REVIEW ARTICLE

Pharmaceutical Applications of Cyclodextrins. 2. *In Vivo* Drug Delivery

ROGER A. RAJEWSKI[x] AND VALENTINO J. STELLA

Received February 9, 1996, from the *Higuchi Biosciences Center for Drug Delivery Research and the Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, KS 66047.* Final revised manuscript received September 6, 1996. Accepted for publication September 9, 1996[⊗].

Abstract □ The objective of this Review is to summarize and critique recent findings and applications of both unmodified and modified cyclodextrins for *in vivo* drug delivery. This review focuses on the use of cyclodextrins for parenteral, oral, ophthalmic, and nasal drug delivery. Other routes including dermal, rectal, and pulmonary delivery are also briefly addressed. This Review primarily focuses on newer findings concerning cyclodextrin derivatives which are likely to receive regulatory acceptance due to improved aqueous solubility and safety profiles as compared to the unmodified cyclodextrins. Many of the applications reviewed involve the use of hydroxypropyl-β-cyclodextrins (HP-β-CDs) and sulfobutylether-β-cyclodextrins (SBE-β-CDs) which show promise of greater safety while maintaining the ability to form inclusion complexes. The advantages and limitations of HP-β-CD, SBE-β-CD, and other cyclodextrins are addressed.

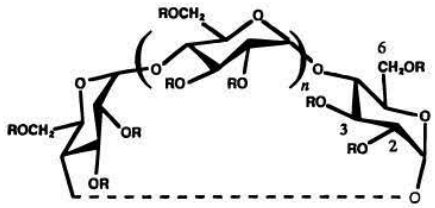
Introduction

The objective of this Review is to summarize and critique recent findings and applications of the use of unmodified and modified cyclodextrins for *in vivo* drug delivery. As part of this series, Loftssen and Brewster[1] reviewed the use of cyclodextrins for the solubilization, stabilization, and formulation of drugs through the formation of inclusion complexes while Uekama et al.[2] will summarize findings on the safety profile of cyclodextrins. Numerous other major reviews on the actual and potential pharmaceutical uses of cyclodextrins have been published.[3−11] Recently, as stated by Duchêne and Wouessidjewe,[3] the availability of new derivatives with better safety profiles has renewed interest in the *in vivo* uses of cyclodextrins. Also, as more products containing cyclodextrins move toward regulatory approval in the U.S. and elsewhere, the general acceptance by researchers and the pharmaceutical industry of specific cyclodextrins as enabling excipients is likely to increase. Although a number of products containing cyclodextrins have been approved for human use in Japan and Europe, no product has yet to be approved in the U.S. The approval of specific products by the Food and Drug Administration (FDA) in the U.S. will be of paramount importance to the commercial viability of cyclodextrins for worldwide pharmaceutical use. It is generally accepted that the lack of an FDA approved product, presumably due to actual or perceived safety concerns, continues to inhibit the universal acceptance of these valuable materials.

Cyclodextrin's Pharmaceutical Niche—In the early 1980s the high incidence of an anaphylactic reaction accompanying the parenteral administration of selected formulations led to questioning the use of surfactants which had been employed to solubilize or stabilize these formulations. This idiosyncratic histamine release was especially evident with the increased clinical use of the solubilizers Cremophor-EL present in cyclosporin A and taxol formulations, and Tween 80 which was used in an etoposide product. Other than the use of cosolvents, microemulsion dosage forms, pH adjustment for ionizable drugs, and experimental dosage forms such as microparticulates and liposomes, few new viable formulation options had been made available to address the problems associated with administering sparingly water soluble drugs in solution form. Although the use of cyclodextrins as potential solubilizing and stabilizing agents had been well recognized earlier, safety concerns limited their use for parenteral administration.

Cyclodextrins of pharmaceutical relevance are cyclic oligosaccharides composed of dextrose units joined through a 1−4 bond. Cyclodextrins with six to eight dextrose units have been named α-, β-, and γ-cyclodextrin, respectively (α-, β-, and γ-CD; Table 1). As discussed by Loftssen and Brewster,[1] cyclodextrins are capable of forming inclusion complexes with drugs. These noncovalent, inclusion complexes can have physical, chemical, and biological properties that are dramatically different from those of either the parent drug or cyclodextrin. These complexes can be used to increase solubility and dissolution rate, decrease volatility, alter release rates, modify local irritation, and increase the stability of drugs. The driving forces for inclusion complexation, including the re-

Table 1—General Structures[a] of Cyclodextrins Referred to in This Review and Their Abbreviated Names

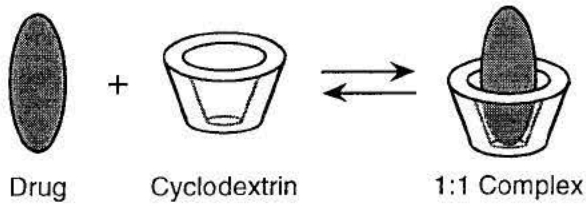


Cyclodextrin	Abbrevia ion	R	*n*
α-Cyclodextrin	α-CD	H	4
β-Cyclodextrin	β-CD	H	5
γ-Cyclodextrin	γ-CD	H	6
Carboxymethyl-β-cyclodextrin	CM-β-CD	CH_2CO_2H or H	5
Carboxymethyl-ethyl-β-cyclodextrin	CME-β-CD	CH_2CO_2H, CH_2CH_3 or H	5
Diethyl-β-cyclodextrin	DE-β-CD	CH_2CH_3 or H	5
Dimethyl-β-cyclodextrin	DM-β-CD	CH_3 or H	5
Me hyl-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
Sulfobutyle her-β-cyclodextrin	SBE-β-CD	$(CH_2)_4SO_3Na$ or H	5

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

[⊗] Abstract published in *Advance ACS Abstracts,* October 15, 1996.

S0022-3549(96)00075-5 CCC: $12.00



Scheme 1—Scheme illustrating equilibrium binding of drug and cyclodextrin to form a 1:1 complex.

quirement of the drug to "fit" into the cyclodextrin cavity, have been discussed elsewhere.[1,12–24]

Mechanisms of Drug Release from Inclusion Complexes—The rational design of formulations which take advantage of cyclodextrin inclusion complexation requires an understanding of the relationship between intrinsic drug solubility, the magnitude of the binding constant for the inclusion complex, and dilution effects. Most pharmaceutical agents form 1:1 complexes with cyclodextrins as described by Scheme 1. On the basis of the structure and properties of the drug as well as the cyclodextrin, higher order complexes are also possible.

The magnitude of the binding constant, $K_{1:1}$, defined by eq 1 for the interaction described by Scheme 1, is generally in the range 0–100 000 M^{-1}, with 0 being the value for a drug that is incapable of forming an inclusion complex and 100 000 M^{-1} being near the upper value observed experimentally for cyclodextrin complexes of drugs. In eq 1, $[drug]_{complex}$ 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.

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

For illustration of the relationship between drug solubility, magnitude of the binding constant, and dilution, a hypothetical drug (MW 400) with an intrinsic solubility of 10 $\mu g \cdot mL^{-1}$ (2.5×10^{-5} M) and a $K_{1:1}$ value of 10 000 M^{-1} for its interaction with a cyclodextrin of unlimited solubility will be examined. In the presence of the cyclodextrin, the solubility of the drug would be defined by eq 2. In eq 2, $[drug]_{total}$ represents the

$$[drug]_{total} = [drug]_{intrinsic} + \frac{K_{1:1}[drug]_{intrinsic}[cyclodextrin]_{total}}{K_{1:1}[drug]_{intrinsic} + 1} \quad (2)$$

total drug solubility, $[drug]_{intrinsic}$ represents the intrinsic solubility of the drug in the absence of the cyclodextrin, and $[cyclodextrin]_{total}$ represents the total molar concentration of cyclodextrin in the solution. In the presence of 0.1 M cyclodextrin, the solubility of the drug would be 8 $mg \cdot mL^{-1}$. An injectable dosage form containing 40 mg of this drug in 5 mL of 0.1 M cyclodextrin would contain only 50 μg of free or noncomplexed drug (0.125%), while the remaining 39.95 mg (99.875%) would be in the form of the inclusion complex. The ratio of free to complexed drug will change when this 5 mL formulation is injected intravenously by bolus dosing. For example, when this formulation is injected into a 70 kg subject with a plasma volume of about 3.5 L, the total drug and cyclodextrin concentrations would be 11.4 $\mu g \cdot mL^{-1}$ (2.85×10^{-5} M) and 0.143 mM, respectively. At these concentrations the percent free drug would be 43.9% with the balance still bound to the cyclodextrin. These values do not reflect drug and cyclodextrin binding to plasma proteins, uptake of drug into red blood cells or other tissues, and competitive displace-

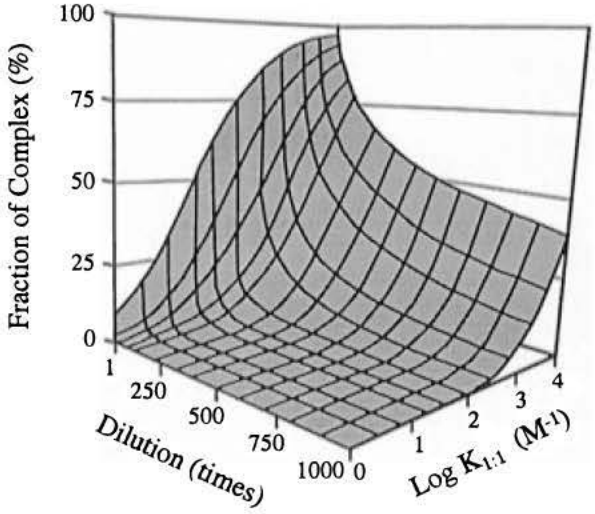


Figure 1—Relationship between fractional percent of a drug in its complex form as a function of the strength of the association constant, $K_{1:1}$, and dilution. The initial drug and cyclodextrin concentrations were set at 0.1 M, the range of $K_{1:1}$ values was 1–10 000 M^{-1}, and dilutions ranged over 1–1000 times. Reprinted with permission from ref 25. Copyright 1994 Harwood.

the drug has a more extensive volume of distribution (V_d), further dilution would occur and a smaller percentage would remain bound. Uekama et al.[25] have quantified the free and bound fractions of drugs to cyclodextrins as a function of drug concentration, binding constant, cyclodextrin concentration, and dilution. A graphical representation is shown in Figure 1. The kinetics of drug binding to cyclodextrins has been studied, and equilibrium binding is usually established with half-lives of much less than 1 s.[26–29] Therefore, the kinetics of dissociation is generally much faster than most physiological processes.

Frijlink et al.[30] studied the effect of dilution with plasma on hydroxypropyl-β-cyclodextrin (HP-β-CD) complexes of naproxen or flurbiprofen. They found experimentally that only small fractions of the drugs remained bound to the cyclodextrin in plasma *in vitro*. This effect was due not only to dilution but also to the competition between albumin binding of the two drugs and cyclodextrin binding. Also contributing to the low fraction bound was displacement of the drugs from cyclodextrin by a competing agent, plasma cholesterol.

The importance of changes in the ratio of free to complexed drug upon dilution of a sparingly water soluble drug in a cyclodextrin complex depends on the phase–solubility behavior of the system. If the cyclodextrin complex of a drug results from a 1:1 interaction, there is a linear increase in drug solubility with increasing cyclodextrin concentration (Figure 2A). Therefore, dilution of a true solution of the drug/cyclodextrin complex will not result in drug precipitation regardless of the extent of dilution. In the example discussed above where the 8 $mg \cdot mL^{-1}$ solution was diluted to 3.5 L, the final drug concentration was 11.4 $\mu g \cdot mL^{-1}$, of which the free drug concentration was 4.6 $\mu g \cdot mL^{-1}$ and the bound concentration was 6.8 $\mu g \cdot mL^{-1}$. The 4.6 $\mu g \cdot mL^{-1}$ free drug concentration is below the intrinsic solubility of the drug, set at 10 $\mu g \cdot mL^{-1}$, and precipitation of the drug will not occur.

Precipitation of the drug may occur on dilution, however, if there is a nonlinear relationship between drug solubility and cyclodextrin concentration. Figure 2B is a plot of solubility versus cyclodextrin concentration for the hypothetical drug described earlier where the solubility of 8 $mg \cdot mL^{-1}$ was achieved at 0.1 M cyclodextrin with a 1:1 interaction constant of 2000 M^{-1} (eq 1) and a 1:2 interaction constant, $K_{1:2}$, of 50

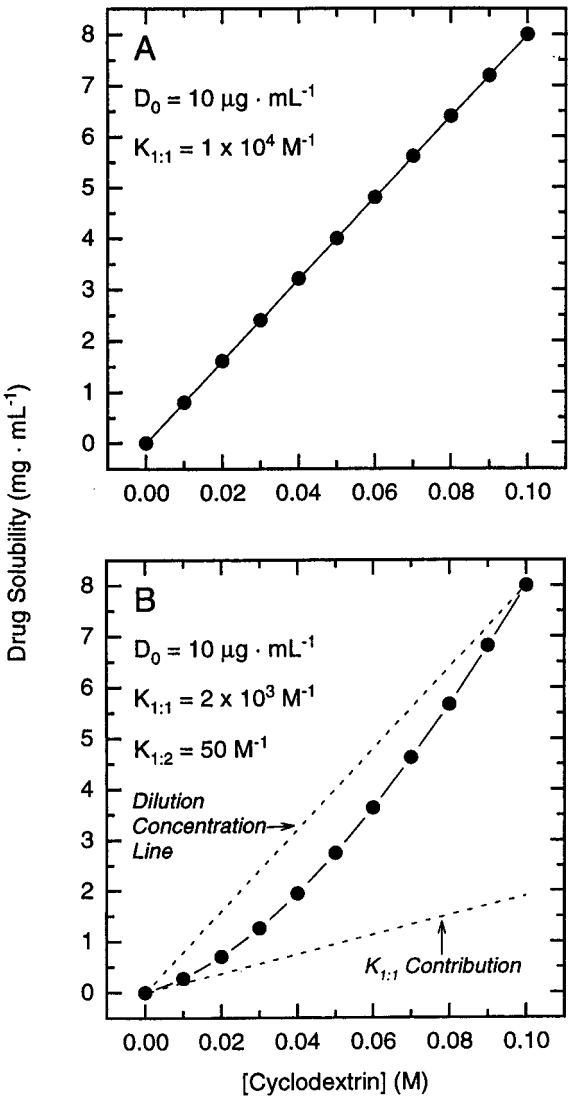
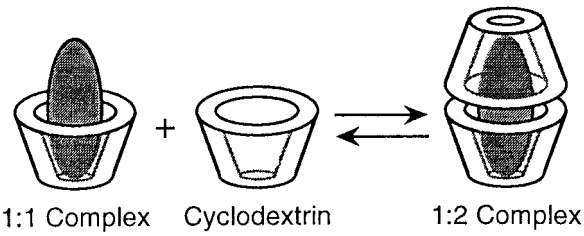


Figure 2—(A) Solubility versus cyclodextrin concentration for a hypothetical drug of MW 400 with an intrinsic water solubility of 10 μg·mL^{-1} (2.5×10^{-5} M) forming a 1:1 cyclodextrin complex with a drug with a $K_{1:1}$ association constant of 10 000 M^{-1}. (B) Solubility versus cyclodextrin concentration for a hypothetical drug of molecular weight 400 with an intrinsic water solubility of 10 μg·mL^{-1} (2.5×10^{-5} M) forming 1:1 and 1:2 cyclodextrin complexes with the drug wi h $K_{1:1}$ and $K_{1:2}$ constants of 2000 and 50 M^{-1}, respectively.



Scheme 2—Scheme illustrating equilibrium binding of a 1:1 complex of drug and cyclodextrin with a second molecule of cyclodextrin to form a 1 2 complex.

As can be seen from Figure 2B, there is a nonlinear increase in solubility with increasing cyclodextrin concentration. If we assume that an 8 mg·mL^{-1} solution of the drug in 0.1 M cyclodextrin is diluted 1:5 into a minibag, the final drug concentration would be 1.6 mg·mL^{-1} while the cyclodextrin concentration would be 0.02 M. According to the data in Figure 2B, the solubility of the drug in 0.02 M cyclodextrin is may occur. Precipitation may occur in such systems at any dilution where the equilibrium drug solubility is lower than the dilution concentration line at a given cyclodextrin concentration. The problem of precipitation on dilution for those drugs which display the behavior just illustrated has recently been documented in the literature.[31] Theoretically, similar precipitation could also occur *in vivo* when such solutions are injected intravenously or by other parenteral routes.

Modified Cyclodextrins—Prior to the mid-1970s most pharmaceutical research on cyclodextrins focused on the unmodified α-, β-, and γ-CDs. The work of Frank et al.[32] and others[33] showing the nephrotoxicity of the unmodified cyclodextrins limited further studies on the parent cyclodextrins to those routes where systemic cyclodextrin absorption was limited, namely, nonparenteral routes.

Most drug molecules tend to interact more favorably with β-CD than α-CD because the 6 Å cavity diameter for β-CD accommodates aromatic groups found in many drug molecules. In contrast, the cavity diameter for α-CD tends to be too small for a favorable fit. Interactions can also be seen between many drugs and γ-CD. However, the cost of γ-CD has made its extensive use economically unfavorable. A severe limitation of β-CD is its limited water solubility of 18.6 mg·mL^{-1} or 16.4 mM. For example, a hypothetical drug with an aqueous solubility of 10 µg·mL^{-1} and a 1:1 binding constant with β-CD of 1×10^4 M^{-1} would have a maximum obtainable solubility of 1.3 mg·mL^{-1} in the presence of 16.4 mM β-CD. In addition, β-CD often forms B-type phase−solubility diagrams where the complexes themselves have limited aqueous solubility.[34]

Because of the solubility limits and the safety concerns with β-CD, numerous chemical modifications of the cyclodextrins have been made. Since the focus of this Review is on the *in vivo* applications of cyclodextrins, only those cyclodextrins which have been studied for their pharmaceutical utility will be discussed. The cyclodextrins of prime interest to pharmaceutical scientists consist of five general types. The first type consists of various methylated and alkylated cyclodextrins, especially 2,6-dimethyl-β-cyclodextrin (DM-β-CD) and randomly methylated β-cyclodextrins (RM-β-CD). The second type consists of the hydroxypropyl and hydroxyethyl cyclodextrins, especially 2-hydroxypropyl-β-cyclodextrins (HP-β-CD). Specific products include Encapsin and Molecusol. The third type consists of various branched cyclodextrins, especially glucosyl, diglucosyl (G_2-β-CD), maltosyl, and dimaltosyl cyclodextrins. The fourth type consists of carboxymethyl cyclodextrins, e.g., CM-β-CD, and associated derivatives. The fifth type consists of the sulfoalkylether cyclodextrins, especially sulfobutyl ethers (SBE-β-CD) of β-CD with degrees of substitution of 4 and 7, SBE4-β-CD and SBE7-β-CD, respectively. Specific products include Captisol, an SBE7-β-CD. The cyclodextrin derivatives discussed in this Review may be found in Table 1.

Pharmaceutical scientists have also investigated the antiangiogenic and antiviral properties of sulfated cyclodextrins; however, the ability of these derivatives to form inclusion complexes is rather minimal.[35−44] In addition, they have heparin-like activity resulting in an increase in blood clotting times which limits the cyclodextrin dose that can be administered to patients. Therefore, the use of sulfated cyclodextrins as potential complexing agents will not be discussed further. As noted for the sulfated cyclodextrins, safety is a primary concern when the advantages and disadvantages of the various cyclodextrins are considered. Uekama et al.[2] will address in detail the safety status of the various cyclodextrins in a Review to be published in a future issue. Questions on the safety of the various derivatives will be addressed briefly in this paper and then only as they affect the performance of

Another very important factor in considering the pharmaceutical use of cyclodextrins is cost. Because cyclodextrins have molecular weights in the range of 1000−2000, 0.1 M solutions require 10−20% (w/v) cyclodextrin. Production of dosage forms on a commercial scale would quickly consume very large amounts of the cyclodextrin. Therefore the cyclodextrin must be reasonably inexpensive for the dosage form to be economically feasible. β-CD itself is quite inexpensive, and the costs of α- and γ-CDs are declining. Any modification of the cyclodextrin structure must entail relatively inexpensive reagents and purification procedures. However, well-characterized, pure, single-component materials are rare.

β-CD contains 21 hydroxyl groups, seven primary (the 6-hydroxy) and 14 secondary (the 2- and 3-hydroxyls). Methods have been developed with varying degrees of success either to derivatize all 21 of the hydroxyls or to selectively derivatize from one to seven of a particular hydroxyl group. Claims of selective derivatization are often overstated, and most claimed derivatives are mixtures. It may be very difficult to justify economically the development of a pure derivative unless it can be accomplished with a high yield, using simple and inexpensive reagents, and employing a purification procedure that can be easily scaled to produce metric ton quantities. The use of complex mixtures is not unknown to the pharmaceutical community. However, the methods used to characterize such mixtures need to be refined so that lot to lot reproducibility can be verified.

From the pharmaceutical viewpoint, not only must these complex mixtures be reproducible and well characterized lot to lot, but they must be free of all potentially reactive and toxic components. This is especially important in the case of unreacted parent cyclodextrin in products intended for parenteral administration. It is critical to have materials free of pyrogens and foreign proteins for cyclodextrins which are intended for parenteral use and to have the ability to sterilize the solution either by heat or filtration. These issues are not trivial and must be addressed before a particular cyclodextrin can be considered for pharmaceutical use.

Parenteral Applications of Cyclodextrins

Introduction—The major anticipated uses of cyclodextrins in parenteral drug delivery include solubilization of drugs, allowing for rapid and quantitative delivery of sparingly water soluble drugs for intravenous and intramuscular dosing, decreasing irritation at the site of administration of parenterally administered drugs, and stabilization of drugs unstable in an aqueous environment.

To date two types of parenteral studies have been published. In the first type a cyclodextrin has been used during animal testing to allow for a solution dosage form to be administered. Some of these studies have used cyclodextrins of questionable safety while other studies have not run controls which might have allowed the researcher to determine if the cyclodextrin altered the pharmacodynamics of the drug. In these cases the cyclodextrin was used as a tool and was not intended as a prototypical formulation for ultimate scaling to humans. In the second type of study the cyclodextrin was being evaluated as a potential tool for improved parenteral delivery of either a model drug or an actual clinical candidate. Nevertheless, both types of studies provide valuable insight into the potential uses of cyclodextrins as enabling excipients for parenteral drug delivery.

Aspects of the use of cyclodextrins to effect parenteral delivery of drugs have been reviewed previously.[3−11,25,45−60] The safety record of the cyclodextrin is perhaps more critical with parenteral delivery than with other routes of administra- delivery of little or no cyclodextrin. Parenteral delivery, on the other hand, guarantees systemic delivery. Although the parenteral use of unmodified cyclodextrins and some modified cyclodextrins such as DM-β-CD has been attempted, their systemic safety records are unacceptable. Since the safety records of HP-β-CDs and SBE-β-CDs appear more promising, this section will focus primarily on their use.

The earlier Review in this series by Loftsson and Brewster[1] focused on the solubilization and stabilization of drugs. Although most of the examples in the current literature on *in vivo* applications have focused on the use of cyclodextrins to solubilize and/or to decrease the irritancy of drugs, future uses will also focus on their ability to stabilize drugs in aqueous solution, allowing for parenteral delivery. This is especially important for those unstable drugs for which long-term infusions might be desirable. For example, cyclodextrins are currently being studied extensively for their ability to stabilize a number of very unstable cytotoxic drugs.

Parenteral Delivery of Insoluble Drugs—Even though the safety of a particular cyclodextrin is the critical factor in its potential parenteral use, other factors also limit whether a cyclodextrin can be used to administer a given drug. One such factor is whether the target drug solubility can be achieved with the use of an acceptable cyclodextrin concentration. In addition, the cyclodextrin safety data must support the concentration and total dose of cyclodextrin required to solubilize the desired amount of drug. Other factors such as the linearity of the relationship between drug solubility and cyclodextrin concentration might also affect the acceptability of a given concentration or dose. If a nonlinear relationship exists and a very high concentration of cyclodextrin is needed to solubilize the drug, dilution of that sample either in a large volume parenteral (LVP) or on iv or im administration could lead to drug precipitation and complications. For example, the authors have noticed that some cyclodextrins could be used to solubilize the anticancer drug taxol (unpublished data). However, the relationships between taxol solubility and cyclodextrin concentration were such that any attempt to dilute the samples resulted in erratic precipitation of the taxol. Because nucleation either in an LVP or *in vivo* is a time dependent phenomenon, it might be possible to consider such metastable dosage forms even though precipitation can occur.[31]

Another critical factor would be whether the drug was completely released from the cyclodextrin dosage form. Drug release from the cyclodextrin dosage form can be determined by assessing the pharmacokinetics of the drug from the cyclodextrin solution as compared to other dosage forms. The pharmacokinetic studies would also indicate if the cyclodextrin altered the temporal pattern of the drug in plasma or blood, or the drug excretion profile. Either effect could lead to a change in pharmacodynamics and perhaps therapeutic efficacy and toxicity. Time profiles of the drug in various tissues would also be helpful in assessing the role of the dosage form. Few well-designed studies have addressed these latter issues to date.

Intravenous Administration—Most recent studies on the use of cyclodextrins to allow iv administration have utilized SBE4-β-CD or HP-β-CD since safety concerns with other cyclodextrins preclude their parenteral use. However, an early study by Shirakura et al.[61] involving β-CD is noted because the results demonstrated that iv β-CD significantly shortened the sleeping time induced by a series of barbituric acid derivatives. The amount of β-CD administered with the barbiturates, however, was about 0.244 mg·kg^{-1}. This dose will show some significant renal toxicity. The possible mechanisms for the altered sleep times were speculated on by the

which utilizes one of the safer cyclodextrins would provide valuable insight to the altered barbiturate activity.

Significant alteration in the pharmacokinetics of a drug was also demonstrated in the work of Frijlink et al.[30] This study evaluated 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 in brain, liver, kidney, spleen, muscle, and plasma of naproxen 10 and 60 min after iv administration was unaffected by coadministration of 7% HP-β-CD. For flurbiprofen, however, at 10 min postdosing HP-β-CD produced significantly higher tissue levels in the brain, liver (most significant), kidney, and spleen but at 60 min postadministration only slightly higher, yet significant, levels in the brain tissue alone. Frijlink et al. speculated that the higher levels in some tissues reflected a transitory alteration in protein binding when HP-β-CD was used as the vehicle. In an *in vitro* study, HP-β-CD was able to compete with the protein binding for both naproxen and flurbiprofen but the effect was more pronounced with the flurbiprofen. Another control experiment where flurbiprofen was administered in a purely aqueous solution might have indicated whether administration in rat plasma also affected the relative results.

LaHann et al.[62,63] have studied the pharmacokinetics in dogs of *p*-boronophenylalanine following iv administration of 4.43 mg·kg^{-1} drug in an aqueous HP-β-CD solution (to effect greater solubility) versus a more dilute 0.96 mg·kg^{-1} aqueous solution. The pharmacokinetics of *p*-boronophenylalanine were found to be significantly different from the two dosage forms. The authors intimated that the pharmacokinetics of *p*-boronophenylalanine was dose dependent (nonlinear). Therefore, differences observed in the pharmacokinetics including longer half-life at the higher dose and a disproportionate increase in AUC with dose might be due to the dose differences. However, a direct effect of the HP-β-CD could not be ruled out. This issue could have been clarified by studying the pharmacokinetics of the drug at increasing doses in the presence of a fixed HP-β-CD dose level. Greater toxicity was seen with the HP-β-CD formulation, but this may have been due to the higher dose levels. Some toxicity from the HP-β-CD vehicle itself was noted in a few dogs. The etiology of this response was not assessed.

In those studies where control experiments could be performed, i.e., where the drug could be given by means other than the cyclodextrins, cyclodextrins have been found to not alter the intrinsic pharmacokinetics of the drug. For example, Arimori et al. showed that γ-CD did not alter the pharmacokinetics of thiopental in rabbits after iv administration.[64] The activity of the anesthetic propofol (2,6-diisopropylphenol) was no different when administered iv as a HP-β-CD solution versus a commercial oil in water emulsion.[65] The responses to increasing doses of the anesthetic isoflurane from a HP-β-CD solution were similar to those after inhalation of the agent.[66] Estes et al.[67] evaluated a nonsurfactant formulation that contained HP-β-CD for administration of alfaxalone (3α-hydroxy-5α-pregnane-11,20-dione, a steroid anesthetic) to rats and dogs. This formulation was compared to a veterinary product containing the surfactant Cremophor-EL. No difference in anesthetic activity was seen between the two formulations in rats. In dogs, the HP-β-CD formulation did not cause the significant histamine release and depressed respiratory rate and blood pressure drop seen with the surfactant formulation. More recently, the same research group provided additional data showing the usefulness of HP-β-CD in the parenteral administration of a series of other steroidal anesthetic agents.[68]

Doenicke et al.[69] compared the iv bolus pharmacokinetics and activity of the hypnotic agent etomidate (2 mg·mL^{-1}) from HP-β-CD solution. The pharmacokinetics of etomidate were identical from the two solutions, and no differences in hypnotic effects were observed. A higher incidence of pain on injection was noted in patients receiving the propylene glycol solution (58% of the patients) as compared to patients receiving the HP-β-CD formulation (8% of the patients). Another study[70] did show a high incidence of pain (52%) from the HP-β-CD formulation when it is was assessed alone. Etomidate itself caused irritation and pain on injection.

Brewster et al.[71] were able to develop a parenteral formulation of the anticonvulsant drug carbamazepine through the use of HP-β-CD. Carbamazepine solubility increased nonlinearly with increasing HP-β-CD concentrations, suggesting complexes of higher order than 1:1 between carbamazepine and HP-β-CD. A tolerability and pharmacokinetic study was performed in epileptic patients by Löscher et al.[72] by comparing a 10 mg·mL^{-1} carbamazepine solution in 20% HP-β-CD to a 65% aqueous glycofural (PEG monotetrahydrofurfuryl ether) solution. The half-lives and AUC values for carbamazepine from HP-β-CD and glycofural were 0.603 $\pm$ 0.043 h versus 1.0 $\pm$ 0.014 h and 3.70 $\pm$ 0.72 μg·h·mL^{-1} versus 7.37 $\pm$ 0.72 μg·h·mL^{-1}, respectively. The longer half-life and higher AUC value (and therefore slower clearance) of carbamazepine and the delayed appearance of the epoxide metabolite of carbamazepine from the glycofural formulation strongly suggested that glycofural was an inhibitor of carbamazepine metabolism. Therefore, the nonidentical pharmacokinetics of carbamazepine from the HP-β-CD solution was most probably due to the negative effect of the glycofural in the control formulation rather than any catalytic effect of the HP-β-CD on carbamazepine elimination.

The pharmacokinetics of the steroids methylprednisolone, dexamethasone, and prednisolone have been evaluated from solutions of cyclodextrins compared to either cosolvent solutions or from water soluble prodrugs of the steroids. Arimori and Uekama[73] studied the iv pharmacokinetics of prednisolone in rabbits from β-CD and γ-CD aqueous solutions as compared to an aqueous solution of its phosphate ester prodrug. The cyclodextrin solutions and the solution of the prodrug showed identical pharmacokinetics. Dietzel et al.[74] compared the iv bolus pharmacokinetics in dogs of dexamethasone (5 mg·kg^{-1} from a 25 mg·mL^{-1} solution) from a 40% HP-β-CD solution compared to a molar equivalent of a water soluble dexamethasone phosphate prodrug. This work has been reviewed by Loftsson et al.[8]

For the phosphate ester prodrug to release dexamethasone it must be cleaved *in vivo* by phosphatase enzymes. The plasma concentration versus time curves for the dexamethasone from the two dosage forms were not identical. Plasma levels during the first hour were significantly higher from the HP-β-CD solution. However, the curves were superimposable after 1 h. There was no significant difference between the plasma AUC values ($\pm$SD) to infinity from the prodrug and the HP-β-CD formulation (5.48 $\pm$ 0.67 μg·h·mL^{-1} versus 6.67 $\pm$ 1.69 μg·h·mL^{-1}). The AUC values over the first hour were significantly lower from the prodrug formulation than from the HP-β-CD solution (1.04 $\pm$ 0.10 μg·h·mL^{-1} versus 1.63 $\pm$ 0.13 μg·h·mL^{-1}). The authors concluded that the lower early plasma concentrations may have been due to slow conversion of the prodrug to dexamethasone. Although the differences between the curves were not significant, there was a trend in the AUC values to infinity which suggested incomplete overall conversion of the phosphate ester prodrug to dexamethasone. This incomplete conversion may have been due to both slow and incomplete conversion of the prodrug. It is possible that metabolic or elimination pathways may have been competing for prodrug conversion to parent drug. Of additional interest was the higher renal clearance of dexamethasone with the

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.