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*Review*

# Cyclodextrins: Their Future in Drug Formulation and Delivery

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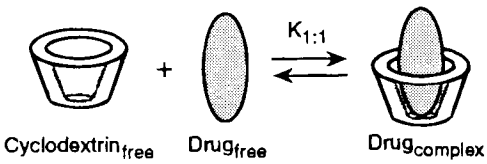
Since their discovery, cyclodextrins and their ability to form inclusion complexes have fascinated chemists, formulators and recently, entrepreneurs. This mini-review has as its objective, a critical assessment of the current status of cyclodextrins in the formulation and delivery of pharmaceuticals and commentary on their potential future uses. The emphasis will be on answers to common questions often asked of pharmaceutical scientists working in this area. Why use cyclodextrins for drug solubilization and stabilization when alternative techniques are available? Why the greater interest in modified cyclodextrins and not the parent cyclodextrins? If a drug forms a strong cyclodextrin inclusion complex, how is the drug released *in vivo*? Does the injection of a cyclodextrin/drug complex alter the pharmacokinetics of the drug? Are there drug products on the market which contain cyclodextrins? What is the regulatory status of cyclodextrins? Although definitive answers to all these questions are not possible at this time, many of these questions are answerable, and educated and informed responses are possible for the rest.

**KEY WORDS:** cyclodextrins; drug formulation; drug delivery; pharmacokinetics.

## INTRODUCTION

Pharmaceutical applications of cyclodextrins have been considered for over 30 years. Many major reviews (1–8) have appeared on this subject with the most recent being a series of three articles by Loftsson and Brewster (1), who reviewed the use of cyclodextrins for the solubilization and stabilization of drugs, Rajewski and Stella (8), who reviewed the *in vivo* applications of cyclodextrins and, Irie and Uekama (2), who reviewed the safety issues associated with the use of cyclodextrins. In addition, Thompson (9) has recently provided a major, comprehensive contribution to the cyclodextrin literature. Another excellent recent paper by Uekama *et al.* (10) and the books by Frömming and Szejtli (3) and Szejtli (4) have a wealth of information and provide useful historical perspectives.

What are cyclodextrins and why have they captured our imagination? Cyclodextrins are cyclic oligosaccharides composed of 6–8 dextrose units (α-, β- and γ-cyclodextrins, respectively) joined through 1–4 bonds. Because the interior of these molecules are relatively lipophilic and the exterior relatively hydrophilic, they tend to form inclusion complexes of the type illustrated by Scheme 1. The driving forces for inclusion complexation are both enthalpic and entropic in nature and not fully understood. Although the ability of a drug molecule to "fit" into the cyclodextrin torus is critical with the 6.0–6.5 Å opening of β-cyclodextrin being optimal for many biomedically relevant molecules, "fit" by itself is not the only consideration. Qualitatively, it also appears that the properties of both the part of the molecule that interacts with the cyclodextrin and the portion that is likely to be "outside" the cyclodextrin may be as critical. We and others are exploring the predictability of inclusion complexation based on structural as well as other considerations. Table 1 gives the schematic structures of the commonly used cyclodextrins and various modified cyclodextrins that have found some pharmaceutical utility. In forming inclusion complexes, the physical and chemical properties of both the drug molecule and the cyclodextrin molecule can be altered. Inclusion complexation has been used to solubilize, stabilize and decrease the volatility of drug molecules. Additionally, it has been used to ameliorate the irritancy and toxicity of drug molecules.




**Scheme 1.** Scheme illustrating the association of free cyclodextrin and drug to form a drug:cyclodextrin complex.

It might be argued that other techniques can achieve these same goals, so why use cyclodextrins? Most other excipients used to solubilize and stabilize drugs do so because of changes in the bulk properties of the resultant solvent. For example, co-solvents like various alcohols and glycols will increase the solubility of a poorly water soluble drug in a non-linear fashion with respect to co-solvent concentration. A drug with a solubility of 0.1 mg/ml in water and 10 mg/ml in pure propylene glycol, for example, does not translate to a 5 mg/ml solubility

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in 50% propylene glycol/water mixture. As illustrated in Scheme 1, most drugs form 1:1 complexes with various cyclodextrins. This complexation can be defined by a binding constant, $K_{1:1}$ and Eq. 1, where $[Drug]_{complex}$ represents the concentration of drug in the complex form, $[Drug]_{free}$ represents the free drug concentration and $[Cyclodextrin]_{free}$ represents the concentration of free cyclodextrin.

$$K_{1:1} = \frac{[Drug]_{complex}}{[Drug]_{free}[Cyclodextrin]_{free}} \quad (1)$$

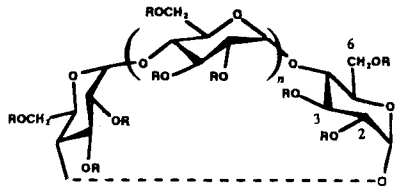
In solubility considerations, if $[Drug]_{free}$ represents the solubility of a drug in the absence of a cyclodextrin, then the increase in solubility of a drug is largely driven by the product of $K_{1:1}$ and $[Cyclodextrin]_{free}$, with $[Cyclodextrin]_{free}$ equal to $[Cyclodextrin]_{total}$ minus $[Drug]_{complex}$. Since most values of $K_{1:1}$ fall within the range of 100–20,000 $M^{-1}$ and $[Cyclodextrin]_{total}$ usually is less than 0.1–0.2 M, the maximum increases in solubility that can be expected from 1:1 interactions with a cyclodextrin are in the range of 1,000–2,000. Although this range may seem quite large, it should be remembered that the intrinsic solubility of the drug in the absence of the cyclodextrin also plays a role in the solubility that can be achieved. If the intrinsic solubility of a drug is 10 μg/ml, then a solubility of 10–20 mg/ml might be attainable. However, if the intrinsic solubility of the drug is 10 ng/ml, no known cyclodextrin is capable of raising the solubility of this drug into the mg/ml range through just a 1:1 interaction. Additionally, if only 1:1 interactions are possible, the solubility of a drug in the presence of a cyclodextrin cannot be any greater than the molar concentration of the cyclodextrin used to solubilize the drug and even this assumes that the binding constant is infinitely large. Therefore, if we assume that we would not want to use a concentration above 0.1 M for a particular cyclodextrin, and if we assume that $K_{1:1}$ is less than 20,000 $M^{-1}$, then the upper limit of solubility of a drug is either about 1,000–2,000 times the intrinsic solubility of the drug, or less than 0.1 M for a drug whose intrinsic solubility is greater than $1 \times 10^{-4}$ M. These simple calculations allow one to determine whether a particular solubility goal is potentially realizable using a cyclodextrin formulation without the need for unnecessary experimentation.

Consider a formulation challenge for a neutral drug (M.W. 250) having an intrinsic aqueous solubility of 0.1 mg/ml solubilized to 5 mg/ml by a 0.1 M cyclodextrin ($K_{1:1}$ = 610 $M^{-1}$) solution. The linear relationship between solubility and cyclodextrin concentration has a number of advantages, one of which is the lack of precipitation of the formulation on dilution. Consider the 5 mg/ml drug solution diluted 1:5 for infusion purposes. If the 5 mg/ml solubility was achieved through a co-solvent mixture, the 1:5 dilution would probably result in drug precipitation. However, on diluting the cyclodextrin formulation, the final drug concentration is 1 mg/ml and the cyclodextrin concentration is 0.02 M. The solubility of this drug in a 0.02 M cyclodextrin solution is 1.08 mg/ml, a concentration above the 1 mg/ml. In our earlier review (8) we did discuss the complications, namely possible drug precipitation on dilution, of drug/cyclodextrin solutions where solubility is achieved through 1:1 and 1:2 or higher order drug/cyclodextrin interactions.

## Drug Dissociation from Cyclodextrin Inclusion Complexes: *In Vivo* Implications

It is important to realize that the kinetics of inclusion complex formation and dissociation between a cyclodextrin and a drug molecule is fast (11,12). Where these events have been measured by various perturbation and competitive binding techniques, the half-lives for formation/dissociation are much less than one second and occur at rates very close to diffusion

**Table 1.** General Structures[a] of Commonly Used Cyclodextrins and Their Abbreviated Names




| Cyclodextrin | Abbreviation | *R* | *n* |
|---|---|---|---|
| α-cyclodextrin | α-CD | H | 4 |
| β-cyclodextrin | β-CD | H | 5 |
| γ-cyclodextrin | γ-CD | H | 6 |
| Carboxymethyl-β-cyclodextrin | CM-β-CD | $CH_2CO_2H$ or H | 5 |
| Carboxymethyl-ethyl-β-cyclodextrin | CME-β-CD | $CH_2CO_2H$, $CH_2CH_3$ or H | 5 |
| Diethyl-β-cyclodextrin | DE-β-CD | $CH_2CH_3$ or H | 5 |
| Dimethyl-β-cyclodextrin | DM-β-CD | $CH_3$ or H | 5 |
| Methyl-β-cyclodextrin | M-β-CD | $CH_3$ or H | 5 |
| Random methyl-β-cyclodextrin | RM-β-CD | $CH_3$ or H | 5 |
| Glucosyl-β-cyclodextrin | $G_1$-β-CD | glucosyl or H | 5 |
| Maltosyl-β-cyclodextrin | $G_2$-β-CD | maltosyl or H | 5 |
| Hydroxyethyl-β-cyclodextrin | HE-β-CD | $CH_2CH_2OH$ or H | 5 |
| Hydroxypropyl β-cyclodextrin | HP-β-CD | $CH_2CHOHCH_3$ or H | 5 |
| Sulfobutylether-β-cyclodextrin | SBE-β-CD | $(CH_2)_4SO_3Na$ or H | 5 |

[a] Derivatives may have differing degrees of substitution on the 2, 3 and 6 positions.

controlled limits with the complexes being continually formed and broken down. That is, inclusion complexation is a very dynamic process and in no way does the complex specie/s resemble a covalent specie. Also, although the complex is usually depicted as a single specie, it really should be viewed as a family of species with the complex illustrated in Scheme 1 representing some average. When complexation is viewed in this context, it is relatively easy to picture the two major mechanisms that contribute to drug/cyclodextrin inclusion complex dissociation.

Consider the drug described earlier with an intrinsic solubility of 0.1 mg/ml (400 μM) solubilized by 0.1 M cyclodextrin to 5 mg/ml (20 mM) through a 1:1 inclusion complex with a $K_{1:1}$ of 610 $M^{-1}$. Figure 1A shows the fraction of the drug that is free (non-complexed) when the 5 mg/ml solution is diluted to varying degrees. A dilution of 1:700 assumes that 5 ml of the 5 mg/ml solution was injected and the distribution volume of the complex/cyclodextrin was only plasma volume, assumed to be about 3.5 L in a 70 kg subject. This volume is the minimum volume of distribution that a drug can have. Even with this minimal dilution volume, the complex will be 92.1% dissociated due to dilution effects alone. If the volume of distribution is extracellular water (about 30% of body weight), a volume of distribution attributed to $(SBE)_{7M}$-β-CD (Captisol™), then a 1:4,200 dilution is reasonable. In this example the drug is 98.6% free. With a relatively weakly bound drug like this case, competition for binding by a similarly bound molecule has little effect on the free fraction. That is, simple dissociation due to dilution is sufficient to cause complete and rapid release of the drug. As illustrated in Figure 1A, this is true for all but very highly bound drugs (K > 10,000 $M^{-1}$). If the drug is highly bound, however, simple dilution effects are still significant. For example, cyclodextrin:drug complexes with K = 10,000 $M^{-1}$ would be 81.3% dissociated after a 1:4,200 dilution (Figure 1A).

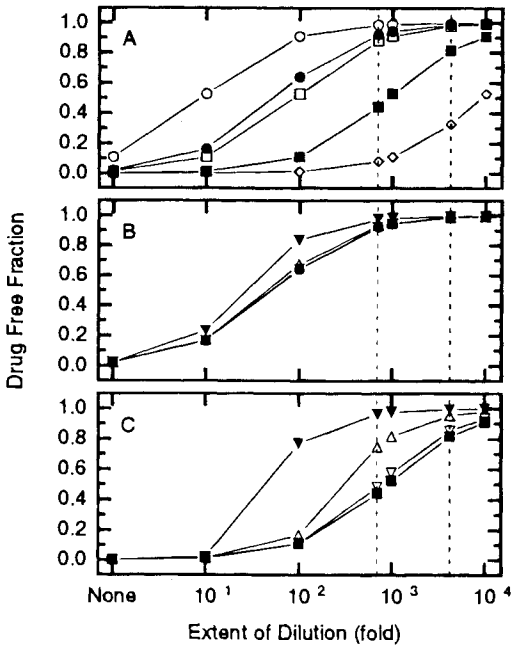



**Fig. 1.** Effect of solution dilution on the free fraction of drug. Dotted lines represent 700 and 4200 fold dilutions. (A) Effect of binding constant; ○ K = 100 $M^{-1}$, ● K = 610 $M^{-1}$, □ K = 1000 $M^{-1}$, ■ K = 10000 $M^{-1}$, ◇ K = 100000 $M^{-1}$. (B) Effect of competing binding agent concentration; K = 610 $M^{-1}$ for drug and agent, ● No competing agent, ▽ 40 μM, △ 400 μM, ▼ 4 mM. (C) Effect of competing binding agent concentration; K = 10000 $M^{-1}$ for drug and agent, ■ No competing agent, ▽ 40 μM, △ 400 μM, ▼ 4 mM.

Agents which compete with the drug for the cyclodextrin cavity may also influence the free fraction of drug (Figures 1B and 1C). If the binding constant of the drug and competing agent are low, the free fraction of drug largely results from dilution effects (Figure 1B). If the binding constants are high, however, the free fraction of drug is significantly influenced by the competing agent. For example, in the presence of 400 μM of a competing agent/s with a comparable binding constant for the cyclodextrin, the free fraction increases to 95.3% (Figure 1C). These free fractions do not take into account the possibility of the free drug being capable of accessing tissues not available to the more polar cyclodextrins which may further increase dissociation.

If the binding constant were to reach a value of $1 \times 10^5$ $M^{-1}$, a binding constant rarely if ever seen between a drug and a cyclodextrin, then a 1:4,200 dilution results in dissociation of only 32.7% of the complex due to dilution effects alone. Therefore, competitive displacement, drug uptake in tissues inaccessible to the cyclodextrin, and binding of the drug to plasma and tissue proteins may be very important for complete and rapid dissociation. A specific illustration of how physiological factors can contribute to drug release was illustrated in the work of Frijlink *et al.* (13) who studied the effect of *in vitro* dilution with plasma on the dissociation of hydroxypropyl-β-cyclodextrin (HP-β-CD) complexes of naproxen or flurbiprofen. Through experimental observations they found that only small fractions of the drugs remained bound to the cyclodextrin in plasma. Albumin binding of the two drugs was able to compete effectively with cyclodextrin binding (13). Displacement of the drugs from cyclodextrin by a competing agent such as plasma cholesterol may have also contributed to the low fraction of drug retained by the cyclodextrin.

In summary, for weakly bound drugs, dilution is sufficient to account for rapid and complete dissociation; for highly bound drugs, it may be that earlier time point pharmacokinetics may be perturbed. Uekama *et al.*, (10) and Thompson (9) have presented more general solutions to the dilution effects and complex dissociation in their reviews and the reader is directed to these excellent papers for additional information and discussion.

## Why Modified Cyclodextrins?

Safety is a major issue with any new enabling agent. Two of the parent cyclodextrins, α- and β-cyclodextrin, are known to be parenterally unsafe due to severe nephrotoxicity (14). Although α- and β-cyclodextrin have been used orally in both food products and in various approved pharmaceuticals, only one product uses α-cyclodextrin parenterally, namely, a $PGE_1$ product available in Japan and Germany. There are no β-cyclodextrin containing parenteral products to our knowledge. Approval of the acute use $PGE_1$ product was possible due to the very low dose of α-cyclodextrin used in this preparation.

The etiology of the nephrotoxicity of both α- and β-cyclodextrin is unknown but appears to be related to either cyclodextrin uptake by the kidney tubule cells followed by disruption of intracellular function, or the extraction of lipid membrane

components by the cyclodextrin. This last hypothesis has some validity since there seems to be a rank order correlation between the ability of various cyclodextrins to disrupt cellular membranes and kidney nephrotoxicity (4,9,15). The ability of cyclodextrins to cause red blood cell hemolysis and membrane irritation also appears to correlate with their ability to extract lipid membrane components, mainly cholesterol and phospholipids. γ-Cyclodextrin is considerably less toxic than either α- or β-cyclodextrin presumably due to its lower ability to affect cellular lipids (16). Alpha through gamma cyclodextrins are more likely to find use in oral products and those dosage forms for which systemic delivery of the cyclodextrin is unlikely.

Modification of the parent cyclodextrins to improve safety while maintaining the ability to form inclusion complexes with various substrates has been the goal of numerous research groups. Some groups have also focused on improving the interaction between the pharmaceuticals and the cyclodextrins while others have attempted to prepare materials that can be chemically defined more precisely. Table 1 lists some of the derivatives that have received the greatest attention. It was found that partial methylation of the hydroxyls at the 2-, 3- and/or 6-position of β-cyclodextrin generally leads to stronger drug binding but greater toxicity. It seemed, therefore, that improved interactions might lead to greater toxicity implication, begging the question, "is it possible to design a cyclodextrin that has a high affinity for drug molecules while having minimal membrane disrupting capability?". The two modified cyclodextrins that have received the greatest attention in the last few years are the hydroxypropyl-β-cyclodextrins (HP-β-CDs) and sulfobutylether-β-cyclodextrins (SBE-β-CDs, mainly as $(SBE)_{7M}$-β-CD). For $(SBE)_{7M}$-β-CD, the number seven refers to the average degree of substitution on the cyclodextrin nucleus while the letter *M* refers to the fact that this material contains multiple bands. The $(SBE)_{7M}$-β-CD referred to in this review is the same as SBE7-β-CD referred to in some earlier papers.

HP-β-CDs have the advantage of greater aqueous solubility and parenteral safety in comparison to β-cyclodextrin, however, the binding constants between drugs and HP-β-CDs is usually less than those with the parent cyclodextrin. The higher the degree of hydroxypropyl substitution the poorer the drug binding (17,18). The greater solubility and safety for HP-β-CDs is assumed to be due to their amorphous, non-crystalline, nature (19). SBE-β-CDs are also water miscible and parenterally safe, but unlike HP-β-CDs, higher sulfobutyl group substitution often results in higher rather than lower drug binding (20). Also, the inability of the SBE-β-CDs, especially $(SBE)_{7M}$-β-CD, to form strong 1:2 complexes with cholesterol and other membrane lipids, probably due to their polyanionic nature giving rise to coulombic repulsion, results in little or no membrane disruption (9,15). This behavior provides a sound mechanistic basis for the greater safety of $(SBE)_{7M}$-β-CD compared to some of the other cyclodextrin derivatives. The work with $(SBE)_{7M}$-β-CD suggests that cyclodextrins with good binding and greater safety are possible.

Economics and quality control issues also play a role in considering which cyclodextrins might be pharmaceutically useful. Alpha, beta and gamma cyclodextrins contain 18, 21 and 24 hydroxyl groups, respectively. Selective derivatization of a specific hydroxyl or family of hydroxyls is possible but claims of selective derivatization are often overstated. For a given modified cyclodextrin to be commercially viable, its synthesis and purification must also be relatively inexpensive and scalable. This will probably preclude many derivatives that involve multiple synthesis and purification steps. Therefore, most modified cyclodextrins of pharmaceutical interest are likely to be complex mixtures. Methods to characterize these mixtures, therefore, will be needed to assure lot to lot reproducibility including possible positional and regio-substitution. These materials also need to be free of pyrogens and foreign particles if they are to be used parenterally. The cost of acute and chronic safety studies will limit the number of cyclodextrins likely to be seriously evaluated for pharmaceutical usage.

## *IN VIVO* APPLICATIONS OF CYCLODEXTRINS

### Parenteral Delivery of Insoluble Drugs

Even though the release of drugs from drug/cyclodextrin complexes is expected to be rapid and quantitative based on simple dissociation and competitive displacement mechanisms, concerns are still raised as to whether drug pharmacokinetics will be perturbed by the presence of the cyclodextrins. We have extensively reviewed the major literature on this subject and concluded that except for local drug delivery where high concentrations of both drug and cyclodextrins can be maintained, drugs are qualitatively and quantitatively released from their inclusion complexes with little if any perturbation of the pharmacokinetics of the drug (8). A complication in reaching this conclusion is how to run the proper control experiments. For example, if a drug is sparingly water soluble, how do you administer the drug without the cyclodextrin? If you use a co-solvent, a surfactant, an emulsion or some other exotic dosage form, how do you know if these alternative dosage forms do not themselves perturb the kinetics? This issue was highlighted in a study by Löscher *et al.* (21) where the pharmacokinetics of carbamazepine was significantly perturbed by the use of the co-solvent, glycofural, through of its inhibition of carbamazepine epoxide formation compared to HP-β-CD which did not apparently perturb this metabolic step. A brief summary of some reliable papers that address the issue of cyclodextrins and drug pharmacokinetics follows.

γ-CD did not alter the pharmacokinetics of thiopental in rabbits after i.v. administration (22) while propofol (2,6-diisopropylphenol) pharmacodynamics were identical after i.v. administration as a HP-β-CD solution versus a commercial oil-in-water emulsion (23). The pharmacodynamics of a number of anesthetic steroids was unaffected by inclusion complexation with HP-β-CD (24,25).

The i.v. bolus pharmacokinetics and activity of the hypnotic agent etomidate (2 mg/ml) from a 35% propylene glycol aqueous solution were identical to a 3% HP-β-CD solution (26), however, a higher incidence of pain on injection was noted with the propylene glycol solution (58% of the patients) relative to the HP-β-CD formulation (8% of the patients).

The pharmacokinetics of some steroidal anti-inflammatory agents were comparable from some cyclodextrins to a series of steroidal prodrugs (27,28). Stella *et al.* (29) compared the i.v. bolus pharmacokinetics in rats of methylprednisolone from an $(SBE)_{4M}$-β-CD solution (0.075 M) and a co-solvent solution (60% PEG400, 12% ethanol, made up to 100% volume with water). Figure 2 shows the plasma concentration versus time profiles for the two formulations. There were no significant

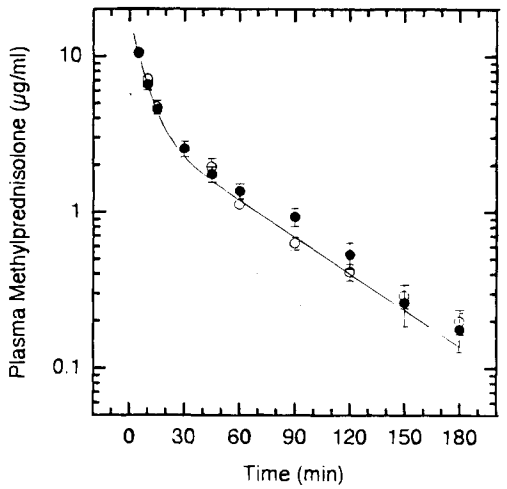



**Fig. 2.** Plasma concentration (±SE) versus time profiles of methylprednisolone after 20 mg/kg i.v. dosing of methylprednisolone in anesthetized rats ($n$ = 6). The solid line is the curve fit for the co-solvent data to a biexponential equation; ● co-solvent mixture, ○ 0.075 M $(SBE)_{4M}$-β-CD. Reproduced with permission (29).

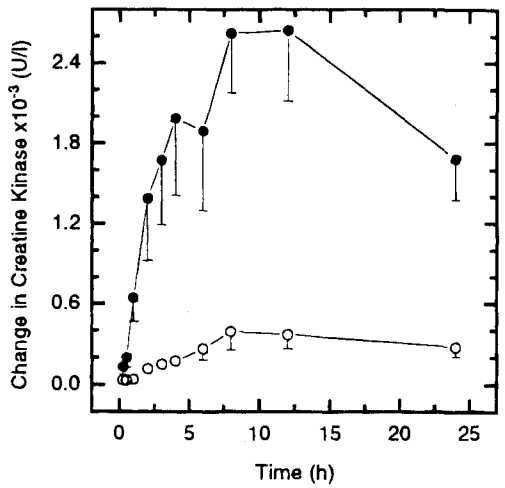



**Fig. 3.** Change in plasma CK levels (±SE) after i.m. injection of 1 ml into both the right and left lumbar muscles of prednisolone to rabbits ($n$ = 8); ● PEG400/ethanol/water (40:10:50) mixture, ○ 0.09 M $(SBE)_{4M}$-β-CD solution. Reproduced with permission (31).

differences in any of the estimated pharmacokinetic parameters between the two formulations. Järvinen *et al.* (30) were able to administer the very water insoluble drug, cinnarizine, i.v. to dogs and to follow its pharmacokinetics from a pH 4.5 $(SBE)_{4M}$-β-CD solution allowing the determination of the absolute oral bioavailability of cinnarizine from a series of potential oral dosage forms.

There are some reliable studies where the apparent pharmacokinetics have been apparently perturbed by cyclodextrins. Frijlink *et al.* (13) studied the tissue distribution in rats of naproxen and flurbiprofen from HP-β-CD containing solutions as compared to solutions of the drugs dissolved in rat plasma. The tissue distribution of naproxen was unaffected by administration in HP-β-CD. At ten minutes post-dosing significantly higher flurbiprofen levels in the brain, liver, kidney and spleen were seen with the HP-β-CD formulation. At sixty minutes post dosing only slightly elevated flurbiprofen levels were seen in the brain. Frijlink *et al.* (13) attributed the higher early time point differences to a transitory alteration in protein binding by HP-β-CD. It would have been interesting to see if these differences would have also been seen if flurbiprofen was administered in a purely aqueous vehicle instead of from a vehicle consisting of rat plasma.

The pharmacokinetics of carbamazepine was also different between a 65% aqueous glycofural solution (PEG monotetrahydrofurfuryl ether) and a HP-β-CD solution (21). The slower clearance of carbamazepine and the delayed appearance of the epoxide metabolite of carbamazepine from the glycofural formulation was attributed to the inhibition of carbamazepine metabolism by glycofural and not a perturbation of carbamazepine kinetics by the HP-β-CD.

Only a limited number of i.m. studies have been published on the use of cyclodextrins. An early paper by Arimori and Uekama (27) attributed the faster release rate of prednisolone from β-CD and γ-CD complexes to the greater solubility of prednisolone in the complexes. Stella *et al.* (31) recently published the pharmacokinetics in rabbits of prednisolone administered i.m. from an $(SBE)_{4M}$-β-CD solution compared to a PEG400/alcohol/water mixture (4:1:5). $(SBE)_{4M}$-β-CD was shown to not cause elevation of the intracellular marker, creatine kinase (CK), compared to an isotonic aqueous control solution (31) while the co-solvent significantly raised CK levels, suggesting much greater tissue irritation from the co-solvent (Figure 3). Plasma concentration time profiles for prednisolone from the $(SBE)_{4M}$-β-CD formulation and the co-solvent are shown in Figure 4. No differences in *AUC* values were seen between the two formulations while a significantly higher $C_{max}$ value was seen from the cyclodextrin solution. Deconvolution of the data suggested that 20–30% of the prednisolone may have precipitated at the injection site from the co-solvent formulation compared to the $(SBE)_{4M}$-β-CD solution.

## Oral Applications of Cyclodextrins

The primary use of cyclodextrins in oral formulations is to increase bioavailability through increased rate and extent of

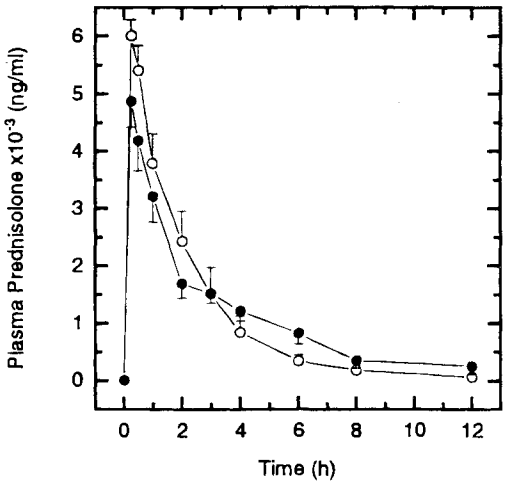



**Fig. 4.** Concentration (±SE) versus time profiles for prednisolone after 5 mg/kg i.m. injections of a 1 ml solution into both the right and left lumbar muscles of rabbits ($n$ = 8); ● co-solvent mixture, ○ 0.09 M $(SBE)_{4M}$-β-CD solution. Reproduced with permission (31).

drug dissolution. Cyclodextrins have also been used to modify the time of drug release during GI transit and decrease local irritation. Numerous examples have been published and reviewed in previous papers (3–5,8,9). Recent examples are summarized below.

An example of the use of cyclodextrins to improve dissolution rate and bioavailability was reported by Panini *et al.* (32) who used HP-β-CD to increase the bioavailability of ursodeoxycholic acid (UDCA) in human volunteers. UDCA is prescribed in the treatment of cholesterol gallstones and is available commercially as Ursacol tablets. Panini *et al.* prepared tablets containing the HP-β-CD complex of UDCA, starch and microcrystalline cellulose. The tablets exhibited disintegration times which were equivalent to the commercial tablets while the dissolution profiles were dramatically different. The cyclodextrin tablets demonstrated much faster and more complete dissolution and produced $AUC$ and $C_{max}$ values twice those of the Ursacol tablets (Figure 5).

The bioavailability effect of increased drug dissolution rate and extent in the presence of cyclodextrins is most apparent in studies which administer the cyclodextrin drug complex as a solid and in solution. For example, Järvinen *et al.* (30) reported on the use of HP-β-CD and $(SBE)_{4M}$-β-CD to modify the bioavailability of cinnarizine in beagle dogs. Cinnarizine is a weak base and is subject to variable and low bioavailability, especially in subjects with high stomach pH. Järvinen *et al.* administered cinnarizine by gastric tube to beagle dogs in a crossover study. The drug was given as a suspension in phosphate buffer, solutions of the HP-β-CD or $(SBE)_{4M}$-β-CD complex, and in a capsules as the solid $(SBE)_{4M}$-β-CD complex or neat. Figure 6 illustrates the effect of cyclodextrin on the observed bioavailabilities. The absolute bioavailabilities of the suspension, the neat capsule and the $(SBE)_{4M}$-β-CD complex capsule were 8 ± 4%, 0.8 ± 0.4% and 38 ± 12%, respectively. The HP-β-CD and $(SBE)_{4M}$-β-CD solutions gave absolute bioavailabilities of 55 ± 11% and 60 ± 13%, respectively.

In another example, Studenberg *et al.* (33) studied the pharmacokinetics and bioavailability of atovaquone in dogs

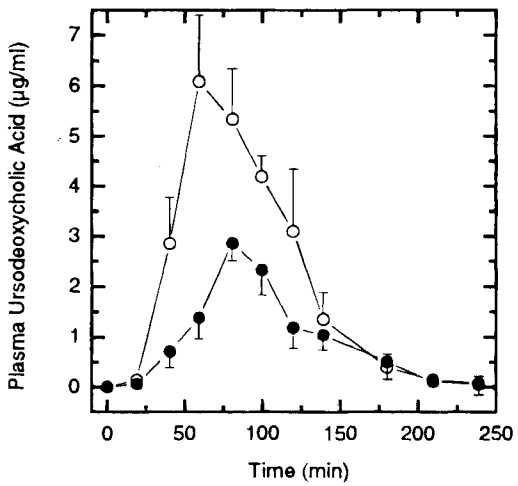



**Fig. 5.** Ursodeoxycholic acid (UDCA) plasma concentrations in six healthy volunteers following oral administration; ○ tablets containing 425 mg of UDCA in the inclusion complex of HP-β-CD; ● commercial tablets containing 450 mg of free UDCA. Bars represent SD. Reproduced with permission (32).

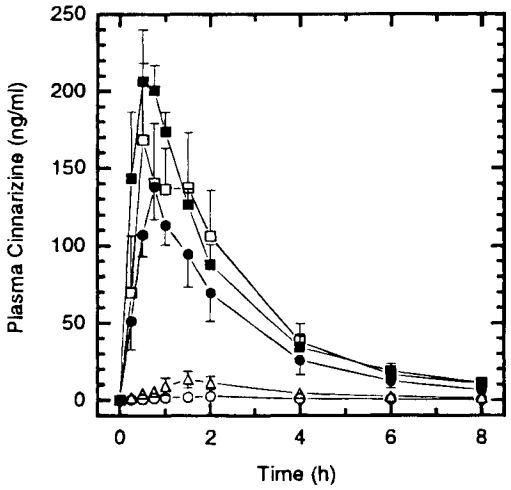



**Fig. 6.** Cinnarizine plasma concentration in dogs (mean ± SE, $n$ = 4) after oral administration of 25 mg cinnarizine; ■ HP-β-CD solution, □ $(SBE)_{4M}$-β-CD solution, ● capsule containing solid $(SBE)_{4M}$-β-CD complex of cinnarizine, △ cinnarizine aqueous suspension (pH 4.5), ○ capsule containing cinnarizine but no $(SBE)_{4M}$-β-CD. Reproduced with permission (30).

following administration of the atovaquone $(SBE)_{7M}$-β-CD or HP-β-CD complex in gelatin capsules. Atovaquone is practically insoluble in water and as the currently available microfluidized suspension (Mepron®) displays dissolution rate limited bioavailability. The absolute bioavailabilities of the modified cyclodextrin complexes were two to three fold greater than the Mepron® formulation while the pharmacokinetic parameters were similar to those for a co-solvent formulation.

Cyclodextrins may also alter oral absorption of drugs through mucosal membrane permeation enhancement. For example, Haeberlin *et al.* (34) recently reported on the cyclodextrin associated absorption enhancement of a modified calcitonin and the octapeptide octreotide (Sandostatin®) *in vitro* using a Caco-2 cell monolayer and *in situ* using isolated rat jejunal sections. α-, β- and γ-cyclodextrin along with HP-β-CD and DM-β-CD were studied. The authors found that β-cyclodextrin and HP-β-CD exhibited octreotide absorption enhancing properties in the *in situ* system (439 and 352%, respectively). β-cyclodextrin, γ-cyclodextrin, HP-β-CD and DM-β-CD showed calcitonin absorption enhancing properties in the *in situ* system (205, 596, 375 and 470%, respectively). The unmodified cyclodextrins provided the greatest increases in peptide permeation in the Caco-2 cell monolayer model. The observed permeation increases paralleled permeation increases for PEG-4000 suggesting that opening of cellular tight junctions may have been occurring. Based on the results the authors concluded that while cyclodextrins may be beneficial for promoting peptide absorption, the results obtained will be highly dependent on the combination of peptide and cyclodextrin.

Several cyclodextrin derivatives have been developed to exhibit pH dependent solubility for use in selective dissolution of the drug cyclodextrin complex. One such example is that of the *O*-carboxymethyl-*O*-ethyl-β-CD (CME-β-CD) which has an estimated $pK_a$ of 3.7 and displays pH dependent solubility (35). The CME-β-CD displays limited solubility under acidic conditions such as the stomach with the complex solubility

increasing as the pH passes through the pKa of the CME-β-CD. Under the control of this pH dependence a dosage form of the CME-β-CD complex which passes from the stomach into the higher pH environment of the upper small intestine would experience increased solubility with increased drug dissolution and release. CME-β-CD complexes have been used in *in vitro* and *in vivo* studies with diltiazem (35) and molsidomine (36) to investigate potential acid protection.

The diltiazem studies (35) were carried out in gastric acidity controlled fasting dogs with gastric pH controlled to less than two or greater than six. Diltiazem absorption was slower at high gastric acidity ($t_{max}$ = 4.0 ± 0.0 h) than at low gastric acidity ($t_{max}$ = 2.3 ± 0.5 h) (Figure 7). The *in vitro* release data measured using a pH changeable dissolution apparatus were in good agreement with the *in vivo* data. Molsidomine absorption from tablets containing CME-β-CD was studied in gastric acidity controlled dogs in the fasted and fed states (36). Under high gastric acidity the molsidomine absorption was significantly retarded relative to the low gastric acidity condition. The delayed absorption effect under high gastric acidity was more pronounced under fasted conditions. As in the diltiazem studies, good agreement was seen between the *in vivo* studies and the *in vitro* release measured with the pH changeable dissolution apparatus.

## Ophthalmic Applications of Cyclodextrins

The use of cyclodextrins in ophthalmic preparations has received some attention (7). Of obvious concern with the use of cyclodextrins is whether they cause any irreversible damage to the cornea. Jansen *et al.* (37) demonstrated that dimethyl-β-cyclodextrin (DM-β-CD) was not suitable for ophthalmic formulations, while up to 12.5% HP-β-CD caused no irritation to the corneal tissue.

If it is assumed that only free drug and not the cyclodextrin complex of a drug penetrates across biological membranes, then ophthalmic drug delivery from cyclodextrin solutions may be somewhat limited by the dissociation of the complex that occurs in the precorneal area (8). Much more limited dilution would occur from ophthalmic administration than from oral or parenteral drug delivery. Therefore, drug dissociation from the complex will be more dependent on drug binding to precorneal proteins, absorption by the corneal tissue itself, and drug displacement from the complex by other molecules present in the precorneal fluid. If a large excess, due to solubility, stability or irritancy considerations, of a cyclodextrin is present in a ophthalmic formulation, corneal delivery of the drug will probably be inhibited.

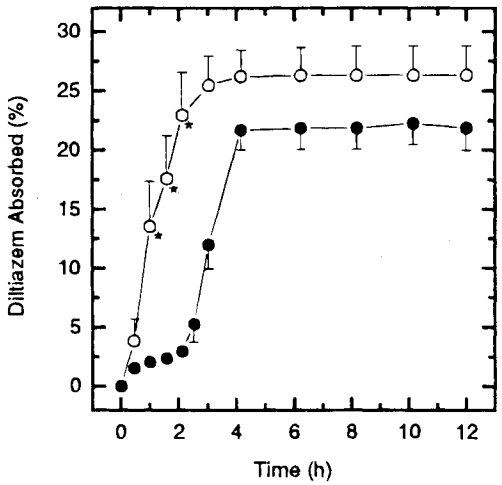



**Fig. 7.** Absorptivity curves generated by deconvolution of diltiazem plasma level-time curves; ● high gastric acidity, ○ low gastric acidity. *$p < 0.05$ compared to high gastric acidity dogs. Reproduced with permission (35).

To be truly considered safe, it is best that intrinsic corneal permeability not be modified by the cyclodextrin. For this reason, DM-β-CD should not be considered for ophthalmic preparations. Similar irritancy might be expected with α- and β-cyclodextrins. Both $(SBE)_{4M}$-β-CD and HP-β-CD have been shown to not alter the corneal permeability of the relatively polar drug, pilocarpine suggesting no irritancy by these cyclodextrins (38). These observations bring into question the observations of Freedman *et al.* (39) who reported an increased miotic response to 50 μg pilocarpine in 5% HP-β-CD as compared to pilocarpine alone. Järvinen *et al.* (38) could not repeat the observations of Freedman *et al.*

Järvinen *et al.* showed that high concentrations of cyclodextrins could decrease the miotic response to pilocarpine (38), a drug which only weakly associates with cyclodextrins ($K < 200\ M^{-1}$). Similar observations were seen by Reer *et al.* on the *in vitro* corneal permeability of diclofenac in the presence of HP-β-CD (40).

An area where cyclodextrins may have a significant therapeutic benefit is the solubilization of poorly water soluble drugs intended for ophthalmic use. Some encouraging data has been seen with cyclosporine A (CsA) and α-cyclodextrin (41). Perhaps the best examples of the use of cyclodextrins with poorly water soluble drugs have been the work with steroids, especially dexamethasone and its acetate ester, dexamethasone acetate (42,43). Usayapant *et al.* (42) studied the solubility, chemical stability and improved ophthalmic delivery of dexamethasone and dexamethasone acetate in the presence of HP-β-CD. Loftsson *et al.* (44) also increased the ophthalmic effectiveness of two carbonic anhydrase inhibitors, acetazolamide and ethoxyzolamide, using HP-β-CD while similar results were seen with the sparingly soluble drug arachidonylethanolamide (45).

Järvinen *et al.* were able to show that $(SBE)_{4M}$-β-CD, $(SBE)_{7M}$-β-CD and HP-β-CD decreased the ophthalmic irritation of a lipophilic pilocarpine prodrug, *O,O'*-diproprionyl-(1,4-xylylene)bispilocarpate (46,47). They observed a selective decrease in irritation with no decrease in miotic effectiveness if the cyclodextrins were present at approximately one to two molar equivalent levels to the drug. When excess cyclodextrin was present, drug effectiveness decreased, as expected. These negative effects with excess cyclodextrin concentrations could be overcome, however, when the viscosity of the ophthalmic drops was increased (Figure 8). Interestingly, the decreases in miotic effect with increasing cyclodextrin concentration reversed by the PVA did not lead to a re-occurance of severe irritation seen in the absence of $(SBE)_{7M}$-β-CD (47).

## Nasal Applications of Cyclodextrins

Uekama *et al.* (10) as part of a larger review, has recently reviewed the use of cyclodextrins in nasal drug delivery. Like ophthalmic drug delivery, nasal delivery may benefit from the

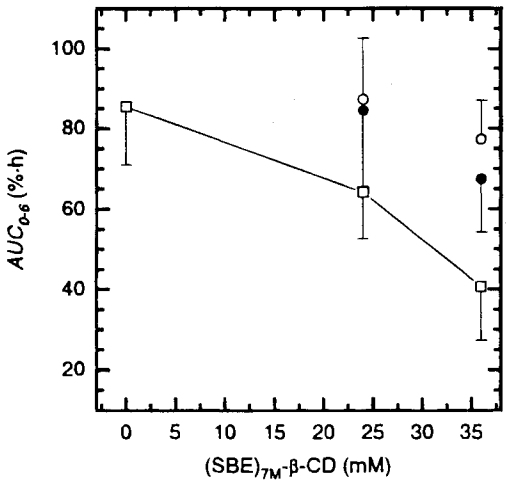



**Fig. 8.** Effect of increasing $(SBE)_{7M}$-β-CD concentration on the area under miotic activity curves ($AUC_{0-6}$) (±SE) following ocular administration of 12 mM *O,O'*-dipropriony-(1,4-xylylene)bispilocarpate to rabbits ($n$ = 6); □ no polyvinyl alcohol (PVA), ● 2% PVA, ○ 3% PVA. Plotted from data in reference (47).

presence of cyclodextrins by changes in nasal mucosa permeability, enhanced drug solubility or a change in the metabolism rate of the drugs at the site of delivery. Balanced against these possible positive effects are possible concerns with nasal ciliary damage that could lead to long term toxicity questions. For example, high DM-β-CD doses have been shown to adversely affect the nasal mucosa in both *in vitro* and some *in vivo* experiments. However, it was much less damaging than the surfactants, sodium glycocholate and laureth-9, and the phospholipid, L-α-lysophosphatidylcholine (48). Nevertheless, many researchers have focused on the use of DM-β-CD for the nasal delivery of a number of agents even though some results suggest potential changes in nasal membranes occur at high levels of exposure to this cyclodextrin derivative. The major focus of these studies is the use of DM-β-CD to enhance the delivery of various steroids, proteins and peptides (10,49,50).

### Other *in Vivo* Applications of Cyclodextrins

Cyclodextrins have been used in dermal, rectal and pulmonary applications to improve either the local action of the drug, increase solubility and/or stability or to alter membrane permeability. The reader is directed to the two reviews by Uekama *et al.* (10) and Rajewski and Stella (8) for a comprehensive coverage of these uses.

## SOME CASE STUDIES ON THE USE OF CYCLODEXTRINS

### Approved Products

No drug product has received regulatory approval in the USA as of late 1996 although a Garlic oil product containing β-cyclodextrin is available and there are two known products in final consideration by the FDA. There are also a number of products in Phase II/III studies with NDA filings expected to take place in 1997/98. Table II lists some of the approved and marketed cyclodextrin/containing pharmaceutical products. Most of the approved products involve the oral use of either α- or β-cyclodextrin.

### Specific Examples

The prostaglandin products marketed by Ono, a Japanese company, have been approved for quite some time and represent, to our knowledge, the first major pharmaceutical products containing cyclodextrins. The parenteral products containing α-cyclodextrin were allowed because of the very low levels of α-cyclodextrin used in these products. The major purpose of the cyclodextrin in these products is to stabilize the prostaglandin from chemical degradation.

The cefotiam hexetil HCl product is interesting in that the role of the cyclodextrin in this oral product is to facilitate dissolution. Specifically, cefotiam hexetil HCl gels on the addition to water causing the product to have a very slow dissolution behavior even though its intrinsic solubility is such that dissolution would not be expected to be rate controlling. Interaction with α-cyclodextrin prevents gel development and promotes dissolution and improved *in vivo* behavior (51). The nitroglycerin/β-cyclodextrin product, nitropen, presumably results in not only improved sublingual release, but probably also the decreased volatility of the nitroglycerin from the complex.

The itraconazole product by Janssen is an oral liquid product that utilizes HP-β-CD and is used in the treatment of fungal infections especially in immune compromised patients. The liquid product allows local oral treatment and dosing in those patients unable to swallow solid dosage forms (52). A parenteral itraconazole/HP-β-CD solution is in development and being considered for regulatory approval.

The list of approved products that utilize cyclodextrins is likely to grow rapidly over the next few years especially after an FDA approved product begins marketing. It is generally accepted that the lack of a major FDA approved product has inhibited a number of companies from utilizing cyclodextrins as enabling agents.

## SAFETY ISSUES ASSOCIATED WITH THE USE OF CYCLODEXTRINS

The safety of the parent cyclodextrins and various derivatives has been reviewed in detail recently by Thompson (9). The Thompson paper contains detailed reviews of issues specific to the oral and parenteral safety of various cyclodextrins along with discussion of mutagenicity, carcinogenicity and reproductive safety where appropriate.

The use of the parent cyclodextrins in parenteral formulations is limited by the renal toxicity observed when α- and β-cyclodextrin are administered by this route (14). Parenteral administration of α- and β-cyclodextrin causes necrosis of the proximal tubule of the kidney with $LD_{50}$ values for i.v. administration in rats reported to be 1 gm/kg and 0.79 g/kg, respectively (14). The necrosis associated with administration of α- and β-cyclodextrin is characterized by the presence of apical vacuoles and lysozomes in the epithelial cells of the proximal tubule. A dose dependent presence of acicular crystals has been observed in the lysozomes and it was believed that the observed toxicity

**Table 2.** A Listing of Approved Pharmaceutical Products Containing Cyclodextrins[a]

| Drug | Trade name | Formulation type | Company | Country |
|---|---|---|---|---|
| $PGE_1$/α-CD 20 μg/ampoule | Prostavasin | i.a. | Ono | Japan |
| | | | Schwarz | Germany |
| $PGE_1$/α-CD 500 μg/ampoule | Prostandin 500 | infusion | Ono | Japan |
| $PGE_2$/β-CD | Prostarmon | sublingual tablet | Ono | Japan |
| OP-1206/α-CD | Opalmon | sublingual tablet | Ono | Japan |
| Piroxicam/β-CD | Brexin | tablet | Chiesi | Italy |
| | | | Robapharm | France |
| | | | Promedica | France |
| | Brexidol | | Nycomed | Scandanavia |
| | | | Lauder | Germany |
| | Cycladol | suppository | Masterpharm | Italy |
| | | | | Belgium |
| | | | | Netherlands |
| | | | | Switzerland |
| Benexate/β-CD | Ulgut | capsule | Shionogi | Japan |
| | Lonmiel | capsule | Teikoku | Japan |
| Iodine/β-CD | Mena-Gargle | gargling solution | Kyushin | Japan |
| Dexamethasone Glyteer/β-CD | Glymesason Ointment | ointment | Fujinaga | Japan |
| Nitroglycerin/β-CD | Nitropen | sublingual | Nippon Kayaku | Japan |
| Cefotiam hexetil HCl/α-CD | Pansporin T | tablet | Takeda | Japan |
| ME 1207/β-CD new cephalosporin | Meiact | tablet | Meiji Seika | Japan |
| Thyaprofenic acid/β-CD | Suramyl | tablet | Roussel-Maestrelli | Italy |
| Chlordiazepoxide/β-CD | Transillium | tablet | Gador | Argentina |
| Hydrocortisone/HP-β-CD | Dexocort | mouth wash | Icelandic Pharm. | Iceland |
| Itraconazole/HP-β-CD | Sporanox | liquid | Janssen | Belgium |
| Garlic oil/β-CD | Xund, Tegra | dragees | Bipharm, Hermes | Germany |
| | Allidex | | Pharmafontana | |
| | Garlessence | tablet | CTD | USA |

[a] Much of the information for this table was supplied by Professor Josef Szejtli, Budapest, Hungary.

was related to the aqueous solubility of the respective cyclodextrin. In contrast to α- and β-cyclodextrin, the $LD_{50}$ for γ-cyclodextrin in rats has been reported to be 3.75 g/kg (53). While the presence of vacuoles was noted with the parenteral administration of γ-cyclodextrin, the effects appear to be reversible when administration is stopped.

The renal toxicity observed with the parenteral administration of the parent cyclodextrins was one of the major driving forces for the development of various modified cyclodextrins. Cyclodextrins modified with the intention of alleviating the renal toxicity of the parent cyclodextrins generally exhibited greater water solubility. One of the earliest cyclodextrin derivatives investigated was DM-β-CD. The renal toxicity of DM-β-CD was greater than that of β-cyclodextrin (54), however, even though it exhibited higher aqueous solubility and was renally eliminated faster and to a greater extent, it proved more toxic.

Two of the more promising cyclodextrin derivatives for parenteral administration are HP-β-CD and $(SBE)_{7M}$-β-CD. HP-β-CD has generally been found to be safe when administered parenterally in animals and humans (55–57). While minor reversible histological changes were observed in high dose animal studies (100–400 mg/kg), more significant hematological changes were observed suggesting red blood cell damage. No adverse effects were observed in the human studies. $(SBE)_{7M}$-β-CD has also been found to be safe when administered parenterally (15) with doses greater than 10 g/kg causing no toxic effects in mice.

In general, cyclodextrins are poorly adsorbed from the GI tract following oral administration. For example, the oral bioavailability of β-CD in animals has been reported to range from 0.1% (58) to 4% (59). The mode of absorption of the cyclodextrins is probably passive (60,61) with the majority of an orally administered cyclodextrin dose being metabolized by GI flora (62,63). The administration of the three parent cyclodextrins does cause minor species dependent physiological changes consistent with oral administration of other carbohydrates which are poorly digested (64). Minimal studies have been performed on the oral absorption of DM-β-CD, however, results obtained suggest that the oral bioavailability of DM-β-CD is in the same range as the parent cyclodextrins (65). Likewise, the oral absorption of HP-β-CD is limited (66) with no detectable plasma or urine levels found in human studies (55). Long term oral administration in rats (2 year studies), however, did produce pancreatic hyperplasia (67). However, this effect appears to be animal species specific.

While the oral administration of cyclodextrins raises minimal safety concerns from systemic absorption of the cyclodextrins themselves, cyclodextrins may cause secondary systemic effects through increased GI elimination of certain nutrients and bile acids. This effect is most notable for β-cyclodextrin assisted fecal elimination of bile acids (68). The increased elimination, however, was only observed at very high oral doses of the cyclodextrin (up to 20% of diet). The secondary effects of the increased bile acid elimination are increased conversion

of serum cholesterol to the bile acids with subsequent lowering of plasma cholesterol levels.

As discussed earlier, the ability of cyclodextrins to complex cholesterol may also play a role in the ability of certain cyclodextrins to cause membrane destabilization. These effects may be directly related to the ability of certain cyclodextrin derivatives to act as membrane permeation enhancers or cause tissue irritation upon injection. Red blood cell lysis has historically be employed as a model to measure the relative ability of cyclodextrins to cause membrane destabilization. For example, Shiotani *et al.* (69) investigated the lysis of rabbit erythrocytes by various cyclodextrins and found that β-CD>HP-β-CD>$(SBE)_{4M}$-β-CD>S1-β-CD. It has also been demonstrated that increases in the molar degree of substitution for the sulfobutyl ether cyclodextrins decreases the membrane destabilization ability (15). This effect is illustrated in Figure 9 for studies using human erythrocytes. These studies demonstrated that $(SBE)_{7M}$-β-CD caused almost no membrane destabilization with the order of membrane damage for the cyclodextrins studied being β-CD>$(SBE)_{1M}$-β-CD>HP-β-CD>$(SBE)_{4M}$-β-CD>$(SBE)_{7M}$-β-CD.

## REGULATORY ISSUES

### Safety and Quality

The regulatory acceptance of finished drug products which contain cyclodextrins will depend in part on the cyclodextrin manufacturers' ability to provide safety and quality control data in support of the administration route and cyclodextrin dosage level for that product. In the United States this information would be included in a Drug Master File (DMF) filed by the cyclodextrin manufacturer and referenced by the drug product manufacturer in their particular regulatory document. For the newer cyclodextrin derivatives such as Captisol™ and Encapsin™ which exist as mixtures of derivatives with varying degrees of substitution, the quality data may require documentation of the batch to batch reproducibility of the substitution pattern to insure that the material is analogous to that which was used to generate the safety data.

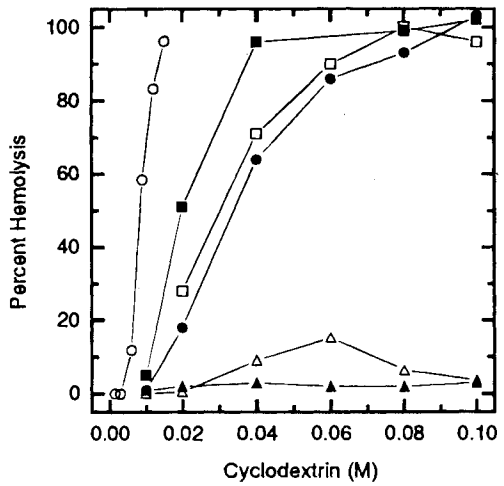



**Fig. 9.** Hemolytic behavior of cyclodextrins with human erythrocytes; ○ β-CD; ● HP-β-CD (Encapsin HPB™); □ HP-β-CD (Molecusol™); ■ $(SBE)_{1M}$-β-CD; △ $(SBE)_{4M}$-β-CD; ▲ $(SBE)_{7M}$-β-CD. Reproduced with permission (15).

### Current Regulatory Status

The review by Thompson (9) contains a detailed discussion of the current global regulatory status of cyclodextrins. In the US, standards for β-CD quality are defined in a National Formulary monograph and DMF's have been or will be submitted for the commercially available cyclodextrins. The existence of a DMF for a specific cyclodextrin derivative, however, does not guarantee regulatory acceptance for the use of that cyclodextrin with a given medicinal agent. The safety data for a specific cyclodextrin derivative provided in the DMF needs to support the administration route, cyclodextrin dosing level and dosing frequency. In addition, the regulatory document referencing the DMF will need to provide supporting safety data on the cyclodextrin/drug combination. The concern of the pharmaceutical industry regarding the former requirement will decrease as approved applications are attained for specific cyclodextrin derivatives and they are accepted as safe enabling excipients.

## SUMMARY

The identification of some modified cyclodextrins with better safety records has renewed interest in the use of cyclodextrins as solubilizing, stabilizing, etc. agents for multiple pharmaceutical applications. As regulatory approval by the FDA of a number of products approaches, interest is likely to increase as the "risk factor" to employing specific cyclodextrins diminishes. It is accepted that the lack of an approved product by the FDA has probably inhibited the universal acceptance of cyclodextrins as pharmaceutical enabling agents. We hope this mini-review has helped answer some of the questions on the issues facing the pharmaceutical development and uses of cyclodextrins.

## ACKNOWLEDGMENTS

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