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RESEARCH ARTICLE

INVESTIGATION OF INCLUSION COMPLEXES OF SODIUM VALPROATE INSIDE INTO α AND β-CYCLODEXTRINS

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ABSTRACT

Molecular assemblies in α and β-cyclodextrin with most important anticonvulsant drug sodium valproate in aqueous medium and solid phases have been explored by reliable spectroscopic and physicochemical techniques as potentially important controlled drug delivery systems. Host–guest inclusion complexes of 1:1 stoichiometry have been determined by surface tension, conductivity studies and inclusion phenomena was confirmed by ^{1}H NMR, FT-IR studies. The results indicated a higher degree of encapsulation in the case of α-cyclodextrin than that in β-cyclodextrin. The formation of the inclusion complexes was elucidated by hydrophobic effects, structural effects, electrostatic forces and H-bonding interactions.

INTRODUCTION

Sodium valproate (SV) is an anticonvulsant drug which is used in epilepsy and bipolar disorder (Johannessen, 2000). It is also used for neuropathic pain and migraine prophylaxis. SV is an extremely hygroscopic solid and completely ionized to form highly active mode of administration (Abuhijleh, 1996). Clinically high doses consideration for use that's why drug present high side effect known as black box warning for hepatotoxicity, pancreatitis and fetal abnormalities (Hadjikostas *et al*., 1990). The search for lead to reduction. Cyclodextrins (CDs) are cyclic oligosaccharide of glucopyranose units with lipophilic inner cavities and hydrophilic outer surfaces, are capable of interacting with a large variety of guest molecules to form non-covalent inclusion complexes that plays an important role in host-guest chemistry (Saha *et al*., 2016). They contains six (*α*-CD), seven (*β*-CD) glucopyranose units (sachem-1), which are bound by *α*-(1–4) linkages forming a truncated conical structure. CDs have been widely employed for encapsulation of several substances (Goodman, 1996), being used in food, cosmetic and pharmaceutical industries, pesticides, toilet articles, textile processing and other industry (Rang, 1998), supramolecular and host-guest chemistry, models for studying enzyme activity, molecular recognition and molecular encapsulation, studying intermolecular interactions and chemical stabilization (Szejtli, 1998).

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In addition, cyclodextrins can be used to reduce gastrointestinal drug irritation (Pralhad, 2004), convert liquid drugs into microcrystalline or amorphous powder, and prevent drug–drug and drug–recipient interactions (Roy *et al*., 2016). The electro chemical and spectrophotometric studies of the interaction between SV and CD. In the present article formation of inclusion complexes have been explored by surface tension, conductivity, IR, ^{1}H NMR study.

Experimental

MATERIALS

Valporic acid sodium salt, Cyclodextrinne α and β (scheme 1) of highly pure were purchased form Sigma –Aldrich .The purities of sodium valporate, α-cyclodextrine and β-cyclodextrine were-99.1%.

Apparatus and procedure

Surface tensions of the solution were measured by tensiometer (K9, KRUSS; Germany) in platinum ring detachment technique using at 298.15K. Accurecy of the study was ±0.1 m. N m^{-1}. A circulating auto thermo stated water through a double- walled glass vessel holding the solution 298.15K. The specific conductivities of the studied solutions were measured with a Mettler-Toledo Seven Multi conductivity meter with an uncertainty of ±1.0 mSm^{-1}. The experiments were carried out in an auto thermo stated water bath held at298.15 K using HPLC-grade water with a specific conductance of 6.0 μS m^{-1}. Calibration of the cell was achieved using a 0.01M aqueous KCl solution.

NMR spectra were recorded in D_2O unless otherwise stated. ^1H NMR spectra were recorded using BrukerADVANCE 350. Signals are quoted as δ values in ppm using residual protonated solvent signals as internal standard (D_2O: δ 4.79 ppm). Data are reported as chemical shift. FTIR Spectra were recorded in KBr disk method by Perkin-Elmer FTIR Spectometer. KBr disks were made in 1:100 ratio of sample and KBr. FT-IR Stuides were carried out in the scaning range of 4000-400 cm-^{1} at room temperature.

RESULT AND DISCUSSION

Surface tension study

Surface tension gives precious information about the nature and formation of inclusion complex (Roy *et al*., 2015). The aqueous solution of α and β-CD do not show any considerable change of surface tension.

The valporic acid shows COO^- group and their side group being non polar shows surfactant like behavior and it has a tendency to decrease the surface tension of aqueous solutions like other surfactants (Pineiro 2007) (Roy, 2016). Here surface tension (γ) is measured for a series of solution with increasing concentration of both host α and β cyclodextrin at 298.15K. The γ values shows increasing trend in case of both the guests (Table 3).

Perhaps it is due to the formation of inclusion complex between VA and CD because due to the removal of the surface active VA molecules from the surface of the solution into the hydrophobic cavity α and β CD. In the two surface tension plots appearance of single break point indicates formation of inclusion complex in both cases (Figure 1). The values of surface tension with corresponding concentration of α and β CD and concentration of VD at each break have been listed in Table 1.

Table 1. Data for surface tension study of aqueous sodium valproate with *α*-CD and β-CD system at 298.15K[a]

Volm of CD (mL)	Total volm (mL)	Conc of sodium valproate (mM)	Conc of CD (mM)	Surface tension in α-CD (mN m^{-1})	Surface tension in β-CD (mN m^{-1})
0	10	10.000	0.000	52.1	52.1
1	11	9.091	0.909	54.8	54.9
2	12	8.333	1.667	57.3	57.4
3	13	7.692	2.308	59.9	59
4	14	7.143	2.857	61.5	61.2
5	15	6.667	3.333	63	63
6	16	6.250	3.750	64.7	64.4
7	17	5.882	4.118	66.2	66.4
8	18	5.556	4.444	67.7	67.9
9	19	5.263	4.737	69.3	69.1
10	20	5.000	5.000	70.5	70.6
11	21	4.762	5.238	70.7	70.8
12	22	4.545	5.455	70.9	71
13	23	4.348	5.652	71	71.1
14	24	4.167	5.833	71.1	71.2
15	25	4.000	6.000	71.2	71.3
16	26	3.846	6.154	71.3	71.4
17	27	3.704	6.296	71.4	71.5
18	28	3.571	6.429	71.6	71.6
19	29	3.448	6.552	71.7	71.7
20	30	3.333	6.667	71.8	71.9

a Standard uncertainties in temperature u are: u(T) = ±0.01 K.

Table 2. Data for conductivity study of aqueous sodium valproate with α and *β*-CD system at 298.15K[a]

Volm of *β*-CD (mL)	Total volm (mL)	Conc of sodium valproate (mM)	Conc of -CD (mM)	Contuctance of α-CD(mSm^{-1})	Conductance of β-CD(mSm^{-1})
0	10	10.000	0.000	0.81	0.81
1	11	9.091	0.909	0.74	0.72
2	12	8.333	1.667	0.66	0.65
3	13	7.692	2.308	0.60	0.59
4	14	7.143	2.857	0.54	0.54
5	15	6.667	3.333	0.49	0.49
6	16	6.250	3.750	0.45	0.44
7	17	5.882	4.118	0.41	0.40
8	18	5.556	4.444	0.38	0.36
9	19	5.263	4.737	0.35	0.33
10	20	5.000	5.000	0.32	0.30
11	21	4.762	5.238	0.31	0.295
12	22	4.545	5.455	0.30	0.287
13	23	4.348	5.652	0.30	0.280
14	24	4.167	5.833	0.29	0.275
15	25	4.000	6.000	0.29	0.271
16	26	3.846	6.154	0.28	0.269
17	27	3.704	6.296	0.28	0.264
18	28	3.571	6.429	0.28	0.260
19	29	3.448	6.552	0.27	0.255
20	30	3.333	6.667	0.27	0.250

a Standard uncertainties in temperature u are: u(T) = ±0.01 K.

Over all variation of γ and one beak point clearly show that at certain concentration of VA and CD where their concentration ratio in solution was almost 1:1, thus the study proves 1:1 ratio in both α and β CD.

Conductance study

Coductivity (κ) of aqueous solution of sodium valproate has been measured with both α and β CD solution to find out whether inclusion have been formed. During experiment k-value of the solution have been decreased in both cases enacapsulation of the VA molecules inside into cavity of the CD-molecule was observed (Table-3)(12).

In both cases after certain concentration breaking of the curve was observed which may indication of the formation of inclusion complex (Fig-2). The experimental curve showed only one beak, which indicates 1:1 inclusion in both α and β CD cases, suggesting the host-guest ratio to be 1:1. At certain concentration the break point is found where maximum inclusion occur through dynamic equilibrium between the host and the guest molecules (12).

^{1}H NMR study

^{1}H NMR spectrum of VA/α-CD and VA /β-CD is small shifts to higher frequencies are observed for VA signals.

Table 3. Values of surface tension (γ) at the break point with corresponding concentrations of cyclodextrins and sodium valproate and values of conductivity (κ) at the break point with corresponding concentrations of cyclodextrins and sodium valproate at 298.15 K

Conc. of α-CD/mM	Conc. of sodium valproate/mM	γ^a /mNm^{-1}
4.74	5.01	69.3
Conc. of β-CD/mM	Conc. of sodium valproate /mM	γ^a /mNm^{-1}
4.91	5.1	70.4
Conc. of α-CD/mM	Conc. of sodium valproate /mM	κ^a /mSm^{-1}
4.74	5.26	0.33
Conc. of β-CD/mM	Conc. of sodium valproate /mM	κ^a /mSm^{-1}
5.1	4.9	0.31

[a] Standard uncertainties (u): temperature: u(T) = ±0.01 K, surface tension: $u(\gamma)$ = ±0.1 mN·m^{-1}, conductivity: $u(\kappa)$ = ±0.001 mS·m^{-1}.

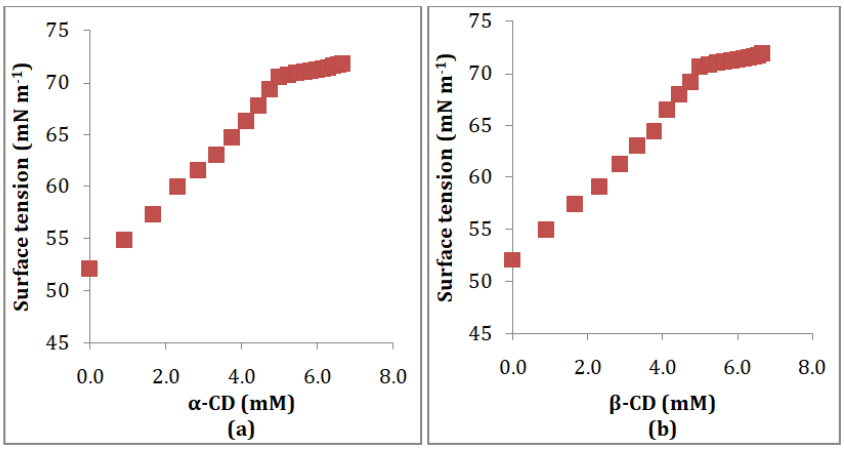


Figure 1. Variation of surface tension of aqueous (a) sodium valproate-α-CD and (b) sodium valproate-β-CD systems respectively at 298.15 K

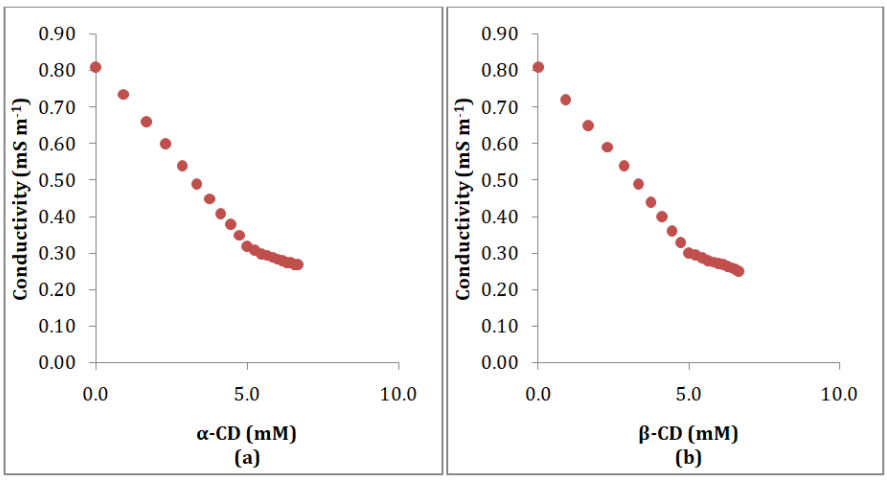


Figure 2. Variation of conductivity of aqueous (a) sodium valproate-α-CD and (b) sodium valproate-β-CD systems respectively at 298.15 K

Table 4. Estimated vibrational frequencies for [α-CD : Sodium Valproate] Complex formation

Sodium Valproate	
wave number / cm^{-1}	Group
3082-2875	–C-H from various –CH3 and methylene groups
1700.60	Streching for -C=O
1560.01	Symmetrical Stretching of $–COO^-$
1412.45	Anti-symmetrical stretching of –COO-
α-CD	
wave number / cm-1	Group
3412.10	stretching of -O-H
2930.79	stretching of –C-H from –CH2
1406.76	bending of –C-H from –CH2 and bending of O-H
1154.39	bending of -C-O-C
1030.39	stretching of -C-C-O
952.36	skeletal vibration involving α-1,4linkage
α-CD +[Sodium Valproate]	
wave number / cm-1	Group
3366.45	stretching of -O-H of α-CD
2948.52	Symmetrical stretching of –C-H from –CH3 Of Sodium valproate
1662.75	-C=O from sodium valporate
1538.74	Stretching of -COO- from sodium valporate
1046.03	Bending of C-C-O Of α-CD
984.46	stretching of C-C-O of α-CD

Table 5. Estimated vibrational frequencies for [β-CD : Sodium Valproate] Complex formation

Sodium Valproate	
wave number / cm^{-1}	Group
3000-2800	–C-H from various –CH3 and methylene groups
1700	Streching for C=O
1560	Symmetrical Stretching of $–COO^-$
β-CD	
wave number / cm-1	Group
3349.23	stretching of O-H
2919.12	stretching of –C-H from –CH2
1409.18	bending of –C-H from –CH2 and bending of O-H
1153.17	bending of C-O-C
1033.02	stretching of C-C-O
938.64	skeletal vibration involving α-1,4linkage
β-CD +[Sodium Valproate]	
wave number / cm-1	Group
3326.18	stretching of O-H of β-CD
2958.13	stretching of –C-H from –CH3 and –CH2 Of sodium valproate
1722.67	Streching for C=O of sodium valproate
1678.56	Symmetrical stretch of –COO- of sodium valproate
1384.41	Anti- symmetrical Stretching of COO^- of sodium valproate
1158.05	bending of C-O-C Of β-CD
1072.56	stretching of C-C-O Of β-CD

The protons of the CD molecule shows considerable chemical shift due to inclusion of the guest VA in to the hydrophobic cavity. In CD structure H3 andH5 are situated inside the wider rim of the cavity, while H1, H2 and H5 are found narrow rim cavity of the CD molecule (Roy *et al*., 2016).During the insertion of the VA molecule inside the cavity of CD, the H3 and H5 protons show up field chemical shifts which conforms the interaction of the host–guest molecule occur(13). The COO^- group of VA interact with H5 and H3 of the CD molecules. The interaction of H1, H2, H2', H3, H3', H4, H4' of VA and H3 located inside the CD cavity. Interaction between H2, H2 and H4, H4'of VA with H5 of the CD cavity and H4, H4' of VA and H2, H4of CD, occur which show that formation of the inclusion compound (Fig-3) .

FTIR study

The formation of inclusion complex of Sodium valporate with α and β-CD in solid state is supported by FT-IR study.

There are many changes in the FT-IR spectra of solid inclusion complexes due to the changes of bending and vibrating peaks of the guest also arosed due to the symmetrical and anti-symmetrical stretching vibrations of the COO^- grouping. The various frequencies of sodium valporate, α-CD, β-CD, sodium valporate + α-CD and sodium valporate + β-CD are reported in (Table -3). The –O-H frequency of both α and β-CD are shifted to lower region most likely due to involvement of the –O-H groups of the host molecules in hydrogen bonding molecule after Complexation. The IR spectra of SV with the hosts presented in figure-4. The spectrum was measured in the solid state of the sample as a KBr dispersion. The following bands in (cm^{-1}) have been assigned in the Tables-2. The inclusion complex formation due to strong bands caused by overlapping of C-H stretching vibrations of various methyl and methylene groups of the guest molecule with cyclodextrins. Moreover strong bands included in the Tables and figures with the guest molecule.

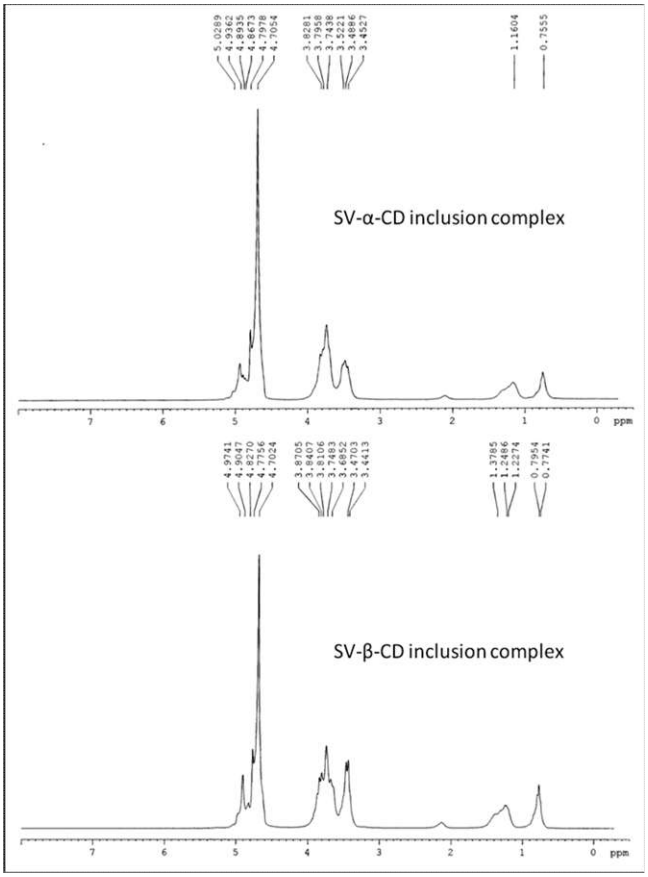


Figure 3. [1]H NMR spectra of sodium valporate-α-CD and sodium valproate-β-CD inclusion complexes

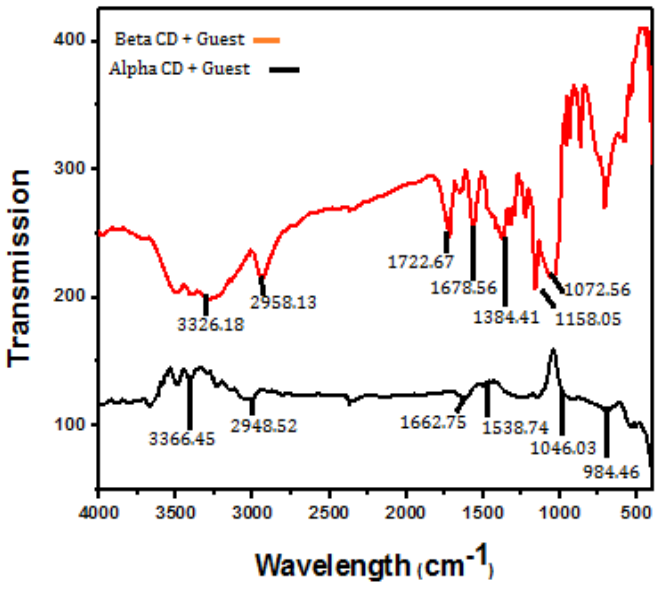
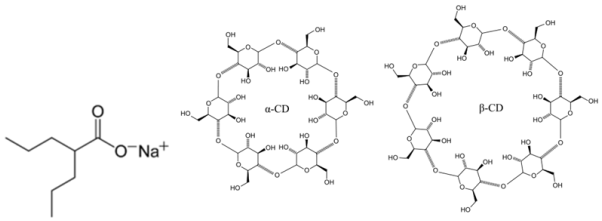


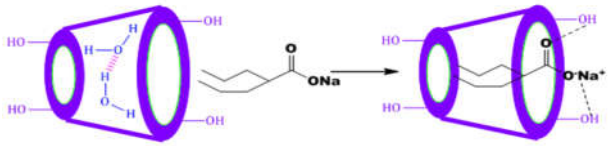
Figure 4. FTIR spectra of sodium valproate-α-CD and sodium valproate-β-CD inclusion complexes

Moreover the spectra of the two inclusion complexes are dissimilar to CD. Additional peaks are recognized in the solid inclusion complexes which means chemical reaction occurred between the guest and CD. However, quite a lot of peaks of sodium valporate are absent or somewhere shifted which is due to the change in environment after inclusion in the cavity of α- CD, these changes was more appropriately noticed in β-CD than α-CD. So, we conclude that the encapsulation is better with β-CD.

Schemes



Scheme 1. Structure of sodium valproate and cyclodextrins



Scheme 2. Plausible schematic representation of mechanism for the formation of 1:1 inclusion complex of sodium valproate with both *α* and *β*-cyclodextrin

Cyclodextrin and sodium valproate: the structural suitability

Cyclodextrin provide great opportunity to act as a host molecules due to inner hydrophobic cavity and hydrophilic rims. A non polar part of guest molecules inside the cavity and polar part of the guest molecule makes association with the polar rims , forming a sTable inclusion complex(scheme-2) .The apolar cavity diameter of α -CD is 4.7-5.3Å and β- CD is 6-6.5Årespectively (Roy *et al*., 2016). The valporic acid size and apolar part of propayl group and polar part COO^- which can be easily encapsulated inside the cavity of CD (Sinisterra *et al*., 2018) . The formation of inclusion complex no covalent bond formation or breaking occur (Roy, 2016). The polar water molecules are present inside the slightly apolar cavity of cyclodextrine. This is generally energetically unflavored. So the polar water molecules are readily substituted by hydrophobic chains of the VA. This results a more sTable energy state. The stoichiometry of the inclusion complex is found as 1:1, which is supported by conductivity and surface tension measurements (Roy *et al*., 2016). So after inclusion of one VA molecule COO^- the zwitterionic part blocks the rim by making hydrogen bonding with the rim –OH groups, so second molecule cannot enter. Propyl group hydrophobic part of VA was found to be inserted through the wider rim of cyclodextrin (Roy *et al*., 2015).

Conclusion

With the help of spectroscopic and physicochemical studies we reached the conclusion that the Valporic acid form host–guest ICs with both α and β-CD both in solution and the solid state. [1]H NMR confirms the inclusion in the apolar cavity of both CD molecules, while surface tension and conductivity measurements suggest a 1: 1 stoichiometry. Solid state characterisations have been carried out by FT-IR, confirming their formation also in the solid state. The inclusion phenomenon has been found to be more favorable in the case of β-CD than the α-CD. In the present study we investigate the nature of formation and stoichiometry of inclusion complexs of α and β-CD with VA in the aqueous medium can be used as controlled delivery systems in the field of modern biomedical sciences.

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