

**Various Interactions Prevailing in
Supramolecular Assembly and Different
Liquid Systems Probed by Experimental and
Theoretical Studies for Innovative Applications**

Abstract of the Thesis submitted to the
UNIVERSITY OF NORTH BENGAL

For the Award of
DOCTOR OF PHILOSOPHY(Ph.D.)
in
CHEMISTRY

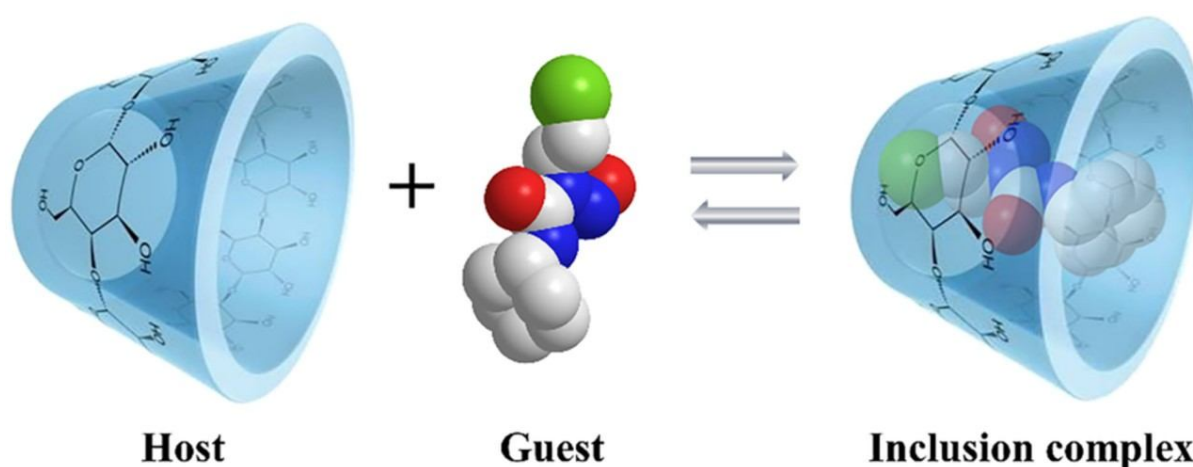
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ABSTRACT

According to the thesis title, I want to demonstrate my extensive knowledge in the fields of amino acid-ionic liquid/drug interaction in aqueous medium and supramolecular host-guest inclusion complexation. Supramolecular assembly has become increasingly important in drug release these days because of its exceptional bioavailability and unique capacity to change the solubility, stability, pharmacokinetics, and pharmacodynamics of the medication. They also show improved encapsulation, controlled release, and benign qualities.



The spectroscopic contribution validates the distinct photophysical characteristics of bioactive compounds and their inclusion complexation in aqueous media. Studies using fluorescence emission spectroscopy, ^1H -NMR, FTIR, and UV-visible light may all satisfactorily describe the inclusion phenomenon. Supramolecular assembly formation can be inferred qualitatively from surface tension, powder XRD, and SEM analyses. The data from the experimental research are validated by theoretical molecular modeling studies of the supramolecular system.

The examination of the physicochemical characteristics of solutions yields important insights into the thermodynamic properties of both electrolytes and non-electrolytes, the impact of varying ionic compositions, and the mobility of individual ions as well as those of their common ions. Measurements of the apparent molar volume (ϕ_v), limiting apparent molar volume (ϕ_v^0), molar refraction (R_M), limiting molar refraction (R_M^0), molar conductance (Λ), and viscosity B coefficients obtained

from various physicochemical methodologies are typically used to reveal the genesis of diverse interactions between amino acids-ionic liquid/drug in aqueous phase.

This work examined the encapsulation of different biologically active compounds, including Valacyclovir and Brilliant Blue FCF, with host molecules, beta- and gamma-cyclodextrins (β - and γ -CD). There may be uses for these bioactive compounds in biological systems. Pharmacological activity is frequently used to characterize the beneficial effects of bioactive compounds.

There has been a lot of interest in host-guest chemistry about the use of macrocyclic hosts in controlled drug release, molecular recognition, *In-vitro* drug release studies, ex-vivo skin permeation analysis, and cytotoxicity investigations. The introduction of guest molecules into the cavity of host molecules, such as β - or γ -cyclodextrin, in an aqueous environment offers fresh insights into molecular recognition through non-covalent interactions, such as inclusion or complexation.

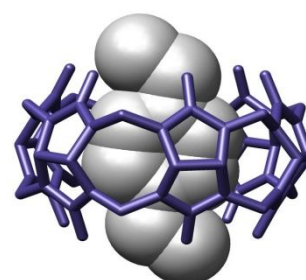
A general understanding of the development of inclusion complexes between host and guest molecules can be obtained through the study of supramolecular host-guest chemistry. The hydrophobic cavities of the host can bind various guest compounds. The supramolecular assembly has recently been extensively researched in several domains, including analytical chemistry and medication delivery. Cyclodextrins appear to be the most promising host molecule to build inclusion complexes, especially when combined with different guest molecules of the right size.

Because supramolecular recognition and solution chemistry have so many applications in a variety of sectors, from the pharmaceutical to the biological sciences, the main goal of this thesis is to determine their influence.

SUMMARY OF THE WORKS

CHAPTER I

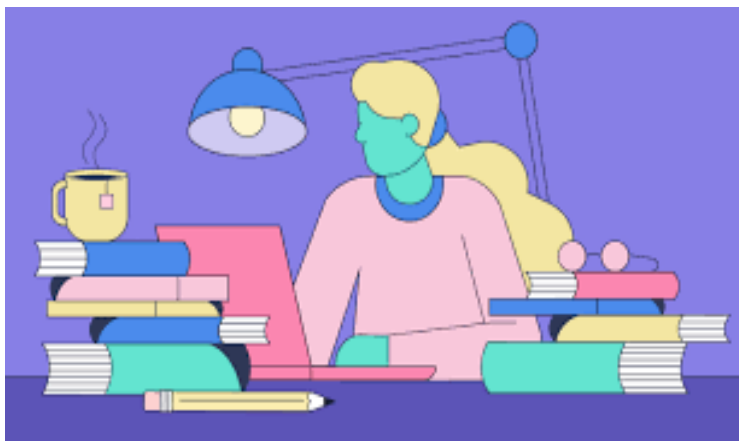
This chapter includes the particular investigation topic, its scope, and its applications in modern science. It also covers the reasons behind the selection of solvent systems, ionic liquid,



cyclodextrins, and bioactive compounds. A summary of all the investigation techniques used in the research study is provided in this chapter.

CHAPTER II

The earlier study on this topic, conducted by different scientists and researchers worldwide, is reviewed in this chapter. Additionally, a detailed explanation of the findings is provided in this chapter, which describes the forces that interact between



the molecules. The present study covers the theoretical underpinnings of all the investigative techniques, including ^1H -NMR, FTIR, UV-visible, Fluorescence, Scanning Electron Microscopy, Powder XRD, Molecular Docking, Cytotoxicity, DNA binding, Photostability, In-vitro drug release studies, and Ex-vivo skin permeation analysis. Surface tension, conductivity, density, viscosity, and refractive index have all been extensively examined, and it has been demonstrated how important it is to employ them in the research project that is the subject of this thesis.

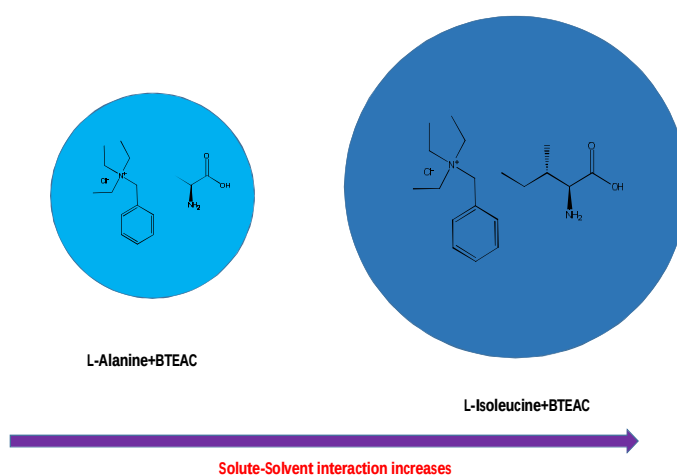
CHAPTER III

The experimental section is covered in this chapter. It discusses the names, structures, characteristics, and uses of cyclodextrins, ionic liquids, and solvents that are employed in research as well as biologically active compounds. It also contains information about the instruments used in the study task, their descriptions, and the specifics of the experimental procedures.



CHAPTER IV

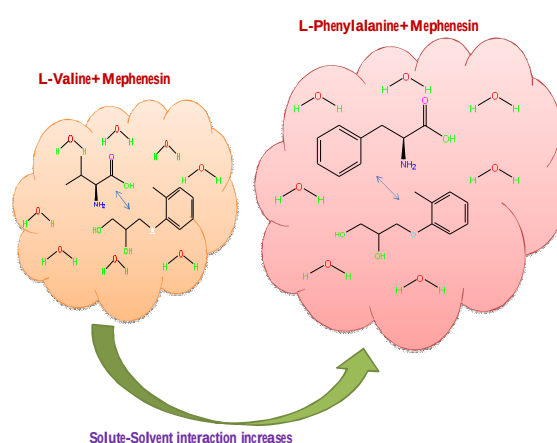
By investigation of different evaluated physico-chemical parameters; density study, viscosity study, refractive index values, conductance study (at four different temperatures) and measurement of surface tension (at 298.15K), the molecular interactions of two different amino acids L-Alanine & L-Isoleucine in an aqueous ionic liquid Benzyltriethylammonium chloride have been studied & explained which is supported by UV-vis and NMR studies. The strong solute-solvent interaction taking place in the solution have been identified depending on the apparent molar volume (ϕ_V) obtained from Masson equation, viscosity B-coefficient obtained from Jones-Doles equation, molar refraction(R_M), limiting molar refraction (R_M^0) from the Lorentz-Lorenz equation at 298.15 K, 303.15 K, 308.15 K, 313.15 K and at 0.001 m, 0.003 m, 0.005 m concentrations of solutions. Hepler's technique and positive value of (dB/dT) data suggest the structure breaking (chaotropic) nature. Specific conductivity measurement helps to explain the ionic nature of the system. The strong interactions present in the system are also suggested by the different thermodynamic data $\Delta\mu_1^{0\neq}$, $\Delta\mu_2^{0\neq}$, $\Delta H_2^{0\neq}$ and $T\Delta S_2^{0\neq}$. UV-visible absorption study helps to understand the structural change & the nature of interactions of the solute amino acids with the solvent BTEAC obtained from association constant data. The change in chemical shift value in NMR gives us valuable insight about hydrophobic interactions and obtained a good agreement. The interaction of (L-Isoleucine + BTEAC) is stronger than (L-Alanine + BTEAC) according to the investigation & theoretical result. Moreover, employing Density functional theory, adsorption energies, electrostatic potential maps (ESP), reduced density gradient plots and different thermodynamic parameters are analyzed to validate experimental observations.



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CHAPTER V

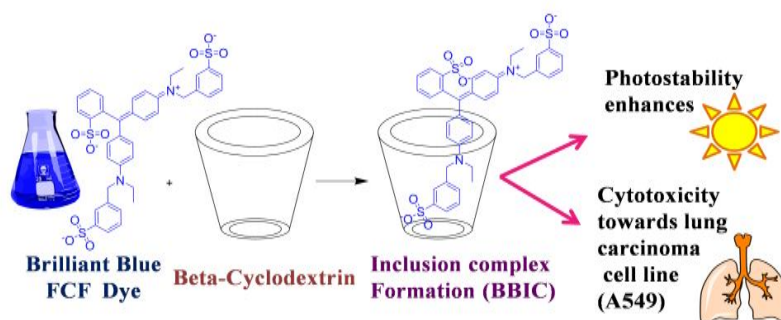
A complete chemical analysis of significant intermolecular interactions of L-Valine (L-Val) and L-Phenylalanine (L-Phe) with Mephenesin (MEPN) molecules in aqueous solution has been studied by different physicochemical methodologies at various temperatures ($T=298.15$ K- 313.15 K at an interval of 5 K) and concentrations (0.001 mol.kg⁻¹, 0.003 mol.kg⁻¹, 0.005 mol.kg⁻¹) of aqueous MEPN solution. The limiting apparent molar volume (ϕ_V^0) and experimental slope (S_V^*) values are found from the equation of Masson, viscosity A and B -coefficient determined using the equation of Jones-Doles, molar refraction (R_M) and limiting molar refraction (R_M^0) derived by the Lorentz-Lorenz equation, express that in our experimental solution of amino acids (AAs) in aqueous MEPN, the solute-solvent interaction predominates over the solute-solute and solvent-solvent interactions for these ternary solutions. These are also justified by the measurement of various thermodynamic parameters, free energy of activation of viscous flow per mole of solvent ($\Delta\mu_1^\circ\#$) and solute ($\Delta\mu_2^\circ\#$), activation of viscous flow of enthalpies ($\Delta H^\circ\#$) and entropies ($\Delta S^\circ\#$). The characteristics of structure-breaking of solutes in the aqueous drug solution have been identified by Hepler's method and dB/dT value. The spectroscopic methods like UV-visible and proton-NMR studies help to explicate the strong AA-MEPN interactions in the solution phase and obtain a good correlation with theoretical studies. Theoretical investigations are checked to authenticate the experimental observations and according to both studies, L-Phe-MEPN interaction is greater than L-Val-MEPN interaction. The experimental and correlated research data are useful for the development of model combinations of AAs with drug molecules in pharmaceutical and medicinal chemistry.



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CHAPTER VI

This research delved into the Brilliant Blue FCF (BB) dye encapsulation within the nano hydrophobic cavity of β -cyclodextrin (β -CD) utilizing various spectroscopic and physicochemical techniques. Job's plot using UV-visible and Fluorescence spectroscopy, surface tension, and conductance study confirmed 1:1 stoichiometry of the inclusion complex (BBIC). ^1H NMR and FT-IR studies demonstrated the possible binding mode of BB into the β -CD cavity, which was in good agreement with the DFT study. The degree of affinity of β -CD for BB in the ground state and excited state were estimated from UV-visible and Fluorescence spectroscopy (binding constant = 8113.9451 M^{-1} and 10199.563 M^{-1}), and the negative free binding energy showed the encapsulation process to be thermodynamically feasible. PXRD analysis and SEM image studies revealed the formation of the BBIC. After complexation with β -CD, the photostability of BB was found to be enhanced. The interaction study of BB and BBIC with CT-DNA revealed the sustained release of BB from the complex. Furthermore, neither BBIC nor free BB exhibited a significant cytotoxic effect on the normal cell line HEK-293. However, BBIC complex ($\text{IC}_{50} = 6.15\text{ }\mu\text{M}$) showed significant *in-vitro* cytotoxic activity compared to pure BB ($\text{IC}_{50} = 8.90\text{ }\mu\text{M}$) towards cancer cell line A549.

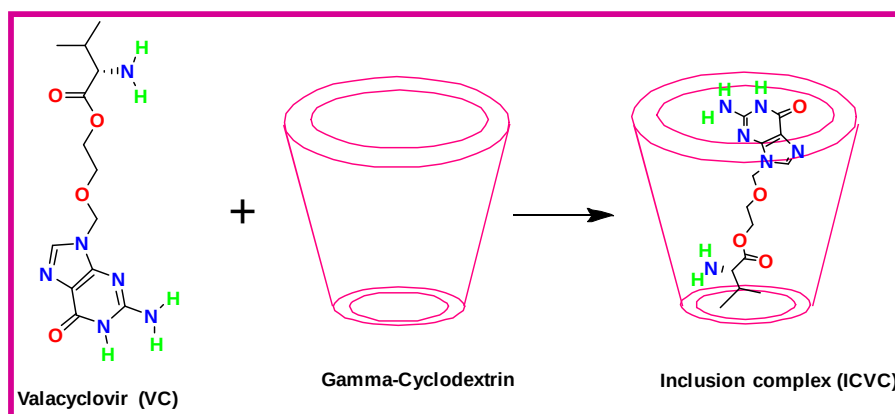


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CHAPTER VII

Herpes Simplex, commonly known as herpes simplex virus, can cause painful blisters or sores around the mouth or genitals. Valacyclovir (VC) possesses 55-70% oral bioavailability among all the anti-herpes drugs and shows more effective performance than Acyclovir (15-20% oral bioavailability). The goal of the current research was to synthesize and characterize the inclusion complex of VC (ICVC) with Gamma-Cyclodextrin (γ -CD) utilizing various spectroscopic and physicochemical techniques like

UV-vis, $^1\text{H-NMR}$, FTIR, conductance, surface tension, SEM analysis. The studies confirmed that the 1:1 stoichiometry of the formed ICVC was also well supported by molecular docking study. After complexation with $\gamma\text{-CD}$, the photostability was enhanced. The purpose of the current study was to create topical gels loaded with VC and ICVC and assess their potential to increase VC penetration through the topical route by enhancing their pharmacokinetic profile. The optimized topical gels containing VC and ICVC have zeta potentials of $-3.8\pm 1.0\text{ mV}$ and $-5.7\pm 0.9\text{ mV}$ respectively. *In-vitro* drug release study showed that at the end of 8h, 32.3% and 23.38% release of VC from the VC-loaded and ICVC-loaded gel. Ex-vivo skin permeation study of ICVC-loaded gel showed poor permeability and negligible flux value in comparison to VC-loaded gel that infers the retainability of the drug to the dermal site as depot formulation from which drug will release and act in a sustained manner. Based on the findings, it was confirmed that the efficacy of VC can be much improved as the topical delivery of ICVC-loaded gel for the treatment of herpes with minimum dose requirements, less toxicity, rapid action, and improved bioavailability of the VC.



**Communicated*

CHAPTER IX

This chapter includes the concluding remarks about the research works done in this thesis.

CHAPTER X

Bibliography and references of all the previous chapters has been included in this chapter.