

CHAPTER I

Necessity of the Research Work

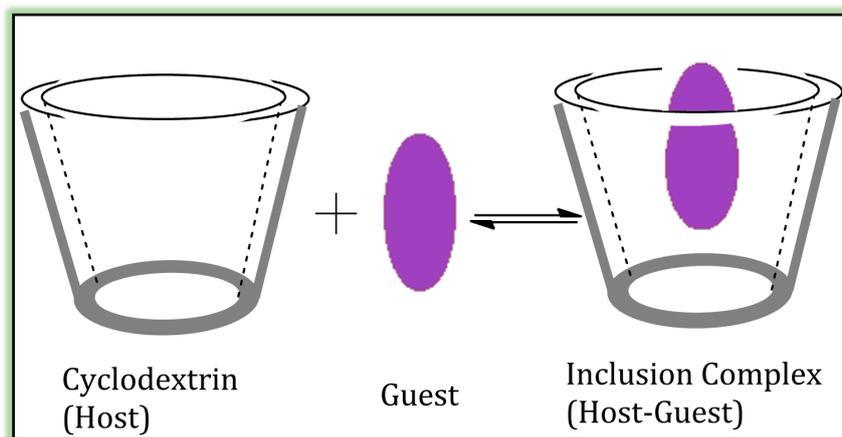
1.1. OBJECTIVE, IMPORTANCE AND APPLICATION OF THE RESEARCH WORK

In host-guest or supramolecular chemistry, an inclusion complex is a compound in which one chemical compound that known as “Host” having cavity like character in which molecules of a second “Guest” compound can be encapsulated [1-2]. Host-guest chemistry describes about the complexes that are held together in unique structural relationship by some non-covalent bonds rather than full covalent bonds. There are four commonly mentioned types of non-covalent interactions: hydrogen bonds, ionic- bonds, vander Waals forces, and hydrophobic interactions [3].

The studies on supramolecular chemistry give a broad idea about the formation of inclusion complex between the host and the guest molecules. Thus, most of this interaction has been performed by host-guest interaction. Among the host molecules, cyclodextrin seems to be the most promising to form inclusion complexes, especially with various guest molecules (drugs, amino acids, ionic liquids, vitamins, etc.) with suitable polarity and dimensions. Here I have investigated the inclusion behavior of some drug molecules, amino acids, ionic liquid (guest) with β -cyclodextrin, α -cyclodextrin and crown ethers in my various works.

Cyclodextrins (CDs) are cyclic oligosaccharide of glucopyranose units that play an important role as a host in inclusion complexes, where non-covalent interactions are involved. Cyclodextrins (cyds) are well known non-toxic truncated macrocyclic host molecules, consisting of (α -1, 4) linked by glucopyranose units [4]. Cyds are commercially accessible in the form of α , β and γ with varying the number of glucose units namely six, seven and eight respectively. Cyds with lipophilic inner cavities and hydrophilic outer surfaces are capable of interacting with a large variety of

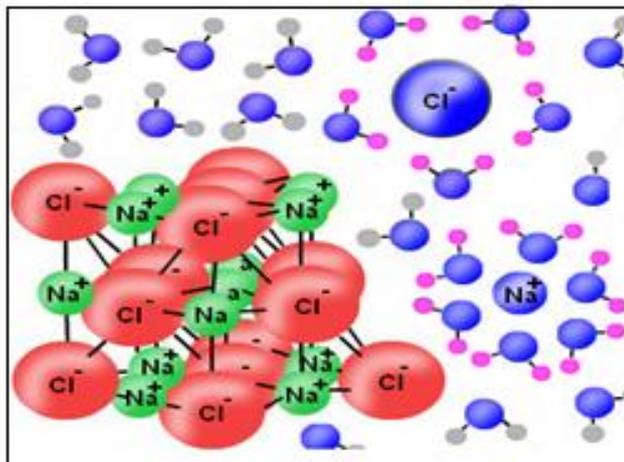
polar and non-polar guest molecules to form inclusion complexes. No covalent bonds are formed or broken during complex formation and in aqueous solution, the complexes are readily dissociated and free guest molecules are in equilibrium with the molecules bound within the cycl cavity. This is a dynamic process whereby the guest molecule continuously associated and dissociated from the host cycl. Cyds are proficient enough to form water soluble inclusion complexes with many lipophilic water insoluble guest molecules and also improve the physicochemical properties of guest molecules [5-7]. CDs have been widely employed for encapsulation of several substances, being used in food, cosmetic and pharmaceutical industries, pesticides, toilet articles, textile processing and other industry, supramolecular and host-guest chemistry, models for studying enzyme activity, molecular recognition and molecular encapsulation, studying intermolecular interactions and chemical stabilization. In addition, cyclodextrins can be used to reduce gastrointestinal drug irritation, convert liquid drugs into microcrystalline or amorphous powder, and prevent drug–drug and drug–excipient interactions.



Crown ethers are the macrocyclic polyether and one of the most prominent molecules in host–guest chemistry, often called the simplest benchmark substrates resembling the general features of key-pocket inclusion complexes [8]. The most

significant and exceptional property of the macrocyclic “crown compounds” is their affinity to form complexes with various class of guest species e.g. metal ions, amino acids, ionic liquids [9-13]. Crown compounds have many applications in analytical chemistry. Cyclic polyethers have been used largely in the determination and separation of first and second main group elements of the periodic table [14-16]. Applications of crown ethers such as phase transfer catalyst [17-18], photo-switching devices [19] and drug carrier [20] have been in progress on the basis of the inclusion phenomena. Different ring sizes as well as type, number, ring substitution(s), and position of the donor atoms in the ring also allow adapting a heterocyclic carbocation through the developing of π -stacking, charge-transfer, H-bonds, ion-dipole interactions between the binding partners [21-24].

A “solution” is a homogeneous mixture of two or more substances, i.e. when small amount of a substance, called solute (solid, liquid and gas) dissolves to a certain limit in liquid or solid substance called solvent. Solvation is the process of strong attraction and association of molecules of a solvent with molecules or ions of a solute, and the strength and nature of this interaction influences many properties of the solute, including stability, solubility, and reactivity in the solution. One may also refer to the solvated state, whereby an ion in a solution is surrounded or complexed by solvent molecules. Solvation is the process of reorganizing solvent and solute molecules into solvation complexes. Solvation involves bond formation, hydrogen bonding, and van der Waals forces (which consist of dipole-dipole, dipole-induced dipole, and induced dipole- induced dipole interactions). Ion solvation is important to many topics of chemical interest, including surface chemistry, environmental chemistry, industrial chemistry, engineering field and the study of molecules such as surfactants, polyelectrolytes etc.



In “solution Chemistry”, there are three different kinds of methods have been used to characterize the solvation behavior. The first method have been used to study conductance, density, viscosity, surface tension etc. of electrolytes and the derivation of various factors associated with ionic solvation, 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, and the third is to use spectroscopic measurements where the spectral solvent shifts or the chemical shifts determine their qualitative and quantitative nature.

In recent year, there are many interesting works has been reported based on the study of interactions and physicochemical properties of solvent-solvent and solute-solvent systems. In order to the gain the mechanism of such interactions thermodynamics, transport and spectroscopic studies on ternary solvent systems are extremely valuable. These properties provide important information about the strength and nature of the intermolecular forces operating among mixed components [25-29].

Drugs, amino acids and Ionic liquids that have been used in my research work considered as the vital compounds. The term 'vital' is mostly used for the special

case of important compounds. To understand the physicochemical properties of these vital compounds in different environments i.e. in solution as well as in solid state, I have measured various experiments.

Drug(s) transport across the biological cell and membranes is dependent on its physicochemical properties. But direct study of the physicochemical properties in physiological media such as blood, intracellular fluids is difficult to understand. One of the well-organized approaches is the study of molecular interactions in both solution and solid states by different physicochemical contrivances are convenient for interpreting the intermolecular interactions. The study of thermodynamic and other properties such as stability, solubility, bioavailability, etc of a drug in suitable medium can be correlated to its therapeutic effects and potentially introduced a new prospect and hope in drug delivery systems and also in research field [30-33].

Amino acids are the building blocks of proteins and muscles tissue and they also play a vital role in physiological process relating to our energy, mood, brain function, and muscle and strength gains and also in our quest for fat loss. There are 23 amino acids 9 of these are classified as essential or indispensable amino acids (IAA) that must be supplied from our outside nutritional intake. The others are termed as non-essential or dispensable amino acids (DAA) as body being able to synthesize them itself from other amino acids. Among them six amino acids are considered as conditionally essential, meaning their synthesis can be limited under special pathophysiological conditions, such as prematurity in the infant or individuals in severe carbolic distress then body demands them in larger amount [34-35]. So, careful use of amino acids can slow or temporarily prevent our many health problems. In this purpose cyclodextrin may play an important role as it acts as an efficient good and safe drug carrier in human body [36-38].

Ionic liquids (ILs) belong to the family of those organic compounds which are nano-structured molten salts at room temperature and having cationic organic part and anionic inorganic/organic part and are liquid at ambient temperature. IL(s) has been widely studied as replacement for volatile organic solvent in various reactions. An essentially attractive advantage of ionic liquids is their non-flammability, negligible vapor pressure, high electrical conductivity, adjustable polarity, selective catalytic effects, ability of dissolving large variety of compounds [39-43] and solvation interactions with organic and inorganic compounds can be generated significant interesting applications in wide range of industries and science [44-46] and process such as biology, supramolecular chemistry [47-49], separation of amino acids, electrochemistry, synthesis etc [50-53].

The understanding of the behavior of ILs and their properties is vital for any practical application. But the available chemical and physical data are unfortunately limited in comparison to the amount of already commercially available ILs. Moreover, the existing data are often inconsistent. In this work we pay attention on the reliable determination of thermodynamic properties of ILs using different independent methods.

The physical and chemical properties between the selected molecules in both solution and solid phase are a result of the strength of their intermolecular interactions and the forces between molecules arise from the same source: different charges on adjacent molecules that lead to electrostatic attractions and governed by Coulomb's law. Partial charges acquired by molecules result in dipole-dipole forces, dipole-induced dipole interactions, hydrogen bonding, etc. and are jointly termed as intermolecular interactions. Intermolecular interactions in a solution control their thermodynamic properties that are measurable and

understanding of the solvation thermodynamics is essential to the characterization and interpretation of any process carried out in the solution phase. We are focusing on different binding interactions and trying to develop scientific experiments to specify the fundamental origins of these non-covalent interactions by utilizing various techniques such as conductance, surface tension, density, NMR spectroscopy, fluorescence and UV-Vis spectroscopy along with powder XRD, SEM, TGA methods. The experimental data are used to measure qualitatively and quantitatively the ion-solvent ion-ion and molecular interaction in different ion-association and host-guest inclusion complex systems and also used to explain binding constants K_a , Gibbs free energy (ΔG_o), Enthalpy (ΔH_o), and entropy (ΔS_o).

Hence, the main objectives of the present research works are

- ✓ To investigate and understand the formation of inclusion complexes and their mechanism, behaviour and importance which may helpful in various field of science.
- ✓ To understand the different type of interactions present in the inclusion complexes.
- ✓ To perform stability studies on guest and its complex with host.
- ✓ To collect detailed information about the nature and strength of various interactions prevailing by physicochemical and transport properties of ionic liquids to understand molecular interactions in solutions.

I.2. SELECTION AND IMPORTANCE OF CHEMICALS USED

In host- guest phenomena water, acetonitrile, ethanol has been chosen as solvent in this research work because these solvents are industrially very important and dielectric constants giving us an optimum environment for the study.

As “Host” I have chosen crown ether (18-Crown-6, Dibenzo-18-Crown-6), alpha cyclodextrin, beta cyclodextrin, because they have polar hydrophilic outer shell and relatively hydrophobic inner cavity and they can build up stable host-guest inclusion complexes by accommodating the non-polar component of the guest molecule in their hydrophobic cavity and stabilizing the polar part of the guest molecule by their polar part and obviously because of their biocompatibility, relatively non-toxicity and relatively low price.

As “Guest” I have preferred various vital molecules such as: amino acids (L-Methionine, L-Proline, L-Glutamine); different drugs molecules (Diethyl phenylmalonate, nortriptyline hydrochloride, Padimate O), ionic liquid (1-ethyl-1-methylpyrrolidinium hexafluorophosphate) because of their huge applications in pharmaceutical, medicinal and cosmetics industries.

In solvation effect study I have selected amino acids (L-tyrosine and L-phenylalanine) as solute and aqueous solution of ionic liquid (1-butyl-3-methylimidazolium octylsulphate and 1-methyl-3-octylimidazolium chloride) as solvent because both have enormous applications in different field and industries.

The detailed descriptions have been given in **CHAPTER III**.

I.3. METHODS OF INVESTIGATIONS

It is of interest to utilize different experimental techniques to get a better approaching into the phenomena of host-guest inclusion complex and different

interactions prevailing in solution. I have, therefore, performed the following important methods to explore the inclusion phenomena and solvation effect.

- Conductometry
- Surface tension
- Densitometry
- NMR (1H NMR, 2D ROESY and ¹³C NMR) spectroscopy
- FTIR spectroscopy
- UV-Vis spectroscopy
- Fluorescence spectroscopy
- Powder x-ray diffraction (PXRD),
- Scanning Electron Microscopy (SEM),
- Mass analysis (ESI-MS) and
- Thermal gravimetric analysis (TGA)

I.4. PHYSICOCHEMICAL PARAMETERS AND METHODS OF INVESTIGATIONS

➤ Limiting molar conductance (Λ_0) obtained from specific conductance as well as molar conductance gives a central idea about the formation of inclusion complexes and interaction of ion-solvent in the solution. More the magnitude of conductance of the solution less is the ion-solvent interaction. Another parameter obtained from the conductance study i.e. association constant (K_a) gives an idea about the binding behaviour of a molecule or ions with solvent molecules.

➤ The surface tension experiment has been done by platinum ring detachment method using a Tensiometer (K9, KRÜSS; Germany) at the experimental temperature. The accuracy of the measurement is within $\pm 0.1 \text{ mN}\cdot\text{m}^{-1}$. Temperature

of the system has been maintained by circulating auto-thermostated water through a double-wall glass vessel containing the solution.

➤ Apparent molar volume (ϕ_{v^0}) is calculated from experimental density results. The sign and magnitude of apparent molar volume (ϕ_{v^0}) provides information about the nature and magnitude of solute-solvent interaction while the experimental slope (S_v^*) provides information about solute-solute interactions.

➤ Nuclear Magnetic Resonance (NMR) spectroscopy is a research technique that exploits the magnetic properties of certain atomic nuclei. It determines the physical and chemical properties of atoms or molecules. It can provide the thorough information about the structure, the kinetics or dynamics of molecules, reaction state and chemical environment of molecules. NMR spectra are unique, well resolved and highly predictable for sample molecules. Thus, NMR spectroscopy ($^1\text{HNMR}$, 2D ROESY and $^{13}\text{CNMR}$) analysis is used to confirm the identity of a given sample.

$^1\text{HNMR}$ is the application of NMR spectroscopy to hydrogen-1 nuclei within a molecule in order to determine the structure of the given molecule.

2D ROESY (Rotating-frame Overhauser Spectroscopy) experiment is useful for determining which signals arise from protons that are close to each other in space although they are not bonded. ROESY spectrum contains a diagonal and cross peaks. The diagonal consists of the 1D spectrum and the cross peak signals arising from protons that are close in space.

$^{13}\text{CNMR}$ is the application of NMR spectroscopy to carbon. It is just analogous to $^1\text{HNMR}$ spectroscopy and allows the identification of carbon atoms in a given sample as the detection of hydrogen atoms in $^1\text{HNMR}$.

➤ Fourier transform infrared spectroscopy (FTIR) is a method which is used to get an infrared spectrum of absorption or emission of a solid, liquid or gas. An FTIR

spectrometer collects high spectral resolution data over a wide spectral range at the same time. Infrared spectroscopy involves the interaction of infrared radiation with the given sample. It exploits the fact that molecules absorb frequencies that are attribute of their structure. These absorption occur at resonance frequencies i.e. the frequency of the absorbed radiation matches the vibrational frequency.

➤ Ultraviolet-visible spectroscopy or ultraviolet-visible spectrophotometry (UV-Vis) indicates absorption spectroscopy or reflectance spectroscopy in the ultraviolet-visible spectral region. This means it uses light in the visible and adjacent (near-UV and near-infrared) ranges. The absorption or reflectance in the visible range directly affects the supposed color of the chemicals involved. In this region of the electromagnetic spectrum, molecules undergo electronic transitions. Molecules containing π -electrons or non-bonding electrons (n-electrons) can absorb the energy in the form of ultraviolet or visible light to excite these electrons to higher anti-bonding molecular orbital. The more easily excited the electrons (i.e. lower energy gap between the HOMO and the LUMO), the longer the wavelength of light it can absorb. There are four possible category of transitions viz. π - π^* , n- π^* , σ - σ^* , n- σ^* . The term λ_{\max} indicates the wavelength of the most intense Uv-Vis absorption. The value of λ_{\max} has been used to correlate the types of bonds and functional group(s) in a given molecule. The spectrum by itself is not a definite test for any given sample, the nature of solvent, pH of solution, temperature, high electrolyte concentrations and the presence of interfering substances can influence the absorption spectrum. Thus, these variables must be taken into account for in order to identify the absorption for any given sample.

➤ Fluorescence spectroscopy (fluorometry or spectrofluorometry) is one kind of electromagnetic spectroscopy that analyzes fluorescence from a given sample. It involves using a beam of light, usually ultraviolet light, that excites the electrons

in molecules of certain compounds and causes them to emit light; typically, but not necessarily, visible light. A complementary technique is absorption spectroscopy. In the special case of single molecule fluorescence spectroscopy, intensity fluctuations from the emitted light are measured from either single fluorophores, or pairs of fluorophores. In fluorescence spectra measurement, the wavelength of the excitation light is kept constant, preferably at wavelength of high absorption, and the emission monochromator scans the spectrum.

➤ X-ray powder diffraction (PXRD) is a common analytical methods mostly applied for phase identification of a crystalline or microcrystalline material. It can provide information on unit-cell dimensions. The diffraction technique is based on generation of X-ray in X-ray tube. These X-rays are directed at the sample and the diffracted X-rays are then detected, processed and counted. By scanning the sample through the range of 2θ angles, all probable diffractions of the sample are obtained due to the random orientation of the powdered material. The direct proof for the complexation between host and guest molecule can be obtained from the analysis of powder XRD spectrum.

➤ Scanning electron microscope (SEM) is a form of electron microscope that creates images of a sample by scanning the surface with a focused beam of electrons. The electrons interact with atoms in the sample, producing various signals that contain information about the sample's surface topography and composition. The electron beam is scanned in a raster scan pattern, and the beam's position is combined with the detected signal to produce an image. SEM can achieve resolution better than 1 nm (nanometer). Specimens can be observed in high vacuum in conventional SEM, or in low vacuum or wet conditions in variable pressure or environmental SEM and at a wide range of cryogenic or elevated temperatures with

specialized instruments. It is very well known technique for analyzing the surface morphological texture and particle size of solid materials.

➤ Mass spectrometry (MS) is an analytical technique that ionizes chemical species and the spectrum is a plot, representing intensity vs. m/z (mass-to-charge ratio) of a sample. In simpler terms, a mass spectrum measures the masses within a sample. Mass spectrometry is applied in many different fields. It is very useful method to characterise the stoichiometry of the systems involving mixed host-guest stoichiometry (1:1, 1:2, 2:1) or mixtures of guests competing for a single host molecule. These spectra are used to determine the elemental or isotopic signature of a sample, the masses of particles and of molecules and to clarify the chemical structures of molecules.

➤ Thermo (or thermal) gravimetric analysis (TGA) is a technique of thermal analysis in which the mass of a sample is considered over time as the temperature changes. This analysis provides information about chemical and physical phenomena such as: thermal decomposition, chemisorptions, phase transition, absorption and desorption. TGA is used to evaluate thermal stability of a given sample, therefore, in a desired temperature range, if a material is thermally stable, there will be no observed mass change. TGA is considered as reliable and relatively fast method to measure the thermal properties of host-guest inclusion complex materials.

I.5. REFERENCES

References of CHAPTER I are given in BIBLOGRAPHY (Page: 217-219).