INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Cyclodextrins in Formulation Development: Complexation and Stability Enhance

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ARTICLE INFO

Published: 20 Sept 2025
Keywords:
Cyclodextrins (CDs), solubility, CD inclusion complexes, bioavailability, drug delivery platforms
DOI:
10.5281/zenodo.17165811

ABSTRACT

Cyclodextrins (CDs), a class of cyclic oligosaccharides, have gained recognition as versatile excipients within the pharmaceutical sciences due to their distinctive capacity to form inclusion complexes with a diverse array of drug molecules. This review provides a thorough examination of the various roles that CDs play in drug delivery systems, with a particular emphasis on their physicochemical properties, mechanisms of complexation, and structural variants, which include native, chemically modified, and polymeric forms. The enhancement of solubility, stability, and bioavailability of poorly water-soluble drugs through CD inclusion complexes is a focal point, alongside their application in both traditional and advanced drug delivery platforms, such as nanosponges, liposomes, and supramolecular systems. Furthermore, the article discusses several FDA-approved formulations that utilize CDs, including Vfend®, Geodon®, and Sporanox®, thereby highlighting their clinical significance and therapeutic advantages. Despite their potential, challenges such as inconsistent complexation efficiency, cost considerations, toxicity associated with certain derivatives, and regulatory obstacles hinder their wider application. The future prospects for CDs are centered on the development of stimuli-responsive delivery systems, gene delivery vectors, and multifunctional nanocarriers, thereby positioning CDs not merely as passive carriers but also as active therapeutic agents. This review serves as a contemporary reference on recent advancements, commercial significance, limitations, and future trajectories in CD-based drug delivery systems, with implications for both industrial applications and translational research.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides widely used in pharmaceutical formulations to enhance drug solubility, stability, and

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

bioavailability[12]. They form inclusion complexes with poorly water-soluble drugs, improving their physicochemical properties without molecular modifications[2]. While CDs generally increase drug stability, they can sometimes promote degradation, depending on the CD type and complex structure[3]. Recent research focuses on ternary complexes, incorporating auxiliary agents like water-soluble polymers or amino acids, which offer advantages over binary complexes, including better complexation efficiency and stability constants[4]. Ternary complexes also reduce the required CD concentration for maximum solubility and stability. In silico molecular modeling has emerged as a valuable tool for preliminary evaluation of CD-based complexes[4].

Poor drug solubility remains a significant challenge in pharmaceutical development, affecting bioavailability and efficacy[5]. Over 60% of marketed drugs and many promising new compounds face solubility issues[6]. Nanotechnology offers potential solutions by increasing surface area and improving drug dissolution[7]. Nanonization techniques, including nanoparticles and lipid-based nanosystems, can enhance solubility and dissolution rates of poorly water-soluble drugs[8]. Various approaches like solid dispersions, nano-suspensions, and cyclodextrin complexes aim to increase drug solubility[7]. Microarray patches (MAPs) have emerged as a promising strategy for delivering poorly soluble drugs through the skin, offering advantages over oral and parenteral routes[6]. Cyclodextrins (CDs) are cyclic oligosaccharides with a hydrophobic cavity and hydrophilic exterior, widely used in pharmaceutical formulations to enhance drug properties [93]. They form inclusion complexes with poorly water-soluble drugs, improving solubility, bioavailability, and stability[10]. CDs can be used in their natural form (α-, β-, γ-CD) or as chemically-modified derivatives for various drug delivery routes[9]. While CDs generally stabilize drugs, they may promote degradation in some cases, depending on the CD type and complex structure[3]. Multicomponent complexes, formed by adding auxiliary substances like amino acids, organic acids, or water-soluble polymers, can enhance complexation efficiency and therapeutic applicability[3]. CDs offer numerous advantages in pharmaceutical development, including taste masking, prevention of drug incompatibilities, and extended shelf life[10].

III. Chemistry and Classification of Cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides composed of glucopyranose units linked by α-1,4-glycosidic bonds, featuring a hydrophobic cavity and hydrophilic surface[11,12]. This unique structure allows CDs to form inclusion complexes with various compounds, making them valuable in multiple industries, including pharmaceuticals, food, and agriculture[12]. CDs are particularly useful in drug delivery systems due to their biocompatibility, safety, and ability to improve drug solubility[9,13]. CD-based drug delivery systems include complexes, nanocarriers, hydrogels, and inserts, which can be administered through various routes such as oral, ocular, dermal, nasal, and rectal[9,13]. Cyclodextrins (CDs) are cyclic oligosaccharides that occur naturally in three main types: α-CD (6 glucose units), β-CD (7 units), and γ-CD (8 units) [14,15]. These CDs have a unique structure with a hydrophilic exterior and a lipophilic cavity, allowing them to form inclusion complexes with various molecules[14]. Recent research has shown that CDs and their complexes can self-assemble in aqueous solutions, forming clusters and nanoparticles[16]. This property has led to the development of CD-based supramolecular hydrogels for local drug delivery applications[16].

Additionally, modified CDs, such as hydroxypropyl-β-CD, sulfobutyl ether-β-CD, and methylated CDs, offer improved properties over native CDs[17]. These derivatives can form inclusion complexes with poorly water-soluble drugs, mask unpleasant tastes and odors, and prevent drug degradation[10]. Recent developments include CD-based polyrotaxanes, CD-polymer conjugates, and thiolated CDs, which show promise for innovative drug delivery systems[18]. The selective modification of CDs at different positions has led to the creation of new derivatives with enhanced properties and applications[19]. Clinical trials have demonstrated various new applications of CDs, including the formation of nanoparticles and stabilization of protein drugs[18].

Cyclodextrins (CDs) are cyclic oligosaccharides widely used in pharmaceutical formulations to enhance drug properties through complexation[3,10]. They can improve drug solubility, bioavailability, and stability while reducing irritation[10]. CDs form inclusion complexes with appropriately sized molecules, which can stabilize or destabilize drugs depending on the CD type and complex structure[3]. Multicomponent complexes, incorporating auxiliary substances, can further enhance complexation efficiency and drug properties[3]. CDs are particularly valuable in parenteral formulations due to their favorable toxicological and pharmacokinetic profiles, often preferred over other solubilizing techniques[20]. They can temporarily camouflage undesirable physicochemical drug properties without using organic solvents or surface-active agents[20]. Various CD derivatives, such as captisol and sulfobutyl ether-β-CD, are used in different dosage forms to address specific formulation challenges[10].

Table 1: Cyclodextrin Derivatives and Their Pharmaceutical Properties

Cyclodextrin Type	Ring Size	Water Solubility	Use in Drug Delivery	Regulatory Status
α-CD	6	Low	Food, minimal pharma	GRAS
β-CD	7	Moderate	Taste masking, tablets	GRAS (limited parenteral use)
γ-CD	8	High	Parenteral, nasal, ocular	Approved
HP-β-CD	7	Very high	Injectable, oral	FDA-approved
SBE-β-CD (Captisol)	7	Very high	Injectable, parenteral	FDA-approved

IV. Mechanism of Inclusion Complexation

Cyclodextrins (CDs) are versatile molecules that form host-guest complexes through noncovalent interactions, enabling various applications in pharmaceuticals, cosmetics, and other industries[21]. Their ability to form inclusion complexes has been extensively studied using techniques like NMR and X-ray crystallography[21]. CDs are biocompatible, biodegradable, and have low toxicity, making them suitable for drug delivery and biomedical applications[22]. CD-based supramolecular hydrogels exhibit unique properties such as stimuli-responsiveness, self-healing, and shape memory[23]. These hydrogels have been explored for local drug delivery through various administration routes, including intra-tumoral, subcutaneous, and ocular[24]. The shear-thinning nature and stimuli-responsiveness of CD-based hydrogels make them particularly attractive for controlled drug release[24]. Despite their potential, challenges remain in the clinical translation of CD-based host-guest supramolecular hydrogels[24].

Cyclodextrins (CDs) form inclusion complexes with various compounds through non-covalent interactions. The primary driving force for

complex formation is van der Waals interactions, followed by hydrophobic interactions and Coulomb forces[2526]. Hydrogen bonding also plays a role in stabilizing the complexes and influencing their conformation[2626]. These interactions contribute to the spontaneous formation and stability of inclusion complexes[26]. The complexation process typically follows a 1:1 stoichiometry, as confirmed by various analytical methods[2527]. Molecular dynamics simulations and computational approaches have been used to elucidate the mechanisms of complex formation and stability[252626]. Inclusion complexes with CDs can improve the solubility, thermal stability, and biological activities of guest molecules [2827]. These complexes, typically in 1:1 stoichiometry, can significantly improve the solubility and stability of poorly soluble compounds like 2R,3R-dihydromyricetin and praziquantel[2729]. The inclusion mechanism involves non-covalent interactions, with guest molecules partially or fully embedded in the CD cavity[27]. Different CD derivatives, such as hydroxypropyl-β-cyclodextrin and randomly methylated β-CD, can enhance solubility to varying degrees[27,29]. Phase solubility diagrams are used to characterize these complexes, with AL and AP types indicating increased drug solubility[30–32]. Different CDs exhibit varying effects on drug solubility, with some increasing and others decreasing it[32]. The stability constants and complexation efficiency of drug-CD complexes can be determined through phase solubility studies[30,33]. Various analytical techniques, including NMR, IR, XRD, and DSC, are employed to characterize these complexes and confirm their formation[30,31,33]. The choice of CD can significantly impact the solubility enhancement of drugs, with some CDs, like HPβ-CD, showing superior performance compared to others[33]. These inclusion complexes can lead to improved dissolution rates and potential enhancements in drug bioavailability[31,33].

V. Methods of Preparation of CD Complexes

Cyclodextrin (CD) complexes can be prepared using various methods to enhance drug solubility and dissolution[34]. Various methods for preparing CD complexes have been investigated, including physical mixing, kneading, co-precipitation, spray drying, freeze drying, and supercritical fluid techniques[353637]. These methods can significantly improve drug solubility and dissolution rates. For instance, kneading and co-precipitation methods achieved complete dissolution of pterostilbene within 20-40 minutes when complexed with β-CD and γ-CD[37]. Spray-freeze drying has been shown to enhance permeation and stability of cannabinoid acids in CD complexes[36]. The choice of CD derivative and preparation method can greatly impact complex formation and drug solubilization, as demonstrated with lopinavir complexation using HP17-γ-CD and supercritical assisted spray drying[35]. The effectiveness of these methods in improving drug properties often follows the order: supercritical CO2 processing > spray-drying > freeze-drying > co-evaporation > physical mixing[38]. Various analytical techniques, such as DSC, SEM, and XRD, are employed to characterize and confirm the formation of CD complexes[39]. Ultraviolet-visible spectroscopy, Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD) are used to analyze flavonoid/hydroxypropyl-β-cyclodextrin complexes[40]. Solid-state nuclear magnetic resonance (ssNMR) is valuable for characterizing CD-including systems[41]. These techniques, along with scanning electron microscopy (SEM), help confirm complex formation and study their properties[42].

Table 2: Preparation Methods for CD Complexes

Method	Description	Advantages	Disadvantages	Example Drugs
Kneading	Wet grinding with water or alcohol	Simple, economical	Low yield	Pterostilbene
Co-precipitation	CD + drug + solvent precipitation	Higher inclusion efficiency	Residual solvent issues	Pterostilbene
Spray drying	Atomizing into hot air chamber	Scalable, fast	Thermal degradation risk	Cannabinoid acids
Freeze drying	Drug/CD solution frozen & sublimated	Preserves thermolabile drugs	Expensive, time-consuming	Various
Supercritical CO2	Uses CO2 as solvent	High inclusion efficiency, green	High cost, requires special equipment	Lopinavir with HP-γ-CD

VII. Applications in Formulation Development

Cyclodextrins (CDs) are versatile excipients widely used in pharmaceutical formulations to enhance drug solubility, stability, and bioavailability [431]. They form inclusion complexes with lipophilic drug moieties and can create non-inclusion complexes and self-assembled aggregates[44]. In tablet formulations, CDs serve as complexing agents, fillers, disintegrants, and binders[45]. Their applications extend beyond pharmaceuticals to food, cosmetics, agriculture, and environmental remediation[46]. Various techniques are employed to incorporate CDs into different matrices and enhance their solubilizing effects[44]. Natural CDs and some derivatives [1]have pharmacopeia monographs and are used in food and toiletry products. However, careful consideration of CD concentration is crucial, as both excessive and insufficient amounts can affect drug bioavailability[44]. Overall, CDs play a significant role in addressing poor aqueous solubility and improving drug delivery in various administration routes[1].

1. Solubility Enhancement

Cyclodextrins, particularly β-cyclodextrin (βCD) and its derivatives, have shown significant potential in enhancing the solubility and dissolution rates of poorly soluble drugs. Two recent studies explored novel approaches using cyclodextrins for BCS Class II and IV drugs. El Baraka et al. (2024) demonstrated that combinations of βCD with PEG 6000 and PVP significantly improved solubility and dissolution rates of celecoxib, furosemide, and valsartan. The most effective combinations varied by drug, with improvements ranging from 3.54 to 25.52-fold[47]. Balenzano et al. (2023) introduced cyclodextrin-based supramolecular deep eutectic solvents (CycloDES) using hydroxypropyl-β-cyclodextrin (HPβCD). This approach achieved at least 100-fold solubility improvements for cannabidiol, indomethacin, and dexamethasone. CycloDES also showed superior resistance to dilution compared to standard glucose-choline chloride DES, maintaining high drug solubility (e.g., 93% for indomethacin) upon water addition[48]. These studies highlight the versatility of cyclodextrin-based systems in addressing solubility challenges for poorly soluble drugs.

Cyclodextrins, particularly β-cyclodextrin and its derivatives, have shown significant potential in enhancing the solubility and dissolution rates of poorly soluble drugs like itraconazole and fenofibrate. Binary and ternary complexes of itraconazole with β-cyclodextrin and polyvinylpyrrolidone demonstrated improved solubility and dissolution behavior[49]. Similarly, fenofibrate complexation with hydroxypropyl-β-cyclodextrin resulted in enhanced dissolution rates and decreased mean dissolution time[50]. Itraconazole-β-cyclodextrin complexes

incorporated into orally disintegrating tablets exhibited higher dissolution rates compared to pure itraconazole formulations, potentially improving bioavailability and reducing dosage requirements[51]. Cyclodextrins form inclusion complexes with guest molecules, enhancing their physicochemical properties such as solubility, stability, and bioavailability. Various methods for complex production and characterization techniques are available, with applications extending beyond pharmaceuticals to other fields[52].

2. Stability Enhancement

Cyclodextrins (CDs) have been shown to enhance the stability and pharmaceutical properties of various active ingredients. Studies demonstrate that CDs can improve photostability of compounds like trans-polydatin[53], roflumilast[54], and nabumetone[55]. In addition to photostability, CDs can enhance thermal stability and solubility of drugs[56]. They also protect against hydrolysis, oxidation, and thermolysis[56]. Formation of inclusion complexes with CDs can improve drug bioavailability, mask taste and smell, and modify biological properties[56]. Specific CD derivatives like hydroxypropyl-β-cyclodextrin (HP-β-CD) have shown superior performance in some cases, such as increasing water solubility and providing photoprotection in gel formulations[55]. Overall, CDs serve as multifunctional excipients that can significantly enhance drug stability and performance across various applications.

Cyclodextrins (CDs) have shown promise in enhancing drug stability and solubility, particularly for poorly soluble drugs like nimodipine (NIMO) and omeprazole (OME). Inclusion complexes of NIMO with sulfobutylether-β-cyclodextrin significantly improved solubility and stability while maintaining bioequivalence with commercial formulations[57]. Similarly, OME stability was enhanced in mucoadhesive buccal films using β-cyclodextrin and l-arginine[58]. A nano-controlled release agent of NIMO modified with hydroxypropyl-β-cyclodextrin demonstrated improved plasma stability and bioavailability in rats[59]. However, CDs can also promote drug degradation in some cases, highlighting the importance of evaluating the specific CD-drug interaction[3].

3. Taste Masking

Cyclodextrins, particularly β-cyclodextrin derivatives, have shown promise in taste-masking applications for pharmaceuticals. They can form inclusion complexes with bitter drugs like ranitidine hydrochloride, effectively reducing their unpleasant taste[60]. The taste-masking efficiency of these complexes can be evaluated using electronic taste sensing systems, providing a rapid and objective assessment method[60]. Cyclodextrins offer a safe and cost-effective approach to taste masking, although their application is not always straightforward and requires careful consideration of factors such as cyclodextrin type and guest-host molar ratio[61]. In addition to cyclodextrins, other taste-masking techniques for traditional Chinese medicines include functional masking with sweeteners, physical masking via polymer film-coating, and biochemical masking through intermolecular interactions[62]. These approaches aim to improve patient compliance, particularly among pediatric and elderly populations.

4. Controlled Release Formulations

Cyclodextrins (CDs) are versatile oligosaccharides widely used in pharmaceutical applications for controlled drug delivery[63]. Their unique structure allows formation of inclusion complexes with various poorly soluble compounds, improving drug solubility, stability,

and bioavailability[64]. CDs, particularly β-CD, can form different nanoarchitectures through self-assembly and host-guest interactions, enhancing loading capacity and enabling targeted and controlled release[65]. Various CD-based controlled release systems, including inclusion complexes, coupling, supramolecular hydrogels, and micelles, are employed in practical applications[63]. CD derivatives, such as hydroxypropyl and sulfobutyl ether CDs, further enhance these properties[65]. CDs have shown promise in non-invasive drug delivery platforms, including ophthalmic and nasal applications[66]. Recent advancements have expanded CD applications to various drug delivery systems, including ocular, osmotic, mucoadhesive, transdermal, nasal, and targeted delivery[64].

5. Parenteral Formulations

Cyclodextrins (CDs), particularly sulfobutylether-β-cyclodextrin (SBE-β-CD) or Captisol®, have emerged as valuable excipients in parenteral formulations due to their ability to enhance drug solubility and stability[6768]. CDs form inclusion complexes with poorly water-soluble drugs, improving their bioavailability and reducing tissue irritation upon injection[68]. Their favorable toxicological and pharmacokinetic profiles often make them preferable to other solubilizing techniques[20]. Sulfobutyl ether-β-CD (SBE-β-CD, Captisol) and hydroxypropyl-β-CD (HP-β-CD) are particularly useful for injectable formulations, with several FDA-approved products[68]. These modified CDs improve drug solubility, chemical stability, and bioavailability while reducing tissue irritation. CDs can also be used to develop more complex drug delivery systems like nanoparticles and supramolecular hydrogels, which are beneficial for anticancer drugs[69]. Additionally, CDs can prevent drug degradation, extend shelf life, and mask undesirable drug properties[10]. Their wide-ranging applications have led to increased acceptance by health authorities, promoting the development of safer and more efficient injectable drug delivery systems[69].

6. Nasal, Ocular, and Transdermal Delivery

Cyclodextrins (CDs) in ocular drug delivery, thiolated β-CD has shown promising results as a mucoadhesive and permeation-enhancing excipient, improving drug residence time and penetration across ocular tissues[70]. CDs, combined with mucoadhesive polymers, can overcome challenges in ocular drug delivery by enhancing permeability and increasing retention time on the ocular surface[71]. Additionally, CDs have been explored for non-invasive drug delivery platforms, including ophthalmic and nasal applications, due to their ability to form water-soluble inclusion complexes with poorly soluble compounds[66]. Recent developments in CD-based nanocarrier systems have further expanded their potential for targeted drug delivery and controlled release, offering improved bioavailability across various administration routes[6466]. CDs are utilized in various formulations, including hydrogels, gel patches, microneedles, and liposome microemulsions for transdermal delivery[72]. These formulations demonstrate improved drug penetration, sustained release, and targeted delivery. CDs also play a role in taste masking and reducing side effects[73]. Recent advancements have explored CD-based nanocarrier systems for targeted drug delivery[66] and the potential of CDs to self-assemble into stable nanoaggregates[64]. The versatility of CDs has expanded their applications in drug delivery systems, including ocular, osmotic, mucoadhesive, transdermal, and nasal routes.

V. Cyclodextrin-Based Novel Drug Delivery Systems

A. Nanoparticles and Nanosponges

Cyclodextrin-based nanosponges (CDNS) are emerging as versatile nanocarriers for drug delivery, offering numerous advantages over conventional systems[7475]. These three-dimensional, porous structures are formed by cross-linking cyclodextrin molecules, resulting in a large surface area capable of encapsulating various drug molecules[7476]. CDNS can enhance drug solubility, bioavailability, and stability while providing controlled release kinetics[75]. Their flexibility allows for targeted drug delivery when coupled with appropriate ligands[75]. CDNS have shown promise in delivering hydrophilic and hydrophobic compounds, proteins, enzymes, and even gaseous substances[77]. The technology's potential extends beyond pharmaceuticals, with applications in nanodiagnostics, nanosensors, and environmental cleanup[74]. As research in this field rapidly expands, CDNS-based products are expected to enter the market soon.

B. Micelles and Liposomes

Cyclodextrins (CDs) are versatile excipients in pharmaceutical applications, enhancing drug solubility, stability, and bioavailability[44]. Their unique structure allows for the formation of inclusion complexes with lipophilic molecules, making them valuable in nanoparticle-based drug delivery systems[78]. Combining CDs with various nanocarriers, such as liposomes, polymeric nanoparticles, and micelles, can overcome limitations of individual carriers and improve drug delivery performance[79]. CD-modified nanomaterials have shown promise in controlled release and increased bioavailability during in vivo studies[80]. These hybrid systems can enhance drug encapsulation efficiency, reduce toxicity to normal cells, and enable targeted delivery to specific locations like cancer cells[78]. However, careful consideration of CD concentration is crucial, as too much or too little can affect drug bioavailability[44].

C. Hydrogels

Cyclodextrin (CD)-based hydrogels have emerged as promising materials for wound healing and transdermal drug delivery. These hydrogels offer excellent biocompatibility, hydrophilicity, and drug encapsulation capabilities[81]. CD's unique structure allows for host-guest interactions, enabling stimulus-responsive and controlled drug release properties[24]. In transdermal applications, CD-based systems, including hydrogels, gel patches, and microneedles, demonstrate improved drug penetration and sustained release[82]. The versatility of CD-based hydrogels extends to various biomedical fields, such as oncology, bone repair, and myocardial tissue engineering[81]. These hydrogels can be designed with different cross-linking methods, allowing for tailored mechanical properties and drug loading capacities[8182]. Despite their potential, challenges remain in translating CD-based hydrogels from laboratory to clinical applications, necessitating further research to optimize their performance and safety profiles[24,81].

D. In Situ Gels and Mucoadhesive Systems

Cyclodextrins (CDs) have emerged as versatile pharmaceutical excipients for enhancing drug delivery, particularly in ocular, nasal, and buccal applications. In ocular drug delivery, CDs combined with mucoadhesive polymers increase drug permeability and retention time on the ocular surface[71]. Various CD-based systems have been developed, including nanocarriers, hydrogels, and inserts, to overcome the challenges of ocular drug delivery[13]. These systems have shown promise in targeted drug delivery and controlled release, leading to improved bioavailability[66]. The unique properties of CDs, such as their biocompatibility and ability to form stable nanoaggregates, have

expanded their applications in drug delivery systems[64]. Ongoing research continues to explore the potential of CD-based formulations in non-invasive drug delivery platforms.

E. Cyclodextrin-Conjugates for Targeted Delivery

Cyclodextrin-based drug delivery systems have gained significant attention in cancer treatment due to their unique properties and versatility. Cyclodextrins (CDs) can form host-guest complexes, enhance drug solubility, and prolong drug half-life[8384]. Various CD-based nanocarriers, including graphenes, carbon nanotubes, nanosponges, hydrogels, dendrimers, and polymers, have been developed to achieve targeted and responsive drug delivery[8485]. These systems offer advantages such as enhanced drug solubility, site-specific action, prolonged release, and reduced toxicity to normal cells[86]. CD-based nanoparticles have shown promise in chemotherapy, gene therapy, and protein/peptide drug delivery. Recent advancements include the development of amphiphilic CD nanoparticles and exploration of various administration routes[87]. Despite their potential, challenges remain in optimizing CD-based delivery systems for clinical translation and improving their efficacy in cancer treatment.

VII. Commercial Applications and Approved Products

Cyclodextrins are cyclic oligosaccharides that can form inclusion complexes with drugs, enhancing their solubility and stability[44]. Some notable commercially approved cyclodextrin-based drugs are Vfend® (voriconazole), Geodon® (ziprasidone) and Sporanox® (itraconazole). Voriconazole is a broad-spectrum triazole antifungal approved for treating invasive aspergillosis and other serious fungal infections[88]. A liposomal voriconazole formulation has shown improved pharmacokinetics, tissue distribution, and antifungal activity compared to the commercial product, potentially offering a safer and more effective treatment option[89]. This liposomal formulation demonstrated higher drug accumulation in the liver and kidneys, a 2.5-fold increase in AUC0-24/MIC ratio, and a 30% reduction in the inactive metabolite voriconazole-N-oxide, indicating enhanced antimicrobial activity and reduced metabolism[89]. Ziprasidone formulated with cyclodextrin showed improved dissolution rates and increased absorption in fasted dogs compared to Geodon® capsules[90]. For itraconazole, ternary complexes with cyclodextrins and water-soluble polymers demonstrated enhanced solubility and dissolution compared to Sporanox®[91]. Hydroxybutenyl-β-cyclodextrin (HBenBCD) formulations of itraconazole exhibited higher bioavailability and reduced food effects compared to Sporanox® in rats[92]. These studies highlight the potential of cyclodextrin-based formulations to improve the pharmacokinetics of poorly soluble drugs, potentially reducing food effects and enhancing bioavailability.

Captisol® and HP-β-CD, have emerged as important excipients in pharmaceutical formulations. These modified cyclodextrins enhance drug solubility, stability, and bioavailability while demonstrating improved safety profiles compared to parent cyclodextrins[93]. Captisol®, developed through academic research, is now used in 13 FDA-approved injectable products[67]. Both Captisol® and HP-β-CD have undergone extensive safety studies and are well-tolerated in humans, showing no adverse effects on kidneys or other organs following oral or intravenous administration[93]. These cyclodextrins rapidly form and dissociate complexes with various drugs, enhancing their solubility and

stability[68]. HP-β-CD has been particularly useful in developing brain-targeting chemical delivery systems, providing stable and water-soluble formulations for parenteral administration of drugs such as estradiol, zidovudine, dexamethasone, and enkephalin derivatives[94].

Table 3: FDA-Approved Drugs Using Cyclodextrins

Drug Name	API	Cyclodextrin Used	Route	Therapeutic Area
Vfend®	Voriconazole	SBE-β-CD (Captisol)	IV	Antifungal
Geodon®	Ziprasidone	SBE-β-CD (Captisol)	IM	Antipsychotic
Sporanox®	Itraconazole	HP-β-CD	Oral	Antifungal
Nexterone®	Amiodarone	HP-β-CD	IV	Antiarrhythmic
Omnipaque®	Iohexol	HP-β-CD	IV	Imaging Contrast

IX. Challenges and Limitations

While CDs offer benefits such as improved solubility, stability, and bioavailability of drugs[95], their use in pharmaceutical compounding faces challenges. These include inconsistent complexation at laboratory scale, variations across suppliers and batches, hygroscopicity and storage challenges and the need for additional quality control analyses. Cost is a significant limitation, with CDs increasing global compounding expenses and presenting purchasing difficulties from recognized suppliers[96]. Natural CDs tend to self-aggregate in aqueous media, limiting their solubility[97]. The complexation efficiency of CDs varies depending on the drug and CD type, often requiring additional excipients[96]. Inconsistencies in complexation at laboratory scale and variations across suppliers and batches necessitate more rigorous quality control analyses. The hygroscopic nature of some CDs, particularly trehalose, can lead to high water absorption during storage, potentially affecting stability[98]. While CDs generally have a good safety profile, exceeding certain dosage thresholds may cause adverse effects[96]. some CD derivatives have shown potential nephrotoxicity, limiting their applications[99]. Recent research has focused on developing safer CD-based materials, such as epichlorohydrin-crosslinked β-cyclodextrin nanoparticles (βCDNPs), which demonstrate reduced nephrotoxicity and enhanced binding with hydrophobic compounds[100]. These advanced CD-based polymers show promise in various food-related applications, including cholesterol complexation and use as sensors[101]. Despite their potential, more studies are needed to fully assess the toxicity of CD derivatives[101]. The integration of CDs in biomedical applications requires careful consideration of their associated toxicities, including cytotoxicity and ototoxicity, which can vary depending on the route of administration[99]. Regulatory issues and safety concerns also need to be addressed for their successful implementation[1]. Nevertheless, CDs continue to be explored for their potential as novel therapeutic agents and carriers for bioactive compounds from natural sources[10299]. Ongoing research aims to overcome these challenges and expand the applications of CDs in drug delivery systems.

X. Future Prospects and Research Trends

Recent research has focused on developing stimuli-responsive CD-based drug delivery systems that respond to environmental factors such as pH, light, and temperature[103]. The evolution of CD research has progressed through distinct phases, from initial focus on β-CD inclusion complexes to the exploration of CD derivatives and their integration into novel delivery systems[104]. The future of CD-based drug delivery systems looks promising, with ongoing research exploring their applications in various delivery

routes, including ocular, transdermal, and targeted delivery systems. Additionally, CDs show potential as nanocarriers and in forming stable nanoaggregates, expanding their utility for new drug entities[64]. CD-based nanosystems, including polymers, supramolecular necklaces, and hydrogels, show promise in cancer treatment[105]. The evolution of CD research has progressed from simple inclusion complexes to sophisticated nanocarriers and conjugates[104]. Recent advancements have led to the development of CD-based nanostructures such as nanoparticles, nanorods, nanomicelles, and nanofibers, expanding their applications beyond drug delivery to areas like food packaging, antibacterial coatings, and environmental remediation[106]. Apart from these CDs are also proving to be a valuable component in non-viral gene delivery systems, offering reduced toxicity and controlled release[106]. CD-based nanoparticles provide synergistic advantages, including targeted delivery and improved stability compared to conventional formulations[86]. Recent research has highlighted CDs' potential as active therapeutic agents, not just inert carriers. Their ability to interact with lipids and proteins, particularly through cholesterol depletion from cellular membranes, shows promise in treating disorders such as Niemann-Pick type C disease, atherosclerosis, and neurodegenerative diseases[107]. As research progresses, CD-based delivery systems continue to evolve, offering opportunities for combination therapies and personalized medicine[108].

CONCLUSION

Cyclodextrins have significantly transformed the field of drug formulation and delivery by facilitating the effective solubilization, stabilization, and controlled release of a diverse array of therapeutic agents. Their distinctive ability to form inclusion complexes, along with their structural adaptability through chemical modifications, renders them essential tools for improving the pharmacokinetic and pharmacodynamic profiles of poorly soluble pharmaceuticals. The commercial success of cyclodextrin-based formulations, such as Vfend®, Geodon®, and Sporanox®, highlights their translational significance and clinical applicability.

Nonetheless, challenges such as elevated production costs, variability between batches, and the potential toxicity associated with certain cyclodextrin derivatives continue to hinder their widespread use. Addressing these challenges through innovative strategies—such as the development of stimuli-responsive cyclodextrin systems, nano-formulations, and safer derivatives—remains a critical focus of ongoing research.

Looking ahead, the prospects for cyclodextrin-based drug delivery systems appear promising. With their expanding applications in targeted delivery, gene therapy, and even as active therapeutic agents, cyclodextrins are positioned to play a crucial role in the advancement of personalized and precision medicine. Continued interdisciplinary research and regulatory progress will be essential for realizing the full therapeutic potential of cyclodextrins within contemporary pharmaceutical science.

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HOW TO CITE: D. Sruthi, Dr. Annie Vijetha, Deekshitha Reddy Padidham, Cyclodextrins in Formulation Development: Complexation and Stability Enhance, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 9, 2274-2290. https://doi.org/10.5281/zenodo.17165811