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Review

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Pharmaceutical applications of cyclodextrins: basic science and product development

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Abstract

Objectives Drug pipelines are becoming increasingly difficult to formulate. This is punctuated by both retrospective and prospective analyses that show that while 40% of currently marketed drugs are poorly soluble based on the definition of the biopharmaceutical classification system (BCS), about 90% of drugs in development can be characterized as poorly soluble. Although a number of techniques have been suggested for increasing oral bioavailability and for enabling parenteral formulations, cyclodextrins have emerged as a productive approach. This short review is intended to provide both some basic science information as well as data on the ability to develop drugs in cyclodextrin-containing formulations.

Key findings There are currently a number of marketed products that make use of these functional solubilizing excipients and new product introduction continues to demonstrate their high added value. The ability to predict whether cyclodextrins will be of benefit in creating a dosage form for a particular drug candidate requires a good working knowledge of the properties of cyclodextrins, their mechanism of solubilization and factors that contribute to, or detract from, the biopharmaceutical characteristics of the formed complexes.

Summary We provide basic science information as well as data on the development of drugs in cyclodextrin-containing formulations. Cyclodextrins have emerged as an important tool in the formulator's armamentarium to improve apparent solubility and dissolution rate for poorly water-soluble drug candidates. The continued interest and productivity of these materials bode well for future application and their currency as excipients in research, development and drug product marketing.

Keywords biopharmaceutical characteristics; cyclodextrins; cyclodextrin-containing formulations; pharmaceutical applications; solubilization

Introduction

In 1891 a French scientist, A. Villiers, published a short note on his isolation of a bacterial digest which he named 'cellobiosine'.[1] The compound was stable towards acid hydrolysis and, like starch, did not display reducing properties. It is now thought that Villiers had isolated a mixture of α- and β-cyclodextrin (αCD and βCD). Later an Austrian microbiologist, Franz Schardinger, described two compounds that he had isolated from bacterial digest of potato starch,which he designated α-dextrin and β-dextrin.[2] It was not until the 1940s, however, that the structure and physicochemical properties of cyclodextrins (CDs) were described in detail.[3,4] The first CD-related patent was issued in Germany in 1953.[5] In this patent, the basic properties of the natural αCD, βCD and γ-cyclodextrin (γCD) are described and how, through complex formation, these CDs can enhance aqueous solubility and chemical stability of biologically active compounds. Bacterial digests of starch consist of a crude mixture of cyclic and linear dextrins as well as proteins and other impurities. It was difficult to isolate pure CDs from the digests and, as a result, only very small amounts of pure natural αCD, βCD and γCD were available at that time. This hampered industrial exploitation of CDs. Biotechnological advances that occurred in the early 1970s led to dramatic improvement in CD production and pharmaceutical-grade CDs can now be obtained at relatively low prices. The first pharmaceutical product containing CD, prostaglandin E_2/βCD sublingual tablets (Prostarmon E, Ono), was marketed in Japan in 1976. Worldwide there are currently about 35 different CD containing drug products on various world markets (Table 1).

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Table 1 Some marketed pharmaceutical products that contain cyclodextrins

Drug/cyclodextrin	Trade name	Formulation	Company (country)
α-Cyclodextrin (αCD)			
Alprostadil	Caverject Dual	Intravenous solution	Pfizer (Europe)
Cefotiam-hexetil HCl	Pansporin T	Tablet	Takeda (Japan)
Limaprost	Opalmon	Tablet	Ono (Japan)
PGE1	Prostavastin	Parenteral solution	Ono (Japan); Schwarz (Europe)
β-Cyclodextrin (βCD)			
Benexate HCl	Ulgut, Lonmiel	Capsule	Teikoku (Japan); Shionogi (Japan)
Cephalosporin	Meiact	Tablet	Meiji Seika (Japan)
Cetirzine	Cetrizin	Chewable tablet	Losan Pharma (Germany)
Chlordiazepoxide	Transillium	Tablet	Gador (Argentina)
Dexamethasone	Glymesason	Ointment, tablet	Fujinaga (Japan)
Dextromethorphan	Rynathisol	Synthelabo (Europe)	
Diphenhydramine and chlortheophylline	Stada-Travel	Chewable tablet	Stada (Europe)
Ethinylestradiol and drospirenone	Yaz	Tablet	Bayer (Europe, USA)
Iodine	Mena-Gargle	Solution	Kyushin (Japan)
Meloxicam	Mobitil	Tablet and suppository	Medical Union (Egypt)
Nicotine	Nicorette	Sublingual tablet	Pfizer (Europe)
Nimesulide	Nimedex	Tablets	Novartis (Europe)
Nitroglycerin	Nitropen	Sublingual tablet	Nihon Kayaku (Japan)
Omeprazole	Omebeta	Tablet	Betafarm (Europe)
PGE2	Prostarmon E	Sublingual tablet	Ono (Japan)
Piroxicam	Brexin, Flogene, Cicladon	Tablet, suppository	Chiesi (Europe); Aché (Brazil)
Tiaprofenic acid	Surgamyl	Tablet	Roussel-Maestrelli (Europe)
2-Hydroxypropyl-β-cyclodextrin (HPβCD)			
Cisapride	Propulsid	Suppository	Janssen (Europe)
Indometacin	Indocid	Eye drop solution	Chauvin (Europe)
Itraconazole	Sporanox	Oral and intravenous solution	Janssen (Europe, USA)
Mitomycin	MitoExtra, Mitozytrex	Intravenous infusion	Novartis (Europe)
Sulfobutylether β-cyclodextrin sodium salt (SBEβCD)			
Aripiprazole	Abilify	Intramuscular solution	Bristol-Myers Squibb (USA); Otsuka Pharm. (USA)
Maropitant	Cerenia	Parenteral solution	Pfizer Animal Health (USA)
Voriconazole	Vfend	Intravenous solution	Pfizer (USA, Europe, Japan)
Ziprasidone mesylate	Geodon, Zeldox	Intramuscular solution	Pfizer (USA, Europe)
Randomly methylated β-cyclodextrin (RMβCD)			
17β-Estradiol	Aerodiol	Nasal spray	Servier (Europe)
Chloramphenicol	Clorocil	Eye drop solution	Oftalder (Europe)
γ-Cyclodextrin (γCD)			
Tc-99 Teboroxime[a]	CardioTec	Intravenous solution	Squibb Diagnostics (USA)
2-Hydroxypropyl-γ-cyclodextrin (HPγCD)			
Diclofenac sodium salt	Voltaren Ophtha	Eye drop solution	Novartis (Europe)
Tc-99 Teboroxime[a]	CardioTec	Intravenous solution	Bracco (USA)

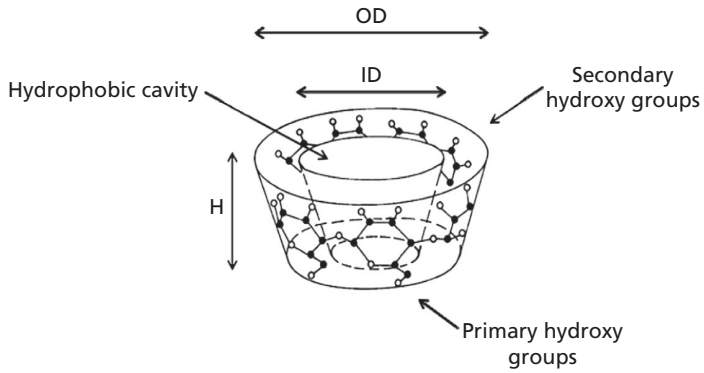
[a]An older product contained γCD but has been replaced by HPγCD in the current product.

The following is intended to be a short introduction on CDs and their pharmaceutical applications. For more comprehensive reviews of their chemistry, physicochemical properties and applications the reader is referred to several books and review articles that have been published in recent years.[4,6–21]

Chemistry

CDs are cyclic oligosaccharides containing six (αCD), seven (βCD), eight (γCD), or more (α-1,4-)-linked D-glucopyranose units (Table 2). Manufacturing of the three most common natural CDs (i.e. αCD, βCD and γCD) is a three step process: (1) bacterial fermentation and extraction of CD glycosyltransferase; (2) enzymatic CD production from starch and precipitation of CD through complexation; and (3) removal of the complexing agent and product purification. CDs with more than eight glucopyranose units (i.e. the large-ring CDs) are usually produced through chromatographic separation of the enzymatic product without precipitation. The large-ring CDs are more expensive, have generally less complexation capacity than αCD, βCD and γCD and are less relevant pharmaceutically, and therefore will not be covered in this short compilation.[22,23] Due to the chair structure of the

Table 2 Characteristics of the natural αCD, βCD and γCD

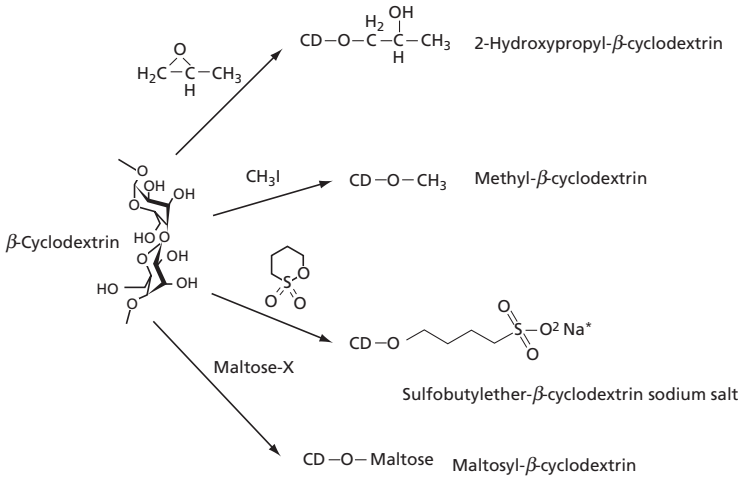


Property	α-Cyclodextrin	β-Cyclodextrin	γ-Cyclodextrin
Synonyms	Cyclo-α-(1 → 4)-D-hexaglucopyranoside Cyclomaltohexaose Cyclohexaamylose Alfadex (Ph.Eur.)	Cyclo-α-(1 → 4)-D-heptaglucopyranoside Cyclomaltoheptose Cycloheptaamylose Betadex (Ph.Eur.)	Cyclo-α-(1 → 4)-D-octaglucopyranoside Cyclomaltooctaose Cyclooctaamylose Gammadex
Molecular weight of anhydrous compound (Da)	972.84	1134.98	1297.12
No. of glucopyranose units	6	7	8
Moisture content (% w/w)	10.2	13.0–15.0	8–18
Approximate dimensions (nm)[a]			
Height (H)	0.78	0.78	0.78
Inner diameter (ID)	0.50	0.62	0.80
Outer diameter (OD)	1.46	1.54	1.75
Solubility in water at 25°C (mg/ml)[b]	129.5 ± 0.7	18.4 ± 0.2	249.2 ± 0.2
Specific rotation $[\alpha]^{25}_{D}$	+147.8	+161.1	+175.9
Calculated LogKo/w (octanol–water partition coefficient) at 25°C[c]	−7.8	−10.7	−12
$K_{1:1}$ (population mean ± SD, 25°C)[d]	130 ± 8	490 ± 8	350 ± 9

[a]From Dodziuk[18]; [b]from Sabadini *et al.*[119]; [c]Calculated $LogK_{o/w}$ (octanol–water partition coefficient) at 25°C (www.syrres.com); [d]from Connors.[120,121]

glucopyranose units, CD molecules are shaped like cones with secondary hydroxy groups extending from the wider edge and the primary groups from the narrow edge (Table 2). This gives the CD molecule a hydrophilic outer surface while the lipophilicity of their central cavity has been estimated to be comparable with an aqueous ethanolic solution.[24] Although the natural CDs and their complexes are hydrophilic, their aqueous solubility can be rather limited, especially in the case of βCD. This is thought to be due to relatively strong binding of the CD molecules in the crystal state (i.e. relatively high crystal lattice energy). Random substitution of the hydroxy groups, even by hydrophobic moieties like methoxy functions, will result in dramatic improvements in their solubility. CD derivatives of pharmaceutical interest include the hydroxypropyl derivatives of β- and γCD (HPβCD and HPγCD), randomly methylated βCD (RMβCD), sulfobutylether βCD sodium salt (SBEβCD) and the so-called branched cyclodextrins, such as maltosyl-βCD (MβCD) (Table 3).[6,17,20] The physicochemical properties of the CD derivatives, including their aqueous solubility and complexation capabilities, not only depend on the structure of the appended substituent but also on their location within the CD molecule and the number of substituents per CD molecule. The molar degree of substitution (MS) is defined as the average number of substituents that have reacted with one glucopyranose repeat unit (Table 3). In some cases, as in hydroxypropylation, the electrophile (propylene oxide) can react with hydroxyl groups of the substituents forming a polymeric side chain (polypropylene glycol). Thus, the MS value can range from 0 (no substitution) to over 3 when two or more substituents react to form oligomeric or polymeric side chains. The number represents the average MS of a mixture of isomers. Hence, MS does not necessarily describe how many hydroxyl groups on each glucopyranose unit have been substituted. In carbohydrate chemistry, the degree of substitution (DS) is defined as the number of hydroxyl groups per anhydroglucose unit that have been substituted. The values can range from 0 (no substitution) to 3 when all three hydroxyl groups are substituted. By contrast, in CD chemistry, DS frequently represents the average number of substituents per CD molecule.

Table 3 Characteristics of some common cyclodextrins that can be found in marketed pharmaceutical products or that are being investigated as pharmaceutical excipients



Cyclodextrin	Trade name and manufacturer	MS	MW (Da)	Solubility (mg/ml)	$LogK_{o/w}$[a]
2-Hydroxypropyl-α-cyclodextrin (HPαCD)	Cavasol W6 HP (Wacker, Germany)	0.65	1199	>500	<–10
2-Hydroxypropyl-β-cyclodextrin (HPβCD) (Hydroxypropylbetadex, Ph.Eur.)	Cavasol W7 HP (Wacker, Germany)	0.65	1400	>600	–8.5
	Kleptose HPB (Roquette, France)	0.65	1400	>600	–8.5
Sulfobutylether β-cyclodextrin Na (SBEβCD)	Captisol (CyDex Pharmaceuticals, USA)	0.9	2163	>500	<–10
Randomly methylated β-cyclodextrin (RMβCD)	Cavasol W7 M (Wacker, Germany)	1.8	1312	>600	–2.4
	Kleptose Crysmeb (Roquette, France)	0.57	1191	200	
Maltosyl β-cyclodextrin (MβCD)	(Ensuiko Sugar Refining Co., Japan)	0.14	1459	>500	<–10
2-Hydroxypropyl-γ-cyclodextrin (HPγCD)	Cavasol W8 HP (Wacker, Germany)	0.6	1576	>600	<–10

[a]Calculated LogKo/w (octanol–water partition coefficient) at 25°C (www.syrres.com). These are approximate values. The exact values will depend on the molar degree of substitution (MS) well as the location of the substituents.

Natural αCD, βCD and γCD are more resistant towards starch hydrolysing enzymes, and two to five times more resistant towards non-enzymatic hydrolysis than the linear oligosaccharides.[24] In the solid state, CDs are at least as stable as sucrose or starch and can be stored for several years at room temperature without detectable degradation.[25] The predominating non-enzymatic degradation of CDs in aqueous solutions is specific acid-catalysed hydrolysis of the α-acetal linkages to form glucose, maltose and non-cyclic oligosaccharides.[26] The half-life ($t_{1/2}$) for the ring-opening of βCD was determined to be about 15 h at 70°C and pH 1.1.[26] The CD derivatives are hydrolysed at about the same rate, ring-opening being the dominant degradation pathway. In aqueous media, CDs are chemically stable under neutral and basic conditions. CDs are resistant to β-amylases that hydrolyse starch from the non-reducing end, but are slowly hydrolysed by α-amylases that hydrolyse starch from within the carbohydrate chain. α-Amylases are present in humans, mainly in pancreatic juice and saliva. The hydrolytic rate depends on the ring size and on the fraction of free CD. For example, αCD and βCD are essentially stable towards α-amylase in saliva while γCD is rapidly digested by salivary and pancreatic amylase.[27,28] αCD and βCD are not digested after oral administration to germ-free rats while γCD is completely digested.[29] In general, free CD is hydrolysed more rapidly than CD bound in a complex. After oral administration, γCD is almost completely digested in the gastrointestinal tract while both αCD and βCD are, to a large extent, digested by bacteria in the colon. αCD is, however, digested more slowly than βCD. The CD derivatives are also susceptible to bacterial digestion in the gastrointestinal tract (Table 4).[8,14,21,29–33]

Pharmacokinetics and toxicology

Most CDs of current pharmaceutical interest (Table 1) are hydrophilic and, due to their bacterial digestion, high molecular weight (973–2163 Da), large number of hydrogen donors and acceptors, and high hydrophilicity ($logK_{o/w}$ between −8 and −12), their oral bioavailability is generally below 4% (Table 4). The oral bioavailability of HPβCD in humans is between 0.5 and 3.3% with 50–65% of the oral dose excreted intact in the faeces and the remainder mainly being metabolized by bacteria in the colon. CD absorbed intact is rapidly excreted in the urine. Toxicological studies have demonstrated that orally administered CDs of pharmaceutical interest are practically nontoxic due to lack of absorption from the gastrointestinal tract.[8] However, there is one exception, that being RMβCD. This methylated βCD derivative (DS of 1.8) is somewhat more lipophilic ($LogK_{o/w} = -2.4$) and has fewer hydrogen-bond donors than the other CDs. Consequently its oral bioavailability

Table 4 Some pharmacokinetic data on common cyclodextrins and cyclodextrin derivatives[8,14,21,29–33]

Cyclodextrin	Rats	After intravenous injection to rats[b]			After intravenous injection to humans[c]		Max. dosage in marketed drug products[d]	
	f_{oral}[a] (%)	V_D[a] (l/kg)	$t^1/_2$[a] (h)	$f_{urine\ unch.}$[a] (%)	V_D[a] (l/kg)	$t^1/_2$[a] (h)	Oral (mg/day)	Intravenous (mg/day)
αCD	2–3		0.4	~90			1	1
βCD	~0.6	0.2	0.4	~90			170	No use[a]
HPβCD	≤3	0.2	0.4	~90	0.2	1.9	8000	16 000
SBEβCD	1.6	0.3	0.3	≥90	0.2	1.4		14 000
RMβCD	0.5–15	~2.5	0.3	~95				No use[a]
γCD	<0.1		0.3	~90				~50
HPγCD								~50

[a]f_{oral}, fraction absorbed intact after oral administration (i.e. oral bioavailability); V_D, volume of distribution; $t_{1/2}$, biological half-life; $f_{urine\ unch}$, fraction excreted unchanged with urine; No use, not for parenteral usage. [b]From Antlsperger[30]; Antlsperger & Schmid[29]; Irie & Uekama[8]; De Bie *et al*.[31]; Davis & Brewster[14]; Van Ommen *et al*.[32]. [c]From Zhou *et al*.[33]; Stella & He.[21] [d]As dietary supplement the daily oral dose of αCD has been reported to be as high as 6000 mg/day, for βCD as high as 500 mg/day and for γCD as high as 10 000 mg/day.

is slightly higher, or up to 12% in rats.[29] Presently, oral administration of methylated βCDs is limited by their potential toxicity. Oral administration of αCD is well tolerated and is not associated with any observable adverse effects.[34,35] The same applies to βCD,[36] γCD,[28] HPβCD[37] and SBEβCD.[21] The main side effects of oral administration of high doses of these CDs are similar to those related to poorly digestible carbohydrates and include flatulence and soft stools. αCD, βCD and HPβCD can all be found in various oral drug products and all three parent cyclodextrins (i.e. αCD, βCD and γCD) are being used in dietary products. The maximum CD dose that can be found in oral drug products is shown in Table 4. However, the CD dose found in approved dietary products can be much higher. For example, the daily dose of αCD in FBC_X tablets (ArtJen, Canada) is 6000 mg while the daily dose in registered drug products is only about 1 mg.

Parenteral administration of CDs can be somewhat more limited. The haemolytic effect of CDs on human erythrocytes in phosphate-buffered saline are in the order methylated βCDs > βCD > HPβCD > αCD > γCD > HPγCD > SBEβCD.[8,9,16] There appears to be a correlation between the haemolytic activity and the ability of the CDs to bind or extract cholesterol from the membranes.[8] This in-vitro cellular lysis study, as well as other comparable in-vitro studies using intestinal cells, *Escherichia coli*, human skin fibroblasts and liposomes, do not indicate in-vivo toxicity but rather provide a method to classify CDs according to their potential to destabilize or disrupt cellular membranes.[9] Furthermore, βCD cannot be given parenterally due to its low aqueous solubility and related adverse effects (e.g. nephrotoxicity). These studies and other in-vivo studies in laboratory animals have shown that the methylated βCDs and βCD cannot be used in parenteral formulations while HPβCD, αCD, γCD, HPγCD and SBEβCD can all be found in marketed parenteral formulations (Table 1) with intravenous dosing of up to 16 g HPβCD daily (Sporanox; Janssen Pharmaceutica, Belgium) and 14 g SBEβCD daily (Vfend; Pfizer, USA). The parent γCD could be found in one parenteral diagnostic product (CardioTec Kit for the preparation of technetium Tc-99m teboroxime; Squibb Diagnostics, USA) but it has been replaced by HPγCD in the current product (CardioTec; Bracco, USA).[38] Aqueous γCD solutions tend to turn opalescent due to γCD aggregation while HPγCD solutions remain clear. The parenteral dose of γCD and HPγCD in CardioTec appears to be about 50 mg. Due to their favourable toxicological profile, CDs are frequently preferred to organic solvents during in-vitro/in-vivo evaluation of new chemical entities.

HPβCD has a small volume of distribution ($V_D \approx 0.2$ l/kg) and a short half-life ($t_{1/2} \approx 1.7$ h), and is mainly excreted unchanged in the urine after parenteral administration to humans (Table 4; Figure 1).[21,33] In humans there is a linear relationship between the parenterally administered HPβCD dose and the area under the plasma concentration–time curve (AUC). No side effects were observed after parenteral administration of up to 24 g of HPβCD daily (12 g twice daily) for 15 days. The pharmacokinetics of SBEβCD is very similar to that of HPβCD (Stella & He 2008).[21] The total plasma clearance of both HPβCD and SBEβCD is similar to the glomerular filtration rate and since CDs are predominately eliminated unchanged in urine (see Table 4), their elimination half-life ($t_{1/2}$) will increase with impaired or reduced kidney function. However, in individuals with normal kidney function, about 90% of parenterally administered CD will be excreted within 6 h of the administration and about 99% within 12 h. Thus, administration of CD

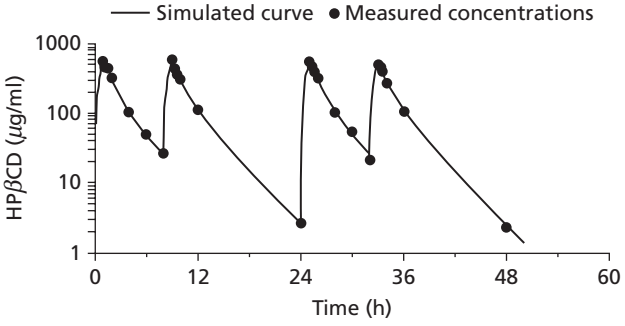


Figure 1 Plasma concentration–time profile after repeated intravenous administration of 8 g of HPβCD twice a day in humans.

containing drug formulations will result in negligible accumulation of CD in individuals with normal kidney function.

Regulatory status

The regulatory status of CDs is evolving as more and more products are approved. Both αCD and βCD are listed in a number of pharmacopoeial sources, including the European Pharmacopoeia (Ph.Eur.), US Pharmacopeia/National Formulary (USP/NF) and Japanese Pharmaceutical Codex (JPC). γCD is referenced in the JPC and will soon be included in the Ph.Eur. and USP/NF. A monograph for HPβCD is available in the Ph.Eur. and a draft has been circulated for the USP/NF. Other derivatives are not yet compendial but efforts are underway for their inclusion. HPβCD and SBEβCD are both cited in the FDA's list of inactive pharmaceutical ingredients. In the food industry, the regulatory status of an additive is based on toxicity studies in animals, which include determination of the no-observable-effect level (NOEL; the highest administered dose that does not cause any detectable adverse effect). The acceptable daily intake (ADI) for humans is calculated from the overall NOEL obtained from the most sensitive species divided by a safety factor. The Joint (FAO/ WHO) Expert Committee on Food Additives (JECFA) has recommended ADI of 5 mg/kg per day for βCD in food products but due to their favourable toxicological profile, no ADI was defined for both αCD and γCD. This 'not specified' ADI of αCD and γCD is considered the most desirable value and is limited to low-toxicity compounds. In the US, αCD, βCD and γCD have been included in the 'generally recognized as safe' (GRAS) list of the FDA as flavour stabilizers. A consensus seems to be building among regulators that CDs are excipients and not integral to the drug substance although various opinions have been given and interpretation related to this point can be division- and product-specific.

Cyclodextrin complexes

The central cavity of the CD molecule provides a somewhat lipophilic nanoenvironment into which suitably sized drug moieties (or even small drug molecules) may enter and be included. No covalent bonds are formed or broken during formation of the drug–CD complexes and in aqueous solutions drug molecules located within the CD cavity are in dynamic equilibrium with free drug molecules. The rates for formation and dissociation of drug–CD complexes are very close to the diffusion-controlled limits and drug–CD complexes are continuously being formed and dissociated.[39] The affinity of a drug for a given CD is determined by the stability constant (equilibrium constant) of the drug–CD complex (K). Most methods for determination of the K-values are based on titrating changes in the physicochemical properties of the guest molecule (i.e. the drug molecule) within the CD and then analysing the concentration dependencies. Properties that can be titrated in this way include aqueous solubility, chemical reactivity (stability), molar absorptivity, NMR chemical shifts, pKa values and HPLC retention times.[6,20,40] It is also possible to titrate changes in the physicochemical properties of the host molecule (i.e. CD molecule) but the guest properties are usually more accessible.

Phase-solubility diagrams

The two most important characteristics of the complexes are their stoichiometry and the numerical values of their stability constants. If m drug molecules (D) associate with n CD molecules (CD) to form a complex (D_m/CD_n), the following overall equilibrium is attained:

$$m \cdot D + n \cdot CD \underset{}{\overset{k_{m:n}}{\rightleftharpoons}} D_m/CD_n \quad (1)$$

where $K_{m:n}$ is the stability constant of the drug–CD complex. The stoichiometry of drug–CD complexes and the numerical values of their stability constants are frequently obtained from phase-solubility diagrams where the drug solubility is monitored as a function of total CD added to the complexation medium as shown in Figure 2.[20,41,42] Linear phase-solubility diagrams (A_L-type) indicate that the complex is first order with respect to the CD ($n = 1$ in Equation 1) and first or higher order with respect to the drug ($m \geq 1$). In this case the apparent drug solubility (S_{tot}) will be given by:

$$S_{tot} = S_0 + m[D_m/CD] \quad (2)$$

where S_0 is the intrinsic solubility of the drug in the aqueous complexation medium. If one drug molecule forms a water-soluble complex with one CD molecule (i.e. 1 : 1 complex) then the slope of the linear phase-solubility diagram will be determined by the equation:

$$\text{Slope} = \frac{S_0 K_{1:1}}{(S_0 K_{1:1} + 1)} \quad (3)$$

where $K_{1:1}$ is the stability constant for the complex. In this case, the slope is always less than unity and the following equation can be applied to calculate $K_{1:1}$:

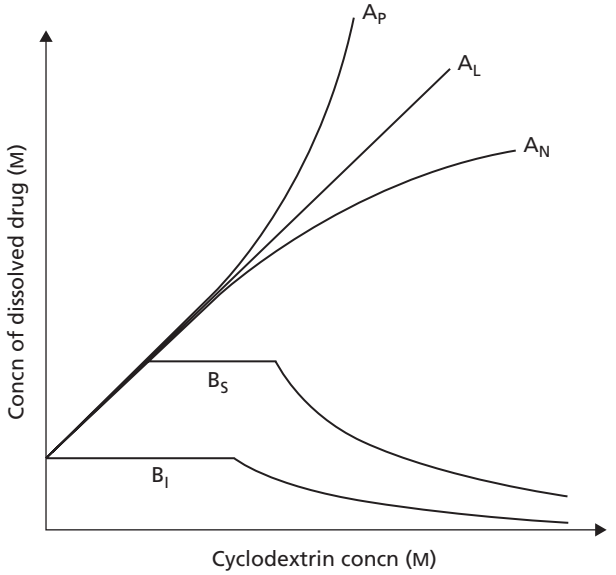


Figure 2 Phase-solubility diagrams. Plots of total drug solubility (S_{tot}) vs total amount of dissolved cyclodextrin, and their classification according to Higuchi & Connors.[41]

$$K_{1:1} = \frac{\text{Slope}}{S_0(1-\text{Slope})} \quad (4)$$

If a 2 : 1 drug–cyclodextrin complex is formed then the slope of the linear phase-solubility diagram will be determined by the equation:

$$\text{Slope} = \frac{2S_0{}^2K_{2:1}}{(S_0{}^2K_{2:1}+1)} \quad (5)$$

where $K_{2:1}$ is the stability constant of the complex. In this case, the slope of the linear phase-solubility diagram is always less than two.

Positive deviation from linearity (A_P-type phase-solubility diagrams) suggests formation of a higher-order complex with respect to CD. The stoichiometry of the system can be probed by curve fitting with a quadratic model. A good fit to this model could suggest formation of a 1 : 2 drug–CD complex:

$$S_{tot} = S_0 + K_{1:1}S_0[CD] + K_{1:1}K_{1:2}S_0[CD]^2 \quad (6)$$

where [CD] represents the concentration of free CD. A third-order model is suggestive of a 1 : 3 complex, etc.[20] Here, consecutive complexation is assumed where, for example, a 1 : 2 complex is formed when one additional CD molecule forms a complex with an existing 1 : 1 complex. Again, it is important to remember that this technique does not indicate whether a given drug forms an inclusion complex with CD, but only how the CD influences the drug solubility. Phase-solubility studies are performed in aqueous solutions saturated with the drug where formation of higher-order complex aggregates is more likely than in diluted (i.e. more ideal) solutions. The natural CDs and their derivatives, as well as their complexes, are known to form aggregates.[43–45] Formation of non-inclusion complexes and CD aggregates contribute to the overall drug solubilization in aqueous CD solutions.[46–53] A_N-type profiles have been explained by changes in the complexation media and self-association of CD molecules or their complexes at higher CD concentrations.

B-type phase-solubility diagrams (Figure 2) indicate formation of complexes with limited aqueous solubility and they are commonly observed in complexationmedia containing the natural αCD, βCD and γCD. B_S-type phase-solubility diagrams are thought to be formed when the drug–CD complex has limited solubility in the complexation medium and then the plateau indicates the total drug solubility (i.e. the intrinsic drug solubility plus the drug solubility in the form of CD-complexes). The ascending part of the profile can mathematically be treated as A-type and the previously described techniques used to gain information on the complex stoichiometry. The loss of total drug solubility at higher CD concentrations has been explained by completion of available drug in the complexation media. However, this decline in concentration is frequently observed when excess drug is available and, thus, these stoichiometric explanations can be inadequate. B_I-type profiles are similar to those of the B_S-type except that the drug–CD complexes formed are insoluble in the complexation media.

Again, it should be emphasized that phase-solubility studies are performed in drug-saturated media, most commonly drug-saturated aqueous CD solutions, and that such solutions are non-ideal. Frequently, drug–CD complexes are characterized by NMR or other spectrophotometric studies of dilute aqueous CD solutions or under 'ideal' conditions. Results obtained under such conditions cannot readily be used to explain complexation phenomena under non-ideal conditions. Furthermore, most aqueous drug formulations contain excipients such as polymers, buffer salts and preservatives, all of which can influence the drug complexation. Thus, during drug formulation the aqueous complexation media should closely resemble the composition of the final formulation. Finally, stability constants such as $K_{1:1}$ and $K_{1:2}$ are frequently used to compare the solubilizing effects of different CDs on a specific drug. However, values of these stability constants are very sensitive to external conditions (such as presence of minor impurities), the method applied and mathematical interpretation of experimental results.

According to the previously described phase-solubility technique the intrinsic solubility (S_0) should be identical to the intercept (S_{int}). However, this is rarely the case for poorly soluble drugs. Thus, complexation efficacy (CE) is frequently a better measure for comparison of solubilization effects of different CDs.[54] If the slope of a linear phasesolubility diagram is less than unity the CE can be calculated from the following equation (Table 5):

$$CE = S_0K_{1:1} = \frac{[D/CD]}{[D]} = \frac{\text{Slope}}{(1-\text{Slope})} \quad (7)$$

Where [D/CD] is the concentration of dissolved complex, [CD] is the concentration of dissolved free cyclodextrin and Slope is the slope of the phase-solubility profile. The complexation efficiency can be used to calculate the D : CD ratio, which can be correlated to the expected increase in formulation bulk:

$$D{:}D = 1{:}\left(1+\frac{1}{CE}\right) \quad (8)$$

Equation 9 shows the correlation between the increase in formulation bulk and molecular weights of the cyclodextrin (MW_{CD}) and the drug (MW_{Drug}), and the value of CE:

$$\text{Relative increase in formulation bulk} = \frac{MW_{CD}}{MW_{Drug}}\left(1+\frac{1}{CE}\right) \quad (9)$$

The new formulation bulk can be found by multiplying the number obtained from Equation 9 with the drug dose (Table 5). The molecular weight of the natural βCD is 1135 Da and those of the three most common βCD derivatives are 1310 Da for RMβCD, 1400 Da for HPβCD and 2163 Da for SBEβCD (Tables 2 and 3). The formulation bulk will increase with increasing molecular weight of the CD used (MW_{CD}) and decrease with increasing CE. Thus, all things being equal, the CD derivatives will result in greater increase in the formulation bulk than their parent CDs. Therefore, while the aqueous solubility of drug complexes of the parent αCD, βCD and γCD may be much lower than those of their derivatives, their solubilities are frequently sufficient to prevent dissolution-rate-limited drug absorption from the gastrointestinal tract.

Table 5 Intrinsic solubility (S_0), stability constant ($K_{1:1}$), complexation efficiency (CE), the drug : CD molar ratio in a drug saturated aqueous CD solution, the oral dose and the formulation bulk (i.e. the minimum weight of a drug–CD complex containing a given oral drug dose)

Druga	Cyclodextrin[a]	S_0 (mg/ml)[b]	$K_{1:1}$ ($M^{(1)}$)[c]	CE[d]	Molar ratio[e]	Dose (mg)[f]	Formulation bulk[g] (mg)
Estradiol	HPβCD	0.078	1120	0.322	1 : 4	0.5	10
(MW 272 Da)	RMβCD	0.078	3300	0.946	1 : 2	0.5	5
Hydrocortisone	HPβCD	0.42	1010	1.16	1 : 2	5	40
(MW 363 Da)	RMβCD	0.42	1650	1.90	2 : 3	5	30
Propofol	RMβCD	0.16	2450	2.21	2 : 3	10	110
(MW 178 Da)	SBEβCD	0.16	4560	4.11	4 : 5	10	150
	HPβCD	0.16	1600	1.44	1 : 2	10	130

Partly based on data from Loftsson *et al*.[54,122] [a]2-Hydroxypropyl-β-cyclodextrin (HPβCD); randomly methylated β-cyclodextrin (RMβCD); sulfobutylether β-cyclodextrin sodium salt (SBEβCD). See Table 3. [b]Drug solubility in the complexation medium when no cyclodextrin is present. [c]Calculated from the experimental determined solubility and Equation 4. [d]The complexation efficiency calculated from the slope of a phase solubility diagram according to Equation 7. [e]The drug : CD molar ratio based on the calculated CE according to Equation 8. [f]Single oral dosage, estimated values or literature values. [g]The formulation bulk of a solid dose containing the drug–cyclodextrin complex equivalent to the oral drug dose (see Equation 9).

Cyclodextrins and drug degradation

CD complexation can retard and sometimes accelerate chemical decomposition of drugs. Due to saturation kinetics, the observed first-order rate constants for a reaction (k_{obs}) asymptotically approaches a minimum value for stabilizing effect (inhibition) or a maximum value for destabilizing effect (catalysis) with increasing CD concentration. The value of k_{obs} at a given CD concentration is the weighted average of the first-order rate constants for degradation of the free (k_f) and the bound (k_c) drug (Table 6):

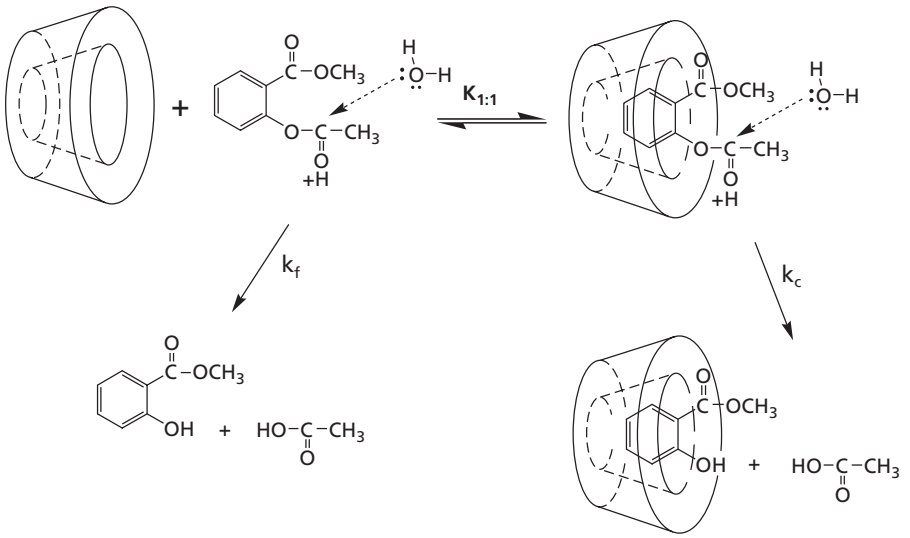
$$k_{obs} = k_f f_f + k_c f_c \quad (10)$$

where f_f is the fraction of free drug and f_c is the fraction of drug in complex. The concentration dependency of k_{obs} can be used to determine $K_{1:1}$[20,55] If we assume that only 1 : 1 drug–CD complex is being formed the following equations are obtained:

$$-\frac{d[D]}{dt} = k_{obs}[D]_T = \left(\frac{k_f + k_c K_{1:1}[CD]}{1 + K_{1:1}[CD]}\right)[D]_T \quad (11)$$

If the total CD concentration is much greater than the total drug concentration ($[CD]_T \geq 10 \cdot [D]_T$) then it can be assumed that $[CD] \approx [CD]_T$:

Table 6 The stabilizing effect of cyclodextrins on the hydrolytic degradation of methyl salicylate in dilute aqueous hydrochloric acid solutions (pH 1.0; 65°C)



k_f (min^{-1})	Cyclodextrin	k_c (min^{-1})	k_f/k_c	$K_{1:1}$ (M^{-1})
4.6×10^{-3}	HPβCD	1.1×10^{-3}	4.2	63
4.6×10^{-3}	HPγCD	1.5×10^{-3}	3.1	33

Data from Loftsson *et al*.[124]

$$k_{obs} = \frac{k_f + k_c K_{1:1}[CD]_T}{1 + K_{1:1}[CD]_T} \quad (12)$$

Equation 12 can then be rearranged into several different formats, including those suggested by Lineweaver–Burk (i.e. a plot of $(k_f - k_{obs})^{-1}$ versus $([CD]_T)^{-1}$ that gives a straight line). In such relationships, k_c can be obtained from the intercept of the graph and $K_{1:1}$ from the slope:

$$\frac{1}{k_f - k_{obs}} = \frac{1}{K_{1:1}(k_r - k_c)}\frac{1}{[CD]_T} + \frac{1}{(k_r - k_c)} \quad (13)$$

Alternatively, k_c and $K_{1:1}$ can be obtained by non-linear fitting of k_{obs} according to Equation 12. The Lineweaver–Burk plot was used to obtain the values of k_f, k_c and $K_{1:1}$ in Table 6. The stabilizing abilitiy of different CDs does not only depend on the degree of complexation, that is the fraction of the drug which resides within the complex (which again depends on the value of $K_{1:1}$), but also on the rate of degradation within the complex (i.e. the value of k_c). Therefore, the larger the value of $K_{1:1}$ and the smaller the value of k_c compared with k_f, the better is the degree of stabilization. Methyl salicylate is hydrolysed about 4.2 and 3.1 times slower within the HPβCD and HPγCD complex, respectively, than the unbound drug in the solution. Methyl salicylate forms a less stable complex with HPγCD ($K_{1:1}$ = 33 M^{-1}) than with HPβCD ($K_{1:1}$ = 63 M^{-1}). The difference in the k_c value could be due to the fit and position of the molecule within the CD cavity.

Other methods are also applied for determination of the stability constant of drug–CD complexes, such as UV/Vis spectrophotometry and fluorometry, which monitor changes in the drug spectra as a function of the guest–host (i.e. drug–CD) interaction, and NMR, which can be used to determine the value of the stability constants (such as $K_{1:1}$) and gives at the same time the solution geometry of the complexes.[20,40] CDs and their complexes tend to self-associate in aqueous solutions to formaggregates and the aggregate formation is concentration dependent, increasing with increasing CD concentration. Consequently, the numerical values of the complex stability constants (e.g. $K_{1:1}$ and $K_{1:2}$) are method sensitive. For example, values obtained by spectrophotometric methods (i.e., Benesi–Hildebrand analysis) can differ from those obtained by the phase-solubility method.

The effect of temperature

The thermodynamic parameters for CD complexation (i.e. the standard free energy change ($\Delta G°$), the standard enthalpy change ($\Delta H°$) and the standard entropy change($\Delta S°$)) can be obtained from the temperature dependence of the stability constant (K) of the CD complex:[56]

$$\Delta G° = -RT \ln K \quad (14)$$

Where R is the gas constant and T is the temperature in Kelvin. $\Delta H°$ is obtained by the temperature dependency of K:

$$\ln K = -\frac{\Delta H°}{R}\frac{1}{T} + \text{constant} \quad (15)$$

Then $\Delta S°$ is obtained from equation 16:

$$\Delta G° = \Delta H - T\Delta S° \quad (16)$$

The complex formation is almost always associated with a relatively large negative $\Delta H°$ while the $\Delta S°$ can be either positive or negative.[6,57–63] Also, the complex formation is largely independent of the chemical properties of the guest (i.e. drug) molecules The association of binding constants with substrate polarizability suggest that van der Waal's forces are important in the complex formation.[64] Based on the relatively hydrophobic environment of the CD cavity, it may be expected that the water molecules situated therein do not have a full complement of hydrogen bonds and are at higher energy than those in the bulk media. Liberation of these '$\Delta H°$-rich' molecules may represent a driving force in this perspective.[64] On the other hand, some have argued that while cavity-bound water may be of higher energy, it may also be more entropically flexible due to the absence of hydrogen bonding.[13] Thus, while release of cavity-bound water may be associated with a negative $\Delta H°$, its overall free energy contribution may be small. It has been observed that for a series of guests and CDs there tends to be a linear relationship between $\Delta H°$ and $\Delta S°$, with increasing $\Delta H°$ related with less negative $\Delta S°$ values.[65] Linear plots of $T\Delta S°$ versus $\Delta H°$ reveal an enthalpy–entropy compensation and suggest that CDs undergo substantial solvent restructuring with both guest and host being desolvated during the complex formation.[63]

While the aqueous solubility of relatively lipophilic drugs most often decreases with decreasing temperature (i.e. they have positive heat of solution (ΔH_{soln})), the value of complex stability constants (e.g. $K_{1:1}$) increases (i.e. they have negative $\Delta H°$ value). In other words, S_0 decreases and $K_{1:1}$ increases with decreasing temperature (Equation 7). Thus, in most cases no drug precipitation is observed when the temperature of drug-saturated aqueous CD solutions is lowered from room temperature (20–25°C) to refrigerator storage conditions (~5°C).

Enhancement of cyclodextrin complexation

For various reasons, including formulation bulk, production capacities and cost, the amount of CD that can be included in most drug formulations is limited. According to Equation 9, the increase in the formulation weight is proportional to the molecular weight of the CD and inversely proportional to the value of the CE. The mean CE (CE ± standard deviation) of 24 different drugs (MW 359 ± 197 Da) with HPβCD (MW 1400 Da) was determined to be 0.44 ± 0.55 in pure water or aqueous buffer solutions.[54] This indicates that only one out of every three or four CD molecules is forming a pharmaceutically relevant complex with the drug. Only 5 out of 24 drugs had CE greater than unity and 10 had CE of 0.1 or lower. HPβCD complexation of a drug with molecular weight 359 Da and CE 0.44 will result in 13-fold increase in the formulation bulk and if the CE is 0.1 then over 40-fold increase in the formulation bulk will be observed. Several methods can be applied to increase the CE and several are listed in Table 7.[66] It should also be emphasized that numerous pharmaceutical excipients have been found to reduce the CE and, thus, it is important to determine the CE in an aqueous environment that resembles the final formulation as closely as possible.

Table 7 Methods that have been used to enhance the complexation efficiency (CE) of cyclodextrins in aqueous solutions by increasing either the apparent intrinsic solubility (S_0) of the drug or increasing the apparent stability constant ($K_{1:1}$) of the complex (see Equation 7)

Effect	Consequences
Dug ionization	Un-ionized drugs do usually form more stable complexes than their ionic counterparts. However, ionization of a drug increases its apparent intrinsic solubility that can result in enhanced complexation. $S_0\uparrow$[67–70]
Salt formation	It is sometimes possible to enhance the apparent intrinsic solubility of a drug through salt formation (i.e. forming a more water-soluble salt of the drug without significantly reducing its ability to form CD complexes). $S_0\uparrow$[71–74]
Acid–base ternary complexes	It has been shown that certain organic hydroxy acids (such as citric acid) and certain organic bases are able to enhance the complexation efficiency by formation of ternary drug–CD–acid or base complexes. $S_0\uparrow$ and/or $K_{1:1}\uparrow$[75–79]
Polymer complexes	Water-soluble polymers form a ternary complex with drug–CD complexes increasing the observed stability constant of the drug–CD complex. $K_{1:1}\uparrow$[80]
Metal complexes	Many drugs are able to form somewhat water-soluble metal complexes without decreasing the drug's ability to form complexes with CDs. Thus, the complexation efficiency can be enhanced by formation of drug–metal ion–CD complexes. $S_0\uparrow$[81]
Co-solvents	Addition of co-solvents to the complexation media can increase the apparent intrinsic solubility of the drug that can lead to enhanced CE. $S_0\uparrow$[82,83]
Ion pairing	Ion pairing of positively charged compounds with negatively charged CDs enhances the complexation efficiency. $K_{1:1}\uparrow$[84]
Combination of two or more methods	Frequently the complexation efficiency can be enhanced even further by combining two or more of the above mentioned methods. For example drug ionization and the polymer method, or solubilization of the CD aggregates by adding both polymers and cations or anions to the aqueous complexation medium. $S_0\uparrow$ and/or $K_{1:1}\uparrow$[73,81,80]

Drug delivery through biological membranes

Most biological membranes consist of aqueous exterior and a lipophilic membrane barrier and drugs are mainly transported through the membranes via passive diffusion (Figure 3). Drug permeation through such multi-layer barriers has been described as series of additive resistances analogous to electric circuits.[85–87] Assuming independent and additive resistances of the individual layers, the total resistance (R_T) of a simple bilayer membrane can be defined as (Figure 3):

$$J = P_T C_v = R_T{}^{-1} C_V = \left(R_{Aq} + R_M\right)^{-1} C_V = \left(1/P_{Aq} + 1/P_M\right)^{-1} C_V \quad (17)$$

where J is the flux of the drug through the membrane, P_T is the overall permeability coefficient, C_V is the drug concentration in the vehicle (i.e. donor phase), R_{Aq} and R_M, and P_{Aq} and P_M are the resistances and permeability coefficients in the aqueous exterior and within the membrane, respectively.[88] Equation 17 can be rewritten as:

$$J = \left[R_{Aq} R_M / \left(P_{Aq} P_M\right)\right] C_V \quad (18)$$

The aqueous exterior layer consists of a stagnant water layer that is frequently referred to as the unstirred water layer (UWL). For example, mucous membranes comprise an inner connective tissue layer and an outer epithelial layer that is most often covered by an external mucus layer. Mucus is present as either an aqueous gel layer attached to the mucosal surface or as an aqueous luminal component in soluble or suspended form.[89] The thickness of the mucous layer that represents the UWL depends on its location, varying from 50 to 450 μm in the stomach to less than 1 μm in the oral cavity.[90] Conventional penetration enhancers, such as fatty acids and surfactants, enhance drug delivery by decreasing the barrier properties of the lipophilic membrane (i.e. by increasing P_M). In contrast, hydrophilic CDs, such as the parent αCD, βCD and γCD, and CD derivatives, such as HPβCD and SBEβCD, increase drug delivery through

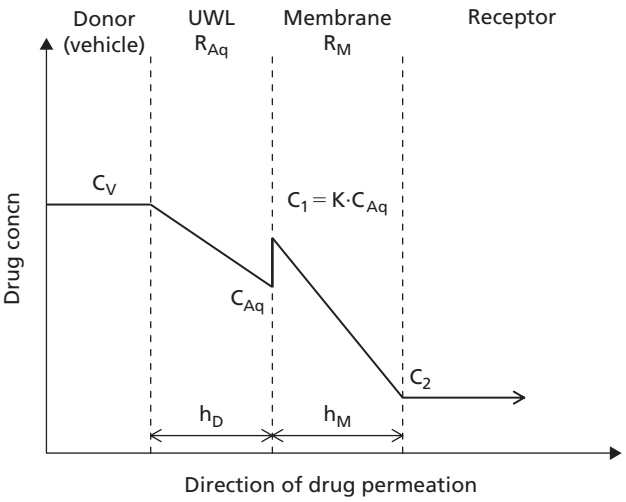


Figure 3 Schematic drawing of drug permeation from a donor through the unstirred water layer and then through membrane to a receptor. UWL, unstirred water layer; C_V, drug concentration in the donor (vehicle); C_{Aq}, drug concentration in the UWL immediate to the membrane surface; C_1, drug concentration within the membrane at the donor side; K, the drug partition coefficient between UWL and the membrane; h_D, thickness of the UWL on the donor side; h_M, thickness of the membrane. R_D, and R_M are the resistances in the UWL at the donor side and within the membrane, respectively. From Konrádsdóttir & Loftsson.[117]

biological membranes by enhancing drug permeation through the UWL (i.e. by increasing P_{Aq}). In general, hydrophilic CDs can only enhance drug delivery through biological membranes when P_{Aq} is relatively small compared with P_M. Hydrophilic CDs do not in general enhance drug delivery through membranes if the lipophilic membrane barrier is the main permeation barrier. When aqueous vehicles, such as hydrogels and oil-in-water creams, are applied to membranes, the UWL is extended into the vehicle and under such conditions CDs can increase drug delivery from the vehicle through the membrane.

Analysis of literature reports on the effects of CDs on oral bioavailability of drugs illustrate this basic relationship between P_{Aq}, P_M and the effects of CDs on drug absorption.[88] According to the Biopharmaceutics Classification System (BCS) oral drugs are classified according to their aqueous solubility characteristics and their ability to permeate the intestinal mucosa.[91] Class I comprises relatively water-soluble drugs that are well absorbed from the gastrointestinal tract and, in general, possess the preferred physicochemical properties for optimum oral bioavailability, which is over 90% according to the definition of BCS Class I. Class II consists of relatively water-insoluble drugs (i.e. generally aqueous solubility $\leq$0.1 mg/ml) that, when dissolved, are well absorbed from the gastrointestinal tract. Class III consists of water-soluble drugs that do not readily permeate mucous membranes and, thus, have low oral bioavailability. Finally, Class IV consists of water-insoluble drugs that do not easily permeate mucous membranes. Data suggest that CDs have little effect or even decrease oral bioavailability of BCS Class I drugs. They enhance the oral bioavailability of Class II drugs and Class IV drugs, frequently providing up to a 4- to 6-fold increase in the oral bioavailability. On the other hand, CDs do not enhance bioavailability of the water-soluble Class III drugs. The negligible effect of CDs on the bioavailability of BCS Class III drugs and the large effects they have on Class II and Class IV drugs support the notion that hydrophilic CDs do not enhance drug bioavailability by reducing the barrier properties of the lipophilic epithelium. Rather, the principal mechanism appears to be an increase in drug solubility and enhanced drug permeation through the aqueous mucus upon formation of water-soluble drug–CD complexes. CD enhancement of oral bioavailability allows for a lower drug dose to be administered and results in more consistent drug plasma profiles.

Release of drugs from the complex

The major driving force for drug release from the CD complexes is simple dilution although other mechanisms, such as drug–protein binding, direct drug partition from the complex to tissue and competitive binding, do contribute to rapid drug release from the complexes.[16,20,21,92] Thus, with only few exceptions, administration of drugs in the form of drug–CD complexes does not hamper their therapeutic effect. In the majority of cases CDs increase the oral absorption of drugs, but there are a couple of reports of reduced bioavailability. For example, oral absorption of [^{3}H]benzo[a]pyrene was reduced upon simultaneous administration of the compound and relatively large doses of βCD[93] and large oral dosages of αCD are used to reduce oral absorption of dietary fat (FBC$_X$ tablets; ArtJen, Canada). Several studies in both animals and humans have indicated that drug–HPβCD and drug–SBEβCD complexation has negligible effects on the drug pharmacokinetics after parenteral administration.[94–101] It has been shown that the binding constant of drug–CD complexes must be greater than about 10^5 M^{-1} to have any effect on the drug pharmacokinetics after parenteral administration.[21] Most commonly, drug–cyclodextrin binding constants have values between 10 and 2000 M^{-1} and binding constants much greater than 5000 M^{-1} are very rarely observed. Two exceptions are, however, known. Sugammadex (Bridion; N.V. Organon, Netherlands) is a γCD derivative that was designed to specifically bind rocuronium, a neuromuscular blocking agent. The binding constant of the rocuronium–sugammadex complex has been determined to be 1.8×10^7 M^{-1} and sugammadex is therefore able to reverse rocuronium-induced neuromuscular blockade after intravenous administration.[102,103] Another example is complexation of SBEβCD with certain ozonide antimalarial drug candidates possessing binding constants of about 10^6 M^{-1}.[104] The pharmacokinetics of these ozonide drug candidates in rats have been shown to be affected by the SBEβCD complexation.[105]

Product development

A search of the literature (SciFinder Scholar, American Chemical Society, USA) shows that CDs are widely used during pharmaceutical product development. In 2008 alone, there were about 600 published patents and patent applications on drugs and drug formulations in which CDs were mentioned and over 500 scientific articles included CD in their studies. Although the main theme of many of these publications is not CD per se, the sheer number of patents and published research articles shows the extent of this field within the pharmaceutical sciences. The applications of CDs in various drug formulations have been previously reviewed.[15,17,106–110] We provide a few examples in the context of this review to give a flavour of their drug enablement.

Piroxicam

Piroxicam is a non-steroidal anti-inflammatory drug that is practically insoluble in water, based on the USP definitions (Figure 4). It is a borderline BCS Class I drug, relatively potent, with a biological half-life ($t_{1/2}$) of 30–60 h but it can cause some upper gastrointestinal side effects such as bleeding. The oral dose is 20 mg piroxicam once a day. A piroxicam–βCD complex can be prepared by dissolving piroxicam and βCD (molar ratio 1 : 2.5) in aqueous ammonium hydroxide solution, followed by lyophilization or spray drying to form white

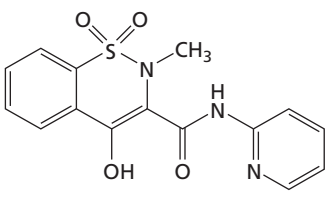


Figure 4 Piroxicam. Piroxicam is a weak acid: pKa 6.3, MW 331.3 Da, m.p. 198–300°C, log$K_{octanol/water}$ 3.1. Data from Moffat *et al.*[118]

complex powder.[111] The aqueous solubility of un-ionized piroxicamis about 0.02 mg/ml. Ionization of the drug increases the apparent S_0, which leads to an enhanced CE (Equation 7, Table 7). Since ammonia has a low vapour pressure, it is almost completely removed during lyophilization or spray drying.[74] The product is a true piroxicam–βCD inclusion complex.[112] The stability constant ($K_{1:1}$) of the piroxicam–βCD complex is 90 M^{-1} and 191.3 mg of the complex powder is equivalent to 20.0 mg of pure piroxicam. Formation of the complex increases the aqueous solubility of the drug from about 0.02 mg/ml to about 0.15 mg/ml (pH 5 and 37°C) as well as its wettability and thus the drug dissolution rate is enhanced.[113] The advantages of tablets containing the piroxicam–βCD complex (Brexin tablets) over tablets containing un-manipulated piroxicam, were more rapid absorption, more rapid onset of analgesia and apparently reduced gastrointestinal irritation, but the complexation did not affect the absolute bioavailability of this BCS Class I drug.[113,114]

Table 8 The effect of salt formation on ziprasidone solubility in pure water and in aqueous solutions containing either 40% (w/v) HPβCD (MW1309) or 40% (w/v) SBEβCD (MW 2163)

Salt	Solubility corresponding to weight of ziprasidone free base (mg/ml)		
	Pure water	40% (w/v) HPβCD	40% (w/v) SBEβCD
Free base	0.0003	0.26	0.35
Hydrochloride	0.08	2.4	4.0
Aspartate	0.17	1.3	9.3
Tartrate	0.18	12.4	26
Esylate	0.36	13.7	15
Mesylate	1.0	17.3	44

The solubility values represent mg free base dissolved in 1 ml. The pH of the salt solutions was 2.3→2.8 pH units below the apparent pKa of the drug molecule. Modified from Kim *et al*.[115,116]

Ziprasidone

Ziprasidone is an antipsychotic drug that is marketed as an oral capsule containing 20–80 mg as ziprasidone hydrochloride (Figure 5). However, the aqueous solubility of the free base is only 0.003 mg/ml and that of the hydrochloride salt 0.08 mg/ ml. Consequently, the drug cannot easily be formulated as a solution for injection. In addition, it is not possible to obtain sufficient aqueous solubility through simple CD complexation of the free base. Formation of ziprasidone salt increased the apparent intrinsic solubility (S_0) of the drug (Table 8) that led to an increase in CE (Equation 7) from about 0.002 for the free base to 0.15 for the mesylate salt in the case of HPβCD and from about 0.05 for the free base to 1.4 for the mesylate salt in the case of SBEβCD. The higher affinity for the SBEβCD cavity can, at least partly, be explained by ion pair formation between the protonated ziprasidone molecule and the negatively charged SBEβCD molecule.[116] Thus, even though SBEβCD has a much higher molecular weight than HPβCD, SBEβCD dissolves 2.5 times more of the drug (Table 8) and consequently ziprasidone mesylate and SBEβCD were used to formulate the drug as an aqueous solution for injection. Ziprasidone for injection (Geodon) is a lyophilized powder that when reconstituted contains ziprasidone mesylate corresponding to 20 mg of the free base and 294 mg of SBEβCD in 1 ml of water. To prevent drug precipitation, due to, for example, temperature changes and changes in pH, it is common to use excess CD in aqueous drug formulations and for that reason Geodon contains about 50% excess SBEβCD. According to the instructions for administration, the reconstituted solution can be stored, when protected from light, for up to 24 h at 15–30°C or up to 7 days refrigerated at 2–8°C.

Itraconazole

Itraconazole (Sporanox) is an antifungal drug and marketed as an HPβCD-based oral solution and a solution for injection. The aqueous solubility of itraconazole at room temperature is estimated to be about 1 ng/ml at pH 7 and about 4 μg/ml in aqueous 0.1 N hydrochloric acid solution (Figure 6). The desired parenteral dose is 200 mg twice a day. However, the solubility of crystalline itraconazole in aqueous 40% (w/v) solution is only about 3 mg/ml (Figure 7). The HPβCD solubilization of itraconazole is enhanced by converting the crystalline drug to its amorphous form. The crystalline form of the drug was dissolved in acidic polyethylene glycol and then this solution was added to an HPβCD-containing aqueous solution. Sporanox solution for injection is marketed as a kit containing a 25-ml ampoule of itraconazole concentrate (10 mg/ml) and a plastic bag containing 50 ml of saline. One millilitre of the concentrate contains 10 mg of itraconazole, 25 μl of polyethylene glycol, 3.8 μl of concentrated hydrochloric acid, 400 mg of HPβCD and sufficient sodium hydroxide to adjust the pH to 4.5. A similar formulation technique is used prepare Sporanox oral.

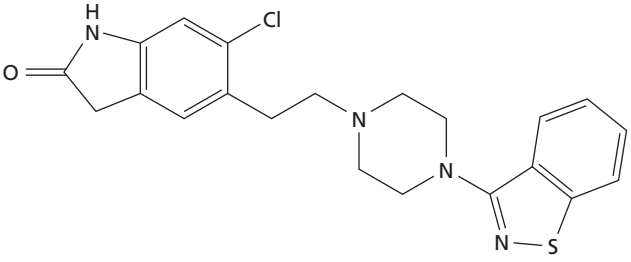


Figure 5 Ziprasidone. Ziprasidone is a weak base: pKa 6.5, MW 412.9 Da (free base) or 467.4 Da (hydrochloride), oral bioavailability 59%. Data from Moffat *et al*.[118]

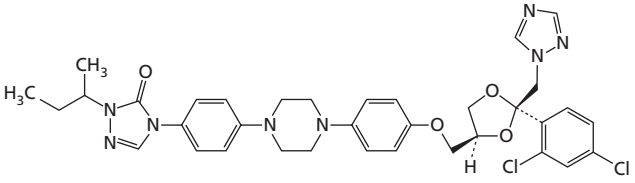


Figure 6 Itraconazole. Itraconazole is a weak base: pKa 3.7, MW 705.6 Da, m.p. 166.2°C, $\log K_{\text{octanol/buffer pH 8.1}}$ 5.66. Data from Moffat *et al*.[118]

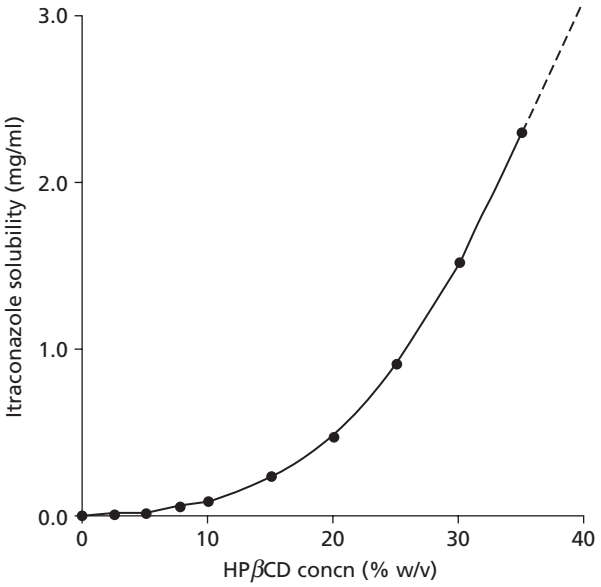


Figure 7 Phase-solubility profile of crystalline itraconazole in aqueous HPβCD solution at 25°C and pH 4. Based on Peeters *et al*.[123]

Conclusions

CDs have emerged as an important tool in the formulator's armamentarium to improve apparent solubility and dissolution rate for poorly water-soluble drug candidates, an important and growing component of contemporary drug pipelines. The cyclic starch derivatives interact through inclusion- and non-inclusion-based mechanism to improve oral bioavailability and enable parenteral dosage form configuration for molecules with less than optimal physicochemical properties. While the parent CDs are well represented inmarketed formulations, the greatest growth area at present is represented by the use of chemically modified CDs, including HPβCD and SBEβCD. These materials are associated with a very low toxicity potential, are not orally bioavailable (making them true oral carriers) and are affordable as enabling excipients. A monograph for HPβCD is available in the European Pharmacopoeia (EP) while both HPβCD and SBEβCD are listed in the FDA's compilation of inactive pharmaceutical ingredients. The continued interest in, and productivity of, these materials bode well for the future application and their currency as excipients in research, development and drug product marketing.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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