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Cyclodextrins in Drug Delivery: An Updated Review

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ABSTRACT

The purpose of this review is to discuss and summarize some of the interesting findings and applications of cyclodextrins (CDs) and their derivatives in different areas of drug delivery, particularly in protein and peptide drug delivery and gene delivery. The article highlights important CD applications in the design of various novel delivery systems like liposomes, microspheres, microcapsules, and nanoparticles. In addition to their well-known effects on drug solubility and dissolution, bioavailability, safety, and stability, their use as excipients in drug formulation are also discussed in this article. The article also focuses on various factors influencing inclusion complex formation because an understanding of the same is necessary for proper handling of these versatile materials. Some important considerations in selecting CDs in drug formulation such as their commercial availability, regulatory status, and patent status are also summarized. CDs, because of their continuing ability to find several novel applications in drug delivery, are expected to solve many problems associated with the delivery of different novel drugs through different delivery routes.

KEYWORDS: cyclodextrins, drug formulation, drug delivery, novel delivery systems, excipients.

INTRODUCTION

Cyclodextrins (CDs), with lipophilic inner cavities and hydrophilic outer surfaces, are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes (Figure 1). Chemically they are cyclic oligosaccharides containing at least 6 D-(+) glucopyranose units attached by α-(1, 4) glucosidic bonds. CDs and their derivatives discussed in this article along with their abbreviations are given in Table 1. The 3 natural CDs, α-, β-, and γ-CDs (with 6, 7, or 8 glucose units respectively), differ in their ring size and solubility (Table 2).[1] CDs with fewer than 6 units cannot be formed due to steric hindrances while the higher homologs with 9 or more glucose units are very difficult to purify. However, recently Endo et al established an isolation and purification method for several kinds of large ring CDs and also obtained a relatively large amount of δ-CD (Cyclomaltonose) with 9 glucose units.[2-4]

The cavity size of α-CD is insufficient for many drugs and γ-CD is expensive. In general, δ-CD has weaker complex forming ability than conventional CDs. With drugs like digitoxin and spiranolactone, δ-CD showed greater solubilizing effect than α-CD but the effect of δ-CD was less than that of β- and γ-CDs. β-CD has been widely used in the early stages of pharmaceutical applications because of its ready availability and cavity size suitable for the widest range of drugs. But the low aqueous solubility and nephrotoxicity limited the use of β-CD especially in parenteral drug delivery.[5]

Chemically modified CD derivatives have been prepared with a view to extend the physicochemical properties and inclusion capacity of parent CDs. Several amorphous, noncrystallizable CD derivatives with enhanced aqueous solubility, physical and microbiological stability, and reduced parenteral toxicity have been developed by chemical modification of parenteral CDs.[6,7]

STUDY OF CD COMPLEXATION AND DILUTION EFFECTS

The most widely used approach to study inclusion complexation (Figure 2) is the phase solubility method described by Higuchi and Connors,[8] which examines the effect of a solubilizer, ie, CD or ligand, on the drug being solubilized, ie, the substrate. Phase solubility diagrams are categorized into A and B types; A type curves indicate the formation of soluble inclusion complexes while B type suggest the formation of inclusion complexes with poor solubility. A B_S type response denotes complexes of limited solubility and a B_I curve indicates insoluble complexes. A-type curves are subdivided into A_L (linear increases of drug solubility as a function of CD concentration), A_P (positively deviating isotherms), and A_N (negatively deviating isotherms) subtypes. β-CD often gives rise to B-type curves due to their poor water solubility whereas the chemically modified CDs like HP-β-CD and SBE-β-CD usually produce soluble complexes and thus give A-type systems.

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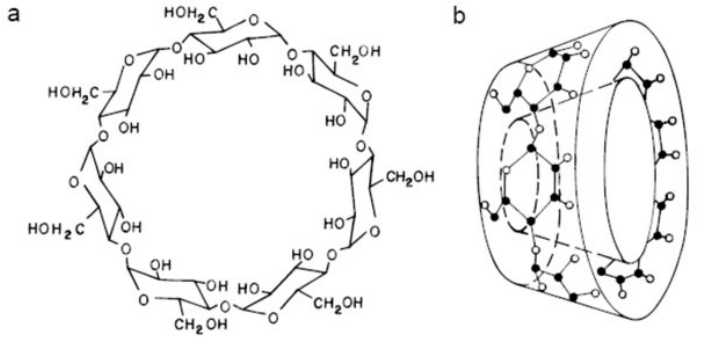

Figure 1. The chemical structure (A) and the toroidal shape (B) of the â-cyclodextrin molecule.

In the case of a 1:1 complex, using the following equation one can determine the equilibrium binding or association constant, *K*, from the slope of the linear portion of the curve.

$$K_{a:b} = \frac{slope}{S_0\ (1 - slope)} \qquad (1)$$

Where S_o is the intrinsic solubility of the drug studied under the conditions.

For many drug/CD complexes, binding constant values are in the range of 100 to 20000M^{-1}. It has been demonstrated that even with tightly bound drugs, a 1:100 dilution reduces the percentage of the complexed drug from 100% to 30%,

Table 1. Abbreviations of CDs Discussed in this Article

Cyclodextrin (CD)	Abbrevation
α- cyclodextrin	α- CD
β- cyclodextrin	β- CD
γ- cyclodextrin	γ- CD
Hydroxyethyl-β-CD	HE -β-CD
Hydroxypropyl-β-CD	HP-β-CD
Sulfobutylether-β-CD	SBE-β-CD
Methyl-β-CD	M-β-CD
Dimethyl-β-CD	DM-β–CD (DIMEB)
Randomly dimethylated -β-CD	RDM-β-CD
Randomly methylated-β-CD	RM-β−CD (RAMEB)
Carboxymethyl - β -CD	CM-β-CD
Carboxymethyl ethyl- β-CD	CME-β-CD
Diethyl-β-CD	DE-β-CD
Tri-O-methyl-β- CD	TRIMEB
Tri-O-ethyl–β-CD	TE-β-CD
Tri-O-butyryl–β-CD	TB-β-CD
Tri-O-valeryl–β-CD	TV-β-CD
Di-O-hexanoyl–β-CD	DH-β-CD
Glucosyl-β-CD	G_1-β-CD
Maltosyl-β-CD	G_2 -β-CD
2-hydroxy-3-trimethyl-ammoniopropyl-β-CD	HTMAPCD

Table 2. Some characteristics of α-, β-, γ-, and δ-CD[1,2]

Type of CD	Cavity Diameter Å	Molecular Weight	Solubility (g/100 mL)
α-CD	4.7–5.3	972	14.5
β-CD	6.0–6.5	1135	1.85
γ-CD	7.5–8.3	1297	23.2
δ-CD	10.3–11.2	1459	8.19

releasing the free drug that can permeate through biological membranes. A 1:100 dilution can be readily attainable on injection or dilution in the stomach and intestinal contents. Although the competing lipophiles present at ophthalmic, transmucosal, and transdermal delivery sites can displace drugs, the products to these delivery sites are more sensitive to strength of binding or association due to minimal dilution possible. The ratio of free-to-complexed drug upon dilution of a sparingly water-soluble drug/CD complex depends on the phase solubility behavior of the system. Dilution will not result in drug precipitation when the relationship between drug solubility and CD concentration is linear, eg, in a 1:1 interaction of CD and drug. However, dilution may cause drug precipitation when the relationship between drug solubility and CD concentration is nonlinear.[9] Hence, effects of dilution must be studied before the clinical use of the products containing drug/CD complexes.

Equilibrium binding of drug and CD to form a 1:1 complex can be represented as

$$Drug\ +\ CD \rightleftharpoons Drug\colon\ CD\ Complex \qquad (2)$$

Since equilibrium binding usually establishes with half-lives of much less than 1 second, the kinetics of dissociation of

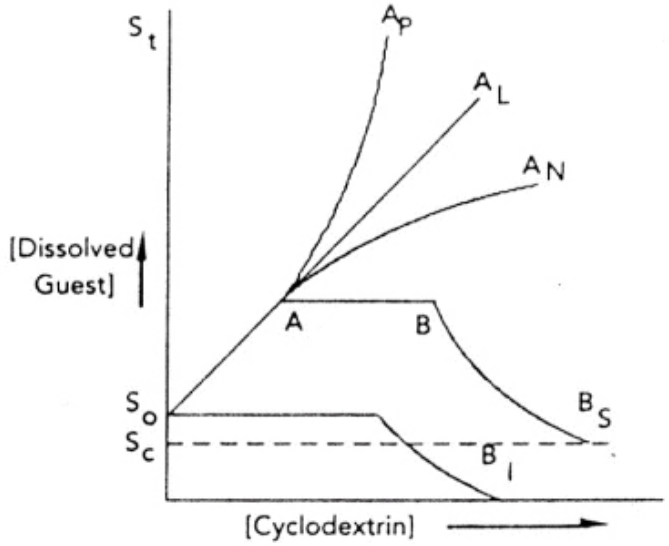

Figure 2. Theoretical phase solubility diagram.[8]

drug/CD complexes are generally expected to be much faster than many physiological processes.[10,11]

CDs and their derivatives have received considerable attention in the pharmaceutical field for the past few years and an increased number of reviews have been dedicated to their industrial and pharmaceutical applications.[1,12-20]

FACTORS INFLUENCING INCLUSION COMPLEX FORMATION

Type of CD can influence the formation as well as the performance of drug/CD complexes (Tables 3, 4, and 5).[21-23] For complexation, the cavity size of CD should be suitable to accommodate a drug molecule of particular size.[25-29] Compared with neutral CDs, complexation can be better when the CD and the drug carry opposite charge but may decrease when they carry the same charge (Figure 3).[30,31] For many acidic drugs forming anions, the cationic (2-hydroxy-3-[trimethylammonio] propyl)-β-CD acted as an excellent solubilizer.[1] In the case of ionisable drugs, the presence of charge may play a significant role in drug/CD complexation and hence a change in the solution pH can vary the complex constant. In general, ionic forms of drugs are weaker complex forming agents than their nonionic forms.[35,36] but in the case of mebendazole, the un-ionized form was less included in HP-β-CD than the cationic form.[37]

Temperature changes can affect drug/CD complexation. In most cases, increasing the temperature decreased the magnitude of the apparent stability constant of the drug/CD complex and the effect was reported to be a result of possible reduction of drug/CD interaction forces, such as van der Waals and hydrophobic forces with rise of temperature.[36,38,39] However, temperature changes may have negligible effect when the drug/CD interaction is predominantly entropy driven (ie, resulting from the liberation of water molecules hydrated around the charges of guest and host molecules through inclusion complexation).[30]

Method of preparation, viz co-grinding, kneading, solid dispersion, solvent evaporation, co-precipitation, spray drying, or freeze drying can affect drug/CD complexation. The effectiveness of a method depends on the nature of the drug and CD.[28,40,41] In many cases, spray drying,[41-43] and freeze drying[21,22,44] were found to be most effective for drug complexation. However, method of preparation showed no influence on the dissolution performance of tolbutamide: β-CD complexes.[53]

When added in small amounts, water-soluble polymers or ion pairing agents enhance CD solubilizing effect by increasing the apparent complex stability constant. The polymers or ion pairing agents due to their direct participation in drug complexation, improve both pharmaceutical and biological properties of drug/CD complexes, independent of drug's physiochemical properties.[20,32,47-51] Certain additives may compete with drug molecules for CD cavities and thus decrease the apparent complex stability constant, eg, additives with positive and negative hydrotropic effect.[54,55] Though water structure forming agents added to CD solutions generally increase the total drug solubility, they showed opposite effects with clotrimazole.[52] Simultaneous complexation and salt formation with hydroxy carboxylic acid (HA) significantly increased the CD solubilizing power for a sparingly water-soluble amine type drug by forming drug/CD/HA multicomponent systems.[56] Co-solvents can improve the solubilizing and stabilizing effects of CDs, eg, use of 10% propylene glycol in development of an oral itraconazole preparation containing 40% of HP-β-CD.[57] Sometimes co-solvents may hinder drug complexation by competitive inclusion, eg, presence of 10% propylene glycol decreased the solubilizing effect of HP-β-CD for itraconazole . On dilution, the presence of propylene glycol favored absorption and precipitation of itraconazole in GI fluids and formulation by providing increased percentage of the free drug. The increased percentage of the free drug in presence of co-solvent was reported to be a result of lesser intrinsic solubility of the drug compared with the dilution concentration line at a given HP-β-CD concentration.[58]

Degree of Substitution

The physicochemical properties of CDs, including their complexation ability, may be greatly affected by the type, number, and position of the substituents on the parent CD molecule. The "degree of substitution" per se does not uniquely characterize a β-CD derivative such as HP-β-CD. When produced under different conditions, the physicochemical properties of HP-β-CD samples with same degree of substitution may not be identical owing to the possible occupancy of hydroxypropyl groups at different positions on the parent CD molecule. Since the purity of CD can have a significant effect on the final quality of the drug product and its marketability, it is necessary to have a proper understanding of the following terms that are used in identification of CD purity.[59]

Degree of substitution (DS): the average number of substituted hydroxyls per glucopyranose unit of CD ring. Since the number of reactive hydroxyls per mole of glucopyranose unit is 3, the maximum numbers of substituents possible for α-, β-, and γ-CDs are 18, 21, and 24, respectively.

Average molar degree of substitution (MS): the average number of moles of the substituting agent, eg, hydroxypropyl, per mole of glucopyranose. It may not necessarily

Table 3. Factors Affecting Inclusion Complexation

Factor	Drug	CDs Studied	Observation	Ref.
Type of CD	Albendazole, Mebendazole, Ricobendazole	β-, HP-β-, M-β-CDs	More effective enhancement of solubility with substituted CDs.	21
	Fenoprofen	α-, β-, γ-, HP-β-CDs	Better stability constant values of pharmaceutical interest with only β-CD and HP-β-CD complexes.	22
	Ketoprofen	M-β-, β-CDs	Better dissolution performance of M-β-CD complex.	23
	Cocaine	α-, β-, γ- CDs	Drug binding with reasonable affinity only to β-CD in aqueous solution.	24
Cavity size	Gliclazide	β-, α- CDs	Cavity size of β-CD was suitable for complexation while that of α-CD was insufficient to include GL rings.	25
	Digitoxin	δ- CD	Enhanced solubility due to partial inclusion of the drug in CD cavity.	26
	Macrocyclic compounds (MCCs)	α-, β-, γ-, δ-CDs	Complexes of smaller MCCs with α- and β-CDs and those of larger MCCs with γ- and δ-CDs were relatively stable.	27
	Ibuproxam	α-, β-, γ- CDs	Effective enhancement of dissolution rate with only with β- and γ-CDs but the cavity of α-CD was less suitable.	28
	Prochloro-methazine	β-, HP-β-, DM-β-CDs	Decreased solubility due to failure of the CD cavities to include phenothiazine ring.	29
pH and ionization state	DY– 9760e	SBE-β-CD	Strong drug/CD interaction in acidic region, at pH 4.	30
	NSC-639829	SBE-β-CD	Increased solubility of the cationic drug at pH 1.	31
	ETH–615	HP- β-, RM-β-, CM-β-, SBE-β-HTMAP-β-CDs	Increased solubility with uncharged RM-β-CD. Complex stability constants were low with the highly polar drug at pH 5 due to its lesser ability to enter the CD cavity but were high with anionic less polar form at pH 10.	32
	Piroxicam	β-CD	Effective complexation at low pH	33
	Levemopamil HCl	HP-β-CD	Enhancement of solubility (mg/mL) was 3-fold with the charged drug (by 7.88 to 25.62 at pH 4) and 525-fold with the neutral form (0.0026 to 1.37 at pH 10.6).	34
	Ziprasdone mesylate	SBE-β-CD	Complexation was more favored with the ion pair over the dissociated ionic form.	35
	Sulindac	β-CD	Complexation was easier with nonionized form.	36
	Mebendazole	HP-β-CD	Un-ionized form was less included than the ionized form.	37
Temperature	DY–9760e	SBE-β-CD	Temperature change showed negligible effect on the stability constant.	30
	Sulindac	β-CD	Increasing the temperature decreased the apparent stability constant.	36
	Phenolphthalein	β-CD	Increasing the temperature decreased association constant for binding.	38
	Danazol	SBE-β-CD	Increasing the temperature decreased the complex stability constant.	39

describe the extent to which the reactive sites are substituted when the substituting agent itself has reactive sites, or when new reactive sites are generated during the substitution reaction. Thus the value of MS can be more than 3 for each glycopyranose unit of substituted CDs, or more than 18, 21, and 24 for α-, β-, and γ-CDs, respectively.

Degree of polymerization (DP): the ratio of MS to DS (MS/DS). If no additional reactive sites are produced during the substitution, MS and DS are equal and the DP becomes 1.

Total Degree of Substitution (TDS): It avoids the confusion between DS and MS and represents the average number of substituted groups (eg, hydroxypropyl) per CD molecule. If the MS and DS are known, one can calculate the molecular weight (Mw) of HP-β-CD from the following equation

$$Mw = 58.08 * (TSD) + 1135 \quad (3)$$

where 1135 and 58.08 are the molecular weights of β-CD and propylene oxide respectively. In the case of β-CD with 7 glycopyranose units, the TDS is 7*MS and hence the equation becomes

$$Mw = 406.56 * (MS) + 1135. \quad (4)$$

Table 4. Effect Preparation Method

Drug	CD	Effect	Ref.
Albendazole, Mebendazole, and Ribendazole	β-, HP-β-, M-β-CDs	Effective inclusion complexation only with freeze-drying but not with coprecipitation	21
Ketoprofen	β -, DM-β-CDs	Better dissolution with co-lyophilized and sealed heated products than kneaded ones	23
Ibuproxam	α-, β-, γ-CDs	With β- and γ-CDs, spray drying and sealed heating resulted in true complexation but kneading was ineffective	28
Nimesulide	β-CD	Drug dissolution was higher with kneading than coevaporation	40
Methoxybutropate	β-CD, HP-β-CD	Solid dispersion gave most effective complexation but kneading was ineffective. With spray drying complete complexation occurred only when the drug/CD molar ratio was 1:4.	41
Vitamin D_2	β-CD	Kneading gave good yield but spray drying gave complete complexation and best dissolution.	42
Oxazepam	DM-β-CD	Dissolution behavior was better with spray-dried systems than the kneaded ones.	43
Sulfamethoxazole	β -, HP-β−CDs	Increased dissolution rate with solid complexes prepared by freeze drying.	44
Glibenclamide	β-CD	Superior dissolution with ground mixture, physical mixture, and kneaded product.	45
Tenoxicam	β-CD	Neutralization method showed better dissolution performance and complex stability than common solvent and kneading methods.	46

HP-β-CDs

Degree of substitution (DS) plays an important role in balancing the CD water solubility and its complexing ability. It was reported that increasing the degree of substitution up to an optimum level improves the CD aqueous solubility, but beyond that, the steric hindrances of the host molecule impair CD complexing (efficiency) capacity. HP-β-CD derivatives with a low degree of substitution showed the best complexing properties with low surface activities. Binding of guests to these CD derivatives was very similar to β-CD at low degrees of substitution, but, as the substitution increased, the steric hindrances weakened the binding and the effect was dependent upon the particular guest. Though increasing the degree of substitution can increase the binding of guests to CDs by increasing the surface area of binding, in many cases the differences in the binding of guests with degree of substitution were small, if detectable.[60]

Table 5. Effect of Various Additives

Effect	Drug	CD	Additive	Ref.
Increased solubilizing effect of CDs (with water-soluble polymers and ionpairing agents)	ETH-615	CM-β-CD, SBE-β-CD, HP-β-CD, RM- β -CD and HTMAPCD	Cationic polymer hexadimethrine bromide (0.25%)	32
	Acetazolamide, Prazepam, and Sulfamethoxazole	HP-β-CD	HPMC, PVP, CMC	47
	Meloxicam	β-CD	PVP (0.1 to 0.25%)	48
	Tropicamide	HP-β-CD	HPMC (0.1%)	49
	Naproxen	β-, M-β-, HP-β-CDs	Sodium CMC, HPMC, PVP K30, PEG 6000	50
	Naphthoquinone	HP-β-CD	PVP K30	51
Increased intrinsic solubility	Clotrimazole	β-CD	Water structure disruptors, urea, and nicotinamide	52
Decreased intrinsic solubility	Clotrimazole	β-CD	Water structure forming agents, sorbitol, and fructose	52
Inhibitory effect on drug/CD association	Phenolphthalein	β-CD	Tetrahydrofuran	38

HPMC, Hydroxyl propyl methyl cellulose; PVP, polyvinyl pyrollidone; CMC, carboxymethyl cellulose; PEG, polyoxyethyleneglycol.

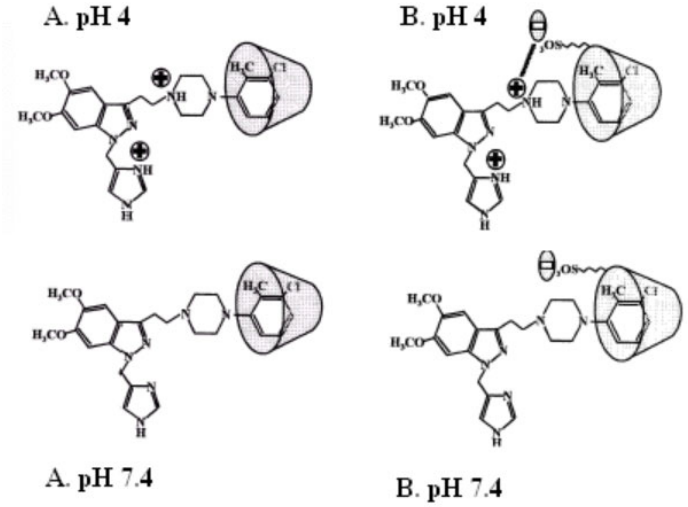

Figure 3. Proposed modes for the inclusion complexes of DY-9760e with HP-β-CD (A) and SBE-β-CD (B) at pH 4.0 (upper) and 7.4 (lower).[30]

Sulfoalkyl Ether-β-CDs

The complexation potential of sulfoalkyl ether-β-CDs for the model drugs, testosterone and progesterone, decreased with reduction in the alkyl chain length from butyl (SBE-β-CD) to propyl (sulfopropyl ether-β-CD, SPE-β-CD), but was assisted by increased DS up to a limited extent. With SPE-β-CD, binding constants of the steroids reached an apparent maximum at a DS of 4, but with SBE-β-CD, the same increased until the constants reached a plateau at a DS of ~7. Complexation is an enthalpy-driven process involving expulsion of enthalpy-rich water molecules. Chemical modification of CDs with charged substituents may lower complexation by providing a hydrogen bonding source for the water molecules that decreases the energy difference between the included water molecules and bulk of the solution. It was found that presence of bulky, highly charged, and hydrated sulfonate groups near the CD cavity entrance inhibits the approach of hydrophobic molecules. On the other hand, increasing the distance between the charged substituents on the CD torus by spacer groups reduced the steric interference and raised the CD binding potential, the effect was also sensitive to the substrate structure.[61]

Some Important Considerations for CD Selection in Drug Formulation

Commercial Availability

Out of various CDs discussed in this article, the natural CDs and hydroxypropyl, hydroxylethyl, sulfobutyl, and various methylated CD derivatives are available in bulk quantities. Other CD derivatives are either synthesized in the laboratory for the study or available on laboratory scale. Some of the companies providing CDs and their derivatives are listed in Table 6. For research and investigational purposes, various CDs, natural and modified, including some sugar branched derivatives like Glucosyl and Maltosyl-β-CDs can be obtained from "cyclodex" under the trade name "trappsol."[66]

Regulatory Status

The global regulatory status of CDs was discussed in the review by Thomson.[14] Regulatory status of natural CDs is given in Table 7. Oral and IV solutions of itraconazole containing 3HP-β -CD (Sporanox, Janssen Pharmaceutica Inc, Titusville, NJ) were approved for marketing in United States and Belgium. 3HP-β-CD containing cisapride suppositories (Prepulsid, Janssen-Cilag) and diclofenac eye-drops (Ciba Vision) were also approved for marketing in Belgium and Switzerland, respectively.[68] In the United States, in August 1999, a type V DMF, containing information and safety data package of captisol (SBE7-β-CD with average degree of substitution of 6.5 from CyDex) was filed. An intramuscular Captisol-Enabled ziprasidone formulation (Geodon, Zeldox) was the first captisol-containing formulation to receive regulatory approval in Sweden (September 2000), also approved in the United States and the rest of Europe. Pfizer has also obtained European and United States approval for a captisol-enabled IV formulation of voriconazole (Vfend).[65]

Patent Status

Being known for several years, natural CDs would not ordinarily be considered as patentable subject matter, however, there are many unexpired patents claiming specific complexes of drugs with natural CDs, particularly with β-CD.

Table 6. Some CD-supplying Companies

Co	CDs	Ref
Cyclolab (Hungary)	α-, β-, γ-CDs, CD derivatives 2HP-β-CD (DS 4.1–5.1) 2HP-γ-CD (DS 4.1–5.6), RAMEB (DS 11.9–13.3), DIMEB, TRIMEB	62
Wacker Chemie	α-, β-, γ-CDs (CAVAMAX) CD derivatives (CAVASOL) HP-β-CD, HE-β-CD, RAMEB, per-Ac-β-CD, β-CD polymer	63
Sigma-Aldrich	α-, β-, γ-CD more than 200 derivatives	64
CyDex	Sufobutylether-β-CD (captisol)	65

Table 7. Summary of Regulatory Status of Parent CDs[67]

Food Approval				Pharmacopeia Monographs		
Product	United States	Europe	Japan	USP/NF	Ph.Eur	JP
α-CD	In preparation	Planned	Yes	No	Yes	Yes
β-CD	GRAS	Food additive	Yes	Yes	Yes	Yes
γ-CD	GRAS	Pending	Yes	No	In Process	No

The patent situation for CD derivatives varies for known derivatives and complexes. HP-β-CD and other hydroxyalkylated β-CD derivatives have been known for nearly 20 years and their basic patents have expired. However, potentially patentable drug complexes of HP-CDs and related derivatives have been developed. In the United States, a patent claiming compositions containing an amorphous drug/CD complex and a method of producing such a complex with description of HP-β-CD as the most promising amorphous CD, was granted to the United States Department of Health and Human Services on 23 February 1988 (United States patent 727 064). In Europe, the dominant patent position with respect to HP-β-CD belongs to Janssen Pharmaceutical Co of Belgium. The Janssen application relates to pharmaceutical compositions containing drugs, which are unstable or sparingly soluble in water, complexed with HP-β-CD or a related β-CD derivative. A European patent was issued to Janssen in 1990 with claims narrowed in the light of earlier work by Pitha.[69] Between 1996 and 1999, Procter and Gamble filed and received at least 100 patents related to CD use in laundry and deodorizing applications.[66] CyDex has exclusive rights to patents protecting the use and composition of matter of captisol. Exclusive rights to use captisol for antifungal and some specific ophthalmic applications have been granted by CyDex to its client companies.[66] Pfizer undertook, in the mid 1990s, to obtain patent protection for another chemically modified β-CD (sulfobutylether) for its own use.[66]

CD Effects on Important Drug Properties in Formulation

Effect on Drug Solubility and Dissolution

CDs have been playing a very important role in formulation of poorly water-soluble drugs by improving apparent drug solubility and/or dissolution through inclusion complexation or solid dispersion, by acting as hydrophilic carriers for drugs with inadequate molecular characteristics for complexation, or as tablet dissolution enhancers for drugs with high dose, with which use of a drug/CD complex is difficult, eg, paracetamol.[70] The magnitude of apparent stability constant for several drug/CD complexes, K in M^{-1}, ranges from 0 to 100 000.[8] CD applications as solubilizing agents are summarized in Table 8.

Out of various commercially available CDs, methylated CDs with a relatively low molar substitution appear to be the most powerful solubilizers. Reduction of drug crystallinity on complexation or solid dispersion with CDs also contributes to the CD increased apparent drug solubility and dissolution rate.[83,87] CDs, as a result of their ability to form in situ inclusion complexes in dissolution medium, can enhance drug dissolution even when there is no complexation in the solid state.[75] SBE-β-CD was shown to be an excellent solubilizer for several drugs and was more effective than β-CD but not as effective as DM-β-CD.[93] CDs can also act as release enhancers, for example β-CD enhanced the release rate of poorly soluble naproxen and

Table 8. Examples of CD-enhanced Solubility and Dissolution

CD	Drug(s)	Ref.
β-CD	Nimesulide, Sulfomethiazole, Lorazepam, Ketoprofen, Griseofulvin, Praziquantel, Chlorthalidone, Etodolac, Piroxicam,, Itraconazole, Ibuprofen	40,44,71-80
α-CD	Praziquantel	75
γ-CD	Praziquantel, Omeprazole, Digoxin	75,81,82
HP-β-CD	Albendazole, DY–9760e, ETH–615, Levemopamil HCl, Sulfomethiazole, Ketoprofen, Griseofulvin, Itraconazole, Carbamazepine Zolpidem, Phenytoin, Rutin	21,30,32,34,44, 72,74,79,83-86
DM-β-CD	Naproxen, Camptothesin	87,88
SBE-β-CD	DY– 9760e, Danazol, Fluasterone, Spiranolactone	30,39,89,90
RM-β-CD	ETH–615, Tacrolimus	32,91
Randomly acetylated amorphous-β-CD (AC-β-CD)	Naproxen	92

ketoprofen from inert acrylic resins and hydrophilic swellable (high-viscosity hydroxy propyl methyl cellulose [HPMC]) tableted matrices. β-CD also enhanced the release of theophylline from HPMC matrix by increasing the apparent solubility and dissolution rate of the drug.[94,95]

Effect on Drug Bioavailability

CDs enhance the bioavailability of insoluble drugs by increasing the drug solubility, dissolution, and/or drug permeability. CDs increase the permeability of insoluble, hydrophobic drugs by making the drug available at the surface of the biological barrier, eg, skin, mucosa, or the eye cornea, from where it partitions into the membrane without disrupting the lipid layers of the barrier. In such cases it is important to use just enough CD to solubilize the drug in the aqueous vehicle since excess may decrease the drug availability (Figure 4).[8,96,97] At low RM-β-CD concentrations, when hydrocortisone was in suspension, increasing the CD concentration increased the drug flux. At higher CD concentrations, when the drug was in solution, increasing the CD concentration decreased the flux.[98] It was found that addition of polymers can further enhance the drug permeability from aqueous CD solutions. Carboxy methyl cellulose (CMC) enhanced triclosan bioavailability from toothpastes containing β-CD by forming a drug/CD/CMC complex with improved substantivity.[99] CDs increased the bioavailability of lipophilic itraconazole from both an oral solution and an intravenous formulation by improving the drug solubility and absorption.[100]

In the case of water-soluble drugs, CDs increase drug permeability by direct action on mucosal membranes and enhance drug absorption and/or bioavailability.[7,8] Solubilization of specific membrane lipids of human erythrocytes through inclusion complexation with CDs and their ability to cause perturbation of membrane integrity, were suggested to contribute to CD-induced promotion of drug absorption and toxicity. It was reported that CDs, because of their ability to remove cholesterol, may increase membrane fluidity and induce membrane invagination through a loss of bending resistance and cause cell lysis. On the other hand, removal of phospholipids, especially phosphatidylcholine and sphingomyelin from the outer half of the membrane bilayer by CDs causes bilayer imbalance; the removal may also contribute in part to the formation of stomatocytes through an inward bending of membranes. CD induced lysis of artificial membranes composed of lecithin and cholesterol by a similar solubilization process. Detergents first incorporate themselves into membranes, then extract the membrane components into micelles and cause membrane solubilization/lysis. However, unlike detergents, CDs were reported to solubilize membrane components without entering into the membrane, and hence the perturbing effects of CDs can be mild and reversible. In the presence of CDs, the new lipid-containing compartment in the aqueous phase with extracted components from the erythrocyte surface equilibrated freely with the cell surface by a reversible process. Compared with other absorption-promoting agents and preservatives commonly used in nasal formulations, CDs exerted a rather mild and reversible effect on the ciliary beat frequency of both chicken embryo trachea and human nasal adenoid tissue in vitro in a concentration-dependent manner.[16] DM-β-CD caused enhancement of enoxaparin nasal absorption by solubilizing membrane components and opening tight junctions but the effect was reversible after 6 hours.[101] Watanabe et al[102] reported that rectal membrane recovers its barrier function probably ~24 hours after the administration of DM-β-CD (at least 30 mg).[7] Even at high doses, the effects of HP-β-CD on kidneys were reversible and similar to those of osmotic agents currently used in parenteral formulations.[8]

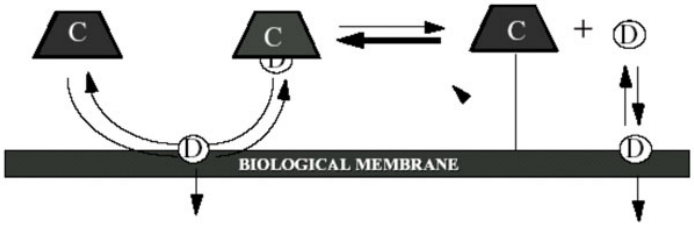

Figure 4. Mode of penetration enhancement by CDs.[96]

Labile drug stabilization by CDs[82,86] and their ability to ameliorate drug irritation, and thus improve drug contact time at the absorption site in nasal, ocular, rectal, and transdermal delivery,[8] are some other important factors that contribute to the CD-improved bioavailability. α-CD improved the rectal bioavailability of morphine by inhibiting the drug's upward movement from areas impacted by first pass metabolism.[7]

Effect on Drug Safety

CDs have been used to ameliorate the irritation caused by drugs.[9] The increased drug efficacy and potency (ie, reduction of the dose required for optimum therapeutic activity), caused by CD-increased drug solubility, may reduce drug toxicity by making the drug effective at lower doses. β-CD enhanced the antiviral activity of ganciclovir on human cytomegalovirus clinical strains and the resultant increase in the drug potency reduced the drug toxicity.[103] The toxicities associated with crystallization of poorly water-soluble drugs in parenteral formulations can often be reduced by formation of soluble drug:CD complexes. Formulation of phenytoin with HP2-β-CD showed considerably reduced tissue irritation compared with a commercial

injection of the drug in a BALB/c mouse model.[104] Further CD entrapment of drugs at the molecular level prevents their direct contact with biological membranes and thus reduces their side effects (by decreasing drug entry into the cells of nontargeted tissues) and local irritation with no drastic loss of therapeutic benefits.[18] Inclusion complexation with HP-β-CD reduced the side effects of 2–ethyl hexyl–p–dimethyl aminobenzoate (a UV filter) by limiting the interaction of the UV filter with skin.[105] In a study with patients, piroxicam/β-CD inclusion complex showed better tolerance with lower incidence and severity of gastrointestinal side effects compared with the free drug.[106] HP-β-CD alleviated the intrinsic irritancy effect observed on IV administration of CKD-732 hemioxalate against blood vessels.[107] SBE7-β-CD inhibited DY-9760e-induced cytotoxicity toward human umbilical vein endothelial cells and significantly suppressed the drug-induced vascular damage in rabbits.[108] Inclusion complexation with CDs also reduces ocular drug irritation by limiting the free drug concentration on the precorneal area to a nonirritating level.[109]

Effect on Drug Stability

CDs can improve the stability of several labile drugs against dehydration, hydrolysis, oxidation, and photodecomposition and thus increase the shelf life of drugs.[1] Table 9 summarizes CD effects on drug stability. It was reported that CD-induced enhancement of drug stability may be a result of inhibition of drug interaction with vehicles and/or inhibition of drug bioconversion at the absorption site.[7] By providing a molecular shield, CD complexation encapsulates labile drug molecules at the molecular level and thus insulates them against various degradation processes. SBE-β-CD showed greater stability enhancement of many chemically unstable drugs than other CDs.[93]

The stabilizing effect of CDs depends on the nature and effect of the included functional group on the drug stability and the nature of the vehicle. Both the catalyzing effect of the nitro group as well as the stabilizing effect of the halogen and cyanogen groups on photodegradation of 1,4 dihydropyrimidine derivatives were reduced by complexation with CDs.[118] HP-β-CD significantly reduced the photodegradation of 2–ethyl hexyl p–dimethyl aminobenzoate in solution than in emulsion vehicle.[105] CDs improved the photostability of trimeprazine (when the solution pH is reduced)[119] and promethazine.[29] CDs also enhanced the solid state stability and shelf life of drugs.[110-112] CDs were reported to enhance the physical stability of viral vectors for gene therapy, and the formulations containing sucrose and CDs were stable for 2 years when stored at 20°C.[120]

Since the hydrolysis of drugs encapsulated in CDs is slower than that of free drugs,[113] the stability of the drug/CD complex, ie, the magnitude of the complex stability constant, plays a significant role in determining the extent of protection.[30,88,114,121] Very low concentrations of HP-β-CD (1% or lower), due to formation of a more physically unstable complex, did not protect taxol as effectively as

Table 9. CD Effect on Drug Stability

Effect	Drug	CD	Ref.
↑Photostability	Promethazine	HP-β-CD, DM-β-CD	32
	DY–9760e	SBE-β-CD	30
	2–ethyl hexyl p–dimethyl aminobenzoate	HP-β-CD	105
↑ Shelf life with unaffected dissolution rates for 4 years	Glibenclamide	β-CD	110
↑ Thermal stability in solid state	Diclofenac sodium	β-CD	111
↑Stability against intramolecular cyclization in solid state	Quinaril	β-CD, HP-β-CD	112
↑Stability to acid hydrolysis and photodecomposition	Doxorubicin	HP-β-CD, HP-γ-CD	113
↑Stability against hydrolysis	acyl ester prodrugs of Ganciclovir	HP-β-CD	72
	Digoxin	γ-CD	82
	Rutin	HP-β-CD	86
	Camptothesin	RDM-β-CD	88
	Melphalan and Carmustine	SBE -β-CD, HP-β -CD	114
	Paclitaxel	γ-CD, HP-γ-CD, HP-β-CD	115
↑ Deacetylation or degradation	Spiranolactone	SBE-α-CD, SBE-β-CD, HP-β-CD, γ-CD,β-CD	116
↑Photoreactivity	Flutamide	β-CD	117

↑, increased effect

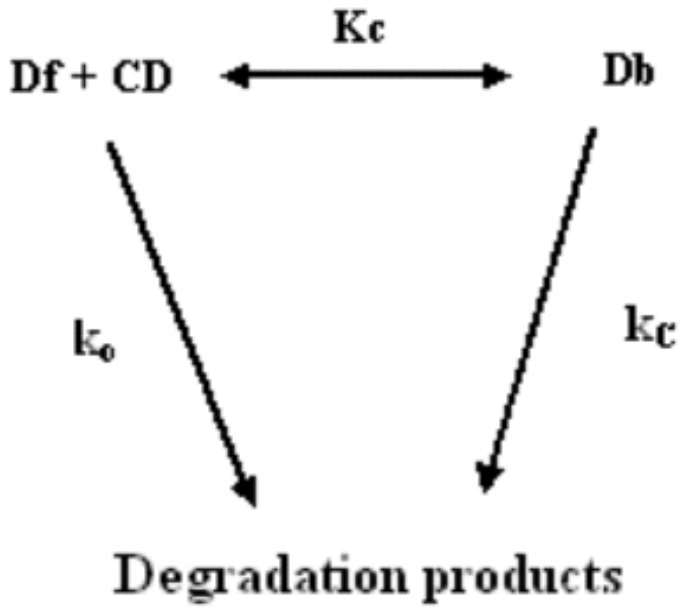

Figure 5. A simple model representing the effect of complex stability constant on drug degradation.[115]

higher CD concentrations. The effect of complexation on drug stability can be represented by the following equation (Figure 5):

$$\frac{1}{k_0 - k_{obs}} = \frac{1}{K_c\ (k_0 - k_c)\ [CD]} + \frac{1}{(k_0 - k_c)}\ , \qquad (5)$$

where k_o is the degradation rate constant of free drug, k_{obs} is the observed degradation rate constant in the presence of CD, k_c is the degradation rate constant of the drug within CD, K_c is the stability constant for the complex, and $[CD]$ is the concentration of CD.[115]

Under specific conditions, CD complexation may accelerate drug degradation depending on the type of the CD. CDs catalyzed deacetylation and degradation of spironolactone, the effect was qualitatively correlated with the ionization state of hydroxyl groups on CDs that were lower in SBE–CDs.[116] Structural changes in drug molecules on CD complexation can also accelerate drug degradation.[117] β-CD did not improve the photostability of oflaxacin as there was only a partial inclusion of the methyl piperazinyl moiety in the CD.[122]

CD Applications in Drug Delivery

Oral Drug Delivery

Applications of CDs in oral drug delivery include improvement of drug bioavailability due to increased drug solubility, improvement of rate and extent of dissolution, and/or stability of the drug at the absorption site, eg, the gastrointestinal tract (GIT) or in formulation, reduction of drug-induced irritation, and taste masking (Table 10). CD complexation was found to decrease local drug irritation and also modify the time of drug release during GI transit.[8,17]An itraconazole oral preparation containing 40% (wt/vol) of HP-β-CD (with reduced drug irritation) has been commercialized in the United States and Europe.[30]

CDs enhance the mucosal drug permeability mainly by increasing the free drug availability at the absorptive surface.[127,128] CD complexation can provide better and uniform absorption of low-soluble drugs with poor and erratic absorption[91] and also enhance the drug activity on oral administration[123,125,126] CD complexation increased the anthelmentic activity of albendazole and provided a high plasma concentration of the active metabolite.[133] CD complexation increased the absorption of poorly water-soluble

Table 10. Applications of CDs in Oral Delivery

Effect	Drug	CD	Ref.
↑ Bioavailability by	β-CD	Ketoprofen, Griseofulvin, Terfenadine	72,73,123
↑Solubility and dissolution rate	HP-β-CD	Albendazole, Ketoprofen, Phenytoin, Gliclazide	21,72,85,124
	SBE7–β-CD	Spiranolactone	90
	DM-β-CD	Tacrolimus	91
	M-β-CD	Albendazole	21
	ME-β-CD	Phenytoin	85
↑ Intensity or duration of therapeutic activity	β-CD	Terfenadine, Tolbutamide	123,125
	HP- β-CD	Tolbutamide, Amylobarbitone	125,126
↑ Permeability	HP-β-CD	Flutamide	127
↑Gastrointestinal stability	γ-CD	Digoxin	82
	HP-β-CD	Rutin	86
↑Sublingual bioavailability	HP-β-CD	Clomipramine, Testosterone	128-130
↑Buccal bioavailability	SBE7-β-CD, HP-β-CD	Danazole	131,132

↑, increased effect

drugs, delivered via buccal or sublingual mucosa.[129-132] Complexation of miconazole, econazole, and clotrimazole with HP-β-CD and genuine CDs increased the toxicity of these drugs on a human buccal cell culture model (TR_{146}) by causing drug supersaturation.[134]

Captisol or (SBE)7m-beta-CD, a solubilizer with osmotic property, was used to design osmotic pump tablets of chlorpromazine and prednisolone.[135,136] Complexation can also mask the undesirable taste of drugs. Complexation with CDs suppressed the bitter taste of oxyphenonium bromide. With the assumption that only the free drug molecule exhibits bitter taste, the extent of the suppression was reported to be dependent on the availability of free drug, regardless of the kind and concentration of CD.[137]

The relative safety, efficacy in terms of complexation, cost, and acceptance in pharmacopeias are some important factors to be considered in selecting a CD for drug complexation. HP-β-CDs were shown to have a better oral safety profile than β-CD and other parent CDs, but only limited data are available on the oral safety of the methylated CDs. However, for oral administration all CDs can be considered practically nontoxic due to lack of CD absorption through GIT and, hence, the relative safety profile of CDs is a concern of drug doses used in drug/CD complexes and the LD50 of CD.[8] β-CD is the most cost-effective compound of all CDs, whereas HP-β- and SBE-β-CDs are more expensive. Monograph of β-CD is already incorporated in various pharmacopeias and national formularies (NF).[1] Hence, β-CD can be considered optimum for oral use when it is effective for drug complexation and modified CDs like HP-, SBE-β-, and DM-β-CDs may be used when they are more effective and when their peculiar property is required in formulation, eg, SBE-β-CD, owing to its osmotic property, was used in the preparation of osmotic pump tablets.[135,136]

Parenteral Drug Delivery

CD derivatives such as amorphous HP-β- and SBE-β-CDs have been widely investigated for parenteral use on account of their high aqueous solubility and minimal toxicity. HP-β-CD with much higher aqueous solubility allows parenteral administration of various drugs with no significant toxicity problems and hence is more often used in parenteral formulations. An itraconazole parenteral injection containing HP-β-CD (40% wt/vol) has been commercialized in the United States and Europe.[138] The solubilizing potentials of both SBE-β- and HP-β-CDs for the drugs melphalan and carmustine were qualitatively similar but the intrinsic reactivities were significantly less with SBE-β-CD.[114] Applications of CDs in parenteral delivery are solubilization of drugs, reduction of drug irritation at the site of administration, and stabilization of drugs unstable in the aqueous environment. Singla et al discussed the use of CDs to enhance the solubility and stability of paclitaxel in formulations and mentioned that the approach needs further research to overcome the serious limitations of CD-based formulations.[115] An IM dosage form of ziprasidone mesylate with targeted concentration of of 20 to 40 mg/mL was developed by inclusion complexation of the drug with SBE-β-CD.[35] Formation of a stable, water-soluble dexamethsone complex with sugar branched β-CDs suggested the potential of these CDs as excellent carriers in steroidal injectable formulations.[139] Aqueous phenytoin parenteral formulations containing HP-β-CD exhibited reduced drug tissue irritation and precipitating tendency because their pH values were significantly closer to the physiological value (7.4).[140] SBE-β-CD was found to be useful in the preparation of parenteral solutions of poorly water-soluble drugs with positive charge, such as DY–9760e.[30]

Effects of CDs on drug pharmacokinetics were discussed by Rajewski and Stella.[9] Miconazole formulations solubilized by HP-β- and SBE7-β-CDs showed no significant effect on the drug pharmacokinetics in sheep compared with the drug micellar solution solubilized by cremophor EL (polyoxyl-35 caster oil). The synergistic effect of CDs with acids like lactic acid was used to solubilize miconazole for safe parenteral delivery.[141] In some cases complexation may affect drug pharmacokinetics, eg, complexation with sugar branched β-CDs altered the disposition of dexamethsone in mice. The binding values of diflunisal in plasma solutions containing HP-β-CD were found to be lower than the theoretical because of competitive displacement of the drug from the CD by plasma cholesterol.[142] In rabbits, coadministration of M-β-CD with doxorubicin resulted in reduced distribution half-life and modified renal and hepatic distribution profiles of the drug, but the main pharmacokinetic parameters of the CD were unaltered.[143]

A water-soluble CD derivative with low hemolytic activity was synthesized by substituting acetyl groups for hydroxyl groups of DM-β-CD. The inclusion ability of the obtained heptakis (2,6 di-O-methyl-3-O-acetyl)-β-CD (DMA-β-CD) was the same as that of DM-β-CD, but the new derivative showed less irritation in rabbits with no hemolysis even at 0.1 M concentration.[144]

Ocular Delivery

Applications of CDs in aqueous eye drop preparations include solubilization and chemical stabilization of drugs, reduction of ocular drug irritation, and enhancement of ocular drug permeability. Vehicles used in ophthalmic preparations should be nonirritating to the ocular surface to prevent fast washout of the instilled drug by reflex tearing and blinking. Hydrophilic CDs, especially 2HP-β- and SBE-β-CDs, are shown to be nontoxic to the eye and are well

tolerated in aqueous eye drop formulations, eg, increased ocular absorption and shelf life of pilocarpine in eye drop solutions by SBE-β-CD and decreased ocular irritation of a lipophilic pilocarpine prodrug by SBE-β- and HP-β-CDs.[1] Reviews on the effects of CDs and aqueous CD-containing formulations on the acular drug bioavailability[96,109] have already discussed the effect of polymers on CD-induced drug solubilization and permeability enhancement (Table 11). The cytotoxicity order of CDs on the human corneal cell line was found to be α-CD > DM-β-CD > SBE-β-CD = HP-β-CD > γ-CD. It was suggested that ocular toxicity with SBE-β-CD (100 mM) after 1 hour of its exposure could be possibly a result of its high osmotic pressure. However, the toxicity with negatively charged SBE-β-CD was greater than that with the control, a neutral hypertonic mannitol solution.[145]

CDs enhance drug permeability by making the drug available at the ocular surface. HP-β-CD enhanced the ocular permeability of dexamethasone acetate and also inhibited the conversion of acetate salt to less permeable dexamethasone.[11] Since only the free drug can permeate biological membranes, ophthalmic delivery of drugs can be limited by the dissociation of drug/CD complexes in the precorneal area due to the limited dilution in this area. The dissociation of drug/CD complexes depends more on the binding of drugs to precorneal proteins, absorption by corneal tissue, and displacement of drugs from CD complexes by precorneal fluid components.[17] The ability of CDs to decrease membrane lipophilicity by interacting with the lipophilic compounds of epithelium was indicated by the reduction in the bioavailability of highly lipophilic pilocarpine prodrugs on addition of CDs.[146] Complexation with HP-β-CD significantly decreased hydrocortisone (HC) transport from the aqueous to the organic phase, the effect was dependent on the drug partition coefficient and the relative magnitude of the stability constant of the inclusion complex. The polymer interactions with the drug, HC, and its complex in each system were reported to be responsible for the observed solubility and different release behaviors of HC and its inclusion complex from high molecular weight cellulose and polyvinyl alcohol (PVA) polymeric films for ocular delivery.[147] Formulation with HP-β-CD, with and without HPMC, improved the bioavailability and maximal mydriatic response of tropicamide by enhancing the drug's ocular permeability, but reduced the ocular drug irritation probably by maintaining the pH in physiologic range.[50] HP-β-CD also enhanced the permeability and miotic response of pilocarpine nitrate without damaging the rabbit corneal tissue.[148]

Table 11. Some of the Examples of Usage of CDs in Aqueous Eye Drop Solutions[96]

Drug	CD
Acetazolamide	HP-β-CD, α-CD, HP-β-CD
Arachidonylethanolamide	HP-β-CD
Cyclosporine	α-CD
Dexamethasone	HP-β-CD
Dexamethasone acetate	HP-β-CD
Diclofenac	HP-β-CD, M-β-CD
Ethoxyzolamide	
Pilocarpine	HP-β-CD, α-CD, β-CD, HP-β-CD, SBE-β-CD
Pilocarpine prodrugs	HP-β-CD

Nasal Drug Delivery

CDs are effective excipients in nasal drug delivery. CDs improve nasal drug absorption either by increasing aqueous drug solubility and/or by enhancing nasal drug permeability. However, large interspecies differences were found in CD-enhanced nasal drug absorption. The safety and nontoxicity of CDs in nasal drug formulations have been demonstrated by the clinical data with CDs showing no adverse effects. Merkus et al[149] demonstrated that CDs can be safely used to improve nasal bioavailability of drugs, especially peptides. DM-β-CD improved the nasal bioavailability of estradiol in rats and rabbits. Nasal absorption of melatonin, a drug with high first pass metabolism was rapid and efficient when administered with β-CD and the peak levels were ~50 times higher than those observed after oral administration. Midazolam was absorbed rapidly when administered as an aqueous nasal spray (pH 4.3) containing SBE-β-CD (14% wt/vol), HPMC (0.1% wt/vol), and other additives.[150]

CDs can also be used to reduce the nasal toxicity of other enhancers without affecting their absorption-enhancing property. β-CD or DM-β-CD reduced the serious nasal toxicity of sodium deoxycholate by inhibiting the leucine aminopeptidase activity in nasal mucosa without affecting the absorption-enhancing property of the bile salt for insulin.[151] Salbutamol release from the powder inhaler formulations containing γ-CD and DM-β-CD was faster than that from control with lactose; at the amount studied γ-CD was safer than DM-β-CD.[152] Midazolam nasal formulation in aqueous SBE-β-CD solution approached an IV form of the drug in speed of absorption, serum concentration, and sedation effect, with no serious side effects.[153]

Rectal Drug Delivery

Applications of CDs in rectal delivery include enhancing drug absorption from a suppository base either by enhancing drug release from the base or by increasing drug mucosal permeability, increasing drug stability in the base or at the absorption site, providing sustained drug release, and alleviating drug-induced irritation.[7,11]

Drug release from the suppository base is important in rectal absorption because of the high viscosity of rectal fluids. The effect of CDs on rectal drug absorption can be influenced by partition coefficient of the drug and its CD complex, magnitude of the complex stability constant, and nature of the suppository base (oleaginous or hydrophilic). Hydrophilic CDs (especially methylated and hydroxylpropyl CDs) enhance the absorption of lipophilic drugs by improving the drug release from oleaginous vehicles and/or by increasing the drug dissolution rate in rectal fluids. Formation of hydrophilic CD complexes was found to inhibit the reverse diffusion of drugs into oleaginous vehicles by reducing the drug/vehicle interaction. Rectal absorptions of flurbiprofen and biphenylacetic acid were improved by DM-β-CD and HP-β-CD, respectively. CDs may not affect drug release if the drug/CD complex dissociates in the vehicle itself. For example, although the dissolution rate of ethyl 4-biphenylylacetate (EBA) was highest from the DM-β-CD complex, only the HP-β-CD complex enhanced EBA release from the oleaginous suppository base because of lower dissociation of the HP-β-CD complex in the vehicle. The CD complex, once released from the base, mostly releases the free drug for absorption. The competing sites for the free drug released at the absorption site are CD cavity, suppository base, and the rectal mucosa. The extent of drug diffusion into these sites depends on drug's partition coefficient, magnitude of the stability constant of the drug/CD complex, and the relative lipophilicity of the competing sites. In the case of lipophilic drugs with a high partition coefficient, there might be some back diffusion of the released free drug into the lipophilic base. Since a part of drug may get absorbed as the CD complex, the partition coefficient of the complex also becomes important, eg, rectal absorption of a part of EBA as HP-β-CD complex. In the presence of hydroxyl propyl methyl cellulose (HPMC), β-CD markedly reduced the bioavailability of acetaminophen from both aqueous solution and hydrogels by forming a complex with a lower partition coefficient or higher hydrophilicity.[7]

CDs enhance the rectal absorption of inabsorbable, hydrophilic drugs such as antibiotics, peptides, and proteins by their direct action on the rectal epithelial cells.[7] α-CD enhanced the rectal absorption of morphine and human chorionic gonadotropin by increasing their mucosal permeability and reducing their degradation.[154,155]

CDs enhance rectal drug stability either by inhibiting the drug/vehicle interaction (by making the drug insoluble in oleaginous base) or by inhibiting the drug bioconversion in the rectum. α-CD improved the rectal bioavailability of morphine by inhibiting the upward movement of the drug from areas impacted by first pass metabolism.[7]

Controlled Drug Delivery

CDs, due to their ability either to complex drugs or to act as functional carrier materials in pharmaceutical formulations, can serve as potential candidates for efficient and precise delivery of required amounts of drugs to targeted site for a necessary period of time. β-CD derivatives are classified as hydrophilic, hydrophobic, and ionizable derivatives. The hydrophilic derivatives improve the aqueous solubility and dissolution rate of poorly soluble drugs, while the hydrophobic derivatives retard the dissolution rate of water-soluble drugs from vehicles. Hence hydrophilic and hydrophobic CD derivatives are used in immediate and prolonged release type formulations, respectively. The ionizable CD derivatives, on the other hand, improve inclusion capacity, modify drug dissolution rate, and alleviate drug irritation, eg, use of CME-β-CD to obtain delayed release–type formulations. Highly hydrophilic derivatives, such as 2HP-β-, G2-β-, and SBE-β-CDs were used in immediate release formulations that dissolve readily in the GIT and enhance the oral bioavailability of poorly soluble drugs. CDs, both natural and chemically modified, are used in the design of immediate, delayed release, and targeted drug delivery systems (Table 12).

The pH-dependent solubility of CME-β-CD (ie, limited solubility under the acidic conditions of stomach with the complex solubility increasing with pH), which provides selective dissolution of drug/CD complex, makes it useful in the design of enteric formulations. When molsidomine

Table 12. Modification of the Drug Release Site and/or Time Profile by CDs[156]

Release Pattern	Aim	Use of CD
Immediate realease	Enhanced dissolution and absorption of poorly water-soluble drugs	HP-β-, DM-β-, SB-β-, and branched-β-CDs
Prolonged release	Sustained release of water-soluble drugs	Ethylated β-CDs, acylated β-CDs
Modified release	More balanced oral bioavailability with prolonged therapeutic effects	Simultaneous use of different CDs and/or other excipients
Delayed, pH-dependent release	(Enteric) Acid protection of drugs	CME-β-CD
Site-specific release	Colon-targeting	Drug/CD conjugate

Table 13. Applications of Various CD Derivatives in the Formulation of Modified Release Preparations[156,157]

Derivative	Drug	Summary
Diethyl-β-CD	Diltiazem	Sustained release for oral use
	Buserelin acetate	Sustained release for subcutaneous use
	Nitroglycerine	Sustained release for percutaneous use
	Isosorbide dinitrate	Sustained release
	Tiaprofenic acid	Delayed release
Triacetyl-β-CD	Flufenamic acid	Prolonged release for oral use
Peracylated-β-CD (TB-β-CD)	Molsidomine	Sustained release for oral use
	Salbutamol	Prolonged release for oral use
	Captopril	Sustained release
Al-β-CD-sulfate	Recombinant human basic fibroblast growth factor	Sustained release for oral use; enhanced stability
O-carboxymethyl-O-β-CD	Molsidomine Diltiazem HCl	Delayed release

tablets containing CME-β-CD were studied in gastric acidity–controlled dogs, the absorption of the drug was significantly retarded under high gastric acidity compared with low gastric acidity conditions.[156,157]

Hydrophobic CDs, such as alkylated and acylated derivatives, are useful as slow-release carriers in prolonged release formulations of water-soluble drugs. Applications of various CD derivatives in formulation of modified-release preparations are summarized in Table 13. Among the alkylated CDs, DE-β- and TE- β-CDs were the first used slow release carriers and their hydrophobic complexes with diltiazem[158] and isosorbide dinitrate[159] provided slow drug release on oral administration in dogs. Peracylated CDs, particularly those with medium alkyl chain lengths (C_4–C_6) are useful as hydrophobic carriers (Table 14) and have broad applicability in various routes of administration. Combination of short-chain and long-chain peracylated β-CDs in an appropriate molar ratio was suggested to be useful to provide an effectively controlled release rate of water-soluble drugs, eg, markedly retarded release rate of molsidomine on complexation with peracylated β-CDs.[160] TB-β-CD was suggested to be a useful carrier for oral administration of water-soluble drugs, especially those that are metabolized in the GIT. In beagle dogs, oral administration molsidomine as TB-β-CD complexes resulted in suppressed peak plasma level of the drug while maintaining sufficient drug levels for long periods. The increased hydrophobicity and mucoadhesive properties on complexation were reported to be responsible for the observed sustained effect with TB-β-CD. Nanospheres of amphiphilic CDs such as DH-β-CD were also reported to have bioadhesive effects on gastrointestinal mucosa.[156]

CDs can also be used along with other carrier materials to optimize drug release rate. Improved nifedipine bioavailability with reduced first pass metabolism was observed from a modified oral dosage form containing a fast release

Table 14. Some Physicochemical Properties of Acylated β-CDs[156]

Compound	R	Melting Point (8C)	[M]* D	Solubility† (mg/dL)
β-CD	H	280	+11850§	119.0
TA-; peracetyl– β-CD	$COCH_3$	201–202	+12522	823.0
TP-; perpropionyl– β-CD	COC_2H_5	168–169	+12450	423.5
TB-; perbutyryl– β-CD	COC_3H_7	126–127	+12607	219.8
TV-; pervaleryl– β-CD	COC_4H_9	54–56	+12640	283.0
TH-; perhexanoyl– β-CD	COC_5H_{11}	‡	+12620	3.7
TO-; peroctanoyl– β-CD	COC_7H_{15}	‡	+12763	‖
TD-; perdecanoyl– β-CD	COC_9H_{19}	‡	+12668	‖
TL-; perlauroyl– β-CD	$COC_{11}H_{23}$	‡	+12829	‖

*In chloroform at 25°C

†In 80% (v/v) ethanol–water at 25°C

‡Oily substance

§In water

‖Could not be determined because of the low solubility

portion of the drug with HP–β-CD and HCO-60, a nonionic surfactant (ie, amorphous drug form obtained by spray drying with the CD and surfactant) and a slow release portion with hydroxy propyl celluloses (HPCs) of different viscosity grades.[161] Quaglia et al[162] reported that CDs can be used to modulate drug delivery from swellable systems, eg, β-CD significantly affected the delivery of nicardipine from swellable crosslinked polyethylene glycol matrix by decreasing effective drug diffusivity through the matrix. SBE-β-CD has been used in the design of sustained release matrix tablets of poorly soluble drugs. Directly compressed tablets containing prednisolone with SBE-β-CD and polymer physical mixture showed more enhanced drug release than the control (with lactose instead of the CD) due to formation of an in situ drug:CD complex in the gel layer.[163] HP-β-CD, because of its dissolution enhancing effect, was found to be more effective than β-CD in the development of controlled release nicardipine formulations.[164]

Combination of drug complexes with hydrophilic and hydrophobic CDs in appropriate ratios can be a promising drug delivery system for prolonged therapeutic effect and balanced bioavailability. In rabbits, a sustained release nicardipine formulation, developed by mixing the drug complexes with HP-β-CD (fast release fraction) and with hydrophobic TA-β-CD (sustained releasing portion) in appropriate ratios, showed markedly retarded drug release with prolonged maintenance of plasma levels.[165] A sustained release 2-layered nifedipine tablet formulation was developed by using the drug complexes with β- and HP-β-CDs.[166] Use of CDs with a hydroxyapatite matrix was indicated to control the release of chemotherapeutic agents containing toxic metals, such as Rhodium II citrate and butyrate, and to provide localized antitumor chemotherapy with minimal side effects.[167]

Colon-Specific Drug Delivery

CDs are barely hydrolyzed and only slightly absorbed in the stomach and small intestine but are absorbed in the large intestine after fermentation into small saccharides by colonic microbial flora. The peculiar hydrolyzing property of CDs makes them useful for colon drug targeting. Biphenyl acetic acid (BPAA) prodrugs for colon-specific delivery were developed by conjugation of the drug onto one of the primary hydroxyl groups of α-, β-, and γ-CDs through an ester or amide linkage. In the case of ester prodrugs, the maltose and triose conjugates released the free drug after initial hydrolysis of the susceptibile ester linkage, but in the case of amide prodrugs, the conjugates remained as such providing delayed release due to the resistance of the amide bond to hydrolysis. The CD-based prodrug approach was used for colon-specific and delayed drug delivery, eg, when tested in rats with carageenan-induced inflammation, the absorption of BPAA from γ-CD prodrugs was found to be from cecum and colon in contrast to that from the highly soluble β-CD complex, which was mainly from the small intestine.[168] When studied in rats, it was found that both sugar-degrading and ester-hydrolyzing enzymes are necessary for colon-specific release of butyric acid from its β-CD ester conjugates.[169] Drug conjugation with α-CD resulted in a delayed release–type prodrug formulation for colon-specific delivery that alleviates the side effects of drugs while maintaining their therapeutic effect, eg, site-specific degradation of prednisolone/α-CD conjugates in the large intestine alleviated the side effects of the drug while maintaining its anti-inflammatory action.[170]

Complexation of triamcinolone acetonide (TA) with β-CD improved the sphericity of microcrystalline cellulose (MCC)–β-CD-TA spherical pellets (5:90:5) prepared by extrusion and spheronization for colon targeting. TA complexation with the CD also facilitated the application of coating resistant to gastric and small intestinal media and maintained the pellet integrity in dissolution medium with no premature bursting of coatings on granule swelling.[171]

Peptide and Protein Delivery

Various problems associated in practical use of therapeutic peptides and proteins are their chemical and enzymatic instability, poor absorption through biological membranes, rapid plasma clearance, peculiar dose response curves, and immunogenicity. CDs, because of their bioadaptability in pharmaceutical use and ability to interact with cellular membranes, can act as potential carriers for the delivery of proteins, peptides, and oligonucleotide drugs.[172]

The existence of efflux pumps may serve as an additional barrier for nonspecific uptake of peptides and thus can cause low peptide bioavailability. P-glycoprotein (P-gp) is an efflux transporter present in the apical region of epithelial cells in the brain, kidney, liver, and GI tract. P-gp opposes the transcellular drug movement in the epithelial cells and many peptide drugs, especially hydrophobic peptides like cyclosporin A,[173] D, N-acetyl-leucyl-leucylnorleucinal,[174] valinomycin,[175] gramicidin,[176] and ditekiren[177] are reported to be substrates for this efflux transporter. Therapeutic use of peptides across the blood brain barrier (BBB) is greatly hindered by their very low penetration and it was reported that P-gp substrates, such as synthetic hydrophobic peptides, can stimulate the transport of drugs across the BBB. An apically polarized verapamil sensitive efflux system for small hydrophobic peptides has been found in the BBB of rats. It was also reported that P-gp–mediated transport of peptides might play an important role in greatly reducing their delivery to the central nervous system in vivo.[178] Hence, whenever unexplainable poor

peptide absorption is seen, the role of efflux pumps should be examined.[179]

It was found that CDs can inhibit or impair the efflux function of P-gp and multidrug resistance associated proteins (MRP2). Out of various β-CD derivatives studied, DM-β-CD was found to be most effective and significantly impaired the efflux function of P-gp and MRP2 in Caco cell monolayers (Caco2, Caco-2R) without changing the cell viability and membrane integrity. The inclusion ability of DM-β-CD, causing the release of the transporters (P-gp, MRP2) from the apical membranes of monolayers, was reported to be the possible reason for the observed impaired efflux function of the transporters in the presence of the CD. Not only the extraction of cholesterol but also that of phospholipids from the monolayers were found to be required for the CD-induced inhibitory effect on the efflux function.[180] In addition to the solubilizing effect of DM-β-CD, its ability to inhibit P-gp efflux of tacrolimus from intestinal epithelial cells contributed to the CD-induced enhancement of the drug's oral bioavailability. Pretreatment of the apical membranes of the Caco cell monolayers with DM-β-CD decreased the efflux of tacrolimus and rhodamine with no associated cytotoxicity. DM-β-CD also decreased the level of P-gp in the apical membranes of the monolayers probably by allowing its release from the apical membranes into the transport buffer.[181]

CDs were found to be useful in the absorption enhancement of calcitonin, glucagon, insulin, and recombinant human granulocyte colony-stimulating factor. DM-β-CD (5%) enhanced the intranasal calcitonin absorption in rats and rabbits. In rabbits the intranasal absorption was comparable to intravenous or subcutaneous calcitonin absorption. In rabbits, a nasal spray of liquid and powder formulations of glucagons containing DM-β-CD provided improved bioavailability (> 80%) of glucagons compared with their subcutaneous administration. The absolute bioavailability of insulin in rats was also increased to ~100% on nasal administration with DM-β-CD (3% to 5%).[149] β-CD or DM-β-CD reduced the serious nasal toxicity of sodium-deoxycholate (a bile salt) by inhibiting the leucine aminopeptidase activity in the nasal mucosa without affecting the absorption-enhancing property of the bile salt for insulin.[151] The various established mechanisms for CD-improved nasal absorption of peptides are interaction with membrane lipids and proteins in the nasal epithelium that reduces the membrane barrier function, inhibition of proteolytic enzyme activities in the nasal mucosa, and finally inhibition of protein or peptide aggregation by direct action upon these molecules. Since the absorption-enhancing effects of CDs are reversible, as enhancers they are less toxic than other widely used enhancers, eg, the effect of CDs on the nasal cilliary beat frequency were observed to be mild, reversible, and less toxic. However, substantial interspecies differences were observed in the absorption enhancement of peptides from CD solutions. DM-β-CD, the only effective nasal absorption enhancer out of the CDs studied (β-, HP-β-, γ-, and DM-β-CDs), largely improved the nasal absorption of insulin and adreno crotico tropic hormone (ACTH) from solutions in rats (bioavailability ~70% to 100%) but in rabbits and healthy human volunteers, the same CD/insulin solution was found to be ineffective. Improved bioavailability of insulin (up to 13%) was observed on nasal administration of powder formulations containing DM-β-CD compared with the control containing lactose instead of the CD.[182]

CDs can enhance physical and chemical stability of protein and peptide drugs, and the maximum enhancing effects were reported at low CD concentrations. The proteolytic degradation of basic fibroblast growth factor was decreased by water-soluble β-CD sulfate.[1]

β-CD improved insulin loading of alginate microspheres prepared by an emulsion-based process. The process was suggested to be useful in the development of an oral insulin drug delivery system as the absorption of insulin from optimized microspheres was found to take place from the GI region.[183]

Gene and Oligonucleotide Delivery

The toxicity and immunogenicity associated with viral vectors led to the development of nonviral vectors for gene delivery. Besides the plasmid or virus-based vector systems, "naked" nucleotide derivatives have also been investigated for possible use as therapeutic agents through several routes of administration. Gene delivery technologists are now testing CD molecules in the hope of finding an optimal carrier for the delivery of therapeutic nucleic acids, however, the limitations of CDs, such as CD-associated toxicity (eg, DM-β-CD) have to be considered before their clinical use.[184]

CDs can solve many of the problems associated with in vivo delivery of oligonucleotides (Ons), such as their limited ability to extravasate from blood stream and traverse cellular membranes, high degree of susceptibility to endonucleases with potential toxicity of their breakdown products, polyanionic nature leading to nonspecific interactions with extracellular and intracellular cationic molecules, and potential immunogenicity. CDs can improve cellular uptake of ONs and also delay their degradation by increasing their stability against endonucleases. ON-adamatane conjugates associated with HP-β-CD provided significantly increased cellular uptake of ONs. Substitution of at least a single nucleotide of ONs with CDs improved the cellular uptake and/or stability of ONs. On conjugation with CDs, ONs may be delivered to the colon, an advantageous absorption site to

achieve acceptable therapeutic levels of ONs. CDs can also modulate undesirable side effects of ON treatment such as immune stimulation and reduction of platelet counts.[185,186]

Neutral and amphipilic as well as cationic CDs have been used for synthesis of novel gene delivery vectors. Neutral CDs like β-, DM-β-, and HP-β-CDs were reported to increase DNA cellular uptake by increasing its permeability. The increased DNA permeability was reported to be a result of interaction of the CDs with membrane components such as cholesterol, but not due to their complexing ability for DNA. Cationic polyamino CDs, because of their polycationic polyanionic interaction with mononucleotides, neutralized the multiple charges on DNA and thus made DNA compact into a particle of suitable size for cellular internalization. Amphiphilic CDs, because of their vesicle-forming potential, offer an additional possibility for polar nucleotides to complex into aqueous vesicle core while allowing hydrophobic agents to complex into individual cavities or interior of the bilayer with multiple lipophilic hydrocarbon chains.[186] Polyplexes (polycation polymer/DNA composite structures) of linear, cationic, β-CD–containing polymers (βCDPs) were found to be suitable for DNA delivery due to their increased transfection efficiency and stability against enzymatic degradation with low in vitro and in vivo toxicity.[187] The ability of CDs to complex hydrophobic adamantane was exploited for steric stabilization of βCDPs with hydrophilic polymers like poly(ethylene glycol). Steric stabilization of βCDPs prevents their self-aggregation but facilitates their targeted delivery by preventing their undesired interactions with non–self-entities.[188]

CDs were also found to enhance plasmid or viral-vector–based delivery of genes. Positively charged quarternary amino and tertiary amino β-CDs significantly enhanced the transfection efficiency of negatively charged adenoviral vector-based gene formulations. It was reported that the transfection enhancement by the cationic β-CDs could be a result of increased viral internalization caused by increased viral binding to cell and improved cell membrane permeability.[189] CDs also enhanced the physical stability of viral vector formulations for gene therapy.[120]

Dermal and Transdermal Delivery

CDs have been used to optimize local and systemic dermal drug delivery. Applications of CDs in transdermal drug delivery include enhancement of drug release and/or permeation, drug stabilization in formulation or at absorptive site, alleviation of drug-induced local irritation, sustaining of drug release from vehicle, and alteration of drug bioconversion in the viable skin. Parent CDs (α-, β-, and γ-CDs) and various chemically modified CD derivatives with extended physicochemical properties and inclusion capacity have been used in transdermal drug delivery.[7]

Drug thermodynamic activity in vehicles as well as its skin/vehicle partition coefficients can significantly affect CD-induced changes in the drug permeability through skin. CDs, by enhancing apparent drug solubility, enhance the drug thermodynamic activity in vehicles and thus cause enhancement of drug release from vehicles. The enhancement of drug release from vehicles by CDs in turn enhances the dermal drug absorption by improving the drug availability at the lipophilic absorptive barrier surface (ie, skin).[7,18] Although the drug partition coefficient (eg, a lipophilic drug) may be decreased on complexation with CDs (eg, with hydrophilic CDs), the increased drug solubility and thermodynamic activity in vehicles can lead to increased drug permeability through skin, eg, increased skin permeability of dexamethasone by HP-β-CD.[190] The vehicle type used, because of its main influence on the drug's membrane/vehicle partition coefficient, can markedly affect CD-induced enhancement of drug release. Diffusion rate of ketoprofen from its β-CD and HP-β-CD inclusion complexes was in the order of carbopol gel > oil/water emulsion > fatty ointment.[191] Hydrophilic CDs improve the release rate of lipophilic drugs from hydrophilic aqueous vehicles. Hydrophilic CDs markedly increased the in vitro release rate of corticosteroids from aqueous bases (hydrophilic, absorptive, or polyacrylic) but retarded the same from nonaqueous bases (fatty alcohol, propylene glycol, or macrogol). Complexation with β-, DM-β-, and HP-β-CDs increased the release of 4-biphenylacetic acid from hydrophilic ointment. β- and HP-β-CDs significantly enhanced the anti-inflammatory effects of indomethacin in hydroxyethyl cellulose hydrogels in healthy volunteers.[18] It was reported that CDs may not affect or even hamper drug release from nonaqueous vehicles and the effect may be due to lowered drug solubility in vehicle on complexation. The release of prednisolone from non–water-containing ointment bases was abated on complexation with DM-β-CD. Hydrophilic β- and HP-β-CDs enhanced the release of hydrocortisone from oil/water cream and hydrogel but retarded the same from petrolatum vehicle or water/oil cream.[192]

CDs enhance drug delivery by increasing the drug availability at the barrier surface, where the free drug partitions from the CD cavity into lipophilic barrier. The free drug fraction at the barrier surface depends on the drug dissolution rate, relative magnitude of the stability constants of the CD complexes with the drug and the competing agent at the absorption site, and the drug absorption rate constant. In ointments, just as in suppositories, a drug in the CD complex may be displaced by ointment components, depending on the magnitude of the stability constant of the drug/CD complex. Hence, for optimum drug release, the vehicle or the CD complex chosen should be such that the complex barely dissociates but still maintains a high

drug thermodynamic activity in the vehicle.[18] The order of prednisolone release rate from a hydrophilic ointment was drug alone < γ-CD complex < β-CD complex < DM-β-CD complex, which was reflective of the order of the complex stability constants.[7] For absorption, the CD complex has to dissociate to release free drug, the actual absorbable species and the dissociation of CD complex depends on the magnitude of the complex stability constant. If the complex stability constant is too high, the complex may not release the free drug at the absorptive site and thus may decrease or inhibit drug absorption.[18] The effect of HP-β-CD concentration on the iontophoretic delivery of hydrocortisone (ie, higher drug amount delivered at lower CD concentration [1%] compared with higher CD concentrations [3% or 5%]) indicated the delivery of only the free drug with the CD acting as a carrier.[193]

CDs have also been used to reduce drug degradation in topical preparations. β-CD maintained the stability of tixoxortol 17-butyrate 21-propionate in vaseline and oil/water emulsion bases even after 30 days.[7] Complexation with CDs was suggested to be a rational way to improve physicochemical properties of drugs for transdermal delivery. β- and HP-β-CDs increased the skin permeability of dexamethasone and also improved its stability in skin by protecting it against skin metabolism.[190] CDs, by increasing solubility, facilitate drug incorporation into formulation and thus increase the drug concentration in the formulation. HP-β-CD increased the amount of piroxicam transported through skin but pretreatment of skin with the CD showed no effect on drug retention in skin. Hence the CD effect on the drug's skin permeability was reported to be due to increased drug concentration in gel and not due to enhancement of drug iontophoretic flux.[194]

CDs may alleviate drug-induced skin irritation by lowering the extent of free drug resulting from inclusion equilibrium. β- and DM-β-CDs significantly reduced chlorpromazine-induced skin irritation and their alleviating efficacy; DM-β-CD > β-CD was consistent with the magnitude of their complex stability constants. Suppression of drug penetration into skin caused by the reduction of drug/skin partition coefficient on CD complexation was reported to be the possible reason for the reduction of chlorpromazine-induced skin irritation. β-CD also attenuated the skin irritation induced by tretinoin and menadione.[7]

Hydrophobic CDs can modulate drug release from vehicles. Nitroglycerin complexation with DE-β-CD accelerated the drug release rate from ointments but the same with β-CD retarded the drug release. Hence a combination of the drug complexes with DE-β-CD and β-CD was suggested to obtain sustained release percutaneous preparations of the drug.[7]

Though only insignificant amounts of CDs and drug/CD complexes can penetrate into biological barriers because of their size and hydrophilicity, CDs may interact with some of the skin components. It was reported that the free CDs released on complex dissociation, due to their ability to remove some membrane surface components, can modify the membrane transport properties and thus can facilitate absorption of drugs, especially water-soluble drugs. Interaction of RM-β-CD with skin components was directly implicated to its effect on drug diffusion. It is also important to pay careful attention toward possible irritation effects of CDs on skin, eg, RM-β-CD extracted all major classes of lipids from an isolated stratum corneum of hairless rats and thereby reduced the barrier function of the skin.[18]

CDs, the safer solubilizing agents with bioadaptability and multifunctional characteristics, have been evaluated for formulation of poorly water-soluble cosmetic materials. HP-CDs increased the aqueous solubility of cosmetic materials, retarded the release rate of fragrance materials with no toxicity in topical liquid preparations,[7,195] and also reduced permeation rate of eugenol and methyl paraben through hairless mouse skin. Other CD applications in cosmetics include masking of smell and stench, stabilization of cosmetic materials (eg, loyal jelly and antiplasmin drugs), assisting in preparation of stable emulsion and suspension, inhibition of foaming caused by amphiphilic materials, and powderization of oily materials.[7] Being nontoxic polysaccharides with solubilizing and stabilizing effects and further advantages, CDs and their complexes have been used to formulate cosmetic products, making possible those effects that were not realizable with common techniques. The ability of CDs to increase stability (against light and oxygen) and solubility of sparingly water-soluble molecules made them useful in the formulation of cosmetic products.[196]

Brain Drug Delivery or Brain Targetting

The concept of Bodor's chemical delivery system (CDS) (ie, covalent coupling of drugs to 1-methyl-1, 4-dihydronicotinic acid through an enzymatically labile linkage, which increases drug lipophilicity) was applied for targeting drugs such as steroids, antitumor agents, and calcium channel antagonists to brain. However, presence of the lipophilic moiety makes prodrugs of CDS poorly water-soluble. HP-β-CD, due to its ability to solubilize drugs and also to enhance the chemical stability of dihydronicotinic acid in aqueous solution solved the solubility problems of CDS.[156] Formulation is an important and integral concern in the development of CDS, especially those for brain targeting. Formulation development of CDS is based on the need for appropriate dosage form, stability, solubility, and dissolution characteristics. Brewster and Loftsson[197] discussed the use

of chemically modified, especially water-soluble, CD derivatives such as HP-β-CD in the formulation development of CDS. HP-β-CD contributed to the development and preclinical testing of several CDS by providing a stable and water-soluble dosage form suitable for parenteral administration. Use of CDs in the formulation of CDS can be demonstrated by the significantly improved solubility, stability, and pharmacologic activity of CDS of thyrotropin-releasing hormone analogs on complexation with HP-β-CD.[198]

The very low penetration across the BBB greatly hinders the therapeutic use of peptides, and whenever unexplainable poor peptide absorption is seen the role of the efflux pumps should be examined. It was reported that P-gp–mediated peptide transport may play an important role in greatly reducing the peptide delivery to the central nervous system in vivo.[178,179] It was also indicated that CDs such as DM-β-CD, due to their inhibitory effect on P-gp efflux function, may enhance drug delivery to brain.[181]

CD Applications in the Design of Some Novel Delivery Systems

Liposomes

In drug delivery, the concept of entrapping CD-drug complexes into liposomes combines the advantages of both CDs (such as increasing the solubility of drugs) and liposomes (such as targeting of drugs) into a single system and thus circumvents the problems associated with each system. Liposomes entrap hydrophilic drugs in the aqueous phase and hydrophobic drugs in the lipid bilayers and retain drugs en route to their destination. The fact that some lipophilic drugs may interfere with bilayer formation and stability limits the range and amount of valuable drugs that can be associated with liposomes. By forming water-soluble complexes, CDs would allow insoluble drugs to accommodate in the aqueous phase of vesicles and thus potentially increase drug-to-lipid mass ratio levels, enlarge the range of insoluble drugs amenable for encapsulation (ie, membrane-destabilizing agents), allow drug targeting, and reduce drug toxicity. Problems associated with intravenous administration of CD complexes such as their rapid removal into urine and toxicity to kidneys, especially after chronic use, can be circumvented by their entrapment in liposomes.[199-202]

When the concept of entrapping CD complexes into liposomes was applied to HP-β-CD complexes of dexamethasone, dehydroepiandrosterone, retinal, and retinoic acid, the obtained dehydration-rehydration vesicles (DRV liposomes) retained their stability in the presence of blood plasma.[199] Liposomal entrapment can also alter the pharmacokinetics of inclusion complexes. Liposomal entrapment drastically reduced the urinary loss of HP-β-CD/drug complexes but augmented the uptake of the complexes by liver and spleen, where after liposomal disintegration in tissues, drugs were metabolized at rates dependent on the stability of the complexes.[200,203]

CD complexation can increase liposomal entrapment of lipophilic drugs and also reduce their release from the carrier, ie, liposomes. Complexation with CDs increased the liposomal entrapment of nifedipine by reducing its interaction with lipid bilayers and also improved the liposomal stability in plasma.[204] To encapsulate large amounts of lipophilic drugs in liposomes, a CD molecule forming an inclusion complex with a high drug:CD ratio should be selected. Liposomal entrapment of prednisolone was higher when incorporated as HP-β-CD complex than as free drug. Selection of CD can also have a significant effect on the amount of drug associated with vesicles, eg, HP-β-CD, with a more lipophilic interior and considerably higher aqueous solubility incorporated higher drug amounts in vesicles than β-CD. However, HP-β-CD, as a result of its ability to get entrapped in higher amounts in the vesicles, also showed a higher velocity of destabilizing effect on vesicles than β-CD.[205]

Complexation with CDs can improve the stability of liposomes, eg, most stable liposomal formulations of metronidazole and verapamil were obtained by direct spray drying of lipid, drug, and HP-β-CD mixture.[206] Inclusion complexation can greatly increase the chemical stability of labile drugs in multilamellar liposomes. Multilamellar DRV liposomes containing a riboflavin/γ-CD complex provided optimal protection to the photosensitive drug.[207] Similarly, multilamellar liposomes containing indomethacin/HP-β-CD inclusion complex showed increased stability of the hydrolysable drug (~75-fold).[208]

Parent CDs (α-, β-, and γ-) along with sulfated glycolipids were used as starting materials in the synthesis of specific erythrocyte-like liposomes having excellent self-assembling capacity to form stable monolayers at an air water interface.[209]

Microspheres

In the presence of a high percentage of highly soluble hydrophilic excipients, complexation may not improve the drug dissolution rate from microspheres. Nifedipine release from chitosan microspheres was slowed down on complexation with HP-β-CD in spite of the improved drug-loading efficiency. Since it is highly unlikely for CD molecules to diffuse out of the microspheres, even with a low stability constant, the complex must first release the free drug that can permeate out of the microspheres. Hence the observed slow nifedipine release from the microspheres was reported to be due to lesser drug availability from the complex and

also due to formation of hydrophilic chitosan/CD matrix layer around the lipophilic drug that further decreases the drug matrix permeability.[210] Sustained hydrocortisone release with no enhancement of its dissolution rate was observed from chitosan microspheres containing its HP-β-CD complex. The sustained hydrocortisone release was reported to be due to formation of a layer adjacent to the interface by the slowly dissolving drug during the dissolution process that makes the microsphere surface increasingly hydrophobic.[211]

Study of in vivo release behavior (over 24 hours) of β-CD from β-CD/poly (acrylic acid) (PAA) microspheres, prepared by a water/oil solvent evaporation technique, indicated a high encapsulating efficiency (>90%) with potential covalent binding of the CD.[212] β-CD caused no alteration of the in vitro release kinetics of dyes, phenolphthalein, and rhodamine B (with different solubilities and strengths of association with β-CD) from the microspheres. The reasons suggested for the unaltered release kinetics were rapid hydration of the polymer matrix because of limited crosslinking; perturbation of dye/β-CD complex by oil, organic solvent residues and/or conformational changes; and reduction of β-CD complexing ability on covalent binding with PAA due to steric hindrance of its cavity.[213]

HP-β-CD acted as a promising agent for stabilizing lysozyme and bovine serum albumin (BSA) during primary emulsification of poly (d, l-lactide-co-glycolide) (PLGA) microsphere preparation. The stabilizing effect was reported to be a result of increased hydrophilicity of the proteins caused by shielding of their hydrophobic residues by HP-β-CD; this also reduces their aggregation and denaturation by keeping them away from methylene chloride water interface. HP-β-CD enhanced BSA conformational stability and also increased its recovery from water/oil emulsion by preventing the adsorption of the protein to PLGA.[214,215] CDs were also used to modulate peptide release rate from microspheres, eg, HP-β-CD co-encapsulation in PLGA microspheres slowed down insulin release rate. Microspheres, prepared by spray drying of a water/oil emulsion containing the CD provided a constant insulin release up to 45 days without initial burst and maintained the peptide stability during the entire release phase. The slowing down of overall release rate of the peptide was reported to be due to its decreased matrix diffusivity caused by its higher apparent molecular weight and size on complexation. Co-encapsulation of the CD also reduced the apparent particle size of the microspheres.[216]

A high entrapment efficiency of gabexate mesylate (GM) was observed with all types of bioadhesive and biodegradable starch/CD microspheres prepared by chemical crosslinking of an alkaline solution of a mixture of starch and CD (α-, β-, or γ-CD) with epichlorohydrin. The amount of GM included and its proportion in microspheres after storage were in agreement with its affinity for the CDs and the order of association constants of its complexes.[217] All PVA/CD microspheres, prepared by crosslinking of an acidified aqueous mixture solution of PVA and CD (α-, β-, or γ-CD) with gluteraldehyde, displayed good affinity for different drugs (diclofenac, indomethacin, metronidazole, and propranolol).[218] The amount of CD linked in microspheres was in the order β- > γ- > α-CD and the dimensions of the microspheres with γ-CD were much higher than those with α- or β-CDs.

Microcapsules

It was suggested that crosslinked β-CD microcapsules, because of their ability to retard the release of water-soluble drugs through semipermeable membranes, can act as release modulators to provide efficiently controlled release of drugs. Terephthaloyl chloride (TC) crosslinked β-CD microcapsules were found to complex p-nitrophenol rapidly and the amount complexed increased as the size of the microcapsules decreased. TC crosslinked β-CD microcapsules retarded the diffusion of propranolol hydrochloride through dialysis membrane. Double microcapsules, prepared by encapsulating methylene blue with different amounts of β-CD microcapsules inside a crosslinked human serum albumin (HSA), showed decreasing release rate of methylene blue with increasing amount of β-CD microcapsules. Dissociation of methylene blue complex with β-CD microcapsules was found to serve as an additional mechanism in controlling the release kinetics of HSA double microcapsules. In the case of HSA microcapsules with parent β-CD, the hydrating property of the CD, by promoting the diffusion of water into the microcapsules, caused an increased release rate of methylene blue compared with those without the CD. However, in the case of HSA double microcapsules (ie, with β-CD microcapsules), the hydrophobic groups introduced during crosslinking suppressed the CD hydration and provided controlled release without enhancing the diffusion of water that can impair the complexation of methylene blue.[219]

Nanoparticles

Nanoparticles are stable systems suitable to provide targeted drug delivery and to enhance the efficacy and bioavailability of poorly soluble drugs. However, the safety and efficacy of nanoparticles are limited by their very low drug loading and limited entrapment efficiency (with classical water emulsion polymerization procedures) that may lead to excessive administration of polymeric material.[220,221] Two applications of CDs have been found very promising in the design of nanoparticles: one is increasing the loading

capacity of nanoparticles and the other is spontaneous formation of either nanocapsules or nanospheres by nanoprecipitation of amphiphilic CDs diesters. Both the new techniques were reported to be useful due to great interest of nanoparticles in oral and parenteral drug administration. CDs increased the loading capacity of poly (isobutylcyanoacrylate) nanoparticles. The increased loading capacity was reported to be a result of increased drug concentration in the polymerization medium on addition of the drug:CD complex and increased number of hydrophobic sites in the nanosphere structure on association of large amounts of CDs to the nanoparticles.[221,222] HP-β-CD increased saquinavir loading into poly (alkylcyanoacrylate) nanoparticles by providing a soluble drug reservoir in polymerization medium that feeds the nanoparticle-formation process. A dynamic equilibrium was observed between the complex, the dissociated species, and the forming polymeric particle. It was indicated that during nanoparticle formation the free drug gets progressively incorporated into polymer network, driven by the drug partition coefficient between the polymer and polymerization medium though there may be a simultaneous direct entrapment of some drug/CD complex.[222,223]

Addition of HP-β-CD in the polymerization medium of poly (ethylcyanoacrylate) (PECA) nanospheres improved the subcutaneous absorption of metoclopramide in rats. PECA nanospheres with HP-β-CD provided the highest drug concentration and enhanced drug absorption compared with those with dextran or with drug solution. However, in addition to drug absorption from subcutaneous (sc) sites, HP-β-CD also enhanced the drug elimination by enhancing the drug absorption to reticluoendothelial tissues.[224]

Addition of steroid drugs, hydrocortisone (HC), and progesterone (PN) as β-CD or HP-β-CD complexes maintained the sizes of solid lipid nanoparticles (SLN) below 100 nm with the steroids dispersed in an amorphous state. CD complexation increased the incorporation of the more hydrophilic drug, HC than PN but provided lower release of both the drugs from SLN compared with the release from SLN containing the free drugs. It was suggested that the process of incorporating drugs partly in free form and partly in complexed form may be used to modulate release kinetics of drugs from SLN.[225]

Amphiphilic β-CDs (β-CDsa), synthesized by introducing substituents of varying chain lengths (C_6-C_{14}) and bond types (ester and amide) on the primary face of the CD, have been characterized and evaluated as potential novel excipients in the preparation of nanocapsules.[226] Compared with natural CDs, β-CDsa, particularly those derivatives with 6C aliphatic chains on the primary face, form biodegradable, nonsurfactant, highly loaded nanospheres and nanocapsules with low hemolytic activity.[220,226,227] The chemical structure of β-CDsa derivatives was found to influence their ability to nanoassociate or form stable nanospheres. Partial acylation of β-CDsa allowed self-assembly into stable nanosphere suspension but peracylation with 14 alkyl chains on secondary hydroxyl groups failed to do the same even in the presence of a nonionic surfactant in the aqueous phase. The amount of partially acylated species in β-CDsa was also found to play an important role in regulating the mean diameter size and suspension stability of nanospheres.[228]

Amphiphilic β-CD (β-CDa) derivatives, 6-N-CAPRO-β-CD and β-CDC6 with 6C aliphatic chains on the primary and secondary face respectively, enhanced the solubility and therapeutic efficacy of model drugs, bifonazole and clotrimazole. The β-CDa derivatives formed inclusion complexes with the drugs and with the nanoprecipitation technique the derivatives gave nanospheres of less than 300 nm with no use of surfactants. 6-N-CAPRO-β-CD, due to its ability to hold drugs longer in its cavity, displayed a higher loading capacity and slower release profile than β-CDC6. A slightly higher loading capacity observed with 6-N-CAPRO-β-CD was attributed to the higher drug adsorption onto its particle surface caused by the higher affinity of the 14 alkyl chains surrounding the CD molecule. Affinity of β-CD to model drugs also played a major role in affecting the drug release from the β-CDa nanospheres.[227] Loading techniques and also the type of β-CDa can influence the loading and release properties of the nanospheres. Inclusion complexation of progesterone with β-CDa prior to its entrapment in nanospheres increased the drug loading into nanospheres. Progesterone-loaded β-CDa nanospheres acted as a promising nonsurfactant injectable delivery system to provide rapidly a high quantity of the water-insoluble drug (within 1 hour).[220]

CD Use as Excipients in Drug Formulation

As excipients, CDs have been finding different applications in the formulation and processing of drugs. β-CD, due to its excellent compactability (varied with source) and minimal lubrication requirements, showed considerable promise as a filler binder in tablet manufacturing but its fluidity was insufficient for routine direct compression. β-CD was also found to be useful as a solubility enhancer in tablets. The ability of β-CD to complex progesterone by wet granulation was found to be dependent on both binder solution and mixture type.[229] Complexation can cause subtle changes in the tabletting properties of drugs or CDs that can substantially affect the stability and tabletting performance of tablet formulations containing drug/CD complexes. Complexation of tolbutamide with HP-β-CD (freeze-dried or spray-dried) altered the water sorption-desorption and tabletting properties of the CD, and the resultant complex showed worse compactability than the pure CD or the drug/

CD physical mixture.[230] CDs also affect the tabletting properties of other excipients, eg, microcrystalline cellulose codried with β-CD showed improved flowability, compactability, and disintegration properties suitable for direct compression.[231] In the case of high-swelling wheat starches, β-CD (1%) increased the peak viscosity (PV) but decreased the cool paste viscosity (CPV) and in the case of low-swelling starches, the same CD slightly decreased the PV but increased the CPV. However, β-CD reduced the heat paste viscosity of both the starches.[232] Avicel/β-CD codried product showed improved flowability and disintegration properties but its rounder particles, because of their sensitivity to lubrication, gave tablets weaker than those with avicel. But on addition of magnesium stearate, the codried excipient with improved powder flowability served as a better excipient in wet granulation.[233]

CDs can be used to mask the taste of drugs in solutions, eg, suppression of bitter taste of 4 mm oxyphenonium bromide by CDs. With the assumption that only the free drug molecule exhibits bitter taste regardless of the kind and concentration of CD, the suppression of drug bitter taste by CDs was reported to be in the order of α-CD < γ-CD < β-CD, reflecting the stability constants of the complexes.[137]

CDs were used as pellatization agents in extrusion and spheronization processes and in the presence of β-CD up to 90% by weight, the process provided satisfactory products.[234] CDs were also indicated to stabilize protein and peptide pharmaceuticals during spray drying, eg, inhibition of spray drying induced inactivation of β-galactoside by HP-β-CD.[235]

CDs were found to inhibit adsorption or absorption of drugs to container walls. SBE-β-CD and HP-β-CD reduced the adsorption of DY-9760e to PVC tubes but the effect was more significant with SBE-β-CD reflecting the stability constants of the CD complexes. Compared with HP-β-CD, SBE-β-CD was found to exhibit a greater masking effect against the hydrophobic interaction between the surface of PVC tubes and the drug.[30] Hydrophilic CDs, including maltosyl-β-CD, inhibited the adsorption of bovine insulin to containers and also inhibited insulin aggregation by interacting with the hydrophilic regions of the peptide.[236] β-CD inhibited the adsorption of FK 906, a surface active drug, from aqueous solution onto container walls by shifting the critical micellar concentration of the drug to a higher value.[237]

Carbomers, owing to their ionic nature and large number of acidic groups, tend to interact with cationic substances and hydrophilic polymers with alcoholic groups. CDs were found to inhibit carbomer-drug interactions in hydrogel. Carbopol, as a result of its interaction with the cationic drug, propranolol HCl, formed an insoluble complex that causes modification of all the hydrogel properties of the polymer. β-CD, by reducing carbopol interaction with the cationic drug, maintained the hydrogel properties of carbopol.[238]

Large differences were observed in the powder and particle characteristics of β-, α-, γ-, and HP-β-CDs. With these CDs, the order of sphericity was β-CD < α-CD < γ-CD < HP-β-CD and that of shape uniformity was α-CD < β-CD < γ-CD < HP-β-CD. Water content of CDs was found to be variable with storage conditions and can be removed by evaporation at 160°C. It was reported that a characteristic peak shown in the DSC profile of α-CD, unaffected even at high temperature, was representative of a "feasible structural change" in the CD molecule.[239]

The osmolality of SBE-CDs was found to increase with the total degree of substitution and was also considerably higher than that of HP-CDs. The observations with these CD derivatives provided a useful insight into their behavior in solutions and in characterization of drug release mechanisms from osmotic pump tablets.[240] SBE- and HP-derivatives of β- and α-CDs, with different total degree of substitution (TDS), exhibited different colligative properties, especially their osmotic pressure (OP) increased with their TDS. With substituted CDs, the OP was above their theoretical values but with unsubstituted γ-CD, the OP was below the expected value. Self-association of the unsubstituted γ-CD molecules was reported to be the possible reason for the observed low OP value of the CD. These findings relating the OP properties of CDs can be useful in the formulation of parenteral and ophthalmic solutions, where maintenance of OP is an important consideration.[241]

Interaction of CDs with the preservatives in the formulation is an important factor and should be investigated. It was reported that such interaction can result in reduction of both the solubilizing effect of CD and the antimicrobial activity of preservatives, eg, interaction of HP-β-CD with preservatives like benzalkonium chloride, chlorhexidine gluconate, chlorambutanol, methylparaben, and propylparaben.[242]

CONCLUSION

CDs, as a result of their complexation ability and other versatile characteristics, are continuing to have different applications in different areas of drug delivery and pharmaceutical industry. However, it is necessary to find out any possible interaction between these agents and other formulation additives because the interaction can adversely affect the performance of both. It is also important to have knowledge of different factors that can influence complex formation in order to prepare economically drug/CD complexes with desirable properties. Since CDs continue to find several novel applications in drug delivery, we may expect these polymers to solve many problems associated with the delivery of different novel drugs through different delivery routes.

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