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Micellar Solubilization of Carbamazepine

Majda Srabovic[1*], Melita Poljakovic[1] and Ekrem Pehlic[2]

[1]Faculty of Science, Department of Chemistry, University of Tuzla, Bosnia and Herzegovina.
[2]Faculty of Biotechnical, University of Bihac, Bosnia and Herzegovina.

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: An important property of micelles with particular significance in pharmacy is their ability to increase the solubility of poorly soluble drugs in water thus increasing their bioavailability. It was of interest to increase the solubility of carbamazepine (CBZ) in aqueous media. Therefore, solubilization of carbamazepine (CBZ) in variety of surfactants was investigated.
Study Design: In this work the solubilization of carbamazepine (CBZ) was studied in micellar solutions of different anionic and cationic surfactants.
Place and Duration of Study: Department of Chemistry, University in Tuzla, between January 2012 and June 2012.
Methodology: The solubilization data were analyzed on the basis of a pseudo-phase model. An ultraviolet–visible spectrophotometry was used to analyze carbamazepine

**Corresponding author: E-mail: majda.srabovic@untz.ba;*

solubility and its molecular location in the micelles.
Results: It was found that carbamazepine solubility increases due to an increase in the carbon length of cationic surfactants. This indicates that carbamazepine is solubilized primarily in the hydrophobic micellar core. Of all surfactants used, the one that gives the highest solubilization of carbamazepine is SDS with value of molar solubilization capacity 0.163 and the lowest is DTAB and SDBS with value of molar solubilization capacity 0.090 nad 0.092.
Conclusion: The results confirm that SDS micelles can solubilize carbamazepine and significantly increase its total aqueous solubility. The solubility of carbamazepine is present only at a concentration of surfactants exceeding the critical micellar concentration (cmc).

Keywords: Carbamazepine; micelles; solubilization; anionic surfactants; cationic surfactants.

1. INTRODUCTION

Carbamazepine (CBZ), a dibenzazepine derivative with structure resembling the tricyclic antidepressans is a first-generation anticonvulsant drug that has been used to treat partial seizures, trigeminal neuralgia, manic-depressive illness, and explosive aggression for nearly 40 years. Carbamazepine (CBZ) is a white or almost white powdered crystal, chemical name 5-H-dibenz(b,f)-azepine-5-carboxamide. The chemical structure of CBZ is illustrated in Fig. 1.

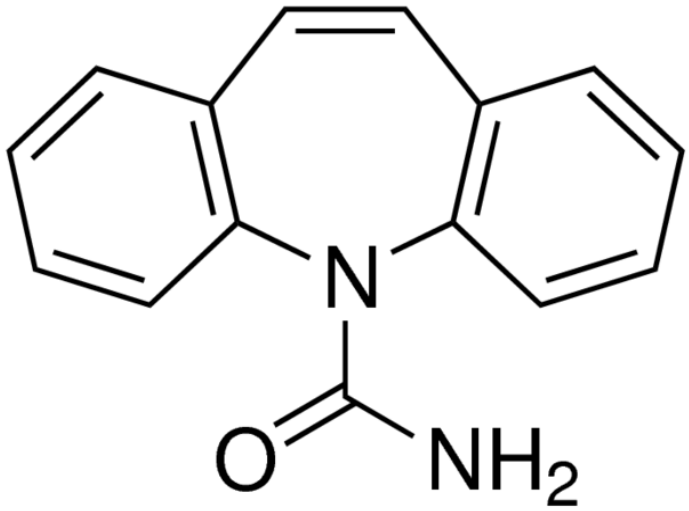

Fig. 1. Carbamazepine chemical structure

Four well-characterized anhydrous polymorphs and a dihydrate as well as other solvates of carbamazepine have been reported in the literature [1,2]. Differences due to polymorphism and pseudopolymorphism in pharmaceuticals are of importance, as physicochemical properties (e.g. solubility) can affect bioavailability and effective clinical use [3,4].

Carbamazepine (CBZ) is a commonly used anticonvulsant drug and belongs to class II of the Biopharmaceutical classification system (BCS). Compounds belonging to class II have

high intestinal permeability and low water solubility. Subsequently, the bioavailability of such compounds is limited by their solubility in water.

Carbamazepine is a poorly water-soluble drug, practically insoluble in water (about 113 µg/mL at 25ºC) [5].

Micellar solubilization is an area of investigation for the improvement of pharmaceutical formulations. Surfactants are amphiphilic molecules, consisting of both hydrophilic and hydrophobic regions. They are widely used to improve the solubility of poorly soluble drugs and also have the advantage of protecting the drug against hydrolysis. Solubilization by surfactant systems was discussed thoroughly by previous investigators [6-8].

One important property of surfactants is the formation of colloidal-sized clusters in solutions, known as micelles, which have particular significance in pharmacy because of their ability to increase the solubility of sparingly soluble substances in water [9]. The utilization of aqueous micellar solutions for drug solubilization can be advantageous for drug delivery purposes, with the possibility of increasing water solubility of poorly soluble drugs, improving bioavailability, reducing toxicity and other side effects, enhancing permeability across the physiological barriers, and substantial change in drug distribution [10].

Usually, the solubilization of a molecule by a surfactant can be evaluated based on two descriptors: molar solubilization capacity (χ) and micelle-water partition coefficient, (*K*) [11]. The (χ) value is defined as the number of moles of the solute (drug) that can be solubilized by one mol of micellar surfactant, and characterizes the ability of the surfactant to solubilize the drug. It can be calculated based on the general equation for micellar solubilization:

$$\chi = (S_{tot} - S_0) / (C_{surf} - CMC) \quad (1)$$

where S_{tot} is the total drug solubility, S_0 is the water drug solubility, C_{surf} is the molar concentration of surfactant in solution, and *CMC* is the critical micelle concentration.

Since above the *CMC* the surfactant monomer concentration is approximately equal to the *CMC*, the term (C_{surf} -CMC) is approximately equal to the surfactant concentration in the micellar form and, therefore, (χ) is equal to the ratio of drug concentration in the micelles to the surfactant concentration in the micellar form. On the other hand, the micelle-water partition coefficient is the ratio of drug concentration in the micelle to the drug concentration in water for a particular surfactant concentration, as follows:

$$K = (S_{tot} – S_0)/ S_0 \quad (2)$$

Combining equations (1) and (2), we can relate the two solubility descriptors. Accordingly, for a given surfactant concentration:

$$K = \chi\ (C_{surf} - CMC) / S_0 \quad (3)$$

As it can be seen, K is related to the water solubility of the compound, in contrary to (χ) [12]. In order to eliminate the dependence of K on the surfactant concentration, a molar micelle-water partition coefficient, K_m , can be defined as follows:

$$K_m = \chi\ (1\text{-}CMC) / S_0 \quad (4)$$

2. MATERIALS AND METHODS

Carbamazepine (CBZ), decyltrimethyl ammonium bromide (DTAB) (98% pure), tetradecyl trimethyl ammonium bromide (TTAB) (99% pure), hexadecyl trimethyl ammonium bromide (CTAB) (99% pure), sodium dodecyl sulfate (SDS) (99% pure), sodium dodecyl benzene sulfonate (SDBS- pharmaceutical secondary standard), sodium laurylether sulfate (SLES) (95% pure) ethanol, hexane and methanol (99,8%) were purchased from Sigma Aldrich. Deionisated water was used in all the experiments.

2.1 Determination of Critical Micelle Concentrations (*CMC*)

The *CMC* of the surfactants at 25ºC was determined in water. The *CMC* determinations for anionic and cationic surfactants were based on the change in conductance with surfactant concentration, with the measurements performed in a Eutech PCD 6500 conductivimeter. Each conductivity measurement was repeated three times, and the typical error in the *CMC* determination was less than 5%. Table 1 gives the CMC for the used surfactants under experimental conditions. Obtained CMC surfactants values were in accordance with literature data [13,14].

Table 1. CMCs of the used surfactants at experimental conditions

Surfactants	CMC (M)($\cdot 10^{-3}$)	Conditions
$CH_3(CH_2)_9N(CH_3)_3(Br)$ (DTAB)	53,52	25℃, H_2O
$CH_3(CH_2)_{13}N(CH_3)_3(Br)$ (TTAB)	3,27	25℃, H_2O
$CH_3(CH_2)_{15}N(CH_3)_3(Br)$ (CTAB)	0,93	25℃, H_2O
$CH_3(CH_2)_{11}OSO_3Na$ (SDS)	7,98	25℃, H_2O
$CH_3(CH_2)_{11}C_6H_4SO_3Na$ (SDBS)	1,88	25℃, H_2O
$CH_3(CH_2)_{11}(OCH_2CH_2)OSO_3Na$ (SLES)	2,9	25℃, H_2O

2.2 Ultraviolet Assay

An ultraviolet – visible (UV – Vis) spectrophotometer (Perkin-Elmer, Model Lambda 25), controlled by Perkin Elmer UV WinLab Software at the interface, was used to analyze carbamazepine solubility and its molecular location in the micelles. Preliminary UV scanning of pure aqueous carbamazepine yielded a stable peak at 285 nm. A series of drug – surfactants solutions was diluted as needed with respective solvents and analyzed by UV - Vis spectrophotometer. Fig. 2 show an excellent correlation (r^2>0.998) indicated that the Beer–Lambert law was obeyed in the carbamazepine concentration ranges of interest.

2.3 Solubility Determination

The solubility of carbamazepine in anionic and cationic surfactants solutions was measured at surfactant concentrations between 0 and 100 mM. Excess amounts of carbamazepine were added to vials containing 10.0 mL of anionic and cationic surfactant solutions. The resulting suspension was treated at room temperature (25ºC) with 100 rpm in an incubator orbital shaker for 24 hours. The solutions were allowed to equilibrate and analyzed on the basis of a pseudo-phase model [15]. After 24 hours, the samples were filtrated and the concentration of solubilized carbamazepine determined spectrophotometrically as described above. All the solubility experiments were carried out in triplicate.

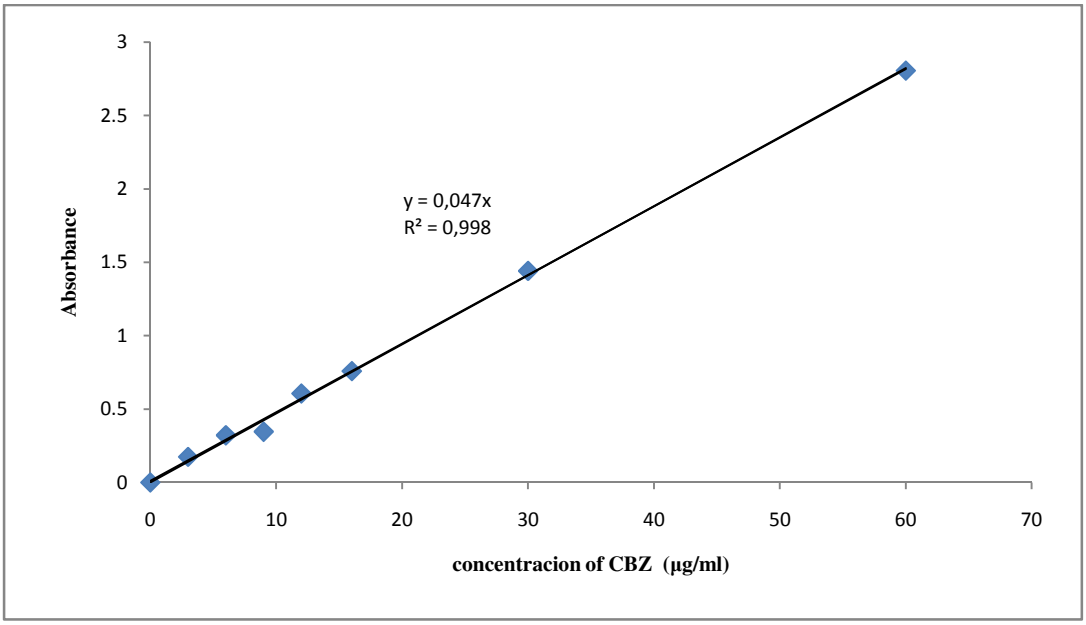

Fig. 2. Calibration curve of carbamazepine

2.4 Spectral Test

The spectral test was done to investigate the location of carbamazepine in the micelles of different surfactant solutions. The ultraviolet spectrum (Perkin-Elmer, Model Lambda 25) was used to determine the wavelength at maximum absorption λ_{max} of carbamazepine in each solvent or solution. SDS, SLES, SDBS, DTAB, TTAB, CTAB, heptane, water, methanol, ethanol were all used in this experiment. The solubilization test was done for each solvent. The absorbances at fixed range of wavelength were obtained using the solvents and solution as the blanks. If dilution was needed, the original solvent was used.

3. RESULTS AND DISCUSSION

In the present work, a number of anionic surfactants (SDS, SDBS, SLES) and cationic surfactants (DTAB, TTAB, CTAB) showed significant solubilizing ability of carbamazepine at 25ºC (Figs. 3 and 4., respectively). Results show that the solubility of carbamazepine linearly increases with increasing concentration of anionic surfactants: sodium dodecyl benzene sulfonate (SDBS) < sodium lauriletersulfat (SLES) < sodium dodecyl sulfate (SDS).

Figs. 3. and 4 explain that solubility is present only at a concentration of surfactants exceeding the critical micellar concentration for anionic surfactants (7.98 x 10^{-3}M SDS, 2.9 x 10^{-3}M for SLES 1.88 x 10^{-3}M of SDBS at 25ºC) and cationic surfactants (0,93 x 10^{-3}M for CTAB; 3,27 x 10^{-3}M for TTAB i 53,52 x 10^{-3}M for DTAB) which indicates the phenomenon of micellar solubilization.

Surfactant chain length effect on solubilization carbamazepine is shown in Fig. 4. For alkyl trimethyl ammonium bromides, the solubilization of carbamazepine has a significant chain length effect : DTAB <TTAB< CTAB . An increase in the hydrocarbon chain length of cationic

surfactant results in an increase in the degree of carbamazepine solubilization. This indicates that carbamazepine is solubilized primarily in the hydrophobic micellar core

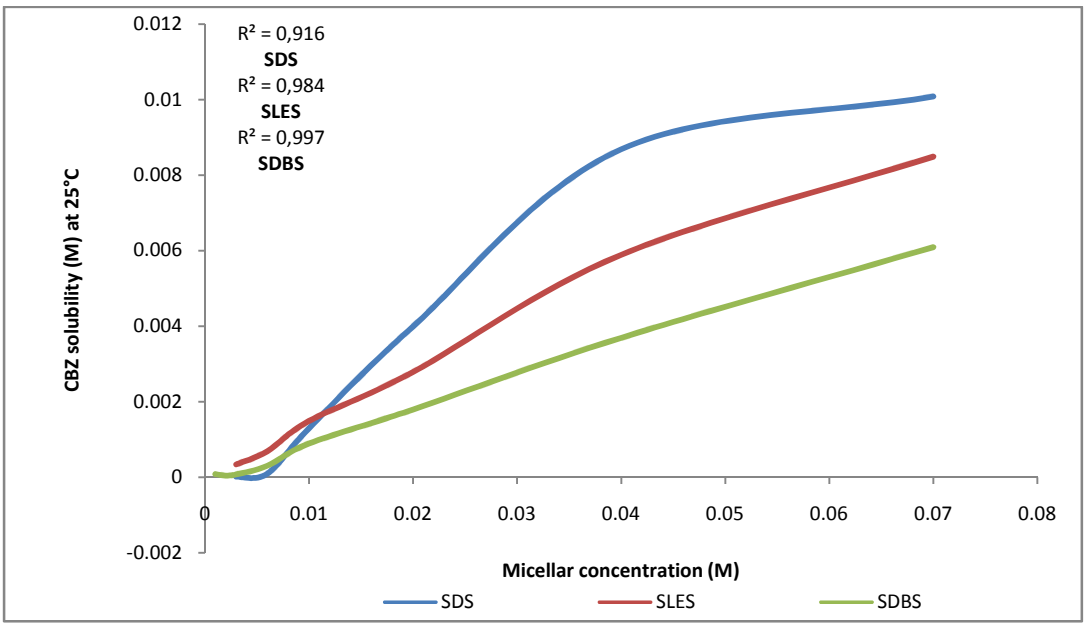

Fig. 3. Carbamazepine solubility versus micellar concentration (C-CMC) for anionic surfactants at 25°C

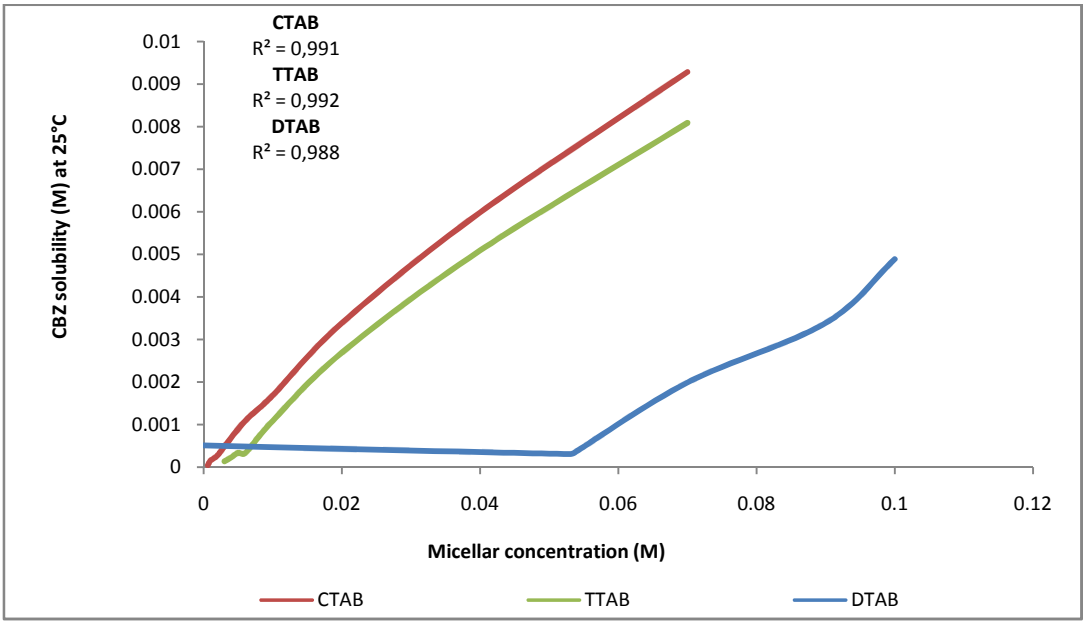

Fig. 4. Carbamazepine solubility versus micellar concentration (C-CMC) for cationic surfactants at 25°C

The best carbamazepine solubilization profile has sodium dodecyl sulfate (SDS). UV analysis of solubilized carbamazepine in sodium dodecyl sulfate (SDS) is display in Fig. 5. indicates a strong interaction between the pharmaceutically active compound and surfactant, with increasing of concentration sodium dodecyl sulfate. Obtained UV spectra of solubilized carbamazepine in sodium dodecyl sulfate (SDS) were in accordance with literature data [16].

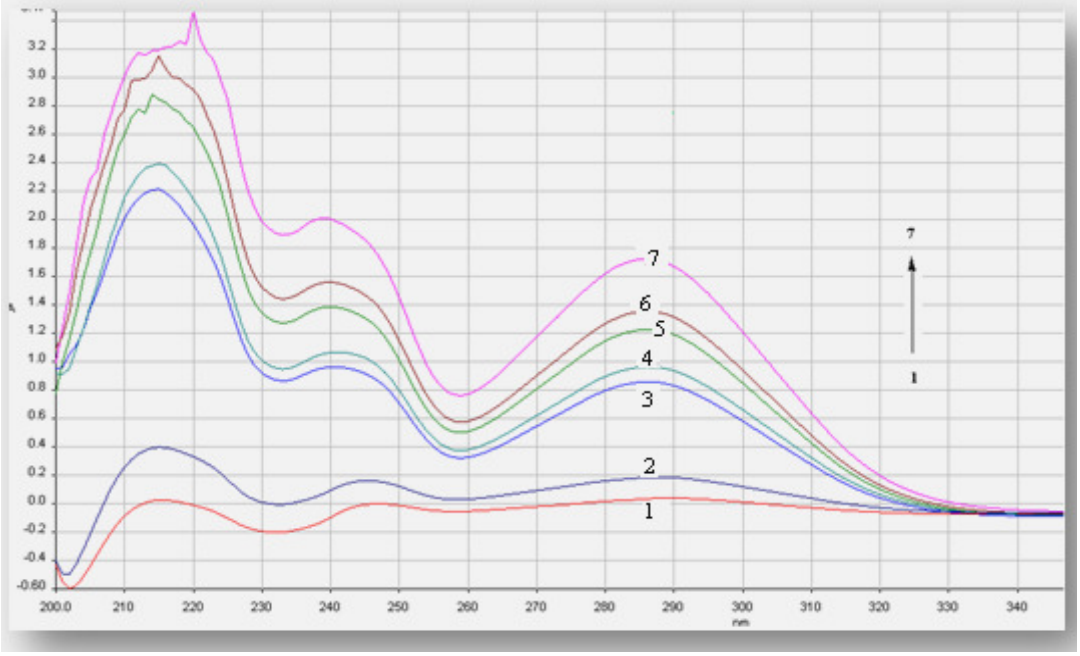

Fig. 5. UV spectra solubilized carbamazepine in sodium dodecyl sulfate (SDS) at 25ºC. Concentration values of SDS systems: (1) 0 (CBZ in water), (2) 3 mM, (3) 6 mM, (4) 10 mM, (5) 20 mM, (6) 40 mM, (7) 70 mM

The slope of each curve plotting carbamazepine solubility versus micellar concentration of different surfactants at 25℃ was used to calculate molar solubilization capacity (χ) with corelation of eq. 1. Table 2 gives values of molar solubilization capacity of all surfactants, the one that gives the highest solubilization of carbamazepine is SDS, and the lowest is DTAB and SDBS.

Table 2. Molar solubilization capacity (χ) carbamazepine in different surfactants system at 25ºC

Surfactants	Molar solubilization capacity (χ) (25ºC)
$CH_3(CH_2)_{15}N(CH_3)_3(Br)$ (CTAB)	0.135
$CH_3(CH_2)_{13}N(CH_3)_3(Br)$ (TTAB)	0.122
$CH_3(CH_2)_9N(CH_3)_3(Br)$ (DTAB)	0.090
$CH_3(CH_2)_{11}OSO_3Na$ (SDS)	0.163
$CH_3(CH_2)_{11}(OCH_2CH_2)OSO_3Na$ (SLES)	0.124
$CH_3(CH_2)_{11}C_6H_4SO_3Na$ (SDBS)	0.092

In the Fig. 6. the slope of each curve plotting relative solubility of carbamazepine versus micellar concentration was used to calculate the molar micelle-water partition coefficient, K_m using pseudophase model. The calculated molar micelle-water partition coefficient, K_m of carbamazepine in SDS is 1274.35 and carbamazepine in DTAB is 357,26.

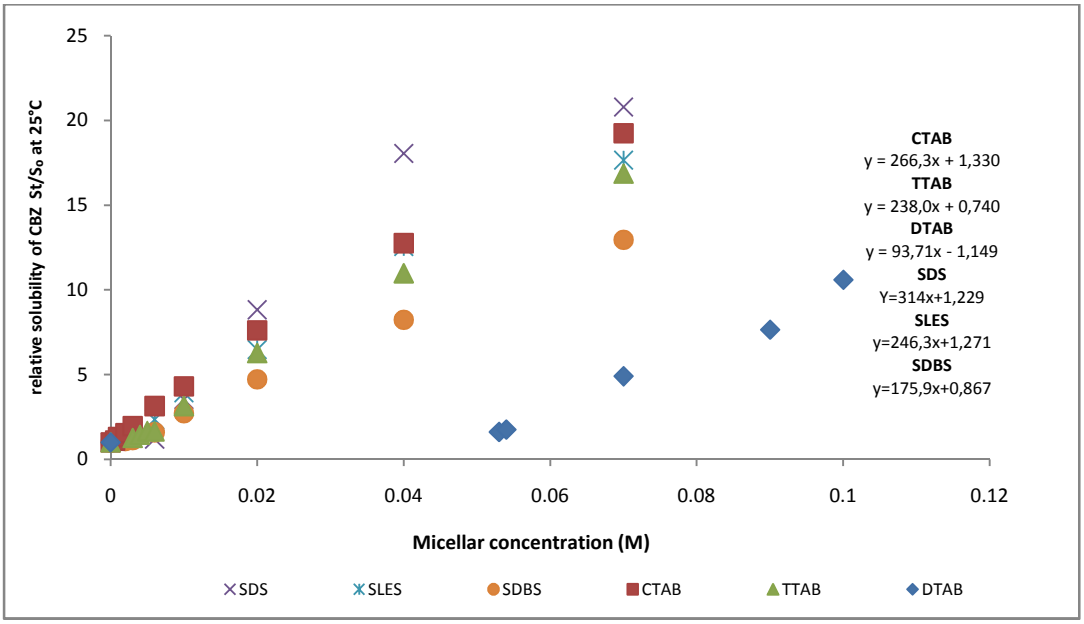

Fig. 6. Relative solubility of carbamazepine versus micellar concentration of various surfactants

Ultraviolet spectroscopy can be used to determine the location of solubilizate in the micelle. The exact location in the micelle at which solubilization occurs varies with the nature of the material solubilized. If carbamazepine as nonpolar drug were to be solubilized in the inner core of the micelle, its ultraviolet spectra must indicate a nonpolar environment on solubilization.

Fig. 7. represents the absorption spectra of carbamazepine in water, methanol, ethanol, water:methanol (1:1) and hexane at different wavelengths. Absorption maximum of carbamazepine in water was λ_{max}-285.02 nm, while in hexane as the non-polar solvent has a λ_{max} value of 286 nm.

The absorption spectra of carbamazepine in anionic and cationic surfactants are shifted more toward heptane than water, which leads to the conclusion that the solubilization environment is nonpolar. The absorption spectra of carbamazepine in anionic surfactants SDS, SLES and SDBS are shown in Fig. 8. The maximum wavelengths are 286.18, 286.42 and 286.64 nm, respectively.

The absorption spectra of carbamazepine in cationic surfactants CTAB and TTAB are shown in Fig. 9. The maximum wavelengths are 286.05 and 286.28 nm, respectively.

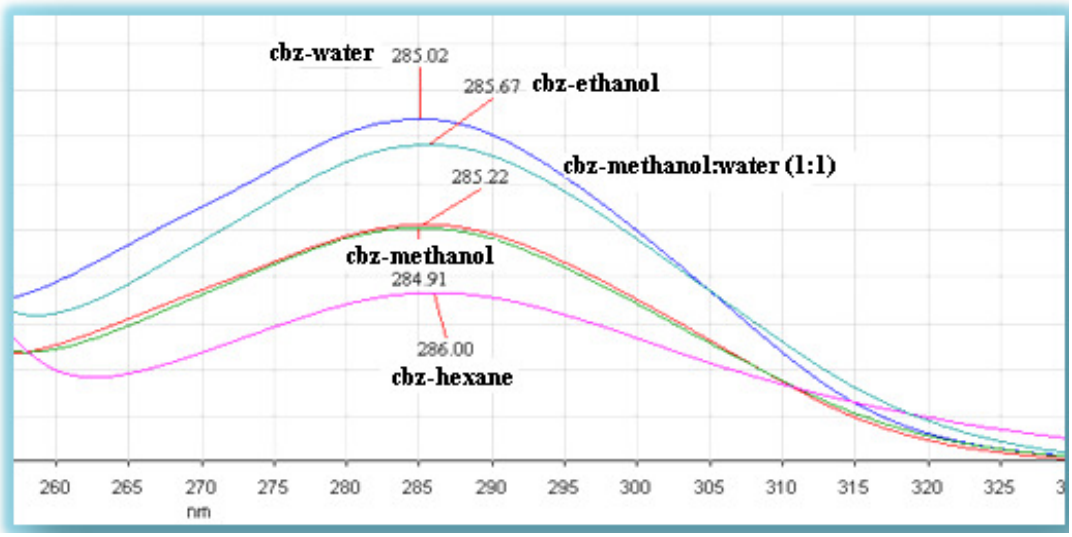

Fig. 7. Absorption spectra of carbamazepine in water, methanol, ethanol, water:methanol (1:1) and hexane

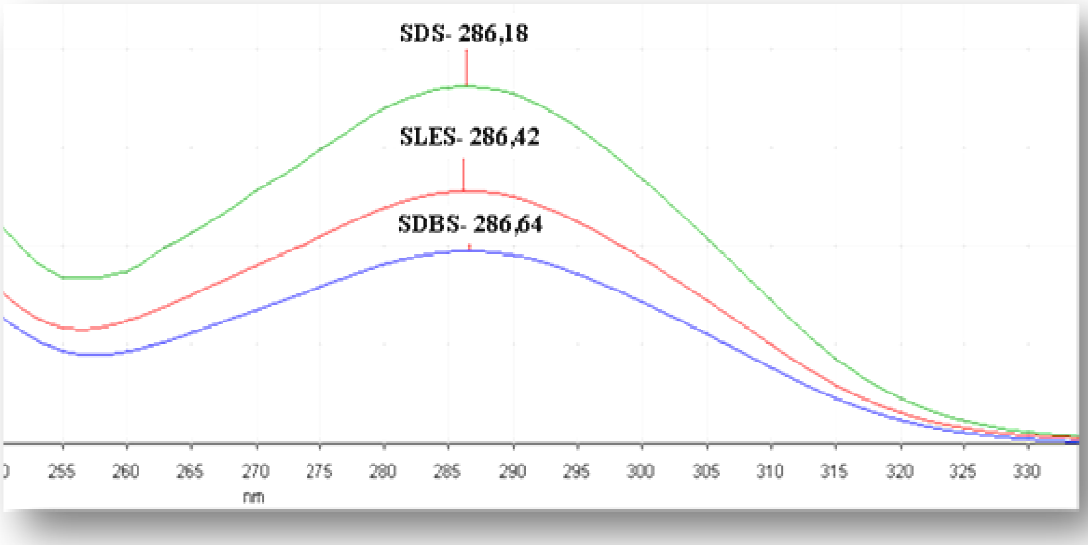

Fig. 8. UV Carbamazepine spectra in the anionic surfactants (0,1 mM)

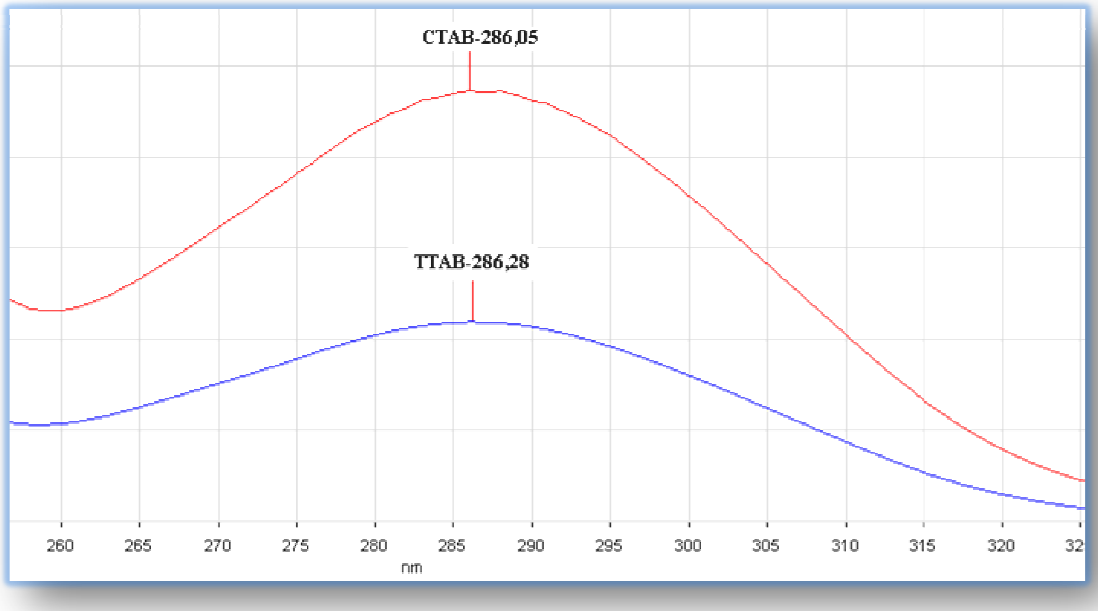

Fig. 9. UV carbamazepine spectra in the cationic surfactants (0,1 mM)

4. CONCLUSION

It was of interest to increase the solubility of carbamazepine in aqueous media. The solubility of carbamazepine is present only at a concentration of surfactants exceeding the critical micellar concentration (cmc). Of all surfactants used, the one that gives the highest solubilization of carbamazepine is SDS with value of molar solubilization capacity 0.163 and the lowest is DTAB and SDBS with value of molar solubilization capacity 0.090 nad 0.092.

It was found that carbamazepine solubility increases with increasing the carbon chain length of cationic surfactants.The results confirm that SDS micelles can solubilize carbamazepine and significantly increase its total aqueous solubility. UV analysis of solubilized carbamazepine in sodium dodecyl sulfate (SDS) indicates a strong interaction between the pharmaceutically active compound and surfactant, with increasing of surfactants concentration.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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