[Chem. Pharm. Bull. 30(8)2912—2918(1982)]

Influence of Surfactants, Polymers, and Concentration of the Water Phase on *in Vitro* Drug Release from Emulsion-Type Suppositories[1)]

Shun'ich Noro,* Yoshihito Komatsu, and Takashi Uesugi

Meiji College of Pharmacy, Yato-cho 1-22-1, Tanashi, Tokyo 188, Japan

(Received November 13, 1981)

Generally, drug release from the base is considered to be one of the most important parameters in evaluating the pharmaceutical usefulness of suppositories *in vivo* and *in vitro*. In spite of the therapeutic importance and wide applications of suppositories, the absorption mechanisms and the factors determining their absorption characteristics have not been established. The present study was undertaken to investigate the effects of surfactants, polymers, and concentration of the water phase on *in vitro* drug release emulsion-type suppositories. N_1-(2′-furanidyl)-5-fluorouracil (FT-207), theophylline and indomethacin were chosen as model compounds. In order to clarify the behavior of the rectal membrane, the following three different methods for studying drug release (*in vitro*) were selected: (1) the filter membrane technique, (2) the use of membranes of animal origin, (3) *in situ* rectal recirculation technique.

The following results were obtained. (1) In the case of readily water-soluble compounds such as FT-207, the amount of drug released increased with increase of the water content in the suppository base. (2) On the other hand, no significant effect of concentration of the water phase in the suppository base was found for fatty drugs such as indomethacin. (3) By the addition of aqueous polymer, the amount of drug released could be controlled and the release prolonged in the emulsion-type suppository base.

Keywords——drug release; emulsion; filter membrane; FT-207; indomethacin; passive transport; recirculation technique; rectal membrane; suppository; theophylline

It is well known that the elucidation of the *in vivo* mechanism of drug release from the verhicle is one of the most important aspects of pharmaceutical evaluation of suppositories from the veiw point of dosage schedule.[2)] In general, the drug release pattern from bases may be described by a three-step model,[3)] *i.e.* transport of the drug to the interface between the melted suppository and rectal fluid, transport across this interface and dissolution of the drugs in the rectal fluid. Depending on the physical and chemical properties of the drug, the rate-limiting step for rectal absorption may be any one of the three steps.[4)] The drug release rate is markedly influenced by the physicochemical properties of both drugs and bases.[5)]

In this study, the influence of surfactant,[6)] polymers, and the concentration of water phase on *in vitro* drug release from emulsion-type suppositories was investigated. The optimum conditions for preparation of the suppositories were described in detail in our previous paper.[7)] In order to clarify the behavior of the rectal membrane, the following three different methods of drug release (*in vitro*) were selected: (1) the filter membrane technique,[8)] (2) the use of membranes of animal origin,[9)] (3) *in situ* rectal recirculation technique.[10)] As model drugs we chose N_1-(2′-furanidyl)-5-fluorouracil,[11)] theophylline[12)] and indomethacin.[13)] N_1-(2′-furanidyl)-5-fluorouracil (FT-207) is a water-soluble 5-fluorouracil (5-FU) derivative. Some studies have suggested that preoperative intrarectal administration of 5-FU emulsion may be effective as an adjunct to surgery for rectal cancer[11)] with lymph node metastasis, because a high concentration can be maintained for a long period in the rectal lymphatics and rectal wall.

Theophylline (TP) is an effective bronchodilator[12)] used widely for the treatment of asthma and has a partition coefficient of about unity. TP has a narrow therapeutic index, and in

order to maintain the optimum blood level, it is necessary to improve the dosage form or to use the prodrug approach.

Indomethacin (IM) is an analgesic or anti-inflammatory agent used to treat rheumatoid arthritis and other joint diseases, and is an oily compound. Some reports have suggested that IM can be completely absorbed from the rectum.[13]

Experimental

1. **Materials and Methods**——N_1-(2′-furanidyl)-5-fluorouracil (FT-207), theophylline (TP) and indomethacin (IM) were chosen as model compounds.

Emulsion-type bases were used as suppository bases in this experiment. The preparation procedures and the physicochemical properties of these bases have already been described in our previous paper.[7] The volume ratios of the dispersed phase to the continuous phase were in the range between 4: 6 and 7: 3. The bases were stored in a constant temperature room (21—23°C) until the drug release experiment in order to obtain uniform suspensions and equilibrium solubilities of the drugs without degradation.

2. **Partition Coefficients of Drugs**——Benzene, chloroform or *n*-octanol was used as the organic phase, and pH 7.4 isotonic buffer solution was used as the aqueous phase. The drug was dissolved at a concentration of 0.5 molar conc. in the aqueous solution, and 10 ml portions of the aqueous solution were equilibrated with equal volumes of the organic solvents. These were kept in a constant-temperature water-bath at 37 ± 0.1°C and were vigorously agitated in an A-14 type mixer (Kaiyō Chemical Co., Tokyo) for 3 h. The drug contents in the aqueous phase were determined by a spectrophotometric method with a Hitachi ESP-3T spectrophotometer and the partition coefficients were calculated. The absorptions of theophylline, FT-207 and indomethacin were measured at wavelengths of 276, 270 and 260 nm, respectively.

3. **Solubility of Drugs**——Isotonic buffer solution of pH 7.4 containing 10 mg of drug was placed in a glass-stoppered flask. The flask was immersed in a water bath (37 ± 0.1°C) and stirred vigorously in an A-14 type mixer for 60 min. After equilibration, an aliquot of the supernatant was removed with the aid of a cotton filter and the solubility of the drug was determined by the spectrophotometric method.

4. **Drug Release During *in Situ* Recirculation**——Male rats weighing 200 to 230 g were fasted for one night prior to the experiment but allowed water freely. The animals were anesthetized with sodium pentobarbital by interperitoneal injection at 40 mg per 1.0 kg, and were cannulated at the end of the colon with polyvinyl tubing. A glass cannula was then inserted into the anus, and the exposed end was connected to polyvinyl tubing by means of a ligature. The length of the rectum was 3 cm. The incision was closed and tubings attached to the cannulated inflow and outflow were then transferred to a flask containing 20 ml of drug solution. This solution was then continuously circulated through the rectum lumen by means of an RV-2 type roller pump (Furue Science Co., Tokyo) with a circulation flow rate of 1.3 ml/min at 37°C. The drug solution was prepared with isotonic buffered solution. A half milliliter of the sample solution was pipetted out at 20, 40, 60, 90, and 120 min after the start of recirculation, and the absorption rate constant was calculated from the decrease of concentration in the drug solution. The pH value of the solution after recirculation remained almost constant or changed by less than 0.4.

5. **Drug Release through a Millipore Filter Membrane**——The drug powders were sieved to obtain accurately sized fractions through 200—250 mesh screens. The apparatus used in studying the drug release from a suppository was a dissolution test instrument (Toyama Sangyo Co., Tokyo). It consisted of an inner cylindrical cell, a Millipore filter membrane and an external cylindrical cell. The inner water, in which a suppository was immersed, was stirred with a Teflon-coated magnetic stirring bar, which was driven at 50 rpm by a synchronous motor placed at the bottom of the inner cell. The apparatus was kept in a constant-temperature water bath maintained at 37 ± 0.1°C. The release of drug from various suppository bases was examined. Half milliliter samples were withdrawn from the sink nine times during 5—180 min. The volume of receptor phase was kept constant throughout the release run by replacing the removed sample with an equal volume of distilled water. The drug concentration was determined with a UV spectrometer (ESP-3T, Hitachi Seisakusho Co., Tokyo).

6. **Drug Release through Rectal Membrane *in Vitro***——A pH 7.2 isotonic buffer solution (20 ml) containing 0.1% glucose was transferred into the chamber immersed in a water bath maintained at 37 ± 0.1°C. The chamber was continuously gassed with 5% (v/v) CO_2 and 95% (v/v) O_2.

Wistar adult male rats weighing 200—230 g were killed, and the rectums were isolated and washed out with 20 ml of saline pre-warmed to body temperature. The lower side of the rectal lumen was closed, and suppository base containing 0.2 g of drug was poured into other side. Both sides of the rectal lumen were closed, and this lumen was immediately placed in the chamber maintained at 37 ± 0.1°C. One-half milliliter of the outer solution was pipetted out at 20, 40, 60, 90, and 120 min, and the drug concentration was determined.

Results and Discussion

1. Solubilities and Partition Coefficients of Drugs

Some physicochemical properties, such as partition coefficient, solubility and pK_a value, for FT-207, theophylline and indomethacin are summarized in Table I. FT-207 is the most water-soluble compound, indomethacin is the most oily substance and theophylline is intermediate in properties.

TABLE I. Some Physicochemical Properties of FT-207, TP, and IM

	Partition coefficient (C_o/C_w)			Solubility (mg/ml)	pK_a
	Benzene	Chloroform	*n*-Octanol		
FT-207[a]	0.26	0.56	0.88	20.1	7.8
TP[b]	0.35	0.78	1.86	8.39	8.8
MI[c]	2.36	6.99	16.09	0.41	4.5

a) N_1-(2'-Furanidyl)-5-fluorouracil.
b) Theophylline.
c) Indomethacin.

2. The Characteristics of Drug Release during *in Situ* Recirculation

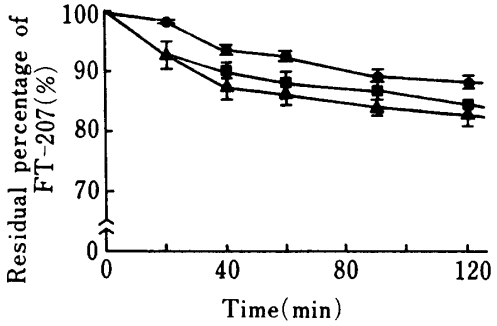

Fig. 1. Effect of Various Surfactants on Rectal Absorption of FT-207 during *in Situ* Recirculation

●, CS-11, 1%; ▲, SDS, 1%; ■, Tween, 1%.

The effect of various surfactants on the rectal absorption of FT-207 during *in situ* recirculation is shown in Fig. 1. The drug release from the suppository base was affected by the kind of surfactant, and it was found to decrease in the order CS-11, Tween 80 and SDS.

Figure 2 indicates the effect of CS-11 as a surfactant on rectal absorptions of FT-207, theophylline, and indomethacin during *in situ* recirculation. In the case of FT-207, the presence of surfactant in buffer solution had little effect on the drug release at the initial stage, but it increased the rate of drug release at later stages. For theophylline, no apparent difference was observed between the releases from buffer solu-

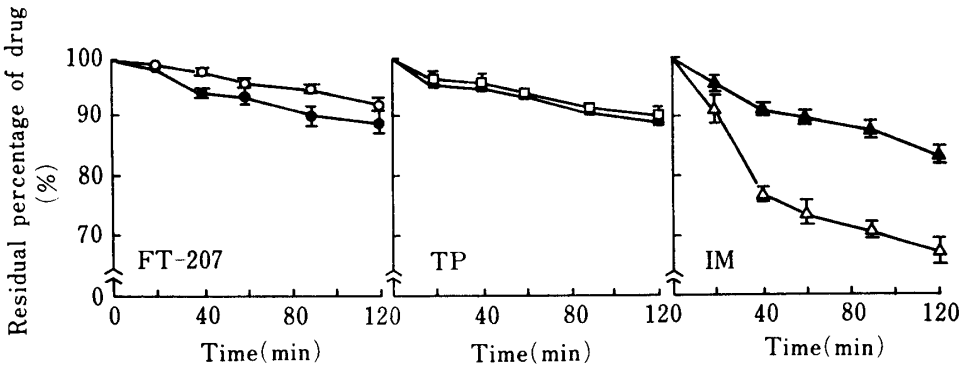

Fig. 2. Effect of CS-11 on the Rectal Absorption of FT-207, TP, and IM during *in Situ* Recirculation

●: 1% CS-11 in buffer solution. ○: Buffer solution. ■: 1% CS-11 in buffer solution. □: Buffer solution. ▲: 1% CS-11 in buffer solution. △: Buffer solution.

tions with and without the surfactant. In contrast, the absorption was considerably higher from buffer solution with the surfactant than from that without it for indomethacin. These findings suggest that drugs such as indomethacin, which are strongly lipophilic as compared with FT-207 or theophylline, are more readily soluble in micelles formed by the surfactant molecules of CS-11 than the hydrophilic substances. In addition, the amount of drug released was closely related to the partition coefficient. Thus, the drug release was observed to decrease in the order indomethacin, theophylline and FT-207, in accordance with the order of partition coefficient.

3. The Characteristics of Drug Release through a Millipore Filter Membrane *in Vitro*

The effects of the water content in suppository bases on the release patterns of FT-207, theophylline and indomethacin *in vitro* through a Millipore filter are shown in Fig. 3. Although the release curves for the three drugs were not linear they were all similar in shape. The drug release from the suppository base increased markedly at the early stage of dissolution, and gradually levelled off as the release time increased. In every case, a higher release was observed at a higher concentration of water phase at all stages of dissolution because the base containing a larger amount of water had a higher solubility in the emulsion-type suppository. In addition, the amounts of drug release were closely related to the solubility since they decreased in the order FT-207, theophylline and indomethacin.

Figure 4 indicates the effect of polymers on the release patterns of FT-207, theophylline and indomethacin through a Millipore filter. The drug release decreased in the order sodium alginate, sodium carboxymethyl cellulose and sodium polyacrylate. These results suggest that the molecular weight and solubility of polymers influence the drug release pattern from the suppository base.

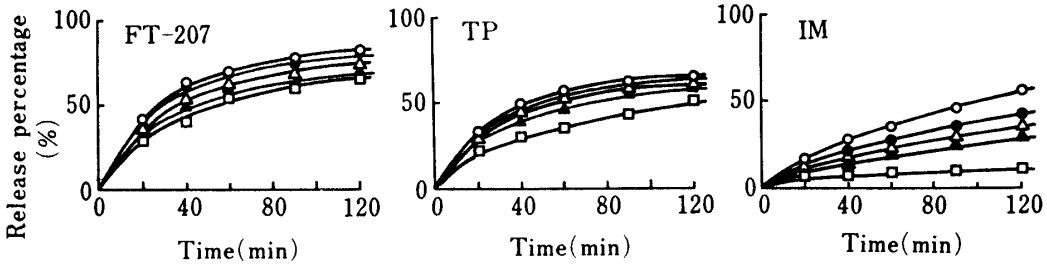

Fig. 3. Effect of Water Content in Suppository Bases on the Release Patterns of FT-207, TP, and IM with the Millipore Filter Technique

□, 0%; ▲, 40%; △, 50%; ●, 60%; ○, 70%.

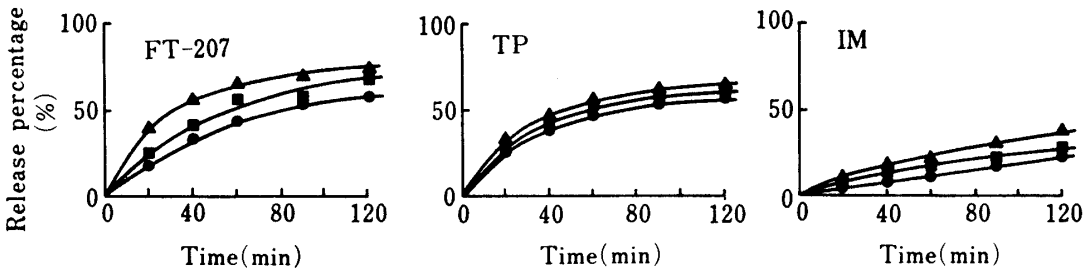

Fig. 4. Effect of Polymers on the Release Patterns of FT-207, TP, and IM with the Millipore Filter Technique

▲, Alg-Na; ●, PAA-Na; ■, CMC-Na.

The relations between the initial release rate and the water content in the suppository base for the three different drugs are shown in Fig. 5. Here, the release rate was calculated from the change in the amount of drug released during the period of time from zero to 20 min

based on the curves in Fig. 3. With increasing concentration of water phase, a linear increase in the release rate was found for all three drugs. As the release rate at the initial stage was related to the drug solubility it was predicted to decrease in the order FT-207, theophylline and indomethacin. On the basis of the results of the Millipore filter membrane technique, we propose the following model for the drug release process *in vitro* in emulsion-type suppository bases. The drug release from an emulsion base occurs in two steps: (1) transport of the drug dissolved in droplets of oil to the aqueous medium, and (2) transport of the drug in the continuous aqueous phase across the the Millipore membrane. Depending on the physical and chemical properties of the drug, the rate-limiting step for the release may be either of the steps.

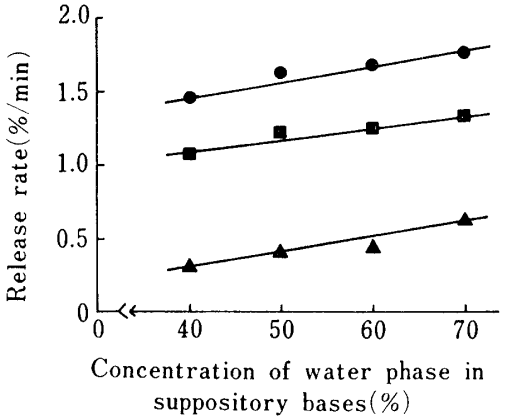

Fig. 5. Effect of Water Content in Suppository Bases on the Release Rates of FT-207, TP, and IM at the Initial Stage of Dissolution

●, FT-207; ■, TP; ▲, IM.

Compounds such as indomethacin are strongly lipophilic and have a high partition coefficient. Since indomethacin dissolves completely in Witepsol S-55 of the dispersed phase, the former step, *i.e.* the transport of the drug from the oil phase to the water phase, is considered to be the rate-limiting step. On the other hand, water-soluble substances such as FT-207 are hardly soluble in the oil phase, and hence, they are suspended in the external water phase. For these substances, therefore, the latter step, *i.e.*, transport across the Millipore membrane, may be the rate-governing step in the process of drug release. In addition, since the partition coefficient of theophylline lies in the range of 0.35 to 1.86, the drug release properties are intermediate between those of FT-207 and indomethacin.

4. The Characteristics of Drug Release through the Rectal Membrane *in Vitro*

The effects of the water content in suppository bases on the releases of FT-207, theophylline and indomethacin through the rectal membrane *in vitro* are shown in Fig. 6. The drug release patterns for the three drugs from the rectal membrane *in vitro* were similar, through indomethacin showed lower release rates at five different concentrations of water in the bases than FT-207 and theophylline. The drug release was increased by increasing the concentration

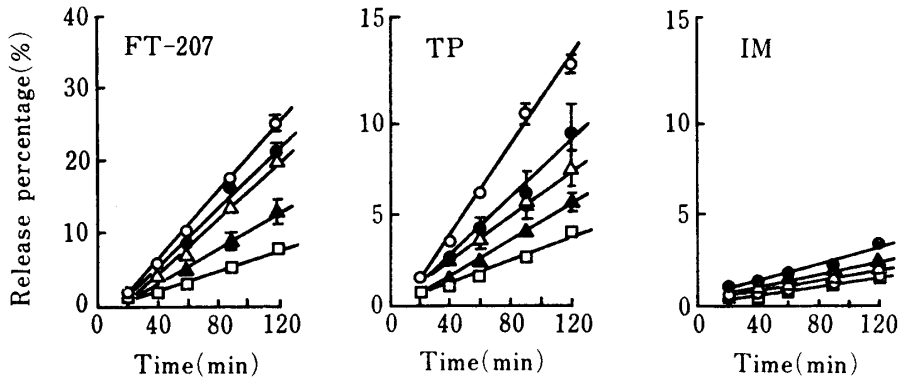

Fig. 6. Effect of Water Content in Suppository Bases on the Release Patterns of FT-207, TP, and IM through Rectal Membrane *in Vitro*

□, 0%; ▲, 40%; △, 50%; ●, 60%; ○, 70%.

of continuous phase. The amount of drug released was linearly related to the dissolution time. The line was extrapolated to the abscissa and the lag time of drug release was determined. The lag time is considered to be the time necessary for the establishment of a quasistationary state and is a function of the mean distance between the suspended particles, the diffusion constant of the drug and so on.

The influence of polymers was also investigated, as shown in Fig. 7. The rate of drug release through the rectal membrane *in vitro* depended upon the water content, and a similar tendency was found in the release through the Millipore filter. As shown in Figs. 6 and 7, there was a linear relationship between the amount of drug released and dissolution time in all cases. Therefore, it can be considered that the process of drug release through the rectal membrane *in vitro* depends on passive transport[14] governed by the concentration gradient of drugs across the membrane. It is likely that many drugs penetrate the solution-rectal barrier by passive diffusion across a membrane having lipoid characteristics and are absorbed at the rectal epithelial border, which resembles the blood-small intestine and blood-colon barriers.[15]

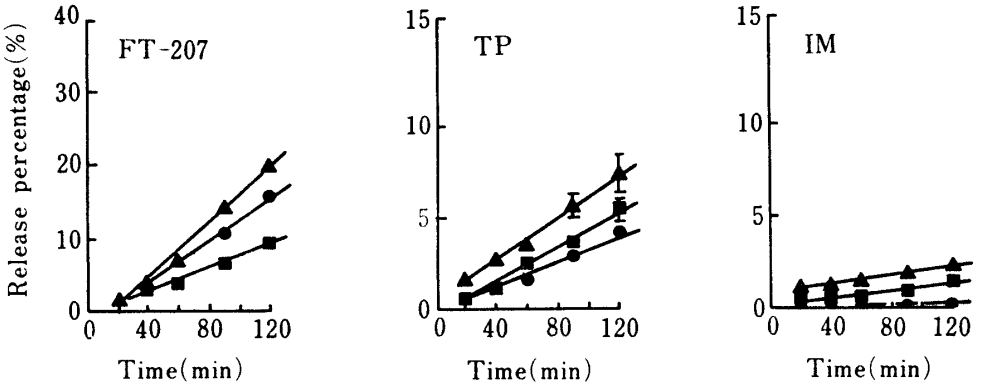

Fig. 7. Effect of Polymers on the Release Patterns of FT-207, TP, and IM through Rectal Membrane *in Vitro*

▲, Alg-Na; ■, PAA-Na; ●, CMC-Na.

The drug diffusion rate was plotted against the water content in the suppository bases (Fig. 8), and good linearity was seen for all three drugs. Here, the diffusion rate constants were calculated from the slopes of the lines in Fig. 6. From these results, it was apparent that the diffusion rate of drug through the rectal membrane *in vitro* is influenced by the water content in the emulsion-type suppository. Highly water-soluble drugs such as FT-207 penetrate slowly into the blood through the rectal membrane. Therefore, the diffusion rate of drug through the rectal membrane would be expected to increase with increase of the water content in the suppository base. On the other hand, drugs having an extremely high partition coefficient (*i.e.* very oil-soluble drugs such as indomethacin) showed a low trans-membrane transfer rate and would remain localized in the lipid layer of the rectum.

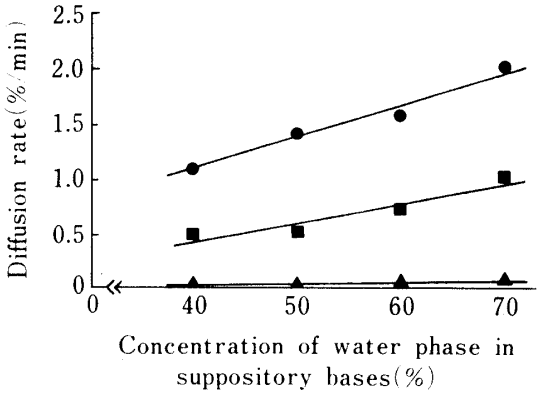

Fig. 8. Effect of Water Content in Suppository Bases on the Diffusion Rates of FT-207, TP, and IM through Rectal Membrane *in Vitro*

●, FT-207; ■, TP; ▲, IM.

Conclusions

The results on drug release *in vitro* from the suppository bases can be summarized as follows.

1. In the case of readily water-soluble FT-207, the amount of drug released increased with increase of the water content in the suppository base.

2. A similar release pattern was found for theophylline which has solubility properties intermediate between those of FT-207 and indomethacin. However, the amount of drug released was lower than in the case of FT-207.

3. For indomethacin, which is strongly lipophilic, no or little effect of the water content in the suppository base was found.

4. The amount of drug released could be controlled and the release prolonged in emulsion-type suppository bases by the addition of aqueous polymer.

5. The transport process of drug through the rectal membrane is considered to be a passive one, which means that the release of drug from the suppository bases proceeds in a zero-order process.

6. In the case of drug release through a Millipore filter membrane, since the emulsion-type suppository bases prepared in this experiment contained a sufficient amount of water, the drug release rate was high at the initial stage of dissolution.

These bases should be practically useful for drug delivery by means of suppositories.

References and Notes

1) Part III. "Studies on Pharmaceutical Drug Design for Suppositories."
2) M. Yasuhara, Y. Miyoshi, A. Yuasa, T. Kimura, S. Muranishi, and H. Sezaki, *Chem. Pharm. Bull.*, **25**, 675 (1977).
3) J.J. Rutten-Kingma, C.J. Blaey, and J. Polderman, *Inter. J. Pharm.*, **3**, 179 (1979).
4) S. Tsuchiya, M. Hiura, and H. Matsumaru, *Chem. Pharm. Bull.*, **25**, 667 (1977).
5) H.I. Silverman, *J. Am. Pharm. Assoc.*, **49**, 716 (1960).
6) J.H. Fincher, D.N. Entrekin, and C.W. Hartman, *J. Pharm. Sci.*, **55**, 23 (1966).
6) J.H. Fincher, D.N. Entrekin, and C.W. Hartman, *J. Pharm. Sci.*, **55**, 23 (1966).
7) S. Noro, Y. Komatsu, and T. Uesugi, *Chem. Pharm. Bull.*, **30**, 2906 (1982)
8) S. Muranishi, Y. Okubo, and H. Sezaki, *Yakuzaigaku*, **39**, 1 (1979).
9) S. Komori, H. Ohashi, T. Okada, and T. Takewaki, *Brit. J. Pharmacol.*, **65**, 261 (1979).
10) T. Koizumi, T. Arita, and K. Kakemi, *Chem. Pharm. Bull.*, **12**, 421 (1964).
11) S. Watanabe, B. Nishioka, Y. Fujita, T. Ueda, O. Kojima, K. Morisawa, E. Yamane, M. Umehara, and S. Majima, *Jpn. J. Surg.*, **10**, 105 (1980).
12) L. K. Paalzow, *J. Pharmacol. Biopharm.*, **3**, 25 (1975).
13) N.M. Curran, E.G. Lovering, K.M. McErlance, and J.R. Watson, *J. Pharm. Sci.*, **67**, 187 (1980).
14) S.K. Chandrasekaran, H. Benson, and J. Urquhart, "Sustained and Controlled Release Drug Delivery Systems," ed. by J.R. Robinson, Marcel Dekker Inc., New York, (1978), pp. 561—564.
15) K. Kamei, T. Arita, and S. Muranishi, *Chem. Pharm. Bull.*, **13**, 861 (1965).