ABSTRACT

As outlined in the thesis title, I would like to demonstrate my extensive knowledge of supramolecular host-guest inclusion complexation and amino acid-ionic liquid interaction in aqueous medium. Supramolecular assembly is becoming increasingly important in drug release because to its outstanding bioavailability and exceptional capacity to change many drug properties such as solubility, stability within the body, pharmacokinetics, and pharmacodynamics. They also have non-toxic characteristics, improved encapsulation, and controlled release.

The spectroscopic contribution validates the inclusion complexation of several bioactive compounds and their distinct photophysical characteristics in aqueous media. The inclusion phenomena can be satisfactorily expressed by UV-visible, ^{1}H-NMR, FTIR and mass spectrometry . Surface tension, Powder XRD, and SEM studies provide qualitative information about the formation of supramolecular assemblies. The thermal stability of such an arrangement can be described using TGA and DSC analysis. Theoretical molecular modelling investigations of the supramolecular system confirm the experimental results.

The study of physicochemical properties of solutions provides substantial knowledge on numerous thermodynamic properties of electrolytes and non-electrolytes, the impact of variations in ionic structures, mobility of ions along with their common ions.. The genesis of diverse interactions between amino acids-ionic liquid in aqueous phase is usually exposed by measurement of the apparent molar volume (ϕ_v), limiting apparent molar volume (ϕ_v^0), molar refraction (R_M), limiting molar refraction (R_M^0), molar conductance (Λ), viscosity B coefficients obtained from different physicochemical methodologies.

This thesis presents research on the formation of host-guest inclusion complexes of the oligosaccharide cyclodextrin with vital guest molecules, as well as the investigation of interactions of ionic liquids with bio-active molecules in solution phase using various spectroscopic and physicochemical techniques.

To achieve the goal, the inclusion complex formation of bioactive guest molecules such as Adiphenine hydrochloride (ADP), Benserazide hydrochloride (BNZ), D Pantothenic acid hemicalcium salt (DPAH) with host molecules such as α-cyclodextrin (α-CD) and HP-β-cyclodextrin (HP-β-CD) has been studied.

Host-guest chemistry has diverse application in the field of modern biochemistry as it covers the area of complexes formed by two or more molecules joined together by forces other than covalent bonds. It is very difficult to explain the 3D structure of large biomolecules by non covalent bonding; rather it is involved in biological processes in which molecules bind specifically but transiently to another molecule. Inclusion complex formation is one type of host–guest chemistry. Common host molecules are cyclodextrin, crown ether, cucurbit, porphyrins etc. while amino acids, vitamins, ionic liquids, drugs etc can act as guest molecules. The guest molecules are encapsulated in the cavity of host molecules and bound by some non-covalent interactions such as hydrogen bonding, van der Waals force and hydrophobic interactions. The thermodynamic driving force for the formation of host-guest inclusion complex is the lowering of Gibb's free energy of the system.

Since supramolecular recognition and solution chemistry have so many applications in a variety of sectors, from the pharmaceutical to the biological sciences, the main goal of this thesis is to explore their effect.

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 and the solvent systems.

Chapter II

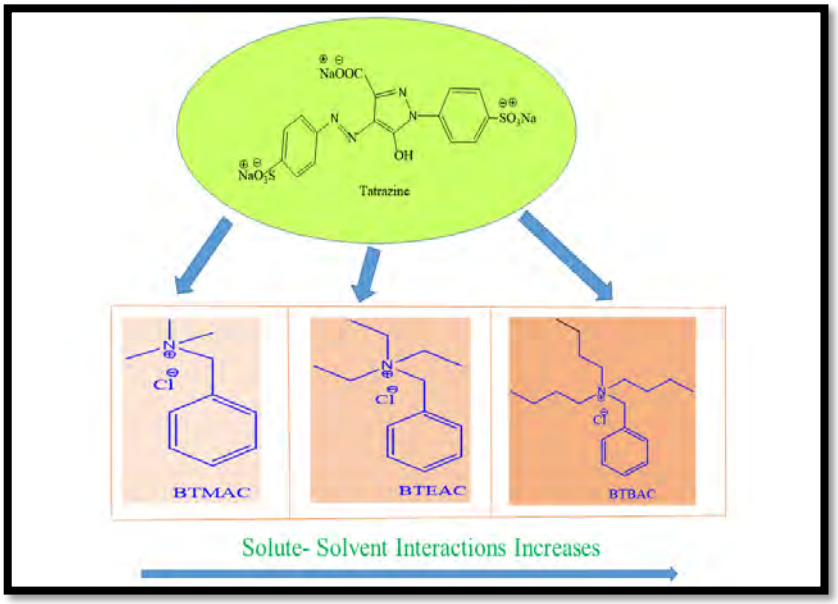
This chapter includes the general introduction about the research work in this thesis. All the methods used to ascertain the various molecular level interactions among the hosts and guests have also shown comprehensively and their background theories have been explained. The parameters based on ^{1}H NMR spectroscopy, 2D ROESY, FTIR spectroscopy, UV-visible spectroscopy, high resolution mass spectrometry, surface tension study, conductivity study, pH study, solution density, viscosity, refractive index have been discussed thoroughly. It also shows the detail review of the earlier related works in the similar field by different workers worldwide.

Chapter III

This chapter contains the experimental section. It covers the source, purity, purification, structure of various bio-molecules, ionic liquids, cyclodextrins, crown ethers and the solvents used in the research work. It also includes the details about various instruments used in this research work.

Chapter IV

Different physicochemical parameters of the food additive azo dye, viz., tartrazine (TZ) were thoroughly examined using three important ionic liquids (ILs) in aqueous solutions, viz., benzyl tri-methyl ammonium chloride (BTMAC), benzyl tri-ethyl ammonium chloride (BTEAC), and benzyl tri-butyl ammonium chloride (BTBAC). In order to understand the plausible interactions of TZ with the ILs,



various physicochemical properties have been studied, including viscosity (η), density (ρ), refractive index (n_D), surface tension and conductance at different temperatures. Moreover, the apparent molar volume (Φ_v) derived from the Masson equation, molar refraction (R_M), limiting molar refraction (R_M^0) from Lorentz-Lorenz equation and coefficient of viscosity (B) from the Jones-Dole equation were applied to criticize the molecular interactions involving the TZ and the ILs at different concentrations and temperatures. Various thermodynamic parameters, such as $\Delta\mu_1^{0\#}$, $\Delta\mu_2^{0\#}$, $T\Delta S_2^{0\#}$, and $\Delta H_2^{0\#}$ which, suggest the strong interactions observed in these systems. Gibbs's free energy change suggests the spontaneity of the system. The ^{1}H- NMR and UV-Vis spectroscopy data also support our theoretical and experimental findings. Density functional theory was used to determine the optimum energies with optimized geometries for the molecular assembly of the ternary system (TZ+IL+H_2O) in order to validate the experimental observations.

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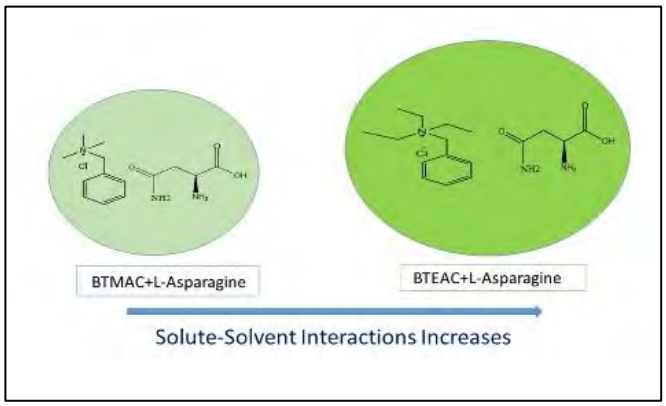
Chapter V

Solution behaviour prevailing in L-Asparagine in two aqueous ionic liquid solutions, namely (Benzyl tri–methyl ammonium chloride; Benzyl tri-ethyl ammonium chloride) have been studied by investigation of physicochemical parameters; density, viscosity, refractive index, conductance and surface tension measurement respectively. The nature of interactions occurring in the solution has been calculated based on apparent molar volume, viscosity A and B-coefficient, molar refraction at 298.15K,303.15K,308.15K and at 0.001m, 0.003m, 0.005m concentrations. The limiting apparent molar volumes (φ_V^0) obtained from the Masson equation, viscosity parameters, A and B coefficients obtained from the Jones-Doles equation, Molar refraction(R_M) from the Lorentz-Lorenz equation that describe the nature of solute-solute and solute-solvent interactions in the solution. Specific Conductance of the experimental solution was



applied to ascertain the ionic nature of the system. The different thermodynamic data, $\Delta\mu_1^{0\neq}$, $\Delta\mu_2^{0\neq}$, $\Delta H^{0\neq}$, and $T\Delta S^{0\neq}$ also suggest the presence of strong interactions in the studied systems. The various types of interactions existing among amino acids in the presence of ionic liquids which are the protein backbone, would advance a many-dimensional challenge in the arena of solution chemistry. Studies of such systems could be forward-thinking further using the correlated results of the investigation.

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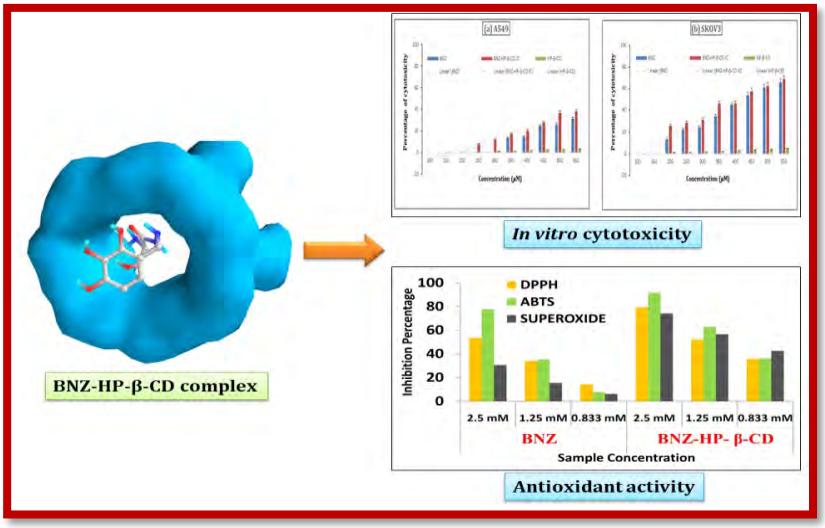
Chapter VI

Herein, we explore the supramolecular complexation of Benserazide hydrochloride (BNZ) with Hydroxypropyl-β-cyclodextrin (HP-β-CD) in an aqueous medium by means of UV-visible, surface tension, FT-IR, ^{1}H NMR, 2D ROESY, DSC, PXRD and molecular docking study. These studies suggest the effective complexation of BNZ with HP-β-CD resulting in the formation of BNZ-HP-β-CD complex. Surface tension study and Job's plot confirm 1:1 stoichiometry of BNZ-HP-β-CD complex. FT-IR, ^{1}H NMR and 2D ROESY studies suggest the possible binding mode of BNZ into the cavity of HP-β-CD. The binding constant (K_a) of BNZ-HP-β-CD complex indicates the affinity of HP-β-CD for BNZ. The estimated negative free energy of binding reveals that the complexation process is thermodynamically feasible. PXRD analysis confirms the formation of BNZ-HP-β-CD inclusion complex. DSC analysis shows the enhancement in the thermal stability of BNZ after complexation with HP-β-CD. The molecular docking study introduces the most stable binding orientation of BNZ within the cavity of HP-β-CD. The complex expresses better cytotoxic effect than free BNZ on bothlung carcinomic A549



cell line and ovarian SKOV3 cancer cell line. Furthermore, the considerable improvement in the antioxidant activity of BNZ is registered after encapsulation.

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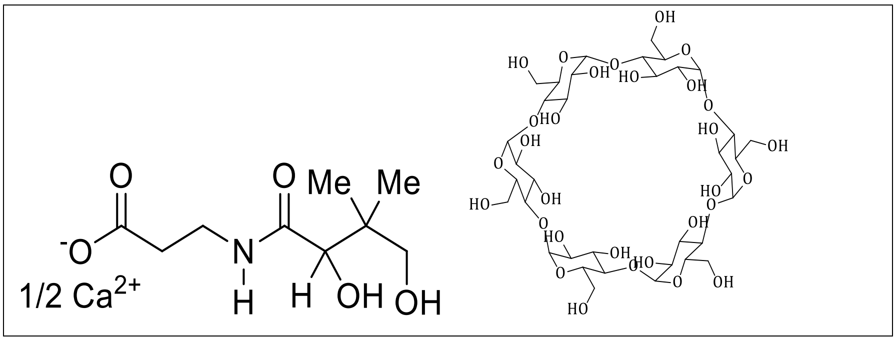
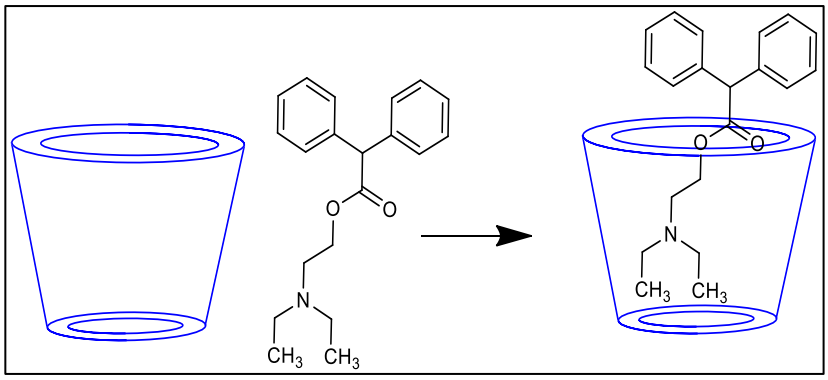
Chapter VII

Herein, we aim to form the inclusion complex (IC) of of D-Pantothenic acid hemicalcium salt with α-cyclodextrin (α-CD) and to analyse it by means of FT-IR,^{1}H NMR HRMS, DSC, TGA, molecular docking study and cytotoxic studies. The DPAH-α-CD complex was synthesized by following the co-precipitation method with a molar ratio of 1:1. The formed complex was characterized by employing several spectroscopic techniques such as nuclear magnetic resonance (^{1}H NMR), fourier transform infrared (FTIR), differential scanning calorimetry (DSC), thermo-gravimetric analysis (TGA) and scanning electron microscopy (SEM) which indicated the successful encapsulation of drug DPAH into the nano cage of α-CD. TGA and DSC study demonstrated how the complexation improved the thermal stability of DPAH. The 1:1 M ratio of host (α-CD) and guest (DPAH) during IC production was verified by mass spectrometry.A molecular modeling study conjectured the most desirable orientation of the DPAH molecule within the non-polar binding pocket of the α-CD cavity. The molecular docking analysis presents the most stable DPAH binding orientation inside the α-CD cavity. The DPAH-α-CD complex (IC_{50} = 113.09 μg/mL) also displayed noteworthy in vitro cytotoxic activity than pure DPAH (IC_{50} = 137.17μg/mL) towards Neuroblastoma cancer cell line (SHSY5Y) .Ultimately, these results show that DPAH complexation with α-CD may improve DPAH stability and show a range of related applications.



Chapter VIII

It has been proven that an inclusion complex may be assembled in an aqueous medium using HP-β-cyclodextrin as the host and a metabolizer drug (Adiphenine hydrochloride) as the guest. This assembly is highly suitable for a range of applications in the contemporary biomedical sciences. The generation of the inclusion complex is confirmed by ^{1}H NMR, and surface tension measurements which demonstrate that a 1:1 stoichiometry was used in its creation. Numerous spectroscopic techniques, including nuclear magnetic resonance (^{1}H NMR), two-dimensional ROESY, fourier transform infrared (FTIR), differential scanning calorimetry (DSC), powder XRD, thermogravimetric analysis (TGA), and scanning electron microscopy (SEM), were used to characterize the formed complex. These methods showed that the drug ADP may be successfully encapsulated within the HP-β-CD nanocage. The results of TGA and DSC research demonstrated the improvement in ADP's thermal stability following complexation. The affinity of HP-β-CD for ADP is shown by the binding constant (K_a) of the ADP-HP-β-CD complex.. The predicted negative free energy of binding indicates that the complexation is feasible thermodynamically. PXRD analysis confirms the formation of the ADP-HP-β-CD inclusion complex. In vitro cytotoxicity, the ADP-HP-β-CD combination was significantly more potent than pure ADP against the SHSY5Y neuroblastoma cell line. Enhancement of antibacterial activity towards a wide range of important bacteria is seen for the encapsulated ADP than the free one.



Chapter IX

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