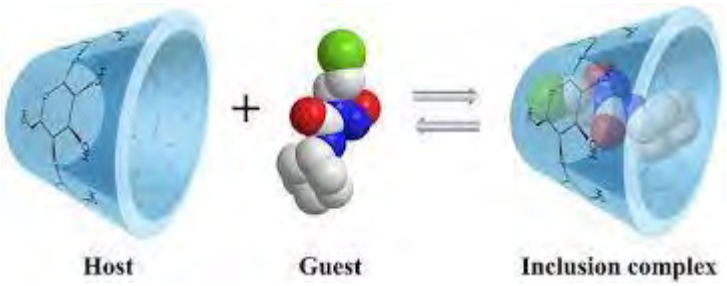
ABSTRACT

Proposed work covers the Supramolecular Host-Guest Inclusion Complexation of some bioactive molecules and the solute-solvent interaction of amino acids (AA) with ionic liquids (ILs) aiming to compare the molecular interaction existing among these different chemical compounds and resulting molecular synergism in solution phase.

Supramolecular assemblage has garnered a huge importance during recent years in the field of drug delivery owing to their significant biocompatibility and excellent potential



to expand the spectrum of medical application in pharmaceutical industries and biomedical sciences.

The spectroscopic techniques confirm the inclusion complex formation of numerous bioactive molecules and their photophysical properties in solution phase. The UV-Visible, ^{1}H NMR and FT-IR spectroscopy along with mass spectrometry studies supports the formation of inclusion complex. Further, SEM and PXRD analysis implements the qualitative aspect for the generation of supramolecular framework. Thermal and photostability of such assembly have been examined through DSC and UV- visible studies. Computational and theoretical molecular modelling studies of this system reaffirms the results observed in the experimental studies.

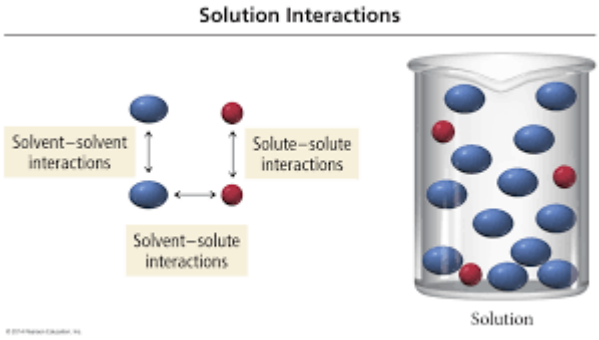
In this study, inclusion of variety of biologically potent molecules such as, Rodanine, Gemcitabine and Nitrofurantoin have been examined. These compounds find significant medicinal applications. Pharmacological aspect is specifically considered to illustrate the biocompatibility of such biologically active molecules.

Molecular recognition, controlled release of a drug and sensing field have received the great consideration under host–guest chemistry. Encapsulation of guest molecules in aqueous phase inside the nanocage of host molecules, such as

cyclodextrins and several other water-soluble hosts lights up an advanced technique into the field of molecular recognition (inclusion or complexation) owing to extensive non-covalent interactions. The potent pharmacological activity of bioactive compounds often gets influenced through molecular recognition.

Supramolecular host-guest chemistry covers a broad aspect related to the inclusion complex formation between the host and the guest molecules. Hydrophobic nanocage of host molecules are very efficient in binding variety of guest molecules. Over the past few decades, the supramolecular assembly has been extensively investigated in several fields including analytical chemistry and drug-delivery. Cyclodextrins (CDs), are the most suitable host compounds owing to their ability for controlled passage of guest molecules after inclusion complex formation thereby increasing bioavailability of the compound.

Ionic liquids (IL) or famously known as molten salts at room temperature currently received great consideration in many areas of chemistry by the researchers across the globe. The most significant characteristic of ILs is the “tunability” of various physical and chemical properties by modifying structure. Many reviews have highlighted the different characteristics of ILs and their potential application. ILs are blessed with some exceptional properties as most of them have a negligible vapor pressure, unparalleled thermal and electrochemical stability, low flammability and commending dissolution properties with large variety of organic/inorganic compounds. ILs mainly consist of different category of cations and anions. They found significant applications as biphasic systems for separation, solvents for many synthetic and catalytic applications, lubricants, extensively in lithium batteries, supercapacitors, actuators, substitute for conventional solvents, alternative for reaction media and active pharmaceutical ingredients. However, the most important characteristic associated with ILs is the “tunability” of their structure. They can easily modify their structure to achieve the specific chemical or electrochemical applications.



In order to investigate the stability of proteins, (ILs) are generally employed as a novel medium . Amino acids are considered ideal system for investigating the characteristics of proteins. Further denaturation, solvation and dissociation of enzyme are highly affected by the neighbouring environment. The emergence of assorted interactions is conventionally examined by estimation of the apparent molar volume (ϕ_v), limiting apparent molar volume (ϕ_v^0), molar refraction (R_M), limiting molar refraction (R_M^0) viscosity B coefficients obtained from different physicochemical methodologies. This study features the variety of physicochemical characteristics of amino acid in solution of Ionic liquid in water. This work helps in interpretating the behaviour of these compounds in complex structures of proteins. Here we have selected an Ionic liquid as an additive (electrolyte) as they are blessed with various advantages as a function of concentration, temperature, and ambient pressure. Thermodynamic, viscometry, volumetric, refractometric, surface tension measurements have been carried out as these properties are susceptible towards the solute-solute and solute-solvent interaction. Investigation of these properties greatly support to understand the structure and characteristics of solutes in aqueous medium and gives a reliable explanation for the complicated nature of molecular interactions in various biochemical processes occurring in the human body.

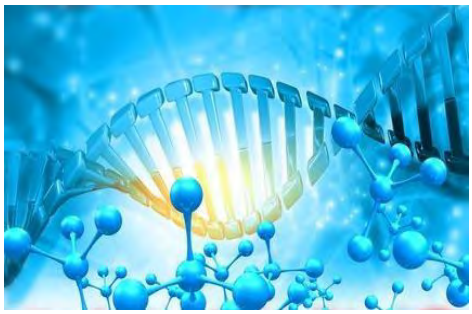
Therefore, the objective of this thesis is to

(1) investigate and understand the significance of supramolecular recognition owing to their diverse range of applications in varied fields such as pharmaceutical, biomedical sciences etc.

(2) understand and evaluate the molecular interactions between ionic liquid and various biomolecules in order to manifest the behaviour of these compounds in complex structures of proteins for further application.

Summary of work done

Chapter I



This chapter contains the details of the research work, their objective, scope and applications in the modern science. A detailed discussion about the scope of selecting the biologically active molecules, cyclodextrins, amino acids and ionic liquids have been included. This chapter consist a brief list of all the techniques of investigations i in the research work.

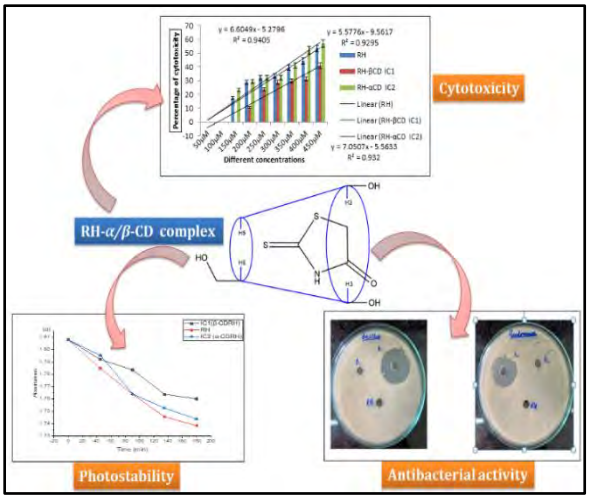
Chapter II

This chapter consist the review of the previous works reported by scientists and researchers in the field of supramolecular and solution chemistry around the world. This chapter also includes the detail of theories of investigation. The interactive forces existing among the various molecules have been discussed in detail. The underlying theories of investigating techniques, i.e., theory of ^{1}H NMR , FT-IR, Fluorescence, UV-Visible spectroscopy, Mass spectrometry and Thermogravimetric analysis, Powder X-ray Diffraction, Scanning Electron Microscopy, Surface tension study, Molecular docking study, Antibacterial activity study, Cytotoxicity study, CT-DNA interaction study, Photostability study, Surface tension, Conductivity, Density, Viscosity, Refractive index studies have been discussed thoroughly and the importance of this research work also included in this thesis.

Chapter III

This chapter presents the experimental section. It includes the details of name, structure, physical properties and applications of the biologically active molecules, cyclodextrins, amino acids, ionic liquids and solvents used in the research work. It consists the briefing about the experimental methodologies.

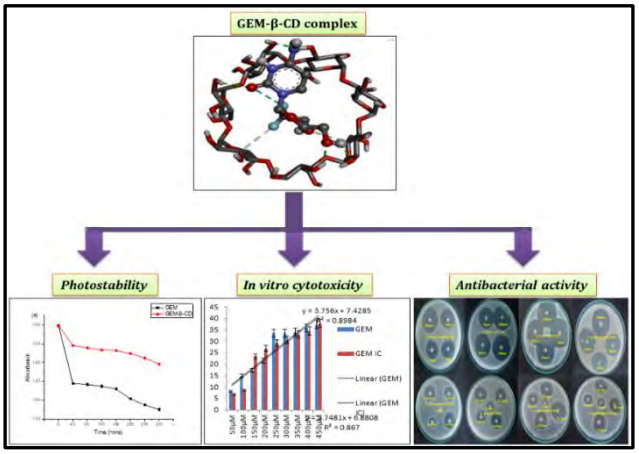
Chapter IV



This chapter contains of the encapsulation of rhodanine within the cavity of α-cyclodextrin and β-cyclodextrin. This work has been investigated by spectroscopic, physicochemical methods. Job plots using UV-Visible spectroscopy confirms the 1:1 stoichiometry of the host-guest molecular assembly. This observation was again supported by mass spectrometric analysis. UV-Visible spectroscopy has been employed to calculate association constants for the inclusion complexes using Benesi–Hildebrand method. Thermodynamic parameters have been calculated and it ascertains the thermodynamically spontaneity of the overall inclusion processes. ^{1}H NMR and FT-IR investigations illustrates the quantitative insight on the possible mode of encapsulation in inclusion complexes. Thermal stability of rhodanine on inclusion with cyclodextrins has been evaluated by DSC analysis. Computational study further provides the useful understanding on the inclusion mode of rhodanine molecule into the nanocage of cyclodextrins. The surface morphology of the inclusion complexes was investigated by SEM. Photostability and CT-DNA interaction studies are investigated by UV Visible spectroscopy. Finally, the biological activity namely; cytotoxicity and

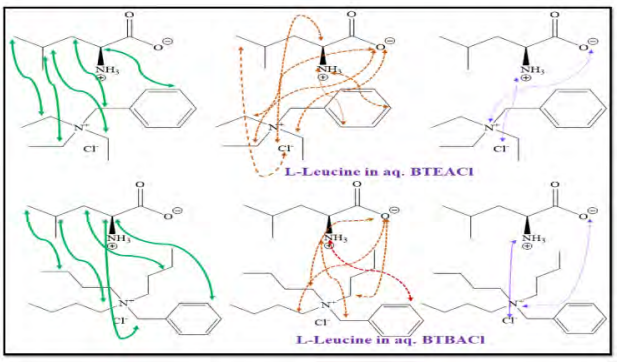
antimicrobial activity of the inclusion complexes were evaluated and a comparative study was carried out with respect to pure rhodanine.

Chapter V



This chapter presents the study of the host-guest inclusion complex of gemcitabine with β-cyclodextrin, photostability, CT-DNA study and its biological activity. The prepared complex was characterized by numerous physicochemical and spectroscopic methods. Job plot, and mass spectrometric analysis confirms the 1:1 ratio host-guest inclusion complex. Association constant has been determined by Benesi–Hildebrand method. The Gibb's free energy of binding has been calculated by evaluating the binding constant which confirms the inclusion process is spontaneous. The mode of inclusion was investigated by ^{1}H NMR and FT-IR spectroscopic analysis. PXRD and SEM analysis have been carried to reaffirm the inclusion complex formation. The enhancement in the photo stability of gemcitabine through complexation was investigated by UV-visible spectroscopic analysis. Molecular docking study presented the most preferred site for binding of gemcitabine molecule within the cavity of β-cyclodextrin. The apoptosis and antibacterial activity of the inclusion complex was investigated in detail and subsequently compared with free gemcitabine.

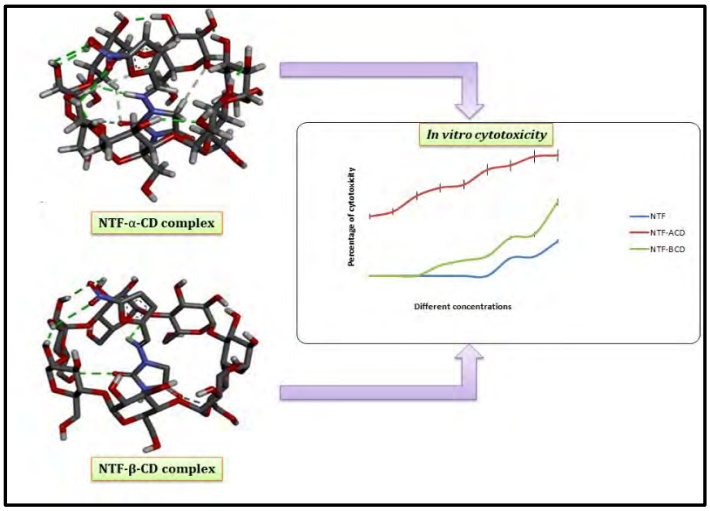
Chapter VI



This chapter presents the thorough analysis on the diverse molecular interactions of implausible amino acid, L-leucine (AA) in the aqueous solution of Benzyltriethylammoniun chloride (BTEACl), Benzyltributylammoniun chloride (BTBACl) have been carried

out by numerous physicochemical techniques such as Density, Refractive index, Viscosity, Electrical conductivity, at four different temperatures ranging from 298.15 K to 318.15 K. ^{1}HNMR and UV-visible analysis were carried out to investigate the solute- solvent interaction. Association constant for L-Leucine-BTBACl system as well as for L-Leucine-BTEACl system were evaluated to understand the diverse intermolecular interactions in the solution phase using UV-vis spectroscopy. Formation of thermodynamic background owing to different interactions occurring in the ternary mixtures were studied by evaluating the free energies of numerous molecular interactions. The source of various interactions is evaluated by calculating the apparent molar volume (ϕ_V), limiting apparent molar volume (ϕ_V^0), viscosity *B*-coefficients, molar refraction (R_M), limiting molar refraction (R_M^0), molar conductivity (Λ) and surface tension (σ)volume, molar refraction, limiting molar refraction, viscosity B coefficients. Furthermore, adsorption energy, molecular electrostatic potential (MESP) maps and reduced density gradient (RDG) obtained by the application of density functional theory (DFT), have been used to determine the type of interactions which are consistent with the experimental observations.

Chapter VII



This chapter provides the detail analysis and application of supramolecular complexations of a very important antibiotic and a potential acetylcholine esterase inhibitor nitrofurantoin with α and β-cyclodextrins in aqueous medium. The molecular interactions have been investigated using ^{1}HNMR spectroscopic studies, Job plot confirms the 1:1 stoichiometry of host with guest in the inclusion complexes. Binding constants for the formation of inclusion complexes have been determined using Benesi–Hildebrand method with the help of UV-visible spectroscopy. Free energy of binding of nitrofurantoin with cyclodextrins have been calculated from the binding constant value. This information subsequently

determines the thermodynamic feasibility of the encapsulation process. PXRD and SEM studies further supports the inclusion complexes formation. Photo stability, CT-DNA interaction studies of the inclusion complexes was carried out using UV-visible spectroscopy. Molecular docking study indicates the most preferable binding orientation of nitrofurantoin within the cavity of cyclodextrins.

Chapter VIII

This chapter contains the concluding remarks related the research works carried out in this thesis.