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Preparation of Sustained-Release Suppositories of Indomethacin Using a Solid Dispersion System and Evaluation of Bioavailability in Rabbits[1)]

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Sustained-release suppositories of indomethacin (IM) were prepared by the use of a solid dispersion system. As the suppository base, we used a solid matrix of polyethylene glycol 2000 (PEG) as a water-soluble carrier and hydroxypropylmethylcellulose phthalate (HP55) as a poorly water-soluble carrier. It was observed by X-ray diffractometry that IM was uniformly dispersed in amorphous state in the matrix suppositories. The rectal administration of 20% HP55 matrix suppositories (M-20-5) in rabbits resulted in both fast-release and sustained-release characteristics as well as good bioavailability. The sustained release of IM from the matrix suppositories was attributed to the formation of a network structure of HP55 which dissolved more slowly than PEG.

Keywords——indomethacin; sustained-release suppository; solid dispersion; hydroxypropylmethylcellulose phthalate–polyethylene glycol matrix; X-ray diffraction; *in vitro* release rate; rectal administration; bioavailability

In the previous work, we prepared sustained-release suppositories of indomethacin (IM) by mixing microcapsulated IM with intact IM.[2,3)] We also prepared sustained-release suppositories of nifedipine by using a solid dispersion matrix of polyethylene glycol 4000 as a water-soluble carrier and cellulose acetate phthalate (CAP) as a poorly water-soluble carrier, and found that these suppositories presented both fast-release and sustained-release characteristics as well as good bioavailability in rabbits.[4)]

In this study, sustained-release suppositories of IM were prepared by the fusion method, using a solid matrix of hydroxypropylmethylcellulose phthalate 200731 (HP55) and polyethylene glycol 2000 (PEG), and the release behavior and bioavailability of the suppositories were investigated in rabbits.

Experimental

Materials——IM was a gift from Sumitomo Pharmaceutical Co., Ltd., HP55 (kinematic viscosity: 40 cSt) was purchased from Shin-etsu Chemical Co., Ltd., and PEG was supplied by Wako Pure Chemical Ind., Ltd. All other chemicals were reagent-grade commercial products.

Preparation of Suppositories——1) Conventional Suppositories (C-0): C-0 was prepared using IM and PEG as a base by the fusion method. The weight of C-0 was 1 g.

2) Matrix Suppositories (M-10, M-15, M-20 and M-20-5): The matrix suppositories were prepared as follows. Physical mixtures of specified proportions of HP55 and PEG were prepared. These mixtures were heated at 120 °C in a thermostated oven with occasional stirrings until clear homogeneous fusions were formed. Then, IM was melted in the HP55–PEG fusions, and these were quickly poured into steel molds and allowed to solidify at room temperature. M-10, M-15 and M-20 contained 10, 15 and 20% HP55 in the matrix base, respectively, and the weight of them was 1 g. M-20-5 contained 20% HP55 in the base and its weight was 0.5 g.

The formulae of suppositories prepared in this work are listed in Table I. The content of IM in all suppositories

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was 25 mg. All suppositories were stored in a desiccator at room temperature, and were administered within 24 h after preparation.

X-Ray Diffractometry——For measurements of the crystallinity of IM in the matrices, parts of the fusions prepared as described above were poured into aluminum holders, then solidified at room temperature (Table I). All matrices were stored in a desiccator at room temperature.

A Rigaku Denki Miniflex diffractometer was used under the following conditions: source, Cu-K_α radiation; filter, Ni-filter; voltage, 30 kV; current, 10 mA; range, 120000 or 240000 cpm; time constant, 1 s; scanning speed, 2.4° (2θ)/min; chart speed, 24 mm/min; divergence slit, 1°; scatter slit, 1°; receiving slit, 0.3 mm; detector, sealed proportional counter.

Release Test of Suppositories——The release test was performed as previously reported.[4] Five hundred ml of 0.1 M phosphate buffer solution (pH 7.2, $\mu=0.5$, NaCl) was used as the test solution. Each suppository was placed directly on a metallic net in a plastic cylindrical cell without an artificial membrane. This cell was immersed in the test solution at 37 ± 0.5 °C and a magnetic stirring bar in the test solution was rotated at 150 rpm. Released IM was assayed spectrophotometrically at 318 nm with a spectrophotometer (Hitachi, model 200-20) by circulating the test solution continuously through the micro flow cell.

Scanning Electron Microscopy——The surface of matrix suppositories was observed with a scanning electron microscope (Nihon Denshi, JSM-T20).

Animal Experiment——White male rabbits weighing from 3.0 to 3.7 kg were fasted for 36 h prior to the experiments but were allowed free access to water. After rectal administration, blood samples were collected from the ear vein at regular intervals. The plasma samples were frozen and stored at -5 °C until assay.

Measurements of IM in Plasma——The high-performance liquid chromatography (HPLC) reported by Kazmi *et al.*[5] was applied with a slight modification as follows: 0.5 ml of plasma was placed in a test tube, and 1 ml of 1 N HCl, 6 ml of benzene and 100 μl of internal standard solution (1 μg of diazepam) were added. After being shaken for 10 min, the mixture was centrifuged at 3500 rpm for 10 min. Then 5 ml of the organic phase was transferred to another tube and evaporated to dryness under a stream of nitrogen. The residue was reconstituted with 100 μl of methanol, and 25 μl of the sample was injected into an HPLC apparatus (Shimadzu, LC-3A) equipped with a detector (Shimadzu, SPD-2A). The conditions for analysis were as follows: column, 25 cm/4 mm i.d.; packing, Partisil 10 ODS; mobile phase, acetonitrile–0.1 M acetic acid (1 : 1); flow rate, 1 ml/min; wavelength, 254 nm; sensitivity, 0.005 a.u.f.s.

TABLE I. Formulae of Suppositories[a] and Matrices

	IM (g)	HP55 (g)	PEG (g)
C-0	0.25	—	9.75
M-10	0.25	1.00	8.75
M-15	0.25	1.50	8.25
M-20	0.25	2.00	7.75
M-20-5	0.50	2.00	7.50
M-20-10	1.00	2.00	7.00

a) The suppository weight of C-0, M-10, M-15 and M-20 was 1 g, and that of M-20-5 was 0.5 g. The content of IM in all suppositories was 25 mg.

Results and Discussion

Crystallinity of IM in Matrices

The crystallinity of IM in the HP55–PEG matrix was investigated by X-ray diffractometry.

Figure 1 shows the X-ray diffraction spectra of the IM–HP55–PEG physical mixture (IM: 2.5%, HP55: 20%) and the corresponding solid dispersion. The former exhibited the characteristic peaks of IM crystals at 11.5, 16.6 and 21.8° (2θ), but the latter did not. These results suggest that IM is present in an amorphous state in the HP55–PEG matrix.

The effect of HP55 content on the crystallinity of IM in matrices during storage is shown in Fig. 2. In the case of C-0, a characteristic diffraction peak (11.5°: 2θ) of IM crystals was clearly observed after storage for 1 month. On the other hand, M-10, M-15 and M-20 stored

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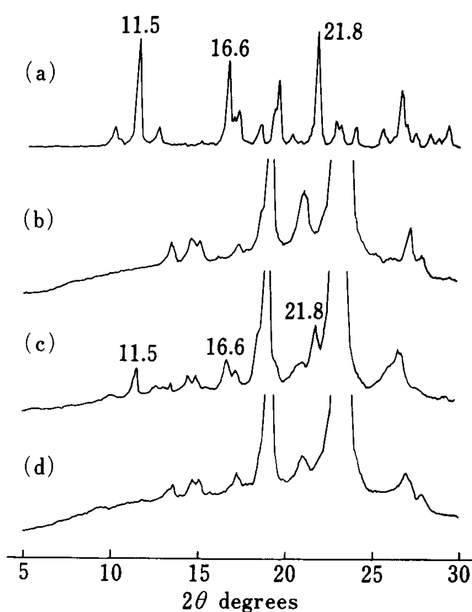

Fig. 1. X-Ray Diffraction Spectra of Various Samples

(a) IM alone, (b) HP55–PEG matrix, (c) IM–HP55–PEG physical mixture, (d) IM–HP55–PEG solid dispersion, IM content 2.5%, HP55 content 20%. Range: (a) 240000 cpm; (b—d) 120000 cpm.

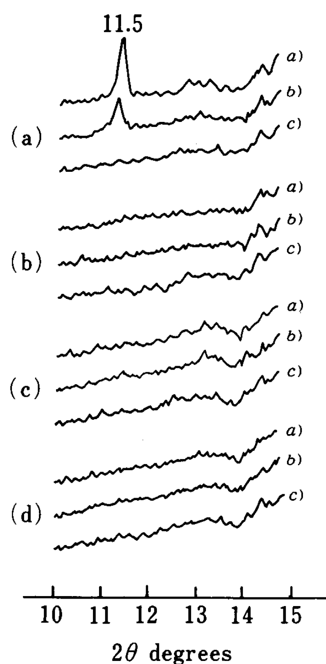

Fig. 2. Effect of HP55 Content on the Crystallinity of IM in Matrices during Storage

(a) C-0, (b) M-10, (c) M-15, (d) M-20. Range: 120000 cpm.

a) After storage for 2 months. *b)* After storage for 1 month. *c)* Before storage.

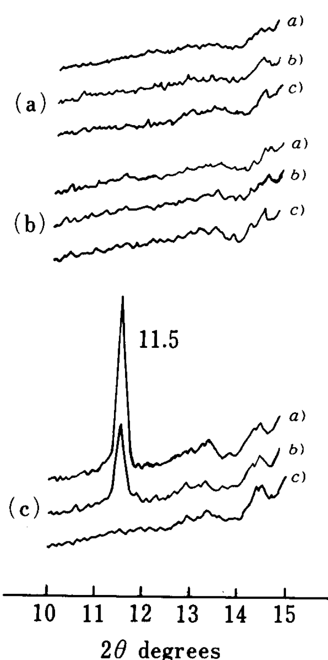

Fig. 3. Effect of IM Content on the Crystallinity of IM in Matrices during Storage

(a) M-20, (b) M-20-5, (c) M-20-10. Range: 120000 cpm.

a) After storage for 2 months. *b)* After storage for 1 month. *c)* Before storage.

for 2 months did not show any peak due to IM crystals. These results indicate that HP55 has the ability to inhibit the crystal growth of IM in HP55–PEG matrices.

Figure 3 shows the effect of IM content on the crystallinity of IM in matrices during storage. The X-ray spectra of M-20 and M-20-5 had no characteristic peak of IM crystals after storage for 2 months. In the case of M-20-10, a peak at 11.5° (2θ) attributable to IM crystals appeared after storage for 3 d, and its intensity gradually increased, depending on the storage period. These results indicate that IM in M-20-10 transforms from an amorphous state to a crystalline form during storage. Accordingly, it is considered that the content of IM

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in a suppository must be restricted to under 5% in order to maintain an amorphous state of IM in the HP55–PEG matrix for a long time.

Release Behavior of IM from Suppositories *in Vitro*

Figure 4 shows the effect of HP55 content on the release behavior of IM from suppositories. The release rate of IM from C-0 was very high, but that of IM from matrix suppositories was markedly low and decreased with increase of HP55 content; *i.e.*, the release rate of IM from matrix suppositories is controlled by HP55 content. M-20-5 tended to dissolve faster than M-20, as shown in Fig. 5. The surface area of M-20-5 is about three-fifths of that of M-20, and the weight of M-20-5 is half that of M-20.

On the other hand, the release rate of IM from C-0 after storage decreased, and it was confirmed that this was attributable to the crystallization of IM. The release behavior of M-10, M-15, M-20 and M-20-5, however, did not change during storage. From these results and the X-ray diffraction data described previously, it was concluded that the matrix suppositories except M-20-10 were physicochemically stable for a long time under these conditions.

Release Mechanism of IM from Matrix Suppositories

The release mechanism of IM from matrix suppositories was investigated by scanning electron microscopy. As shown in Fig. 6, pore formation and the development of a network

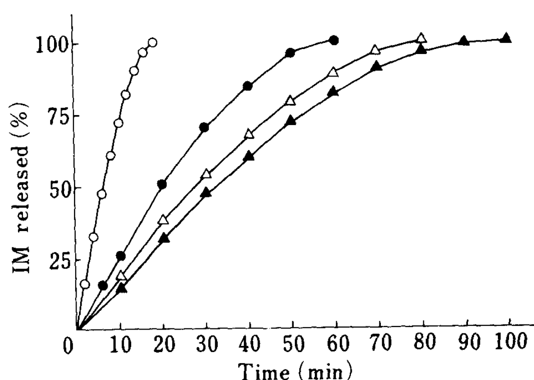


Fig. 4. Effect of HP55 Content on the Release Behavior of IM from Matrix Suppositories *in Vitro*

○, C-0; ●, M-10; △, M-15; ▲, M-20. Each point represents the mean of three experiments.

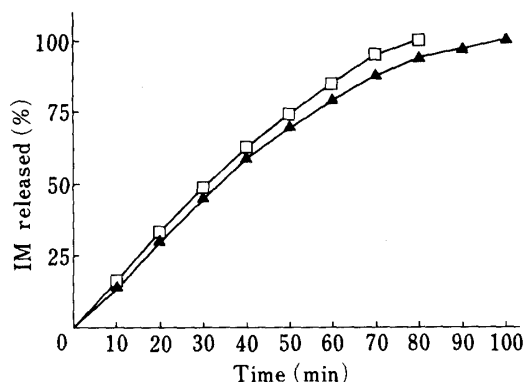
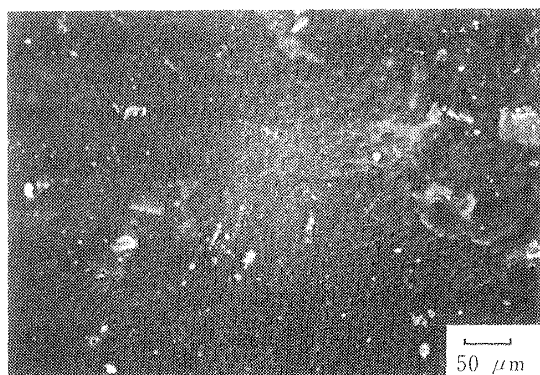
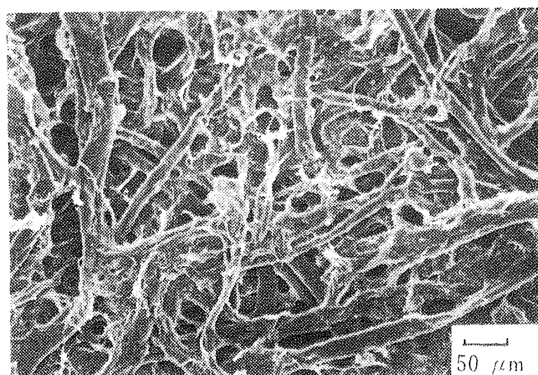


Fig. 5. Release Behavior of IM from M-20 and M-20-5 *in Vitro*

▲, M-20; □, M-20-5. Each point represents the mean of three experiments.



(a)



(b)

Fig. 6. Scanning Electron Microphotographs of the Surface of M-20-5

(a) Before the release test. (b) At 15 min after the start of the release test in 0.1 M phosphate buffer solution (pH 7.2) at 37 °C.

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structure could be observed at the surface of M-20 at 15 min after the start of the release test. It is considered that pore formation and the development of a network structure are attributable to the difference of dissolution rates of HP55 and PEG. Thus, the controlled release of IM from matrix suppositories may be explained as follows. First, PEG which entraps IM dissolves faster than HP55 at the surface of the suppository. Secondly, a network structure of HP55 appears at the surface. Owing to this network structure, the release of PEG-entrapped IM at the inner portion of the suppository is controlled. Thirdly, the superficial erosion of HP55 proceeds very slowly. These phenomena continue until the suppository is completely dissolved. This sustained-release mechanism is similar to that proposed in the previous study.[4)]

Plasma Levels of IM after Rectal Administration and Bioavailability in Rabbits

In this work using rabbits, we assumed that the maximal plasma concentration was below 5 μg/ml and the effective plasma level was above 2 μg/ml, and that the time for which an effective plasma level was maintained was 6—8 h as described previously.[2)]

The plasma levels of IM after rectal administration of C-0, M-10, M-15 and M-20 in rabbits are shown in Fig. 7. The absorption of IM after administration of C-0 was very fast, and the plasma level reached a peak of 22.2 μg/ml at 45 min and then decreased rapidly. M-10 and M-15 gave peaks of 10.7 μg/ml at 60 min and 7.3 μg/ml at 90 min, respectively. The administration of M-20 resulted in a low plateau plasma level from 15 min to 10 h. This markedly low plasma level appears to be attributable to a decreased release rate of IM due to the high content of HP55.

The area under the plasma concentration–time curve (AUC) and the extent of bioavailability (EBA) after rectal administration of the suppositories are listed in Table II. The EBAs of M-10 and M-15 were 90.0 and 77.6%, respectively. The EBA of M-20 was much

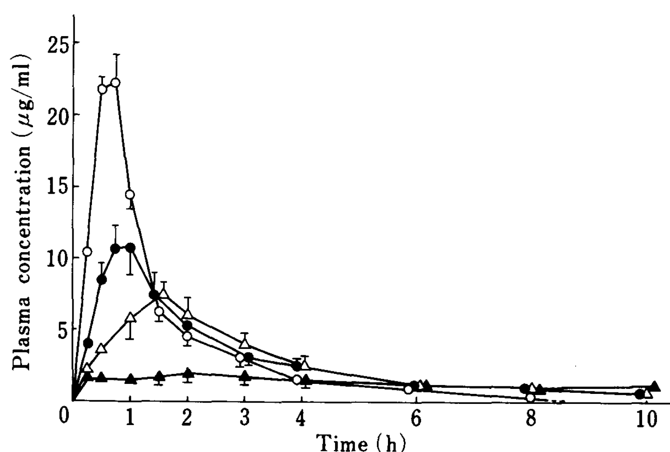

Fig. 7. Plasma Levels of IM after Rectal Administration of Matrix Suppositories in Rabbits

○, C-0; ●, M-10; △, M-15; ▲, M-20. Each point represents the mean ± S.E.

TABLE II. Bioavailability Parameters[a)] after Rectal Administration of IM (25 mg) in Rabbits

Suppositories	C-0	M-10	M-15	M-20	M-20-5
n[b)]	4	4	4	7	6
Body weight (kg)	3.5±0.1	3.6±0.1	3.6±0.1	3.5±0.1	3.6±0.1
C_{max} (μg/ml)	22.2±2.0	10.7±2.2	7.3±1.9	1.9±0.7	4.9±0.6
$[AUC]_0^{10}$ (μg·h/ml)[c)]	32.1±2.1	28.9±4.4	24.9±4.5	12.8±2.1	22.8±2.2
EBA (%)	100.0	90.0	77.6	39.9	71.0

a) Each value represents the mean ± S.E. *b*) The number of rabbits used. *c*) Calcd. by use of the trapezoidal rule from 0 to 10 h.

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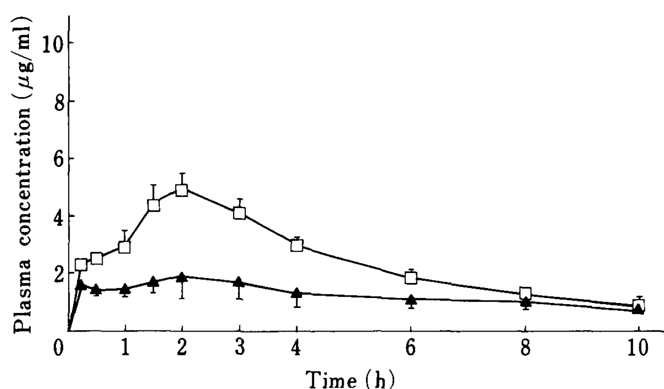

Fig. 8. Plasma Levels of IM after Rectal Administration of M-20 and M-20-5 in Rabbits

▲, M-20; □, M-20-5. Each point represents the mean±S.E.

smaller than the others. The reason for the small [AUC] of M-20 may be that the content of HP55 is so high that the PEG-entrapped IM at the inner portion of the suppository is unable to be released, and the superficial erosion proceeds more slowly. It was observed that about one-third of M-20 remained in the rectum of a rabbit at 10 h after administration.

To enhance the [AUC] of M-20, we designed M-20-5 by miniaturizing M-20. M-20-5 should dissolve in the rectal fluid of a rabbit within 10 h, because it dissolves out earlier than M-20 *in vitro* (Fig. 5). As shown in Fig. 8, M-20-5 presented a sustained-release property without an excessively high peak concentration. Furthermore, its [AUC] value was about twice that of M-20 (Table II). It appeared that this suppository was a suitable preparation for a sustained-release dosage form.

Conclusion

It was concluded that in HP55–PEG matrix suppositories, PEG enhances the bioavailability of IM, and HP55 controls the release rate of the PEG-entrapped IM by the formation of a network structure. M-20-5 gave both fast-release and sustained-release effects without a decrease of bioavailability. Accordingly, the HP55–PEG matrix as well as the CAP–PEG 4000 matrix[4)] appears to be suitable for development of a rectal drug-delivery preparation offering sustained release and excellent bioavailability.

References and Notes

1) This paper forms Part V of "Studies on Sustained-Release Dosage Forms." The preceding paper, Part IV: T. Kuroda, T. Yokoyama, T. Umeda, N. Ohnishi, K. Kuroda and S. Asada, *Kobe J. Med. Sci.*, **31**, 117 (1985). This work was presented at the 35th Meeting of the Kinki Branch, Pharmaceutical Society of Japan, Kyoto, November 1985.
2) T. Umeda, A. Matsuzawa, T. Yokoyama, K. Kuroda and T. Kuroda, *Chem. Pharm. Bull.*, **31**, 2793 (1983).
3) T. Kuroda, T. Yokoyama, T. Umeda, A. Matsuzawa, K. Kuroda and S. Asada, *Chem. Pharm. Bull.*, **31**, 3319 (1983).
4) T. Umeda, T. Yokoyama, N. Ohnishi, T. Kuroda, Y. Kita, K. Kuroda and S. Asada, *Chem. Pharm. Bull.*, **33**, 3953 (1985).
5) S. Kazmi, A. Ali and F. M. Plakogiannis, *Drug. Der. Ind. Pharm.*, **7**, 359 (1981).

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