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# An Organic Acid-Induced Sigmoidal Release System for Oral Controlled-Release Preparations

**Shinji Narisawa,[1] Minako Nagata,[1] Chieko Danyoshi,[1] Hiroyuki Yoshino,[1,2] Kazuo Murata,[1] Yoshiyuki Hirakawa,[1] and Kazuo Noda[1]**

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To achieve time-controlled or site-specific drug delivery in the gastrointestinal tract, a sigmoidal release system (SRS) was developed, which achieved a prolonged lag time, followed by rapid release. The theophylline beads with a thick Eudragit RS film coating showed very low drug release in water, whereas the release rate increased considerably in organic acid solutions. A hydration study of Eudragit RS films suggested that the increase in drug release was attributable to structural changes of the film induced by polymer–acid interactions. When succinic acid was incorporated into the core of Eudragit RS-coated theophylline beads, the drug release profile showed a typical sigmoidal pattern. SRS beads containing acetaminophen were also prepared by the same technique. Again, a sigmoidal release pattern was observed in which the lag time was prolonged with an increase in the coating level, whereas the drug release rate thereafter was almost constant irrespective of the coating level. Acetaminophen-containing SRS beads with different coating thickness were orally administered to beagle dogs. The drug plasma concentration curves showed lag periods similar to the *in vitro* lag time.

KEY WORDS: controlled release; organic acid; release-enhancing; sigmoidal release; lag time; film coating.

## INTRODUCTION

Various orally applicable drug delivery systems have been developed, mostly for sustained release, including osmotic devices (1), film-coated preparations (2), matrix systems (3), floating systems (4), and bioadhesive systems (5). Drug release should be controlled in accordance with the therapeutic purpose and the pharmacological properties of an active substance (6). Accordingly, the maintenance of a constant drug blood level is not always desirable. For instance, nitrates (7), antibiotics, and contraceptive steroids may require rhythmic variations of the blood concentration in order to avoid the development of tolerance. In addition, to reduce the nocturnal or early morning symptoms of some chronic diseases, such as ischemic heart disease, asthma (8), and arthritis, drugs should be administered so as to achieve a therapeutic level only at the required time, so that side effects can be minimized. In such cases, drug release should be "time controlled" instead of "rate controlled."

A sigmoidal release system (SRS), which rapidly releases a drug from a multiple-unit device after a predetermined lag time, can achieve both time-controlled release and rhythmic release by the appropriate combination of systems with different lag times. SRSs with different lag times release a drug repeatedly at different positions during gastrointestinal (GI) passage. Moreover, considering the fact that multiple-unit dosage forms have less variation in GI transit time (9), use of an SRS may provide a convenient method of site-specific drug delivery for the treatment of colonic disease or for the colonic absorption of peptide drugs.

The objective of the present study was to develop a new type of orally applicable SRS capable of time-controlled or "site-specific" drug delivery. To achieve ideal sigmoidal release from a coated agent, it is necessary to determine how to keep the lag time in the desired range and how to produce rapid drug release after the lag period. Eudragit RS is a copolymer synthesized from acrylic and methacrylic acid esters with a low content of quarternary ammonium groups, and it seems to have suitable physicochemical properties for use as an SRS coating material, because the film formed by this polymer is insoluble and has a low water permeability but swells in water by incorporating $H_2O$ molecules into its hydrophilic groups. The low water permeability of the film suggests that the desired lag time can be obtained by varying the thickness of the film and that drug release after the lag period can be enhanced by electrostatic or other physicochemical interactions between the polymer and organic acids. On the basis of these concepts, the changes in drug permeability of Eudragit RS film were investigated in various organic acid solutions. Then, SRS technology based on the polymer–acid interactions was applied to two model drugs, and the *in vivo* performance of the model SRS was investigated.

## MATERIALS AND METHODS

### Materials

Anhydrous theophylline (TP; Tokyo Kasei Kogyo Co., Tokyo) and acetaminophen (AA; Yamamoto Chemical Ind. Co., Wakayama, Japan) used as the model drugs were of JP grade. They were used after grinding by a hammer mill. Nonpareil-103 (24–32 mesh, Freund Industrial Co., Tokyo) was used as the core material for the construction of beads. Sucrose (Taito Co., Ltd., Japan) or hydroxypropylcellulose (HPC; Nisso Co., Tokyo) were used as the binders and were of JP grade. Eudragit RS 30D (Röhm Pharma, Germany), ethylcellulose (EC; Ethocel standard premium, 10 cP, Dow Chemical Co.), talc (Nippon Talc Co., Tokyo), and triethylcitrate (TEC; Pfizer Co., Tokyo) were used as received. The six organic acids used (acetic acid, succinic acid, glutaric acid, DL-tartaric acid, DL-malic acid, and citric acid monohydrate) and all other chemicals were of reagent grade.

### Preparation of Beads

Uncoated drug beads were prepared from a powder mixture of the drug and sucrose or the drug and succinic acid using a CF-granulator (CF-360EX, Freund Industrial Co.). The powder mixture was slowly applied to the Nonpareil seeds while continuously spraying a binder solution to obtain drug beads. The conditions used were as follows: spray so-

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[1] Pharmaceutics Research Laboratory, Tanabe Seiyaku Co., Ltd., 16-89, Kashima 3-chome, Yodogawa-ku, Osaka 532, Japan.

[2] To whom correspondence should be addressed.

lution feed, 2–7 mL/min; spray air pressure, 0.8 kg/cm$^2$; blower rate, 150–250 L/min; blower temperature, 60°C; and rotating speed, 150 rpm. The beads were then dried for 18 hr at 45°C. After drying, the beads were sieved to remove both agglomerate and fine particles. Then the beads were coated by spraying with a mixture of Eudragit RS 30D, talc, TEC, and water (39.0:5.7:1.2:54.1) using a fluid-bed coater (Flow coater mini, Freund Industrial Co.). The size of the beads and the ultimate film thickness (70% coating) were approximately 1100 and 90 μm, respectively. The coating conditions were as follows: spray air pressure, 1 kg/cm$^2$; inlet temperature, 50–60°C; outlet temperature, 30–37°C; and spray solution feed, 5 mL/min. The coated beads were oven-cured at 60°C for 16 hr. EC-coated beads were prepared by spray coating of an aqueous ethanolic solution of EC (concentration: 5% EC and 65% ethanol) with a CF-granulator. The coating conditions were as follows: spray solution feed, 6 mL/min; spray air pressure, 1 kg/cm$^2$; blower rate, 100–200 L/min; blower temperature, 50°C; and rotating speed, 150 rpm. The coating thickness was expressed as the coating level ($M_C$) defined as Eq. (1):

$$M_C = (M_f/M_b) \times 100 \tag{1}$$

where $M_f$ is the amount of solid materials deposited and $M_b$ is the weight of uncoated beads.

### Dissolution Studies

Dissolution experiments were performed by the JP paddle method in 900 mL of water at 37°C with constant stirring at 100 rpm. Aliquots were removed at specified times and assayed with a spectrophotometer (UV-160, Shimadzu Co., Kyoto, Japan) to determine the drug concentration. To examine the release-enhancing effect of the various organic acids, the test fluid was replaced with the same amount of a 0.5 *M* aqueous solution of various organic acids.

### Film Preparation

An aqueous mixture of Eudragit RS 30D (41.4%), TEC (1.2%) and water (57.4%) was spread on a Teflon sheet fixed on a glass plate and dried for 3 days at 25°C. After drying, the film was oven-cured at 60°C for 16 hr.

### Hydration Study

Eudragit RS films (10 × 10 mm) were immersed in 50 mL of water or in 0.5 *M* aqueous organic acid solutions for 24 hr at 37°C. After equilibration, the wet films were quickly blotted to remove excess surface water and then weighed. The percentage hydration ($H_m$) was then calculated according to Eq. (2):

$$H_m = (W_w - W_d)/W_d \times 100 \tag{2}$$

where $W_w$ is the wet weight of the film and $W_d$ is the dry weight, respectively.

### Determination of Solubility

The solubility of TP in water or 0.5 *M* organic acid aqueous solutions was determined at 37°C. An excess of TP was added to 20 mL of each solution in jacketed beakers which were heated by external water circulation to maintain a constant temperature. The solutions were stirred constantly for several hours. After equilibration, an aliquot of each solution was removed and filtered for analysis of the drug concentration with a spectrophotometer (U-2000, Hitachi, Ltd., Tokyo).

### *In Vivo* Absorption Study

Three male beagle dogs (weighing 10–12 kg) were used in the single-dose study. The dogs were fasted for 20 hr before drug administration, while receiving water *ad libitum*. AA-SRSs (30, 50, and 70% coating) or EC-coated AA beads (4% coating) were orally administered with 30 mL of water (equivalent to 200 mg of AA). After dosing, blood samples (4 mL) were collected at predetermined times and centrifuged, and the plasma thus obtained was frozen until analysis. Plasma samples were analyzed to determine AA concentration by HPLC. The plasma sample (0.5 mL), 0.1 mL of internal standard solution (TP, 50 μg/mL), and 0.3 g of sodium chloride were vortexed briefly, and then 5 mL of ethyl acetate was added. This mixture was shaken for 10 min and then centrifuged. The ethyl acetate layer (4 mL) was transferred and the solvent was evaporated under nitrogen gas. Then the residue was dissolved in 0.5 mL of methanol, and 20 μL of the resulting solution was injected into the HPLC apparatus (Shimadzu Co.). An acidified (pH 4) aqueous solution of acetonitrile:0.01 *M* sodium acetate (1:20) was used as the mobile phase at a flow rate of 1.0 mL/min. The column was a reverse-phase column (CAPCELL PAK C18 SG120, 4.6 × 250 mm, Shiseido, Co., Tokyo), and UV detection and quantification were performed at 254 nm. A linear detector response ($r$ = 0.9999) was observed over the concentration range of 0.1–250 μg/mL.

### Pharmacokinetic and Statistical Analysis

The maximum plasma concentration ($C_{max}$), the time to reach the maximum concentration ($T_{max}$), and the lag time were obtained directly from the observed values. The area under the curve until 24 hr after oral administration (AUC) was calculated by the trapezoidal rule from the observed values, and the mean residence time (MRT) was computed by moment analysis (10).

Pharmacokinetic parameters were statistically com-

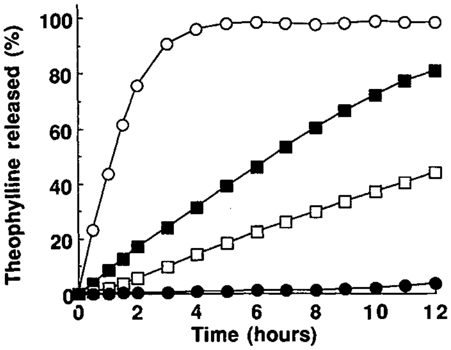


Fig. 1. Effect of coating level on theophylline release from Eudragit RS-coated beads in water. Coating level: (○) 10%; (■) 15%; (□) 20%; (●) 30%.

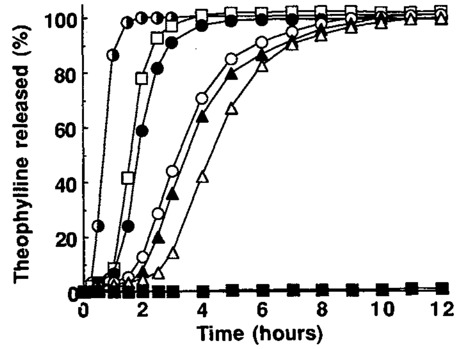


Fig. 2. Theophylline release from Eudragit RS-coated beads in aqueous solutions of various organic acids (0.5 *M*). Coating level: 40%. Organic acids: (◑) acetic acid; (□) succinic acid; (●) glutaric acid; (○) tartaric acid; (▲) malic acid; (△) citric acid; (■) no organic acids (water).

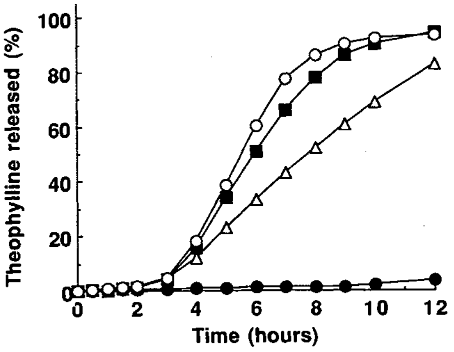


Fig. 4. Changes in the theophylline release profiles in water as a function of the succinic acid content. Coating level: 30%. Succinic acid content in beads: (●) 0%; (△) 10%; (■) 20%; (○) 33%.

pared by the paired *t* test, and $P < 0.05$ was used to indicate statistical significance.

## RESULTS AND DISCUSSION

### Drug Release from Eudragit RS-Coated Beads

Uncoated beads containing TP and sucrose were coated with an aqueous dispersion of Eudragit RS containing talc and TEC. Figure 1 shows the drug release profiles for the coated beads as a function of the coating level. The profiles of beads with 10–20% coating suggested that drug release obeyed zero- or first-order kinetics. In contrast, there was little TP released from 30%-coated beads until 12 hr. When drug release occurred after a prolonged period of time, however, the rate of release was very low. Therefore, to produce rapid release after the lag period, the drug permeability of the film must be drastically increased. An alteration in permeability may be achieved by inducing structural changes of the barrier based on polymer–drug or polymer–additive interactions. Since Eudragit RS possesses quarternary ammonium groups in its polymer chain, organic acids might induce a change in film permeability by electrostatic interactions, and optimum sigmoidal release might be achieved by incorporating such acids into the cores of Eudragit RS-coated beads. Concerning drug–polymer interactions, Jenquin *et al.* recently reported that salicylic acid could reduce the glass transition temperature of Eudragit RS by electrostatic interactions between salicylate anion and the cationic groups of the polymer (11).

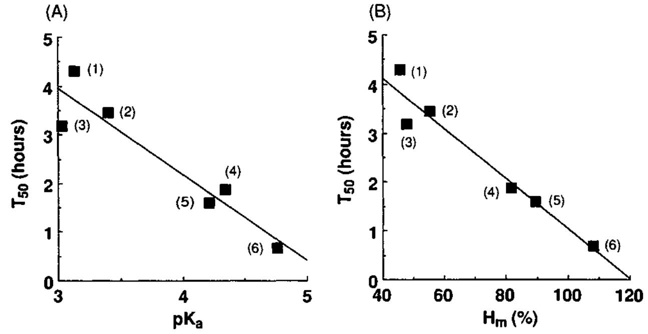


Fig. 3. (A) Relationship between the p$K_a$ values of organic acids and the $T_{50}$. (B) Relationship between the hydration percentage ($H_m$) of Eudragit RS film and the $T_{50}$. Organic acids: (1) citric acid; (2) malic acid; (3) tartaric acid; (4) glutaric acid; (5) succinic acid; (6) acetic acid. The $T_{50}$ values are the time for 50% drug release calculated from each curve in Fig. 2.

### Effect of Organic Acids on Drug Release

Therefore, to find suitable additives capable of increasing the drug release rate, a series of dissolution studies was conducted using TP beads with a 40% coating. Six organic acids (acetic acid, succinic acid, glutaric acid, DL-tartaric acid, DL-malic acid, and citric acid monohydrate) were selected as potential release enhancers, and a 0.5 *M* solution of each acid was used for the dissolution fluid. The effect of these organic acids on TP release is shown in Fig. 2. In water, the drug was not released for many hours due to the thick coating. On the other hand, drug release was considerably enhanced in organic acid solutions, with the degree of enhancement depending on the acid used. Among the solid acids studied, succinic acid had the most marked release-enhancing effect.

To examine quantitatively the relationship between the release-enhancing effect and the p$K_a$ of organic acids, the time for 50% drug release ($T_{50}$) was calculated from each curve in Fig. 2 and plotted against the p$K_a$ value (Fig. 3A). It was found that $T_{50}$ values decreased with increasing p$K_a$, suggesting that weaker acids were generally more effective.

Table I. Formulae of the Uncoated Beads[a]

| Component | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 |
|---|---|---|---|---|---|---|
| Theophylline | 20 | 20 | 20 | 20 | | |
| Acetaminophen | | | | | 36 | 36 |
| Nonpareil-103 | 33 | 33 | 33 | 33 | 10 | 10 |
| Succinic acid | | 10 | 20 | 33 | 35 | |
| Sucrose[b] | 47 | 37 | 27 | 14 | 15 | 50 |
| HPC-SL[c] | | | | | 4 | 4 |

[a] All quantities are percentages (w/w).

[b] Sucrose was used as a filler and binder. The binder solution was 25% (w/w) aqueous ethanol containing 25% (w/w) sucrose.

[c] The binder solution was 30% (w/w) aqueous ethanol containing 3% (w/w) HPC-SL.

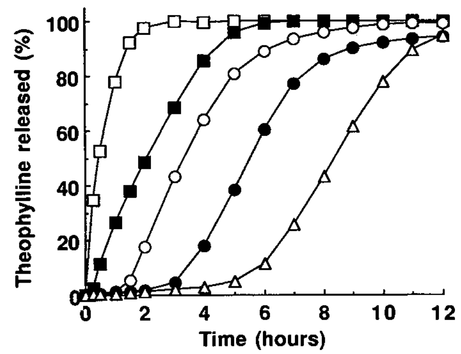


Fig. 5. Effect of coating level on drug release from theophylline-SRS in water. Content of succinic acid: 33%. Coating level: (□) 5%; (■) 10%; (○) 20%; (●) 30%; (△) 40%.

This relationship implies that electrostatic interactions between the quarternary ammonium groups of the polymer and organic acids are not necessarily the major mechanism of the release-enhancing effect, because all of the 0.5 $M$ organic acid solutions had a pH in the range of 1 to 2 and the concentration of reactable anions decreases with increasing $pK_a$ under such conditions. Thus, partition of the undissociated compound into the matrix phase of the polymer film seems to be a more likely mechanism, but further investigation will be necessary to clarify this issue.

### Hydration Study of Eudragit RS Free Films

The release-enhancing effect of organic acids could have been brought about by an increase in the permeability of the coating, because a marked increase in bead size was observed visually during the dissolution process, which suggested that some structural changes of the coating might occur in the organic acid solutions. To examine whether organic acids actually had the ability to induce structural changes of the coating, a hydration study was conducted using Eudragit RS films (Eudragit RS:TEC = 10.2:1).

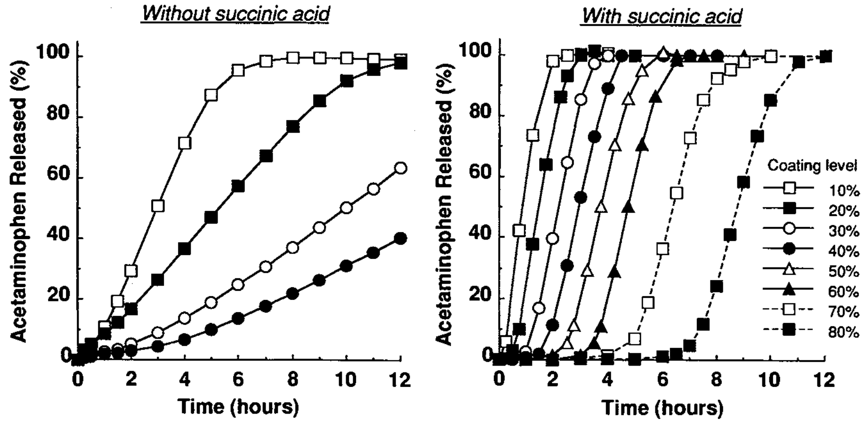
When placed in water, the film absorbed about 31% of its dry weight, whereas the $H_m$ values for organic acid solutions were in the range of 1.5- to 3.5-fold, depending on the organic acid used. Okor *et al.* reported that a film formed from Eudragit RS and RL can be hydrated in water because of its hydrophilic quarternary ammonium groups (12). A positive relationship between solute permeability and the hydration of a film has been proposed as the "free-volume" theory (13). Thus, the enhancement of permeability by the organic acids was thought to be directly related to changes in $H_m$. Figure 3B shows the relationship between $H_m$ and the $T_{50}$ values found in the dissolution study shown in Fig. 2. The $T_{50}$ value increased as the $H_m$ decreased, meaning that the release-enhancing effect of organic acids was related to their facilitation of the hydration of the Eudragit RS coating.

Another possible reason for the release-enhancing effect of organic acids could be an increase in the solubility of TP, because increased drug solubility can boost the driving force for drug release. The solubility in acid solutions (0.5 $M$) increased to 1.49–1.99% (w/v) from 1.16 in water at 37°C. Although an increase in solubility was observed in the presence of organic acids, the change was so small that this cannot be considered the major reason for the drastic increase in drug release.

### Formulation Study of Succinic Acid-Induced SRS

Because succinic acid had a marked release-enhancing effect, formulation study were performed to fabricate an SRS incorporating succinic acid. The formula of the uncoated beads used in this study is summarized in Table I. Uncoated beads were coated by spraying with the same aqueous dispersion containing Eudragit RS–talc–TEC (11.7:5.7:1.2) as used in the other studies.

Figure 4 shows a comparison of the drug release profiles in water for four kinds of TP beads coated with the Eudragit RS-based dispersion (30% coating). Each preparation had a different core, 0, 10, 20, and 33% succinic acid (C-1, C-2, C-3, and C-4 in Table I). The drug was not released from the acid-free beads for many hours. On the other hand, all of the beads containing succinic acid released the drug content after a 3-hr lag time (Fig. 4). Release after the lag period became faster as the succinic acid content increased, and the overall release profile showed a typical sigmoid shape. Thus, it was shown that incorporation of succinic acid into the core could effectively produce sigmoidal drug release, with 20% succinic acid being sufficient to obtain the maximum release-enhancing effect.


Without succinic acid

With succinic acid

Fig. 6. Comparison of acetaminophen release in water from Eudragit RS-coated beads with or without succinic acid.

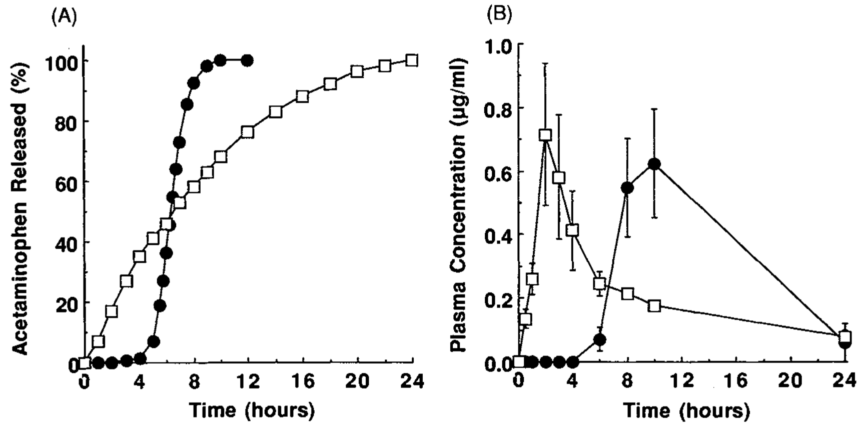


Fig. 7. Release profiles in water (A) and plasma concentration–time profiles (B) of acetaminophen following oral administration to beagles of EC-coated beads or SRS with the same $T_{50}$. Preparations: (□) EC-coated beads (4% coating); (●) SRS (70% coating). The release profile for the SRS is identical to that in Fig. 6.

Figure 5 shows the effect of the coating on release from TP beads, each of which had a 33% succinic acid core and was coated with the Eudragit RS-based dispersion at 10, 20, 30, or 40%. The lag time was prolonged up to 5 hr with an increase in the coating level, and it is notable that release after the lag period was almost constant irrespective of the coating level. This suggests that the lag time until drug release can be varied by altering the coating level with little effect on the subsequent rate of drug release.

To examine the applicability of the succinic acid-induced SRS, AA was also used to formulate an SRS. The formula of the uncoated beads is shown in Table I (C-5 and C-6), and the drug release behavior of the preparation in water is shown as a function of the coating level in Fig. 6. In the absence of succinic acid, the release profile was close to a zero- or first-order curve. On the other hand, in the presence of succinic acid, the drug release profiles changed to a typical sigmoidal pattern with a distinctive lag period followed by rapid release.

### *In Vivo* Performance of the SRS

To clarify the *in vivo* performance of the SRS, the plasma concentration–time profile was examined in beagle dogs. Figure 7A shows the *in vitro* AA release profile of an AA-SRS (70% coating) and that of EC-coated AA beads (4% coating) exhibiting conventional zero- or first-order release. Both dosage forms have an identical $T_{50}$ (6 hr), but their profiles are quite different. Figure 7B shows a comparison of the plasma concentration–time profiles after the oral administration of each formulation to beagle dogs. The EC-coated beads did not exhibit any lag time before drug release. On the other hand, the SRS exhibited an abrupt increase in the AA plasma concentration following a lag period of about 5 hr. This indicates that the *in vivo* performance of SRS is clearly different from that of a conventional controlled-release preparation.

Figure 8 compares the mean AA plasma concentration–time profiles after oral administration of three AA-SRSs with various *in vitro* lag times (30, 50, and 70% coatings). A clear lag period was observed at the initial stage in each case, and it became longer with an increase of the coating thickness. Table II compares the *in vitro* lag times obtained from the drug release profiles (Fig. 6) and the *in vivo* lag times obtained from the plasma concentration profiles (Fig. 8). It was found that the *in vivo* lag times were almost coincident with the *in vitro* lag times, indicating that the starting time of AA release was well controlled in the GI tract. The pharmacokinetic parameters calculated from the plasma concentration curves are summarized in Table III. The $T_{\max}$ value and MRT were significantly delayed with an increase in coating level, corresponding to the increase in the *in vivo* lag time. On the other hand, the $C_{\max}$ and AUC values did not show

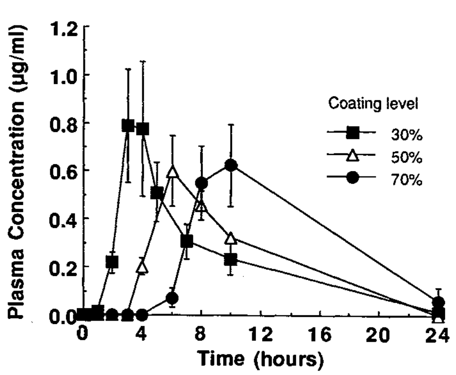


Fig. 8. Mean plasma concentration–time profiles of acetaminophen following oral administration of acetaminophen-SRS (equivalent to 200 mg of the drug) with different coating levels (30, 50, and 70%) to beagle dogs. The vertical lines show the SE. The profile for 70% coating is identical to that in Fig. 7.

Table II. Comparison of the *in Vitro* and *in Vivo* Lag Times

| Coating (%) | Lag time (hr) | |
|---|---|---|
| | *In vitro* | *In vivo*[a] |
| 30 | 1.2 | 1.1 |
| 50 | 2.5 | 3.0 |
| 70 | 5.0 | 5.4 |

[a] Mean value ($n = 3$).

**Table III.** Pharmacokinetic Parameters Obtained Following Oral Administration of SRS Beads Containing 200 mg of Acetaminophen to Beagles (mean ± SD; $n = 3$)

| Coating (%) | $T_{max}$ (hr) | $C_{max}$ (μg/mL) | AUC (μg · hr/mL) | MRT (hr) |
|---|---|---|---|---|
| 30 | 3.7 ± 0.6* | 0.9 ± 0.4 | 5.5 ± 2.2 | 6.9 ± 0.3* |
| 50 | 6.0 ± 0.0** | 0.6 ± 0.2 | 5.0 ± 0.6 | 8.3 ± 0.3** |
| 70 | 9.3 ± 1.2 | 0.6 ± 0.3 | 6.7 ± 2.3 | 9.5 ± 0.1 |

* Significant difference from 50% coating ($P < 0.05$) or 70% coating ($P < 0.01$).

** Significant difference from 70% coating ($P < 0.05$).

significant changes. The MRT increased with an increase in the coating level, and fair agreement of values (MRT–*in vivo* lag time) was observed at every coating levels (5.8, 5.3, and 5.4 hr for 30, 50, and 70% coating, respectively). These results indicate that the differences in MRT of the beads with different coating thickness were due to differences in *in vivo* lag time.

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