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The effects of organic salts on the cyclodextrin solubilization of drugs

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Abstract

Previous studies have indicated that conventional description of drug/cyclodextrin complexes in aqueous solutions as inclusion complexes are not as unambiguous as one might think. It has been shown that in some cases drug/cyclodextrin complexes consist of a mixture of inclusion and non-inclusion complexes. Furthermore it has been shown that drug/cyclodextrin complexes can form aggregates containing up to couple of hundred complexes. In this present study β-cyclodextrin (βCD) solubilization of hydrocortisone is enhanced by including short-chain anionic and cationic species in the aqueous complexation medium. For example, maximum hydrocortisone solubility in pure aqueous βCD solutions or suspensions is 2.2 mg/ml. Addition of 1% (w/v) sodium acetate to the complexation medium increases this value to 7.1 mg/ml (or over 220%). Further addition of 0.25% (w/v) hydroxypropyl methylcellulose to the medium increased the hydrocortisone solubility to over 9 mg/ml. Similar results were obtained when sodium salicylate or benzalkonium chloride were added to the complexation medium. It is also shown that cyclodextrin complexes of lipophilic compounds that have good affinity for the cyclodextrin cavity can be used to enhance cyclodextrin solubilization of drugs that have low affinity for the cavity. All these observations can be explained by formation of drug/cyclodextrin complex aggregates.

Keywords: Cyclodextrin; Solubility; Aggregate; Self-association; Complexation

1. Introduction

Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. In aqueous solutions cyclodextrins are able to solubilize lipophilic water-insoluble drugs by taking some lipophilic moiety of the drug molecule into the central cavity (Loftsson and Brewster, 1996). Such complexes are called inclusion complexes. However, non-cyclic oligosaccharides are also known to form water-soluble complexes with lipophilic water-insoluble compounds (Komiyama et al., 1986; Rácz, 1989; Aoyama et al., 1992; Kano et al., 1995; Loftsson et al., 1996; Tomasik and Schilling, 1998; Gabelica et al., 2002). Thus, cyclodextrin complexes do not have to be inclusion complexes. For example, Gabelica et al. have shown that α-cyclodextrin (αCD) forms both inclusion and non-inclusion complexes with dicarboxylic acids and that the two types of complexes coexist in aqueous solutions (Gabelica et al., 2002). By comparing αCD complexes with those of maltohexaose, which is a linear analog of αCD, the

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authors were able to show that the 1:1 dicarboxylic acid/αCD complexes are mainly inclusion complexes while 2:1 complexes, formed by additional complex formation between a given acid and an 1:1 complex, are non-inclusion complexes. Even the 1:1 complexes consisted of a mixture of inclusion and non-inclusion complexes.

Cyclodextrins and cyclodextrin complexes are known to self-associate to form aggregates or micelle-like structures consisting of two to several hundred cyclodextrin molecules and/or cyclodextrin complexes (Suzuki et al., 1994). For example, spontaneous opalescence of aqueous γ-cyclodextrin (γCD) solutions is due to self-aggregation of γCD (Szente et al., 1998). In aqueous solutions 2,5-diphenyloxazole/γCD complexes form aggregates consisting of 60–500 2,5-diphenyloxazole/γCD complex units (Agbaria and Gill, 1988; Agnew et al., 1995). The aggregates dissociate upon heating increasing the relative concentration of complex monomers. Likewise β-carotene complexes with β-cyclodextrin (βCD) or γCD form aggregates in aqueous solutions (Mele et al., 1998). Water-soluble polymers are used to stabilize all kinds of aggregates and micelle-like structures as well as drug/cyclodextrin complexes (Malmsten, 2002; Yamakawa and Nishimura, 2003). The polymers are also known to increase the solubilizing effects of surfactants (Attwood and Florence, 1983). Previously we have shown that water-soluble polymers do enhance the solubilizing effect of cyclodextrins and the aqueous solubility of βCD (Loftsson, 1998; Loftsson and Friðriksdóttir, 1998). We have also shown that drug/cyclodextrin complexes can self-associate to form water-soluble aggregates (or microaggregates) of several drug/cyclodextrin complex units and that these aggregates can solubilize lipophilic water-insoluble drugs through non-inclusion complexation (Loftsson et al., 2002a,b). Thus, the conventional description of drug/cyclodextrin complexes in aqueous solutions is not as unambiguous as one might think.

The purpose of the present study was to determine the effects of anionic and cationic species, such as sodium acetate and benzalkonium chloride, on the solubilizing effects of the natural βCD. Furthermore the effect of one lipophilic water-insoluble compound on the cyclodextrin solubilization of a second compound was investigated.

2. Materials and methods

2.1. Materials

Alprazolam was kindly donated by Delta (Iceland). Diflunisal and hydrocortisone were purchased from ICN Pharmaceuticals (USA), sodium acetate and hydroxypropyl methylcellulose 4000 (HPMC) from Norsk Medisinaldepot (Norway), sodium salicylate from Merck (Germany), benzalkonium chloride and cholesterol from Sigma Chemical Co. (USA), and Cyclosporin A from Poli Industria Chimica (Italy). 2-Hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) 0.64 was purchased from Janssen Biotech (Belgium) and βCD from Wacker Chemie (Germany). All other chemicals and solvents used in this study were commercialy available products of analytical or of special reagent grade. The sodium salt of diflunisal was prepared by a previously described method (Loftsson et al., 2002a). The moisture content of the cyclodextrins was periodically determined and corrected for (Scaltec SMO 01 Moisture Analyzer, Germany).

2.2. Solubility studies

The solubility studies are listed in Table 1. The solubility of alprazolam, hydrocortisone, or cyclosporin A was determined in water, 10% (w/v) HPβCD solution or 0–8% (w/v) solution/suspension of βCD in water or aqueous 0.25% (w/v) HPMC solution. Also aqueous HPβCD solution, which had been previously saturated with the sodium salt of diflunisal or cholesterol, was saturated with alprazolam or cyclosporin A, respectively (Loftsson et al., 2002a). An excess of the drug was added to the aqueous cyclodextrin solution/suspension and the drug suspension formed heated in a sealed vial in an autoclave (121 °C for 20 min) or in case of cyclosporin A in an ultrasonic bath (70 °C for 60 min). The suspension was heated to promote drug, and in some cases cyclodextrin, saturation of the aqueous complexation medium. After equilibration at room temperature (22–23 °C) over night the vials were opened, small amount of solid drug was added to each vial and the aqueous drug suspensions were allowed to equilibrate at room temperature under constant agitation for additional 6 days. This was done to promote drug precipitation. Preliminary

Table 1
The solubility studies

Drug	Intrinsic solubility[a] (mg/ml)	Cyclodextrin concentration (% w/v)	HPMC[b] (% w/v)	Salt[c] (% w/v)	Medium
Alprazolam	0.1	No cyclodextrin	0.00	No salt	Pure water
		10% HPβCD	0.00	No salt	Pure water
		10% HPβCD	0.00	No salt	The aqueous cyclodextrin solution was first saturated with sodium diflunisal and then with alprazolam
Cholesterol	0.6	10% HPβCD	0.00	No salt	Pure water
Cyclosporin A		10% HPβCD	0.00	No salt	Pure water
		10% HPβCD	0.00	No salt	The aqueous cyclodextrin solution was first saturated with cholesterol and then with cyclosporin A
Hydrocortisone	0.4	No cyclodextrin	0.00	0.0–4.3% sodium salicylate	Pure water
		No cyclodextrin	0.25	0.0–4.3% sodium salicylate	Pure water
		4% βCD	0.00	0.0–4.3% sodium salicylate	Pure water
		4% βCD	0.25	0.0–4.3% sodium salicylate	Pure water
		4% βCD	0.00	0.0–4.0% sodium acetate	Pure water
		0.0–8.0% βCD	0.00	No salt	Pure water
		0.0–7.0% βCD	0.25	No salt	Pure water
		0.0–5.0% βCD	0.00	1.0% sodium acetate	Pure water
		0.0–5.0% βCD	0.25	1.0% sodium acetate	Pure water
		No cyclodextrin	0.00	No salt	Pure water
		No cyclodextrin	0.25	No salt	Pure water
		No cyclodextrin	0.00	1.0% benzalkonium chloride	Pure water
		No cyclodextrin	0.25	1.0% benzalkonium chloride	Pure water
		1% βCD	0.00	No salt	Pure water
		1% βCD	0.25	No salt	Pure water
		1% βCD	0.00	1.0% benzalkonium chloride	Pure water
		1% βCD	0.25	1.0% benzalkonium chloride	Pure water
Sodium diflunisal		10% HPβCD	0.00	No salt	Pure water

[a] The solubility of the drug in pure water at ambient temperature.
[b] HPMC: hydoxypropyl methylcellulose.
[c] The salt added to the aqueous medium before saturation with the drug.

experiments showed that 6 days are more than enough time to reach solubility equilibrium. The chemical stability of the drugs was also monitored during heating and equilibration period and in all cases less that 1% degradation was observed. After equilibration the suspensions were filtered through 0.45 μm nylon membrane filters and the filtrate analyzed by HPLC.

Cholesterol is a very hydrophobic compound with a low solubility in water and therefore it is difficult to saturate aqueous solutions with cholesterol. Thus, in the case of cholesterol the solubility was determined by dissolving cholesterol in methylene chloride and then evaporating this solution under flow of nitrogen in a cylindrical vial. This left a very thin layer of cholesterol on the inner surface of the vial. Aqueous cyclodextrin solution was then added to the vial and the tightly sealed vials heated in an autoclave as previously described.

2.3. Quantitative determinations

Quantitative determinations were performed in a high performance liquid chromatographic (HPLC) system from Merck-Hitachi (Germany) consisting of

L 4250 UV-Vis detector, L 6200A Intelligent pump, AS-2000A Autosampler, L 2500 Cromato-Integrator and Phenomex Luna 5 μ C18 reversed phase column (150 mm × 4.6 mm). The composition of the mobile phases and wavelengths, respectively, used for quantitative determination of the various compounds were as follows. Cholesterol: methanol, acetonitrile, isopropyl alcohol, and tetrahydrofuran (50:25:25:0.1), 203 nm. Diflunisal: acetonitrile, acetic acid, and water (65:2:33), 254 nm. Alprazolam: methanol and water (70:30), 254 nm. Hydrocortisone: acetonitrile, tetrahydrofuran, and water (35:1:64), 254 nm. Cyclosporin A: methanol and water (82:18), 215 nm.

3. Results and discussion

The solubility of sodium diflunisal and alprazolam was determined in water or aqueous 10% (w/v) HPβCD solution. Also, aqueous 10% (w/v) HPβCD solution, which previously had been saturated with the sodium diflunisal, was saturated with alprazolam. The pK_a value of alprazolam (a base) and diflunisal (a carboxylic acid) are 2.4 and 3.0, respectively (Cho et al., 1983; Zornoza et al., 1999). The pH of the unbuffered solutions was monitored and determined to be 8.36 ± 0.09 (mean ± S.D.). The solubility of alprazolam in 10% aqueous HPβCD solution was determined to be 0.59 mg/ml, but 1.23 mg/ml in 10% (w/v) HPβCD solution that had been previously saturated with sodium diflunisal. The solubility of alprazolam in water was determined to be about 0.1 mg/ml when no diflunisal was present and about 0.3 mg/ml in water saturated with sodium diflunisal. The saturation concentration of sodium diflunisal in 10% (w/v) HPβCD solution was unaffected by the presence of alprazolam, it was about 47 mg/ml in both cases, determined as the free acid. If the two compounds would compete for a space in the HPβCD central cavity then less solubilization of alprazolam in 10% HPβCD solution would be expected when both drugs are present in a mixture compared to the alprazolam solubility when no sodium diflunisal is present. Here, 108% increase in the alprazolam solubility is observed.

The solubility of cyclosporin A was determined in pure aqueous unbuffered solution containing 10% (w/v) HPβCD as well as in aqueous 10% (w/v) HPβCD solution, which had been previously saturated with cholesterol. The concentration of dissolved cyclosporin A in the solution that had not been saturated with cholesterol was determined to be 0.09 mg/ml but 0.12 mg/ml in the solution that had been saturated with cholesterol. Thus, addition of cholesterol increased the HPβCD solubilization of cyclosporin A. The concentration of cholesterol was not affected by cyclosporin A, remaining at about 0.6 mg/ml. The results obtained for alprazolam and cyclosporin A can indicate self-association of the diflunisal/HPβCD and cholesterol/HPβCD complexes, respectively, to form water-soluble microaggregates. These aggregates can then solubilize the drugs through non-inclusion complexation (Loftsson et al., 2002a).

The solubility of hydrocortisone was determined in aqueous unbuffered solution containing either pure water or 4% (w/v) βCD in a suspension, with and without the presence of 0.25% (w/v) HPMC, and sodium salicylate concentrations from 0 to 4.3% (w/v). The pH of the unbuffered solutions was about 7.4. The results in Table 2 show that both sodium salicylate and HPMC have solubilizing effect on hydrocortisone. However, in the presence of βCD, both sodium salicylate and HPMC give a synergistic effect. For example, if additive effects would be observed, then the solubility of hydrocortisone in 4% (w/v) βCD suspension containing 4.3% (w/v) of sodium salicylate should be 2.1 mg/ml (contribution from βCD and the intrinsic solubility) + 1.1 mg/ml (contribution from the salicylate; 1.5–0.4 mg/ml) or 3.2 mg/ml. The observed value is 7.2 mg/ml or 125% higher than the expected value. Likewise when HPMC is present one would expect hydrocortisone solubility of 3.4 mg/ml + 5.4 mg/ml − 1.1 mg/ml or 7.7 mg/ml. The observed value is 17 mg/ml or 121% higher than the expected additive value, and much higher than can be expected by formation of 1:1 drug/cyclodextrin complex. Previously, it has been shown that one molecule of sodium salicylate forms an inclusion complex with one molecule of βCD and that the value of the stability constant of the complex ($K_{1:1}$) is 51 M^{-1} (Loftsson and Friðriksdóttir, 1998). Thus, due to competition between the hydrocortisone and salicylate molecules for a space in the cyclodextrin cavity addition of sodium salicylate to the aqueous complexation media should result in reduced complexation and cyclodextrin solubilization of hydrocortisone. However, enhanced solubilization

Table 2
The effect of sodium salicylate and 0.25% (w/v) HPMC on the solubilization of hydrocortisone in aqueous βCD suspensions at ambient temperature and pH 7.4

Sodium salicylate concentration	Solubility of hydrocortisone			
	Pure water		4% (w/v) (35 mM) βCD suspension	
	No polymer	HPMC	No polymer	HPMC
0.0% (w/v) (0 mM)	0.4 mg/ml (1.1 mM)	1.1 mg/ml (3.0 mM)	2.1 mg/ml (5.9 mM)	3.4 mg/ml (9.3 mM)
0.4% (w/v) (32 mM)	n.d.[a]	n.d.	2.3 mg/ml (6.2 mM)	3.7 mg/ml (10 mM)
0.9% (w/v) (63 mM)	0.7 mg/ml (1.8 mM)	1.6 mg/ml (4.4 mM)	2.9 mg/ml (8.1 mM)	4.9 mg/ml (13 mM)
2.6% (w/v) (187 mM)	1.2 mg/ml (3.4 mM)	3.1 mg/ml (8.5 mM)	4.5 mg/ml (12 mM)	6.8 mg/ml (19 mM)
4.3% (w/v) (312 mM)	1.5 mg/ml (4.0 mM)	5.4 mg/ml (15 mM)	7.2 mg/ml (20 mM)	17 mg/ml (46 mM)

[a] Not determined.

is observed in the presence of sodium salicylate. This observation cannot be explained by simple inclusion complex formation.

The solubility of hydrocortisone was determined in an aqueous 4% (w/v) βCD suspension containing from 0 to 4% (w/v) sodium acetate at pH 6.9 (Fig. 1). The results show that, like in the case of sodium salicylate, sodium acetate can enhance the βCD solubilization of hydrocortisone. The decreased hydrocortisone solubility observed at 4% (w/v) sodium acetate is most probably due to medium effects such as increased ionic strength with increasing sodium acetate concentration.

The solubility of hydrocortisone was also determined in aqueous unbuffered 0–8% (w/v) βCD solutions or suspensions containing either no or 1% (w/v) sodium acetate, with or without the presence of 0.25% (w/v) HPMC. The pH of the unbuffered solutions was about 6.9. Both βCD and the hydrocortisone/βCD complex have a limited solubility in water (Fig. 2). Addition of HPMC increases the solubility. Hydrocortisone, βCD, and HPMC are all uncharged compounds that do not contain moieties capable of ionization (i.e. proton acceptors or donators) at pH ranging from 1 to 11. Thus, addition of sodium acetate does not result in

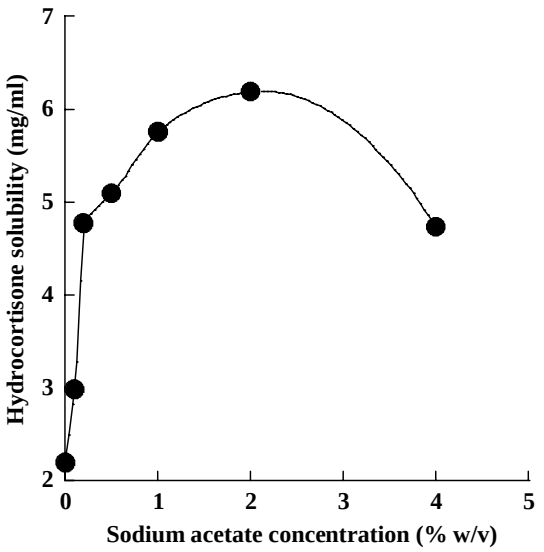

Fig. 1. The effect of the sodium acetate concentration on the solubility of hydrocortisone in aqueous 4% (w/v) βCD suspension at ambient temperature and pH 6.9.

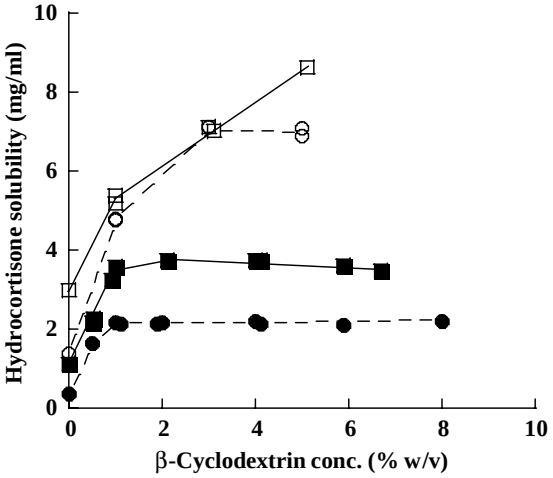

Fig. 2. Phase–solubility diagrams of hydrocortisone in aqueous βCD solutions or suspensions at pH 6.9 and ambient temperature. Pure water (●), aqueous 0.25% (w/v) hydroxypropyl methylcellulose solution (HPMC) (■), aqueous 1% (w/v) sodium acetate solution (○), and aqueous 1% (w/v) sodium acetate solution containing 0.25% (w/v) HPMC (□).

Table 3
The solubility of hydrocortisone in the aqueous complexation medium when no βCD is present in the medium and when 1% (w/v) (8.8 mM) βCD is present and no or 1% (w/v) (about 25 mM) benzalkonium chloride, with and without the presence of 0.25% (w/v) HPMC, at ambient temperature and neutral pH

Concentration of βCD (% w/v)	Solubility of hydrocortisone			
	No benzalkonium chloride		1.0% benzalkonium chloride	
	No polymer	HPMC	No polymer	HPMC
0	0.4 mg/ml (1.1 mM)	1.1 mg/ml (3.0 mM)	2.6 mg/ml (7.2 mM)	3.1 mg/ml (8.6 mM)
1.0 (8.8 mM)	2.2 mg/ml (6.1 mM)	3.6 mg/ml (9.9 mM)	2.5 mg/ml (6.9 mM)	6.0 mg/ml (17 mM)

ionization of these compounds. However, addition of relatively small amounts of sodium acetate resulted in dramatic increase in the βCD solubilization of the drugs. The aqueous solubility of hydrocortisone is 0.4 mg/ml in pure water. The maximum obtainable hydrocortisone solubility in pure aqueous βCD solutions or suspensions is 2.2 mg/ml. Including 0.25% HPMC increases this value to 3.6 mg/ml, but addition of 1% sodium acetate to the complexation medium increases the hydrocortisone solubility to 7.1 mg/ml. This is over 220% increase in the hydrocortisone solubility over the basic value of 2.2 mg/ml obtained with pure βCD. Even further solubilization is observed when both acetate and HPMC are present in the aqueous complexation medium. The solubilization levels off at approximately 3% βCD concentration when acetate is present, but at 1% when no acetate is present (Fig. 2). This shows that the enhanced solubilization is partly due to increased βCD solubility and the solubility of the hydrocortisone/βCD complex. The acetate ions solubilize the hydrocortisone/βCD microaggregates formed in the aqueous solutions. Addition of HPMC to the complexation media enhances this solubilization even further.

The solubility of hydrocortisone was determined in aqueous unbuffered 0 or 1% (w/v) βCD solutions or suspensions containing either no or 1% (w/v) benzalkonium chloride, with and without the presence of 0.25% (w/v) HPMC. Table 3 shows that when no polymer is present, adding 1% (w/v) benzalkonium chloride to aqueous 1% (w/v) βCD only results in slight enhancement the solubilization (increasing from 2.2 to 2.5 mg/ml or 14%). The solubilization enhancement is small, possibly due to competing effects between benzalkonium and hydrocortisone for a space in the cyclodextrin cavity. In fact, in absence of HPMC adding 1% (w/v) βCD to the 1% (w/v) benzalkonium chloride solution reduces somewhat the solubility of hydrocortisone (from 2.6 to 2.5 mg/ml, see Table 3). It has been shown that cyclodextrins form complexes with benzalkonium chloride and that the complexation decreases its antibacterial effect (Loftsson et al., 1992; Dechandt et al., 1994). Likewise, when no βCD is present addition of HPMC to the benzalkonium chloride solution only results in relatively small increase in the hydrocortisone solubility (increasing from 2.6 to 3.1 mg/ml). However, when the polymer is present, including benzalkonium chloride increases the drug solubility from 3.6 to 6.0 mg/ml, or almost 70%. Interestingly, the hydrocortisone/βCD molar ratio in the solution containing βCD, HPMC, and benzalkonium chloride is about two, which shows that the solubilization mechanism involves more than just simple 1:1 hydrocortisone/βCD complex formation.

The solubility studies presented show that, in general, simple drug/cyclodextrin inclusion complex formation cannot fully explain the solubilizing effects of cyclodextrins. Non-inclusion complex formation, such as formation of water-soluble microaggregates of drug and drug/cyclodextrin complexes, can contribute to the overall solubility. In such aqueous systems water-soluble polymers, such as HPMC, and anionic and cationic molecules appear to enhance the contribution of the non-inclusion complexation to the overall drug solubility, as well as solubilize and stabilize drug/βCD complexes.

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