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### **REVIEW ARTICLE**

### Pharmaceutical Applications of Cyclodextrins. 1. Drug Solubilization and Stabilization

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Abstract 
Cyclodextrins are cyclic oligosaccharides which have recently been recognized as useful pharmaceutical excipients. The molecular structure of these glucose derivatives, which approximates a truncated cone or torus, generates a hydrophilic exterior surface and a nonpolar cavity interior. As such, cyclodextrins can interact with appropriately sized molecules to result in the formation of inclusion complexes. These noncovalent complexes offer a variety of physicochemical advantages over the unmanipulated drugs including the possibility for increased water solubility and solution stability. Further, chemical modification to the parent cyclodextrin can result in an increase in the extent of drug complexation and interaction. In this short review, the effects of substitution on various cyclodextrin properties and the forces involved in the drug-cyclodextrin complex formation are discussed. Some general observations are made predicting drug solubilization by cyclodextrins. In addition, methods which are useful in the optimization of complexation efficacy are reviewed. Finally, the stabilizing/destabilizing effects of cyclodextrins on chemically labile drugs are evaluated.

#### Introduction

Although cyclodextrins are frequently regarded as a new group of pharmaceutical excipients, they have been known for over 100 years.<sup>1</sup> The foundations of cyclodextrin chemistry were laid down in the first part of this century<sup>2,3</sup> and the first patent on cyclodextrins and their complexes was registered in 1953.<sup>4</sup> However, until 1970 only small amounts of cyclodextrins could be produced and high production costs prevented their widespread usage in pharmaceutical formulations. Recent biotechnological advancements have resulted in dramatic improvements in cyclodextrin production, which has lowered their production costs. This has led to the availability of highly purified cyclodextrins and cyclodextrin derivatives which are well suited as pharmaceutical excipi-

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ents. These carbohydrates are mainly used to increase the aqueous solubility, stability, and bioavailability of drugs, but they can also, for example, be used to convert liquid drugs into microcrystalline powders, prevent drug-drug or drug-additive interactions, reduce gastrointestinal or ocular irritation, and reduce or eliminate unpleasant taste and smell.

The following is a short review of the effects of cyclodextrins on the solubility and stability of drugs in aqueous solutions with emphasis on the more recent developments. For further information on cyclodextrins and their physicochemical properties the reader is referred to several excellent books and reviews published in recent years.<sup>5-13</sup>

### Structure and Physicochemical Properties

Cyclodextrins are cyclic (α-1,4)-linked oligosaccharides of  $\alpha\text{-}\text{p-glucopyranose}$  containing a relatively hydrophobic central cavity and hydrophilic outer surface. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are toroidal or cone shaped. Based on this architecture, the primary hydroxyl groups are located on the narrow side of the torus while the secondary hydroxyl groups are located on the wider edge (Figure 1). The most common cyclodextrins are  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin, and  $\gamma$ -cyclodextrin, which consist of six, seven, and eight glucopyranose units, respectively. While it is thought that, due to steric factors, cyclodextrins having fewer than six glucopyranose units cannot exist, cyclodextrins containing nine, ten, eleven, twelve, and thirteen glucopyranose units, which are designated  $\delta$ -,  $\epsilon$ -,  $\zeta$ -,  $\eta$ -, and  $\theta$ -cyclodextrin, respectively, have been reported.<sup>14,15</sup> Of these large-ring cyclodextrins only  $\delta$ -cyclodextrin has been well characterized.<sup>16,17</sup> Chemical and physical properties of the four most common cyclodextrins are given in Table 1. The melting points of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrin are between 240 and 265 °C, consistent with their stable crystal lattice structure.18

The parent cyclodextrins, in particular  $\beta\text{-cyclodextrin},$  have limited aqueous solubility, and their complex formation with

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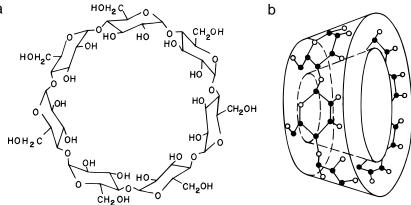


Figure 1–(a) The chemical structure and (b) the toroidal shape of the  $\beta$ -cyclodextrin molecule.

Table 1—Some Characteristics of  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -Cyclodextrin<sup>a</sup>

	α	β	γ	δ
No. of glucopyranose units	6	7	8	9
Molecular weight	972	1135	1297	1459
Central cavity diameter (Å)	4.7–5.3	6.0–6.5	7.5–8.3	10.3–11.2
Water solubility at 25 °C (g/100 mL)	14.5	1.85	23.2	8.19

<sup>a</sup> Modified from refs 5 and 17.

lipophilic drugs, and other compounds with limited aqueous solubility, frequently gives rise to B-type phase-solubility diagrams as defined by Higuchi.<sup>19</sup> That is, addition of these unmodified cyclodextrins to aqueous drug solutions or drug suspensions often results in precipitation of solid drugcyclodextrin complexes. The aqueous solubility of the parent cyclodextrins is much lower than that of comparable acyclic saccharides, and this could partly be due to relatively strong binding of the cyclodextrin molecules in the crystal state (i.e., relatively high crystal lattice energy). In addition,  $\beta$ - and  $\delta$ -cyclodextrin form intramolecular hydrogen bonds between secondary OH groups, which detracts from hydrogen bond formation with surrounding water molecules, resulting in less negative heats of hydration.<sup>5,17</sup> Thus, intramolecular hydrogen bonding can result in relatively unfavorable enthalpies of solution and low aqueous solubilities. Substitution of any of the hydrogen bond forming hydroxyl groups, even by hydrophobic moieties such as methoxy and ethoxy functions, will result in a dramatic increase in water solubility.<sup>5</sup> For example, the aqueous solubility of  $\beta$ -cyclodextrin is only 1.85% (w/v) at room temperature but increases with increasing degree of methylation. The highest solubility is obtained when two-thirds of the hydroxyl groups (i.e., 14 of 21) are methylated, but then falls upon more complete alkylation. That is, the permethylated derivative has a solubility that is lower than that of, e.g., heptakis(2,6-O-dimethyl)- $\beta$ -cyclodextrin but that is still considerably higher than that of unsubstituted  $\beta$ -cyclodextrin.<sup>7</sup> Other common cyclodextrin derivatives are formed by other types of alkylation or hydroxy-alkylation of the hydroxyl groups.<sup>5,20</sup> The main reason for the solubility enhancement in these derivatives is that chemical manipulation frequently transforms the crystalline cyclodextrins into amorphous mixtures of isomeric derivatives. For example, (2-hydroxypropyl)- $\beta$ -cyclodextrin is obtained by treating a base-solubilized solution of  $\beta$ -cyclodextrin with propylene oxide, resulting in an isomeric system that has an aqueous solubility well in excess of 60% (w/v).<sup>21</sup> The number of isomers generated based on random substitution is very large. Statistically, for example, there are about 130 000 possible heptakis(2-O-(hydroxypropyl))- $\beta$ -cyclodextrin derivatives, and given that introduction of the 2-hydroxypropyl function also

introduced an optically active center, the number of total isomers, i.e., geometrical and optical, is even much greater.

In reality, the chemical alkylation of cyclodextrins is not totally random, based on relative reactivities of the hydroxy functions in the molecule. The secondary OH groups on the cyclodextrin molecule (i.e., OH-2 and OH-3 on the glucopyranose units) are somewhat more acidic than the primary OH group (i.e., OH-6). Thus, alkylation of OH-6, the least sterically crowded functionality, is favored in strong basic solutions while alkylation of OH-2, the most acidic of the hydroxyl groups but also the most hindered, is favored in a weak basic solution.<sup>22</sup> Thus, some degree of regioselectivity is possible. Both the molar substitution, i.e., the average number of alkyl or hydroxyalkyl groups that have been reacted with one glucopyranose unit, and the location of the alkyl or hydroxyalkyl groups on the cyclodextrin molecule will affect the physicochemical properties of the derivatives including their ability to form drug complexes.23 However, theoretical studies have shown that the alkylation and hydroxyalkylation of the cyclodextrins should not introduce significant steric hindrance.<sup>24</sup> Some of the commercially available cyclodextrins are listed in Table 2.

### **Cyclodextrin Complexes**

The central cavity of the cyclodextrin molecule is lined with skeletal carbons and ethereal oxygens of the glucose residues. It is therefore lipophilic. The polarity of the cavity has been estimated to be similar to that of aqueous ethanolic solution.<sup>5</sup> It provides a lipophilic microenvironment into which suitably sized drug molecules may enter and be included. No covalent bonds are formed or broken during drug-cyclodextrin complex formation, and in aqueous solutions, the complexes are readily dissociated. Free drug molecules are in equilibrium with the molecules bound within the cyclodextrin cavity. Measurements of stability or equilibrium constants  $(K_c)$  or the dissociation constants ( $K_d$ ) of the drug-cyclodextrin complexes are important since this is an index of changes in physicochemical properties of a compound upon inclusion. Most methods for determining the K values are based on titrating changes in the physicochemical properties of the guest molecule, i.e., the drug molecule, with the cyclodextrin and then analyzing the concentration dependencies. Additive properties that can be titrated in this way to provide information on the K values include<sup>25</sup> aqueous solubility, 19,26-28tion on the A values include- aqueous solubility, chemical reactivity,<sup>10,29,30</sup> molar absorptivity and other optical properties (CD, ORD),<sup>31–34</sup> phase solubility measurements,<sup>35</sup> NMR chemical shifts,<sup>23,36</sup> pH-metric methods,<sup>37</sup> calorimetric titration,<sup>38</sup> freezing point depression,<sup>39</sup> and LC chromato-

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Table 2—Some Currently Available Cyclodextrins Obtained by
Substitution of the OH Groups Located on the Edge of the Cyclodextrin
Ring <sup>a</sup>

Cyclodextrin Derivatives			
α	β	γ	
	Alkylated:		
Methyl	Methyl Ethyl	Methyl	
Butyl	Butyl	Butyl Pentyl	
	Hydroxylalkylated:		
	Hydroxyethyl	Hydroxyethyl	
2-Hydroxypropyl	2-Hydroxypropyl 2-Hydroxybutyl	2-Hydroxypropyl	
	Esterified:		
Acetyl	Acetyl Propionyl Buttand	Acetyl	
Succinyl	Butyryl Succinyl Benzoyl Palmityl Toluenesulfonyl	Succinyl	
	Esterified and Alkylated: Acetyl methyl Acetyl butyl		
	Branched:		
Glucosyl	Glucosyl	Glucosyl	
Maltosyl	Maltosyl	Maltosyl	
	Ionic:		
Carboxymethyl ether	Carboxymethyl ether Carboxymethyl ethyl	Carboxymethyl ether	
Phosphate ester	Phosphate ester 3-Trimethylammonium-2- hydroxypropyl ether Sulfobutyl ether	Phosphate ester	
	Polymerized:		
Simple polymers Carboxymethyl	Simple polymers Carboxymethyl	Simple polymers Carboxymethyl	

<sup>a</sup> Since both the number of substitutes and their location will affect the physicochemical properties of the cyclodextrin molecules, such as their aqueous solubility and complexing abilities, each derivative listed should be regarded as a group of closely related cyclodextrin derivatives.

graphic retention times.<sup>40</sup> While it is possible to use both guest or host changes to generate equilibrium constants, guest properties are usually most easily assessed. Connors has evaluated the population characteristics of cyclodextrin complex stabilities in aqueous solution.<sup>41</sup>

The thermodynamic parameters, i.e., the standard free energy change ( $\Delta G$ ), the standard enthalpy change ( $\Delta H$ ), and the standard entropy change ( $\Delta S$ ), can be obtained from the temperature dependence of the stability constant of the cyclodextrin complex.<sup>42</sup> The thermodynamic parameters for several series of drugs and other compounds have been determined and analyzed.<sup>43-45</sup> The thermodynamic parameters of several other drugs are listed in Table 3. The complex formation is almost always associated with a relatively large negative  $\Delta H$  and a  $\Delta S$  that can be either positive or negative. Also, complex formation is largely independent of the chemical properties of the guest (i.e., drug) molecules. The association of binding constants with substrate polarizability suggests that van der Waals forces are important in complex formation.<sup>50</sup> Hydrophobic interactions are associated with a slightly positive  $\Delta H$  and a large positive  $\Delta S$ ; therefore, classical hydrophobic interactions are entropy driven, suggesting that they are not involved with cyclodextrin complexation since, as indicated, these are enthalpically driven processes. Furthermore, for a series of guests there tends to be a linear relationship between enthalpy and entropy, with increasing

Table 3—Standard Enthalpy Change ( $\Delta {\it H}$ ) and Standard Entropy Change ( $\Delta {\it S}$ ) for Several Drug–Cyclodextrin Complexes

Cyclodextrin <sup>a</sup>	Drug	pН	$\Delta H$ (kJ/mol)	$\Delta S$ (J/(mol K))	Ref
HP-α-CD	Hydrocortisone		-32	-70	49
$\beta$ -CD	Phenytoin, un-ionized	7	-38	-67	46
<i>p</i> -00	Phenytoin, ionized	7	-21	-21	46
β-CD	Naproxen	'	-13	18	31
β-CD	Adenine arabinoside	7	-28	-64	32
β-CD	Adenosine	7	-21	-53	32
β-CD	Ibuprofen (pKa 5.2)	2	-29	15	47
<i>p</i> -00		4	-32	4	47
		5		3	47
		6	-17	34	47
$\beta$ -CD	Diazepam (pKa 3.3)	2	-0.2	70	47
<i>p</i> -00	Diazopani (pria 0.0)	3	-3.3	69	47
		4	-17	22	47
		6	-18	19	47
$\beta$ -CD	Hydrochlorothiazide	5	-40	62	47
ρΟD	$(pK_a 8.8 \text{ and } 10.4)$	8	-39	59	47
	(pria oto ana rotr)	9	-42	70	47
HP- $\beta$ -CD	Acetylsalicylic acid	1	-68	-166	48
HP-β-CD	Acetazolamide	•	-18	-26	49
HP-β-CD	$17\beta$ -Estradiol		-71	-151	49
HP-β-CD	Hydrocortisone		-20	-6	49
HP-β-CD	Methyl acetylsalicylate	1	-55	-127	48
HP-β-CD	Methyl salicylate	1	-63	-144	48
M/DM-β-CD	Acetylsalicylic acid	1	-57	-134	48
M/DM-β-CD	Methyl acetylsalicylate	1	-20	-28	48
HP-γ-CD	Acetylsalicylic acid	1	-28	-56	48
HP-γ-CD	Methyl acetylsalicylate	1	-75	-194	48
HP-γ-CD	Methyl salicylate	1	-73	-176	48

<sup>a</sup> HP-α-CD: (2-hydroxypropyl)-α-cyclodextrin . β-CD: β-cyclodextrin. HP-β-CD: (2-hydroxypropyl)-β-cyclodextrin. M/DM-β-CD: mixture of maltosyl- and dimaltosyl-β-cyclodextrin (3:7). HP- $\gamma$ -CD: (2-hydroxypropyl)- $\gamma$ -cyclodextrin.

enthalpy related to less negative entropy values.<sup>43-45,48</sup> This effect, termed compensation, is often correlated with water acting as a driving force in complex formation. The main driving force for complex formation could, therefore, be the release of enthalpy-rich water from the cyclodextrin cavity.47 The water molecules located inside the cavity cannot satisfy their hydrogen-bonding potentials; therefore, they are of higher enthalpy.<sup>51</sup> The energy of the system is lowered when these enthalpy-rich water molecules are replaced by suitable guest molecules which are less polar than water. Other mechanisms that are thought to be involved with complex formation have been identified in the case of  $\alpha$ -cyclodextrin. In this instance, release of ring strain is thought to be involved with the driving force for compound-cyclodextrin interaction. Hydrated  $\alpha$ -cyclodextrin is associated with an internal hydrogen bond to an included water molecule which perturbs the cyclic structure of the macrocycle. Elimination of the included water and the associated hydrogen bond is related to a significant release of steric strain decreasing the system enthalpy.<sup>52</sup> In addition, "nonclassical hydrophobic effects" have been invoked to explain complexation. These nonclassical hydrophobic effects are a composite force in which the classic hydrophobic effects (characterized by large positive  $\Delta S$ ) and van der Waals effects (characterized by negative  $\Delta H$  and negative  $\Delta S$ ) are operating in the same system. Using adamantanecarboxylates as probes,  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrins were examined.<sup>53</sup> In the case of  $\alpha$ -cyclodextrin, experimental data indicated small changes in  $\Delta H$  and  $\Delta S$  consistent with little interaction between the bulky probe and the small cavity. In the case of  $\beta$ -cyclodextrin, a deep and snug-fitting complex was formed leading to a large negative  $\Delta H$  and a near zero  $\Delta S$ . Finally, complexation with  $\gamma$ -cyclodextrin demonstrated near zero  $\Delta H$  values and large positive  $\Delta S$  values consistent with a classical hydrophobic interaction. Evidently, the cavity size of  $\gamma$ -cyclodextrin was too large to provide for a significant

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Table 4—Effect of Poly(vinylpyrrolidone) Concentration on the Value of the Apparent Stability Constant (K<sub>c</sub>) of Some Drug–(2-Hydroxypropyl)- $\beta$ -cyclodextrin (1:1) Complexes at Room Temperature (20–23 °C)<sup>a</sup>

	$K_{\rm c}~({\rm M}^{-1})$		
PVP (% w/v)	Acetazolamide	Hydrocortisone	17 $\beta$ -Estradiol
0.00 0.10 0.25 0.50	86.2 95.4 97.0 96.2	1010 1450 <i>c</i> 1190	52900 58800 78200 80400

<sup>a</sup> From ref 49. <sup>b</sup> Poly(vinylpyrrolidone). <sup>c</sup> Not determined.

contribution by van der Waals-type interactions. These various explanations show that there is no simple construct to describe the driving force for complexation. Although release of enthalpy-rich water molecules from the cyclodextrin cavity is probably an important driving force for drug-cyclodextrin complex formation, other forces may be important. These forces include van der Waals interactions,<sup>34,54</sup> hydrogen bonding,<sup>55,56</sup> hydrophobic interactions,<sup>34,57</sup> release of ring strain in the cyclodextrin molecule,<sup>56</sup> and changes in solvent-surface tensions.<sup>58</sup>

Methods of preparing drug-cyclodextrin complexes have been reviewed.<sup>25</sup> In the solution phase, the procedure is generally as follows: an excess amount of the drug is added to an aqueous cyclodextrin solution, and the suspension is agitated for up to 1 week at the desired temperature. The suspension is then filtered or centrifuged to form a clear drugcyclodextrin complex solution. For preparation of solid formulations of the drug-cyclodextrin complex, the water is removed from the aqueous drug-cyclodextrin complex solution by evaporation or sublimation. It is sometimes possible to shorten this process by formation of supersaturated solutions through sonication followed by precipitation at the desired temperature. In some cases, the efficiency of complexation is not very high, and therefore, relatively large amounts of cyclodextrins must be used to complex small amounts of drug. To add to this difficulty, vehicle additives, osmolality modifiers, and pH adjustments commonly used in drug formulations, such as sodium chloride, buffer salts, surfactants, preservatives, and organic solvents, very often reduce the efficiency. For example, in aqueous solutions, ethanol and propylene glycol at low concentrations have been shown to reduce the cyclodextrin complexation of testosterone and ibuprofen by acting as competing guest molecules while at higher concentrations they can reduce complexation through a manipulation of solvent dielectric constant.<sup>48,59</sup> Likewise, non-ionic surfactants have been shown to reduce cyclodextrin complexation of diazepam<sup>60</sup> and preservatives to reduce the cyclodextrin complexation of various steroids.<sup>61</sup> On the other hand, additives such as ethanol can promote complex forma-tion in the solid or semisolid state.<sup>62</sup> Un-ionized drugs usually form a more stable cyclodextrin complex than their ionic counterparts; thus, the complexation efficiency of basic drugs can be enhanced by addition of ammonia to the aqueous complexation media.

For example, solubilization of pancratistatin with (hydroxypropyl)-cyclodextrins was optimized upon addition of ammonium hydroxide.<sup>63</sup> Freeze-drying of the solutions removed ammonia, resulting in ammonia-free solid complex preparations which dissolved rapidly to form clear supersaturated pancratistatin solutions. The resulting solutions were stable for a few hours, time sufficient for potential use in parenteral preparations. Finally, enhanced complexation can be obtained by formation of ternary complexes (or cocomplexes) between a drug molecule, a cyclodextrin molecule, and a third component. For instance, addition of a small amount of various

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water-soluble polymers to an aqueous complexation medium, followed by heating of the medium in an autoclave, can significantly increase the apparent stability constant of the drug-cyclodextrin complex (Table 4).<sup>49,64,65</sup> A somewhat similar effect has been obtained through formation of drughydroxy acid-cyclodextrin ternary complexes or salts with basic drugs.<sup>66-68</sup>

### Drug Solubilization

The most common pharmaceutical application of cyclodextrins is to enhance drug solubility in aqueous solutions. Some of the reports generated on this topic have been reviewed,<sup>5-9</sup> and additional data is available from the individual cyclodextrin manufacturers. The solubilizing effects of various cyclodextrins on three different drugs are listed in Table 5. Although prediction of compound solubilization by cyclodextrins continues to be highly empirical, various historical observations permit several general statements. First, the lower the aqueous solubility of the pure drug, the greater the relative solubility enhancement obtained through cyclodextrin complexation. Drugs that possess aqueous solubility in the micromole/liter range generally demonstrate much greater enhancement than drugs possessing solubility in the micromole/liter range or higher. In Table 5, the enhancement factor, i.e., the solubility in the aqueous cyclodextrin solution divided by the solubility in pure water, for paclitaxel, for example, is much larger than the enhancement factors for hydrocortisone and pancratistatin. A similar observation was made when the solubilizing effect of (2-hydroxypropyl)- $\beta$ -cyclodextrin on 53 different drugs was investigated.<sup>9</sup> Second, cyclodextrin derivatives of lower molar substitution are better solubilizers than the same type of derivatives of higher molar substitution. In Table 5, both randomly methylated  $\beta$ - and  $\gamma$ -cyclodextrins with molar substitution 0.6 provide for better solubilization than the same type of randomly methylated cyclodextrins with molar substitution 1.8. With the exception of  $\alpha$ -cyclodextrin, permethylated derivatives (of  $\beta$ - and  $\bar{\gamma}$ -cyclodextrin) possess a lower complexing potential (lower  $K_c$  value) than the parent cyclodextrins.<sup>23</sup> Of the commercially available materials, the methylated cyclodextrins with relatively low molar substitution appear to be the most powerful solubilizers. The chain length of the alkyl group, on the other hand, appears to be of less importance. $^{24,70}$  Third, charged cyclodextrins can be powerful solubilizers, but their solubilizing effect appears to depend on the relative proximity of the charge to the cyclodextrin cavity. The farther away the charge is located, the better the complexing abilities. For example, (2-hydroxy-3-(trimethylammonio)propyl)- $\beta$ - and - $\gamma$ -cyclodextrin possess excellent solubilizing effects while  $\beta$ -cyclodextrin sulfate has a relatively low complexation potential (Table 5). Sulfobutyl ether  $\beta$ -cyclodextrin, where the anion has been moved away from the cavity by a butyl ether spacer group, is an excellent solubilizer.<sup>71</sup> (Carboxymethyl)- $\beta$ -cyclodextrin is another interesting anionic cyclodextrin derivative.72 Compared to neutral cyclodextrins, enhanced complexation is frequently observed when the drug and cyclodextrin molecules have opposite charge but decreased complexation is observed if they carry same type of charge. For example, (2-hydroxy-3-(trimethylammonio)propyl)- $\beta$ -cyclodextrin is an excellent solubilizer for many acidic drugs capable of forming anions.

Another finding is that while many ionizable drugs are able to form cyclodextrin complexes, the stability constant of the complex is much larger for the un-ionized than for the ionized form. For example, both the un-ionized and the cationic (i.e., the protonated) form of chlorpromazine give rise to 1:1 complexes with  $\beta$ -cyclodextrin but the stability constant for the un-ionized form is 4 times larger than for the cationic

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Drug	Cyclodextrin <sup>a</sup>	Concn <sup>b</sup> (% w/v)	Solubility (mM)	Enhancement <sup>c</sup> Factor	Re
Hydrocortisone (MW 362)	None		0.993		49
	Glucosyl-a-CD	10	7.45	7.50	49
	Maltosyl-α-CD	10	11.3	11.4	49
	HP-β-ĆD MS 0.6	10	33.7	33.9	49
	HE-β-CD	10	48.3	48.6	49
	$RM-\beta$ -CD MS 0.6	10	72.2	72.7	27
	$RM-\beta$ -CD MS 1.8	10	50.8	51.2	27
	HTMAP- $\beta$ -CD MS 0.5	10	30.3	30.1	27
	CM- $\beta$ -CD MS 0.6	10	44.6	44.9	27
	Glucosyl-β-CD	10	46.9	47.2	49
	Maltosyl- $\beta$ -CD	10	28.7	28.9	49
	$RM-\gamma$ -CD MS 0.6	10	58.8	55.2	27
	$RM-\gamma$ -CD MS 1.8	10	38.6	38.9	27
Paclitaxel (Taxol, MW 854) <sup>d</sup>	None		$4 \times 10^{-4}$		69
	β-CD	1.5	0.005	13	69
	Dimaltosyl-β-CD	50	0.115	288	69
	HE-β-CD	50	0.914	2285	69
	HP-β-CD	50	0.856	2140	69
	DM-β-CD	50	39.6	99.000	69
	γ-CD	15	0.020	50	69
	ΉΡ-γ-CD	50	0.080	200	69
Pancratistatin (MW 325)	None		0.16		63
	HTMAP- $\beta$ -CD MS 1.4	10	0.86	5.4	63
	S- $\beta$ -CD Na-salt MS 2.3	10	0.28	1.8	63
	$CM-\beta$ -CD Na-salt MS 0.6	10	0.83	5.2	63
	HP- $\beta$ -CD MS 0.5	10	1.0	6.3	63
	Maltosyl- $\beta$ -CD MS 0.14	10	0.95	5.9	63
	$DM-\beta-CD$ MS 2.0	10	1.2	7.5	63
	HE-β-CD	10	0.83	5.2	63
	γ-CD	10	0.80	5.0	63
	HTMAP-γ-CD MS 0.3	10	0.49	3.1	63
	HP-γ-CD MS 0.7	10	0.83	5.2	63
	TM-γ-CD MS 3.0	10	0.49	3.1	63

#### Table 5—Solubility of Drugs in Different Cyclodextrin Solutions at Room Temperature

<sup>a</sup> β-CD: β-cyclodextrin. HP-β-CD: (2-hydroxypropyl)-β-cyclodextrin. HE-β-CD: (hydroxyethyl)-β-cyclodextrin. RM-β-CD: randomly methylated β-cyclodextrin. HTMAP-β-CD: (2-hydroxy-3-(trimethylammonio)propyl)-β-cyclodextrin. CM-β-CD: (carboxymethyl)-β-cyclodextrin. Glucosyl-β-CD: glucosyl-β-CD: glucosyl-β-CD: glucosyl-β-CD: andomly methylated β-cyclodextrin. Maltosyl-β-CD: maltosyl-β-cyclodextrin. DM-β-CD: 2,6-O-dimethyl-β-cyclodextrin. S-β-CD: β-cyclodextrin sulfate. γ-CD: γ-cyclodextrin. RM-γ-CD: randomly methylated γ-cyclodextrin. HT-γ-CD: (2-hydroxy-3-(trimethylammonio)propyl)-γ-cyclodextrin. TM-γ-CD: trimethyl γ-cyclodextrin. MS: molar substitution (i.e., the average number of OH groups on each glucose repeat unit that have been substituted). Na salt: sodium salt. <sup>b</sup> Concentration of the aqueous cyclodextrin solution. <sup>c</sup>The solubility in the aqueous cyclodextrin solution divided by the solubility in water. <sup>d</sup> pH 7.4

form.<sup>37</sup> The  $K_c$  for the phenytoin- $\beta$ -cyclodextrin complex is over 3 times larger for the un-ionized form than for the anionic form.<sup>46</sup> However, it is frequently possible to enhance cyclodextrin solubilization of ionizable drugs by appropriate pH adjustments. Thus, the solubilizing effects of both (2-hydroxypropyl)- $\beta$ -cyclodextrin and dimethyl- $\beta$ -cyclodextrin on dihydroergotamine mesylate have been found to increase with decreasing pH (i.e., formation of the cationic form). Both the saturation solubility and the slopes of the phase-solubility diagrams increase with decreasing pH.<sup>73</sup> Similar results have been reported for the complexation of phenytoin with  $\beta$ -cyclodextrin<sup>46</sup> and for the complexation of indomethacin,<sup>74</sup> prazepam, acetazolamide, and sulfamethoxazole<sup>75</sup> with (2hydroxypropyl)- $\beta$ -cyclodextrin.

As mentioned before, it is also possible to enhance complexation and, thus, the solubilizing effect of cyclodextrins by addition of polymers or hydroxy acids to the cyclodextrin solutions. It has been shown that polymers, such as water-soluble cellulose derivatives and other rheological agents, can form complexes with cyclodextrins and that such complexes possess physicochemical properties different from those of individual cyclodextrin molecules.<sup>49,76</sup> In aqueous solutions water-soluble polymers increase the solubilizing effect of cyclodextrins on various hydrophobic drugs by increasing the apparent stability constants of the drug–cyclodextrin complexes. For example, the solubilizing effect of 10% (w/v) (2-hydroxypropyl)- $\beta$ -cyclodextrin solution on a series of drugs and other compounds was increased from 12 to 129% when 0.25%

(w/v) poly(vinylpyrrolidone) was added to the aqueous cyclodextrin solution.<sup>49</sup> Water-soluble polymers are also capable of increasing aqueous solubilities of the parent cyclodextrins without decreasing their complexing abilities, thus making them more feasible as pharmaceutical excipients. Likewise, addition of hydroxy acids, such as citric, malic, or tartaric acid, can enhance the solubilizing effect of cyclodextrins through formation of super complexes or salts.<sup>67</sup> It is frequently possible to obtain even larger solubilization enhancement by applying several methods simultaneously. For instance, prazepam is a benzodiazepine with a  $pK_a$  of about 3. (2-Hydroxypropyl)- $\beta$ -cyclodextrin has a solubilizing effect on both the un-ionized and the ionized form of the drug, and as expected, hydroxypropyl methylcellulose has a synergistic effect on the solubilization. However, the synergistic effect was more pronounced for the ionized form (Figure 2).75 Finally, pharmaceutical formulations should contain as small an amount of cyclodextrin as possible since excess cyclodextrin can reduce, e.g., drug bioavailability and preservative efficacy. Drug solubility should be determined in the final formulation and under normal production conditions to determine if too much, or too little, cyclodextrin is being used.

### Effect on Drug Stability

The effects of cyclodextrins on the chemical stability of drugs is another useful property of these excipients and has been extensively examined in the literature.<sup>10</sup> Cyclodextrin

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