American Journal of Engineering Research (AJER)
e-ISSN: 2320-0847 p-ISSN : 2320-0936
Volume-11, Issue-09, pp-17-25
www.ajer.org
Research Paper Open Access

# Carbamazepine-α-cyclodextrin inclusion complexes

*Majda Srabovic[1], Melita Huremovic[1], Mirsada Salihovic[2]
[1]University of Tuzla, Faculty of Natural Sciences and Mathematics, Department of Chemistry, Bosnia and Herzegovina
[2]University of Sarajevo, Faculty of Pharmacy, Department of Chemistry, Bosnia and Herzegovina
Corresponding Author: Majda Srabovic,

***ABSTRACT :****According to the biopharmaceutical classification system (BCS) drugs in Class II, as carbamazepine, have inadequate aqueous solubility, but good permeability when in solution. Thus, their absorption from the gastrointestinal tract is slow and dissolution dependent. It is of great importance to increase the aqueous solubility of the drug for better efficancy and chemical availability. Due to its low solubility, carbamazepine oral administration is marred. Cyclodextrins (CDs) act as a drug carrier to improve solubility and stability, enhancement of dissolution rate and bioavailability, reduction in volatility etc. CDs are capable of forming inclusion complexes with compounds having a size compatible with the dimensions of the cavity. The aim of this study was to investigate the effect of different aqueous and buffer CDs solutions (pH-6.8) on the phase solubility of carabamzepine. Use of α-CD as a natural cyclodextrin and it synthetic derivatives, 2-hydroxypropyl-α-cyclodextrin, increases the solubility of carbamazepine. The UV-VIS spectrophotometric method was used as a method to confirm the complexation effect of α-cyclodextrin and 2 hydroxypropyl-α-cyclodextin on increasing the solubility of carbamazepine. Using the FTIR method, the more significant interactions in the formation of inclusion complexes were observed.*

***KEYWORDS: solubility, complexation, carbamazepine,α-cyclodextrin, 2-hydroxypropyl α-cyclodextrin***

---

Date of Submission: 01-09-2022 Date of acceptance: 13-09-2022

---

## I. INTRODUCTION

Carbamazepine (Fig. 1.), 5*H*-dibenz-(*b*,*f*)azepine-5-carboxamide, can crystallize and exhibits four polymorphic forms and one dihydrate form. It iswhite or almost white crystalline powder that is used as a anticonvulsant drug to treat epilepsy, trigeminal neuralgia, manic-depressive illness, and explosive aggression.The efficacy of carbamazepine was confirmed in the 1960s, when it was launched onto the commercial market [1].

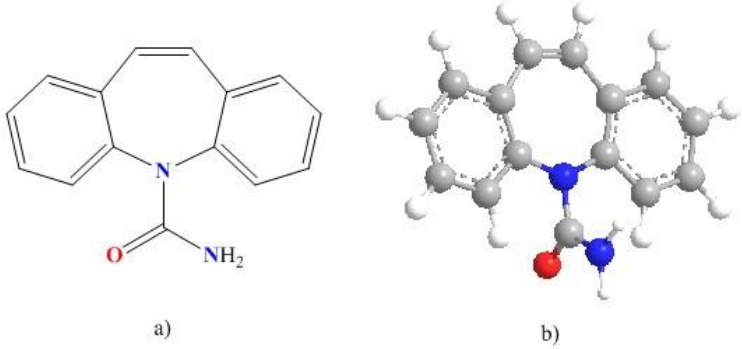


**Fig.1. Molecular (a) and three-dimensional (b) structure of carbamazepine**

Oral administration of carbamazepine is marred by poor solubility of carbamazepine (~ 120 μg/mL) leading to lower bioavailability[2].Variable absorption and low bioavailability can be attribute to the slower dissolution rate of carbamazepine. The problem of increasing solubility of activesubstances is old as pharmacy itself, and the efforts focused on carbamazepine were acontinuous concern of pharmacists in the last fifty

years[3]. It is most appropriate to design an siutable approach to increase the solubility of carbamazepine as an essential method to improve its bioavailability.Therefore, efforts have been made by trying to increase the solubility of carbamazepine by incorporating it into cyclodextrins.Cyclodextrins (CDs) are cyclic oligosaccharides composed of 6, 7 or 8 D-glucopyranoside units (glucose), joined together by a-1,4 glycosidic bonds and are respectively called as α-CD, β-CD and γ- CDs[4]. Due to the lack of free rotation about the glycosidic bondsand chain conformation of glucose units, CDs display a torus-like or hollow truncated cone shape(Fig. 2.)[5-6]. In this peculiar structure the secondary hydroxyl groups can be found at the broadest end, bonded to the C2 and C3 atoms of the glucose units, while the primary hydroxyl groups are located at the narrower opposite end, bonded to the C6 atoms of the glucose units[7].The outer surface od CD's is hydrophilic due to the presence of hydroxyl groups and the interior of the cone is hydrophobic due to presence of glycosidic ether oxygen at O-4 and the hydrogen attached to C-3 and C-5 and thereby provides a lipophillic microenvironment into which drug can enter and can be partially or fully included without covalent bonding, while outer hydrophilic environment contributes to drug dissolution.

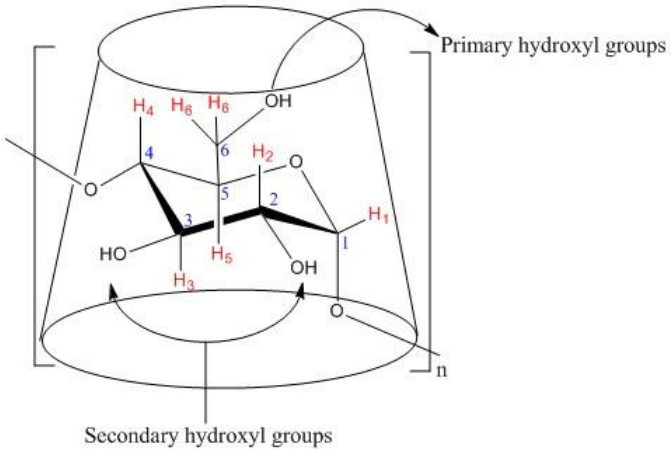


**Fig.2. Native α, β and γ-cyclodextrins form a "truncated" cone (n = 6, 7, and 8, for α-CD, β-CD, and γ-CD, respectively)**

CDs act as a drug carrier to improve solubility and stability, enhancement of dissolution rate and bioavailability, reduction in volatility etc[8].CDs are capable of forming inclusion complexes with compounds having a size compatible with the dimensions of the cavity.The *α, β,* and γ-CDs, with different internal diameters, are able to accommodate molecules of different size.The size properties of α-CD, β-CD, and γ-CD arelisted in Table I[9].

**Table I.Size properties of α-CD, β-CD, and γ-CD**

| Cyclodextrin | No. of Glucose Units | Molecular Weight | Cavity Diameter (Å) | Outer Diameter (Å) | Height (Å) | Cavity Volume ($Å^3$) |
|---|---|---|---|---|---|---|
| α | 6 | 972 | 4,7-5,2 | 14,6 | 7,8 | 174 |
| β | 7 | 1135 | 6,0-6,4 | 15,4 | 7,8 | 262 |
| γ | 8 | 1297 | 7,5-8,3 | 17,5 | 7,8 | 427 |

Natural cyclodextrins (such as β-CD ~ 2 g/100 mL) have low solubility in aqueous media, which limits their use as drug carriers. Chemically modified CD derivatives have been synthesized to offer high-water solubility, increased inclusion ability, and minimal toxicity.CDs can be modified by substituting various functional groups on the primary and/or the secondary face of the molecule. This substitution could occur to any glucosyl residue, and the ligands need not be attached to the same glucose unit. Modified CDs have found uses in pharmaceuticals, foods, and separations[9]. CD derivatives can be obtained by substitution with methyl, ethyl, carboxymethyl, hydroxyethyl, hydroxypropyl, sulfobutyl, or saccharide groups or even by polymerization of CDs. Hydroxyalkyl derivatives are one of the derivative groups most commonly used in drug complexation.Figure 3. shows the structures of α-CD and 2-hydroxypropyl α-CD.

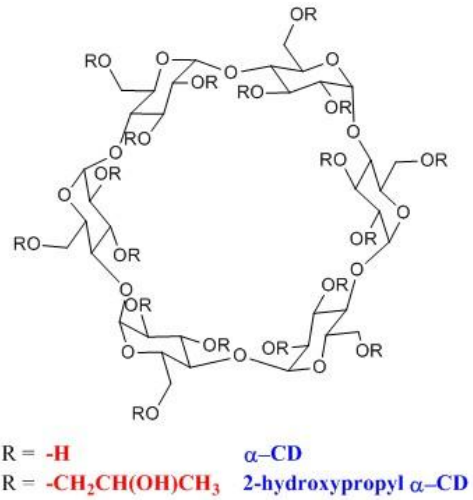


**Fig.3. Structure of α-cyclodextrin and 2-hydroxypropyl α- cyclodextrin**

Interaction of drug molecule and CDs leads to the formation of host-guest complexes also known as inclusion complexes. The truncated cone structure of CDs (host molecule), which are open at both ends, enables the inclusion of organic molecules (poorly aqueous soluble drugs) in their central lipophilic cavities(Fig. 4.). In aqueous solutions of CDs, polar water molecules enter the CD cavity.If drug molecules are found in such a medium, water molecules are replaced by relatively less polar drug molecules. Hydrogen bonding between drug and CDs, van der walls interaction, charge transfer reactions, and replacement of polar water molecules by the less polar guest molecules act as the driving forces for the formation of inclusion complexes[6]. The most common type of CDs complex is the 1:1 drug/cyclodextrin (D/CD) complex, where one molecule of the drug forms a complex with one molecule of cyclodextrin.

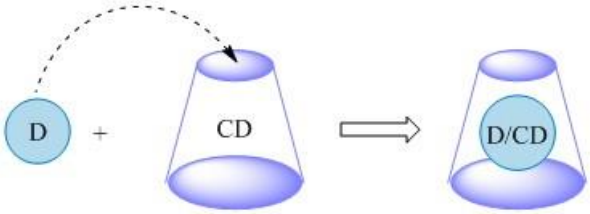


**Fig.4. Mechanism drug-cyclodextrin complexation**

## II. MATERIAL AND METHODS(10 BOLD)

Various methods have been used to form drug-CD complexes such as: physical blending, co-precipitation, spray-drying, freeze-drying, kneading and solvent evaporation[10]. Higuchi and Connors classified the complexes based on their influence on the solubility of the substrate (guest molecule)[11], as shown the phase solubility profilein Fig.5.

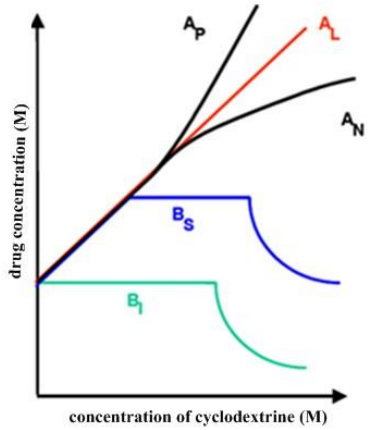


**Fig.5. Types of phase-solubility diagrams according to Higuchi and Connors**[11]

The utility of cyclodextrins in pharmaceutical dosage forms comes from the fact that they interact with one or more drug molecules to form inclusion complexes. However, most common stoichiometry type of drug/cyclodextrin complex, is then 1:1 with the equilibrium constant ($K_{1:1}$) defined as:

$$(Drug)_{free} + (Cyclodextrin)_{free} \overset{K_{1:1}}{\rightleftarrows} (Drug-Cyclodextrin)_{complex}$$

The value of $K_{1:1}$can be calculated by Equation (1) where $S_0$ is the intrinsic solubility of the drug (i.e., the solubility in the aqueous media when no CD is present), and Slope is the slope of the linear (i.e., $A_L$-type) drug-CD phase solubility diagram (Fig. 5.):

$$K_{1:1} = \frac{\text{Slope}}{S_0 \cdot (1 - \text{Slope})} \quad (1)$$

The value of $K_{1:1}$ is highly sensitive towards small changes in $S_0$ and for poorly-soluble drugs it can be complicated to obtain accurate $S_0$ values. Accordingly, a definition for complexation efficiency (CE) as a more precise method for evaluating the solubilizing effect of CDs has been proposed[12]:

$$CE = K_{1:1} \cdot S_0 = \frac{\text{Slope}}{(1 - \text{Slope})} \quad (2)$$

The apparent stability constant ($K_{1:1}$) and the CE were determined from the slope of the linear phase-solubility diagrams plots of the total drug solubility versus total concentration of CD in liquid phase in moles per liter.Carbamazepine was kindly provided by from Bosnalijek d.o.o (Bosnia and Herzegovina). α-cyclodextrin, 2-hydroxypropyl-α-cyclodextrin, sodium hydroxide and potassium dihydrogen phosphate was purchased from Sigma Aldrich. All other chemicals used in this study were of analytical grade.Carbamazepine -cyclodextrin physical mixtures were prepared using a certain amount of drug and cyclodextrin for molar ratios of 1:1, 1:2 and 2:1. Mixtures were blended for 10 min and transferred to an air tight container and stored. After drying, a FTIR analysis of samples was performed.

For the purpose of analysis and characterization of carbamazepine inclusion complex, were applied following instrumental methods:

- Fourier transform infrared spectroscopy (FTIR)

FTIR spectra carbamazepine inclusion complexes with different CDs were analyzed on a Perkin-Elmer Spectrum 1000 system, equipped with a deuterium triglycine sulfate detector. The scan range was 350–4000 $cm^{-1}$, usingeight scans per spectrum with a resolution of 4 $cm^{-1}$. Spectra were obtained in the transmission mode in KBr pellets.by FTIR spectrophotometric analysis and spectra obtained.

- Ultraviolet Assay

The UV spectrophotometric method based on the measurement of absorbance at 285 nm was used to estimate the quantity of the sample quantified in µg/ml.The method was in accordance with the Beer-Lambert law in the concentration range of 3-60 µg/mL based to the calibration curve and the correlation coefficient 0,998884 (Fig.6.).A Perkin-Elmer UV-Vis spectrophotometer, model lambda 25 with UV WinLab software was used to examine complexation and solubility of carbamazepine in aqueous and buffer solutions (pH=6,8) of α-cyclodextrin and 2-hydroxypropyl α-cyclodextrin.After preparing the samples according to the method of Higuchi and Connors (solubility method), a suitable suspension of carbamazepine in CDs solutions is obtained.Solid carbamazepine was added in excess to each vial along with 5 mL of CD aqueous and buffersolution of a given concentration.This methodology was performed in triplicate.The formed suspensions were kept at 25°C with constant stirring.After reaching equilibrium (48 h), the mixture was centrifuged.The liquid phases were filtered and the clear solutions were analyzed by UV-VIS spectrophotometry at a recording speed of 240 nm/min.

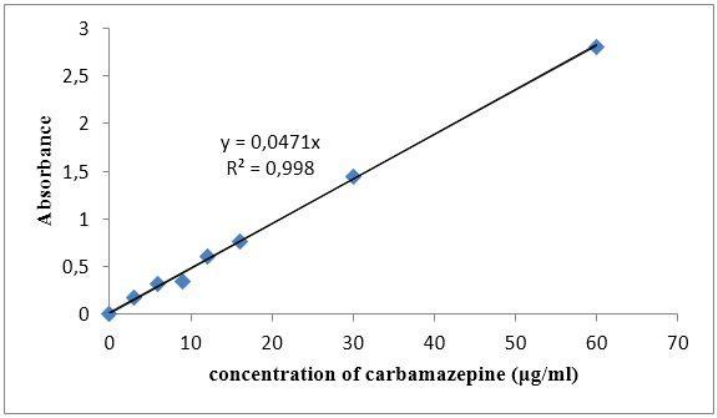


**Fig.6. Calibration curve of carbamazepine in methanol**

## III. RESULTS AND DISCUSSION(10 BOLD)

The biopharmaceutical classification system (BCS) divides orally-administered drugs into four cases based on their solubility and intestinal permeability[13]. Drugs in Class II, as carbamazepine, have inadequate aqueous solubility, but good permeability when in solution. Thus, their absorption from the gastrointestinal tract is slow and dissolution dependent. It is of great importance to increase the aqueous solubility of the drug for better efficancy and chemical availability.

The aim of this study was to investigate the effect of different aqueous and buffer CDssolutions (pH-6.8) on the phase solubility of carabamzepine.Use of α-CD as a natural cyclodextrin and it synthetic derivatives, 2-hydroxypropyl-α-cyclodextrin, increases the solubility of carbamazepine. According to Higuchi and Connors, the phase solubility diagrams (Fig. 7.) obtained for carbamazepine inα-cyclodextrin buffer (pH-6,8) and aqueous solutiongave lines characteristic for $A_L$-type profiles.The stability constant $K_{1:1}$ is calculated from Higuchi and Connors equation using parameters obtained from the phase solubility diagram. Diagrams of phase solubility of carbamazepine and aqueous and buffer solutions of α-cyclodextrin indicate a very weak linear correlation between "host" and "guest" with increasing concentration of α-cyclodextrin.$K_{1:1}$stability constants obtained from the slope of the phase solubility diagram are 32.13 $M^{-1}$ for aqueous solutions of α-cyclodextrin, while for buffer solutions $K_{1:1}$ is 66.03 $M^{-1}$.The apparent carbamazepine complexation efficiency was found to be 0,014 and 0,029 for aqueous and buffer α-CDs solutions, retrospectively.

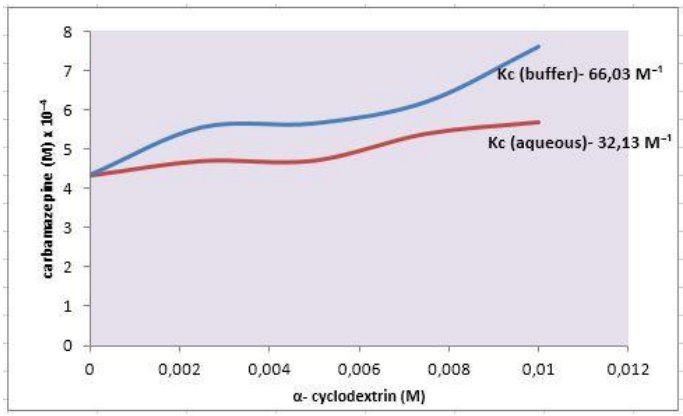


**Fig.7. Phase solubility diagram for carbamazepine inα-cyclodextrin buffer (pH-6,8) and aqueous solution**

The results of ANOVA analysis with p-value of 3,61 x $10^{-6}$ show that there is obvious statistical difference at the level of significance of 0.05 between increasing concentrations of buffer solutions α-cyclodextrin and the carbamazepine concentration. The results of ANOVA analysis with p-value of 4,02 x $10^{-8}$ show that there is obvious statistical difference at the level of significance of 0.05 between increasing concentrations of aqueous solutions α-cyclodextrin and the carbamazepine concentration.

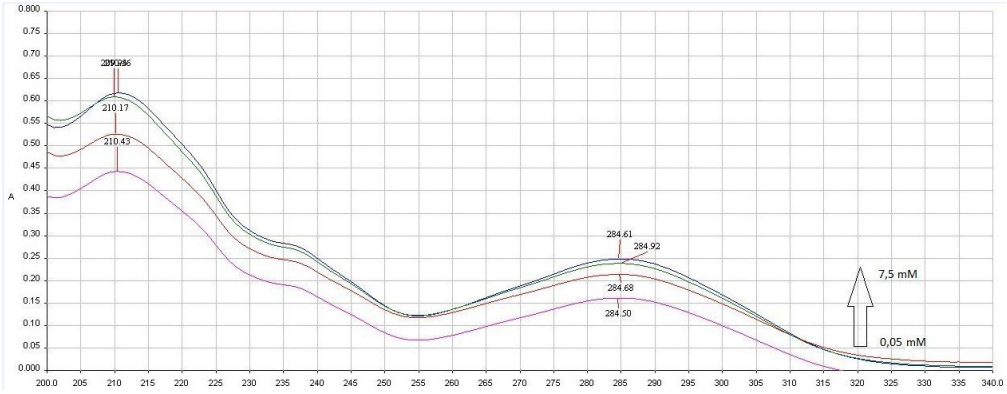


**Fig.8. UV-VIS spectra of carbamazepine indifferent α-cyclodextrin aqueous solutions**

The analysis of the UV spectra of the aqueous samples of carbamazepine and α-cyclodextrin (Fig. 8.) shows a very weak increase in absorbance intensity with increasing concentration of α-cyclodextrin, which results in a weak complexation effect.From a geometric point of view, the diameter of the inner cavity of α-cyclodextrin is 4,7-5.2 Å[9], which certainly represents a spatial limitation for the complexation of carbamazepine, which has a vertical distance between the aromatic rings of 7.5 Å[14]. Since the lenghts between the carbamazepine aromatic rings are greater than that of α-CD cavity, it cannot encapsulate completely within the one α-CD cavity. Therefore, it is possible to assume that more than one molecule of α-CD is needed for the inclusion complexation.

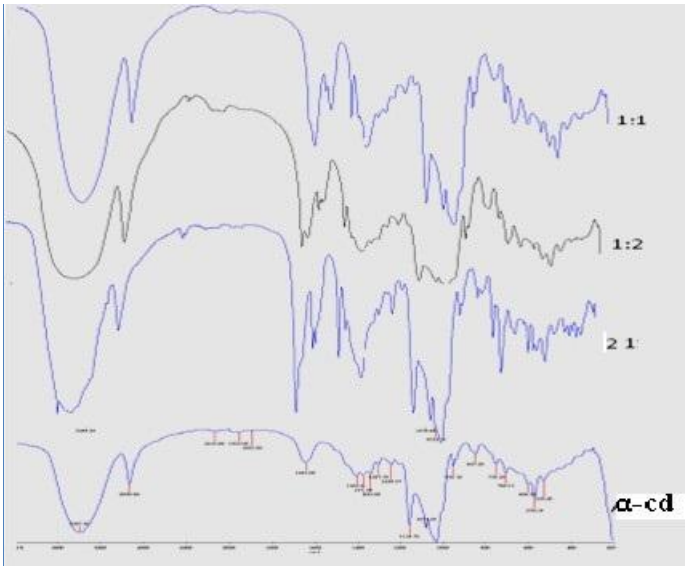


**Fig.9. FTIR spectra of α-cyclodextrin (1) and complexes (physical mixtures) of carbamazepine and α-cyclodextrin in the ratios: (2) 2: 1, (3) 1: 2, (4) 1:1**

The FTIR spectrum of carbamazepine exhibited major peaks at 3466 $cm^{-1}$ (–NH stretching vibrations), 1678 $cm^{-1}$ and 1598 $cm^{-1}$ (strong –C=O and –C=C– vibrations), and 1384 $cm^{-1}$ (–NH deformation)[15]. The characteristic changes on the FTIR spectra of physical mixtures samples are visible in Figure 9.In the IR spectra of α-cyclodextrin (Fig. 9.), a broad band with an absorption maximum at 3400 $cm^{-1}$ corresponding to the valence vibrations of O–H bonds was observed. An absorption band belonging to the valence vibrations of C–H bonds in CH and $CH_2$ groups with a maximum at 2930 $cm^{-1}$ was also observed. Absorption bands from deformation vibrations of C–H bonds in primary and secondary hydroxyl groups were observed in the region 1405–1239 $cm^{-1}$. Bands of valence vibrations of C–O bonds in ether and hydroxyl groups of CD were observed in the region 1154–1000 $cm^{-1}$.Absorption bands in the region 950–850 $cm^{-1}$ belong to deformation vibrations of C–H bonds.However, the characteristic absorption maximum of the valence vibration ($\nu$C=O) of the carbonyl group at 1679 $cm^{-1}$, which occurs in the samples of the physical mixture of the ratio 1:2, indicates the possible formation of a complex.

Modified CDs,2-hydoxypropyl α-cyclodextrin was capable of solubilizing carbamazepine and slightly increase its apparent solubility with increasing concentracion CDs.Based on the slope of the phase solubility diagram of carbamazepine and 2-hydroxypropyl α-cyclodextrin (fig. 10.), smaller Cds cavity size probably hinders the interaction as revealed by the calculated parameters (i.e., $K_{1:1}$=17.46 $M^{-1}$and CE= 0.01 for aqueous solutions and $K_{1:1}$=48.08 $M^{-1}$and CE= 0,026 for buffer solutions).The stability constants were obtainedindicating very weak interactions between the pharmaceutically active compound and 2-hydroxypropyl α-cyclodextrin.The results of ANOVA analysis with p-value of 8,6 x $10^{-7}$ and 8,29 x $10^{-9}$show that there is obvious statistical difference at the level of significance of 0.05 between increasing concentrations of buffer and aqueous solutions 2-hydroxypropyl α-cyclodextrin and the carbamazepine concentration,retrospectively.

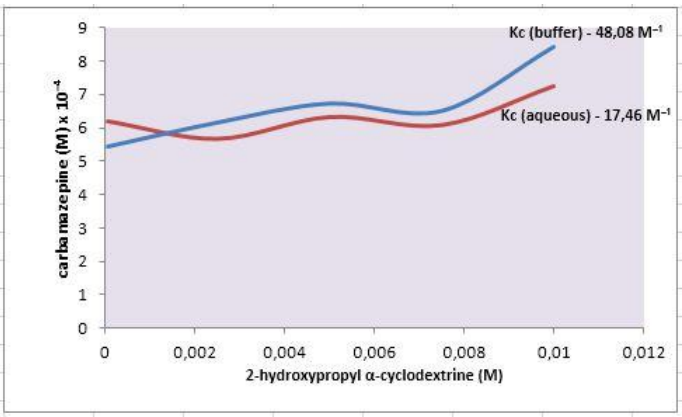


**Fig.10. Phase solubility diagram for carbamazepine in2-hydroxypropyl α-cyclodextrin buffer (pH-6,8) and aqueous solution**

Based on the analysis of the results of UV spectroscopy of aqueous samples of carbamazepine and 2-hydroxypropyl α-cyclodextrin shown in the fig. 11., we see that 10 mM solution of 2-hydroxypropyl α-cyclodextrin achieves a increase in absorbance.

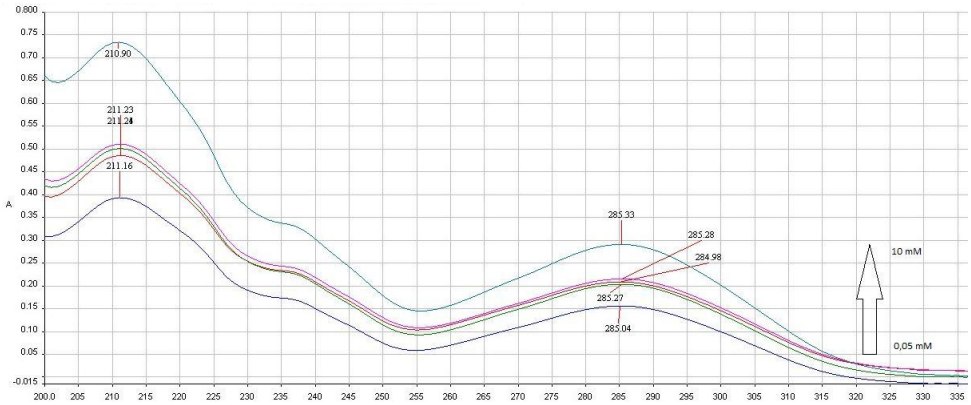


**Fig.11. UV-VIS spectra of carbamazepine indifferent2-hydroxypropyl α-cyclodextrin aqueous solutions**

In the IR spectra of 2-hydroxypropyl-α-cyclodextrin (Fig. 12.), a broad band with an absorption maximum at 3400 $cm^{-1}$ corresponding to the valence vibrations of O–H bonds was observed. An absorption band belonging to the valence vibrations of C–H bonds in CH and $CH_2$ groups with a maximum at 2931 $cm^{-1}$ was also observed. Absorption bands from deformation vibrations of C–H bonds in primary and secondary hydroxyl groups were observed in the region 1400–1200 $cm^{-1}$. Bands of valence vibrations of C–O bonds in ether and hydroxyl groups of CD were observed in the region 1200–1000 $cm^{-1}$.Absorption bands in the region 950–850 $cm^{-1}$ belong to deformation vibrations of C–H bonds.

FTIR spectra of physical mixtures of carbamazepine and 2-hydroxypropyl α-cyclodextrin (Fig. 12.) indicate a peak at about 1700 $cm^{-1}$ originating from the vibrational band of the carbonyl group in a 1:2 sample ratio, which is also evidence that there wereinteractions between carbamazepine and2-hydroxypropyl α cyclodextrin.

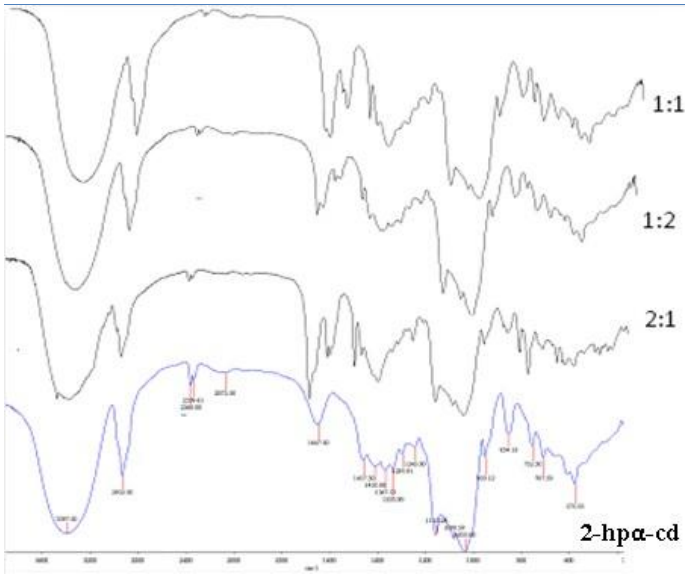


**Fig.12. FTIR spectra of α-cyclodextrin (1) and complexes (physical mixtures) of carbamazepine and 2-hydroxypropyl α-cyclodextrin in the ratios: (2) 2:1, (3) 1: 2, (4) 1:1**

## IV. CONCLUSION

Various physiochemical properties of drugs can be altered through CD complexation, especiallydrug solubility in aqueous biological media. In aqueous media, drug molecules of appropriate sizeand structure will enter into the central cavity of CD molecules to form water-soluble complexesand, frequently, enhanced total drug solubility is observed. $A_L$-type phase solubility diagramsrepresent linear relationships between concentrations of dissolved drug and amounts of CD addedto an medium.

The phase solubility study of carbamazepine and aqueous and buffer solutions of alpha-cyclodextrin and 2-hydroxypropyl cyclodextrin indicated a weak linear correlation between "host" and "guest" with increasing concentration of cyclodextrin in the form of AL profile type. The solubility of carbamazepine increases with the concentration of cyclodextrin in each case, with solubility studies showing that the effect of 2 hydroxypropyl α-cyclodextrin is slightly greater.

The UV-VIS spectrophotometric method was used as a method to confirm the complexation effect of α-cyclodextrin and 2-hydroxypropyl α-cyclodextin on increasing the solubility of carbamazepine. Using the FTIR method, the most significant interactions in the formation of inclusion complexes were observed in the complexation ratio 1:2 which is in accordance with the geometric limitations of the central cavity of the examined cyclodextrins.

## REFERENCES

[1]. Pinto, M., Ambrozini, B., Ferreira, A.P.G., Cavalheiro É. T. G.: Thermoanalytical Studies of Carbamazepine: Hydration/ Dehydration, Thermal Decomposition, and Solid Phase Transitions.Brazilian Journal of Pharmaceutical Sciences 50, 877-884 (2014).
[2]. Alrashood ST. Carbamazepine. In: Brittain HG, editor. Profiles of drug substances, excipients and related methodology, vol. 41, pp. 133–321. Academic Press (2016)
[3]. Musuc, A.M., Anuta, V., Atkinson, I., Sarbu, I., Popa, V.T., Munteanu, C.; Mircioiu, C., Ozon, E.A., Nitulescu, G.M., Mitu, M.A.: Formulation of Chewable Tablets Containing Carbamazepine-β-cyclodextrin Inclusion Complex and F-Melt Disintegration Excipient. The Mathematical Modeling of the Release Kinetics of Carbamazepine. Pharmaceutics 13, 915 (2021).
[4]. Heise, H.M., Kuckuk. R., Bereck, A., Riegel. D.:Infrared spectroscopy and Raman spectroscopy of cyclodextrin derivatives and their ferrocene inclusion complexes. Vibrational Spectroscopy 53, 19-23, (2010).
[5]. Parmar, V., Patel, G., Abu-Thabit, N.Y.: Responsive Cyclodextrins as Polymeric Carriers for Drug Delivery Applications. In: Makhlouf, A.S.H., Abu-Thabit, N.Y., (eds.) Woodhead Publishing Series in Biomaterials, vol. 1, pp. 555–580. Woodhead Publishing: Sawston, UK, (2018).
[6]. Loftsson, T., Jarho, P., Másson, M., Järvinen, T.: Cyclodextrins in Drug Delivery. Expert OpiniononDrug Delivery2,335–351 (2005).
[7]. Crestani de Miranda, J., Martins, T. E.A., Veiga, F., Ferraz, H.G.:Cyclodextrins and ternary complexes: technology to improve solubility of poorly soluble drugs.Brazilian Journal of Pharmaceutical Sciences 47, 4, (2020).
[8]. Saharan V. A., Kukkar V., Kataria M., Gera M., Choudhury P. K. : Dissolution Enhancement of Drugs Part II: Effect of Carrier. International Journal of Health Research 2, 207-223 (2009).
[9]. Poulson, B.G., Alsulami, Q.A., Sharfalddin, A., El Agammy, E.F., Mouffouk, F., Emwas, A.-H., Jaremko, L., Jaremko, M.: Cyclodextrins: Structural, Chemical and Physical Properties, andApplications. Polysaccharides3,1–31 (2022).
[10]. Tasic, LJ., Ciklodekstrini u savremenoj farmaceutskoj tehnologiji, Zadružbina, 22-24, Andrejević, Beograd (1999).
[11]. HiguchiT., Connors,K.A.:Phase Solubility Techniques.Advanced Analytical Chemistry of Instrumentation 4, 117 (1965).

[12]. Loftsson, T., Duchêne, D.: Cyclodextrins and their pharmaceutical applications. International Journal of Pharmaceutics329, 1-11 (2007).
[13]. Saokham, P., Muankaew, C., Jansook, P., Loftsson, T.: Solubility of Cyclodextrins andDrug/Cyclodextrin Complexes.Molecules23, 1161 (2018).
[14]. Prabhu, A.A.M., Venkatesh, G., Rajendiran N.: Unusual Spectral Shifts of Imipramine and Carbamazepine Drugs. Journal of Fluorescence 20, 1199-1210 (2010).
[15]. Koester,L.S., Xavier, CR., Mayorga,P., Bassani,VL.,Influence of β-cyclodextrin complexation on carbamazepine release from hydroxypropyl methylcellulose matrix tablets. European Journalof Pharmaceutics and Biopharmaceutics55, 85–91, (2003).

Majda Srabovic, et. al. "Carbamazepine-α-cyclodextrin inclusion complexes."*American Journal of Engineering Research (AJER)*, vol. 11(09), 2022, pp. 17-25.