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COMMUNICATION

Evaluation of a Sulfobutyl Ether β-Cyclodextrin as a Solubilizing/Stabilizing Agent for Several Drugs

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ABSTRACT

To evaluate the potential use of β-cyclodextrin sulfobutyl ether, 7 sodium salt (SBE7–β-CD) as a drug solubilizing and stabilizing agent, the solubilizing effects of SBE7–β-CD on 22 different poorly water-soluble drugs were compared with those of intact β-CD and heptakis-(2,6-di-O-methyl)–β-CD (DMCD). SBE7–β-CD was generally a more effective solubilizer for poorly water-soluble drugs than was intact β-CD, but SBE7–β-CD was not as effective as DMCD. The effects of SBE7–β-CD on the acid hydrolysis rate of prostaglandin I_2, the alkaline hydrolysis rate of indomethacin, the dehydration of prostaglandin E_1, and the isomerization of prostaglandin A_1 were also investigated and compared to those for intact β-CD, DMCD, and 2,3,6 partially methylated–β-CD (PMCD). The stabilizing effects of SBE7–β-CD on chemically unstable drugs were generally higher than those of other CDs.

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INTRODUCTION

Sulfoalkyl ether cyclodextrin (CD) derivatives have recently attracted considerable attention in the pharmaceutical field because of their high aqueous solubility and low toxicity (1). β-Cyclodextrin sulfobutyl ether, 7 sodium salt (SBE7–β-CD) seems to be one of the most useful sulfoalkyl ether CD derivatives (2). To evaluate the potential use of SBE7–β-CD as a drug solubilizing and stabilizing agent, the solubilizing effects of SBE7–β-CD on 22 different poorly water-soluble drugs were compared with those of intact β-CD and heptakis-(2,6-di-*O*-methyl)–β-CD (DMCD). The effects of SBE7–β-CD on the acid hydrolysis rate of prostaglandin I_2 (PGI_2), alkaline hydrolysis rate of indomethacin, the dehydration of prostaglandin E_1 (PGE_1), and the isomerization of prostaglandin A_1 (PGA_1) were investigated and compared to those for intact β-CD, DMCD, and 2,3,6 partially methylated–β-CD (PMCD) (3).

METHODS

Materials

β-CD and DMCD were supplied by Nihon Shokuhin Kako Co. Ltd. (Tokyo, Japan). SBE7–β-CD was donated by CyDex, Inc. (Overland Park, KS). PMCD was donated by Mercian Corp. (Tokyo, Japan). All other chemicals and solvents were from commercial sources and were used without further purification. Milli-Q water was used in all of the experiments.

Solubility Studies for Poorly Water-Soluble Drugs

Excess amounts of drug were added to aqueous solutions containing SBE7–β-CD (15 mg/ml). The solutions were sonicated three times for 10 min at 30-min intervals and then shaken at 25°C. After equilibrium was attained

Table 1

Effects of CDs on the Solubility of Slightly Soluble or Insoluble Drugs in Water at 25°C

Drug	Solubility in Water (μg/ml)	Solubility in 15 mg/ml CD Solution (μg/ml)		
		SBE7–β-CD	β-CD	DMCD
Testosterone propionate	1.2	1946 (1622)	6.9 (5.7)	3460 (2845)
Nifedipine	5.4	14.8 (2.7)	10.8 (2.0)	27.7 (5.1)
Benzthiazid	5.5	41.2 (7.5)	44.7 (8.1)	73.4 (13)
Indomethacin	6.9	29.5 (4.3)	12.9 (1.9)	56.0 (8.0)
Digitoxin	9.7	1470 (152)	533 (55)	4469 (460)
Progesterone	11.7	1161 (99)	12.5 (2.1)	2173 (186)
Piroxicam	13.6	73.4 (5.4)	61.5 (4.5)	80.1 (5.9)
Polythiazide	14.6	74.8 (5.1)	71.1 (4.9)	187.4 (13)
Acetohexamid	17.4	82.7 (4.8)	55.9 (3.2)	130.7 (7.5)
Griseofulvin	21.2	83.3 (3.9)	26.5 (1.7)	33.5 (1.3)
Spironolactone	24.2	2018 (83)	2174 (90)	4323 (180)
Sulfadimethoxin	28.2	87.8 (3.1)	121 (4.3)	210.6 (7.5)
Flurbiprofen	31.3	914.3 (29)	81.4 (2.6)	1721 (55)
Furosemide	32.5	108.5 (3.3)	67.3 (2.1)	121.2 (3.7)
Digoxin	33.8	1925 (57)	5226 (154)	5193 (154)
17α-Methyltestosterone	34.0	1314 (39)	204.7 (6.0)	2340 (69)
Sulfadiazine	90.0	180.2 (2.0)	360.7 (4.0)	347.6 (3.9)
Tolbutamid	105.3	264.1 (2.5)	206.5 (2.0)	470.8 (4.5)
Ketoprofen	133.0	866.8 (6.5)	1151 (8.7)	1756 (13)
Trichlormethiazide	148.9	156.8 (1.1)	245.7 (1.7)	255.1 (1.7)
Carbamazepine	167.0	821.5 (4.9)	1108 (6.6)	1975 (12)
Sulfathiazol	441.7	1352 (3.1)	2910 (6.6)	2892 (6.5)

(about 24 hr), the solutions were filtered through a 0.45-μm membrane filter. A portion of each sample was diluted and analyzed by spectrophotometry at suitable wavelengths, and then the solubility was calculated. For reference, the solubilization ability of other CDs was determined in the same manner.

The Effect of CDs on the Acid Hydrolysis Rate of PGI_2

The acid hydrolysis rate of PGI_2 in the absence and presence of CDs was spectrophotometrically monitored by measuring the decrease in absorbance at 230 nm. The reaction was initiated by the addition of 0.1 ml of stock solution of PGI_2 sodium salt (ca. 9×10^{-3} M) into 3 ml of phosphate buffer solution (pH 7.4, $\mu = 0.2$) containing CDs at a constant temperature (20°C). The final concentration of PGI_2 was adjusted to about 3.0×10^{-4} M. The pH of the sample solution was the same before and after the reaction. The plot of the logarithm of the concentration against time for the acid hydrolysis of PGI_2 was a straight line, indicating that the reaction was first-order. The rate constant was then calculated from the slope of the line.

The Effect of CDs on the Alkaline Hydrolysis Rate of Indomethacin

The alkaline hydrolysis rate of indomethacin in the absence and presence of CDs was spectrophotometrically monitored by measuring the decrease in the absorbance at 319 nm. The reaction was initiated by the addition of 0.1 ml of stock solution of indomethacin (5×10^{-4} M) into 3 ml of a Na_2HPO_4–NaOH buffer solution (pH 11, $\mu = 0.2$) containing CDs at a constant temperature (20°C). The final concentration of indomethacin was adjusted to about 1.6×10^{-5} M. The pH of the sample solution was the same before and after the reaction. The calculation of the rate constant for the alkaline hydrolysis of indomethacin was similar to that for PGI_2.

The Effect of CDs on the Dehydration of PGE_1

The dehydration of PGE_1 in the absence and presence of CDs was spectrophotometrically monitored by measuring the increase in absorbance at 218 nm. The reaction was initiated by the addition of 0.1 ml of methanol stock solution of PGE_1 (ca. 3×10^{-2} M) to 3 ml of a 0.1 M HCl solution containing CDs at a constant temperature (55°C). The pH of the sample solution was identical to

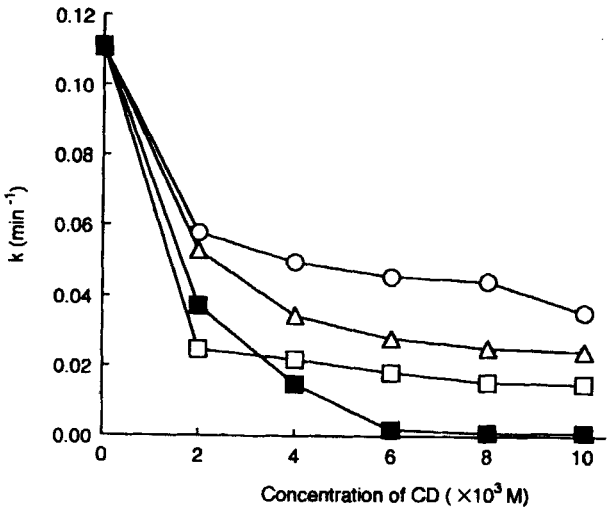

Figure 1. Rate constants for the hydrolysis of PGI_2 as a function of CD concentration in phosphate buffer (pH 7.4, $\mu = 0.2$) at 20°C. Key: (■), SBE7–β-CD; (△), PMCD; (□), DMCD; (○), β-CD.

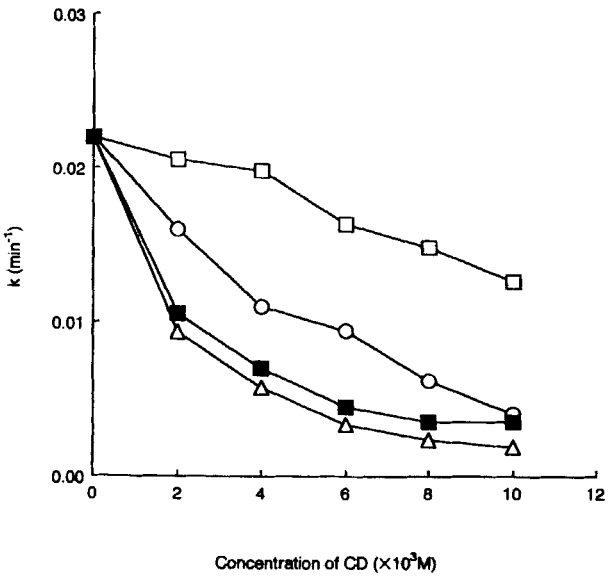

Figure 2. Rate constants for the hydrolysis of indomethacin as a function of CD concentration in phosphate buffer (pH 11.0, $\mu = 0.2$) at 20°C. Key: (■), SBE7–β-CD; (△), PMCD; (□), DMCD; (○), β-CD.

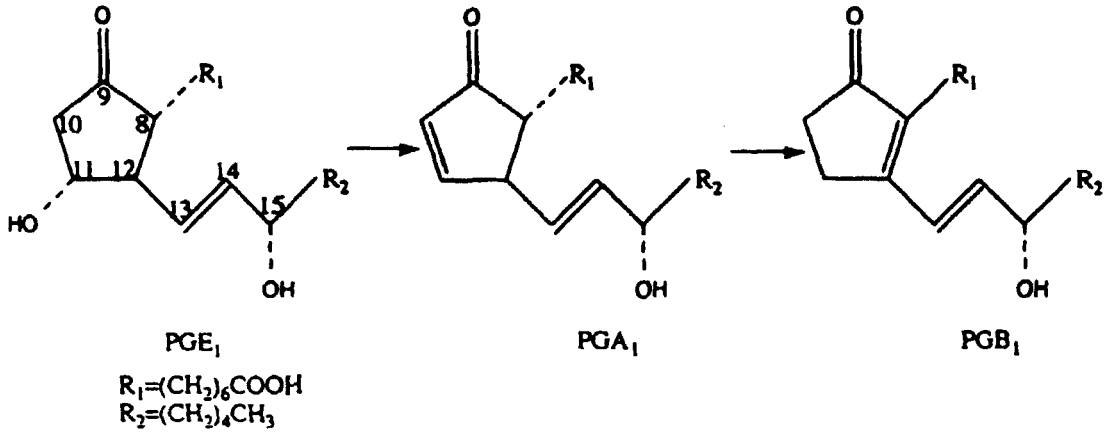

Figure 3. Dehydration and isomerization of PGE_1.

the initial pH. The calculation of the rate constant for the dehydration of PGE_1 was similar to that for PGI_2.

The Effect of CDs on the Isomerization of PGA_1

An aqueous solution of PGE_1 was kept in the dark for at least 48 hr so that the PGE_1 was completely converted to PGA_1. The solution was then adjusted to a pH of 9.0 by the addition of NaOH. Isomerization of PGA_1 in absence and presence of CDs was spectrophotometrically monitored by measuring the increase in absorbance at 278 nm at a constant temperature (20°C). The pH of sample solution was identical to the initial pH. The calculation of the rate constant for the isomerization of PGA_1 was similar to that for PGI_2.

RESULTS AND DISCUSSION

Table 1 summarizes the effects of CDs on the solubility of slightly soluble or insoluble drugs in water at 25°C. The solubilizing effects of SBE7–β-CD and DMCD were much higher than that of the parent β-CD because their aqueous solubilities were much higher. However, SBE7–β-CD was not as effective as DMCD. The above results did not suggest that the drug dissolving ability of SBE7–β-CD was weaker than that of DMCD. The average molecular weight of SBE7–β-CD is 2113 and the molecular weight of DMCD is 1331. The effects of CDs on the solubility of drugs used in this study were expressed in units per mole of CD; thus, there was no large difference between SBE7–β-CD and DMCD.

Prostacyclin (PGI_2) undergoes extremely facile hydrolysis of the vinyl ether moiety to yield 6-keto-prostaglandin $F_{1\alpha}$ in aqueous solution, and it loses its activity within a few minutes (4). Figure 1 summarizes the effects of CDs on the hydrolysis rate of PGI_2. All of the CDs examined in this study slowed the hydrolysis rate. Among these CDs, SBE7–β-CD exhibited the largest stabilization effect. These findings suggested that the effects of SBE7–β-CD and PGI_2 are greater than those of other CDs.

Indomethacin is stable under acidic conditions, but it is immediately hydrolyzed under neutral or alkaline con-

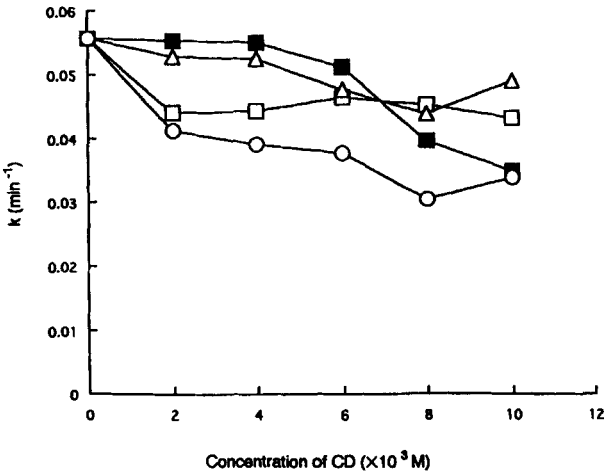

Figure 4. Rate constants for the dehydration of PGE_1 as a function of CD concentration in HCl (pH 1) at 55°C. Key: (■), SBE7–β-CD; (△), PMCD; (□), DMCD; (○), β-CD.

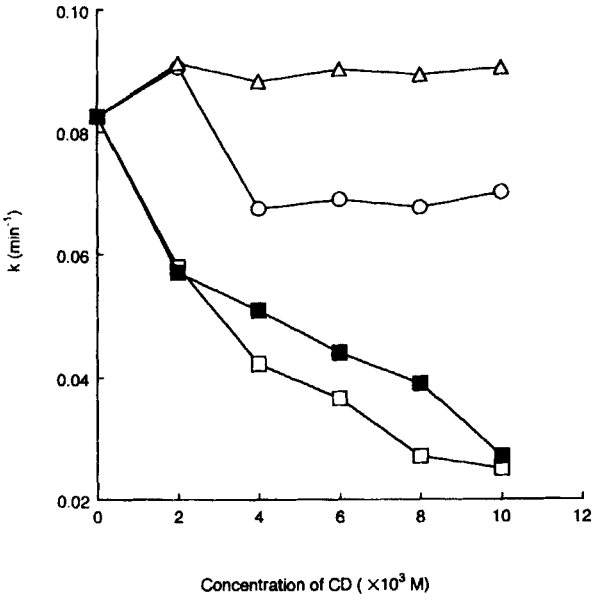

Figure 5. Rate constants for the isomerization of PGA_1 as a function of CD concentration in sodium hydroxide (pH 9) at 20°C. Key: (■), SBE7–β-CD; (△), PMCD; (□), DMCD; (○), β-CD.

ditions (5). Figure 2 summarizes the effects of CDs on the hydrolysis rate of indomethacin. Among these CDs, SBE7–β-CD and PMCD exhibited marked stabilization effects. Despite the higher solubilizing effects of DMCD on indomethacin, this CD exhibited a weaker stabilization effect. The reason for this is not clear, but may be related to differences in the solubilization mechanism.

As shown in Fig. 3, PGE_1 undergoes dehydration and isomerization in aqueous solution. It was confirmed that the reaction of $PGE_1 \rightarrow PGA_1$ showed first-order kinetics under these experimental conditions (6). Figure 4 shows the effects of CDs on the dehydration of PGE_1 in HCl at 55°C. β-CD had a relatively large stabilization effect, but there were no marked differences among the CDs examined in this study.

Above pH 4, the isomerization of $PGA_1 \rightarrow PGB_1$ became marked. Figure 5 shows the effects of CDs on isomerization of PGA_1 at pH 9 at 20°C. DMCD and SBE7–β-CD exhibited large stabilization effects, but β-CD showed minimal stabilization effects. PMCD had no effect on the isomerization of PGA_1. These observations suggested that the structural component which affects the dehydration and isomerization of PGE_1 differed from that of β-CD. Thus, the effects of CDs on dehydration and isomerization of PGE_1 yielded different results.

CONCLUSIONS

There were no large differences among SBE7-β-CD, β-CD, and DMCD on inclusion behavior toward most chemical compounds which were examined in this study. Its effect on poorly water-soluble drugs was greater than that of β-CD, but less than that of DMCD in units per weight of CDs. SBE7–β-CD, like β-CD and DMCD, prevented the hydrolysis of prostacyclin and indomethacin and the dehydration and isomerization of PGE_1. The stabilizing effects of SBE7–β-CD on unstable drugs were generally higher than those of other CDs.

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