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The Influence of Water-Soluble Polymers and pH on Hydroxypropyl-β-Cyclodextrin Complexation of Drugs

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ABSTRACT

The effect of water-soluble polymers and ionization of the drug molecules on the cyclodextrin, mainly 2-hydroxypropyl-β-cyclodextrin (HPβCD), solubilization of drugs was investigated. HPβCD has significant solubilizing effect on acetazolamide, prazepam, and sulfamethoxazole in aqueous solutions. All three polymers tested—i.e., hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and carboxymethylcellulose—increase the solubilizing effect of HPβCD. The polymers increase the solubilization by increasing the apparent stability constant (K_c) of the drug–HPβCD complex. Thus, addition of 0.10% (w/v) HPMC to the aqueous complexation medium results in a 56% increase in K_c for the acetazolamide–HPβCD complex and a 200% increase in K_c for the prazepam–HPβCD complex. Addition of 0.25% (w/v) PVP to the complexation medium results in a 138% increase in K_c for the sulfamethoxazole–HPβCD complex. The HPβCD solubilization of the drugs can also be improved by ionization of the drug molecule through pH adjustments. However, larger improvements of the HPβCD solubilization are obtained when both methods are used simultaneously compared to when either method is used separately.

INTRODUCTION

Various methods can be used to increase aqueous solubility of drugs, such as addition of water-miscible organic liquids; formation of emulsions, liposomes, or micelles; adjustment of pH and/or the dielectric constant of the aqueous solution medium; chemical modification of the drug molecule (e.g., prodrug formation); and formation of a drug complex with appropriate inorganic or organic complexing agent. It is frequently possible to obtain better solubilization by using two or even three methods simultaneously rather than using only one single method. Recently, we have shown, for example, that water-soluble polymers have a synergistic effect on the solubilizing

abilities of cyclodextrins (1–3). Enhanced cyclodextrin solubilization of drugs can also be obtained by addition of some organic acids (4,5) or through pH adjustments of the aqueous media (6–11). In aqueous cyclodextrin solutions, ionization of the drug molecule, through salt formation and/or pH adjustments, can result in both higher saturation solubility and an increased slope of the phase-solubility curve. Consequently, synergistic effect on the drug solubilization is frequently observed. The purpose of this study was to investigate the effect of water-soluble polymers and ionization of drug molecules on the cyclodextrin solubilization of drugs.

EXPERIMENTAL

Materials

Materials were acetazolamide (Agrar, Italy), prazepam (Fabbrica Italiana sintetia, Italy), sulfamethoxazole (Icelandic Pharmaceuticals, Iceland), 2-hydroxypropyl-β-cyclodextrin with molar substitution of 0.6 (Wacker-Chemie, Germany), randomly methylated β-cyclodextrin with degree of substitution 1.8 (Wacker-Chemie, Germany), glucosyl-β-cyclodextrin of molecular weight 1452 g/mol (Ensuiko Sugar Refining Co., Japan), carboxymethylcellulose sodium (Norsk Medicinaldepot, Norway), polyvinylpyrrolidone MW 40,000 (Mecobenzon, Denmark), and hydroxypropyl methylcellulose 4000 (Mecobenzon). All other chemicals were commercially available products of special reagent grade.

Solubility Studies

An excess amount of the drug to be tested was added to aqueous 2-hydroxypropyl-β-cyclodextrin (HPβCD)-buffered solution or unbuffered solution containing no polymer, 0.10%, 0.25%, or 0.50% (w/v) polyvinylpyrrolidone (PVP), 0.10% (w/v) hydroxypropyl methylcellulose (HPMC), or 0.25% (w/v) carboxymethylcellulose sodium (CMC). The suspension formed was heated in an autoclave (M7 Speed Clave from Midmark Corporation, USA) 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, USA), diluted with a mixture of methanol and water (7:3 v/v) and analyzed by a high-performance liquid chromatography (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 whole 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 following buffers were used: hydrochloric acid (pH 1), 0.11 M acetate (pH 3.5 and 5.6), 0.20 M acetate (pH 4.6), buffer (phosphate) solution pH 7.2 (Ph. Eur., 2nd ed., VII.1.3), buffer (ammonium chloride) solution pH 10.0 (Ph. Eur., 2nd ed., VII.1.3), and sodium hydroxide (pH 11 to 12). The pH of the final solution was determined after the heating process.

The phase-solubility diagrams in the pure (i.e., unbuffered) aqueous solutions containing HPβCD, HPβCD and PVP, HPMC or CMC, methyl-β-cyclodextrin (MβCD) or glucosyl-β-cyclodextrin (glucosylβCD) were determined. An excess amount of the drug was added to aqueous solutions containing from 0% to 20% (w/v) HPβCD and from 0.00% to 0.25% (w/v) polymer. The solutions were saturated by heating in a sealed container to 120°C for 20 min. After equilibration at room temperature (22° to 23°C) from at least 3 days, the suspensions were filtered and analyzed as described above. The apparent 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_0):

$$K_c = \text{slope} \; x \; [S_0 \; x \; (1 - \text{slope})]^{-1}$$

according to method of Higuchi and Connors (12).

Quantitative Determinations

The quantitative determinations of the individual drugs were performed by on a reversed-phase high-performance liquid chromatographic (HPLC) component system consisting of a Milton Roy ConstaMetric 3200 solvent delivery system operated at 1.50 ml/min, a Rheodyne 7125 injector, a Spectro Monitor 3200 UV/vis variable wavelength detector, and a Waters ODS 3.9 × 150 4 μm (acetazolamide) or Beckman ODS 4.5 × 150 4 μm (prazepam and sulfamethoxazole) column. For acetazolamide the mobile phase consisted of acetonitrile, acetic acid, and water (10:2:88) containing 0.015% (w/v) 1-octanesulfonate and the retention time was 1.7 min. For prazepam the mobile phase consisted of methanol, tetrahydrofuran, and water (85:1:14) and the retention time was 1.7 min. For sulfamethoxazole the mobile phase consisted of acetonitrile, acetic acid, and water (30:1:69) and the retention time was 3.0 min.

RESULTS AND DISCUSSION

Prazepam

Prazepam is a benzodiazepine possessing a protonable nitrogen group, pK_a 3.0 (13). The solubility of the unprotonized form was determined to be only 5 μg/ml at 23°C. Even the protonized (i.e., the positively charged) form appears to have very low aqueous solubility. For example, at pH 1.0, where the drug mainly exists in the protonized form, the aqueous solubility was determined to be only 0.7 mg/ml.

The effect of cyclodextrins on the aqueous solubility of prazepam was investigated. At high cyclodextrin concentrations, MβCD has the most pronounced effect of the three β-cyclodextrin derivatives tested (Fig. 1). The other two derivatives, i.e., HPβCD and glucosylβCD, also have a significant effect. Addition of small amount of a water-soluble polymer enhances the solubilizing effects of the cyclodextrins (Figs. 1 and 2). The aqueous solubility of prazepam increases linearly as a function of HPβCD or glucosylβCD concentration (Fig. 1). Thus, the phase-solubility diagrams are of Higuchi's A_L type and formation of 1:1 prazepam–HPβCD and 1:1 prazepam–glucosylβCD complexes can be assumed (12). Of the three polymers tested, HPMC has the largest enhancing effect on the HPβCD solubilization of prazepam, and protonization of the drug molecule appeared to have synergistic effect on the HPMC effect (Fig. 2). Thus, in the aqueous 10% (w/v) HPβCD solution the solubility increases from 0.3 mg/ml to 0.8 mg/ml when the pH is lowered from 4.6 to 1.0, which is a 2.7-fold increase; but in the aqueous solution containing both 0.10% (w/v) HPMC and 10% (w/v) HPβCD, the solubility of prazepam increases from 0.7 mg/ml to 5.2 mg/ml when the pH is lowered from 4.6 to 1.0, which is a 7.4-fold increase.

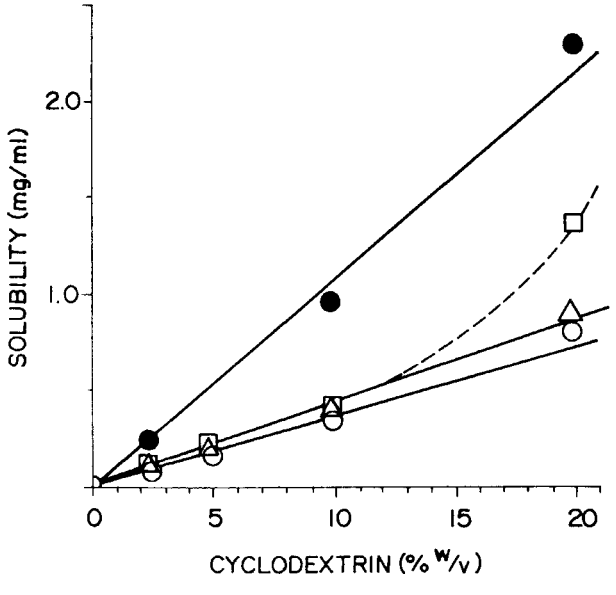

Figure 1. Phase-solubility diagrams of prazepam in aqueous cyclodextrin solutions at room temperature (23°C): (○) HPβCD, (●) HPβCD containing 0.1% (w/v) HPMC, (Δ) glucosylβCD, (□) MβCD.

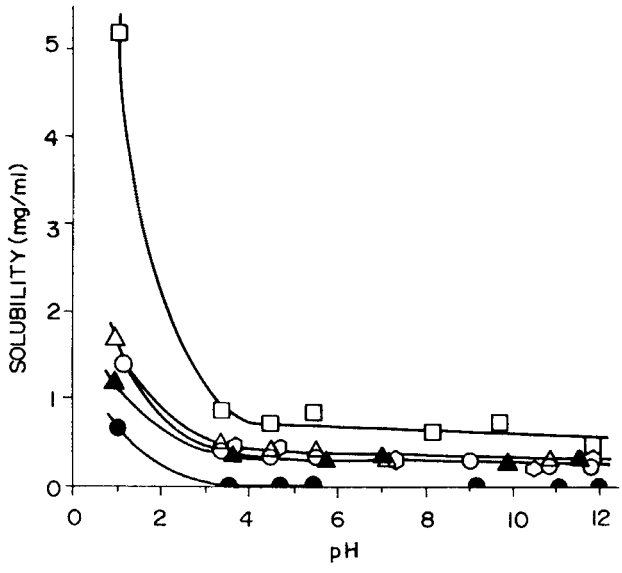

Figure 2. Effect of water-soluble polymers an pH on the solubility of prazepam (at 23°C) in aqueous buffer solutions containing 10% (w/v) HPβCD: reference buffer solution containing no polymer or HPβCD (●), HPβCD solution containing no polymer (○), HPβCD and 0.1% (w/v) HPMC (□), HPβCD and 0.10% (w/v) PVP (Δ), HPβCD and 0.25% (w/v) PVP (▲), HPβCD and 0.25% (w/v) CMC ( ).

Acetazolamide

Acetazolamide is a sulfonamide capable of forming an anion upon release of a proton from the acetamido group, pK_a 7.4 (14). The solubility of the unionized form was determined to be 0.5 mg/ml at 23°C. The sodium salt (i.e., the anionic form) of acetazolamide is water soluble.

The effect of pH on the solubility of acetazolamide in water is shown in Fig. 3. The solubility is pH independent in the pH range from about 1.5 to about 6. It increases when the pH is lowered below 1.5, probably due protonization of one of the nitrogens of the thiadiazole ring (i.e., cation formation), and increases when the pH is raised above 6 due to anion formation. HPβCD is able

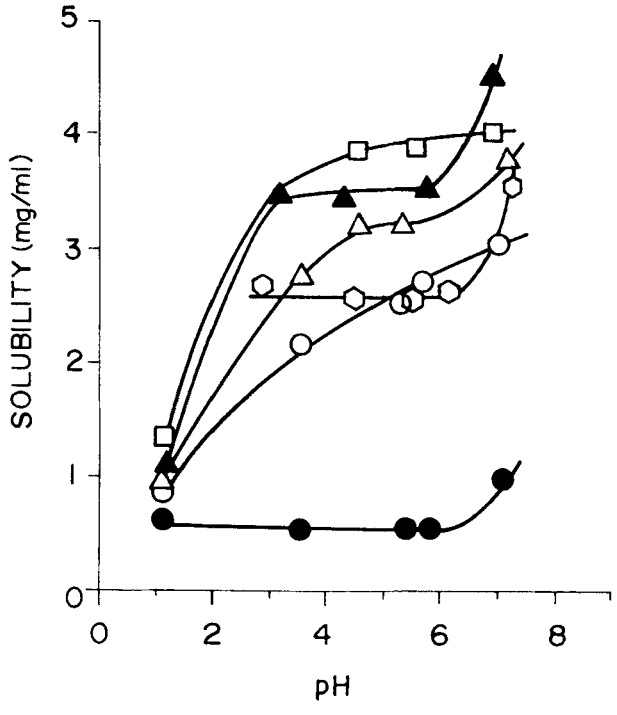

Figure 3. Effect of water-soluble polymers an pH on the solubility of acetazolamide (at 23°C) in aqueous buffer solutions containing 10% (w/v) HPβCD: reference buffer solution containing no polymer or HPβCD (●), HPβCD solution containing no polymer (○), HPβCD and 0.1% (w/v) HPMC (□), HPβCD and 0.10% (w/v) PVP (Δ), HPβCD and 0.25% (w/v) PVP (▲), HPβCD and 0.25% (w/v) CMC ( ).

to solubilize both the nonionised and the anionic form of the drug, but it has much less effect on the cationic form. All the polymers tested increase the solubilizing effect of HPβCD. However, the effect is pH dependent and CMC reduces the solubilizing effect at pH ~6. Again, it is possible to obtain greater solubilization by combining the two methods—i.e., pH adjustments and addition of HPβCD—than when either method is used separately.

Sulfamethoxazole

Sulfamethoxazole is a sulfonamide with a protonable primary amino group and an ionizable sulfoamido group. The cationic form of the drug molecule is the dominating form at pH below about 1.5, the nonionised form dominates between pH 2 and 6, and the anionic form dominates above pH about 7. The solubility of the nonionised form was determined to be 0.4 mg/ml. Both the cationic and the anionic form of the drug are soluble in water. The effect of pH on the solubility of sulfamethoxazole in water is shown in Fig. 4. HPβCD is able to solubilize both the nonionised and the anionic form of the drug but it has no effect, or even a small desolubilising effect, on the cationic form. All polymers tested increase the solubilizing effect of HPβCD and, again, the anion formation has a synergistic effect on the effect of polymers on the HPβCD solubilization.

Effect of Polymers on the Stability Constant

The apparent stability constants (K_c) of the drug–HPβCD complexes were determined at room temperature, both when no polymer was present in the aqueous HPβCD solution and when small amounts of the three different polymers were present (see Table 1). Addition of very small amount of a water-soluble polymer results in a significant increase in K_c. For example, addition of 0.10% (w/v) of HPMC to the aqueous unbuffered complexation medium results in a 56% increase in K_c for the acetazolamide–HPβCD complex and a 200% increase in K_c for the parzepam–HPβCD complex. Addition of 0.25% (w/v) PVP to the complexation medium results in a 138% increase in K_c for the sulfamethoxazole–HPβCD complex. Both HPMC and PVP are neutral polymers which have little or no effect on the pH of the complexation medium.

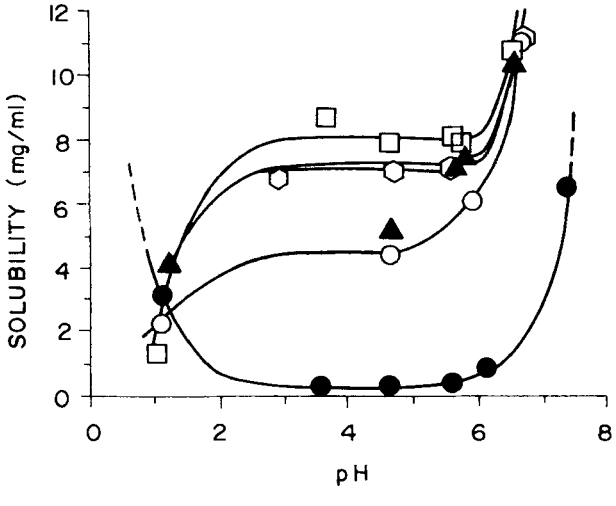

Figure 4. Effect of water-soluble polymers an pH on the solubility of sulfamethoxazole (at 23°C) in aqueous buffer solutions containing 10% (w/v) HPβCD: reference buffer solution containing no polymer or HPβCD (●), HPβCD solution containing no polymer (○), HPβCD and 0.1% (w/v) HPMC (□), HPβCD and 0.25% (w/v) PVP (▲), HPβCD and 0.25% (w/v) CMC ( ).

Table 1

Effect of Water-Soluble Polymers on the Hydroxypropyl-β-Cyclodextrin (HPβCD) Solubilization of Acetazolamide, Prazepam, and Sulfamethoxazole in Aqueous Solutions at Room Temperature (22–23°C): K_c Is the Apparent Stability Constant of the Drug–HPβCD Complex

	Acetazolamide		Prazepam		Sulfamethoxazole	
Polymer	Solubility in 20% HPβCD (mg/ml)	K_c (M^{-1})	Solubility in 20% HPβCD (mg/ml)	K_c (M^{-1})	Solubility in 10% HPβCD (mg/ml)	K_c (M^{-1})
No polymer	6.82	64	0.80	1200	7.15	370
0.10% PVP	7.10	67	0.80	1200	6.60	300
0.25% PVP	7.55	73	0.81	1200	10.7	880
0.10% HPMC	10.2	100	2.30	3600	10.3	570
0.25% CMC	7.49	75	0.75	1100	7.57	350

Note. The solubility of acetazolamide in pure water at 22°C was determined to be 0.86 mg/ml, that of prazepam to be 5×10^{-3} mg/ml, and that of sulfamethoxazole to be 0.45 mg/ml.

CONCLUSIONS

The HPβCD solubilization of drugs in aqueous solutions can be improved by addition of a small amount of a water-soluble polymer to the complexation medium or by ionization of the drug molecule through pH adjustments. However, larger improvement is obtained when both methods are used simultaneously, compared to use of either method separately. Water-soluble polymers increase the solubilizing effect of HPβCD by increasing K_c of the water-soluble drug–HPβCD complexes.

ACKNOWLEDGMENTS

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