**Multi-faceting Cyclodextrin Matrix: Physicochemical and theoretical /Cheminformatics Portfolio**

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**Abstract:**

Cyclodextrin (CDs) has gained prevalence as functional solubilizing excipients with an perpetually increasing list of advantageous properties and functionalities. This is an insight aiming to evaluate the properties of CDs and their vast functionalities in science and technology. The purpose of the article is to scrutinize the nature of chemical aspects of CDs, the way in which they were petitioned in cheminformatics system. In cheminformatics the abstraction is performed to acquire knowledge about compound properties of CDs. The formation of Inclusion complex of beta-CD and heterocycles can be further studied by phase solubility techniques were the stability constant and free energies of heterocyclic molecule from aqueous solution to the cavity of CDs can be calculated, Thermodynamic study(∆G,∆H,∆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.

**Graphical abstract:**

**Keywords:** Cyclodextrin, Bioavailability, Inclusion complex, Host-guest interaction, API, Molecular docking, In-silico Drug design, QSAR, Cheminformatics

**INTRODUCTION**

History of Cyclodextrin In 1891 a French scientist, A. Villiers, isolated bacterial digest from starch and this substance was found to be dextrin & Villiers named it as “cellulosine”1 . Afterward an Austrian microbiologist, Franz Schardinger, reported two crystalline compounds α & β dextrin which was been isolated from a bacterial digests of

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**Figure 1 : 3D structure of Cyclodextrin**

Potato starch. Schrodinger identified β-dextrin as “Villiers” “cellulosine”. These compounds are commonly called Cyclodextrin (α & β- Cyclodextrin types) 2. Figure1: (Beta-Cyclodextrin complex) β-CD. In medicinal chemistry and allied systems these CDs are acknowledged as useful pharmaceutical excipients and due to their comprehensive studies, intensive basic research & industrial production, they can be used extensively in pharmaceutical/biomedical industries. Their molecular structures impart them with a unique property like lipophilc outward lipophilc & central cavity3,4,5. This enables CDs to form non-covalent Inclusion complexes by entrapping drug into their cavities. 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. Formation of Inclusion complex of drug with innocuous agent is a promising approach used to ameliorate the dissolution properties of drug, 12,13,14. Cyclodextrin a kind of pharmaceutical adaptor for solubilizing countless inadequately soluble species including drugs through the CDs complexes. CDs being family of oligosaccharides constitute one of the most widely used molecular hosts in supramolecular chemistry. Encapsulation in the lipophilc (hydrophobic) cavity of CDs firmly affects the physicochemical characteristics of the guest upon the formation of (IC) Inclusion complexes 4. Extensively used natural CDs exists as α, β and Ꝩ consisting of 6, 7, 8 glucopyranose units in their skeleton mentioned in the figure. Throughout the course of complexation procedure, no covalent bond is formed or broken, which strains the physical rather than that the chemical character of process. The Inclusion complexes ameliorate the characteristics of the drug molecule like solubility, the reducing of side effects, Chemical stability and bioavailability, 6,8, 9. The propulsion for drug-CD complex formation are hydrogen bonds, van der Waals forces, hydrophobic interactions between the host and guest molecules and entropy released by uncomplexed water molecules from the CD cavity. During the last few years, computational practice in combination with experimental techniques has been mostly focused on the conformational study of inclusion complex of natural CDs (CD-IC) or their derivatives. There are several computational techniques that are used in molecular modeling studies(MM)69, for the complexes of Cyclodextrin or their derivatives with guest molecules (host–guest chemistry) such as, 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 (lipophilc) cavities & boost the solubility and stability of guest molecules in solvent system like water, these molecules are utilized in a great many chemical fields, including analytical, organic chemistry & bio-chemistry etc.

The characteristic cone-like conformation of sugar ring, expressing a lipophilc (hydrophobic) cavity & hydrophilic (lipophobic) outer surface allows Cyclodextrin matrix to spontaneous complex even poorly soluble compounds in an aqueous environment. Although, the natural Cyclodextrin and their allied complexes are lipophobic, yet their aqueous solubility is limited that is mainly in β- CD system,8. This is because Cyclodextrin molecules bind relatively strongly in their crystal structure. Numerous techniques of manifold nature are being presently utilized for intensifying the solubility of drugs,9.

Complexation is one of the several ways to sympathetically strengthen the physicochemical properties of pharmaceutical compound. It is based on the potentiality of many well known drugs to interact & form new complex drugs, with altered properties in comparison with drug alone. Complexation is the thermodynamic interaction between different constituents of CDs the active drug parts,10. The net energetic driving force must be vital for such complexation, which drags the active drugs into CDs skeleton. Even though the chemical structure of CDs may appear rather simple, the complete characterization & understanding of CDs the chemical properties was a research enterprise, which required more than half a century to be completed. Figure 2 given below includes Cyclodextrin structures with their NMR spectra.

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|  |  |

**Figure 2:** α,β and Ꝩ Cyclodextrin NMR spectra

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Structure of α,β,Ꝩ Cyclodextrin | Cavity diameter (Å)(µm) | Cavity volume (Å3) | Water molecule in cavity (nr) | Aqueous solubility (M) | Gibbs free energy of dissolution KJ/mol |
| C:\Users\HP\Desktop\alpha.tif | ͌  5.2 | 100 | 2.5 | 0.12 | 15 |
| C:\Users\HP\Downloads\MolView (model).png | 6.6 | 160 | 5.0 | 0.016 | 20 |
| C:\Users\HP\Downloads\Gamma cyclodextrin (model) (1).png | ͌  8.4 | 250 | 8.5 | 0.17 | 14 |

**Table 1:** α,β and Ꝩ-Cyclodextrin characteristics

**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 deer 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 reassure a condition that they must fit utterly / partially into CDs cavity18,19.

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 deer 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. There is no breakage or formation of covalent bond involved in the formation of inclusion complexation 21. Selectivity of host-guest recognition arises from size/shape matching mechanism requires the guest molecule to be trapped entirely / partially into a -polar CDs cavity/voids. Figure 3 shows the inclusion complexation of host and guest molecule in CDs networking framework.

**Figure 3:** Beta-Cyclodextrin with N-methylitribulin and Inclusion complex

The internal cavity being lipophilc in nature being hallmark of Cyclodextrin in order to providing the ability of forming complexes to encompass variety of guest molecules 20,22. CDs inclusion is a stoichiometric molecular phenomenon in which usually only a molecule interacts with the cavity of CDs molecule to become entrapped 4, 5,10,23. A variety of non-covalent forces, such as van der Waals forces, hydrophobic interactions & other forces are responsible for the formation of stable complex. It is regarded as encapsulation of drug molecules, or at least the unsteady part of the molecule 16. Encapsulation shield the drug molecule against attack by numerous reactive molecules & so on reduces the rate of hydrolysis, oxidation, steric rearrangement, racemization & even enzymatic decomposition 23. Figure 4 explains the functions of Cyclodextrin and complex formation11,12 .

**Figure 4:** Functions of Cyclodextrin Inclusion complex.

**Methodology used for Inclusion Complex formation**

|  |  |
| --- | --- |
| Methods | Instrumentation |
| 1)Co-precipitation method |  |
| 2)Kneading method |  |
| 3) Microwave irradiation | Optimization of biodiesel synthesis under simultaneous ultrasound-microwave  irradiation using response surface methodology (RSM) |
| 4)Sonnication method | https://m.media-amazon.com/images/I/51QUmYsYdbL.jpg |

**Tools and Description employed in CD analysis and Description6.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Apache** | **My SOL** | **Babel** | **JMol** | **Chemaxon marvin** | **Chemaxon Jchem** | **Auto dock** |

***Docking***

***Structure editing***

***3D molecule viewer***

viewer

***File format converter***

***SQL server***

***HTTP server***

***Ligand physicochemical***

**Cyclodextrin in Pharmaceutics/Biological aspects**

1. **In Vivo CDs Studies**

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

* **Anti-Inflammatory Activities of Cyclodextrin Inclusion Complex**

There are several diseases activates inflammatory process, and consequently attentiveness in substances with anti-inflammatory properties, in particular Cyclodextrin-Inclusion complexes used innovative biotechnology to increase the bioavailability, solubility and pharmacological effects of drugs. The Cyclodextrin most often found in studies of Cyclodextrin-Inclusion complex with anti-inflammatory is beta-Cyclodextrin because of its virtuous capacity for complexation with anti-inflammatory drugs, its appreciable oral acceptability and affordable cost 9,15.

In an attempt to treat inflammatory disorders, an anti-inflammatory compound has been used; these drugs are normally classified as non-steroidal anti-inflammatory drugs and corticosteroids. Many of these drugs have serious side effects, such as gastrointestinal disturbances and cardiovascular risks. Cyclodextrin enhance the effect of anti-inflammatory drugs and refine the side effect profile9,16,17,18.

* **Antinociceptive Activities of Cyclodextrin Inclusion Complex**

Search for product with upgraded Antinociceptive properties has intensified, with the insertion of active principles into substances such as Cyclodextrin to form Inclusion Complex in order to develop more effective products, with better stability, solubility and bioavailability, and a consequent improvement in their pharmacological activities 7,9,18.

* **Anticancer Activities of Cyclodextrin Inclusion Complex**

To enhance the bioavailability and solubility, Betulinic acid, a very auspicious anti-melanoma agent was complexed with water soluble gamma-Cyclodextrin. The physicochemical characterization was done by differential scanning calorimeter (DSC), X-ray and Scanning electron microscope (SEM) 9. Animal model of murine melanoma in mice has been used to test the complex. The results showed depletion in tumor volume and weight, showing that this complexation was beneficial in ant proliferative activity and reduction of tumor development in vivo, 9,25.

* **Intestinal Absorption of Cyclodextrin Inclusion Complex**

Cyclodextrin complex formation could be the solution of many active substances presenting low bioavailability. A study evaluated the intestinal permeability of tanshinone IIA, a substance with cardiovascular benefits complexed with HP-β-CD. The complexes are acquired by co-evaporation. It was observed that increase in the dosage of the complex caused saturation, proposing that the transport mechanism in vivo is related to passive transport. Higher permeability was found for TSIIA in the intestinal membrane with increased oral bioavailability23,24,26.

1. **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 assays9,10,11.



* **Antimicrobial Activities of Cyclodextrin Inclusion Complexes**

2-pentanoylfuran complexed with Cyclodextrin and their solubility and antimicrobial activities against Staphylococcus, aureus, Bacillus subtilis, Escherichia coli were evaluated. The Cyclodextrin increase the solubility of compounds in an hydrated environment and increased their antimicrobial activity26.

* **Anticancer activity of Cyclodextrin Inclusion Complexes**

Aphidicolin, a tetra cyclic diterpene, show specific cytotoxic action against neuroblast cells. This diterpene is important for the evolution of new antitumor drugs because treatment failure is most patients with NB is related to primary or acquired resistance to conventional chemotherapeutic agents. Cyclodextrin decrease the growth of NB cells in vitro9,23,27.

* **Antichagasic Activity of Cyclodextrin Inclusion Complex**

Benznidazole has less solubility and higher toxicity but a very promising drug for the treatment of Chagas disease, and it is essential to find technological solutions for these problems of solubility and toxicity. Therefore Inclusion complex were formed9,10.

* **Antioxidant Activity of Cyclodextrin Inclusion Complexes**

Antioxidant has limited applicability due to their instability in light and oxygen, as well as their low solubility in water. Complexation with CDs can provide higher stability to these molecules which have significant therapeutic potential.

**Cyclodextrin in Drug Formulations and Drug Delivery Systems**

Complexation of guest molecules and Cyclodextrin in aqueous solution results in a considerable rearrangement salvation of water and the removal of the water molecules from the Cyclodextrin cavity and salvation water of guest molecules, with remarkable entropic gain. For relatively small hosts, a 1:1 complex if formed lipophilc molecules displaying a strong lipophilc effect are preferred and the result is a substantial increase in the water solubility of compounds, which constitute the basis for using Cyclodextrin as solubility enhancers for hydrophobic drugs. The nanometric dimensions of Cyclodextrin ensure a high dispersion of lipophilc drugs in water, preventing their crystallization in aqueous media and enhancing their bioavailability. The encapsulated drug can be released upon contact with the lipophilc cell membrane, with CD acting as a drug nanocarriers and delivery systems27,28,29.

**Futuristic prospects of Cyclodextrin**

The subsequent of Cyclodextrin in the pharma industry seems to be intense. There are number of traditional as well as non-traditional applications that are on the scope for commercialization. Novel uses of Cyclodextrin are likely to be explored as the properties of Cyclodextrin are expanded and the number of commercialized and Food and Drug Administration-approved form increases. At present only conventional formulations like tablets, capsules, solutions, ointment and Intravenous solutions have been commercialized using Cyclodextrin29,30. These days, Cyclodextrin are extensively being studied for their application in Novel (DD) drug delivery such as Nanoparticles, Liposome’s, Microspheres and targeted drug delivery that become commercially available in future. Gene therapy is also taken up to generate interest with Cyclodextrin. With the reported difficulties of viral gene delivery, non-viral methods are being further explored. (CD)Cyclodextrin containing polycations have distinctive properties that could be useful in the non-viral delivery of (NA) nucleic acids. These materials show potential for gene delivery in animals, although their utility in humans remains to be proven31.



**Figure 5:** Ꝩ-Cyclodextrin Inclusion complex with heterocyclic molecule

The range of the host molecules is not limited to solid compounds. Liquid and gaseous compounds can be encapsulated in CDs and delivered in aqueous solution16,31,32. CDs can significantly reduce the volatility of low boiling point liquids through host-guest complex formation, and thus can either mask unpleasant odors generated by them or encapsulate and slowly released pleasant odor. Water plays an important role in the formation and stability of host-guest complexes of Cyclodextrin33,34. The affinity of host for their guests usually decreases when the water is removed and decomplexation can occur, especially for compounds with low hydrophobicity, resulting in molecular dispersion of host and guest30,32,35. The phenomenon is reversible and complexes are formed spontaneously when water is added to these dispersions. The very lipophilc drugs do not decomplex from their CD host even in dry form and the CD complex36.

**CDs utilities in Cheminformatics**

The sphere of what now refer to as cheminformatics started some fifty years ago with first strives to explore sub-structural patterns in molecules & tally organic activity with structural information . Cheminformatics had expanded an intact range of tools & techniques for the discovery of new molecules with significant, commercially valuable, properties. Objective of this review is to inspect nature of chemical concepts & the way in which they are applied in cheminformatics systems 25,30,70 . An account of concepts in beliefs & in the information science leads to a study of chemical concepts & their interpretation. Attention is focused on the basis of concepts of subject reaction & property on the organizing concepts of chemical structure, structural similarity, periodicity an on more precise concepts including 2D & 3D structural patterns, reaction types & property concepts etc .Figure 6,shown below shows the cheminformatics data analysis methods70**.**

**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 process36,37,38.

**In-sillico Molecular Docking Study:**

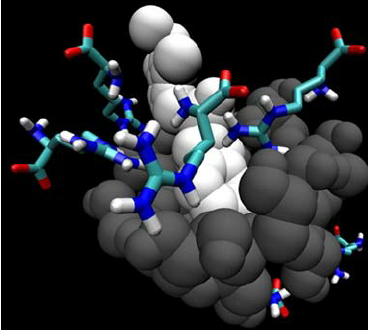
Drug development requires detailed information about the biological activity of the pharmacological compounds against selected targets. The application of computational method to study the formation of intermolecular complexes has been the subject of intensive research70,71. It is widely accepted that drug activity is obtained through the molecular binding of one molecule i.e., ligand to the pocket of another, usually larger molecule i.e., the receptor. The computational process of searching for a ligand that is able to fit both geometrically and energetically the binds called molecular docking site of a protein 44,70,71. Figure 7 gives an idea about drug discovery process.



**Figure7:** Drug discovery process

### Molecular Docking and Simulations

In supramolecular chemistry, molecular docking is a computational process of searching for a guest that is able to fit both geometrically and energetically in the cavity of the host moiety74. This is a process by which two molecules fit together in 3D space. The aim of docking is to predict the predominant binding mode for a guest with a host of a known three-dimensional structure. An established docking protocol for host–guest system implemented in MOE was applied. The docking was carried out with the default parameters, that is, with the triangle matcher method and ordered with the London Δ*G* scoring function. The top five produced poses were ranked as per their docking scores and saved in a separate database file in a .mdb format. The build-in scoring function of MOE, S-score, was used to predict the binding affinity (kcal·mol–1) of the optimized structure of the inclusion complex62,63.Figure 8 shown below is the docking study of CD-IC.



**Figure 8:** Molecular docking study of CD-IC heterocycles

Cheminformatics analytical tools. The development of software and tools for computer assisted organic synthesis are under vast development. This has resulted in many tools and representation for chemical structure. Some of the prominent tools are listed below65, 66,67,70,71,72.

Allied application

Types of tools

Types of tools

|  |  |
| --- | --- |
| * ISIS-Draw | Chemical structure drawing program for windows, published by MDL information system |
| * Chem. Draw | Molecular editor developed by cheminformatics company Cambridge Soft |
| * Chem3D & Chem. finder | Part of chem. office suits program available for Macintosh and Microsoft Windows |
| * Chem. Window | Chemical structure drawing program with several templates. The template is created by customer saved in template folder & opened in preference Dialogue box. |
| * Chem. Sketch | More powerful, user friendly tools for drawing structure |
| * Chem. Reader | Software developer toolkit for translating digital raster images of chemical structure into standard |
| * Log Chem. | Inductive Logical Program based tools for discriminative interactive mining of chemical fragments |
| * Pub Chem. | Open repository for small molecule & their experimental biological activity. It integrates, provides search ,retrieval, visualization, analysis, programmatic access tools in an effort to maximize utility of contributed information |

**Conclusion**: CDs had been known worldwide & beneficial additive used in field of pharmaceuticals & other industries75,78,79. Numerous uses of CDs had been attributed to its proclivity of complexion with varied drug molecules resulting in the formation of corresponding inclusion complex 1,2,3,10 . CDs are also known for its profile as molecular chelating agents with great demand in the area of food, pharmaceuticals & chromatographic techniques (entrenched & also known worldwide for its toxicity modifier)15,16,17,39,45. Single interaction between host-guest molecules is sufficient to change the physicochemical & pharmaceutical properties of drug molecule in the CD network in the form of enhanced water stability of drug stabilization of drugs under different environmental circumstances Types of tools Allied applications like light, heat & oxidizing conditions, i.e. avoids the deterioration of drugs in these sources & also reduction in volatility of drugs 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 formation50,51,52, . 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 users74,76. 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 an emerging field which is used for better understanding of molecules70,72. Given review primarily focuses on cheminformatics and application on drug discovery, issues of traditional discovery, which in turn helps chemists & researchers for developing drugs without side effects. It seems essential for explicit inclusion of such concepts within modern information systems, indeed concepts plays significant role in cheminformatics system65,66,69. Perhaps a combination of the relatively new philosophical interest in concepts in the information sciences and interest of researcher of science in chemical concepts, which finds fruitful utility in the field cheminformatics in the future36,37,39,71.

**References:**