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Study on Slow-Release of Indomethacin from Suppositories Containing Hydrogenated Soybean Lecithin[1)]

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Indomethacin (IM) slow-release suppositories were prepared using hydrogenated soybean lecithin (HL) as an additive. The suppositories were prepared by the fusion method with IM, HL and Witepsol H-15. The suppositories were evaluated by *in vitro* release testing, X-ray diffractometry, differential scanning calorimetry and penetrometry. IM existed in an amorphous state in the suppositories.

The melting point and hardness of the suppositories increased with increasing HL content. Slow release from suppositories in which the IM content was 10 mg was obtained when the HL content was over 300 mg. When the IM content was 20 mg, the HL content required to obtain the slow-release profile was more than 600 mg. The slow-release suppositories did not melt or disintegrate entirely in the test solution in the cylindrical cell of the releasing apparatus in the course of testing. It was considered that IM dissolved gradually from the surface of the suppositories, because HL at the levels giving slow release of IM made the suppositories hard.

Keywords——indomethacin; hydrogenated soybean lecithin; suppository; slow release suppository; *in vitro* release test; X-ray diffraction

In the previous paper,[2)] we reported the preparation of sustained-release suppositories containing surface-modified indomethacin (IM) microcapsules. The release profile of IM from the suppositories was shown to be zero-order. In a test using a rabbit, however, the plasma level of IM did not show a sustained profile because the IM absorption after administration was considerably affected by the suppository base. Thus, we investigated the preparation of a sustained-release suppository without using microcapsules.

There are several reports concerning sustained-release suppositories using additives. Ohnishi *et al.*[3)] used hydroxypropylmethylcellulose phthalate and hydroxypropylmethylcellulose acetate succinate to prepare IM sustained-release suppositories. Cellulose acetate phthalate[4)] was used to prepare nifedipine sustained-release suppositories. Enomoto *et al.*[5)] used cyclodextrin, ethylcellulose, and glyceride to prepare IM sustained-release suppositories. Kamada *et al.* used beeswax,[6)] glycerin monostearate,[7)] and Aerosil® and sodium bisulfate[8)] to prepare sulpyrine sustained-release suppositories. Lecithin was used to prepare flufenamic acid[9)] and sodium diclofenac[10)] sustained-release suppositories. There are, however, few reports[11)] concerning a sustained-release suppository using hydrogenated soybean lecithin (HL) as an additive.

In this study, we investigated the preparation of slow-release suppositories containing HL. The slow-release suppositories were evaluated by *in vitro* release testing, X-ray diffractometry, differential scanning calorimetry (DSC) and penetrometry.

Experimental

Materials——The sources of the materials used in this work were as follows: IM from Sumitomo Chemical Co.,

TABLE I. Formulae of Suppositories

Rp.	IM (mg)	HL (mg)	H-15 (mg)	Rp.	IM (mg)	HL (mg)	H-15 (mg)
1	10	0	Total 1000	5	20	0	Total 1000
2		200		6		350	
3		300		7		500	
4		350		8		600	
				9	30	350	

Ltd., HL (Lecinol S-10) from Nikko Chemicals Co., Ltd., Witepsol H-15 (H-15) from Dynamit Nobel Co., Ltd. The phosphatidylcholine content of HL was about 30% and its fatty acid components measured by gas chromatography were as follows: palmitic acid, stearic acid and oleic acid, 19.9, 72.3 and 7.8%, respectively. The iodine value of HL was 8. All other chemicals were reagent-grade commercial products.

Preparation of IM Suppositories——Suppositories were prepared as follows: H-15 (20—49.5 g) and HL (0—30 g) were fused in a beaker on an oil bath at 80 °C. Then, IM (0.5—1.5 g) was added and dissolved (with HL) or suspended (without HL) in the fused bases. The fused bases containing IM with and without HL were cooled to 70 °C and poured into suppository molds (1.0 ml in volume), which were quickly placed in a refrigerator at 5 °C. Table I shows the formulae of the suppositories. The samples were stored at 5 °C and were used for experiments within 1 week.

Release of IM from Suppositories——The release of IM was measured by the following two methods: 1) the Muranishi method[12] as described previously,[2] 2) the Thomas method[13]: A suppository was put in Visking tubing, 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 was agitated at 30 rev/min. In both release test, IM concentration was assayed spectrophotometrically at 318 nm.

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

The fused mixtures were prepared in the same manner as the suppositories, and the physical mixtures were prepared with an agate mortar by hand. The crystallinity of the IM in the bases was measured with a Rigaku Geigerflex 2027 (Rigaku Denki Co., Ltd.). The measurement conditions were as follows: source, Cu-K_α radiation; filter, Ni filter; voltage, 30 kV; current, 40 mA; time constant, 0.5 s; scanning speed, 4° (2θ)/min; chart speed, 20 mm/min.

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.

Measurement of Penetration Time——The penetration time of the suppositories was measured with the penetrometer[14] to evaluate the softening point.

Results and Discussion

Crystallinity of IM in Bases

The crystallinity of IM in the suppository bases and in the physical mixture of IM, HL 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 ($2\theta = 11.5°$) of IM crystals did not overlap the peaks due to H-15 and HL, the peak ($2\theta = 11.5°$) was regarded as the characteristic peak of IM crystals in bases. The physical mixture (H-15 : IM = 99 : 1), which had the same component ratio as the Rp.1 suppository did not show the peak ($2\theta = 11.5°$), although IM was in the crystal form in the mixture, because almost all IM was not dissolved in H-15. Thus, an increased content of IM in the mixture was used to see clearly the X-ray patterns. The physical mixture containing HL (H-15 : HL : IM = 5.5 : 3.5 : 1, Fig. 1e) showed the characteristic peak, but the fused mixture (Fig. 1f) scarcely showed the peak. These results indicate that IM was in the amorphous state in the fused mixture of H-15, HL and IM. Although the data are not shown, both physical mixtures (H-15 : HL : IM = 5.7 : 3.5 : 0.8 and 6.1 : 3.5 : 0.4) showed the characteristic peak, but neither of the fused mixtures did so. Thus, IM in the suppository containing HL (prepared as described in Experimental) was also considered to be amorphous.

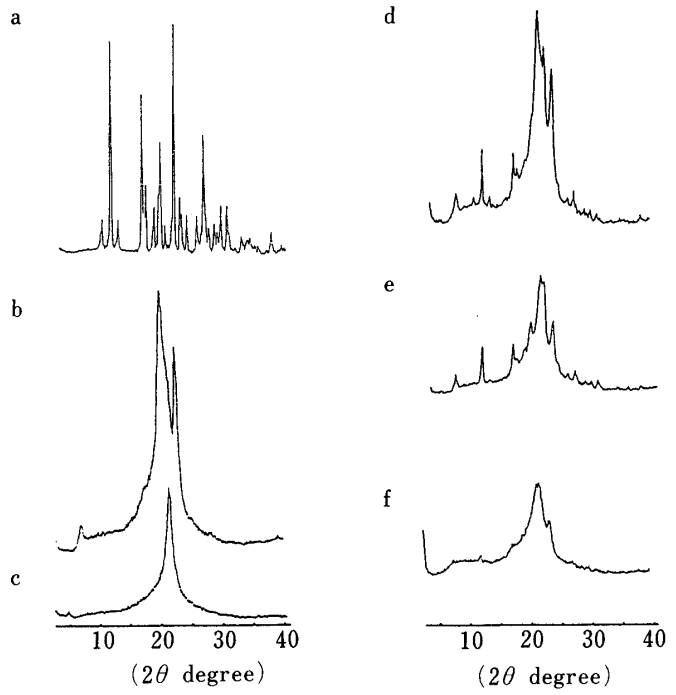

Fig. 1. X-Ray Diffraction Patterns

Alone: a, IM; b, H-15; c, HL. Physical mixture: d, H-15 : HL : IM = 5.5 : 3.5 : 1. Fused mixture: e, H-15 : IM = 9 : 1; f, H-15 : HL : IM = 5.5 : 3.5 : 1.

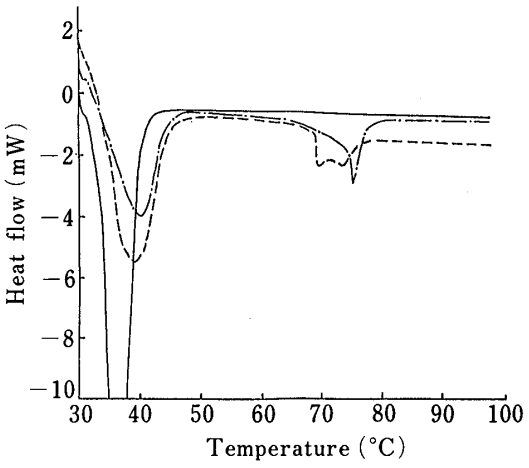

Fig. 2. Differential Scanning Calorimetry Thermograms

IM content: 10 mg. HL content: ——, 0 mg (Rp. 1); – – – –, 200 mg (Rp. 2); —·—, 350 mg (Rp. 4).

TABLE II. Penetration Time of Various Suppositories

Rp.	HL content (mg)	At 37 °C (s)	At 50 °C (s)
1	0	302 ± 6	82 ± 6
2	200	—[a]	79 ± 5
3	300	—[a]	134 ± 4
4	350	—[a]	648 ± 419

Each value represents the mean ± S.D. ($n = 3$). *a*) Suppository was not penetrated within 1 h. Penetration time means the time taken for a rod, weighing 7.0 g and 2 mm in diameter, to penetrate the suppository and reach the bottom of a glass tube with a rubber stopper in the penetrometer at 37 or 50 °C.

Penetration Time of Suppositories

Table II shows the results obtained with the penetrometer. Suppositories Rp.2, Rp.3 and Rp.4 were not penetrated at 37 °C within 1 h. At 50 °C, however, the suppositories were penetrated and the penetration time increased with increasing HL content. These results indicate that HL made the suppositories harder.

Thermotropic Properties of Suppositories

There was no significant difference among suppositories Rp.2, Rp.3 and Rp.4 concerning penetrating time at 37 °C. Thus, the thermotropic properties were examined by DSC. Figure 2 shows the DSC pattern of various suppositories with and without HL. The Rp.1 suppository without HL showed an endothermic peak at about 36 °C. Suppositories Rp.2 and Rp.4 showed an endothermic peak at about 38 and 39 °C, respectively, and small endothermic peaks were also seen at about 70—75 °C. The melting point of the suppositories increased with increasing HL content in the suppositories.

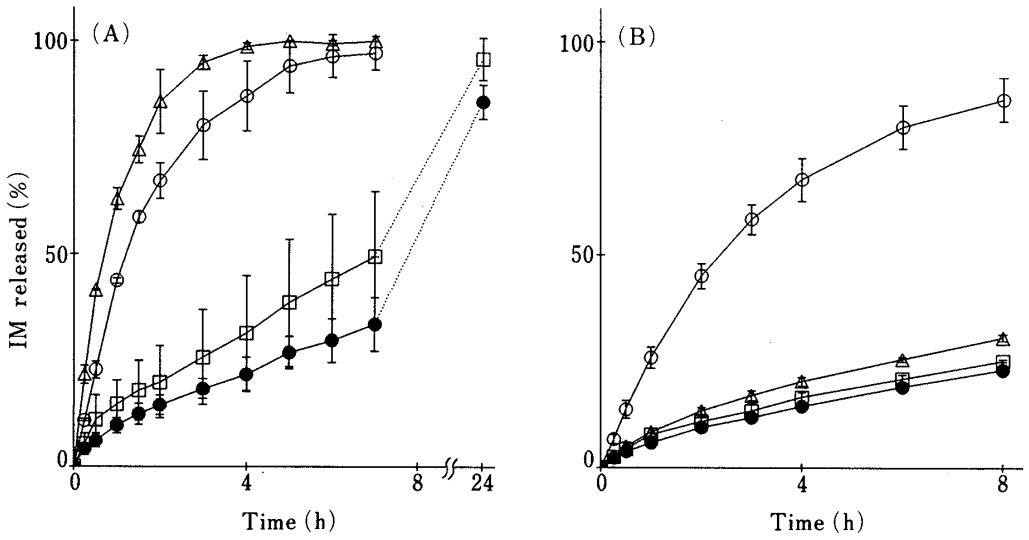

Fig. 3. Release Profiles of IM from Various Suppositories by the Muranishi Method (A) and the Thomas Method (B)

IM content: 10 mg. HL content: ○, 0 mg (Rp. 1); △, 200 mg (Rp. 2); □, 300 mg (Rp. 3); ●, 350 mg (Rp. 4).

Release of IM from Suppositories

Figure 3 shows the effect of HL content on the release of IM from suppositories containing 10 mg of IM. As determined by the Muranishi method, the release rate of IM from Rp.2 (HL 200 mg) was faster than that from Rp.1 (HL 0 mg) up to 4 h ($p<0.05$). Rp.3 (HL 300 mg) and Rp.4 (HL 350 mg) suppositories showed slow release. The release rate of IM from suppositories was controlled by the HL content, and slow release suppositories were obtained by adding more than 300 mg of HL. The Rp.1 suppository melted completely within 15 min in a cylindrical cell. The Rp.2 suppository also disintegrated and melted within 15 min, although it contained 200 mg of HL and was not penetrated within 1 h at 37 °C. On the other hand, the Rp.3 and Rp.4 suppositories did not disintegrate or melt entirely, and the shape of the suppositories was maintained (naked eye observation). It was considered that IM was released gradually from the surface of the Rp.3 and Rp.4 suppositories because a sufficient content of HL increased the melting point and hardness of the suppositories. On the other hand, 200 mg of HL (Rp.2) was insufficient to provide a slow-release suppository.

Tanabe *et al.*[15] examined the release of IM from vegetable oil using the Muranishi method. They thought that the main release process of IM particles from the vegetable oil was the migration of IM particles to the water phase from the interface between water and oil and then the dissolution of IM particles in water phase owing to mechanical stirring or sedimentation of IM particles. They also reported that the release of IM from olive oil was enhanced by adding a nonionic surfactant.

In this experiment, although the Rp.2 suppository had a higher endothermic point in DSC and a longer penetration time than those of the Rp.1 suppository, the release rate of the Rp.2 suppository was faster than that of the Rp.1 suppository. This is because the stirring stress and shear imposed by the rod of the release machine of the Muranishi method were greater than the weight of the rod of the penetrometer. Thus, the Rp.2 suppository disintegrated and melted early in the release testing. After disintegration and melting, the release of IM from the Rp.2 suppository seemed to be fast because HL seemed to act as a surfactant (its content was below the slow-release level).

Figure 3B shows the results of the release test when the Thomas method was used. In this case, the IM release rates from suppositories of Rp.2, Rp.3 and Rp.4 were slow and were

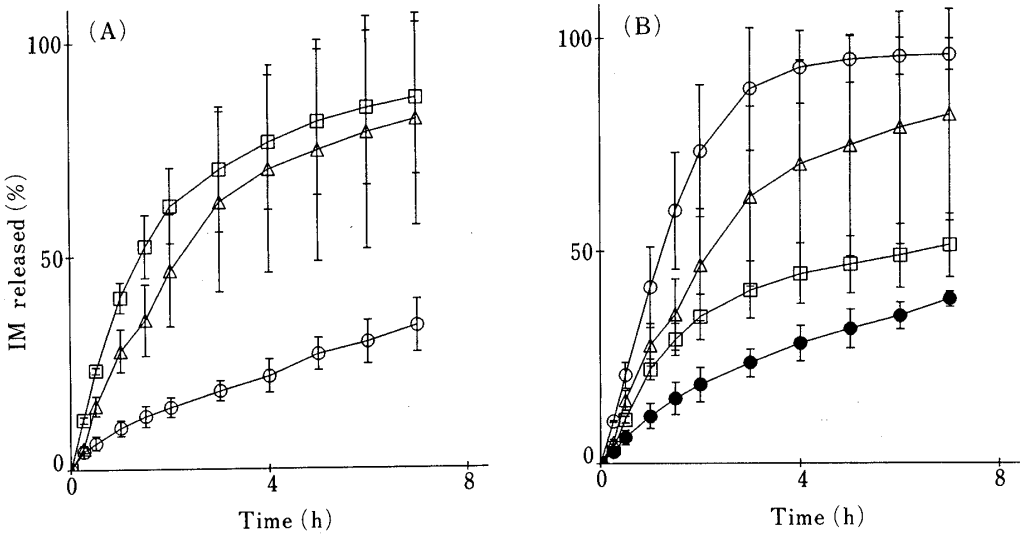

Fig. 4. Release Profiles of IM from Various Suppositories by the Muranishi Method

(A) IM content: ○, 10 mg (Rp. 4); △, 20 mg (Rp. 6); □, 30 mg (Rp. 9). HL content: 350 mg. (B) IM content: 20 mg. HL content: ○, 0 mg (Rp. 5); △, 350 mg (Rp. 6); □, 500 mg (Rp. 7); ●, 600 mg (Rp. 8).

almost the same. The shape of these suppositories, even Rp.2 which disintegrated and melted in the Muranishi method, was maintained during testing (naked eye observation). It was thought that the stirring stress or the force imposed on the suppository was greater in the Muranishi method than in the Thomas method. Thus, the Rp.2 suppository was not disintegrated and IM was released gradually from the surface of the suppository.

Figure 4A shows the effect of IM content on the release of IM from suppositories containing 350 mg of HL (Rp.4, 6 and 9). The IM release rates from suppositories Rp.6 (IM 20 mg) and Rp.9 (IM 30 mg) were fast, and a slow release profile like that of Rp.4 (IM 10 mg) was not obtained. These suppositories (Rp.6 and 9) disintegrated. When the stirring rate of the rod in the release test apparatus was reduced from 25 to 10 rpm, the release profile hardly changed (not shown), and the suppositories still disintegrated. These results suggest that increased IM content makes the suppositories fragile, and the IM release rate becomes faster.

Then, the effect of HL content on the release of IM from suppositories (IM 20 mg) was investigated. Figure 4B shows the results following the Muranishi method. The IM release rate from the suppositories decreased with increasing HL content. The IM release rate from the Rp.8 suppository (IM 20 mg, HL 600 mg) showed a slow-release profile which was almost the same as that of the Rp.3 suppository (IM 10 mg, HL 300 mg), as shown in Fig. 3A. This indicates that when the IM content increases, the HL content also needs to be increased to produce a slow-release suppository. In this case, twice the content of HL is needed since the IM content is doubled. Although the detailed mechanism is not clear, it was speculated that an interaction occurs between IM and HL in H-15 base.

In conclusion, when HL and IM were dissolved in H-15 (clear to the naked eye) and the fused mixture was cooled to solidify it, the mixture became harder and had a high melting point; this is supported by the results of DSC and the penetrometry test. As to the role of HL, IM crystals are converted to an amorphous state by HL in the suppositories, and HL contributes to the hardness or high melting point of the suppositories. Furthermore, HL seemed to act as a surface-active agent or a dispersing agent after the melting or disintegration of the suppositories when the HL content was rather low. Thus, slow-release suppositories able to release IM gradually from the surface of the suppositories were obtained when the HL

content was high enough in relation to IM.

References and Notes

1) A part of this work was presented at the 107th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April, 1987.
2) T. Nakajima, Y. Takashima, K. Iida, H. Mitsuta and M. Koishi, *Chem. Pharm. Bull.*, **35**, 1201 (1987); T. Nakajima, Y. Takashima, K. Iida, H. Mitsuta, A. Furuya and M. Koishi; *ibid.*, **35**, 4249 (1987).
3) N. Ohnishi, T. Yokoyama, T. Umeda, Y. Kiyohara, T. Kuroda, Y. Kita and K. Kuroda, *Chem. Pharm. Bull.*, **34**, 2999 (1986); N. Ohnishi, Y. Kiyohara, Y. Kita, K. Kuroda and T. Yokoyama, *ibid.*, **35**, 3935 (1987).
4) T. Umeda, T. Yokoyama, N. Ohnishi, T. Kuroda, Y. Kita, K. Kuroda and S. Asada, *Chem. Pharm. Bull.*, **33**, 3953 (1985); N. Ohnishi, T. Yokoyama, T. Umeda, Y. Kiyohara, T. Kuroda, Y. Kita and K. Kuroda, *ibid.*, **35**, 1294 (1987).
5) H. Enomoto, T. Ichiba and T. Sumi, Japan. Patent Kokai 83140012 (1983) [*Chem. Abstr.*, **99**, 181504 (1983)].
6) K. Tanabe, Y. Furuich, R. Inaba, Y. Takeda, S. Itoh, M. Sawanoi, M. Yamazaki and A. Kamada, *Yakuzaigaku*, **45**, 91 (1985).
7) K. Tanabe, R. Inaba, Y. Furuichi, S. Itoh, M. Yamazaki, A. Kamada and M. Sawanoi, *Yakuzaigaku*, **46**, 1 (1986).
8) K. Tanabe, Y. Furuichi, R. Inaba, S. Itoh, M. Sawanoi, M. Yamazaki and A. Kamada, *Yakuzaigaku*, **46**, 23 (1986).
9) S. Gülhan, J. Akbuga and G. B-Alpmen, *Sci. Pharm.*, **51**, 184 (1983).
10) T. Nishihata, H. Wada and A. Kamada, Int. J. Pharmaceut., **27**, 245 (1985).
11) T. Nishihata, M. Sudho, A. Kamada, M. Keigami, T. Fujimoto, S. Kamide and N. Tatsumi, *Int. J. Pharmaceut.*, **33**, 181 (1986); T. Nishihata, M. Keigami, A. Kamada, T. Fujimoto, S. Kamide and N. Tatsumi, *ibid.*, **42**, 251 (1988).
12) S. Muranishi, Y. Okubo and H. Sezaki, *Yakuzaigaku*, **39**, 1 (1979).
13) W. H. Thomas and R. McCormack, *J. Pharm. Pharmacol.*, **23**, 490 (1971).
14) S. Muranishi, "Suppository," Nanzando, Tokyo, 1985.
15) K. Tanabe, M. Sawanoi, M. Yamazaki and A. Kamada, *Yokuzaigaku*, **44**, 115 (1984).