

CHAPTER: I

NECESSITY OF THE RESEARCH WORK

I.1. AIMS AND OBJECTIVES

Scientific research work motivated by discovery of unknown. It is especially pleasing when the work offers the promise of new knowledge, as well as imminent applications.

Supramolecular chemistry is often defined as “the chemistry beyond the molecule” or “the chemistry of the noncovalent bond”. One of the forefront contributions of supramolecular chemistry is in designing and synthesizing macrocycles that can selectively bind a particular guest. This is extremely important especially in our pursuit of knowledge in biological systems. Where it is difficult to study the humongous molecules such as enzyme, it is much easier to simulate the studies in smaller molecules that have the same properties. This is where supramolecules come in useful; where it can mimic the features of biosystems.

Majority of drug products available in market suffer from solubility problems. Because of poor solubility, good numbers of new molecules are not reaching the market. The solubility can be enhanced by several techniques. One of the prominent approaches to enhance solubility is the complexation with cyclodextrin (CD) and formation of solid inclusion complex [1]. Cyclodextrins are employed as complex forming agents thereby enhancing the aqueous solubility of poorly soluble drugs [2,3]. Thus they improve the bioavailability and stability of drugs, reduce gastrointestinal drug irritation, prevent drug–excipient and drug–drug interactions. To overcome gastrointestinal tract irritant effects caused by many of nonsteroidal anti-inflammatory drugs, it becomes necessary to formulate the drug in an appropriate dosage form which can be administered through skin. Due to the major advantage of CDs to act as drug delivery vehicles, it is proposed to study CD complexation of various significant molecules, an important constituent of numerous pharmaceutical products, by using

analytical techniques. The proposed studies employ cyclodextrins as potential drug delivery vehicles [4-6] as they can change the physical, chemical and biological activities of guest molecules by forming inclusion complexes. The principal advantages of natural cyclodextrins as drug carriers are the following: (1) well-defined chemical structure (2) availability of cyclodextrins having appropriate cavity size (3) low toxicity and low pharmacological activity (4) certain water solubility (5) they can protect included drugs from biodegradation.

The Host-guest complex formation based on the macrocyclic molecules is a facile and reversible process, which organise for the feasibilities to design stimuli-responsive supramolecular systems and these macrocyclic molecules are basically friendly to the biological environment and exhibit good biocompatibilities [7-9]. Crown ether-based host-guest interactions, which show good selectivity, high efficiency, and reversibility, have been structurally characterized and the underlying supramolecular chemistry has been presented in our work. Supramolecular chemistry i.e. host-guest complex formation through noncovalent interactions offer the basis for novel approaches in medicine and also helps in understanding the interactions present in living systems. It was also found that host-guest complexation with crown ethers resembles an established principle i.e. the hydrogen bonding acceptance as well as the donation propensity of crown ethers.

To understand the binding behavior of the different unique host system, "Inclusion complex", will be prepared and it is proposed to characterize them by various analytical tools such as IR, UV, fluorescence, NMR, conductance and surface tension studies. This will throw light not only on the role of host molecule in offering protection against degradations but also on stabilising potential conformers *via* various interactions such as hydrogen bonding *etc.*

When one substance dissolves in another the properties of the substances changes. Solution chemistry is the branch of physical chemistry where this type of changes are studied. In '**Solution Chemistry**' broadly three types of approaches have been made to estimate the extent of solvation. The first is the ionic solvation of the electrolytes involving the studies of viscosity, conductance [10], the second is the thermodynamic approach by measuring the free energies, enthalpies and entropies of

solvation of ions from which factors associated with solvation can be elucidated [11], and the third is to use spectroscopic measurements where the spectral solvent shifts or the chemical shifts determine their qualitative and quantitative nature [12]. Interactions taking place between solute-solute, solute-solvent, solvent-solvent species govern the strength of ion-solvation [13,14]. The interpretation of solute-solute, solute-solvent and solvent-solvent interactions gives a complete information about the phenomena of solution chemistry. Hence we have concentrated on the studies of solute-solute, and solvent-solvent interactions in some industrially important liquid systems.

The molecular interaction in liquids explored by physicochemical methods has paying attention, as thermodynamic parameters are appropriate to interpret intermolecular interaction patterns in non-electrolytic solvent mixtures [15]. The different sequence of solubility, difference in solvating power and possibilities of chemical or electrochemical reactions unaware in aqueous chemistry have open vistas for chemists and interest in the organic solvents transcends the traditional boundaries of physical, inorganic, organic, analytical and electrochemistry.

Solvation behaviour is one of the most essential properties of any liquid as it regulates more complex processes such as solvation and reaction dynamics. The physico chemical properties of a solution (liquid) is a outcome of the strength of their intermolecular forces. The molecules are acquired partial charges through the *intermolecular forces*, e.g., dipole-dipole forces, dipole-induced dipole forces, hydrogen bonding, Van der Waal forces and electrostatic interaction etc. *Intermolecular forces* in a solution control their thermodynamic properties and the understanding of the solvation thermodynamics is essential to the characterization and interpretation of any process performed in the liquid systems. Therefore, the studies on the thermodynamic along with the transport and spectral properties of solutions would provide a clear idea about the nature of the forces, interacting manner existing between the constituents of solution. This type of study thus opens a path for research in solution chemistry to discover the nature of interaction through experimental studies involving density, viscosity, refractive index, conductometry, spectroscopy study and to interpret the experimental data collected.

Due to significant physicochemical properties such as negligible vapour pressure, high thermal and electrochemical stability, high solvating power, etc. the ionic liquids (ILs) are advantageous in various fields. The choice of the cation and the anion constituting an ionic liquid has a profound effect on the physicochemical properties such as density, viscosity, conductivity and polarity. This variety opens wide opportunities in the tailoring of ILs suitable for practical applications. The understanding of the behaviour of ILs and their properties is crucial for any practical application. But the available chemical and physical data are unfortunately inadequate in comparison to the amount of already commercially available ILs. Moreover, the existing data are often inconsistent. In this perspective, we focused on the reliable determination of physicochemical, transport and spectral properties of ILs in various solvent systems to explore and to understand the molecular as well as ionic level of interfaces of ILs prevailing in solvent systems by studying their thermodynamic properties based on various physicochemical approach.

1.1.1 Importance of Physicochemical Parameters

The nature of intermolecular interactions present in the studied system can be understood in terms of derived parameters based on the physicochemical approach.

Apparent molar volumes obtained from density measurements, are usually expedient parameters for interpreting ion-solvent/solute-solvent and ion-ion/solute-solute interactions in solution. Ionic apparent molar volume for the individual ions has been obtained with the help of “*reference electrolyte*” method. The compressibility, a second derivative to Gibbs energy, is also a sensitive indicator of molecular interactions, which provide useful information in such cases where partial molar volume data alone cannot provide an unequivocal interpretation of these interactions.

The change in viscosity of solutions by the addition of electrolyte is attributed to inter-ionic and ion-solvent effects. The viscosity *B*-coefficients are also separated into ionic components by the ‘*reference electrolyte*’ method and from the temperature dependence of ionic values, a satisfactory interpretation of ion-solvent interactions such as the effects of solvation, structure-breaking or structure-making, polarization, etc. has been given.

The transport properties in most cases are studied using the conductance data, especially the conductance at infinite dilution. Conductance data obtained as a function of concentration can be used to study the ion-association with the help of appropriate equations. The limiting ionic conductance of the each ion has been calculated from the same method “*reference electrolyte*” using tetrabutylammonium tetraphenylborate. The ionic conductances also play the crucial role to the interpretation of the ionic level of interaction, association or ion-solvent interactions of ions as well as molecules.

The spectroscopic study has been established by the investigation of FTIR spectroscopy. The study has been taking into account to qualitative interpreting the molecular as well as ionic association of the electrolytes in the solutions.

1.1.2 The main objectives of our work

My research work is:

- ✓ To investigate the host-guest inclusion complex formation between cyclic Host and various significant Guest molecules by suitable technique.
- ✓ To perform stability studies on guest and its complex with cyclodextrin.
- ✓ To find out solvation behaviour of some significant molecules.
- ✓ To understand the different type of interactions present in the inclusion complexes.
- ✓ To collect detailed information about the nature and strength of various interactions.
- ✓ To employ Host-Guest complexes in various field of science.
- ✓ To examine the transport properties of ionic liquids in industrially important solvents along with thermodynamic studies to characterize molecular interactions in solutions.

I.2. CHEMICALS USED

The name of the significant molecules which have been used throughout the research work are ionic liquids (Benzyltrimethylammonium chloride, Benzyltriethylammonium chloride, Benzyltributylammonium chloride, 1-ethyl-3-

methyylimidazolium chloride, 1-methyl-3-octylimidazolium tetrafluoroborate), drug molecules (Amantadine hydrochloride, Sulfanilamide, Metoclopramide Hydrochloride), cyclic compounds (α -cyclodextrin, β -cyclodextrin, 18-crown-6, Dibenzo-18-crown-6, Dicyclo-18-crown-6)

The solvents which have been used during the research work are Water, Methanol, Acetonitrile, Dichloromethane, Tetrahydrofuran. The detailed description has been given in *Chapter III*.

I.3. METHODS OF INVESTIGATION

Existence of free ions, solvated ions, ion-pairs and triple-ions of the electrolytes/non-electrolytes in aqueous and non-aqueous media depends upon the concentrations of the solution, size of ions, and *intermolecular forces*, e.g., electronegativity of the atom, dipole-dipole forces, dipole-induced dipole forces, H-bonding, Van der Waal forces, columbic forces and electrostriction, +I, -I effect, side chain effect etc. Hence, the study of assorted interfaces and equilibrium of ions in diverse concentration regions are of immense importance to the technologist, theoretician, industrialist, researchers as most of the chemical processes take place in these systems.

Interestingly the different experimental techniques have been employed to find out a better understanding the occurrence of solvation and different interactions prevailing in solution. Therefore, we have employed the five significant physicochemical methods, viz., conductometry, volumetry, viscometry, and refractometry to explore the solvation phenomena and NMR, FT-IR, UV-vis and Fluorescence spectroscopy to characterize the inclusion complex.

I.4. SCOPE OF THE PRESENT WORK

Among the macrocycles constituting the great class of 'hosts' in supramolecular chemistry, cyclodextrins are the most attractive as they possess a unique molecular architecture, with a hydrophilic exterior and a hydrophobic interior. Though there are many cavitand host molecules such as calixarenes, crown ethers, cucurbiturils *etc.*,

cyclodextrins are very special as they can complex with a broad spectrum of guest molecules of appropriate size, shape and polarity. The physicochemical characteristics of guest molecules are beneficially modified after inclusion into these elegant 'organized' assemblies. Among all potential hosts, cyclodextrins have been extensively utilized as confined media to modify organic reactions, to achieve selectivity to a greater extent and this plays a key role in organic syntheses.

Cyclodextrin can form inclusion complexes with various biologically active guest molecules, among them drug-CD formulations are very significant and important because of the enhanced solubility, bioavailability and stability of drug molecules after complexation with CD. Structural characterization is of particular significance for these supramolecular host-guest complexes, which are the basis of most CD applications in medicine, catalysis or in food chemistry, separation and sensor technology. Pharmaceutical uses of CDs for drug protection or targeting now legally require structural characterization of the administered compounds. To gain insight of reactivity and selectivity in organic reactions and also to understand the binding behavior of this unique host system, the present work "Inclusion complex formation", is carried out by physicochemical characterization of CD complexes with various analytical techniques.

Supramolecular chemistry i.e. host-guest complex formation through noncovalent interactions offer the basis for novel approaches in medicine and also helps in understanding the interactions present in living systems. Hence in **Chapter IV** size, shape, structural effect of ionic liquids in the formation of the inclusion complexes have been studied quantitatively and qualitatively to find the nature of host-guest inclusion complexes of consecutive cationic surface active ionic liquids, benzyltrialkylammonium chloride with β -cyclodextrin in aqueous media using surface tension, conductance and NMR study. It is expected to provide important conclusions and results on binding behavior, importance of hydrogen bonding and the role of hydrophobic group in complex formation.

Crown ether-ammonium complexes are of fundamental interest as prototypical systems involving multiple hydrogen bonds. Study of these simple multiply-bound complexes is a promising means of gaining insight into much more complex macromolecular systems, such as those involved in protein folding or in the pairing of

nucleo bases in polynuclear nucleic acids. In **Chapter V** conductance study, surface tension study and density study of the complex formed between amantadine hydrochloride (ADH) and 18-crown-6 (18C6) in methanol solution was reported and discuss the influence of several structural and medium parameters on the complexation reaction. The study (carried out for the first time) is expected to provide information on the potential utility of this substrate for optoelectronic applications. It was also found that host-guest complexation with crown ethers resembles an established principle i.e. the hydrogen bonding acceptance as well as the donation propensity of crown ethers.

In **Chapter VI**, we have investigated on conductometric properties of the ionic liquid 1-butyl-3-methylimidazolium chloride in polar aprotic solvents acetonitrile (ACN), tetrahydrofuran (THF), dichloromethane (DCM) at different temperatures. The experimental data was analysed using Fuoss conductance equation and Fuoss-Kraus theory to calculate the ion pair formation constant K_p and triple ion formation constants K_T . The main purpose of this study is to obtain experimental and quantitative information for the interactions between the ions. Here the ion pair formation constants are expected to reflect strongly the direct interactions between the ions.

Crown ethers have proved to be unique cyclic molecules for molecular recognition of suitable substrates by hydrogen bonds, ionic interactions and hydrophobic interactions. The study of interactions involved in the complex formation is important for a better understanding of the mechanism of biological transport, molecular recognition, and other analytical applications. In this **Chapter (VII)**, we have studied the complexation of Sulfanilamide with three different crown ethers (1) Dicyclohexano-18-crown-6 (DC18C6) (2) 18-crown-6 (18C6) and (3) Dibenzo-18-crown-6 (DB18C6) in acetonitrile (ACN). The complexes were characterized by ^1H NMR, IR and UV-visible spectra.

Metoclopramide hydrochloride is used as an anti-emetic in the treatment of some forms of nausea and vomiting and to treat heartburn caused by gastroesophageal reflux in people who have used other medications without relief of symptoms. Metoclopramide hydrochloride have a greater impact on the treatment of disorders of the gastrointestinal tract. Since metoclopramide has been confirmed as an effective drug in treating and preventing various types of disease hence the stabilization and

regulatory release of this drug is of great concern in pharmacology. Thus to protect these drugs from external effects and to reduce side effects for their regulatory release, it is crucial to investigate whether they can be encapsulated into the cyclodextrin molecule. Hence in **Chapter VIII**, the inclusion complex formation of metoclopramide hydrochloride with both α and β -cyclodextrins (CDs) was studied in detail based on physicochemical and spectroscopic measurements. The factors affecting the inclusion process were discussed. Enhanced fluorescence and absorption characteristics served as an aid for better understanding the inclusion mechanism, including the size/shape-fit, hydrophobicity. Especially, detailed spatial information in solution has been studied by ^1H NMR.