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RESEARCH PAPER

# Physical Properties of Solid Dispersion of a Nonsteroidal Anti-inflammatory Drug (M-5011) with Eudragit E

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**ABSTRACT**

*Some acidic nonsteroidal anti-inflammatory drugs (NSAIDs) are poorly soluble in the stomach. In this study, M-5011, d-2-[4-(3-methyl-2-thienyl) phenyl] propionic acid, was used as a model substance. To increase the dissolution rate of M-5011, a solid dispersion of M-5011 was prepared by the powder mixing method using Eudragit E-100 (aminoacryl methacrylate copolymer) as a carrier. Evaluation by X-ray diffraction and differential scanning calorimetry (DSC) revealed that M-5011 easily formed a solid dispersion with E-100. The dissolution behavior of a physical mixture prepared immediately after mixing and the mixture stored for 14 days at 40°C were examined. It was observed that the former, containing a great deal of E-100, showed a fairly good dissolution behavior, and the latter had a better dissolution rate. The mechanism of the interaction of M-5011 and E-100 was investigated by infrared (IR) spectroscopy and nuclear magnetic resonance (NMR). The interaction was simulated by NMR using a monomer of Eudragit E-100.*

***Key Words:*** *Aminoacryl methacrylate copolymer; Hydrogen bond; Interaction; d-2-[4-(3-Methyl-2-thienyl)phenyl] propionic acid; Powder mixing method; Solid dispersion.*

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## INTRODUCTION

To increase the dissolution rate of poorly water soluble drugs, various methods have been examined. The most common method is particle size reduction by comminution (1). However, a decrease in the particle size sometimes causes agglomeration of particles and results in poor powder wettability, reducing the effective surface area. The most promising method for promoting dissolution at present is the formation of a solid dispersion (2,3) using an excellent carrier. Ford (4) classified the process of producing a solid dispersion into melting (fusion) and solvent methods, as well as the melting-solvent method. Macrogols (polyethylene glycol [PEG]) (5) and polyvinylpyrrolidone (PVP) (6–8) with intrinsic rapid dissolution properties have been used frequently as carriers. Other macromolecules (9–11) or phospholipids (12,13) also were often used. The organic solvent method, which is considered to be the most possible method to obtain solid dispersions, suffers some serious disadvantages, such as pollution, explosion, and residual solvent.

It has been reported by Nakai et al. (14) that some of the crystalline materials decrease in crystallinity by ball mill grinding with microcrystalline cellulose. The ground mixture of phenytoin and microcrystalline cellulose significantly improved the dissolution rate and bioavailability of phenytoin (15). Recently, Danjo et al. (16) found that ibuprofen became amorphous when it was merely mixed with PVP using a test tube mixer and allowed to stand at an appropriate temperature. The purpose of the present study was to find a useful method to improve the dissolution rate of M-5011 by the preparation of a solid dispersion without using any organic solvent. A cationic polymer, Eudragit E-100, was selected as a carrier, and the powder mixing method was examined.

## EXPERIMENTAL

### Materials

The sample powder used was M-5011, d-2-[4-(3-methyl-2-thienyl)phenyl] propionic acid ($C_{14}H_{14}O_2S$) (Maruho, Japan), which was developed as a nonsteroidal, anti-inflammatory, antipyretic analgesic. The average particle diameter (Heywood diameter) determined by an image analyzer (Luzex 500, Nireco, Tokyo, Japan) was 11.1 μm. The carrier used was Eudragit E-100 (Röhrm Pharma, Darmstadt, Germany); it is an aminoacryl methacrylate copolymer with a molecular weight of $1.5 \times 10^5$ (manufacturer's data) and a Heywood diameter of 109 μm (Luzex 500). The monomer sample used was 2-(dimethylamino)ethyl methacrylate (DAEM, Wako Chemical, Osaka, Japan), with a molecular weight of 157 (Fig. 1). The $^1$H-NMR (nuclear magnetic resonance) spectral data of M-5011 and DAEM are shown in Table 1.

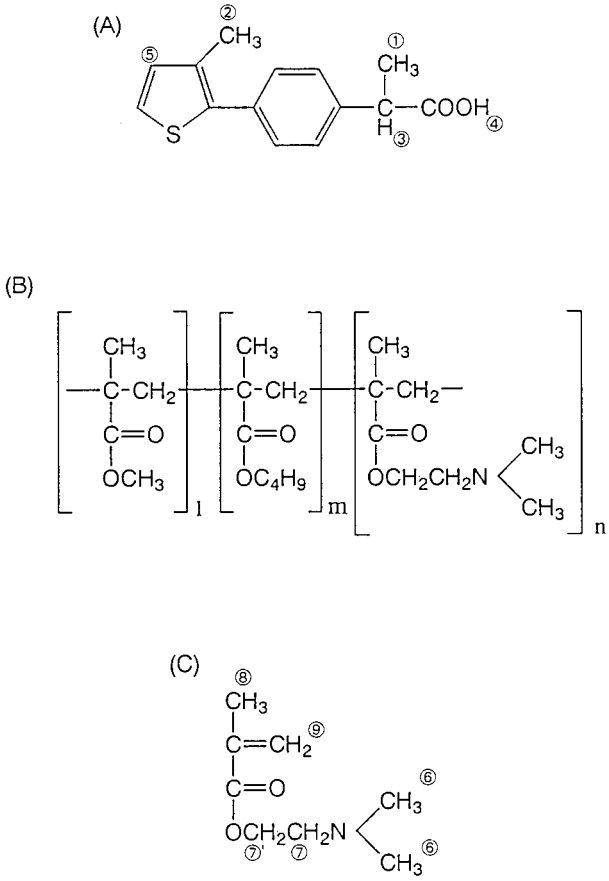


**Figure 1.** Chemical structure of materials: (A) M-5011; (B) Eudragit E-100; (C) DAEM.

### Methods

#### Preparation of Solid Dispersions

M-5011 and Eudragit E-100 were weighted in various weight proportions (1/3, 1/1, 3/1) and mixed with a tube mixer (Automatic Mixer, Yamato, Tokyo, Japan) for 10 min at a constant rate of 500 rpm. After mixing, the physical mixtures were stored at the following conditions: 25°C (33%, 53%, 75%, 93% relative humidity [RH]), 40°C (7% RH), and 50°C (7% RH).

#### X-Ray Diffraction Analysis (Powder Method)

X-ray diffraction analysis was performed with a Rigaku Geiger-Flex diffractometer (RAD-IIVC, Rigaku-denki, Tokyo, Japan) using nickel-filtered $CuK_\alpha$ radiation

***Table 1***

*$^1$H-NMR Spectral Data for (A) and (C)*

| Proton No. | (A)[a] | (C)[a] |
|---|---|---|
| 1 | 1.39 (3H, d, J = 7.3) | |
| 2 | 2.28 (3H, s) | |
| 3 | 3.72 (1H, q, J = 7.3) | |
| 4 | 12.38 (1H, br.s) | |
| 5 | 6.98–7.46 (6H) | |
| 6 | | 2.18 (6H, s) |
| 7 | | 2.52 (2H, t, J = 5.5) |
| 7′ | | 4.18 (2H, t, J = 5.5) |
| 8 | | 1.88 (3H, s) |
| 9 | | 5.68 (1H), 6.02 (1H) |

[a] δ value, J = Hz.

(a voltage of 40 kV and a current of 20 mA). The scanning rate was 2°/min over a 2θ range of 2°–60° and with an interval of 0.02°.

## Thermal Analysis

Differential scanning calorimetry (DSC) was carried out with a heating rate of 10°C/min using a type of DSC-50 instrument (Shimadzu, Kyoto, Japan).

## Dissolution Studies

Dissolution tests were carried out at 37°C by the JP 12 paddle method. Each sample powder containing 50 mg of M-5011 was put into a hard capsule (No. 2), which was immersed in 900 ml of the first fluid (pH 1.2) of the JP 12 disintegration test. The stirring rate of the paddle was 100 rpm. At given intervals, 5 ml of the fluid were withdrawn through a 0.45-μm membrane filter (Ekikuro-disk, Gerumann, Tokyo, Japan) and replaced by an equal

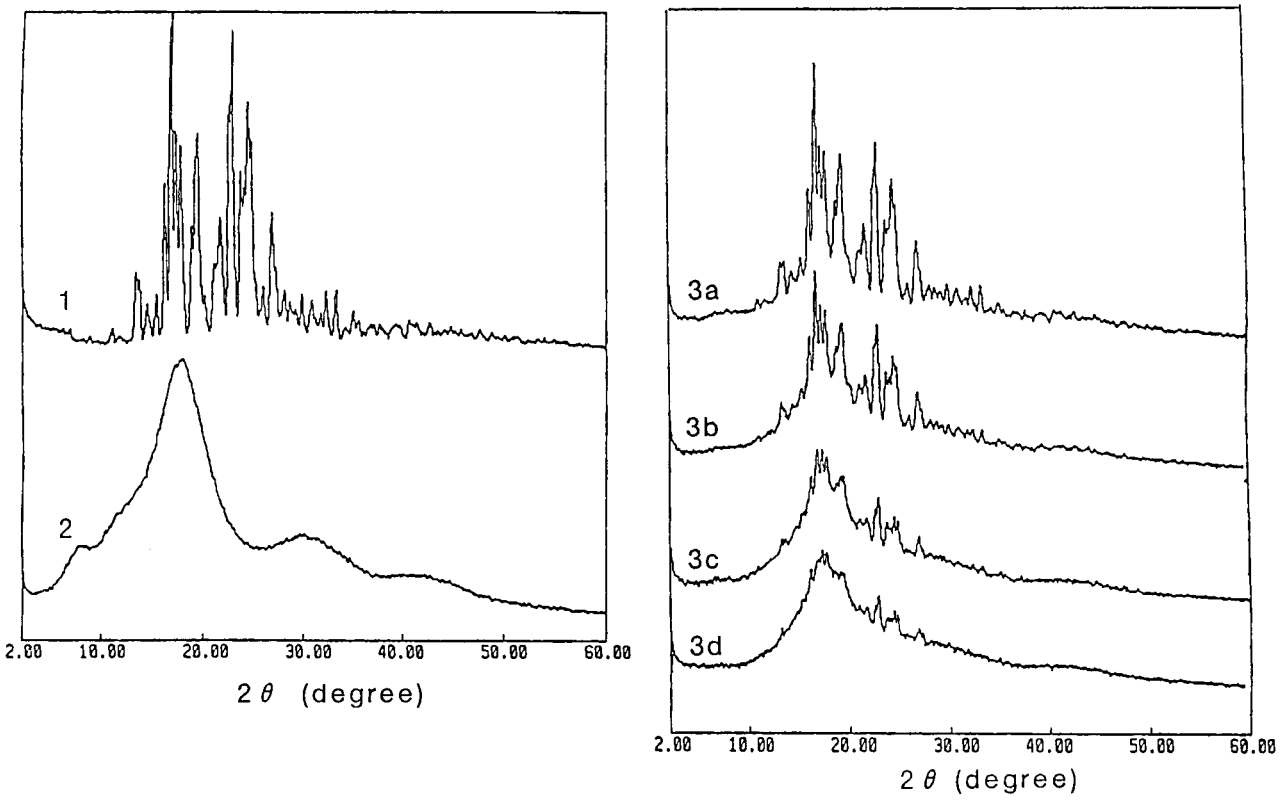


**Figure 2.** Powder X-ray diffraction patterns of M-5011, Eudragit E-100, and M-5011/Eudragit E-100 systems (storage condition 40°C, 7% RH): 1, M-5011; 2, Eudragit E-100; 3a, M-5011/E-100 (1/1) immediately after mixing; 3b, M-5011/E-100 (1/1) after 1 day; 3c, M-5011/E-100 (1/1) after 6 days; 3d, M-5011/E-100 (1/1) after 14 days.

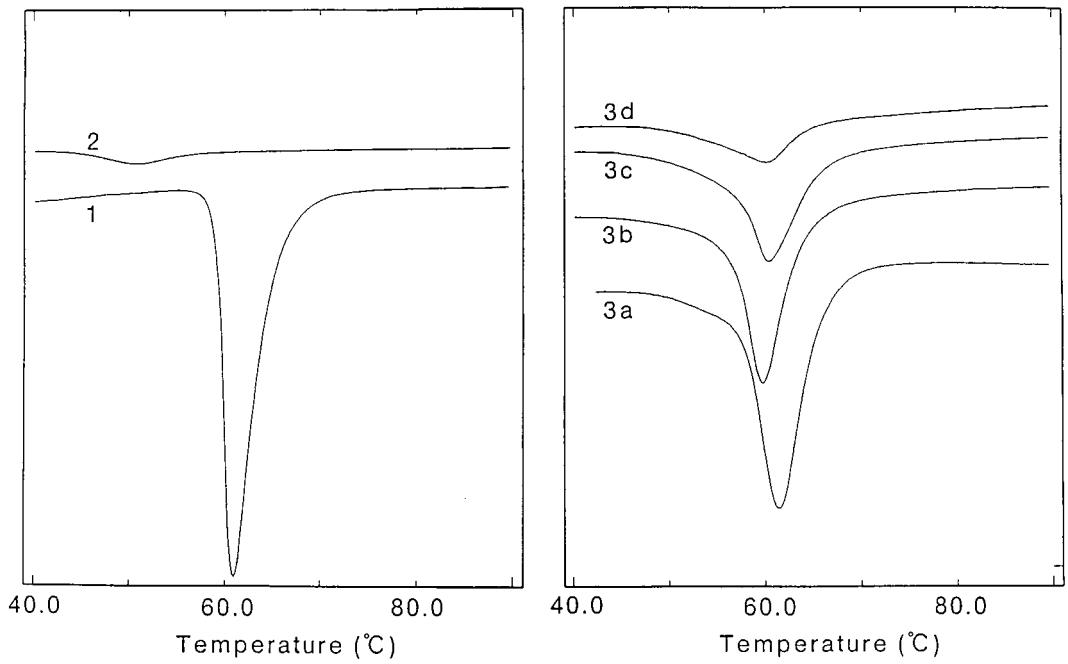


**Figure 3.** DSC curves of M-5011, Eudragit E-100, and M-5011/Eudragit E-100 systems (storage condition 40°C, 7% RH): 1, M-5011; 2, Eudragit E-100; 3a, M-5011/E-100 (1/1) immediately after mixing; 3b, M-5011/E-100 (1/1) after 1 day; 3c, M-5011/E-100 (1/1) after 6 days; 3d, M-5011/E-100 (1/1) after 14 days.

volume of fresh test fluid. The M-5011 content was assayed using ultraviolet (UV) spectroscopy at 253 nm (UV-2200A, Shimadzu).

### Infrared Spectra

Infrared (IR) spectra were obtained with an IR spectrophotometer (IR-270, Hitachi, Tokyo, Japan) by the KBr semimicrodisk technique.

### Nuclear Magnetic Resonance Spectra

NMR spectra were recorded on an NMR spectrometer (GSX-270, JEOL, Tokyo, Japan). Proton NMR spectra were recorded with a JEOL GSX-270 spectrometer using tetramethyl silane as an internal standard. Splitting patterns were as follows: s, singlet; d, doublet; t, triplet; q, quartet; br. s, broad singlet.

## RESULTS AND DISCUSSION

### Physicochemical Properties of Solid Dispersions

### Changes in X-Ray Diffraction Patterns

Figure 2 shows the X-ray spectra of M-5011, Eudragit E-100, and the mixture of M-5011 and E-100 (1/1). The crystallinity of M-5011 in the mixture decreased with standing time. These findings suggested that the physical mixture of M-5011 and E-100 easily formed a solid dispersion at 40°C (7% RH).

### Changes in Thermograms

Figure 3 shows DSC spectra of M-5011, E-100, and the mixture of M-5011 and E-100 (1/1). When the mixed sample was stored at 40°C (7% RH), the peak intensity around the melting point of M-5011 was reduced. Figure 4 shows the effect of the mixing ratio of M-5011 to E-100 on the heat of fusion. With an increase in the mixing ratio of E-100, the heat of fusion of M-5011 rapidly decreased, indicating the promotion of formation of a solid dispersion. Figures 5a and 5b show the effect of storage conditions (temperature and relative humidity) on the heat of fusion of the sample. The abscissa shows a mixing ratio of E-100. The formation of a solid dispersion was enhanced with increasing temperature and relative humidity.

### Dissolution Studies

The dissolution curves of the sample obtained immediately after mixing in the first fluid (pH 1.2) in JP 12 are shown in Fig. 6a. With the physical mixture containing a large amount of E-100, a fairly rapid release of M-5011

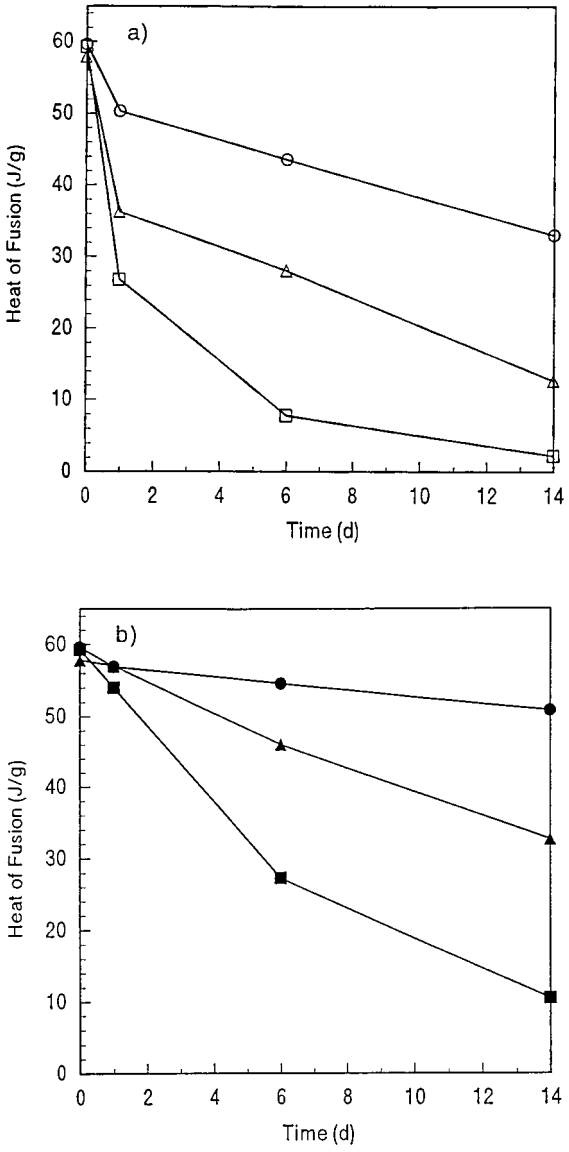


**Figure 4.** Change in heat of fusion of M-5011 in various mixing ratios (M-5011/Eudragit E-100): (a) storage condition 40°C, 7% RH with ○ M-5011/E-100 (3/1), △ M-5011/E-100 (1/1), □ M-5011/E-100 (1/3); (b) storage condition 25°C, 75% RH with ● M-5011/E-100 (3/1), ▲ M-5011/E-100 (1/1), ■ M-5011/E-100 (1/3).

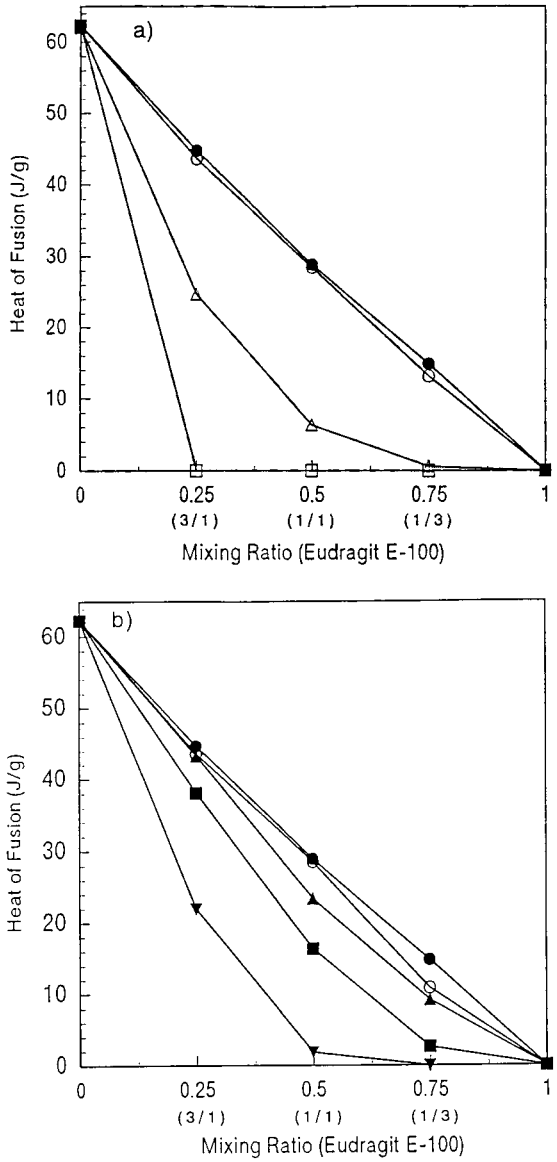


**Figure 5.** Effect of storage conditions on heat of fusion of M-5011 in physical mixture and solid dispersions with Eudragit E-100: (a) ● immediately after mixing, ○ stored for 14 days at 25°C (33% RH), △ 40°C (7% RH), □ 50°C (7% RH); (b) ● immediately after mixing, ○ stored for 14 days at 25°C (33% RH), ▲ 25°C (53% RH), ■ 25°C (75% RH), ▼ 25°C (93% RH).

was observed, suggesting that the proton transfer from M-5011 to E-100 easily occurred in the dissolution fluid. Figure 6b shows dissolution curves of the samples stored at 40°C (7% RH). In this case, the presence of E-100 was more effective for the dissolution of M-5011. It was supposed that the proton transfer had already occurred even in the solid state.

## Mechanism of the Formation of Solid Dispersion

### Infrared Spectra

To clarify the mechanism of the formation of solid dispersion, IR spectra were compared among M-5011, E-100, the initial physical mixture of M-5011 and E-100 (1/3), and the mixture stored at 40°C (7% RH) for 14

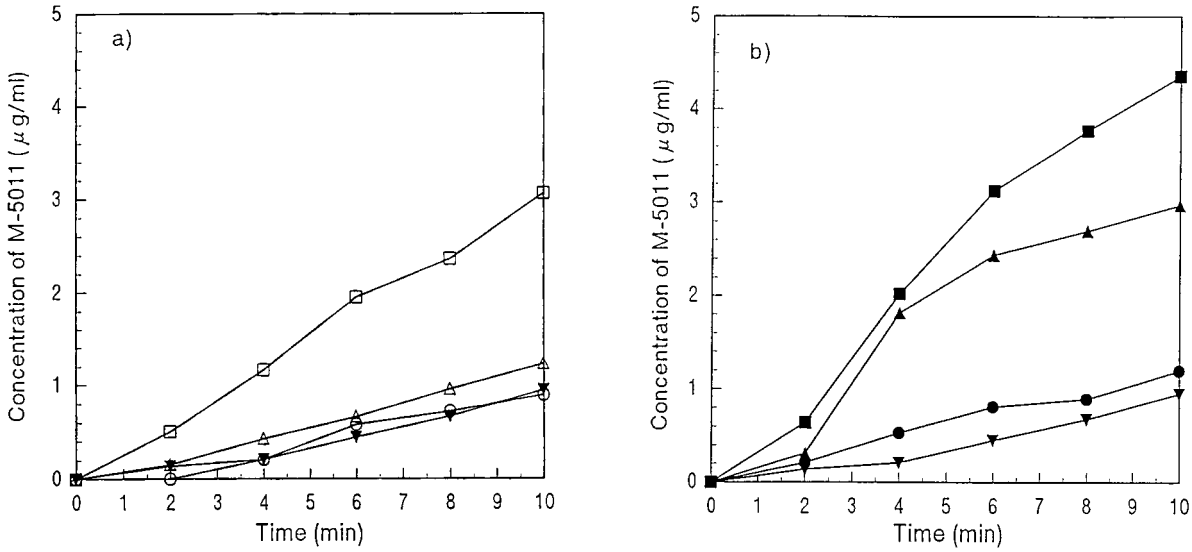


**Figure 6.** Dissolution profiles of M-5011 from physical mixtures and solid dispersions with Eudragit E-100: (a) immediately after mixing, with ▼ M-5011, ○ M-5011/E-100 (3/1), △ M-5011/E-100 (1/1), □ M-5011/E-100 (1/3); (b) stored at 40°C (7% RH) for 14 days, with ▼ M-5011, ● M-5011/E-100 (3/1), △ M-5011/E-100 (1/1), ■ M-5011/E-100 (1/3).

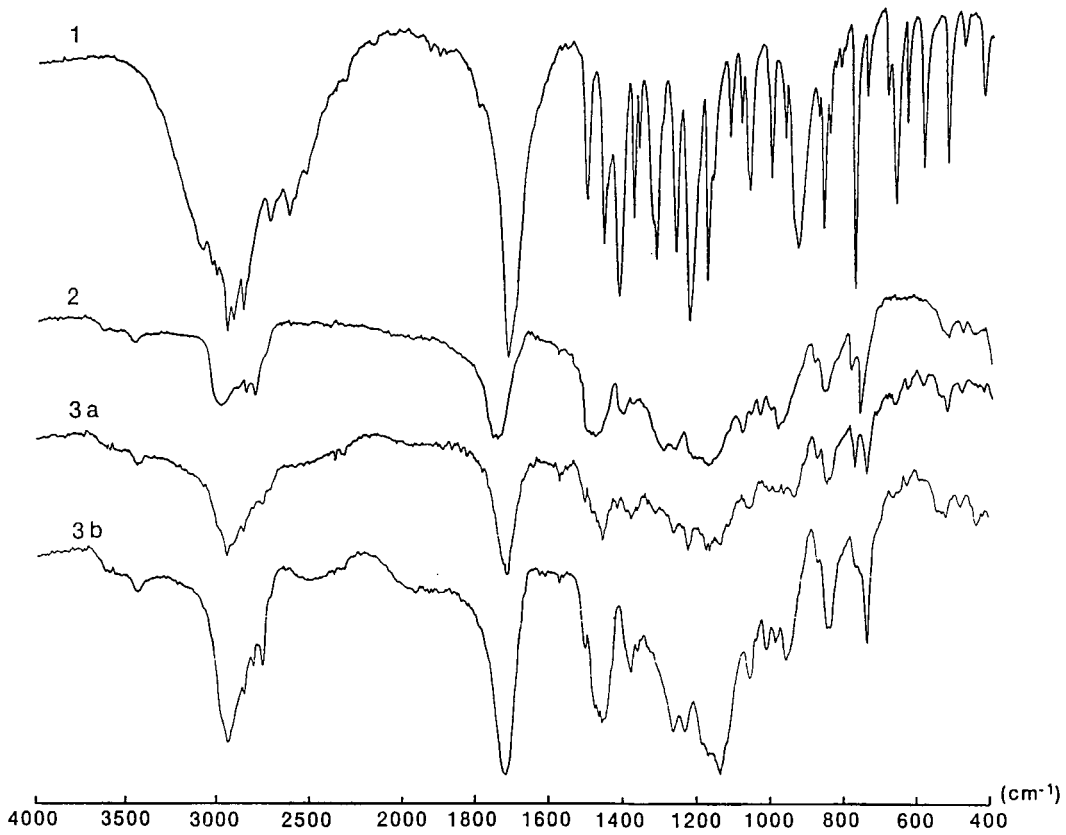


**Figure 7.** IR spectra of M-5011, Eudragit E-100, and M-5011/E-100 systems (40°C, 7% RH): 1, M-5011; 2, Eudragit E-100; 3a, M-5011/E-100 (1/3) immediately after mixing; 3b, M-5011/E-100 (1/3) after 14 days.

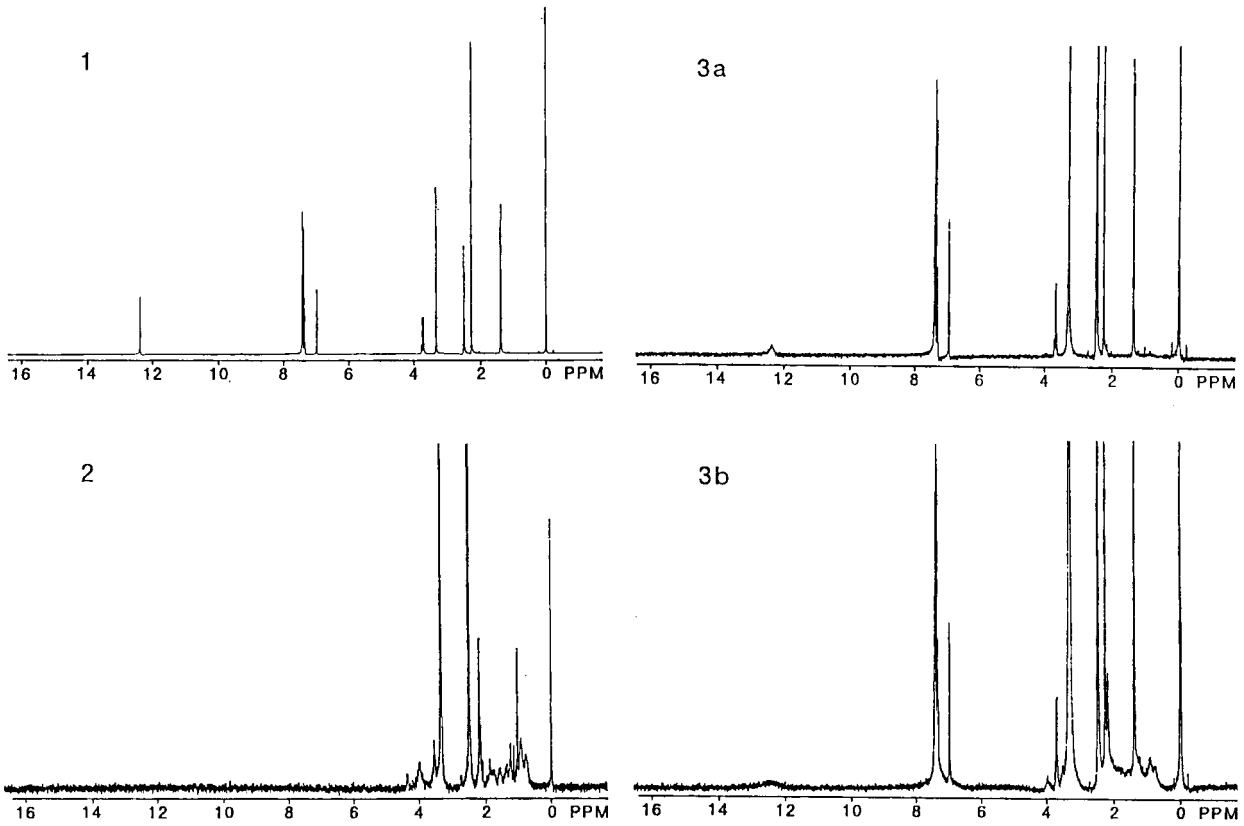


**Figure 8.** NMR spectra of M-5011, Eudragit E-100, and M-5011/E-100 systems (40°C, 7% RH): 1, M-5011; 2, Eudragit E-100; 3a, M-5011/E-100 (1/3) immediately after mixing; 3b, M-5011/E-100 (1/3) after 14 days.

days (Fig. 7). The absorption of the carboxyl group (–COOH) of M-5011 at 3500–2200 and 1250 $cm^{-1}$ was observed to be smaller than that of the samples after storage. (In general, a compound with a carboxyl group was formed the stable dimer by the hydrogen bond each other in the solid state.) As shown in Fig. 7, the absorption of the hydrogen bonding carboxyl group in M-5011 and the initial physical mixture (1/3) was observed at 1700 $cm^{-1}$, whereas the absorption of that in the stored mixture shifted slightly, to 1735 $cm^{-1}$. These findings suggested that the hydrogen bond of each M-5011 was transformed to the more stable complex between the tertiary amine in the polymer and the carboxyl group in M-5011.

### Nuclear Magnetic Resonance Spectra

Comparison of the carboxyl group in the initial physical mixture of M-5011 and E-100 (1/3) and the mixture after storage were examined by NMR spectra to determine the interaction of the carboxyl group in M-5011 against the tertiary amine in the polymer. The signal of a hydrogen bond between each M-5011 in the initial mixture was observed at δ12.38, whereas the broad signal was shown at the same position in the NMR spectrum of the mixture after storage (Fig. 8). El-Hinnawi and Najib (17) and Sekizaki et al. (16) reported that the carboxyl group of ibuprofen interacts with PVP through a hydrogen bond. From the above data, the interaction between the carboxyl group in M-5011 and the tertiary amine of the polymer resulted from the storage of the mixture. The interaction with M-5011 and DAEM as a model compound instead of the polymer was then examined by NMR spectra. As shown in Fig. 9, the signal (δ12.38) of the hydrogen bond of the carboxyl group of M-5011 was shifted to the higher field at δ11.75, 9.70, and 9.05 according to the mixture ratio of 20/1, 3/1, and 1/1 of M-5011/DAEM, respectively. Furthermore, the methylene signal at δ2.52 was shifted to the low field at δ2.53, 2.57, 2.61, and 2.86 by the increasing mixing ratio of M-5011. These findings indicated that the acidic protons of the carboxyl group in M-5011 were trapped with the tertiary

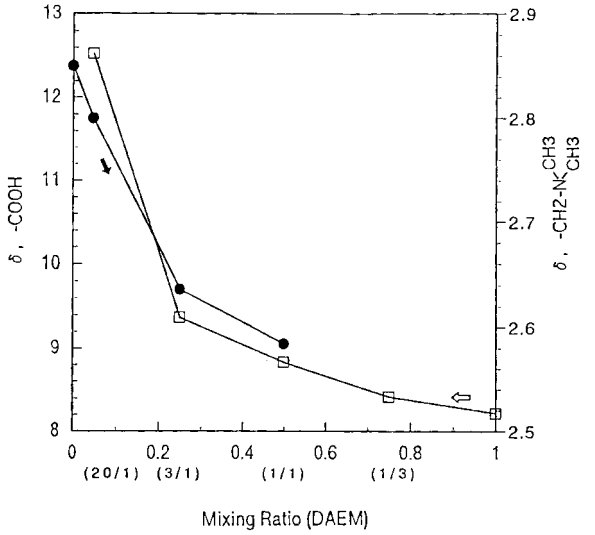


**Figure 9.** Changes in chemical shifts of the hydrogen bond of carboxyl group in M-5011 and the methylene signal of DAEM: ● –COOH; □ $-CH_2N(CH_3)CH_3$

amine in DAEM to form the quaternary ammonium through the hydrogen bond.

From the above results, the mixture of the powdered Eudragit E-100 and the crystallized M-5011 caused the formation of solid dispersion with more stable electrostatic effect by the formation of a hydrogen bond between the carboxyl group in M-5011 and the tertiary amine in Eudragit E-100. These findings revealed the configuration of M-5011 in the solid state was influenced by the addition of the polymers containing a tertiary amine in their structures.

## CONCLUSION

First, M-5011, a nonsteroidal anti-inflammatory drug, was mixed with Eudragit E-100, aminoacryl methacrylate copolymer, and stored. The X-ray diffraction pattern and DSC curve changed with time, indicating the formation of a solid dispersion in the solid state.

Second, the dissolution rate of M-5011 from the solid dispersion was higher than that from M-5011 crystal or from the physical mixture.

Third, IR and NMR analyses suggested that M-5011 interacted with Eudragit E-100 by the formation of a hydrogen bond between the carboxyl group in M-5011 and the tertiary amine in Eudragit E-100.

## ACKNOWLEDGMENT

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