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OVERVIEW

Cyclodextrin complexes: Perspective from drug delivery and formulation

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Abstract

Cyclodextrins (CDs) have been widely investigated as a unique pharmaceutical excipient for past few decades and is still explored for new applications. They are highly versatile oligosaccharides which possess multifunctional characteristics, and are mainly used to improve the physicochemical stability, solubility, dissolution rate, and bioavailability of drugs. Stability constant, factors affecting complexation, techniques to enhance complexation efficiency, the preparation methods for molecular inclusion complexes and release of guest molecules are discussed in brief. In addition, different CD derivatives and their pharmacokinetics are elaborated. Further, the significance of CD complex in aqueous solubility, dissolution and bioavailability, stability, and taste masking is explained. The recent advancement of CDs in developing various drug delivery systems is enlightened. Indeed, the potential of CDs by means of inclusion complex formation have widen the applicability of these materials in various drug delivery systems including ocular, osmotic, mucoadhesive, transdermal, nasal, and targeted delivery systems. Feasibility studies have been performed on the benefit of these cyclic oligomers as nanocarriers, a strategy that can modify the drugs with improved physicochemical properties. Studies also demonstrated the feasibility of CDs to self-assemble in the form of stable nanoaggregates, which may extend the scope of CDs in drug delivery to the continually expanding list of new drug entities.

KEYWORDS

bioavailability, complexation efficiency, dissolution, nanoparticles, ocular, solubility, stability

1 | INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides assembled of D-(+) glucopyranose units connected by α-(1,4) glucosidic bonds to form a torus like macro rings. Naturally occurring α, β, and γ CDs consists of 6, 7, and 8 glucopyranose units, respectively, and differ in their molecular weight, cavity size, and solubility. The CDs capacity to form inclusion complexes in aqueous solution results more from its toroidal structure. The core CDs is relatively hydrophobic due to the presence of CH_2 groups, whereas the hydrophilicity at the cavity entrances are attributed to the occupancy of primary and secondary hydroxyl functional groups (Figure 1). Thus, molecules of proper size and stereochemistry can only be accommodated in the CD cavity by hydrophobic interactions. β-CD and γ-CD and their derivatives are the most prominent complexing agent for formulations owing to their large hydrophobic cavity size (internal diameter ≅ 6 Å and 8 Å, respectively). The popularity of CDs is primarily due to its availability, cost, and biocompatibility. Indeed, the potential of CDs to improve the therapeutic utility of existing and emerging drug candidates by enhancing the bioavailability, solubility and dissolution rate, intensity or duration of therapeutic activity, permeability, physicochemical stability, and reduction of tissue irritation/toxicity has been demonstrated (Diniz et al., 2018). Moreover, the CDs are highly versatile oligosaccharides which can be easily modified to change their physicochemical properties and could be combined with other excipients like polymers to achieve synergetic effect.

2 | ASSOCIATION CONSTANT AND STOICHIOMETRIC RATIO

Determination of association or stability constant (*K*), and complexation efficiency (CE) for CD complexes are utmost important (Jambhekar &

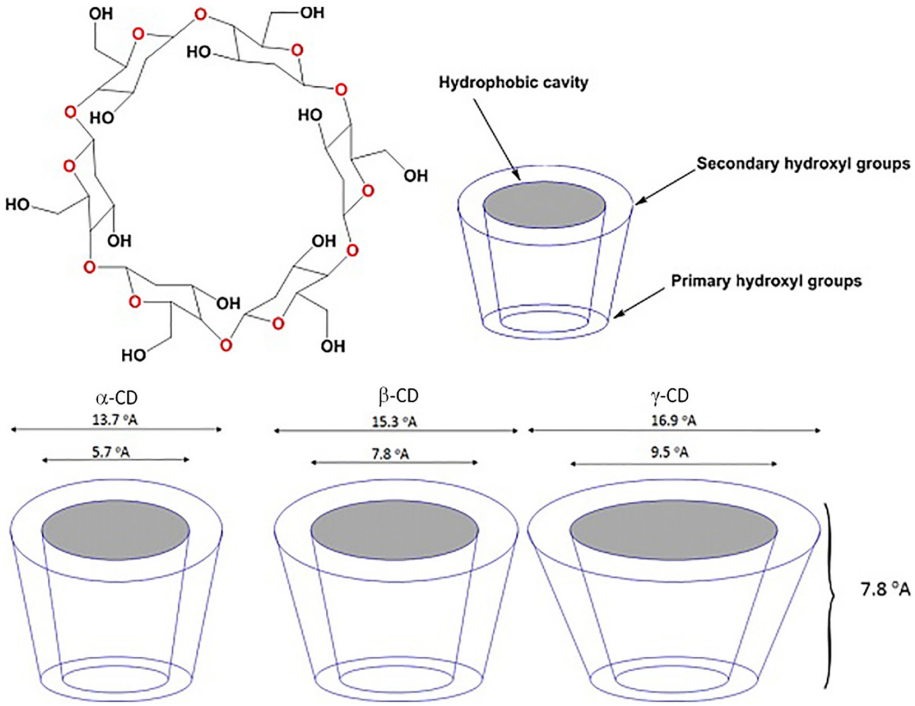

FIGURE 1 A graphical representation of chemical structure and the molecular shape of α, β, and γ cyclodextrins [Color figure can be viewed at wileyonlinelibrary.com]

Breen, 2016a). As a result of inclusion and noninclusion complex formation in aqueous solution, the stoichiometry of the inclusion complex ($K_{a:b}$) frequently depends on concentration of the complex, conditions of the study, and the techniques applied for evaluation. The magnitude of binding affinity as interpreted by association or stability constant, $K_{a:b}$ is given in below equation, where the symbol "a" and "b" specifies the molar ratio of the drug molecule to the CD.

$$K_{a:b} = \frac{[\mathrm{Drug_aCD_b}]}{[\mathrm{Drug}]^a[\mathrm{CD}]^b}.$$

One of the most frequently used methods of determining association constant and stoichiometric ratio is the phase-solubility technique, illustrated by Higuchi and Connors (1965). Additional methods that are available to determine these stability constants include fluorescence, Nuclear magnetic resonance spectroscopy, circular dichroism, micro calorimetry, electrophoresis, and various chromatographic methods (Junquera & Aicart, 2015). In phase solubility technique, a phase graph is made by plotting the molar concentration of solubilized drug on *y* axis and concentration of complexing agent on *x* axis. Typically, phase solubility curves are characterized into A and B types and their subclasses as shown in Figure 2. The A type curve, usually observed with water soluble complexes, is further subcategorized into A_L (linear), A_P (positive-type isotherm), and A_N (negative type isotherm) based on drug solubility as a function of CD. Type B curve is usually observed with β-CD which can be further subclassified into B_S (limited solubility) and B_I (insoluble). Indeed, a linear curve A_L, indicates the presence of one molecule of complexing agent, A_P type plot shows the presence of more than one complexing agent and A_N type can occur in presence of self-association or high concentration of complexing agent. In case of a 1:1 complex, equilibrium binding or association constant, *K*, can be determined from the slope of the curve using the following equation, where S_0 represents the intrinsic solubility of the compound.

$$K = \frac{\mathrm{Slope}}{S_0\,(1-\mathrm{Slope})}$$

A range of *K* values (0–100,000 M^{-1}) have been described for CD complexes. However, one can easily assess the binding characteristics of the observed value by considering 0 (absence of binding), <500 M^{-1} (very weak binding), 500–1,000 M^{-1} (weak binding),

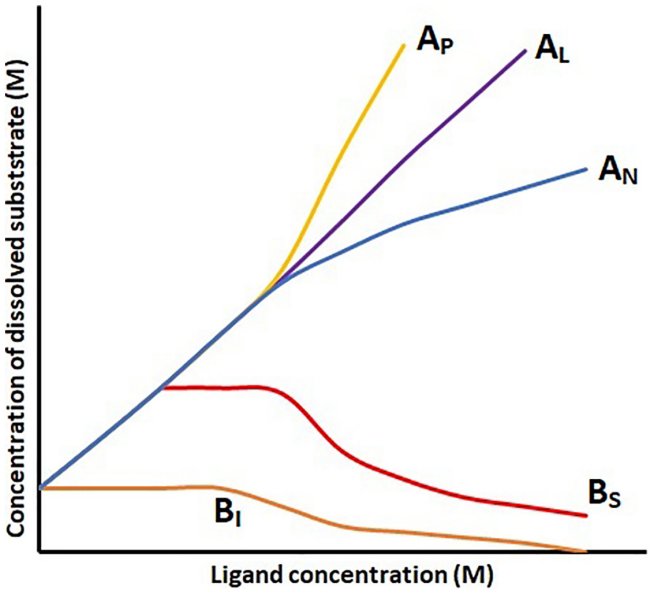

FIGURE 2 An illustration of typical phase solubility profile [Color figure can be viewed at wileyonlinelibrary.com]

1,000–5,000 M^{-1} (moderate binding), 5,000–20,000 M^{-1} (strong binding), and >20,000 M^{-1} (very strong binding).

In the pharmaceutical formulation development, the CE of the CD has more significant role than the *K* and is determined from slope of the phase solubility graph using the following equation (Loftsson, Hreinsdóttir, & Másson, 2005);

$$CE = \frac{Slope}{1 - Slope}.$$

A low value of CE indicates large amounts of CD need for formulation. For instance, CE value of ~0.3 means one out of four CD molecules is involved in forming a complex with a drug. The CE value has been used to investigate the influence of various pharmaceutical additives like preservatives, antioxidants, polymers, and buffer agents on the solubilizing capacity of CDs.

2.1 | Mechanisms of CD inclusion complexation

In an aqueous solution, the slightly apolar CD cavity is entrapped by high enthalpy water molecules due to noncovalent interaction. These water molecules can be readily replaced by less polar "guest molecules" of suitable size. CD complexation process involving host and guest is usually a 1:1 ratio, though 2:1, 1:2, 2:2, or higher order complexation and complicated associations occurs concurrently.

3 | FACTORS TO BE CONSIDERED IN COMPLEXATION

The formation of drug–CD complex in an intended formulation or final composition is of paramount important. It depends on various factors like chemical structures as well as physicochemical properties of both the drug and the CD, solvents, thermodynamic interactions between CD, guest molecule and solvent, method of preparation, additives, temperature, and so forth. One should remember that all the drug moieties are not ideal substrates for CD complexation and should have certain characteristics like skeleton with more than 5 atoms (C, P, S, N), less than 5 condensed rings, melting point <250 °C and structure with a key functional group (hydrophilic moiety), which enable inclusion in the hydrophobic CD cavity. Typically, guest molecules with straight or branched chain hydrocarbons, aldehydes, ketones, alcohols, organic acids, fatty acids, aromatic compounds, gases, and polar compounds, such as halogens, oxyacids, and amines, promote complexation (Loftsson, Sigurđsson, Másson, & Schipper, 2004). Further, lower the aqueous solubility of a drug, the greater the relative enhancement in drug solubility due to complexation. However, one should remember that the low aqueous solubility is not always associated to the lipophilicity of the drug. In addition, ionic drugs generally form weaker complex as compared with nonionic drugs. In case of ionizable drugs, the presence of charge will influence the drug–CD complexation and therefore a variation in the solution pH can alter the complexation. Moreover, it should be remembered that an appropriate salt selection for the drug can improve binding behavior, although counter ion of CD can inhibit solubility due to common ion effect. Various factors to be considered in selecting CDs are:

Type of CDs: Despite the fact that the natural CDs and their complexes are hydrophilic in nature, their aqueous solubility is limited predominantly because of comparatively high crystal lattice and intermolecular hydrogen bond formation within the CD molecules. However, substitution with polar hydroxyl groups or hydrophobic methoxy groups will transform them from crystalline to amorphous state, hence remarkably increases aqueous solubility.

Cavity size: Cavity size of the host and the preparation methods can affect the physicochemical properties of drug–CD complex. The size of the CD cavity should be sufficient to incorporate a drug molecule of proper dimension (Lutka, 2002).

Charge: Charged CD can be very effective solubilizers, however, it depends on the relative proximity of the charge to the CD cavity. The general observation with ionic CDs is opposite charge (CD and guest molecules) leads to efficient complexation. For instance, anionic CDs [SBE-β-CD, carboxymethyl (CM)-β-CD], forms good complexation (due to attraction and high-binding constant) with cationic drugs, while they form weak complexation with neutral drugs and no complexation with anionic drugs (due to electrostatic interaction). A key disadvantage of ionic CDs is their inability to form higher order complex, such as 1:2 or 1:3 due to increase in charge density and electrostatic repulsion. Conversely, the neutral charged CDs (HP-β-CD) usually show good complexation with neutral drugs as compared with anionic and cationic drugs.

Molar substitution: CD derivatives of lower molar substitutions are better drug solubilizers (complexation agents) when compared with the same type of derivatives with higher molar substitutions.

pH and ionization: Variation in drug–CD interaction is observed with change in the pH and ionization (Gladys, Claudia, & Marcela, 2003).

Various formulation ingredients as well as processing and formulation factors which could influence the complexation are:

Formulation bulk: A major limitation of CDs in pharmaceutical formulations is their inherent nature to enlarge the formulation size owing to large molecular weight which is generally determined using equation;

$$\text{Increase in formulation bulk} = \frac{MW_{CD}}{MW_{Drug}} \times \left(1 + \frac{1}{CE}\right).$$

The upper limit of the dosage form (including drug dose and excipients) is ~800 mg. Consequently, the routine use of CD as solubility enhancers is therefore limited to potent (~5 mg) and medium potent drugs (~50 mg), provided that they have relatively high CE.

Solvent: Solvent plays significant role in complexation as both guest molecule and CD are required to dissolve. Indeed, the more soluble the CD in the solvent, the more molecules becomes available for complexation. Water is the most ideal solvent for performing complexation reactions as CDs have good solubility and the guest molecules can easily displace it from the CD cavity. Parent CDs exhibit high solubility in water, partial solubility in glycols and are insoluble in most of the organic solvents (except dimethylformamide). Conversely, guest molecules with low aqueous solubility could be improved using co-solvents like propylene glycol. Unfortunately, organic solvents reduce the complexation, because of hydrophobic effect, and thereby solubility. However, not all guests are readily solubilized in water,

making complexation either very slow or impossible. In such cases, the use of an organic solvent, which do not form complex with CD and can be easily removed, to dissolve the guest is desirable. Ethanol and diethyl ether are good examples of such solvents.

Additives: In general, additives alter the formation of complex, hence solubility studies are required using the expected formulation. Few additives like urea and nicotinamide seems to increase the solubility of drug when used with certain CDs. However, common additives (sodium chloride, buffer salts, surfactants, preservatives, and organic solvents) decrease the prospective of CDs to solubilize drugs. They can even compete with drug molecules of similar size for CD cavities and consequently decrease the apparent *K*, for example, adjuvants having positive and negative hydrotropic effects. Therefore, the optimal use of drug salts, polymers, low molecular weight organic acids or surfactants and co-solvents may be useful to enhance both apparent drug solubility and CE.

Method of preparation: The performance of the method depends up on the physicochemical nature of the drug as well as the CD. The removal of solvent from the drug–CD complex can also influences the complexation. Method, such as spray drying and freeze drying are most effective for drug complexation.

Temperature: Processing factors, such as temperature, should be considered so as to make CD function as better solubilizers. In general, increasing the temperature increases intrinsic solubility of drug as well as drug–CD complex, whereas it decreases the magnitude of the apparent stability constant (destabilizes the complex), hence need to be balanced. As heat stability of the complex varies from guest to guest, most complexes start to decompose at 50–60 °C, while some complexes are stable at higher temperatures, especially if the guest is strongly bound or the complex is highly insoluble.

4 | ENHANCEMENT OF COMPLEXATION EFFICIENCY

Various methods which improve the CE of drug–CD are described below (Loftsson & Brewster, 2012).

Drug ionization: Ionization of weakly acidic and basic drugs increases its apparent intrinsic solubility which in turn enhances complexation.

Salt formation: Apparent intrinsic solubility of acidic and basic drugs is often enhanced due to water soluble salt formation without compromising CE. The aqueous solubility of the salt is driven by factors, such as the solubility product constant of the salt, the pKa, and solubility of the unionized drug.

Amorphous form: Complexation can convert the crystalline drug to more soluble amorphous form and hence the CE.

Polymer complexes: Incorporation of water-soluble polymers like carboxymethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol 6,000, polyvinylpyrrolidone K30, serum albumin, and so forth, increase complexation efficiency when combined with certain parent CDs or their substitutes. This is perhaps due to the formation of a ternary complex by these water-soluble polymers with drug–CD complex.

Acid–base complexes: Hydroxy acids in the CD solutions enhance CE and there by solubility of drugs.

Metal complexes: Drugs which can form a water-soluble complex with metal ion and with CDs will improve the CE.

Co-solvents: Use of co-solvents like propylene glycol that can improve drug solubility will also enhance the CE.

Ion pairing: Opposite charged drug and CDs increase the complexation, while identical charges decrease.

A combination of two or more approaches described above has been often used and demonstrated synergetic effect in improving the CE.

5 | METHODS OF PREPARING CD COMPLEXES

Method of preparation of CD-complex considerably influences the final product. Indeed, the optimization of water content, degree and time of mixing, temperature and time of heating are critical for efficient inclusion complexation. It should be kept in mind that the final product in most of the approaches (except precipitation) will have the free guest, empty CD, and complex. Different approaches have been described to prepare molecular inclusion compounds of CDs and are briefed below.

5.1 | Kneading or slurry method

This method involves the addition of CD powder to a high-shear mixer followed by gradual addition of water while mixing in a specific ratio. The mixing is continued until a homogeneous viscous paste is obtained. Then, the guest molecule to be complexed can be gradually added to the mixing paste, the product is kept for 24 hr to equilibrate. This is followed by washing, filtration, drying, grinding, and sieving of the powder.

5.2 | Solution or co-precipitation method

Precipitation method is probably the most commonly used approach in research laboratories. This method is simple to perform wherein drug in water miscible solvent is mixed with CD in water. They are dispersed in hot to obtain a concentrated, viscous, and translucent solution. The equilibrated mixture is then allowed to cool to precipitate a highly crystalline and pure inclusion complex. Similarly, precipitation of drug–CD complex can be achieved by adding antisolvent, which precipitates the complex.

5.3 | Solvent evaporation

In solvent evaporation method, both the drug and the CD are generally dissolved in water by mixing it for hours. Then, the solvent is removed at stable temperature under vacuum. Alternatively, it can be spray dried or freeze dried.

5.4 | Dry mixture

Typically, inclusion complexes with oils or liquid guests can be prepared by directly adding and mixing the guest to the CD. This method does not result in immediate inclusion complex but encapsulation depends on the type of active ingredient. Dry mixture when dissolved in situ (e.g., in the mouth or GI tract) will equilibrate and form the required complex. Unlike simple mixing, high-energy grinding can yield true inclusion complex with activated residual moisture content.

5.5 | Damp mixing

The drug and CD are efficiently mixed with minimum volume of water and kept in a sealed container. The mixture is then heated at a high temperature (~100 °C), subsequently removed from the container and dried.

5.6 | Extrusion

The CD, guest and water are either premixed or mixed when added to the extruder. The extruded materials may be allowed to dry at room temperature or in a hot air or vacuum oven.

6 | GUEST MOLECULE RELEASE

Dissociation of drug–CD complex is equally important as that of their association. A simple dissolution of the guest-CD complexes and their subsequent dilution in aqueous environment is the process involved in the guest release from CD complexes. Hence, CD-based complexes are widely investigated to improve the solubility of BCS class II drugs. In oral delivery, the drug–CD complex is expected to release the guest rapidly in the gastro intestinal tract (GIT). A rapid dissolution of drug in GIT has several significances; for instance the rapid dissolution may make the transporters saturate and improve permeability of drugs undergoing apical efflux. In intravenous (IV) administration, the drug is both rapidly and quantitatively released from drug–CD complex. This rapid release of drug from CD complexes is attributed to competitive replacement, partitioning of drug from complex as well as binding with plasma protein and tissues. It is also reported that the CD complex usually influence the pharmacokinetics of drug when the stability constant value is $>10^5\ M^{-1}$ (Kurkov, Loftsson, Messner, & Madden, 2010).

7 | DERIVATIVES OF CD

Biotechnological advancement has resulted in the development of nonhygroscopic, highly purified CDs and its derivatives that are most acceptable for various pharmaceutical, industrial and scientific applications (Jambhekar & Breen, 2016a, 2016b; Stella & He, 2008). Due to the presence of numerous hydroxyl groups in CDs, it is easy to introduce different types of linkages for specific purpose. CDs can also be easily cross-linked or derivatized to yield monomers which can give raise to either linear or branched networks. The CD derivatives currently used as pharmaceutical excipients for commercial applications are α, β, γ-CD and methyl (M), hydroxypropyl (HP), and sulfobutyl ether (SBE) substituents.

7.1 | Methylated CD

The aqueous solubility increases as the methylated substitution increases up to 14 groups for the β-CD ring. The M14-β-CD, a random methylated β-CD (RM-β-CD) demonstrates an increase in aqueous solubility as temperature rises and significantly improves the solubility of various drugs. A partially methylated (MS 1.8-2) β-CD that has an aqueous solubility that increases with increase in temperature. However, a low substituted (MS = 0.57) methylated β-CD exhibits a better biocompatibility even in elevated temperature.

7.2 | Hydroxypropyl CD

The 2-HP derivatives of both β and γ-CD are commercially available as pharmaceutical excipients. Monosubstituted derivative, 2-HP-β-CD, a neutral CD, shows good complexation with neutral drugs. HP-β-CD derivatives, with DS of 2.7 or more shown less water uptake, improved aqueous solubility (>50% w/v) and complexing ability with minimum surface activities.

7.3 | Sulfobutyl ether

The sulfonate and sulfoalkyl ether (SAE) derivatives with varying solubility are typically synthesized by reacting sultone with a CD in the presence of base. Due to amorphous characteristics, SBE-β-CD are highly water soluble (>50% w/v). SBE-β-CD is anionic in nature and have poor complex with neutral and anionic drugs because of electrostatic interaction. However, it shows good complexation with cationic drugs because of high binding constant. The binding capacity of the SAE-β-CD derivatives is based on the guest compound, the DS and the alkyl ether chain length.

8 | PHARMACOKINETICS OF CDS

The major fraction of orally administered α and β-CD are degraded in the colon because of the digestive activity of bacterial enzymes. The percentage oral absorption value of γ-CD is negligible (0.02%) due to rapid degradation by the gut wall enzymes of upper GI tract (Munro, Newberne, Young, & Bär, 2004). However, the derivatives of CD are strongly resistant to hydrolytic decomposition than parent CD. Conversely, after IV administration, significant amount of α and β-CD are excreted unchanged while limited metabolism was demonstrated with γ-CD. In humans, the average values of half-life, volume of distribution, and clearance in HP-β-CD has been reported as high when compared with SBE-β-CD.

Safety after peroral administration of α, β, and γ-CD as well as CD derivatives (M12-β-CD, HP3-β-CD, and SBE7-β-CD) was investigated in various animals like mice, rats, or dogs, including detailed evaluation of haematology and pathophysiology (Stella & He, 2008). A number of safety evaluations have shown that γ-CD, 2-HP-β-CD, SBE-β-CD, sulphated β-CD, and maltosyl β-CD are practically nontoxic and safe

TABLE 1 Pharmaceutical and pharmacokinetic properties of cyclodextrins

CD	Molecular weight (Da)	Degree of substitution	Molar degree of substitution[a]	Approximate cavity diameter (°A)	Oral absorption (in rats) %	Aqueous solubility % w w^{-1}[b]	Pharmacokinetic parameters (in rats)		Current pharmaceutical use
							$t_{1/2}$ (min)	CL_T (ml h^{-1} kg^{-1})	
α-CD	972	>18	0	4.7–5.3	1	13	*	*	Oral and parenteral products
β-CD	1,135	>21	0	6–6.5	0.6	2	23.9–50.2	204–372	Oral, buccal, and topical products
2-HP-β-CD	1,400	2.7	0.4–1.5	6.2	3	>60	24	512	Oral, parenteral, rectal, and ophthalmic products
SBE-β-CD	2,163	7	0.9	6–7.1	1.6	>50	18	588	Parenteral products
Methylated-β-CD	1,312	10.4	1.8	4–7	≤12	23.2	420 (rabbit)	228 (rabbit)	Ophthalmic and nasal products
γ-CD	1,297	>24	0	7.5–8.3	0.02	26	15–20	*	Parenteral products
2-HP-γ-CD	1,576	0.6	0.6	10.75	<0.1	>50	*	*	Parenteral and ophthalmic products

[a] Average number of substituents per glucose repeat unit.
[b] Solubility in pure water at ~25 °C.
*Not available.

when administered parenteral. The pharmacokinetic properties of CDs and CD derivatives are listed in Table 1.

9 | SIGNIFICANCE OF CD COMPLEXATION

9.1 | Aqueous solubility, dissolution, and bioavailability

Typically, the drug properties such as low aqueous solubility and low dissolution in biorelevant dissolution media demands CD complexation to enhance their solubility and dissolution efficiency. Therefore, the drug–CD complexes are expected to offer a dose solubility ratio ≤250 ml or more precisely the complex should exhibit sufficient solubility in the GI fluid. Further, a rapid drug dissolution (>0.1 mg ml^{-1}) in GI fluid is expected from such complexes to overcome dissolution rate-limited drug absorption. In addition, low molecular weight (100–500 Da) and low dose (5–50 mg) drugs are good candidates for CD complexation to improve both solubility and dissolution. In aqueous solutions, CDs can form inclusion, noninclusion complexes and hydrogen bond formation with adjacent CD molecules (Sallas & Darcy, 2008). However, the extent of solubility enhancement is limited by the drug molecular weight and CD concentration. For instance, a 1:1 complex between drug (MW 350 Da) and CD (0.1 M) can dissolve only up to 0.1 M drug or 35 mg ml^{-1} (assuming the *K* value is infinitely large). Thus, the possible enhancement in solubility can be predicted before performing the experiment.

Poorly soluble drugs generally display inadequate or highly variable absorption following oral delivery. However, the solubility enabling CD complex shows enhanced aqueous solubility and dissolution characteristics of hydrophobic drugs without changing their molecular structure. This characteristic feature can significantly contribute toward an improvement of oral bioavailability of drugs whose absorption is dissolution rate limited (Nair et al., 2014). In general, complexation using CD to enhance oral bioavailability is usually investigated for drugs with high lipophilicity (log p > 2.5), poor water solubility (1 μg ml^{-1} – 1 mg ml^{-1}) and low dose (<100 mg). The formulator should keep in mind that if a factor other than dissolution kinetics is resulting in poor bioavailability (e.g., low permeability of the intestinal membrane to the compound being studied), it is unlikely that formulation with CD will result in bioavailability enhancement. Hence, interpreting the release kinetics and appropriately controlling the thermodynamic activity by optimizing the molar ratio of drug:CD complex are the key factors that can improve oral bioavailability. The utility of CDs for enhancing oral bioavailability, the mechanism by which they influence these processes has been reviewed elsewhere (Carrier, Miller, & Ahmed, 2007). In aqueous CD solutions, the bioavailability of a drug is influenced by its potential to interact with CD molecules as well as their concentration ratio. Therefore, an optimum concentration of drug:CD is important to achieve maximum bioavailability. Typically, a drug:CD ratio of 1:2 or less has been used in most of the oral formulations aimed to improve bioavailability. One should also remember that the formulation ingredients can influence the drug–CD interaction and therefore consider optimizing final formulation with regard to the amount of CD (Loftsson & Brewster, 2011, 2012). CD complexes were also combined with other excipients (polymers, lipids, surfactants, ion exchange resins) to improve the solubility or dissolution of therapeutic actives (Di Cagno, Nielsen, Larsen, Kuntsche, & Bauer-Brandl, 2014). Table 2 summarizes the list of drugs which are investigated to improve aqueous solubility, dissolution rate, absorption, permeability, or oral bioavailability using various CDs. CDs are also widely investigated to enhance the bioavailability of pharmaceutical actives in other routes like ophthalmic, nasal (Kulkarni & Avachat, 2017), buccal, transdermal, and so forth. (Yang, Hussain, Paulson, Abbruscato, & Ahsan, 2004).

As compared with the other solubilization techniques, the drug–CD complexes have several advantages. In general, the common solubilization techniques contain nonaqueous solvents, surfactants, or emulsifying agents which cause tissue irritation and other adverse reactions (Del Valle, 2004). In addition, these products on dilution with aqueous solvent generally cause precipitation of drug, unlike drug–CD complexes. Conversely, as no covalent bonds are involved,

TABLE 2 List of drugs complexed with various CDs to improve aqueous solubility, dissolution rate, absorption, permeability, or oral bioavailability

CDs	Drugs
α-CD	α-Methylstilbene, β-lapachone, Alprostadil, Apigenin, artemisinin, Astemizole, Azadirachtin, Baicalein, beclomethasone dipropionate, betamethasone, Bromazepam, Camptothecin, Cefotiam hexetil HCl, celecoxib, cetirizine, Chlordiazepoxide, Clobazem, clonazepam, coenzyme Q10, cortisone, curcumin, dexamethasone, diazepam, Droepiandrosterone, Econazole, Fludiazepam, Flunitrazepam, Fluocinolone acetonide, Flurazepam, Glibenclamide, Griseofulvin, hydrocortisone, Ibuproxam, isotretinoin, Ketoprofen, Limaprost, limonene, Loratadine, lorazepam, Medazepam, Melarsoprol, meloxicam, Nerolidol, Nimesulide, Nimetazepam, Nitrazepam, Oxazepam, Paramethasone, Praziquantel, prednisolone, progesterone, risperidone, R-α-lipoic acid, salbutamol, sildenafil, simvastatin, spironolactone, Sulfadimethoxine, Terfenadine, testosterone, triamcinolone
β-CD	α-Methylstilbene, β-lapachone, 5-fluorouracil, Aceclofenac, acyclovir, Albendazole, Altretamine, amiodarone, amitriptyline, amlodipine Besylate, Apigenin, aripiprazole, artemisinin, Astemizole, atenolol, atorvastatin, Azadirachtin, Baicalein, beclomethasone dipropionate, Bendazac, Benexate HCl, Benznidazole, Berberine hydrochloride, betamethasone, Borneol, Bromazepam, Camptothecin, candesartan Cilexetil, Carvacrol, carvedilol, Cefdinir, Cefixime, cefuroxime axetil, celecoxib, cetirizine, Cetirzine, Chlodizepoxide, Chlordiazepoxide, Chlorogenic acid, Chlorthalidone, Cilostazol, Clobazem, clonazepam, clove oil, coenzyme Q10, copaiba, cortisone, curcumin, cyclobenzaprine, dexamethasone, diazepam, Diosgenin, doxorubicin, Econazole, Efavirenz, Epothilone A, Eslicarbazepine acetate, estradiol, Ethionamide, Etodolac, famotidine, Felodipine, Fexofenadin, finasteride, Fludiazepam, Flunitrazepam, Fluocinolone acetonide, Flurazepam, Flutamide, fluticasone propionate, furosemide, Gefitinib, gemfibrozil, Glibenclamide, Gliclazide, Griseofulvin, haloperidol, Hesperetin, hydrochlorothiazide, hydrocortisone, Hypericin, ibuprofen, Ibuproxam, Imatinib, indomethacin, insulin, Irbesartan, Itraconazole, Itraconazolium, Ketoconazol, Ketoprofen, Ketotifen, lansoprazole, leuprolide acetate, Limaprost, limonene, Lonidamine, Loratadine, lorazepam, Manidipine, Mebendazole, Medazepam, Melarsoprol, meloxicam, Meropenem, methotrexate, Methoxybutropate, metronidazole, naproxen, Naringenin, Naringin, Natamycin, Nerolidol, Niclosamide, nicotine, Nimesulide, Nimetazepam, Nitrazepam, nitroglycerin, Norfloxacin, nystatin, olanzapine, Oridonin, Oxaliplatin, Oxatomide, Oxazepam, paclitaxel, Paramethasone, Pedunculoside, phenylalanine, pioglitazone, Piperine, Piroxicam, Pizatifen, polyphenols, Posaconazole, Praziquantel, prednisolone, progesterone, propyl gallate, Racecadotril, Raloxifene, Regorafenib, Repaglinide, resveratrol, Rhein, Ribendazole, Rifabutin, Rifaximin, risperidone, Rofecoxib, Rosmarinic acid, R-α-lipoic acid, salbutamol, sildenafil, simvastatin, siRNA, sodium Diflunisal, spironolactone, squalene, Sulfadimethoxine, Sulfamerazine, sulfamethazine, sulfamethoxazole, tacrolimus, Tadalafil, Telmisartan, Tenoxicam, Teprenone, Terfanidine, testosterone, Tetracaine, theophylline, thymol, Tiaprofenic acid, Tocotrienol, Tolbutamide, triamcinolone, vanillin, vitamin D2, warfarin, Zaltoprofen
2-HP-β-CD	α-Methylstilbene, β-lapachone, 5-fluorouracil, 9-nitro camptothecin, Aceclofenac, acetazolamide, Acetohexamide, Acitretin, acyclovir, Albendazole, Alfaxalone, alprazolam, Amylobarbitone, Andragrapholide, Apigenin, aripiprazole, Artemether, artemisinin, Astemizole, Azadirachtin, Baicalein, Barbigerone, Bendazac, Benznidazole, Brinzolamide, Bromazepam, Bropirimine, Camptothecin, Canthaxanthin, carbamazepine, Carbendazim, carvedilol, Cefdinir, Cefixime, celecoxib, Chlorzoxazone, Cilnidipine, Cilostazol, Cinnarizine, Cisapride, clomipramine, Clotrimazole, clozapine, coenzyme Q10, copaiba, curcumin, Cyproterone acetate, Daidzein, Danazole, Dantrolene sodium, Darifenacin, dexamethasone, diazepam, diclofenac, digoxin, Dihydroartemisinin, diphenhydramine HCl, disulphiram, docetaxel, doxorubicin, Dutasteride, DY-9760e, Econazole nitrate, Efavirenz, Epothilone A, estradiol, ETH-615, Etodolac, etomidate, Fexofenadin, finasteride, Fisetin, Flavopiridol, Flurbiprofen, Flutamide, fluticasone propionate, furosemide, Gallic acid, Gefitinib, Glibenclamide, Gliclazide, glutathione, glyburide, Gonadorelin, Griseofulvin, Hesperetin, hydrocortisone, ibuprofen, Iloperidone, indomethacin, insulin, isotretinoin, Itraconazole, Ketoprofen, Ketotifen, lansoprazole, Levemopamil HCl, Ligustilide, Loratadine, Mebendazole, meclizine HCl, Melarsoprol, meloxicam, Melphalan, methotrexate, Methoxybutropate, miconazole, Mitomycin, Myricetin, Naftifine, naproxen, Naringenin, Natamycin, Nerolidol, Nicardipine, Niclosamide, Nifedipine, Nimesulide, Nitrazepam, olanzapine, Oxaliplatin, oxcarbazepine, paclitaxel, Perphenazine, phenytoin, Phloridzin, pioglitazone, Piroxicam, Pizatifen, prednisolone, Pregnenolone, progesterone, Propofol, propyl gallate, quercetin, Raloxifene, Regorafenib, Repaglinide, resveratrol, Rhein, Ribendazole, risperidone, Rutin, Saquinavir, SID530, sildenafil, sodium Diflunisal, spironolactone, Sulfamerazine, sulfamethoxazole, Sulfisoxazole, tacrine HCl, Tadalafil, Tanshinone IIA, Telmisartan, testosterone, Tetracaine, theophylline, Tolbutamide, triamcinolone acetonide, Triazolam, Triclosan, trimethoprim, Valdecoxib, Voriconazole, Vorinostat, Zerumbone, zolpidem
SBE-β-CD	7-hydroxy-4-methylcoumarin, acetazolamide, Alphaxalone, amiodarone hydrochloride, Apigenin, Aprepitant, aripiprazole, artemisinin, Asenapine, Berbamine, Camptothecin, carbamazepine, chlorpromazine hydrochloride, Danazol, dexamethasone, docetaxel, dopamine, DY-9760e, Econazole nitrate, Edaravone, estradiol, etomidate, finasteride, Fluasterone, Flunitrazepam, fluticasone propionate, Glaucocalyxin A, Glibenclamide, hydrocortisone, insulin, Ketoprofen, Maropitant, methylprednisolone, miconazole, naproxen, Naringenin, Nerolidol, Nitrazepam, phenytoin, pioglitazone, prednisone, progesterone, Propofol, propyl gallate, quercetin, Spiranolactone, tacrine HCl, testosterone, Voriconazole, ziprasidone
Methylated-β-CD	α-Methylstilbene, β-carotene, Aceclofenac, Albendazole, Ambenonium, Azadirachtin, Benznidazole, Camptothecin, curcumin, Daidzein, estradiol, Exemestane, finasteride, Flurbiprofen, Hesperetin, ibuprofen, ketoconazole, Ketoprofen, Mebendazole, meloxicam, Naftifine, naproxen, Nimesulide, olanzapine, omeprazole, phenytoin, pioglitazone, quercetin, rapamycin, Ribendazole, salbutamol, Sulfamerazine, sulfamethazine, valsartan
RM-β-CD	17β-Oestradiol, Albendazole, Apigenin, chloramphenicol, Cyproterone acetate, ETH-615, Glibenclamide, Hesperetin, Imatinib, Melarsoprol, midazolam, Nerolidol, Repaglinide, rifampicin, tacrolimus, Vorinostat
DM-β-CD	α-Tocopheryl nicotinate, Azadirachtin, Baicalein, Camptothesin, carbamazepine, Cilostazol, Clotrimazole, Cyclosporin A, diphenhydramine HCl, finasteride, Flutamide, Isoquercitin, Ketoprofen, leuprolide acetate, Loratadine, midazolam, naproxen, Naringenin, Oxazepam, paclitaxel, Posaconazole, propyl gallate, spironolactone, tacrolimus, Tadalafil
γ-CD	α-Methylstilbene, β-lapachone, Amisulpride, amphotericin B, artemisinin, Astemizole, Azadirachtin, Baicalein, beclomethasone dipropionate, Bendazac, betamethasone, Bromazepam, Camptothecin, celecoxib, cetirizine, Chlordiazepoxide, Cilostazol, Clobazem, clonazepam, coenzyme Q10, cortisone, curcumin, Cyproterone acetate, dexamethasone, diazepam, diclofenac sodium, digoxin, doxorubicin, Epothilone A, Fludiazepam, Fluocinolone acetonide, Flurazepam, Flutamide, gemfibrozil, Glaucocalyxin A, Glibenclamide, hydrocortisone, Ibuproxam, indomethacin, Irbesartan, Josamycin, Ketotifen, lorazepam, Medazepam, meloxicam, midazolam, Naftifine, Natamycin, Nimesulide, Nimetazepam, Nitrazepam, nystatin, omeprazole, Oxaliplatin, Oxazepam, Paramethasone, peptides, Picoplatin, pioglitazone, Piroxicam, Pizatifen, Praziquantel, prednisolone, progesterone, Regorafenib, risperidone, R-α-lipoic acid, salbutamol, salicylic acid, sildenafil, sodium Diflunisal, squalene, Telmisartan, Teprenone, testosterone, Tocotrienol, triamcinolone
2-HP-γ-CD	Amphotericin B, Camptothecin, curcumin, Cyproterone acetate, dexamethasone, diclofenac sodium, gemfibrozil, hydrocortisone, indomethacin, phenytoin

the integrity of the active pharmaceutical ingredient is well preserved in drug–CD complexation.

9.2 | Tissue irritation

CDs are frequently used to reduce tissue irritation and toxicity produced by drugs when administered by various routes. Increasing the drug solubility by complexation can reduce the dose required for optimum therapeutic activity as demonstrated in various studies. In one attempt Nicolazzi, Venard, Le Faou, and Finance (2002) have demonstrated that the complexation of ganciclovir with β-CD magnified the antiviral activity on human cytomegalovirus which in turn drastically reduced tissue toxicity. Similarly, soluble drug–CD complexes diminish the toxicity due to precipitation of a sparingly soluble drug, phenytoin, when formulated as parenteral dosage (Blanchard, Ugwu, Bhardwaj, & Dorr, 2000). SBE7-β-CD inhibited the DY-970e-induced cellular damage and thus reduced the drug-induced vascular damage in rabbits (Nagase et al., 2003). In addition, hydrophilic CDs like 2-HP-β-CD had been reported to promote the chemical stability, minimize local drug irritation as well as toxicity to the eye. Similarly, less tissue irritation was noticed for ophthalmic, IV, and intramuscular (IM) route of administration and in cellular injury screening tests. Combination of CD with naproxen, indomethacin, and piroxicam induce less GI irritations than drug given individually (Alsarra et al., 2010).

9.3 | Stability

Both parent and CD derivatives can protect the susceptible drugs against hydrolysis, oxidation, photodecomposition, as well as increase the drug shelf-life. The magnitude of stabilization/destabilization of a drug complexing with a CD depends on the degradation rate, the fraction of drug that is complexed and the stoichiometry. In addition, the nature of the functional group as well as the type of the vehicle controls the stabilizing effect of CDs. The stabilization potential of CDs against degradation has been reported for number of drugs including nicardipine, prostaglandin E1, and glucagon (Matilainen et al., 2009). The potential of β-CD inclusion complex to improve the photochemical stability was demonstrated with trimethoprim and promethazine (Lutka, 2002). Development of formulation containing CDs to improve the physical stability of viral vectors for gene therapy has been reviewed elsewhere (Croyle, Cheng, & Wilson, 2001).

9.4 | Taste masking

The inclusion complexation of drugs with CDs can contribute satisfactory taste masking effects without altering the dissolution and drug release performance of drugs. Both native and derivatives of CDs are used in masking the bitter taste of drugs like meloxicam, cetirizine, fluconazole, and so forth (Samprasit et al., 2015). Evaluating the host-guest kinetic interactions between drugs and HP-β-CD for the prediction of taste masking properties has been explored. It was established that a relationship constructed between K_a, K_d, and $K_{a:b}$ has the potential to project the magnitude of taste masking (Guo et al., 2017). Recently, the potential of hot melt extrusion technique has been demonstrated to mask the bitter taste of drugs using β-CD and HP-β-CD (Malaquias et al., 2018). In addition, the CDs are also combined with other approaches such as ion exchange resin to reduce the bitter taste as well as to improve solubility of poorly soluble drugs (Samprasit et al., 2015). Suppression of bitter taste of drugs by CD complexation with its performance, evaluations, and mechanisms were detailed elsewhere (Arima et al., 2012).

10 | CD IN DRUG DELIVERY SYSTEMS

The contribution of CD and their derivatives in various drug delivery systems has been reviewed elsewhere (Palem, Chopparapu, Subrahmanyam, & Yamsani, 2012). Numerous drug delivery applications have been reported with CDs when used alone or in combination with polymers, which in turn contributed synergistically. Indeed, the extensive studies carried out by combining CDs with both natural and synthetic polymers demonstrated the CDs compatibility with large number of polymers. This versatile additive is frequently used to modify drug release from different systems and is discussed in the following sections.

10.1 | Immediate release

In general, poorly soluble BCS Class II and BCS Class IV drugs can form inclusion complexes with hydrophilic CDs derivatives like HP-β-CD, SBE-β-CD, RM-β-CD, and TM-β-CD, and subsequently improved dissolution rate and oral bioavailability. Thus, CD–drug inclusion complexes included in immediate release dosage forms allows the drug to dissolve promptly in the GI fluid. Practical considerations of CDs in development of solid dosage forms and flow chart that outlines the various critical steps are illustrated by Miller, Carrier, and Ahmed (2007). The application of β-CD in formulating novel fast disintegrating tablets has been reported (Jacob, Shirwaikar, & Nair, 2009; Late & Banga, 2010). An overview on CDs-based oral drug delivery nanosystems has been reviewed recently (Adeoye & Cabral-Marques, 2017).

10.2 | Modified release

CDs can be considered as promising modified release carriers as they form inclusion complexes with especially hydrophilic drugs, including protein and peptides in solution as well as in solid state. Hydrophobic derivatives like acylated β-CD and cationic trimethyl-ammonium-β-CD are included in the formulation for prolonged release of drugs. in vitro release and bioavailability studies in rabbits suggested that the appropriate ratios of hydrophilic (HP-β-CD) and hydrophobic Triacetyl-β-CD (TA-β-CD) complexes could be used as a potential sustained release carrier (Fernandes, Carvalho, da Costa, & Veiga, 2003). The drug release pattern of silymarin in floating tablets was efficiently controlled by changing ratio of β-CD with other ingredients (Garg & Gupta, 2009). Goindi, Mann, and Aggarwal (2011) have formulated sustained release floating tablets incorporating curcumin in to β-CD and demonstrated exceptional gastro retentive behavior. In another attempt, the aqueous solubility, bioavailability and release of risperidone was improved from floating microparticles using complexing agents like HP-β-CD or M-β-CD (Ammar, Ghorab, Mahmoud, & Noshi, 2016).

10.3 | Delayed release

Hydrophobic CDs, such as O-Carboxymethyl-O-ethyl-β-CD (CME-β-CD) are preferred in delayed dosage forms because they show pH-dependent solubility due to the dissociation of the acidic group. Typically delayed release behavior demonstrates the suitability of CME-β-CD complex for drug targeting at specific regions of GI tract, such as colon (Sinha & Kumria, 2001). Ikeda et al. (2002) have demonstrated that the appropriate amounts of HP-β-CD in hydrophobic matrix of ethyl cellulose can be used as release retardant for highly water-soluble drugs. Delayed release behavior from 5-Flurouracil-β-CD conjugate was observed in large intestinal tract and cecum (Udo et al., 2010).

10.4 | Controlled release

Oral controlled delivery system has many advantages including fewer dose administration and minimum fluctuation of plasma drug concentration (Aldhubiab, Nair, Kumria, Attimarad, & Harsha, 2015; Nair, Gupta, & Vasanti, 2007). CDs and their hydrophilic/hydrophobic derivatives are frequently used to achieve controlled release of drugs from drug–CD complexes of solid dosage forms. Controlled release adhesive buccal tablets of piroxicam were developed with HP-β-CD and hydrophilic HPMC and carbopol polymer (Jug & Bećirević-Laćan, 2004). Control of release rate and membrane transport of drug incorporated in hydrophilic CDs in hydrophilic matrices, such as polyethylene oxide intended for oral drug delivery was studied (Miro et al., 2009). The feasibility of CD derivatives as release control agent in HPMC matrix tablets depends on the molecular size, nature of the CD, and physicochemical nature of the drug (Pose-Vilarnovo et al., 2004). in vitro release profile showed that the aldronate-β-CD-dexamethasone complexes bound to hydroxyapatite constantly release the drug in phosphate buffer saline (Liu, Reinhardt, & Wang, 2006). Enhanced pharmacological effect and reduced haemolytic effect was observed after controlled drug release from ropivacaine-2-HP-β-CD inclusion complexes (de Araujo et al., 2008).

Directly compressed, sustained release matrix tablet of metformin has been designed based on a combination of hydrophobic TA-β-CD dispersed in a polymeric material (Corti, Cirri, Maestrelli, Mennini, & Mura, 2008). Sustained release applications of hydrophobic alkylated and acylated-CD derivatives forming inclusion complexes with highly water-soluble drugs have been disclosed (Ganapathy, Lee, Park, & Lim, 2008). Siemoneit et al. (2006) examined the practicability of CD-PEG-based hydrogels for the rate-controlled delivery of lysozyme, beta-estradiol, and quinine.

10.5 | Osmotic drug delivery

Understanding the osmolality of CDs is important to characterize the release mechanisms from osmotic pump tablets. It was demonstrated that SBE7m-β-CD in controlled porosity osmotic pump tablet can serve as solubility modulator and osmotic releasing agent for different types of drugs (Okimoto et al., 2004). Notably, SBE7m-β-CD affects the release rate in a similar fashion for both hydrophilic and hydrophobic drugs. Studies in prednisolone-SBE7m-β-CD complexes indicated that, the release rate depends on the molar ratio between CD and drug, the microporous membrane thickness and the pressure difference across the barrier (Sotthivirat, Haslam, Lee, Rao, & Stella, 2009). The results from another study indicated that solubility and dissolution rate of lovastatin-β-CD were greatly improved in elementary osmotic pump tablet formulations (Mehramizi, Asgari, Pourfarzib, Kh, & Dorkoosh, 2007).

10.6 | Ocular drug delivery

The clinical efficacy of several therapeutic agents in the management of ocular disorders have been significantly improved by complexation using CDs. Table 3 summarizes the list of drug–CD inclusion complex investigated in the last decade in ocular delivery. Both native (α, β, γ) and CD derivatives (HP-β-CD, SBE-β-CD, TM-β-CD, DM-β-CD, RM-β-CD, and HP-γ-CD) were used in preparing various drug–CD complexes. Among the CD derivatives, HP-β-CD has been widely investigated owing to its potential to solubilize and stabilize drugs, reduces ocular irritation, and enhances ocular drug permeability while offering low toxicity (El, Soliman, El-Dahan, & Al-Zuhairy, 2017). Indeed, the utility of CD-drug complex to increase aqueous solubility, drug release, corneal permeability, bioavailability, and clinical efficacy of various categories of drugs including corneal inflammation, glaucoma, fungal infection, and age-related macular degeneration were demonstrated (Ahn et al., 2017). The literature also suggests that the drug–CD complexes have been effectively utilized in the management of local and systemic ophthalmic diseases and deliver greater amount of drug to various regions of eye. Additionally, the complex enhances stability, prolongs residence time, and improved bioadhesion, when prepared as various ocular formulations. Interestingly, it was demonstrated the complex have considerably improved safety, visual acuity, patient tolerance, and adherence, while reducing the incidence of adverse side effects like macular thickness, ocular irritation, and toxicity. CD–drug complex has been incorporated into various conventional and drug delivery systems including contact lens, ocuserts, nanoliposomes, nanospheres, microspheres, nanogels, in situ gels, and so forth. It is generally admitted that only the free drug, and not the complex HP-β-CD-drug, can penetrate the lipophilic barrier (Shimpi, Chauhan, & Shimpi, 2005). If a large excess of HP-β-CD is present, then insufficient free fraction of drug will be available for corneal permeation. Commercial pharmaceutical ophthalmic products of indocid (indomethacin) and Voltranen Ophtha (Diclofenac sodium) contain HP-β-CD and HP-γ-CD as solubilizing agent, respectively. in vivo toxicologic studies in rabbits with aqueous ophthalmic drops containing cyclosporin A-CD nanoparticles have been performed (Jóhannsdóttir et al., 2017). An in situ antifungal ophthalmic gelling formulation of HP-β-CD-voriconazole complexes was prepared using pluronic polymers and sodium alginate by cold gelation technique.

10.7 | Transdermal delivery

Few studies were reported on the transdermal drug delivery using CDs. In general, β-CDs and its derivatives have been investigated in transdermal systems to improve the solubility, permeation, bioavailability, and stability of pharmaceutical actives. The drug deposition using nanocarriers have been extensively studied to enhance the

TABLE 3 Applications of cyclodextrins in ocular drug delivery

Drug	CD	Outcome	References
Acetazolamide	HP-β-CD	Hyaluronic acid-itaconic acid films loaded with acetazolamide-CD-triethanolamine complexes showed strong bioadhesion and hypotensive effect in glaucoma	Calles et al. (2018)
Acyclovir	HP-β-CD	In situ gel ophthalmic formulation improved permeability of acyclovir	Li et al. (2018)
Brinzolamide	HP-β-CD	Nanoliposome showed ~10-fold increase in the apparent permeability and enhanced intraocular pressure reduction efficacy	Wang et al. (2018)
Ciprofloxacin	HP-β-CD	Increases solubility, stability, and in vitro release	Bozkir, Denli, and Basaran (2012)
Cyclosporin A	α-CD, γ-CD	Enhanced the drug solubility and the eye drop formulation did not cause ocular irritation or toxic side effects to the rabbit eyes	Jóhannsdóttir et al. (2017)
Dexamethasone	β-CD, γ-CD,	Effective transocular delivery of dexamethasone into the eye	Bucatariu, Constantin, Ascenzi, and Fundueanu (2016); Fiorica, Palumbo, Pitarresi, Bongiovì, and Giammona (2017)
Dexamethasone, amphotericin B	γ-CD, HP-β-CD	Developed CD-poloxamer self-assembled nanocarriers for ophthalmic drug delivery	Jansook, Pichayakorn, Muankaew, and Loftsson (2016)
Disulphiram	HP-β-CD	Colloid dispersions increased the AUC and mean corneal residence time	Nagai et al. (2015)
Dorzolamide	γ-CD, RM-β-CD	Increases solubility, permeability, and delivered drug to the posterior segment of eye	Jóhannesson et al. (2014); Loftsson, Jansook, and Stefansson (2012)
Doxycycline	HP-β-CD	Complex showed better stability and antibacterial activity	Zhang et al. (2013)
Econazole	SBE-β-CD	Chitosan-SBE-β-CD nanoparticles developed had the tendency to act as a carrier for controlled delivery of drug to eyes	Mahmoud, El-Feky, Kamel, and Awad (2011)
Honokiol	SBE-β-CD	Chitosan-SBE-β-CD nanoparticles exhibited good ocular tolerability and improve ophthalmic bioavailability	Deng, Hu, Chen, Tang, and Zhang (2018)
Indomethacin	HP-β-CD	Enhanced solubility, stability, safety, and management of corneal inflammation	Halim Mohamed and Mahmoud (2011)
Loteprednol Etabonate	β-CD, HP-β-CD	Gels, drops, and ocuserts significantly enhanced stability, ocular anti-inflammatory efficacy, and ocular bioavailability	Soliman et al. (2017)
Naringenin	SBE-β-CD	CD-chitosan nanoparticles provides sustained release, prolong residence time	Zhang, Liu, Hu, Bai, and Zhang (2016)
Natamycin	β-CD, HP-β-CD	Developed contact lens contain drug–CD complex	Phan, Subbaraman, and Jones (2014)
Riboflavin	α-CD, β-CD	Enhances solubility and permeability	Morrison, Connon, and Khutoryanskiy (2013)
Telmisartan	γ-CD	Suspension with higher stability and greater mucoadhesion was developed	Muankaew, Jansook, Sigurcrossed, Signsson, and Loftsson (2016)
Thiosemicarbazone	β-CD	β-CD-drug hydrogels provided controlled ocular release with optimal therapeutic range for 2 weeks	Glisoni et al. (2013)

clinical efficacy of therapeutic molecules (Jacob, Nair, & Al-Dhubiab, 2017). The CDs have also been combined with polymers or lipids to formulate nanocarriers (e.g., nanospheres, liposomes, or nanoemulsions) to provide cutaneous deposition of clonazepam, flurbiprofen, isotretinoin, itraconazole, meloxicam and so forth. Table 4 summarizes the list of drug–CD inclusion complex investigated in the last decade in transdermal delivery. Improved dermal permeation and stability of dexamethasone indicated that complexation significantly improve the physicochemical nature of the drugs (Lopez, Collett, & Bentley, 2000). Due to increased solubility as well as direct action on the stratum corneum, HP-β-CD/DM-β-CD-celecoxib complexes demonstrated an enhanced percutaneous absorption (Ventura et al., 2006). Attempt was also made to enhance the transdermal delivery from propofol-CD complex by iontophoresis, a physical enhancement technique (Juluri, Peddikotla, Repka, & Murthy, 2013). The prospective of drug–CD in enhancing the transungual delivery of terbinafine was also demonstrated (Chouhan & Saini, 2014; Nair, Sammeta, Vaka, & Murthy, 2009).

10.8 | Mucoadhesive delivery

The mucoadhesive properties of CDs have been already established in both buccal and vaginal drug delivery systems. A fivefold increase in mucoadhesion time by thiolated carboxymethyl chitosan-*g*-β-CD was noticed as compared to chitosan (Prabaharan & Gong, 2008). Similarly, bupivacaine HCl-β-CD-soluble β-CD-epichlorohydrin complexes was

TABLE 4 Applications of cyclodextrins in transdermal drug delivery system

Drug	CD	Outcome	References
Clonazepam	Me-β-CD	Liposomal and microemulsion formulations contain drug–CD complex showed greater solubility and permeation	Mura, Bragagni, Mennini, Cirri, and Maestrelli (2014)
Curcumin	HP-β-CD	Increases solubility, transdermal permeation of curcumin, and demonstrated better anti-inflammatory effect	Ghanghoria, Kesharwani, Agashe, and Jain (2013)
Diclofenac sodium	HP-β-CD	HP-β-CD grafted polyethyleneimine has proved as a potent skin penetration enhancer with no toxicity or skin irritation	Yan et al. (2014)
Epalrestat	ME-β-CD	Enhanced dissolution and skin permeation through hairless mouse skin	Furuishi et al. (2017)
Flurbiprofen	HP-β-CD	Polymeric nanospheres with drug–CD complex showed greater retention of drug in skin as well as stronger anti-inflammatory effect	Vega et al. (2013)
Isotretinoin	HP-β-CD	Elastic liposomes significantly increased the skin deposition, prolonged drug release and reduce skin irritation	Kaur, Puri, and Jain (2010)
Itraconazole	HP-β-CD	Deformable liposomes contain drug–CD complex showed greater cutaneous drug deposition	Alomrani, Shazly, Amara, and Badran (2014)
Levodopa	β-CD	Stability of levodopa was enhanced when complexed with β-CD in transdermal patches	Obaidat, Al-Shar'i, Tashtoush, and Athamneh (2016)
Lornoxicam	HP-β-CD	Incorporation of CD and propylene glycol in gel improved the skin permeation	Al-Suwayeh, Taha, Al-Qahtani, Ahmed, and Badran (2014)
Propofol	SBE-β-CD	Complexation significantly improved the passive and iontophoretic transdermal flux	Juluri, Peddikotla, Repka, and Murthy (2013)
Terbinafine	HP-β-CD	Demonstrated the potential of CD as a transungual permeation enhancer	Chouhan and Saini (2014)

found appropriate for the successful development of mucoadhesive buccal delivery (Jug, Maestrelli, Bragagni, & Mura, 2010). It was proved that a cationic polymer, hexadimethrine bromide, and an anionic CD, SBE-β-CD, exhibited mucoadhesion better than a buccal delivery system containing cationic polymer and a neutral CD, such as HP-β-CD (Sigurdsson et al., 2002). Literature also indicates that there are several mucoadhesive formulations where in various CDs are utilized to improve their efficacy (d'Angelo, Fraix, Ungaro, Quaglia, & Miro, 2017). Choi et al. (2014) have developed a thermo-mucoadhesive composite buccal formulation containing paclitaxel-DM-β-CD complex, Pluronic F127, and polyethylene oxide. A mucoadhesive buccal film incorporating flufenamic acid utilizing HP-β-CD, chitosan, and Kollicoat IR has been developed (Mura et al., 2010).

Mucoadhesive vaginal delivery system for acyclovir based on thiolated CD (β-CD-SH1563) complex has been formulated (Ijaz, Griessinger, Mahmood, Laffleur, & Bernkop-Schnürch, 2016). Hydrogel vaginal delivery system for a sustained release of HP-β-CD-dehydroepiandrosterone for the treatment of postmenopausal syndrome has also been formulated (Mennini, Casella, Cirri, Maestrelli, & Mura, 2016). Mucoadhesive vaginal gel having extended release and thermosensitive characteristics was prepared using clotrimazole-β-CD complex and a mucoadhesive polymer (Bilensoy, Rouf, Vural, Šen, & Hincal, 2006). Mucoadhesive gel formulation loaded with 5-fluorouracil-HP-β-CD complex showed better therapeutic efficacy during the treatment of human papilloma-induced cervical cancer (Bilensoy, Cırpanlı, Şen, Doğan, & Çalış, 2007). An attempt has been also made to develop bilayer gastroretentive dosage form for furosemide using HP-β-CD complex (Darandale & Vavia, 2012). Bioadhesive tablets containing itraconazole-CD complex for the treatment of vaginal candidiasis has been explored (Cevher et al., 2014).

10.9 | Nasal drug delivery

The β-CD and HP-β-CD complex coupled with alginate or chitosan polymer have been investigated for treating various neurodegenerative diseases via nasal drug delivery system (Gavini et al., 2009). Albumin nanoparticles containing β-CD, SBE-β-CD, HP-β-CD, and anti-Alzheimer's drug, tacrine for brain targeting have been explored (Luppi et al., 2011). Polymeric nanospheres contain HP-β-CD for brain targeting showed significant neuroprotective effects on β-amyloid (1–42) induced toxicity (Yalcin et al., 2016). Intranasal targeting to striatum using thiomer-based dopamine nanoparticle using SBE-β-CD, chitosan, glycol chitosan, and polyanion crosslinking agent has been developed (Di Gioia et al., 2015). Pharmacokinetic studies showed that intranasal delivery of carfentanil-DM-β-CD absorbed more promptly and has higher bioavailability as compared to IM injection or oral administration (Yang et al., 2018). Permeation of HPMC-based pH-triggered in situ gel containing paliperidone-HP-β-CD across sheep mucosa demonstrates the potential role of HP-β-CD as nasal permeation enhancer (Sherje & Londhe, 2018). Similarly, rapid nasal absorption after administration of CD-mediated asenapine, an atypical antipsychotic psychiatric medication as in situ gel was reported (Kulkarni & Avachat, 2017). CD-based microemulsion and microparticles were also developed for intranasal administration to improve bioavailability and higher targeting efficiency.

10.10 | Drug targeting

Increasing the drug lipophilicity based on the concept of Bodor's chemical delivery system is exploited for brain targeting in CD-based drug formulations (Buchwald & Bodor, 2016). Oral administration of chitosan/alginate/phospholipid in combination with β-CD was explored for brain targeting (Shan et al., 2016). Promising results were

shown after clinical trials of KLEPTOSE CRYSMEB and 2-HP-β-CD-based therapy as cholesterol-chelating agent in atherosclerosis and Niemann-Pick type C disease (Coisne et al., 2016). β-CD-based inclusion complexes for targeted drug delivery system incorporating aspirin (Ma et al., 2015) and diclofenac (Vieira et al., 2016) have been demonstrated. Advantages of modified β-CDs as brain delivery vectors for RNAi-based therapies in Huntington's disease were investigated (Godinho, Ogier, Darcy, O'Driscoll, & Cryan, 2013). The role of ligand-attached CD-based tumor targeting has been reviewed by Yin, Zhou, and Zhou (2013). Potential use of folate-conjugated β-CD-based amphiphilic polymeric micelles containing doxorubicin as promising nanocarriers for enhanced targeted antitumor drug delivery has been reported (Zhang, Lu, Jin, & Qiu, 2014). Erdogar, Varan, and Bilensoy (2017) have described the potential uses and pharmaceutical applications of amphiphilic CD for targeted drug delivery in tumor. Lactoferrin conjugated to β-CD via polyethylene glycol linker is used for brain targeting of hydrophobic drugs and diagnostic agents (Ye et al., 2013). CDs also find their ways in gene delivery and have been reviewed elsewhere (Mellet, Fernández, & Benito, 2011).

10.11 | Nanoparticles and self-aggregates

Extensive studies signified that amphiphilicity is important for self-assembling characteristics and are imparted by the chemical modification of CDs (Bonnet, Gervaise, Djedaïni-Pilard, Furlan, & Sarazin, 2015). Particulate drug delivery systems made of CD molecules frequently has a particle size of 1 nm and self-assembled CD aggregates have diameter of about 100 nm. In case of amphiphilic CDs, the stability of nanoparticles formed are directly proportional to the hydrophobicity of the derivatives. Hydrophobic β-CD linked chitosan were shown to form pendant core cavities, while surface active guest such as hydrophobic drug form inclusion complex or mixed micelle like formation. It has the potential applications in drug delivery system due to preservation of conformation as well as integrity of inclusion complexes (Auzély-Velty & Rinaudo, 2002). Fatty acid-CD complexes also form polymer micelle-like structures that enhance the solubility of poorly soluble drug in aqueous solutions (Bochot et al., 2007).

CDs also found extensive application as a multifaceted drug delivery carrier in nanotechnology drug delivery system. Generally, nanoparticles are formed by incorporating previously formed CD-drug inclusion complexes into polymeric nanoparticles. Drugs with both hydrophilic and lipophilic characteristics can be included to design such as versatile drug delivery systems. It was suggested that the self-assembled nanoparticles prepared from carboxymethyl dextran-γ-CD conjugate could be considered as a potential carrier for the delivery of poorly soluble drugs (Sivasubramanian et al., 2013). Investigation of inclusion complexes of doxorubicin with oligomeric β-CD nanoparticles and fibrin gel as biomaterial hold great promise for clinical use in local anticancer therapy for tumors that are resistant to surgical treatment (Viale et al., 2017).

Solid-lipid nanoparticles prepared with hydrocortisone and progesterone using β-CD and HP-β-CD shown slower release profile from inclusion complexes as compared with free drug when administered orally (Kamboj, Bala, & Nair, 2010). Anionic polymerization technique using HP-β-CD for the preparation of nanospheres and nanoprecipitation technique used for the preparation of amphiphilic diesters were reported. Tozuka et al. (2004) has demonstrated that nanoparticle formation by co-grinding technique with CD can be successfully used for improving aqueous solubility of poorly soluble drugs. It was revealed that 6-guanidino-6-deoxy CDs can interact strongly with DNA and can be compressed into nanoparticles, which can be used in DNA transfection studies (Mourtzis et al., 2007). An increase in entrapment efficiency was observed as compared with chitosan-based nanocapsules because of greater molecular interaction between the drug and HP-β-CD (Du, Xu, Wang, Yuan, & Hu, 2009). in vitro and ex vivo studies demonstrated that dried solid-lipid nanoparticles consists of HP-β-CD and diclofenac sodium can be proposed for colon targeted delivery systems (Spada, Gavini, Cossu, Rassu, & Giunchedi, 2012).

Controlled oral insulin release from cationic-β-CD-insulin retained in the core of alginate/chitosan nanoparticles has been demonstrated (Zhang et al., 2010). Mucoadhesive property of poly(anhydride) nanoparticles was increased by the incorporation of CDs in GantrzAN nanoparticles, which in turn improve the interactions with mucosal components (Agüeros et al., 2009). Amphiphilic CD nanoparticles seem to be a promising substitute for parenteral paclitaxel formulation with minimum toxicity and comparable therapeutic efficacy (Bilensoy et al., 2006). It was recommended that amphiphilic CD nanoparticles with different surface charges can be used for safe and effective chemotherapy (Varan, Benito, Mellet, & Bilensoy, 2017). Paclitaxel-β-CD nanoparticles showed higher bioavailability as compared with paclitaxel-6-monodeoxy-6-monoamino-β-CD nanoparticles (Agüeros, Zabaleta, Espuelas, Campanero, & Irache, 2010). Biodegradable self-assembled macromolecular micelles prepared from carboxymethyl-β-CD is also a promising nanocarrier platform for drug delivery applications (Chen et al., 2016).

Amphiphilic CDs that self-assemble to form stable nanocarriers with distinctive structures and properties has been described (Trapani, Garcia-Fuentes, & Alonso, 2008). The aliphatic and hydrophobic functional groups can influence the surface characteristics of amphiphilic CDs and subsequent interaction with membrane. Investigations revealed that unsubstituted secondary amphiphilic CDs could be an ideal choice for targeted drug delivery (Bonnet et al., 2015). It was shown that the inclusion of HP-β-CD enhanced the solubilizing efficiency of γ-CD and HP-γ-CD nanoparticles. The results from another study suggested that hybrid CD-camptothecin nanocapsules could be used for oral chemotherapy (Ünal, Öztürk, & Bilensoy, 2015).

It was reported that molecularly imprinted CD nanosponges is a potential carrier for an extended stability and delivery of drugs (Trotta et al., 2016). Recently, suitability of inclusion complexation between β-CD and slightly water-soluble drug, atorvastatin calcium was developed for improving dissolution rate and subsequent oral bioavailability (Zidan, Ibrahim, Afouna, & Ibrahim, 2018). Improvement of oral bioavailability with anti-HIV drug rilpivirine HCl was also reported through nanosponge formulation (Zainuddin, Zaheer, Sangshetti, & Momin, 2017). A nanosized colloidal carrier was used for the targeted and prolonged delivery of poorly soluble antirestenotic agent, DB103 for the local delivery to vessel wall (Coviello et al., 2017).

The characteristics of liposomes incorporating CD-drug inclusion complex along with its advantages and disadvantages has been

reviewed elsewhere (Gharib, Greige-Gerges, Fourmentin, Charcosset, & Auezova, 2015). In one attempt, Ascenso et al. (2013) have prepared and characterized tretinoin formulations based on the novel drug-in-CD in liposomes. The same strategy was used by Chen et al. (2016), which was beneficial in improving the drug solubility, drug loading capacity, and vesicles stability. Combinatorial therapy of docetaxel and gemcitabine co-loaded PEGylated liposome was demonstrated to enhance the cytotoxic effect in osteosarcoma. Inclusion complex of 2-HP-γ-CD-liposome was prepared to overcome the poor aqueous solubility of docetaxel (Sun, Zhou, Zhang, Li, & Liu, 2015). Enhanced drug loading with improved cytotoxic and haemolytic potential of PEGylated liposome-DM-β-CD encapsulated paclitaxel demonstrated its superiority over current marketed paclitaxel formulation (Bhatt et al., 2018).

10.12 | Challenges, issues, and future perspectives in various drug delivery systems

Dose escalation in preclinical toxicological studies can proportionately increase the concentration of CD. Being hypertonic, oral administration of these complexes can result in reduced free drug concentration up on dilution in GI tract, short GI transit time, and thereby limited GI absorption. It was demonstrated that pharmacokinetic and pharmacodynamics parameters of a drug is not generally influenced by the use of CDs, whenever the association constant between drug–CD complex is less than 1×10^5 M^{-1}. γ-CD and few of its derivatives, as well as HP-β-CD and SBE-β-CD, are considered to be much safer as compared with other CDs. The major strength of CD is their peculiar nature to interact noncovalently with drug molecules, while weakness is that only molecules with suitable size, geometry, and inherent solubility can complexes with CD.

The future prospects of CD and its derivatives are encouraging as CDs and their derivatives can contribute as a valuable tool for optimizing the drug delivery of intractable drugs as well as for drugs having undesirable properties. Even though, only conventional formulations have been commercialized using CDs so far, they are extensively being studied for their utilization in novel drug delivery systems. However, it is necessary to understand the binding mechanism between the drug and CD to rule out any possible interaction between these agents and other formulation ingredients, which may adversely impact the performance. It is essential to have insight on different factors that can affect complex formation in order to formulate drug–CD complexes with unique and desirable properties.

10.13 | Potential commercial applications of CD

The applications of CDs to improve the performance of solid and liquid pharmaceutical dosage forms (including oral and parenteral) have been established in more than 40 commercial pharmaceutical products. Being a safe excipient, parental both parent and CD derivatives have been frequently used in various dosage forms including capsule, chewing tablet, eye drops, nasal spray, ointment, oral solution, parenteral solution, sublingual tablet, suppository, and tablet. In many of these products, they are frequently used as solubilizers, to improve physical and stability of various compounds including proteins. Other potential uses are to mask the unpleasant taste, to reduce tissue irritation, convert liquid drug to solid, and to achieve controlled, sustained, or targeted release of drugs. Currently approved marketed products use native CDs, α-CD, and β-CD and their derivatives including 2-HP-β-CD, RM-β-CD, and SBE-β-CD.

11 | CONCLUSIONS

It is evident from the details provided in this review that CDs by virtue of distinct molecular structure and physicochemical properties can be recommended as a valuable tool for formulation scientist to overcome many formulation and drug delivery issues pertaining to various drug molecules. CD-drug conjugate fulfills the requirement of the potential drug carrier as it has the capacity to maintain the release rate as well as deliver the drug to the targeted site. Recently, CDs ability to form nanoparticles and microparticles by supramolecular self-assembles and its significance as a potential tool for drug delivery is highlighted. As more pharmaceutical products using CDs are approved by regulatory authorities, there is still more scope for further research and various potential applications as excipients in formulation, and product life cycle management. The application of CDs is not limited to the topics discussed above, but also have been extended to cosmetics, food, textiles, agriculture industries, and so forth.

CONFLICT OF INTEREST

The authors report no declarations of interest.

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