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The effect of water-soluble polymers on drug-cyclodextrin complexation

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Abstract

In aqueous solutions water-soluble polymers were shown to increase the solubilising effect of cyclodextrins on drugs. For example, the solubilising effect of 2-hydroxypropyl-β-cyclodextrin (HPβCD) with molar substitution of 0.6 was improved by 6–57% (on average 27%) when 0.25% (w/v) carboxymethylcellulose was present in the solution and 12–129% (on average 49%) when 0.25% (w/v) polyvinylpyrrolidone (PVP) was present. Similar results were obtained with other cyclodextrins and other polymers. For PVP and 10% (w/v) HPβCD the PVP concentration for maximum solubilisation appeared to be between 0.05 to 0.25% (w/v). At this low concentration PVP had insignificant effect on the viscosity of the aqueous HPβCD solution. The polymers increased the stability constants of the drug-cyclodextrin complexes. Addition of PVP to the aqueous complexation medium resulted in an increased negative enthalpy change, together with an increased negative entropy change.

Key words: Keywords: Complexation; Cyclodextrin; Drug; Polymer; Solubilization

1. Introduction

Cyclodextrins form a group of structurally related oligosaccharides. The important characteristics of the cyclodextrin molecules are their cylindrical shape, somewhat hydrophobic central cavity and hydrophilic outer surface (Szejtli, 1988). Cyclodextrins are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or some part of it, into the cavity (Pitha et al., 1986; Duchêne, 1987). No covalent bonds are formed or broken during formation of the complex. The complexes are readily dissociated and free drug molecules are in a rapid equilibrium with the drug molecules bound within the cyclodextrin cavity. This type of molecular encapsulation will affect many of the physicochemical properties of the drugs, such as their solubility and stability. Thus, cyclodextrins are of potential importance as excipients in drug formulations (Loftsson et al., 1991; Duchêne and Wouessidjewe, 1993).

The most common method for preparing drug-cyclodextrin complexes on a laboratory scale is to add an excess of the drug to an aqueous

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cyclodextrin solution. The suspension formed is then agitated for up to 1 week at room temperature. The suspension is then filtered or centrifuged to form a clear drug-cyclodextrin 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 in a rotary evaporator, in a spray dryer or by lyophilisation. Frequently, the efficiency of complexation is not very high and, therefore, relatively large amounts of cyclodextrins must be used to complex small amounts of the drug. Vehicle additives commonly used in drug formulations, additives such as sodium chloride, buffer salts, surfactants, preservatives and organic solvents, reduce the efficiency. For example, in aqueous solutions, low concentrations of ethanol or propylene glycol have been shown to reduce the cyclodextrin complexation of testosterone and ibuprofen by acting as a competing guest molecule (Pitha and Hoshino, 1992; Loftsson et al., 1993). In the same manner, non-ionic surfactants have been shown to reduce the cyclodextrin complexation of diazepam (Kraus et al., 1991) and preservatives to reduce the cyclodextrin complexation of various steroids (Loftsson et al., 1992). However, hydroxypropyl methylcellulose has been demonstrated to increase the complexation of dexamethasone with 2-hydroxypropyl-β-cyclodextrin (Loftsson et al., 1994).

There are several reasons why increased efficiency of cyclodextrin complexation of drugs is desirable. For example, only a limited amount of cyclodextrin can be used in many drug formulations, such as in aqueous isotonic solutions and tablets, and increased efficiency will mean that less cyclodextrin can be used to achieve the same or even greater solubilising effect. Also, since cyclodextrins are still relatively expensive, reduction in the amount of cyclodextrin in drug formulations will result in lower production costs. The purpose of this study was to investigate further the effects of various water-soluble polymers on the cyclodextrin complexation of drugs. The efficiency of complexation was mainly evaluated by determining the solubilising effects of the cyclodextrins, however, the stability constants of the drug-cyclodextrin complexes and their thermodynamics were also determined.

2. Materials and methods

2.1. Materials

The following drugs were obtained from Sigma Chemical Co. (U.S.A.): alprazolam, clotrimazole, econazole, 17β-estradiol, ethoxyzolamide, hydrocortisone, miconazole and progesterone. The following drugs were purchased from Lyfjaverslun rikisins (Iceland): acetazolamide, diazepam, oxazepam, prednisolone, sulfamethoxazole, temazepam and triamcinolone acetonide. Carbamazepine was obtained from Aldrich Chemical Co. (U.S.A.). 2-Hydroxypropyl-β-cyclodextrin with molar substitution of 0.6 or 0.9 (HPβCD MS 0.6 or 0.9), hydroxyethyl-β-cyclodextrin with molar substitution of 0.6 (HEβCD) and randomly methylated β-cyclodextrin with degree of substitution of 1.8 (RMβCD) were supplied by Wacker-Chemie (Germany). Glucosyl-α-cyclodextrin (glucosyl-αCD), glucosyl-β-cyclodextrin (glucosyl-βCD), maltosyl-α-cyclodextrin (maltosyl-αCD) and maltosyl-β-cyclodextrin (maltosyl-βCD), all monosubstituted, were obtained from Pharmatec (U.S.A.). Carboxymethylcellulose sodium of medium viscosity (CMC), polyvinylpyrrolidone (PVP) of molecular weight (Mol. Wt) 40 000 or 360 000 and hydroxypropyl methylcellulose of 4000 cP (HPMC) were obtained from Sigma. All other chemicals were commercially available products of special reagent grade.

2.2. Solubility studies

An excess amount of the drug to be tested was added to water, aqueous polymer solution, aqueous cyclodextrin solution, or aqueous solution containing both a polymer and cyclodextrin. The suspension formed was sonicated in an ultrasonic bath (Kerry, U.K.) for 1 h and then heated in an autoclave (M7 Speed Clave from Midmark Corp., U.S.A.), in a sealed container to 120°C for 20 min. After equilibration at room temperature (23°C) for at least 3 days, the suspension was

filtered through a 0.45 μm membrane filter (Millex-HV filter units from Millipore, U.S.A.), diluted with a mixture of methanol and water (7:3 v/v) and analysed by an HPLC method. Significant excess of the drug was always used in these studies and, thus, solid drug particles were always present in the aqueous cyclodextrin solution during the entire equilibration period. The 3 day equilibration was considered sufficient, since further equilibration of selected drug suspensions for up to 10 days did not result in any further drug precipitation.

The phase-solubility diagrams in aqueous cyclodextrin solutions with or without polymer were determined at various temperatures. An excess amount of the drug was added to aqueous solutions containing from 0 to 20% (w/v) cyclodextrin and from 0 to 0.7% (w/v) polymer. The solutions were saturated by sonication and heating. After equilibration at the desired temperature (from 6 to 50°C) for 7 days, the suspensions were filtered and analysed as described above. The stability constants (K_c) of the drug-cyclodextrin complexes were calculated from the slope of the phase-solubility diagrams and the drug solubility in water (S_o):

$$K_c = \text{slope} \times \left(S_o \times (1 - \text{slope})\right)^{-1}$$

according to method of Higuchi and Connors (1965). The effect of PVP on the enthalpy (ΔH°) and the entropy (ΔS°) of K_c for the drug-cyclodextrin complex was determined according to Martin (1993).

2.3. Quantitative determinations

Quantitative determinations of the individual drugs were performed on a reversed-phase high-performance liquid chromatographic (HPLC) component system consisting of a Milton Roy ConstaMetric 3200 solvent delivery system, a Rheodyne 7125 injector, a Spectro Monitor 3200 UV/Vis variable-wavelength detector and a LiChrosorb RP-18 5 μ (125 × 4 mm) column. For other HPLC conditions, see Table 1.

Table 1
Conditions of quantitative drug determination by HPLC

Drug	Mobile phase	Flow rate (ml/min)	Wave-length (nm)	Retention time (min)
Acetazolamide	acetonitrile, acetic acid, water (10:20:88) containing 0.015% 1-octanesulfonate	1.5	263	4.0
Alprazolam	methanol, water (70:30)	1.5	254	2.8
Carbamazepine	acetonitrile, tetrahydrofuran, water (35:1:64)	2.0	278	2.8
Clotrimazole	methanol, 0.01 M aqueous potassium phosphate solution (pH 4.5) (90:10)	1.5	210	2.0
Diazepam	methanol, water (72:25)	1.5	226	4.0
Econazole	methanol, 0.01 M aqueous potassium phosphate solution (pH 4.5) (90:10)	1.5	226	2.0
17β-Estradiol	acetonitrile, ethanol, water (54:1:45)	1.5	285	2.0
Ethoxyzolamide	acetonitrile, water (35:65) containing 0.1% 1-hexanesulfonate	1.0	254	3.2
Hydrocortisone	acetonitrile, tetrahydrofuran, water (30:1:69)	1.5	254	2.6
Miconazole	methanol, 0.01 M aqueous potassium phosphate solution (pH 4.5) (90:10)	1.5	272	2.6
Oxazepam	methanol, tetrahydrofuran, water (55:2:43)	1.5	226	2.8
Prednisolone	acetonitrile, acetic acid, water (17:0.5:82.5)	1.5	242	4.0
Progesterone	acetonitrile, ethanol, water (54:1:45)	1.5	235	5.2
Sulfamethoxazole	acetonitrile, acetic acid, water (30:1:69)	1.5	253	2.4
Temazepam	methanol, water (70:30)	1.5	275	2.8
Triamcinolone acetonide	acetonitrile, water (42:58)	1.5	254	2.8

2.4. Viscosity measurements

The viscosity of the aqueous HPβCD MS 0.6 solutions at room temperature was determined in a Brookfield digital viscometer Model DV-1 + (Brookfield, U.S.A.) equipped with a Brookfield UL adapter. HPβCD MS 0.6 and/or polymer was dissolved in water and the solution heated in a sealed container as previously described (120°C for 20 min). After equilibration at room temperature and appropriate adjustments of the viscometer the viscosity of the solutions was determined.

3. Results

Various cyclodextrins and cyclodextrin derivatives have been shown to be powerful solubilizers of drugs. The most common cyclodextrin derivatives presently used in drug formulation are the hydroxypropyl derivatives of β-cyclodextrin (Pitha et al., 1986; Loftsson et al. 1991), however, their complexing abilities and, hence, their solubilising effects, are affected by both the average number of hydroxypropyl groups on each glucopyranose repeat unit, i.e., the molar substitution (MS), and the location of the hydroxypropyl groups on the HPβCD molecule (Rao et al., 1991; Loftsson and Baldvinsdóttir, 1992; Loftsson and Jóhannesson, 1994). To a certain limit, HPβCD's complexing ability increases when its MS decreases. For example, in aqueous 10% (w/v) HPβCD solution, the solubility of prednisolone was determined to be 12.7 mg/ml when the MS 0.9 derivative was used compared to 13.6 mg/ml in the case of the MS 0.6 derivative and that of sulfamethoxazole 6.08 mg/ml compared to 10.0 mg/ml. Therefore, we mainly used HPβCD MS 0.6 in our studies. The effect of CMC on the solubilising effect of HPβCD MS 0.6 is shown in Table 2. Solubilities of the drugs in aqueous 10% (w/v) HPβCD solutions (S_{co}) were from 3.6-fold (acetazolamide) to 510-fold (17β-estradiol) greater than in water (S_o) but introduction of a small amount of CMC into the solution medium improved the solubility even further. Thus, the solubilising effect of HPβCD MS 0.6 was improved by 6–57% (S_{cp}/S_{co} = 1.06–1.57) when 0.25% CMC was present in the solution, on average the solubilising effect being improved by 27%. An even greater

Table 2
Effect of addition of 0.25% (w/v) CMC to aqueous 10% (w/v) HPβCD MS 0.6 solution on HPβCD's solubilization of various drugs

Drug	S_0 (mg/ml) [a]	S_p (mg/ml) [b]	S_{co} (mg/ml) [c]	S_{cp} (mg/ml) [d]	S_{cp}/S_{co} [e]
Acetazolamide	0.70	0.84	2.52	3.11	1.23
Alprazolam	0.07	0.18	1.28	1.55	1.21
Carbamazepine	0.11	0.20	7.00	9.20	1.31
Clotrimazole	0.00	0.00	1.20	1.40	1.17
Diazepam	0.69	0.81	9.14	9.70	1.06
Econazole	0.57	0.60	5.03	7.41	1.47
17β-Estradiol	0.01	0.17	4.78	5.35	1.12
Ethoxyzolamide	0.04	0.07	1.36	1.66	1.22
Hydrocortisone	0.36	1.10	12.2	17.0	1.39
Miconazole	0.04	0.06	1.98	2.50	1.26
Oxzazepam	0.03	0.04	0.90	1.42	1.57
Prenisolone	0.38	0.53	13.6	15.3	1.13
Progesterone	0.00	0.00	4.39	6.11	1.39
Sulfamethoxazole	0.36	0.69	10.0	12.6	1.26
Temazepam	0.60	0.65	3.01	3.48	1.16
Triamcinolone acetonide	0.03	0.07	1.84	2.58	1.40

[a] Solubility in pure water. [b] Solubility in aqueous 0.25% (w/v) solution of the polymer. [c] Solubility in aqueous 10% (w/v) cyclodextrin solution. [d] Solubility in aqueous solution containing both 0.25% (w/v) polymer and 10% (w/v) cyclodextrin. [e] Solubility ratio.

Table 3
Effect of addition of 0.25% (w/v) PVP Mol. Wt 40000 to aqueous 10% (w/v) HPβCD MS 0.6 solution on HPβCD's solubilization of various drugs

Drug	S_0 (mg/ml) [a]	S_p (mg/ml) [b]	S_{co} (mg/ml) [c]	S_{cp} (mg/ml) [d]	S_{cp}/S_{co} [e]
Acetazolamide	0.70	1.05	2.52	3.92	1.56
Carbamazepine	0.11	0.31	7.00	8.50	1.21
Clotrimazole	0.00	0.00	1.20	1.80	1.50
Econazole	0.57	0.64	5.03	5.65	1.12
Ethoxyzolamide	0.04	0.06	1.36	2.72	2.00
Oxazepam	0.03	0.04	0.90	1.14	1.27
Progesterone	0.00	0.00	4.39	5.71	1.30
Sulfamethoxazole	0.36	0.86	10.0	14.8	1.48
Trimethoprim	0.82	1.35	2.83	6.47	2.29

[a] Solubility in pure water. [b] Solubility in aqueous 0.25% (w/v) solution of the polymer. [c] Solubility in aqueous 10% (w/v) cyclodextrin solution. [d] Solubility in aqueous solution containing both 0.25% (w/v) polymer and 10% (w/v) cyclodextrin. [e] Solubility ratio.

effect was obtained when CMC was replaced by PVP Mol. Wt 40000 (Table 3). In this case the solubilising effect was improved from 12 to 129% ($S_{cp}/S_{co} = 1.12–2.29$), or on average about 49%. Similar results were obtained with other cyclodextrin derivatives and polymers (Table 4). The optimal polymer concentration appeared to be below 1% (w/v). By comparing the solubility of the drugs in water (S_0) with that in aqueous 0.25% solutions of the polymers (S_p) in Tables 2 and 3, it can be seen that the polymers possess a significant solubilising effect themselves. Both the polymers and the cyclodextrins form water-soluble complexes with various drug molecules and can be used to solubilize drugs. However, when polymer and cyclodextrin are mixed together as described above, one achieves a greater extent of solubilization than when the polymer and cy-

Table 4
Effect of polymers on the solubilization of hydrocortisone in aqueous cyclodextrin solutions

Cyclodextrin	Polymer	S_{co} (mg/ml) [a]	S_{cp} (mg/ml) [b]	S_{cp}/S_{co} [c]
HEβCD	CMC	17.5	26.8	1.53
RMβCD	CMC	18.6	20.1	1.08
RMβCD	PVP Mol. Wt 40000	18.6	20.2	1.09
RMβCD	HPMC	18.6	21.8	1.17
Glycosyl-αCD	CMC	2.7	5.4	2.00
Glycosyl-αCD	PVP Mol. Wt 40000	2.7	3.6	1.33
Glycosyl-αCD	HPMC	2.7	5.4	2.00
Glycosyl-βCD	CMC	17.0	20.2	1.19
Glycosyl-βCD	PVP Mol. Wt 40000	17.0	22.2	1.31
Maltosyl-αCD	CMC	4.1	6.1	1.49
Maltosyl-βCD	CMC	10.4	18.3	1.76
Maltosyl-βCD	PVP Mol. Wt 40000	10.4	19.5	1.88
Maltosyl-βCD	HPMC	10.4	17.9	1.72

[a] Solubility in aqueous 10% (w/v) cyclodextrin solution. [b] Solubility in aqueous solution containing both 0.25% (w/v) of the given polymer and 10% (w/v) cyclodextrin. [c] Solubility ratio.

clodextrin are used separately. This solubilization enhancement is more than simply additive, it is synergistic.

The optimum amount of the polymer in the aqueous cyclodextrin solutions appeared to be between 0.05 and 0.25% (w/v) polymer concentration, since higher concentrations usually lead to some decrease in drug solubility. Fig. 1 shows the effect of increasing concentration of PVP Mol. Wt 360000 on the solubility of hydrocortisone, 17β-estradiol and triamcinolone acetonide in an aqueous 10% (w/v) HPβCD MS 0.6 solution. The solubility increases sharply with maximum solubility between 0.05 and 0.2% (w/v)

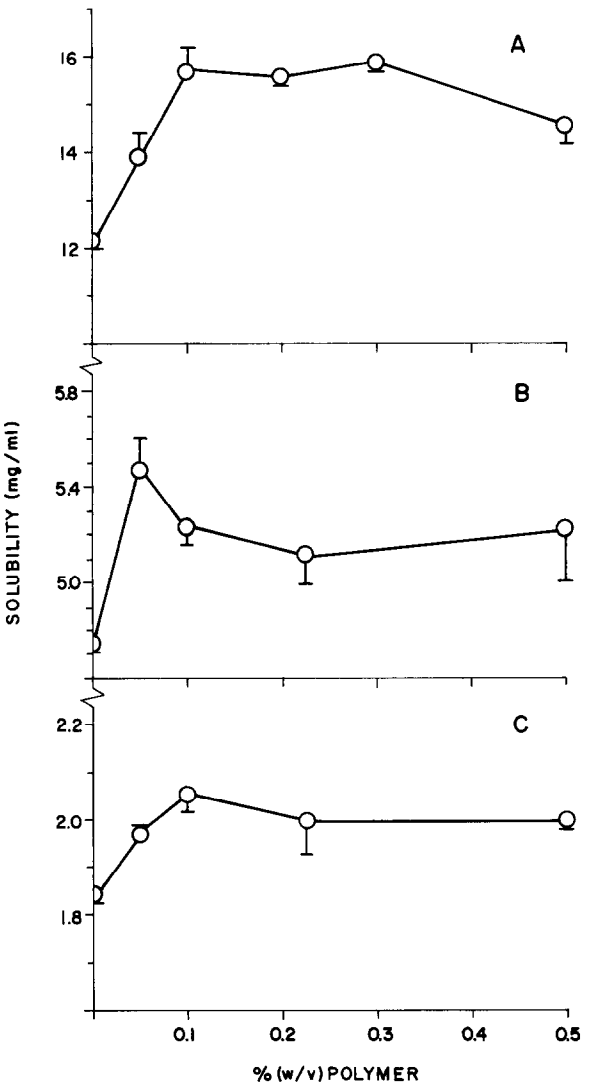

Fig. 1. The effect of increasing concentration of PVP Mol. Wt 360000 on the solubility of hydrocortisone (A), 17β-estradiol (B) and triamcinolone acetonide (C) in an aqueous 10% (w/v) HPβCD MS 0.6 solution at room temperature. Each point represents the mean of three measurments and the vertical lines represent the standard error of the mean.

Table 5
Viscosity of water and aqueous HPβCD MS 0.6, RMβCD DS 1.8, PVP Mol. Wt 360000, CMC and/or HPMC solutions at room temperature (23°C)

Aqueous solution	Viscosity (mPa s)
Pure water	1.00
0.10% (w/v) PVP	1.16
1.00% (w/v) PVP	4.15
1.00% (w/v) CMC	52.9
10% (w/v) HPβCD MS 0.6	1.47
10% (w/v) HPβCD MS 0.6 and 0.05% (w/v) PVP	1.62
10% (w/v) HPβCD MS 0.6 and 0.10% (w/v) PVP	1.72
10% (w/v) HPβCD MS 0.6 and 0.25% (w/v) PVP	2.17
10% (w/v) HPβCD MS 0.6 and 0.05% (w/v) CMC	3.66
10% (w/v) HPβCD MS 0.6 and 0.10% (w/v) CMC	5.40
10% (w/v) HPβCD MS 0.6 and 0.25% (w/v) CMC	10.8
10% (w/v) HPβCD MS 0.6 and 0.50% (w/v) CMC	17.0
10% (w/v) HPβCD MS 0.6 and 0.05% (w/v) HPMC	1.78
10% (w/v) HPβCD MS 0.6 and 0.10% (w/v) HPMC	2.75
10% (w/v) HPβCD MS 0.6 and 0.10% (w/v) HPMC	6.44
25% (w/v) HPβCD MS 0.6	3.07
25% (w/v) HPβCD MS	3.04

Table 6
Effect of PVP Mol. Wt 360000 on the stability constant (K_c) of the hydrocortisone-HPβCD MS 0.6 complex at room temperature (23°C)

PVP concentration (% w/v)	Slope	Corr.	K_c (l/mol)
0	0.502	0.988	1010
0.01	0.528	0.972	1120
0.025	0.532	0.994	1140
0.05	0.544	0.977	1190
0.1	0.591	0.999	1450
0.15	0.577	0.999	1390
0.2	0.548	0.999	1290
0.5	0.544	0.998	1190
0.7	0.543	0.999	1190

Table 7
Effect of PVP Mol. Wt 360 000 on ΔH° and ΔS° for the stability constant (K_c) of various drug-cyclodextrin complexes

	PVP concentration (% w/v)	ΔH° (kJ mol^{-1} K^{-1})	ΔS° (J mol^{-1} K^{-1})
Acetazolamide-HPβCD MS 0.6 complex	0.00	−18.4	−26.0
(K_c = 86.2 M^{-1} at 0% PVP and 20°C)	0.10	−25.8	−49.6
	0.25	−24.8	−46.2
	0.50	−25.8	−49.9
Hydrocortisone-HPαCD MS 0.6 complex	0.00	−32.1	−70.2
(K_c = 112.0 M^{-1} at 0% PVP and 20°C)	0.10	−39.3	−94.5
	0.25	−48.4	−124.2
	0.50	−35.7	−81.9
Hydrocortisone-HPβCD MS 0.6 complex	0.00	−20.4	−6.2
(K_c = 2100 M^{-1} at 0% PVP and 20°C)	0.10	−41.0	−68.6
	0.25	−36.5	−56.4
	0.50	−38.8	−64.9
17β-Estradiol-HPβCD MS 0.6 complex	0.00	−71.1	−151
(K_c = 52 880 M^{-1} at 0% PVP and 20°C)	0.10	−75.3	−166
	0.25	−89.5	−213
	0.50	−81.2	−185

PVP Mol. Wt 360 000 and then decreases slowly (Fig. 1). The viscosity of the aqueous 10% (w/v) HPβCD MS 0.6 solutions remained essentially constant, being 1.47 mPa s when no PVP Mol. Wt 360 000 was present in the solution but 2.17 mPa s when the PVP concentration was 0.25% (w/v). Addition of CMC or HPMC resulted in somewhat larger viscosity increase but the HPβCD solutions were never viscous (Table 5).

The effect of increasing concentration of PVP Mol. Wt 360 000 on the stability constant (K_c) of the hydrocortisone-HPβCD MS 0.6 complex was determined at room temperature. As expected from Fig. 1, initially the value of K_c did increase with increasing PVP concentration, reached its maximum at 0.1% PVP and then decreased slowly upon further addition of PVP. Also, addition of PVP Mol. Wt 360 000 to the aqueous complexation medium resulted in more negative standard free energy changes (Table 7).

4. Discussion

Water-soluble polymers have been used in pharmaceutical formulations for many years and although the polymers are usually considered to be chemically inert, they are known to form complexes with small molecules in aqueous solutions. About 40 years ago Takeru Higuchi and coworkers (Riley et al., 1991) investigated interactions of various drugs with a number of water-soluble polymers, i.e., polyethylene glycols, polypropylene glycols, PVP and CMC. In aqueous solutions, they frequently observed a marked increase in drug solubility due to the formation of water-soluble drug-polymer complexes, however, phase separation was sometimes observed which was characterised in pharmaceutical systems as rather embarrassing incompatibilities. In our study, the addition of a very small amount (0.25% w/v) of PVP, CMC or HPMC resulted in a significant increase in the aqueous solubility of most of the drugs tested. The solubility enhancement of both CMC and PVP was on average about 1.7-fold (Tables 2 and 3). HPMC was also shown to increase the aqueous solubility of various drugs. The polymers mainly interact with drug molecules via electrostatic bonds, i.e., ion-to-ion (in the case of CMC), ion-to-dipole and dipole-to-dipole bonds, but other types of forces, such as van der Waals forces and hydrogen bridges, frequently participate in complex formation (Rácz, 1989). In aqueous solutions, the poly-

mer molecules also tend to form electrostatic bonds between themselves and at high concentrations heat-reversible gels.

Monomeric cyclodextrins are powerful drug solubilizers which do not form gels at high concentrations. Even aqueous 25% (w/v) HPβCD and RMβCD solutions have low viscosity (Table 5). In aqueous solutions, water-soluble polymers increased the solubilising effect of cyclodextrins. Our results show that the polymers increased the efficiency of the complexation by increasing K_c. In the case of hydrocortisone, addition of 0.1% (w/v) PVP Mol. Wt 360 000 results in about 45% increase in the value of K_c (Table 6).

The driving force for drug-cyclodextrin complex formation is thought to be the release of enthalpy-rich water molecules from the cyclodextrin cavity. The water molecules located inside the cavity cannot satisfy their hydrogen bonding potentials and therefore exist in a higher energy state compared to those in the aqueous cyclodextrin solution (Bergeron, 1984, García Sánchez et al., 1990). These enthalpy-rich water molecules are readily replaced by suitable guest molecules which are less polar than water. The expulsion of the water molecules from the cyclodextrin cavity results in a negative enthalpy (Table 7). The large negative ΔH° value outweighs the unfavourable negative ΔS° value. However, a variety of other physicochemical phenomena have been proposed as driving forces for cyclodextrin complexation, such as the release of strain in the cyclodextrin ring, hydrophobic effect, hydrogen bonding, and van der Waals and London dispersion forces. Addition of PVP to the aqueous complexation medium results in an increased negative enthalpy change, together with an increased negative entropy change (Table 7). Again the unfavourable ΔS° changes were outweighed by the large ΔH° values and the net results were more negative ΔG° values. Thus, the compexation was enhanced (i.e., K_c was increased) upon addition of PVP to the complexation medium. This is consistent with the general observation that the values of ΔH° and ΔS° become more negative as K_c for molecular complexation increases (Andrews and Keefer, 1964). The stronger binding between the complexing agent and the drug is reflected in a more negative ΔH° value and a greater structural restraint in a more negative ΔS° value. PVP complexation of hydrophobic drugs is usually characterised by a small positive (or negative) ΔH° value and a positive ΔS° value (Martin, 1993). The binding can be considered as a kind of hydrophobic interaction with the partial destruction of the iceberg-like structure surrounding the molecules and, thus, an increase in entropy. The fact that both ΔH° and ΔS° become more negative in the presence of PVP supports the previous observation that the effect of PVP on the cyclodextrin complexation is not a simple additive effect.

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