International Journal of Engineering and Science Invention (IJESI)
ISSN (Online): 2319-6734, ISSN (Print): 2319-6726
www.ijesi.org ||Volume 12 Issue 6 June 2023 || PP 21-29

Solubilization of carbamazepine in surfactant solutions with addition of sodium chloride electrolyte

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ABSTRACT: *Carbamazepine is a poorly water-soluble drug. Some of the approaches commonly used to enhance the solubility of poorly soluble drugs include use of co-solvents, selection of salt form, micellar solubilization, complexation etc. The aim of this research was investigated the solubilization of carbamazepine in different surfactants solutions. A number of anionic surfactants (SDS, SDBS, SLES) and cationic surfactants (TTAB, CTAB) showed significant solubilizing ability of carbamazepine at 37°C according to the obtained results of solubilization capacity (κ) and micellar partition coefficient, (K_M). Increasing the concentration of the surfactants, increased the solubilized amount of carbamazepine. The effect of adding a small amount of electrolyte (NaCl) to ionic surfactants solutions on the carbamazepine solubilization was investigated and the results indicate an increase carbamazepine solubility in aqueous solutions of TTAB with the addition of NaCl.*

KEYWORDS *– carbamazepine, solubilization, anionic and cationic surfactants, sodium chloride*

Date of Submission: 22-05-2023 Date of Acceptance: 03-06-2023

I. INTRODUCTION

Carbamazepine is an organic compound, molecular formula $C_{15}H_{12}N_2O$, which occurs as white or almost white powdered crystals soluble in polar solvents (glycol, ethanol and acetone), but very poorly soluble in water. Iupac name of carbamazepine is 5H-dibenz[b,f]azepine-5-carboxamide. Carbamazepine is commonly used to prevent seizure episodes in patients diagnosed with epilepsy, as well as to relieve the pain associated with trigeminal neuralgia. [1] Structurally, carbamazepine is a molecularly simple active pharmaceutical ingredient (API) with a nonpolar tricyclic backbone and one polar amide functional group (Fig 1.). that is available under the trade name Tegretol.

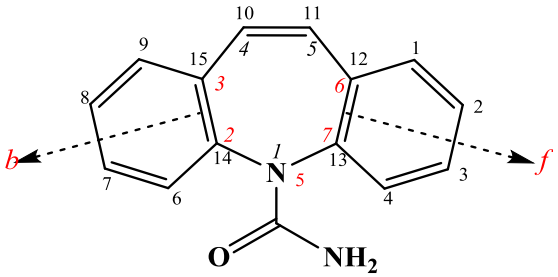

Figure 1. Molecular structure of carbamazepine

Carbamazepine is a poorly water-soluble drug, practically insoluble in water (about 113 μg/mL at 25°C). [2] The characteristics of the drug substance are used to classify drugs in the Biopharmaceutical Classification System (BCS). Carbamazepine is a BCS Class II drug that shows high permeability and low solubility. [3] Subsequently, the bioavailability of such compounds is limited by their solubility in water. Poor aqueous solubility is usually a major obstacle in the development of therapeutic agents. Some of the approaches commonly used to enhance the solubility of poorly soluble drugs include use of co-solvents, selection of salt form, increase of specific surface area by reduction of particle size, complex formation with excipients such as hydrophilic polymers and cyclodextrins, change of crystal form (polymorphism/amorphism) and preparation of solid dispersions. Micellar solubilization is a widely used alternative for the dissolution of poorly soluble drugs. [4]

Surfactant molecules are amphiphilic i.e., they possess hydrophilic and hydrophobic regions having a long hydrocarbon tail and a relatively small ionic or polar head group. [5] Depending on the charge of head groups, the surfactants are classified as: cationic, anionic (Fig 2.), zwitterionic, or nonionic.

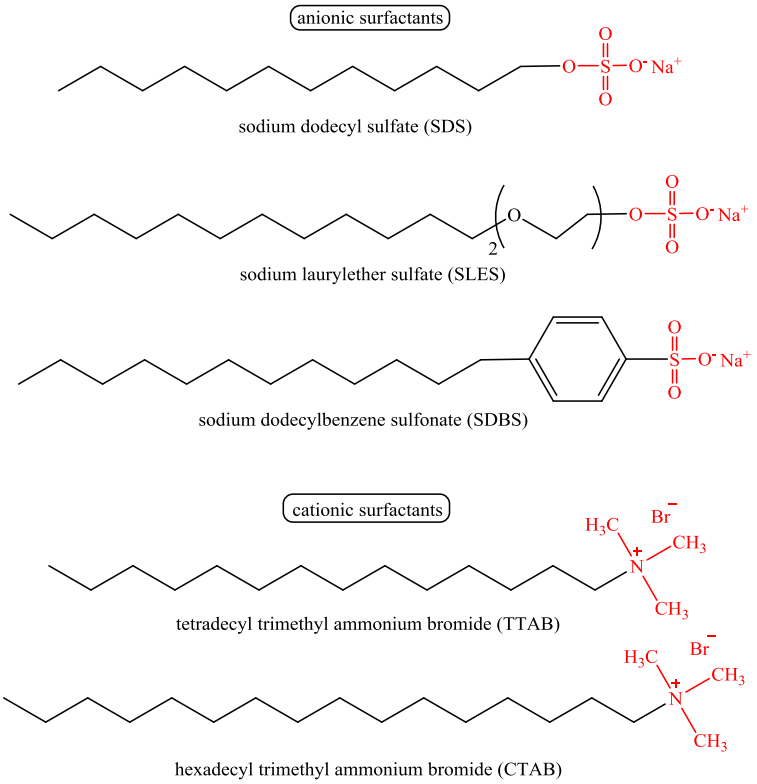

Figure 2. Molecular structure of different anionic and cationic surfactants

In polar solvents such as water, amphiphilic surfactant monomers assemble to form a micelle (Fig 3.) in such a way that their hydrocarbon tails huddle in the core of the micelle, and the polar head groups project outwards into the polar bulk solution and locate at the micelle-water interface such that the hydrophobic tails are shielded from water. Micelles often drawn as static structures of spherical aggregates of oriented surfactant molecules. However, micelles are in dynamic equilibrium with surfactant monomers in the bulk, which are frequently being exchanged with the surfactant molecule in micelles. [5]

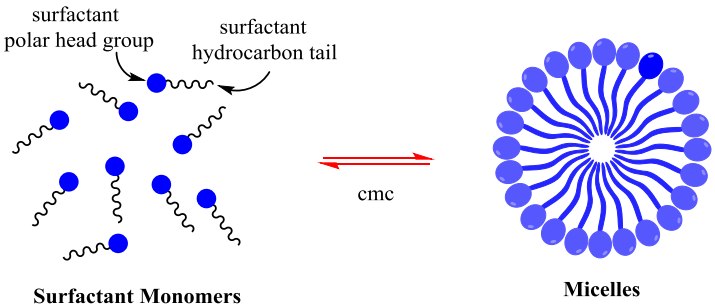

Figure 3. Schematic illustration of micelles

At low concentrations in the aqueous medium, molecules of surfactants are completely dissociated and do not tend to form aggregates. At higher concentrations, their spontaneous aggregation and formation of first small aggregates occur, which, in a narrow temperature range, turn into larger aggregates-micelles. The concentration at which the phenomenon of micelle formation occurs is called the critical micellar concentration (CMC).

Various factors effects the CMC values e.g., temperature, the length of the hydrocarbon tail, the nature of the counterions and the existence of salts and organic additives; and thus amphiphiles have characteristic CMC values under given conditions. [5] Depending upon the drug hydrophobicity, it can be solubilized in the inner core

of the micelle, on the surface of the micelle or at an intermediate location in the palisade layer. [4] Solubilization in micellar systems is an important method for dissolving hydrophobic pharmaceutical active compounds in aqueous and non-aqueous environments. [6]

1.1. Factors determining the extent of solubilization

1.1.1. Solubilization capacity and micellar partition coefficient

The most commonly used descriptors are: solubilization capacity (κ) and micellar partition coefficient, (K_M). [7] Solubilization capacity is the most commonly used means of characterizing the ability of a surfactants to solubilize a solute. The solubilization capacity (κ) or solubilizing power of the micelle is defined as the number of moles of solubilizate per mole of micellized surfactant, given by the ratio

$$(S_{tot} - S_w) / (C_{surf} - CMC) \qquad (1)$$

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

It often remains constant for a particular surfactant over a wide concentration range above the CMC, although some surfactants show increasing solubilizing power at higher concentrations. In general, solubilization capacity is greater for polar solubilizates than for nonpolar ones, especially for spherical micelles (because of the larger volume available at the surface of the micelle than in the interior), and decreases with increase in the molar volume of the solubilizate. Also, factors that promote micellization (e.g., electrolyte addition to ionic surfactants) increase solubilization capacity. [8] The molar solubilzation capacity is equal to the slope of the S_{tot} versus C_{surf} line if both solute concentration and surfactant concentration are expressed in moles per liter. 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, (κ) is equal to the ratio of drug concentration in the micelles to the surfactant concentration in the micellar form.

The micellar partition coefficient (K_M) is another measure of affinity of a solute for a micelle. [7] It is defined as the ratio of solute concentration in the micelle to that in water for a particular concentration of surfactant, as follows:

$$K_M = (S_{tot} - S_w)/ S_w \qquad (2)$$

The micellar partition coefficient can be related to the solubilization capacity combining equations (1) and (2). Accordingly, for a given surfactant concentration:

$$K_M = (\kappa) (C_{surf} - CMC) / S_w \qquad (3)$$

As can be seen, K_M is related to the water solubility of the compound, in contrary to (k). [9] In order to eliminate the dependence of K_M on the surfactant concentration, a molar micelle-water partition coefficient, K_m , can be defined as follows:

$$K_m = (\kappa) (1-CMC) / S_W \qquad (4)$$

1.1.2. Effect of electrolyte

Electrolytes and organic compounds as additives surfactants solutions can also cause changes in solubilization capabilities. The addition of small amounts of neutral electrolyte to solutions of ionic surfactants appears to increase the extent of solubilization of hydrocarbons that are solubilized in the inner core of the micelle and to decrease that of polar compounds that are solubilized in the outer portion of the palisade layer. [8] The effect of neutral electrolyte addition on the ionic surfactant solution is to decrease the repulsion between the similarly charged ionic surfactant head groups, thereby decreasing the CMC and increasing the aggregation number and volume of the micelles. The increase in aggregation number of the micelles presumably results in an increase in hydrocarbon solubilization in the inner core of the micelle. The decrease in mutual repulsion of the ionic head groups causes closer packing of the surfactant molecules in the palisade layer and a resulting decrease in the volume available there for solubilization of polar compounds.

1.1.3. Effect of temperature

The temperature is one of the significant factors that affects the power of solubilization. For ionic surfactants an increase in temperature generally results in an increase in the extent of solubilization for both polar and nonpolar solubilizates, possibly because increased thermal agitation increases the space available for solubilization in the micelle. Thus, the solubilization of cyclohexane in an aqueous solution of sodium di(2-ethylhexyl) sulfosuccinate above 50°C increases with increase in the temperature. [8]

II. EXPERIMENTAL

2.1. Chemicals

In this study, the following chemicals were used for experimental work:

- carbamazepine (CBZ),
- tetradecyl trimethyl ammonium bromide (TTAB) (99% pure),
- hexadecyl trimethyl ammonium bromide (CTAB) (99% pure),
- sodium dodecyl sulfate (SDS) (99% pure),
- sodium dodecylbenzene sulfonate (SDBS- pharmaceutical secondary standard),
- sodium laurylether sulfate (SLES) (95% pure)
- methanol (99,8%)
- sodium chloride (99% pure)

Deionisated water was used in all the experiments.

2.2. Experimental procedure

2.2.1. Determination of critical micelle concentrations (CMC)

The *CMC* of the surfactants at 37 °C 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 CMCs for the used surfactants under experimental conditions.

Table 1. Critical micelle concentrations of the used surfactants at experimental conditions

Surfactants	CMC (M)($\cdot 10^{-3}$)	Conditions
$CH_3(CH_2)_{11}OSO_3Na$ (SDS)	8,32	37 °C, H_2O
$CH_3(CH_2)_{11}C_6H_4SO_3Na$ (SDBS)	2,32	37 °C, H_2O
$CH_3(CH_2)_{11}(OCH_2CH_2)OSO_3Na$ (SLES)	3,24	37 °C, H_2O
$CH_3(CH_2)_{13}N(CH_3)_3(Br)$ (TTAB)	3,57	37 °C, H_2O
$CH_3(CH_2)_{15}N(CH_3)_3(Br)$ (CTAB)	1,04	37 °C, H_2O

2.2.2. Determination of drug solubility

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. Determination of the carbamazepine solubility in anionic and cationic surfactants solutions (0-100 mM) was performed by UV spectrophotometry. After preparing the samples according to the method of Higuchi and Connors [10], a suitable suspension of the pharmaceutical active compound in surfactants solutions is obtained. The resulting suspension is equilibrated at 37 °C and then analyzed. All the solubility experiments were carried out in triplicate.

Concentration of sample was determined quantitatively in μg/ml (mg/ml), based on a calibration curve of carbamazepine (3-60 μg/ml). Preliminary UV scanning of pure aqueous carbamazepine yielded a stable peak at 285 nm. Fig 4. show an excellent correlation (r^2 >0.998) indicated that the Beer–Lambert law was obeyed in the carbamazepine concentration ranges of interest.

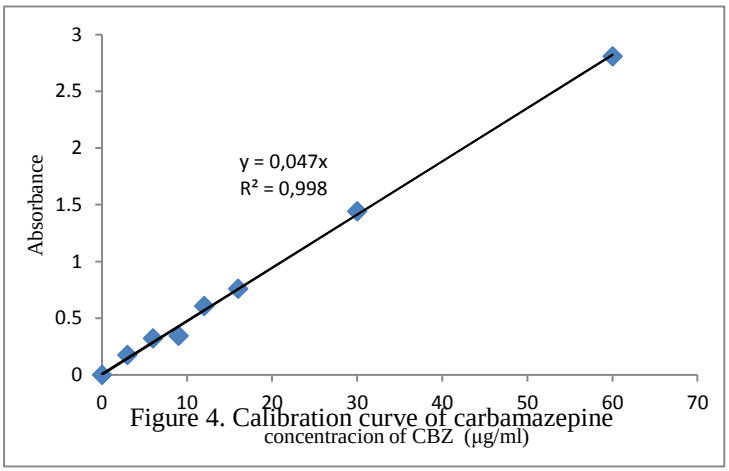

Figure 4. Calibration curve of carbamazepine

III. RESULTS AND DISCUSSION

Surfactants are used as excipients to improve the solubility of pharmaceutical active ingredients. According to the USP solubility criteria, carbamazepine is very poorly soluble in water, while it has moderate solubility in methanol. It is of great importance to increase the water solubility of the drug for better efficiency and chemical availability. Micellar solubilization is a significant alternative way to increase the solubility of hydrophobic organic compounds in an aqueous medium. The aim of this research was investigated the solubilization of carbamazepine in different surfactants solutions. A number of anionic surfactants (SDS, SDBS, SLES) and cationic surfactants (TTAB, CTAB) showed significant solubilizing ability of carbamazepine at 37°C (Fig 5 and 6., respectively). Results show that the solubility of carbamazepine linearly increases with increasing concentration of anionic surfactants: sodium dodecyl benzene sulfonate (SDBS) < sodium laurilетersulfat (SLES) <sodium dodecyl sulfate (SDS). Fig 5. and fig 6. explain that solubility is present only at a concentration of surfactants exceeding the critical micellar concentration for anionic surfactants (8,32 x 10^{-3}M SDS, 3,24 x 10^{-3}M for SLES 2,32 x 10^{-3}M of SDBS at 37°C) and cationic surfactants (1,04 x 10^{-3}M for CTAB; 3,57 x 10^{-3}M for TTAB) which indicates the phenomenon of micellar solubilization.

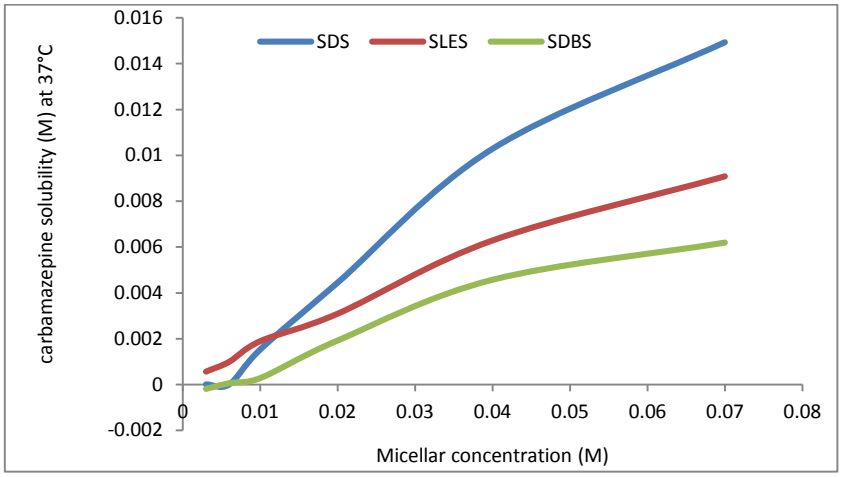

Figure 5. Carbamazepine solubility for anionic surfactants at 37°C

The best solubilization profile of carbamazepine is shown by sodium dodecyl sulfate (SDS), which can be explained by the existence of sufficient available space for solubilization, due to the larger volume of the hydrophobic core of the SDS micelle compared to the sodium lauryl ether sulfate (SLES) and sodium dodecyl benzene sulfonate (SDBS) micelles. Although SDS and SLES have the same polar group and the same hydrocarbon length chain, they show a different solubility profile for carbamazepine. The presence of oxyethylene units in the SLES structure is a structural factor that affects to hydrophobic region of the micelle. SDBS gives the lowest solubility profile of carbamazepine probably due to the steric influence of the benzene core and the presence of the sulfone group.

Considering that most surfactants solubilized lower polarity compounds in the non-polar area of the micelle, this region is directly determined based on the solubilization capacity (κ). The non-polar area of surfactants is determined based on the number of carbon atoms in the hydrocarbon chain. This is in accordance with the obtained results of the carbamazepine solubilization capacity at 37°C in the presence of CTAB with longer hydrocarbon chain (Fig 6.).

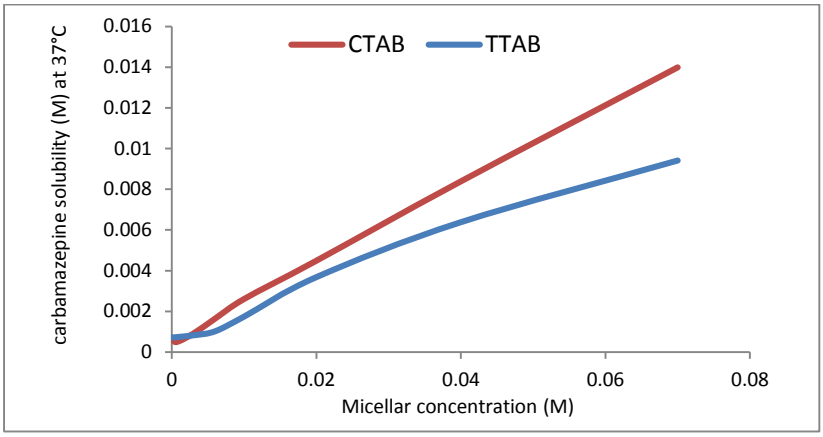

Figure 6. Carbamazepine solubility for cationic surfactants at 37°C

Table 2. shows the results of the solubilization capacity (κ), where the highest value is achieved using SDS as a surfactant and the lowest with SDBS. The slope of each curve plotting carbamazepine solubility versus micellar concentration of different surfactants at 37°C was used to calculate molar solubilization capacity (κ) with corelation of eq. 1.

Table 2. Carbamazepine molar solubilization capacity (κ) in used surfactants at 37°C

Surfactants	molar solubilization capacity (κ), (37°C)
$CH_3(CH_2)_{11}OSO_3Na$ (SDS)	0,235
$CH_3(CH_2)_{11}(OCH_2CH_2)OSO_3Na$ (SLES)	0,129
$CH_3(CH_2)_{11}C_6H_4SO_3Na$ (SDBS)	0,101
$CH_3(CH_2)_{15}N(CH_3)_3(Br)$ (CTAB)	0,193
$CH_3(CH_2)_{13}N(CH_3)_3(Br)$ (TTAB)	0,131

In the figure 7. 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 1316,96 and carbamazepine in SDBS is 492.

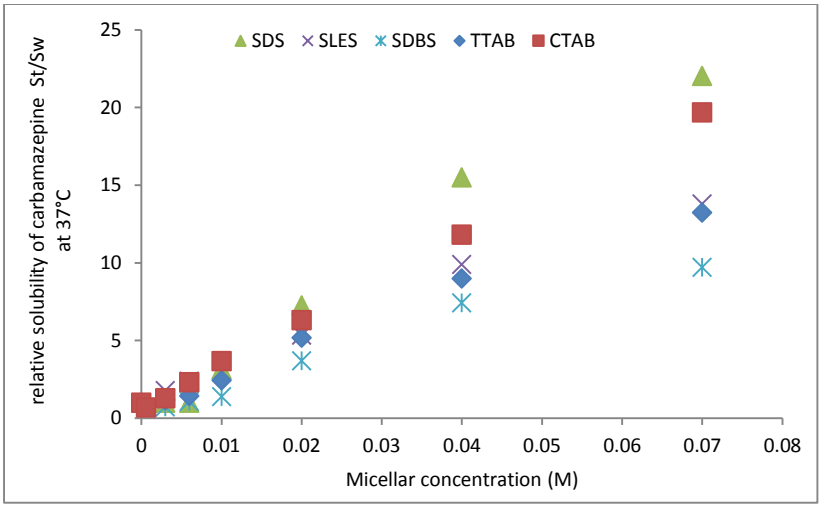

Figure 7. Relative carbamazepine solubility versus micellar concentrations of different surfactants at 37°C

The effect of adding a small amount of electrolyte (NaCl) to ionic surfactants solutions on the carbamazepine solubilization was investigated. Fig 8. shows the increase of carbamazepine solubility in aqueous solutions of TTAB with the addition of NaCl as an electrolyte. A better solubility profile of carbamazepine was observed in TTAB solutions with 0.5 M NaCl compared to solutions without salt. This is in accordance with literature data [11] in which the addition of small amounts of electrolytes to solutions of ionic surfactants increases the extent of solubilization of non-polar compounds that are solubilized in the hydrophobic interior of the micelle core.

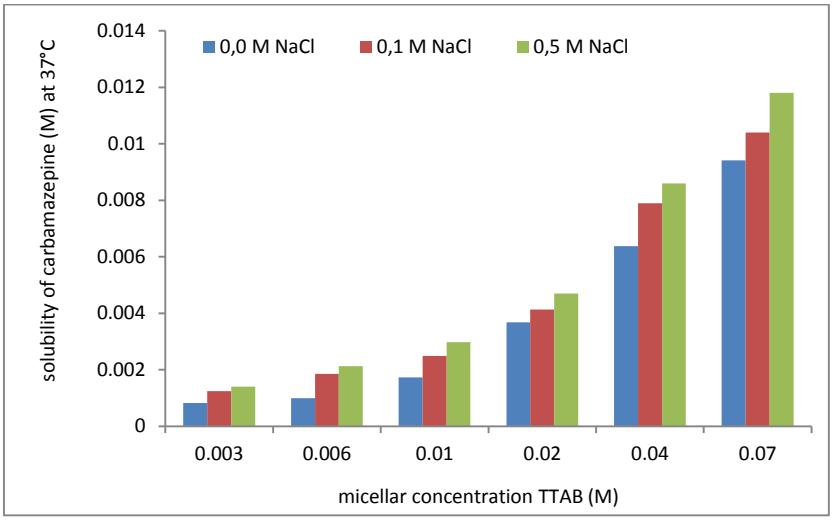

Figure 8. Carbamazepine solubilization profile in cationic surfactant (TTAB) in different concentrations of NaCl at 37°C

It was found that increasing the ionic strength does not significantly affect to the carbamazepine solubilization in sodium dodecyl sulfate. Although the addition of NaCl decreases the critical micellar concentration of SDS and increases the aggregation number, the solubilization of carbamazepine does not significant increase (Fig 9.). It was observed that at a concentration of 0.07 M SDS with the addition of a higher concentration of salt, the extent of carbamazepine solubilization decreases, most likely due to salting out of the surfactant from the solution.

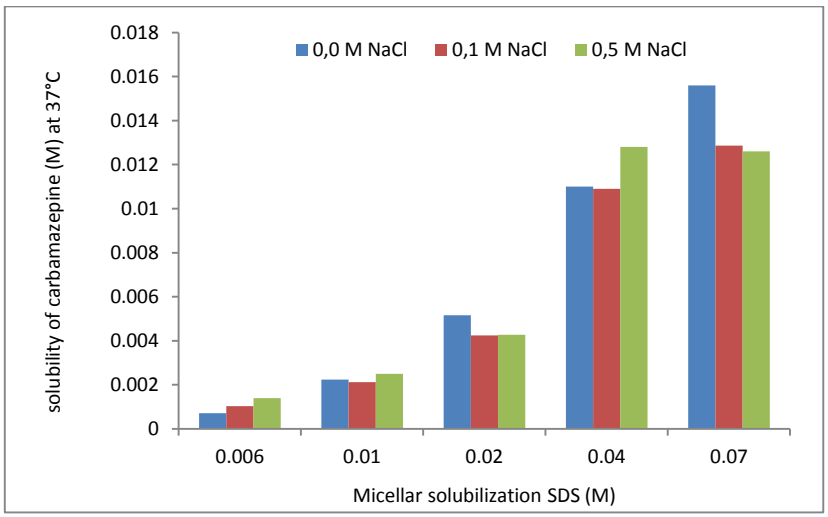

Figure 9. Carbamazepine solubilization profile in anionic surfactant (SDS) in different concentrations of NaCl at 37°C

Determination of the carbamazepine solubilization capacity (k) in sodium dodecyl sulfate (SDS) and tetradecyl trimethyl ammonium bromide (TTAB) solutions at temperatures of 25°C and 37°C was performed on the data basis of the curves slope from the diagrams (Fig 10. and Fig 11.). Solubilization capacity of carbamazepine in sodium dodecyl sulfate (SDS) at 37˚C is higher than capacity at 25°C and it is 0.235 and 0,163 respectively. An increase in temperature, in the case of ionic surfactants, causes a greater extent of solubilization of both polar and non-polar solubilizers.

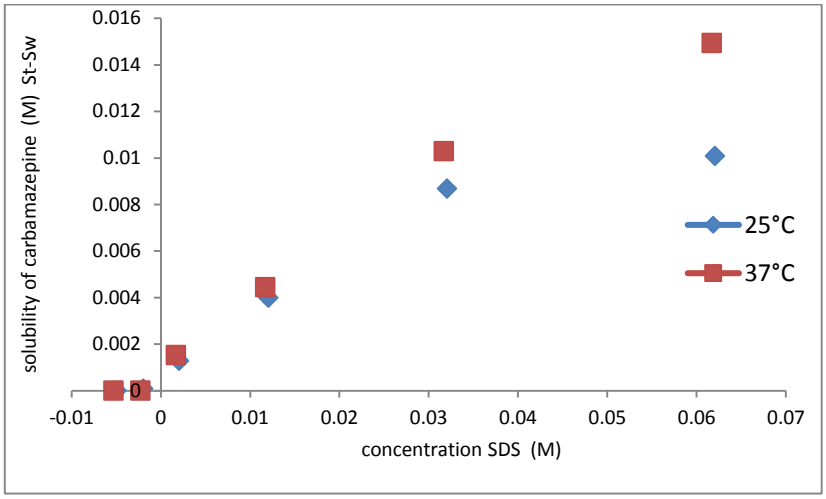

Figure 10. Carbamazepine solubility as a function of micellar concentration (C-CMC) of sodium dodecyl sulfate (SDS) at 25°C and 37°C.

The results indicate a positive influence of the thermal effect on the carbamazepine solubility in TTAB solutions at a temperature of 37°C with a capacity of 0.131 compared to 0.122 at 25°C.(Fig 11.)

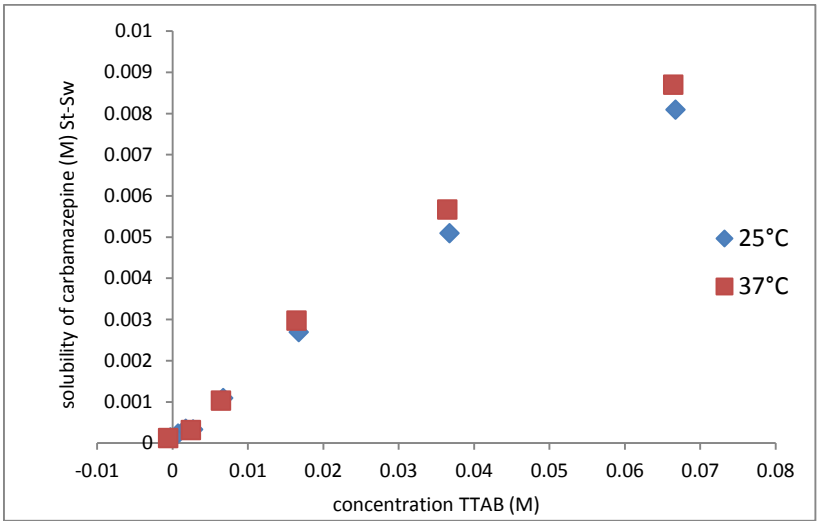

Figure 11. Carbamazepine solubility as a function of micellar concentration (C-CMC) of tetradecyl trimethyl ammonium bromide (TTAB) at 25°C and 37°C.

IV. CONCLUSION

Micellar solubilization is a method by which it is possible to improve the poor water solubility of carbamazepine. The solubility of carbamazepine increases linearly with increasing concentration of anionic surfactants in the order: sodium dodecyl benzene sulfonate (SDBS) < sodium lauryl ether sulfate (SLES) < sodium dodecyl sulfate (SDS). For alkyl trimethyl ammonium bromides (cationic surfactants), the range of micellar solubilization of carbamazepine increases in the order TTAB<CTAB. Obtained molar solubilization capacities (κ) of carbamazepine in the tested micellar systems at 37°C indicate the fact that sodium dodecyl sulfate (SDS) and hexadecyltrimethylammonium bromide (CTAB) have the highest ability to solubilize the tested pharmaceutical active compound. The addition of small amounts of electrolytes to solutions of cationic surfactants (TTAB) increases the extent of solubilization of carbamazepine, which is probably solubilized in the hydrophobic interior of the micelle core. Increasing the ionic strength does not significantly affect the extent of solubilization of carbamazepine in sodium dodecyl sulfate (SDS). An increase in temperature, in the case of ionic surfactants, causes a greater extent of solubilization of carbamazepine.

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Majda Srabovic, et. al. "Solubilization of carbamazepine in surfactant solutions with addition of sodium chloride electrolyte". *International Journal of Engineering Science Invention (IJESI)*, Vol. 12(6), 2023, PP 21-29. Journal DOI- 10.35629/6734