Cyclodextrins in pharmaceutical formulations I: structure and physicochemical properties, formation of complexes, and types of complex

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Cyclodextrins are cyclic oligosaccharides that have been recognized as pharmaceutical adjuvants for the past 20 years. The molecular structure of these glucose derivatives, which approximates a truncated cone, bucket, or torus, generates a hydrophilic exterior surface and a nonpolar interior cavity. Cyclodextrins can interact with appropriately sized drug molecules to yield an inclusion complex. These noncovalent inclusion complexes offer a variety of advantages over the noncomplexed form of a drug. Cyclodextrins are primarily used to enhance the aqueous solubility, physical chemical stability, and bioavailability of drugs. Their other applications include preventing drug–drug interactions, converting liquid drugs into microcrystalline powders, minimizing gastrointestinal and ocular irritation, and reducing or eliminating unpleasant taste and smell. Here, we discuss the physical chemical properties of various cyclodextrins, including the effects of substitutions on these properties. Additionally, we report on the regulatory status of their use, commercial products containing cyclodextrins, toxicological considerations, and the forces involved in complex formation. We also highlight the types of complex formed and discuss the methods used to determine the types of complex present.

Introduction

Although cyclodextrins are regarded by pharmaceutical scientists as a new group of pharmaceutical excipients, they have been in existence for over 100 years. The reader is referred to [1–28] for additional information on cyclodextrins and their physicochemical properties and pharmaceutical applications to augment that discussed here. The foundations of cyclodextrin chemistry were laid over 100 years ago by Villiers and Schardinger [29–31] and the first patent on cyclodextrins was registered in 1953 [32]. For many years following their discovery, only small amounts of cyclodextrins could be produced because of the expense of their manufacture, and this precluded their widespread use in pharmaceutical formulations or dosage forms. The biotechnological advances of the past 30 years have resulted in dramatic improvements in production, and an associated reduction in production costs. This has also contributed to the ready availability of highly purified cyclodextrins and cyclodextrin derivatives that are well suited for use in pharmaceutical applications.

Structure and physicochemical properties

Cyclodextrins are a group of structurally related natural products formed during the bacterial digestion of cellulose. These bucket-shaped [33–35] cyclic oligosaccharides comprise (α-1,4)-linked α-D glucopyranose units and have a lipophilic central cavity and a hydrophilic outer surface (Fig. 1a). The most common naturally occurring cyclodextrins are α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, comprising six, seven, and eight glucopyranose units, respectively (Table 1). Given the chair conformation of the glucopyranose units, cyclodextrins are shaped like a truncated cone rather than as perfect cylinders (Fig. 1b).

The hydroxyl functions are oriented to the cone exterior, with the primary hydroxyl groups of the sugar residues at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge (Fig. 1b). The central cavity is lined with the skeletal carbons and ethereal oxygen of the glucose residues, which impart a
lipophilic character. The polarity of the cavity has been estimated to be similar to that of an aqueous ethanolic solution.

As a result of its molecular shape and structure, cyclodextrin exhibits the unique ability to trap a guest molecule inside its cavity and act as a molecular container (Fig. 2). The inclusion complexes formed have several applications in pharmaceutical formulations. For example, cyclodextrins enhance the water solubility of poorly soluble drugs and improve their bioavailability [36], mask the bitter taste of the active ingredient [37], enable the development of chewable and orally disintegrating tablet formulations [38], and stabilize drugs from light, thermal, and oxidative degradation [33].

The natural α- and β-cyclodextrins, unlike γ-cyclodextrin, cannot be hydrolyzed by human saliva and pancreatic amylase [35,39]. However, both α- and β-cyclodextrins can be fermented by the intestinal microflora. Cyclodextrins are both large (molecule weight from almost 1000 to over 2000 Da) and hydrophilic, with a significant number of hydrogen donors and acceptors; therefore, they cannot be absorbed from the gastrointestinal tract in their intact form. Hydrophilic cyclodextrins are considered nontoxic at low to moderate oral dosages.

Aqueous solutions of cyclodextrins have been regarded as true solutions, whereas solutions of individual cyclodextrin molecules and cyclodextrin complexes are considered as homogeneous molecular dispersions in an aqueous system. Recently, it was shown that cyclodextrins and cyclodextrin complexes self-associate to form an aggregate or micelle-like structure [40-43]. Furthermore, polymers have been shown to interact with such a system [44,45] and the aggregates formed can solubilize drugs through noninclusion complex formation [46].

The natural cyclodextrins, in particular β-cyclodextrin, have limited aqueous solubility (18.5 mg/ml) and, therefore, do so the complexes formed with these cyclodextrins. This results in precipitation of solid cyclodextrin complexes from water and other aqueous systems. Several techniques can be used to enhance the water solubility of drug–cyclodextrin complexes (aggregates). The

![Diagram of cyclodextrin structure](drugdiscoverytoday.com)

**Figure 1**
The chemical structure (a) and the toroidal shape (b) of the β-cyclodextrin molecule. Source: Reproduced, with permission, from [33].

**Table 1**

<table>
<thead>
<tr>
<th>Type of cyclodextrin</th>
<th>Number of glucose units</th>
<th>Cavity diameter (Å)</th>
<th>Cavity height (Å)</th>
<th>Cavity volume (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>6</td>
<td>4.7–5.3</td>
<td>7.9</td>
<td>174</td>
</tr>
<tr>
<td>β</td>
<td>7</td>
<td>6.0–6.5</td>
<td>7.9</td>
<td>262</td>
</tr>
<tr>
<td>γ</td>
<td>8</td>
<td>7.7–8.3</td>
<td>7.9</td>
<td>427</td>
</tr>
</tbody>
</table>

![Diagram of doxorubicin-γ-cyclodextrin complex](drugdiscoverytoday.com)

**Figure 2**
Proposed structure of the doxorubicin–γ-cyclodextrin complex. Source: Reproduced, with permission, from [33].
addition of a small amount of water-soluble polymer to an aqueous complexation media, for instance, increases the solubility of aggregates [46]. Analogously, addition of various salts, such as sodium acetate and benzalkonium chloride, can also enhance the solubility of drug–cyclodextrin complexes.

The poor aqueous solubility of cyclodextrins is attributed to the presence of relatively strong intermolecular hydrogen bonding in the crystal state (https://www.eurocdsoc.com/index.php). Substitution of any hydrogen bond-forming hydroxyl group, even the lipophilic methoxy function, results in dramatic improvement in the aqueous solubility of these compounds. Although natural cyclodextrins exhibit lower aqueous solubility compared with cyclodextrin derivatives, their solubility is often enough to prevent dissolution rate-limited drug absorption from the gastrointestinal tract [47]. Moreover, because the molecular weights of natural cyclodextrins are lower than those of their derivatives, complexes formed with natural cyclodextrins are less bulky than those formed with derivatives.

Given the poor aqueous solubility of natural cyclodextrins as well as their toxicity when administered parenterally, several researchers have attempted to identify, prepare, and evaluate other cyclodextrin derivatives of pharmaceutical interest. These include the hydroxypropyl derivatives of β- and γ-cyclodextrins, the randomly methylated β-cyclodextrin, sulfobutylether β-cyclodextrin (SBE-β-cyclodextrin), and the branched cyclodextrins (Table 2). SBE-β-cyclodextrin, a polyanionic variably substituted SBE of β-cyclodextrin, and hydroxypropyl β-cyclodextrins have undergone extensive safety studies [47] and are currently used in many marketed products approved by the US Food and Drug Administration (FDA; Table 3). Additionally, they in use in numerous clinical and preclinical studies. Pitha et al. [48] and Casella et al. [49,50] described the preparation and characterization of drugs from hydroxypropyl β-cyclodextrin, and Jambhekar et al. [51] evaluated hydroxypropyl-β-cyclodextrin-indomethacin complexes for the bioavailability of indomethacin.

Cyclodextrins listed in Table 2 have been shown to enhance the aqueous solubility of biopharmaceutical classification system class II and class IV drugs [36,52]. The natural β- and γ-cyclodextrins have been approved as food additives, with some restrictions, and cyclodextrins listed in Table 3 are all found in one or more pharmaceutical products in Europe, the USA, or Japan.

Although it is thought that cyclodextrins with fewer than six glucopyranose units cannot exist because of steric factors, cyclodextrins containing 9–13 glucopyranose units have been reported [42,43]; however, of these large-ring cyclodextrins, only δ-cyclodextrin has been well characterized [44,45]. The physical and chemical properties of the four most common cyclodextrins are reported in Table 4.

### Table 2

<table>
<thead>
<tr>
<th>Cyclodextrin</th>
<th>Substitution(s)a</th>
<th>Molecular weightb</th>
<th>Solubility in waterc (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Cyclodextrin</td>
<td>–</td>
<td>972</td>
<td>145</td>
</tr>
<tr>
<td>β-Cyclodextrin</td>
<td>–</td>
<td>1135</td>
<td>18.5</td>
</tr>
<tr>
<td>HP-β-cyclodextrin</td>
<td>0.65</td>
<td>1400</td>
<td>&gt;600</td>
</tr>
<tr>
<td>Randomly methylated β-cyclodextrin</td>
<td>1.8</td>
<td>1312</td>
<td>&gt;500</td>
</tr>
<tr>
<td>β-Cyclodextrin SBE sodium salt</td>
<td>0.9</td>
<td>2163</td>
<td>&gt;500</td>
</tr>
<tr>
<td>γ-Cyclodextrin</td>
<td>–</td>
<td>1297</td>
<td>232</td>
</tr>
<tr>
<td>HP-γ-cyclodextrin</td>
<td>0.6</td>
<td>1576</td>
<td>&gt;500</td>
</tr>
</tbody>
</table>

*a Average number of substitution per glucopyranose repeat unit.

*b Provided by the supplier or value calculated based on average degree of substitution.

*c Solubility in pure water at 25°C.

### Table 3

| Examples of marketed products containing cyclodextrinsa. |
|-------------------|-------------------|-------------------|-------------------|
| Type of cyclodextrin | Drug name | Route of administration | Trade name | Market |
| α-Cyclodextrin | Cefotiam hexetil hydrochloride | Oral | Pansporin T | Japan |
| β-Cyclodextrin | Benexate hydrochloride | Oral | Ulgut, Lonmil | Japan |
| | Omeprazole | Oral | Omebeta | Europe |
| | Piroxicam | Oral | Brexin | Europe |
| HP-β-cyclodextrin | Cisapride | Rectal | Propulsid | Europe |
| | Itraconazole | Oral, Intravenous | Sporanox | Europe, USA |
| | Mitomycin | Intravenous | Mitozytrex | USA |
| Randomly methylated β-cyclodextrin | 17β-Estradiol | Nasal drops | Aerodiol | Europe |
| SBE-β-cyclodextrin | Voriconazole | Intravenous | Vfend | Europe, USA |
| | Ziprasidone maleate | Intramuscular | Geodon, Zeldox | Europe, USA |
| HP-γ-cyclodextrin | Diclofenac sodium | Eye drops | Voltaren | Europe |

*a Adapted from https://www.eurocdsoc.com/index.php.
TABLE 4
Selected properties of α-, β-, γ-, and δ-cyclodextrins.

<table>
<thead>
<tr>
<th>Type of cyclodextrin</th>
<th>Number of glucopyranose units</th>
<th>Molecular weight (Da)</th>
<th>Central cavity diameter (Å)</th>
<th>Water solubility at 25 °C (g/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>6</td>
<td>972</td>
<td>4.7–5.3</td>
<td>14.5</td>
</tr>
<tr>
<td>β</td>
<td>7</td>
<td>1135</td>
<td>6.0–6.5</td>
<td>1.85</td>
</tr>
<tr>
<td>γ</td>
<td>8</td>
<td>1297</td>
<td>7.5–8.3</td>
<td>23.2</td>
</tr>
<tr>
<td>δ</td>
<td>9</td>
<td>1459</td>
<td>10.3–11.2</td>
<td>8.19</td>
</tr>
</tbody>
</table>

*Adapted from [33].

Regulatory status

The regulatory status of cyclodextrins continues to change (https://www.eurocdsoc.com/index.php). α-Cyclodextrin and β-cyclodextrin are included in several pharmacopoeias, including the US Pharmacopoeia, European Pharmacopoeia, and Japanese Pharmacopoeia. γ-cyclodextrin will soon be included in the US Pharmacopoeia and subsequently the European Pharmacopoeia as well. A monograph for 2-hydroxypropyl-β-cyclodextrin (HP-β-cyclodextrin) has appeared in both the European Pharmacopoeia and US Pharmacopoeia 28/National Formulary 23. Moreover, efforts are under way to include other derivatives in pharmacopoeias (https://www.eurocdsoc.com/index.php). β-Cyclodextrin and γ-cyclodextrin are also listed in the generally regarded as safe (GRAS) list of the FDA for use as a food additives.

Regulatory agencies still appear to be skeptical [47] regarding the use of cyclodextrins in pharmaceuticals. This appears to be a bigger issue for the FDA than for other regulatory agencies, particularly in Europe and Japan. With time, the availability of more data, and the expanding use of cyclodextrins in pharmaceutical drug formulations used to treat acute and life-threatening diseases, these compounds might encounter less regulatory resistance. Several pharmaceutical products containing cyclodextrins are currently on the market, and examples are listed in Table 3.

Toxicological considerations

α-Cyclodextrin is well tolerated when administered orally and is not associated with significant adverse effects [53,54]. Only a small fraction of α-cyclodextrin is absorbed intact from the gastrointestinal tract and is mainly excreted unchanged in the urine following intravenous administration. By contrast, β-cyclodextrin cannot be administered parenterally because of its low aqueous solubility and nephrotoxicity. However, it is nontoxic when administered orally. The renal toxicity of α- and β-cyclodextrins, following parenteral administration, [55] as well as problems with several modified cyclodextrins, have been well documented [35,56,57].

Following oral administration, the nontoxic effect level of β-cyclodextrin was determined to be 0.7–0.8 g kg⁻¹ day⁻¹ in rats and approximately 2 g kg⁻¹ day⁻¹ in dogs [58]. The metabolism of γ-cyclodextrin closely resembles that of starch and other linear dextrans [59], and only small amounts of γ-cyclodextrin are absorbed intact from the gastrointestinal tract. Following intravenous injection, γ-cyclodextrin is mainly excreted in an unchanged form in the urine.

Hydrophilic cyclodextrins, namely HP-β-cyclodextrin and SBE-β-cyclodextrin, are considered nontoxic when administered in low to moderate doses by oral and intravenous routes [35,56]. HP-β-cyclodextrin is more water soluble and, toxicologically, more benign than the natural β-cyclodextrin [57,60]. HP-β-cyclodextrin has been shown to be well tolerated in humans, with the main adverse effect being the increased incidence of soft stool or diarrhea [35,57,60]. There are several additional publications [61–63] that provide useful information related to the toxicity of cyclodextrins.

Lipophilic cyclodextrin derivatives, such as methylated cyclodextrin, are absorbed to a greater extent from the gastrointestinal tract into the systemic circulation and have been shown to be toxic after parenteral administration [35]. Presently, oral administration of methylated β-cyclodextrin is limited because of its potential toxicity.

One relative incompatibility for a cyclodextrin molecule appears in the literature. SBE-β-cyclodextrin is used as a solvent for the poorly water-soluble antifungal voriconazole. In one study [64], patients with renal failure receiving intermittent dialysis as well as intravenous doses of the complex of voriconazole, showed an accumulation of SBE β-cyclodextrin in plasma; however, no toxic effects were reported. This observation underscores the need to carefully monitor SBE β-cyclodextrin levels in dialysis patients receiving voriconazole. Intravenous voriconazole is not recommended by the manufacturer for patients with creatinine clearances less than 50 ml/min [65]. However, it has been shown that continuous venovenous hemofiltration (CVVH) can safely remove SBE β-cyclodextrin in patients with renal failure receiving voriconazole [66].

Complex formation

Mechanism: guest molecule consideration

Cyclodextrins in aqueous solution are capable of forming inclusion complexes with many drugs by accepting into their central cavity (Fig. 2) a drug molecule or, more frequently, only the lipophilic portion of the therapeutics moiety. While the complex is being formed, no covalent bonds are formed or broken, and drug molecules in the complex are in rapid equilibrium with free molecules in the solution. Whereas the initial equilibrium to form a complex is rapid, the final equilibrium takes longer time to attain. Drug molecules, once inside the cyclodextrin cavity, undergo conformational adjustments to take maximum advantage of the presence of weak van der Waal’s forces. The driving forces behind complex formation are reported to be release of enthalpy-rich water molecules from the cavity, electrostatic interactions, van der Waals interactions, hydrophobic interactions, hydrogen bonding, and release of conformational strain and charge-transfer interactions (https://www.eurocdsoc.com/index.php).
The ability of cyclodextrins to form an inclusion complex with the active drug rests upon several factors. The first is steric and depends on the relative size of cyclodextrin to the size of the drug molecule or certain key functional groups of the active ingredients. If the active ingredient is too large in size, it will not fit properly into the cyclodextrin cavity (Fig. 2). In addition, although the height of three natural cyclodextrins might be the same, they differ in the number of glucose units and diameter of the cavity. Table 1 provides the dimensions of three natural cyclodextrins (α-, β-, and γ-cyclodextrins).

Based on dimensions, α-cyclodextrin can typically form a complex with compounds of lower molecular weight or compounds with an aliphatic side chain. β-Cyclodextrin will complex with aromatic and heterocyclic molecules, and γ-cyclodextrin will accommodate larger molecules, such as macrocycles and steroids [67].

Another key factor for complex formation is the thermodynamic interaction between different components of the chosen cyclodextrin and the drug molecule. For a complexation to occur, there must be a favorable net energetic driving force that pulls the drug molecule into the cyclodextrin cavity [67]. The most stable 3D structure of cyclodextrin is a toroid, with the larger and smaller openings presenting hydroxyl groups to the external environment and mostly hydrophobic functionality lining the interior of the cavity (Fig. 1). This unique configuration imparts cyclodextrins with their interesting properties and creates the thermodynamic driving force required to form a drug–cyclodextrin complex. There are four energetically favorable interactions that help shift the equilibrium towards complex formation [67]: (i) the displacement of polar water molecules from the apolar cyclodextrin cavity; (ii) the increased number of hydrogen bonds formed as the displaced water returns to the larger pool; (iii) a reduction in the repulsive interactions between the hydrophobic guest and the aqueous environment; and (iv) an increase in hydrophobic interactions as the guest molecule inserts itself into the apolar cyclodextrin cavity.

The physicochemical properties of the free drug molecule and the free cyclodextrin molecule are different from their counterparts in the complexed form (https://www.eurocdsoc.com/index.php). The changes in the physicochemical properties of drugs can be observed using several methods. Typically, these methods measure changes in solubility, chemical reactivity, ultraviolet/visible spectrum (UV/VIS) absorbance, fluorescence, NMR chemical shifts, drug retention, pKa value, potentiometric measurements, and chemical stability, and effects on drug permeability, through an artificial membrane (https://www.eurocdsoc.com/index.php). Furthermore, because complexation influences the physicochemical properties of the aqueous complexation media, methods that monitor media changes can be applied to study complexation, including measurement of conductive changes, determination of freezing point depression, viscosity measurements, and calorimetric titration. However, only a few of these methods can be applied to obtain structural information on drug–cyclodextrin complexes.

**Types of complex**

The stoichiometry of drug–cyclodextrin complexes and the numerical values of their stability or binding constants are frequently obtained from plots of drug solubility against cyclodextrin concentration. This phase-solubility technique was first developed by Higuchi and Connors [68] and reported by Riley et al. [69].

Higuchi and Connors [68] classified complexes by studying the effects of ligand (solubilizer) concentration on the solubility of a substrate (drug), as illustrated in Fig. 3, which is referred to as the phase-solubility profile. A-type phase-solubility profiles are obtained when the solubility of the substrate (drug) increases with an increase in ligand (cyclodextrin) concentration. The A-type profile is further subdivided into three profiles. The Aπ profile indicates that there is a linear increase in solubility as a function of ligand or solubilizer concentration; the Aπ profile indicates an isotherm, wherein the curve deviates from linearity in a positive manner, suggesting that ligand or solubilizer is proportionately more effective at higher concentrations. Conversely, the AN type relation indicates a negative deviation from linearity, which means that the ligand or solubilizer is proportionately less effective at higher concentration [68,69].

Collectively, all three curves (Fig. 3) indicate that water-soluble complexes are being formed with solubilities higher than that of the uncomplexed substrate. If the slope of the Aπ type plot is less than unity, a 1:1 complex is formed. If the slope is greater than unity, higher order complexes are assumed to be involved in the solubilization process (https://www.eurocdsoc.com/index.php). Although a slope of less than unity does not exclude the possibility of higher order complexes, a 1:1 complex is often assumed to form in the absence of other information.

When the complex is first order in nature with respect to ligand (complexing agent) and first order with respect to substrate (drug), then the Aπ-type (Fig. 3) phase solubility profile is obtained. If the complex is first order with respect to substrate but second or higher order with respect to the ligand, then the Aπ-type (Fig. 3) phase solubility profile is obtained. The third type, the AN-type phase solubility profile, is difficult to interpret.

**FIGURE 3**

Graphical representation of A and B type phase-solubility profiles with applicable subtypes (Aπ, AN, Bσ, and Bτ). Source: Reproduced, with permission, from [70].
In general, the water-soluble cyclodextrins form A-type phase solubility profiles, whereas the less-soluble natural cyclodextrins frequently form B-type profiles. Type B phase-solubility profiles indicate the formation of a complex with limited water solubility and are traditionally observed with naturally occurring cyclodextrins, in particular β-cyclodextrin. Type B complexes are further subdivided into two subtypes: Bₐ and Bₜ (for further details, see [68–70]). Most drug–cyclodextrin complexes are thought to be inclusion complexes; however, cyclodextrins are also known to form noninclusion complexes and complex aggregates capable of dissolving drug through micelle-like structures. Phase-solubility profiles are incapable of verifying formation of inclusion complexes, and describe only how the increasing concentration of cyclodextrin influences drug solubility [33].

Concluding remarks

It is clear from the information presented here that cyclodextrins, because of their unique structure and physicochemical properties, offer an additional tool to pharmaceutical scientists to overcome some of the formulation and drug delivery challenges for problematic drugs. These starch derivatives are useful solubilizers, enabling the preparation of liquid oral, solid, and parenteral dosage forms. Additionally, cyclodextrins can improve the bioavailability of problematic drugs through increases in aqueous solubility and dissolution rates. Many cyclodextrins such as α, β, γ, randomly methylated β-cyclodextrin, HP-β-cyclodextrin, and SBE-β-cyclodextrins have become standard tools in formulation development. Although both α- and β-cyclodextrins as well as several alkylated cyclodextrins are known to be renally toxic and disruptive of biological membranes, γ-cyclodextrin as well as HP-β-cyclodextrin and SBE-β-cyclodextrin appear to be safer. Phase-solubility plots of drug solubility against concentration of cyclodextrin permit determination of the type of complex formed.

As is the case with the use of any new technology, cyclodextrins have both strengths and weaknesses. Their major strengths are how they interact with drug molecules and their ability to safely deliver intractable drug molecules. The specific nature of their interaction becomes a weakness in that only those drug molecules with the right size, geometry, and intrinsic solubility characteristics benefit from their use.

Given that there are currently more commercial products that contain cyclodextrins than 20 years ago, the future for pharmaceutical applications of cyclodextrins as solubilizers appears bright. As more products containing cyclodextrins are evaluated and approved following their rigorous and robust evaluation by the regulatory agencies for their use in food and pharmaceuticals, concerns about their safety will likely be attenuated.

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