

MULTI-FACETING CYCLODEXTRIN MATRIX: PHYSICOCHEMICAL AND THEORETICAL /CHEMINFORMATICS PORTFOLIO

Abstract

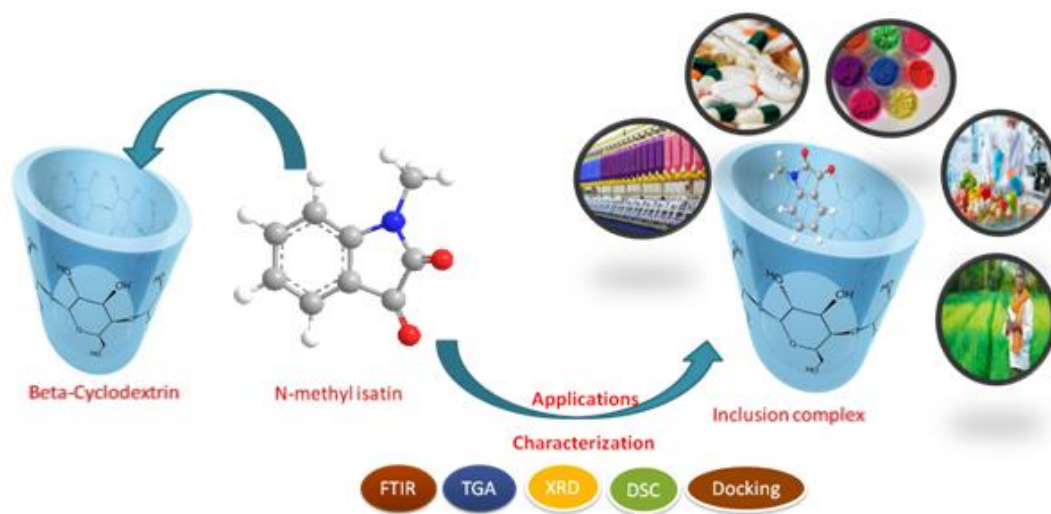
Cyclodextrin (CDs) has gained prevalence as functional dissolving additives with an perpetually expanding records of advantageous traits and capabilities. This is an insight aiming to evaluate the properties of CDs and their vast functionalities in science and technology. Objective of this article is to scrutinize the chemical nature of CDs, the way they were petitioned in cheminformatics system. To acquire knowledge about compound properties of Cyclodextrin, the abstraction is performed. Inclusion complex formation of beta-CD and heterocycles can be studied by phase solubility techniques to calculate stability constant and free energies of heterocyclic molecule from aqueous solution to the cavity of CDs. Thermodynamic study($\Delta G, \Delta H, \Delta S$), QSAR, and computational analysis(Molecular docking). Computational analysis has been widely used for predicting binding constant and studying driving forces. Cheminformatics techniques were initially developed for the construction & penetrating huge achievement of chemical structure but they were soon applied to complication in drug discovery and are now playing an increasingly important role in many additional zone of chemistry. This article is the short review, includes the applications of Inclusion complex of Cyclodextrin-Heterocycles and their combinatorial chemistry.

Keywords: Cyclodextrin, Bioavailability, Inclusion Complex, Host-Guest Interaction, API, Molecular Docking, In-Silico Drug Design, QSAR, Cheminformatics.

Author

Prachi P. Khobragade
Department of Chemistry
R.T.M. Nagpur University
Nagpur, India.
khobragadeprachi3@gmail.com

Graphical Abstract



I. INTRODUCTION

In 1891, A. Villiers, a french scientist segregated bacterial digest from starch and the substance was found to be dextrin and named it as “Cellulosine” by Villiers. Afterwards two crystalline compounds alpha and beta dextrin had been isolated from bacterial digest of starch present in potato by Franz Schardinger an Austrian microbiologist. He called beta-cyclodextrin as a “Villiers” “Cellulosine” and these compounds are commonly called as Cyclodextrin. In medicinal chemistry and allied system the cyclodextrin are acknowledged as important pharmaceutical ingredients and because of their comprehensive analysis, intense research and

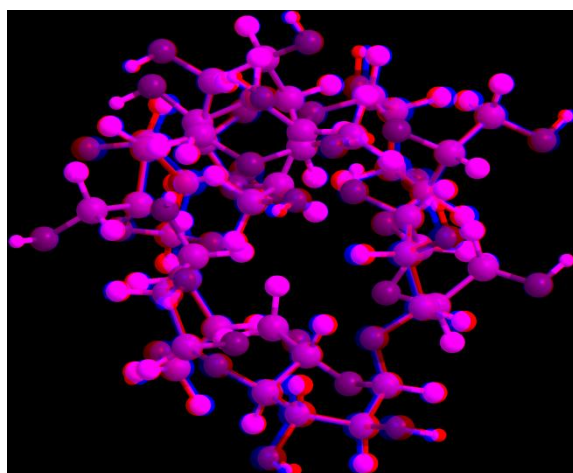


Figure 1: 3D Structure of Cyclodextrin

& industrial production, they can be used extensively in biomedical industries. Their chemical architecture endow them with a special quality like core cavity^{3,4,5} and outward lipophilia. By trapping the medication in their cavities, CDs can then create non-covalent inclusion complexes. They dramatically alter the physicochemical & biological properties of parent drug &/ CD) ^{5,6}. CDs gets shielded when administered through various routes e.g. dilution, protein binding, competitive displacement etc. A possible method for improving the medication's ability to dissolve is the formation of inclusion complexes of the drug with harmless agents, ^{12,13,14}. Through the use of CDs complexes, cyclodextrin is a type of pharmacological adapter used to dissolve several species that are insufficiently soluble. In supramolecular chemistry, CDs, a family of oligosaccharides, are one of the most often employed molecular hosts. The creation of (IC) Inclusion complexes strongly influences the physicochemical properties of the guest when it is encapsulated in the lipophilic (hydrophobic) cavity of CDs. ⁴. Extensively used natural CDs exists as α , β and γ consisting of 6, 7, 8 glucopyranose units in their skeleton mentioned in the figure. No covalent bonds are created or broken during the complexation process, which puts more strain on the physical than the chemical nature of the process. The inclusion complexes improve the solubility, chemical stability, and bioavailability of the therapeutic molecule, as well as its potential to reduce side effects. Hydrogen bonds, van der Waals forces, hydrophobic contacts between the host and guest molecules, and entropy released by uncomplexed water molecules from the

CD cavity all contribute to the drug-CD complex's formation. The structural analysis of inclusion complexes of native CDs (CD-IC) or their derivatives has been the main focus of computational practice combined with experimental methods over the past few years. For the complexes of Cyclodextrin or their derivatives with guest molecules (host-guest chemistry), several computational techniques are used, including molecular dynamics (MD)¹³, semi-empirical method, hybrid own N-layer Integrated Orbital Molecular mechanics, Hartree Fock, and density functional theory⁷⁴.

As Cyclodextrin comprise organic molecules in their hydrophobic^{5,6,7} (lipophilic) cavities & boost the bioaccessibility of heterocyclic guest molecules in solvent system like water, these molecules are utilized in numerous chemical fields, which includes analytical, organic chemistry & bio-chemistry etc.

Cyclodextrin matrix can spontaneously bind even weakly soluble molecules in an aqueous environment thanks to the distinctive cone-like shape of the sugar ring, expressing a lipophilic (hydrophobic) interior & hydrophilic (lipophobic) outer surface. Even though Cyclodextrin and its related complexes are lipophobic in nature, their solubility in water is restricted, with a focus on the -CD system. This is due to the Cyclodextrin molecules' relatively strong crystal-structured bonds. Currently, a variety of methods of various kinds are being used to increase the solubility of pharmaceuticals.⁹.

One of the many methods for harmonizingly enhancing the physicochemical characteristics of a medicinal molecule is complexation. It is predicated on the possibility of numerous well-known medications interacting and forming new complex pharmaceuticals with different qualities from the properties of the individual drugs. Complexation is the thermodynamic interaction of various CDs (the active ingredient components) constituents,¹⁰. For such complexation, which pulls the active medications into the skeleton of CDs, the net energetic driving force must be essential. Despite the fact that CDs' chemical structure may appear to be quite straightforward, it took more than 50 years of research to fully characterize and comprehend CDs' chemical properties. Figure 2 given below includes Cyclodextrin structures with their NMR spectra.

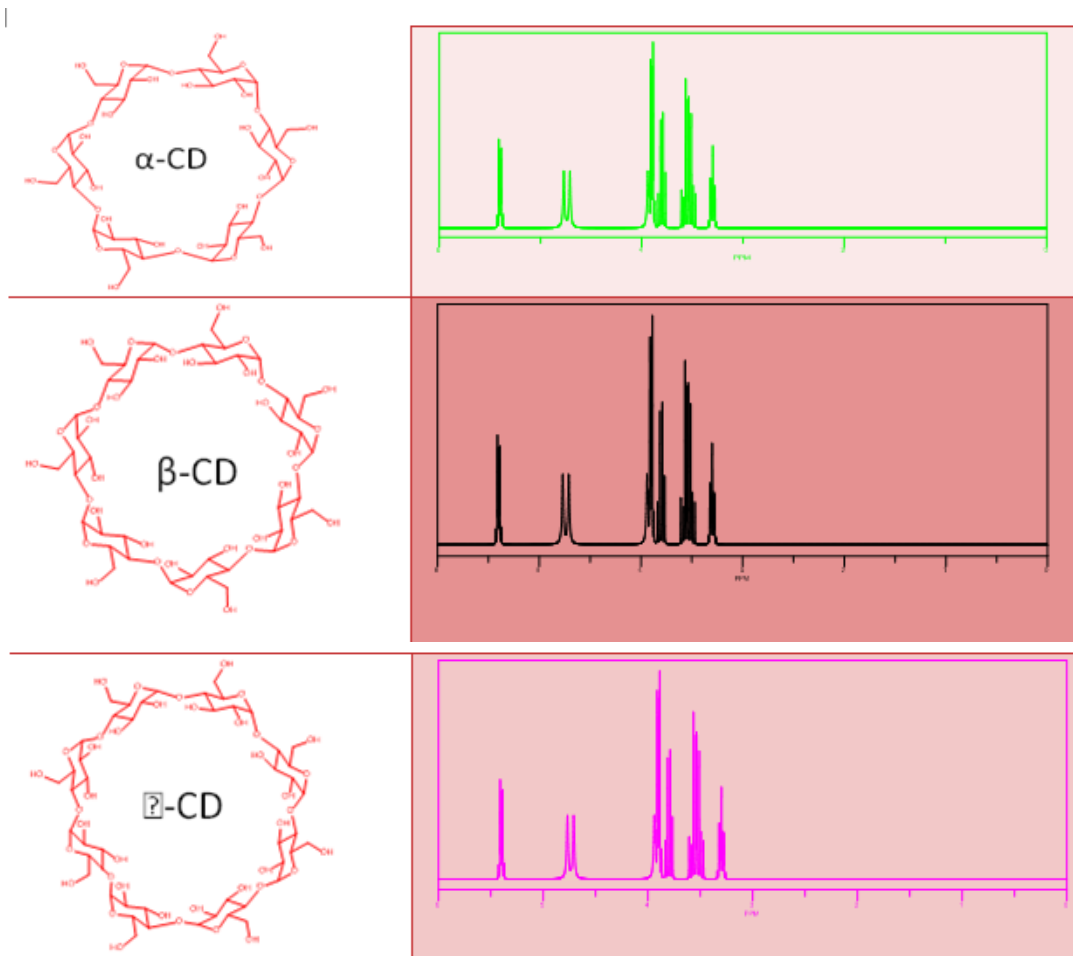
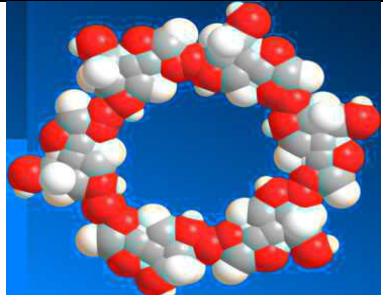
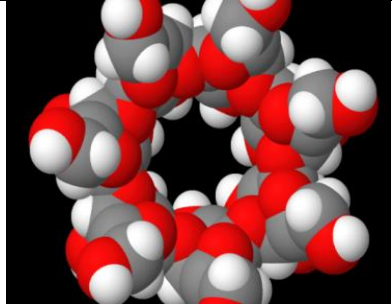
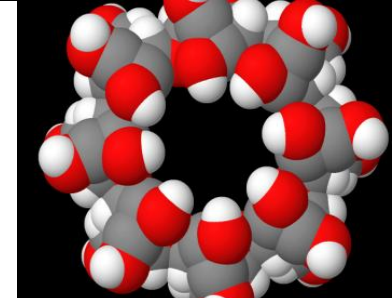


Figure 2: α , β and η Cyclodextrin NMR Spectra

Table 1: α , β and η -Cyclodextrin Characteristics

Structure of α, β, η Cyclodextrin	Cavity Diameter (\AA)(μm)	Cavity Volume(\AA^3)	Water Molecule in Cavity (n^r)	Aqueous Solubility(M)	Gibbs Free Energy Dissolution KJ/mol
	5.2	100	2.5	0.12	15

	6.6	160	5.0	0.016	20
	8.4	250	8.5	0.17	14

Inclusion complex formation: Host guest chemistry

Foremost property of Inclusion compounds: host components can admit "guest" species/ components into its cavity without forming any covalent bond i.e by means of non-covalent bonding like Van der Waal, H-bonding etc. Most remarkable property of CDs is their ability to form inclusion compounds with heterogeneity of molecules which apparently only have to assure a condition that they must fit utterly / partially into CDs cavity^{18,19}.

CDs had a central non- polar hole and hydroxyl groups placed on the facet, Inclusion of hydrophobic interconnection between guests molecules & walls of CDs cavity,^{15,20}. Even so, other forces, like van der Waals and dipole-dipole interaction, may be involved in the binding of the guests^{3, 4,5,10}. Inclusion complex formation can be confirmed by studying interaction between a guest's molecules & CDs using various techniques. Inclusion complexation does not result in a covalent bond breaking or being formed. 21. The guest molecule must be fully or partially trapped in a -polar CDs cavity or voids in order for the selectivity of host-guest recognition to be achieved. Figure 3 shows the inclusion complexation of host and guest molecule in CDs networking framework.

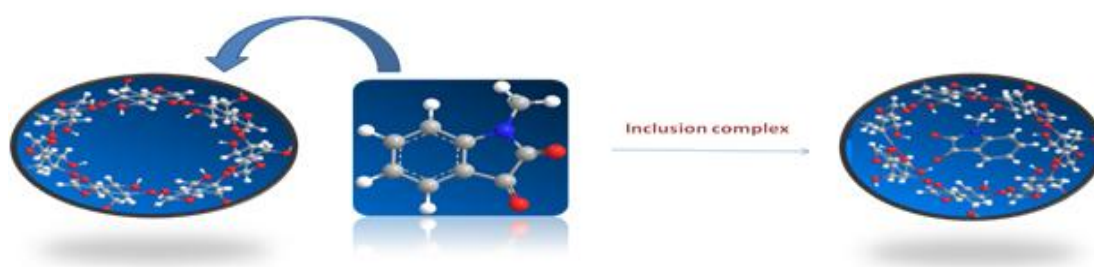


Figure 3: Beta-Cyclodextrin with N-Methyltribulin and Inclusion Complex

The internal cavity being lipophilic in nature being hallmark of Cyclodextrin in order to providing the ability of forming complexes to encompass various guest molecules^{20,22}. A molecule often interacts with the CDs molecule's cavity to become trapped in CDs inclusion, which is a stoichiometric molecular phenomena 4, 5, 10, and 23. The development of stable complexes is caused by a number of non-covalent forces, including van der Waals forces, hydrophobic contacts, and other factors. It is thought to contain medication molecules, or at the very least the unstable portion of the molecule¹⁶. Encapsulation slows down the rate of hydrolysis, oxidation, steric rearrangement, racemization, and even enzymatic degradation by protecting the drug molecule from attack by multiple reactive chemicals²³. Figure 4 explains the functions of Cyclodextrin and complex formation^{11,12}.

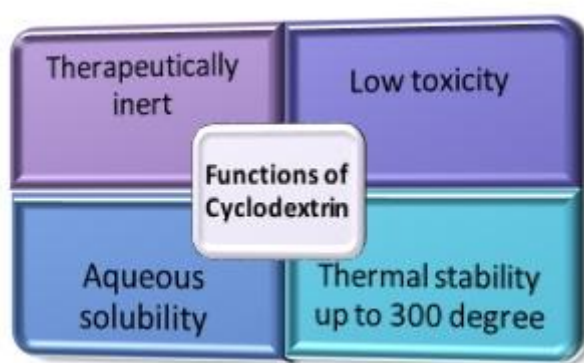



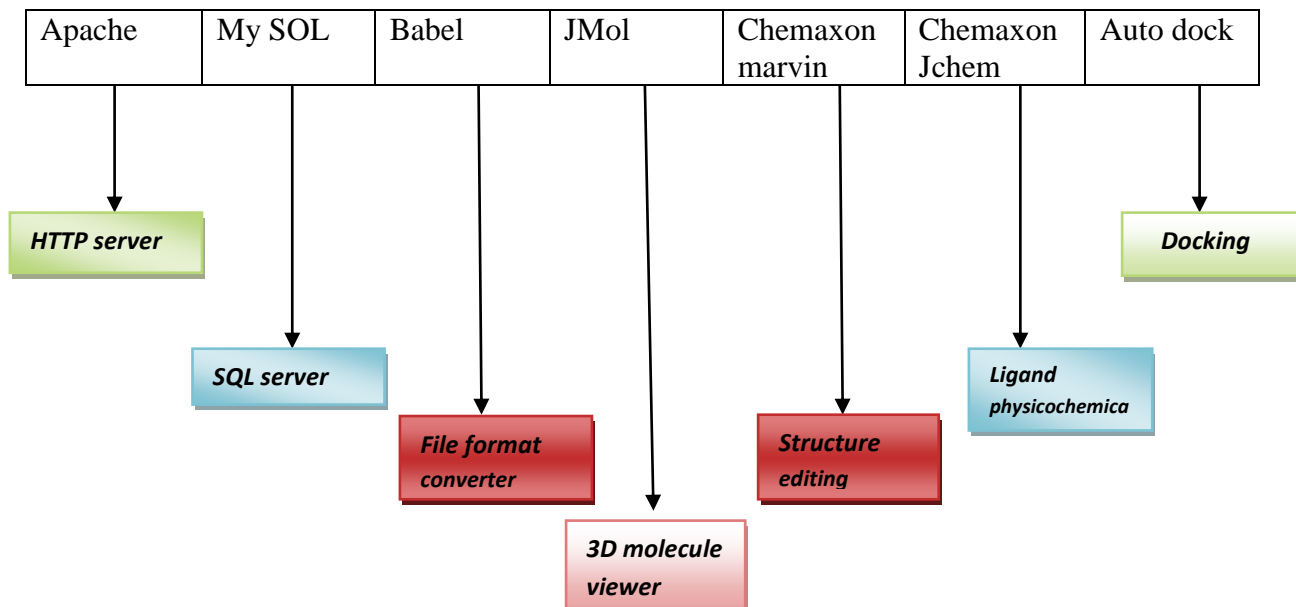


Figure 4: Functions of Cyclodextrin Inclusion Complex

II. METHODOLOGY USED FOR INCLUSION COMPLEX FORMATION

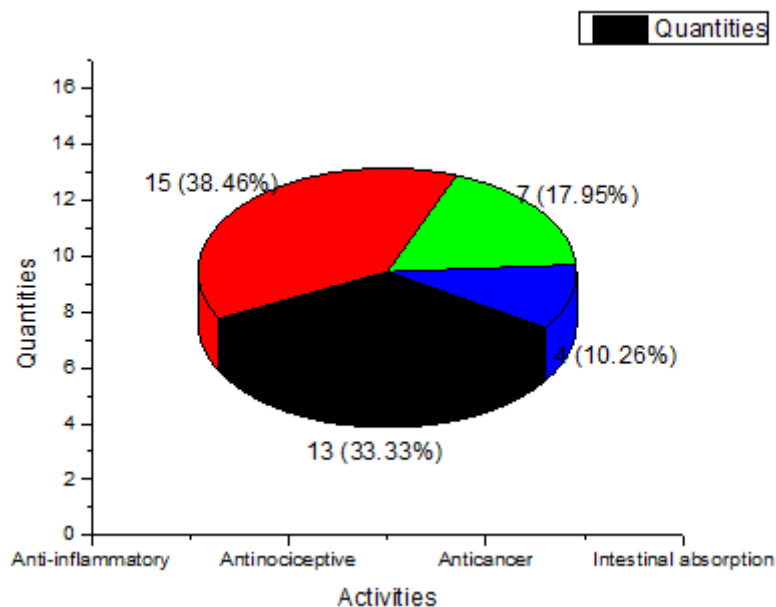
Methods	Instrumentation
1)Co-precipitation method	
2)Kneading method	
3) Microwave irradiation	
4)Sonication method	

III. TOOLS AND DESCRIPTION EMPLOYED IN CD ANALYSIS AND DESCRIPTION⁶



IV. CYCLODEXTRIN IN PHARMACEUTICS/BIOLOGICAL ASPECTS

1. In Vivo CDS Studies



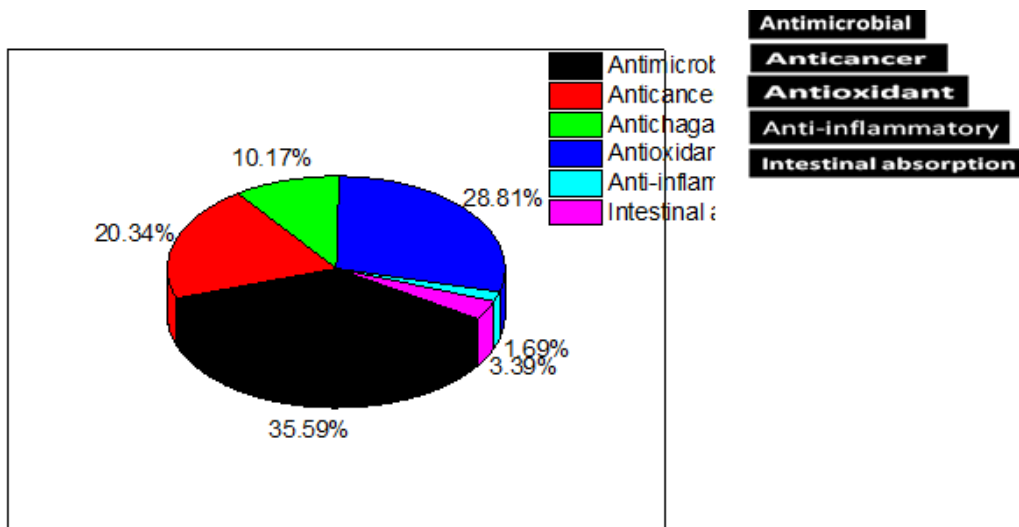
Quantities of in vivo studies performed with substances in an inclusion complex with Cyclodextrin.

- **Anti-Inflammatory Activities of Cyclodextrin Inclusion Complex:** Many diseases trigger the inflammatory response, thus it is important to pay attention to substances with anti-inflammatory qualities. In particular, Cyclodextrin-Inclusion complexes use cutting-edge biotechnology to boost the bioavailability, solubility, and pharmacological effects of medications. Beta-Cyclodextrin is the cyclodextrin that is most frequently discovered in research of cyclodextrin-inclusion complex with anti-inflammatory because of its virtue for complexation with anti-inflammatory medications, its notable oral acceptance, and its reasonable price 9,15.

Anti-inflammatory medicines, which are typically categorized as corticosteroids and non-steroidal anti-inflammatory drugs, have been utilized in an effort to treat inflammatory illnesses. Many of these medications have detrimental side effects, like cardiovascular risks and gastrointestinal problems. Anti-inflammatory medicine effectiveness is increased by cyclodextrin, and the adverse effect profile is improved^{9,16,17,18}.

The incorporation of active principles into compounds like cyclodextrin to create inclusion complex has increased the search for products with improved antinociceptive properties. This has led to the development of more potent products with better stability, solubility, and bioavailability, which have improved pharmacological activities.^{7,9,18}

- **The Cyclodextrin Inclusion Complex has Anticancer Properties:** Betulinic acid, a highly effective anti-melanoma drug, was complexed with water-soluble gamma-Cyclodextrin to increase the bioavailability and solubility. By using a differential scanning calorimeter (DSC), X-rays, and a scanning electron microscope (SEM), the physicochemical characterization was carried out 9. A murine melanoma in mice animal model has been utilized to investigate the complex. The outcomes demonstrated a decrease in tumor volume and weight, demonstrating that this complexation was advantageous in reducing ant proliferative activity and tumor development in vivo,^{9,25}.
 - **Intestinal Absorption of Cyclodextrin Inclusion Complex:** The creation of cyclodextrin complexes may be the answer for many active compounds with poor bioavailability. Tanshinone IIA, a compound complexed with HP-CD that has positive effects on the cardiovascular system, was tested for intestinal permeability. Co-evaporation is used to acquire the complexes. It was shown that increasing the dosage of the complex led to saturation, indicating that passive transport may be the in vivo transport mechanism. With improved oral bioavailability, TSIIA was found to have greater intestinal membrane permeability^{23,24,26}.
- 2. In Vitro CDs Studies:** The insufficiency of solubility reduces the pliability for drug formulation and administration, thus solubility. Non-polar drugs are usually more soluble in in vitro assays after complexation with Cyclodextrin than non-polar drugs alone, although some compounds are strongly bound to CDs, limiting their availability in in vitro assays and consequently the biological assays^{9,10,11}.



Cyclodextrin Inclusion Complex Antimicrobial Activities Evaluation of the solubility and antibacterial efficacy of 2-pentanoylfuran complexed with Cyclodextrin against *Staphylococcus aureus*, *Bacillus subtilis*, and *Escherichia coli*. In a hydrated environment, cyclodextrin makes substances more soluble and increases their antibacterial action.²⁶

- **Cyclodextrin Inclusion Complex Antimicrobial Activities:** Evaluation of the solubility and antibacterial efficacy of 2-pentanoylfuran complexed with Cyclodextrin against *Staphylococcus aureus*, *Bacillus subtilis*, and *Escherichia coli*. In a hydrated environment, cyclodextrin makes substances more soluble and increases their antibacter • Cyclodextrin Inclusion Complexes' anti-cancer properties^{9,23,27}.
- **Cyclodextrin Inclusion Complex has Antichagasic Activity:** It is crucial to develop technological solutions for the solubility and toxicity issues associated with benzodazole since it is a very promising medicine for the treatment of Chagas disease despite having lower solubility and increased toxicity. Consequently, inclusion complexes were created.^{9,10}
- **The Antioxidant Activity of Complexes Including Cyclodextrin:** Due to their low solubility in water and instability in light and oxygen, antioxidants have a limited range of applications. These compounds, which have a great deal of medicinal potential, can become more stable through complexation with CDs.

V. DRUG FORMULATIONS IN CYCLODEXTRIN AND DRUG DELIVERY SYSTEMS

When guest molecules and Cyclodextrin are combined in aqueous solution, there is an impressive entropic benefit due to the water's significant rearrangement salvation, removal of water molecules from the Cyclodextrin cavity, and water salvation of guest molecules. In order to significantly increase the solubility of compounds in water, 1:1 complexes of lipophilic molecules with a strong lipophilic effect are preferable for relatively small hosts,

which is the rationale for the use of Cyclodextrin as solubility enhancers for hydrophobic pharmaceuticals. The great dispersion of lipophilic medications in water is made possible by cyclodextrin's nanometric dimensions, which also inhibit the crystallization of these pharmaceuticals in aqueous conditions and increase their bioavailability. When the lipophilic cell membrane comes into touch with the encapsulated drug, the medication can be released, and CD serves as a drug nanocarrier and delivery mechanism^{27,28,29}.

VI. FUTURISTIC PROSPECTS OF CYCLODEXTRIN

In the pharmaceutical sector, cyclodextrin seems to have a strong following. Numerous conventional and non-traditional uses are in the running to become profitable. As the characteristics of cyclodextrin are enhanced and more marketed and FDA-approved forms are produced, novel uses of cyclodextrin are expected to be investigated. Cyclodextrin has only currently been sold in traditional forms such as tablets, capsules, solutions, ointments, and intravenous solutions^{29,30}. The use of Cyclodextrin in novel (DD) drug delivery systems, such as nanoparticles, liposomes, microspheres, and targeted drug delivery, is currently the subject of substantial research. In order to increase interest in Cyclodextrin, gene therapy is also being used. Since viral gene delivery has been proven to be challenging, non-viral techniques are being investigated further. The unique features of polycations made of (CD) Cyclodextrin may be advantageous in the non-viral delivery of (NA) nucleic acids. Although their usefulness for humans has not yet been established, these materials demonstrate the potential for gene delivery in animals³¹.

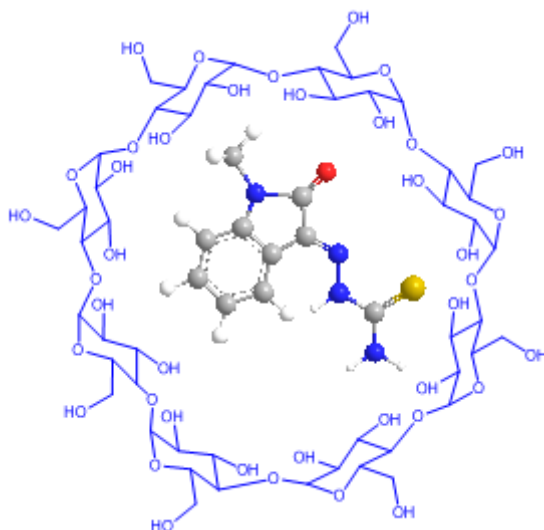


Figure 5: η -Cyclodextrin Inclusion Complex with Heterocyclic Molecule

The host molecules' repertoire is not restricted to solid-state substances. Aqueous solutions can be used to distribute liquid and gaseous substances that have been packaged in CDs^{16,31,32}. Through the development of host-guest complexes, CDs can dramatically lower the volatility of low boiling point liquids, which allows them to either conceal disagreeable aromas they produce or enclose and release pleasant odors over time. The development and stability of host-guest complexes of Cyclodextrin are significantly influenced by water^{33,34}. When the water is withdrawn, the affinity of the host for its guests

often declines, and decomplexation might happen, especially for compounds with poor hydrophobicity, leading to molecular dispersion of the host and guest^{30,32,35}. When water is given to these dispersions, the phenomena can be reversed, and complexes develop on their own. Even in dry form, the highly lipophilic medicines do not decomplex from their CD host, and the CD complex³⁶.

VII. CDS UTILITIES IN CHEMINFORMATICS

Around fifty years ago, efforts were made to investigate sub-structural patterns in molecules and add up organic activity using structural data. This field is today known as cheminformatics. An extensive set of tools and strategies for the discovery of novel compounds with noteworthy, economically beneficial features had been expanded by cheminformatics. This review's goal is to examine the nature of chemical ideas and how they are used in cheminformatics systems^{25,30,70}. A review of chemical concepts and their interpretation follows a discussion of concepts in beliefs and information science. The organizing concepts of chemical structure, structural similarity, periodicity, as well as more detailed concepts like 2D & 3D structural patterns, reaction types & property notions, etc., are the main areas of concentration. The techniques for cheminformatics data analysis are displayed in Figure 6 below.⁷⁰

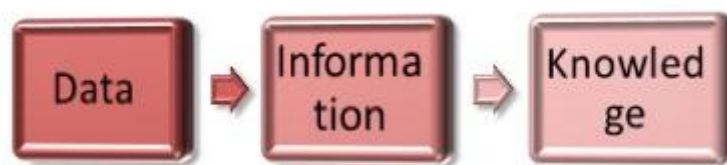


Figure 6: Cheminformatics Data Analysis Method

Cheminformatics plays a vital role in maintaining and accessing huge amount of chemical data, assemble by chemists using a proper data base, figure 8 shown below shows various field in cheminformatics. The field of chemistry needs emerging techniques for knowledge extrication from data to model complex relationship between structure of chemical compounds & bioactivity. Cheminformatics is a remarkable application of information Application of CDs Chemical Industry Catalytic uses Separation process Agriculture Cosmetics & dyes 12 technology (IT) to help chemists & researchers to investigate problems, organize, and analyze & to understand scientific data in the development of new compound, material and process^{36,37,38}.

VIII. IN-SILICO MOLECULAR DOCKING STUDY

Detailed knowledge of the biological activity of pharmacological substances against chosen targets is necessary for drug development. In-depth research has been done on the use of computational methods to analyze the development of intermolecular complexes^{70,71}. It is generally acknowledged that the chemical binding of one molecule, the ligand, to the pocket of another, typically bigger molecule, the receptor, produces the drug's activity. The computational process of looking for a ligand that can suit the molecular docking site—also

known as the location where a protein binds—both geometrically and energetically 44,70,71. Figure 7 illustrates the process of finding new drugs.

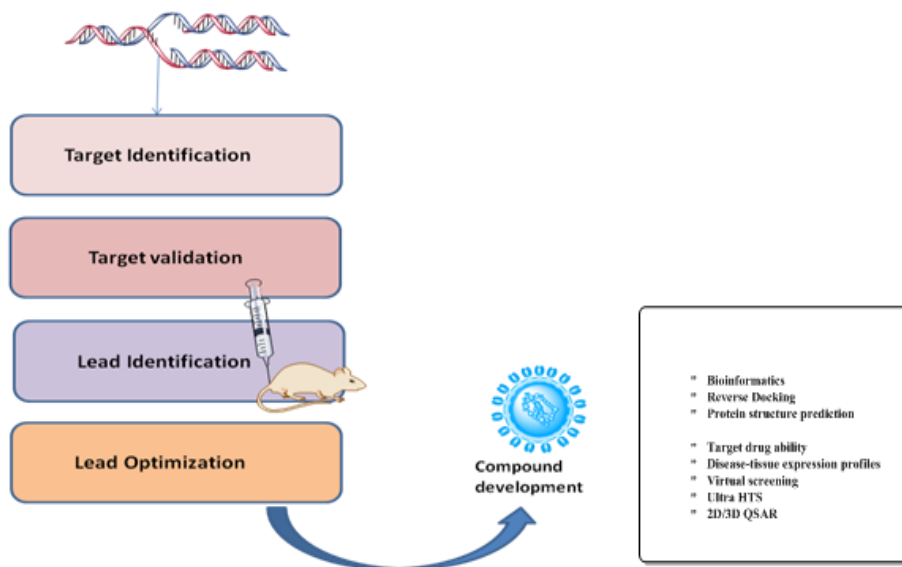


Figure 7: Drug Discovery Process

IX. MOLECULAR DOCKING AND SIMULATIONS

Molecular docking is a computational approach used in supramolecular chemistry to find a guest that can fit both geometrically and energetically in the host moiety's cavity⁷⁴. This is how two molecules fit together in three dimensions. The purpose of docking is to foretell the main form of binding between a guest and a host with a recognized three-dimensional structure. Application of a well-established docking procedure for the host-guest system in MOE. The triangle matcher method and the London G scoring function were used to organize the docking, which was performed with the default parameters. The top five created poses were recorded in a separate database file with a.mdb extension and sorted according to their docking scores. The binding affinity ($\text{kcal}\cdot\text{mol}^{-1}$) of the optimized structure of the inclusion complex was predicted using the built-in scoring function of MOE, S-score^{62,63}. Figure 8 depicts the CD-IC docking investigation.

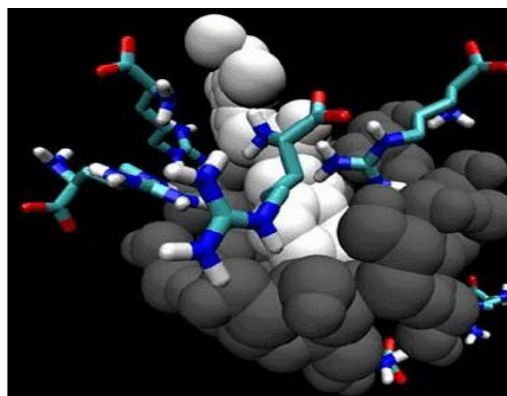


Figure 8: Molecular Docking Study of CD-IC Heterocycles

(Snapshot from the molecular dynamics simulation of the multicomponent inclusion complex formed between OME (light gray) and β CD (dark gray) in the presence of ARG (colored))

Cheminformatics research instruments. Software and equipment for computer-assisted organic synthesis are now being developed extensively. Chemical structure now has a wide variety of instruments and representations because to this. The following list includes some of the most popular utilities^{65, 66,67,70,71,72}.

Types of Tools	Allied Application
ISIS-Draw	A Windows software for sketching chemical structures is available from MDL Information System.
Chem. Draw	Cambridge Soft, a cheminformatics business, created a molecular editor
Chem3D & Chem. finder	Part of chem. office suits program available for Macintosh and Microsoft Windows
Chem. Window	An application with many templates for drawing chemical structures. The customer creates the template, saves it in the template folder, and opens it in the preference dialogue box.
Chem. Sketch	More powerful, user friendly tools for drawing structure
Chem. Reader	A toolbox for software developers to convert digitized raster representations of chemical structures into standard
Log Chem.	Tools based on an inductive logical program for selective, interactive mining of chemical fragments
Pub Chem.	Small molecules and their experimental biological action are stored in an open repository. It combines, offers tools for search, retrieval, visualization, analysis, and programmatic access in an effort to make the most of the information that has been donated.

X. CONCLUSION

The use of CDs as an advantageous addition in the pharmaceutical industry and other sectors is well known and widespread^{75,78,79}. The propensity of CDs to interact with various medicinal compounds and generate the appropriate inclusion complex 1,2,3,10 has been attributed to a variety of purposes. In addition to being well-established and well-known internationally for its toxicity modifier, CDs are also known for their profile as molecular chelating agents with high demand in the fields of food, medicines, and chromatographic procedures.^{15,16,17,39,45} In the CD network, a single interaction between host and guest molecules is sufficient to alter the physicochemical and pharmacological properties of the drug molecule in the form of improved water stability and drug stabilization under various environmental conditions. Allied tool types prevent the degradation of pharmaceuticals in various sources by avoiding light, heat, and oxidizing environments.^{46,47,48,49} . One of the most important application of CD known from the different experiments carried out in human and animals, enhancing drug delivery of majority of the formation^{50,51,52} . As compared to drug alone the field of cheminformatics helps to get computational data of the Inclusion complexes and allied use of cheminformatics tools made available by the molecular modeling

and cheminformatics cluster with more users^{74,76}. Identifying & understanding structural & functional behavior of chemical host species (Cyclodextrin/ Inclusion complex)^{53,54,63} are one of the challenging issues for medical researchers. Cheminformatics is a new field that helps people understand chemicals better^{70,72}. The review in question largely focuses on cheminformatics and its applications to problems with traditional drug discovery, which in turn aids chemists and researchers in creating medicines with no adverse effects. Such notions should be explicitly included in contemporary information systems, as they play a crucial role in cheminformatics systems^{65,66,69}. Perhaps a combination of the recently developed philosophical interest in information science concepts and the scientific researchers' interest in chemical notions could one day prove useful in the field of cheminformatics^{36,37,39,71}.