ABSTRACT

This thesis expresses the research works involving systematic exploration of formation of host-guest inclusion complexes of various cyclodextrins and crown ethers with vitamins, neurotransmitters, amino acids, drugs, nucleosides and ionic liquids by various calorimetric, spectroscopic and physicochemical techniques.

Importance of host-guest chemistry of cyclodextrins: Molecular encapsulation and release are exceptionally significant in pharmacology and drug delivery science in recent years. For this purpose various host molecules, such as calixarenes, pillararenes, cucurbiturils, cyclodextrins, etc. have been widely used as excellent receptors for guest recognition. The host-guest complexes could be applied to construct stimuli-responsive supramolecular materials, where series of external stimuli, such as, enzyme activation, photo sensing, temperature dependence, changes in pH/redox and competitive binding may be employed to operate the release of guest molecules from the inclusion complexes. In the last decade attention has been focused on molecular sensing, anti-cancer drug release, gene transfection etc. with the help of mechanized nanoparticles capable of trapping and regulating the release of cargo molecules by a range of external stimuli. Macrocyclic host molecules are of immense importance in inclusion complexes as the cyclized and constrained conformation offer the benefit of molecular selectivity. The cyclodextrins are exclusively interesting in this regard, due to their amphiphilic nature. The interest in amphiphiles comes up from their self-assembly in aqueous systems to form well defined structures, such as micelles, nanotubes, nanorods, nanosheets and vesicles, which can be applied in several grounds ranging from nano-devices, drug delivery and cell imaging. In recent times cyclodextrin modified nanoparticles are of great attention as they appreciably improve the characteristics of the assemblies, such as the electronic, conductance, thermal, fluorescence and catalytic properties improving their potential applications as nanosensors and drug delivery vehicles. Various sophisticated probes have been designed for this purpose for their applications in the manufacture of molecular switches, molecular machines, supramolecular polymers, chemosensors, transmembrane channels, molecule-based logic gates and other interesting host–guest systems. Cyclodextrins are the cyclic oligosaccharides having six (α-CD), seven (β-CD) and eight (γ-

CD) glucopyranose units which are bound together by α-(1–4) linkages making a truncated conical structure, which allows cyclodextrins to form host–guest inclusion complexes with different sized guest molecules. The structures and the properties of the inclusion complexes formed by cyclodextrins are determined by their architectures, i.e., interplay between the hydrophilic–hydrophobic balance and geometric packing constraints. The experimental conditions, such as concentration, temperature, pH, etc. also play crucial roles exhibiting their potential applications in gene and drug delivery. Due to their above mentioned advantages, the inclusion complexes are being widely investigated in materials and biomedical sciences, especially, the applications in biologically and pharmaceutically relevant fields have produced tremendous interest of researchers in recent years. The exterior of the cyclodextrin cavity is highly polar due to the hydroxyl groups, while the interior is non-polar, making them suitable and fascinating hosts for supramolecular chemistry. The chemical stability of guest molecule also increases due to encapsulation inside the cavity.

Importance of host-guest chemistry of crown ethers: Crown ethers are used as important hosts in supramolecular chemistry, where the host–guest interaction mimics natural systems as well as constructs various materials. Crown ethers are macromolecular heterocyclic compounds with essential repeating unit -CH_2CH_2O-. A number of researchers are working on fabrication of crown-ether-based stimuli-responsive materials that have unique characters of ion recognize ability. A variety of current supramolecular materials, for instance rotaxanes are made on these unique recognition properties of CEs. Binding of CEs with cations with high selectivity and affinity has found remarkable importance in chemistry. Formation of molecular assemblies has vast implication for the building of molecular machines having plausible use as analogous to sophisticated machines of natural systems. Hence, fundamental investigations of the interactions between CEs and cationic species are important for their advanced applications.

Importance of vitamins as guest molecules: Nicotinic acid and ascorbic acid are the essential human nutrients with many important functions in biological systems. Nicotinic acid is used to treat hypercholesterolemia and pellagra while its deficiency causes nausea, skin and mouth lesions, anemia, headaches, and tiredness. On the other hand

scurvy, fatigue, depression, and connective tissue defects are the common syndromes caused by deficiency of ascorbic acid. Thus to protect these important bio-molecules from external effects (*e.g.*, oxidation, structural modification etc.) and for their regulatory release, it is crucial to investigate whether these molecules can be encapsulated into the CD molecule and to explore the thermodynamic aspect of the process.

Importance of neurotransmitters as guest molecules: Dopamine is an important neurotransmitter in the mammalian central nervous system and is a member of catecholamines. It is involved in neuropsychiatric disorders such as Perkinson's disease, which is the second most common central nervous system disorder. Tyramine is also a neurotransmitter and acts as a catecholamine releasing agent, having nonpsychoactive peripheral sympathomimetic effects. Epinephrine is a hormone and a neurotransmitter, serves as chemical mediators for conveying the nerve impulses to effectors organs. Epinephrine remains a useful medicine for several emergency indications and is used as a drug to treat cardiac arrest and other cardiac dysrhythmias.

Importance of sulfa-drugs as guest molecules: The stabilization and regulatory release of the sulfa-drugs are of great concern in pharmacology. Thus to protect these drugs from external effects and for their regulatory release, it is crucial to investigate whether they can be encapsulated into the CD molecule. Sulfonamides are bacteriostatic material and their range of activity is analogous for all. Sulfonamides restrain bacterial synthesis of dihydrofolic acid by inhibiting the condensation of the pteridine with aminobenzoic acid by competitive inhibition of the enzyme dihydropteroate synthetase. Topically applied sulfonamides act against vulnerable strains of various bacterial eye pathogens, for example, Escherichia coli, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus, Haemophilus influenzae, Klebsiella species, Enterobacter species, etc. Sulfacetamide sodium 10% topical lotion is approved for the treatment of acne, seborrheic dermatitis, conjunctivitis and various external visual infections due to susceptible for microorganisms. It has been considered in the treatment of pityriasis versicolor and rosacea. It also has anti-inflammatory property while used to treat conjunctivitis. It is found that sulfacetamide sodium may be used in the treatment of mild

forms of hidradenitis suppurativa. There are a number of topical products containing sulfacetamide sodium, e.g., foams, shampoos, cream, etc. Sulfacetamide is a competitive inhibitor of bacterial para-aminobenzoic acid, which is necessary for bacterial synthesis of folic acid, a vital constituent for bacterial growth. The multiplication of bacteria is thus inhibited by the action of sulfacetamide. Sulfacetamide sodium can also be used orally to treat urinary tract infections and the oral absorption of sulfacetamide sodium is found to be 100%. Sulfacetamide causes slight irritation in presence of UV-A light, as it gets sensitized and degraded leading to toxicity when used continuously.

Importance of RNA nucleosides as guest molecules: RNA nucleosides are very important biomolecules having enormous applications in the field of modern biological sciences, for example, RNA-based information technologies, RNA cloning, recombinant RNA technology and other genetic engineering processes.

Importance of amino acids as guest molecules: Amino acids play a crucial role in almost all biological processes and they are the building blocks of proteins. A large proportion of our cells, muscles and tissue are made up of amino acids. There are different types of amino acids. The polar amino acids include serine, threonine, asparagine, glutamine, histidine and tyrosine. The hydrophobic amino acids include alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophane, cysteine and methionine. The role of amino acids goes ahead of building blocks. They are essential for the synthesis of proteins, enzymes, hormones, neurotransmitters, metabolic pathways, mental stabilization and just about every function that takes place within the human body.

Importance of ionic liquids as guest molecules: The ionic liquids, namely, 1-butyl-3-methylimidazolium chloride [BMIm]Cl, 1-butyl-4-methylpyridinium chloride [BMPy]Cl and 1-butyl-1-methylpyrrolidinium chloride [BMP]Cl are biologically highly significant as they play important roles in enzymatic reactions. They are also important in organometallic, organic and material chemistry for their exceptional physical, chemical and electrical properties. Cetylpyridinium chloride is structurally significant because of having long lipophilic chain and pyridinium cationic head and also has medicinal applications. Pyridinium based ionic liquids are biologically extremely significant and also have role in

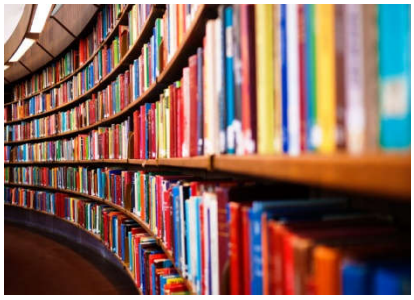
material chemistry for their extraordinary properties. The structure of cetylpyridinium chloride is very important to make supramolecular materials and also has biological and medicinal functions.

Summary of work done

Chapter I

This chapter contains the detail object of the research work, their scope and applications in the contemporary science. It also includes the reason of choosing the bio-molecules, ionic liquids, cyclodextrins, crown ethers and the solvent systems. This chapter has a short list of all the methods of investigations used in the research work.

Chapter II

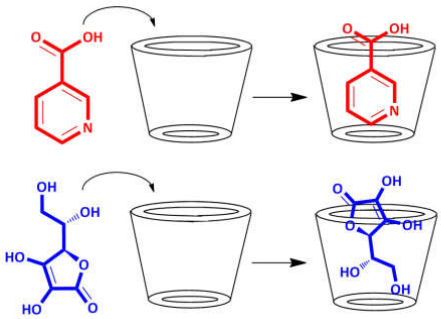


This chapter includes the review of the earlier works in this field of research done by various scientists and researchers across the world. This chapter also provides a detail theory of investigations, where the interacting forces among the molecules have been described. Here, the background theory of all the investigating methods, i.e., theory of ^{1}H NMR spectroscopy, 2D ROESY, FTIR spectroscopy, UV-visible spectroscopy, high resolution mass spectrometry, isothermal titration calorimetry, surface tension study, conductivity study, pH study, solution density, viscosity, refractive index, ultrasonic speed study have been discussed thoroughly and the significance of their use in the research work described in this thesis have been shown.

Chapter III

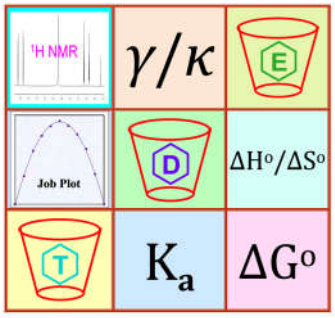
This chapter contains the experimental section. It covers the name, structure, physical properties and applications of the biologically active molecules, cyclodextrins, ionic liquids, crown ethers and solvents used in the research work. It also includes the details about the experimental methods and the description and use of the instruments involved in the research work.

Chapter IV



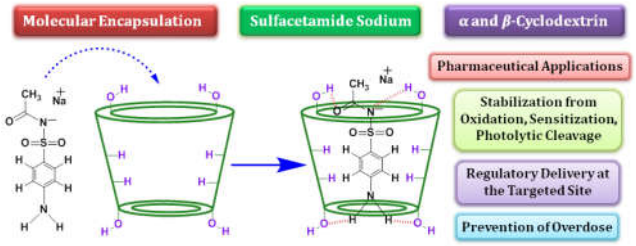
This chapter includes the host–guest inclusion complexes of β-cyclodextrin with two vitamins namely, nicotinic acid and ascorbic acid in aqueous medium. The work has been explored by spectroscopic, physicochemical and calorimetric methods. Job plots have been drawn by UV-visible spectroscopy to confirm the 1:1 stoichiometry of the host-guest assembly. Stereo-chemical nature of the inclusion complexes has been explained by 2D NMR spectroscopy. Surface tension and conductivity studies further support the inclusion process. Association constants for the vitamin-β-CD inclusion complexes have been calculated by UV-visible spectroscopy using both Benesi–Hildebrand method and non-linear programme, while the thermodynamic parameters have been estimated with the help of van't Hoff equation. Isothermal titration calorimetric studies have been performed to determine the stoichiometry, association constant and thermodynamic parameters with high accuracy. The outcomes reveal that there is a drop in ΔS^0, which is overcome by higher negative value of ΔH^0, making the overall inclusion process thermodynamically favorable. The association constant is found to be higher for ascorbic acid than that for nicotinic acid, which has been explained on the basis of their molecular structures.

Chapter V



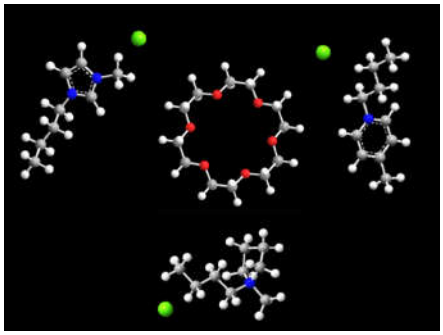
This chapter comprises the molecular assemblies of *β*-cyclodextrin with few of the most important neurotransmitters, namely, dopamine hydrochloride, tyramine hydrochloride and (±)-epinephrine hydrochloride in aqueous medium. The work has been explored by spectroscopic and physicochemical techniques as potential drug delivery systems. Job plots confirm the 1:1 host-guest inclusion complexes, while surface tension and conductivity studies illustrate the inclusion process. The inclusion complexes were characterized by ^{1}H NMR spectroscopy and association constants have been calculated by using Benesi–Hildebrand method. Thermodynamic parameters for the formation of inclusion complexes have been derived by van't Hoff equation, which demonstrate that the overall inclusion processes are thermodynamically favorable.

Chapter VI



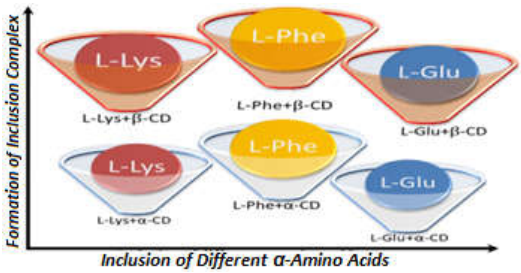
This chapter consists of the molecular encapsulation of one of the most important sulfa-drugs, namely, sulfacetamide sodium in solution and solid phase within the cavity of α and *β*-cyclodextrins. Various physicochemical techniques have been employed to establish the outcome of the work. Isothermal titration calorimetric method has been used to evaluate the stoichiometry, association constant and thermodynamic parameters with high accuracy. The solid inclusion complexes have been analyzed by spectroscopic technique, which ascertain the encapsulation of the investigating drug into the cavity of α and *β*-cyclodextrins. This inclusion phenomenon of the drug is exceedingly significant for its stabilization from external hazards, like oxidation, sensitization, photolytic cleavage etc., for regulatory release of essential amount of drug at the targeted site for a period of time proficiently and accurately and for preventing overdose when applied as ophthalmic solution and ointment.

Chapter VII



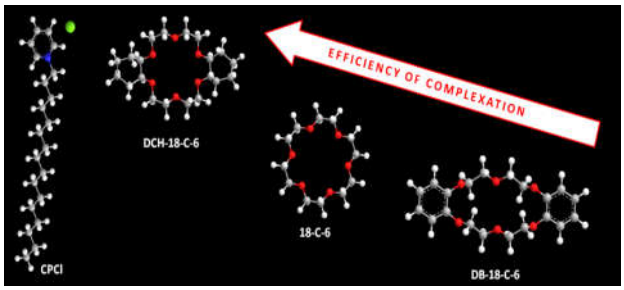
This chapter contains supramolecular host-guest complexation with excellent comparison among three similarly substituted ionic liquids, namely, 1-butyl-3-methylimidazolium chloride, 1-butyl-4-methylpyridinium chloride and 1-butyl-1-methylpyrrolidinium chloride with 18-crown-6 in acetonitrile medium by conductivity in a range of temperature to elucidate the stoichiometry of the complexes. The programmed mathematical study with the help of conductivity data provides association constants for the complexes, by which the thermodynamic properties have been evaluated for improved understanding about complexation. The molecular interactions have been explained and critically discussed with the help of FT-IR and ^{1}H NMR spectroscopic studies, which illustrate H-bond and ion-dipolar attractions primarily exist in complexation.

Chapter VIII



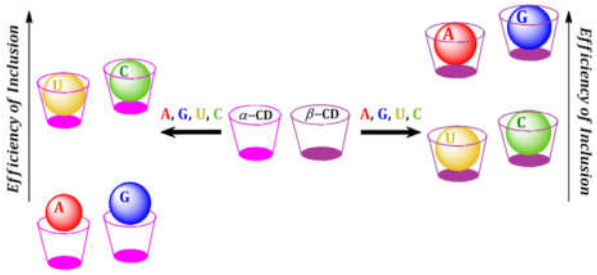
This chapter includes the studies of molecular inclusions of a congener series of guest amino acid molecules into the host cavity of α and β-cyclodextrins in aqueous solution focusing on modern research gaining far reaching effect. With both the α and β-cyclodextrins, it is found that 1 : 1 host–guest inclusion complexes are formed with all the guest molecules at both low and high pH. The variation of the thermodynamic parameters with guest size and state are used to draw inferences about contributions to the overall binding from the driving forces, namely, hydrophobic effect, van der Waals forces, H-bonds, electrostatic forces, structural effect and configurational theory. The formation and comparative study of inclusion complexes have been analyzed by available data supplemented with surface tension, pH, density, viscosity and refractive index.

Chapter IX



This chapter incorporates the supramolecular complexations of cetylpyridinium chloride with three comparable cavity dimension based crown ethers, namely, dibenzo-18-crown-6, 18-crown-6 and dicyclohexano-18-crown-6 in acetonitrile with the help of conductivity in a series of temperatures to reveal the stoichiometry of the three host-guest complexes. Programme based mathematical treatment of the conductivity data affords association constants for complexations from which the thermodynamic parameters were derived for better comprehension about the process. The interactions at molecular level have been explained and decisively discussed by means of FT-IR and ^{1}H NMR spectroscopic studies that demonstrate H-bond type interactions as the primarily force of attraction for the investigated supramolecular complexations.

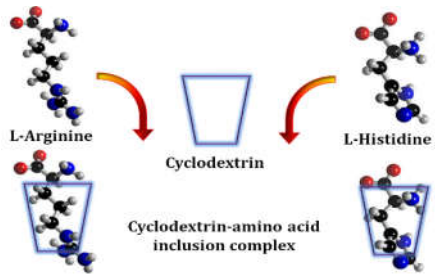
Chapter X



This chapter comprises the exploration of stable host-guest inclusion complexes with the guest RNA nucleosides inside aqueous α and β-cyclodextrins. α-cyclodextrin has been found to have favorable structural features for inclusion with uridine and cytidine, whereas β-cyclodextrin has that with all the four nucleosides, namely, adenosine, guanosine, uridine and cytidine. The formation and nature of the inclusion complexes have been characterized using surface tension study, Job's method by ultraviolet spectroscopy and pH measurements. The limiting apparent molar volume, viscosity B-coefficient, limiting apparent molar adiabatic compressibility and limiting molar refraction data have been used to characterize the interaction between nucleosides and cyclodextrins in the experimental ternary solution systems. The inclusion phenomenon has been confirmed by

proton NMR study. Association constants and thermodynamic parameters have been evaluated for the formed inclusion complexes by ultraviolet spectroscopy.

Chapter XI



This chapter contains assembly of two natural amino acids namely, L-arginine and L-histidine as guests with α and β-cyclodextrins as hosts to form inclusion complexes in aqueous medium which are highly suitable for diverse applications in modern bio-medical sciences. ^{1}H NMR study establishes the formation of inclusion complexes, while surface tension and conductivity studies confirm that the inclusion complexes have been formed with 1:1 stoichiometry. Nature of the complexes has been established by thermodynamic parameters, based on density, viscosity, and refractive index measurements. Contributions of different groups of the guest molecules towards the limiting apparent molar volume and viscosity-B coefficient are determined and solvation numbers are calculated. All the parameters support the formation of the inclusion complexes, which are explained basing upon hydrophobic effect, H-bonds, electrostatic forces and structural effects.

Chapter XII

This chapter includes the concluding remarks about the research works done in this thesis.