

Indomethacin Sustained-Release Suppositories Containing Sugar Ester

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We prepared indomethacin (IM) sustained-release suppositories using sugar ester (SE) as an additive. The suppositories were prepared by the fusion method with IM, SE, and Witepsol® H-15 (H-15) and their availabilities *in vitro* and *in vivo* were evaluated mainly by the drug release test and the absorption test in rabbits, respectively.

The softening point of the suppositories increased with increasing SE content. In the release test with the Muranishi method, slow-release profiles were obtained when the SE content was more than 52.5%. The absorption of IM from these suppositories, however, was very little. In the other release test, *e.g.* immersion method with gauze, all of the suppositories with SE showed slow-release profiles, and the drug release rates clearly depended on the SE content. The drug was released from the suppositories by the following leaching-type mechanism proposed by Higuchi. The suppository with a 30% SE content showed a sustained-plasma level of IM, but the other suppositories did not. It was concluded that an appropriate content of SE (*i.e.* 30%) in the suppository base was required to obtain sustained-release because it reasonably regulated the infiltration of rectal fluid into the suppository and the mechanical strength of the suppository against disintegration.

Keywords indomethacin; sucrose fatty acid ester; sugar ester; sustained-release suppository; rabbit

In previous papers¹⁾ we reported that indomethacin (IM) sustained-release suppositories containing hydrogenated soybean lecithin (HL) were obtained when more than 30% of HL was added to a Witepsol® H-15 (H-15) base. The mechanism of the sustained-release of IM was thought to be that HL raised the softening point of the suppositories and that IM dissolved gradually from them. From this point of view, we tried to use sucrose fatty acid ester (sugar ester, SE) as an additive with the aim of producing sustained-release suppositories. We used SE, whose ester value and hydrophile-lipophile balance (HLB) were 2.08 and 2, respectively. The SE has similar properties to lecithin; for example, SE forms vesicles²⁾ in water, so-called niosomes, as does lecithin. SE was used for many purposes, such as an emulsifier, an additive for solid dosage forms, and so on.³⁾ In suppositories, SE was used to enhance the crystallization of IM contained to prolong shelflife.⁴⁾ It has also been used to improve the disintegration of suppositories and to reduce irritation of the rectal mucosa.⁵⁾ Moreover, SE has been used in suppositories to enhance both the absorption of drugs⁶⁾ and the release of drugs.⁷⁾

Yonezawa *et al.*⁸⁾ reported that 5% of SE, whose HLB was more than 11, was added to a digoxin suppository to increase its solubility with the aim of producing a sustained-release suppository. The digoxin plasma concentration, however, was not well sustained.

In this paper, we investigated the preparation of IM sustained-release suppositories containing SE. The physicochemical properties of suppositories containing SE were evaluated by *in vitro* release test, X-ray analysis, differential scanning calorimetry (DSC), penetrometry and *in vivo* absorption behaviour in rabbits.

Experimental

Materials The sources of the materials used in this work are as follows: IM from Sumitomo Chemical Co., Ltd.; H-15 from Dynamit Nobel; and SE (DK ester F-20w) from Daiichikogyoseiyaku Co., Ltd. The ester value and the HLB of the SE were 2.08 and 2, respectively. The ester composition was as follows: mono ester (9.2%) and diester or poly ester (90.8%). The fatty acid of the SE was derived from tallow, and its components in the SE were as follows: stearic acid and palmitic acid were 70% and 30%,

respectively.³⁾ All other chemicals were reagent-grade commercial products.

Preparation of IM Suppositories Suppositories were prepared as follows: H-15 (19.5–49.5 g) and SE (0–30 g) were fused in a beaker in an oil bath at 90°C. Then IM (0.5 g) was added and dissolved or suspended in the fused bases. The fused bases were cooled to 60°C and poured into suppository molds (1.0 ml in volume) which were quickly refrigerated at 5°C. Table I shows the formulae of the suppositories. The samples were stored at 5°C and used for experiments within 1 week.

Release of IM from Suppositories The release of IM was measured using the following three methods: 1) the Muranishi method⁹⁾ with 3 ml of test solution in a cell as described previously¹⁾; 2) the modified Thomas method¹⁰⁾ with a Visking tube: a suppository was put in a Visking tube which was then placed in 120 ml of the test solution in a flask. The flask was incubated at 37°C in a shaker (Eyela shaker SS-8, Tokyo Rikakikai Co., Ltd.) and agitated at 30 rev/min; and 3) a gauze method¹¹⁾: a suppository wrapped with two sheets of gauze was placed in 120 ml of the test solution in a flask. The flask was incubated without shaking at 37°C. At appropriate sampling times, 1 ml of the releasing fluid was removed and one ml of fresh test solution was added to the flask.

In each test, the IM concentration was assayed spectrophotometrically at 318 nm.

Release of Base Components from Suppository After weighing initially a suppository and two sheets of gauze, the suppository, wrapped with the two sheets of gauze, was immersed in the test solution in the flask, as described in the release test (3). In the release test, the suppository and the gauze were taken out of the flask every hour after discarding the test solution. The suppository and the gauze were dried at room temperature for 1 d, and then in a desiccator for 2 d. After weighing them, the amount of released base was calculated by subtracting the dried weight of the suppository and gauze from their initial weight.

Measurement of Softening Point of Suppository by Penetration Time The penetration time of the suppositories was measured with the penetrometer¹⁾ to evaluate the softening point (*i.e.* a kind of hardness). Penetration time is the time required for a rod, weighing 7.0 g and measuring 2 mm in diameter, to penetrate a suppository which is immersed

TABLE I. Formulae of Suppositories

Rp.	IM (mg)	SE (mg)	H-15 (mg)
1	10	0	Total 1000
2		200	
3		300	
4		500	
5		525	
6		600	

in 5 ml distilled water in a glass tube, and to reach the rubber stopper at the bottom of the tube. The tube was maintained in a water bath at 37 or 50 °C.

Calorimetric Study A differential scanning calorimeter (Du Pont Instrument Co., thermal analyzer 1090B) was used for examining the thermotropic properties of suppositories with a heating rate of 10 K/min. Samples weighing about 5 mg were used.

X-Ray Diffraction Analysis The X-ray diffraction patterns of the fused and physical mixtures (IM, SE, and H-15) were measured to investigate their crystallinity.

The fused mixtures were prepared like suppositories as described before, and the physical mixtures were prepared by hand with an agate mortar and pestle. The crystallinity of the IM in the bases was measured using a Rigaku Geigerflex 2027 (Rigaku Denki Co., Ltd.). The measurement conditions have been described previously.¹⁾

Animal Experiments White male rabbits, each weighing 2.8–3.6 kg, were fasted for a 48 h period before the experiments but were allowed free access to water. The suppositories (IM, 3 mg/kg) were inserted manually. Retention of the suppositories by the rabbits was ensured by fastening the anus with a clip after insertion. Blood (2 ml) was taken from the rabbits by cardiac puncture at different time intervals. The plasma was obtained by centrifugation at 3000 rpm for 10 min. The value of the area under the plasma concentration–time curve (AUC) was calculated by means of the trapezoidal method, from 0 to 10 h.

Assay of IM in Plasma Plasma (0.7 ml) was pipetted into a glass-stoppered centrifuged tube containing 2 ml of 0.2 M citrate buffer (pH 3.6) and 10 ml of ethyl acetate. The test tube was mechanically shaken for 10 min and then centrifuged at 3000 rpm for 10 min. Eight milliliters of the ethyl acetate was pipetted into another centrifuged tube and evaporated to dryness under reduced pressure.

The residue was dissolved in 250 μ l in the mobile phase. A 20 μ l sample was injected into a high-performance liquid chromatography apparatus (Hitachi 655-12 liquid chromatograph with a Hitachi 655A variable-wavelength ultraviolet (UV) monitor). The conditions for analysis were as follows: column, 15 cm \times 4 mm i.d.; packing, TSK-LS410 (5 μ m) ODS; mobile phase, methanol–water–acetic acid–triethanolamine (74.3 : 25 : 0.5 : 0.2); flow rate, 0.5 ml/min; wavelength, UV at 260 nm; column temperature, 50 °C.

Results and Discussion

Crystallinity of IM in Bases The crystallinity of IM in the suppository bases and in the physical mixture of IM, SE, and H-15 was investigated by X-ray diffractometry. Figure 1 shows the X-ray diffraction spectra of various samples. Since the characteristic diffraction peak ($2\theta = 11.5^\circ$) of IM crystals did not overlap the peaks derived from SE and H-15, it was regarded as the characteristic peak of IM crystals in bases. As described previously,¹⁾ due to the low sensitivity of IM, an increased content of IM in the mixture was used to see the X-ray patterns clearly. Both the physical mixture and the fused mixture (SE:H-15:IM=6:4:1) showed a characteristic peak. Thus, IM in a suppository containing SE that was prepared as described in the experimental section was considered to be crystalline although IM existed in an amorphous state in the suppository containing HL.¹⁾

Penetration Time of Suppositories Table II shows the results obtained with the penetrometer. The Rp. 2 suppository was penetrated within 350 s at 37 °C. The Rp. 3–6 suppositories were not penetrated at 37 °C within 1 h, although the Rp. 3 suppository had swelled considerably (macroscopic observation). At 50 °C, the Rp. 1–4 suppositories were penetrated within 170 s and the penetration time increased with increasing SE content. The Rp. 5 and 6 suppositories, however, were not penetrated within 30 min at 50 °C.

These results indicate that the increase of SE content raised the softening point of the suppositories like HL.¹⁾

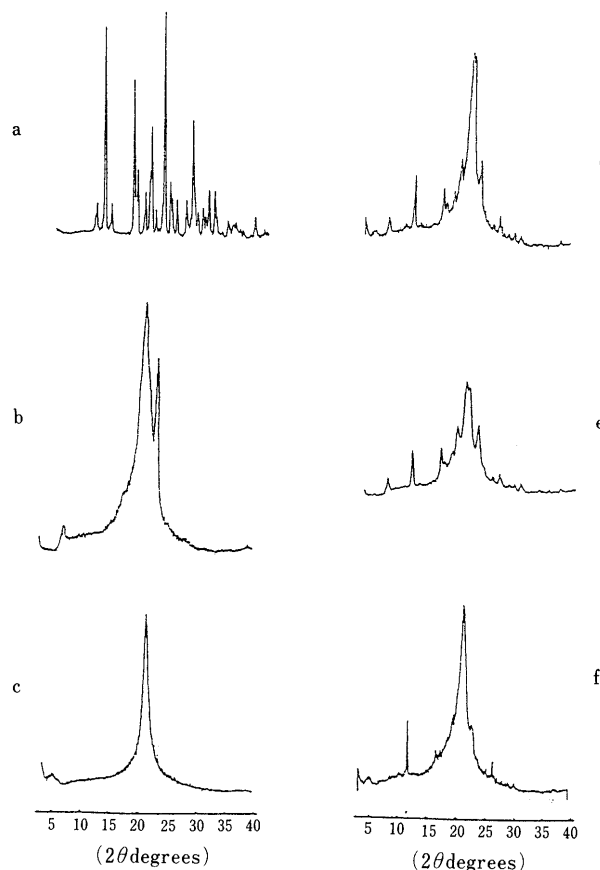


Fig. 1. X-Ray Diffraction Patterns

Alone: a, IM; b, H-15; c, SE. Physical mixture: d, SE:H-15:IM=6:4:1. Fused mixture: e, H-15:IM=9:1; f, SE:H-15:IM=6:4:1.

TABLE II. Penetration Time of Various Suppositories

Rp.	SE content (mg)	At 37 °C (s)	At 50 °C (s)
1	0	302 \pm 6	82 \pm 6
2	200	350 \pm 20	85 \pm 5
3	300	a)	130 \pm 9
4	500	a)	160 \pm 6
5	525	a)	b)
6	600	a)	b)

Suppositories were not penetrated within 1 h^{a)} and 0.5 h^{b)}.

although HL raised the softening point more than SE did.

Thermotropic Properties of Suppositories Figure 2 shows the DSC pattern of SE and the suppositories with various SE content. The endothermic peak of SE was approximately 62 °C. The Rp. 1 suppository showed an endothermic peak at approximately 36 °C derived from H-15. The Rp. 2 suppository (SE 200 mg) showed an endothermic peak at approximately 36 and 62 °C. The Rp. 3, 4, 5 and 6 suppositories, whose SE contents were from 300 to 600 mg, showed almost the same DSC pattern as each other. The endothermic peak at approximately 62 °C derived from SE did not increase with an increasing SE content of 300 to 600 mg.

On the other hand, an endothermic peak at 36 °C in a control suppository without HL shifted to a higher temperature with an increasing HL content. The suppository containing 350 mg of HL showed the peak at approximately 39 °C.¹⁾

Release of IM from Suppository Figure 3 shows the

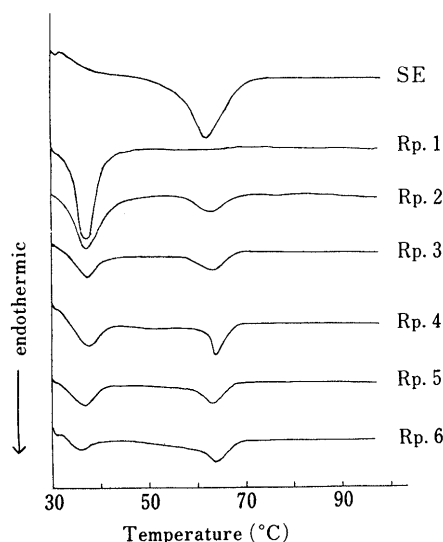


Fig. 2. DSC Thermograms

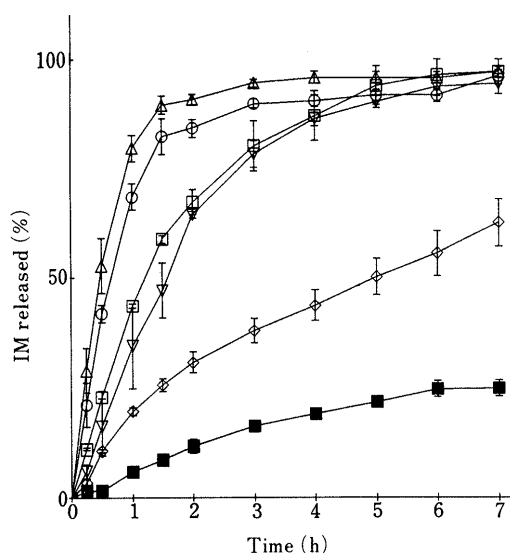


Fig. 3. Release Profiles of IM from Various Suppositories Using the Muranishi Method

SE content: □, 0 mg, 0%; ○, 200 mg, 20%; △, 300 mg, 30%; ▽, 500 mg, 50%; ◇, 525 mg, 52.5%; ■, 600 mg, 60%. Each value represents the mean \pm S.E. ($n=3$).

effect of SE content on the release of IM from suppositories using the Muranishi method. The release rates of IM from the Rp. 2 and 3 suppositories were faster than that of the Rp. 1 suppository. The Rp. 1, 2 and 3 suppositories disintegrated and melted within 15 min in the cell of the release apparatus. Since SE could act as a surfactant or a dispersing agent as well as increase the softening point of the suppository, the release of IM from the Rp. 2 and 3 suppositories having insufficient hardness (softening point) against mechanical stress by agitation was enhanced. The release profile of the Rp. 4 suppository was almost the same as that of the Rp. 1 suppository. The Rp. 4 suppository also disintegrated and melted within 15 min. The Rp. 5 and 6 suppositories did not melt or disintegrate entirely during testing, and their shape was maintained, as seen by macroscopic observation. The Rp. 5 and 6 suppositories showed slow release profiles.

Although the penetration time of the Rp. 3 and 4 suppositories was more than 1 h at 37°C, these suppositories disintegrated or melted within 15 min in the cell

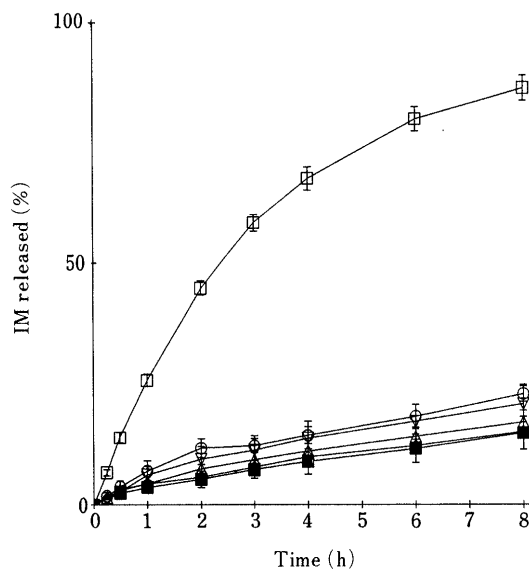


Fig. 4. Release Profiles of IM from Various Suppositories Using the Visking Tube Method

Symbols are the same as in Fig. 3. Each value represents the mean \pm S.E. ($n=3$).

of the release apparatus. This is due to the fact that the stirring and the shear stresses imposed by the rod of the release apparatus were greater than that applied by the rod of the penetrometer. Thus, the Rp. 3 and 4 suppositories showed fast release profiles with disintegration and melting of the suppositories. On the other hand, the Rp. 5 and 6 suppositories did not disintegrate or melt entirely with the Muranishi method during testing because their penetration time was more than 30 min at 50°C. Thus, the gradual dissolution of IM from the suppositories occurred with the gradual melting and disintegration of the base component from the surface of the suppositories.

Figure 4 shows the results of the release test using a Visking tube method. The Rp. 2–6 suppositories showed considerably slow-release profiles. This is because the suppository was maintained statically in the Visking tube and the tube acted as a barrier and a cushion during shaking. Although the suppositories swelled, they did not disintegrate or melt entirely and their shape was maintained during testing. Thus, the Rp. 2–6 suppositories showed considerably slow-release profiles.

Figure 5A shows the results of the release test using the gauze method. The release rate of IM from the suppositories decreased with increasing SE content. Even the Rp. 2 and 3 suppositories showed slow release profiles and the t_{50} was 3.5 and 4.5 h, respectively, although only 20% of IM was released from these suppositories at 8 h in the Visking tube method. This is because the gauze did not act as a barrier, unlike the Visking tube method, although there was no shaking in the gauze method.

Release of Base Components from Suppository In the gauze method the amount of the released base components from the Rp. 3 suppository was measured. Figure 6 shows the results.

The release profile of the base components from the suppository was similar to that of IM from the suppository. The main base components released seemed to be H-15 because oil droplets appeared on the surface of the test solution during testing. These results indicate that IM

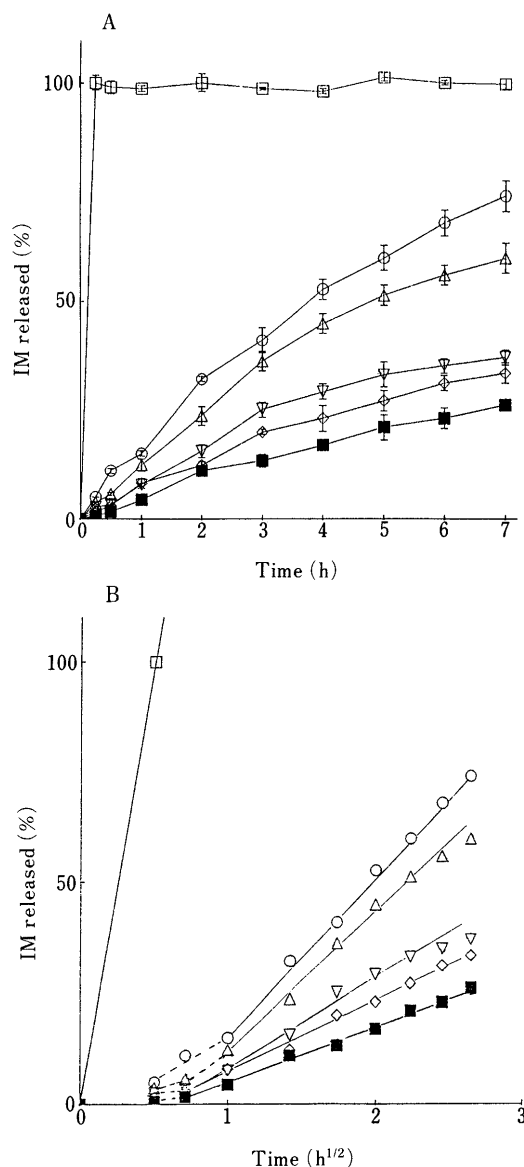


Fig. 5. Release Profiles of IM from Various Suppositories Using the Gauze Method

A: time, h; B: time, $h^{1/2}$. Symbols are the same as in Fig. 3. Each value represents the mean \pm S.E. ($n=3$).

dissolved gradually from the suppository with gradual melting or disintegration of the base component of the suppository.

Figure 5B shows the results of the release test when the unit of the stem of Fig. 5A is represented by the square root of h . The Rp. 2–6 suppositories are represented by a straight line in Fig. 5B. These data indicate that an apparent leaching-type of release mechanism proposed by Higuchi¹²⁾ may be applied.

This agreed with the results of the release test of sodium diclofenac from suppositories containing HL reported by Nishihata *et al.*¹¹⁾

Absorption Studies on Suppositories Containing SE

Figure 7 and Table III show the results of the absorption study of IM from the suppositories containing SE. The Rp. 2 suppository was not sustained and showed almost the same plasma level of IM as the Rp. 1 suppository. The IM plasma level of the Rp. 3 suppository was well sustained, and the T_{max} was 1 h, although that of other suppositories was 0.5 h. The IM plasma levels of the Rp. 4,

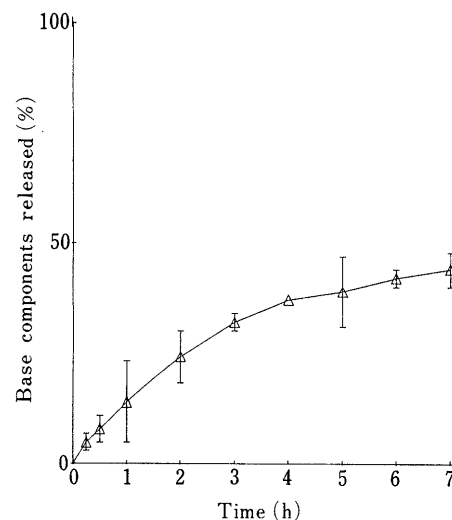


Fig. 6. Release Profile of Base Components from the Rp. 3 Suppository Using the Gauze Method

Value represents the mean \pm S.E. ($n=3$).

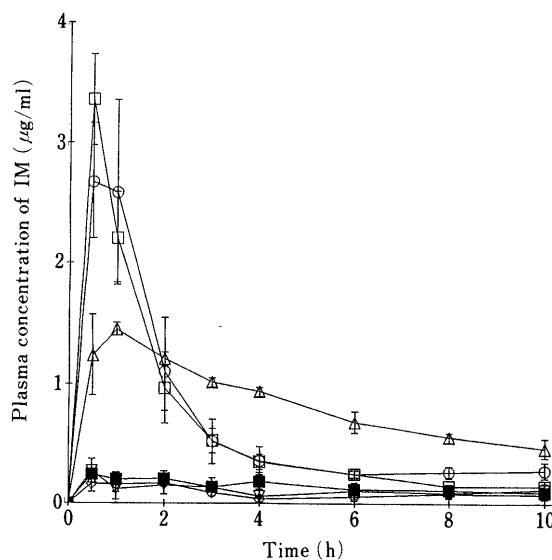


Fig. 7. Plasma Concentration of IM after Rectal Administration of Various Suppositories

Symbols are the same as in Fig. 3. Each value represents the mean \pm S.E. ($n=3$).

TABLE III. Pharmacokinetic Parameters of Various Suppositories

Rp.	IM (mg)	SE (mg)	Base (mg)	C_{max} (μ g/ml)	T_{max} (h)	AUC_0^{10} ($h \cdot \mu$ g/ml)
1	10	0	Total 1000	3.36 ± 0.38	0.5	6.31 ± 0.72
2		200		2.80 ± 0.57	0.5	6.77 ± 1.75
3		300		1.52 ± 0.11	1.0	8.30 ± 0.60
4		500		0.28 ± 0.05	0.5	1.13 ± 0.10
5		525		0.23 ± 0.05	0.5	0.89 ± 0.09
6		600		0.30 ± 0.03	0.5	1.46 ± 0.23

Each value of C_{max} and AUC_0^{10} represents the mean \pm S.E. ($n=3-5$).

5 and 6 suppositories were considerably low and the AUC value was also significantly low ($p < 0.05$) compared with the Rp. 1 suppository. These results indicate that SE 200 mg was insufficient, that SE 300 mg was appropriate, and that over 500 mg of SE was excessive for attaining a sustained-release suppository. When the results of the absorption test were compared with those of the release test using the

Muranishi method, a good correlation was not obtained. The Rp. 5 and 6 suppositories, which showed good slow-release profiles, released very little IM in the rectum of the rabbit. Even the Rp. 4 suppository released very little IM in the rectum, although the release rate of IM was almost the same as that of the Rp. 1 suppository. Although the release rate of IM from the Rp. 3 suppository was fast in the Muranishi Method, the IM plasma level was well sustained.

The results of the absorption test was good corresponding to the results of the softening point rather than to the release test. The Rp. 5 and 6 suppositories were not penetrated within 30 min at 50°C, and both suppositories showed low plasma levels of IM. The Rp. 3 suppository, which showed a sustained-plasma level of IM, was not penetrated within 1 h at 37°C and was penetrated 130 s at 50°C, although the Rp. 1 and 2 suppositories were penetrated within 350 s at 37°C.

The release test using the Visking tube method could not obtain a good correspondence to the absorption test. In the gauze method, the Rp. 3 suppository showed a good correspondence to the results of the absorption test. The IM plasma level of the Rp. 2 suppository, showing a slow-release profile in the gauze method, was not sustained. This is because there was peristalsis in the rectum although it might have been weaker than that imposed by the rod of the release apparatus of the Muranishi method. Therefore, the Rp. 2 suppository might disintegrate and melt, quickly releasing IM in the rectum and causing its rapid absorption. On the other hand, the Rp. 4, 5 and 6 suppositories seemed not to disintegrate or melt, and the release of IM was suppressed in the rectum because of their higher softening points and less rectal fluid, thereby also suppressing the absorption of IM. The Rp. 3 suppository had an appropriate softening point and released IM gradually in the rectum. Thus the plasma level of IM was sustained.

Nishihata *et al.* reported the influence of HL on the release of sodium diclofenac from suppositories containing HL and H-15,¹¹⁾ and from vehicles prepared with HL and methyl palmitate.¹³⁾ In the reports they described that HL regulated the infiltration of the dissolution medium into the matrices of suppositories or vehicles, and HL protected the matrices from disintegration according to its gel-forming property. They also reported that a leaching-type drug release process as proposed by Higuchi might be applied for the release of sodium diclofenac from the matrices, and that HL influenced the tortuosity and porosity of the matrices. In our previous reports,¹⁾ we investigated the release and absorption of IM from the suppository containing HL and H-15, and a sustained-release suppository was obtained. In this paper we investigated the influence of SE on the release and absorption of IM from the suppositories containing SE and H-15 compared with HL. The results of the release test using the gauze method indicated that SE,

similarly to HL, regulated the infiltration of the medium into the suppositories and the drug release mechanism was the apparent leaching-type. The protecting ability of SE from disintegration of the suppositories was rather weak compared with that of HL in the Muranishi method, but it was relatively strong in the Visking tube method and in the gauze method. These results indicate that SE also regulates the infiltration of the medium and protects suppositories from disintegration although the protection ability of SE is weaker than that of HL. The protection ability of SE or HL from disintegration corresponded to the results of the softening point or DSC patterns of the suppositories containing HL or SE. The Rp. 5 suppository, in which IM was crystalline, was compared with the suppository containing 300 mg of HL, in which IM was amorphous, to take account of the influence of crystallinity of IM on the absorption of IM in rabbits. Both suppositories showed slow-release profiles in the Muranishi method. The plasma level of IM from the suppository containing 300 mg of HL was well sustained, but the absorption of IM from the Rp. 5 suppository was very little. The amorphous state of IM seemed to enhance the dissolution or the absorption of IM from suppositories in the rectum in which the dissolution medium was little.

In conclusion, we were able to prepare the sustained-release suppositories containing SE with a drug release mechanism similar to suppositories containing HL.

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