Absorption, Distribution and Excretion of Galactosyl- β -cyclodextrin and Mannosyl- β -cyclodextrin in Rats

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Microanalytical methods were developed for measuring galactosyl- β -cyclodextrin (Gal- β CD) and mannosyl (Man)- β CD in biological matrices of the rat by HPLC with pulsed amperometric detection. Then, using these methods, the absorption, distribution and excretion of intravenously and orally administered Gal- β CD and Man- β CD were determined in rats, and compared with those of glucosyl (Glc)- β CD. The pharmacokinetic behavior of Gal- β CD, Man- β CD and Glc- β CD after intravenous administration (50 mg/kg) was very similar. Within 6 h after intravenous administration, unchanged Gal- β CD and Man- β CD recovered in urine accounted for about 90% of each dose. After oral administration (500 mg/kg), 0.37% and 0.38% of Gal- β CD and Man- β CD, respectively, were excreted in urine. After intravenous and oral administration of Gal- β CD and Man- β CD, the decomposition of Gal- β CD and Man- β CD to β CD in the urine, kidney and liver was greater than that of Glc- β CD. The sum of the molar concentrations of branched CDs and their decomposition product, β CD, in the liver at 4 h after intravenous administration of Gal- β CD and Man- β CD was greater than that of Glc- β CD. Furthermore, the inclusion complexes of estriol and betamethasone with Gal- β CD, Man- β CD and Glc- β CD were prepared and their absorption was evaluated after oral administration in rats. The plasma concentrations of the drugs after oral administration of drug-Gal- β CD and drug-Man- β CD complexes were the same as those after the administration of drug-Glc- β CD complexes.

Key words galactosyl- β -cyclodextrin; mannosyl- β -cyclodextrin; microanalysis; absorption; distribution; excretion

Generally, in the development of effective and safe drugs, dosage forms must be designed to guarantee adequate bioavailability. Cyclodextrins (CDs) are known to form inclusion complexes with various drugs and to increase aqueous solubility and bioavailability.^{1,2)} Recently, studies on the application of branched CDs have been performed because of their high water solubility and low haemolytic activity, compared with the parent CDs.^{3–5)} In particular, galactosyl (Gal)- β CD and mannosyl (Man)- β CD are expected to be used as targeting carriers in drug delivery systems,⁶⁾ and it has been already reported that Gal-CDs interact with hepatocytes *in vitro*.⁷⁾

In a previous paper,^{8–10)} we applied HPLC with pulsed amperometric detection to the analysis of β CD and glucosyl (Glc)- β CD, and determined their absorption, distribution and excretion in rats.

In the present paper, we report an HPLC assay for Gal- β CD and Man- β CD in biological matrices, and the pharmacokinetic behavior of Gal- β CD and Man- β CD after intravenous administration to rats as well as the absorption of orally administered Gal- β CD and Man- β CD, compared with Glc- β CD. Furthermore, the absorption and excretion of two drugs (estriol and betamethasone), after oral administration of drug-CD complexes, were evaluated.

MATERIALS AND METHODS

Materials Gal- β CD, Man- β CD, and Glc- β CD were kindly donated by Bio Research Corporation of Yokohama (Yokohama, Japan) and were purified by HPLC. β CD was a gift from Mercian (Tokyo, Japan) and was recrystallized from hot water. Estriol and betamethasone were obtained from Sigma Chemical Co. (St. Louis, MO, U.S.A.) and Wako Pure Chemical Industries, Ltd. (Osaka, Japan), respectively. All other reagents were of analytical reagent grade. Water

used for the preparation of the eluents was distilled, deionized and purified (18 M Ω cm) using NANO-pure II equipment (Barnstead, Newton, MA, U.S.A.). Sodium hydroxide solutions used for preparation of the eluent and for pH adjustment of the effluent were prepared by dilution of carbonate-free 50% sodium hydroxide using purified water. The eluents were filtered through a 0.2- μ m membrane filter. Reagent grade organic solvents used were freshly distilled and filtered through a 0.2- μ m membrane filter.

Apparatus and Columns HPLC analyses of branched CDs were performed on a Dionex BioLC Model 4000i system equipped with a Model PAD 2 pulsed amperometric detector (both from Dionex, Sunnyvale, CA, U.S.A.) consisting of an amperometric flow-through cell with a gold working electrode, a silver-silver chloride reference electrode, and a potentiostat. The columns used were a Shodex Asahipak C8P-50 (5 μ m, 250 $\times$ 6 mm i.d.) for Gal- β CD and Glc- β CD, and a Shodex Asahipak ODP-50 (5 μ m, 250 $\times$ 6 mm i.d.) (both from Showa Denko, Tokyo, Japan) for Man- β CD. The determination of estriol and betamethasone was carried out as described in a previous paper.¹⁰⁾

Chromatographic Conditions For the determination of branched CDs, the following pulse potentials (E) and durations (t) were used at range 2 (sampling period, 200 ms): $E_1=0.10$ V ($t_1=300$ ms); $E_2=0.60$ V ($t_2=120$ ms); $E_3=-0.80$ V ($t_3=300$ ms). The response time of the PAD 2 detector was set at 1.0 s. Eluents prepared daily were degassed by bubbling helium gas through them and kept under helium. All separations were carried out using a TU-100 column oven (Jasco, Tokyo, Japan). Branched CDs were eluted with an aqueous acetonitrile solution containing sodium hydroxide. The weakly alkaline eluate from the column was adjusted to a pH of more than 13 with 1.5 M sodium hydroxide solution using an AMMS-1 anion micromembrane suppressor (Dionex)¹¹⁾ prior to detection. The peak areas were calcu-

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lated using a Model 807-IT integrator (Jasco).

Intravenous Administration of Branched CDs Male Wistar rats, weighing between 190 and 230 g, were used. The jugular vein was cannulated at least 1 d before the experiment was carried out. CDs were dissolved in normal sterile saline to give a 1.5% (w/v) solution, and then the solution (0.7 ml/210 g) was administered intravenously through the cannula. At appropriate intervals, blood samples (0.3 ml) were taken from the cannula. Plasma samples were obtained after centrifugation at $1350\times g$ for 5 min, and stored at -20°C until analysis. Other rats were placed in metabolic cages, and their urine was collected at appropriate intervals after administration and stored at -20°C until analysis. The rats were killed, their kidneys and liver received, and after pretreatment for HPLC, the samples were stored at -20°C until analysis.

Oral Administration of Branched CDs Male Wistar rats were starved 16 h prior to the experiment, and then given food 6 h following administration. The animals received drinking water *ad libitum* before and during the experiment. Branched CDs were dissolved in water and the solution (3.5 ml/210 g) given as a single oral administration through a stomach sonde. Biological samples (plasma, urine, kidney and liver) were obtained in the same manner as in the intravenous experiment.

Preparation and Oral Administration of Inclusion Complexes Solid complexes were prepared as follows: a branched CD and a drug whose molar ratio was calculated from the solubility isotherm¹²⁾ (estriol/branched CD and betamethasone/branched CD were 1/1.7 and 1/2.6, respectively) were mixed in water, dissolved with stirring, and the solution then lyophilized. The composition of the freeze-dried product was confirmed by HPLC. The products obtained were used for oral administration as solid inclusion complexes. Inclusion complexes were dissolved in water to give 0.42 and 0.39% (w/v) solutions of estriol and betamethasone, respectively; each of them (3.5 ml/210 g) was given as a single oral administration through a stomach sonde.

Pharmacokinetic Analysis The time-course of the plasma concentrations of branched CDs after intravenous administration was fitted to a two-compartment open model by nonlinear least-squares regression analysis (MULTI¹³⁾) to obtain the pharmacokinetic parameters. The maximum plasma concentration ($C_{\max}$) and the time to reach the $C_{\max}$ ($T_{\max}$) after oral administration were determined directly from the observed values. The area under the plasma concentration-time curve (AUC) was calculated by the trapezoidal method using plasma concentrations over to the measured time periods after oral administration.

RESULTS AND DISCUSSION

Chromatographic Conditions Analyses of Gal- β CD and Man- β CD were carried out by HPLC on a Shodex Asahipak C8P-50 column using 0.8% acetonitrile solution containing 10 mM sodium hydroxide as the eluent.¹⁰⁾ Previously, microanalyses of Glc- β CD and β CD in biological matrices had been performed by HPLC and, after intravenous and oral administration of Glc- β CD, slight decomposition to β CD was observed.¹⁰⁾ However, under these conditions, the retention times of Man- β CD and β CD were almost the same

Fig. 1. Chromatogram of Man- β CD Standard (2 nmol), Glc- β CD Standard (2 nmol) and β CD Standard (2 nmol) in Kidney

Chromatographic conditions: column, Shodex Asahipak ODP-50 (5 μm , $250\times 6\text{ mm}$ i.d.); eluent, 1.0% acetonitrile solution containing 15 mM sodium hydroxide; flow rate, 0.6 ml/min; temperature, 55°C ; post-column addition, 1.5 M sodium hydroxide solution at a flow rate of 1.0 ml/min; attenuation 1 μA full scale.

and so the degradation of Man- β CD to β CD was not detectable. Then, separation of Man- β CD and β CD on a Shodex Asahipak ODP-50 column was tried and a favorable result was obtained (Fig. 1). The Shodex Asahipak C8P-50 and ODP-50 columns were packed with C_8 - and C_{18} -bonded vinyl alcohol copolymer gel, respectively. These columns have a wider pH range (2–13) for separation than that of silica-based columns, and, therefore, sodium hydroxide solution of up to *ca.* 100 mM can be used as the eluent. Consequently, 1.0% acetonitrile solution containing 15 mM sodium hydroxide was employed as the eluent. The sensitivity of the pulsed amperometric detector increases on lowering the flow rate.⁸⁾ Nevertheless, a flow rate of 0.6 ml/min at 55°C was adopted to shorten the time required for analysis. The chromatographic conditions for Gal- β CD were the same as those for Glc- β CD, using a Shodex Asahipak C8P-50 column.

Preparation of Biological Samples For the determination of Gal- β CD and Man- β CD, a fixed amount of α CD and Glc- β CD, respectively, as internal standards was added to the biological samples after administration of the branched CDs. Extraction of the branched CDs from biological matrices (urine, kidney and liver) was performed by solid-phase extraction through a minicolumn packed with 0.5 g YMC ODS-A (40–63 μm) (YMC, Kyoto, Japan).⁹⁾ The extract from the minicolumn was evaporated, the residue dissolved in 5 ml water and treated batchwise with strong cation exchange resin (Dowex 50W, 3 g). The mixture was filtered through a sintered glass filter, the filtrate evaporated, and the residue dissolved in 0.5–1 ml water and 50- μl aliquots were loaded onto the HPLC column for analysis. The recovery of Gal- β CD, Man- β CD and Glc- β CD from biological matrices

(urine, kidney and liver) was $>80\%$, $<50\%$ and $>80\%$, respectively. The reason for the low recovery of Man- β CD was thought to be its weak retention on the ODS minicolumn: the retention time of CDs on C_{18} -bonded silica columns increased in the order of Man- β CD $<$ Gal- β CD $<$ Glc- β CD $<$ β CD. Although C_8 - and C_{18} -bonded vinyl alcohol copolymer gel packings were examined, the recovery of Man- β CD was also low. However, a minicolumn packed with 1 g YMC ODS-A gave satisfactory results and the recovery of Man- β CD was above 80%. Furthermore, no decomposition of Gal- β CD and Man- β CD occurred during the processing of biological samples. Plasma underwent ultrafiltration using an MPS-1 micropartition system (molecular weight cut-off 10000, Amicon, Lexington, MA, U.S.A.) and 50- μ l aliquots were loaded onto the HPLC column for analysis.⁸⁾

Intravenous Administration of Branched CDs Figure 2 shows the plasma concentrations of branched CDs after in-

Fig. 2. Plasma Concentrations of Branched CDs after Intravenous Administration of Branched CDs (50 mg/kg)

○, Gal- β CD; Δ , Man- β CD; ●, Glc- β CD. Each point and vertical bar indicates the mean $\pm$ S.E. of 6 rats.

Table 1. Pharmacokinetic Parameters of Branched CDs after Intravenous Administration of Branched CDs (50 mg/kg)

Parameter	Gal- β CD	Man- β CD	Glc- β CD
$t_{1/2\alpha}$ (min)	7.5 $\pm$ 2.0	6.9 $\pm$ 1.7	4.8 $\pm$ 2.0
$t_{1/2\beta}$ (min)	16.1 $\pm$ 0.3	24.3 $\pm$ 2.2	17.7 $\pm$ 1.5
V_{dss} (ml/kg)	265.4 $\pm$ 10.0	310.6 $\pm$ 16.2	345.1 $\pm$ 25.3
CL_r (ml/h/kg)	570.2 $\pm$ 61.6	264.1 $\pm$ 15.1	541.4 $\pm$ 62.6
AUC_{0-2} (μ g $\cdot$ h/ml)	77.4 $\pm$ 7.2	151.0 $\pm$ 15.9	81.3 $\pm$ 10.1

Each value represents the mean $\pm$ S.E. of 5 rats.

travenous administration of Gal- β CD, Man- β CD or Glc- β CD (50 mg/kg) to rats. The limits for the determination of Gal- β CD, Man- β CD and Glc- β CD in plasma were 0.2, 0.4 and 0.3 μ g/ml, respectively. The plasma concentration-time profiles of branched CDs were fitted to a two-compartment open model, which was used to calculate the half-life for the distribution phase ($t_{1/2\alpha}$), the half-life for the elimination phase ($t_{1/2\beta}$), the steady-state distribution volume (V_{dss}) and the total clearance (CL_r) and these are listed in Table 1. Figure 3 and Table 2 show the urinary excretion and tissue distribution, respectively, of the CDs after administration of the branched CDs. Gal- β CD disappeared rapidly from the plasma in the same way as Glc- β CD, and the plasma concentrations fell to below the detection limit at 3 h after administration. On the other hand, the disappearance of Man- β CD from plasma was slower than that of Gal- β CD and Glc- β CD, and the plasma concentrations were about 2.0 μ g/ml even 4 h after administration. Furthermore, the urinary excretion of Man- β CD within 2 h of administration was slower than that of Gal- β CD and Glc- β CD (Fig. 3) and β CD, produced from Man- β CD at 4 h after administration, was detected in the urine (Table 2). These results may be attributable to the enzymatic degradation of Man- β CD, as described later, and to the binding of Man- β CD in blood or various tissues. The recovery of intact Gal- β CD, Man- β CD and Glc- β CD was about 90% in the urine within 6 h. The remainder (about 10%) of the dose is probably widely distributed in various organ of the rat. After administration of branched CDs, their concen-

Fig. 3. Cumulative Urinary Excretions of Branched CDs after Intravenous Administration of Branched CDs (50 mg/kg)

○, Gal- β CD; Δ , Man- β CD; ●, Glc- β CD. Each point and vertical bar indicates the mean $\pm$ S.E. of 6 rats.

Table 2. Tissue Distribution and Cumulative Urinary Excretion of CDs (% of Dose $\times$ 10) after Intravenous Administration of Branched CDs (50 mg/kg)

Sample	CDs	4 h			24 h		
		Kidney	Liver	Urine	Kidney	Liver	Urine
Gal- β CD	Gal- β CD	1.79 $\pm$ 0.22	0.97 $\pm$ 0.68	887.48 $\pm$ 22.56	0.02 $\pm$ 0.01	0.04 $\pm$ 0.02	950.07 $\pm$ 22.78
	β CD	6.71 $\pm$ 0.83	4.58 $\pm$ 0.79	— ^{a)}	4.55 $\pm$ 0.33	1.40 $\pm$ 0.11	1.10 $\pm$ 0.28
Man- β CD	Man- β CD	1.39 $\pm$ 0.55	0.66 $\pm$ 0.20	869.28 $\pm$ 53.23	0.79 $\pm$ 0.23	0.17 $\pm$ 0.03	951.33 $\pm$ 33.96
	β CD	5.73 $\pm$ 1.90	3.72 $\pm$ 0.22	3.08 $\pm$ 1.82	5.65 $\pm$ 2.07	1.39 $\pm$ 0.13	9.99 $\pm$ 2.75
Glc- β CD	Glc- β CD	9.80 $\pm$ 0.75	1.43 $\pm$ 0.27	883.30 $\pm$ 16.28	6.87 $\pm$ 0.34	1.09 $\pm$ 0.07	944.79 $\pm$ 14.83
	β CD	0.15 $\pm$ 0.04	0.39 $\pm$ 0.05	— ^{a)}	0.18 $\pm$ 0.04	0.19 $\pm$ 0.02	0.21 $\pm$ 0.06

Each value represents the mean $\pm$ S.E. of 6 rats. a) Below the detection limit.

trations in the kidney were higher than in the liver. The concentrations of β CD in the kidney and liver after the administration of Gal- β CD and Man- β CD were higher than that of Glc- β CD. This may be due to the action of debranching enzymes on Gal- β CD and Man- β CD being stronger than on Glc- β CD in rat tissues. It is known that α -galactosidase, α -mannosidase and α -glucosidase are widely distributed throughout mammalian tissues¹⁴⁾ and a debranching enzyme for branched CD exists in yeast and in rabbit skeletal muscle.¹⁵⁾ The decomposition of Gal- β CD and Man- β CD to β CD may lead to renal toxicity, compared with Glc- β CD, because β CD is nephrotoxic at higher doses.¹⁶⁾ However, the absolute amount of β CD produced from Gal- β CD or Man-

β CD was very low (less than 0.7% of the dose). The sum of the molar concentrations of branched CDs and their decomposition product, β CD, in the liver at 4 h after the administration of Gal- β CD and Man- β CD was 3.0-fold and 2.4-fold, respectively, that of Glc- β CD. These results suggest that Gal- β CD and Man- β CD might be useful as drug carriers targeting the liver, compared with Glc- β CD.

Oral Administration of Branched CDs The plasma concentrations (Fig. 4), pharmacokinetic parameters (Table 3) and cumulative urinary excretion (Fig. 5) of Gal- β CD and Man- β CD obtained following the oral administration of Gal- β CD and Man- β CD (500 mg/kg) to rats were similar to those of Glc- β CD. The bioavailability (urinary recovery after oral administration/urinary recovery after intravenous administration) of Gal- β CD, Man- β CD and Glc- β CD was about 0.4%. Table 4 shows the tissue distribution and cumulative urinary excretion of branched CDs and β CD (% of dose and extent of bioavailability) after the administration of branched CDs. Branched CDs underwent no significant first-pass effect in the liver following oral administration. The urinary excretion of branched CDs after oral administration was slower than that after intravenous administration. At 24 h after the administration of Gal- β CD and Man- β CD, the concentrations of

Fig. 4. Plasma Concentrations of Branched CDs after Oral Administration of Branched CDs (500 mg/kg)

○, Gal- β CD; Δ , Man- β CD; ●, Glc- β CD. Each point and vertical bar indicates the mean $\pm$ S.E. of 5 rats.

Table 3. Pharmacokinetic Parameters of Branched CDs after Oral Administration of Branched CDs (500 mg/kg)

Parameter	Gal- β CD	Man- β CD	Glc- β CD
$T_{\max}$ (min)	12.0 $\pm$ 2.0	19.2 $\pm$ 5.5	16.0 $\pm$ 2.4
$C_{\max}$ (μ g/ml)	2.52 $\pm$ 0.36	3.65 $\pm$ 0.41	2.90 $\pm$ 0.14
AUC_{0-2} (μ g $\cdot$ h/ml)	2.40 $\pm$ 0.22	3.17 $\pm$ 0.49	2.49 $\pm$ 0.12

Each value represents the mean $\pm$ S.E. of 5 rats.

Fig. 5. Cumulative Urinary Excretions of Branched CDs after Oral Administration of Branched CDs (500 mg/kg)

○, Gal- β CD; Δ , Man- β CD; ●, Glc- β CD. Each point and vertical bar indicates the mean $\pm$ S.E. of 5–6 rats.

Table 4. Tissue Distribution and Cumulative Urinary Excretion of CDs [% of Dose $\times 10^2$ (% Bioavailability)] after Oral Administration of Branched CDs (500 mg/kg)

Sample	CDs	4 h			24 h		
		Kidney	Liver	Urine	Kidney	Liver	Urine
Gal- β CD	Gal- β CD	0.34 $\pm$ 0.08 (0.85)	0.08 $\pm$ 0.01 (0.19)	26.98 $\pm$ 3.29 (67.45)	— ^{a)} (— ^{a)}	0.06 $\pm$ 0.02 (0.14)	37.42 $\pm$ 2.80 (92.87)
	β CD	0.16 $\pm$ 0.02 (0.39)	0.05 $\pm$ 0.01 (0.12)	— ^{a)} (— ^{a)}	0.11 $\pm$ 0.02 (0.28)	0.07 $\pm$ 0.01 (0.18)	0.08 $\pm$ 0.07 (0.20)
Man- β CD	Man- β CD	0.37 $\pm$ 0.08 (0.93)	0.10 $\pm$ 0.03 (0.26)	29.27 $\pm$ 2.86 (73.16)	— ^{a)} (— ^{a)}	— ^{a)} (— ^{a)}	37.75 $\pm$ 3.85 (94.38)
	β CD	0.29 $\pm$ 0.05 (0.72)	0.14 $\pm$ 0.07 (0.34)	0.06 $\pm$ 0.04 (0.16)	0.26 $\pm$ 0.03 (0.66)	0.30 $\pm$ 0.03 (0.75)	14.6 $\pm$ 0.54 (3.65)
Glc- β CD	Glc- β CD	0.60 $\pm$ 0.04 (1.50)	0.12 $\pm$ 0.03 (0.30)	24.63 $\pm$ 1.80 (61.57)	0.26 $\pm$ 0.03 (0.64)	0.04 $\pm$ 0.01 (0.11)	36.60 $\pm$ 3.26 (91.51)
	β CD	— ^{a)} (— ^{a)}	— ^{a)} (— ^{a)}	— ^{a)} (— ^{a)}	— ^{a)} (— ^{a)}	— ^{a)} (— ^{a)}	0.14 $\pm$ 0.08 (0.35)

Each value represents the mean $\pm$ S.E. of 5 rats. ^{a)} Below the detection limit.

Table 5. Dose and Pharmacokinetic Parameters of Drugs after Oral Administration of Drug-Branched CDs Complexes

Sample	Dose (mg/kg) CD+drug	$T_{\max}$ (h)	$C_{\max}$ ($\mu\text{g/ml}$)	$AUC_{0-t}^{a)}$ ($\mu\text{g}\cdot\text{h/ml}$)
Estriol-Gal- β CD complex	535+70	0.54 ± 0.04	2.13 ± 0.27	2.14 ± 0.12
Estriol-Man- β CD complex	535+70	0.50 ± 0.07	2.27 ± 0.10	2.36 ± 0.13
Estriol-Glc- β CD complex	535+70	0.54 ± 0.09	2.11 ± 0.33	2.10 ± 0.23
Betamethasone-Gal- β CD complex	558+65	1.15 ± 0.13	56.17 ± 2.60	178.34 ± 12.22
Betamethasone-Man- β CD complex	558+65	1.00 ± 0.11	57.54 ± 3.60	171.42 ± 8.36
Betamethasone-Glc- β CD complex	558+65	0.95 ± 0.10	59.27 ± 2.70	180.88 ± 8.75

Each value represents the mean $\pm$ S.E. of 5 rats. a) t : 2 h for the estriol series and 5 h for the betamethasone series.

Gal- β CD in the kidney and Man- β CD in the kidney and liver were below the detection limit. On the other hand, a small amount of β CD, produced from Gal- β CD and Man- β CD, was present in almost the same concentration as that following intravenous administration. However, although Glc- β CD was detected in the kidney and liver after 24 h, no β CD was produced from Glc- β CD.

Oral Administration of Inclusion Complex The model drugs, estriol and betamethasone, were selected because their solubility in water was significantly enhanced by complexation with CDs¹²⁾ and their toxicity following oral administration in rats was low.¹⁷⁾ The dose of the inclusion complex was the same as in a previous paper¹⁰⁾ (Table 5). The plasma concentrations of the drugs were determined after oral administration of the drug-branched- β CD complexes to rats. The pharmacokinetic parameters of the drugs obtained from administration of drug-Gal- β CD and drug-Man- β CD were almost the same as those of drug-Glc- β CD (Table 5). Complexation markedly improves the solubility of poorly water-soluble drugs,¹⁰⁾ and results in an increase in gastrointestinal absorption. The absorption of drug from drug-Gal- β CD and drug-Man- β CD was almost the same as that of drug-Glc- β CD, because the solubilities of Gal- β CD, Man- β CD and Glc- β CD are very similar.⁵⁾

CONCLUSION

The bioavailability of Gal- β CD and Man- β CD was almost 0.4% and the same as that of Glc- β CD. The decomposition of Gal- β CD and Man- β CD to β CD was greater than that of Glc- β CD. However, the amount of β CD produced from Gal- β CD or Man- β CD was not likely to induce renal toxicity. The sum of the molar concentrations of branched CDs and their decomposition product, β CD, in the liver at 4 h after intravenous administration of Gal- β CD and Man- β CD was higher than that of Glc- β CD. These results, together with those of a previous paper^{5,7)} on the characteristics of Gal- β CD and Man- β CD, suggest that they will be useful as drug carriers targeting the liver following intravenous administration, compared with Glc- β CD. Furthermore, after oral ad-

ministration of drug-Gal- β CD and drug-Man- β CD, the absorption increased to the same extent as that of drug-Glc- β CD. Complexation of poorly water-soluble drugs with Gal- β CD and Man- β CD produces dosage forms with adequate bioavailability.

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