CHAPTER IX

INCLUSION OF TYROSINE DERIVATIVES WITH α-CYCLODEXTRIN IN AQUEOUS MEDIUM OF VARIOUS p^H CONDITIONS BY SURFACE TENSION, CONDUCTANCE, UV-VIS AND NMR STUDIES

9.1. Introduction

pH-sensitive drug delivery in aqueous systems are gaining importance as these systems deliver the drug on specific site as per the physiological need of the diseases, resulting in improved patient therapeutic efficiency and compliance[1]. Although, significant progress has been made in the cyclodextrins based controlled drug delivery systems [2-5], more advancement are required for treating many clinical disorders, such as diabetes, rhythmic heart disorders and neuropsychiatric disorders, etc. However, dopamine hydrochloride (DH), tyramine hydrochloride (TH) and epinephrine hydrochlorides (EH) are important biogenic amine group of naturally occurring molecules and acts as neurotransmitters that allow the transmission of signals from a neuron to target cells across synapse. Dopamine is one of the most physiologically important biogenic amines and, its regulation in the central nervous system is prerequisite for homeostasis [6, 7]. Tyramine is also a neurotransmitter and act as a catecholamine releasing agent [8]. Epinephrine is a hormone and a neurotransmitter, which function as chemical mediators for turning over the nerve impulses to effective organs [9]. Epinephrine is also used as a drug to treat cardiac arrest and other cardiac disorders [10].

Generally, Cyclodextrins (CDs) (Scheme1) are known to complex a wide variety of molecules in their hydrophobic interior [11-15]. The most likely mode of binding consists of inclusion of the less polar portion of the guest within the cavity while the polar or hydrophilic part of the guest remains in the bulk [16, 17]. It has been recognized that the binding forces involved in the inclusion are hydrophobic interactions, hydrogen bonding, van der Waals forces, the relief of high energy water from the CDs cavity and the relief of conformational strain upon guest incorporation [13-16]. It is important to study these weak interactions by physicochemical method in various aqueous conditions, for our further understanding the nature of the

Published in J. Mol. Liquids 230 (2017) 104-112

Inclusion complexes (ICs) to predict new approaches in controlled drug delivery and release [16, 17], analytical [18], material [19, 20], pesticides, foodstuffs, textile processing and other industries, *etc*. For a variety of reasons, including toxicological considerations, formulation, bulk, drug bioavibility and production cost. It is more important to use as small amount of CDs as possible in pharmaceutical formulations. In this respect, aqueous solubility of α-CD is higher than β-CD, taking more advantages for this study (solubility in water (w/v) at 25^0C: for α-CD is 14.5 mg/mL and β-CD is 1.85mg/mL). Moreover, α-CD favors to form stable ICs with the neurotransmitters. This is obviously due to the fact that α-CD provides more viable features (cavity diameter and cavity volume) for formation of feasible ICs with the neurotransmitters so as to make close contact with α-CD than β-CD [21, 22]. The determinations of a variety of guest compounds have been developed by exploiting the β-CDs [23-25], whereas only a few biological and analytical applications of α-CD [7, 8, and 26] have been developed.

The aim of this work is to investigate the formation of inclusion complexes (ICs) of tyrosine derivatives (DH, TH and EH) with α-CD in aqueous media at pH=7.4 and at pH=9.0 and compare their efficiency of inclusion with respect to the pure water medium. Triply distilled degassed water was used for a reference solution (specific conductivity: 1×10^{-6} S·cm^{-1}). It is mentioned that, hydrophobicity and the ability of neurotransmitters to form hydrogen bonds vary with the change in pH medium [27]. Therefore, efficiency of inclusion of the neurotransmitters directly depends on the medium of the solution. All these guest molecules have a common aromatic ring containing two adjacent -OH groups for DH and EH, and one –OH group for TH which may attribute towards the formation of intermolecular and intramolecular hydrogen bonds (Scheme 2). They are suitable for the study of the effects of polarity, hydrogen bonding and position of the substituent on the host–guest system.

9.2. Experimental Section

9. 2.1. Materials

Dopamine hydrochloride, tyramine hydrochloride, (±)-epinephrine hydrochloride and α-cyclodextrin of puriss grade were procured from Sigma-Aldrich Company, Germany and used as received. Purity of dopamine hydrochloride,

tyramine hydrochloride, (±)-epinephrine hydrochloride and α-cyclodextrin were 99%, 98%, 99% and 0.98% respectively. The selected phosphate buffers were procured from Merck, India.

9. 2.2. Apparatus and procedure

Prior to the start of the experimental work solubility of α-CD and chosen neurotransmitters have been precisely checked in triply distilled and degassed water (specific conductance is 1×10^{-6} $S\cdot cm^{-1}$). Stock solution of pH=7.4 and pH=9.0 were prepared by adding the appropriate amount of buffer into the aqueous solution. The pH of the solutions were re-checked and adjusted. All the stock solutions were prepared by mass (weighed by Mettler Toledo AG-285 with uncertainty 0.0003 g), and then the working solutions were obtained by mass dilution at 298.15K. Adequate precautions (viz., maintaining room temperature at 298.15K through the preparation of the solution, sample kept in a P_2O_5 Containing vacuum desiccator, instant preparation of the solution mixture etc.) for the preparation of solutions were made to reduce evaporation losses during mixing.

The surface tension experiments were done by platinum ring detachment method using a Tensiometer (K9, KRŰSS; Germany) at 298.15K. The accuracy of the measurement was within ±0.1 $mN\cdot m^{-1}$. Temperature was maintained by circulating auto-thermostat water through a double-wall glass vessel containing the 5 mM stock solution of neurotransmitters with increment addition of α-CD. Break points are calculated by considering the intersection points of each curve.

The specific conductance measurements were carried out in a Systronic-308 conductivity meter (accuracy ±0.01%) using a dip-type immersion conductivity cell, CD-10, having a cell constant of approximately (0.1 ± 0.001) cm−1. Measurements were completed in a water bath maintained within T = (298.15 ± 0.01)K.

UV-visible spectra were recorded by JASCO V-530 UV/VIS Spectrophotometer, with an uncertainty of wavelength resolution of ±2 nm. The measuring temperature was monitored by an automated digital thermostat.

^{1}H-NMR spectra were recorded at 500 MHz and 400 MHz using Bruker ADVANCE 500 MHz & 400MHz instruments respectively using D_2O at 298.15K. All the signals are assigned with respect to the residual protonated solvent signals (D_2O: δ 4.79 ppm).

9. 3. Result and Discussion

9.3.1. Surface Tension

Surface tension (γ) measurement provides significant idea about the formation of ICs as well as stoichiometry of the host-guest complexes [28]. In aqueous medium α-CD does not show any change in surface tension in significant range of concentration [29, 30]. Therefore, surface activity of α-CD is negligible in the studied medium. On the other hand, neurotransmitters (Scheme 2) have a common characteristics in their structures, *i.e.*, they have a hydrophobic $–CH_2–CH_2–Ph$ [$CH_2–CH$ (OH)–Ph for EH] part and a terminal "$-NH_3^+$ [$-NH_2^+$ for EH]" part, which makes them surface active materials. Hence, γ of aqueous solution as well as pH solutions of each of the neurotransmitters are found to be lower than that of pure water and are shown in Fig. 1. The increasing trend of γ with increasing concentration of α-CD is due to the inclusion of neurotransmitters into the hydrophobic cavity of α-CD. Each curve also shows that there is a single break point at certain concentration after which the curve becomes linear. Sighting of break point in surface tension curve not only indicates formation of IC but also provides information about its stoichiometry,i.e., appearance of single, double and so on break point in the plot indicates 1:1, 1:2 and so on stoichiometry of host : guest ICs (Scheme 3)[31]. The γ values are reported in Table1 as a function of corresponding concentrations of α-CD at each break point. Hence this study proves formation of 1:1 ICs between neurotransmitters and α-CD. From the details of γ-values (Table 1) it is understood that neurotransmitters are more efficient for the formation of ICs with α-CD in aqueous medium than the other two pH medium. This is obviously due to the fact that phenyl part of neurotransmitters provides maximum hydrophobic nature in aqueous environment for the formation of feasible ICs with α-CD. The insertion of neurotransmitters occurs via the wider rim (inclusion via narrower rim is sterically hindered) through hydrophobic and hydrophilic interaction, while the charged polar head part remains either in the wider rim of α-CD or in the bulk solution through H-bonding interaction (Scheme3)[32].

9.**3.2. Conductivity**

The specific conductivity (κ) of neurotransmitters in the experimental solution has been measured to get the information about transport property of ICs as well as the stoichiometry of the complexes [33]. The considered guest molecules are

charged structures (Scheme2) in all the solvent media and have considerable conductivity. Conductivity of the experimental solution arises from the ionic mobility of ions of the neurotransmitters in presence of α-CD (Fig. 2). The decrease in conductivity is due to the inclusion of hydrophobic part of neurotransmitter molecules one by one into the apolar cavity of α-CD. The markedly change in solution conductivity with the increment addition of α-CD corresponds to the formation of ICs between neurotransmitters and α-CD molecules. After a certain concentration of α-CD, a marked changed, i.e., a break point, was observed in conductivity curve indicating the formation of 1:1 ICs. An unusual break in the conductivity curve occurred at a concentration of about 2.5mmol L^{-1} for α-CD in each solvent systems, suggesting that the stoichiometry of the inclusion complex is almost equimolar [31, 34]. Conductivity values of each IC are tabulated in Table 2. Therefore, the main inclusion complexes of α-CD with neurotransmitters in this concentration range are of 1:1 molar ratio which point out that the neurotransmitters are almost totally in complexed situation.

9.3.3. ^{1}H-NMR Study

Insertion of a guest molecule into the hydrophobic cavity of a cyclodextrin results in the modification of the NMR frequencies of the signals of both the host. ^{1}H-NMR study was used to confirm the host-guest interaction of ICs in the cyclodextrin based systems [35]. In the α-CD, the H3 and H5 protons are located inside the cavity, mainly; H3 is placed near the wider rim while H5 is placed near the narrower rim. The other H1, H2 and H4 hydrogens are situated at the exterior of the α-CD molecule (Scheme 1) [36]. Thus when a guest enters into the cavity of α-CD molecule it interacts with the H3 and H5 protons, resulting in the upfield chemical shift of these protons. The shift is higher for H3 proton as it is located near the wider rim of α-CD, through which usually the guest enters, than that of H5 proton which is situated near the narrower rim at the interior of α-CD molecule. The other protons e.g., H1, H2 and H4 also shows upfield chemical shifts, but the shift is lower compared to H3 and H5 protons [37]. In our work, neurotransmitters are inserted into the α-CD cavity. Hence, chemical shift of the α-CD protons and protons of the neurotransmitters are well established for the formation of 1:1 ICs (Figs. 3-5). Thus, it holds the conductometric and surface tension investigation.

9.3.4. UV-Vis Study

9.3.4.1. Job's method (to determine stoichiometry between host and guests)

Job's method of continuous variation was useful to distinguish the stoichiometry of the host–guest systems by studying UV–visible spectroscopic investigation [38]. Job plots were obtained by plotting ΔA vs R, where ΔA is the difference in absorbance of neurotransmitters with and without α-CD and R= [Guests]/([Guests] + [CD]), by varying the mole fraction of the guests (neurotransmitters) in the range of 0–1 (Tables S1–S3, supporting information)[39,40]. Absorbance values were considered at corresponding λ_{max} for each series of solutions at 298.15 K. Maximum deviation of 'R' gives the information about the stoichiometry of the inclusion complex (IC) (e.g., R= 0.5 for 1:1 complexes; R= 0.33 for 1:2 complexes; R= 0.66 for 2:1 complexes, etc.). Thus, from Fig. 6, maxima of each plots were attained at R=0.5, which definitely point out 1:1 stoichiometric inclusion between host and neurotransmitters.

9.3.4.2. Stability studies

UV-Vis spectroscopy is an important method to measure not only the absorbance of ICs but also we obtain the comparative binding stability of the neurotransmitters with α-CD [22, 34, 41]. Since, α-CD has almost no absorption throughout the wavelength; hence the absorption of the α-CD can be neglected [34]. Therefore, absorption of the guest molecules are taken into consideration [42]. Absorption spectra for each neurotransmitter in every solvent medium found similar at most of the points along the wavelengths recorded which shows that the absorbance arises from neurotransmitters only. Whereas, ICs show increased intensity at a fixed wavelength due to the inclusion phenomena between α-CD and neurotransmitters (Fig. 7)[43]. The spectra show that the absorbance values increase at a particular wavelength with increasing α-CD concentrations while the concentration of neurotransmitters remains the same. It signifies that the molecular interaction occurs between the neurotransmitters and α-CD molecules, and their solubility increases upon forming the inclusion complexes [44]. Gablica et. al demonstrated that α-CD forms both inclusion and non-inclusion complexes. Non-inclusion complexes are those in which the guest molecules are linked at the external part of the CDs [45]. The prominent increases in molar absorption of

neurotransmitters at a particular wavelength with in concentration of α-CD are the direct evidence of inclusion complex formation. Other type of non-inclusion complex (viz., 1:2 or 2:1) can only form when a neurotransmitters or α-CD can interact externally with the 1:1 inclusion complexes. Thus, appearance of 1:1 complexes from Job's method successfully signifies the formation of ICs chiefly [46]. Since, the guest molecules have aromatic ring having phenolic –OH group therefore it is possible to make them as different ionic structures by changing the pH of the medium [27,47]. As a result, their hydrophobicity is to some extent modified and it directly influences the binding stability of the inclusion complexes. From the Hildebrand–Benesi equation [48], a very good linear relationship was obtained for 1/A vs. 1/T [α-CD] and the reciprocal plot obviously indicates the stoichiometry ratio for the formation of ICs between neurotransmitters and α-CD is 1:1 M ratio [49, 50].

From the reciprocal plot (Table S4 & Fig. S1) the apparent formation constant (K) for each ICs were obtained and are reported in Table 3. Thermodynamic parameters for the formation of ICs have also been evaluated from the plot of LnK Vs $1/T$ at 298.15, 303.15 and 308.15 K with the help of Van't Hoff eq. [51] (Table 3). The large negative value of standard free energy change (ΔG^0) comprises the inclusion process is thermodynamically favorable, where as the negative standard enthalpy change (ΔH^0) and standard entropy change (ΔS^0) values respectively suggested that the formation of IC is enthalpy driven and entropic forbidden. The higher negative value of standard enthalpy change (ΔH^0) overcome the unfavorable spontaneity (ΔS^0) of the system and favors the overall process for the formation of ICs.

The results shown in Table 3 indicate that order of K for ICs with α-CD and the order of $-\Delta G^O$ is EH>DH> TH. This can be elucidated on relation of the difference in the structures of three neurotransmitters, which have almost similar hydrophobic moiety, but EH can form extra H-bonds with α-CD because of having one extra alcoholic –OH groups along with two phenolic –OH group; thus, it forms strongest complex among the three. Likewise, the consequences for DH and TH can be explained because of having two and one –OH groups in their structures respectively. All the favorable inclusions in different medium are being explained as follows:

In aqueous solution

All the studied neurotransmitters in aqueous solution are in acidic form, i.e, amine part is protonated [27] in this state. The apparent formation constant for the inclusion complex follows the trends, EH> DH>TH. The standard free energy, ΔG^0 values also support the same sequence (Table3). Thus, from the overall experimental results the following contribution can be made, (i) removal of water molecules from the hydrophobic cavity of α-CD (ii) extended H-bonding for primary and secondary –OH group of the α-CD which unlock the rims for incoming hydrophobic moiety (iii) reduction of repulsive force from the solvent and guest molecules in the bulk of the solution (iv) hydrophobic-hydrophobic interaction increases in the cavity of the α-CD after getting inclusion.

At pH=7.4 solution

At pH=7.4, the neurotransmitters are in almost similar state as described in above aqueous medium (Scheme 2). In this pH=7.4 medium, –OH group of the phenyl ring may partially ionize and thus hydrophobicity may decrease compared to that in aqueous medium. As such, some polarity may develop in the hydrophobic moiety of neurotransmitters [27]. Therefore, the binding stability for this system is reduced and values of formation constant are lower than the aqueous medium. Standard free energy (ΔG^0) values for the neurotransmitters supported the facts obtained from the results (Table 3). The smaller negative value of ΔG^0 is responsible for the loss of hydrophobic nature of neurotransmitters.

At pH=9.0 solution

In this pH ranges one of the -OH group of the phenyl ring of neurotransmitters gets ionize to $-O^-$ ion [26]. Ionic nature of phenyl ring also reduces the binding stability of the neurotransmitters with α-CD than aqueous medium. However, the extra stability of inclusion complexes in this medium than pH=7.4 medium is due the following additional contribution: (i) strong H-bonding between the O^- ion and the –OH of the narrower rim (Scheme 3) of the α-CD (ii) remove of repulsion from the anionic neurotransmitters and hydroxide ion containing bulk solution.

9.4. Conclusion

Structural features and aqueous solubility of α-CD promote to obtain the efficiency of inclusion complexes with tyrosine derivatives. Various characterization techniques have been executed to determine the exclusive formation and stability of the 1:1 ICs. The results showed that with increase in pH of the medium stabilities of ICs decreases however an extra stability was found at pH 9.0. Therefore, the pH responsive inclusion of drug molecules will be an active area of research that will result in the development of novel systems with possible commercial and biological applications. As an extra stability obtained at pH 9.0, the drugs are more effective if administered by parental route.

Tables

Table 1. Values of break points for the surface tension of neurotransmitters with the corresponding concentration of α-CD in aqueous medium of various pH conditions at 298.15K[a]. (Initial concentration of each neurotransmitter is 5 mM)

	Conc. /mM	Surface Tension /mNm^{-1}		
		In aqueous	At pH=7.4	At pH=9.0
EH	2.5	70.7±0.1	71.1±0.2	71.2±0.1
DH	2.5	70.8±0.2	71.2±0.1	71.3±0.1
TH	2.5	71.1±0.1	71.5±0.1	71.7±0.2

[a] Average standard uncertainties (*u*): temperature: *u*(T) = ±0.01 K

Table 2. Values of break points for the conductance of neurotransmitters with the corresponding concentration of α-CD in aqueous medium of various pH conditions at 298.15K. (Initial concentration of each neurotransmitter is 5 mM)

	Conc. /mM	Conductance /mScm^{-1}		
		In aqueous	At pH=7.4	At pH=9.0
EH	2.5	0.165±0.004	0.121±0.002	0.162±0.005
DH	2.5	0.178±0.005	0.123±0.003	0.169±0.003
TH	2.5	0.181±0.004	0.127±0.002	0.174±0.002

[a] Average standard uncertainties (*u*): temperature: *u*(T) = ±0.01 K

Table 3. Values of apparent formation constant (K) and thermodynamic parameters for the formation of ICs of neurotransmitters with α-CD.

Host-Guest complex	T/K[a]	K/M^{-1}	ΔH^0/KJmol^{-1}	ΔS^0/Jmol^{-1}	ΔG^0/KJmol^{-1}
	298.15	2978.29±0.15	-22.87±0.12	-11.47±0.04	-19.41±0.06
EH+α-CD in aqueous	303.15	2419.02±0.11			
	308.15	1806.15±0.12			
	298.15	1916.51±0.15	-19.10±0.11	-2.09±0.17	-18.48±0.13
DH+α-CD in aqueous	303.15	1598.01±0.11			
	308.15	1282.41±0.13			
	298.15	1067.01±0.11	-19.10±0.19	-7.91±0.09	-16.74±0.14
TH+α-CD in aqueous	303.15	754.02±0.17			
	308.15	566.42±0.13			
	298.15	616.58±0.11	-19.00±0.01	-11.48±0.07	-15.58±0.05
EH+α-CD at pH=7.4	303.15	494.82±0.10			
	308.15	396.73±0.09			
	298.15	509.29±0.06	-17.85±0.12	-9.03±0.17	-15.16±0.08
DH+α-CD at pH=7.4	303.15	408.71±0.11			
	308.15	318.66±0.13			
	298.15	189.89±0.16	-15.24±0.09	-8.75±0.13	-12.63±0.07
TH+α-CD at pH=7.4	303.15	157.92±0.01			
	308.15	117.62±0.03			
	298.15	1312.98±0.07	-19.10±0.08	-5.4±0.18	-17.48±0.10
EH+α-CD at pH=9.0	303.15	1100.54±0.10			
	308.15	814.01±0.05			
	298.15	1161.45±0.11	-18.80±0.05	-5.4±0.05	-17.19±0.06
DH+α-CD at pH=9.0	303.15	921.24±0.06			
	308.15	7.893±0.14			
	298.15	958.29±0.05	-17.55±0.03	-2.92±0.02	-16.68±0.05
TH+α-CD at pH=9.0	303.15	719.44±0.12			
	308.15	579.27±0.08			

[a]Average standard uncertainties in temperature *u* are: *u*(T) = ±0.01 K.

Figures

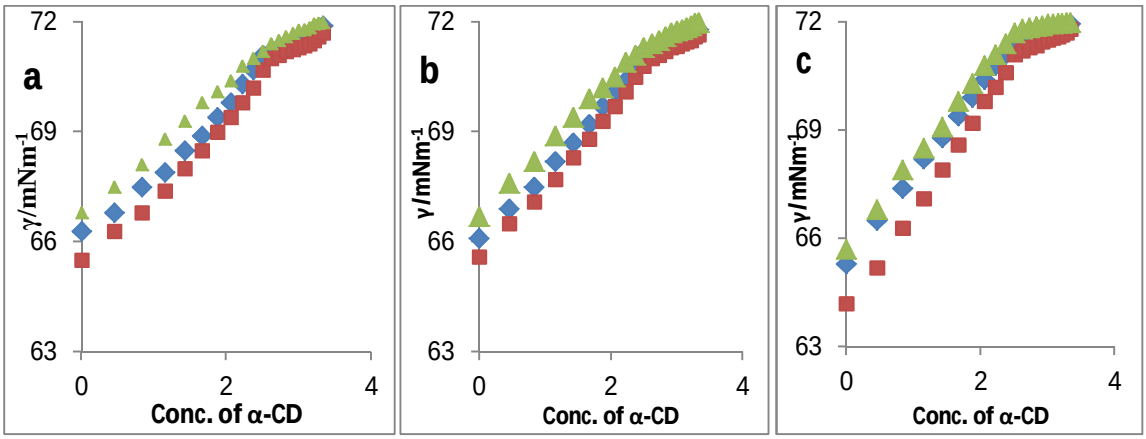
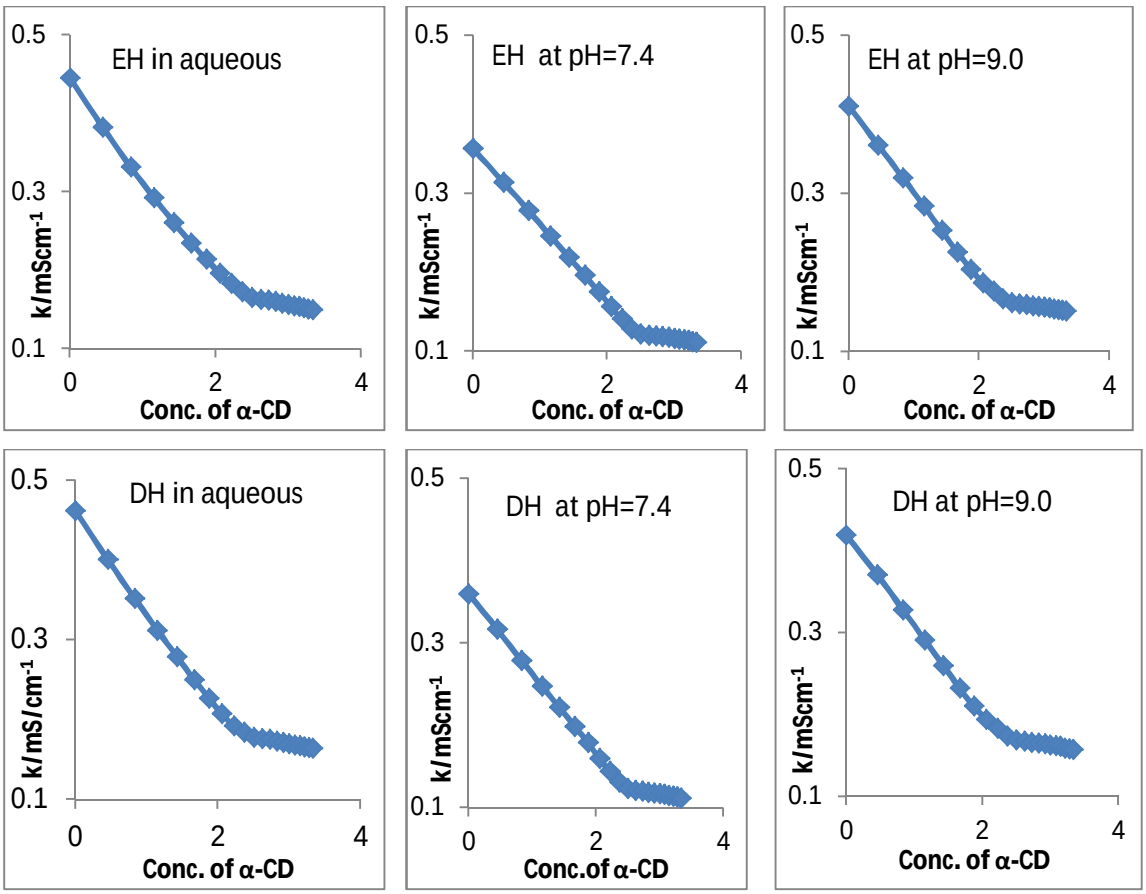


Figure 1. Surface tension of (a) epinephrine,(b) dopamine and (c) tyramine hydrochloride with α-CD at 298.15K [red line (■) for aqueous solution, blue(♦) for pH=7.4 and green line (▲) for pH=9.0 solutions)].



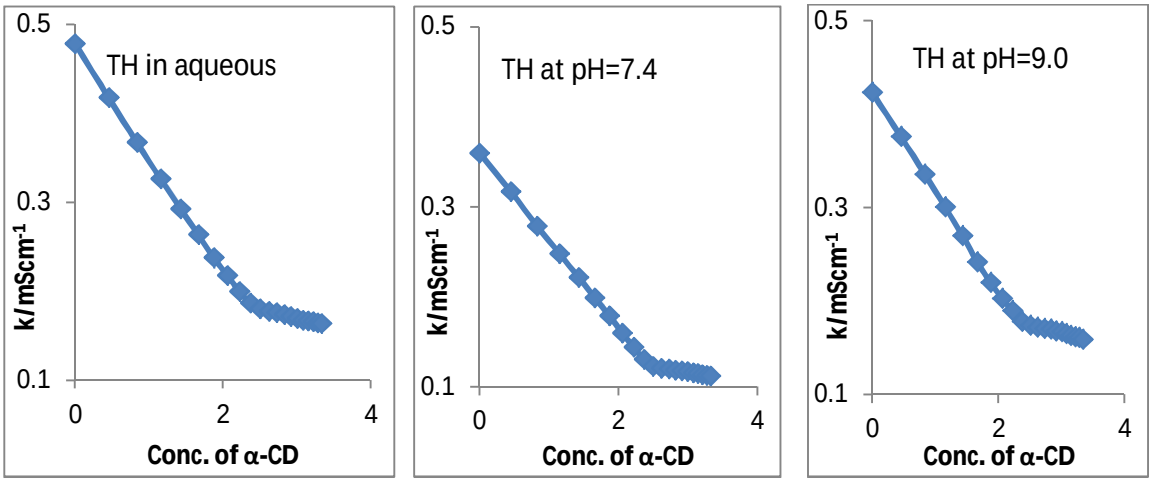


Figure 2. Conductance of neurotransmitters with the corresponding concentration of α-CD at 298.15K.

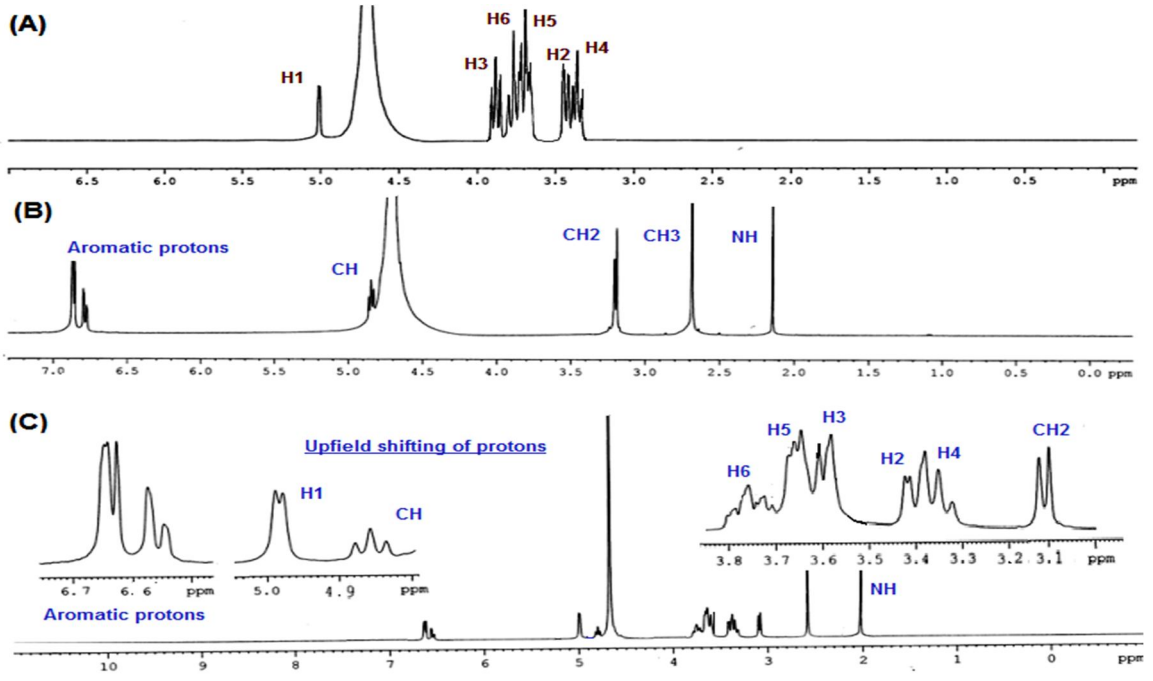


Figure 3. ^{1}H-NMR spectra of (A) α-CD, (B) epinephrine hydrochloride and (C) α-CD + epinephrine hydrochloride in D_2O.

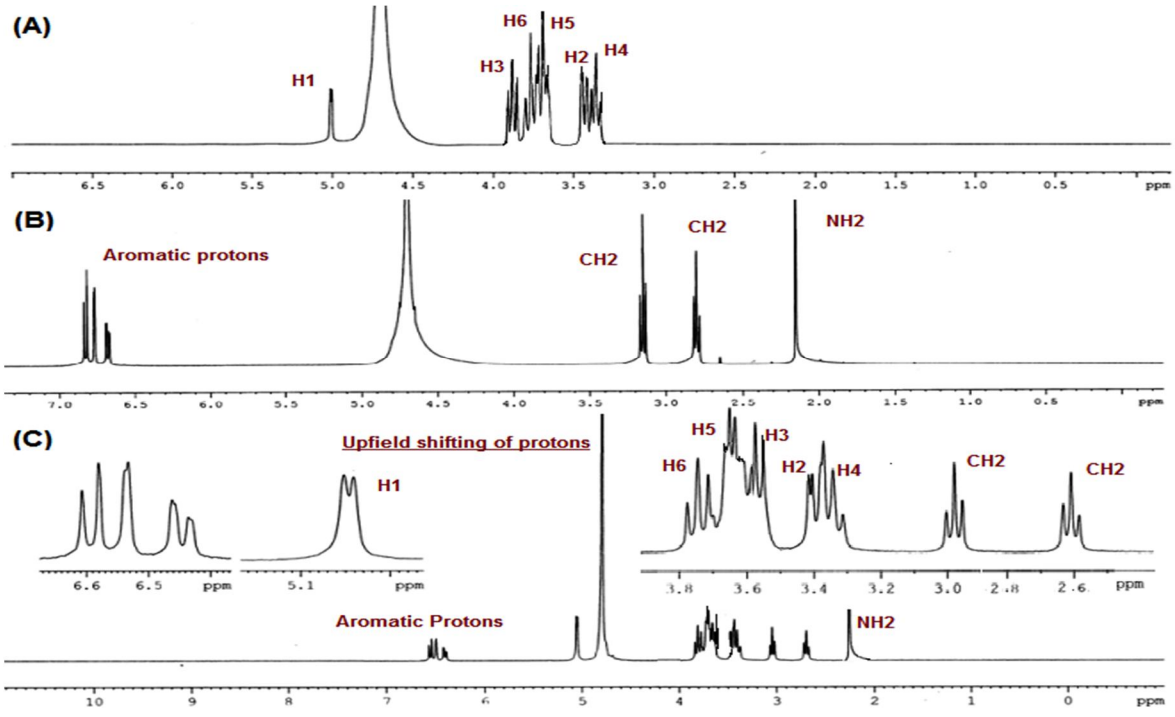


Figure 4. ^{1}H-NMR spectra of (A) α-CD, (B) dopamine hydrochloride and (C) α-CD + dopamine hydrochloride in D_2O.

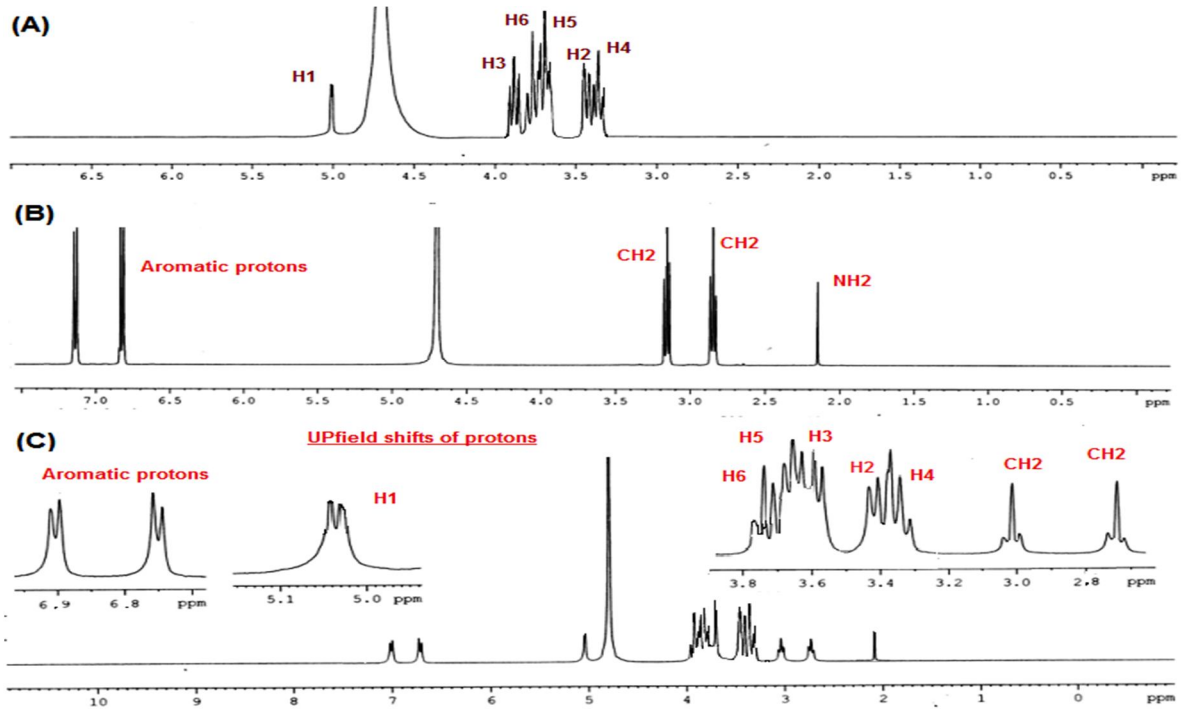


Figure 5. ^{1}H-NMR spectra of (A) α-CD, (B) tyramine hydrochloride and (C) α-CD + tyramine hydrochloride in D_2O.

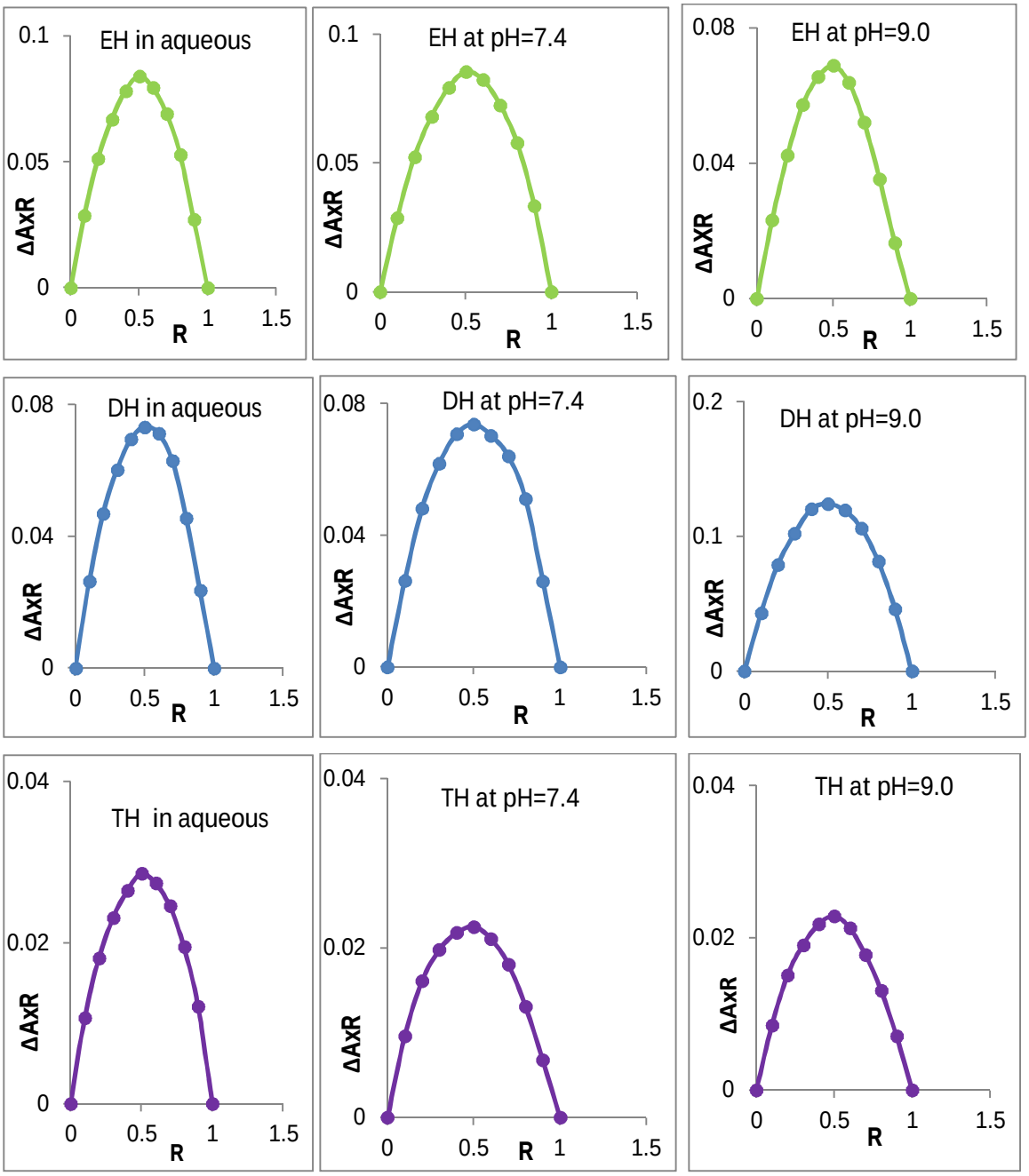


Figure 6. Job plot of different neurotransmitter-α-CD systems at 298.15 K. Where, R= [Guest]/([Guest] + [α-CD]), ΔA= absorbance difference of the Guests without and with α-CD.

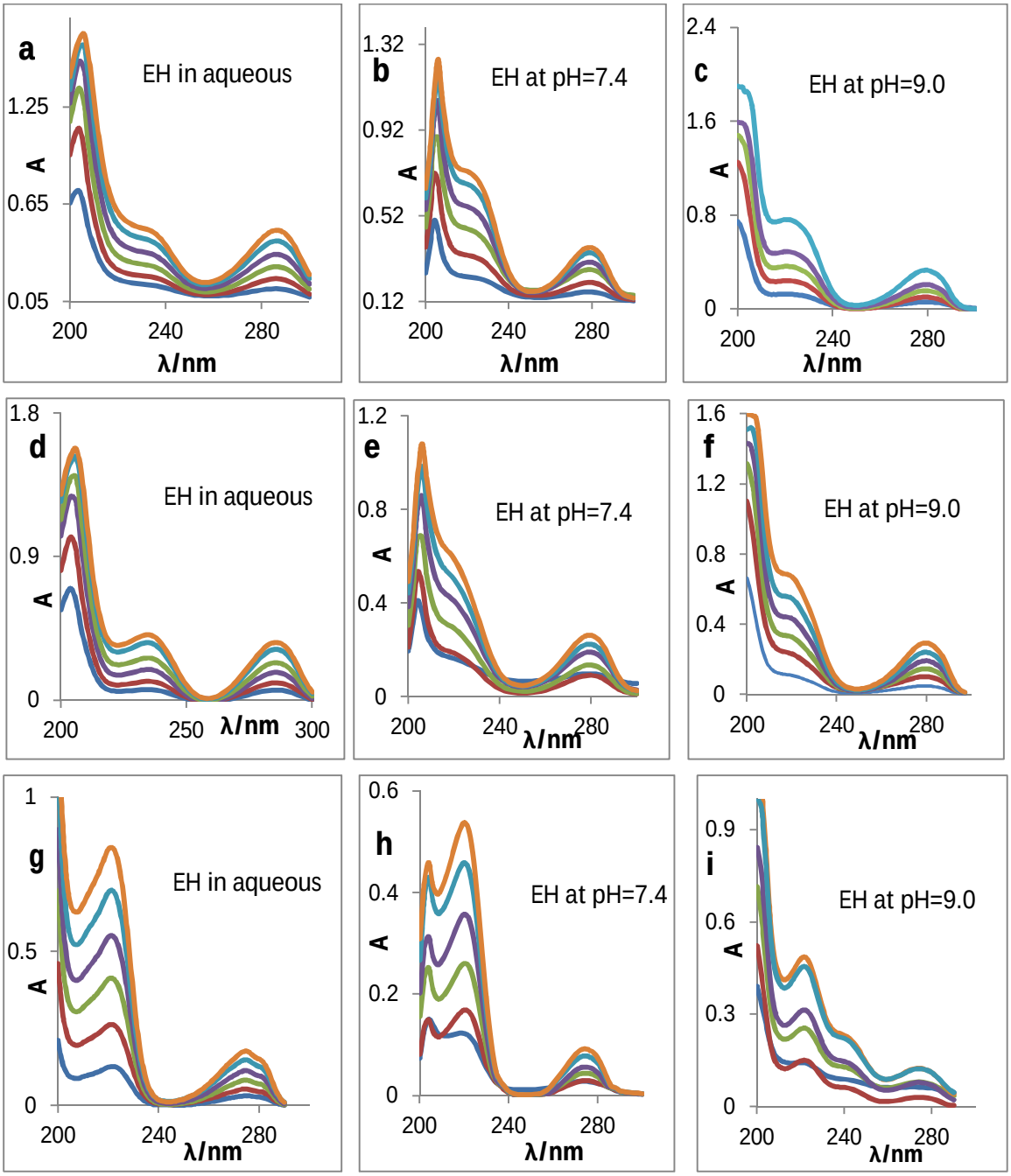
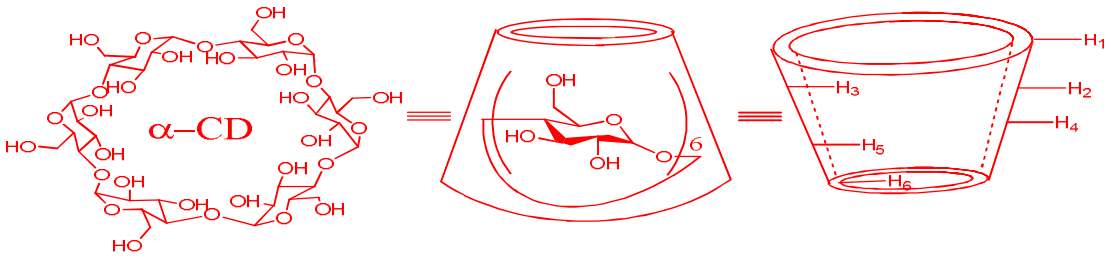
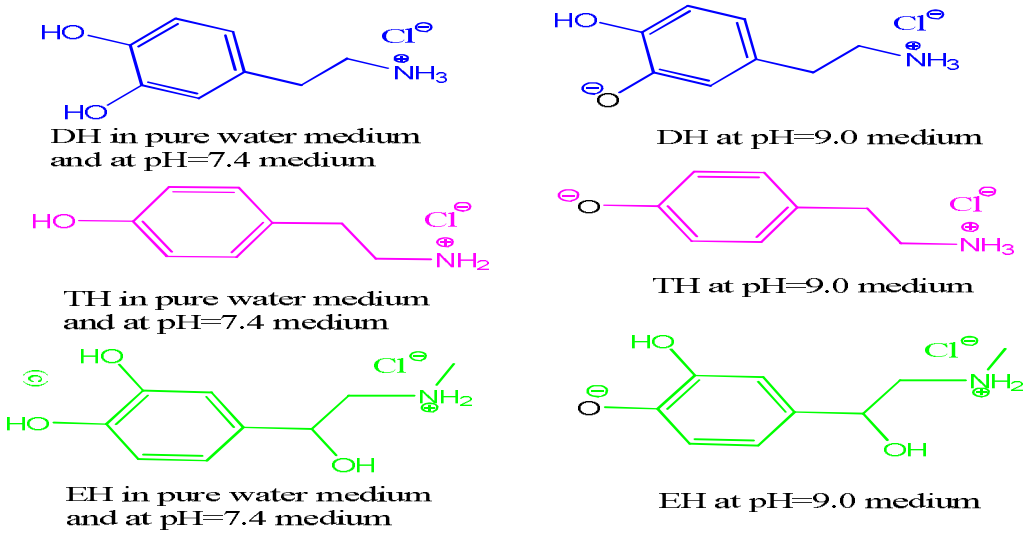


Figure 7: UV-Vis spectra of neurotransmitters with the increasing concentration of α-CD at 298.15K.

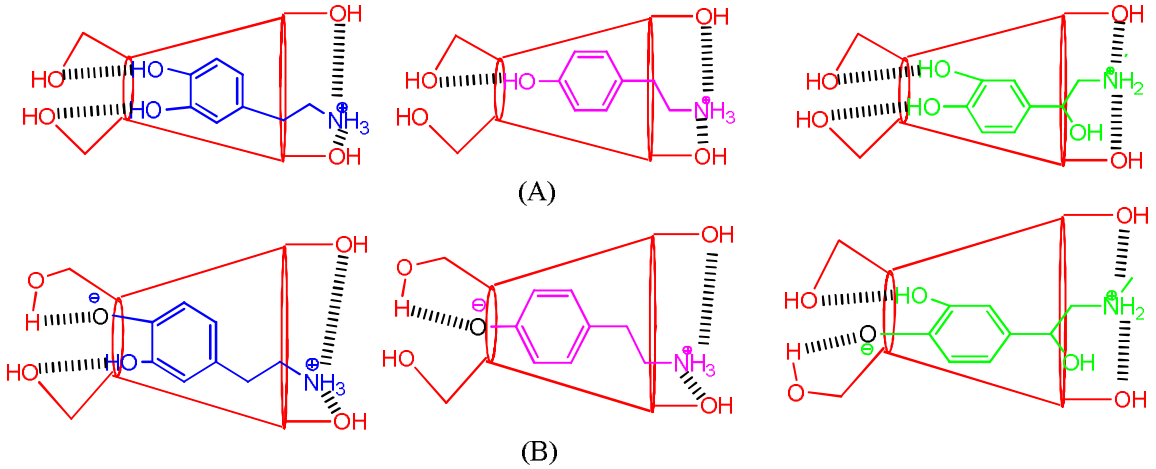
Schemes



Schemes 1. Molecular structure of α-CD



Scheme 2. Molecular structures of dopamine hydrochloride (DH), tyramine hydrochloride (TH) and epinephrine hydrochloride (EH).



Scheme 3. Plausible schematic mechanism of inclusion of neurotransmitters into the α-CD cavity (A) in aqueous (reference medium), (B) at pH=7.4 and (C) at pH=9.0.

CHAPTER X

CONCLUDIGNG REMARKS

In this thesis, I have endeavoured to ascertain the various non-covalent interactions of ionic liquids and some bioactive molecules in various aqueous and non-aqueous liquid systems. The observed phenomena have been explained by the solute-solute, solute-solvent and solvent-solvent interactions. Molecular interactions and favourable host-guest inclusion have been scrutinizing with the help of thermodynamic and transport properties of solutions.

Different types of interactions exist between the ions in solutions. These types of non-covalent interactions are of current interest in solution and supra-molecular chemistry. These interactions help in better understanding of salvation consequences of ionic liquid and bio-molecules in various liquid environments. Volumetric, viscometric, conductometric, refractive index and surface tension studies confirm the extent of molecular interactions in a particular solution system. Spectroscopic investigation such as, Uv-Visible, FT-IR and NMR method indicates an insight into the molecular interaction occurring in particular group or site of a given system.

In Chapter IV, from thermodynamical, structural and the experimental evidences it can generally be concluded that the ionic liquid 1-butyl-4-methylpyridinium iodide form inclusion complex with both the α- and β-Cyclodextrins through non-covalent interactions. Four energetically favorable interactions that shift the equilibrium towards the formation of inclusion complex: one, the displacement of existing polar water molecules from the apolar cavity of CDs. Two, the formation of extended hydrogen bonds by the primary and secondary hydroxyl (-OH) groups and rest of the water molecules that open a face for incoming the guest molecule. Three, a reduction of the repulsive interactions between the hydrophobic guest and the aqueous surroundings. And finally, there is an increased hydrophobic interaction as the guest inserts itself into the apolar cyclodextrin

cavity. Also, the bindings of IL molecule with the CDs are not fixed or permanent but a dynamic equilibrium and the binding strength depend on the specific local interactions between surface atoms. The key factor that stabilises the inclusion complexes is the steric effect and it depends on the relative size of the CD to the size of the guest molecule or certain key functional groups within the guest molecule. Since, the IL molecule is the mark on size; it gets fitted properly into the CD cavity and form selectively stable1:1 inclusion complex .Thus, in a word the inclusion of α-CD is comparatively less than that of the β-CD.

In Chapter V, extensive study reveals that the ionic liquid, 1,3-dimethyl imidazolium methyl sulfate mainly exists as Ion pair in the studied alkoxy alcohols. Λ-values suggested that molecular interaction increases from ME to PE. The results of K_A indicate IL is more associated in the PE than the other two solvents. G^o values imply the overall process for ion-dipole interaction and ion-association of the IL in the studied solvents are feasible. Density and viscosity measurements provide the information about ion-dipole interaction, and show the solute-solvent interaction for this system is higher than the solute-solute interaction. FT-IR studies definitely recommend the ion-dipole interaction in each binary system (IL+alkoxy alcohols).Formation of Ion pair was confirmed and well established from the transport, volumetric and spectroscopic studies.

Chapter VI dealt with the inclusion of 2-pyridine aldoxime methochloride inside the Cucurbit [6]uril cavity. The molecular interactions provides evidence for the 1:1 stoichiometric inclusion mechanism between the drug and Cucurbit [6]uril. The structural viability of the guest in accordance with CB[6], and the position of the positive charge on the guest encourage inclusion route. The supramolecular assembly of the drug, envisioned in this work, is very potent and promising for pharmacological applications and as well as for designing tunable artificial molecular devices or nano-materials. The low cytotoxicity and bio-adaptability of CB[6]-decorated stimuli responsive drug systems investigated here may have potential applications in bio-systems for therapeutics.

Chapter VII concludes that the selected ionic liquid, 1-butyl pyridinium bromide forms 1:1 stoichiometric complexes with both the 18-crown-6 and dibenzo-18-crown-6 through ionic-interaction. Physicochemical investigation for complex formation in ternary system by surface tension, conductometric volumetric and refractrometric method is already proved the details. Thermodynamic contribution confirms the feasible mechanism of complexation. Further, this outcome reveals that complex formation between IL and 18C6 is more efficient than IL and DBz-18C6. All the findings support the complexation process and thus the current work describes its appropriateness towards assorted applications in the field of modern biomedical as well as industrial areas.

Chapter VIII, from the thorough study it is evident that the ion-solvent interaction increases for both the investigated ILs with increasing temperature. It is also pronounced that the ion-solvent interactions is greater for [BMPyrr][Br] compared to [BMPyrr][Cl] and it can be modulated by changing the anion for a particular cation in the same solvent.

Chapter IX, Structural features and aqueous solubility of α-CD promote to obtain the efficiency of inclusion complexes with tyrosine derivatives. Various characterization techniques have been executed to determine the exclusive formation and stability of the 1:1 ICs. The results showed that with increase in pH of the medium stabilities of ICs decreases however an extra stability was found at pH 9.0. Therefore, the pH responsive inclusion of drug molecules will be an active area of research that will result in the development of novel systems with possible commercial and biological applications. As an extra stability obtained at pH 9.0, the drugs are more effective if administered by parental route.

In conclusion it is generalised that inclusion complexations an solvation consequences of ionic liquids and bio active molecules will be of immense help in understanding the nature of various interactions existing in liquid environments.