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Indomethacin (IM) sustained-release suppositories were prepared by using a solid matrix of cellulose acetate phthalate (CAP) or hydroxypropylmethylcellulose acetate succinate (AS·MF) as a poorly soluble carrier and polyethylene glycol 2000 (PEG 2000) as a soluble carrier, and the utility of AS·MF as a poorly soluble carrier was compared with that of CAP. The release rate of IM from the AS·MF matrix suppositories, as well as that from the CAP matrix suppositories, decreased with increase of the content of AS·MF. The sustained release of IM from the AS·MF matrix suppositories was attributed to the formation of a network structure of AS·MF. Rectal administrations of the CAP or AS·MF matrix suppositories in rabbits resulted in good sustained-release characteristics. The bioavailability of the AS·MF matrix suppositories was higher than that of the CAP matrix suppositories.

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

In the previous papers,2,3) we reported that nifedipine suppositories prepared by using a solid matrix of cellulose acetate phthalate (CAP) as a poorly water-soluble carrier and polyethylene glycol 4000 (PEG 4000) as a water-soluble carrier showed a sustained-release characteristic and good bioavailability in rabbits and humans. Furthermore, we reported that indomethacin (IM) sustained-release suppositories prepared with a hydroxypropylmethylcellulose phthalate 200731 (HP55)–PEG 2000 solid matrix showed good bioavailability in rabbits.4)

In this study, we examined the utility of hydroxypropylmethylcellulose acetate succinate (AS·MF), a newly developed enteric coating agent, as a poorly soluble carrier in IM sustained-release suppositories.

Experimental

Materials—IM and AS·MF were gifts from Sumitomo Pharmaceutical Co., Ltd. and Shin-etsu Chemical Co., Ltd., respectively. CAP and PEG 2000 were supplied by Wako Pure Chemical Ind., Ltd. All other chemicals were reagent-grade commercial products.

Preparation of Suppositories—Conventional Suppositories (C-0): C-0 was prepared by the fusion method using IM and PEG 2000 as a base.

Matrix Suppositories: Matrix suppositories were prepared by using CAP–PEG 2000 and AS·MF–PEG 2000 matrices as a base according to the fusion method as previously reported.4) The matrix suppositories containing 5, 10 and 15% CAP were termed CAP-5, CAP-10 and CAP-15, and those containing 5, 10 and 15% AS·MF were termed AS·MF-5, AS·MF-10 and AS·MF-15, respectively.
The formulae of suppositories prepared in this study are listed in Table I. The content of IM in all suppositories and the suppository weight were 25 mg and 1 g, respectively. All suppositories were stored in a desiccator at room temperature, and were administered within 24 h after preparation.

X-Ray Diffractometry——The samples for determination of the crystallinity of IM in a matrix were prepared according to the same method as described in the previous paper.4) The formulae of matrices are listed in Table I. All matrices were stored in a desiccator at room temperature. The X-ray diffraction spectra were determined with an X-ray diffractometer (Miniflex, Rigaku Denki, Ltd.; Cu-Kα radiation, 30 kV, 10 mA).

Release Test of Suppositories in Vitro——The release test was performed at 37 °C with a suppository release test apparatus (Toyama Ind., Ltd.) according to the same method as reported previously.5) Five hundred milliliters of 0.1 M phosphate buffer solution (pH 7.2; µ = 0.5, NaCl) was used as the test solution.

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

Animal Experiments——White male rabbits weighing from 2.6 to 4.0 kg were fasted for 36 h prior to the experiments but were allowed free access to water. After rectal administration of a test suppository, blood samples were collected from the ear vein at regular intervals. The plasma samples were frozen and stored at −5 ºC until assay.

Assay of IM in Plasma——The concentrations of IM in the plasma were determined by high-performance liquid chromatography as reported in the previous paper.5)

Results and Discussion

Crystallinity of IM in Matrices

Figure 1 shows the X-ray diffraction spectra of IM powder, CAP-15 and AS·MF-15. There were no characteristic peaks of IM crystals (e.g., 11.5, 16.6 and 21.8 ° (2θ)) in the spectra of CAP-15 and AS·MF-15. Two major peaks at about 19 and 23 ° (2θ) in these spectra were identified as being attributable to PEG 2000. These results indicate that IM is present in an amorphous state in these matrices.

The effect of the content of CAP or AS·MF on the crystallinity of IM in matrices during storage is shown in Table II. C-0 showed characteristic peaks due to IM crystals after storage for 1 month. On the other hand, CAP-5, CAP-10 and CAP-15, as well as AS·MF-5, AS·MF-10 and AS·MF-15, did not show any peak attributable to IM crystals after storage for 2 months. These results suggest that CAP and AS·MF are able to inhibit the crystallization of IM in these matrices. Sugimoto et al.5) reported that the crystallization of a poorly water-soluble drug in a polymer might be related to the hygroscopicity of the polymer. Therefore, the hygroscopicity of PEG 2000 may have been decreased because of the addition of CAP or AS·MF to PEG 2000 in this study.

Release Patterns of IM from Suppositories in Vitro

Figure 2 shows the effect of the content of CAP or AS·MF on the release patterns of IM from suppositories. The release rate of IM from C-0 was very high and C-0 was dissolved within 20 min. However, the release rates of IM from the CAP or AS·MF matrix sup-
repositories were low, and decreased with increase of CAP or AS·MF content. The release rate of the AS·MF matrix suppositories tended to be higher than that of the CAP matrix suppositories at the same content of CAP and AS·MF. This may be due to the difference of dissolution rates of CAP and AS·MF in the test solution. These results indicate that the content and species of the poorly soluble carrier affect the release rate of IM from the matrix suppositories.

On the other hand, the release behavior of the matrix suppositories stored for 2 months was the same as that before storage (the data were not shown). From these results and the X-ray diffraction data (Table II), it was concluded that the matrix suppositories were physically stable for at least 2 months in a desiccator at room temperature.

**Table II. Crystallinity of IM in Matrices Stored in a Desiccator at Room Temperature**

<table>
<thead>
<tr>
<th>Matrix</th>
<th>Before storage</th>
<th>After 1 month</th>
<th>After 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-0</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CAP-5</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CAP-10</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CAP-15</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>AS·MF-5</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>AS·MF-10</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>AS·MF-15</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

+ X-ray diffraction peaks of IM crystals appeared; −, no X-ray diffraction peaks of IM crystals appeared.

![Fig. 1. X-Ray Diffraction Spectra of Matrices](image)

(a) IM powder, (b) CAP-15, (c) AS·MF-15, IM content 2.5%, CAP and AS·MF content 15%. Range: (a) 240000 cpm; (b, c) 120000 cpm.

![Fig. 2. Effect of the Content of CAP or AS·MF on the Release Behavior of IM from Suppositories in Vitro](image)

(a) ○, C-0; ●, CAP-5; △, CAP-10; ▲, CAP-15. (b) ○, C-0; ●, AS·MF-5; △, AS·MF-10; ▲, AS·MF-15. Each point represents the mean of three experiments.
Release Mechanism of IM from Matrix Suppositories

The sustained-release mechanism of a drug from the CAP matrix suppositories has already been elucidated in the previous paper. In this study, the release mechanism of IM from the AS·MF matrix suppositories was investigated by scanning electron microscopy. As shown in Fig. 3, many pores could be observed at the surface of AS·MF-15 at 15 min after the start of the release test. These results show that the sustained-release mechanism in this case is similar to that of the CAP or HP55 matrix suppositories.

Plasma Levels of IM after Rectal Administration and Bioavailability in Rabbits

The plasma levels of IM after rectal administration of suppositories in rabbits are shown...
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 declined rapidly. CAP-5 and CAP-10 gave peaks of 14.4 μg/ml at 60 min and 4.4 μg/ml at 90 min, respectively. The administration of CAP-15 resulted in a low plasma level from 15 min to 10 h (Fig. 4a). On the other hand, AS-EMF-5 showed a high peak of 13.9 μg/ml at 45 min and AS-EMF-10 gave a peak of 6.8 μg/ml at 60 min. The administration of AS-EMF-15 resulted in a low plasma level from 15 min to 10 h (Fig. 4b).

The area under the plasma concentration–time curve (AUC) and the extent of bioavailability (EBA) after rectal administration are listed in Table III. The EBA of the CAP or AS-EMF matrix suppositories decreased with increase of the content of CAP or AS-EMF, and also the EBA of the AS-EMF matrix suppositories was higher than that of the CAP matrix suppositories. For instance, the EBA of AS-EMF-15 with a good sustained-release characteristic was about 1.6 times that of CAP-15. These results suggest that AS-EMF-15 is superior to CAP-15. However, the EBA of AS-EMF-15 was only half that of C-0. It may be that the content of AS-EMF is so high that the PEG-entrapped IM at the inner portion of the suppository can not be released, and the superficial erosion proceeds more slowly as described in the previous paper. Therefore, it should be possible to enhance the bioavailability of AS-EMF-15 by incorporating IM in the outside layer of AS-EMF-15 or by miniaturizing AS-EMF-15, as reported in the previous papers.

Consequently, it appears that AS-EMF is useful as a poorly soluble carrier in IM sustained-release suppositories with a combination of a poorly soluble carrier and PEG.

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References