The Controlled Release of Prednisolone Using Alginate Gel

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In a release study of alginate gel beads, swelling and erosion of the beads were observed at pH 6.8, whereas no swelling occurred at pH 1.2. The amount of released prednisolone (PL) was greater at pH 6.8 than at pH 1.2. The lower the ratio of mannuronic acid block to guluronic acid block in alginate, the slower the release of PL. An increase in loaded PL in the beads resulted in a slower release of PL. The decrease in bead size caused a rapid release of PL. The addition of sodium alginate propylene glycol ester elevated the extent of PL release. The plasma profile of PL showed sustained-release behavior after the oral administration of the beads to beagles. Furthermore, the correlation between *in vitro* release and *in vivo* absorption of PL for various alginate gel beads was evaluated using deconvolution and convolution methods. The *in vivo* absorption of PL was correlated with the PL release at pH 1.2, and it differed from that at pH 6.8. The release of PL from alginate gel beads *in vivo* appeared to occur under conditions that cause little swelling.

KEY WORDS: alginate; gel beads; controlled release; prednisolone; *in vitro/in vivo* correlation; beagle.

INTRODUCTION

Alginic acid, which is a polysaccharide originally obtained from marine brown-algae, is a linear copolymer consisting of β-(1–4)-D-mannuronic acid (M) and α-(1–4)-L-guluronic acid (G) residues, arranged in homopolymeric blocks of each type (MM, GG) and in heteropolymeric blocks (MG) (1,2). A remarkable property of alginate is its ability to form a gel with divalent or multivalent metal ions (3). It has been proposed that gelation takes place by forming an egg-box junction to associate the metal ions with the GG blocks of alginate chain (4).

Alginate has been used in food additives as a stabilizer, viscosifier, and gelling agent and, also, in pharmaceutical formulations as an antiulcer agent, antacid agent, and wound protectant. In addition, it has been utilized for the immobilization of microorganisms, cells, and enzymes by taking advantage of its gelling property.

Recently, the alginate gel bead, which is a spherical gel prepared by dropping sodium alginate solution into calcium chloride solution, has received attention as an oral drug delivery vehicle for controlled-release preparations. The *in vitro* release of several substances from alginate gel beads has been investigated (5–7). The amount of drug released from alginate gel beads depends on the swelling of the beads and the diffusion of the drug in the gel matrix. However, the factors that affect release of drug from the alginate gel beads and drug absorption after oral administration of the beads are unknown. Similarly, the correlation between the *in vitro* release and the *in vivo* absorption behavior of drug is unclear.

In the present study, prednisolone, as a neutral model drug, was incorporated into alginate to prepare beads. We clarified the effect of composition of uronic acid block (MM/GG ratio), the drug content, the size of the beads, and the addition of alginate propylene glycol ester on the release of drug. Furthermore, the releasing behavior of the drug from alginate gel beads *in vivo* was discussed and correlated with *in vitro* release of the drug.

MATERIALS AND METHODS

Materials

Prednisolone (PL) and sodium prednisolone phosphate were purchased from Uclaf Japan (Tokyo) and Dojin Iyaku Kako (Tokyo), respectively. Sodium alginate and sodium alginate propylene glycol ester (PGA) were donated by Kimitsu Chemical Industries Co., Ltd. (Tokyo) and Kibun Food Chemifa Co., Ltd. (Tokyo), respectively. The physicochemical properties of alginates and PGA used in this study are shown in Table I. All other reagents and solvents were of analytical grade, and deionized-distilled water was used throughout the study.

Preparation of Alginate Gel Beads

PL powder (<100 mesh) was added to a 4% (w/w) solution of sodium alginate, at a PL:sodium alginate weight ratio of 1:2, 1:4, or 1:10, and dispersed homogeneously. The dispersions were dropped using a nozzle (0.65-mm i.d.) or sprayed using an air-spray into gently agitated 0.2 *M* calcium chloride solution. The beads formed were allowed to stand in the solution for 72 hr to be fully cured. The separated and washed beads were dried in air for 48 hr, and then *in vacuo* at room temperature for 24 hr. The gel beads comprised of PGA and sodium alginate were prepared in the same manner as described above, using a 2% (w/w) solution of the mixture of these alginates at a weight ratio of 1:1. The PL content in various alginate gel beads was 6.3 to 24.8%. The ranges of diameters of the dried gel beads prepared by nozzle and by air-spray were 1–2 mm and 100–200 μm, respectively.

Release Studies

The release of PL from PL powder or alginate gel beads (equivalent to 10 mg PL) was examined according to the paddle method of the JP XII dissolution test (100 rpm, 37°C) in 500 mL of first fluid for the disintegration test (pH 1.2) according to JP XII, 1/500 *M* phosphate buffer (pH 6.8). The 5-mL aliquots were withdrawn periodically and immediately filtered through a 0.45-μm membrane filter (Toyo Roshi Kaisha, Ltd., Tokyo). The same volume of fresh medium was added to the test medium. The concentration of PL in the filtrate was determined spectrophotometrically at 250 nm. Mean dissolution time (MDT) was calculated using statistical moment analysis (8).

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Table I. Characteristics of Sodium Alginates and PGA

Alginate	Composition (%) MM	GG	MG	MM/GG ratio	Viscosity (cp)[a]	Degree of esterification (%)
A	8.3	62.8	28.9	0.13	13.3	
B	25.2	38.1	36.7	0.66	13.7	
C	40.1	22.7	37.2	1.77	12.1	
PGA	28.2	31.4	40.4	0.89	102.0	50

[a] A 1% alginate solution at 25°C.

In Vivo Absorption Studies

To four male beagles (9–13 kg), fasted for 24 hr, PL powder (2 mg/kg) or alginate gel beads (equivalent to 4 mg/kg of PL) were administered orally together with 20 mL of water. The suspension of PL in 0.5% sodium carboxymethylcellulose solution and the solution of sodium prednisolone phosphate (equivalent to 2 mg/kg of PL) were administered to the stomach of beagles through a rubber tube and intravenously, respectively. At appropriate intervals a 3-mL blood sample was withdrawn into heparinized syringes from the forefoot vein and immediately centrifuged for 10 min at 3000 rpm to obtain plasma. During the experimental period, no food was allowed, but water was available ad libitum. The drug samples were administered according to a randomized crossover design with a 2-week washout interval.

The plasma concentration of PL was determined by HPLC. One milliliter of plasma was mixed with 6 mL of dichloromethane, with 100 μL of methanolic solution of β-methasone (12 μg/mL) as internal standard. The mixture was centrifuged at 3000 rpm for 5 min after vortex mixing for 10 min. Four milliliters of the dichloromethane phase was evaporated and the residue was redissolved in 100 μL of mobile phase of HPLC, 10 μL of which was injected for the determination of PL. The HPLC conditions were as follows: pump and UV detector, LC-6A type and SPO-6A type (Shimadzu Corporation, Kyoto, Japan); column, Inertsil ODS-2 (5 μm, 4.6-mm i.d. × 150 mm; GL Science Inc., Tokyo); mobile phase, methanol:water (1:1); flow rate, 1 mL/min; detection, 250 nm; and column temperature, 40°C.

Pharmacokinetic Analysis

The pharmacokinetic parameters of PL after oral administration of PL suspension and intravenous administration of sodium prednisolone phosphate were calculated using the MULTI program (9). The area under the plasma concentration–time curve (AUC) was calculated by means of the trapezoidal method. Mean residence time (MRT) was calculated using statistical moment analysis (8).

The cumulative amount of PL absorbed *in vivo* was estimated by the deconvolution method (10) using plasma levels data of PL after oral administration of alginate gel beads as the output function and those after intravenous administration of sodium prednisolone phosphate as the weighting function. The simulated amount of the PL absorbed was calculated by the convolution method of Katori *et al.* (11), using PL release data from alginate gel beads as the input function and the absorption rate constant calculated from the plasma level data obtained after oral administration of PL suspension as the weighting function.

RESULTS AND DISCUSSION

Effect of Uronic Acid Composition of Alginate

The PL release profiles from alginate gel beads of varying uronic acid composition are shown in Fig. 1. PL release from alginate beads was slower than from PL powder at pH 1.2 and 6.8. The plot of PL released from the beads at pH 1.2 against the square root of time gave a straight line (12). The alginate gel is thought to form insoluble matrices of alginate polymer because the alginate carboxylic acid is nonionized at acidic pH (13). We also observed that no bead swelling occurred during the release of PL at pH 1.2. Therefore, PL release from beads at pH 1.2 depends on diffusion through the insoluble matrices of the alginate polymer. The PL release differed slightly among different beads. This result suggests that the difference in the uronic acid composition of alginate may have a rather small effect on the matrix structure of the alginate polymer.

On the other hand, because the plots of the fraction of PL released from the beads at pH 6.8 against the square root of time did not demonstrate a straight line, a different release mechanism of PL at pH 6.8 and pH 1.2 was suspected. PL release from the alginate B or C bead at pH 6.8 demonstrated a sigmoidal profile, characterized by a slow release of PL at the beginning, which increased remarkably at a later stage. Since the gel forming ability with calcium cations was higher for alginate with a lower MM/GG ratio (14–17), swelling and

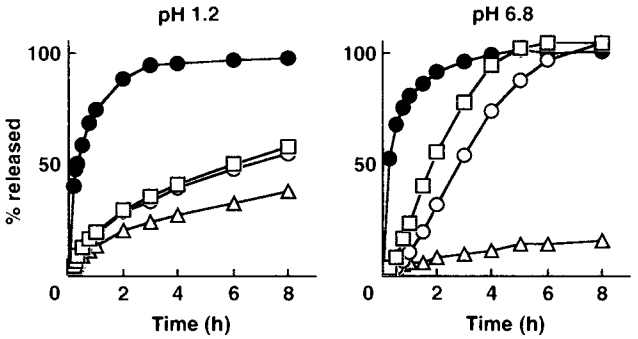

Fig. 1. Effect of alginate composition on the PL release from alginate gel beads at pH 1.2 (left) and pH 6.8 (right), 37°C, and 100 rpm. PL powder (●); alginate gel beads prepared with alginate A (△), alginate B (○), and alginate C (□). All gel beads consisted of each alginate:PL at 4:1.

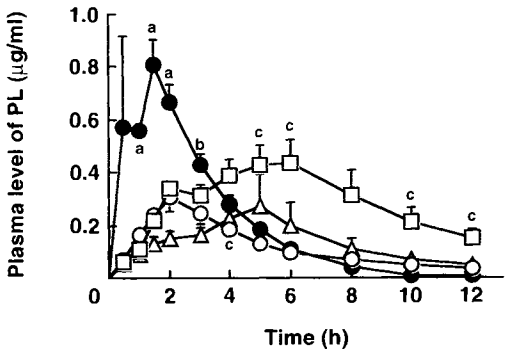

Fig. 2. Effect of alginate composition on the plasma level of PL after oral administration of alginate gel beads to beagles. PL powder (●); alginate gel beads prepared with alginate A (△), alginate B (○), and alginate C (□). All gel beads consisted of each alginate:PL at 4:1. Data represent the mean ± SE (n = 4). (a) $P < 0.05$ vs all beads; (b) $P < 0.05$ vs beads prepared with alginate A and B; (c) $P < 0.05$ vs PL powder.

erosion of the bead prepared by alginate with a high MM/GG ratio occur easily at a neutral pH above the pK_a of alginate (18). In fact, rapid swelling and erosion of the beads prepared from alginate B or C with a high MM/GG ratio were observed at pH 6.8. Therefore, the release of PL from these beads would be depressed by the formation of the gel layer at the initial stage but gradually enhanced by the increasing water content and the erosion of the swollen gel phase at the later stage. The bead prepared by alginate A, which has a low MM/GG ratio, slowly swelled but did not erode because of its strong gel formation. Therefore, the release of PL from this bead was remarkably lower than from other beads at pH 6.8. The release from bead A at pH 6.8 was even slower than from the same bead at pH 1.2.

The mean plasma PL level–time profiles after oral administration of PL powder and the beads to beagles are shown in Fig. 2, with the pharmacokinetic parameters summarized in Table II. When the beads were administered, a delayed peak level time (t_{max}) and lower maximum plasma level (C_{max}) of PL were observed compared with those after administration of PL powder. These plasma level profiles of PL reflected the results of PL release *in vitro*. Administration of the alginate C beads provided satisfactory sustained plasma level profiles of PL, with AUC and t_{max} values higher than those of the alginate A or B beads.

Effect of PL Content in Beads

The release profiles of PL from beads prepared at various ratios of alginate and PL (alginate:PL = 10:1, 4:1, and 2:1) are shown in Fig. 3. The profiles at ratios of 10:1 and 4:1 were similar, but somewhat higher than obtained at a 2:1 ratio at both pH values. As shown in Fig. 4, the beads prepared at a 4:1 ratio of alginate:PL maintained the PL plasma level for a longer period of time *in vivo*. There was no significant difference in the AUC between the beads with alginate:PL ratios of 4:1 and 10:1, whereas the AUC after the administration of the beads with a 2:1 ratio was significantly smaller than the AUC obtained after the administration of the beads with a 4:1 ratio. The results may be explained by the decrease in the surface area of bead per amount of PL in the bead with a high PL content. Therefore, an appropriate ratio of alginate:PL (4:1) must be selected to control PL release from the beads.

Effect of the Size of Beads

The bead prepared by spraying was smaller (diameter, 100–200 μm) than that prepared using a nozzle (diameter, 1–2 mm). The smaller-sized bead showed immediate release of PL, similar to that of PL powder, in both media (Fig. 5). Similarly, *in vivo*, the administration of the smaller beads showed rapid PL absorption, comparable to PL powder (Fig. 6). The rapid release and absorption of PL from smaller beads may be due to the increase in bead surface area. Thus, the critical bead size for sustained release is between 100–200 μm and 1–2 mm in diameter.

Table II. *In Vivo* Pharmacokinetic Parameters and *in Vitro* Release Parameters of PL Preparations at pH 1.2

	In vivo[a]				*In vitro* (pH 1.2)[b]	
Dosage form	t_{max} (hr)	C_{max} (μg/mL)	AUC_{0-12} (hr · μg/mL)	MRT (hr)	Released amount (%)	MDT (hr)
PL powder	1.0 ± 0.5	1.98 ± 0.39[c]	5.28 ± 0.63[c]	2.77 ± 0.25	84.89	0.37
Alginate A:PL, 4:1	3.5 ± 1.7*	0.31 ± 0.20*	1.61 ± 0.98*,**	5.02 ± 0.73*	32.97	6.38
Alginate B:PL, 4:1	1.8 ± 0.5**	0.31 ± 0.09*	1.43 ± 0.29*,**	4.28 ± 0.26*,**	28.62	8.38
Alginate C:PL, 4:1	4.3 ± 2.1*	0.48 ± 0.16*	3.43 ± 1.06	5.83 ± 0.60*	50.27	12.02
Alginate C:PL, 10:1	3.8 ± 1.0*	0.51 ± 0.22*	2.84 ± 1.95*	4.58 ± 0.82*,**	52.53	4.24
Alginate C:PL, 2:1	2.5 ± 0.6	0.42 ± 0.03*	1.62 ± 0.19*,**	3.97 ± 0.34*,**,***	30.47	6.27
Alginate C:PL, 4:1, of smaller size	2.0	0.91	3.69	3.42	76.95	1.33
Alginate B:PGA:PL, 2:2:1	1.8 ± 1.0	0.49 ± 0.12*	2.14 ± 0.71*	3.74 ± 0.42*,**,***	42.41	5.19

[a] Values represent the mean ± SE (n = 4) except for alginate C:PL, 4:1, of a smaller size (n = 1).
[b] Values represent the mean (n = 3).
[c] Corrected for the dose by multiplying by 2.
* $P < 0.01$ vs PL powder.
** $P < 0.01$ vs alginate C:PL, 4:1.
*** $P < 0.01$ vs alginate A, PL = 4:1.

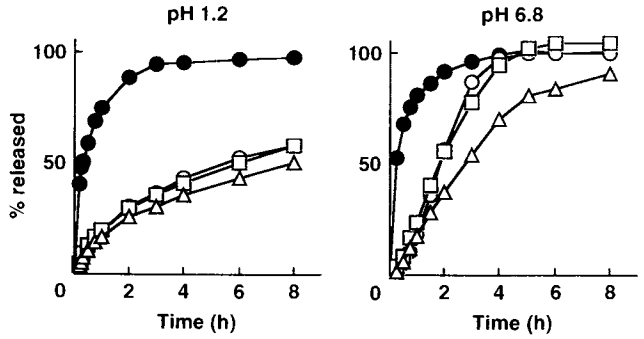

Fig. 3. Effect of the PL content in alginate gel beads on PL release from alginate gel beads at pH 1.2 (left) and pH 6.8 (right), 37°C, and 100 rpm. PL powder (●); alginate gel beads consisting of alginate C:PL at 10:1 (○), 4:1 (□), and 2:1 (△).

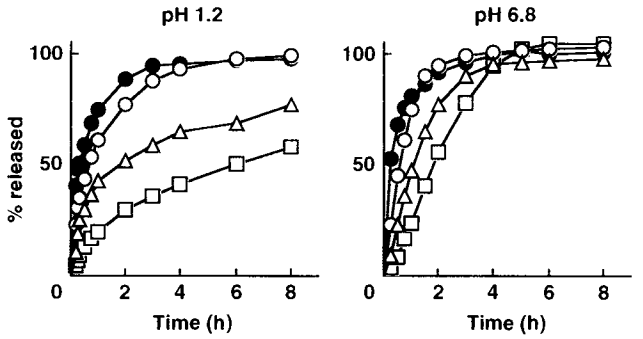

Fig. 5. Effects of the size of gel beads and PGA addition to alginate on the PL release from alginate gel beads at pH 1.2 (left) and pH 6.8 (right), 37°C, and 100 rpm. PL powder (●); alginate gel beads consisting of alginate C:PL at 4:1 with a diameter of 1–2 mm (□) and 100–200 μm (○) and consisting of alginate B:PGA:PL at 2:2:1 (△).

Effect of PGA Addition

The PL release profile from the bead comprised of PGA and alginate B with a similar uronic acid composition is shown in Fig. 5. The release of PL from the bead containing PGA was faster than from the bead prepared by alginate alone in both media. As shown in Fig. 6, a rapid increase in the plasma level of PL was observed compared with the bead prepared by alginate alone. This result reflects the *in vitro* PL release profile.

PGA has less ability to form gel with divalent cations than intact alginate because 50% of the carboxyl groups related to binding with divalent cation are esterified with propylene glycol (19). Therefore, the rapid swelling and erosion of the bead may be attributed to the increase in the release rate of PL from the bead consisting of PGA and alginate.

In Vitro/in Vivo Correlation

The release behavior of PL *in vitro* was compared with the absorption behavior of PL *in vivo* to explore the drug release pattern from the beads in the gastrointestinal tract. Several methods have been reported to compare the amount of drug release *in vitro* and drug absorption *in vivo* (20,21). Recently, Katori *et al.* (11) studied the *in vitro/in vivo* correlation for a controlled-release formulation of *d*-chlorpheniramine maleate using convolution and deconvolution to simulate the drug absorption from *in vitro* release data and to estimate the drug absorption from *in vivo* plasma level data, respectively. They demonstrated that convolution and deconvolution are useful for evaluation of the *in vitro/in vivo* correlation, especially if the drug absorption or the drug release from a formulation is hard to fit to a certain mathematical model.

As shown in Fig. 7, absorption of PL *in vivo* was terminated within 2 to 6 hr after dosing of any bead. PL absorption after administration of the beads was incomplete. The estimated total amounts of PL absorbed *in vivo* fitted well with the simulated absorption curves using the release data at pH 1.2 in comparison with those at pH 6.8. The correlations between the estimated amounts of absorbed PL *in vivo* and the simulated absorption amounts *in vitro* at both pH's until the time of absorption termination *in vivo* are displayed in

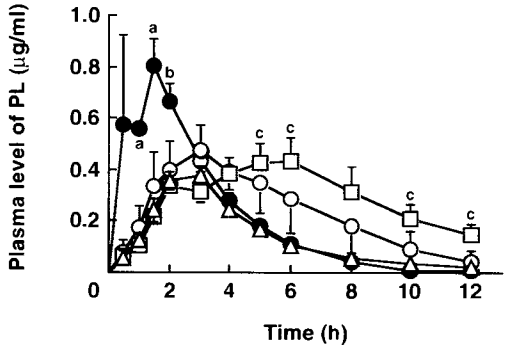

Fig. 4. Effect of the PL content in alginate gel beads on the plasma level of PL after oral administration of alginate gel beads to beagles. PL powder (●); alginate gel beads consisting of alginate C:PL at 10:1 (○), 4:1 (□), and 2:1 (△). Data represent the mean ± SE (n = 4). (a) $P < 0.05$ vs all beads; (b) $P < 0.05$ vs beads consisting of alginate C:PL at 4:1 and 2:1; (c) $P < 0.05$ vs PL powder.

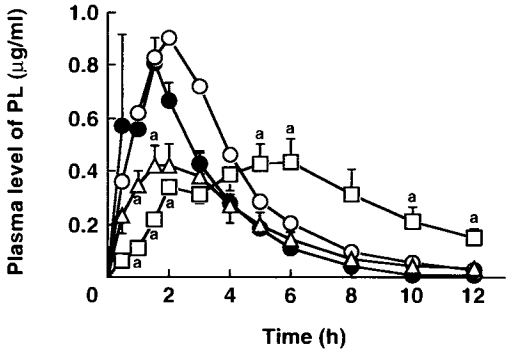

Fig. 6. Effects of the size of gel beads and PGA addition to alginate on the plasma level of PL after oral administration of alginate gel beads to beagles. PL powder (●); alginate gel beads consisting of alginate C:PL = 4:1 with a diameter of 1–2 mm (□) and 100–200 μm (○) and consisting of alginate B:PGA:PL at 2:2:1 (△) with a diameter of 1–2 mm. Data represent the mean ± SE (n = 4) except for alginate beads consisting of alginate C:PL at 4:1 with a diameter of 100–200 μm (n = 1). (a) $P < 0.05$ vs PL powder.

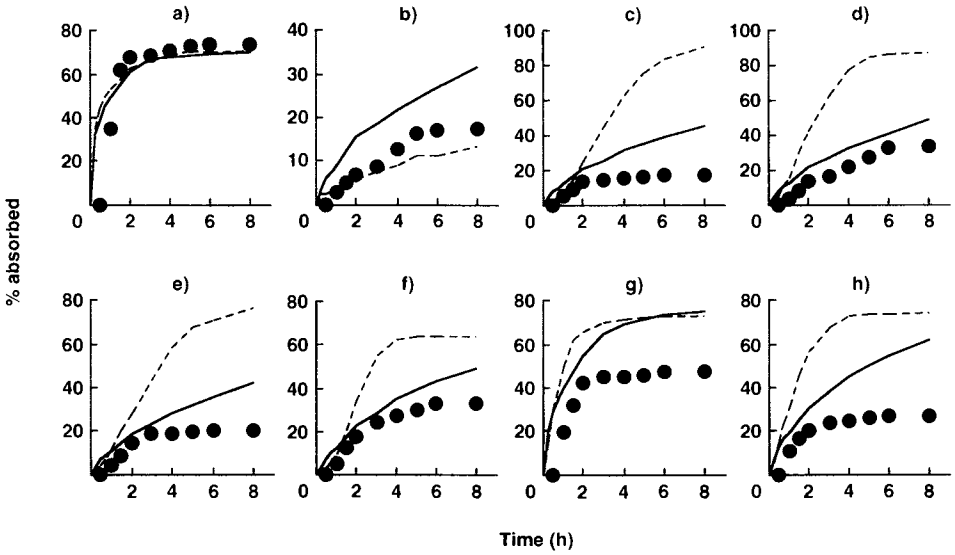

Fig. 7. Comparison of the mean cumulative amount of PL absorbed *in vivo* calculated by deconvolution (●) and the simulated absorbed amount *in vitro* calculated by convolution (pH 1.2, ——; pH 6.8, ----). (a) PL powder; alginate gel beads consisting of (b) alginate A:PL at 4:1, (c) alginate B:PL at 4:1, (d) alginate C:PL at 4:1, (e) alginate C:PL at 2:1, (f) alginate C:PL at 10:1, (g) alginate C:PL at 4:1 with a diameter of 100–200 μm, and (h) alginate B:PGA:PL at 2:2:1.

Fig. 8. A better correlation was obtained at pH 1.2 than at pH 6.8 *in vitro*. This result indicates that the beads in the gastrointestinal tract are exposed to conditions that cause little swelling and erosion of the beads. However, the reason for this phenomenon is not clear. The long residence of the beads in the stomach by adhesion to the gastric mucosa, the short residence of the beads in the intestinal tract, and/or the small and viscous digestive juice may cause insufficient swelling and erosion of the beads. The beads did not adhere to the gastric mucosa after administration to rat (data not shown), arguing against protracted residence in the stomach.

The correlations between *in vivo* pharmacokinetic parameters and *in vitro* release parameters at pH 1.2 were examined. The AUC and the cumulative amount of released PL until the time of absorption termination, and the MRT and MDT were compared (Table II). Good correlations ($r = 0.96$ in the former and $r = 0.87$ in the later) were obtained. These release parameters obtained under conditions without swelling will be useful in predicting *in vivo* drug absorption.

In conclusion, drug release *in vitro* and drug absorption *in vivo* from alginate gel beads are both influenced by the composition of the beads, and the *in vivo* drug absorption correlated well with the *in vitro* drug release from the beads at pH 1.2. In the present study, a satisfactory sustained-release formulation of PL demonstrating a large AUC, t_{max}, and MRT was obtained using the bead consisting of alginate C:PL at 4:1 with a diameter of 1–2 mm, suggesting that alginate gel beads might be useful as vehicles for controlled-release formulations.

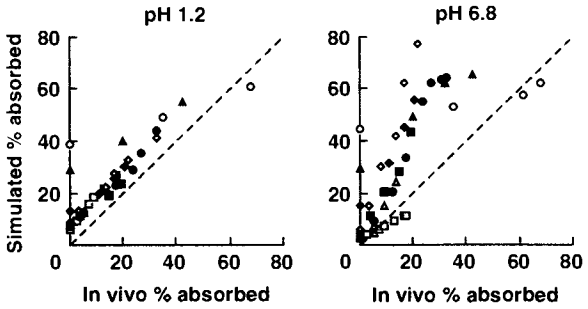

Fig. 8. Relationship between the mean cumulative amount of PL absorbed *in vivo* calculated by deconvolution and the simulated absorbed amount *in vitro* calculated by convolution at pH 1.2 (left) and pH 6.8 (right). Symbols represent the alginate gel beads described in the legend to Fig. 7 as follows: ○ (a), □ (b), △ (c), ◇ (d), ● (e), ■ (f), ▲ (g), and ◆ (h).

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