CHAPTER I

INTRODUCTION

This section offers an introduction to the realms of supramolecular and solution chemistry. It delves into the comprehensive exploration of cyclodextrin-based supramolecular assembly, highlighting its diverse applications, notably in drug delivery and various biological contexts, as well as the myriad molecular interactions occurring between drug and amino acids in aqueous environments. Additionally, it addresses the fundamental characteristics of cyclodextrin-based inclusion complexes, their analysis, and the significance of their hybrids, alongside outlining the primary goals of the thesis. Concluding the chapter, it outlines the rationale behind our research, identifies the research problem, delineates the scope and objectives, and anticipates the outcomes of the proposed work.

NECESSITY OF THE RESEARCH WORK

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

Research is systematically conducted to contribute to science by collecting, interpreting, and evaluating data. This process generates new knowledge and understanding. As humanity progresses, research remains integral to exploring the interactions between matter and living organisms, which constitute the world.

Jean-Marie Lehn first introduced the term "supramolecular chemistry" and, along with Pedersen and Cram, received the Nobel Prize in 1987 for extensive work in this field [1]. Supramolecular chemistry, an emerging discipline in chemistry and material science, involves the study of molecular assemblies and non-covalent bonds. The foundation of this field dates back to 1894 when Fischer introduced the lock and key principle. By the 1930s, the term supramolecule was coined following the discovery of molecular aggregation via intermolecular interactions [2]. Significant contributions to this field were made in the 1950s by Cramer on cyclodextrins, Pedersen in the 1960s on host-guest complexes of crown ether compounds, and Cram on spherands and cavitands, with recent advancements by Stoddart on box-like container molecules [3, 4].

Supramolecular chemistry now includes three broad categories: (a) host-guest chemistry, (b) clathrates, and (c) self-assembly. In host-guest chemistry, host molecules (cavitands) possess permanent intramolecular cavities to encapsulate guest molecules (e.g., cyclodextrins,

calixarenes, and cucurbiturils) [5]. Clathrates are lattice-structured complexes with extramolecular cavities created by multiple host molecules. Self-assembly involves the formation of supramolecular entities by molecules that do not fit the typical host-guest definitions.

Supramolecular complexes offer unique advantages, such as elucidating the existence and limitations of binding energy additivity, crucial for rational drug design. These complexes benefit from multiple interactions, and the entropy loss of translation in intermolecular associations is mitigated by a single association step. Non-covalent forces stabilizing inclusion complexes include Van der Waals forces, hydrogen bonding, π-π stacking, electrostatic interactions, and hydrophobic interactions [6]. Supramolecular chemistry encompasses various aspects, including molecular self-assembly, molecular recognition, host-guest chemistry, molecular machines, and dynamic covalent chemistry.

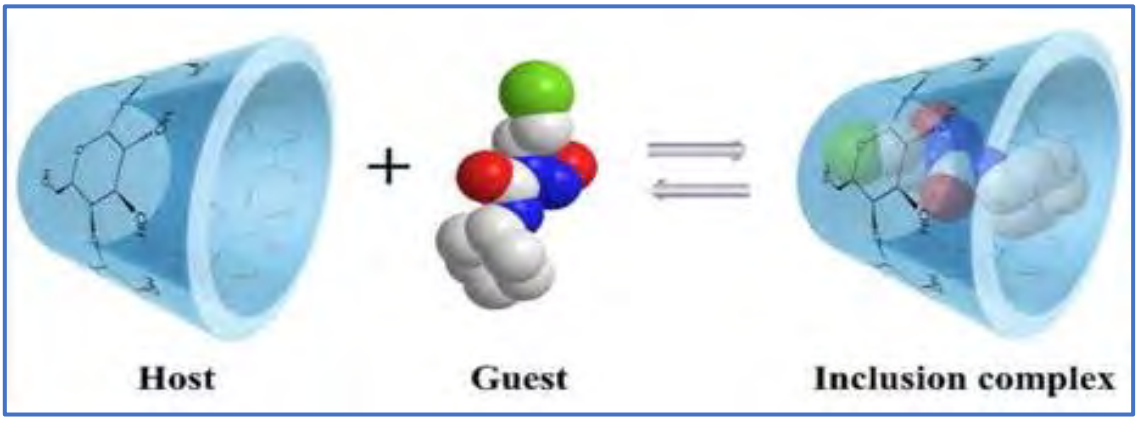

Figure 1: Diagram showing a host-guest supramolecular inclusion complex.

Host-guest supramolecular chemistry involves non-covalent binding between a host and a guest, as illustrated in **Figure 1**. Hosts are large molecules or aggregates, such as enzymes or synthetic cyclic compounds, with sizeable pre-organized cavities (e.g., cyclodextrins, calixarenes, crown ethers) [7, 8]. Guests can be organic or inorganic cations, simple inorganic anions, ion pairs, or complex organic molecules like anticancer drugs [9, 10]. Natural host-guest systems include antigen-antibody, DNA-ligand, enzyme-substrate, and protein-carbohydrate complexes.

Advancements in supramolecular chemistry have been driven by macrocycle-based host-guest chemistry, with macrocyclic hosts such as cyclodextrins, calixarenes, crown ethers, and cucurbiturils [11]. Cyclodextrins (CDs) are particularly noteworthy due to their amphiphilic nature, which enables self-assembly in aqueous systems to form structures like nanotubes,

nanorods, nanosheets, micelles, and vesicles, applicable in drug delivery, nanodevices, and cell imaging [12, 13]. Recently, cyclodextrin-modified nanoparticles have gained attention for improving assembly properties such as conductance, electronic, fluorescence, catalytic, and thermal properties, enhancing their potential as nanosensors and drug delivery vehicles [14-16]. These developments have led to sophisticated probes for molecular machines, switches, supramolecular polymers, chemosensors, transmembrane channels, and molecular logic gates 17-20].

Cyclodextrins, derived from starch, contain six (α-CD), seven (β-CD), eight (γ-CD), or more (α-1,4)-linked α-D-glucopyranose units and are nontoxic nanocarriers known as cyclic oligosaccharides [21]. Their hydrophilic outer surface and hydrophobic internal cavities allow them to host both polar and nonpolar guests, including small molecules and various drugs [22-25]. CDs form stable inclusion complexes with biologically active compounds, enhancing their stability, water solubility, bioavailability, and reducing side effects [26]. Inclusion complexation within the non-polar CD cavities is utilized to protect the hydrophobic components of various bioactive molecules, enzymes, drugs, volatile organic compounds, flavors, essential oils, taxols, flavonoids, vitamins, and more, thereby enhancing their stability against light, air, and heat, improving water solubility, increasing bioavailability, and mitigating adverse effects. This has led to widespread applications in pharmaceuticals, food industries, cosmetics, tissue engineering, and biomedical devices [27].

In pharmacology, the stabilization and controlled release of drugs are critical concerns today. Protecting drug molecules from environmental impacts and minimizing side effects through controlled release requires exploring their encapsulation within cyclodextrin molecules. To address this, research has been conducted on the formation of inclusion complexes involving bioactive guest molecules like Tartrazine (TZ), 6-Mercaptopurine Monohydrate (6-MP), Dyphylline, and Bisphenol A with host molecules such as α-cyclodextrin (α-CD), β-cyclodextrin (β-CD). This study aims to achieve effective stabilization and controlled release of these drugs.

In my first study, we aimed to create inclusion complexes (ICs) with α-Cyclodextrin (α-CD) and β-Cyclodextrin (β-CD) to encapsulate Tartrazine (TZ), a common dye. TZ, also known as FD&C Yellow No. 5, is widely used in various products but has been associated with health and environmental concerns [28, 29]. Encapsulation in cyclodextrins could expand TZ's applications, offering benefits such as controlled release and reduced environmental impact.

Previous research has highlighted the potential of cyclodextrin inclusion complexes, including improved solubility and controlled release, among other advantages [30, 31]. Understanding the release behavior of TZ from cyclodextrins in the body can inform pharmaceutical and food industry formulations [32, 33]. Additionally, we explored the degradation properties of the complexes compared to pure TZ, considering the challenges of treating wastewater containing organic dyes [34, 35]. Furthermore, we investigated the *in vitro* cytotoxic activity of the complexes on a human kidney cell line to assess the potential benefits of TZ encapsulation.

In my second study, β-Cyclodextrin (β-CD) with its advantageous properties was chosen as the host molecule. Cyclodextrins are preferred for inclusion complex (IC) development to enhance the physicochemical properties of medicinal compounds. 6-Mercaptopurine Monohydrate (6-MP), an adenine analogue used in leukemia treatment, faces challenges due to its low absorption and therapeutic index [36]. Encapsulation within β-CD nanocavities offers a promising strategy to improve drug bioavailability and stability while reducing toxicity. The encapsulation process enhances pharmacological properties, including solubility, stability, and anticancer activity, making it a novel treatment approach [37, 38]. β-CD's characteristics make it an ideal matrix for drug delivery, protecting medications from degradation and ensuring stability under various conditions [39]. Controlled release using β-CD can mitigate 6-MP's negative effects and facilitate its delivery to physiological sites while maintaining bioactivity [40]. Additionally, the antibacterial activity of encapsulated 6-MP was evaluated, highlighting the potential benefits of 6-MP inclusion complexes.

Bisphenol A (BPA), a widely used industrial chemical, poses health and environmental risks due to its hormone-disrupting properties and widespread consumption [41]. With increasing demand, there's a need for sensitive analytical methods to monitor BPA pollution in groundwater and drinking water [42]. Scientists are exploring eco-friendly solutions, such as Cyclomaltooligosaccharides (CDs), for removing pollutants like BPA from the environment [43]. In my third piece of study, we investigated the development of inclusion complexes (IC) between β-CD and BPA to address industrial and medicinal challenges. β-CD's ability to encapsulate BPA can reduce its toxicity and enhance its solubility, making it a promising approach for drug delivery [44]. Additionally, IC formation can preserve BPA's bioactivity, offering novel applications in chemistry and engineering. Antioxidant and antibacterial activities of BPA and IC were evaluated, highlighting potential therapeutic benefits [45]. Density functional theory (DFT) calculations were conducted to complement experimental findings, providing insights into molecular interactions.

My fourth article describes, Cyclodextrins (CDs), first described in 1891 by A. Villiers as "Cellulosine," are cyclic oligosaccharides with 6 (α-CD), 7 (β-CD), and 8 (γ-CD) glucopyranose units [46]. Their torus-shaped ring structure features polar hydrophilic rims and a moderately hydrophobic core, allowing them to form host-guest inclusion complexes (ICs) with various hydrophobic guests. These ICs are gaining attention for their potential in releasing bioactive compounds and removing pollutants [47]. Dyphylline, a xanthine derivative used in respiratory illnesses, is being replaced due to its availability and low cost. This study investigates the formation of ICs between β-CD and dyphylline, focusing on encapsulation, stabilization, and controlled release without chemical modification [48, 49]. Thermodynamic analysis, density, viscosity, refractive index, conductance, and surface tension measurements characterize the ICs and their interactions. UV-visible spectroscopy and Job's plot confirm the 1:1 inclusion phenomenon, with binding constants estimated using the Benesi-Hildebrand method. Antibacterial activity against pathogenic bacteria was evaluated to assess pharmacological benefits. Density functional theory calculations were employed to correlate with experimental results. Ultimately, this research aims to develop controlled-release systems to enhance therapeutic effectiveness and reduce dosing frequency, advancing pharmaceutical science [50].

My last work i.e., fifth research related to solution thermodynamics included drug-molecular molecular interaction in solution phase. Drug-macromolecular interactions in water are crucial for drug transport and protein binding, providing insights into therapeutic mechanisms [51]. Proteins act as receptors for drugs, but their complex structure makes studying their behavior in water challenging [52]. However, it's known that drugs must undergo chemical or physico-chemical reactions with substances like proteins and phospholipids before exerting their effects [53]. Non-covalent interactions in solutions, such as ionic, hydrophobic, hydrophilic, and hydrogen bonding, stabilize protein structures and increase stability. Experimental and theoretical studies on amino acids like L-Alanine and L-Valine in Chloroquine diphosphate (CDP) solutions provide valuable data for pharmaceutical and medicinal chemistry. CDP is mainly used to prevent and treat malaria and is occasionally used for other conditions like amebiasis and rheumatoid arthritis [54]. The interactions between CDP and amino acids in water were investigated using various measurements and spectroscopic techniques, revealing the importance of electrostatic and hydrophobic interactions, which contribute to the understanding of the system's behavior and its potential applications in medicinal chemistry and biomedicine [56, 57].

I.2. Choice of Environmental Significant Guest molecules (Drug/ Dye/Pollutant), Host Molecules and Solvents Used in the Research Work

Names of the Host Molecules, Significant Guest Molecules (Drugs/Dye/ Pollutant), Amino Acids and Solvent molecules are listed below

Significant Guest Molecules:

- Tartrazine (TZ)
- 6-Mercaptopurine Monohydrate (6-MP)
- Bisphenol A (BPA)
- 7-(2,3-Dihydroxypropyl)theophylline (Dyphylline)

Host Molecules:

- ✓ α-Cyclodextrin
- ✓ β-Cyclodextrin

Significant Drug for Solution Chemistry Research:

- ➢ Chloroquine diphosphate (CDP)

Amino Acids:

- ❖ L-Alanine
- ❖ L-Valine

Solvents:

- o Water
- o Ethanol
- o Dimethyl sulfoxide
- o Acetonitrile

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

Name of the Investigation Methods are listed below:

- UV-vis spectroscopy
- Differential Scanning Calorimetry (DSC)
- Thermogravimetric Analysis (TGA)
- Powder X-Ray Diffraction (PXRD)
- Scanning Electron Microscopy (SEM)
- FTIR spectroscopy
- ^{1}H NMR spectroscopy
- Surface tension study
- Conductivity study
- Density study
- Viscosity study
- Refractive Index study
- Advanced Oxidation Processes (Fenton and Photo Fenton)
- Photostability study
- Antimicrobial activity
- Antioxidant activity
- MTT and Cytotoxicity Assay