Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

Multi-Purpose Cyclodextrin Metal-Complexes: Physicochemical and Theoretical Portfolio in Drug Domain

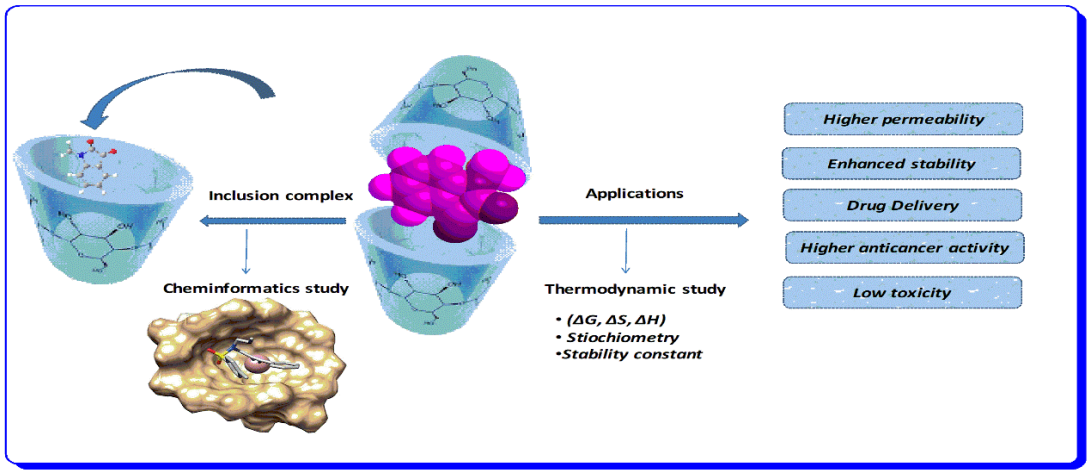
Prachi P. Khobragade[a,d*], Varsha Manvatkar[b,d], Pankaj Meshram[c,d], Rajendra Dongre[d*]

[a]Shri Shivaji Science College, Congrees Nagar, Nagpur
[b]G. D. M. Arts, K. R. N. Commerce & M. D. Science College, Jamner, Jalgaon (M.S.)-424206, India.
[c]Shri. Lemdeo Patil Mahavidyalaya, Mandhal, Nagpur (M. S.)-441210, India.
[d] PGTD Chemistry, R. T. M. Nagpur University, Nagpur, (M.S.)-440033, India.

(Received: 27 October 2023 Revised: 22 November Accepted: 26 December)

KEYWORDS
Host-guest Chemistry, Encapsulation, Inclusion Complex, Metal Complex, Cheminformatics (In-silico study).

Graphical abstract:



ABSTRACT: Organic-inorganic assemblies like host-guest Cyclodextrin (CDs) milieus and specific MOFs or metal complexes found to act as functionally attenuated soluble excipients to offer innate perpetually beneficial features due to dynamic portfolio in the domain of functional drugs. This is an insight aiming to evaluate the properties of CDs and their functionalities in sci-tech. The article aims to scrutinize the nature of the chemical aspects of CDs and to use the system in cheminformatics modules. In cheminformatics, the abstraction is performed to acquire knowledge about the compound properties of CDs. Phase solubility techniques, thermodynamic studies (G, H, S), stability constant, and QSAR can all be used to investigate the development of the cyclodextrin inclusion complex and heterocycles. The review mainly focuses on the synthesis, susceptivity and distinct structure of definitive metal complexes procure essentially from indigenous Cyclodextrin. The pattern and diversity in complexes with respect to cyclodextrin, which ranges from diverse motifs, were displayed.

Introduction:

In 1891, A. Villiers, a French scientist segregated bacterial digest from starch and named as "Cellulosine". Afterwards, two crystalline compounds alpha and beta dextrin were present and isolated from potatoes by Franz Schardinger an Austrian microbiologist. He called beta-cyclodextrin a "Villiers"

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

or “Cellulosine” and these compounds are commonly called Cyclodextrin. In medicinal chemistry and allied systems, cyclodextrin is acknowledged as an important pharmaceutical ingredient.(Carneiro et al. 2019; Păduraru et al. 2022; Sharma and Baldi 2016).Figure 1 shows the 3-dimensional structure of Cyclodextrin.

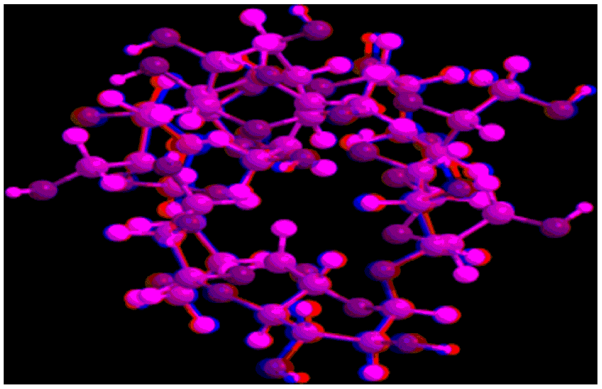


Figure 1: 3D Structure of Cyclodextrin

Their chemical architecture endows them with a special quality like core cavity and outward lipophilia by trapping the medication in their cavities, CDs can then create non-covalent inclusion complexes (Yuan Liu †, Ting Lin † and, Qiaowen Wang, Shujin Lin 2021). They dramatically modify the physico-bio-chemical attributes of the parent drug & CD(Zhou et al. 2023). The CDs get 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 the drug-inclusion complexes with harmless agents (Loftsson et al. 2005). Through the use of CD complexes, Cyclodextrin is a type of pharmacological adapter used to dissolve several species that are insufficiently soluble(Di Cagno 2017; Fatiha et al. 2013). In supramolecular chemistry, CDs belong to the branch of oligosaccharides to show the host-guest compatibility with a supramolecular framework (Chaudhary and Pharmacy 2013). The creation of (IC) Inclusion complexes strongly influences the guest physicochemical properties to entice within the lipophilic void of CDs. Extensively used natural CDs with gluco-pyranose parts in their skeleton are mentioned in the table1**.** The covalent bonds remain untouched throughout the complexation process, the physical properties are under high stress while the chemical attributes remain unchanged (Simanchal Dash1 2017). The solubility is enhanced by the inclusion of complexes., chemical stability and bioavailability of the therapeutic molecule as well as its potential to reduce side effects(Goran M. Petrović1, Gordana S. Stojanović1, Olga P. Jovanović1, Aleksandra S. Đorđević1, Ivan R. Palić1 2012; Jambhekar, Casella, and Maher 2004; Nguyen et al. 2013). The bonding interactions and thermodynamic properties contribute to the drug-CD complex's development (Kfoury, Landy, and Fourmentin 2018; Khemtong et al. 2005; Sambasevam et al. 2013)(Saokham et al. 2018). The structural analysis 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(Chatzidaki et al. 2020). Many computational techniques are used for the Cyclodextrin complexes or their derivatives (host-guest chemistry), such as density functional theory, hybrid own N-layer Integrated Orbital Molecular mechanics, semi-empirical method, & molecular dynamics (MD)(Alvira 2017; Butnariu et al. 2021; Chakraborty et al. 2019; Sandilya, Natarajan, and Priya 2020).

One popular synthetic cyclodextrin derivative is called hydroxypropyl-β-cyclodextrin. HP-βCD has significantly higher water solubility as compared to native cyclodextrin. Hydroxypropyl-β-cyclodextrin being dissolution and drug excipients, widely utilized in the food, cosmetic, and medical industries. HP-βCD systems produced flawless, consistent nanofibrous structures with no defects. Furthermore, the IC of cortisol with HP-βCD exists in an amorphous state in the Cortisol/HP-βCD nanofibers, according to the structural and thermal characterization of the nanofibers. The thiabendazole/HP-βCD combination was effectively synthesized in earlier study, this complexed nanofibrous structure was created by electro-spinning, showed improved antifungal activity and drug’s solubility(Munnangi et al. 2023).

Generally speaking, thiram's thermal stability, solvability, and fungicidal activity were all enhanced by the synthesis of thiram/HP-βCD-IC-NF. This work represented a significant attempt at creating water-based pesticide formulations and offered a useful resource for future formulation work. It is consistent with the safe, environmentally friendly, and water-soluble pesticide formulation that agriculture supports. It offers fresh concepts for the creation of pesticides(Gao et al. 2021). One popular synthetic cyclodextrin derivative is called hydroxypropyl-β-cyclodextrin (HP-βCD). HP-βCD has

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

significantly higher water solubility as compared to native cyclodextrin. The product is a perfect pharmaceutical excipient and solubilizer, with widespread applications in the food, cosmetic, and medical industries.

In this work, the solution of HP-β-CD was prepared to improve the oral biological availability of nitrendipine (NT). The spectroscopic technique was used to analyses of the collected particles revealed the development of complex in non-polar solvent. The stoichiometry ration is 1:1 between the inclusion complexes as revealed by phase solubility test(Liang et al. 2023). The remarkable application of such inclusion complexes from food to pharmaceutical and cosmetics industries. Due to enhanced solubility of HP-β-CD, it is effective to used in drug delivery mechanism.

In pharmaceutical formulations, hydroxypropyl-beta-cyclodextrin, a cyclic oligosaccharide, is extensively used as an enabling excipient and cholesterol modulator. With the recent license to treat lysosomal lipid storage disorders, the inclusion complex are now used in Sphingolipidoses disease. Given that leukaemia and other cancers have been linked to dysregulated cholesterol metabolism and/or cholesterol buildup, we postulated that HP-β-CyD may possess anticancer properties in and of itself. This work shows that the accessibility to use the β CD to suppresses at physiologically accessible levels, HP-β-CyD suppresses blood cancer cell. Also the treatment with HP-β-CyD decreased intracellular cholesterol, which significantly inhibited the development of leukemic cells.

A chronic, inflammatory skin condition that is challenging to treat is psoriasis. Dietary flavonoid quercetin (QT) is well-known for its anti-inflammatory properties and safe application to people. However, due to its low stability in semisolid preparations, where it tends to recrystallize, and poor water solubility, quercetin poses a significant challenge when applied topically for the treatment of psoriasis. A novel liposome-in-gel formulation for the topical treatment of psoriasis based on quercetin is presented in this work. Hydroxypropyl-β-cyclodextrin (HP-CD) stabilizes quercetin-loading liposomes by forming a layer of HP-CD coating on the liposome interface through hydrogen bonding with phospholipids. This process improves liposome stability. Several analytical methods, including TEM, Raman, and FTIR spectroscopy, were employed to describe the molecular coordination patterns between cyclodextrin.

As Cyclodextrin comprise organic molecules in their hydrophobic (lipophilic) cavities & boosts the inaccessibility of heterocyclic guest molecules in the solvent system like water, these molecules are utilized in numerous chemical fields, including analytical, organic chemistry & bio-chemistry etc.

Cyclodextrin matrix can spontaneously bind even weakly soluble molecules in an aqueous environment thanks to the distinctive toroid shape, expressing a hydrophobic interior & lipophobic outer rims(Manvatkar et al. 2023; Szente and Fenyvesi 2018). Even though Cyclodextrin and its related complexes are lipophobic in nature, their solubility in water is restricted, with a focus on the CD system(Christaki et al. 2023). 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(Cheirsilp and Rakmai 2017; Psimadas et al. 2012).

One of the many methods for harmonizing and 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(Abou-Okeil et al. 2018; Heinrich, Pajaziti, and Roziev 2014; Santos et al. 2016). Complexation is the thermodynamic interaction of various CDs (the active ingredient components) constituents. For such complexation, which pulls the active medications into the skeleton of CDs(Ghuzlaan, Al Omari, and Al-Sou'od 2009; Yang et al. 2012), the net energetic driving force must be essential(Abbasi 2017). Even though 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(García et al. 2014).

In Cyclodextrin, the glucose units are connected via α-1,4-glycosidic bonds to form cyclic oligosaccharides(Hazai et al. 2010). They have an exclusive toroidal assembly with a lipophilic centre and lipophobic exterior surface. Because of their structural characteristics, Cyclodextrin shows the ability to form IC with host-guest chemistry built with supramolecular entities (Cid-Samamed et al. 2022; Louiz, Labiadh, and Abderrahim 2015). These cyclodextrins also can form

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

coordinated complexes with metal ions. These complexes demand implementation in various fields, including the chemical industry, pharmaceutics, and environmental science(Iacovino et al. 2016).

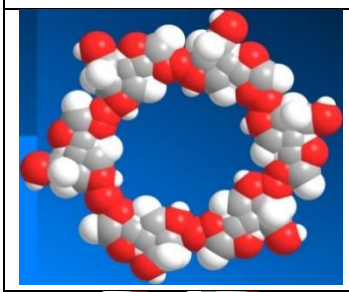
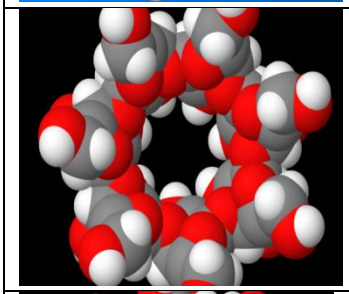
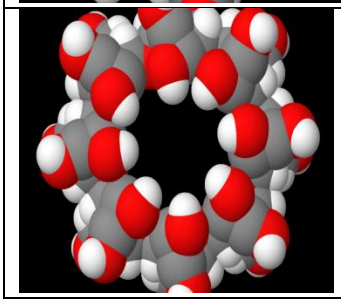
Structure of α,β,γ Cyclodextrin	Cavity diameter (Å)(µm)	Cavity volume ($Å^3$)	Water molecule in cavity (n^r)	Aqueous solubility (M)	Gibbs free energy of dissolution KJ/mol
	≈ 5.2	100	2.5	0.12	15
	6.6	160	5.0	0.016	20
	≈ 8.4	250	8.5	0.17	14

Table 1: α,β and γ-Cyclodextrin characteristics(Di Cagno 2017; Shimpi, Chauhan, and Shimpi 2005)

Formation of the complex:

The capability to form inclusion complexes is the most important feature of CDs. Such complexes are named "host-guest complexes" and can be made with an extremely broad variety of different natures and states of composites(Hazai et al. 2010; Nan et al. 2015). The host fitted the guest moiety inside the void of the Cyclodextrin by a supramolecular dimension fit between the two molecules(Iacovino et al. 2016).

Cyclodextrin can form complexes with metal ions by encapsulating the metal ions within their hydrophobic cavities. The formation of these complexes is driven by various intermolecular forces. These complexes show a wide range of potential applications with enhancing properties and reactivity of metal ions tailored to suit the hydrophobic cavities of Cyclodextrin (Soares et al. 2009).

Diversification in structural entity and bonding ability makes CDs important tools for forming various complexes. Overall the 2° -OH groups on CDs get deprotonated which leads to forming a host that enables guest molecules connected through a multidentate metallo-macrocycle sphere. These cavities contain metal ions of different sizes. Two types of sandwich complexes shown in Figure 2 are reported as homo-

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

metallic and hetero-metallic systems where metals are distributed in various patterns depending upon the density that appears in the CD molecules. The groups on CDs show bonding with solvents which resembles the noncovalent structure resulting in constructing supramolecular moiety with layered networks. (Prochowicz et al. 2016).

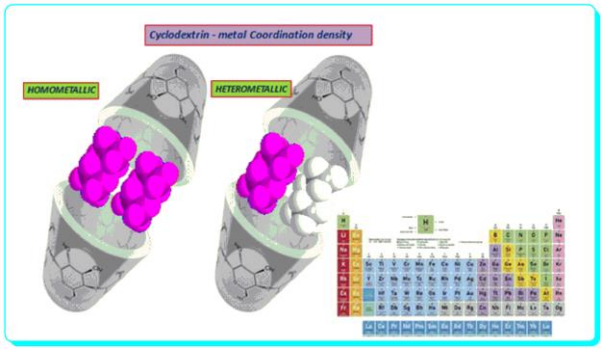


Figure 2: Cyclodextrin-metal complex in sandwich form.

CDs complexes with metals:

The range of their macrocyclic topologies and molecular structures is discussed in this part, with an emphasis on the methods used to synthesize native and CD-based metal–organic complexes. The adaptability of CD-metal ion coordination and the geometric array of related compounds (Lippold et al. 2009). Generally, when CDs' secondary hydroxyl groups deprotonate and combine with metal ions, sandwich-type complexes are formed (Bellia et al. 2009; Sivakumar and Parinamachivayam 2022). These complexes consist of partially or completely deprotonated CD molecules joined by a multidentate metallo-macrocycle sphere. Such macro-molecules encompassed either 1 or 2, different kinds of cationic species. Only two homo-metallic sandwich-type compounds with structural characterization are known at this time. In a family of heterometallic sandwich-type compounds, the metals undergo sequential reactions. Different patterns can be seen in the distribution of metal ions inside the metallo-macrocycle ring in heterometallic systems, liable on the intrinsic sum of coordination spots in cyclodextrin and the variety of metal ions used. Specifically, using Li^+ as auxiliary ions results in double-decker molecules which encompass the cationic species within the rings or a metallomacrocycle with alternating metal centres of {M, Li}n type. Conversely, using Na+ as a secondary cation typically encourages the metallomacrocycle {M, Na}n to develop. Due to their bigger sizes, these ions—K+ and Rb+ in particular—are found outside the sandwich-type complex cavity and connect the nearby molecules in cylindrical, longer structures. The establishment of hydrogen bonds by solvent molecules with the free -OH moiety in CDs influences architectural noncovalent assembly. The morphological analysis reveals that sandwich-type topologies with nonporous close-packing assembly inside layered systems are preferred (Inoue et al. 2022). Mono- and dinuclear systems creating an assembly resembling a bucket wheel comprise another family of CD-metal-based compounds. Complexes based on ˛-CD metals A natural -CD is found to be an effective ligand for metal, according to a literature search. There have been reports of several heterometallic sandwich-type complexes wherein multinuclear metallomacrocycle rings link partially or completely deprotonated -CD molecules. Nevertheless, homo-metallic -CD-based complex examples are scarce. Depending on the auxiliary ions employed, the macrocycle loop of heterometallic systems exhibits distinct patterns. Sandwich-type compounds with a {M, Li}n-type by employing the auxiliary Li^+ ion. CD molecules can partially or completely deprotonate with the Na^+ metal ions, allowing them to template transition metal ions and form {M, Na}n-type rings. Alternatively, dinuclear sandwich-type complexes are formed upon the coordination of alkali metal ions. In these complexes, auxiliary ions situated beyond the void of -CDs covalently connected with the neighbouring molecules shown above in Figure 3, within a longer framework curiously, the crystal studies reveal a bonding relationship between host-guest molecules with varied networking capabilities inside CD complexes. The initial structurally characterized metallic complexes of CD were created by treating -CD with $Cu(NO_3)_2 \cdot 3H_2O$ in a range of alkaline medium.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

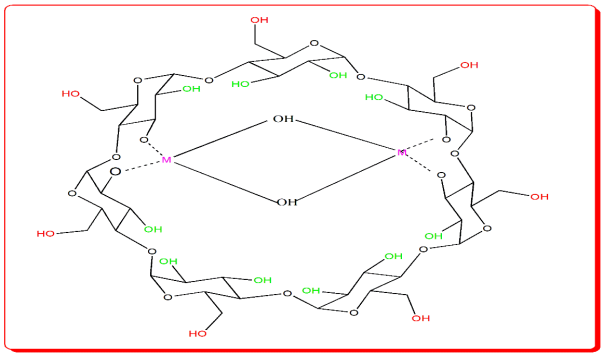


Figure 3: β -CD metal complex formation

The heterometallic Cu − Li − -CD molecules $Li_3[(-CD)_2Cu_3Li_3(H_2O)_3]$ •$41H_2O$ with Li^+ as the auxiliary ion was synthesised. A six-membered heterometallic ring unites two six-time deprotonated chemical structures of one to form a double-toroidal structure. The metallomacrocycle is formed by combining 3 Cu^{2+} and Li^+ ions to generate 3 {Cu, Li} units. The complexes show square pyramidal distortion with OH- group at the base and H_2O ligand at the apex connected well within the CD cavity and form sandwich-type complexes, each Cu^{2+} centre adopts non-ideal square planar arrangement with the CuO_4 environment. The development of shorter intramolecular O H• • O− hydrogen bonds modifies the conical shape of -CD. In the presence of Na+ as the auxiliary ions, a similar sandwich-type combination with the formula $Na_3[(-CD)_2Cu_3Na_3(H_2O)_3]$•32H2O•acetone (2) was produced. Notably, a thorough examination of the crystal structure indicates that the sandwich-type complexes 1 and 2 have distinct stacking in their crystal lattices. A nonporous supramolecular architecture was formed as a result of the neighbouring molecules of 1 being arranged in a herring-bone pattern, according to an examination of the crystal structure. Nonetheless, the creation of a more extended shape in the crystal structure of 2 is facilitated by auxiliary ions that are situated beyond the cavity of sandwich-type complexes. Specifically, these Na^+ ions formed a deformed hexagonal 2D sheet by forming coordination connections between the neighbouring sandwich-type complexes via the free main and 2˚ hydroxyl groups of the glucopyranose ring(Prochowicz et al. 2016).

Complexation Methods:

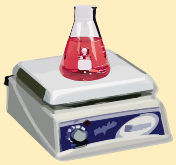
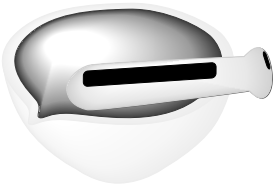
Methods	Instrumentation
1)Co-precipitation method	
2)Kneading method	
3) Microwave irradiation	
4)Sonication method	

Table 2: Methodology used for formation of Host-guest complex(Birhade et al. 2010).

Characterization of Complex:

1. Quantitative analysis of Guests in the complexes: Analytical techniques for quantitative determination including Spectroscopic data obtained by UV-visible radiations and chromatography techniques . The

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

complexation of a guest often induces a slight change in λ_{max}.

2. Thermogravimetric analysis: The difference in weight with respect to temperature changes is noted between inclusion complexes and adsorbates, and then it has been utilized to define the unique thermal effects resulting from molecular entrapment. Techniques like thermography (TG, DTG) are often utilized. Analysis of Thermal Evolution (TEA) Calorimetric using DSC and vacuum sublimation.

DSC measures the rate at which heat is absorbed or evolved by the sample throughout the course of a temperature program, for example. The DSC thermograph of paracetamol reveals that it melts and starts to decompose at 168°C. The simple mixture's DSC curves are similar to the total of the cures of two pure drugs. A little exothermic peak is observed upon melting, indicating complex creation. The breakdown of paracetamol only began at roughly 220°C, and the complex did not exhibit the melting peak of the guest material. Many visitors exhibit this behaviour, melting or re-crystallizing before reaching the temperature at which -CD decomposes.

3. Infra-Red Spectroscopy: The complex formation hardly has any effect on the CD distinctive bands, which comprise the majority of the complex. IR spectroscopy studies of such CD complexes with a guest containing a carbonyl group are typically published in the literature. This is because complexation with CD greatly covers and shifts the carbonyls' bands, which are sufficiently spaced and well-separated (approximately 1680–1700 cm–1).

4. X-ray Powder Diffraction: Liquid guest molecules do not generate diffraction patterns. When dealing with a solid guest molecule, it is essential to compare the anticipated complex diffractogram with a physical combination of the guest and Cyclodextrin. Complex creation is quite likely when the diffractograms differ, meaning that the distinctive peaks of one or more components vanish and new ones emerge as a result of the intricate tests.

5. Scanning Electron Microscopy: One kind of electron microscope is the scanning electron microscope (SEM), which uses a high-energy electron beam to scan a sample surface in a raster scan pattern. A scanning electron microscope was utilized to examine the surface morphology of various raw materials such as drugs, Cyclodextrin, and binary systems (Prabu et al. 2015; Shinde, Jeong, and Jung 2018; Spulber et al. 2008).

Double-sided tape was used to secure the samples to a brass stub. A tiny layer of copper was then vacuum-coated to make the samples electrically conductive, and pictures were taken.

Nevertheless, the acquired microphotographs corroborate the concept of consecutively integrating new individual components, along with the utilization of SEM techniques, which proves to be inadequate for achieving genuine complex innovation. The common examples are:

1. Cyclodextrin-Silver Complexes: Antimicrobial properties(Yang et al. 2023)
2. Cyclodextrin-Gold Complexes: explored for their potential in drug delivery and cancer therapy. Gold nanoparticles can be functionalized with cyclodextrins to improve drug solubility and targeting(Abdellatif et al. 2023).
3. Cyclodextrin-Copper Complexes: Analytical chemistry for the pre-concentration and separation of copper ions from solutions(Bucur et al. 2021).
4. Cyclodextrin-Iron Complexes: the removal of iron from industrial wastewater and used as a catalyst(Meymand et al. 2022).
5. Cyclodextrin-Platinum Complexes: drug delivery for cancer treatment as cytotoxic properties(Giglio et al. 2015; Tang et al. 2014).
6. Cyclodextrin-Zinc Complexes: for application in analytical chemistry and drug stability(Ding et al. 2010).
7. Cyclodextrin-Heavy Metal Complexes: removal of hazardous chemicals from the environment like Pb, Cd, Hg etc(Kurup, Parmar, and Mayilswamy 2021).
8. Cyclodextrin-Rare Earth Metal Complexes: selective extraction with high-tech applications(Iacovino et al. 2016; Yunling et al. 2007).

Porous coordination polymer (PCPs), are a rapidly emerging class of crystalline and porous materials that are attracting a lot of interest for a variety of uses. There have been attempts on examining the PCPs generation

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

twenty-six, twenty-seven nucleation stage and the linking and severing of the fundamental elements throughout PCPs expansion(Smaldone et al. 2010).

Cyclodextrin-based porous coordination polymer (PCPs) are a type of biofriendly PCPs that incorporate CDs as a coordinating component. Due to their exceptional ability for inclusion, lipophobic nature, versatile aptitude in forming supramolecular complexes, CD-PCPs have drawn significant attention across diverse fields such as capturing carbon-dioxide, selective adsorption of small molecules, sensing technologies, and biomedical fields. Nevertheless, the aqueous vulnerability of CD-PCP-based material presents a challenge. To gain a better understanding of how the structure influences the function of CD-PCPs and to further investigate the disintegration and liberation processes in comprehensive studies focusing on the kinetics of CD-PCPs dissolution can enhance our comprehension.

Porous coordination polymer (PCPs), are extensively used as encapsulating matrices for a variety of guest molecules, with applications ranging from drug delivery to chemical sensing. PCPs stand out for their remarkable permeability, extensive interfacial region, and variety of active sites. These characteristics allow PCPs to stabilize guest molecules in the confined pores of PCPs through multi-site non-covalent interactions and high encapsulation efficiency **(Danyu, Wenqian, & Yongguang, 2021)**. Interestingly, alkali metal ions and naturally occurring γ-cyclodextrin (γ-CD) building blocks assemble which use for food applications(Su et al. 2024).

Complexation mechanism of drug release from CD complexes:

The inner cavity being lipophilic in nature is the hallmark of Cyclodextrin providing the capability to form complexes to encompass a variety of guest molecules (Rong et al. 2014). A stoichiometric molecular phenomenon known as CD inclusion occurs when a molecule primarily interacts with the CD molecule's cavity to become imprisoned. Stable complex formation is caused by a multitude of intermolecular forces, including hydrophobic contacts, van der Waals forces, and others. It is thought to encapsulate drug molecules, or at the very least, the erratic portion of the molecule (Agrawal and Gupta 2012; Boczar and Michalska 2022). Encapsulation slows down the rate of hydrolysis, oxidation, steric rearrangement, racemization, and even enzymatic breakdown by protecting the drug molecule from several reactive chemicals (Christaki et al. 2023). Figure 4 shows the IC formation of beta Cyclodextrin with N-methyl isatin and Figure 5 shows the various applications of Cyclodextrin in numerous fields.

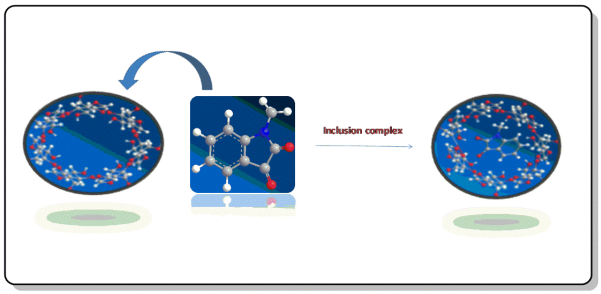


Figure 4: IC formation of β-CD-N-methyl-Isatin

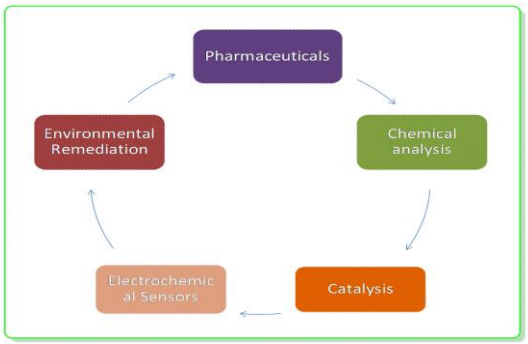


Figure 5:Applications of Cyclodextrin in numerous fields

Stability constant (Ks) and allied thermodynamic parameters (ΔG°, ΔH° and ΔS°): An essential component of the inclusion phenomenon that gauges how well host-guest complexation is working is the stability constant (Ks). By utilizing the variations in guest molecule absorbance (ΔA) in relation to β-Cyclodextrin concentration at varying temperatures, one may compute the stability constants (Ks). The absorbance results for different β-CD concentrations showed that the guest molecule's aqueous solubility steadily increased as the β-CD concentration rose. An equation was used to get the stability constant (Ks) for the temperature range under study(Chang et al. 2023; Sanku et al. 2019; Siva, Thulasidhasan, and Rajendiran 2013).

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

Ks = $\boldsymbol{Intercept}$ /$\boldsymbol{Slope}$

The host-guest connection is significantly impacted by temperature, as the research indicates that guests from the β-CD cavity are de-capsulated at higher temperatures. It was discovered that when temperature increased, stability constant values decreased. Using calculated Ks values, the thermodynamic parameters related to the inclusion of complex formation at the studied temperature range were found, including free energy change (ΔG), enthalpy change (ΔH), and entropy change (ΔS). The change in free energy was computed using the relation.

$\Delta \boldsymbol{G} = -\boldsymbol{RTlnk}$…… (1)

Using Vant't Hoff equation 4, enthalpy and entropy changes have been determined.

$\boldsymbol{lnK} = -\Delta \boldsymbol{H}\ \boldsymbol{RT} + \Delta \boldsymbol{S}\ \boldsymbol{R}$…… (2)

R is the gas constant (8.314 J K-1 mol−1), and T is the absolute temperature.

From Vant Hoff's equation 4, the plot between ln Ks and 1/T shows a linear relationship. The interaction between IPH and β-CD was an exothermic process that occurred spontaneously within the investigated temperature range. The thermodynamic parameter changes specify that the host-guest association is mainly driven by weak forces such as Vander Waal, hydrogen bonding, etc. between the interacting species. When compared to the guest alone, the inclusion complex's rotational and vibrational degrees of freedom are assumed to be lower (Meshram, Manwatkar, and Dongre 2023; Prabu et al. 2015).

CDs utilities in Cheminformatics:

The sphere of what is now referred to as cheminformatics started some fifty years ago with first strives to explore sub-structural patterns in molecules & and tally organic activity with structural information. Cheminformatics has expanded an intact range of tools & techniques with significant and commercially valuable for material development(Ertl 2008; Firdaus Begam and Satheesh Kumar 2012). The objective of this review is to inspect the nature of the molecules & their application in cheminformatics systems. A study of chemical concepts and their interpretation follows an analysis of concepts in information science and beliefs. The organizational notions for molecular patterns such as 2D and 3D and reaction specificity are the basis for the focus of attention, along with the concepts of subject reaction & property(GUHA RAJARSHI & BENDER ANDREAS 2012). The approaches for cheminformatics data analysis are depicted in Figure 6 below.

Figure 6: Cheminformatics data analysis

Figure 6: Cheminformatics data analysis

Cheminformatics with huge amounts of chemical data, assembled by chemists using a proper database, figure 8 shown below shows various fields in cheminformatics. The field of chemistry needs emerging techniques for knowledge extrication from data to model complex relationships between the structure of chemical compounds & and bioactivity. Cheminformatics is an amazing way that information technology (IT) is used to support chemists and researchers in problem-solving, data organization, analysis, and comprehension for the creation of new compounds, materials, and processes.

Cheminformatics analytical tools.

Software and tools for computer-assisted organic synthesis are now undergoing extensive development. Numerous tools and representations for chemical structure are the consequence of this. The following is a list of some of the well-known tools.

S. No.	Types of tools	Allied Applications
1.	**ISIS-Draw**	Chemical structure sketching software for Windows is offered by MDL Information System.
2.	**Chem. Draw**	Cambridge Soft, a cheminformatics business, created a molecular editor
3.	**Chem3D & Chem. finder**	A portion of the Microsoft Windows

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

		and Macintosh Chemical Office suite software
4.	**Chem. Window**	A program that provides a large number of chemical structure templates. The client builds the template, opens the preference dialogue box, and saves it in the template folder.
5.	**Chem. Sketch**	More powerful, user-friendly tools for drawing structure
6.	**Chem. Reader**	A toolbox for software developers to convert digitized raster representations of chemical structures into standard
7.	**Log Chem.**	Tools based on an inductive logical program for selective, interactive mining of chemical fragments
8.	**Pub Chem.**	An open repository which offers data on chemicals and biological actions of the molecules.

In-silico Molecular Docking Study

Comprehensive data regarding the biological activity of pharmacological substances against specific targets is necessary for drug development. Much research has been done on the application of computational approaches to the study of the formation of intermolecular complexes. It is commonly acknowledged that the chemical binding of one molecule, the ligand, to the pocket of another, typically a bigger molecule, the receptor, results in pharmacological activity. The computational procedure of looking for a ligand that can match a protein's molecular docking site both energetically and geometrically(Garg, Ahmad, and Hassan 2021; Roy et al. 2020; Sompornpisut, Deechalao, and Vongsvivut 2002). An overview of the drug discovery process is shown in Figure 7.

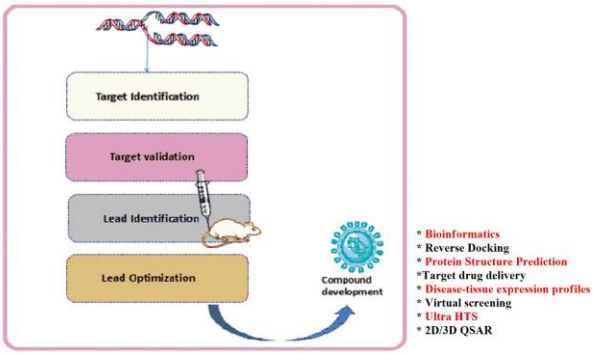


Figure 7: Drug discovery process

Abbreviations:

CD: Cyclodextrin

IC: Inclusion complex

MOFs: Metal-organic framework

Conclusion: In summary, Cyclodextrin is an effective molecule showing supramolecular entities due to host-guest interaction with drug moiety leads applied in the administration of drugs and the medical field. The other dimension of Cyclodextrin is to form complexes with metal ions which is helpful for extraction and environmental remediation. Nowadays, Cyclodextrin is frequently utilized to stabilize medications by providing incredibly selective and non-toxic options. This complexation method creates new opportunities for improving the anti-microbial properties of bioactive substances. This brief review covers the development of Cyclodextrin complexes with different metal ions and heterocyclic molecules that have multiple applications in various fields. Additionally, a study conducted in cheminformatics demonstrates the non-covalent bonding that results in the intermolecular structure of the host-guest compound. The ratio and stability constant of the complex can be estimated using thermodynamics research.

Conflict of Interest:

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

References:

1. Abbasi, Mohsen. 2017. "β-Cyclodextrin as an Efficient and Recyclable Supramolecular Catalyst for the Synthesis of Heterocyclic Compounds." Journal of the Chinese Chemical Society 64(8):896–917. doi: 10.1002/jccs.201600887.
2. Abdellatif, AHmed A. H., Fatma Ahmed, Ahmed M. Mohammed, Mansour Alsharidah, Amal Al-Subaiyel, Waad A. Samman, Aisha A. Alhaddad, Samiah Hamad Al-Mijalli, Mohammed A. Amin, Hassan Barakat, and Shaaban K. Osman. 2023. "Recent Advances in the Pharmaceutical and Biomedical Applications of Cyclodextrin-Capped Gold Nanoparticles." International Journal of Nanomedicine 18:3247–81. doi: 10.2147/IJN.S405964.
3. Abou-Okeil, A., M. Rehan, S. M. El-Sawy, M. K. El-bisi, O. A. Ahmed-Farid, and F. A. Abdel-Mohdy. 2018. "Lidocaine/β-Cyclodextrin Inclusion Complex as Drug Delivery System." European Polymer Journal 108(September):304–10. doi: 10.1016/j.eurpolymj.2018.09.016.
4. Agrawal, Rajesh, and Vishal Gupta. 2012. "Cyclodextrins – a Review on Pharmaceutical Application for Drug Delivery." International Journal of Pharmaceutical Frontier Research 2(1):95–112.
5. Alvira, E. 2017. "Molecular Dynamics Study of the Factors Influencing the β-Cyclodextrin Inclusion Complex Formation of the Isomers of Linear Molecules." Journal of Chemistry 2017. doi: 10.1155/2017/6907421.
6. Bellia, Francesco, Diego La Mendola, Carlo Pedone, Enrico Rizzarelli, Michele Saviano, and Graziella Vecchio. 2009. "Selectively Functionalized Cyclodextrins and Their Metal Complexes." Chemical Society Reviews 38(9):2756–81. doi: 10.1039/b718436k.
7. Birhade, S. T., V. H. Bankar, P. D. Gaikwad, and S. P. Pawar. 2010. "Preparation and Evaluation of Cyclodextrin Based Binary Systems for Taste Masking." International Journal of Pharmaceutical Sciences and Drug Research 2(3):199–203.
8. Boczar, Dariusz, and Katarzyna Michalska. 2022. "Cyclodextrin Inclusion Complexes with Antibiotics and Antibacterial Agents as Drug-Delivery Systems—A Pharmaceutical Perspective." Pharmaceutics 14(7). doi: 10.3390/pharmaceutics14071389.
9. Bucur, Stefan, Marius Niculaua, Catalina Ionica Ciobanu, Neculai Catalin Lungu, and Ionel Mangalagiu. 2021. "A Simple Synthesis Route for Selectively Methylated β-Cyclodextrin Using a Copper Complex Sandwich Protecting Strategy." Molecules 26(18). doi: 10.3390/molecules26185669.
10. Butnariu, Monica, Massimiliano Peana, Ioan Sarac, Salvatore Chirumbolo, and Haralampos Tzoupis. 2021. "Analytical and in Silico Study of the Inclusion Complexes between Tropane Alkaloids Atropine and Scopolamine with Cyclodextrins." Chemical Papers 75(10):5523–33. doi: 10.1007/s11696-021-01742-4.
11. Di Cagno, Massimiliano Pio. 2017. "The Potential of Cyclodextrins as Novel Active Pharmaceutical Ingredients: A Short Overview." Molecules 22(1):1–14. doi: 10.3390/molecules22010001.
12. Carneiro, Simone Braga, Fernanda Ílary Costa Duarte, Luana Heimfarth, Jullyana De Souza Siqueira Quintans, Lucindo José Quintans-Júnior, Valdir Florêncio Da Veiga Júnior, and Ádley Antonini Neves De Lima. 2019. "Cyclodextrin-Drug Inclusion Complexes: In Vivo and in Vitro Approaches." International Journal of Molecular Sciences 20(3):1–23. doi: 10.3390/ijms20030642.
13. Chakraborty, Susama, Pranab Ghosh, Basudeb Basu, and Amitava Mandal. 2019. "Inclusion Complex of β-Cyclodextrin with Tetrabutylammonium Bromide: Synthesis, Characterization and Interaction with Calf Thymus DNA." Journal of Molecular Liquids 293:111525. doi: 10.1016/j.molliq.2019.111525.
14. Chang, Chaokang, Meng Song, Mingxing Ma, Jihong Song, Fengyi Cao, and Qi Qin. 2023. "Preparation, Characterization and Molecular Dynamics Simulation of Rutin–Cyclodextrin Inclusion Complexes." Molecules 28(3). doi: 10.3390/molecules28030955.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

15. Chatzidaki, Maria, Ioanna Kostopoulou, Chryssa Kourtesi, Ioanna Pitterou, Spyridon Avramiotis, Aristotelis Xenakis, and Anastasia Detsi. 2020. “β-Cyclodextrin as Carrier of Novel Antioxidants: A Structural and Efficacy Study.” Colloids and Surfaces A: Physicochemical and Engineering Aspects 603(June):125262. doi: 10.1016/j.colsurfa.2020.125262.
16. Chaudhary, V. B., and Shri Sarvajanik Pharmacy. 2013. “Chaudhary & Patel,.” Cyclodextrin Inclusion Complex To Enhance Solubility of Poorly Water Soluble Drugs: A Review 4(1):68–76.
17. Cheirsilp, Benjamas, and Jaruporn Rakmai. 2017. “Inclusion Complex Formation of Cyclodextrin with Its Guest and Their Applications.” Biology, Engineering and Medicine 2(1):1–6. doi: 10.15761/bem.1000108.
18. Christaki, Stamatia, Revekka Kelesidou, Vaia Pargana, Evangelia Tzimopoulou, Magdalini Hatzikamari, and Ioannis Mourtzinos. 2023. “Inclusion Complexes of β-Cyclodextrin with Salvia Officinalis Bioactive Compounds and Their Antibacterial Activities.” Plants 12(13). doi: 10.3390/plants12132518.
19. Cid-Samamed, Antonio, Jaruporn Rakmai, Juan Carlos Mejuto, Jesus Simal-Gandara, and Gonzalo Astray. 2022. “Cyclodextrins Inclusion Complex: Preparation Methods, Analytical Techniques and Food Industry Applications.” Food Chemistry 384(August 2021):132467. doi: 10.1016/j.foodchem.2022.132467.
20. Ding, Lixiu, Jiang He, Junkai Fu, and Jinlong Zhang. 2010. “Study on β-Cyclodextrin Inclusion of Zn(II) Aromatic Complex and Its Analytical Application.” Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy 75(2):604–9. doi: 10.1016/j.saa.2009.11.025.
21. Ertl, Peter. 2008. “Cheminformatics and Its Role in the Modern Drug Discovery Process.” (June):0–28.
22. Fatiha, Madi, Largate Leila, Nouar Leila, and Khatmi Djamel Eddine. 2013. “Computational Study on the Encapsulation of Ethylparaben into β-Cyclodextrin.” Journal of Inclusion Phenomena and Macrocyclic Chemistry 76(3–4):379–84. doi: 10.1007/s10847-012-0209-6.
23. Firdaus Begam, B., and J. Satheesh Kumar. 2012. “A Study on Cheminformatics and Its Applications on Modern Drug Discovery.” Procedia Engineering 38(Icmoc):1264–75. doi: 10.1016/j.proeng.2012.06.156.
24. Gao, Shuang, Yanyan Liu, Jingyu Jiang, Xiaoming Li, Fei Ye, Ying Fu, and Lixia Zhao. 2021. “Thiram/Hydroxypropyl-β-Cyclodextrin Inclusion Complex Electrospun Nanofibers for a Fast Dissolving Water-Based Drug Delivery System.” Colloids and Surfaces B: Biointerfaces 201(October 2020):111625. doi: 10.1016/j.colsurfb.2021.111625.
25. García, Agustina, Darío Leonardi, Mario Oscar Salazar, and María Celina Lamas. 2014. “Modified β-Cyclodextrin Inclusion Complex to Improve the Physicochemical Properties of Albendazole. Complete in Vitro Evaluation and Characterization.” PLoS ONE 9(2):3–10. doi: 10.1371/journal.pone.0088234.
26. Garg, Anuj, Javed Ahmad, and Mohd Zaheen Hassan. 2021. “Inclusion Complex of Thymol and Hydroxypropyl-β-Cyclodextrin (HP-β-CD) in Polymeric Hydrogel for Topical Application: Physicochemical Characterization, Molecular Docking, and Stability Evaluation.” Journal of Drug Delivery Science and Technology 64(March):102609. doi: 10.1016/j.jddst.2021.102609.
27. Ghuzlaan, Ameer, Mahmoud M. Al Omari, and Khaldoun A. Al-Sou’od. 2009. “Prednisone/Cyclodextrin Inclusion Complexation: Phase Solubility, Thermodynamic, Physicochemical and Computational Analysis.” Journal of Solution Chemistry 38(1):83–94. doi: 10.1007/s10953-008-9349-0.
28. Giglio, Valentina, Valentina Oliveri, Maurizio Viale, Rosaria Gangemi, Giovanni Natile, Francesco P. Intini, and Graziella Vecchio. 2015. “Folate-Cyclodextrin Conjugates as Carriers of the Platinum(IV) Complex LA-12.” ChemPlusChem 80(3):536–43. doi: 10.1002/cplu.201402342.
29. Goran M. Petrović1, Gordana S. Stojanović1, Olga P. Jovanović1, Aleksandra S. Đorđević1, Ivan R. Palić1, Sofija V. Sovilj2. 2012.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

"Inclusion Complexes of Pesticides in Aqueous Solutions of Methylated-?-Cyclodextrin Goran." (April):1–24.

30. GUHA RAJARSHI & BENDER ANDREAS. 2012. APPROACHES IN COMPUTATIONAL APPROACHES IN Edited By.
31. Hazai, Eszter, Istvan Hazai, Laszlo Demko, Sandor Kovacs, David Malik, Peter Akli, Peter Hari, Julianna Szeman, Eva Fenyvesi, Edina Benes, Lajos Szente, and Zsolt Bikadi. 2010. "Cyclodextrin Knowledgebase a Web-Based Service Managing CD-Ligand Complexation Data." Journal of Computer-Aided Molecular Design 24(8):713–17. doi: 10.1007/s10822-010-9368-y.
32. Heinrich, Lothar A., Betina Pajaziti, and Rakhimdzhan Roziev. 2014. "Drug Delivery System of a Radio-Protective Inclusion Complex." Advanced Materials Research 872:231–36. doi: 10.4028/www.scientific.net/AMR.872.231.
33. Iacovino, Rosa, Jolanda Caso, Cristina Donato, Gaetano Malgieri, Maddalena Palmieri, Luigi Russo, and Carla Isernia. 2016. "Cyclodextrins as Complexing Agents: Preparation and Applications." Current Organic Chemistry 21(2):162–76. doi: 10.2174/1385272820666160909111842.
34. Inoue, Yutaka, Masaaki Yoshida, Toshinari Ezawa, Takashi Tanikawa, Florencio Arce, Gerard Lee See, Junki Tomita, Mitsuaki Suzuki, and Toshio Oguchi. 2022. "Inclusion Complexes of Daidzein with Cyclodextrin-Based Metal–Organic Framework-1 Enhance Its Solubility and Antioxidant Capacity." AAPS PharmSciTech 23(1):1–14. doi: 10.1208/s12249-021-02151-2.
35. Jambhekar, Sunil, R. Casella, and T. Maher. 2004. "The Physicochemical Characteristics and Bioavailability of Indomethacin from β-Cyclodextrin, Hydroxyethyl-β-Cyclodextrin, and Hydroxypropyl-β-Cyclodextrin Complexes." International Journal of Pharmaceutics 270(1–2):149–66. doi: 10.1016/j.ijpharm.2003.10.012.
36. Kfoury, Miriana, David Landy, and Sophie Fourmentin. 2018. "Characterization of Cyclodextrin/Volatile Inclusion Complexes: A Review." Molecules 23(5):1–23. doi: 10.3390/molecules23051204.
37. Khemtong, Chalermchai, Debasish Banerjee, Yubiao Liu, Jouliana M. El Khoury, Peter L. Rinaldi, and Jun Hu. 2005. "Formation of an Inclusion Complex of a New Transition Metal Ligand in β-Cyclodextrin." Supramolecular Chemistry 17(4):335–41. doi: 10.1080/10610270500115563.
38. Kurup, Swati, Dhruvesh V Parmar, and Neelaambhigai Mayilswamy. 2021. "Removal of Heavy Metal Ions from Water Using Beta-Cyclodextrin: A Review." International Research Journal of Engineering and Technology 878–89.
39. Liang, Bingchan, Jianxia Hao, Ning Zhu, Limin Han, Lijun Song, and Hailong Hong. 2023. "Formulation of Nitrendipine/Hydroxypropyl-β-Cyclodextrin Inclusion Complex as a Drug Delivery System to Enhance the Solubility and Bioavailability by Supercritical Fluid Technology." European Polymer Journal 187:111880. doi: 10.1016/J.EURPOLYMJ.2023.111880.
40. Lippold, Ines, Kristin Vlay, Helmar Görls, and Winfried Plass. 2009. "Cyclodextrin Inclusion Compounds of Vanadium Complexes: Structural Characterization and Catalytic Sulfoxidation." Journal of Inorganic Biochemistry 103(4):480–86. doi: 10.1016/j.jinorgbio.2008.12.014.
41. Loftsson, Thorsteinn, Pekka Jarho, Már Másson, and Tomi Järvinen. 2005. "Cyclodextrins in Drug Delivery." Expert Opinion on Drug Delivery 2(2):335–51. doi: 10.1517/17425247.2.1.335.
42. Louiz, S., H. Labiadh, and R. Abderrahim. 2015. "Spectrochimica Acta Part A : Molecular and Biomolecular Spectroscopy Synthesis and Spectroscopy Studies of the Inclusion Complex of 3-Amino-5-Methyl Pyrazole with Beta-Cyclodextrin." Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 134:276–82. doi: 10.1016/j.saa.2014.06.028.
43. Manvatkar, V. D., R. Y. Patle, P. H. Meshram, and R. S. Dongre. 2023. "Azomethine-Functionalized Organic–Inorganic Framework: An Overview." Chemical Papers

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

77(10):5641–62. doi: 10.1007/s11696-023-02889-y.

44. Meshram, Pankaj, Varsha Manwatkar, and Rajendra Dongre. 2023. “B - CYCLODEXTRIN ENCAPSULATED INCLUSION COMPLEX OF ISATIN PHENYLHYDRAZONE : SPECTROSCOPIC , STOICHIOMETRIC , THERMODYNAMIC , AND BIOLOGICAL.” 441210(10):1435–45.
45. Meymand, Mahdieh Abbasi, Maryam Kazemipour, Mehdi Shahidi, and Mehdi Ansari. 2022. “Synthesis of Bentonite-β-Cyclodextrin-Iron Nanoparticles Composite as a Magnetic Adsorbent in Solid-Phase Extraction for Separation of Nicotinic Acid N-Methylbetaine: An Optimized Process.” Polymer Bulletin 79(10):9093–9110. doi: 10.1007/s00289-021-03944-y.
46. Munnangi, Siva Ram, Ahmed Adel Ali Youssef, Nagarjuna Narala, Preethi Lakkala, Sagar Narala, Sateesh Kumar Vemula, and Michael Repka. 2023. “Drug Complexes: Perspective from Academic Research and Pharmaceutical Market.” Pharmaceutical Research 40(6):1519–40. doi: 10.1007/s11095-023-03517-w.
47. Nan, Song Ya, Zhou Yu Fang, Zhen Wei Jun, Song Ya Nan, Zhou Yu Fang, and Zhen Wei Jun. 2015. “β -Cyclodextrin 과 Polylactic Acid 간의 포접화합물 제조 및 특성 분석 Preparation and Characterization of Inclusion Complex between β -Cyclodextrin and Polylactic Acid.” 39(2):261–67.
48. Nguyen, Tien An, Benguo Liu, Jian Zhao, Donald S. Thomas, and James M. Hook. 2013. “An Investigation into the Supramolecular Structure, Solubility, Stability and Antioxidant Activity of Rutin/Cyclodextrin Inclusion Complex.” Food Chemistry 136(1):186–92. doi: 10.1016/j.foodchem.2012.07.104.
49. Păduraru, Dan Nicolae, Adelina Gabriela Niculescu, Alexandra Bolocan, Octavian Andronic, Alexandru Mihai Grumezescu, and Rodica Bîrlă. 2022. “An Updated Overview of Cyclodextrin-Based Drug Delivery Systems for Cancer Therapy.” Pharmaceutics 14(8). doi: 10.3390/pharmaceutics14081748.
50. Prabu, Samikannu, Meenakshisundaram Swaminathan, Krishnamoorthy Sivakumar, and Rajaram Rajamohan. 2015. Preparation, Characterization and Molecular Modeling Studies of the Inclusion Complex of Caffeine with Beta-Cyclodextrin. Vol. 1099. Elsevier Ltd.
51. Prochowicz, Daniel, Arkadiusz Kornowicz, Iwona Justyniak, and Janusz Lewiński. 2016. “Metal Complexes Based on Native Cyclodextrins: Synthesis and Structural Diversity.” Coordination Chemistry Reviews 306(P1):331–45. doi: 10.1016/j.ccr.2015.07.016.
52. Psimadas, Dimitrios, Panagiotis Georgoulias, Varvara Valotassiou, and George Loudos. 2012. “Molecular Nanomedicine Towards Cancer :” Journal of Pharmaceutical Sciences 101(7):2271–80. doi: 10.1002/jps.
53. Rong, Wen Ting, Ya Peng Lu, Qing Tao, Miao Guo, Yu Lu, Yong Ren, and Shu Qin Yu. 2014. “Hydroxypropyl-Sulfobutyl-β-Cyclodextrin Improves the Oral Bioavailability of Edaravone by Modulating Drug Efflux Pump of Enterocytes.” Journal of Pharmaceutical Sciences 103(2):730–42. doi: 10.1002/jps.23807.
54. Roy, Niloy, Biswajit Ghosh, Debadrita Roy, Biswajit Bhaumik, and Mahendra Nath Roy. 2020. “Exploring the Inclusion Complex of a Drug (Umbelliferone) with α-Cyclodextrin Optimized by Molecular Docking and Increasing Bioavailability with Minimizing the Doses in Human Body.” ACS Omega 5(46):30243–51. doi: 10.1021/acsomega.0c04716.
55. Sambasevam, Kavirajaa Pandian, Sharifah Mohamad, Norazilawati Muhamad Sarih, and Nor Atiqah Ismail. 2013. “Synthesis and Characterization of the Inclusion Complex of β-Cyclodextrin and Azomethine.” International Journal of Molecular Sciences 14(2):3671–82. doi: 10.3390/ijms14023671.
56. Sandilya, Avilasha A., Upendra Natarajan, and M. Hamsa Priya. 2020. “Molecular View into the Cyclodextrin Cavity: Structure and Hydration.” ACS Omega 5(40):25655–67. doi: 10.1021/acsomega.0c02760.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 1121-1136 | ISSN:2251-6727

57. Sanku, Rajesh K. K., Ozlem O. Karakus, Monica Ilies, and Marc A. Ilies. 2019. “Inclusion Complexes in Drug Delivery and Drug Targeting: Formation, Characterization, and Biological Applications.” ACS Symposium Series 1309(March):188–221. doi: 10.1021/bk-2019-1309.ch009.
58. Santos, Cecília I. A. V., Carmen Teijeiro, Ana C. F. Ribeiro, Daniela F. S. L. Rodrigues, Carmen M. Romero, and Miguel A. Esteso. 2016. “Drug Delivery Systems: Study of Inclusion Complex Formation for Ternary Caffeine–β-Cyclodextrin–Water Mixtures from Apparent Molar Volume Values at 298.15 K and 310.15 K.” Journal of Molecular Liquids 223:209–16. doi: 10.1016/j.molliq.2016.08.035.
59. Saokham, Phennapha, Chutimon Muankaew, Phatsawee Jansook, and Thorsteinn Loftsson. 2018. “Solubility of Cyclodextrins and Drug/Cyclodextrin Complexes.” Molecules 23(5):1–15. doi: 10.3390/molecules23051161.
60. Sharma, Neha, and Ashish Baldi. 2016. “Exploring Versatile Applications of Cyclodextrins: An Overview.” Drug Delivery 23(3):739–57. doi: 10.3109/10717544.2014.938839.
61. Shimpi, Shyam, Bhaskar Chauhan, and Prajakta Shimpi. 2005. “Cyclodextrins: Application in Different Routes of Drug Administration.” Acta Pharmaceutica 55(2):139–56.
62. Shinde, Vijay Vilas, Daham Jeong, and Seunho Jung. 2018. “Supramolecular Aminocatalysis via Inclusion Complex: Amino-Doped β-Cyclodextrin as an Efficient Supramolecular Catalyst for the Synthesis of Chromeno Pyrimido[1,2-b]Indazol in Water.” Journal of Industrial and Engineering Chemistry 68:6–13. doi: 10.1016/j.jiec.2018.08.010.
63. Simanchal Dash1, B. K. Garnaik2*. 2017. “Antioxidant Activities of Inclusion Complexes of 2-(Benzothiazolyl-2) Hydrazono-3-Phenyl 5-Arylidene- 4-Thiazolidinone Derivatives with ?-Cyclodextrin.” International Journal of Pharmaceutical Sciences and Drug Research 9(01):17–21. doi: 10.25004/ijpsdr.2017.090103.
64. Siva, S., J. Thulasidhasan, and N. Rajendiran. 2013. “Host-Guest Inclusion Complex of Propafenone Hydrochloride with α- and β-Cyclodextrins: Spectral and Molecular Modeling Studies.” Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy 115:559–67. doi: 10.1016/j.saa.2013.06.079.
65. Sivakumar, K., and G. Parinamachivayam. 2022. “Review on β-Cyclodextrin Inclusion Complex Based Chemosensors for Heavy Metals.” Journal of Inclusion Phenomena and Macrocyclic Chemistry 102(7–8):603–18. doi: 10.1007/s10847-022-01153-2.
66. Smaldone, Ronald A., Ross S. Forgan, Hiroyasu Furukawa, Jeremiah J. Gassensmith, Alexandra M. Z. Slawin, Omar M. Yaghi, and J. Fraser Stoddart. 2010. “Metalorganic Frameworks from Edible Natural Products.” Angewandte Chemie - International Edition 49(46):8630–34. doi: 10.1002/anie.201002343.
67. Soares, Líllian Amélia, Ana Flávia Vasconcelos Borges Leal, Leonardo Fernandes Fraceto, Elaine Rose Maia, Inês Sabioni Resck, Massuo Jorge Kato, Eric De Sousa Gil, Aparecido Ribeiro De Sousa, Luiz Carlos Da Cunha, and Kênnia Rocha Rezende. 2009. “Host-Guest System of 4-Nerolidylcatechol in 2-Hydroxypropyl-β- Cyclodextrin: Preparation, Characterization and Molecular Modeling.” Journal of Inclusion Phenomena and Macrocyclic Chemistry 64(1–2):23–35. doi: 10.1007/s10847-009-9532-y.
68. Sompornpisut, Pornthep, Nutsima Deechalao, and Jitraporn Vongsvivut. 2002. “An Inclusion Complex of -Cyclodextrin-L-Phenylalanine: 1H NMR and Molecular Docking Studies.” ScienceAsia 28(3):263–70. doi: 10.2306/scienceasia1513-1874.2002.28.263.
69. Spulber, Mariana, Mariana Pinteala, Valeria Harbagiu, and Bogdan C. Simionescu. 2008. “Inclusion Complexes of Sulconazole with β-Cyclodextrin and Hydroxypropyl β-Cyclodextrin: Characterization in Aqueous Solution and in Solid State.” Journal of Inclusion Phenomena and Macrocyclic Chemistry 61(1–2):41–51. doi: 10.1007/s10847-007-9391-3.

70. Su, Qimeng, Wentao Su, Shanghua Xing, and Mingqian Tan. 2024. "Enhanced Stability of Anthocyanins by Cyclodextrin–Metal Organic Frameworks: Encapsulation Mechanism and Application as Protecting Agent for Grape Preservation." Carbohydrate Polymers 326(August 2023):121645. doi: 10.1016/j.carbpol.2023.121645.
71. Szente, Lajos, and Éva Fenyvesi. 2018. "Cyclodextrin-Enabled Polymer Composites for Packaging." Molecules 23(7). doi: 10.3390/molecules23071556.
72. Tang, Siping, Yonglan Feng, Zhifeng Xu, and Deping Wang. 2014. "Synthesis and Dna Binding Studies of Platinum (Ii) Complexes Based on Cyclodextrin." Key Engineering Materials 575–576:280–86. doi: 10.4028/www.scientific.net/KEM.575-576.280.
73. Yang, Haitao, Michael A. Parniak, Sharon L. Hillier, and Lisa C. Rohan. 2012. "A Thermodynamic Study of the Cyclodextrin-UC781 Inclusion Complex Using a HPLC Method." Journal of Inclusion Phenomena and Macrocyclic Chemistry 72(3–4):459–65. doi: 10.1007/s10847-011-0019-2.
74. Yang, Ke, Junfeng Liu, Laichun Luo, Meilin Li, Tanfang Xu, and Junfeng Zan. 2023. "Synthesis of Cationic β-Cyclodextrin Functionalized Silver Nanoparticles and Their Drug-Loading Applications." RSC Advances 13(11):7250–56. doi: 10.1039/d2ra08216k.
75. Yuan Liu †, Ting Lin †, Cui Cheng *., and Chun Liu *. and Xiao Han *. , Qiaowen Wang, Shujin Lin. 2021. "Research Progress on Synthesis and Application of Cyclodextrin Polymers." Molecules 26(1090).
76. Yunling, Jia, Shang Yanli, Ma Yun, Li Junran, Wang Juan, Zhang Shaohua, and Li Mingxiu. 2007. "Electrorheological Property of Rare Earth Complexes Based on β-Cyclodextrin Inclusion." Journal of Rare Earths 25(SUPPL. 1):9–14. doi: 10.1016/S1002-0721(07)60513-4.
77. Zhou, Wenshuai, Yanlong Feng, Meng Li, Chengxiao Zhang, and Honglan Qi. 2023. "Tracking the Dissolution Surface Kinetics of a Single Fluorescent Cyclodextrin Metal-Organic Framework by Confocal Laser Scanning Microscopy." Langmuir 39(19):6681–90. doi: 10.1021/acs.langmuir.3c00018.