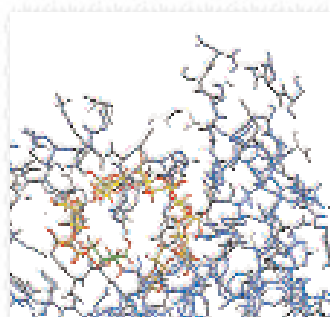


Cyclodextrins as Sustained-Release Carriers

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The use of cyclodextrins (CDs) is a **practical and economical way to improve**

the physicochemical and pharmaceutical properties of administered drug molecules.

CDs can improve properties such as solubility, stability, and bioavailability of various drugs, thereby potentially serving as novel drug carriers. In addition, the hydrophobic and ionizable derivatives of CDs are being tested for use in the preparation of sustained-release or delayed-release formulations. This review article describes the complexation of drug molecules with CDs to improve the properties of various formulations.

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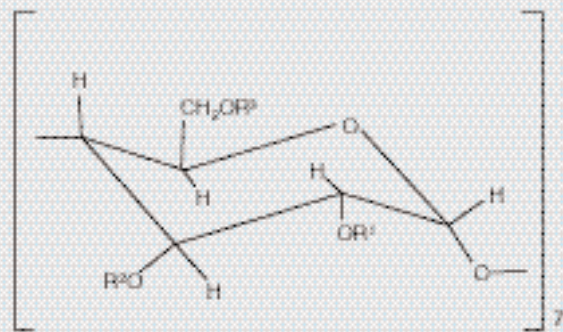
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Cyclodextrins (CDs) have immense potential as carrier molecules in the formulation of novel drug delivery systems. These substances can alter the physicochemical properties of guest molecules by forming inclusion complexes with the molecules that fit within the hydrophobic cavity of CDs (1,2). Commercially available CDs can be used for the complexation of drug molecules that are poorly soluble and unstable and hence difficult to formulate. Complexation with a CD results in improved wettability, dissolution, and stability of this type of drug (3). Despite these well-documented applications of CDs, few reports exist that document the use of CDs to develop sustained-release formulations. Hydrophobic CDs such as alkylated and acylated derivatives have been used as slow-release carriers for water-soluble drugs (4). This article summarizes the physicochemical properties of hydrophobic CDs and investigates their use in sustained drug delivery.

Hydrophobic derivatives of CDs and their physicochemical properties

CDs are cyclic (α -1,4)-linked oligosaccharides of α -D-glucopyranose units that have a relatively hydrophobic central cavity and hydrophilic outer surface (5). The α -, β -, and γ -CDs are the most common natural CDs consisting of six, seven, and eight D-glucopyranose residues, respectively, linked by α -1,4 glycosidic bonds into a macro cycle (6). Several reviews describe the physicochemical aspects and application of these CDs (1,2,7,8). To diversify the use of the natural CDs, various kinds of derivatives have been prepared to improve their physicochemical properties and inclusion capacity to enable them to become novel drug carriers (7). The hydrophobic CD derivatives are useful as sustained-release drug carriers for water-soluble drugs and peptides because they tend to decrease the solubility of the guest molecule (4). Natural CDs such as β -CD have 21 hydroxyl groups that can be exploited for the structural modifications of CDs by introducing various functional groups into the CD molecules. Such structural modifications can optimize the desirable properties of CDs (1).

Ethylation of the hydroxyl groups of β -CDs decreases their aqueous solubility, which in turn is proportional to the degree of substitution (10). The available hydrophobic ethylated derivatives are heptakis-(2,6-di-O-ethyl)- β -cyclodextrins (diethyl- β -cyclodextrins) and heptakis (2,3,6-tri-O-ethyl)- β -cyclodextrins (triethyl- β -cyclodextrins) (10). Studies have shown that these



Derivative of cyclodextrin	R ¹	R ²	R ³
β-cyclodextrin	H	H	H
Diethyl-β-cyclodextrin	C ₂ H ₅	H	C ₂ H ₅
Triethyl-β-cyclodextrin	C ₂ H ₅	C ₂ H ₅	C ₂ H ₅
Triacetyl-β-cyclodextrin	COCH ₃	COCH ₃	COCH ₃
Tripropanoyl-β-cyclodextrin	COC ₂ H ₅	COC ₂ H ₅	COC ₂ H ₅
Tributanoyl-β-cyclodextrin	COC ₃ H ₇	COC ₃ H ₇	COC ₃ H ₇
Trivaleryl-β-cyclodextrin	COC ₄ H ₉	COC ₄ H ₉	COC ₄ H ₉
Trihexanoyl-β-cyclodextrin	COC ₅ H ₁₁	COC ₅ H ₁₁	COC ₅ H ₁₁
Triocanoyl-β-cyclodextrin	COC ₇ H ₁₅	COC ₇ H ₁₅	COC ₇ H ₁₅
Carboxymethyl-ethyl-β-cyclodextrin	C ₂ H ₅	C ₂ H ₅	H/CH ₂ COONa/C ₂ H ₅

Figure 1: β-cyclodextrin and its hydrophobic derivatives.

cyclodextrin induced sufficient plasma levels as compared with the other derivatives that had shorter or longer chain lengths.

In addition to these derivatives, an insoluble aluminum salt of β-cyclodextrin sulphate was prepared from sodium-β-cyclodextrin sulphate. Aluminum-β-cyclodextrin sulphate was prepared by dissolving sodium-β-cyclodextrin sulphate and aluminum chloride in water at a pH value of 4.5 adjusted using 2 M sodium hydroxide. After the solution was stirred at 25 °C for 2 h, the precipitate obtained was washed with water and vacuum dried at 60 °C for 24 h. The prepared derivative was used as a stabilizer and as a sustained-release carrier molecule (13).

Another derivative, *O*-carboxymethyl-*O*-ethyl-β-cyclodextrin (CME-β-CD), has proved to be an ideal candidate for the development of delayed-release formulations. Uekama et al. combined the carboxymethyl substituent with an ethylated CD to produce 6-*O*-(carboxymethyl)-*O*-ethyl-β-cyclodextrin (14). This derivative was slightly soluble at low pH values and freely soluble in neutral and alkaline regions as the result of ionization of the carboxyl group. Thus CME-β-CD could serve as an enteric-type drug carrier similar to carboxymethyl ethyl cellulose, with the additional advantage of stabilizing the labile drugs because of its inclusion ability (15).

CDs in sustained-release formulations

Diltiazem. Several researchers have reported the use of the CD derivatives previously mentioned in this article. Uekama et al. prepared the solid

Table I: Solubility of β-cyclodextrin and its hydrophobic derivatives.

Cyclodextrin	Solubility	Solvent System	Ref.
β-cyclodextrin	1.8 g/100 mL	Water	10
Diethyl-β-cyclodextrin	5.0 × 10 ⁻³ g/100 mL	Water	10
Triethyl-β-cyclodextrin	1.8 × 10 ⁻³ g/100 mL	Water	10
Triacetyl-β-cyclodextrin	823.0 mg/dL	80% ethanol/water	1
Tripropanoyl-β-cyclodextrin	423.0 mg/dL	80% ethanol/water	1
Tributanoyl-β-cyclodextrin	219.0 mg/dL	80% ethanol/water	1
Trivaleryl-β-cyclodextrin	283.0 mg/dL	80% ethanol/water	1
Trihexanoyl-β-cyclodextrin	3.7 mg/dL	80% ethanol/water	1
Triocanoyl-β-cyclodextrin	*	80% ethanol/water	1

*Could not be determined because of low solubility.

derivatives sustain the release of various drugs from the inclusion complexes, with varying effects. Thus, a desirable release profile can be obtained by using these derivatives either alone or in combination for the formation of inclusion complexes (11).

The diethyl derivatives of β-CD were prepared by partially ethylating the C₂ secondary and C₆ primary hydroxyl group of β-CD; the C₃ secondary hydroxyl group was left unsubstituted. For preparing triethyl-β-cyclodextrin (TE-β-CD), the primary and secondary hydroxyl groups of β-CD were perethylated. Steric hindrance offered by these groups imparts low-solubility and acid-stability characteristics to these derivatives (10).

In addition to ethylation, acylation has been used to prepare derivatives with differing chain lengths (12). Peracylated β-CD derivatives with various alkyl chains (from acetyl to octanoyl) were prepared by acylating all hydroxyl groups of β-CD using corresponding acid anhydrides in a pyridine solution. Table I shows the solubility behavior of these derivatives. The derivatives retard drug release in proportion to their alkyl chain lengths. Among all the peracylated derivatives, perbutanoyl-β-

complexes of diltiazem with diethyl-β-cyclodextrin (DE-β-CD) and TE-β-CD in a molar ratio of 1:1 using the kneading method (10). The in vitro release profile indicated a slow release of the drug from the complexes, particularly from TE-β-CD as expected because of its aqueous solubility, which is considerably less when compared with that of DE-β-CD (see Table I). Therefore the release of the drug from the derivative was also quite slow. For the in vivo evaluation, a compressed tablet of diltiazem and its ethylated-β-cyclodextrin complex was administered to rats. The pharmacokinetic parameters such as C_{max} and T_{max} suggested that DE-β-CD prolonged the time (T_{max}) required to reach the maximum plasma level (C_{max}) compared with that of diltiazem alone, and it further maintained the plasma concentration for as long as 48 h. For the TE-β-CD complex, the plasma concentration of diltiazem was maintained at a comparatively low and constant level for 48 h after administration. However, the TE-β-CD was inappropriate for practical use because of its low-absorption properties (10).

Buserelin acetate. Buserelin acetate is a highly potent analog

of luteinizing hormone-releasing hormones and is used for the treatment of endocrine-dependent metastatic prostate carcinoma. Because of its short biological half-life, frequent injections and nasal applications of the drug must be administered so that its therapeutic concentration is maintained (16). The solid complex of buserelin acetate with DE- β -CD in a 1:100 weight ratio was prepared using the kneading method. The complex obtained was formulated into an oily suspension using arachis oil as a vehicle. For in vitro dissolution, the extended duration of drug release could be explained by the slow dissolution of the complex owing to the low solubility of DE- β -CD. In the in vivo studies, the oily suspension containing both the drug and its complex was administered subcutaneously to Sprague Dawley male rats. No appreciable difference between the two suspensions in the area under the plasma drug-level time curve (AUC) was seen, which indicated that the complexation did not alter the extent of bioavailability of the drug. The suspension containing the complex provided plasma levels of buserelin that lasted for at least 7 weeks. It provided a 70-fold-longer mean residence time of the drug complex in plasma as compared with that of the drug alone (4).

Flufenamic acid (FA). Studies have shown that FA, which belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs), has limited clinical value because of its gastrointestinal side effects and short biological half-life (17). The complexes of FA with triacetyl- β -cyclodextrin (TA- β -CD) at various molar ratios were prepared using the kneading method. A mixture of drug with glucose also was prepared for comparison with the release rate from the complexes. The in vitro studies of the release rates from the various complexes as well as from the drug-glucose mixture found that the drug release from the complexes was very slow. The release profile consisted of two stages: faster release in the first stage and slower release in the second stage. The fast release in the first stage may be attributable to the presence of free drug in the formulations, and the slow release may be the result of release of drug from the complexes. The estimated free drug in the complexes was 14% for a 1:1 drug-to-CD ratio, 8.8% for a 1:2 ratio, and 5.3% for a 1:3 ratio. These values corresponded to the values obtained in the first stage of the release from the complexes. After the release of the free drug, the drug in the complex dissolved slowly for as long as 8 h. However, 100% of the drug was released from the drug-glucose mixture in 1 h.

In vivo experiments were performed by directly administering the FA-TA- β -CD mixture into the intraduodenal lumen of male Wistar rats (17). The plasma concentration of FA reached a maximum level within 40 min of administration. However, the complex did not show a sharp peak but instead plateaued for 6–8 h. An increased mean residence time (MRT) of FA from the complex was observed, but no changes in the AUC_{0–10} were seen for the complexes as compared with that of the mixture. Therefore it was concluded that FA-TA- β -CD complexes may be useful for achieving prolonged action with fewer side effects.

Nitroglycerine (TNG). The use of DE- β -CD in combination with β -CD has been reported to formulate a sustained-release formulation of TNG (18). The release rate of TNG from ointment formulations was increased by complexation of TNG with

DE- β -CD and retarded by complexation with β -CD. Complexation with DE- β -CD also led to a better dissolution of TNG from the ointment base, giving better percutaneous absorption. β -CD retarded drug release because of its hydrophilic character, which led to decreased solubility of the drug in the ointment base, hence, lower percutaneous absorption. However, from the tablet formulation, the DE- β -CD complexes retarded in vitro release compared with release from the β -CD complexes. Hence a combination of DE- β -CD and β -CD in an optimum ratio could be used to prepare sustained-release formulations for percutaneous administration (18).

Isosorbide dinitrate. Another water-soluble drug, isosorbide dinitrate, was complexed with DE- β -CD in a drug-to-CD molar ratio of 1:2 using the kneading method (19). Researchers performed in vitro release studies of the drug and its complexed form. They observed that the release rate from the capsule containing the complex was very slow compared with that of the capsule containing the free drug. For in vivo experiments, capsules containing the complex and the free drug were administered orally to male Wistar rats. The plasma-concentrations-versus-time graph showed that the time (T_{\max}) required to reach the maximum plasma level (C_{\max}) as well as the MRT values was approximately 1.8 times longer than that of drug alone, producing a sustained-release pattern. In addition, no appreciable decrease in the plasma concentration-time AUC and C_{\max} was observed.

Molsidomine. In addition to the reported use of ethylated derivatives, peracylated derivatives such as heptakis(2,3,6-tri-*O*-butanoyl)- β -cyclodextrin have been used to complex molsidomine, a nitrovasodilator used to treat angina pectoris (12). It was complexed with acylated derivatives having differing alkyl chains (from acetyl to octanoyl). The complexes were prepared in a 1:1 molar ratio using the kneading method. The release studies of the complex were performed using gelatin capsules and compared with those of a drug-starch mixture. The release rate of the drug from the starch mixture was very fast because of its high aqueous solubility. The release was much retarded from the complex. The most-prominent results were obtained with perbutanoyl- β -cyclodextrin as a result of its mucoadhesive property and hydrophobicity. The derivatives with alkyl chains longer than the butanoyl chains released very little molsidomine. The release rate decreased in proportion to the increased length of the alkyl chain.

In vivo studies were conducted using male beagle dogs. The absorption of the drug from capsules containing free drug was rapid and showed short biological half-life in the plasma, whereas a sustained-release pattern was obtained from the complexes. Of all the derivatives, only the perbutanoyl derivative produced an increase in the plasma concentration AUC for as long as 12 h postadministration and significantly prolonged the time (T_{\max}) required to reach the maximum plasma level (C_{\max}). In addition, the MRT of the perbutanoyl complex was twice that of molsidomine alone (12).

bFGF. It has been reported that oral administration of aluminum salt of sucrose sulfate provides selective binding to ulcer lesions and forms a pepsin-resistant barrier over the surface of the lesions (20). On the basis of this finding, the adsorbate of

Table II: Applications of various derivatives of cyclodextrins in the formulation of modified-release preparations.

Derivative	Drug	Category	Method of Complexation	Summary	Ref.
Diethyl- β -CD	Diltiazem	Calcium antagonist	Kneading	Sustained release for oral use	10
	Buserelin acetate	Luteinizing hormone-releasing hormone	Kneading	Sustained release for subcutaneous use	4
	Nitroglycerine	Nitrovasodilator	Kneading	Sustained release for percutaneous use	18
	Isosorbide dinitrate	Nitrovasodilator	Kneading	Sustained release	19
	Tiaprofenic acid	NSAID	Kneading	Delayed release	23
Triacetyl- β -CD	Flufenamic acid	NSAID	Kneading	Prolonged release for oral use	17
Peracylated- β -CD	Molsidomine	Nitro vasodilator	Kneading	Sustained release for oral use	12
	Salbutamol	Bronchodilator	Kneading	Prolonged release for oral use	21
	Captopril	Angiotensin-converting enzyme inhibitor	Kneading	Sustained release	22
Al- β -CD-sulphate	Recombinant human basic fibroblast growth factor	Growth hormone	Kneading	Sustained release for oral use; enhanced stability	13
O-carboxymethyl-O- β -CD	Molsidomine	Nitrovasodilator	Kneading	Delayed release	26
	Diltiazem HCl		Kneading	Delayed release	14,24

recombinant human basic fibroblast growth factor (bFGF) with aluminum- β -cyclodextrin sulphate was expected to have a similar affinity to the ulcer locus so that it could deliver the protein more effectively to the site of action (13). Aluminum- β -cyclodextrin sulphate was used as a stabilizer and sustained-release carrier for bFGF. An adsorbate of bFGF with aluminum- β -cyclodextrin sulphate was prepared by incubating the protein with a suspension of aluminum- β -cyclodextrin sulphate in water at room temperature. The degradation of bFGF in both the absence and presence of aluminum- β -cyclodextrin sulphate was determined. When bFGF was incubated with pepsin at 37 °C and a pH value of 1.2, protein rapidly degraded and was almost completely abolished within 15 min, but the complexed form was protected against peptic digestion. It was noted that the pH value of the medium shifted to 3.8, at which level the catalytic activity of the pepsin was minimal. This shift in the pH value could be attributed to the intrinsic antacid activity of the adsorbate. When incubated with α -chymotrypsin at 37 °C, bFGF was degraded within 1 h at a pH value of 7.0, whereas >70% of the initial amount of bFGF remained after 18 h of incubation encase of the complex. The release profile of bFGF from its aluminum- β -cyclodextrin sulphate adsorbate showed apparent retardation. The rate of retardation depended on the ratio of aluminum- β -cyclodextrin sulphate to the protein in the adsorbate. The degradation of bFGF was <5% of the initial amount. Therefore a stable adsorbate of aluminum- β -cyclodextrin sulphate could provide a formulation having gastro-stable and sustained-release characteristics (13).

TB- β -CD is a useful carrier for orally administered drugs that are metabolized in the gastrointestinal tract (21).

Captopril. Similarly, solid complexes of captopril, an angiotensin-converting enzyme inhibitor, were formed with TB- β -CD using the kneading method. Drug-release studies have shown a retarding effect. The plasma profile obtained from an in vivo analysis was comparable with that of a commercially available sustained-release preparation (Captopril, Sigma Co., St. Louis, MO) (22).

CDs in delayed-release formulations

Tiaprofenic acid (TA). TA, which is an NSAID, is associated with gastrointestinal toxicity and erratic bioavailability. Its inclusion complex was prepared by using DE- β -CD in a 1:1 molar ratio using the kneading method. The dissolution of TA as a powder was tested at pH values of 1.5, 3.0, and 7.4. Both the extent and rate of release from the complex increased by increasing the pH value, with complete release occurring at pH 7.4. In vivo studies carried out on male Sprague Dawley rats involved administration of solid particles of complexes by means of gastric intubation followed by ingestion of 500 μ L of water. The studies showed a prolonged T_{max} , 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 (23).

Diltiazem. The ionizable derivative CME- β -CD was investigated as a delayed-release drug-carrier system for both in vitro and in vivo studies. The water-soluble drug diltiazem HCl was

Salbutamol. Salbutamol is a bronchodilator that is metabolized in the gastrointestinal tract, which is responsible for its drawback of short half-life in plasma. By complexing the drug with tributanoyl- β -cyclodextrin (TB- β -CD), a prolonged release was obtained with high and constant salbutamol levels in plasma. In vivo studies were conducted: The complex was administered orally to male beagle dogs, resulting in a significant decrease in the plasma level of the major metabolite salbutamol glucuronide. This decrease indicated reduced metabolism of the drug in the gastrointestinal tract and showed that

used as a model drug for this study. It was complexed with CME- β -CD and compressed into a tablet. The release rate of the drug was quite low 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 low pH because of the ionization of the carboxyl group (14,24). 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 (25).

Molsidomine. Horikawa et al. studied the release of the water-soluble drug molsidomine from tablets of CME- β -CD complex using male beagle dogs with controlled gastric acidity. The solid complex of molsidomine was prepared with CME- β -CD in a molar ratio of 1:1 using the kneading method. The in vitro release study from the tablet was performed using pH values of 1.2, 4.0, and 6.8. The release rate of molsidomine was suppressed at a lower pH and was increased following an increase in pH, thereby showing a typical delayed-release pattern (26).

Conclusion

A desirable attribute for drug-carrier systems is their ability to control both the rate and time of drug release. Such carriers can be used to control the release of water-soluble drugs, including peptide and protein drugs (see Table II). Although the ethylated and acylated derivatives provide sustained-release

formulations, ionizable derivatives such as CME- β -CD can modify the rate and time of drug release and therefore can be exploited for targeted drug delivery to various regions of the gastrointestinal tracts. From these observations, it can be concluded that CDs can be used as drug carriers in sustained-release formulations for administration through various routes, but considerable effort is required for this facet of cyclodextrin application. Though hydrophilic derivatives of CD already have been proven safe for use as pharmaceutical excipients, their hydrophobic derivatives still require detailed investigation for this application. They have great potential to act as carriers for sustained-release formulations through various routes of administration, but further study must be directed to this aspect of cyclodextrin application.

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