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Evaluation of Indomethacin Sustained-Release Suppositories Prepared with a Methacrylic Acid–Methacrylic Acid Methyl Ester Copolymer–Polyethylene Glycol 2000 Solid Matrix[1)]

NORIAKI OHNISHI,[a] TERUYOSHI YOKOYAMA,[b] YOSHIFUMI KIYOHARA,[a] KATSUHIKO OKUMURA,[a] and KOJI KURODA*,[a]

Hospital Pharmacy, Kobe University School of Medicine,[a] Kusunoki-cho, Chuo-ku, Kobe 650, Japan and Kyoto Pharmaceutical University,[b] 5, Nakauchi-cho, Misasagi, Yamasina-ku, Kyoto 607, Japan

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Indomethacin (IM) sustained-release suppositories were prepared by using a solid matrix of methacrylic acid–methacrylic acid methyl ester copolymer (Eudragit L100®: EL) as a poorly water-soluble carrier and polyethylene glycol 2000 (PEG 2000) as a readily water-soluble carrier. The rate of IM release from the EL–PEG 2000 matrix suppositories decreased with increase of the EL content. The sustained release of IM from these matrix suppositories was attributed to the development of a network structure of EL. Rectal administrations of the matrix suppositories in rabbits resulted in good characteristics for sustained release. The extent of bioavailability of the 20% EL–PEG 2000 matrix suppositories (EL-20) was about 50%.

Keywords——indomethacin; sustained-release suppository; solid dispersion; methacrylic acid–methacrylic acid methyl ester copolymer–polyethylene glycol 2000 matrix; X-ray diffraction; *in vitro* release rate; rectal administration; bioavailability

In the previous papers,[2,3)] we reported that indomethacin (IM) suppositories prepared by the fusion method of the solid dispersion technique[4)] showed sustained-release characteristics; these suppositories were prepared by using a solid matrix of cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose phthalate (HP55) or hydroxypropylmethylcellulose acetate succinate (AS·MF) as a poorly water-soluble carrier and polyethylene glycol 2000 (PEG 2000) as a easily water-soluble carrier.

Eudragit L100® (EL) is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water. It becomes soluble in a neutral to weakly alkaline milieu by forming salts with alkalis, thus affording enteric film coatings which are soluble in intestinal fluid.[5)] In a series of experiments reported herein, we investigated the usefulness of EL as a poorly soluble carrier in IM sustained-release suppositories with a solid dispersion system.

Experimental

Materials——IM was kindly supplied by Sumitomo Pharmaceutical Co., Ltd. EL and PEG 2000 were purchased from Röhm Pharma GmbH (W. Germany) and Wako Pure Chemical Ind., Ltd., respectively. All other chemicals were reagent-grade commercial products.

Preparation of Suppositories——1) Conventional Suppositories (C-0): C-0 was prepared by the fusion method with PEG 2000 as a base.

2) Matrix Suppositories (EL-10, EL-15 and EL-20): These suppositories were prepared by the fusion method with EL and PEG 2000 as a base. Physical mixtures of specified proportions of EL and PEG 2000 were heated at 80 °C in a thermostated oven with occasional stirrings until homogeneous fusions were formed. Then, IM was melted in the EL–PEG 2000 fusions, and the fusions were quickly poured into steel molds and allowed to solidify at a room temperature. EL-10, EL-15 and EL-20 contained 10, 15 and 20% EL in the base, respectively.

The IM content in all suppositories and the suppository weight were 25 mg and 1 g, respectively. All suppositories were stored in a desiccator at a room temperature, and were administered within 24 h after preparation.

X-Ray Diffractometry—— For determinations of the crystallinity of IM in the suppositories, parts of the fusions prepared as described above were poured into the aluminum holders, then solidified therein at room temperature. They were stored in a desiccator at a room temperature. An X-ray diffractometer (Rigaku Denki, Miniflex) was used under the conditions reported previously.[2)]

Release Test of Suppositories——The release tests were carried out with a suppository release test apparatus (Toyama Ind., Ltd.) at 37 °C according to the method reported previously.[2)] The test solution used was 500 ml of 0.1 M phosphate buffer solution (pH 7.2, $\mu=0.5$, NaCl).

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

Animal Experiment——White male rabbits weighing from 2.9 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 suppository, blood samples were collected from the ear vein at regular intervals. The plasma samples were frozen and stored at −20 °C until assay.

Determination of IM in Plasma——Plasma concentrations of IM were determined by high-performance liquid chromatography as reported previously.[2)]

Results and Discussion

Crystallinity of IM in Suppositories

The crystallinity of IM in the suppositories was investigated by X-ray diffractometry. Figure 1 shows the X-ray diffraction spectra of IM powder, EL–PEG 2000 matrix material, IM–EL–PEG 2000 physical mixture and IM–EL–PEG 2000 solid dispersion. The physical mixture showed the characteristic peaks of IM crystals, but the solid dispersion did not. Two peaks at about 19 and 23° (2θ) in these spectra were identified as being attributable to PEG 2000. These results suggest that IM is present in an amorphous form in the EL–PEG 2000 matrix material.

In order to measure the stability of the suppositories, the effect of EL content on the crystallinity of IM in the suppositories during storage was studied. C-0 before storage did not show any peaks due to IM crystals, but C-0 stored for 1 month were found to give them. On the other hand, EL-10, EL-15 and EL-20 before and after storage for 2 months did not show any peaks attributable to IM crystals. From these results, it was concluded that the 10—20% EL–PEG 2000 matrix suppositories were physicochemically stable for at least 2 months in the desiccator at a room temperature.

Release of IM from Suppositories *in Vitro*

The effect of EL content on the release patterns of IM from the suppositories is plotted in

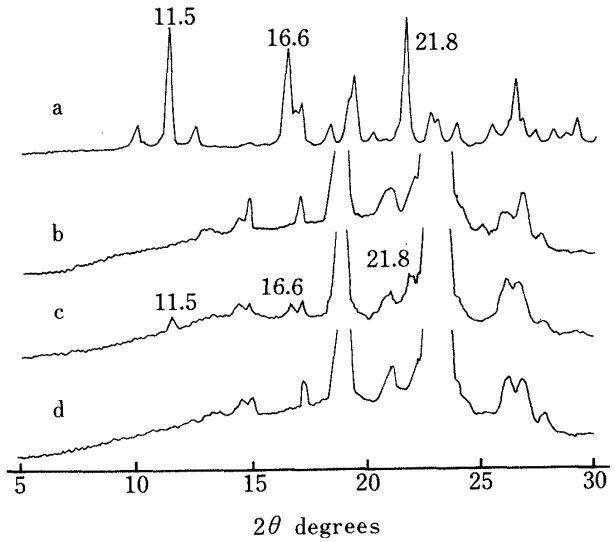

Fig. 1. X-Ray Diffraction Spectra of Various Samples

a, IM powder; b, EL–PEG 2000 matrix material; c, IM–EL–PEG 2000 physical mixture; d, IM–EL–PEG 2000 solid dispersion, IM content 2.5%, EL content 20%. Range: a, 240000 cpm; b—d, 120000 cpm.

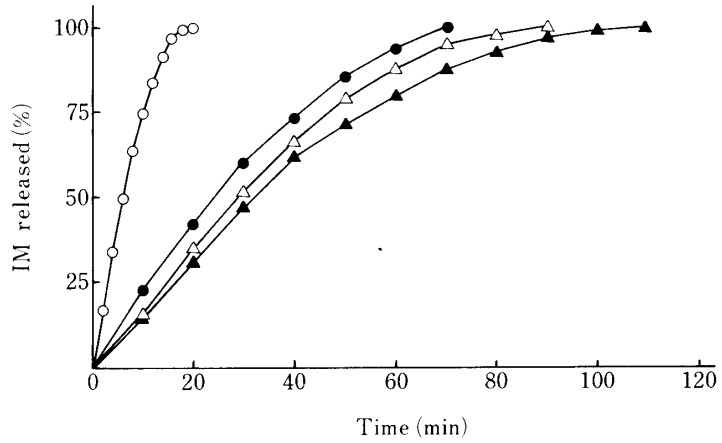

Fig. 2. Effect of EL Content on the Release Pattern of IM from Suppositories *in Vitro*

○, C-0; ●, EL-10; △, EL-15; ▲, EL-20. Each point represents the mean of three experiments. The coefficient of variation of each value was less than 5.7%.

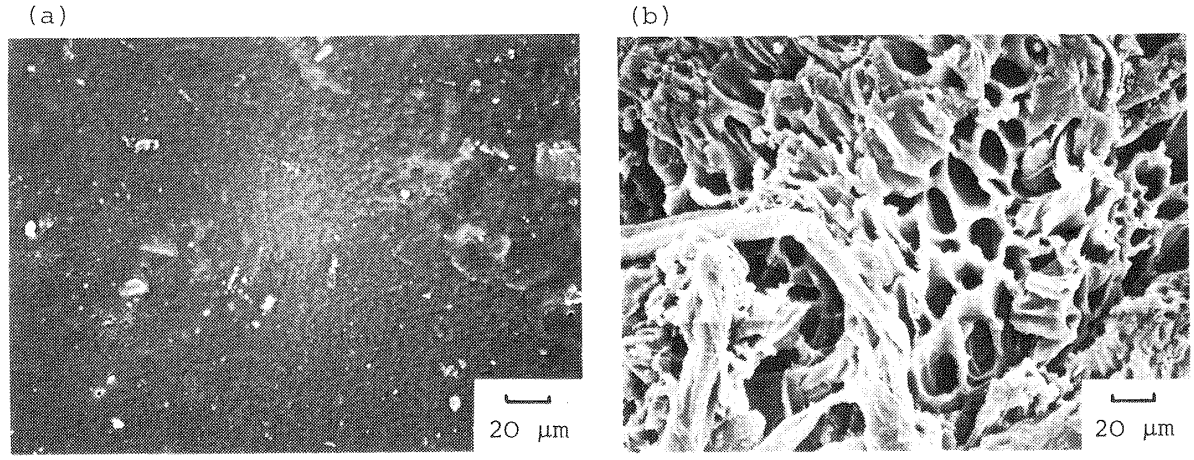

Fig. 3. Scanning Electron Micrographs of the Surface of EL-15

(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.

Fig. 2. The rate of IM release from C-0 was very high and C-0 gave complete drug release within 20 min. On the other hand, the rate of IM release from the matrix suppositories was low, and decreased with increase of the EL content. The matrix suppositories were dissolved out within 70—110 min. These results indicate that the rate of IM release from the matrix suppositories is affected by the EL content.

Mechanism of Sustained Release of IM from Matrix Suppositories

In order to establish the mechanism of sustained release of IM from the matrix suppositories, an investigation by scanning electron microscopy was carried out. As shown in Fig. 3b, a network structure of EL could be seen at the surface of EL-15 at 15 min after the start of the release test. This seems to be attributable to the difference of dissolution rate between EL and PEG 2000. The results illustrated by the photos (Fig. 3) suggest that the mechanism of sustained release of IM from the EL–PEG 2000 matrix suppositories is very similar to that from the suppositories containing CAP–PEG 2000, HP55–PEG 2000 or AS·MF–PEG 2000 matrix base discussed in our previous paper[2,3]; EL controlled the release of the PEG-entrapped IM by developing a network structure.

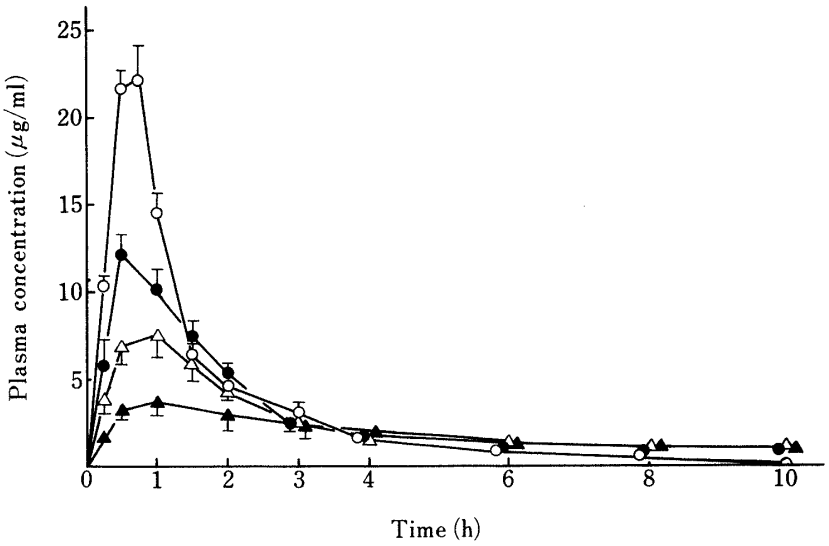

Fig. 4. Plasma Levels of IM after Rectal Administration of Suppositories in Rabbits

○, C-0; ●, EL-10; △, EL-15; ▲, EL-20. Each point represents the mean±S.E. of 4 rabbits.

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

	$n^{b)}$	Body weight (kg)	C_{max} (μg/ml)	$AUC_0^{10\,c)}$ (μg·h/ml)	EBA (%)
C-0	4	3.5±0.1	22.2±2.0	32.1±2.1	100.0
EL-10	4	3.3±0.2	12.1±1.2	28.5±2.4	88.8
EL-15	4	3.3±0.1	7.5±1.1	23.5±2.6	73.2
EL-20	4	3.6±0.2	3.6±0.8	16.1±3.6	50.1

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

Plasma Levels of IM after Rectal Administration and Bioavailability in Rabbits

The plasma levels of IM after rectal administration of suppositories in rabbits are plotted in Fig. 4. The rectal absorption of IM from C-0 preparation was fast, and C-0 showed a high peak (22.2 μg/ml) at 45 min. EL-10 and EL-15 gave peaks of 12.1 μg/ml at 30 min and 7.5 μg/ml at 60 min, respectively. The administration of EL-20 resulted in a low plasma level in the range of 0.7—3.6 μg/ml from 15 min to 10 h. The results indicate that the sustained-release characteristics of the matrix suppositories become appreciable with increase of the EL content.

The area under the plasma concentration–time curve (AUC) and the extent of bioavailability (EBA) within 10 h after rectal administration are listed in Table I; the EBA of the matrix suppositories decreased with increase of the EL content, and the EBA of EL-20 (which showed a marked sustained-release pattern) was about 50%. This may be due to the fact that the EL content is so high that the PEG–entrapped IM in the inner portion of the suppository can not be completely released within 10 h. It was observed that the small part of EL-20 remained in the rectum of a rabbit at 10 h after administration. Therefore, the IM release from EL-20 may continue for several hours after 10 h, so that IM may be detectable in plasma after 10 h, resulting in a greater value of EBA than that of EBA within 10 h.

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References and Notes

1) This paper forms Part X of "Studies on Sustained-Release Dosage Forms."
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