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Cyclodextrins: Application in different routes of drug administration

SHYAM SHIMPI[1]*
BHASKAR CHAUHAN[1]
PRAJAKTA SHIMPI[2]

[1] *Department of Pharmaceutics, Bharati Vidyapeeth Deemed University Poona College of Pharmacy, Erandawane Pune-411 038, Maharashtra, India*

[2] *Nasik District Maratha Vidya Prasarak Samaj's College of Pharmacy, Gangapur Road, Nasik-422002, Maharashtra, India*

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The objective of this review article is to explain the use of cyclodextrin in the different routes of drug administration. The article gives the chemistry of cyclodextrins and addresses the issue of the mechanism of drug release from cyclodextrin complexes. Dilution, competitive displacement, protein binding, change in ionic strength and temperature and drug uptake by tissues are the different release mechanisms of the drug from the drug-cyclodextrin complex discussed here. Use and its limitations in the different drug delivery systems like nasal, ophthalmic, transdermal and rectal drug delivery are explained. The application of the cyclodextrins in the oral drug delivery is detailed in this review. Many studies have shown that cyclodextrins are useful additives in the different routes of drug administration because of increased aqueous solubility, stability, bioavailability and reduced drug irritation.

Keywords: cyclodextrins, release mechanism, nasal drug delivery, ophthalmic drug delivery, transdermal drug delivery, rectal drug delivery, oral drug delivery

INTRODUCTION

Cyclodextrins (CDs), cyclic oligosaccharides, were discovered approximately 100 years ago. CDs have been used as solubilizers, stabilizers for biological active substances, enzyme models, as separating agents in chromatography or batch processes, catalysts and additives (as detergents, viscosity modifiers, *etc.*) (1).

CDs can be used to reduce or prevent gastrointestinal (GI) or ocular irritation, reduce or eliminate unpleasant smell or taste, prevent drug-drug or drug-additive interactions, or even to convert oils and liquid drugs into microcrystalline or amorphous powder. CDs can be also used as processing aid to isolate a specific compound from natural sources and to remove an unwanted compound such as cholesterol from food products.

Marketed CDs are well accepted because of their low oral and local toxicity, low eye and mucous irritability, easy availability, *etc*. Some points must be considered while pre-

* Correspondence, e-mail: shyam_5p@yahoo.com

paring the CD derivatives, such as that they must be produced by a simple reaction, must be non-toxic, must have an acceptable price, must retain the complex forming capacity and must possess advantageous properties for some specific application.

CHEMISTRY AND PROPERTIES OF CDs

More than 1500 different CD derivatives have been described in the literature. Generally, CDs can be divided into naturally occurring and chemically modified CDs (2). Another classification is based on their water solubility (Table 1), so one can distinguish hydrophilic, lipophilic and ionizable derivatives. Pitha (3) classified the two ways of derivatization, vertical (axial) and horizontal cavity modifications. Horizontal modification is done by enzymes cyclodextrin glucanotransferase yielding natural α-, β-, γ- and larger CDs. α-CD, β-CD and γ-CD differ from each other depending on the presence of glucose residue (Fig. 1). Vertical cavity modification is done by chemical substitution, which elongates the CD torus in an axial direction by introducing larger substituents. Some water soluble CD derivatives that are available and expected to have commercial pharmaceutical applications are methylated derivatives of β-CD, 2-hydroxypropylated β- and γ-CDs, sulfobutylated-β-CD, branched CDs (glucosyl- and maltosyl-β-CD), acetylated β- and γ-CD and sulfated CDs (4). When CDs are modified, the solubility can increase or decrease. Modification of the 2- or 3- hydroxyl group results in disruption of the hydrogen bonding occurring around the ring of the CD molecule. The disruption allows more interactions of these hydroxyl groups with water molecules, resulting in altered solubility, *e.g.* methylated β-CD shows an aqueous solubility up to 50 fold higher than that of unsubstituted β-CD (5, 6).

Complexation of molecules to CDs occurs through a non-covalent interaction between the molecule and the CD cavity. This is a dynamic process whereby the guest molecule continuously associates and dissociates from the host CD. CDs are insoluble in most organic solvents; they are soluble in some polar, aprotic solvents. Although the solubility of CDs is higher in some organic solvents than in water, complexation may not occur readily in non-aqueous solvents because of the increased affinity of the guest for the solvent compared to its affinity for water. Also CDs form complexes with lipophilic solvents, even with ethanol and methanol, and these complexes become contaminants in the final product. CDs glass transition occurs at about 225 to 250 °C. The glass transition

Table I. Molecular properties of CDs

Parameter	α-CD	β-CD	γ-CD
Glucose residue	6	7	8
Molecular mass	973	1135	1297
Cavity diameter (nm)	0.47–0.53	0.6–0.66	0.75–0.83
Cavity height (nm)	0.79	0.79	0.79
Cavity volume (mL mol^{-1})	174	262	472
Solubility (mg mL^{-1} at 25 °C)	130	18.5	300

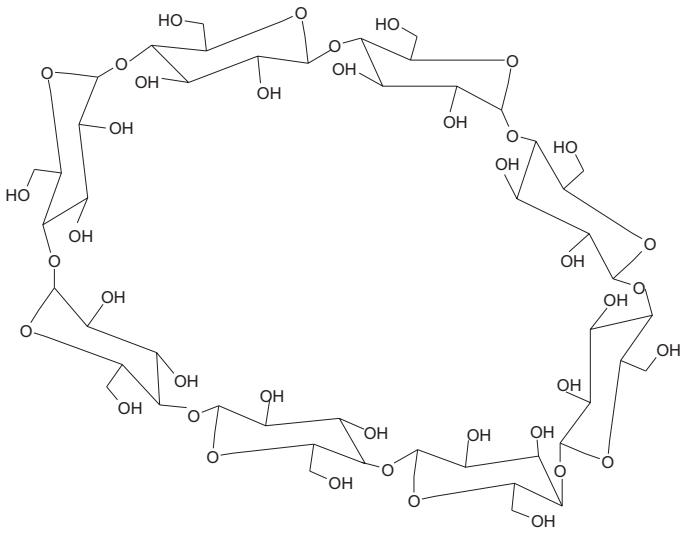

Fig. 1. Structure of β-CD.

temperature varies with the degree of substitution. Thermal decomposition occurs at 308 °C. Strong acids such as hydrochloric acid and sulfuric acid hydrolyze CDs. The rate of hydrolysis is dependent upon temperature and concentration of the acid. CDs are stable against bases. HP-β-CD can be hydrolyzed by some amylases at a very slow rate compared to the corresponding unsubstituted CD. The greater the degree of substitution, the less hydrolysis occurs. Substitution provides hindrance to the binding of CD to the active site of the enzyme; as a result, the extent of hydrolysis is reduced (7).

COMPLEXATION AND THE MECHANISM OF DRUG RELEASE FROM CD COMPLEXES

The internal cavity, hydrophobic in nature, is a key feature of the CDs providing the ability to form complexes, which include a variety of guest molecules. CD inclusion is a stoichiometric molecular phenomenon in which usually only one molecule interacts with the cavity of the CD molecule to become entrapped. A variety of non-covalent forces, such as van der Waals forces, hydrophobic interactions and other forces are responsible for the formation of the stable complex. Inclusion complex formation can be regarded as 'encapsulation' of the drug molecule, or at least the labile part of the molecule. The encapsulation protects the drug molecule against attack by various reactive molecules and in this way reduces the rate of hydrolysis, oxidation, stearic rearrangement, racemization and even enzymatic decomposition (8). In addition, CDs can decrease the photo degradation of various light sensitive drugs (9, 10).

Many techniques are used to form CD complexes, like co-precipitation, slurry complexation, paste complexation, damp mixing, heating method, extrusion and dry mixing. The name itself describes the process of complex formation.

Co-precipitation. – CD is dissolved in water and the guest is added while stirring the CD solution. By heating, more CD can be dissolved (20%) if the guest can tolerate the higher temperature. The CD and guest solution must be cooled under stirring before a precipitate is formed. The precipitate can be collected by decanting, centrifugation or filtration and washed. The main disadvantage of this method lies in the scale-up.

Slurry complexation. – CD can be added to water, as much as 50–60% solids, and stirred. The aqueous phase will be saturated with CD in solution. Guest molecule will complex with the CD in solution and, as the CD complex saturates the water phase, the complex will crystallize or precipitate.

Paste complexation. – A small amount of water is added to the guest to form a paste, which is mixed with the CD using a mortar and pestle. The resulting complex can be dried directly, and milled if hard mass forms.

Damp mixing. – The guest and CD are thoroughly mixed and placed in a sealed container with a small amount of water. The contents are heated to about 100 °C and then removed and dried.

Extrusion. – CD, guest and water can be premixed or mixed as added to the extruder. The extruded complex may dry as it cools or the complex may be placed in an oven to dry. Heat-labile guests can get decomposed.

Dry mixing. – Some guests can be complexed by simply adding the guest to the CD and mixing them together. This works best with oils or liquid guests.

In all above methods, optimization of the amount of water, degree and time of mixing, temperature and heating time is necessary for each guest.

Different mechanisms play an important role in drug release from the drug-CD complex. Complexation of the drug (D) to CD occurs through a non-covalent interaction between the molecule and the CD cavity. This is a dynamic process whereby the drug molecule continuously associates and dissociates from the host CD. Assuming a 1:1 complexation, the interaction will be as follows:

$$D_{free} + CD_{free} \overset{K}{\rightleftharpoons} DCD_{complex}$$

Two parameters, the complexation constant (K) and the lifetime of the complex, are very important for the drug release mechanism.

Dilution. – Dissociation due to dilution appears to be a major release mechanism. The recent example reported by Piel *et al.* (11) for miconazole, a more strongly bound drug compared to prednisolone (12), supports the probable role of dilution. Dilution is minimal when a drug-CD complex is administered ophthalmically. Efficient corneal absorption is further exacerbated by contact time.

Competitive displacement. – Competitive displacement of drugs from their CD complexes probably plays a significant role *in vivo*. Addition of parabens to parenterals not

only leads to decreased antimicrobial activities of the parabens, due to complexation, but also decreases the drug solubility due to its displacement from complexes (13). Van Stam *et al.* (14) showed that alcohol displaces 2-napthol from β-CD complexes. Tokumura *et al.* (15, 16) reported that the β-CD complex of a poorly water-soluble drug, cinnarizine, was more soluble *in vitro* than cinnarizine alone. Oral administration of the complex showed less bioavailability than expected, based on the *in vitro* dissolution experiments. It was suggested that cinnarizine was too strongly bound to the CD so that complex dissociation was limiting oral bioavailability. Co-administration of phenylalanine, a displacing agent, improved the bioavailability of cinnarizine from the complex but not from conventional cinnarizine tablets.

Protein binding. – Drug binding to plasma proteins may be an important mechanism by which the drug may be released from a drug-CD complex. It is evident that proteins may effectively compete with CDs for drug binding and thus facilitate the *in vivo* release of drugs from drug-CD complexes. Dilution alone may be effective in releasing free drugs from weak drug-CD complexes but when the strength of the binding between the drug and CD is increased, a mechanism such as competitive displacement is at work. Plasma and tissue protein binding may also play a significant role. Frijlink *et al.* (17) studied the effect of HP-β-CD on the displacement of both naproxen and flurbiprofen from plasma binding sites *in vivo*. They found that tissue distribution of flurbiprofen and naproxen was higher when HP-β-CD-drug solution was administered compare to drug solution in plasma, 10 minutes after parenteral dose, meaning that more drug was free from CD solution to distribute to the tissues than from the plasma solution.

Drug uptake by tissue. – A potential contributing mechanism for drug release from CD is preferential drug uptake by tissues. When the drug is lipophilic and has access to tissue, and is not available to the CD or the complex, the tissue then acts as a »sink«, causing dissociation of the complex based on simple mass action principles. This mechanism is more relevant for strongly bound drugs or when the complex is administered at a site where dilution is minimal, *e.g.*, ocular, nasal, sublingual, pulmonary, dermal or rectal sites. For example, CD has been used in ophthalmic delivery of poorly water-soluble drugs to increase their solubility and/or stability in the tear fluid, and in some cases to decrease irritation (18, 19).

Change in ionic strength and temperature. – In the case of a weak electrolyte, the strength of binding to CD is dependent on the charged state of the drug, which is dependent on dissociation constant(s) of the drug and the pH of environment. For most molecules, the ionized or charged form of the molecule has poorer binding to CD compared to the non-ionized or neutral form of the drug, especially when bound to a neutral CD (12, 20, 21). Loftsson *et al.* (22) and Inoue *et al.* (23) have shown that binding of substrate to CD is an exothermic process. Hence any increase in temperature results in a weakening of the complex and thus increases the free fraction of substrate. Drug-CD complexes are usually prepared and stored at/or below room temperature. Since the normal body tissue temperature can be as high as 37 °C, this difference in temperature may be another contributing factor to drug dissociation *in vivo*.

CYCLODEXTRINS IN OPHTHALMIC DRUG DELIVERY

Local drug administration to the eye is preferred to systemic drug administration (oral route). This route can avoid the effects influencing gastrointestinal absorption such as pH, food, stomach emptying, *etc*. Topically applied drug formulations such as suspensions, oily drops, gels, ointments and solid inserts have been used, but most of these formulations give rise to unwanted side effects (*e.g.*, eye irritation and blurred vision) (24). Some investigators suggest that CDs enhance drug permeability through biological membranes such as eye cornea and skin by disrupting the membrane, either by permeating into the membrane or by extracting or complexing with some lipophilic components such as cholesterol and phospholipids from the membrane (25). But, the correct mechanism is when CD acts as a true carrier by keeping the hydrophobic drug molecules in solution and delivers them through the aqueous mucin layer to the surface of the ocular barrier (*i.e.*, cornea or conjunctiva) where they partition into the barrier.

Ophthalmic irritation is a common drawback in ophthalmic drug development and in their clinical use. CDs may decrease the irritation of ophthalmic drugs by forming inclusion complexes and thereby masking the irritating drugs or by replacing the irritating additives from the formulation. Co-administration of HP-β-CD (26), SBE4-β-CD (*i.e.*, SBE-β-CD with the average degree of substitution of 4) (27) or SBE7-β-CD (substitution degree 7) (28) significantly decreases eye irritation of the pilocarpin prodrug. Pilocarpin irritation is due to the rapid absorption of the lipophilic prodrug into the lipophilic corneal epithelium and/or precipitation of prodrug molecules in the pre-corneal area. Pilocarpin/SBE 7-β-CD complexes can be considered to act as a depot that limits the free prodrug concentration in the precorneal area to a non-irritating level. Similarly, cetirizine, an antiallergic drug, causes strong irritation after ophthalmic administration but co-administration of α-CD, β-CD and γ-CD eliminates this irritation (29).

Ophthalmic solutions are usually aqueous solutions in which most drugs are subject to chemical degradation. One of the most common pharmaceutical applications of CDs is to enhance drug stability in aqueous solutions. Dipivefrine, a prodrug of epinephrine, has currently replaced epinephrine in the treatment of glaucoma. The main drawback of dipivefrine is its low aqueous stability. In eye drops, this has been overcome by formulating a dipivefrine solution in the pH range of 2.5 to 3.5 (30). However, the eye drop is irritating to the eye, resulting in decreased ocular bioavailability due to induced lacrimation (31). At pH 5 and pH 7.4, the negatively charged SBE7-β-CD increases the aqueous stability of positively charged dipivefrine 15–30 times and 20–200 times, respectively. Commercial pilocarpin eye drops are buffered between pH 4 and 5 for stability. SBE 4-β-CD increases the aqueous stability of pilocarpin at pH 6–8 as much as twofold (32). Hydrocortisone can be formulated as a water solution in the presence of HP-β-CD and the aqueous stability of hydrocortisone was increased approximately twofold at 60 °C due to complexation (33). Considerable improvement in the chemical and enzymatic stability of ganciclovir prodrugs was observed in the presence of HP-β-CD. HP-β-CD was found to enhance the corneal permeation only of the lipophilic prodrugs of ganciclovir (34).

Unfortunately, there are some limitations to the of CDs application in ophthalmic drug delivery. Pilocarpin is stabilized by SBE 4-β-CD in aqueous solution but the bioavailability of the drug is affected. Freedman *et al.* (35) showed that at a low concentration, co-administration of SBE 4-β-CD has no effect on pilocarpin bioavailability and it

has even a slight decreasing effect at higher concentrations (32). Similarly, HP-β-CD has been shown to slightly reduce the efficacy of water-soluble timolol for intraocular pressure in rabbits. The decreased bioavailability is, in most cases, due to a fast clearance of the drug-CD complex from the precorneal area. This problem can be, at least partly, overcome by increasing the viscosity (and hence the residence time) of eye drops. *In vitro* (36–38) and *in vivo* (24, 28) studies have shown that excess complexation of a poorly water-soluble drug will decrease its membrane permeability and ophthalmic viability.

Eye drops are usually delivered in a multi-dose container and thus should contain an antimicrobial preservative. CD complexation with the preservative can reduce their antimicrobial activity. Lipophilic preservatives such as *p*-hydroxy benzoic acid esters form complexes with HP-β-CD and their antimicrobial effect decreases (39–41). Contrary to this, the antimicrobial effect of hydrophilic preservatives like thimerosal, bronopol (41), benzalkonium chloride and chlorohexidine gluconate (40) are not much affected since they are not as effectively bound to CDs.

CYCLODEXTRINS IN NASAL DRUG DELIVERY SYSTEM

Nasal route is an alternative and convenient route for administration of high potency drugs with low oral bioavailability because of their extensive gastrointestinal breakdown and high hepatic first-pass effect. Drugs of a lipophilic nature are difficult to deliver through the nasal route due to their poor water solubility. Large hydrophilic drugs like peptides and proteins show insufficient nasal absorption. One more drawback of this route is large interspecies differences exist in the nasal absorption of drugs. Also, the nasal mucosa possesses enzymatic activity as a protective mechanism against exogenous chemicals.

Methylated derivatives of CD, especially β-CD and α-CD, have been proven to be excellent solubilizer and absorption enhancers. However, studies on RM-β-CD (20% and above) have revealed severe damage to the nasal mucosa integrity (42). Recent investigations of lipophilic drugs in the nasal drug delivery system with CD involved estradiol (decrease in dose) (43, 44), morphine HCl (45), midazolam (46) (enhanced nasal absorption), dihydroergotamine (improved stability) (47). Administration of lipophilic drugs such as female steroid hormones estradiol and progesterone with CDs has shown rapid absorption (43, 44). Intranasal spray of the antiviral lipophilic drug pirodavir with 10% hydroxypropyl-β-CD as solubilizer was effective in preventing rhinovirus infection (50). Side effects such as nasal dryness and blood in mucus were attributed to the viscosity of the formulation vehicle and high frequency of administration. Dimethyl-β-CD and 2-hydroxypropyl-γ-CD has shown an enhanced and sustained level of morphine in the plasma and cerebrospinal fluid (45). CDs have been also shown to enhance the concentration and improve the stability of the antimigraine drug dihydroergotamine. Melatonin in combination with β-CD has been investigated as well. The nasal absorption appeared to be very fast and efficient, in contrast the oral bioavailability of melatonin, which is low and variable due to the first pass metabolism (51).

Hydrophilic drugs, *e.g.*, proteins and peptides, have low nasal absorption in humans that decreases with increasing molecular size. CD has shown increased nasal absorption of oligopeptide drugs like buserelin (52) and leuprolide (53). At a 5% concentra-

tion, methylated-β-CD significantly increased calcitonin nasal absorption compared to intravenous or subcutaneous administration (54). Increased nasal bioavailability of glucagons (55) and insulin (56) with dimethyl-β-CD has been reported. It can be concluded from the various studies that most nasal absorption enhancing CDs for peptides and proteins are methylated β-CD derivatives, DM-β-CD.

Bioavailability after nasal administration of insulin to rats increased up to 100% with dimethyl-β-CD (3–5%) (54). When the concentration of dimethyl-β-CD in nasal liquid formulations was increased to 50%, the insulin bioavailability dropped markedly. The decreased absorption was possibly due to administration of extremely high concentrations of CD or the excess of CD interfered with the insulin transport across the nasal epithelium (57).

CYCLODEXTRINS IN TRANSDERMAL DRUG DELIVERY

Drugs have been delivered by the transdermal route for both local and systemic action. As the drug enters systematic circulation directly, the first pass effect is eliminated; it also eliminates the factors that influence gut absorption. This route can be used for drugs with a low therapeutic index. The transdermal drug transport is greatly limited by stratum corneum permeation characteristics; so attempts at improving topical absorption have been reported. Drugs must retain sufficient stability, not only during storage but also at the site of application. Various studies report CD as a drug stabilizer in dermal drug delivery. Complex of dermatocorticoid, tixoxortol-17-butyrate-21-propionate, with β-CD included in vaseline and o/w emulsion showed stability after 30 days storage at 40 °C (58). Uekama *et al.* (59) reported that CME-β-CD markedly stabilized prostaglandin E_1 (PGE_1) in fatty alcohol/propylene glycol (FAPG) ointment and in aqueous solution. Adachi *et al.* (60) reported stabilizing effects of CD against the decomposition of PGE_1 in the skin. The combination of CME-β-CD and topical permeation enhancer, 1-[2-(decylthio) ethyl]-azacyclopentane-2-one, suppressed the bioconversion of PGE_1 to give less pharmacologically active metabolites during the passage through the skin.

A number of reports reported improved drug release from the vehicle and permeation as CDs complexes. Dermal corticoids like betamethasone (61) and beclamethasone dipropionate (62) showed enhanced release from hydrophilic ointment bases after complexation with β-CD and/or γ-CD. Vehicle types used markedly affect the enhancing effect of CDs on the drug release, *e.g.*, prednisolone complexation with dimethyl β-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 (63). CDs are also able to enhance the dermal delivery of NSAIDs. Arima *et al.* (64) have shown increased *in vivo* absorption of 4-biphenyl acetic acid in rats due to complexation with β-CD, DM-β-CD and HP-β-CD. Lin *et al.* (65) reported that the anti-inflammatory effects of indomethacin in hydroxyethylcellulose hydrogels, a hydrophilic base, were significantly enhanced by complexation with β-CD and HP-β-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. Further addition of CDs to the systems decreases

the permeation rate of lipophilic drugs through the formation of strong complexes (66). In addition, Loftsson *et al.* (67, 68) reported the possibility that addition of ternary materials to the vehicle affected the enhancing effects of CDs on dermal drug delivery. Considering the effects of hydrophilic CDs on drug release, hydrophobic CD may alter the drug release from the vehicle. For example, the release rate of nitroglycerin from ointments was accelerated by complexation with DE-β-CD, and retarded by complexation with β-CD. Therefore, a combination of DE-β-CD and β-CD complexes might be applicable to sustained release preparations for percutaneous administration (69, 70). This increased permeability may be due to CDs interaction with some component of the skin. CDs are also being identified as co-enhancers in dermal drug delivery systems. This statement is supported by Legendre *et al.* (71) who showed that a combination of oleic acid, a permeation enhancer, and RM-β-CD increased the flux of S-9977 hydrochloride 30 fold due to the increase in the diffusion of oleic acid in stratum corneum.

Recently, CDs in dermal delivery of proteins and peptides has been noted. For example, a combination of β-CD and the permeation enhancer Azone achieved higher percutaneous absorption of a peptide drug, nafarelin acetate, and a luteinizing hormone releasing analog (72). CDs may alleviate skin irritation caused by drugs by lowering the extent of free drug resulting from the inclusion equilibrium. Hoshino *et al.* (73) studied the effect of topically applied β-CD and DM-β-CD on photoallergic contact dermatitis of chlorpromazine HCl in guinea pig and found a decreased photosensitizing potential of chlorpromazine HCl with β-CD and DM-β-CD compared to chlorpromazine HCl alone. The alleviating effects of CDs may be explained by the suppression of the penetration of chlorpromazine HCl into the skin via the lower partition coefficient between drug and skin. Studies show that at higher concentrations parent CDs and chemically modified CDs caused skin irritation in guinea pigs in the order γ-CD < α-CD < β-CD; this result largely depends on their abilities to extract lipids from stratum corneum (74). As regards CD derivatives, DM-β-CD is known to extract the components from stratum corneum, which leads to skin irritation.

CYCLODEXTRINS IN RECTAL DRUG DELIVERY

Rectal route is the alternative drug application route for patients who have difficulties in swallowing, nausea or vomiting, for infants or children. However, rectal drug delivery is limited by the dissolution media volume, low rectal bioavailability of some drugs, limited absorbing surface and drug degradation by microorganisms present in the rectum. Usefulness of CDs for rectal drug delivery has been reported with respect to stabilization, improvement in release, bioavailability and alleviation of local irritation (75).

Many reports concluded that the effect of CDs on rectal drug delivery depends solely on the vehicle type (hydrophilic or lipophilic), physicochemical properties of the complexes and addition of ternary excipients such as viscous polymers. Enhancement of rectal absorption of lipophilic drugs is based on the improvement of drug release from vehicles and the dissolution rates in rectal fluid. In the case of inabsorbable drugs like antibiotics, peptides and proteins, CDs directly act on the rectal epithelial cells. CDs drug 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 (76). These stabilizing effects of CDs are attributed to insolubilization of the drugs in the lipophilic suppository base. Arima *et al.* (77) reported inhibition of ethyl-4-biphenylyl acetate (EBA) bioconversion in the rectal lumen of rats by complexation with β-CD, DM-β-CD and HP-β-CD using the *in situ* recirculation technique. Complexed EBA was less absorbable from the rectal lumen in the solution state; this inhibited the bioconversion of EBA to BPAA. These inhibitory effects may also lead to decreased rectal irritation of the drug. α-CD in combination with xanthan gum has been reported to inhibit the bioconversion of morphine in rabbit rectum. CD inhibits the upward movement of morphine from areas affected by the first pass metabolism and thereby conversion to less active morphine-glucoronoid conjugates (78).

Watanabe *et al.* (79, 80) 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 have been also reported as co-enhancers. Along with the fact that CDs reduce gastrointestinal mucosa 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 BPAA and EBA administration of lipophilic suppositories to rats (77, 81).

CYCLODEXTRINS IN ORAL DRUG DELIVERY

Oral modified release is of growing interest because appropriate drug release from dosage forms is of critical importance for their therapeutic efficacy. CDs are potential candidates for modified release carriers because they can form inclusion complexes both in solution and in the solid state, in which the guest molecule is surrounded by the hydrophobic environment of the CD cavity. Chemically modified hydrophobic and hydrophilic CDs may serve as novel slow-release carriers for water-soluble drugs, including proteins and peptide drugs, and enhance drug absorption.

*Immediate release***.** – The dissolution rate of poorly water-soluble drugs is mainly responsible for both the rate and extent of oral bioavailability of drugs. Hydrophilic CDs have been extensively used to enhance the oral bioavailability of steroids, NSAIDs, cardiac glycosides, antiepileptics, benzodiazepines, antidiabetics, vasodilators, *etc.* (82). These improvements are mainly attributed to the increase in solubility and wettability of drugs through the formation of inclusion complexes. Only the free form of the drug, which is in equilibrium with the complexed form of the drug in solution, is capable of penetrating the lipophilic barriers and thus entering the systemic circulation. Displacement of the drug from the CD cavity by exogenous (excipient) and endogenous substances (which compete with the drug for the CD cavity) at the absorption site is one of the factors responsible for acceleration of drug absorption. Therefore, the application is successful when the rate-limiting step in drug absorption is the dissolution of the drug itself and not its absorption across the gastrointestinal tract. Complexation of β-CD with imidazole antifungal agents, such as ketoconazole and econazole, provides enhanced bioavailability (83, 84). The stabilizing effect of CDs on labile drugs is also responsible for the im-

provement of oral bioavailability. For example, the γ-CD complex decreases acid hydrolysis of cardiac glycosides and thus improves the oral absorption of digoxin in dogs (85). Highly hydrophilic CD derivatives, such as HP-β-CD (86), maltosyl-β-CD (87) and SBE-β-CD (88) have been used to obtain an immediate release formulation that is readily dissolved in GIT, enhancing the oral bioavailability of poorly water soluble drugs. Rapidly dissolving complexes of drugs and CDs are well suited for sublingual or buccal administrations, which avoid the hepatic first-pass metabolism of the drug. HP-β-CD and β-CD support the absorption of testosterone from the oral cavity rather than GIT.

*Delayed release***.** – Delayed release can be classified as time controlled release, since the drug is preferentially released in the intestinal tract. Excipients having weak acidic groups are preferable because they are less soluble in water at low pH. CME-β-CD was developed to exhibit pH-dependent solubility for use in selective dissolution of the drug CD-complex. Molsidomine absorption from tablets containing CME-β-CD was studied in gastric acidity-controlled dogs in fasted and fed states. Under high gastric acidity, molsidomine absorption was significantly retarded compared to that found under low gastric acidity conditions. The delayed absorption effect under high gastric acidity was more pronounced under fasted conditions (89).

*Prolonged release***.** – Slow-release preparations have been designed to achieve zero-order or pH-independent release of drugs to provide a constant blood level for a long period of time. These formulations have advantages such as reduced dosing frequency, prolonged drug efficacy and absence of toxicity associated with the administration of a simple plain tablet. Hydrophobic alkylated CDs such as DE-β-CD, TE-β-CD were the first slow-release carriers to be used in conjugation with diltiazem (90).

*Modified release***.** – Nifedipine has low oral bioavailability due to its poor aqueous solubility; hence the release rate of nifedipine must be modified in order to obtain a more balanced oral bioavailability with therapeutic effect. Wang *et al.* (91) developed a double-layer tablet employing an amorphous nifedipine powder prepared by spray drying with HP-β-CD and HCO-60® (non-ionic detergent) as the fast release portion to attain initial rapid dissolution. Recently, Okimoto *et al.* (92) developed a novel osmotic pump tablet for prednisolone using (SBE)7m-β-CD, which acts as a solubilizer and an osmotic agent.

CONCLUSIONS

Dissociation due to dilution appears to be the major release mechanism from CD inclusion complexes. CDs are useful additives in ophthalmic formulations for increasing the aqueous solubility, stability and bioavailability of ophthalmic drugs, and for decreasing drug irritation. Methylated β-CDs have been shown to be useful excipients in nasal drug delivery. The *in vivo* study demonstrates that they can largely improve the nasal absorption of some lipophilic drugs and of oligopeptides. The effects of CDs on the release, topical bioavailability and pharmacological effects of drugs when applied to the skin and into the rectum are considerably influenced by the vehicle type. A desirable attribute to the drug carrier is the ability to control the rate and time of drug release; pera-

cylated CDs may serve as novel hydrophobic carriers to control the release rate of water-soluble drugs. We hope that further investigations on CDs will overcome some of the problems related to producing larger, labile complexes, insoluble and/or inabsorbable drugs in the near future.

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Acronyms. – CD – cyclodextrin; CME-β-CD – *O*-carboxymethyl-*O*-ethyl β-CD; DE-β-CD – 2,6-diethyl-β-CD; HP-β-CD – 2-hydroxypropyl-β-CD; DM-β-CD – 2,6-dimethyl-β-CD; SBE-β-CD – sulfate and sulfobutylether-β-CD; RM-β-CD – randomized methylated-β-CD; BPAA – 4-biphenyl acetic acid; EBA – ethyl 4-biphenylyl acetate; GIT – gastrointestinal tract; NSAID – non-steroidal anti-inflammatory drug.

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SAŽETAK

Ciklodekstrini – primjena u različitim načinima isporuke lijekova

SHYAM SHIMPI, BHASKAR CHAUHAN i PRAJAKTA SHIMPI

U ovom revijalnom radu opisana su fzičko-kemijska svojstva ciklodekstrina, različiti načini njihove primjene te mehanizmi oslobađanja ljekovitih tvari iz kompleksa s ciklodekstrinima (razrjeđenje, kompetitivna zamjena, vezanje na proteine, promjena ionske jakosti i temperature, te unos ljekovite tvari u tkivo). Opisana je uporaba ciklodekstrina i ograničenja uporabe u različitim sustavima za isporuku lijekova za nazalnu, oftalmičku, transdermalnu, rektalnu te detaljno za peroralnu primjenu. Mnogobrojna istraživanja su potvrdila da su ciklodekstrini korisni sastojci pripravaka za različite načine primjene jer povećavaju vodotopljivost, stabilnost i bioraspoloživost ljekovite tvari, a smanjuju njenu iritabilnost.

Ključne riječi: ciklodekstrini, mehanizam oslobađanja, nazalna primjena lijekova, oftalmička primjena lijekova, transdermalna primjena lijekova, rektalna primjena lijekova, peroralna primjena lijekova

Department of Pharmaceutics, Bharati Vidyapeeth Deemed University Poona College of Pharmacy Erandawane, Pune-411 038, Maharashtra, India

Nasik District Maratha Vidya Prasarak Samaj's College of Pharmacy, Gangapur Road, Nasik-422002 Maharashtra, India