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Characterization of organogel as a novel oral controlled release formulation for lipophilic compounds

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ABSTRACT

A low molecular mass gelator can form soft solids in a variety of organic liquids and vegetable oils. These soft solids are generally called organogels. In this study, we prepared organogel using 12-hydroxystearic acid (12-HSA) as a gelator for soybean oil and investigated its characteristics as a controlled release formulation for lipophilic compounds. The release rate of ibuprofen, a model lipophilic compound, from organogel decreased with the increase of 12-HSA concentration in the formulation; however, the difference in the concentration of 12-HSA in the formulation did not affect the diffusivity of ibuprofen in the organogel. The erosion constant of organogel in the intestinal tract was examined by using simulated gastric fluid and intestinal fluid. Regardless of 12-HSA concentration in the formulation, organogel is very stable in the simulated gastric fluid. On the other hand, the erosion constant of organogel in the simulated intestinal fluid increased with the decreasing concentration of 12-HSA. Therefore, it is speculated that the difference in the release rate of ibuprofen among organogels with various concentrations of 12-HSA was mainly caused by the difference in the erosion rate. To characterize the organogel effect *in vivo*, ibuprofen was orally administered to rats in an aqueous suspension or organogel. Ibuprofen concentration in plasma rapidly increased after administration with an aqueous suspension, whereas organogel suppressed the rapid absorption. In conclusion, organogel is clearly useful as an oral controlled release formulation for lipophilic compounds.

1. Introduction

Recently, the strategy for new drug development has been changed by the rapid progress of the technique of combinatorial chemistry, high-throughput screening and structural analysis of the biomembrane, such as receptors and channels, with the result that the number of lipophilic or poorly water-soluble compounds for drug candidates increased (Lipinski et al., 2001). Generally, lipophilic compounds are rapidly absorbed from gastrointestinal tissue after oral administration due to their high membrane permeability. Among these, compounds which are rapidly eliminated from the body need frequent repeated dosing (Malonne et al., 2004; Su et al., 2003). The utilization of a controlled release formulation is considered a good strategy offering many advantages to the patients. A multi-layered hydrophilic matrix (Conte et al., 1993), polyethylene oxide matrix (Choi et al., 2003), three-layer guar gum matrix (Krishnaiah et al., 2002), etc. were investigated as novel controlled release systems, although most are for hydrophilic compounds. In most controlled release formulations for lipophilic compounds, the solid compound is dispersed in the hydrophilic polymer (Cheng et al., 1999; Abrahamsson et al., 1998). However, the dissolution process of lipophilic compounds in the matrix is considered to be affected by various conditions, such as the secreted amount of bile juice and pH in the intestinal tract (Horter and Dressman, 2001), resulting in a large variation of absorption. When lipophilic compounds are administered as a solid, their solubility in the intestinal tract is varied; therefore, administration of a dissolved compound could be appropriate to maintain the stable absorption of compounds.

Oils are safe and interesting materials for formulations, especially lipophilic compounds, because of their very high potential for the solubility of lipophilic compounds. Although they are used as excipients for liquid formulations, such as injection, they are not suitable for oral dosage formulations because of the difficulty in handling liquids. From the viewpoint of production cost, capsules filled with liquid are not the ideal formulation.

12-Hydroxystearic acid (12-HSA) is a low molecular mass gelator (Tamura et al., 1994; Tamura and Ichikawa, 1997). Low molecular mass gelators can form soft solids in a variety of organic liquids, such as benzene, toluene, cyclohexane, vegetable oils and so on, and are generally known as organogels. Regarding the effect of oils, it is reported that 12-HSA organogels form hydrogen bonds between 12-HSA molecules and make a network structure in the oil phase (Tamura et al., 1994). This organogel formed by 12-HSA exists

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in the gel state at room temperature; however, it becomes liquid by heating over the melting point of 12-HSA. If the lipophilic compound can be gradually released from organogels in the dissolved state, it may be used as a controlled release formulation.

In this study, we characterize the organogels formed by 12-HSA as a controlled release formulation for lipophilic compounds.

2. Materials and methods

2.1. Materials

Ibuprofen (Wako Pure Chemical Industries Ltd., Osaka, Japan) was used as a model compound because it was highly lipophilic (Avdeef et al., 1998) and was rapidly excreted from the body (Ghorab and Adeyeye, 2003). The calculated log D (pH 7.0), log P and pK_a values were 1.16, 3.722 and 4.41, respectively (ACD/PhysChem Suite, Advanced Chemistry Development Inc., Ontario, Canada). Solubility of ibuprofen in water and soybean oil measured by the conventional flask-shaking method were 3.7 and 15.4 mg/mL, respectively. Flurbiprofen and soybean oil as well as 12-hydroxystearic acid (12-HSA), a gel-forming agent, were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Sodium taurocholate was from Nacalai Tesque Inc. (Kyoto, Japan). Lipase from porcine pancreas (EC 3.1.1.3) was from Sigma Chemical Co. Ltd. (St. Louis, MO, USA).

2.2. Preparation of organogel

For the formulation including ibuprofen in the organogel, both ibuprofen and 12-HSA were weighed and added to soybean oil. Ibuprofen is easily dissolved in the oil at room temperature, because of its high lipophilicity. The mixture was then heated at 75 °C with gently stirring to melt 12-HSA. After 12-HSA was completely melted, the mixture was poured into the body and cap of a gelatin capsule to be gradually cooled to solidify the soybean oil. The body and cap were adhered to each other just before the organogel was completely solidified. All the organogel used in this study included more than 2% of HSA, was completely solidified and did not show fluidity. It was reported that 12-HSA formed helical structure of fibrous aggregate in soybean organogel (Tachibana and Kambara, 1965, 1967; Tachibana et al., 1970). Therefore, it is speculated that the structure of organogel in this study was similar one. Furthermore, it was also reported that the stiffness of organogel formed by 12-HSA remarkably lowered when lecithin was added to the gel and this was caused by the interaction between 12-HSA and lecithin (Tamura and Ichikawa, 1997). Thus, stiffness of organogel may be altered when contaminants coexisted in organogel. However, all the organogels used in this study were very stiff regardless of 12-HSA amounts. Because organogels used in this study included no contaminant, the helical structure of fibrous aggregate of 12-HSA in gel might be maintained, resulting in the stiff organogel.

2.3. Release of ibuprofen from organogel in vitro

The release of ibuprofen from the formulation was evaluated by the dissolution test (Paddle method) of the Japanese Pharmacopoeia Fifteenth Edition (JP15) with some modification. Phosphate-buffered saline (pH 6.8), including 10 mM of sodium taurocholate and 375 U/mL of lipase from porcine pancreas, was used as simulated intestinal fluid according to the previously published method (Nishihata et al., 1993). The rotation rate of the paddle and the volume of test solution were 50 rpm and 250 mL, respectively. Various organogels formed in capsules (size #1) containing 5 mg ibuprofen were used as test formulations. Five hundred microliters of the test solution were periodically withdrawn and the same volume of simulated intestinal solution was added to correct the volume decrease. The concentration of ibuprofen in each sample was determined by the HPLC method.

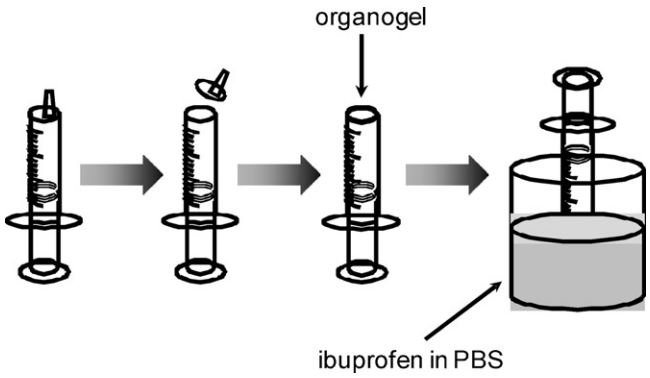

Fig. 1. Diffusion of ibuprofen in organogel.

2.4. Evaluation of diffusivity of ibuprofen in organogel

The diffusion coefficient of ibuprofen in organogel was determined by the previously published method (Upadrashta et al., 1993) with some modification. As shown in Fig. 1, organogel composed of 2%, 3%, 5% and 10% of 12-HSA (without ibuprofen) was formed in the plastic syringe (2.5 mL) with the tip removed. The syringe was vertically fixed and immersed in phosphate-buffered saline (pH 6.8) containing 3.5 mg/mL ibuprofen at 37 °C. The solution was gently stirred at the rate of 50 rpm. Twenty-four hours after starting, the syringe was removed from the solution and organogel was recovered from the syringe by pushing the plunger. Oil matrix was sliced every 1.5 mm and discs of organogel were obtained as shown in Fig. 2. The ibuprofen concentration in each disc was determined. The diffusion of the substances in the gel was considered to follow Fick's low. The solution of Fick's second low was shown by the following equation (1) as previously reported (Upadrashta et al., 1993).

$$\frac{C_i}{C_0} = 1 - \mathrm{erf}\left(\frac{x}{2\sqrt{D_i t}}\right) \quad (1)$$

where C_i is the ibuprofen concentration in #i disc, C_0 is the ibuprofen concentration at the surface of the organogel–PBS border. erf is error function and is basically similar with the standard normal distribution function. In this equation, x is the distance from the organogel–PBS border to the center of #i disc. D_i is the diffusion coefficient and t is time. The error function is as follows:

$$\mathrm{erf}(z) = \frac{2}{\sqrt{\pi}} \int_0^z e^{-y^2}\, dy \quad (2)$$

In the process of calculating the diffusion coefficients, we did not determine C_1 in #1 disc. Ibuprofen remained on the surface

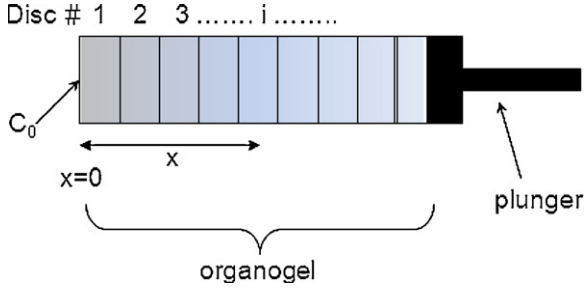

Fig. 2. Determination of ibuprofen concentration in each organogel disc.

of organogel ($x = 0$) could not be completely wiped off because organogel surface directly contacted with the solution. Similarly, C_0 could not also determine directly. Therefore, the diffusion coefficients were obtained by fitting the set of ibuprofen concentration data (except C_0 and C_1) of each experiment to Eq. (1).

2.5. Erosion of organogel

Organogel containing ibuprofen (5 mg/g of gel) was used to evaluate the erosion of the formulations. Organogel containing 2–10% of 12-HSA formed in the gelatin capsule (size #1) was weighed and incubated at 37 °C in 10 mL test solution. The first solution of the disintegration test for JP15 (pH 1.2), PBS (pH 6.8) and PBS (pH 6.8) containing 10 mM sodium taurocholate or 375 U/mL lipase and simulated intestinal solution (PBS (pH 6.8) with 10 mM taurocholate and 375 U/mL lipase) were used as test solutions. The test solution was continuously gently stirred at 50 rpm during incubation period. At 1, 2, 3, 4, 6, 8 h after starting, organogel was removed from the test solution and dried *in vacuo* for 12 h. The weights of organogel before and after incubation were measured and fitted to the following equation to calculate the erosion rate constant (k) according to the previously published method (Kavanagh and Corrigan, 2004).

$$\left(\frac{W_d}{W_i}\right)^{1/3} = 1 - kt \quad (3)$$

where W_d and W_i are the dried weight of organogel after and before incubation, respectively. k is the erosion constant and t is incubation time.

2.6. Experimental animals

Male Wistar rats weighing 250–350 g (Japan SLC Inc., Shizuoka, Japan) were used as experimental animals.

2.7. Oral administration experiment in vivo

The day before the experiment, the rats were lightly anesthetized with ether and were implanted surgically with a combination of Phicon (Fuji Systems Ltd., Tokyo, Japan) and PE50 (Clay Adams, Parsippany, NJ) in a catheter, which was inserted into the right jugular vein for blood sampling. The catheter was externalized through the back of the neck and secured. The rats were fasted 18 h before the experiment, but drinking water was supplied *ad libitum*. Either organogel (10% HSA) or soybean oil with dissolved ibuprofen was orally administered to rats using a stomach catheter. Organogel containing ibuprofen (concentration; 10 mg/g of gel) was formed in the syringe in this experiment. Ibuprofen aqueous suspension was administered to rats in the control experiment. For all experiments, the amounts of formulation and dose of ibuprofen were adjusted to 0.5 g and 5 mg, respectively. Four hundred microliters of blood were periodically withdrawn from the jugular vein for 6 h. Blood was centrifuged at 10,000 rpm for 5 min to obtain a plasma sample. Separately, 0.5 mg of ibuprofen was intravenously administered to rats through the catheter inserted into the jugular vein and plasma samples were obtained by the similar method with oral administration experiment. AUC (0–∞) was calculated for all *in vivo* experiments by extrapolation of terminal phase of plasma concentration–time profile. By using those AUC values, bioavailability was calculated.

2.8. Determination of ibuprofen in the samples

For the *in vitro* release experiment, the sample of the test solution (500 μL) was filtered through a 0.45 μm membrane filter (ADVANTEC, Tokyo, Japan) and 20 μL filtrate was injected into the HPLC system.

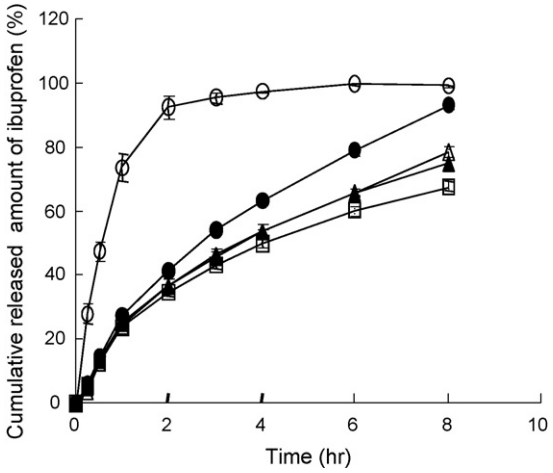

Fig. 3. Release profiles of ibuprofen from organogel including (○) 0%, (●) 2%, (△) 3%, (▲) 5% and (□) 10% of 12-HSA in simulated intestinal fluid. Each value represents the mean ± SE of three experiments.

For the diffusion experiment, sliced discs of organogel were dissolved in chloroform. Flurbiprofen dissolved in acetonitrile (70 μg/mL) was added as an internal standard. The mixture was alkalized by the addition of Tris/HCl buffer (50 mM Tris/5.7 mM HCl), vigorously shaken and centrifuged at 3000 rpm for 10 min. An aliquot of the Tris/HCl phase was taken and 0.1 M HCl and chloroform were added to extract ibuprofen into the chloroform phase. After centrifuging, the chloroform phase was taken and dried *in vacuo*. The residue was reconstituted with the mobile phase of HPLC and 20 μL of the sample was injected to HPLC system.

For the plasma sample obtained from animal experiments, 800 μL methanol was added to 200 μL plasma sample for deproteinization. The mixture was vigorously shaken and centrifuged at 10,000 rpm for 4 min. The supernatant (800 μL) was taken and dried *in vacuo*. The residue was reconstituted with the mobile phase of HPLC and 20 μL of the sample was injected into the HPLC system.

2.9. HPLC condition

Ibuprofen was assayed by reversed phase HPLC on a Mightysil RP-18 GP column (150 mm × 3.0 mm, 5 μm; Kanto Chemical Co., Inc., Tokyo, Japan). HPLC consisted of a LC-10AS pump, SPD-6A spectrophotometric detector and C-R6A integrator (Shimadzu Co., Kyoto, Japan). The mobile phase was acetonitrile:0.12% acetic acid aqueous solution = 2:3 and was run at a flow rate of 1.5 mL/min. The UV detector was set at 220 nm. Column temperature was maintained at 40 °C.

2.10. Data analysis

All values are expressed as the mean ± SE. Statistical analysis was performed using the Mann–Whitney *U*-test. The level of significance was taken as $p < 0.05$.

3. Results and discussion

3.1. Controlled release of ibuprofen from organogel in vitro

The release rate of ibuprofen from organogel was evaluated in the simulated intestinal fluid, including lipase and sodium taurocholate. As shown in Fig. 3, ibuprofen was rapidly released when no gel-forming agent was added to soybean oil. On the other

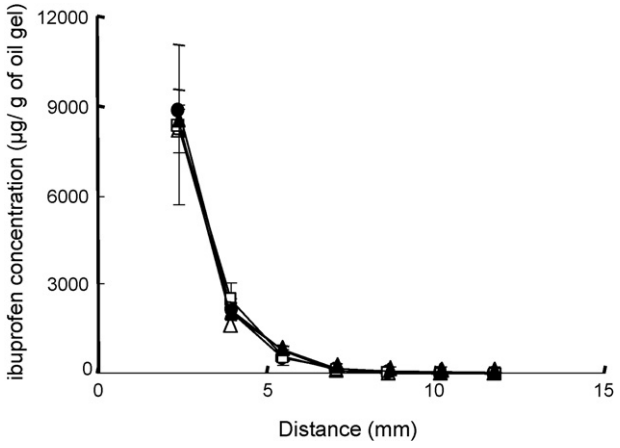

Fig. 4. Relationship between the distance from organogel–ibuprofen solution border and ibuprofen concentration in organogel including (●) 2%, (△) 3%, (▲) 5% and (□) 10% 12-HSA. Each value represents the mean ± SE of three experiments.

hand, the release rate of ibuprofen was significantly decreased for all the organogels. As the 12-HSA concentration in the formulation increased, the release rate decreased. The released amount of ibuprofen from organogels containing 2%, 3%, 5% and 10% of 12-HSA during 8 h reached 93%, 78%, 75% and 68%, respectively. This result shows that the organogel formed by 12-HSA has potential for controlled release.

3.2. Diffusion of ibuprofen in organogel

The mechanism of drug release from the controlled release formulation of the matrix type is generally explained as diffusion-controlled release system or erosion-controlled release system (Miyajima et al., 1998; Mehta et al., 2001). The former controls the release rate by decreasing drug diffusivity in the matrix. In contrast, the latter slowly releases the drug by erosion by water, enzyme and so on. First, the diffusion coefficient of ibuprofen in the organogel composed of various concentrations of 12-HSA was measured. Fig. 4 shows the relationship between the ibuprofen concentration in the discs and the distance from the boundary of ibuprofen solution – organogel surface. Regardless of the concentration of 12-HSA in organogel, the ibuprofen concentration decreased with increasing distance from the boundary. From this result, it is obvious that the driving force of diffusion could be the gradient of ibuprofen concentration in organogel. The diffusion coefficients of ibuprofen in each organogel are listed in Table 1. No significant difference was observed among organogels; therefore, the difference in the concentration of 12-HSA in the range of 2–10% did not affect the diffusivity of ibuprofen in the organogel. It is reported that the diffusion coefficient of salicylic acid in the ethylene glycol dimethacrylate (EGDMA) gel decreased with increasing EGDMA concentration (Wood et al., 1982). They speculated that the area where the salicylic acid molecule can diffuse becomes smaller because the network structure formed by polymer matrix becomes

Table 1
Effect of 12-HSA concentration on the diffusivity of ibuprofen in organogel.

Concentration of 12-HSA (%)	Diffusion coefficient ($\times 10^7$ cm^2/s)
2	1.23 ± 0.27
3	1.14 ± 0.07
5	1.12 ± 0.12
10	1.11 ± 0.31

Each value represents the mean ± SE (n = 3).

Table 2
Effect of 12-HSA concentration on the erosion rate of organogel in the simulated intestinal fluid.

Concentration of 12-HSA (%)	Erosion rate constant ($\times 10^3$ h^{-1})
2	9.29 ± 0.52
3	2.46 ± 0.37
5	1.41 ± 0.55
10	0.04 ± 0.02

Each value represents the mean ± SE (n = 3).

denser as the EGDMA concentration increases. On the other hand, it was also shown that drug diffusivity in the gel has a threshold and the control of diffusivity by increasing the polymer concentration becomes impossible (Chen, 1974). For the organogel used in this study, it is known that 12-HSA molecules also form a network structure (Tamura et al., 1994). Because the network structure in even 2% of 12-HSA organogel reached saturation, the difference in the 12-HSA concentration might not affect the diffusion coefficients of ibuprofen.

3.3. Erosion of organogel in simulated gastrointestinal fluid

The results of the release experiment *in vitro* showed that the release rate of ibuprofen from organogel can be controlled, but the diffusion coefficient of ibuprofen in organogel did not change regardless of the 12-HSA concentration; therefore, we speculated that the erosion of organogel might relate to the release rate of ibuprofen. First, the erosion of oil matrix in the stomach was investigated. The time course of the organogel weight in the simulated gastric fluid (pH 1.2) is shown in Fig. 5(A). No organogel used in this study showed a significant weight change during 8-h incubation. This result suggests that organogel is very stable in the stomach regardless of the 12-HSA concentration and passes into the intestine without disintegration when it is orally administered. Next, we checked the erosion of organogel in the simulated intestinal fluid (pH 6.8). As shown in Fig. 5(B), organogel containing 2% of 12-HSA gradually eroded and the gel weight remaining after 8-h incubation had decreased to about 75% of the initial weight. As the concentration of 12-HSA in gel increased, organogel hardly eroded in the simulated intestinal fluid. The erosion constant of each organogel was calculated and listed in Table 2. The erosion constant decreased with the increasing concentration of 12-HSA in organogel; therefore, the difference in the release rate of ibuprofen among organogels with various concentrations of 12-HSA was mainly caused by the difference in the erosion rate. In order to clarify the mechanism of the erosion of organogel in the simulated intestinal fluid, the effect of lipase and taurocholate on erosion was investigated using organogel with 2% HSA, the formula that eroded most easily. The erosion profiles of organogel with 2% HSA in various test solutions are shown in Fig. 6. In the test solutions without lipase (e.g., containing only taurocholate in PBS), no erosion was observed for 8 h. On the other hand, the weight of gel significantly decreased after 4-h lag time when organogel was incubated in the solution containing only lipase. This result clearly suggests that lipase partly participates in the erosion of organogel. Pancreatic lipase specifically hydrolyzes and severs the esteric bonding of triglyceride included in lipid in foods at 1- and 3-positions in the gastrointestinal tract; therefore, in organogel, esteric bonding of triglycerides in soybean oil is considered to be severed by lipase. When the solution contained both lipase and taurocholate, the erosion of organogel greatly increased compared to that containing only lipase. The weight of organogel remaining after 8-h incubation in the solution with lipase and taurocholate decreased to 75% of the initial weight, suggesting that the erosion of triglyceride by

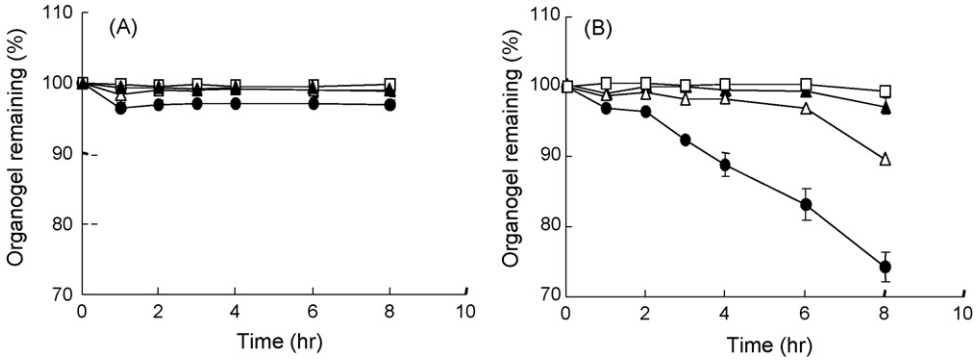

Fig. 5. Erosion of organogel including (●) 2%, (△) 3%, (▲) 5% and (□) 10% 12-HSA in simulated (A) gastric fluid and (B) intestinal fluid. Each value represents the mean ± SE. Each value represents the mean ± SE of three experiments.

lipase was obviously increased with the addition of taurocholate. It is reported that the enzymatic activity of lipase was increased in the presence of taurocholate by lowering its K_m value (Lombardo et al., 1978). It is also reported that the enhancement of the hydrolyzation activity of lipase by taurocholate base was caused by lowering the activating energy of ester hydrolyzation or free energy of the enzyme–substrate complex (Abouakil and Lombardo, 1989). In this experiment, it was speculated that the enzymatic activity of lipase was enhanced in the presence of taurocholate; however, the erosion of organogel in the real intestinal tract is considered to be more complex because not only taurocholate but also many cholates, such as deoxycholate, glycocholate and so on, are present.

3.4. Oral administration of organogel in vivo

From *in vitro* experiments it has been clarified that organogel containing 10% 12-HSA was the most suitable formulation for the controlled release of ibuprofen. Next, we also studied the usefulness of organogel for oral dosage formulation *in vivo*. The ibuprofen concentration in plasma after oral administration with aqueous suspension, soybean oil alone and organogel (10% of 12-HSA) is shown in Fig. 7. When ibuprofen was administered in aqueous suspension form, the ibuprofen concentration in plasma rapidly increased and then disappeared from the body. This result shows that ibuprofen rapidly permeates the intestinal membrane, and the elimination rate from the body is also rapid, as previously reported (Wanger et al., 1984). When ibuprofen was orally administered to rats with organogel, the absorption rate was decreased compared with aqueous suspension or soybean oil. The affinity of ibuprofen to oil is much higher than to intestinal fluid because of its high lipophilicity; therefore, the absorption of ibuprofen was comparably low because ibuprofen remained in oil, resulting in low absorption.

t_{max} after administration with aqueous suspension or soybean oil was <15 min. On the other hand, t_{max} after administration with organogel was around 1 h. This result suggests the possibility that ibuprofen may be absorbed from the stomach because it is an acidic compound. It has also been shown that ferulic acid can be absorbed from rat stomach (Zhao et al., 2004); therefore, when designing a controlled release formulation for acidic compounds such as ibuprofen and ferulic acid, gastric absorption should be considered. When ibuprofen was administered as organogel, the increase of ibuprofen concentration in plasma was further suppressed compared to soybean oil. t_{max} was also significantly delayed and the time course of ibuprofen concentration in plasma showed a typical flip-flop pattern. AUC and bioavailability of ibuprofen were calculated and listed in Table 3. Bioavailability of ibuprofen after administration in soybean oil was slightly higher than that in aqueous suspension. However, administration with organogel significantly increased bioavailability of ibuprofen compared to aqueous suspension and soybean oil (1.5-times and

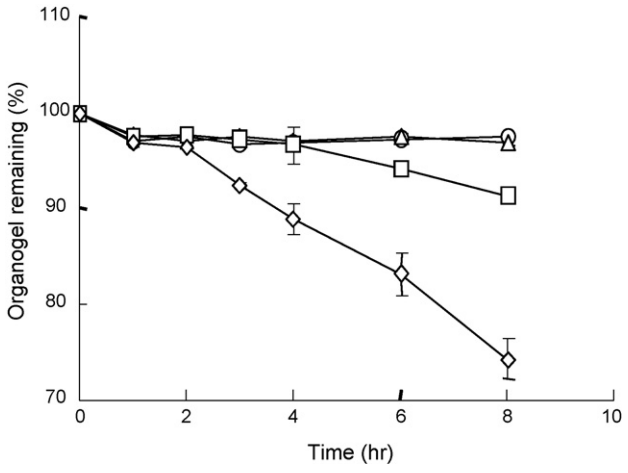

Fig. 6. Erosion of organogel including 2% 12-HSA in (○) PBS (pH 6.8), (△) 10 mM sodium taurocholate in PBS (pH 6.8), (□) 375 U/mL lipase in PBS (pH 6.8) and (◊) 10 mM sodium taurocholate + 375 U/mL lipase in PBS (pH 6.8). Each value represents the mean ± SE of three experiments.

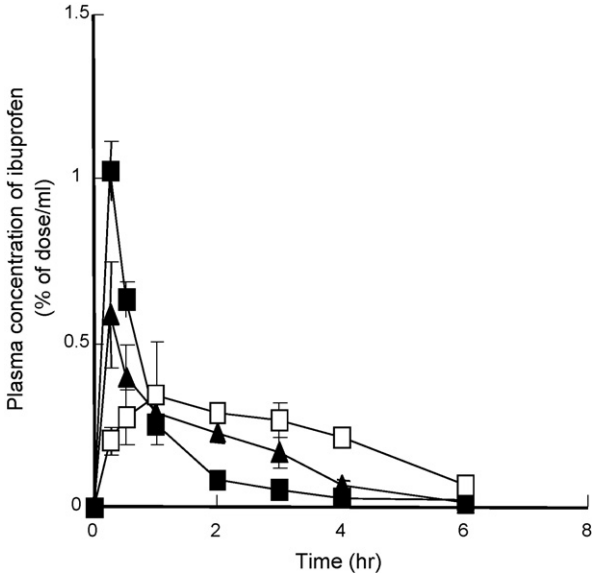

Fig. 7. Time course of ibuprofen concentration in plasma after oral administration to rats with (■) aqueous suspension, (▲) soybean oil and (□) organogel including 10% HSA. Each value represents the mean ± SE of four experiments.

Table 3
Area under the ibuprofen concentration in plasma and bioavailability after oral administration to rats.

Formulations	AUC (% of dose × h/mL)	Bioavailability
i.v. bolus	1.425 ± 0.142	–
Aqueous suspension	0.914 ± 0.128	0.642 ± 0.052
Soybean oil	1.075 ± 0.106	0.754 ± 0.032
Organogel (10% 12-HSA)	1.397 ± 0.158	0.981 ± 0.111*

Each value represents the mean ± SE ($n = 3$).
* Significant at $p < 0.05$ vs aqueous suspension and soybean oil.

1.3-times, respectively). This enhancement of bioavailability was due to the lasted intestinal absorption of ibuprofen by the prolonged release from organogel. Furthermore, the solidification of oil by adding 12-HSA suppressed the spread of oil containing ibuprofen in the gastrointestinal tract and slowly released ibuprofen with erosion, resulting in the slow absorption rate of ibuprofen. From these results, it was clarified that both the slow release of drug from the formulation and decreased gastric absorption of the drug are important for designing a controlled release formulation for acidic drugs.

4. Conclusions

It was found that the release rate of ibuprofen from organogel can be controlled by changing the amount of the low mass gelator and its mechanism is the main difference in the erosion rate of organogels. It was also clarified that lipase is strongly related to the disintegration of organogel and taurocholate enhanced the lipolytic activity of lipase.

Organogel is clearly useful as an oral controlled release formulation for lipophilic compounds.

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