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Article

Investigation of Host–Guest Inclusion Complexes of a Neurotransmitter inside into α- and β-Cyclodextrins through Hydrophobic and Hydrophilic Interactions by Physicochemical Approach

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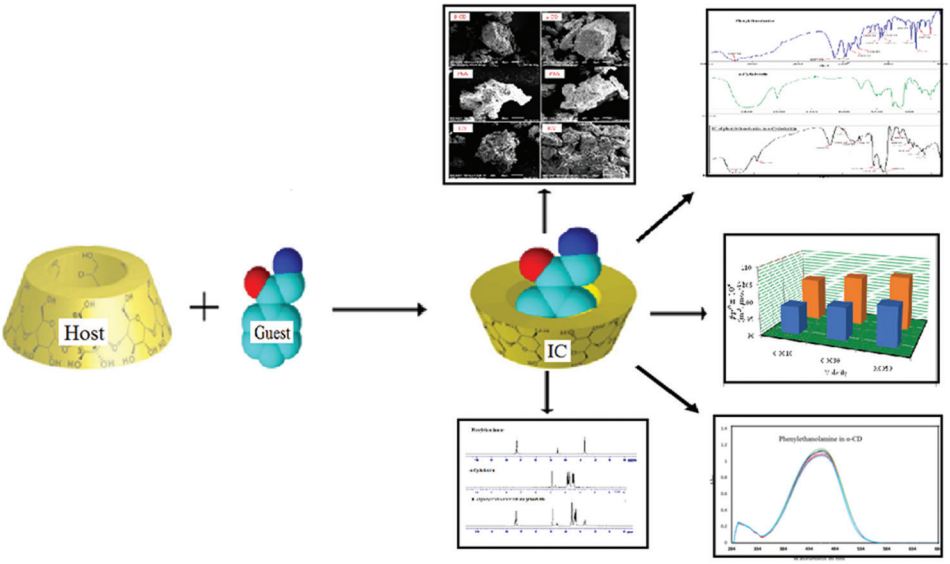
ABSTRACT

In the present work, the formation of inclusion complex of a neurotransmitter, phenylethanolamine with α-cyclodextrin (α-CD) and β-CD (β-CD) was examined from volumetric, viscometric, and spectroscopic studies. The supramolecular interaction between CD and phenylethanolamine has been characterized by volumetric and viscometric and spectral studies. However, the stoichiometry of host–guest of the inclusion complexes was ascertained from Job's plot calculation from ultraviolet–visible spectroscopy. The association/binding constant of the formation of inclusion complex was calculated from Benesi–Hildebrand equation. The infrared (IR) and ^{1}H-NMR spectroscopy also support the formation of inclusion complexes and the probable manner of inclusion was defined from ^{1}H-NMR and two-dimensional Roesy NMR spectroscopies.

Key words: Phenylethanolamine, Job's plot, cyclodextrins, Benesi–Hildebrand equation.



Graphical Abstract

1. INTRODUCTION

Phenylethanolamine is known as β-hydroxyphenethylamine is a neurotransmitter which is structurally similar to others trace amine such as norepinephrine, dopamine, and epinephrine [1,2].

It is endogenous chemical which transmits signal across a chemical synapse from one neuron to another neuron. The neurotransmitters produced from synaptic vesicles are received by specific neurotransmitter receptors on the cell membrane of the postsynaptic neuron as shown in Scheme 1. This neuron may be connected to many more neurons and pass the information to adjacent neuron [3-5].

The neurotransmitters are clinically used for the treatment of several neurological and psychiatric disorders such as schizophrenia, Parkinson's disease, bipolar disorder, attention deficit, Huntington's disease, and hyperactivity disorder. It regulates the blood pressure, respiration, and body

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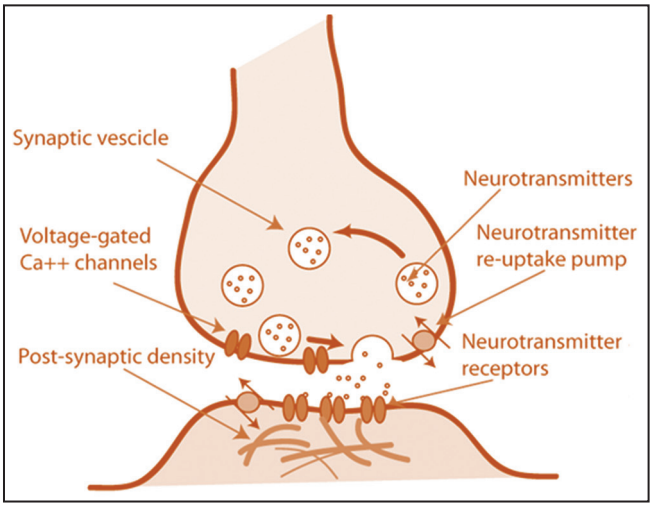
temperature, the secretion of hormones from the pituitary gland, the regulation of α2-adrenoceptors in the hypothalamus, etc. Phenylethanolamine is responsible for the production of enzyme phenylethanolamine-N-methyltransferase for the conversion of norepinephrine into epinephrine [6-8]. Phenylethanolamine-N-methyltransferase catalyzes the biosynthesis of epinephrine from norepinephrine by transferring methyl group from S-adenosyl-l-methionine [9].

The cyclodextrins (CDs) are the cyclic oligosaccharides of glucopyranose units. There are three kinds of CDs, α-CD (α-CD), β-CD (β-CD), and γ-CD (γ-CD) containing 6, 7, and 8 glucopyranose units, respectively, connected with α-(1–4) linkages [10,11]. The two-dimensional (2D) and three-dimensional structures of CDs are shown in Schemes 2 and 3. The special characteristic of CD is that its inner cavity is hydrophobic in nature, whereas exterior side is hydrophilic in nature. This kind of exceptional property allows CD for complexation with diverse molecules such as vitamins, amino acids, drugs, ionic liquids, hormones, polymers, and dyes [12-16]. The H3 and H5 protons of CDs are located inside the cavity and the H1, H2, and H4 protons are located outside the cavity as shown in Scheme 3. Another significant feature of CD is that the H3 proton is situated close to the wider rim and H5 proton is situated close to the narrower rim of the CD. The hydrophobic or alkyl parts of the compound enter inside the hydrophobic cavity of CDs and thus forming a stable inclusion complex [17] and the hydrophilic or ionic part of the compound exposes outside the cavity of CDs, thus forming an inclusion complex. The complexation of any compound inside CD increases the solubility, stability against heat, light, oxidation, and bioavailability and reduces volatility of the encapsulated molecules without disturbing its structure.



Scheme 1: Process of transmission of signals from one neuron to another neuron.

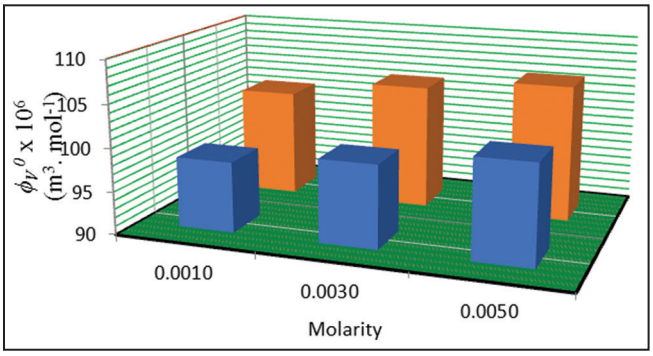


Figure 1: Variation of limiting apparent molar volumes (ϕ_V^0) of phenylethanolamine in aqueous α- and β-CDs solution with molarity (red and blue color for α- and β-CDs, respectively).

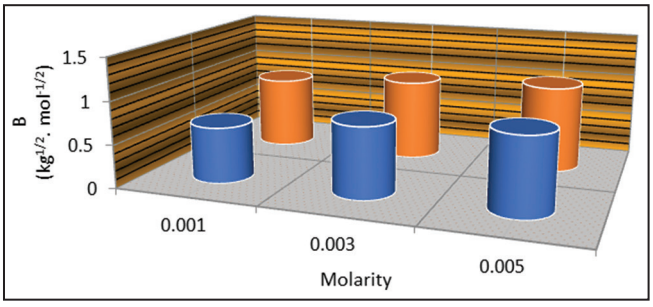


Figure 2: Variation of viscosity B coefficient of phenylethanolamine in aqueous α- and β-CDs solution with molarity (red and blue column for α- and β-CDs, respectively).

In our present work, we studied the formation of inclusion complex of phenylethanolamine inside the cavity of α- and β-CDs. Various physicochemical parameters from volumetric and viscometric studies and spectrometric methods were used to inspect the inclusion phenomenon. The inclusion complexes so formed may be used medically for its better performance as drugs.

2. EXPERIMENTAL SECTION

2.1. Materials

The neurotransmitter, phenylethanolamine was procured from TCI Chemicals (Japan) Pvt. Ltd., and α- and β-CDs were procured from Sigma-Aldrich, Germany. All these chemicals were used as purchased as their mass fraction purity was >0.98.

2.2. Apparatus and Procedure

The solutions were prepared with triply distilled water. The weight was measured with Mettler AG-285 electronic balance having precession $\pm 0.0003 \times 10^{-3}$ kg.

Anton Paar Density Meter (DMA 4500M) with a precision of 0.00001 $\times 10^{-3}$ (kg/m^3) was employed to measure the density (ρ) of the solutions at different temperatures. The calibration of the density meter was done using doubly distilled water and dry air.

The viscosities of the solutions were taken with Brookfield DV-III Ultra Programmable Rheometer with spindle size-42. The viscometer was connected with Brookfield Digital Bath TC-500. The machine was calibrated with doubly distilled water and purified methanol at 298.15 K before recording the viscosities of our studied solutions. The uncertainty in viscosity is within ±0.003 mPa/s.

Ultraviolet (UV)–visible absorption spectra of phenylethanolamine solution with successive addition of CDs were taken at 298.15 K by JASCO V-530 UV–visible spectrophotometer. In our present work, a probe methyl orange (MO) was used since the studied neurotransmitter does not absorb in the UV–visible range.

The Fourier-transform infrared (FT-IR) spectra were recorded with PerkinElmer FT-IR spectrometer after preparing the KBr disk of phenylethanolamine, CDs, and inclusion complexes of it. The KBr disk is prepared by mixing 100 mg of carefully dried pure KBr and 1 mg of the compound to be studied.

^{1}H-NMR and NMR-ROSEY spectra were taken at 298 K in D_2O by Bruker Avance 400 MHz spectrometer.

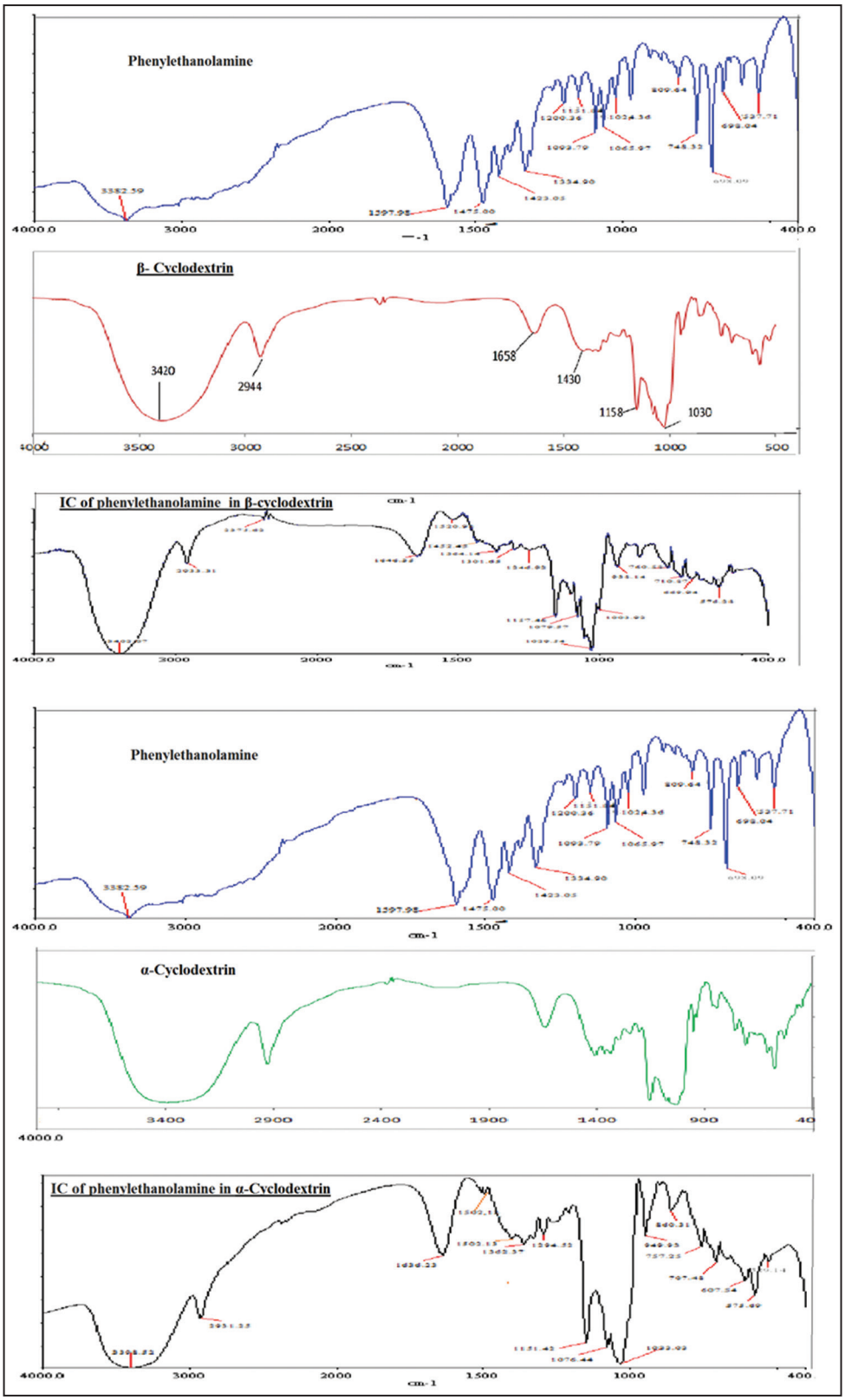


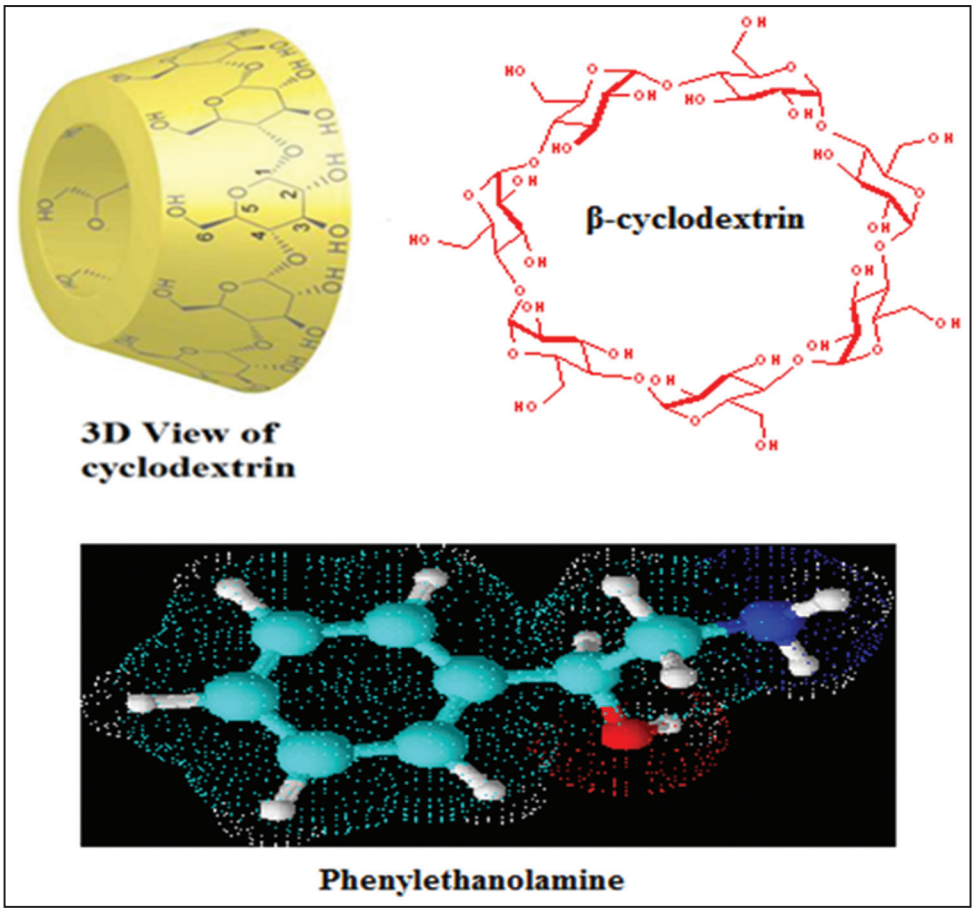
Figure 3: FTIR spectra of phenylethanolamine and inclusion complexes of it in α- and β-CD at 298.15 K.

3. RESULTS AND DISCUSSION

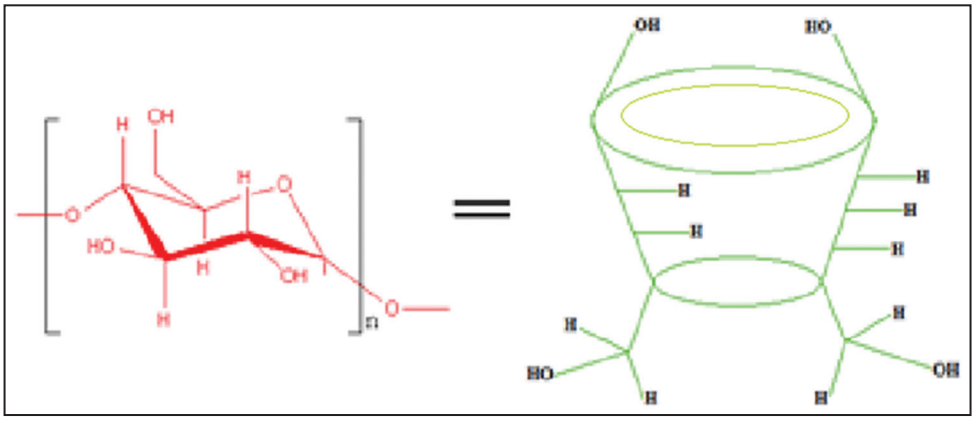
3.1. Density Study

We may get valuable information about the interactions between phenylethanolamine and CD molecules from volumetric study. The values of densities (ρ) and viscosities (η) of different molar aqueous solutions of phenylethanolamine in α- and β-CDs at 298.15 K are shown in Tables S1 and S2, respectively. We calculated the apparent molar volume, ϕ_V from densities of different molarities of phenylethanolamine in aqueous solution of α- and β-CDs of varying molarities from the following equation [18].

$$\phi_V = M/\rho - 1000\,(\rho - \rho_0)/(m\rho\rho_0) \quad (1)$$



Scheme 2: Structure of cyclodextrin and phenylethanolamine.



Scheme 3: Structure of cyclodextrins.

The limiting apparent molar volume, ϕ_V^0 was evaluated by least square treatment of the plots of ϕ_V against $\sqrt{m}$ using the renowned Masson equation [19].

$$\phi_V = \phi_V^0 + S_V^* \sqrt{m} \quad (2)$$

The ϕ_V^0 provides the information about solute-solvent interaction. The variations of limiting apparent molar volumes (ϕ_V^0) of phenylethanolamine are shown in Table S3 and Figure 1. It is noticed that ϕ_V^0 values increase with increase in molarity of phenylethanolamine and CDs which specifies that solute and cosolute interactions increase with increasing concentration of phenylethanolamine and CDs are shown in Table S3 and Figure 1. The interaction is assumed to be arisen from the H-bonding between -NH_2 and -OH groups of phenylethanolamine and -OH group of CDs. The higher ϕ_V^0 value of phenylethanolamine in α-CD than β-CD indicates that the former interacts strongly with phenylethanolamine than later. This cannot be explained with H-bonding only. If the interaction was arisen only from H-bonding, then ϕ_V^0 values for both α-CD and β-CD should be same. The difference in ϕ_V^0 values of phenylethanolamine in α-CD and β-CD can be explained on the basis of formation of inclusion complex which occurs due to another kind of non-bonding interaction known as hydrophobic-hydrophobic interaction. The hydrophobic aryl part of phenylethanolamine enters inside the hydrophobic interior of CD forming inclusion complex and exert hydrophobic-hydrophobic interaction [20]. The higher ϕ_V^0 values of phenylethanolamine in α-CD than β-CD may be explained from their cavity sizes. We know that the

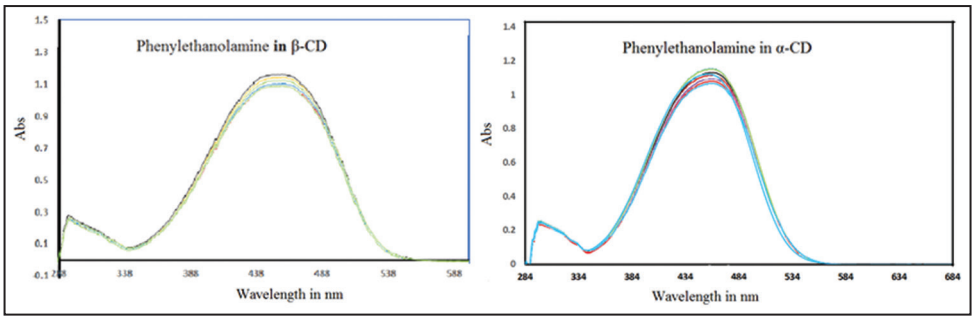


Figure 4: Ultraviolet–visible spectra of phenylethanolamine in different concentrations of CDs using MO as probe.

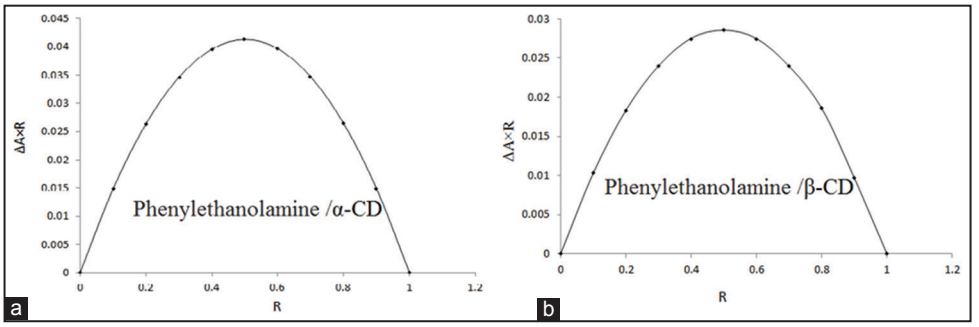


Figure 5: Job's plot of different concentrations of (a) β-CD in phenylethanolamine (b) α-CD in phenylethanolamine using MO as probe.

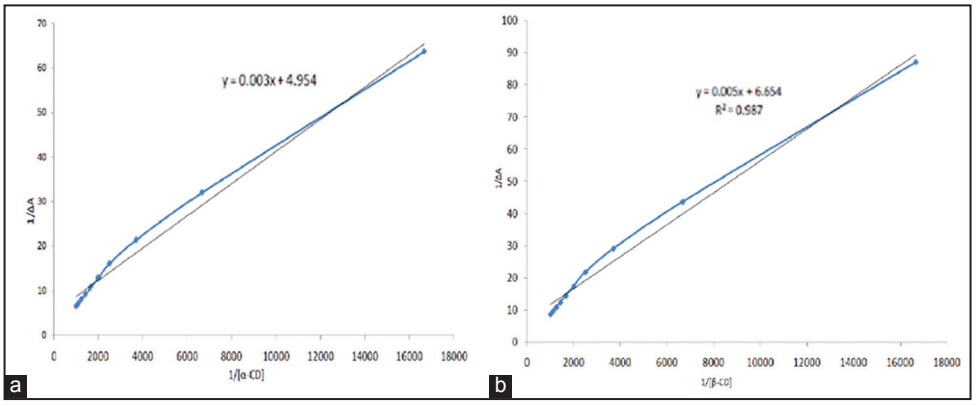


Figure 6: (a) Plot of 1/ΔA against 1/[α-CD]for examining stoichiometry of inclusion complexes. (b) Plot of 1/ΔA against 1/[β-CD] for examining stoichiometry of inclusion complexes.

cavity size of α- and β-CD is 4.7–5.3 Å and 6.0–6.5 Å, respectively. The smaller cavity size of α-CD provides a better situation for hydrophobic-hydrophobic interaction with phenylethanolamine than β-CD which has comparatively larger cavity size. For this reason, ϕ_V^0 of phenylethanolamine is higher in α-CD than in β-CD. Hence, volumetric study gives us an idea about the formation of inclusion of phenylethanolamine with CDs.

3.2. Viscosity Study

Viscosity study is also helpful for inspecting the inclusion complex of phenylethanolamine with CDs [21]. From the viscosities of the phenylethanolamine in different molarities of aqueous CDs solution, we can calculate the viscosity A and B coefficient using famous Jones–Dole equation given below.

$$(\eta/\eta_0 - 1)/\sqrt{m} = A + B\sqrt{m} \quad (3)$$

Where, η_0 and η are the viscosities of the solvent (aqueous solution of cosolute) and solution, respectively. The viscosity coefficients A and B values are obtained from intercept and slope of the straight line obtained from the plot of $(\eta/\eta_0 - 1)$/against $\sqrt{m}$ and reported in Table S3 and Figure 2. The viscosity B coefficient gives the information about the solute-solvent interaction [22,23]. The values of viscosity B coefficients of phenylethanolamine increase with increasing concentration of phenylethanolamine and CDs. This indicates that interaction between phenylethanolamine and the CD increases with increasing concentration of CD. The interaction arises from H-hydrogen bonding between -OH group of CD and -OH and $-NH_2$ groups of phenylethanolamine. It is observed that B values for phenylethanolamine/α-CD and phenylethanolamine/β-CD systems are different which cannot be explained by H-bonding only. Similar kind of observation was obtained in volumetric study also which may be explained by hydrophobic-hydrophobic interaction due to the formation of inclusion complex. The hydrophobic aryl part of phenylethanolamine enters into the hydrophobic interior of CD and forms inclusion complex by hydrophobic-hydrophobic interaction. The higher B value for phenylethanolamine/α-CD system

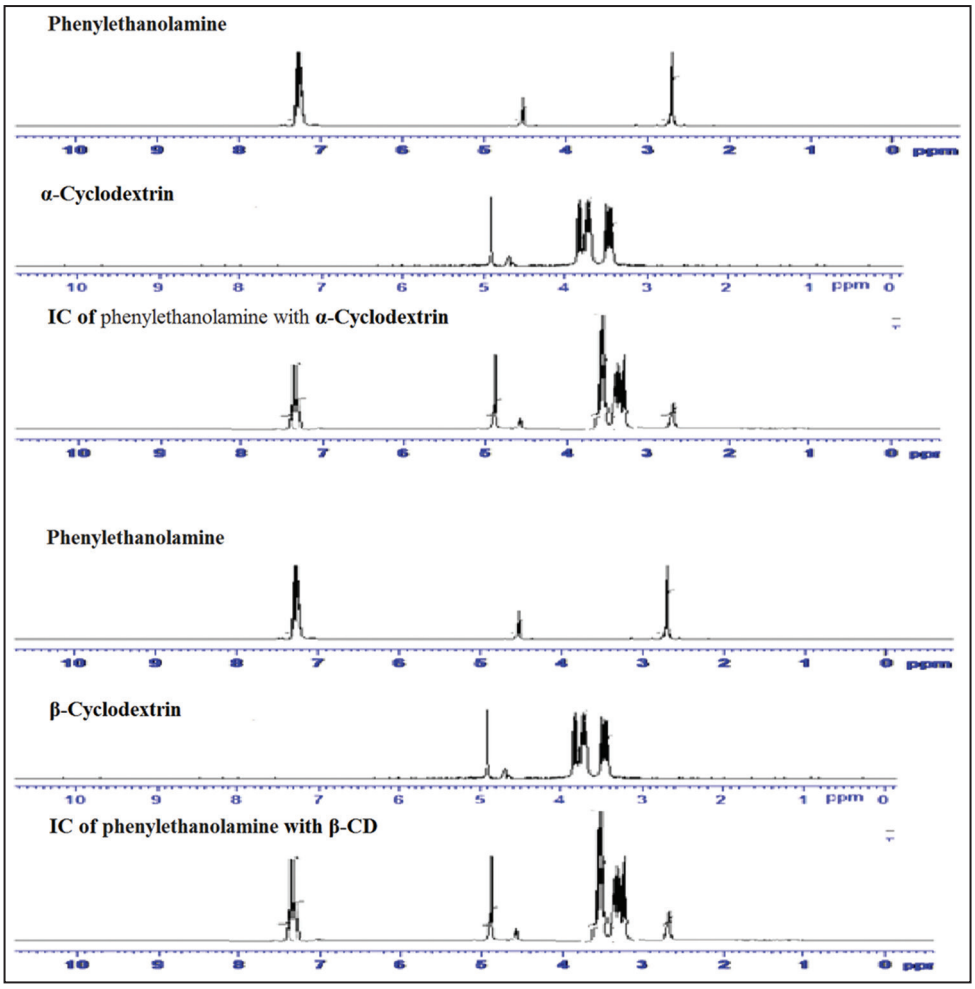


Figure 7: ^{1}H-NMR spectra of phenylethanolamine and inclusion complexes of it with α- and β-CDs in D_2O at 299.15 K.

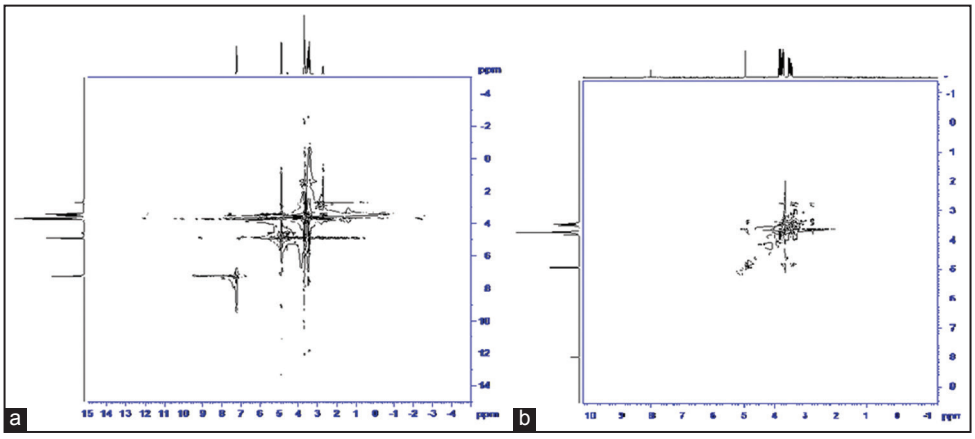


Figure 8: NMR Roesy spectra of inclusion complexes of (a) phenylethanolamine and α-CD (b) phenylethanolamine and β-CD.

than phenylethanolamine/β-CD systems indicates that α-CD is more favorable in forming inclusion complex than β-CD [24]. The smaller cavity size of α-CD provides a better situation for encapsulation than β-CD.

3.3. FT-IR Spectroscopy

The FT-IR study is a very reliable technique for investigation the inclusion phenomena [25-27]. The FT-IR spectra of pure phenylethanolamine, α- and β-CD CDs, and their inclusion complexes are given in Figure 3.

Some characteristic frequencies of phenylethanolamine, α- and β-CD CDs, and their inclusion complexes are given below. The frequencies for –OH group of both the α- and β-CD shifted to the lower frequencies which may be considered due to the presence of H-bonding between -OH groups of the CDs and –OH and $–NH_2$ groups of phenylethanolamine. The peaks positions for aryl part of phenylethanolamine and hydrogen

present in the interior of CDs changed due to encapsulation of aryl group into the cavity of CD.

The frequencies of different groups are as follows:

Phenylethanolamine: 3458 cm^{-1} (O-H stretch), 2813.55 cm^{-1} (C-H stretch for -CH_2), 1597.98 cm^{-1} (-C=C stretch for aromatic), 1589 cm^{-1} (C=C), 1475 cm^{-1} (C-C stretch for aromatic), and 1423.05 cm^{-1} (Bending-CH2), α-CD: 3434 cm^{-1} (stretching of O-H), 2930 cm^{-1} (stretching of –CH from –CH2), 1420 cm^{-1} (bending –CH), 1160 cm^{-1} (bending of C-O-C), 1080 cm^{-1} (stretching of C-C-O), and 956 cm^{-1} (vibration α-1,4 linkage).

β-CD: 3327 cm^{-1} (stretching of O-H), 2944 cm^{-1} (stretching of –CH from –CH2), 1430 cm^{-1} (bending –CH), 1158 cm^{-1} (bending of C-O-C), 1030 cm^{-1} (stretching of C-C-O), and 953 cm^{-1} (vibration α-1,4 linkage).

Phenylethanolamine/α-CD inclusion complex: 3398.52 cm^{-1} (stretching of O-H of α-CD), 2931 cm^{-1} (stretching of –C-H), 1456.02 cm^{-1} (bending of –C-H), and 1502.13 cm^{-1} (C-C stretch for aromatic).

Phenylethanolamine/β-CD inclusion complex: 3402.02 cm^{-1} (stretching of O-H of B-CD), 2922.31 cm^{-1} (stretching of –C-H), 1520 cm^{-1} (C-C stretch for aromatic), and 1452.45 cm^{-1} (bending of –C-H).

3.4. UV–Visible Spectroscopy Investigation

A significant indication about the formation inclusion complex may be obtained from UV–visible spectroscopy [28]. Since our studied compounds phenylethanolamine and CDs do not absorb in the UV–visible range, we used MO as probe.

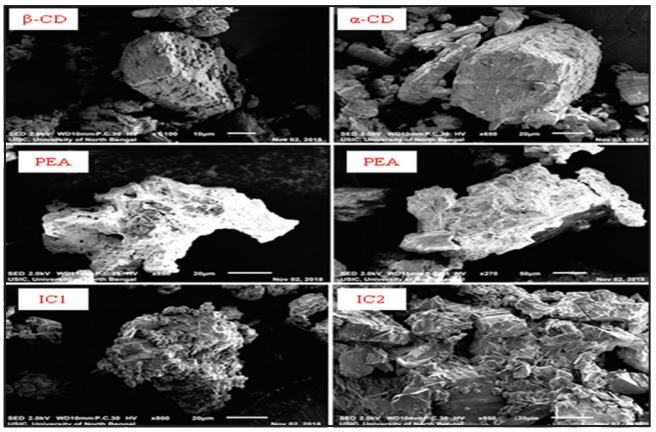


Figure 9: SEM images of α-CD, β-CD, and their inclusion complexes with phenylethanolamine.

The absorption spectra of phenylethanolamine in different molarities of CDs were recorded and shown in Figure 4.

The stoichiometry of host and guest of inclusion complex may be obtained from absorbance values by plotting the graph of ΔA×R against R which is known as Job's plot [29-31] [Figure 5].

Where, R is concentration ratio

R = [PEA]/([PEA]+[CD]) and ΔA represents the difference in absorbance of phenylethanolamine with and without CD at 298.15 K. R values at the maxima of Job's plot indicate the stoichiometry of host and guest of inclusion complexes.

R = 0.5, 0.33, and 0.66 at the maxima indicate the 1:1, 1:2, and 2:1 host–guest stoichiometry of the inclusion complexes.

R value in case of phenylethanolamine/CD system is 0.5 which indicates the 1:1 stoichiometry.

The association constant of inclusion complex formation (Schemes 4 and 5) for phenylethanolamine/CD system, K_a may be determined from the absorptivity values of UV–visible spectra. We used the well-known Benesi–Hildebrand equation to estimate the association constants (K_a) of inclusion complex formation [32].

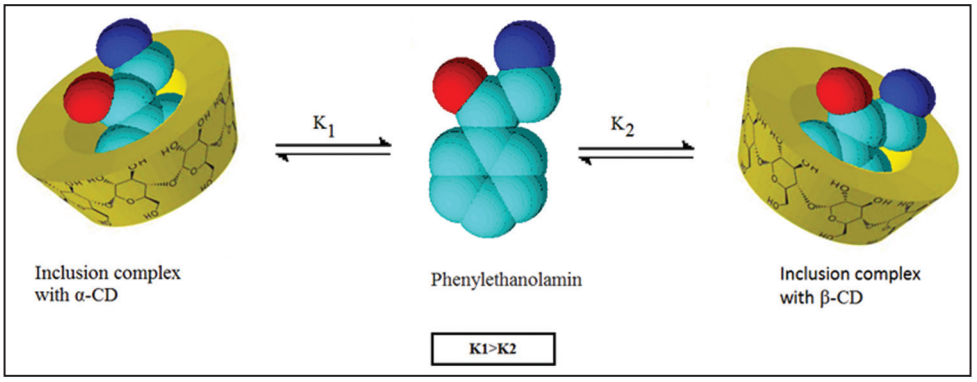
$$\frac{1}{\Delta A} = \frac{1}{\Delta\varepsilon K[\text{Guest}]} \times \frac{1}{[\text{Host}]} + \frac{1}{\Delta\varepsilon}$$

The spectra of phenylethanolamine at constant molarity were recorded with varying concentration of CD in the presence of the probe (MO).

Where, ΔA denotes the difference in absorbance of phenylethanolamine in the presence and absence of CDs, [Guest] and [Host] represent the concentration of phenylethanolamine and CD, respectively, and Δε denotes the molar absorption coefficient difference in the presence and absence of CDs. The plot of 1/ΔA against 1/[CDs] gives a straight line with an intercept 1/Δε and a slope of $\frac{1}{\Delta\varepsilon K[\text{Guest}]}$. The association constant, K_a may be achieved by dividing the intercept with the slope of the plot at a certain concentration of ionic liquid. The K_a evaluated from Benesi–Hildebrand equation for phenylethanolamine/α-CD system is 1.216×10^4 M^{-1} and for phenylethanolamine/β-CD system is 1.331×10^4 M^{-1}.

3.5. ^{1}H-NMR Study

^{1}H-NMR study gives us important information about the formation of host–guest inclusion complex [33]. The ^{1}H-NMR spectra of phenylethanolamine, CDs, and their IC were recorded in D_2O at 298.15 K and are shown in Figure 7. Remarkable chemical shifts of various protons of the inclusion complexes from host and guest molecules noted. It is known that H3 and H5 protons of CDs are positioned inside the

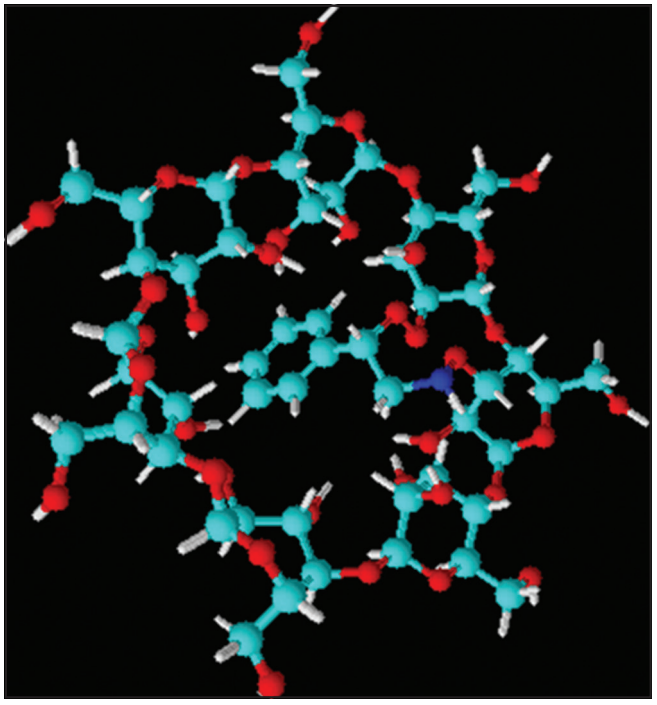


Scheme 4: Formation of inclusion complexes of phenylethanolamine with α- and β-CDs, respectively, and the order of association constants.

cavity, whereas the H1, H2, and H4 protons are positioned outside the cavity [34,35]. Another important feature of CD is that the H3 proton is situated closer to the wide rim and H5 proton is situated closer to the narrow rim of the CD. The alkyl part of phenylethanolamine is assumed to be held inside CD cavity through hydrophobic-hydrophobic interaction without forming or breaking any bond. Due to the encapsulation of aryl part of the phenylethanolamine inside the cavity of CDs, notable upfield chemical shift of the H3 and H5 protons of CDs and downfield chemical shift of protons of aryl part of the ionic liquid took place [33]. Comparatively larger chemical of shift for H3 proton than the H5 proton supports that the encapsulation of aryl part of phenylethanolamine inside CD molecules occurs through the wider rim of CD as shown in Scheme 6.

3.5.1. ^{1}H-NMR data

Phenylethanolamine: [^{1}H-NMR (300 MHz, D2O)]: δ 2.694–2.732 (2H, m), 4.527–4.559 (1H, t), 7.210–7.315 (5H, m).



Scheme 5: Diagrammatic representation showing probable geometrical configurations of inclusion complexes of phenylethanolamine with α- and β-CDs.

α-CD: [^{1}H-NMR (300 MHz, D_2O)]: δ 3.42–3.43 (1H, j=9.00 Hz), 3.51–3.52 (1H, j=10 Hz), 3.74–3.83 (1H, m), 3.87–3.91(1H, J=9 Hz), 4.96–4.97 (1H, J=3 Hz), 7.44–7.535(6H, d).

β-CD: [^{1}H-NMR (300 MHz, D_2O)]: δ 3.41–3.42 (1H, j=9.00 Hz), 3.53–3.56 (1H, j=10 Hz), 3.75–3.77 (2H, m), 3.82–3.83 (1H, J=9 Hz), 4.97–4.98 (1H, J=3 Hz).

Phenylethanolamine/β-CD: [^{1}H-NMR (300 MHz, D_2O)]: δ 2.684–2.711 (2H, m), 3.267–3.275 (1H, m), (1H, m), 3.292–3.298 (1H, m), 3.558–3.567 (1H, m), 3.732–3.748 (1H, m), 4.97–4.98 (1H, d), 7.46–7.543 (6H, d).

Phenylethanolamine/α-CD: [^{1}H-NMR (300 MHz, D_2O)]: δ 2.688–2.716 (2H, m), 3.265–3.272 (1H, m), (1H, m), 3.288–3.292 (1H, m), 3.552–3.563 (1H, m), 3.725–3.774 (1H, m), 4.96–4.97 (1H, d), 7.44–7.535 (6H, d).

3.6. 2D Roesy NMR

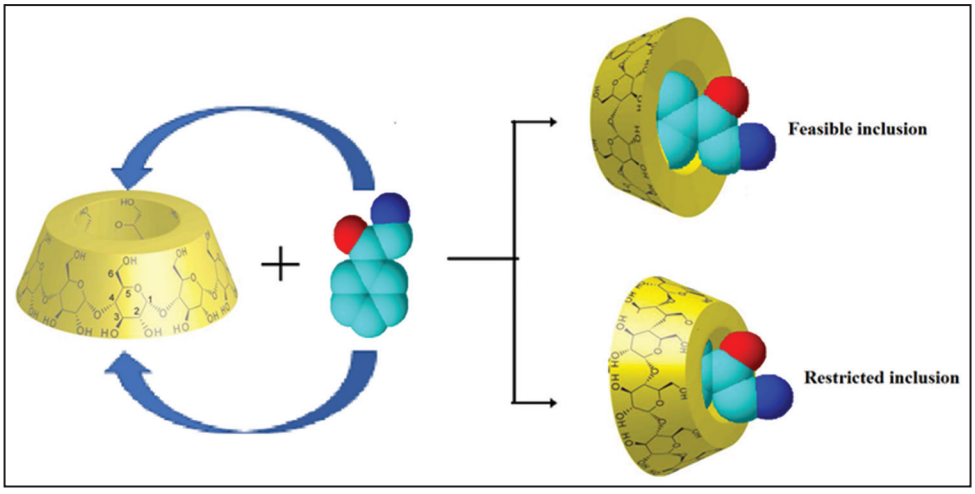
2D ROESY NMR study is another vital technique to investigate the formation of inclusion complexes [36,37]. We are aware that two neighboring protons placed within a distance of 0.4 nm can exert a nuclear Overhauser effect which may be established by 2D ROESY NMR (rotating frame NOE spectroscopy). The ROESY NMR spectra of inclusion complexes of phenylethanolamine inside CDs are displayed in Figure 8. The H3 and H5 protons of CDs situated inside the cavity experience nuclear Overhauser effect with the protons of aryl part of phenylethanolamine showing cross-peaks in the ROESY NMR spectra of inclusion complexes.

3.7. Scanning Electron Microscope (SEM)

SEM is an exceptionally familiar method for examining the surface texture and particle size of solid materials [38-41]. From the SEM images of the drug molecule, α-CD, β-CD, and their complexes, it is clear that the SEM images of pure compounds and their Inclusion complexes (ICs) are totally different. Significant morphological changes and changes of surface structures of pure compounds and their ICs are observed. Changes of SEM images of pure hosts and guest molecule indicate about the formation of inclusion complexes.

4. CONCLUSION

The formation of inclusion complexes of phenylethanolamine inside the cavity of α- and β-CDs has been proved by various physicochemical and spectroscopic studies. The volumetric and viscometric studies reveal the existence of considerable interaction between phenylethanolamine



Scheme 6: Feasible and restricted inclusion complex formation of phenylethanolamine with CD.

and CD in aqueous medium. The UV–visible, ^{1}H-NMR, 2D ROESY NMR, and IR spectroscopy firmly establish the formation of inclusion complexes of phenylethanolamine with both CDs. The Job's plot from UV–visible spectroscopy reveals that the inclusion is of 1:1 stoichiometry; however, ^{1}H-NMR spectroscopy reveals that the encapsulation of aryl part of phenylethanolamine inside the cavity of CDs occurs through the wider rim of CDs.

5. ACKNOWLEDGMENT

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SUPPLEMENTARY FIGURE

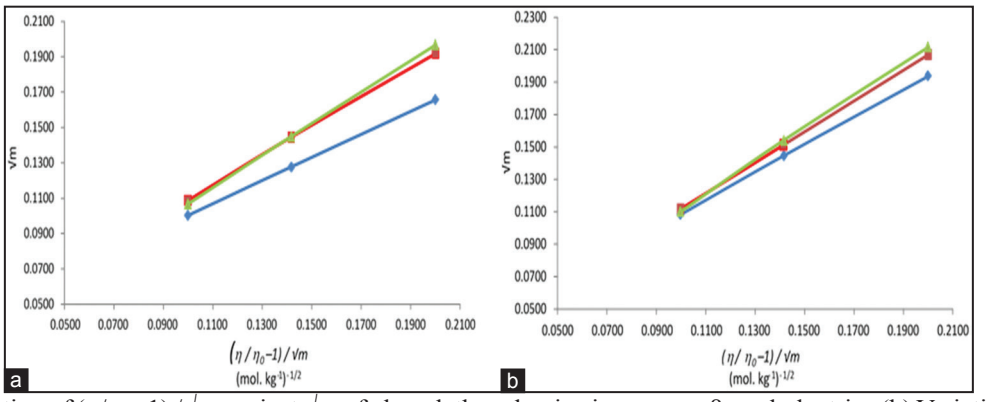

Figure S1: (a) Variation of $(\eta/\eta_0 - 1)/\sqrt{m}$ against $\sqrt{m}$ of phenylethanolamine in aqueous β-cyclodextrins (b) Variation of $(\eta/\eta_0 - 1)/\sqrt{m}$ against $\sqrt{m}$ of phenylethanolamine in aqueous α-cyclodextrins. (Blue line for 0.01 m, red line for 0.03 m and green line for 0.05 m cyclodextirns).

SUPPLEMENTARY TABLE

Table S1: Experimental values of density (ρ) and viscosity (η) of different molarities of phenylethanolamine in aqueous α- and β-cyclodextrins at 298.15 K.

Molarity of α-CD in mol/kg	$\rho\times10^{-3}$ (kg/m^3)	η (mP/s)	Molarity of β-CD in mol/kg	$\rho\times10^{-3}$ (kg/m^3)	η (mP/s)
Molarity of phenylethanolamine=0.001			**Molarity of phenylethanolamine=0.001**		
0.010	0.99910	0.9065	0.001	0.99923	0.8204
0.020	0.99956	0.9137	0.002	0.99970	0.8282
0.030	1.00006	0.9273	0.004	1.00018	0.8431
Molarity of phenylethanolamine=0.003			**Molarity of phenylethanolamine=0.003**		
0.001	0.99933	0.9207	0.001	0.99997	0.8317
0.002	0.99978	0.9294	0.002	1.00043	0.8401
0.004	1.00029	0.9458	0.004	1.00091	0.8566
Molarity of phenylethanolamine=0.005			**Molarity of phenylethanolamine=0.005**		
0.001	0.99979	0.9282	0.001	0.99931	0.8440
0.002	1.00024	0.9372	0.002	0.99978	0.8530
0.004	1.00074	0.9546	0.004	1.00027	0.8702

Table S2: Experimental values of density (ρ) and viscosity (η) of phenylethanolamine in different molarities of aqueous α- and β-cyclodextrin at 298.15 K.

Molarity (mol/kg)	ϕ_V x 10^6 (m^3/mol^{-1})	$(\eta/\eta_0-1)/\sqrt{m}$ $(mol/kg)^{-1/2}$	Molarity mol/kg)	ϕ_V x 10^6 (m^3/mol)	$(\eta/\eta_0-1)/\sqrt{m}$ $(mol/kg)^{-1/2}$
Molarity of phenylethanolamine=0.001			**Molarity of phenylethanolamine=0.001**		
0.001	196.5612	0.642	0.001	196.5100	0.645
0.002	195.6088	0.703	0.002	195.3574	0.701
0.004	194.8903	0.782	0.004	194.5054	0.786
Molarity of phenylethanolamine=0.003			**Molarity of phenylethanolamine=0.001**		
0.001	196.4372	0.647	0.001	196.4214	0.651
0.002	195.2849	0.708	0.002	195.1190	0.712
0.004	194.4333	0.793	0.004	194.0838	0.801
Molarity of phenylethanolamine=0.005			**Molarity of phenylethanolamine=0.001**		
0.001	196.3978	0.6502	0.001	196.2818	0.655
0.002	195.1457	0.7133	0.002	194.7801	0.715
0.004	194.0605	0.8011	0.004	193.6121	0.809

Table S3: Apparent molar volume (ϕ_V) and (η_r-1)/√m of the phenylethanolamine in different molarities of aqueous α- and β-CD mixtures at 298.15 K.

Molarity of phenylethanolamine	$\phi_V{}^0$x 10^6 (m^3/mol)	$S_V{}^*$x 10^6 ($m^3/mol^{-3/2}.kg^{1/2}$)	B ($kg^{1/2}/mol^{-1/2}$)	A (kg/mol)
α-CD				
0.001	102.5	−63.46	0.850	0.023
0.003	104.4	−72.09	0.949	0.017
0.005	105.6	78.98	1.01	0.009
β-CD				
0.001	98.19	−41.02	0.653	0.035
0.003	99.60	−45.56	0.828	0.026
0.005	101.4	−54.79	0.898	0.017

CD: Cyclodextrin