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The effect of water-soluble polymers on the aqueous solubility and complexing abilities of β-cyclodextrin

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Abstract

The purpose of this study was to investigate the effects of both water-soluble polymers and various drugs on the solubility of β-cyclodextrin (βCD) in aqueous solution. The solubility of βCD in water was determined to be 18.6 mg/ml, but addition of 0.25–1.00% (w/v) of polyvinylpyrrolidone, and heating in an autoclave (120–140°C for 20–40 min) increased the solubility to 21 mg/ml. The aqueous solubility of βCD also increased upon drug–βCD complex formation. Both lipophilic and hydrophilic drugs increased the solubility of βCD in water. For example, the solubility of βCD in a saturated aqueous solution of carbamazepine was determined to be 28.4 mg/ml but 53.3 mg/ml when 0.25% (w/v) hydroxypropyl methylcellulose (HPMC) was present in the solutions. The total solubility of βCD in such aqueous systems appeared to be the sum of the intrinsic solubility of βCD and the solubility of the various βCD complexes, i.e. the drug–βCD complexes and the complexes of βCD and drug–βCD complexes with the water-soluble polymers. Not only did the polymer solubilize βCD and its complexes, but was also able to enhance drug–βCD complex formation.

Keywords: Cyclodextrin; Complexation; Drug delivery; Drug formulations; Polymers; Solubility

1. Introduction

Cyclodextrins (CDs) are a group of structurally related cyclic oligosaccharides that are formed by enzymatic cyclization of starch. The three most common naturally occurring CDs are α-cyclodextrin (αCD), β-cyclodextrin (βCD) and γ-cyclodextrin (γCD) consisting of six, seven and eight (α-1,4)-linked α-D-glucopyranose units, respectively. The CD molecules are cone-shaped with a somewhat hydrophobic central cavity and hydrophilic outer surface. They are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or more frequently some hydrophobic part of it, into the cavity. The complexation will affect many of the physicochemical properties of the drugs without

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affecting their intrinsic lipophilicity or pharmacological properties (Frömming and Szejtli, 1994; Duchêne and Wouessidjewe, 1996; Loftsson and Brewster, 1996; Rajewski and Stella, 1996; Irie and Uekama, 1997).

The natural CDs, in particular βCD, have limited solubility in water and their complexes with lipophilic water-insoluble drugs often result in precipitation of solid drug–CD complexes (Szejtli, 1988). Therefore various CD derivatives possessing very high solubility in water have been synthesized. These derivatives include the βCD derivatives which presently are the most common CDs used in experimental drug formulations, i.e. 2-hydroxypropyl-β-cyclodextrin (HPβCD), randomly methylated β-cyclodextrin, sulfobutylether-β-cyclodextrin and maltosyl-β-cyclodextrin. Little attention has been focused on the usage of third component, such as water-soluble polymers, to enhance the aqueous solubility of βCD and its complexes. The purpose of this study was to investigate the effect of water-soluble polymers on the aqueous solubility and complexing abilities of βCD.

Polymers are known to interact with CDs, although the exact nature of the polymer–CD interactions is still not known. Hladon and Cwiertinia (1994) have shown that βCD interacts with a number of water-soluble cellulose derivatives. Other investigators have shown that at low concentrations, polymers increase the complexing abilities of CDs (Loftsson et al., 1994; Ganzerli et al., 1996) and that the polymers enhance the availability of drugs in aqueous CD solutions (Sigurðardóttir and Loftsson, 1995). This indicates that these interactions between water-soluble polymers and CDs are different from those observed in, for example, polyrotaxanes where many CD molecules are threaded onto a linear polymer (see for example Fujita et al., 1996). Such inclusion complex formation between CDs and polymers will reduce the abilities of the CDs to form complexes with other molecules. Polyrotaxanes are prepared at room temperature by gently stirring an aqueous solution containing both the polymer and the CD. Enhancements of the complexation efficacy and increased drug availability in CD solutions are usually obtained by heating aqueous solutions containing polymer, CD and drug in an autoclave (120–140°C for 20–40 min). Simply adding the polymers to the solutions without heating does not enhance the complexation or the drug availability (Loftsson and Sigurðardóttir, 1996).

2. Materials and methods

2.1. Materials

β-Cyclodextrin (βCD) was obtained from Celedex (Japan), 2-hydroxypropyl-β-cyclodextrin MS 0.6 (HPβCD) and γ-cyclodextrin (γCD) from Wacker (Germany), carboxymethylcellulose sodium salt of medium viscosity (CMC) from Norsk Medisinaldepot (Norway), hydroxypropyl methylcellulose 4000 (HPMC) and polyvinylpyrrolidone of molecular weight 40 000 (PVP) from Mecobenzon (Denmark), sodium salicylate and sulfamethoxazole from Icelandic Pharmaceuticals (Iceland), acetazolamide from Agar (Italy), carbamazepine from Aldrich (USA), and alprazolam, dexamethasone, econazole, ethoxyzolamide and methazolamide from Sigma (USA). All other chemicals used were of pharmaceutical or special analytical grade.

2.2. Quantitative determination

The quantitative determination of βCD was performed on a high-performance liquid chromatographic (HPLC) system composed of a Waters Model 501 pump operated at 1.0 ml/min flow rate, a Rheodyne 7125 injector and PAD-2 pulsed amperometric detector from Dionex (USA) with a gold working electrode and a silver–silver chloride reference electrode. The column was a CarboPac PA1 Analytical Column (4×250 mm) from Dionex. The eluent consisted of 150 mM sodium hydroxide and 300 mM sodium acetate in water. Duration times for detection were: $E_1 = 100$ mV ($t_1 = 120$ ms), $E_2 = 600$ mV ($t_2 = 120$ ms) and $E_3 = -800$ mV ($t_3 = 300$ ms). The PAD response time was set at 1 s. Quantitative determinations of the drugs were performed on a reversed-phase HPLC component system consisting of a Milton

Table 1
Conditions of quantitative drug determination by HPLC

Drug	Mobile phase	Flow rate (ml/min)	Wavelength (nm)	Retention time (min)
Acetazolamide	Acetonitrile, acetic acid, water (10:2:88) containing 0.015% 1-octanesulfonate	1.5	263	4.0
Carbamazepine	Acetonitrile, tetrahydrofuran, water (35:1:64)	2.0	278	2.8
Hydrocortisone	Acetonitrile, tetrahydrofuran, water (30:1:69)	1.5	254	2.6
Econazole	Methanol, 0.01 M aqueous potassium phosphate solution (pH 4.5) (90:10)	1.5	226	2.0
Methazolamide	Acetonitrile, acetic acid, water (12:2:86) containing 0.015% (w/v) 1-octanesulfonate	2.0	254	2.5

Roy ConstaMetric 3200 solvent delivery system (USA), a Spectro Monitor 3200 UV/Vis variable-wavelength detector, AS-2000A Hitachi Merck 3200 autosampler (Japan-Germany), and a Beckman Ultraspere ODS 5 μ, 4.6 × 150 mm column (USA). For other HPLC conditions, see Table 1.

2.3. Evaluation of βCD stability during autoclaving

Stability of the βCD was determined by heating pure unbuffered aqueous βCD (0.5% w/v) solutions, at a pH of about 5, to 120°C in an autoclave (M7 Speed Clave from Midmark, USA) for 0 to 80 min (0–4 heating cycles). The solution was heated in closed vials and one vial removed from the autoclave after each heating cycle. After cooling the samples to room temperature, the βCD concentration was determined by HPLC. The experiment was repeated two times. No degradation of βCD could be observed in the three independent experiments.

2.4. Solubility studies

An excess amount of βCD and/or the drug to be tested was added to water or aqueous polymer solution. The suspension formed was heated in an autoclave in sealed containers (120°C for 20 min). After equilibration at room temperature (23°C) for 4–7 days, the suspension was filtered through a 0.45-μm membrane filter (Nylon Acrodisc from Gelman, USA), diluted with water (when the solubility of βCD was to be determined) or methanol–water (7:3) solution (when the solubility of the drug was to be determined) and the βCD and drug concentrations determined by HPLC. The apparent stability constants (K_c) of the drug–βCD (1:1) complexes were determined from the phase-solubility diagrams according to the method of Higuchi and Connors (1965).

2.5. Diffusion through cellophane membrane

The effect of heating the polymer βCD solutions on the diffusion of βCD through cellophane membrane (Spectropore membrane tubing, m.w. cut off 12 000–14 000) was investigated in Franz diffusion cells (Vangard, USA). The aqueous solution to be tested contained 1% (w/v) βCD and 0.25% (w/v) water-soluble polymer. Half of each solution was heated in an autoclave as described in Section 2.4 (the heating promotes the polymer–βCD interaction) and the other half was not heated (minimal polymer–βCD interaction). Water was used as a receptor phase. Samples (200 μl) were withdrawn from the receptor phase every 15 min for 90 min. The βCD concentration was determined by HPLC. Each experiment was repeated at least three times and the results reported are mean values ± standard error of the mean.

3. Results and discussions

3.1. Polymer–βCD interaction

It is possible to enhance aqueous solubility of βCD by forming complexes with water-soluble

drugs like sodium salicylate. For example, the solubility of βCD was determined to be 18.6 mg/ml in pure water but it increased to about 200 mg/ml when the solution contained 5% (w/v) sodium salicylate. The apparent stability constant (K_c) of the salicylate–βCD complex was determined from the linear phase-solubility diagram to be 51 M^{-1} in pure aqueous βCD solutions but it increased to 64, 87 or 80 M^{-1} when 0.25% (w/v) CMC, PVP or HPMC, respectively, were added to the solution. However, solubilization of βCD through complexation with water-soluble drugs is of limited value to the pharmaceutical industry. The observed enhancement of K_c upon addition of the polymers shows that the polymers are able to interact with the anionic salicylate–βCD complex. The polymer–βCD interaction could also be observed by measuring the flux of βCD from aqueous polymer solutions through a semi-permeable membrane which was impermeable to the polymers. Thus the fluxes of βCD from aqueous PVP solutions were $56 \pm 4 \times 10^{-7}$ and $46 \pm 4 \times 10^{-7}$ M min^{-1} cm^{-2} from unheated and heated solutions, respectively. From a CMC-containing solution, the fluxes were determined to be $100 \pm 18 \times 10^{-7}$ and $53 \pm 7 \times 10^{-7}$ M min^{-1} cm^{-2} from an unheated and heated solution, respectively. This indicates that heating in an autoclave enhanced the polymer–CD interaction resulting in slower CD permeability through the membrane. Finally, the polymer–βCD interaction can be observed by measuring the effect of the polymer on the aqueous solubility of βCD itself. For example, addition of a small amount of PVP and heating in an autoclave resulted in notable enhancement of the aqueous solubility of βCD (Fig. 1). The solubility decreases somewhat at higher polymer concentrations, possibly due to formation of water-insoluble inclusion complexes between the polymer and several βCD molecules. Such precipitates are commonly observed when polyrotaxanes of βCD are formed in aqueous solutions (Fujita et al., 1996).

3.2. Effect of lipophilic drugs and polymers on the solubility of βCD

In general, lipophilic drugs possess low intrinsic aqueous solubility and, thus, one would expect that addition of such drugs to aqueous βCD solutions should lower the solubility of βCD. However, the solubility of βCD in such systems should be the sum of the intrinsic solubility of βCD and the solubility of the drug–βCD complex. The solubility of βCD was determined in water and several aqueous polymer solutions and the effect of complex formation between drug and βCD on the solubility investigated (Table 2). Addition of the polymers results in a 3–10% increase in the total aqueous solubility of βCD but the drug–βCD complexation results in a ca 40% to >100% increase in solubility (the solubility ratio in Table 2 is 1.4–2.1). Further solubilization was obtained when a water-soluble polymer was present in the aqueous complexation media resulting in an additional 2–100% increase in the total aqueous solubility of βCD. The total increase in the βCD solubility was in some cases as high as 190% (solubility ratio was up to 2.9). It appears that the total solubility of βCD in such aqueous compositions is the sum of the individual contributions. For example, the total solubility of

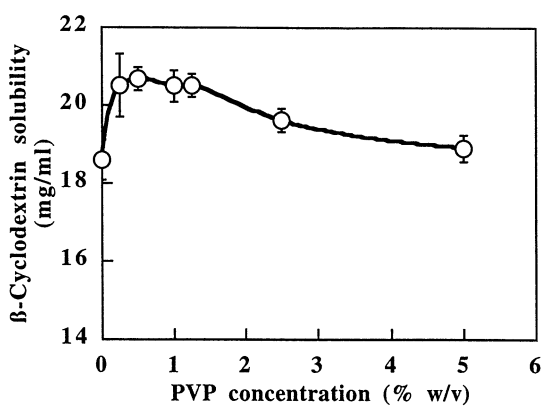

Fig. 1. The effect of increasing PVP concentration on the solubility of βCD in water at room temperature (23°C). The mean ± standard error of the mean of three experiments.

Table 2
The solubility of βCD in water, in aqueous 0.25% (w/v) polymer solution, in water saturated with both βCD and the drug, or in aqueous 0.25% (w/v) polymer solution saturated with both βCD and the drug

Drug (sol. mg/ml)[a]	Polymer	Solubility ± standard deviation (mg/ml)		Solubility ratio[b]
		Polymer	Both polymer and drug	
Acetazolamide	—[c]	18.6 ± 0.4	26.0 ± 0.6	1.4
(0.70)	PVP	20.5 ± 0.8	26.6 ± 2.8	1.4
	HPMC	20.2 ± 1.5	36.8 ± 6.8	2.0
	CMC	19.1 ± 0.1	26.8 ± 1.9	1.4
Alprazolam	PVP	20.5 ± 0.8	24.9 ± 0.4	1.3
(0.07)	HPMC	20.2 ± 1.5	25.2 ± 0.2	1.4
	CMC	19.1 ± 0.1	24.4 ± 0.4	1.3
Carbamazepine	—	18.6 ± 0.4	28.4 ± 0.0	1.5
(0.11)	PVP	20.5 ± 0.8	48.4 ± 0.1	2.6
	HPMC	20.2 ± 1.5	53.3 ± 2.5	2.9
	CMC	19.1 ± 0.1	38.2 ± 4.0	2.1
Dexamethasone	PVP	20.5 ± 0.8	24.9 ± 0.4	1.3
(0.11)	HPMC	20.2 ± 1.5	25.2 ± 0.2	1.4
	CMC	19.1 ± 0.1	24.4 ± 0.4	1.3
Ethoxyzolamide	—	18.6 ± 0.4	25.5 ± 3.5	1.4
(0.04)	PVP	20.5 ± 0.8	28.5 ± 0.5	1.5
	HPMC	20.2 ± 1.5	35.0 ± 2.6	1.9
	CMC	19.1 ± 0.1	37.0 ± 3.0	2.0
Methazolamide	—	18.6 ± 0.4	26.0 ± 0.7	1.4
(0.05)	PVP	20.5 ± 0.8	29.0 ± 2.2	1.6
	HPMC	20.2 ± 1.5	32.3 ± 2.2	1.7
	CMC	19.1 ± 0.1	51.1 ± 0.3	2.8
Sulfamethoxazole	—	18.6 ± 0.4	38.8 ± 0.8	2.1
(0.36)	PVP	20.5 ± 0.8	48.0 ± 2.8	2.6
	HPMC	20.2 ± 1.5	53.0 ± 2.0	2.9
	CMC	19.1 ± 0.1	41.9 ± 2.8	2.3

The solubility is the mean of at least three determinations ± standard deviation.
[a] Solubility (in mg/ml) of the drug in pure water at room temperature.
[b] Solubility of βCD in aqueous solution saturated with both drug and βCD divided by the intrinsic solubility of βCD in pure water.
[c] No polymer.

βCD in aqueous 0.25% HPMC solution which has been saturated with carbamazepine was determined to be 53.3 mg/ml. The individual contributions calculated from Table 2 are as follows: (a) the intrinsic solubility of βCD contributes 18.6 mg/ml, (b) the HPMC–βCD interactions contribute 1.6 mg/ml, (c) the carbamazepine–βCD interactions contribute 8.2 mg/ml, and (d) the HPMC–carbamazepine–βCD interactions contribute 24.9 mg/ml. Only a very small amount of HPMC had to be added to the system to obtain this solubilizing effect (Fig. 2).

3.3. Complexation efficacy

The polymers increase the aqueous solubility of βCD without decreasing its ability to form inclusion complexes. Actually, in most cases, the polymers increase the complexing abilities of βCD. For example, Fig. 3 shows the effect of CMC and HPMC concentrations on the carbamazepine incorporation into βCD, i.e. how many milligrams of carbamazepine forms a complex with one gram of βCD. It can be seen that addition of a small amount of the polymers dramatically increases the

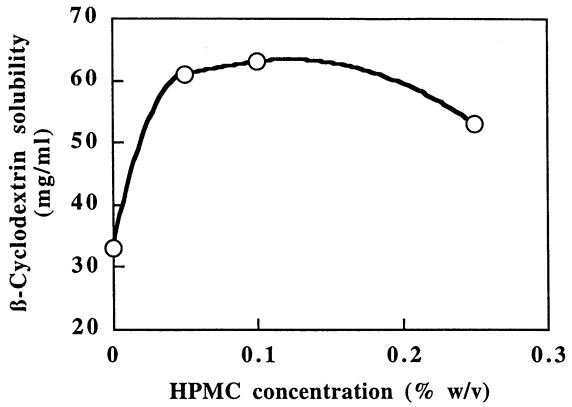

Fig. 2. The effect of HPMC concentration on the solubility of βCD in an aqueous solution which is saturated with both βCD and carbamazepine.

incorporation. Maximum incorporation was about 100 mg carbamazepine per gram βCD, which was obtained in 0.075–0.25% (w/v) HPMC solution. HPMC significantly increased the incorporation of acetazolamide into βCD but PVP was better for both methazolamide and econazole (Fig. 4). In our study βCD was a much better complexing agent than HPβCD (Fig. 4). The polymers were also able to enhance drug incorporation into γCD (Fig. 5). Thus, this effect on drug incorporation appears to be a general effect of the polymers on CD complexation, as previously shown in the case of HPβCD (Loftsson et al., 1994).

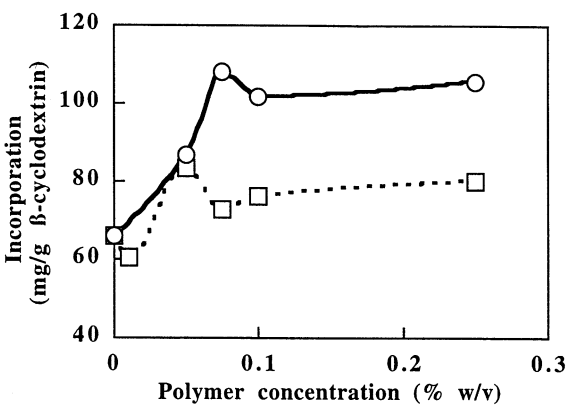

Fig. 3. The effect of CMC (□) and HPMC (○) concentration on carbamazepine incorporation into βCD.

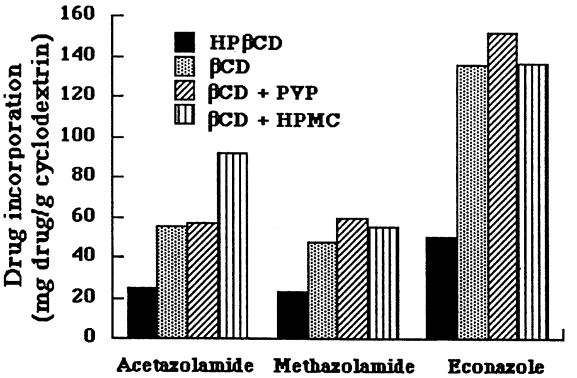

Fig. 4. Drug incorporation into HPβCD and βCD and the effect of addition of 0.25% (w/v) PVP or HPMC on drug incorporation into βCD.

4. Conclusions

The aqueous solubility of βCD in pure water is only 18.6 mg/ml. However, its solubility in aqueous drug formulations will increase significantly upon formation of inclusion complexes with drugs or complex formation with water-soluble polymers. The polymers not only solubilize βCD and its complexes, but they are also able to enhance formation of complexes between drugs and βCD. Thus, it should be possible to form aqueous drug formulations containing a water-soluble polymer and up to 5 or 6% βCD in solution. In such solutions, βCD could be as effective a solubilizer as 10–15% solution of some

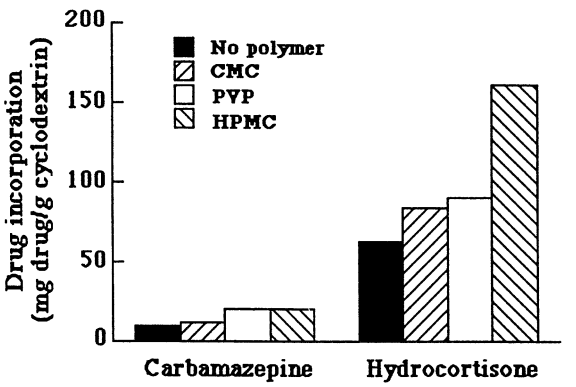

Fig. 5. Effect of addition of 0.25% (w/v) CMC, 0.25% (w/v) PVP, or 0.10% w/v HPMC on the incorporation of carbamazepine and hydrocortisone in a lyophilized γCD complex.

of the more water-soluble βCD derivatives. Finally, addition of a water-soluble polymer could also enhance the efficiency of the complexation when solid βCD complex powder is produced by kneading or co-grinding at elevated temperatures (Loftsson and Brewster, 1997).

Acknowledgements

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