



# Cyclodextrins in pharmaceutical formulations II: solubilization, binding constant, and complexation efficiency

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Cyclodextrins are cyclic oligosaccharides that have been recognized as pharmaceutical adjuvants for the past 20 years. The molecular structure of these glucose derivatives, which approximates a truncated cone, bucket, or torus, generates a hydrophilic exterior surface and a nonpolar interior cavity. Cyclodextrins can interact with appropriately sized drug molecules to yield an inclusion complex. These noncovalent inclusion complexes offer a variety of advantages over noncomplexed forms of a drug. Cyclodextrins are carbohydrates that are primarily used to enhance the aqueous solubility, physical chemical stability, and bioavailability of drugs. Their other applications include preventing drug–drug interactions, converting liquid drugs into microcrystalline powders, minimizing gastrointestinal and ocular irritation, and reducing or eliminating unpleasant taste and smell. Here, we focus on the solubilization of drugs by complexation, and discuss the determination and significance of binding constants for cyclodextrin complexes, and the determination of complexation efficiency and factors that influence it. We also make some general observations on cyclodextrin complexation and the use of cyclodextrins in solid, as well as parenteral, dosage forms.

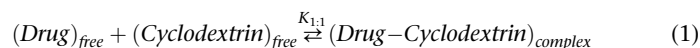
## Introduction

Although cyclodextrins are regarded by pharmaceutical scientists as a new group of pharmaceutical excipients, they have been in existence for over 100 years. For many years following their discovery, only small amounts of cyclodextrins could be produced because of their prohibitive production costs, which precluded their widespread use in pharmaceutical formulations or dosage forms. The biotechnological advances of the past 30 years have resulted in dramatic improvements in production, which have resulted in reduced production costs. This has also contributed to the ready availability of highly purified cyclodextrins and cyclodextrin derivatives that are well suited for pharmaceutical applications. The use of the phase solubility diagram has enabled the calculation of binding constants and the complexation efficiency parameter for cyclodextrin complexes, thus facilitating the evaluation and comparison of these complexes. This knowledge forms

the basis for making a more rational choice of a particular complex for a particular pharmaceutical application.

## Determination of binding constant and total solubility

The utility of cyclodextrins in pharmaceutical dosage forms comes from the fact that they interact with drug molecules to form inclusion complexes. The most common type of cyclodextrin complex is 1:1, where one drug molecule forms a complex with one cyclodextrin molecule. This formation of a complex is usually described by using Eqs. (1) and (2).



The scheme described in Eq. (1) can also be written as:



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where one drug ( $D$ ) molecule forms a complex with one cyclodextrin ( $CD$ ) molecule. Under such conditions, an  $A_L$ -type phase solubility diagram is most likely to be observed [1], although higher order complexes are also hypothesized and observed.

The solubility of a drug in the presence of a cyclodextrin that forms a 1:1 inclusion complex is described by Eq. (3) [2–4]:

$$S_{\text{total}} = S_0 + \frac{K_{1:1} \cdot S_0 [CD_{\text{total}}]}{K_{1:1} \cdot S_0 + 1}, \quad (3)$$

where  $S_{\text{total}}$  refers to the total drug solubility or the drug solubility in the presence of a given total cyclodextrin complexation;  $S_0$  refers to the intrinsic solubility or solubility of a drug in the absence of cyclodextrin;  $[CD_{\text{total}}]$  is the total cyclodextrin added to the solution, and  $K_{1:1}$  is the stability or binding constant [2,4].

Therefore, according to Eq. (3), a plot of total solubility ( $S_{\text{total}}$ ) of a drug against cyclodextrin concentration  $[CD_{\text{total}}]$  will yield a straight line. The slope of the graph will be less than unity and equal to  $K_{1:1} \cdot S_0 / [K_{1:1} \cdot S_0 + 1]$ . By contrast, the intercept of the plot represents the intrinsic solubility ( $S_0$ ) of the drug. The binding or stability constant ( $K_{1:1}$ ) and intrinsic solubility ( $S_0$ ) can be calculated using Eqs. (4) and (5), from knowing the slope and intercept, respectively [2,4,5]:

$$K_{1:1} = \frac{\text{Slope}}{S_0(1 - \text{Slope})}, \quad (4)$$

$$\text{Slope} = \frac{S_0 \cdot K_{1:1}}{S_0 \cdot K_{1:1} + 1}, \quad (5)$$

Eq. (3) suggests that there should be a linear increase in the solubility of the drug ( $S_{\text{total}}$ ) with increasing cyclodextrin concentration  $[CD_{\text{total}}]$ . Therefore, it is clear from Eq. (3) that the ability of a cyclodextrin to enhance drug solubility is a function of both the intrinsic solubility of a drug ( $S_0$ ) and the binding constant ( $K_{1:1}$ ) as well as the total cyclodextrin concentration used. The observed value for the binding or stability constant ( $K_{1:1}$ ) is usually between 50 and 2000  $M^{-1}$ , with reported [6] mean values of 129, 490, and 355  $M^{-1}$  for  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrin, respectively.

It is also apparent from Eq. (4) that the determined value for the stability or binding constant ( $K_{1:1}$ ) is affected by the accuracy of the intercept value ( $S_0$ ). Therefore, the feasibility of using cyclodextrins as solubility enhancers in pharmaceutical formulations can be determined from knowing the stability constant ( $K_{1:1}$ ) and the intrinsic solubility ( $S_0$ ), the latter being the intercept value of the phase-solubility diagram.

The value of the stability constant ( $K_{1:1}$ ) is used to compare the affinity of drugs for different cyclodextrins or cyclodextrin derivatives. In other words, the stability constant ( $K_{1:1}$ ) is a fundamental property that describes the strength of an interaction between a drug and a cyclodextrin. In this case, the slope of the phase-solubility plot is always less than unity. Therefore, for any formulation where complete solubilization is required, the practical utility of cyclodextrins as efficient solubilizers depends on the binding constant, ( $K_{1:1}$ ), between a drug and cyclodextrin and the intrinsic solubility ( $S_0$ ) of the drug.

If a 2:1 drug–cyclodextrin complex is formed, then the slope of the linear phase-solubility diagram is determined by Eq. (6) [5]:

$$\text{Slope} = \frac{2S_0^2 \cdot K_{2:1}}{S_0^2 \cdot K_{2:1} + 1}, \quad (6)$$

where  $K_{2:1}$  is the stability constant of the complex. The slope of the phase-solubility diagram in this case is always less than two.

There are many reports in literature (e.g., [7–30]) documenting that formation of a complex with various cyclodextrins produces several changes in the properties of the drug candidate. This includes enhanced solubility, physical and chemical stability, dissolution, bioavailability, and their many applications in pharmaceutical dosage forms.

Among the many advantages of complexation, by far the greatest has been in the area of the enhanced solubility of problematic drugs [2]. Enhancement of aqueous solubility by formation of an inclusion complex is different from that of the solubility enhancement produced as a result of the use of co-solvents and surfactants. When a co-solvent is used in this manner, the aqueous solubility of the drug is enhanced as a consequence of changes in the bulk properties of the solution. For example, solvents such as polyethylene glycol, propylene glycol, and ethanol will enhance the solubility when mixed with water, but in a very nonlinear fashion [1]. The drug will remain in a solution form in a mixture of solvents as long as the composition is maintained. The dilution of the solvent system with an aqueous solvent will result in separation of the solute from the system because of precipitation. This nonlinearity is not a problem with the use of cyclodextrins, particularly those that form 1:1 complexes [2].

### The complexation efficiency

For several reasons, it is important to use as little cyclodextrin as possible [4] in the pharmaceutical dosage form and, therefore, the solubilizing efficiency of the cyclodextrin becomes a more important aspect than the absolute value of the binding or stability constant ( $K_{1:1}$ ). The solubilizing efficiency is determined [4] either from knowing the slope of the phase solubility profile or from the complex:free cyclodextrin ratio, which is referred to as the ‘complexation efficiency’ ( $CE$ ) [4].

For 1:1 drug–cyclodextrin complexes, the complexation efficiency can be calculated from the slope of the phase-solubility diagram using Eq. (7):

$$CE = S_0 \cdot K_{1:1} = \frac{[D-CD]}{[CD]} = \frac{\text{Slope}}{(1 - \text{Slope})}, \quad (7)$$

where  $[D-CD]$  is the concentration of dissolved complex,  $[CD]$  is the concentration of the dissolved free cyclodextrin, and ‘Slope’ is the slope of the phase solubility profile.

When selecting cyclodextrin or complexation conditions during formulation development work, it might be more convenient to compare the complexation efficiency of cyclodextrin rather than the stability or binding constant ( $K_{1:1}$ ) value between the cyclodextrin and the drug. By using Eq. (7) and knowledge of slopes, which enable the determination of the binding constant ( $K_{1:1}$ ) and complexation efficiency, Loftsson *et al.* [4] determined the complexation efficiency for hydroxypropyl  $\beta$ -cyclodextrin and methylated  $\beta$ -cyclodextrin with 28 different drugs at ambient temperature. The authors reported that, on an average, complexation efficiency was approximately 0.3 [4]. This means that, on an average, only about one out of four cyclodextrin molecules in solution forms a water soluble complex with poorly soluble drugs. It assumes that a 1:1 complex is being formed [4]. Among the drugs that were tested, diethylstilbestrol exhibited the highest complexation efficiency

(2.82), suggesting that three out of four cyclodextrin molecules are involved in forming a complex with a drug. A complexation efficiency of 0.1 suggests that one out of 11 cyclodextrin molecules forms a complex with the drug. If the complexation efficiency is 0.01, then only one out of 100 cyclodextrin molecules forms a complex.

The value of the intercept, and, therefore, of the intrinsic solubility ( $S_0$ ) (Fig. 1) is affected by commonly used pharmaceutical excipients, such as buffer salts, polymers, and preservatives. Therefore, occasionally, the intrinsic solubility ( $S_0$ ) of a drug will be below the detection limit of the analytical method used. Given that the numerical value of the complexation efficiency depends only on the slope of the phase-solubility profile, less variation is usually observed in complexation efficiency values compared with stability constant ( $K_{1:1}$ ) values. In the same study [4], Loftsson *et al.* reported that the value of the binding constant ( $K_{1:1}$ ) was strongly influenced by intrinsic solubility ( $S_0$ ) and the intercept; however, the complexation efficiency values were independent of intrinsic solubility and the intercept. Furthermore, the complexation efficiency values showed that, on an average, addition of polymers to the complexation media had little effect on the complexation efficiency [4].

Rao and Stella [19] introduced a dimensionless number [the cyclodextrin utility number ( $U_{CD}$ )] to assess the feasibility of the use of cyclodextrins in a dosage form. The cyclodextrin utility number can be determined using Eq. (8):

$$U_{CD} = \left( \frac{K_{1:1} \cdot S_0}{1 + K_{1:1} \cdot S_0} \right) \left( \frac{(CD)_t}{(D)_t} \right) = \left( \frac{K_{1:1} \cdot S_0}{1 + K_{1:1} \cdot S_0} \right) \left( \frac{(m)_{CD}}{(m)_D} \right) \left( \frac{(MW)_D}{(MW)_{CD}} \right), \quad (8)$$

where  $K_{1:1}$  is the binding constant;  $S_0$  is the intrinsic solubility of a drug;  $(m)_D$  and  $(m)_{CD}$  are the drug dose and workable amount of cyclodextrin in mg, respectively; and  $(MW)_D$  and

$(MW)_{CD}$  are molecular weights of the drug and cyclodextrin, respectively.

When the numerical value of the dimensionless cyclodextrin utility number ( $U_{CD}$ ) is greater than or equal to 1, solubilization is adequately provided by the complexation with cyclodextrins. When this value is less than one, complexation alone is inadequate for the complete solubilization of a drug [19].

In Eq. (8), intrinsic solubility ( $S_0$ ), molecular weight of cyclodextrin [ $(MW)_{CD}$ ], molecular weight of drug [ $(MW)_D$ ], and the amount of drug [ $(m)_D$ ] are known *a priori* [9]. The workable amount of cyclodextrin [ $(m)_{CD}$ ] can be fixed based on the dosage form type, weight or volume (tablet size), tonicity of the solution (parenteral or ophthalmic), cost, and so on. Therefore, application of Eq. (8) to determine the utility of cyclodextrin for a specific drug formulation depends on the value of the binding constant,  $K_{1:1}$  (Eq. (9)):

$$K_{1:1} = \frac{[Drug-(CD)_{complex}]}{[(Drug)_{free}] \cdot [(CD)_{free}]}, \quad (9)$$

Rao and Stella [19] provide some specific numerical examples of the use of the cyclodextrin utility number in drug formulation.

### Drug solubilization: some general observations

The most common application of cyclodextrins of pharmaceutical interest is in increasing the drug solubility in aqueous solution (reviewed in [7–9,31,32]). There are a few simple guidelines and observations regarding the pharmaceutical applications of cyclodextrins.

The formation of a drug–cyclodextrin complex depends on the chemical structures and physicochemical properties of both the drug and the cyclodextrin [33]. For the formation of the inclusion complex, a hydrophilic moiety of an active pharmaceutical ingredient must be capable of fitting in the hydrophobic cyclodextrin cavity. Furthermore, low aqueous solubility is not always attributed to the lipophilicity of the active pharmaceutical ingredient or drug.

Generally, the lower the aqueous solubility of a pure drug, the greater the relative enhancement in drug solubility attained as a result of cyclodextrin complexation. Drugs whose aqueous solubility is in the range of micromoles/liter generally demonstrate greater enhancement compared with drugs whose aqueous solubility is in the moles/liter range [1].

In addition, cyclodextrin derivatives of lower molar substitutions are better drug solubilizers compared with the same type of derivatives with higher molar substitutions. Of the commercially available cyclodextrins, the methylated cyclodextrins, with relatively low molar substitutions, appear to be more effective solubilizers. By contrast, the chain length of the alkyl groups appears to be less important [34,35].

Charged cyclodextrins can be very effective solubilizers, although their solubilizing effect appears to depend on the relative proximity of the charge to the cyclodextrin cavity. Complexing ability improves as the location of the charge moves farther away from the cavity. For example,  $\beta$ - and  $\gamma$ -cyclodextrin have excellent solubilizing effects, whereas  $\beta$ -cyclodextrin sulfate exhibits low complexation potential. Sulfobutyl ether  $\beta$ -cyclodextrin (SBE- $\beta$ CD), where the anion has been moved from the cavity by the butyl ether spacer group, is an excellent solubilizer [36].

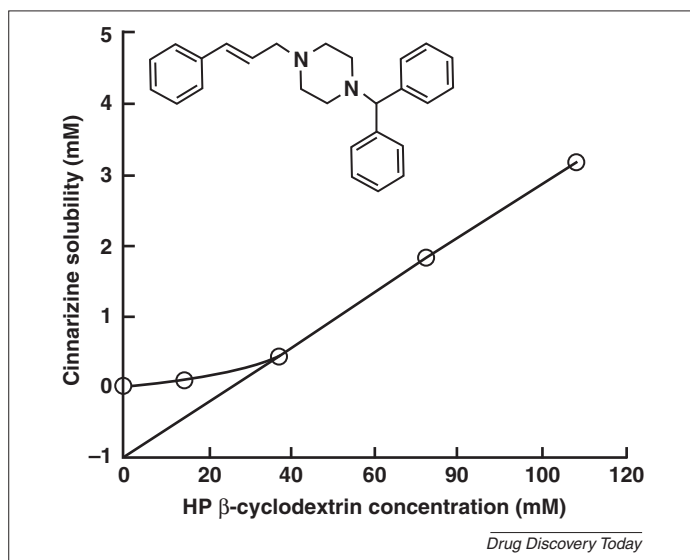


FIGURE 1

The phase-solubility profile of cinnarizine in aqueous 2-hydroxypropyl- $\beta$ -cyclodextrin (HP  $\beta$ -cyclodextrin) solution with a molar substitution of 0.6 in aqueous 0.01 N sodium hydroxide solution (pH 11.9) at ambient temperature. The  $pK_a$  of cinnarizine hydrochloride is 7.5.

Source: Reproduced, with permission, from [2].

Another important finding is that, although many ionizable drugs are capable of forming cyclodextrin complexes, the stability constant ( $K_{1:1}$ ) for the complex is larger for the ionized form of a drug. For example, both the unionized and cationic form of chlorpromazine give rise to a 1:1 complex with  $\beta$ -cyclodextrin; however, the stability constant for the unionized form is four times larger than for the cationic form [37]. The constant for phenytoin  $\beta$ -cyclodextrin is over three times greater for the unionized form than for the anionic form [38]. Nevertheless, the solubilization of ionizable drugs can be enhanced by adjusting the pH appropriately. The solubilizing effect of both  $\beta$ -cyclodextrins and dimethyl- $\beta$ -cyclodextrin on dihydroergotamine mesylate increased with decreasing pH (i.e., formation of cationic form), which was reflected in both saturation solubility and the slope of the phase-solubility diagram [39]. Similar results have been reported for the complexation of phenytoin as well as of indomethacin [40], prazepam, acetazolamide, and sulfamethoxazole with  $\beta$ -cyclodextrin [41]. Table 1 provides a summary of general observations on the effects of molecular structure and physicochemical properties on the formation of drug-cyclodextrin complexes.

Many commonly used additives, such as sodium chloride, buffer salts, surfactants, preservatives, and organic solvents, often attenuate the ability of cyclodextrins to solubilize drugs. Therefore, solubility studies should be conducted using the intended formulation.

It is also possible to enhance complexation efficiency and, therefore, the solubilizing effects of cyclodextrins by incorporating polymers or hydroxyl acids in the cyclodextrin solutions. Complexes have been reported [42,43] to form in the presence of water-soluble cellulose derivatives. The solubilizing effect of 10% (w/v)  $\beta$ -cyclodextrin solution on a series of drugs and other compounds was reported to increase from 12 to 129% when 0.25% (w/v) polyvinylpyrrolidone was added to the aqueous cyclodextrin solution [42]. Water-soluble polymers are also capable of increasing the aqueous solubilities of parent cyclodextrins without decreasing their complexing abilities. Similarly, the addition of hydroxyl acids, such as citric, malic, or tartaric acid, can enhance the solubilizing effect of cyclodextrin via formation of super complexes or salts [44]. In general, the complexation efficacy of

cyclodextrins is low and, therefore, large amounts of cyclodextrins are required for the formation of a complex with a small amount of drug. As a result of toxicological considerations and formulation and production costs, it is important to use as little cyclodextrin as possible in a pharmaceutical preparation.

Complexation efficiency is equal to the intrinsic solubility of a drug multiplied by the stability constant ( $K_{1:1}$ ) of the drug-cyclodextrin complex. Methods that can be used to enhance the complexation efficiencies are listed in Table 2 [45–48].

### The use of cyclodextrins in a solid dosage form

There are three requirements for the formulation of a solid dosage form. First, the dose:solubility ratio must be equal to or less than 250 ml. This simply means that the aqueous solubility of the drug-cyclodextrin complex in the gastrointestinal tract must be sufficient for the active pharmaceutical ingredient to dissolve in the available amount of fluid in the gastrointestinal tract. Second, the upper limit of the drug dose and excipients per tablet is approximately 800 mg. This is relevant because the dosage form contains excipients; for example, 700 mg of a drug:cyclodextrin complex will contain approximately 50–100 mg of the drug. Finally, drug dissolution from the tablet must be sufficiently rapid to prevent dissolution rate-limited drug absorption.

For example, the aqueous solubility of carbamazepine, an anti-convulsant drug, is 0.1 mg/ml and its normal dose is 100–200 mg twice daily. This provides a dose:solubility ratio of 1000–2000 mL, which exceeds the 250 mL guideline. Absorption of carbamazepine from the conventional tablet is slow and erratic. Its bioavailability is approximately 75–80% and peak plasma concentration occurs 4–8 h following the administration of the dose via the immediate release tablet [48]. If this drug is formulated in a tablet dosage form by preparing a cyclodextrin complex, the minimum weight for a 100-mg carbamazepine tablet would be 1500 mg if the complex is formed with 2-hydroxypropyl  $\beta$ -cyclodextrin (HP- $\beta$ CD), and 800 mg if the complex is formed with a natural  $\beta$  cyclodextrin. Although the complex formed with HP- $\beta$ CD is more soluble in water (dose:solubility ratio < 6 ml), the carbamazepine/ $\beta$ -cyclodextrin provides adequate solubility (dose:solubility ratio of 15 ml to prevent dissolution rate-limited absorption).

TABLE 1

#### The effects of the molecular structure and physicochemical properties on the formation of drug-cyclodextrin complexes [48].

Property	Consequences
Size of cyclodextrin cavity	Influence complex formation; for instance, the $\alpha$ -cyclodextrin cavity is too small for naphthalene and only $\gamma$ -cyclodextrin can accommodate anthracene; $\alpha$ -cyclodextrin can be used for small molecules or side chains of larger molecules; $\beta$ -cyclodextrin is useful for complexing molecules containing a phenyl group, which is a group present in many drugs; $\gamma$ -cyclodextrin can be used for complexation of larger molecules, such as macrolide antibiotics
Molar substitution or degree of substitution of cyclodextrin molecule	Chemically modified cyclodextrins of lower molar substitution are frequently better complexation agents than the same derivatives with higher molar substitution
Intrinsic solubility of the drug	The lower the intrinsic solubility of a drug, the greater the relative solubility increase obtained via cyclodextrin complexation; drugs that exhibit intrinsic solubility in the $\mu$ g/ml range generally demonstrate greater increases in solubility compared with drugs with solubility in the mg/ml range
Hydrophilic drugs with low intrinsic aqueous solubility	Zwitterion drugs and other polar drugs with limited aqueous solubility generally have low complexation abilities
Ion pairing	Enhanced complexation is observed when the drug and the cyclodextrin molecules are of opposite charge; when a drug and cyclodextrin carry the identical charge, decreased complexation is observed



TABLE 2

**Methods that can be used to enhance the complexation forming efficiency [46–48].**

Effects	Consequences
<b>Drug ionization</b>	Unionized drugs usually form a more stable complex than their ionic counterparts; however, ionization of a drug increases its apparent intrinsic solubility, resulting in enhanced complexation
<b>Salt formation</b>	It is sometime possible to enhance the apparent intrinsic solubility of a drug via a salt formation
<b>Acid/base ternary complex</b>	Selected organic hydroxyl acids (e.g., citric acid) and organic bases are able to enhance the efficiency of complex formation of ternary drug–cyclodextrin–acid or base complexes
<b>Polymer complexes</b>	Water-soluble polymers form a ternary complex with drug–cyclodextrin complexes, increasing the observed stability constant for the drug–cyclodextrin constant; this increase in the value of the constant improves the complexation efficiency
<b>Solubilities of cyclodextrin aggregates</b>	Organic anions and cations solubilize uncharged drug–cyclodextrin complexes with limited aqueous solubility; this enhances the complexation efficiency during preparation of solid drug–cyclodextrin complex powder
<b>Combination of two or more methods</b>	Frequently, the complexation efficiency can be enhanced further by combining two or more of the methods mentioned here; for example, the drug ionization and polymer methods

**The use of cyclodextrins in a parenteral dosage form**

Cyclodextrins have been used to prepare injectable solutions for poorly soluble drugs. Parenteral (injectable) cyclodextrins are found in several marketed products, including intravenous solutions of etomidate [49], mitomycin [50], voriconazole [50,51], the diagnostic agent <sup>99</sup>Tc teboroxime [50], itraconazole [51], diazepam, and phenytoin sodium [(<https://notendur.hi.is/~thorstlo/injectable.pdf>). Examples of intramuscular solutions include aripiprazole and ziprasidone mesylate [50]. Additionally, cyclodextrins are used in the solubilization of various proteins and peptides [52].

β-Cyclodextrin should not be used in any parenteral formulation [51–53] because it forms a complex with cholesterol that causes nephrotoxicity [53]. α- and methylated β-cyclodextrin have both demonstrated renal toxicity when administered parenterally [50,51]. There is a potential for renal damage if γ-cyclodextrin is used parenterally [51]. By contrast, the soluble cyclodextrins HP-βCD and SBE-βCD are widely used in parenteral products, including intravenous products [51,54], in doses of up to 16 and 14 g per day, respectively [51]. However, these products should not be used for infants under 2 years of age [51]. Finally, one nonclinical study [55] reported that rats given high-dose (200 mg/kg) HP-βCD daily for 4 months developed bone loss.

Intravenously administered HP-βCD and SBE-βCD are quickly removed from the systemic circulation by renal excretion, with elimination half-lives ranging from 20 to 100 min [51]. These soluble cyclodextrins have minimal effect on the pharmacokinetics of drugs [49,56]. It has been shown [49] in a few cases that, when complexed with cyclodextrin, drugs with large cyclodextrin

binding constants along with a low degree of plasma protein binding can exhibit low apparent volumes of distribution and increased renal excretion.

**Concluding remarks**

It is clear from the information presented here that cyclodextrins, because of their unique structure and properties, offer an additional tool to pharmaceutical scientists to overcome some of the formulation and drug delivery challenges for problematic drugs.

Phase-solubility plots of drug solubility against concentration of cyclodextrin enable one to calculate the stability or binding constant ( $K_{1:1}$ ), which, in turn, enables determination of the complexation efficiency of a cyclodextrin. The complexation efficiency values can be used to compare the solubilizing effects of various cyclodextrins and the influence of different excipients on the solubilization. Furthermore, cyclodextrin efficiency is independent of the intrinsic solubility of a drug, although it is influenced by the stability or binding constant. Common pharmaceutical excipients, such as preservatives, water-soluble polymers, and buffer salts, can influence the intrinsic solubility and can induce formation of higher order complexes.

As with the use of any new technology, cyclodextrins have both strengths and weaknesses. Their major strengths are how they interact with drug molecules and their ability to safely deliver the relevant number of intractable drug molecules. The specific nature of their interaction becomes a weakness in that only those drug molecules with the right size, geometry, and intrinsic solubility characteristics benefit from their use.

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