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Delayed-release tablets using hydroxyethylcellulose as a gel-forming matrix

Mitsuyuki Matsuo, Kazuhiko Arimori, Chizuko Nakamura, Masahiro Nakano*

Department of Pharmaceutical Services, Kumamoto University Hospital, 1-1-1 Honjo, Kumamoto 860, Japan

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Abstract

Delayed-release tablets containing diltiazem hydrochloride (DIL) were prepared by using CM-type hydroxyethylcellulose (HEC) of three viscosity grades. The tablets consisted of a core containing 30 mg of DIL and an outer shell formed by compressing HEC. DIL in the core was rapidly released from the tablets after a lag time of several hours in all cases. The lag time to the start of release of DIL was more prolonged with an increase in viscosity of CM-type HEC. The rate of water-uptake was greater in the CM-L4 type HEC tablet of a low viscosity grade (14 cps) than those in CM-L3 and CM-L2 type HEC (27 and 95 cps, respectively) tablets. There was little difference in lag time to the start of release of DIL from CM-type HEC tablets between JP XII 1st (pH 1.2) and 2nd (pH 6.8) fluids. A human volunteer study was performed using the delayed-release tablets prepared with CM-type HEC of two or three viscosity grades. The t_{max} and MRT values of CM-type HEC tablets were significantly increased with an increase in viscosity of HEC and showed only small variations between subjects, respectively. On the other hand, although the AUC values were almost the same, the C_{max} values decreased with prolongation of lag time. The lag time in vivo for appearance of DIL in the blood corresponded well to the lag time in vitro for drug release, but tended to be shortened as compared with the lag time in vitro. These results indicate that the lag time can be optionally controlled by selecting HEC with a proper viscosity and/or by changing the amount of HEC forming the outer shell. This delayed-release tablet using HEC will be useful for control of time-related symptoms which need time-controlled or site-specific delivery in the gastrointestinal tract.

Keywords: Diltiazem hydrochloride; Hydroxyethylcellulose; Lag time; Healthy volunteers; Delayed-release tablet; Swellable matrix; Bioavailability

1. Introduction

The disease symptoms such as hypertension, ischemic heart disease, asthma and rheumatoid arthritis exhibit circadian rhythms (Lemmer, 1991; Traynor et al., 1992). For example, blood

* Corresponding author, Tel: +81 96 373 5820; fax: +81 96 373 5906.

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Table 1
Characteristics of HEC

	AL-15	CM-L4	CM-L3	CM-L2	CM-L	CM-G	CM-H
Ash (%)	11	0.5	0.4	0.8	0.5	0.3	0.3
Viscosity (cps)*	25	14	27	95	148	270	1280

*Viscosity in 2% solution at 20°C.

pressure tends to be lower while asleep and to be elevated in the early morning (Lemmer, 1991). Similarly, the maximum morning occurrence of deaths from heart attack is at 9 a.m., which coincides with peaks in platelet aggregation, plasma catecholamine levels and blood pressure and a trough in fibrinolytic activity (Traynor et al., 1992). From these points of view, development of preparations, in which a required amount of a drug is released only at a required time and effective drug levels are reached, has been desired.

Various approaches to controlled-release delivery systems have been investigated for oral application. Of their approaches, delayed-release preparations have been noted as orally applicable delivery systems which are useful for time-controlled or site specific delivery of a drug to the gastrointestinal tract (Bae et al., 1987; Ishino et al., 1992a,b; Wilding et al., 1992).

In general, cellulose derivatives have been widely used for controlled release formulations because of their low cost and ease of fabrication (Nakano et al., 1983; Padmalatha Devi et al., 1989; Prisant et al., 1992; Nakagami and Nada, 1991a; Nakagami and Nada, 1991b). However, their applications have been mainly limited within sustained-release type preparations until now. Recently, a time-controlled explosion system using cellulose derivatives, such as hydroxypropylcellulose and ethylcellulose has been developed (Ueda et al., 1994; Hata et al., 1994). The system has a four-layered spherical structure, which consists of polystyrene balls or sucrose seeds (Nonpareil®) as core particles, a drug, low-substituted hydroxypropylcellulose as a swelling agent and ethylcellulose as a water-insoluble polymer membrane and is characterized by an initial expansion of the swelling agent by water penetrating through the outer membrane, destruction of the membrane by stress due to swelling force and subsequent rapid drug release. An organic acid-induced sigmoidal release system (Narisawa et al., 1994) presents another development in designing a formulation with lag time in release profiles.

The present study was aimed at the use of hydroxyethylcellulose (HEC) in the design of the delayed-release dosage form. HEC has the characteristics of a wide range of viscosity grades and a poor solubility in organic solvents compared with other cellulose derivatives, such as hydroxypropylcellulose and hydroxypropylmethylcellulose and shows pH-independent release because of the nonionic nature of the polymer. A series of CM-type HEC was selected as the matrix polymer because of appropriate viscosity enough to maintain the gel layer and having low ash contents compared with other types of HEC. CM-type HEC is a water-soluble gel-forming polymer, which includes 30–50% substituted hydroxyethoxy groups in the cellulose and exhibits viscosity of 2% solution from 14 to 1280 cps. Diltiazem hydrochloride (DTL) was chosen as a representative drug, which is a potent calcium-channel blocker and has been effective for angina pectoris and essential hypertension suitable for preventing time-related occurrence of disease symptoms (Lemmer, 1991; Traynor et al., 1992).

2. Materials and methods

2.1. Chemicals

Diltiazem hydrochloride (DIL) and verapamil hydrochloride were kindly supplied by Tanabe Seiyaku Co. (Osaka, Japan) and Eisai Co. (Tokyo, Japan). Three CM-grade HEC (Fuji Chemical Co., Osaka, Japan) with different vis-

cosity values and ash contents were used for tablet formulations. The characteristics of a series of CM-type HEC are given in Table 1. The other materials used were of JP XII or reagent grade.

2.2. Preparation of delayed-release tablets

Schematic representation for the preparation of delayed-release tablets has been described previously (Matsuo et al., 1995). The tablet consists of a core tablet (30 mg of DIL) and an outer shell of HEC (570 mg) wrapping the core tablet. HEC polymers were used after grinding in a ball mill for 8 h. The particle size used in this experiment was within a range of 106–250 μm. All the tableting experiments were performed by using a reciprocating press (potassium bromide press, Shimadzu Corp. Kyoto, Japan) with a flat-faced punch and a die. A core tablet containing 30 mg of DIL with a diameter of 5 mm was compressed at an applied force of 200 kg/cm^2 and compression time of 1 min. A half amount of HEC (285 mg) was filled into the die with a diameter of 13 mm to make the powder bed and then compressed at applied force of 40 kg/cm^2 and compression time of 5 s. The core tablet was placed on the center of the HEC disk. After being filled with the remaining half amount of HEC, the die content was compressed at applied force of 400 kg/cm^2 and compression time of 2 min.

2.3. Drug release in vitro

The dissolution test was carried out using the JP XII paddle method with 900 ml of medium at 37°C. The dissolution medium was JP XII disintegration medium 1st fluid (pH 1.2) or 2nd fluid (pH 6.8). The effects of paddle speed on dissolution profiles of DIL from the tablets prepared with HEC were studied at 50, 100 and 200 rpm using the JP XII 1st and 2nd fluids for the dissolution test. The amount of DIL dissolved was assayed by measuring UV absorbance at a wavelength of 237 nm. All the tests were performed in triplicate. The lag time of drug release was defined as the intersected point on the time axis when the straight line part of the release pattern was extended to the time axis. The release rate was calculated from the slope of the straight line of the release pattern with respect to the time axis.

2.4. Water-uptake study

Water-uptake by the delayed-release tablet was examined at room temperature using the apparatus described by Nogami et al. (1969). Briefly, a tablet was placed in the center of a sample tube, and the amount of water decreased with the elapse of time was measured.

2.5. Study in vivo

Five healthy volunteers with a mean weight of 57 kg (range 51–68 kg) ranging in age from 24 to 42 years old participated in this study after giving informed consents after the objective of the study was explained. Each subject received orally DIL at a dose of 30 mg as the delayed-release preparation or the solution with 200 ml of water in a crossover fashion according to a randomized block design with a 7-day wash-out period between dosing. They were fasted for 12 h prior to the experiment and for 5 h after receiving DIL preparations. Venous blood samples were collected from an indwelling venous cannula introduced into the arm at predetermined times. The serum samples were separated by centrifugation at 3000 rpm for 10 min and kept frozen at −20°C until assay.

2.6. Diltiazem analysis

DIL in the serum was assayed using a reversed phase high performance liquid chromatography (HPLC) (Apparatus: Shimadzu LC-6A, Kyoto, Japan). Into each 10-ml screw cap tube were added 1.0 ml of each serum sample, 0.1 ml of the internal standard solution (1.6 μg/ml of verapamil hydrochloride), 0.4 ml of water, 0.5 ml of 1.0 M dipotassium hydrogen phosphate, and 6.0 ml of cyclohexane/diethyl ether (2:1). The samples were extracted using a reciproshaker. After centrifugation, the organic layer was transferred from each tube into a second set of tubes containing 0.5 ml portions of 0.01 N hydrochloric acid. These tubes were reciproshaken to back-extract the drug. Af-

ter centrifugation, a 100 μl portion of the water layer was injected into the HPLC column. Separation was performed with a reversed phase-type column (LiChrospher 100 RP-18(e), 5 μm, 4.0 mm I.D. × 250 mm l). The mobile phase consisted of acetonitrile and water (adjusted by phosphoric acid to pH 3.0) containing 0.35% of triethylamine (70:30). At a flow rate of 1.0 ml/min, the eluate was monitored for absorbance at 240 nm.

2.7. Data analysis

Pharmacokinetic model-independent parameters including maximum serum concentration (C_{max}) and time to maximum serum concentration (t_{max}) were calculated by a standard method. The areas under the serum concentration-time curve ($AUC_{0-24\ h}$) were calculated by the trapezoidal method. The mean residence time ($MRT_{0-24\ h}$) was calculated using the equation reported by Yamaoka et al. (1978). Release rates in vivo were calculated by the Wagner-Nelson method (Wagner and Nelson, 1964). The pharmacokinetic parameters obtained were statistically estimated by Student's *t*-test.

3. Results and discussion

3.1. Release behavior from delayed-release tablets

Fig. 1 shows the release patterns of DIL from the tablets prepared with CM-type HEC of three viscosity grades in JP XII 2nd fluid (pH 6.8). The drug was rapidly released from the tablets after lag periods of several hours in all cases. The lag time to the start of release of DIL was prolonged with an increase in viscosity of CM-type HEC, and was longest in CM-L2 type HEC tablet of the highest viscosity grade among three CM-type HEC's. On the other hand, the release rate of DIL tended to decrease with the prolongation of lag time. The order for lag time was CM-L4 < CM-L3 < CM-L2 in all cases of the rotating speeds (data only at a rotating speed of 100 rpm are shown). This suggests that the lag time can be controlled by selecting CM-type HEC of various viscosity grades.

It should be considered that a vigorous gastrointestinal peristaltic motion and a change in pH in passing through the gastrointestinal tract may affect the release behavior of a drug from the preparations. Thus, to estimate the effect of the peristaltic motion and pH in the digestive fluid, release tests in vitro were performed by changing the paddle speed and pH in the dissolution medium using the JP XII paddle method.

Figs. 2 and 3 show the effect of rotating speed on release patterns of DIL from the tablets prepared with CM-type HEC of three viscosity grades in JP XII 1st (pH 1.2) and 2nd fluids (pH 6.8), respectively. Table 2 also shows the lag time and the apparent release rate at 50. 100 and 200 rpm of the paddle speed in JP XII 1st and 2nd fluids. As shown in Figs. 2 and 3, the lag time was shortened in all cases with an increase in the paddle speed from 50 to 200 rpm. However, the degree of shortening of the lag time tended to be small with an increase in viscosity. On the other hand, the release rate of DIL after the lag time grew faster with an increase in the paddle speed. In particular, the release rate of DIL from the tablet prepared with CM-L2 type HEC, which is of the highest viscosity grade among the three types of HEC polymers, was greatly affected.

In a case of a gel-forming matrix, the lag time can be controlled by changing the particle size, the thickness of the outer shell and the viscosity of

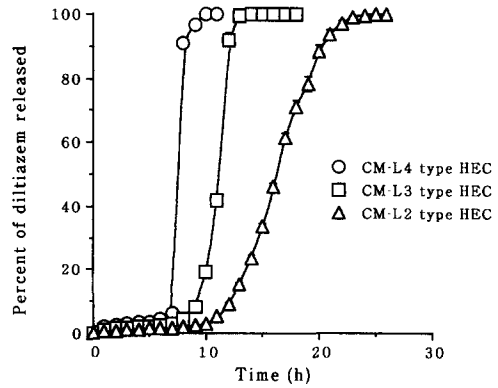

Fig. 1. Release patterns of diltiazem from the tablets prepared with three CM-type HEC in JP XII 2nd fluid (pH 6.8) with a paddle speed of 100 rpm at 37.0 ± 0.5°C. Each bar indicates ± S.E. (n = 3).

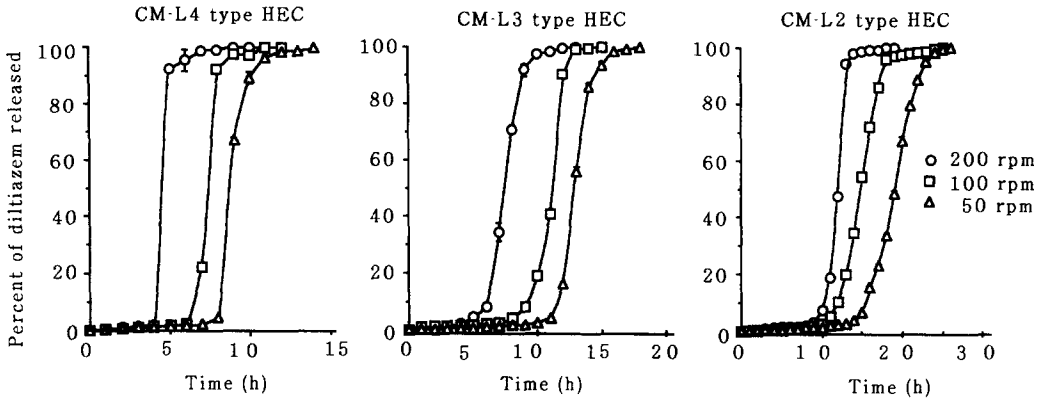

Fig. 2. Effect of paddle speed on release patterns of diltiazem from three CM-type HEC tablets in JP XII 1st fluid (pH 1.2) at 37.0 ± 0.5°C. Each bar indicates ± S.E. (n = 3).

the polymer which influences the penetration of water and drug through the gel layer (Matsuo et al., 1995; Ueda et al., 1994; Gebre-Mariam et al., 1989). On the other hand, drug release from the tablets is generally rate-determined by diffusion of water into the tablet and the diffusion of a dissolved drug through the gel layer and somewhat by tablet erosion (Bamba et al., 1979), furthermore, the diffusion is influenced by viscosity of polymer (Gebre-Mariam et al., 1989). The increase in the rotating speed could facilitate the diffusion of a dissolved drug through the gel layer and the erosion of the outer shell forming the gel layer.

From the external appearance of the tablets, it was confirmed that CM-L2 type HEC formed the gel more firmly than CM-L3 and CM-L4 type HECs since a shape of the tablet prepared with CM-L2 type HEC was kept for a long time after gel formation compared with those with other HECs. Accordingly, it was considered that the thickness of the outer shell did not change much in the tablet prepared with CM-L2 type HEC with high viscosity grades, resulting in a small influence on the lag time due to an insignificant erosion and a relatively large influence on the release rate of the drug from the tablet due to a significant change in diffusion rate of the drug by facilitating the rotating speed. On the other hand, it was observed that the tablet prepared with CM-L4 type HEC formed a fragile gel and became smaller with the lapse of time than those with other HECs. In the case of the tablet prepared with CM-L4 type HEC, therefore, it may be considered that the lag time was influenced by both the erosion of the outer shell and the change in diffusion rate of the drug by facilitating the rotating speed. Consequently, if CM-type HEC polymers of the high viscosity grades are used, it may be harder to be influenced by the rotating force accompanied with gastrointestinal motility since the effect of the rotating speed on lag time becomes smaller with an increase in the viscosity grade of a HEC polymer.

The pH value in the gastrointestinal tract varies greatly when the tablets pass through the lumen. Thus, the release patterns of DIL from CM-type HEC tablets of three viscosity grades were determined in JP XII 1st and 2nd fluids, respectively. As shown in Figs. 2 and 3, there was little difference in the lag time between JP XII 1st and 2nd fluids. These suggest that the lag time is independent of pH in the gastrointestinal tract. However, the release rates of DIL from the tablets tended to be faster in JP XII 1st fluid than those in 2nd fluid, probably owing to greater aqueous solubility of DIL in acid as in JP XII 1st fluid than that in 2nd fluid since DIL behaves as a weak base with pKa value of 7.7.

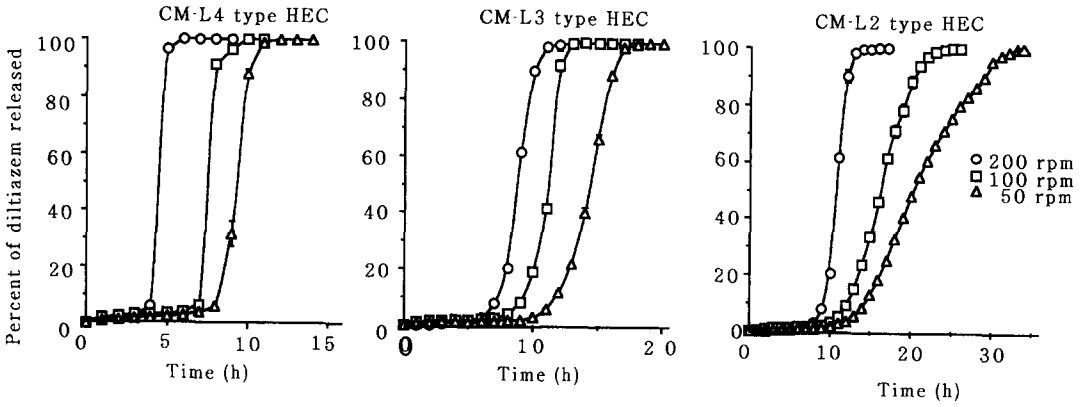

Fig. 3. Effect of paddle speed on release patterns of diltiazem from three CM-type HEC tablets in JP XII 2nd fluid (pH 6.8) at 37.0 ± 0.5°C. Each bar indicates ± S.E. (n = 3).

3.2. Effect of viscosity grade on water-uptake

To estimate penetration of fluid into the gel-matrix tablets, the amount of water-uptake was determined for the tablets prepared with CM-type HEC of three viscosity grades. Fig. 4 shows the effect of viscosity grade of CM-type HEC on water-uptake. There was little difference in the initial rate of water-uptake among CM-type HEC tablets of three viscosity grades. However, after a lapse of a few hours, the rate of water-uptake was decreased with an increase in the viscosity grade of HEC. Consequently, it is suggested that the rate of water-uptake after hydrophilic gel-formation has a close relationship with the viscosity of polymer forming the gel. These results are also supported by the report of Wan et al. (1992) that the rate of water penetration into hydrophilic matrix is determined by the balance of forces promoting water entry and the viscous force opposing it.

3.3. Effect of a water-soluble additive on release patterns

Fig. 5 shows the release patterns of DIL from the tablets prepared by adding lactose to CM-L2 type HEC. The lag time of the tablets containing 20 or 50% lactose was shortened as compared with that of the tablet with only HEC from 12.3 h to 9.5 and 5.1 h, respectively. It is considered that the mechanism of the drug release from the tablets may be explained by a combination of diffusion and a slight erosion of a gel matrix. As the relative content of CM-L2 type HEC was decreased by adding water-soluble lactose, strength of the gel matrix would be decreased, resulting in an increased diffusion rate of the drug and an increased erosion rate of the tablets. Gebre-Mariam et al. (1989) reported that the viscosity of the gel in the diffusional route of a drug affects the release behavior when a drug is released by diffusion through the gel matrix. The change in the lag time and the release rate of DIL from the tablets could be attributed to the decrease in the viscosity in the diffusional route of a drug by addition of lactose.

3.4. Evaluation in vivo

From studies in vitro, it was clarified that the drug release patterns could be controlled by changing the viscosity of the polymer. Thus, evaluation in vivo of the tablets prepared with CM-type HEC of two or three viscosity grades was performed in healthy volunteers. Fig. 6 shows the serum concentration-time profiles of DIL after oral administration of DIL (30 mg) in the dosage form of an aqueous solution and the tablets prepared with CM-type HEC to five healthy volunteers. Table 3 summarizes the pharmacokinetic parameters. The aqueous solution exhibited a

Table 2
Lag time and apparent release rates of diltiazem from CM-type HECs in JP XII 1st (pH 1.2) and 2nd (pH 6.8) fluids with paddle speeds of 50, 100 and 200 rpm at 37°C

HEC type	Paddle speed (rpm)	Lag time (h)		Release rate (%/h)	
		1st fluid	2nd fluid	1st fluid	2nd fluid
CM-L4	50	7.92 ± 0.59	8.43 ± 0.22	42.2 ± 2.39	41.1 ± 0.35
	100	6.70 ± 0.19	6.98 ± 0.01	45.0 ± 0.95	84.9 ± 0.17
	200	3.95 ± 0.48	3.93 ± 0.15	86.4 ± 1.83	90.5 ± 0.33
CM-L3	50	11.5 ± 0.29	10.6 ± 0.29	34.6 ± 1.59	15.4 ± 0.51
	100	8.64 ± 0.43	9.87 ± 0.05	22.8 ± 1.32	20.6 ± 0.92
	200	5.76 ± 0.09	6.74 ± 0.05	27.8 ± 0.69	27.4 ± 0.21
CM-L2	50	15.7 ± 0.71	13.3 ± 0.39	11.0 ± 0.29	5.25 ± 0.31
	100	11.3 ± 0.15	12.3 ± 0.08	14.2 ± 0.50	8.43 ± 0.27
	200	9.78 ± 0.04	8.63 ± 0.18	28.8 ± 0.79	22.6 ± 0.49

Each value represents the mean ± S.E.M. of three experiments.

rapid increase in the serum levels of DIL without any lag time and reached C_{max} in 1 h. On the other hand, a clear lag period was observed in each CM-type HEC tablet. It was observed that the lag time was prolonged with an increase in the viscosity grade of HEC. In addition, with an increase in the viscosity grade of HEC the serum level pattern of DIL became less steep and the peak level values also decreased. The t_{max} and MRT values of CM-type HEC tablets were significantly increased with an increase in the viscosity of HEC and showed only small variations among subjects, indicating that the tablets fulfill their function as a time-controlled release system.

On the other hand, although the AUC values were almost the same, the C_{max} values decreased with prolongation of the lag time.

The lag time of CM-L2 type HEC tablet which was administered to one volunteer (MM) was observed at about 12 h after dose. The lag time was apparently prolonged with an increase in the viscosity in the order: CM-L2 > CM-L3 > CM-L4. Consequently, the CM-L2 type HEC tablet may be considered to be unsuitable for the use in drugs which are expected to exhibit the therapeutic effect several hours after taking medicine, e.g. the midnight to daybreak, since it exhibited too long lag time to the start release of DIL.

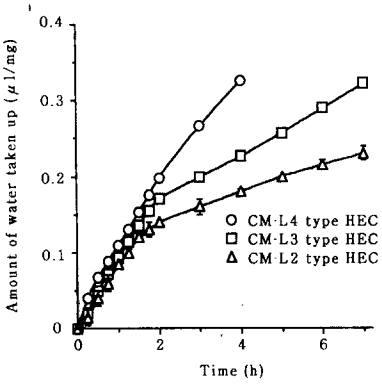

Fig. 4. Effect of viscosity grade on uptake of water in three CM-type HEC tablets in JP XII 2nd fluid (pH 6.8) at room temperature. Each bar indicates ± S.E. (n = 3).

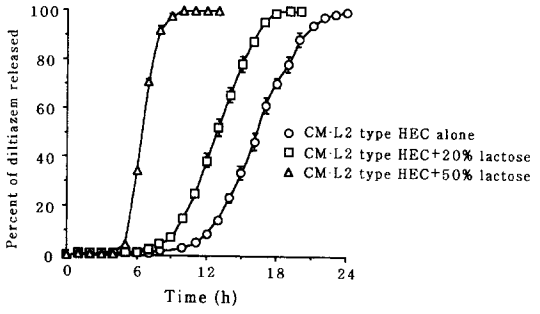

Fig. 5. Effect of lactose on release patterns of diltiazem in JP XII 2nd fluid (pH 6.8) with a paddle speed of 100 rpm at 37.0 ± 0.5°C. Each bar indicates ± S.E. (n = 3).

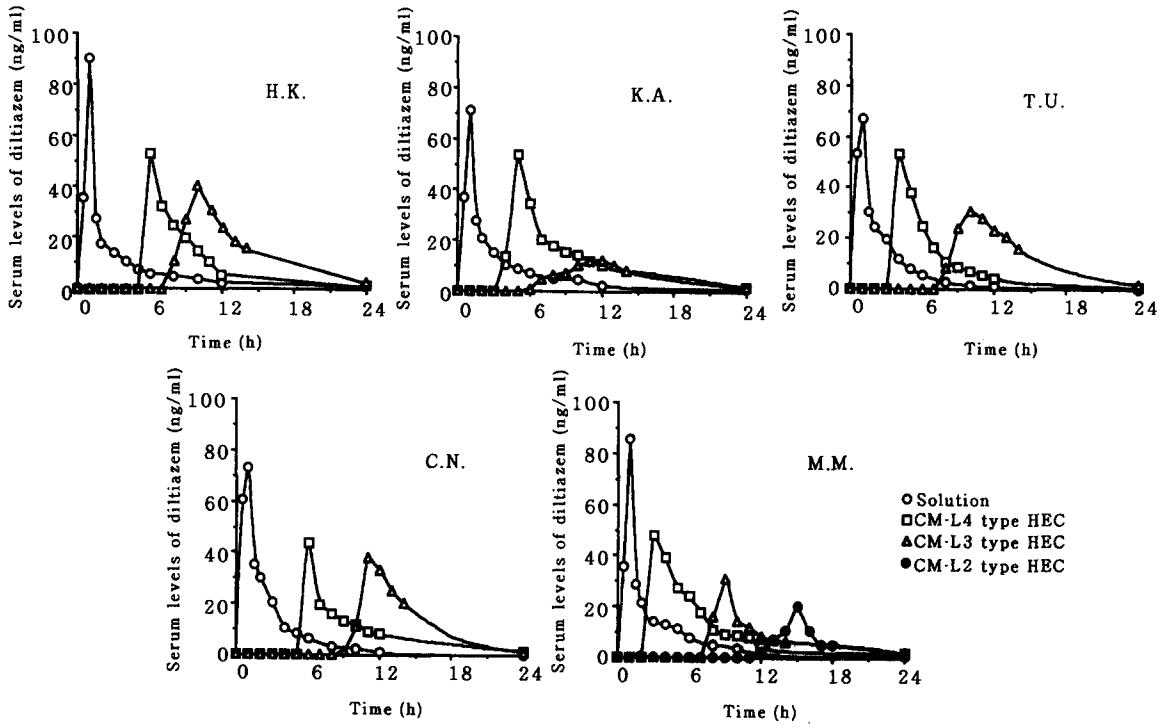

Fig. 6. Serum concentration-time curves of diltiazem after oral administration of CM-type HEC tablet containing 30 mg of diltiazem hydrochloride to five healthy volunteers. CM-L2 type HEC tablet was administered to only one volunteer (Subject M.M.).

The absorption profiles of DIL for three CM-type HEC tablets were calculated by using the Wagner-Nelson method using the systemic elimination rate determined from the serum concentration profile of an aqueous solution. The results of the release profiles in vivo were generally similar to the release profiles in vitro (Fig. 7). Fig. 8 shows the relationship between lag time in vivo and lag time in vitro with paddle speed at 100 rpm in JP XII 2nd fluid on the assumption that the tablets will be burst in the small intestine. The order for the lag time in vivo well corresponded to the order for the lag time in vitro. This suggests that release of DIL from the delayed-release tablet in the gastrointestinal tract could be controlled. However, it was observed that the lag time in vivo was shortened as compared with the lag time in vitro. These results suggest that a erosion of the tablets prepared with HEC was facilitated by a vigorous gastrointestinal peristaltic action.

4. Conclusion

In the present study we evaluated application of HEC as a delayed-release dosage form which rapidly releases a drug from a reservoir device after a predetermined lag time. The system consists of a core containing a drug and an outer shell of CM-type HEC which forms a gel matrix. Prior to drug release, water penetrates through matrix to form a gel in the outer shell. When water reaches the core, a drug compressed in the core dissolves and is rapidly released through the outer gel layer. The lag time could be controlled by changing various conditions of the outer shell, i.e. thickness of the outer shell, viscosity grade of HEC and addition of water-soluble excipients. The study in vivo also indicates that the delayed-release tablets can release DIL in the gastrointestinal tract in a manner similar to that in vitro. HEC has an advantage over hydroxypropylcellulose since the former has more

Table 3
Pharmacokinetic parameters of diltiazem after oral administration of solution and CM-type HEC tablets containing 30 mg diltiazem hydrochloride to healthy volunteers

Dosage form	Lag time (h)			t_{max} (h)			C_{max} (ng/ml)			$AUC_{0-24\ h}$ (ng·h/ml)		$MRT_{0-24\ h}$ (h)		
Solution	0.16 ± 0.02	a	a	1.00	a	a	79.6 ± 4.14	a	a	178.4 ± 6.53	b	3.85 ± 0.38	b	a
CM-L4 tablet	4.43 ± 0.64	a		4.80 ± 0.50	a		52.9 ± 1.7	a		224.6 ± 17.0		8.37 ± 0.53	a	
M-L3 tablet	7.61 ± 0.42			10.4 ± 0.51			32.1 ± 5.01			199.9 ± 24.9		12.6 ± 0.18		

Each value represents the mean ± S.E.M. of five experiments.
[a] $P < 0.01$.
[b] $P < 0.05$.

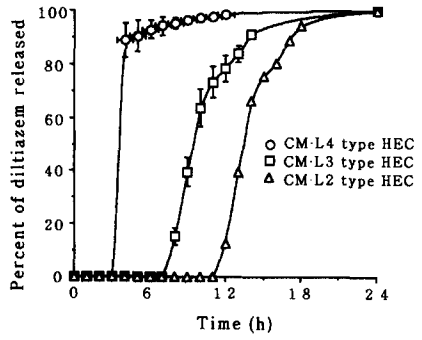

Fig. 7. Release patterns in vivo of diltiazem from CM-type HEC tablets calculated by using a Wagner Nelson method. Each point of CM-L4 and CM-L3 type HEC tablets represents the mean of five subjects and that of CM-L2 type HEC tablet represents the value of subject M.M. The vertical lines show the S.E.M.

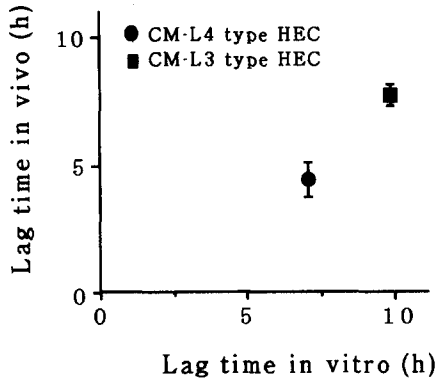

Fig. 8. Relationship between lag time in vivo and lag time in vitro under the condition of a paddle speed of 100 rpm in JP XII 2nd fluid at 37.0 ± 0.5°C. Each bar indicates ± S.E. (in vitro: $n = 3$; in vivo: $n = 5$).

viscosity grades than the latter. Consequently, the delayed-release system using HEC is considered to be applicable to the time-related symptoms which need time-controlled or site-specific delivery in the gastrointestinal tract.

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