Some Pharmaceutical Properties of 3-Hydroxypropyl- and 2,3-Dihydroxypropyl-β-cyclodextrins and Their Solubilizing and Stabilizing Abilities

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3-Hydroxypropyl- and 2,3-dihydroxypropyl-β-cyclodextrins (3-HP- and DHP-β-CyDs) with different degrees of substitution (D.S.) were prepared and their pharmaceutical properties were investigated. The aqueous solubility of 3-HP- and DHP-β-CyDs was much higher than that of the parent β-CyD and the dissolution of DHP-β-CyD in water was endothermic. The acid- and α-amylase-catalyzed hydrolysis rates of 3-HP- and DHP-β-CyDs were slower than those of the parent β-CyD. The hemolytic activity (human erythrocytes) and local irritancy (rabbit muscle) of DHP-β-CyD were considerably less than those of natural, methylated or other hydroxyalkylated β-CyDs, and decreased with increasing D.S. The ability of the hydroxyalkylated β-CyDs to remove cholesterol and proteins from human erythrocytes decreased with increasing D.S., and correlated well with their hemolytic activity. 3-HP-β-CyD was a more effective solubilizer for poorly water-soluble drugs than the parent β-CyD, and its stabilizing effect on chemically instable drugs was higher than that of the parent β-CyD. The above data suggest a considerable pharmaceutical potential of 3-HP- and DHP-β-CyDs as parenteral carriers.

Keywords 3-hydroxypropyl-β-cyclodextrin; 2,3-dihydroxypropyl-β-cyclodextrin; aqueous solubility; moisture sorption; local irritancy; hydrolysis; solubilization; stabilization

Recently, considerable attention has been paid to the utilization of hydrophilic cyclodextrin (CyD) derivatives as parenteral carriers, because of their good solubilizing power and lack of toxicity.[1-4] In a previous paper,[5] we reported that 2-hydroxyethyl- and 2-hydroxypropyl-β-CyDs (2-HE- and 2-HP-β-CyDs) had lower local toxicity, higher aqueous solubility and greater solubilizing ability for poorly water-soluble drugs than the parent β-CyD. In the work presented here, the relevant physicochemical properties of 3-hydroxypropyl- and 2,3-dihydroxypropyl-β-CyDs (3-HP- and DHP-β-CyDs), such as viscosity, hygroscopicity, surface activity, and aqueous solubility, were investigated and compared with those of the parent β-CyD and other hydroxyalkylated β-CyDs. To ensure the safety of 3-HP- and DHP-β-CyDs in parenteral formulations, the hemolytic activity against human erythrocytes and the local irritating effects on muscular tissues were examined. In addition, the solubilization and stabilization of several drugs by 3-HP- and DHP-β-CyDs were studied.

Experimental

Materials β-CyD was supplied by Nihon Shokuhin Kako Co., Ltd. Prostacyclin sodium salt and prostaglandin E_1 (PGE_1) were gifts from Ono Pharmaceutical Co., Ltd. Nimodipine (NM) and carmofur were kindly donated from Bayer Yakuhin, Ltd. and Mitsui Pharmaceutical Co., Ltd., respectively. 3-HP- and DHP-β-CyDs with different degrees of substitution were prepared by condensations of β-CyD in aqueous alkali with 3-chloro-1-propanol and glycerol α-monochlorohydrin, respectively, according to the reported method.[4] The distribution and degree of substitution (D. S.) in 3-HP- and DHP-β-CyDs were evaluated by mass and nuclear magnetic resonance (NMR) spectrometries.[4] The mass spectrum of DHP-β-CyD (D. S. 2.4) is shown in Fig. 1, as an example. The D. S. values calculated by both methods were in good agreement with each other. Other chemicals and drugs were from commercial sources, and deionized, double-distilled water was used.

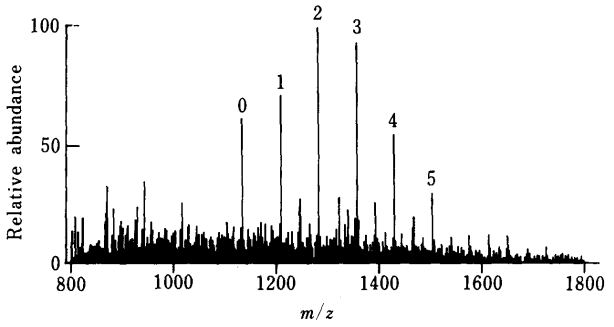

Fig. 1. Mass Spectrum (Negative Ion Detection) of DHP-β-CyD (D.S. 2.4)

Numerals indicate D.S.

Apparatus Optical rotation measurements: a DIP-360 digital polarimeter (Jasco, Tokyo, Japan) with an accuracy of ±0.002°. Surface tension measurements: duNouy surface tensionmeter (Shimadzu Co., Kyoto, Japan) with an accuracy of $\pm 0.5\,mN \cdot m^{-1}$. Viscosity measurements: Low Shear 30 rotational rheometer with an accuracy of ±0.05% (Contraves AG, Zurich, Switzerland). Water content measurements: MKA-3P Karl-Fischer moisture meter (Kyoto Electronics Co., Kyoto, Japan) with an accuracy of ±0.3%. Fast atom bombardment (FAB) mass spectrometry: JEOL JMS-DX 303 HF (Tokyo, Japan) in the negative ion detection mode, with a primary atom beam of Xe (20 keV) and glycerol as a matrix.

Viscosity Studies Rheological properties were measured at 25 °C with a Couette-type rotational rheometer (Low Shear 30, Contraves AG, Zurich, Switzerland). The vicosity was expressed as an average value obtained at various shear rates.

Moisture Sorption These studies were carried out under the same conditions as reported.[5] The water content of the sample was determined by the Karl-Fischer method or from the increase in weight.

Stability Studies of CyDs Acid-catalyzed hydrolysis was carried out in 1 N HCl at 60 °C, and followed by monitoring the change in reducing power of the hydrolyzates by the method of Somogyi–Nelson.[6] α-Amylase-catalyzed hydrolysis was carried out in 0.05 M acetate buffer (pH 5.2) containing 5 mM $CaCl_2$ at 37 °C. The concentrations of the substrates and α-amylase were 25 mM and 0.3 unit/ml, respectively. At appropriate intervals, the reaction was stopped by boiling the sample solution in a water bath, and the resulting reducing sugar was determined according to the method of Somogyi–Nelson.[6]

Hemolysis Studies These studies were carried out according to the method reported previously.[5]

Release of Cholesterol and Protein from Human Erythrocytes The erythrocyte suspension was treated with β-CyDs under conditions similar to those used in the hemolysis studies, except for β-CyD concentration. Cholesterol in the supernatant (3 ml) of the erythrocyte suspension was extracted with ether (6 ml) containing cholesterol acetate as an internal standard for gas chromatography. A 5 ml aliquot of the organic phase was evaporated and the residue was dissolved in 100 μl of chloroform; 2 μl of this solution was subjected to gas chromatography for determination of cholesterol. The chromatograph (Shimadzu GC-6A, Kyoto, Japan), with a hydrogen flame ionization detector, was operated

using N_2 as a carrier gas at a flow rate of 40 ml/min. The column was a coiled column (3 mm diameter × 500 mm) packed with 3% OV-17 on 80—100 mesh Chromosorb WHP (Tokyo, Japan). The temperatures of the injection and column ports were 280 and 250 °C, respectively. Protein in the supernatant of the erythrocyte suspension was determined by the method of Lowry *et al.*[7]

Intramuscular Irritation Studies These studies were carried out by the method of Shintani *et al.*[8] Male albino rabbits weighing 2.5—3.0 kg were used. The compounds were dissolved in a normal sterile saline (1 ml) and injected into the *M. vastus lateralis* using a 23-gauge 0.5 inch needle. Two days after the injection, the rabbits were killed, the muscle was exposed and cut longitudinally, and the lesions were scored as described.[8]

Solubility Studies Solubility measurements were carried out according to Higuchi and Connors.[9] Excess amounts of drugs were added to aqueous solutions containing β-CyDs and shaken at 25 °C. After equilibrium was attained (about 10 d), filtered aliquots were analyzed by spectrophotometry at suitable wavelengths. Apparent 1 : 1 stability constants (K_c) were calculated from the slope and intercept of the linear portion of the phase solubility diagrams.[9]

Kinetics Photolysis of nimodipine (NM): NM in aqueous solution was irradiated through a Pyrex filter by using a medical, ultraviolet (UV) instrument (Toshiba FL20S-BLB, Tokyo, Japan). The radiance of the source averaged 7 mW/cm² at 305 nm. A 0.5 ml aliquot of sample solution was withdrawn at timed intervals and NM was extracted with ethyl acetate containing nifedipine as an internal standard. The residue was dissolved in the mobile phase for high-performance liquid chromatography (HPLC), and 20 μl was subjected to HPLC. The HPLC conditions were as follows: pump, Hitachi 635A; detector, Hitachi 655A; column, ERC-ODS-1282 (6 mm diameter × 150 mm) (Erma Optical Works, Tokyo, Japan); mobile phase, acetonitrile–methanol–water (40 : 40 : 20, v/v); flow rate, 1.0 ml/min; detection, 358 nm. The photolysis of NM obeyed first-order kinetics within one or two half lives. Kinetic studies for other drugs were carried out under the reported conditions as follows: hydrolysis of carmofur,[10] dehydration of PGE_1 and isomerization of prostaglandin A_1 (PGA_1),[11] and hydrolysis of prostacyclin.[12]

Results and Discussion

Physicochemical Properties Optical activity, solubility, and surface activity of 3-HP- and DHP-β-CyDs in water were measured and the results are listed in Table I. The specific rotation, $(\alpha)_D$, of 3-HP- and DHP-β-CyDs tended to decrease with increasing D. S., in analogy with other hydroxyalkylated β-CyDs.[5] 3-HP- and DHP-β-CyDs had much higher aqueous solubility (>50% w/v) than the parent β-CyD, and as shown in Fig. 2, the dissolution of DHP-β-CyD in water was endothermic, which is in sharp contrast to the case of methylated CyDs.[13] The solubility behavior of hydroxyalkylated β-CyDs may be of great advantage in their use in liquid preparations, since no precipitation of the host molecules should occur at high temperatures of sterilization. The surface tension of the solutions of 3-HP- and DHP-β-CyDs decreased with increasing concentrations (Fig. 3), while their surface activities were significantly lower than those of 2-hydroxypropylated, methylated and ethylated β-CyDs reported previously.[5] The surface activity of hydroxyalkylated β-CyDs, as estimated from surface tension, may be affected by the position of the hydroxyl group in the alkyl moiety, *i.e.* 2-HE-, 3-HP- and DHP-β-CyDs having the hydroxyl group at the end of the substituent showed weaker surface activity, whereas 2-HP-β-CyD and methylated and ethylated β-CyDs having a nonpolar methyl group showed higher activity. Figure 4 shows the moisture sorption curves of β-CyD, 3-HP- and DHP-β-CyDs at 25 °C. 3-HP- and DHP-β-CyDs was less hygroscopic than the parent β-CyD at low relative humidity (R. H.), whereas their water content increased abruptly near R. H. 100%, where they were partly dissolved in the sorbed water due to the high aqueous

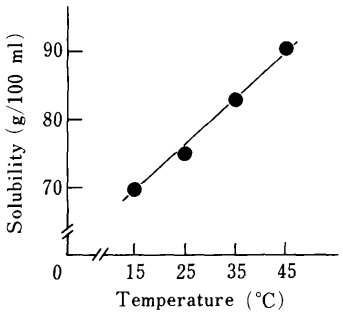

Fig. 2. Effects of Temperature on the Solubility of DHP-β-CyD (D.S. 2.4) in Water

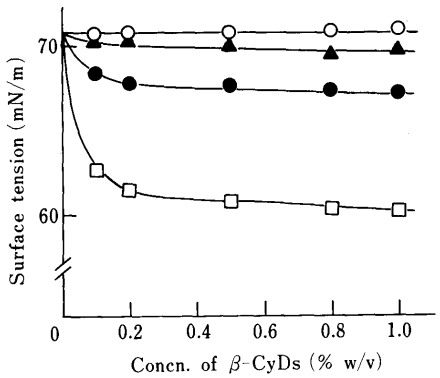

Fig. 3. Surface Tension of Hydroxyalkylated β-CyD Solutions as a Function of Concentration of Hydroxyalkylated β-CyDs in Water at 25 °C

●, 3-HP-β-CyD (D.S. 6.1); ○, DHP-β-CyD (D.S. 5.9); ▲, 2-HE-β-CyD (D.S. 5.8); □, 2-HP-β-CyD (D.S. 5.8).

TABLE I. Some Physicochemical Properties of β-CyDs

Host molecule	Substituent	Degree of[a] substitution	Average molecular weight	Aqueous[b] solubility (g/100 ml)	$[\alpha]_D$[b]	Surface[c] tension (mN/m)
β-CyD			1135	1.85	163	71
3-HP-β-CyD	$-OCH_2CH_2CH_2OH$	1.8	1239	>50	140	71
3-HP-β-CyD	$-OCH_2CH_2CH_2OH$	2.8	1297	>50	136	70
3-HP-β-CyD	$-OCH_2CH_2CH_2OH$	4.5	1396	>50	128	71
3-HP-β-CyD	$-OCH_2CH_2CH_2OH$	6.1	1489	>50	125	70
DHP-β-CyD	$-OCH_2CH(OH)CH_2OH$	2.6	1327	>50	126	71
DHP-β-CyD	$-OCH_2CH(OH)CH_2OH$	4.7	1483	>50	128	71
DHP-β-CyD	$-OCH_2CH(OH)CH_2OH$	5.9	1572	>50	114	71
DHP-β-CyD	$-OCH_2CH(OH)CH_2OH$	9.3	1823	>50	108	70

a) Estimated by mass spectrometry (FAB). *b*) In water at 25 °C. *c*) Concentration of cyclodextrins was 0.1% w/v.

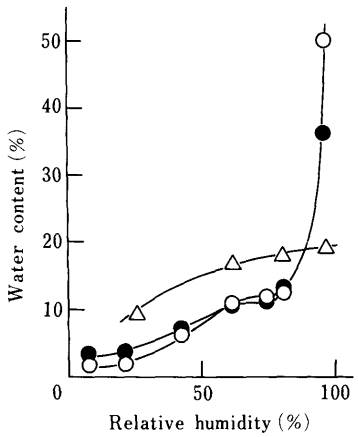

Fig. 4. Moisture Sorption Curves of β-CyDs at 25 °C

△, β-CyD; ●, 3-HP-β-CyD (D.S. 6.1); ○, DHP-β-CyD (D.S. 5.9).

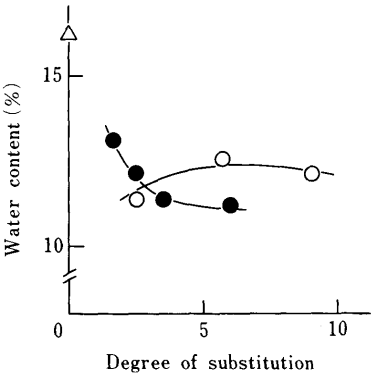

Fig. 5. Relationship between Moisture Sorption and Degree of Substitution of 3-HP- and DHP-β-CyDs at R.H. 75% and 25 °C

△, β-CyD; ●, 3-HP-β-CyD; ○, DHP-β-CyD.

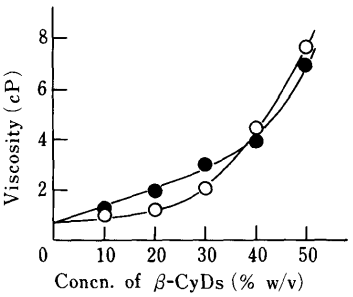

Fig. 6. Viscosity of 3-HP- and DHP-β-CyD Solutions as a Function of Concentration in Water at 25 °C

●, 3-HP-β-CyD (D.S. 6.1); ○, DHP-β-CyD (D.S. 5.9).

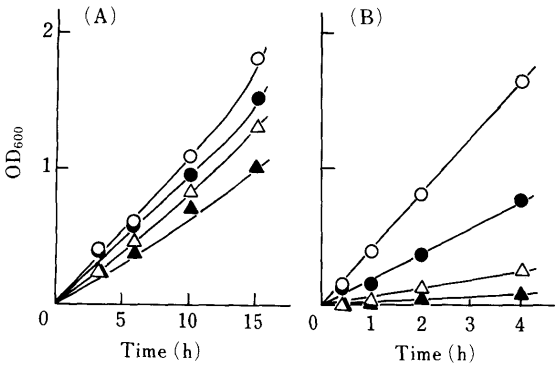

Fig. 7. Acid (A)- or α-Amylase (B)-Catalyzed Hydrolysis of β-CyD and DHP-β-CyD with Different Degrees of Substitution

○, β-CyD; ●, DHP-β-CyD (D.S. 2.6); △, DHP-β-CyD (D.S. 5.9); ▲, DHP-β-CyD (D.S. 9.3). The reaction was followed by measuring change in reducing power of hydrolyzates by the method of Somogyi–Nelson (λ=600 nm).[6] (A) In 1 N HCl at 60 °C. (B) In 50 mM acetate buffer (pH 5.2) containing 5 mM $CaCl_2$ at 37 °C.

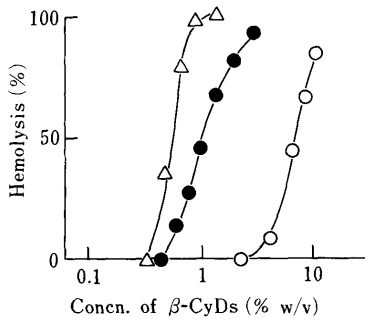

Fig. 8. Hemolytic Effects of β-CyDs on Human Erythrocytes in Isotonic Phosphate Buffer (pH 7.4) at 37 °C

△, β-CyD; ●, 3-HP-β-CyD (D.S. 6.1); ○, DHP-β-CyD (D.S. 5.9).

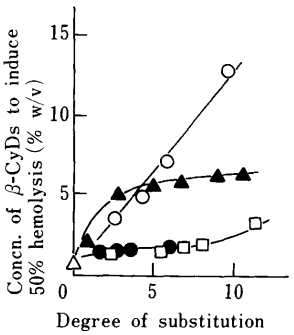

Fig. 9. Relationship between Hemolytic Activity and Degree of Substitution of Hydroxyalkylated β-CyDs

△, β-CyD; ●, 3-HP-β-CyD; ○, DHP-β-CyD; ▲, 2-HE-β-CyD; □, 2-HP-β-CyD.

solubility. Figure 5 shows the dependence of water content sorbed after 3—4 d at 75% R. H. on D. S. The water content of 3-HP-β-CyD decreased with increasing D. S., which may be due to increase in the hydrophobicity of the host molecule by the introduction of the apolar substituent. On the other hand, the water content of DHP-β-CyD was almost constant in the range of D. S. 3—10. Similar tendencies were observed for the 2-HE-β-CyD system as reported previously.[5] Figure 6 shows the viscosity change of 3-HP- and DHP-β-CyDs as a function of concentration in water. The viscosity of the β-CyDs increased exponentially with concentration, but there was no significant difference in the viscosity change between 3-HP- and DHP-β-CyDs.

Chemical and Enzymatic Stabilities CyDs are fairly stable in alkaline media, whereas they are hydrolytically cleaved by strong acids or by α-amylase to give linear oligosaccharides. Thus, the characteristics of acid and enzymatic hydrolyses of 3-HP- and DHP-β-CyDs were investigated and compared with those of β-CyD. The reaction was monitored by measuring reducing power of the hydrolyzates because of the multi-component system of the hydroxyalkylated β-CyDs. Figure 7 shows the time courses of reducing power of the reaction products in the acid-catalyzed and *Aspergillus oryzae* α-amylase-catalyzed hydrolyses, respectively, of DHP-β-CyDs with different D.

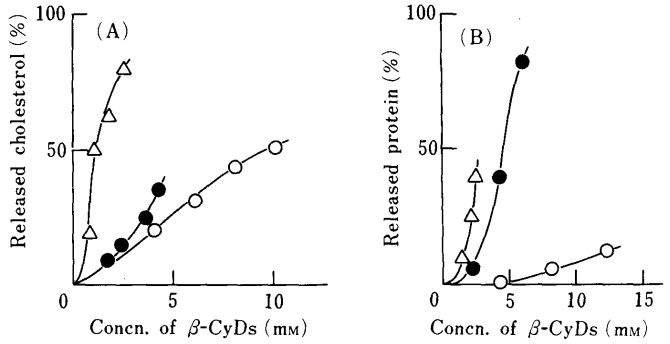

Fig. 10. Release Profiles of Cholesterol (A) and Protein (B) from Human Erythrocytes Treated with β-CyDs

△, β-CyD; ●, 3-HP-β-CyD (D.S. 6.1); ○, DHP-β-CyD (D.S. 5.9).

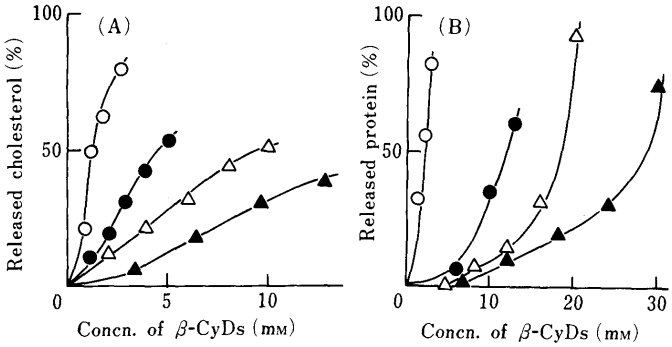

Fig. 11. Release Profiles of Cholesterol (A) and Protein (B) from Human Erythrocytes Treated with β-CyD or DHP-β-CyDs with Different Degrees of Substitution

○, β-CyD; ●, DHP-β-CyD (D.S. 2.6); △, DHP-β-CyD (D.S. 5.9); ▲, DHP-β-CyD (D.S. 9.3).

S. values. In both hydrolyses, the reaction rate of DHP-β-CyDs was slower than that of β-CyD and decreased with increasing D. S., which may be due to the steric hindrance of the dihydroxypropyl group.

Hemolytic Activity Figure 8 shows hemolytic effects of 3-HP- and DHP-β-CyDs on human erythrocytes in isotonic phosphate buffer, and Fig. 9 shows the relationship between their D. S. and the concentrations resulting in 50% hemolysis of human erythrocytes, together with the results on 2-HE- and 2-HP-β-CyDs for comparison. It is of interest that the hemolytic activity of DHP-β-CyD decreased linearly with increasing D. S. and DHP-β-CyDs having high D. S. showed weaker hemolytic activity than β-CyD and other hydroxyalkylated β-CyDs we have so far studied. On the other hand, 3-HP-β-CyD showed hemolytic activity similar to that of 2-HP-β-CyD, in spite of its weaker surface activity (Fig. 3). The CyD-induced hemolysis was reported to be due to the membrane disruption elicited by the dissolution and removal of membrane components.[14] Thus, the membrane-disrupting ability of 3-HP- and DHP-β-CyDs was evaluated by comparing the release profiles of cholesterol and protein, important membrane components, from human erythrocytes treated with these CyDs. As is apparent from Figs. 10 and 11, the ability of DHP-β-CyDs to remove cholesterol and protein was lower than those of β-CyD and 3-HP-β-CyD of corresponding D. S. and decreased with increasing D. S. This behavior was well correlated with the hemolytic activity of 3-HP- and DHP-β-CyDs.

Table II. Intramuscular Irritation[a] of the *M. vastus lateralis* of Rabbit by Natural CyDs and β-CyD Derivatives

CyD system	10 mg/ml	50 mg/ml	100 mg/ml
α-CyD	0.67±0.17	1.50±0.87	3.83±0.17
β-CyD	0.00±0.00	0.25±0.14[f]	—
γ-CyD	0.00±0.00	0.00±0.00	0.25±0.14[g]
DM-β-CyD	2.33±1.17	3.50±0.29	4.33±0.44
2-HE-β-CyD[b]	0.13±0.13	0.20±0.12	0.38±0.24[g]
2-HP-β-CyD[c]	0.00±0.00	0.38±0.24	0.75±0.14[g]
3-HP-β-CyD[d]	0.00±0.00	0.25±0.14	0.75±0.48[g]
DHP-β-CyD[e]	0.00±0.00	0.00±0.00	0.13±0.05[g]

a) Scored according to the method of Shintani *et al.*[8] (maximum score 5). *b*) D.S., 4.0. *c*) D.S., 4.3 *d*) D.S., 4.7. *e*) D.S., 4.5. *f*) 20 mg/ml. *g*) $p<0.001$ *versus* α-CyD.

Table III. Apparent Stability Constants (M^{-1}) for Inclusion Complexes of Various Drugs with β-CyD Derivatives in Water at 25 °C

Drug	β-CyD	3-HP-β-CyD[a]	DHP-β-CyD[b]
Digitoxin	17000	20000	14000
Digoxin	11000	11000	4900
Ethyl 4-biphenyl acetate	3000	6000	2400
Nimodipine	480	830	260
Nisoldipine	780	1500	510
Prednisolone	1600	2000	760
Progesterone	13000	26000	6500
Testosterone	7500	16000	5200

a) D.S., 6.1. *b*) D.S., 5.9.

Damage to Muscle Tissue Table II lists the intramuscular irritation of CyDs in *M. vastus lateralis* of rabbits, in comparison with those of 2-HE- and 2-HP-β-CyDs.[5] The irritancy of 3-HP- and DHP-β-CyDs to muscle tissues was significantly lower than those of methylated β-CyD and α-CyD (dimethyl-β-CyD (DM-β-CyD) > 2-HP-β-CyD ≈ 3-HP-β-CyD > 2-HE-β-CyD ≈ DHP-β-CyD), correlating to their hemolytic activity. Natural β-CyD showed a relatively high irritancy even at a concentration of 20 mg/ml, which corresponded to that of 3-HP-β-CyD at a concentration of 50 mg/ml. DHP-β-CyD caused no irritation to the muscle even at a concentration of 100 mg/ml.

Solubilization of Drugs by 3-HP- and DHP-β-CyDs The effects of 3-HP- and DHP-β-CyDs on the solubility of several drugs were studied and compared with those of the parent β-CyD. Table III summarizes the apparent stability constants of complexes, calculated from the phase solubility diagrams.[9] In general, DHP-β-CyD had a lower solubilizing ability than the parent β-CyD, whereas 3-HP-β-CyD had a slightly higher ability. The decrease in the complexing ability of DHP-β-CyD may be due to the steric hindrance of its dihydroxypropyl group, while in the case of 3-HP-β-CyD this negative effect is compensated by the enhanced complexing ability due to the increase in the hydrophobicity. Figure 12 shows the phase solubility diagrams of digoxin with DHP-β-CyDs of different D. S. The solubilizing ability of DHP-β-CyD decreased remarkably with increasing D. S. The precipitation of the complexes was never observed when 3-HP- and DHP-β-CyDs were used, in contrast to the case of the parent β-CyD.[15] Therefore, it is apparent that 3-HP- and DHP-β-CyDs are good solubilizers for poorly water-soluble drugs, compared

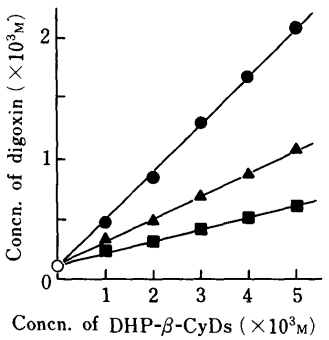

Fig. 12. Phase Solubility Diagrams of Digoxin–DHP-β-CyD Systems in Water at 25 °C

○, solubility of digoxin in water; ●, DHP-β-CyD (D.S. 2.6); ▲, DHP-β-CyD (D.S. 5.9); ■, DHP-β-CyD (D.S. 9.3).

TABLE IV. Rate Constants (h^{-1}) for Degradation of Some Drugs in the Absence and Presence of β-CyDs

	Without CyD	With β-CyD	With[a] 3-HP-β-CyD	With[b] DHP-β-CyD
Hydrolysis of prostacyclin[c]				
k_0	9.72			
k_c		4.68	3.48	4.80
k_0/k_c		2.08	2.79	2.03
Hydrolysis of carmofur[d]				
k_0	5.58			
k_c		3.84	3.48	4.20
k_0/k_c		1.45	1.60	1.33
Photolysis of nimodipine[e]				
k_0	0.174			
k_c		0.142	0.122	0.148
k_0/k_c		1.23	1.42	1.18
Dehydration of PGE_1[f]				
k_0	20.5			
k_c		128.2	73.9	41.3
k_0/k_c		0.160	0.277	0.496
Isomerization of PGA_1[f]				
k_0	1.39			
k_c		6.12	4.08	3.76
k_0/k_c		0.227	0.340	0.370

a) D.S., 6.1. *b*) D.S., 5.9. *c*) In phosphate buffer (pH 7.4, $\mu=0.2$) at 25 °C. Concentration of β-CyDs was 5×10^{-3} M. *d*) In phosphate buffer (pH 7.4, $\mu=0.2$) at 37 °C. Concentration of β-CyDs was 5×10^{-3} M. *e*) In water at 25 °C. Concentration of β-CyDs was 1×10^{-3} M. *f*) In phosphate buffer (pH 11.4, $\mu=0.2$) at 60 °C. Concentration of β-CyDs was 1×10^{-2} M.

to the parent β-CyD.

Stabilization of Drugs by 3-HP- and DHP-β-CyDs The ability of 3-HP- and DHP-β-CyDs to stabilize some drugs was also studied, *i.e.*, the ability to prevent hydrolyses of prostacyclin and carmofur, photooxidation of NM, dehydration of PGE_1 and isomerization of PGA_1. Table IV summarizes the results on k_0, k_c and k_0/k_c (the rate constants in the absence and presence of β-CyDs and the deceleration ratio, respectively). The reaction rates of these drugs, except PGE_1 and PGA_1, were decelerated about 1.2—2.5 times by the addition of 3-HP-or DHP-β-CyDs, and the stabilizing effect was in the order of 3-HP-β-CyD > β-CyD > DHP-β-CyD. This order was well correlated with that of the complexing ability (Table III). The dehydration of PGE_1 and isomerization of PGA_1 were rather accelerated by β-CyDs,[11] in the order of β-CyD > 3-HP-β-CyD > DHP-β-CyD. The smaller accelerating effect of 3-HP- and DHP-β-CyDs may be attributable to the decrease in the number of secondary hydroxyl groups of β-CyDs participating in the reaction as catalysts and/or the decrease in the complexing ability owing to the hydroxyalkylation.

In conclusion, undesirable aspects of β-CyD usage, such as local irritation or poor aqueous solubility, can be considerably diminished by substitution of β-CyD with 3-hydroxypropyl and particularly dihydroxypropyl groups. The solubilizing and stabilizing effects of 3-HP-β-CyD were almost the same as or higher than those of the parent β-CyD, while DHP-β-CyD showed slightly decreased effects. Moreover, 3-HP- and DHP-β-CyDs were more stable to α-amylase than the parent β-CyD. Such data will provide a rational basis for utilizing hydroxyalkylated β-CyDs in the phamaceutical field, particularly as parenteral drug carriers.

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