Cyclodextrins

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Abstract

Cyclodextrins (CDs) were first isolated in 1891 as degradation products of starch from a medium of *Bacillus amylobacter*. They are cyclic water-soluble, nonreducing, macrocycle carbohydrate polymers constructed from α-(1-4)-linked D-glucopyranose units (naturally occurring α, β, and γ formed by 6, 7, and 8 glucose units), in a ring formation and present a toroidal, hollow, truncated cone shape. Their most important property is the ability to establish specific interactions – molecular encapsulation – with various types of molecules through the formation of non-covalently bonded entities, either in the solid phase or in aqueous solution, taking up a whole molecule, or some part of it, into their cavities. This process in part mimics the "lock and key" mechanism of enzyme catalysis. Complexation may cause changes in physicochemical properties of the guest molecule (e.g., solubility, stability, kinetics and bioavailability, toxicity). Their negligible cytotoxic effects promoted them to the GRAS list and led them to be widely used in many industrial products and technologies.

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1 Introduction

1.1 Historical Background

Since the beginning of times, the most important discoveries happen as casual observation due to researchers' curiosity (Table 1). Cyclodextrin (CD) discovery also followed this pattern as they were first isolated in 1891 by Villiers when, in addition to reducing dextrins, beautiful crystals were observed in alcohol waste as degradation products of starch from a medium of *Bacillus amylobacter*. These substances were called "cellulosine" due to its similarity to cellulose (Villiers 1891). In the following years (early twentieth century), another prominent scientist, Schardinger, made important discoveries for CDs' science. In 1903, this author was responsible for the isolation of two crystalline products showing lack of reducing properties: dextrins A and B. In 1904, Schardinger isolated a new organism capable of producing acetone and ethyl alcohol from sugar- and starch-containing plant material (Eastburn and Tao 1994). In 1911, he described that the strain *Bacillus macerans* produces large amounts of crystalline dextrins (25–30 %) from starch. Thus, Schardinger is considered the founder of CD chemistry due to his work to characterize Villiers' "cellulosines" from 1903 to 1911, determining that they were cyclic oligosaccharides (Schardinger 1903a, b, 1904, 1911; Szejtli 1998). It is for this reason that CDs are also termed Schardinger dextrins, especially in the older literature. Since then several fractionation schemes for the production of CDs were also developed (Stella and Rajewski 1997; Matsuda and Arima 1999; Mabuchi and Ngoa 2001). The γ-dextrin was only isolated in 1935.

Pure CDs (i.e., cyclic water-soluble, nonreducing, macrocycle polymers) were prepared in the early part of the last century by Freudenberg and co-workers (Freudenberg and Meyer-Delius 1938; Freudenberg et al. 1947), who reported that CDs are constructed from α-(1-4)-linked D-glucopyranose units, in a ring formation (Saenger 1980; Uekama 1981; Szejtli 1982). In 1948, using X-ray crystallography the γ-CD structure was clarified. Immediately after, the most important property of CDs was recognized: their ability to form inclusion complexes. The general title for this class of complexes, "inclusion compounds" ("einschlussverbindung"), was first used by Schlenk in 1949. Besides the general terms ("occlusion" and "adducts"), other terms that have been used to describe these complexes are "molecular compounds," "cryptates" (Frank 1975; Szejtli 1982), and "clathrates" (Powell 1948). The term "clathrate," derived from the Latin "clathratus," meaning "enclosed or protected by cross bars of a grating," has been used to describe the cage-like structure of the hydroquinone inclusion compounds.

Table 1 Chronological order of cyclodextrin research (Cramer 1954; Bender and Komiyama 1978; Cramer 1987; Frömming and Szejtli 1994; Robyt 1998; Szejtli 1998, 2004; Loftsson and Duchêne 2007; Kurkov and Loftsson 2012)

Historical period	Investigator	Milestones
1808	E-L. Malus	Development of plane polarized light and observation of optical rotation by carbohydrates
1870	Bayer and Fittig	Formula: HO–CH_2–CH(OH)–CH(OH)–CH(OH)–CH(OH)–CHO for glucose
1888–1891	Fisher	Structure determination of several carbohydrates (glucose, fructose, manose, arabinose)
1891	A. Villiers	Discovery of α- and β-CD, pioneering study on composition and chemical properties
1903–1911	F. Schardinger	Isolation of bacteria responsible for CD synthesis; first attempts to distinguish between different CDs
1920–1930	N. Harworth	Proof of hexagonal form for carbohydrate rings
1924		CD first methylation
1930s		Maltose units bound via α-1,4-glycosidic linkages are found to be building blocks for CD molecule; first isolation of pure CDs
1935	K. Freudenberg and Jacobi	γ-CD is discovered
1936		CD cyclic structure is disclosed
1940s	F. Cramer	Idea of inclusion complex formation is suggested
1948	K. Freudenberg	γ-CD structure is clarified
	W. Borchert	Structures of α-, β-, and γ-CDs are determined by X-ray diffraction
1950s	D. French	Discovery of CDs with larger rings
	F. Cramer	Study of inclusion complexation properties of CDs
1953	K. Freudenberg	First patent on CDs
	F. Cramer	
	H. Plieninger	
1954	F. Cramer	Publication of the book "*Einschlussverbindungen*" ("inclusion compounds")
1957	D. French	First fundamental review on CDs containing first misinformation on toxicity of β-CD
1965	T. Higuchi	Development of a mathematical model describing inclusion complexation mechanism
	K. Connors	
1975	M. Furue	First publication on CD polymers
1976	Ono Pharmaceutical Co. Ltd.	Release of the first medicine, Prostarmon E, from CD
1980s		Beginning of industrial application of CDs in food and cosmetics
1981	J. Szejtli	The First International Cyclodextrin Symposium is organized; the first cyclodextrin book is published

(*continued*)

Table 1 (continued)

Historical period	Investigator	Milestones
1983–1985	U. Brauns	HP-β-CD is patented in Europe and the USA
	B. Muller	
	J. Pitha	
1983	K. Miyajima	First suggestion of self-association of parent CDs
1988	Chiesi Farmaceutic (Italy)	Commercialization of Piroxicam/β-CD tablets (Brexin®)
1991	V. Stella	SBE-β-CD is patented
	R. Rajewski	
1994	Oftalder (Portugal)	Commercialization of the first eye drops: chloranphenicol/RM-β-CD (Clorocil®)
1990s	A. Harada	Intensive research activity on CD catenanes and rotaxanes
	M. Kamachi	
2000s	M. Bonini	Intensive research activity on CD aggregation
	A. Coleman	
	G. Gonzalez-Gaitiano	
	T. Loftsson	
	L. Szente	
	A. Wu	

Although Chemical Abstracts and several other reference sources use the term "clathrates" as a general descriptor for inclusion compounds, this term more appropriately describes only cage-like polymolecular inclusion compounds (Cabral-Marques 1994a). In 1961 the existence of larger natural CDs, namely, δ- (delta), ε- (epsilon), ζ- (zeta), and η- (nu) CD, was proved (9–12 glucose residues) (Hirose and Yamamoto 2001). CD chemistry was discussed in detail by Bender and Komiyama (Bender and Komiyama 1978).

1.2 Occurrence/Sources

Although discovered more than 100 years ago as previously referred, the cyclic glucooligosaccharides termed CDs (based on dextrose, which is an old name for glucose) remained laboratory curiosities until the 1970s when they began to be used commercially (Szejtli 1998). Its production results from degrading the starch by the enzyme cyclodextrin glucanotransferase (CGTases), involving excision and reconnection of single turns from the helical α-(1→4)-glucan (amylose) chain (Fig. 1) to provide cyclic α-(1→4)-linked glucooligosaccharides with six (α-CD), seven (β-CD), and eight glucose units (γ-CD) (Rendleman 1999; Lichtenthaler 2010). This intramolecular transglycosylation is called cyclization reaction (Szejtli 1998; Cheirsilp et al. 2010).

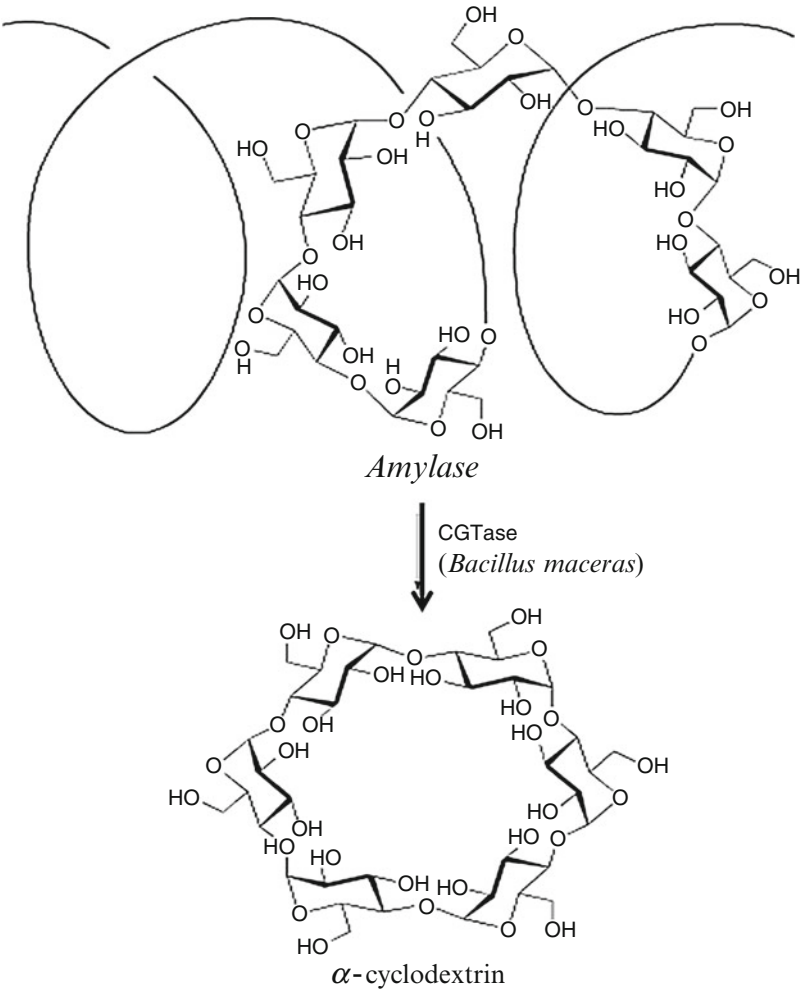

Fig. 1 Representation of a left-handed, single-stranded helix of VH-amylose (*top*) and of α-cyclodextrin (*bottom*), which de facto represents a single turn of the amylose helix excised and reconnected by *Bacillus macerans*-derived enzymes (CGTases). The close analogy allows VH-amylose to be considered as a tubular analogue of *α*-cyclodextrin (Lichtenthaler 2010)

The starch sources used to produce CDs are varied and include according to different authors the following substrates:

- Liquefied starch, maltodextrin, or long-chain maltooligosaccharides (Rendleman 1999)
- Maltodextrin and commercial soluble starch, corn, cassava, sweet potato, and waxy corn starches (Alves-Prado et al. 2008)
- Amaranth starch (Urban et al. 2012)

- Soluble and cocoyam starch (Mora et al. 2012)
- Starch such as potato, tapioca, and corn (Shahrazi et al. 2013)

CGTase is specifically active on both structures of amylose and amylopectin (Shahrazi et al. 2013). Several microorganisms and methods have been used to produce or use CGTase as described in the following:

- *Bacillus amylobacte*r in 1881 (Szejtli 1998).
- *Bacillus macerans* (Rendleman 1999).
- *Bacillus circulans* DF 9R (Rosso et al. 2002).
- *Bacillus clausii* strain E16 (Alves-Prado et al. 2008).
- *Bacillus megaterium* (Zhekova and Stanchev 2011; Sivakumar and Shakilabanu 2013).
- Alkaliphilic *Bacillus licheniformis* (Thombre and Kanekar 2013).
- CGTase was anchored on the surface of *Saccharomyces cerevisiae* and was used as an immobilized enzyme (Wang et al. 2006).
- *Escherichia coli* pAD26 cells immobilized on cotton (Kriaa et al. 2012).
- *Amphibacillus* sp. NPST-10 (Ibrahim et al. 2012).
- *Paenibacillus macerans* CCM 2012 (Urban et al. 2012).
- *Amphibacillus* sp. NRC-WN (Al-Sharawi et al. 2013).

2 Structure and Properties

2.1 Parent Cyclodextrins

The most common of these naturally occurring, ring-shaped molecules are the α- (alpha), β- (beta), and γ- (gamma) CDs formed by six, seven, and eight glucose units (Fig. 2) and cavities' diameters smaller than 0.6, 0.8, and 1.0 nm, respectively (Frank 1975; Szejtli 1982). Because of their sugar backbone, these CDs are also known as cycloamyloses: hexa- (C6A), hepta- (C7A), and octa-amylose (C8A) (Szejtli 1982) or cyclohexa-, cycloheptа-, and cyclooctaglucan and α-, β-, and γ-amylosan (French 1957).

CDs have no well-defined melting point and start to decompose at temperatures above 270 °C, and at 300 °C a sharp endothermic process is detected, which indicates that the melting is accompanied by decomposition (Szejtli 1982). Generally their solubility in water is greatly increased at higher temperatures (except for the dimethyl-β-CD which decreases). The most important characteristics of the natural CDs are summarized in Table 2 (Saenger 1980; Szejtli1998; Pitha et al. 1983; Duchêne et al. 1986; Bas and Rysanek 1987; Uekama and Otagiri 1987; Duchêne and Wouessidjewe 1990a; Salústio et al. 2011).

It is noteworthy that there are differences in the reported central cavity and outer periphery diameters of the CDs. Molecule CDs present a hydrophilic exterior, which can dissolve in water, and an apolar cavity, which provides a hydrophobic matrix, described as a "micro heterogeneous environment" (Szejtli 1989).

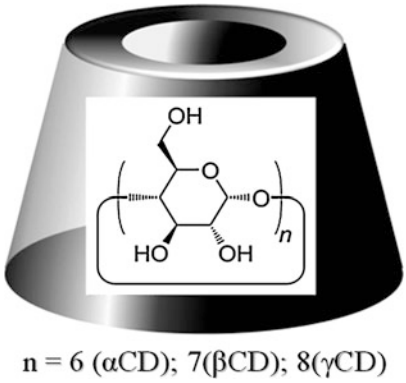

Fig. 2 Schematic cyclodextrins structure (Szejtli 1998; Salústio et al. 2011)

Table 2 Characteristics of α-, *β*-, and *γ*-CDs (Saenger 1980; Szejtli 1998; Pitha et al. 1983; Duchêne et al. 1986; Bas and Rysanek 1987; Uekama and Otagiri 1987; Duchêne and Wouessidjewe 1990; Salústio et al. 2011)

	α	*β*	*γ*
n° of glucose units	6	7	8
mol wt.	972	1,135	1,297
Solubility in water (g/100 ml), 25 °C	14.5	1.85	23.2
$[R]_D$25 °C	150.0 ± 0.5	162.5 ± 0.5	177.4 ± 0.5
Cavity diameter (Å)	4.7–5.3	6.0–6.5	7.5–8.3
Height of torus (Å)	7.9 ± 0.1	7.9 ± 0.1	7.9 ± 0.1
Diameter of outer periphery (Å)	14.6 ± 0.4	15.4 ± 0.4	17.5 ± 0.4
Approx. cavity volume ($Å^3$)	174	262	427
Approx. cavity volume in 1 mol CD (ml)	104	157	256
Approx. cavity volume in 1 g CD (ml)	0.10	0.14	0.20
Crystalline forms (from water)	Hexagonal plates	Monoclinic parallelograms	Quadratic prisms
Crystal water, wt %	10.2	13.2–14.5	8.13–17.7
Diffusion constant at 40 °C	3.443	3.224	3.000
Hydrolysis by *A. oryzae* α-amylase	Negligible	Slow	Rapid
V_{max} value, min^{-1}	5.8	166	2,300
Relative permittivity at pH 5.3, 25 °C (on incorporating the toluidinyl group of 6-*p*-toluidynilnaphthalene 2-sulphonate)	47.5	52.0	70.0
(On incorporating the naphthalene group)	[a]	29.5	39.5
p*K* (by potentiometry) at 25 °C	12.332	12.202	12.081
Partial molar volumes in solution (ml/mol)	611.4	703.8	801.2
Adiabatic compressibility in aqueous solutions ml (mol^{-1} bar^{-1}) × 10^4	7.2	0.4	−5.0

[a]Naphthalene group is too bulky for the α-CD cavity

Nuclear magnetic resonance (NMR) and X-ray diffraction indicate the C-1 chair conformation for the glucose molecule (Rao and Foster 1963). CDs are shown to have a toroidal, hollow, truncated cone structure, where the secondary OH groups on the C-2 and C-3 atoms are located on the wider side of the torus, while the primary OH groups on the C-6 are positioned on the opposite side of the torus (the narrower) and are directed "away" from the cavity except if H-bonded to include guest molecules (Saenger 1982; Szejtli 1988). The CH groups comprising H-1, H-2, and H-4 are located on the exterior of the molecule, while the polar sugar OH groups are oriented to the cone exterior, and as a consequence the external faces of CDs are hydrophilic leading to their aqueous solubility. The interior of the torus offers an environment of much lower polarity than is present in water, so it can be considered as a "hydrophobic cavity," which is lined by two rings of CH groups (H-3 and H-5), and by a ring of glucosidic oxygen-bridge atoms "ether oxygens" (O-4 and O-5) (Saenger 1982; Jones et al. 1984; Uekama and Otagiri 1987), H-6 forms the narrower rim of the truncated cone. The result of this amphipathic property is that CDs can form soluble, reversible inclusion complexes with water-insoluble compounds resulting in compound solubilization.

In all CD crystal structures, H-bonding between adjacent glucoses is found, with O-3....H-O-2 distances in the usually accepted range, 0.28–0.31 nm. H-bonding between these secondary OH groups appears to be preferred because their pKa, around 12.2 (Chin et al. 1968), is relatively low, suggesting enhanced polarization and therefore good H-bond donor and acceptor functions. This ring of H-bonds is, in general, fully established in β- and γ-CDs, but in α-CD, the curvature of the ring produces, on average, longer O-3....H-O-2′ separations, and H-bonding is weaker and can break down, as shown for the "empty" hexahydrate where four O-3....H-O-2′ hydrogen bonds are formed but two are broken. Spectroscopic data also indicate that β-CD is rigid in aqueous solution, whereas α-CD is flexible and undergoes conformational change if inclusion of a guest molecule occurs, as proposed in the "induced-fit" concept for proteins (Saenger 1982; Szejtli 1988). These interactions prevent hydration by water molecules (Szejtli 1985; Uekama and Otagiri 1987) resulting in poor aqueous solubility. In order to improve CDs' aqueous solubility, their structure has been modified via alkylation and hydroxyalkylation (Uekama and Otagiri 1987; Yoshida et al. 1988; Jicsinszky 2014).

The OH groups on C-2, C-3, and C-6 are available as points of structural modification without danger of eliminating the "central void" (MacNicol et al. 1978). The OH groups on C-6 are the most reactive, whereas the OH at C-3 are much less reactive than those at C-2.

2.2 Large Cyclodextrins

CDs with fewer than six glucopyranose residues do not exist, probably for steric reasons (Duchêne and Wouessidjewe 1990b). The existence of CDs comprising more than 8 glycosyl units was referenced in 1948 by Freudenberg and Cramer (Freudenberg and Cramer 1948). A decade later these findings were subsequently

substantiated by French and co-workers, who reported the isolation and partial characterization of large CDs with 9, 10, 11, and 12 glycosyl units in the macrocycle. However, some doubts remained concerning these CDs since they were not able to experimentally distinguish the large CDs from branched CDs (Pulley and French 1961; French et al. 1965; Szejtli 1988). During last decades, the existence of the large CDs has been fully proven. CDs containing up to 31 glycosyl units have been purified and characterized (Koizumi et al. 1999), and the existence of even larger CDs with degrees of polymerization up to several hundreds of glycosyl units has been reported (Kitamura 2000; Larsen 2002). Indeed, large CDs are not commercially exploited due to their extremely small isolation/purification yields and lack of their complexing properties (French 1957; Pulley and French 1961; French et al. 1965; Szejtli 1982).

Large CDs (Table 3) have often been designated "cycloamylose" (abbreviated CD*n*, where *n* designates the number of glucose molecules in the macrocycle) (Kitamura 2000; Larsen 2002).

2.3 Cyclodextrins Derivatives

In order to improve the physicochemical properties (i.e., better solubility, stability, and inclusion formation abilities/release behaviors of the substrate molecules) of the natural CDs, many derivatives were synthesized by various molecular manipulations (Frömming 1987; Frömming et al. 1987).

These derivatives (Table 4) usually are produced by alkylations, aminations, esterifications, or etherifications of their primary and secondary OH groups, leading also to the formation of polymeric and amphiphilic CDs (long alkyl or fluoroalkyl chains at primary and/or secondary sides of the CDs) (Bender and Komiyama 1978; Szejtli 1982; Szente et al. 1999; Sollogoub 2013). Croft and Bartsch (1983) published an interesting review of chemical methods for modifying CDs.

3 Complexation

3.1 Complexes Formation

CDs are able to form inclusion complexes with a wide variety of hydrophobic guest molecules. Thus, guest molecules can be totally or partially entrapped into CDs' cavities and in several molar ratios. The complexation process (Fig. 3) involves the insertion of the less polar part of the guest molecule into the host cavity, while the more polar and often charged group of the guest is exposed to the bulk solvent. During insertion phenomenon the water molecules are removed from the inside of CD cavity due to their thermodynamical instability. The inclusion complex formation is achieved by weak interactions such as van der Waals, hydrogen bonding, and hydrophobic effect, among others (Szejtli 1982; Cabral-Marques 1994a; Rekharsky and Inoue 1998; Sun et al. 2006). This process does not occur by means of ionic,

Table 3 Nomenclature and some properties of large cyclodextrins (Larsen 2002)

Glycosyl units	Semisystematic name	Generic name[a]	Abbreviation	Molecular weight	Aqueous[d,e] solubility (g/100 mL)	Surface[d,e] tension (mN/m^{-1})	Specific[e] rotation $[\alpha]_D^{25}$	Half-life[f] of ring opening (h)	Radius[g] of gyration (Å)
6	Cyclomaltohexaose	α-cyclodextrin	α-CD	972.9[b]	14.5	72	147.8	33	6.0
7	Cyclomaltoheptaose	β-cyclodextrin	β-CD	1135.0[b]	1.85	73	161.1	29	6.7
8	Cyclomaltooctaose	γ-cyclodextrin	γ-CD	1297.2[b]	23.2	73	175.9	15	7.3
9	Cyclomaltononaose	δ-cyclodextrin	CD_9	1459.3[b]	8.19	73	187.5	4.2	–
10	Cyclomaltodecaose	ϵ-cylodextrin	CD_{10}	1621.4[b]	2.82	72	204.9	3.2	–
11	Cyclomaltoundecaose	ζ-cyclodextrin	CD_{11}	1783.6[b]	>150	72	200.8	3.4	–
12	Cyclomaltododecaose	η-cyclodextrin	CD_{12}	1945.7[b]	>150	72	197.3	3.7	–
13	Cyclomaltotridecaose	θ-cyclodextrin	CD_{13}	2107.9[b]	>150	72	198.1	3.7	–
14	Cyclomaltotetradecaose	ι-cyclodextrin	CD_{14}	2270.0[b]	2.30	73	199.7 ± 1.0	3.6	–
15	Cyclomaltopentadecaose	κ-cyclodextrin	CD_{15}	2432.2[b]	>120	73	203.9 ± 0.4	2.9	–
16	Cyclomaltohexadecaose	λ-cyclodextrin	CD_{16}	2594.3[b]	>120	73	204.2 ± 0.7	2.5	–
17	Cyclomaltoheptadecaose	μ-cyclodextrin	CD_{17}	2756.4[b]	>120	72	201.0 ± 0.6	2.5	–
18	Cyclomaltooctadecaose	ν-cyclodextrin	CD_{18}	2918.6[b]	–	–	–	–	–

19	Cyclomaltononadecaose	ξ-cyclodextrin	CD_{19}	3080.7[b]	–	–	–	–	–
20	Cyclomaltoeicosaose	*o*-cyclodextrin	CD_{20}	3242.9[b]	–	–	–	–	–
21	Cyclomaltoheneicosaose	π-cyclodextrin	CD_{21}	3405.0[b]	–	–	–	–	11.5
22	Cyclomaltodoicosaose	–	CD_{22}	3567.2[c]	–	–	–	–	–
23	Cyclomaltotriicosaose	–	CD_{23}	3729.3[c]	–	–	–	–	–
24	Cyclomaltotetraicosaose	–	CD_{24}	3891.4[c]	–	–	–	–	–
25	Cyclomaltopentaicosaose	–	CD_{25}	4053.6[c]	–	–	–	–	–
26	Cyclomaltohexaicosaose	–	CD_{26}	4215.7[c]	–	–	–	–	19.6
27	Cyclomaltoheptaicosaose	–	CD_{27}	4377.9[c]	–	–	–	–	–
28	Cyclomaltooctaicosaose	–	CD_{28}	4540.0[c]	–	–	–	–	–
29	Cyclomaltononaicosaose	–	CD_{29}	4702.2[c]	–	–	–	–	–
30	Cyclomaltotriacontaose	–	CD_{30}	4864.3[c]	–	–	–	–	–
31	Cyclomaltohentriacontaose	–	CD_{31}	5026.5[c]	–	–	–	–	–
n	–	–	CD*n*	$n \cdot 162.14$	–	–	–	–	–

[a]Fujiwara et al. 1990; Endo et al. 1995, 1997a, b, 1998; Miyazawa et al. 1995
[b]Calculated from the molecular formula and confirmed by mass spectrometry (Fujiwara et al. 1990; Endo et al. 1995, 1997a, b, 1998; Miyazawa et al. 1995; Koizumi et al. 1999)
[c]Calculated from the molecular formula and confirmed by mass spectrometry (Koizumi et al. 1999)
[d]Observed at 25 °C
[e]Endo et al. 1995; Ueda et al. 2000
[f]In 1 M HCl at 50 °C
[g]Determined by small angle X-ray scattering at 25 °C (Kitamura 2000)

Table 4 Cyclodextrins derivatives and their release behavior (Salústio et al. 2011)

Hydrophilic derivatives		
Methylated β-cyclodextrin		
Methyl-β-cyclodextrin	Me-β-CD	
Randomly methylated-β-cyclodextrin	RM-β-CD (RAMEB)	
Dimethyl-β-cyclodextrin	DM-β-CD (DIMEB)	
Randomly dimethylated-β-cyclodextrin	RDM-β-CD	
Trimethyl-β-cyclodextrin	TM-β-CD	*Immediate release*
Acetylated dimethyl-β-cyclodextrin	DMA-β-CD	
Hydroxyalkylated β-cyclodextrin		*Enhanced dissolution and absorption of poorly water-soluble drugs*
2-Hydroxyethyl-β-cyclodextrin	2-HE-β-CD	
2-Hydroxypropyl-β-cyclodextrin	2-HP-β-CD	
3-Hydroxypropyl-β-cyclodextrin	3-HP-β-CD	
Hydroxybutenyl-β-cyclodextrin	HBen-β-CD	
2,3-Dihydroxypropyl-β-cyclodextrin	2,3-DHP-β-CD	
Branched β-cyclodextrin		
Glucosyl-β-cyclodextrin	G_1-β-CD	
Maltosyl-β-cyclodextrin	G_2-β-CD	
Glucuronylglucosyl-β-cyclodextrin	GUG-β-CD	
Hydrophobic derivatives		
Alkylated β-cyclodextrin		
2,6-di-*O*-ethyl-β-cyclodextrin	DE-β-CD	
2,3,6-tri-*O*-ethyl-β-cyclodextrin	TE-β-CD	
Acylatedβ-cyclodextrin		*Prolonged release*
2,3,6-tri-*O*-$acyl_{(C2\text{-}C18)}$-β-cyclodextrin	TA-β-CD	
2,3,6-tri-*O*-butanoyl-β-cyclodextrin	TB-β-CD	*Sustained release of water-soluble drugs*
2,3,6-tri-*O*-valeryl-β-cyclodextrin	TV-β-CD	
2,3,6-tri-*O*-octyl-β-cyclodextrin	TO-β-CD	
Ionizable derivatives		
Anionic β-cyclodextrin		
O-carboxymethyl-*O*-ethyl-β-cyclodextrin	CME-β-CD	*Delayed release* (pH-dependent release)
β-cyclodextrin sulfate	β-CD sulfate	
Sulfobutyl ether group-β-cyclodextrin (d.s.4)	SBE_4-β-CD	*Immediate release*
Sulfobutyl ether group-β-cyclodextrin (d.s.7)	SBE_7-β-CD	
Cationic β-cyclodextrin		
Trimethyl-ammonium-β-cyclodextrin	TMA-β-CD	*Prolonged release*
Drug-CD conjugate		*Delayed release* (site-specific release)

d.s. degree of substitution

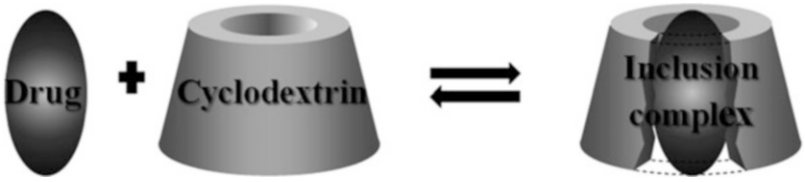

Fig. 3 Interaction of a drug molecule with a CD to form an inclusion complex (Salústio et al. 2011)

covalent, or coordinate covalent bonds (Frank 1975; Cramer 1982; Charoenchaitrakool et al. 2002). The specific association of two molecules results not by a single weak interaction but through the simultaneous cooperation of several weak interactions. Molecular mechanics calculations have also been made to investigate the solute-solvent interactions between CD and water and the molecular interactions in inclusion complexes of CDs. The essential criterion is simply that the enclosed molecule or guest must be of a suitable size and shape (i.e., the best possible filling of space) to fit into a cavity within a solid structure formed by host molecules (Powell 1948, 1954). The main binding contribution between CD and its partners is the geometrical fitting, so complexation occurs in a stereo-specific manner (Cramer 1982). The spatial requirements for the formation of a CD inclusion compound in part mimic the enzyme catalysis "lock-key" mechanism which occurs if the substrate/guest molecule is orientated properly with respect to the active centers of the host (Cramer and Hettler 1967). It is also possible to use the CD to block some reactive sites on the guest and expose others.

CD complex formation, from a pharmaceutical point of view, is equivalent to molecular encapsulation, as the drug molecules are isolated from each other and are dispersed on a molecular level in an oligosaccharide matrix, i.e., a process similar to drug encapsulation in a hydrophilic matrix (e.g., polyvinylpyrrolidine or cellulose) (Pitha et al. 1983; Szejtli 1985).

Inclusion complexes can be obtained by several techniques, such as physical mixing (Menezes et al. 2012), coprecipitation (Sapkal et al. 2007;Nieddu et al. 2014), complexation in a slurry (Fages et al. 2007; Menezes et al. 2012, 2014), complexation in paste (Gil et al. 2004; Menezes et al. 2012, 2014), extrusion (Yano and Kleinebudde 2010), dry mixing (Higashi et al. 2009), solution/suspension with solvents removal by drying methods (spray-drying, freeze-drying) (Salústio et al. 2009), sealed-heating method (Nieddu et al. 2014), and supercritical fluids (Junco et al. 2002). In order to enhance the complex efficiency of the CDs, different methods can be used such as ionization of the drug, salt formation, formation of metal complexes, addition of organic cosolvents to the aqueous complexation media, and the use of supercritical fluids, since all promote an intrinsic solubility enhancement of the drug-favoring complexation (Junco et al. 2002; Loftsson and Duchêne 2007). There are also references to the inclusion of essential oils (EO) into β-CD through a sol-gel process, which consists in the introduction of the suspension containing the EO and β-CD into a colloidal silica, under continuous stirring, at room temperature. This procedure was used to

encapsulate mint and lavender oils, which according to the authors, allowed the EOs to be much more protected against the humidity, temperature, and solar light, among other factors (Răileanu et al. 2013).

3.2 Phase Solubility Studies

Phase solubility studies are a traditional approach to determine not only the stability (also called equilibrium) constant value but also to give insight into the stoichiometry of the equilibrium. Experimentally, an excess of a poorly water-soluble guest molecule (e.g., drug, D, representing the substrate) is introduced into several vials to which a constant volume of an aqueous vehicle containing successively larger concentrations of the CD (representing the ligand) is added. Afterwards the vials are shaken at constant temperature until equilibrium is established. The supernatant is spared and the total concentration of the drug (D_t) is determined by a adequate quantification method (e.g., UV-VIS, HPLC, fluorescence). The phase solubility profile is then constructed by assessing the effect of the CD on the apparent solubility of the drug (D) as shown in Fig. 4 (Higuchi and Connors 1965; Brewster and Loftsson 2007; Cabral-Marques 2010). Several behaviors can be identified between two major types: A and B.

Thus, the following profiles may be described as:

- A-type – formation of soluble inclusion complexes
  - A_L-type – linear increase of drug solubility versus CD concentration
  - A_P-type – positively deviating from the linear profile (i.e., the solubilization is proportionally more effective at higher concentrations)
  - A_N-type – negatively deviating from the linear profile (i.e., the CD is proportionally less effective at higher concentrations)
- B-type – formation of inclusion complexes poorly soluble
  - B_S-type – complexes of limited solubility
  - B_I-type –formation of insoluble complexes

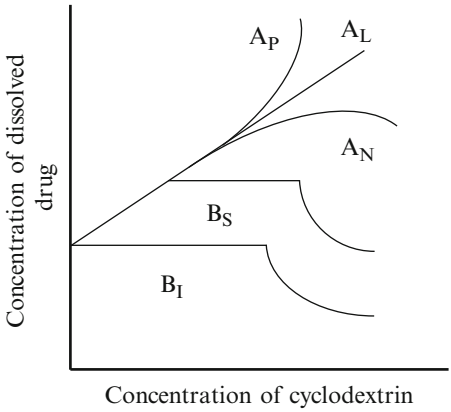

Fig. 4 Profile types in the phase solubility diagrams (Higuchi and Connors 1965)

A_L profiles indicate a linear increase in solubility in function of CD concentration, and water-soluble complexes are being formed with solubilities higher than that of the uncomplexed substrate. A_L-type relationships are first order with respect to the CD and may be of first or higher order with respect to the drug (i.e., *D•CD*, D_2•*CD*, D_3•*CD*, etc.). If the slope of the A_L isotherm is higher than the unity, higher-order complexes are assumed to be involved in the solubilization. Although a slope of less than one does not exclude the occurrence of higher-order complexes, a one-to-one complex is often assumed in the absence of other information. A_P systems suggest the formation of higher-order complexes with respect to the CD, at higher CD concentrations (i.e., *D•CD*, *D•*CD_2, *D•*CD_3, etc.). The stoichiometry of the formed complexes has historically been implied by the extent of curvature of the phase solubility profile. Thus, when an isotherm best fits to a quadratic function, the formation of a one-to-two (*D•*CD_2) complex is suggested, one best fits to a cubic function suggests a one-to-three complex (*D•*CD_3), and so forth. A_N profiles have several explanations including bulk changes imparted to the solvent by the CD at various concentrations (i.e., the CD is acting as a chaotrope or kosmotrope or is altering the bulk properties of the media by changing its viscosity, surface tension, or conductivity) and/or CD self-association at high concentrations. Equilibrium constants can be derived from the linear portion of each phase solubility profile, given by Eq. 2. To this point, intrinsic drug solubility is given as D_o and the formed complex is represented by *D•CD*.

The complexation process is most frequently a 1:1 host/guest ratio; however, 2:1, 1:2, or even higher-order associations may exist at the equilibrium, almost always simultaneously. Equilibrium established between dissociated and associated species can be expressed by the stability (association or equilibrium) constant and designed as K_s or K_a or $K_{1:1}$ (Szejtli 1998). These constants may be determined by several methods, e.g., phase solubility studies (Waleczek et al. 2003; Daletos et al. 2008), NMR, UV-VIS, HPLC (Cabral-Marques 1994a, b), TLC (Lederer and Leipzig-Pagani 1996), and static headspace method (Saito et al. 1999). The CD association with the drug (D) or guest molecules and the dissociation of the formed inclusion complexes are governed by a thermodynamic equilibrium showed by the following equations (Szejtli 1998):

$$\begin{matrix} mD + nCD \overset{K_{m:n}}{\Leftrightarrow} D_mCD_n \\ [a-mx][b-nx]\ [x] \end{matrix} \tag{1}$$

and

$$K_d = \frac{[x]}{[a-mx]^m[b-nx]^n} \tag{2}$$

Then, a dissociation constant can be defined as

$$K_d = \frac{[a-mx]^m[b-nx]^n}{[x]} = \frac{1}{K_{m:n}} \tag{3}$$

Intrinsic drug solubility is given as D_0 and a formed complex is represented by $D{\bullet}CD$.

Since

$$[D] = D_0 \tag{4}$$

$$D_t = D_0 + m[D_m CD_n] \tag{5}$$

$$CD_t = CD + n[D_m CD_n] \tag{6}$$

then the values for $[D_m{\bullet}CD_n]$, $[D]$ and $[CD]$ can be derived as

$$[D_m CD_n] = \frac{D_t - D_0}{m} \tag{7}$$

$$[CD] = CD_t - n[D_m CD_n] \tag{8}$$

where D_0 is the equilibrium solubility of the drug in the absence of CD, D_t is the total concentration of the drug (i.e., the sum of the complexed and uncomplexed forms), and CD_t is the total concentration of CD. For equilibria that are first order with respect to the CD ($n = 1$), the following equation can be obtained:

$$D_t = \frac{mKD_0^m CD_t}{1 + KD_0^m} + D_0 \tag{9}$$

A plot of D_t versus CD_t for the formation of $D_m{\bullet}CD$ should, therefore, give a straight line with the y intercept representing D_0 and the slope defined as

$$\text{slope} = \frac{mKD_0^m}{KD_0^m} \tag{10}$$

Therefore, if m is known, the K can be calculated meaning that for 1:1 complexation, i.e., $m = 1$, the following graphical approach can be applied:

$$K_{1:1} = \frac{\text{slope}}{D_0(1 - \text{slope})} \tag{11}$$

For 1:1 drug $\bullet CD$ complexes, the complexation efficiency (CE) can be calculated from the slope of the phase solubility diagram according to Eq. 12. When selecting CD or complexation conditions during formulation work, it can frequently be more convenient to compare the CE than $K_{1:1}$ values since CE is less sensitive to errors related to estimation of intrinsic drug solubility (Loftsson et al. 2005a):

$$CE = \frac{[D \bullet CD]}{[CD]} = D_0{}^* K_{1:1} = \frac{\text{slope}}{(1 - \text{slope})} \tag{12}$$

The CE is the product of the apparent solubility of the poorly soluble drug (D_0) and the apparent stability constant of the complex ($K_{1:1}$), assuming formation of 1:1 *D•CD*. The CE can be increased by either increasing the value of D_0 or the value of $K_{1:1}$ or both values simultaneously. This parameter increase can be achieved by the use of drug salts, polymers, and cosolvents. In addition, processing approaches to improve CDs, solubilizing functions should be considered, and formulation concepts such as supersaturation may further help in the optimal use and placement of CD in pharmaceutical dosage forms (Loftsson and Brewster 2012; Ciobanu et al. 2013).

4 Biology/Biotechnological Approaches

4.1 Toxicological Considerations

Due to the importance of CDs and the derivatives, their safety and toxicological profiles have been reviewed by several authors (Cabral-Marques 1994b; Irie and Uekama 1997; Thompson 1997; Del Valle 2003; Stella and He 2008; Arima et al. 2011). As CDs possess MW ranging from almost 1,000 to over 2,000 Da and hydrophilicity ($\log_{Ko/w}$ −8 to −12) with a significant number of H-donors and acceptors, they are not significantly absorbed from the gastrointestinal tract (GI) in their intact form. Natural CDs and their hydrophilic derivatives present considerable difficulties to permeate lipophilic biological membranes. Even the somewhat lipophilic randomly methylated β-CD does not readily permeate lipophilic membranes, although it interacts more readily with membranes than the hydrophilic CD derivatives (Totterman et al. 1997); for this reason some β-CD derivatives have been considered skin enhancers due to their ability to complex membrane components causing its disruption (Babu and Pandit 2004; Wang et al. 2014). Several CDs, namely, γ-CD, 2-HP-β-CD, SBE-β-CD, sulphated β-CD, and maltosyl β-CD evaluated in a number of safety studies have proven that they appear to be safe even when administered parenterally. However, these same studies proved that the natural α- and β-CDs and the methylated β-CDs are not suitable for parenteral delivery (Del Valle 2003). The α-CD and β-CD, unlike γ-CD, cannot be hydrolyzed by human salivary and pancreatic amylases even if it can be fermented by the intestinal microflora (Irie and Uekama 1997; WHO 2002). One of the target organs where the toxicity profile of several CDs can be assessed is the kidney (Antlsperger and Schmid1996).

4.1.1 α-CD

Oral administration of α-CD is, in general, well tolerated and is not associated with significant adverse effects (Lina and Bär 2004a, b). Only small fractions of α-CD are absorbed intact from the GI tract, and it is mainly excreted unchanged in the urine after IV injection (Table 5) (Brewster and Loftsson 2007). Studies in rats showed that α-CD p.o. was excreted 60 % as CO_2 (no CO_2 exhalation after p.o. to

Table 5 Safety overview of selected cyclodextrins (Brewster and Loftsson 2007)

	The pharmacokinetics in rats			Acute toxicity, LD50 rat (g/kg)		Maximum dosage in marketed products (mg/day)	
Cyclodextrin	$t_{1/2}$ after IV injection (min)	Fraction excreted unchanged in urine	Oral absorption	IV	Oral	IV	Oral
α-CD	25	≈90 %	2–3 %	0.5–0.8	>10	1.3	
β-CD	20	≈90 %	1–2 %	1	19	Not for parenteral usage	170
HP-β-CD	20	≈90 %	≤3 %	10	>2	16,000	8,000
SBE-β-CD				>15	>10	6,000–14,000	–
RM-β-CD	18	>95 %	0.5–12 %	1.5–2.1	>8	Not for parenteral usage	–
G2-β-CD	23				>5	No product	No product
γ-CD	20	90 %	<0.02 %	4	>8	No product	No product
HP-γ-CD					>2		

germ-free rats), 26–33 % as metabolite incorporation, and 7–14 % as metabolites in feces and urine, being mainly excreted in the unchanged form by the renal route after parenteral injection ($t_{1/2} = 25$ min, LD_{50} oral, rat >10,000 mg/kg, LD_{50} IV, rat between 500 and 750 mg/kg).

Some other relevant characteristics were observed after this CD administration, such as, skin irritation after IM injection, binding with some lipids, eye irritation, and slight absorption (2–3 %) after oral administration in rats. α-CD is not metabolized in the upper intestinal tract and its cleavage is only due to the intestinal flora of cecum and colon (Del Valle 2003).

4.1.2 β-CD

Due to its low aqueous solubility and side effects (e.g., nephrotoxicity), β-CD is not able to be administered by parenteral route but it can be used in p.o. because by this route is normally nontoxic. However, it must be carefully used because in high doses it may be harmful and therefore not recommended. After p.o. administration, the nontoxic effect level of β-CD was determined to be 0.7–0.8 g/kg/day in rats and about 2/g/kg/day in dogs (Bellringer et al. 1995).

It was noticed that β-CD binds cholesterol, is absorbed in small scale (1–2 %) in the upper intestinal tract after oral administration, and is less irritating than α-CD after IM injection. β-CD is not metabolized in the upper intestinal tract, but suffers bacterial degradation and fermentation in cecum and colon which may lead to gas production and diarrhea (LD_{50} oral, rat >5,000 mg\kg; LD_{50} IV, rat = 450–790 mg/kg) (Del Valle 2003). As it will be described in the Regulatory State chapter, β-CD is the most commonly used CD in pharmaceutical formulations, and, thus, it is probably the most studied in humans.

4.1.3 γ-CD

The metabolism of γ-CD closely resembles that of starch and linear dextrins (Munro et al. 2004). Only a small portion of the IV-injected γ-CD is absorbed intact from the GI tract, and it is mostly excreted unchanged in the urine. Oral administration of 8 g γ-CD or 8 g maltodextrin to humans did not reveal any differences in GI tolerance of these two oligosaccharides (Koutsou et al. 1999). The γ-CD showed to promote an insignificant irritation after IM injection and was rapidly and completely degraded by intestinal enzymes in the upper intestinal tract to glucose monomers (even using high daily doses, e.g., 10–20 g/kg). Following p.o. administration γ-CD remained intact, i.e., almost no absorption (0.1 %) was observed and it was practically not metabolized after parenteral administration (LD_{50} oral, rat $\gg$8,000 mg/kg; LD_{50} IV, rat $\approx$4,000 mg/kg) (Del Valle 2003).

Comparing the toxicological profile of the three natural CDs, γ-CD seems to be the least toxic. But its complexes normally have limited solubility in aqueous solutions and tend to self-aggregate; therefore, its complexing abilities are limited compared to those of β-CD and some water-soluble β-CD derivatives (Table 5).

4.2 Metabolism and Pharmacokinetics

4.2.1 Cyclodextrins

Regarding physicochemical and biological characteristics, CDs (ring dextrins) are very similar to water-soluble linear dextrins, but owing to their cyclic structure, they are more resistant to hydrolysis (enzymatic and nonenzymatic) than linear ones (Kurkov and Loftsson 2012). Contrary to starch, CDs are generally resistant to β-amylases, so they are not hydrolyzed from the nonreducing ends, but they cannot resist to the slow hydrolysis caused by α-amylases (hydrolysis from within the carbohydrate chain). α-CD and β-CD are not affected by the stomach acids and salivary and pancreatic enzymes during digestion, but γ-CD is digested partly by these amylases in the GI tract. The mechanism involved in the CDs' hydrolysis resistance is due to all bridge oxygens being hidden within the central cavity; this hydrolytic rate will depend on several factors, namely, the ring size and fraction of free CD (Kurkov and Loftsson 2012).

Linear dextrins as well as starch are digested mainly into glucose through a stepwise enzymatic hydrolysis process which starts when in contact with salivary α-amylase, but by p.o. administration this is overcome as in the stomach the enzyme is inactivated (Dona et al. 2010). Some nonenzymatic specific acid hydrolysis of the dextrins can occur in the stomach, but this phenomena can be delayed by the formation of complexes with food lipids (Singh et al. 2010). In the small intestine (neutral pH), where pancreatic fluid containing α-amylase is released, enzymatic hydrolysis occurs. The dextrin substrates that remained intact along the above enzymatic process are finally submitted to bacterial digestion when they reach the lower sections of the intestine.

Thus, the most important pharmacokinetic parameters for these macromolecules are urinary clearance and hepatic uptake (Nishikawa et al. 1996). As it was shown by several authors, both natural CDs and their derivatives are susceptible to bacterial digestion in the GI tract (Antlsperger and Schmid 1996; Irie and Uekama 1997; Zhou et al. 1998; Zuo et al. 2002; Van Ommen et al. 2004; Stella and He 2008).

Natural CD pharmacokinetics are very similar to each other and to the linear dextrins with similar molecular weights (MW). The insignificant amount that is absorbed from the GI tract after p.o. administration is made by passive diffusion and can be explained by the bulky and hydrophilic nature of the CDs. After absorption, CDs are eliminated by the renal route without undergoing significant metabolism. Any remaining CD is eliminated by other pathways (liver metabolism and biliary excretion) similarly to low MW dextrans.

The main elimination process is dependent on the administration route: Following p.o. administration in rats and dogs, HP-β-CD was mainly excreted via the feces, whereas after IV administration, this CD was excreted via the kidneys. In the case of humans, this excretion process mainly occurs via the kidneys (Gould and Scott 2005). The $t_{1/2}$ of the elimination phase (natural CDs) ranged approx. between 1.4 and 2 h, and the volume of distribution (V_D) was approx. 0.2 L kg^{-1}. The pharmacokinetic studies showed that over 90 % of parenterally administered CD

Table 6 The absorption of cyclodextrins and their derivatives following oral administration (Stella and He 2008)

Cyclodextrin	Species	Dose (mg/kg)	Absorption (% dose)	Reference
α-CD	Rat	200	1	Van Ommen et al. 2004
β-CD	Rat	500	0.6	Kubota et al. 1996
γ-CD	Rat	1,000	0.02	De Bie et al. 1998
G-β-CD	Rat	500	0.3	Kubota et al. 1996
HP-β-CD	Rat	40	3	Gerloczy et al. 1990
SBE-β-CD	Rat	60	1.64	CyDex (unpublished)

will be eliminated from the body within approximately 6 h and over 99.9 % within 24 h (Kurkov and Loftsson 2012). The absorption of natural CDs and their derivatives following oral administration in the rat is summarized in Table 6.

After being absorbed CDs are distributed to several organ tissues, such as the kidney, urinary bladder, liver, adrenal gland, and others (Gerloczy et al. 1990; Monbaliu et al. 1990; Antlsperger and Schmid 1996; Kubota et al. 1996; De Bie et al. 1998; Van Ommen et al. 2004). The absorption of β-CD-methylated derivatives in rats were 6.3–9.6 % for DM-β-CD and 0.5–11.5 % for M-β-CD (Mosher and Thompson 2002). The HP-β-CD oral bioavailability (itraconazoleoral solution) in humans was estimated to be less than 1 % (De Repentigny et al. 1998; Stevens 1999). The IV administration of β-CD and HP-β-CD to permanently cannulated rats resulted in a pharmacokinetic behavior of both CDs similar to that of inulin, showing a rapid distribution over extracellular fluids and elimination through glomerular filtration (Frijlink et al. 1990). CDs via IV route disappeared rapidly from systemic circulation, as they are rapidly eliminated by the kidney, almost in intact form. This makes the kidney the organ with the highest level of CDs among all tissues. Thus, renal insufficiency could result in CD accumulation. As an example, it was observed that after IV bolus administration (10 mg kg^{-1}) of M-β-CD, its concentration in the kidneys (mainly in the renal cortex) remained almost at the same level for at least 6 days (Antlsperger and Schmid 1996; Slain et al. 2001; Gould and Scott 2005; Von Mach et al. 2006; Stella and He 2008).

The β-CD steady-state volume of distribution (V_{dss}) and most of its derivatives in all animal species tested correspond well with the respective extracellular fluid volume (Table 7). Thus, it can be concluded that, after IV administration, CDs distribute mainly in the extracellular compartments without involving the deep compartments or storage pools (Kleijn et al. 2011). Methylated β-CD has a larger V_{dss} and longer $t_{½}$ compared to other CD derivatives which may be due to its ability to interact with cellular membranes and its hemolytic activity (Thompson 1997). The total plasma clearance for HP-β-CD and SBE-β-CD in all species tested is similar to the glomerular filtration rate of individual species (Davies and Morris 1993). In these cases 100 % of an IV dose was recovered in the urine within 6–12 h (Davies and Morris 1993). Most CDs disappear from tissues dramatically within the first several hours after administration. For example, the level of SBE-β-CD in most tissues decreased by more than 90 %; even in the kidney, SBE-β-CD was reduced

Table 7 Pharmacokinetic parameters of some cyclodextrins IV administered (Stella and He 2008)

Cyclodextrin	Species	Dose (mg/kg)	$T_{1/2}$ β (min)	V_{dss} (mL/kg)	Plasma clearance (mL/min/ kg)	Reference
β-CD	Rat	50	21.6	201.8	7.53	Kubota et al. 1996
G-β-CD	Rat	50	17.3	308.1	12.5	Kubota et al. 1996
HP-β-CD	Rat	200	23.9	194	7.2	Frijlink et al. 1990
HP-β-CD[a]	Human	43	102	222	1.57	Szathmary et al. 1990
HP-β-CD[b]	Human	114	114	253	1.54	Zhou et al. 1998
SBE-β-CD	Rat	600	18	300	9.8	CyDex (unpublished)
SBE-β-CD	Rabbit	600	30	200	5.2	CyDex (unpublished)
SBE-β-CD	Dog	240	66	430	4.7	CyDex (unpublished)
SBE-β-CD[c]	Human	100	84	200	1.9	CyDex (unpublished)
M-β-CD[d]	Rabbit	200	420	2,500	3.8	(Grosse et al. 1999)

[a]Calculated as 70 kg body weight. HP-β-CD was administered intravenous injection (IV) at 3 g in normal volunteers

[b]The body weight is calculated as 70 kg. HP-β-CD was administered as itraconazole formulated with HP-β-CD to patients with advanced AIDS at 8 g over 1 h IV infusion

[c]IV infusion for 1 h

[d]Methyl-β-CD with total degree of substitution (DS) of 10.4

by at least 60 % from 0.1 to 1 h following IV bolus injection of 600 mg/kg SBE-β-CD in the rat (Stella and He 2008).

4.2.2 Complexes

The partitioning of the drug in its different forms (dissolved free drug molecules, dissolved complex, solid free drug, and solid complex) depends on the solubility of the free drug and the complexed drug in the given medium, the stability constant of the CD-drug complex, the molar ratio of the components, and the volume of the liquid phase. The same complex may provoke different – enhanced or decreased – biological responses depending on the additional amount of CD or even on the volume of water consumed.

It has generally been believed that following oral administration only an insignificant amount of CD is absorbed simultaneously with the drug, i.e., only free drug molecules can enter the circulation and the increasing excess of the remaining CD will push the equilibrium towards complex formation. CD acts primarily as a carrier agent to the site of absorption transporting the more or less hydrophobic guest

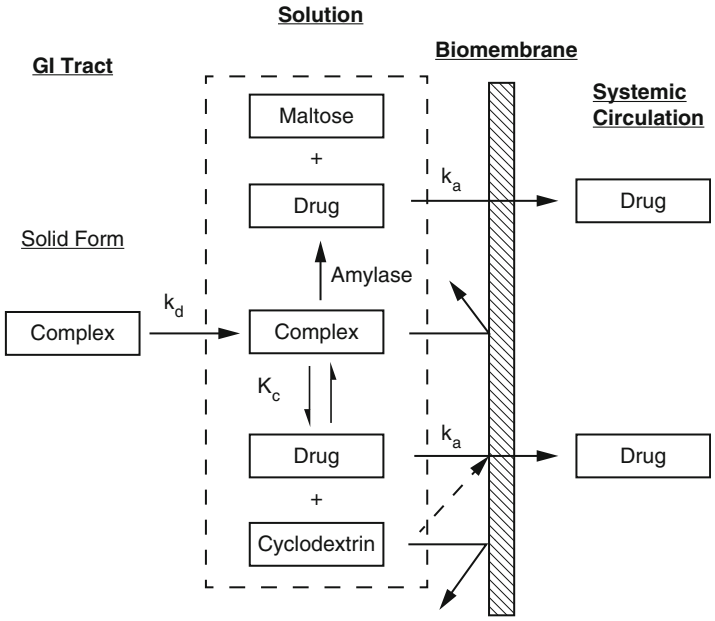

Fig. 5 Mechanism of drug absorption from CD complexes in vivo (where k_d is the rate constant of dissolution, k_a rate constant of absorption, *D* drug in the orally administered dose, *GI* concentration of dissolved drug in the gastrointestinal tract, and *B* concentration of drug in blood) (Cabral-Marques 1994c)

molecule through an aqueous milieu to the lipophilic membrane of cells in the GI tract. There the guest molecule is absorbed, since the membrane has a higher affinity for a lipophilic guest molecule than the CD itself. If the complex is very stable or the CD concentration is high, the equilibrium is greatly shifted towards complexation and absorption is considerably hindered. Some studies have indicated slow absorption of some CDs by passive diffusion across intestinal membranes, which seem to be promoted in the presence of bile salts and Ca^{2+}-chelating agents indicating absorption by the paracellular pathway. It is unclear whether GI tract absorption of drug-CD complexes may constitute a significant level of absorption under certain conditions, but in the case of pulmonary delivery where the barrier membranes are much thinner, this possibility should be considered.

In a model for in vivo drug release, the first step must be the dissolution of the solid adducts (Fig. 5). There then exists an equilibrium between the dissolved complex and the released drug. Only the dissolved, non-complexed drug can be absorbed (Cabral-Marques 1994c).

4.3 Biotechnological/Bioengineering Approaches

CD has been used in several biotechnological/bioengineering studies, some of which are described below:

It is not easy to predict drug absorption after its complexation with CD due to the large range of interacting parameters and their influence on free drug concentration.

Molecular modeling can help by making predictions and providing orientations for the development of new complexes that can be formulated in pharmaceutical dosage forms. Neutral compound complex model demonstrates the mechanism behind a possible variation (increase, decrease or no effect) in the absorption when CD is dosed as an inclusion complex. A model for predicting the CD effect on drug bioavailability, when administered as inclusion complex, was used. This model involved mass transport expressions for drug dissolution and absorption and pseudo-equilibrium *D•CD* complexation. Its predictions were compared with in vitro and in vivo experimental results allowing to predict when CD can be delivered as a preformed complex with drug to enhance bioavailability (Gamsiz et al. 2013).

Different polymers such as plasticized poly (vinyl chloride) (PVC-P), poly (ethylene oxide) (PEO), PEO/poly (propylene oxide) (PPO), and copolymers, e. g., Pluronic F68 (F68), were studied in order to obtain a novel modified biomaterial surface using CDs for increased blood compatibility. The β-CD-PEO and β-CD-F68 associations in certain feeding ratio were synergistic in producing the desired effect (Zhao and Courtney 2006).

Hydrogels have suitable properties for wound-dressing use due to its good biocompatibility and maintenance of a moist environment for better healing. The efficacy of these platforms can be improved by the use of CDs as cross-linking agents. The association hydrogels-CDs may allow the moist environment required for the healing process and the moiety with the ability to protect and modulate the release of bioactive molecules (Pinho et al. 2013). Furthermore, the development of the platforms using CD-containing polyrotaxanes is expected to provide a new paradigm for biomaterials. Thus, the CD-based biodegradable polypseudorotaxane hydrogels could be used as a promising injectable drug delivery system for sustained and controlled drug release. The polyrotaxanes with drug- or ligand-conjugated CDs threaded on a polymer chain with a biodegradable end group could be useful for controlled and multivalent targeted delivery. In the field of gene delivery, cationic polyrotaxanes consisting of multiple OEI-grafted CDs threaded on a block copolymer chain are attractive non-viral gene carries due to the strong DNA-binding ability, low cytotoxicity, and high gene delivery capability (Li et al. 2011).

The bioactive compounds from plants (polyphenolics, alkaloids, and polysaccharides) have well-documented pharmacological properties and have been widely used by the food, cosmetic, and pharmaceutical industries due to its advantages, such as high levels of biocompatibility, low toxicity and good availability. Polyphenolics are currently the major group of interest in view of their anti-inflammatory, antimicrobial, and antioxidant properties, as well as their availability in the human diet (Cowan 1999; Aridogan et al. 2002; Belščak-Cvitanović et al. 2011; Gou et al. 2011). Many studies have been published regarding the encapsulation of natural polyphenolic agents by CDs, for food and drug delivery proposes. CDs have a capacity of improving their aqueous solubility, protect them from elevated temperatures, pH, and light- or moisture-induced degradations

increasing their bioavailability. In the case of flavonoids, the CD derivatives are the best choices to achieve an efficient complexation (Pinho et al. 2014).

Monochlorotriazinyl-β-cyclodextrin (β-CDMCT) has been used as a great tool for surface modification of natural and synthetic fibers (polyester, polyamides, and polyacrylics). These materials after being grafted onto celluloses substrates can be used for fragrance release, odor adsorption (sheets and personal clothing), controlled release (antibacterial, fungicide, or insect repellents), UV protection, and stabilization of active ingredients due to CD cavities. These platforms in β-CD cavities can include an insect repellent and an insecticide. In addition this new tool was designed for the treatment of materials (such as bed nets, curtains, specific clothing, military uniforms, etc.) in order to prevent man-vector contact (Reuscher and Hinsenkorn 1996; Romi et al. 2005).

The structural CD properties make them suitable building blocks to be used in polymeric reactions, since they can be grafted to polymers (natural/synthetic) resulting in different polymer architectures (Zhang and Ma 2013).

Molecular complexation with CDs already cited play an important role in biotechnology and bioengineering area in the domain of selectivity, separation, and solubilization of various biomolecules.

4.4 Applications of CDs

Since CDs are versatile molecules that offer unique features and have negligible cytotoxic effects, they have been widely used in many industrial products, technologies, and analytical methods (Cabral-Marques 1994c; Singh et al. 2002; Del Valle 2003; Cabral-Marques 2008). Some examples of applications are the following.

4.4.1 Pharmaceuticals

CDs have been widely used in pharmaceutical industries, being in the most of the cases as auxiliary substances, improving stability, bioavailability, and organoleptic properties (e.g., palatability, masking odors) of active compounds in multiple pharmaceutical dosage forms (Del Valle 2003; Carrier et al. 2007; Miller et al. 2007; Cabral-Marques 2010). These versatile sugar molecules enabled the production and reintroduction of numerous active substances that, owing to stability, compatibility, or absorption problems, were not in use (Cabral-Marques 1994c). Shortly, the CDs' multifunctional features have been exploited in drug delivery system being potential candidates in many applications because of their ability to alter the physical, chemical, and biological properties of guest molecules through the formation of inclusion complexes (Uekama et al. 1998; Cabral-Marques 2008). All these improvements enabled their application in commercialized pharmaceutical products used in almost every drug delivery systems: α-CD (oral, parenteral), β-CD (dermal, oral, rectal, sublingual), HP-β-CD (ocular, oral, parenteral, rectal), DM-β-CD (dermal, nasal, ocular), SBE-β-CD (parenteral), and HP-γ-CD (ocular) (Cabral-Marques 2008; Tiwari et al. 2010). Among all CDs, β-CD is the most reasonably priced, thus the most used on industrial applications.

Oral delivery: The drug release in this route of administration is controlled either by dissolution, diffusion, osmotic systems, density, or pH (Tiwari et al. 2010).

CDs are particularly useful as they can be used as a way to reduce local drug irritation and increase drug absorption rate (Loftsson et al. 2005b). The hydrophilic CDs provide an enhancement of stability, solubility, dissolution rate, and wettability of poorly water-soluble drugs by means of complex formation (Carrier et al. 2007). CDs are supposed to act only as carriers and help to transport the drug through an aqueous medium to the lipophilic absorption surface in the GI tract. Buccal and sublingual routes have also been an effective way to deliver rapid-dissolving drug-CD complexes. In this case, a rapid increase in the systemic drug concentration takes place along with the avoidance of systemic and hepatic first-pass metabolism (Tiwari et al. 2010).

Pulmonary delivery: Pulmonary administration has been gaining an increased importance for therapeutic usage due to lung's anatomical and physiological characteristics like large surface area available (~100 m^2), high irrigation (5 L/min), very thin absorption membrane (0.1–0.2 μm), and relatively low enzymatic activity (Pilcer and Amighi 2010). This is normally an attractive route for treatment of local diseases (e.g., asthma, DPOC) but is also interesting for systemic delivery. However, this route is usually limited by the characteristics of drugs used, low aqueous solubility, and slow drug dissolution (Loftsson et al. 2005b). CDs are used to solve these drawbacks and to improve the pulmonary delivery of drugs either systemically or locally. Formulations of insulin delivered via pulmonary route (powders and liquids) have low bioavailability (10–15 %), and thus, to get the right dose, a high drug loading is needed in drug delivery system (Ramalhete et al. 2001). Formulations with penetration enhancers (with proven efficacy via other administration routes) such as CDs could help this matter (Cabral-Marques et al. 1991). Current DPIs (Dry Powder Inhalers) for treatment of respiratory diseases generally deliver only 10–20 % of the nominal dose to the site of action. It is possible to engineer particles by spray-drying and using CDs to improve this drawback allowing a more efficient drug delivery to the site of action, with fewer systemic effects than oral therapy (Vozone and Cabral-Marques 2002; Almeida and Cabral-Marques 2004; Drumond et al. 2014).

Nasal delivery: This is another effective route that avoids the extensive GI breakdown and hepatic first-pass metabolism. Due to nasal mucosa's good permeability, this delivery route is a novel approach for systemic delivery of high potency drugs with a low oral bioavailability. As lipophilic CDs can interact with biological barriers (without affecting their barrier function), they have the ability to enhance the drug delivery – a property which makes CDs ideal penetration enhancers for intranasal administration. Methylated CDs are the most commonly used and widely studied. They have shown in several studies very promising results being efficient absorption enhancers, namely, in the delivery of peptides and hormones (Merkus et al. 1999; Loftsson et al. 2005b; Tiwari et al. 2010).

Ocular delivery: In this type of delivery systems, the most used dosage form is the eye drop due to easy instillation in the eye. However, eye drops are a great formulation challenge due to the high probability of its inability to sustain high

local concentration of drug (Tiwari et al. 2010). By this reason CDs have been used to overcome these problems as they present possible advantages in ophthalmic use, such as increase in solubility and/or stability and reduction or avoidance of side effect of drugs (e.g., discomfort and irritation) (Torres Marques et al. 1996; Loftsson et al. 2012). One of the prerequisites for a new vehicle to be used in ophthalmic preparations is that it is not irritating to the ocular surface, because irritation causes reflex tearing and blinking, which result in a fast washout of the instilled drug (SáCouto et al. 2014). Hydrophilic CDs do not penetrate eye cornea biological barriers but enhance the ocular bioavailability of lipophilic drugs by keeping them in solution (Cabral-Marques 2008).

Rectal delivery: This route is by far the chosen one to deliver drugs to the unconscious patients, children and infants. Despite offering a relatively low area for drug absorption, which leads to an erratic release of drugs, the rectal mucosa represents a potential site for delivery of drugs with limitations by the oral route (e.g., organoleptic problems, pH degradation, high first-pass metabolism) (Tiwari et al. 2010). Beraldo et al. (2002) has shown that CDs are quite useful to solve the erratic release problems of this route.

Dermal delivery: This is the most sophisticated and more reliable form to administrate the drug through skin, either for local or systemic action (Tiwari et al. 2010). CDs have a significant safety margin in dermal application and can be used to optimize the transdermal delivery of drugs. CDs improve drugs' solubility and/or stability in topical preparations, consequently enhancing the transdermal absorption of drugs, to sustain the drug release from the vehicle and to avoid undesirable side effects associated with dermally applied drugs (Waleczek et al. 2003; Santos et al. 2004; Loftsson et al. 2005b). CDs may interact with some components of the skin and the lipids such as cholesterol and triglycerides and consequently induce a temporary change in the skin barrier function and an enhancement in the drug absorption. It was shown that DM-β-CD has higher skin permeation effect than HP-β-CD (Cabral-Marques 2008).

4.4.2 Bioconversion and Fermentation

The efficiency of bioconversion and fermentation processes is often restricted by the inhibitory or toxic influence from either the substrate or the conversion products on the biocatalyst. Another problem often found on most organic substrates is their solubility in water which complicates the amount of substrate accessible to the biocatalyst. In order to overcome process limitations such as low solubility of lipophilic substrates, CDs can be added to the bioconversion or fermentation media. In addition CDs may provide a reduction of toxicity by complexation with toxins and biocompatibility improvement (Bar 1989; Cabral-Marques 2010).

4.4.3 Environment Protection

CDs are important to environmental science in terms of remediation by complexation of organic contaminants/pollutants and heavy metals from soil, water, and atmosphere. After treating wastewaters containing environmentally unacceptable aromatic compounds (phenol, p-chlorophenol and benzene) with β-CD, the initial

levels of these aromatic hydrocarbons were significantly reduced. The same CD benefic actions may also be used in the treatment of gaseous effluent from chemical industries (Cabral-Marques 1994b; Del Valle 2003).

4.4.4 Agrochemical Industry

CDs may be used to improve a variety of properties of bactericides, insecticides, herbicides, and fungicides. Complex formation with β-CD has been reported, including examples of increased or decreased activity of pesticides (Cabral-Marques 1994b).

4.4.5 Catalysis

The CDs ability to mimetize enzymes, i.e., molecular recognition phenomenon, led them to be used in catalysis. Thus, CDs have to be modified through substituting various functional compounds or by attaching reactive groups. In addition CDs possess the ability of enantiomeric recognition. Resulting from the chelating effect of the CD catalysts, rates of reaction may be enhanced by almost 1,000-fold when compared to free solution (Del Valle 2003).

4.4.6 Analytical

The CDs are very useful in separation process due to its molecular recognition ability to discriminate positional isomers, functional groups, and homologues/enantiomeric compounds. Depending on the substrate to be separated, the choice of the CDs is essential since shape, size, and selectivity will influence separations. CDs have been used in HPLC and GC (being CDs in the stationary phase columns), in NMR (chiral shift agents), in circular dichroism (selective agents altering spectra), and also in electrochemical chemistry (to mask contaminating compounds) (Del Valle 2003). These substances serve as an ideal selector by molecular recognition and further enhance the complex forming ability and selectivity in various type of separations (Eastburn and Tao 1994; Han 1997; Loung and Nguyen 1997; Szejtli 1998; Del Valle 2003; Cabral-Marques 2010).

4.4.7 Food and Flavors

In food industry the CDs are used as multifunctional food ingredients. They can be used as carriers for molecular encapsulation forming inclusion complexes with a variety of molecules including fats, aromatic agents, flavors, and colors. The inclusion complexes improve both physical and chemical stability of sensitive ingredients leading to better conservation and, consequently, to extended food shelf life. CDs also can act as a controlled release agent of desired food constituents and can provide a promising alternative to the conventional encapsulation technologies by removing and/or masking undesirable components (e.g., removal of cholesterol from butter, eggs, milk; decreasing of juice's bitterness). In addition, CDs can protect the food ingredient throughout many rigorous food-processing methods of freezing, thawing, and microwaving (Prasad et al. 1999; Del Valle 2003; Cabral-Marques 2010).

4.4.8 Cosmetics, Toiletry, and Personal Care

Cosmetic preparations are another area where CDs have been largely used to protect molecules against physical and chemical instabilities (e.g., oxidation, decomposition, hydrolysis). By complex formation included guest molecules may increase their stability, suppress volatility (in the case of perfumes), reduce/prevent skin irritation, and improve room fresheners and detergent's action. Active ingredients are released from inclusion compounds by controlled release. In summary, it is possible to say that major benefits of CDs in the cosmetics, toiletry, and personal care products are stabilization, odor control, process improvement upon conversion of liquids to solids, absorption increase/decrease of various compounds into skin, flavor protection, enhanced water solubility, and thermal stability of oils. Moreover, CDs are used in toothpaste, lipsticks, skin creams, liquid and solid fabric softeners, paper towels, tissues, shampoos, and deodorants (Del Valle 2003; Cabral-Marques 2010).

4.4.9 Packaging and Textile Industry

Textile industry is another area in which CDs are increasingly attracting attention (Cabral-Marques 2010). Fabrics can be imbued with novel properties by means of these substances. In order to permanently transfer the versatile properties of CDs to textiles, Wacker-Chemie (the world's largest producer of γ-CDs) covalently attached reactive CD derivative with monochlorotriazinyl (MCT) substituents to the fiber. This substituted CD provided excellent textile finishing to cottons, blended materials, and woolens. Using hydrophobic tosyl derivative of β-CDs, threefold increase in the binding of fluorescent dye to the polyester fiber was attained.

CDs also play a major role in the packaging industry. Inclusion complex containing oily antimicrobial and volatile agents are coated on a water-absorbing sheet with a natural resin binder, which is used for wrapping fresh products. It was found that food-packaging bag manufactured using CD with ethylene-tetracyclo-3-dodecane copolymer and hinokitiol showed no odor and good antifungal properties after 1 week of storage at room temperature, which proved useful for food-packaging materials (Hedges 1998; Ishibashi et al. 1999; Hirose and Yamamoto 2001).

5 Current Regulatory State

Despite of being characterized as pharmacologically inactive compounds, pharmaceutical excipients are treated as active compounds in the regulatory perspective, especially when used for the first time in humans (Demerlis et al. 2009; Koo 2011; Osterberg et al. 2011). Their acceptance is often supported by previous usage in commercialized pharmaceutical products or in the food industry. This is also valid if the excipient is already being used at the same levels and administration routes as in marketed products. In these cases a full safety evaluation may not be needed (Kurkov and Loftsson 2012).

Table 8 Food approval status of Cyclodextrins (Cabral-Marques 2010)

	α-CD	β-CD	γ-CD
WHO/FAO[a]	ADI = not specified (June 2001 and June 2004)	ADI = 5/mg/kg/day (Jan. 1995)	ADI = not specified (1999 and 2000)
USA	GRAS[b] (Jan. 2004)	GRAS[c] (Oct. 2001)	GRAS[b] (Sept. 2000)
Canada	Filed for novel food status (July 2006)		
EU	Novel food approved (2008)	Carrier for food additives (<g/1 kg)	Novel food filed (Jan. 2010)
Japan	Natural product	Natural product	Natural product
Mexico	Follow FDA approvals with an import license	Follow FDA approvals with an import license	Follow FDA approvals with an import license
Mercosur States[d]	Food approved		
FSANZ[e]	Novel food (Jan. 2004)		Novel food (2003)
Korea	Approved for dietary supplement	Approved for dietary supplement	Approved for dietary supplement
Philippines	Food approved		Food approved
Thailand			Approved for dietary supplement
Taiwan	Approved for dietary supplement		

[a]*WHO*/*FAO* World Health Organization/Food and Agriculture Organization of the United Nations
[b]GRAS in a wide range of intended use in food
[c]GRAS as a flavor protectant
[d]Mercosur States – Argentina, Brazil, Paraguay, Uruguay, and Venezuela
[e]FSANZ – Food Standards Australia New Zealand

The regulatory status of CDs has evolved over the last years even with the skepticism within the regulatory agencies concerning their usage. Consensus seems to be building among regulators that CDs are excipients and not part of the drug substance although divergent opinions exist (Brewster and Loftsson 2007). Products containing CDs undergo rigorous evaluation, and their strengths and weaknesses are understood and agencies will become more comfortable with them and lower the barriers to their use (Davis and Brewster 2004; Loftsson et al. 2004; Stella and He 2008). Table 8 shows an overview of the food approval status of CDs by the different worldwide regulatory agencies.

Monograph for natural β-CD is listed in some pharmacopoeia sources such as the US Pharmacopoeia/National Formulary (USP/NF), European Pharmacopoeia (Ph. Eur.), and Japanese Pharmaceutical Codex (JPC). α-CD is also listed in the Ph. Eur., USP/NF, and JPC; γ-CD is referenced in the JPC and soon will be included in the Ph. Eur. and USP/NF. A monograph for HP-β-CD is available in the Ph. Eur., and a draft has been circulated for the USP/NF; SBE-β-CD can be found in the USP/NF. Other derivatives are not yet compendial but efforts are being made for their inclusion. α-CD, β-CD, and γ-CD were also introduced into the generally regarded as safe (GRAS) list of the FDA for use as a food additive in 2004, 2001,

and 2000, respectively; HP-β-CD and γ-CD are cited in the FDA's list of Inactive Pharmaceutical Ingredients. SBE-β-CD is also available in various dosage forms and listed in the FDA's compilation of Inactive Pharmaceutical Ingredients (Cabral-Marques 2010; Kurkov and Loftsson 2012).

Currently different marketed pharmaceutical products (Table 9) as well as numerous food products (Cabral-Marques 2010) can be found using different CDs: α-CD, β-CD, HP-β-CD, RM-β-CD, SBE-β-CD, γ-CD, and HP-γ-CD.

6 Conclusion/Prospects

Since the begin of nineteenth century CDs have been showing their potentialities, and up to today they have gained a great importance and different applications in distinct areas from pharmaceutical and food to chemical and environmental industries. So a prosperous future can be envisaged to CDs being one of the most adaptable and relevant excipient. All this was only possible due to their remarkable characteristics which make them a versatile compound with the ability to form inclusion complexes with guest molecules possessing a hydrophobic moiety (Tiwari et al. 2010).

Due to science evolution, the discovery of new molecules with solubility, bioavailability, and permeability limitations or other undesirable properties (stability, taste and odor, irritation potential, etc.) raises the need for CDs' usage as they can be useful tools for scientists.

CDs can be useful drug carriers in delivery systems as they are bio-adaptable particularly in parenteral applications (especially HP-β-, SBE-β-, and maltosyl-β-CDs), having the ability to control the rate and time of drug release. Peracylated CDs may serve as novel hydrophobic carriers to control the release of water-soluble drugs including peptides and proteins in various routes of administration. Amphiphilic or ionizable CDs can modify the rate or time of drug release and bind to the surface membrane of cells, which may be used for the enhancement of drug absorption across biological barriers. A combination of molecular encapsulation with other pharmaceutical excipients is effective and valuable in the improvement of carrier properties of CDs. Conjugates of a drug with CDs can be a versatile drug site-specific carrier for colon therapy; they form a new class of colon-targeting prodrugs (Uekama et al. 1998; Uekama 2004; Li and Loh 2008).

There are more than 100 different CD derivatives commercially available as fine chemicals, mainly for use in chromatography, in diagnostics, and as intermediate for further synthesis. The ideal derivative does not exist yet. It is expected that more derivatives will be developed. For organ or receptor targeting, extremely stable, bio-adaptable, and specific affinity-showing CD complexes will be needed (Cabral-Marques 2008; Kurkov and Loftsson 2012).

Despite of all the unique architecture and the chelating properties that CDs present, the usage of this excipient is not by itself a reason to achieve a successful goal without previous studies. In fact a great knowledge of the characteristics of all the compounds intended to be used (CDs, guest molecule, additives to the product)

Table 9 Commercialized pharmaceutical products containing cyclodextrins (Adapted from Szejtli 2005; Hincal et al. 2011; Kurkov and Loftsson 2012)

Cyclodextrin	Drug	Therapeutic usage	Formulation	Trade name
α-CD	Alprostadil	Treatment of erectil dysfunction	Intracavernous solution	Caverject, rigidur, dual, edex
	Alprostadil (PGE1)	Chronic arterial occlusive disease, etc	Intra-arterial infusion	Prostodin
	Alprostadil (PGE1)	IA or IV vasodilator	IV solution	Prostarmon
	Alprostadil (PGE1)	IA or IV vasodilator	IV solution	Prostavasin
	Cefotiam hexetil HCl	Antibiotic	Oral tablet	Pansporin T
	OP-1206	Buerger's disease	Tablet	Opalmon
β-CD	Benexate HCl	Anti-ulcerant	Oral capsule	Ulgut, Lonmiel
	Betahistidine	Antivertigo drug	Tablet	Betahist
	Cetirizine	Antibacterial agent	Chewing tablets	Cetrizin
	Cephalosporin	Antibiotic	Tablet	Meiact
	Chlordiazepoxide	Tranquilizer	Tablet	Transillium
	Dexamethasone	Anti-inflammatory steroid	Ointment, tablets	Glymesason, glyteer
	Dextromethorphan	Antitussive (cough suppressant)	Xyrup	Rynathisol
	Diphenhydramine, chlorotheophylline	Travel sickness	Chewing tablets	Stada travel pill
	Flunarizine	Calcium channel blocker	Tablet	Fluner
	Iodine	Throat disinfectant	Gargle	Mena-Gargle
	Meloxicam	Nonsteroidal anti-inflammatory drug	Tablet, suppository	Mobitil
	Nicotine	Nicotine replacement product	Sublingual tablets	Nicorette, nicogum
	Nimesulide	Nonsteroidal anti-inflammatory drug	Tablets	Nimedex, mesulid fast
	Nitroglycerin	Coronary dilator	Sublingual tablets	Nitropen
	Omeprazole	Proton-pump Inhibitor	Capsule	Omebeta
	PGE2	Induction of labor	Sublingual tablets	Prostarmon E
	Piroxicam	Nonsteroidal anti-inflammatory drug	Tablets	Brexin, brexidol
	Piroxicam		Suppository	Cycladol

(*continued*)

Table 9 (continued)

Cyclodextrin	Drug	Therapeutic usage	Formulation	Trade name
	Piroxicam	Analgesic for pediatric use	Liquid	
	Rofecoxib	Nonsteroidal anti-inflammatory drug	Tablet	Rofizgel
	Tiaprofenic acid	Analgesic	Oral tablet	Surgamyl
	Thiomersal	Antiseptic/ antifungal	Eye drop	Vitaseptol
HP-β-CD	Alfaxalone	Veterinary anesthetic		
	Cisapride	Gastroprokinetic agent	Suppository	Propulsid
	Hydrocortisone	Mouthwash (aphtha, gingivitis, etc.)	Liquid	Dexacort
	Indomethacin	Nonsteroidal anti-inflammatory drug	Eye drop solution	Indocid
	Itraconazole	Antifungal agent	Oral and IV solutions	Sporanox
	Mitomycin	Anticancer agent	IV infusion	Mitozytrex MitoExtra
	Telavancin	Bactericidal lipoglycopeptide	IV infusion	Vibativ
RM-β-CD	17β-Oestradiol	Hormone	Nasal spray	Aerodiol
	Chloramphenicol	Antibiotic	Eye drop solution	Clorocil
SBE-β-CD	Aripiprazole	Antipsychotic drug	IM solution	Abilify
	Amiodarone	Antiarrhythmic agent	IV	Nexterone
	Insulin	Diabetes	Nasal spray	
	Maropitant	Antiemetic drug (motion sickness in dogs)	Parenteral solution	Cerenia
	Voriconazole	Antifungal agent	IV solution	Vfend
	Ziprasidone mesylate	Antipsychotic drug	IM solution	Geodon, Zeldox
γ-CD	Minoxidil	Stimulate hair growth	Solution	Alopexy
	Sugammadex (as sodium salt)	Antidote (modified γ-CD)	IV solution	Bridion
HP-γ-CD	Diclofenac sodium salt	Nonsteroidal anti-inflammatory drug	Eye drop solution	Voltaren Ophtha
	Tc-99 Teoboroxime	Diagnostic aid, cardiac imaging	IV solution	CardioTec
SL-CD	Modified porcine (circovirus inactivated)	PCV2 vaccine	Suspension for injection	Suvaxyn PCV

and prior work are extremely necessary to try to predict and find out any possible interaction between them, just because these interactions can adversely affect the performance of these constituents, which can lead to incompatibilities, formulation problems, lack of stability, etc., and consequently have a great impact in the final commercialized product. In conclusion, the ideal scenario would be to choose the CD that has the most appropriate characteristics to include the desired guest molecule, predict all the different variables that can influence the complex formation process, and in the end be able to prepare a product with the desirable properties that can be an innovation or an improvement and at last but not the least be economically viable.

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