DTAB], 8.92 mM [SDS], and 0.012 mM [Tween-80] and of 0.07 mM [TX-100] solutions, indicate the CMCs of the respective surfactant and adsorption/encapsulation of TQ molecules in the micelles (Fig. 6). The literature reports CMC of DTAB, SDS, Tween-80 and TX-100 as 14.2 mM, 7.19 mM [60], 0.015 mM [61] and 0.2—0.3 mM [62] respectively, at room temperature. TQ is a small hydrophobe having methyl, isopropyl, cyclohexa-2,5-diene hydrophobic moieties and polar > C═O groups at the 1 and 4 positions of cyclohexadiene moiety in TQ. DTAB and SDS ionic micelles can both interact with TQ molecules, but the way they do so and what drives their interaction are different. TQ can interact with

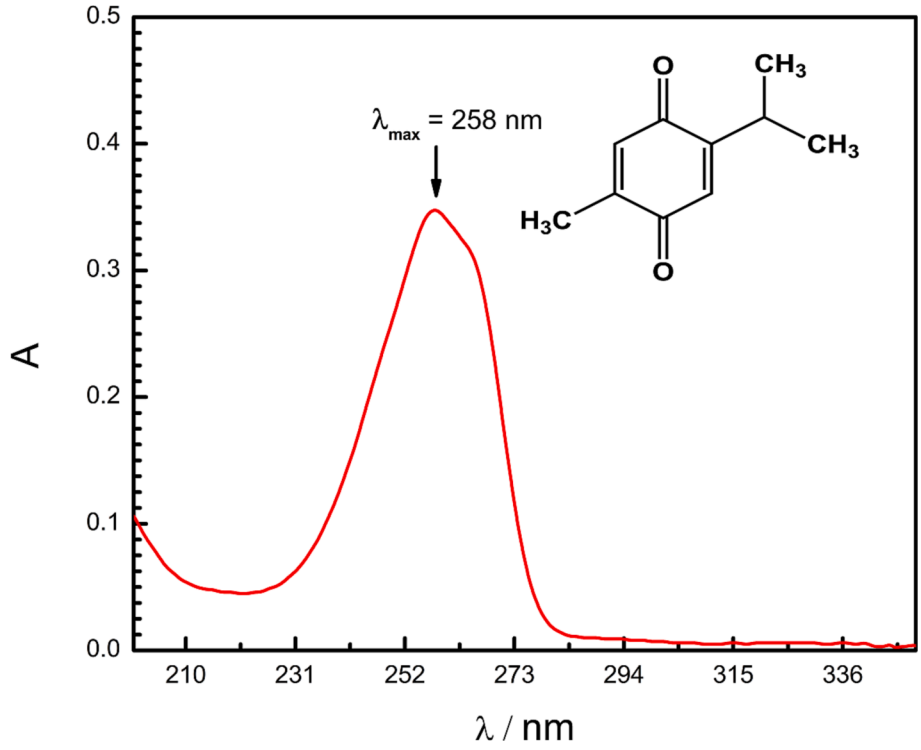

Fig. 5. Normal UV absorption spectrum of 2.09 × 10^{-5} M aqueous solution of TQ. The inset shows the molecular structure of TQ.

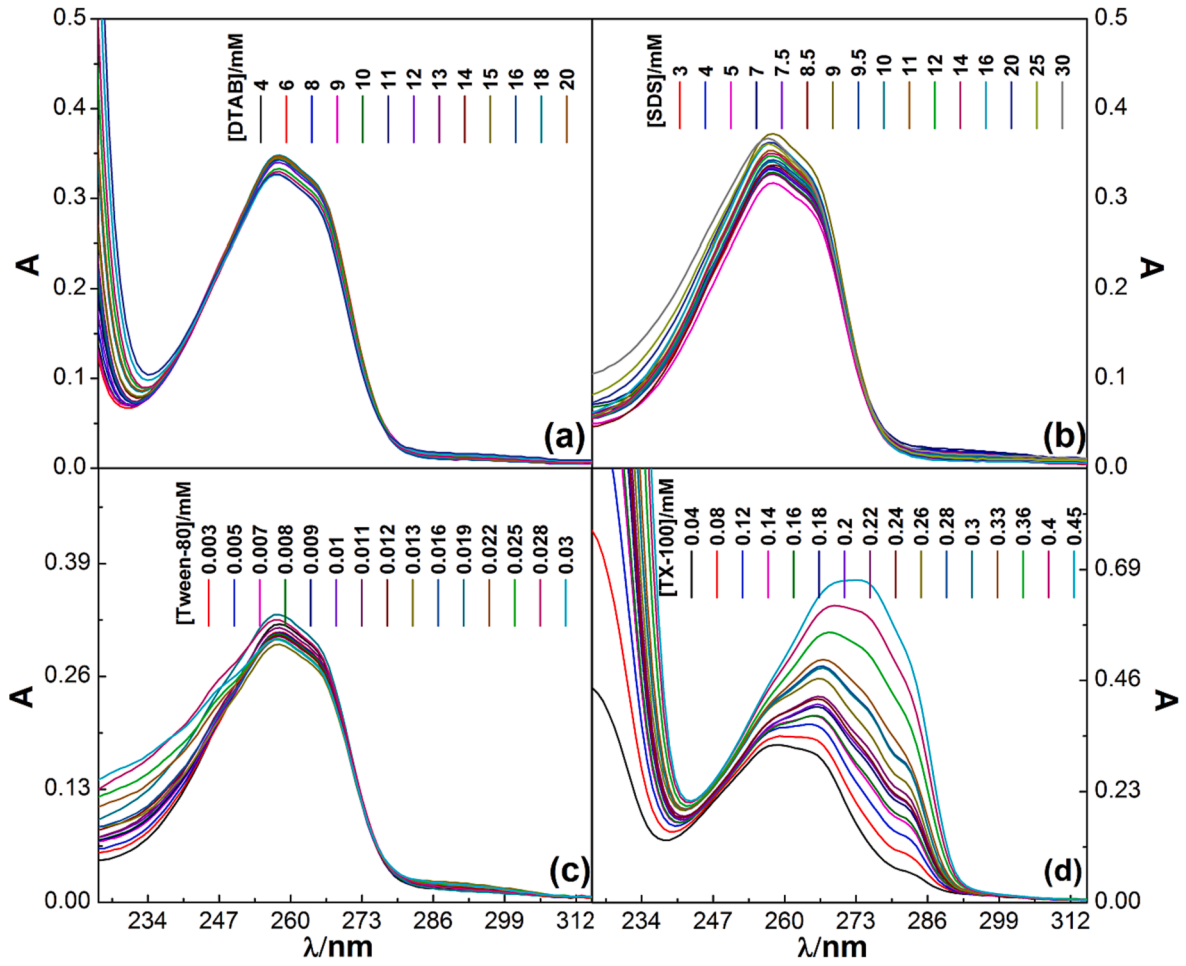

Fig. 6. The UV spectra of TQ-surfactant complex in aqueous medium of varying (a) [DTAB], (b) [SDS], (c) [Tween 80] and (d) [TX-100].

the -$N^+(CH_3)_3$ and -OSO_3 ions of DTAB and SDS, respectively, through hydrogen bonding, and lone pairs on O═C < groups. The comparatively lower CMC value obtained for DTAB illustrates the water structure-making or hydrophobic effect of TQ [63,64], i.e., ability of hydrophobic residues (methyl, isopropyl and cyclohexadiene) to induce self-aggregation and, consequently, reducing the CMC. Additionally, -$N^+(CH_3)_3$ possesses three hydrophobic –CH_3 groups in contrast to the SDS head group containing hydrophilic oxygen moieties with lone pairs, which reduces the extent of hydration around the DTAB head groups [65], making it more hydrophobic. Further, lone pairs of electrons on –OSO_3 of SDS are capable of making hydrogen bonds with any H-bond acceptor like water. In contrast to DTAB, the electrostatic interactions between TQ and the SDS micelles seems to dominate making the micellization more difficult. The hydrophilic keto-moiety of TQ seems to adsorb at the water-DTAB micelle interface due to electrostatic attractions with positively charged head groups and thereby reducing the electrostatic repulsions among head groups and decreasing the CMC. However, in case of TQ-SDS micelle a reverse interaction is seen that results into increase in CMC.

The absorbance of TQ initially increases with increase in [DTAB] in the premicellar region (Fig. 6a), indicating the solubilization of TQ due to water structure breaking effect of added surfactant, however further addition of DTAB allows hydrophobic forces to dominate and facilitate micellization. A sharp decrease in TQ absorbance at [DTAB] > 12 mM with no peak shifting implies the attainment of CMC and adsorption of the drug at the water-micelle interface. Beyond 12.2 mM [DTAB], absorbance again starts increasing indicating the encapsulation of TQ in the micelles, which continues as the number of micelles improves until a steady-state is reached where all the drug molecules are encapsulated. In the case of SDS, the TQ absorbance curve initially rises highlighting the strong TQ-SDS electrostatic engagements; however the sharp rise in the absorbance with a little spectral shift highlights the attainment of CMC. Further increase in [SDS] leads to rise in TQ absorption continually together with incorporation of more drug molecules into the newly-added micelles until a level-off is reached.

In case of interaction with non-ionic surfactants a mixed behavior is observed. Taking into account the higher contribution of oxyethylene units in the chemical make-up of tween-80 and hydrophobic nature of TQ, it seems that TQ-tween-80 system as expected shows a higher decrease in CMC as compared to TQ-TX-100 system. However, for TX-100, a stronger water structure making effect of TQ, relative to tween-80, is noticed. A relatively higher decrease in CMC of TX-100 indicates stronger hydrophobic effect due to non-polar moieties and less hydration of hydrophilic part (oxyethylene) of TX-100 in presence of TQ. Both these factors cumulatively result in comprehensive decrease in the CMC of TX-100. In case of tween-80 in aqueous TQ the CMC is found to be relatively less affected, which be attributed to higher oxyethylene content of tween-80 involving stronger hydration as compared to structure making effect of TQ molecules. It can be seen from the Fig. S5 that though both the surfactant system caused a decrease in the CMC value, the underlying mechanism of TQ-surfactant interaction is different. The initial increase or decrease in the TQ absorbance for non-ionic surfactants may be attributed to the electrostatic interactions among the polar components of TQ-surfactant-water systems. However, a continuous increase in the absorbance in the post-micellar region coupled with a significant spectral shift of 8 nm (from 259 nm to 267

nm) in TQ-TX-100 system may be attributed to shifting of the TQ molecules from a medium of high dielectric constant (bulk water) to a relatively non-polar micellar environment where their chromophoric parts are positioned such that they can still be photo-absorptive. Keeping in view a higher decrease in the CMC for TQ-TX-100 system it may also be inferred that the TQ molecules remain adsorbed at the head group region such that they electrostatically shield the repulsions of polar head groups of TX-100 and thus facilitate micellization process. On the other hand, for TQ-Tween-80, the post-micellar absorbance firstly decreases and then levels off indicating that TQ molecules penetrate somewhat deeper into tween-80 micelles where they are such oriented that they can neither absorb radiations nor shield the repulsions of polar head groups to reduce the CMC appreciably.

The fluctuation in TQ's differential absorbance in aqueous medium as a function of [S] at 298.15 K is shown in Fig. 7. The post-micellar rise in ΔA of TQ with increase in surfactant concentration in the same absorption band reflects the ongoing integration of the drug molecules in the micelles.

Estimation of the partition coefficient (K_c) is important as it indicates not only the magnitude of the solubilizing power of a particular micellar phase, but also helps in understanding the mechanisms of drug-membrane interactions. K_c was determined using the following equation [66]:

$$1/\Delta A = 1/K_c \Delta A_\infty (C_a + C_s^{mo}) + 1/\Delta A_\infty \quad (11)$$

Here, C_s^{mo} stands for C_s- CMC^o (CMC^o is the CMC of the surfactant in water), C_a is the drug concentration, and ΔA_∞ stands for differential absorbance at infinite surfactant concentration (C_s). The linear plot of $1/\Delta A$ *versus* $1/(C_a + C_s^{mo})$ for determining the K_c from the slope and the intercept is shown in the inset graph Fig. S4 of SI. The connection $K_x = K_c \times n_w$, where n_w is the amount of H_2O molecules per cubic meter of pure water (i.e., 55.55 mol/dm^3), was used to determine the dimensionless partition constant (K_x).

Benesi–Hildebrand Equation (12) was used to calculate the binding constant (K_b) of CH with surfactant micelles (Fig. S4 of SI) [67]:

$$dC_a/\Delta A = 1/(\Delta\varepsilon K_b C_s^{mo}) + 1/\Delta\varepsilon \quad (12)$$

where $\Delta\varepsilon$ is the difference in absorption coefficients. The linear plot of $dC_a/\Delta A$ *vs.* $1/C_s^{mo}$ was used to evaluate intercept and slope of the plot for K_b values.

The Gibbs free energy change for binding (ΔG_b) and partitioning (ΔG_p) processes of TQ-surfactant systems were determined using the Equations (13) and (14), respectively:

$$\Delta G_b = -RTlnK_c \quad (13)$$

$$\Delta G_p = -RTlnK_x \quad (14)$$

The values of binding constants, partition coefficient and their corresponding Gibbs free energy changes are listed in Table 2. Though reasonable values of K_x and ΔG_p were obtained for both the ionic surfactants (SDS & DTAB), however, the highest values for K_x (8.686 x 10^{-4}) and ΔG_p (-28.19 kJ mol^{-1}) were achieved for TQ-TX-100 system, signifying the supremacy of the non-ionic system for incorporating spontaneous solubilization of TQ molecules in the micelles. The water structure-breaking effect of aromatic moieties of TQ molecules coupled with the hydrophobic interactions of alkyl chain of TX-100 facilitates the self-aggregation of TX-100 at lower CMC value. The continuous increase

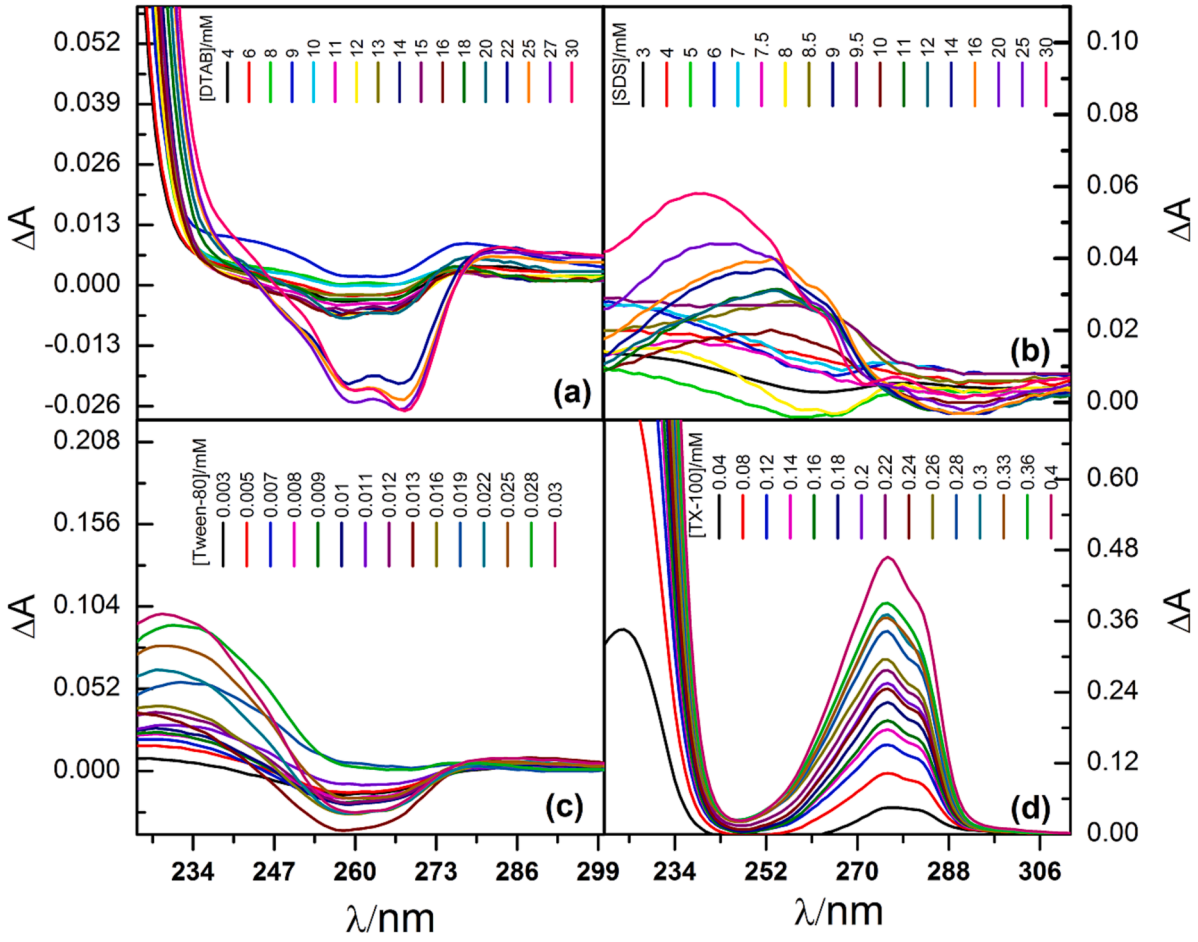

Fig. 7. Differential absorbance spectra of TQ–surfactant in aqueous medium of varying (a) [DTAB], (b) [SDS], (c) [Tween 80] and (d) [Tx-100].

Table 2
Partition coefficient (K_x), binding constant (K_b) and related free energies (ΔG) for CH-surfactant systems.

System	Medium	CMC* (mM)	K_b (M^{-1})	$\Delta G_b°$ ($kJ.mol^{-1}$)	$K_x \times 10^3$	$\Delta G_p°$ ($kJ.mol^{-1}$)
TQ-DTAB	H_2O	12.11	10.00	−5.71	0.478	−15.29
TQ-SDS	H_2O	8.93	300.00	−14.14	20.352	−24.59
TQ-Tween 80	H_2O	0.014	4.79	−3.88	20.351	−24.59
TQ-TX-100	H_2O	0.07	1.14×10^{-5}	−13.13	1818.735	28.07

* The error limit of CMC is ± 3 %.

in the absorbance after CMC further implies that the TQ chromophores are continuously incorporated in the micellar cage. Partition coefficient values serve as indicators of the drug solubilization capacity within a particular surfactant system. The notably higher partition coefficient values, Kx (approximately 20 times and 4000 times greater compared to tween-80/SDS and DTAB, respectively) obtained for TX-100 unequivocally demonstrate the remarkable potential of TX-100 in solubilizing TQ in aqueous media. This highlights its prospective utility in the development of potential formulations of TQ. The post-micellar increase and bathochromic shift in TQ-TX-100 systems suggest electrostatic interactions between the polar $> C{=}O$ moiety of TQ and the hydrophilic ethylene oxide and –OH groups at the water-micellar interface, and hydrophobic linkages between the non-polar methyl, isopropyl and cyclohexadiene moieties of TQ and non-polar alkyl moieties of the outer palisade layer resulting into large partition coefficient and binding energy.

Relatively lower values of K_b were obtained for non-ionic micelles showing the dominating hydrophobic natures of the systems. The substantially stronger electrostatic interaction of TQ with SDS head groups in SDS micelles compared to DTAB and other non-ionic micelles account for the relatively higher K_b value of TQ-SDS system. This significantly stronger contact makes it easier for the drug to enter the micelles, boosting the partition coefficient in the process.

3.5. Conclusion

The objective of the present investigation study was to understand the physic-chemical nature and molecular dynamics of solute–solvent interactions of the TQ-micellar systems in aqueous medium at various surfactant and temperature conditions. The volumetric and acoustic parameters computed for ionic and non-ionic surfactants (DTAB, SDS, tween-80 and TX-100) in the presence of TQ were used to interpret, and correlate the apparent molar volume and acoustic parameters with the solute–solvent interactions using cosphere overlap model and electrostriction effects. The intrinsic hydrophobic nature of TQ demonstrated a vital role in modifying the intermolecular forces among the solution components and thus shaping the trends of these parameters. UV spectroscopy demonstrated higher binding constant and partition coefficient for TQ-TX-100 system implying the greater solubilization power of TX-100 for TQ. A general deduction in view of the results obtained from different techniques is that hydrophobic forces are primarily responsible for binding and partitioning of TQ in ionic and non-ionic micelles. Such studies in drug-model membrane interactions may help design new drugs and drug delivery systems involving surfactant micelles.

CRediT authorship contribution statement

Iram Nadeem: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Farhat Yasmeen:** Conceptualization, Data curation, Project administration, Supervision. **Muhammad Sohail:** Methodology, Validation, Writing – original draft. **Athar Yaseen Khan:** . **Muhammad Nadeem Asghar:** Methodology, Validation, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemphys.2024.112198.

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