Cyclodextrins and their Derivatives in Drug Delivery: A Review

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Abstract
The objective of the present review is to discuss the role and applications of cyclodextrins and their derivatives in drug delivery. Cyclodextrins are useful functional excipients that have enjoyed widespread attention and use. They are a family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. Cyclodextrins have been used in the pharmaceutical industry as complexing agents to increase aqueous solubility of poorly soluble drugs, to increase stability, bioavailability and reduced drug irritation. Applications in the different drug delivery systems like oral, sublingual, buccal, ocular, nasal, transdermal, rectal, pulmonary, parenteral, colon-specific delivery, brain drug delivery, novel delivery systems like liposomes, nanoparticles, microparticles, in gene delivery and oligonucleotide delivery are discussed. Studies in both humans and animals have shown that cyclodextrins can be used to improve drug delivery from almost any type of drug formulation. However, addition of cyclodextrins to existing formulations without further optimization will seldom result in acceptable outcome. A number of cyclodextrin-based products have reached the market based on their ability to camouflage undesirable physicochemical properties.

Keywords: cyclodextrins, drug delivery, formulation, solubility, stability, bioavailability.

Introduction
Cyclodextrins (CDs) are cyclic oligosaccharides consist of (α-1, 4)-linked α-D-glucopyranose units and due to the chair conformation of the glucopyranose units, the cyclodextrins are doughnut in shape rather than perfect cylinders. CDs are produced from starch by enzymatic conversion. As a result of their molecular structure and shape, they possess a unique ability to act as molecular containers by entrapping guest molecules in their internal cavity. The resulting inclusion complexes offer a number of potential advantages in pharmaceutical formulations. Cyclodextrins increase the water solubility of poorly soluble drugs to improve their bioavailability. Stability of the active pharmaceuticals in terms of oxidative, light and thermal stability can be improved through the formation of cyclodextrin inclusion complexes. Cyclodextrins have been using to reduce dermal, gastrointestinal or ocular irritation, mask unpleasant tastes or odors, prevent adverse drug-excipient interactions and useful in converting the oils/liquids into powders to improve handling (6).

Structure, Derivatives, Properties of Cyclodextrins: Cyclodextrins are a general class of molecules composed of glucose units connected by α-1, 4 glycosidic linkages to form a series of oligosaccharide rings and contain a somewhat lipophilic central cavity and a hydrophilic outer surface. Due to the chair conformation of the glucopyranose units, the CDs
take the shape of a truncated cone or torus rather than a perfect cylinder. The hydroxyl functions are orientated to the cone exterior (which gives it a relatively hydrophilic character) with the primary hydroxyl groups of the sugar residues at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge. The central cavity of the CD molecule is lined with skeletal carbons and ethereal oxygens of the glucose residue, which gives it a relatively lipophilic character (7, 8).

In nature, the enzymatic digestion of starch by cyclodextrin glycosyltransferase produces a mixture of cyclodextrins comprised of 6, 7 and 8 glucose units (α, β and γ cyclodextrin, respectively) and were shown in Figure 1. Cyclodextrins are still commercially producing from starch by enzymatic digestion, specific enzymes are used to produce selective α, β or γ-cyclodextrin, as desired (9, 10). These three cyclodextrins are crystalline, homogeneous, non-hygroscopic in nature. The differing number of glucose units leads to slight differences in conformational structure, flexibility and size of the ring in terms of diameter (Fig. 1). While all three major cyclodextrins are water soluble, solubility is differs from one another, these differences result in higher exposure of hydrogen bonding hydroxyl groups to the aqueous environment and higher water solubility for γ and α- cyclodextrins than β-cyclodextrin (11).

Cyclodextrin derivatives can be prepared by chemical or enzymatic reactions. The main objective of such derivatizations may be: 1) to improve the solubility of the CD derivative and its inclusion complexes; 2) to improve the fitting and/or the association between the CD and its guest, with concomitant stabilization of the guest, reducing its reactivity and mobility; 3) to attach specific groups to the binding site (e.g., in enzyme modeling); 4) to form insoluble, immobilized CD-containing structures, polymers (e.g., for chromatographic purposes) (12).

Several chemical modifications techniques were applied cyclodextrins to obtain water-soluble cyclodextrin derivatives. Chemical modification of the hydroxyl groups, even by hydrophobic moieties such as methoxy functions present on the cyclodextrins, resulted in dramatic increase in their aqueous solubility. Later several

Fig. 1. Shape and size of α, β and γ-cyclodextrins

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new derivatives of cyclodextrins for pharmaceutical interest include hydroxypropyl derivatives of β-CD and γ-CD (i.e., HP-β-CD and HP-γ-CD), the randomly methylated β-CD (RM-β-CD), sulfobutylether β-CD (SBE β-CD), Monochlorotriazinyl beta cyclodextrin (MCT-β-CD), Heptakis-β-CD [Heptakis (2-x-amino-O-oligo(ethylene oxide)-6-hexylthio) beta cyclodextrin] and the so called branched CDs such as maltosyl-β-CD (G2-β-CD) etc., came available (13). The main reason for the solubility enhancement in the alkyl derivatives is that chemical manipulation transforms the crystalline α, β or γ-cyclodextrins into amorphous mixtures of isomeric derivatives (7, 14). Properties of natural cyclodextrins and some of their derivatives such as average number of substituents per glucopyranose repeat unit, molecular weight, solubility are shown in Table 1.

Cyclodextrin molecules are relatively high molecular weight ranging from 1000 to 2000 Da with a large number of hydrogen donors and acceptors, and are consequently poorly absorbed through biological membrane. Natural α- and β-cyclodextrins cannot hydrolyze by human salivary and pancreatic amylases, whereas α-cyclodextrin can hydrolyze by human salivary and pancreatic amylases, but all three are subjected to fermentation by the intestinal microflora. Hydrophilic cyclodextrins are non-toxic in nature at low to moderate concentrations in oral dosage forms (15, 16). The natural cyclodextrins and their derivatives are used in topical and oral dosage forms, but only γ-cyclodextrin and the hydrophilic derivatives of β- and γ-cyclodextrin can be used in parenteral formulations. γ-Cyclodextrin forms visible aggregates in aqueous solutions and, thus, is not well suited for parenteral formulations (17). β-cyclodextrin cannot be used in the parenteral formulations because of its nephrotoxicity. Lipophilic cyclodextrin derivatives, such as methylated cyclodextrins, are to some extent absorbed from the gastrointestinal tract into the systemic circulation and have been shown to be toxic after parenteral administration (15). Presently, oral administration of methylated β-cyclodextrin is limited by its potential toxicity.

**Inclusion complex formation:** Cyclodextrins are able to form solid inclusion complexes with active drug moieties (host–guest complexes) with a very wide range of solid, liquid and gaseous compounds by a molecular complexation. In these cyclodextrin inclusion complexes, a guest molecule is held within the cavity of the cyclodextrin cavity.

**Table 1.** Natural cyclodextrins and their derivatives that can be found in marketed pharmaceutical products.

<table>
<thead>
<tr>
<th>Cyclodextrin</th>
<th>Substitutiona</th>
<th>MWb</th>
<th>Solubility in water (mg/mL)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Cyclodextrin</td>
<td>–</td>
<td>972</td>
<td>14.5</td>
</tr>
<tr>
<td>β-Cyclodextrin</td>
<td>–</td>
<td>1135</td>
<td>1.85</td>
</tr>
<tr>
<td>2-Hydroxypropyl-β-cyclodextrin</td>
<td>0.65</td>
<td>1400</td>
<td>&gt;600</td>
</tr>
<tr>
<td>Randomly methylated β-cyclodextrin</td>
<td>1.8</td>
<td>1312</td>
<td>&gt;500</td>
</tr>
<tr>
<td>β-Cyclodextrin sulfobutyl ether sodium salt</td>
<td>0.9</td>
<td>2163</td>
<td>&gt;500</td>
</tr>
<tr>
<td>γ -Cyclodextrin</td>
<td>–</td>
<td>1297</td>
<td>23.3</td>
</tr>
<tr>
<td>2-Hydroxypropyl-γ -cyclodextrin</td>
<td>0.6</td>
<td>1576</td>
<td>&gt;500</td>
</tr>
</tbody>
</table>

a Average number of substituents per glucopyranose repeat unit.
b MW (Molecular Weight) in Daltons.
c Solubility in pure water at approx. 25°C.
cyclodextrin host molecule. Complex formation is a dimensional fit between the host cavity and guest molecule was represented in Fig. 2 (18). The lipophilic inner cavity of the cyclodextrin molecules provide a lipophilic microenvironment, into which appropriately sized non-polar moieties of the guest active moieties can enter to form inclusion complexes (19). No covalent bonds are formed or broken during formation of the inclusion complex (20). Release of enthalpy-rich water molecules from the cavity is the main driving force for complex formation, electrostatic interaction, van der Waals interaction, hydrophobic interaction, hydrogen bonding, release of conformational strain, and charge-transfer interaction. All these forces are relatively weak, allowing free drug molecules in solution to be in rapid equilibrium with drug molecules bound within the cyclodextrin cavity. Water molecules are displaced by more hydrophobic guest molecules present in the solution to attain an apolar-apolar association and decrease of cyclodextrin ring strain resulting in a more stable lower energy state.

The inclusion of guest molecules within the host cyclodextrin is in dynamic equilibrium and not a fixed or permanent. Binding strength depends on how well the 'host–guest' complex fits together and on specific local interactions between surface atoms. Several techniques are used to form CD inclusion complexes, like co-precipitation, slurry complexation, paste complexation, damp mixing, heating method, extrusion and dry mixing.

**Phase Solubility studies**: Phase Solubility studies were first described by Higuchi and Connons in 1964 (21, 22) in their pioneering research work. In phase solubility studies the effect of complexing agents on the compound being solubilized is to determine not only the value of the stability constant but also to give stoichiometry of the equilibrium. Experimentally phase solubility studies were conducted by

![Fig.2. Illustration of cyclodextrin inclusion complex formation](image-url)
adding, an excess of a poorly water-soluble drug into several vials to which a constant volume of an aqueous vehicle containing successively larger concentrations of the cyclodextrins/ cyclodextrin derivatives are added. The need for excess drug is based on the desired to maintain as high a thermodynamic activity of the drug as possible. The vials are shaken at constant temperature until equilibrium is established. The suspensions are then filtered and the total concentration of the drug determined based on appropriate analytical techniques (UV Visible Spectrophotometer or HPLC). The Phase Solubility profile is then constructed by assessing the effect of the cyclodextrin on the apparent solubility of the drug. Based on the shape of the generated Phase Solubility relationships, several types of behaviors can be identified (23) Phase Solubility diagrams fall into two major types: Type A profile and Type B profile (Fig. 3).

**Profiles indicate a linear increase in solubility as a function of solubilizer/cyclodextrin concentration, A_p systems indicate an isotherm wherein the curve deviates in a positive direction from linearity (i.e. the solubilizer/cyclodextrin is proportionally more effective at higher concentrations) and A_n relationships indicate a negative deviation from linearity (i.e. the cyclodextrin is proportionally less effective at higher concentrations). Taken as a whole, these isotherms indicate that water-soluble complexes are being formed with solubilities higher than that of the uncomplexed substrate. Generally A_n-type relationships follows first order with respect to the cyclodextrin and may be first or higher order with respect to the drug. If the slope of the A_n isotherm is greater than one, first order complexes are assumed to be involved in the solubilization and slope value is higher than one indicates higher order complexes are formed.

**B-type phase solubility profiles:** In B type phase solubility profiles are indicative of the formation of complexes with limited water solubility and are generally observed with naturally occurring cyclodextrins, especially with β-CD. Two subclasses have been described in B-type profile including B_s and B_I systems. B_s-type isotherms denote complexes of limited solubility and a B_I-curve are indicative of insoluble complexes.

**Formulation and process variables influencing the cyclodextrin inclusion complexes**

**Type of Cyclodextrin:** Type of cyclodextrin can influence the inclusion complex formation as well as the performance of drug/CD complexes. For better inclusion complexation, the cavity size of cyclodextrin should be suitable to accommodate a drug molecule of particular size. Nagase Y, 2001 et al., (110) reported that inclusion complexation can be better when the cyclodextrin and the drug carry opposite charge but may decrease when they carry the same charge in comparison with neutral cyclodextrins. For many acidic drugs forming anions, the cationic (2-hydroxy-3-[trimethylammonio] propyl)-β-CD...
acted as an excellent solubilizer in comparison to neutral and ionic cyclodextrins. 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, but in the case of mebendazole, the un-ionized form was less included in HP-\(\beta\)-CD than the cationic form (24). Arias-Blanco MJ A, 1998 et al., (111) reported that the cavity size of \(\beta\)-CD was suitable for complexation of gliclazide while that of \(\alpha\)-CD was insufficient to include gliclazide into cyclodextrin ring.

**Process temperature:** Formulation and process temperature changes can affect drug/cyclodextrin complexation. In general most of the cases, increasing in the temperature decreasing the apparent stability constant of the inclusion complex and the effect was reported to be a result of possible reduction of drug/cyclodextrin inclusion complex interaction forces, such as van der Waals and hydrophobic forces with increasing in temperature. However, temperature changes may have negligible effect when the drug/cyclodextrin interaction is predominantly entropy driven (i.e., resulting from the liberation of water molecules hydrated around the charges of guest and host molecules through inclusion complexation).

**Method of preparation:** Method of preparation, viz physical mixing/co-grinding, kneading, solvent evaporation, co-precipitation, spray drying, or freeze drying can affect drug-cyclodextrin complexation. The effectiveness of a method depends on the nature of the drug and cyclodextrin used in the preparation (25, 26). Most of the cases, spray drying and freeze drying were found to be most effective for drug, cyclodextrin inclusion complexation, resulting to improvement of solubility, stability and bioavailability. In spray drying and freeze drying amorphousization of the drug taking place during complexation. In case of tolbutamide:\(\beta\)-CD inclusion complexation method of preparation showed no influence on the dissolution performance.

Water-soluble polymers or ion pairing agents added in small amounts, enhanced cyclodextrin 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/ cyclodextrin complexes. Some of the inactive ingredients/additives may compete with drug molecules for cyclodextrin cavities and thus decrease the apparent complex stability constant. Water structure forming agents when added to cyclodextrin solutions generally increase the total drug solubility, but they showed opposite effects with clotrimazole. Simultaneous complexation and salt formation with hydroxy carboxylic acid (HA) significantly increased the cyclodextrin solubilizing power for a sparingly water-soluble drug by forming drug/CD/HA multicomponent/ ternary complexation systems. Co-solvents can improve the solubilizing and stabilizing effects of CDs, e.g., use of 10% propylene glycol in development of an oral itraconazole preparation containing 40% of HP-\(\beta\)-CD. Sometimes co-solvents may hinder drug complexation by competitive inclusion, e.g., presence of 10% propylene glycol decreased the solubilizing effect of HP-\(\beta\)-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-\(\beta\)-CD concentration (27).

**Role of Cyclodextrin on drug solubility, dissolution rate and stability:** Cyclodextrins (CDs) have been playing an important role in development of poorly aqueous-soluble drugs by improving drug solubility and dissolution rate through inclusion complexation. Reduction of

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drug crystallinity on complexation or solid dispersion with CDs also contributes to the cyclodextrin increased apparent drug solubility and dissolution rate. 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.

CDs can improve the stability of several labile drugs by preventing hydrolysis, oxidation, dehydration, and photodecomposition of the formulation. Role of Cyclodextrin and its derivatives on drug solubility, dissolution rate and stability were represented in Table 2.

Safety and biocompatibility of cyclodextrins and its derivatives: The chemical structure of cyclodextrins (i.e., the large number of hydrogen donors and acceptors), their molecular weight is more than 972 Da and their very low partition coefficient (approximately log Po/w between less than 3 and 0) are all characteristics of compounds that do not readily permeate biological membranes. Studies have shown that only negligible amounts of hydrophilic cyclodextrins and drug/cyclodextrin complexes are able to permeate lipophilic membranes such as gastrointestinal mucosa and skin. All toxicity studies have demonstrated that when administered orally cyclodextrins are practically non-toxic due to lack of absorption from the gastrointestinal tract. However, the lipophilic methylated β-cyclodextrins are surface active and they are to some extent (~10%) absorbed from the gastrointestinal tract and consequently only limited amounts of these lipophilic cyclodextrin derivatives can be included in oral formulations, and they are unsuited for parenteral formulations. Due to toxicological considerations β-cyclodextrin cannot be used in parenteral formulations and

Table 2. Role of cyclodextrin and their derivatives on drug solubility, dissolution rate and stability

<table>
<thead>
<tr>
<th>Cyclodextrins</th>
<th>Examples of CD-enhanced Solubility and Dissolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Cyclodextrin</td>
<td>Praziquantel</td>
</tr>
<tr>
<td>β-Cyclodextrin</td>
<td>Piroxicam, Nimesulide, Lorazepam, Ketoprofen, Praziquantel, Chlorthalidone, Itraconazole, Ibuprofen, Griseofulvin</td>
</tr>
<tr>
<td>Dimethyl-β-cyclodextrin (DM-β-CD)</td>
<td>Naproxen, Camptothesin</td>
</tr>
<tr>
<td>Random methyl-β-cyclodextrin</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Hydroxypropyl-β-cyclodextrin (HP-β-CD)</td>
<td>Griseofulvin, Albendazole, Levemopamil HCl, Sulfomethiazole, Itraconazole, Ketoprofen, Carbamazepine, Zolpidem</td>
</tr>
<tr>
<td>γ-CD</td>
<td>Omeprazole, Digoxin, Praziquantel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cyclodextrins</th>
<th>Examples of CD-enhanced Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Cyclodextrin</td>
<td>Glibenclamide, Diclofenac sodium, Flutamide, Atorvastatin Calcium</td>
</tr>
<tr>
<td>Hydroxypropyl-β-cyclodextrin (HP-β-CD)</td>
<td>Promethazine, Quinaril, Doxorubicin, Rutin, Paclitaxel, Spiranolactone,</td>
</tr>
<tr>
<td>SBE-β-CD</td>
<td>Spiranolactone, Melphalan and Carmustine</td>
</tr>
<tr>
<td>γ-CD</td>
<td>Digoxin</td>
</tr>
</tbody>
</table>

Cyclodextrins and their derivatives in drug delivery
the usage of α-cyclodextrin in parenteral formulations is severely limited although it can already be found in one marketed formulation. In animal studies, β-cyclodextrin has been found to be virtually non-toxic when given intravenously. Extensive toxicological studies have been completed for 2-hydroxypropyl-β-cyclodextrin as well as for sulfobutylether β-cyclodextrin, both of which can be found in marketed parenteral formulations at relatively high concentrations.

**Regulatory status of cyclodextrins:** Cyclodextrin monographs can be found in several pharmacopoeial sources. Their regulatory status continues to evolve (28, 29). β-CD is listed in a number of pharmacopoeial sources including the US Pharmacopoeia/National Formulary (USP/NF), European Pharmacopoeia (Ph.Eur.) and Japanese Pharmaceutical Codex (JPC). α-CD is similarly listed in the Ph.Eur., USP/NF and JPC and β-CD is referenced in the JPC and will soon be included in the Ph.Eur., and USP/NF. A monograph for HP-β-CD is available in the Ph.Eur., and a draft has been circulated for the USP/NF. Other derivatives are not yet compendial but efforts are underway for their inclusion. β-CD, β-CD and α-CD were also introduced into the generally regarded as safe (GRAS) list of the FDA for use as a food additive in 2004, 2001 and 2000, respectively, HP-β-CD and SBE β-CD are cited in the FDA’s list of Inactive Pharmaceutical Ingredients.

**Cyclodextrins in drug delivery:** Cyclodextrins are currently used in the pharmaceuticals to improve the aqueous solubility, stability and bioavailability of poorly aqueous soluble and unstable drugs (7). Cyclodextrins will form hydrophilic inclusion complexes with lipophilic active moieties. In aqueous solutions drug molecules bound with the cyclodextrin in the inclusion complex are in a dynamic equilibrium with the free drug molecule. Thus, cyclodextrins enhance the aqueous solubility of drugs without changing their intrinsic ability to permeate lipophilic membranes (30). Due to their size and hydrophilicity insignificant amounts of cyclodextrins and drug/cyclodextrin complexes are able to penetrate into lipophilic biomembranes, such as intact skin. In general cyclodextrins enhance drug delivery through biomembranes by increasing the drug availability at the membrane surface. At the surface the drug molecules partition from the cyclodextrin cavity into the lipophilic membrane (31, 32). Thus, properly designed cyclodextrin formulation will increase the drug concentration gradient over the membrane, which will increase the drug flux through the membrane. Since drug/cyclodextrin complexes do not readily permeate biomembrane, excess cyclodextrin in pharmaceutical formulations can reduce drug bioavailability. Cyclodextrins are used in almost all drug delivery systems and few important delivery systems were described in the subsequent sections.

**Oral Drug Delivery:** The effect of cyclodextrins on oral drug absorption can be explained in the context of the Biopharmaceutics Classification System (BCS) (28). BCS Class I drugs have good aqueous solubility and permeate easily through the aqueous diffusion layer and possess sufficient lipophilicity to permeate through the gastrointestinal mucosa. In general, hydrophilic cyclodextrins are not able to improve the bioavailability of Class I drugs. However, cyclodextrin can be used to reduce local drug irritation, taste masking and increase rate of drug absorption. BCS Class II drugs have limited aqueous solubility and good permeability, resulting in dissolution-rate limited oral absorption. Thus, permeation through the aqueous diffusion layer adjacent to the mucosal surface will also be slow due to their low aqueous solubility. Water-soluble cyclodextrin complexes of these drugs will enhance their diffusion to the mucosal surface leading to improved oral bioavailability. BCS Class II drugs have limited aqueous solubility and good permeability, resulting in dissolution-rate limited oral absorption. Thus, permeation through the aqueous diffusion layer adjacent to the mucosal surface will also be slow due to their low aqueous solubility. Water-soluble cyclodextrin complexes of these drugs will enhance their diffusion to the mucosal surface leading to improved oral bioavailability. BCS Class III drugs are water soluble, but do not easily permeate biological membranes due to their size and/or extent of hydration. Consequently, formation of hydrophilic drug/cyclodextrin complexes will not enhance their oral bioavailability, but will, if anything, reduce the ability of dissolved drug molecules to
partition from the aqueous exterior into the gastrointestinal mucosa. BCS Class IV drugs are water insoluble and do not readily permeate through biological membranes. These can, for example, be water-insoluble zwitterions or relatively large lipophilic molecules. Hydrophilic water-insoluble compounds such as zwitterions do not readily form cyclodextrin complexes and, thus, hydrophilic cyclodextrins are not likely to improve their oral bioavailability. However, cyclodextrins are capable of increase in aqueous solubility of some large lipophilic molecules leading to increased drug availability at the mucosal membrane. This will frequently lead to increased oral bioavailability. Modification of the drug release site and/or time profile by cyclodextrins is shown in Table 3.

**CDs in Oral Immediate release dosage forms:** CDs have been extensively used to improve the aqueous solubility and the oral bioavailability of poorly aqueous soluble actives such as cardiac glycosides, antiepileptics, benzodiazepines, antidiabetics, vasodilators etc. (33). These improvements are mainly attributed to the increase in solubility and wettability of drugs through the formation of inclusion complexes. Complexation of β-CD with imidazole antifungal agents, such as ketoconazole and econazole, provides increased solubility and enhanced bioavailability (34, 35). Cyclodextrins and their derivatives such as HP-β-CD and randomly methylated β-CDs are utilized in the improvement of solubility, stability and bioavailability of Atorvastatin calcium (36, 37). Chinna Reddy et al reported that the solubility, stability and bioavailability of atorvastatin calcium were significantly improved due to inclusion complexation with cyclodextrins in a 1:1 stoichiometric ratio (38). The stabilizing effect of CDs on unstable drugs is also responsible for the improvement of oral bioavailability. Uekama et al., reported that the γ-CD complex decreases acid hydrolysis of cardiac glycosides and thus improves the oral absorption and bioavailability of digoxin in dogs (38). Highly hydrophilic CD derivatives, such as HP-β-CD (39), maltosyl-β-CD (40) and SBE-β-CD sulfate and sulfobutylether-β-CD; (41) have been used to obtain an immediate release formulation that is readily dissolved in GIT, enhancing the oral bioavailability of poorly water-soluble drugs.

**CDs in Delayed release dosage forms:** Horikawa et al. studied the release of the water soluble drug molsidomine, an orally active, long acting vasodilating agent from the tablets of CME-β-CD complex using male beagle dogs with controlled gastric acidity. Under high gastric acidity, molsidomine absorption was significantly

| Table 3. Modification of the Drug Release Site and/or Time Profile by Cyclodextrins |
|---------------------------------|-------------------|-----------------|
| Release Pattern                  | Aim                | Use of Cyclodextrin                        |
| Immediate release                | Enhanced dissolution and absorption of poorly water soluble drugs | HP-β-CD, Dimethyl-β-CD (DM-β–CD), SBE-β-CD 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 | Carboxymethyl ethyl- β-CD (CME-β-CD) |
| Site-specific release            | Colon-targeting    | Drug/CD conjugate |

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retarded compared to low gastric acidity conditions. The delayed absorption effect under high gastric acidity was more pronounced under fasted conditions (42).

Uekama et al., studied on diltiazem HCl, a water-soluble drug for delayed release formulation. Diltiazem HCl was complexed with CME-β-CD and compressed into a tablet. The drug release rate was quite slow in the low-pH solutions and increased with an increase in pH. The release of water-soluble diltiazem HCl from CME-β-CD was suppressed at a lower pH because of ionization of the carboxyl group. These studies indicated that the release rate of water-soluble drugs can be suppressed in the low-pH region in the stomach and increased at intestinal pH values because of the ionization of the carboxyl group of the drug molecule, thereby showing suitability for drug targeting to specific areas in the intestine (43).

Tiaprofenic acid (TA), an NSAID, is associated with gastrointestinal toxicity and erratic bioavailability. Tiaprofenic acid inclusion complex was prepared by kneading method using DE-β-CD in a 1:1 molar ratio. The dissolution profile of TA as a powder was tested at pH values of 1.5, 3.0, 4.5, 6.8 and 7.4. The in vitro dissolution rate from the TA/DE-β-CD complex increased by increasing the pH value and complete release was observed at a pH of 7.4. In vivo studies in male Sprague Dawley rats administration of solid particles of complexes by means of gastric intubations followed by ingestion of 500µL of water. The studies showed a prolonged Tmax, which most likely resulted from slow or no release of the drug in the stomach and duodenum, both of which have low pH ranges. The drug was released and was absorbed immediately and completely in the distal intestine, which has an alkaline pH (44).

Sublingual and buccal drug delivery:
Sublingual drug delivery is one of the most efficient methods to bypass hepatic first-pass metabolism. In sublingual method the drug dissolves in the mucosa and then enters in to the systemic circulation. Rapidly dissolving complexes of drugs and CDs are well suited for sublingual or buccal administrations, which avoid the hepatic first-pass metabolism. However, in order to enter into the systemic circulation the drug must dissolve in the saliva. Due to the small volume of saliva in the mouth, the therapeutic dose has to be relatively small and usually dissolution enhancers must be included in the formulation. In sublingual formulations the complexation of poorly water-soluble drugs such as 17β-estradiol (47), androstenediol (48), clomipramine (49) and danazol (50) with cyclodextrins has been shown to increase in solubility, permeability and bioavailability. However, the interactions between cyclodextrins and sublingual mucosa (i.e., cyclodextrins acting as conventional penetration enhancers) cannot be excluded. Results from in vivo absorption studies showed that sublingual administration of randomly methylated β-CD (RM-β-CD) containing Δ9-tetrahydrocannabinol (THC) formulation increases the bioavailability of THC compared with oral administration (51).

Jug, M et al., (52) reported that the Influence of hydroxypropyl-β-cyclodextrin complexation on
In their research they found that HP-β-CD can enhance the release rate of piroxicam from tableted matrices formulated with swellable hydrophilic polymers, hydroxypropylmethyl cellulose (HPMC) and Carbopol 940 (C940). The increase in the release rate of piroxicam from buccal tablets could be attributed to the ability of HP-β-CD to form a complex with piroxicam, resulting in an increase of apparent drug solubility. Higher medium penetration rate into the complex containing tablets may also contribute to the improved release rate.

Cappello, B et al., (53) studied the role of HP-β-CD on carvedilol containing poly ethylene oxide (PEO) tablets for buccal delivery system. The amount of carvedilol permeated from PEO tablet was higher in the case of HP-β-CD containing tablets compared to PEO tablets containing only carvedilol. Cyclodextrins are responsible for an increase in the erosion rate of the buccal tablet resulting in an improvement in the dissolution rate of the drug inside the tablet. Piroxicam was released from the polymer matrices in a constant mode over the passage of time, thus providing a prolonged effect.

### Table 4. Marketed pharmaceutical products containing cyclodextrins

<table>
<thead>
<tr>
<th>Drug/cyclodextrin</th>
<th>Trade name</th>
<th>Formulation</th>
<th>Country</th>
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<tr>
<td>α-Cyclodextrin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprostadil (PGE1)</td>
<td>Prostavastin, Rigidur</td>
<td>I.V. solution</td>
<td>Japan, Europe, USA</td>
</tr>
<tr>
<td>OP-1206</td>
<td>Opalmon</td>
<td>Tablet</td>
<td>Japan</td>
</tr>
<tr>
<td>Cefotiamhexetil HCl</td>
<td>Pansporin T</td>
<td>Tablet</td>
<td>Japan</td>
</tr>
<tr>
<td>β-Cyclodextrin</td>
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<td></td>
<td></td>
</tr>
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<td>Benexate HCl</td>
<td>Ulgut, Lonmien</td>
<td>Capsule</td>
<td>Japan</td>
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<td>Melact</td>
<td>Tablet</td>
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<td>Chlordiazepoxide</td>
<td>Transillium</td>
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<td>Glymesason</td>
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<td>Stada-Travel</td>
<td>Chewing tablet</td>
<td>Europe</td>
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<td>Nicotine</td>
<td>Nicorette, Nicogum</td>
<td>chewing gum</td>
<td>Europe</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>Nimedex</td>
<td>Tablet</td>
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<td>Nitopen</td>
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<td>Propulsid</td>
<td>Suppository</td>
<td>Europe</td>
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<td>Itraconazole</td>
<td>Sporulox</td>
<td>Oral and I.V. solutions</td>
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<td>Mitozytrex</td>
<td>I.V. infusion</td>
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<td>Clorocil</td>
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<td>Aerodiol</td>
<td>Nasal spray</td>
<td>Europe</td>
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<td>Sulfobutylether β-CD</td>
<td>Voriconazole</td>
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<td>Ziprasidone mesylate</td>
<td>Vfend</td>
<td>M solution</td>
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<td>Diclofenac sodium</td>
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<td>Tc-99 Teboroxime</td>
<td>Voltaren</td>
<td>I.V. solution</td>
<td>USA</td>
</tr>
<tr>
<td></td>
<td>Cardiotec</td>
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Cyclodextrins and their derivatives in drug delivery.
polymeric matrix. The erosion effect is the crucial factor, which determines the increase of release rate from the tablets in solution. They observed a twenty-fold increase in the amount of carvedilol permeated through porcine buccal mucosa in comparison with absence of cyclodextrin in the formulation.

Chinna Reddy et al., (54) studied the release of felodipine from buccal tablets comprising HP-β-CD - felodipine complex and hydroxypropyl methyl cellulose and reported a complete and sustained release of the drug associated with an enhanced buccal permeation. These results could be attributed to the ability of HP-β-CD to form a complex with felodipine, resulting in an increase of apparent drug solubility, dissolution rate and permeability.

**Ocular Delivery:** In ocular delivery drug administration in the form of topically applied low viscosity aqueous eye drops. Ophthalmic irritation is a common drawback in ophthalmic drug development and in their clinical use. CDs are generally included in the ocular formulations to decrease the irritation effect of ophthalmic drugs by forming inclusion complexes.

HP-β-CD is the most commonly used CDs in aqueous eye drop formulations (55). Numerous studies in animals as well as in human beings have shown that HP-β-CD is well tolerated in aqueous solutions, even at high concentrations as much as 45%. Application of one drop of aqueous eye drop solution containing 18% HP-β-CD to humans, three times a day for 28 days, was well tolerated in the eye (56). Jarho, P et al., studied the effect of SBE7-β-CD on pilocarpine prodrug in rabbits and reported that SBE7-β-CD improved the ocular delivery and tolerability of pilocarpine in aqueous solutions (57). Other CDs and CD derivatives which might be considered safe upon topical administration in aqueous eye drop solutions include maltosyl β-CD, γ-CD and hydroxypropyl- β-cyclodextrin (HP-γ-CD), and, at low concentrations, α-CD and RM-β-CD.

Irritation of pilocarpine in the eye is due to the rapid absorption of the pilocarpine prodrug into the lipophilic corneal epithelium and/or precipitation of prodrug molecules in the precorneal area. Pilocarpine/SBE-β-CD inclusion complexes can be considered to be act as a depot in the precorneal area that limits the free prodrug concentration in that area to a non-irritating level (58). The major ocular drug administration is usually aqueous solutions in which most of the drugs are prone to chemical degradation. One of the most common pharmaceutical advantages of CDs is to increase the drug stability in aqueous solutions. Lee, V.H.L et al., studied on dipivefrine, a prodrug of epinephrine, has currently replaced epinephrine in the treatment of glaucoma. The main drawback of dipivefrine is its low aqueous stability. Dipivefrine is stable at a pH range of 2.5 to 3.5, so the stability problem has been overcome by formulating a dipivefrine solution in this pH range. Lee, et al., reported that inclusion of SBE-β-CD in dipivefrine aqueous ocular formulation at pH 5 and pH 7.4, the negatively charged SBE-β-CD increases the aqueous stability of positively charged dipivefrine 15-30 times and 20-200 times, respectively (59). Cyclodextrin based dexamethasone eye drops are well tolerated in the eye and seem to provide higher bioavailability and clinical efficiency than presently available steroid eye drop formulations (60).

**Nasal Drug Delivery:** The nasal route is one of the effective ways to bypass the hepatic first-pass metabolism. Drugs of highly lipophilic in nature are difficult to deliver through the nasal route due to their poor aqueous solubility. High molecular weight hydrophilic drugs like peptides and proteins show poor nasal absorption. Administration of lipophilic drugs such as steroid hormones estradiol and progesterone along with CDs has shown rapid absorption, this may be due to formation of inclusion complexation with cyclodextrins (61). The estradiol nasal spray Aerodiol® (Servier) represents the successful use of cyclodextrins in nasal applications; each spray delivers 70 μL of solution, which contains 150 μg of estradiol dissolved in aqueous RM-β-CD solution.
Dimethyl-\(\beta\)-CD (DM-\(\beta\)-CD) and HP-\(\beta\)-CD have shown an enhanced and sustained level of morphine in the plasma and cerebrospinal fluid (62). CDs have been shown to enhance the concentration and improve the stability of the antimigraine drug dihydroergotamine (63) and increased nasal absorption of oligopeptide drugs like buserelin (64) and leuprolide (65). Calcitonin, containing a 5% concentration of methylated-\(\beta\)-CD, nasal absorption significantly increased compared to intravenous or subcutaneous administration of the drug (66). Glucagon (67) and insulin (68) nasal bioavailability was significantly improved with incorporation of dimethyl-\(\beta\)-CD (DM-\(\beta\)-CD) in the formulation. It can be concluded from the various studies reported in the literature that methylated-\(\beta\)-CD derivatives, such as DM-\(\beta\)-CD significantly enhances the nasal absorption of peptides and proteins. In addition, the local toxicity of dimethyl-\(\beta\)-cyclodextrin, indicated by ciliary beat frequency, has been shown to be very mild compared with other absorption-enhancing agents and preservatives (e.g., benzalkonium chloride) used in nasal formulations (69).

**Transdermal drug delivery:** Drugs have been delivered by the transdermal route for both local and systemic action. As the drug enters systemic circulation directly, the first pass effect is eliminated; it also eliminates the factors that influence gut absorption. The transdermal drug transport is greatly limited by stratum corneum permeation characteristics; so attempts at improving topical absorption have been reported. Cyclodextrins enhance drug delivery through aqueous diffusion layers (i.e., aqueous diffusion barriers), but not through lipophilic barriers such as the stratum corneum. If the drug release is from an aqueous-based vehicle or if an aqueous diffusion layer at the outer surface of the skin is a rate-determining factor in dermal drug delivery, then cyclodextrins can act as penetration enhancers. However, if drug penetration through the lipophilic stratum corneum is the main rate-determining factor then cyclodextrins are unable to enhance the delivery (54). Through cyclodextrin complexation it is possible to enhance significantly hydrocortisone delivery from cream formulations to the skin (70).

Dermal corticoids like betamethasone (71) and beclamethasone dipropionate (72) showed enhanced release from hydrophilic ointment bases after complexation with \(\beta\)-CD and/or \(\gamma\)-CD. Vehicle types used markedly affect the enhancing effect of CDs on the drug release, e.g., prednisolone complexation with DM-\(\beta\)-CD in non-aqueous ointment bases such as macrogol decreases the release. These decreasing effects of the hydrophilic CDs may be due to the lowering of the drug solubility via the complex formulation (73). CDs are also able to enhance the dermal delivery of NSAIDs. Lin et al. (74) reported that the anti-inflammatory effects of indomethacin in hydroxyethylcellulose hydrogels, a hydrophilic base, were significantly enhanced by complexation with \(\beta\)-CD and HP-\(\beta\)-CD in healthy volunteers. This can be due to permeation enhancement of lipophilic drugs such as corticosteroids and NSAIDs through the skin by increasing the drug thermodynamic activity in water containing vehicles.

Recently, CDs in dermal delivery of proteins and peptides has been noted. For example, a combination of \(\beta\)-CD and the permeation enhancer Azone achieved higher percutaneous absorption of a peptide drug, nafarelin acetate, and a luteinizing hormone releasing analog (75).

Cyclodextrins have also been used to reduce permeability of compounds into skin. For example, addition of an excess of HP-\(\beta\)-CD to a vehicle containing the UV-absorbing compound oxybenzone (a common sunscreen) (more than needed to solubilizing the compound) reduced significantly transdermal permeation of the compound, thus preventing permeation of the sunscreen into skin (76, 77).

Studies show that at higher concentrations parent CDs and chemically modified CDs caused skin irritation in guinea pigs in the order \(\gamma\)-CD \(<\) \(\alpha\)-CD \(<\) \(\beta\)-CD; this result largely depends on their

Cyclodextrins and their derivatives in drug delivery
abilities to extract lipids from stratum corneum (78). As regards CD derivatives, DM-β-CD is known to extract the components from stratum corneum, which leads to skin irritation.

Numerous studies have shown that excess cyclodextrins do, like in the case of ophthalmic drug delivery, decrease drug delivery through excised skin (30). Use of cyclodextrins and their derivatives in transdermal drug delivery are represented in Table-5.

**Rectal Drug Delivery:** Rectal drug delivery is an alternative route of drug administration for patients who have difficulties in swallowing, suffering from nausea or vomiting, for infants or children and old people intended for systemic use. However, rectal delivery is limited by the low media volume, limited absorbing surface area and drug degradation by microorganisms present in the rectum resulting low bioavailability. CDs are useful in rectal delivery to improve the drug release, stability, bioavailability and alleviation of local irritation (79). Enhancement of rectal absorption of lipophilic drugs is based on the improvement of drug release from vehicles and the dissolution rates in rectal fluid. CDs directly act on the rectal epithelial cells in case of unabsorbable drugs like antibiotics, peptides and proteins. Drug-cyclodextrin inclusion complexes improve the chemical stability of the drugs in suppository bases and reduce the drugs bioconversion to pharmacological inactive metabolites in the rectum. For example, AD-1590, an acidic NSAID, with β-CD prevents its auto-oxidation (80). These stabilizing effects of CDs are attributed to insolubilization of the drugs in the lipophilic suppository base. CDs have been reported as co-enhancers. Watanabe et al., (81, 82) reported that CDs enhanced the permeability of proteins such as insulin and recombinant human granulocyte colony stimulating factor through the rectal epithelial cells of rabbits. CDs reduce gastrointestinal mucosal irritation, CDs have also been reported to reduce rectal irritation caused by NSAIDs. For example, HP-β-CD significantly reduced the irritation of rectal mucosa caused by Biphenyl acetic acid (BPAA) and ethyl-4-biphenyl acetate (EBA) administration of lipophilic suppositories to rats (83, 84). Use of cyclodextrins and their derivatives in rectal drug delivery are represented in Table-5.

**Pulmonary drug delivery:** Pulmonary administration of drugs is to treat asthma, chronic obstructive pulmonary disease or other lung diseases (85). Pulmonary drug delivery is an attractive route for systemic drug delivery. However, pulmonary drug delivery can be limited by poor aqueous solubility and slow drug dissolution. Insoluble particles are removed from the lungs by the mucociliary clearance in the upper airways and by macrophages in the alveoli (86). Cyclodextrins can be used in the pulmonary delivery to increase the solubility, stability and dissolution rate of water-insoluble and chemically unstable drugs. Cyclodextrins are capable to reduce the drug clearance resulting that increased drug absorption and faster onset of action. Furthermore, by forming drug/cyclodextrin inclusion complexation, a liquid drug can be converted to a solid form, bad smells and/or tastes can be reduced, two incompatible drugs can be mixed in a dry powder formulation, and local drug irritation in the lungs can be reduced. In general, cyclodextrins that are considered safe for parenteral administration are also considered safe for pulmonary administration (HP-β-CD and SBE-β-CD) (86). The number of studies dealing with pulmonary applications of cyclodextrins is also very limited. Studies have been performed using premetered dry powder inhalers, which emit the dose from a pierced blister or capsule (87). The respirable fraction of salbutamol from Diskhaler® has been increased by complexation with DM-β-CD and γ-CD (88), and the respirable fraction of beclomethasone dipropionate from Microhaler® has been increased by HP-β-CD complexation (89). Furthermore, the absorption of intratracheally administered drugs has been shown to increase in the presence of various cyclodextrins (89-91). A recent study with budesonide also showed that cyclodextrin complexes could be used in an inhalation powder...
Table 5. Use of cyclodextrins and their derivatives in Transdermal and rectal drug delivery

<table>
<thead>
<tr>
<th>Cyclodextrins</th>
<th>Drugs used</th>
<th>Role of cyclodextrins</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Cyclodextrin</td>
<td>Miconazole</td>
<td>Improvement of release and permeation</td>
</tr>
<tr>
<td>β-Cyclodextrin</td>
<td>Tixoxortol 17-butyrate 21-propionate</td>
<td>Improvement of stability</td>
</tr>
<tr>
<td></td>
<td>Betamethasone, Norfloxacin, Indomethacin</td>
<td>Improvement of release and permeation</td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine hydrochloride</td>
<td>Reduction of local irritation</td>
</tr>
<tr>
<td>Dimethyl-β-cyclodextrin</td>
<td>Indomethacin, Predonisolene, Sufanilic acid</td>
<td>Improvement of release and permeation</td>
</tr>
<tr>
<td>(DM-β-CD)</td>
<td>Chlorpromazine</td>
<td>Reduction of local irritation</td>
</tr>
<tr>
<td>Random methyl-β-cyclodextrin</td>
<td>Hydrocortisone, Acitretin</td>
<td>Improvement of release and permeation</td>
</tr>
<tr>
<td>Hydroxypropyl-β-cyclodextrin</td>
<td>Dexamethasone, Miconazole, Liarozole</td>
<td>Improvement of release and permeation</td>
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<td>(HP-β-CD)</td>
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<tr>
<td>Maltosyl-β-cyclodextrin</td>
<td>Hydrocortisone</td>
<td>Improvement permeation</td>
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<td>Diethyl-β-cyclodextrin</td>
<td>Nitroglycerin</td>
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<td>Carboxymethyl-ethyl-β-cyclodextrin</td>
<td>Prostaglandin E</td>
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</tr>
<tr>
<td>γ-Cyclodextrin</td>
<td>Betamethasone, Predonisolone</td>
<td>Improvement of release and permeation</td>
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Use of cyclodextrins & its derivatives in rectal drug delivery

<table>
<thead>
<tr>
<th>Cyclodextrins</th>
<th>Drugs used</th>
<th>Role of cyclodextrins</th>
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</thead>
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<tr>
<td>β-CD</td>
<td>Cefmetazole, Morphine hydrochloride</td>
<td>Improvement of release, stability and permeation</td>
</tr>
<tr>
<td>β-CD</td>
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<tr>
<td>HP-β-CD</td>
<td>Diazepam</td>
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<tr>
<td>DM-β-CD</td>
<td>Carmoful, Diazepam</td>
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<td>4-biphenylacetic acid, Ethyl 4-biphenyl acetate</td>
<td>Reduction of local irritation</td>
</tr>
<tr>
<td>TM-β-CD</td>
<td>Carmoful, Diazepam</td>
<td>Improvement of permeation</td>
</tr>
<tr>
<td>γ-CD</td>
<td>Diazepam, Flurbiprofen</td>
<td>Improvement of release and permeation</td>
</tr>
</tbody>
</table>

Cyclodextrins and their derivatives in drug delivery
without lowering the pulmonary deposition of the drug (92).

**Parenteral Drug Delivery:** Cyclodextrin derivatives such as HP-β-CD and SBE-β-CD have been widely investigated for parenteral use on account of their high aqueous solubility and are safe in parenteral administration. 40% w/v HP-β-CD containing an itraconazole parenteral injection was commercialized in the United States and Europe (93). 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 (94). Ziprasidone mesylate was developed by inclusion complexation with SBE-β-CD for IM administration with targeted concentration of 20 to 40 mg/mL (95).

**Cyclodextrin applications in the design of some novel delivery systems:** Cyclodextrins and their derivatives have been used in novel delivery systems such as nanoparticles, liposomes, microspheres and microcapsules.

**Nanoparticles:** Nanoparticles (Solid Lipid Nanoparticles and Nanostructured Lipid Carriers) are considered to be more stable than liposomal delivery systems. However, a major drawback is associated with the drug loading capacity of polymeric nanoparticles. Cyclodextrins are used in the nanoparticle development to improve water solubility and sometimes the hydrolytic or photolytic stability of drugs for better loading properties. Saquinavir-loaded nanoparticles could be easily prepared in the presence of a drug–cyclodextrin complex. It was found that large amounts of cyclodextrins remained associated with the particles, resulting in a 20-fold increase in saquinavir loading compared to nanoparticles prepared in the absence of cyclodextrins. It was shown that the loading in saquinavir of poly (alkylcyanoacrylate) nanospheres could be dramatically improved by simultaneously increasing the apparent solubility of the drug in the preparation medium and the amount of cyclodextrin associated with the particles, making these nanospheres a promising system for oral application. Thus, cyclodextrins constitute very powerful tools in drug targeting because they can increase dramatically the loading capacity of nanoparticles by improving water solubility and drug stability (96).

**Liposomes:** Cyclodextrin complexation can increase liposomal entrapment of lipophilic drugs. Liposomes entrap hydrophilic drugs in the aqueous phase and hydrophobic drugs in the lipid bilayers and retain drugs en route to their destination with a predetermined rate. By forming water soluble complexes, CD would allow insoluble drugs to accommodate in the aqueous phase of vesicles, thereby potentially increasing the drug-to-lipid mass ratio levels, enlarges the range of insoluble drugs amenable for encapsulation, allows drug targeting and reduce drug toxicity. Complexation with CD can also improve the stability of liposomes. Skalko, N et al., reported that nifedipine inclusion complexation with CDs increased the liposomal entrapment of nifedipine by reducing its interaction with lipid bilayers and also improved the liposomal stability in plasma (97). Stability of liposomes were improved by complexation with CDs. Skalko-Basnet, N et al., (98) reported that the most stable liposomal formulations of metronidazole and verapamil were obtained by direct spray drying of lipid, drug, and HP-β-CD mixture. 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 (99). Liposomal entrapment of prednisolone was higher when incorporated as HP-β-CD complex than free drug. Selection of CD have a significant effect on the amount of drug associated with vesicles, for example, 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.

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Microspheres and Microcapsules: The role of cyclodextrins in microsphere preparation was first studied by Kang et al., (100). 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. Cyclodextrins were also used to modulate peptide release rate from microspheres, e.g., HP-β-CD co-encapsulation in PLGA microspheres slowed down insulin release rate (101, 102).

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 (94). Inclusion complexes of glycerides, fatty acids or fatty alcohols do possess surface activity and this property together with their ability to form aggregates frequently result in formation of dispersed systems (103).

Micro Scale-Interpenetrating Networks (ms-IPNs): Cross-linking of HP-β-CD with ethylene glycol diglycidyl ether (EGDE) in carbopol dispersions enabled the synthesis of cyclodextrin hydrogels with domains of interpenetrating acrylic microgels (micro scale- interpenetrating networks ms-IPNs) in a single step under mild conditions. An adequate design of the HP-β-CD/carbopol ms-IPNs provides a single material with tunable mechanical properties, in which the carbopol microgels provide the ms-IPNs with flexibility, bioadhesion, swelling ability and pH-responsiveness, while the HP-β-CD network is mainly responsible for the drug loading and the control of the release. The ms-IPNs properties can be modulated through an adequate selection of the proportion of both components, which makes them potentially useful as versatile vehicles of relatively hydrophobic substances. The stability against autoclaving also enables the sterilization of ms-IPNs (104).

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. The CD-based prodrug approach was used for delayed release and colon-specific drug delivery, e.g., the absorption of Biphenyl acetic acid from γ-CD prodrugs was found to be from caecum and colon in rats with carrageenan induced inflammation, in contrast to that from the β-CD complex, which was mainly from the small intestine. Rajeswari, C et al., in vivo study in rats revealed that both sugar-degrading and ester-hydrolyzing enzymes are necessary for colon-specific release of butyric acid from its β-CD ester conjugates (94). Drug conjugation with α-CD resulted in a delayed release type prodrug formulation for colon-specific delivery showed the side effects of drugs while maintaining their therapeutic effect, e.g., 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 (105). Cyclodextrin based colon specific drug delivery system best suits for γ-CD prodrugs in comparison to α- and β-CD conjugates.

Brain Targetting or Brain Drug Delivery: Brewster and Loftsson (106) first discussed the use of water-soluble, chemically modified, cyclodextrin derivatives such as HP-β-CD in the formulation development of chemical delivery system (CDS). Formulation development of CDS
is based on the need for appropriate dosage form, solubility, stability, and dissolution characteristics. 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 (94). 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. Arima, H et al., (107) reported that P-gp mediated peptide transport may play an important role in reducing the peptide delivery to the central nervous system in vivo. 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.

**Gene Delivery:** Amphiphilic and neutral as well as cationic CDs have been used for synthesis of novel gene delivery vectors. Neutral CDs like β-CD, DM-β-CD 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. Polycation polymer/DNA composite structures (Polyplexes) 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. CDs were also found to enhance plasmid or viral-vector based delivery of genes. Positively charged quaternary 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. CDs also enhanced the physical stability of viral vector formulations for gene therapy (108).

**Cyclodextrins-Non- inclusion complexes:** In the classical cyclodextrin chemistry, it has generally been assumed that the mechanism whereby cyclodextrins exert their effects, especially their augmentation of solubility, is via the formation of noncovalent, dynamic inclusion complexes. In other words, it is assumed that when a drug molecule forms a complex with cyclodextrin, then some given lipophilic moiety of the drug molecule enters into the hydrophobic cyclodextrin cavity. This is a model, which regards drug-cyclodextrin interactions as a discrete phenomenon and ignores the possible interaction of these complexes with one another. That is the hydrated drug/cyclodextrin complexes are in an ideal solution in which individual complexes are independent of each other. It is becoming increasingly apparent that such assumptions may not be universally applicable or all encompassing. Cyclodextrins are able to form both inclusion and non-inclusion complexes. In saturated aqueous solutions guest/cyclodextrin complexes frequently consist of a mixture of inclusion and non-inclusion complexes. Specifically, there is a growing body of evidence that supports the important contribution of non-inclusion-based aspects for drug solubilization by cyclodextrins including surfactant-like effects and molecular aggregation. Cyclodextrins and their complexes
form water soluble aggregates in aqueous solutions and these aggregates are able to solubilize lipophilic water insoluble drugs through non-inclusion complexation or micelle-like structures (109).

Conclusion
Cyclodextrins are useful functional excipients, which are being used in an ever-increasing way to camouflage undesirable pharmaceutical characteristics, especially poor aqueous solubility. 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. The expanded use of known cyclodextrins as well the development of new derivatives continues to energize this field of study.

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