CHAPTER I

INTRODUCTION

A brief description of solution and supramolecular chemistry is provided in this chapter. The chapter mainly addresses a comprehensive review of supramolecular assembly based on cyclodextrin, its numerous applications, especially with regard to drug delivery and other biological contexts, and the diverse molecular interactions that occur between ionic liquid and amino acids and also with azo dye in aqueous medium. The primary objectives of the thesis are addressed along with the general characteristics of cyclodextrin-based inclusion complexes, their characterization, and the significance of their hybrids. The chapter concludes with a brief discussion of the objective, scope, goals, and applications of our research.

NECESSITY OF THE RESEARCH WORK

I.1. Objective, Scope and Applications of the Research Work

Research is undertaken to contribute to science by the methodical collecting, interpretation, and assessment of data. Research generates fresh knowledge and understanding. Human beings perform research as part of the world's progress. A significant amount of research focuses on the interplay between matter and living things since matter and living beings make up the world.

Jean-Marie Lehn introduced the phrase supramolecular chemistry, and he got the Nobel Prize for his major contribution in this field in 1987, along with Pedersen and Cram[1]. It is a growing subject in chemistry and material science, which can be characterized as the chemistry of molecular assemblages and the chemistry of non-covalent bonds. Supramolecular complexes have a unique advantage of enabling the clarification of the presence and limitations of binding energy additivity, which is generally taken for granted in applications like sensible drug design. Another benefit is because in normal supramolecular complexes, numerous contacts participate, and the translational entropy loss for any intermolecular interaction is already compensated by a single association step. Inclusion complexes are stabilized by non-covalent forces such as Van der Waals contacts, electrostatic interactions, π-π stacking, hydrogen bonding, and hydrophobic interactions (6). Supramolecular chemistry is a vast topic that includes

molecular self-assembly, molecular recognition, host-guest chemistry, molecular machines, and dynamic covalent chemistry.

Fischer recognized the lock and key idea in 1894, which laid the groundwork for supramolecular chemistry.[2] The word supramolecule was coined in the 1930s, following the discovery of molecule aggregation via intermolecular interactions. During the 1950s, comprehensive works on cyclodextrins by Cramer, Pedersen in the 1960s on the host-guest complexes of crown ether compounds, and Cram on spherands, cavitands, and recently box-like container molecules discovered by Stoddart speed up study in the field of supramolecular chemistry.[3,4]

In recent years, supramolecular chemistry is divided into three broad categories; (a) host-guest chemistry (b) clathrates and (c) self-assembly depending on size and shape. In host-guest chemistry, host molecules, also known as cavitands, are molecular entities with persistent intramolecular cavities (e.g., cyclodextrins, calixarenes, and cucurbiturils) that encase guest molecules [5]. Clathrates are lattice-structured complexes formed when two or more host molecules form a gap between them, creating an extramolecular cavity. Self-assembly is another supramolecular structure involving two molecules that do not fit the standard categories of host or guest [6,7]

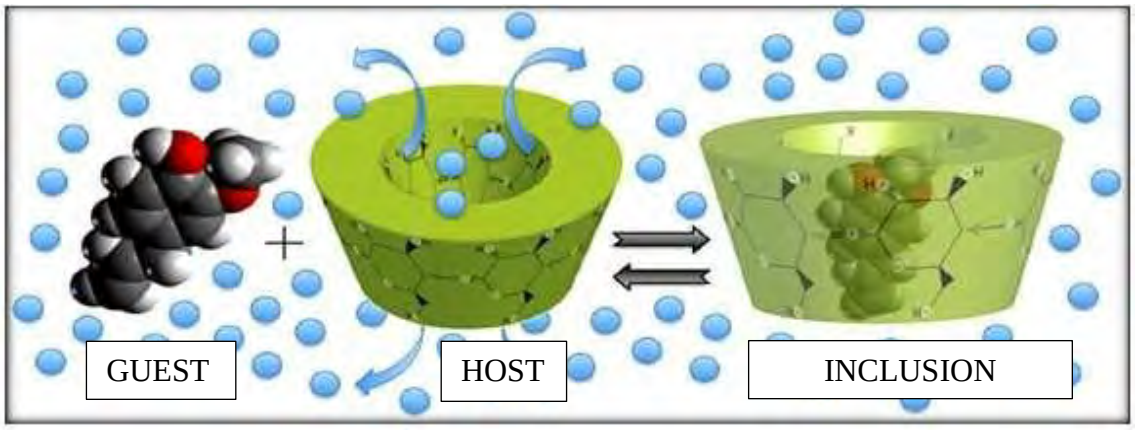

Figure 1: Schematic illustration of host-guest supramolecular inclusion complex

Supramolecular Host-Guest chemistry concerns about non-covalent binding or complexation between a host and a guest as depicted in **Figure 1**. The host is commonly defined as a large molecule or aggregate such as an enzyme or synthetic cyclic compound that possess a sizeable, pre-organized central hole or cavity such as CDs, calix[n]arenes, crown ethers, etc. [8,9]. The guest may be an organic or inorganic cation, a simple inorganic anion, an ion pair, or a more complicated organic molecule such as anticancer

drug [10, 11]. Our mother nature is also full of natural host-guest systems that includes antigen-antibody, DNA-ligand, enzyme-substrate, and protein-carbohydrate complexes [12,13]. Cyclodextrins, calixarenes, crown ethers, cucurbiturils, and other macrocycles are examples of macrocyclic hosts [14,15].

Cyclodextrins (CDs) are particularly noteworthy in this regard due to their amphiphilic properties [16]. Amphiphiles are of interest because of their ability to self-assemble in aqueous systems to create well-defined structures such as nanotubes, nanorods, nanosheets, micelles, and vesicles, which can be used in a variety of disciplines such as drug delivery, nanodevices, and cell imaging [17, 18]. Cyclodextrin-modified nanoparticles have received a lot of attention in recent years due to the fact that they significantly improve the properties of the assemblies, such as conductance, electronic, fluorescence, catalytic, and thermal properties, causing these assemblies more appropriate for use as nanosensors and drug delivery vehicles [19,20]. Consequently, a variety of sophisticated probes have been designed for applications in the manufacturing of molecular machines, molecular switches, supramolecular polymers, chemosensors, transmembrane channels, molecule based logic gates, and other interesting host−guest systems [21,22].

Cyclodextrins (CDs) are Starch-derived molecules that may have six (α-CD), seven (β-CD), eight (γ-CD), or more (α-1,4)-linked α-d-glucopyranose units. They are harmless nanocarriers known as cyclic oligosaccharides [23]. The external surface of CDs is hydrophilic, whereas the interior cavities of cyclodextrins are slightly hydrophobic. CDs can operate as hosts for both polar and nonpolar guests, such as tiny molecules and various medicinal compounds [24]. Because of their binding capabilities, different CDs can form stable inclusion complexes with a variety of biologically active molecules, including medicines and food components [25,26].

In this study, α-cyclodextrin and HP-β-cyclodextrin with 6 and 7 glucopyranose units were chosen as host molecules because of their excellent inclusion efficiency, suitable cavity dimensions, low cost, and low toxicity [27]. CDs have found widespread use in medicines, food industries, cosmetics [28], tissue engineering, and biomedical devices. Inclusion complexation within the non-polar cavity of CDs is used to protect the hydrophobic part of various bioactive molecules, enzymes, drugs, volatile organic compounds, essential oils, taxols, flavonoids, vitamins [29], and so on, in order to

increase their light, air, and thermal stability, improve water solubility, bioavailability, and shield against side effects.

Pharmacology is increasingly concerned with medication stabilization and controlled release. To protect therapeutic molecules from environmental impacts and prevent side effects, controlled release requires encapsulation in cyclodextrin molecules. 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 (β-CD) has been studied.

This thesis explores the encapsulation of BNZ in the HP-β-CD cavity.In this study, we employed Benserazide hydrochloride (BNZ), a medicine used to treat Parkinson's disease, parkinsonism, and restless leg syndrome.[30,31] It is used to treat Parkinson's disease in conjunction with L-DOPA and is listed as an essential drug by the World Health Organization. Benserazide prevents the aforementioned decarboxylation, and because it cannot cross the blood-brain barrier, it permits dopamine to accumulate only in the brain. As a result, the negative effects of peripheral dopamine, such as vasoconstriction, nausea, and arrhythmia, are reduced.[32,33] The incorporation of BNZ into the cavity of HP-β-CD has been investigated in both solid and solution phases. This work explores the development and stabilization of the BNZ-HP-β-CD complex, which will help deploy encapsulated pharmaceuticals in the pharmaceutical industry.

Adiphenine hydrochloride (ADP), also known by the chemical name 2-diethylaminoethyl diphenylacetatehydrochloride, is an antispasmodic with a smooth muscle relaxing effect similar to papaverine and a nicotinic receptor inhibitor [34, 35]. As a result, it is used to relieve uterine, gastrointestinal, and womb spasms [36]. Furthermore, some research [37] look at the treatment of respiratory disorders [38], Parkinson's disease, and antipasmodics.This study examines the integration of Adiphenine hydrochloride into aqueous HP-β-CD, focusing on its encapsulation within the cavity. Several reliable ways have been employed to create, stabilize, transport, and control the release of adiphenine hydrochloride without the need for chemical modification.

D-Pantothenic Acid hemicalcium salt, is a water-soluble B-complex vitamin.. It can be found in a variety of foods. Calcium salt is employed because free acid is

hygroscopic and unstable in a wide range of foods. The calcium salt is used because free acid is unstable and hygroscopic. D-Pantothenic acid hemicalcium salt (Vitamin B5 calcium salt), a vitamin, that can lower the patulin level in apple juice.

The hemi-calcium salt of D-pantothenic acid in water is the amide of pantoic acid and alanine, making it a 99 percent analytical reagent. Pantothenic acid, often known as vitamin B5, is a water-soluble vitamin that is required for optimal nutrition. It is commonly found as an alcohol analogue, a calcium, and the provitamin panthenol. Pantothenic acid is required for the production and metabolism of proteins, carbohydrates, and fats in mammals

This study investigates the incorporation of D-Pantothenic acid hemicalcium salt in aqueous α-CD. Several reliable techniques such as 1H NMR, FT-IR, DSC, SEM, and TGA studies have been employed to create, stabilize, transport, and control the release of D-Pantothenic acid hemicalcium salt without the need for chemical modification.

Ionic liquids (ILs) are employed as greener organic solvents with a broad chemical window and are liquid at or near room temperature in their pure form. They have been widely used in a variety of sectors, both academic and industrial. It has several advantages, including a low melting point (<373 K), being liquid across a wide temperature range, thermal stability, acceptable viscosity, the capacity to dissolve a variety of substances, and minimal vapour pressure [39, 40]. Ionic liquids have been advocated as a green and safe alternative to typical volatile organic solvents. It has an increasing number of applications in several scientific domains, including catalysis, separation processes, chemical reactions, electrochemistry, nanoscience, and bioscience [41,42].

Because proteins' physicochemical properties and interactions cannot be studied directly due to their complicated conformation and configuration, amino acids, the structural building blocks of proteins, are frequently used as model substances to investigate the effects of additives on proteins. The various valuable thermodynamic data of aqueous solutions of small-chain amino acids are very much needed for the pharmaceutical and food industries to develop the design and operation of unit operations, as surface tension and volumetric properties are very important for understanding the multiplied phase transport processes.

The chemicals, which are used in this study, find wide industrial usage. Benzyl tri-methyl ammonium chloride or BTMAC has lyophilic and hydrophilic groups and is soluble in water. In many biphasic organic transitions, it can be used as a phase transfer catalyst. It is also used in the agrochemicals, polymer and pharmaceutical industries. Also, BTMAC is used as a corrosion inhibitor in oilfields. Benzyl tri-ethyl ammonium chloride or BTEAC can be used in phase transfer catalysis (PTC) to catalyse polycondensation reactions to form high molecular weight polymers under bi-phasic conditions. It is used as a lipophilic phase-transfer catalyst.

L-asparaginase is commonly used to treat acute lymphoblastic leukemia, as it is believed that circulating L-asparagine provides energy to leukemic cells, which lack the ability to produce it themselves. However, the demand for L-asparaginase is associated with a number of issues, including hypersensitivity, antibody development, and the rebound phenomenon caused by the fast stimulation of hepatic L-asparagine synthetase [43].

The solution behaviour of L-Asparagine in two aqueous ionic liquid solutions, namely (Benzyl tri-methyl ammonium chloride; Benzyl tri-ethyl ammonium chloride), was investigated by measuring physicochemical parameters such as density, viscosity, refractive index, conductance, and surface tension. The apparent molar volume, viscosity A and B coefficients, and molar refraction at different temperatures and concentrations were used to determine the nature of the solution's interactions. The Masson equation, which explains solute-solute and solute-solvent interactions, is used to calculate the experimental slopes and limiting apparent molar volumes. Hepler's technique and dB/dT values were used to study the solutes' structure-forming and structure-breaking properties in the solvents. The viscosity parameters A and B generated from the Jones-Doles equation explained the solute-solute and solute-solvent interactions in solution.

The behaviour of many other biomolecules may be explained using amino acids as a model, and the technique has been expanded to elucidate the behaviour of other biological systems.

In this study, the interaction between Azo dyes and ILs is critical in the solvolization process to assure the stability of the dye-IL complexes. Taking these types of interactions (dye-macromolecules) in the aqueous medium into account, such physicochemical phenomena play an important role in dye transport and provide very

important information about the mechanism proposed by Betokens, in which the dye delivers its beneficial action to achieve the desired goal.

In acidic pH range, the tartrazine dye's azo group of tartrazine dye can undergo a distinct, two-step, two-electron reduction that is reversible; in a neutral medium, this reduction becomes quasi-reversible.Tartrazine's biological effects and removal from industrial effluents[12] have been the subject of much investigation because of its real-world associations with many health issues, including cancer, hyperactivity, asthma, itching, and headaches. Taking these types of interactions (dye-macromolecules) in the aqueous medium into account, such physicochemical phenomena play an important role in dye transport and provide critical information about the mechanism proposed by Betokens, in which the dye delivers its beneficial action to achieve the desired goal. Electron reduction is reversible in acidic pH ranges but becomes quasi-reversible in neutral media.[44] Tartrazine's biological effects and removal from industrial effluents have been extensively studied since it has been linked to a variety of real-world health issues, including hyperactivity, asthma, itching, migraines, and cancer.[45]

In this context, three ILs (BTMAC, BTEAC, BTBAC) which has long hydrophobic chain structure, and one anionic dye tartrazine in the aqueous medium has been used to determine the molecular interactions of the ternary (IL+H_2O+Azo dye) solutions which play a critical role in the complex's stability. When used in the fields of foodstuffs, cosmetics, textiles, and colouring, it increases the stability of the mentioned field. It is also used in the pharmaceutical industry to make vitamins, antacids, cold medications (including cough drops and throat lozenges), lotions, and prescription drugs that contain tartrazine as a constituent, and it is used in the treatment of cancer and other potential treatments. Several procedures have been used by the researcher to determine the interactions between the dye and ILs. As a result, we conducted various experimental techniques such as viscosity, density, refractive index, conductance, and surface tension of tartrazine in aqueous ILs solutions at various temperatures and molality of ILs to investigate the overall solute-solvent interaction, as well as to evaluate the effect of molality and temperature on the Physico-chemical behaviour of this azo dye (tartrazine) in the presence of ILs to continue our current work. 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.*)*, 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.

I.2. The selection of biologically active molecules, host molecules, ionic liquids, food preservatives, and solvents used in the research

Names of the Biologically Active Molecules, Host Molecules, Ionic Liquids, Amino Acids and Solvent molecules are listed below-

Biologically active Molecules:

- Adiphenine hydrochloride
- Benserazide hydrochloride
- D-Pantothenic acid hemicalcium salt

Host Molecules:

- α-cyclodextrin
- HP- β-cyclodextrin

Ionic Liquids:

- Benzyltrimethylammoniun chloride
- Benzyltriethylammoniun chloride
- Benzyltributylammoniun chloride

Amino Acids:

- L-Asparagine

Azo Dye

- Tartrazine

Solvents:

- Water
- Ethanol

I.3. Methods of Investigations Used in the Research Work

Name of the Investigation Methods are listed below:

- UV-vis Spectroscopy
- Fluorescence Spectroscopy
- Differential Scanning Calorimetry (DSC)
- Powder X-Ray Diffraction (PXRD)
- Scanning Electron Microscopy (SEM)
- FTIR Spectroscopy
- Thermogravimetric Analysis (TGA)
- ^{1}H-NMR Spectroscopy
- HRMS Spectroscopy
- Surface Tension Study
- Conductivity Study
- Density Study
- Viscosity Study
- Refractive Index Study
- Antimicrobial Activity
- Antioxidant Activity
- Cytoxicity study