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RESEARCH PAPER

Evaluation of Hypromellose Acetate Succinate (HPMCAS) as a Carrier in Solid Dispersions

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ABSTRACT

The utility of hypromellose acetate succinate (HPMCAS), a cellulosic enteric coating agent, as a carrier in a solid dispersion of nifedipine (NP) was evaluated in comparison with other polymers, including hypromellose (HPMC), hypromellose phthalate (HPMCP), methacrylic acid ethyl acrylate copolymer (MAEA), and povidone (PVP). An X-ray diffraction study showed that the minimum amount of HPMCAS required to make the drug completely amorphous was the same as that of other cellulosic polymers, and less than that in dispersions using non-cellulosic polymers. Hypromellose acetate succinate showed the highest drug dissolution level from its solid dispersion in a dissolution study using a buffer of pH 6.8. This characteristic was unchanged after a storage test at high temperature and high humidity. The inhibitory effect of HPMCAS on recrystallization of NP from a supersaturated solution was the greatest among all the polymers examined. Further, the drug release pattern could be modulated by altering the ratio of succinoyl and acetyl moieties in the polymer chain. Our results indicate that HPMCAS is an attractive candidate for use as a carrier in solid dispersions.

Key Words: Solid dispersion; Nifedipine; Supersaturation; Hypromellose acetate succinate; Hydroxypropyl methylcellulose acetate succinate; Amorphous; Dissolution.

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INTRODUCTION

Drugs that are poorly soluble in aqueous media are likely to have low bioavailability after oral administration. Many approaches have been used in attempts to improve the solubility of drugs. Leuner and Dressman have published a review of methods for improving drug solubility for oral delivery, focusing on solid dispersion.[1] In that application, the drug is dispersed in amorphous form within a carrier substance. Various methods are available to prepare solid dispersions, including the solvent method, hot-melt extrusion, cogrinding, etc.[2–7] Although environmental problems remain, the solvent method is a simple and relatively easy process; that is, both the drug and the carrier are dissolved in a common solvent and then the solvent is removed to obtain the solid dispersion. Although water-soluble compounds such as urea and sugars were often used as carriers, polymeric carriers such as povidone, polyethylene glycol, and various cellulose derivatives have recently been used to prepare solid dispersions.[8–12]

Selection of a carrier substance is important, because the dissolution behavior of the carrier is a determinant of the drug dissolution. In addition, the drug release may be affected by interaction between the active ingredient and carrier. Hasegawa et al. applied enteric coating agents as carriers for solid dispersions and obtained well-controlled drug release with good bioavailability after oral administration to rats.[13–17] Chutimaworapan et al. prepared a solid dispersion of nifedipine with povidone and Eudragit RS (water-insoluble ammoniomethacrylate copolymer) and achieved good control of drug release.[18]

In 1985, hypromellose acetate succinate (HPMCAS, also known as hydroxypropyl methylcellulose acetate succinate) was developed as an aqueous enteric coating material. This polymer is a cellulose ester bearing acetyl and succinoyl groups.[19] The unique characteristics of this polymer include the feature that its dissolution behavior in buffers of various pH values can be controlled by changing the ratio of succinoyl and acetyl moieties, and that the polymeric powder changes into a film in the absence of water or solvents. The latter characteristic means that the polymer can be used for dry coating,[20] as well as for conventional coating using an aqueous dispersion. There have been several studies of cellulosic enteric coating agents as carriers in solid dispersions, though most of them focused on hypromellose phthalate (HPMCP).

The objectives of this study are to evaluate HPMCAS, a relatively new enteric polymer, as a carrier for solid dispersions. Nifedipine, a typical drug with poor solubility, was used as a model active ingredient.

MATERIALS AND METHODS

Materials

Nifedipine (NP) was obtained from Daito Co., Toyama, Japan. The following materials were used as carriers: hypromellose acetate succinate (HPMCAS: Shin-Etsu AQOAT®, type AS-MF, AS-LF, and AS-HF, Shin-Etsu Chemical Co., Tokyo, Japan), hypromellose phthalate (HPMCP, type HP-55, Shin-Etsu Chemical Co., Japan), hypromellose (HPMC: Pharmacoat® type 606, Shin-Etsu Chemical Co., Japan), povidone K30 (PVP: Kollidon®, BASF JAPAN, Tokyo, Japan), methacrylic acid ethyl acrylate copolymer (MAEA: Eudragit® L 100–55, Röhm Pharma GmbH, Weiterstadt, Germany). For HPMCAS, type AS-MF was used for all the experiments in this study. The other two grades were only used for the study on the effect of succinoyl–acetyl ratio.

Methods

Preparation of Solid Dispersions

All experiments were carried out in a dark room with protection from light to prevent photodegradation of NP.[21]

Solid dispersions were prepared by means of the solvent method. Nifedipine and a carrier polymer were dissolved together in a mixed solvent (ethanol:dichloromethane = 1:1) and then the solvent was sprayed onto a Teflon® sheet heated by a hot plate (60–80° C). The solvent was evaporated, and the residual film was peeled off and dried at 60° C for an hour. The obtained films were kept in a desiccator for 20 minutes and pulverized by using a mortar and pestle. After pulverization, the powder was screened through a 24 mesh sieve. To compare dissolutions of different samples in parallel, samples should have a similar particle size or specific surface area. Therefore, the specific surface area of the samples was measured using a BET surface area analyzer (Gemini 2375, Micromeritics/Shimadzu, Kyoto, Japan), and was determined to be within 0.25 $m^2/g \pm 10\%$ for all the samples prepared.

Preparation of Physical Mixtures

For comparison, physical mixtures of NP and carrier were prepared by mixing for 5 minutes with a mortar and pestle.

X-Ray Diffraction Analysis

X-Ray diffraction analysis was conducted with a diffractometer (MX-Labo, MAC Science, Tokyo, Japan)

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using a copper Kα target with a nickel filter at 30 kV, 40 mA, 2°/min scanning speed, and 5°–40° (2θ) range.

FT-IR Spectrophotometry

Infrared spectra were obtained from KBr disks with an IR spectrophotometer (JIR5500, JEOL, Tokyo, Japan) from 4000 to 400 cm^{-1}.

Dissolution Study

Dissolution tests were carried out at 37° C by the following method. Each sample, containing 5 mg of NP, was placed in 200 mL of a test fluid of pH 6.8 in a beaker. For the study on the effect of succinoyl–acetyl ratio, the load of NP was increased to 10 mg so that clear differences would be obtained. The test fluid was composed of KH_2PO_4 (50 mmol/L) and NaOH (23.6 mmol/L). This is designated as the 2nd fluid of the disintegration test in Japanese Pharmacopeia 14. Its composition is the same as that of Simulated Intestinal Fluid TS in USP 26, except that it does not contain pancreatin. For the study on dissolution in various dissolution media, a test fluid of pH 1.2 was also used. This contains HCl (84 mmol/L) and NaCl (34 mmol/L), and is designated as the 1st fluid of the disintegration test in Japanese Pharmacopeia 14. Its composition is the same as that of Simulated Gastric Fluid TS in USP 26 without pectin. The fluid was stirred with a magnetic stirrer during the test. At specified intervals, 2 mL of the fluid was withdrawn and filtered through a membrane filter (DISMIC-25HP, PTFE-0.45 μm, Advantec, Tokyo, Japan) and replaced with an equal volume of fresh test fluid. Nifedipine was assayed by ultraviolet absorption measurement at 325 nm (UV-160 spectrometer, Shimadzu, Kyoto, Japan). All dissolution tests were carried out in triplicate and the mean and SD were reported. Student's *t*-test was used for statistical analysis.

Inhibitory Effect of Carrier on Recrystallization of NP from a Supersaturated Solution

The method was based on the second method of the dissolution test (''paddle method'') in Japanese Pharmacopeia 14. A solution of 50 mg of NP in methanol (25 mg/mL) was added to 200 mL of the pH 6.8 test fluid, in which a carrier polymer had previously been dissolved at 37° C and the fluid was stirred at 150 rpm. The amounts of dissolved carrier polymers, i.e., HPMCAS, HPMC, HPMCP, PVP, and MEAE, were 50 mg, 50 mg, 50 mg, 100 mg, and-150 mg, respectively. These amounts were equivalent to the full amounts of polymers in their solid dispersions used in the dissolution study. At specified times, 2-mL samples were withdrawn, filtered through a 0.45-μm membrane filter, and replaced by an equal volume of fresh test fluid. The NP was assayed by measuring the UV absorption at 325 nm.

Stability Test

Solid dispersions were stored at 40° C, 75% RH and at 50° C in closed bottles for a month with protection from light. X-ray diffraction and dissolution tests were conducted after the storage.

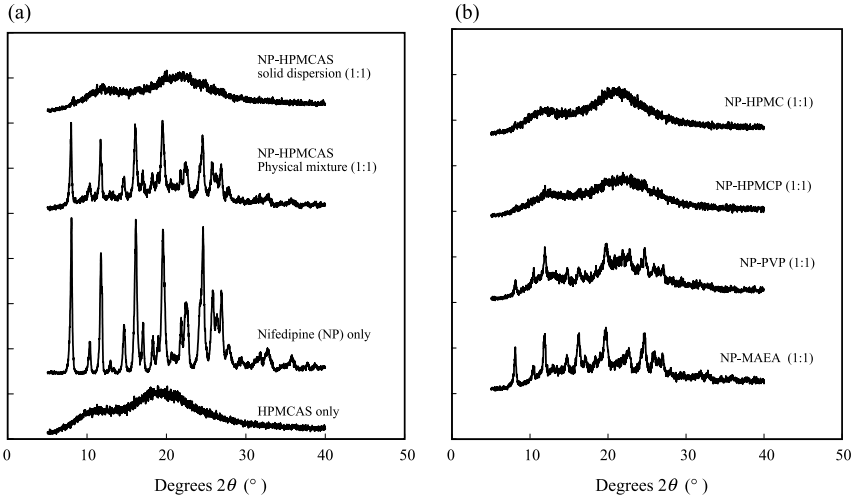

Figure 1. X-ray diffraction patterns of various NP solid dispersions: a) NP–HPMCAS system; b) NP–other polymer (1:1) solid dispersions.

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RESULTS AND DISCUSSION

X-Ray Diffraction Pattern

Figure 1 shows the X-ray diffraction patterns of various samples, including solid dispersions (NP:polymer=1:1), physical mixture, and pure materials. Pure NP showed many sharp peaks, which are attributed to its crystalline structure (Fig. 1a). On the other hand, the diffraction pattern of pure HPMCAS did not show any peaks, which indicates that its polymeric structure is amorphous. In the physical mixture of NP and HPMCAS, there were still peaks due to remaining NP crystals. In the X-ray pattern of the NP–HPMCAS solid dispersion, however, the peaks of crystalline NP had completely disappeared. This indicates that NP was present in amorphous form. Figure 1b shows the x-ray diffraction patterns of solid dispersions with other polymers. The HPMC and HPMCP systems did not show sharp peaks of crystalline NP, similarly to HPMCAS. The PVP and MAEA systems showed sharp peaks, indicating that some crystalline NP existed.

It is important to know how much polymer is required to completely break the crystalline structure of the active ingredient. Samples with various drug–polymer ratios were therefore prepared and their crystallinity was measured. The results are shown in Fig. 2. The diffraction peak intensity at $2\theta=8°$ was chosen as an indicator of crystallinity. The cellulosic and other polymers showed different patterns. Smaller amounts of the cellulosic polymers were required to obtain completely amorphous drug as compared to PVP and MAEA. When the drug–polymer ratio was 1:1 in the case of the cellulosic polymers, crystalline NP was undetectable, whereas ratios of 1:2 and 1:3 were required with PVP and MAEA, respectively.

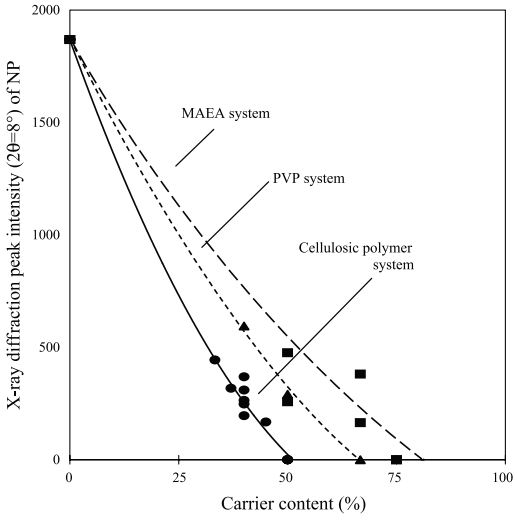

Figure 2. Relationship between crystallinity of NP and carrier content in various solid dispersions.

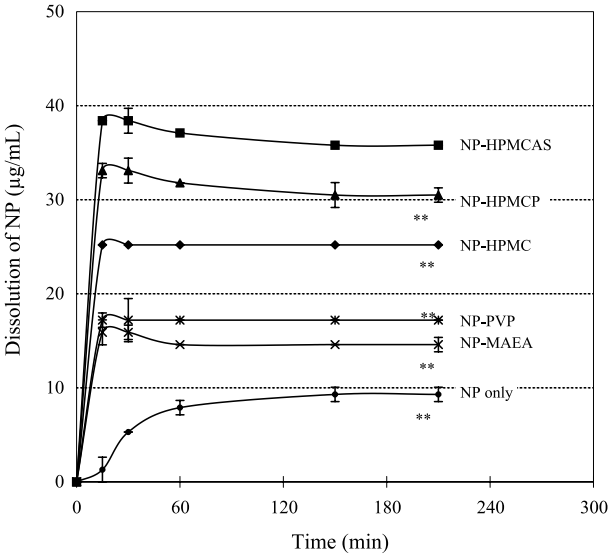

Figure 3. Dissolution of NP from various solid dispersions in the test fluid of pH 6.8. Each point represents the mean ± SD (n=3). Where a bar is not shown, the SD lies within the symbol. **Significantly different from NP–HPMCAS ($P<0.01$).

These results show that the required amount of HPMCAS to obtain an amorphous solid dispersion of NP was the same as that of the other cellulosic polymers, and was less than in the case of PVP or MAEA. In further comparative studies, we used solid dispersion samples prepared with the minimum amount of each polymer required to obtain a completely amorphous dispersion.

Dissolution of NP

Figure 3 shows the dissolution of NP from various solid dispersions in the test fluid (pH 6.8). All solid dispersions released the drug to a higher concentration than the original solubility of the pure drug, presumably by generating a supersaturated state in the test fluid. The cellulosic polymers showed greater NP release than the non-cellulosic polymers (PVP, MAEA). Among the cellulosic polymers, HPMCAS showed the greatest level of drug release in the test fluid.

The order of improvement of drug dissolution was HPMCAS>HPMCP>HPMC>PVP>MAEA.

Inhibition of Recrystallization

The inhibitory effects of polymers on recrystallization of NP in a supersaturated solution were studied by adding a methanol solution of NP to the test fluid with or without carrier polymer. The results are shown in Fig. 4. In the test fluid without carrier, the drug began to recrystallize immediately after the NP solution was added to the fluid. The amount of dissolved NP therefore decreased. However, in the test fluid in which HPMCAS or HPMC had previously been dissolved, the dissolved NP was maintained at a higher level. In the cases of PVP and MAEA, NP recrystallized from the supersaturated solution significantly faster than in the presence of the cellulosic polymers, and the amount of dissolved NP decreased correspondingly. Even though PVP or MAEA were present in larger amounts in the fluid than cellulosic polymers, they were found to be less efficient in the inhibition of the recrystallizaion. Similar results were reported by Hasegawa et al.,[16] who investigated the recrystallization of NP in a supersaturated solution containing polymers such as PVP, MAEA, HPMC, etc. Based on microscopic observation, they suggested a physico-chemical interaction between certain polymers and the drug, i.e., adsorption of drug nuclei on the polymers occurred, thereby inhibiting recrystallization. A similar mechanism may operate in the case of HPMCAS.

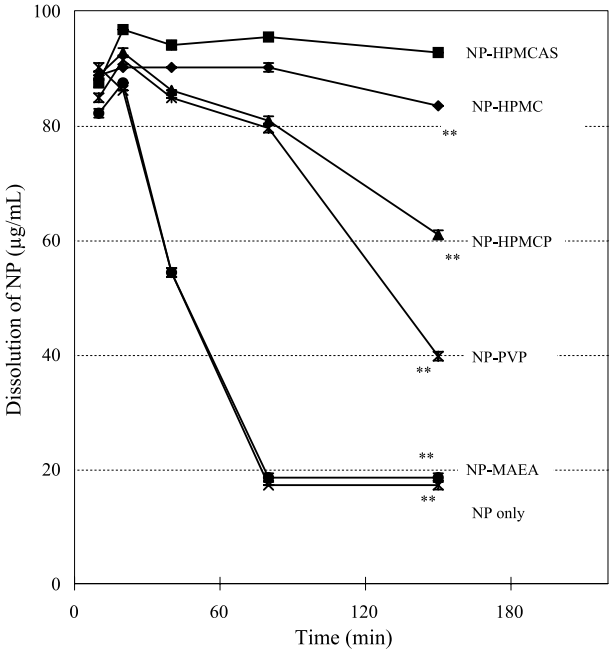

Figure 4. Inhibitory effect of polymer on recrystallization of NP from a supersaturated solution in the test fluid of pH 6.8. Each point represents the mean ± SD (n = 3). Where a bar is not shown, the SD lies within the symbol. **Significantly different from NP–HPMCAS ($P<0.01$).

Infrared Spectrophotometry

Figure 5 shows the infrared (IR) spectra of the pure materials and the solid dispersions with the cellulosic polymers. The original absorptions seen in the pure NP, such as the N–H stretching vibration at 3330 cm^{-1}, a major peak of C═O stretching at 1679 cm^{-1}, C–O ester stretching at 1226 cm^{-1}, and C–H aromatic vibration at 686–794 cm^{-1}, were broadened or shifted to 3334 cm^{-1}, 1704 cm^{-1}, 1214 cm^{-1}, and 684–782 cm^{-1}, respectively, in the solid dispersion. These data indicate that NP may have interactions with each polymer. There was little difference among the spectra of the solid dispersions. It is therefore suggested that the finding that NP–HPMCAS solid dispersion showed the greatest dissolution level is likely to be attributed to HPMCAS having the greatest inhibitory effect on recrystallization of NP, rather than to molecular interactions in the solid state. This idea is supported by the fact that the order of effectiveness is similar to those in Figs. 3 and 4.

Stability

For the stability study, the solid dispersions were stored under two different conditions for a month, and the dissolution of the drug in the test fluid was examined (Table 1).

NP–PVP solid dispersion changed significantly in appearance at 40° C and 75% humidity. It absorbed moisture and aggregated during storage. The others did not change in appearance, but many of them showed a slight reduction in drug release. In X-ray diffraction analysis, these solid dispersions showed peaks due to small amounts of recrystallized NP. However, the NP–HPMCAS solid dispersion retained the highest level of NP dissolution even after storage under high temperature and high humidity conditions.

Effect of Test Fluid on Dissolution of NP

To study the influence of media on the dissolution of NP from the solid dispersions, dissolution tests were carried out using various test fluids including purified water, the test fluid of pH 1.2, and the test fluid of pH 6.8. Figure 6 shows the dissolution amount of NP from

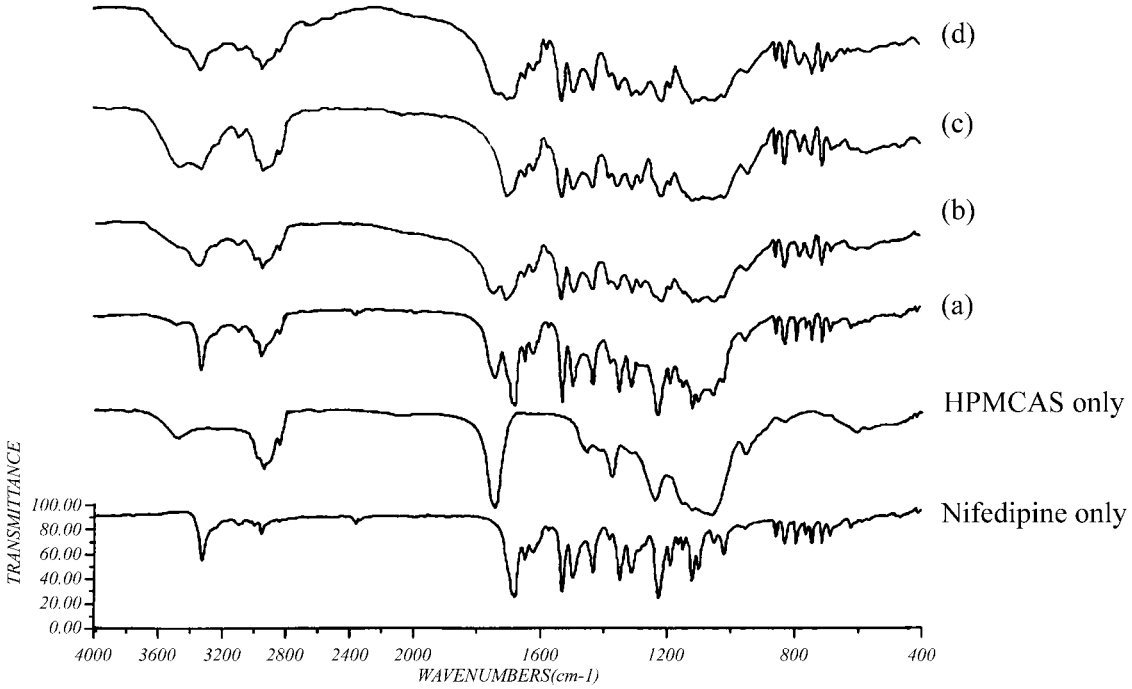

Figure 5. IR spectra of NP-cellulosic polymer solid dispersions: (a) NP-HPMCAS physical mixture (1:1); (b) NP-HPMCAS solid dispersion (1:1); (c) NP-HPMC solid dispersion (1:1); (d) NP-HPMCP solid dispersion (1:1).

the solid dispersions at 60 minutes in the test fluids. Pure NP showed the same solubility in the three test fluids (10 μg/mL). The solid dispersions showed different dissolution behaviors depending upon their polymer characteristics. Since HPMCAS, HPMCP, and MAEA are enteric polymers and dissolve in basic buffers, they were insoluble in the acidic fluid and in purified water. Nifedipine was released in only small amounts from the solid dispersions using these polymers. Both HPMC and PVP are pH-independent polymers and dissolve in all three test fluids, so essentially the same dissolution of NP was obtained in the three fluids, as shown in Fig. 7. Enteric polymer can be used for a pH-dependent controlled release dosage form,[12–17,22] and gives better bioavailability because it prevents recrystallization of the drug in the gastric juice,[12–15,17,22] as well as acid decomposition of drugs.

Table 1. Dissolution of NP from various solid dispersions before and after 1-month storage.

	Dissolution of NP (μg/mL)[a]		
	Initial	40° C, 75% RH	50° C in closed bottle
NP only	8	8	8
NP-HPMCAS	47 (0.8)	42 (0.8)[d]	45 (1.4)
NP-HPMCP	34 (0.7)	34 (0.8)	32 (0.8)[c]
NP-HPMC	39 (0.4)	27 (0.8)[d]	39 (0.8)
NP-PVP	17 (0.1)	15 (0.8)[b,d]	17 (0.7)
NP-MAEA	17 (1.6)	12 (0.8)[d]	13 (0.8)[d]

[a]Dissolution at 60 min in the test fluid of pH 6.8. Data represents the mean of triplicate determinations, with the SD in parenthesis.
[b]Aggregation was observed.
[c]$P<0.05$ compared to initial value.
[d]$P<0.01$ compared to initial value.

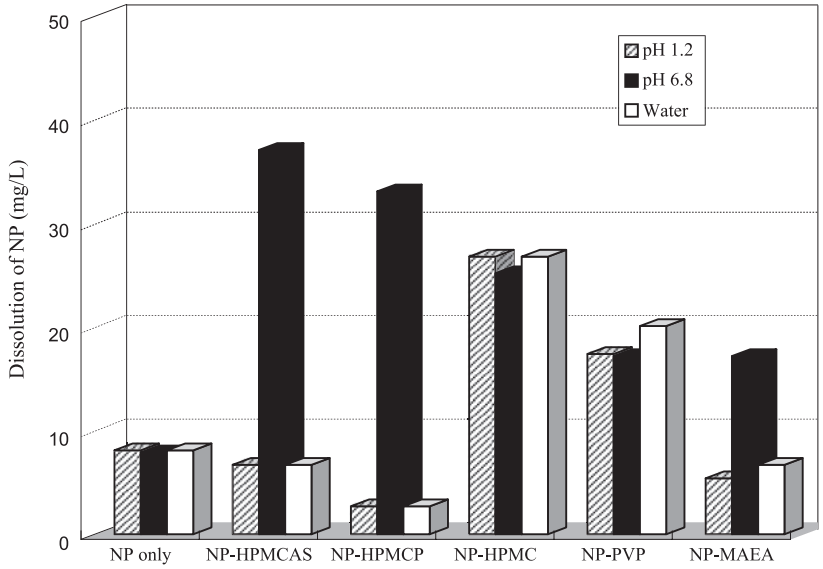

Figure 6. Effect of the test fluid on the dissolution amount of NP from various solid dispersions. See the text for details of the test fluids.

Effect of Succinoyl–Acetyl Ratio of HPMCAS on Dissolution of NP

To investigate if the chemical composition of HPMCAS affects the drug release, the proportions of the two substituent groups of HPMCAS, i.e., succinoyl and acetyl groups were varied and solid dispersions were prepared using these samples. Currently, three types with different ratios of succinoyl and acetyl groups are commercially available, i.e., AS-LF, AS-MF, and AS-HF (Table 2). The proportion of succinoyl substitution to acetyl substitution (SA ratio) is highest in AS-LF, which is soluble at lower pH, whereas AS-HF, having a low SA ratio, dissolves at higher pH.

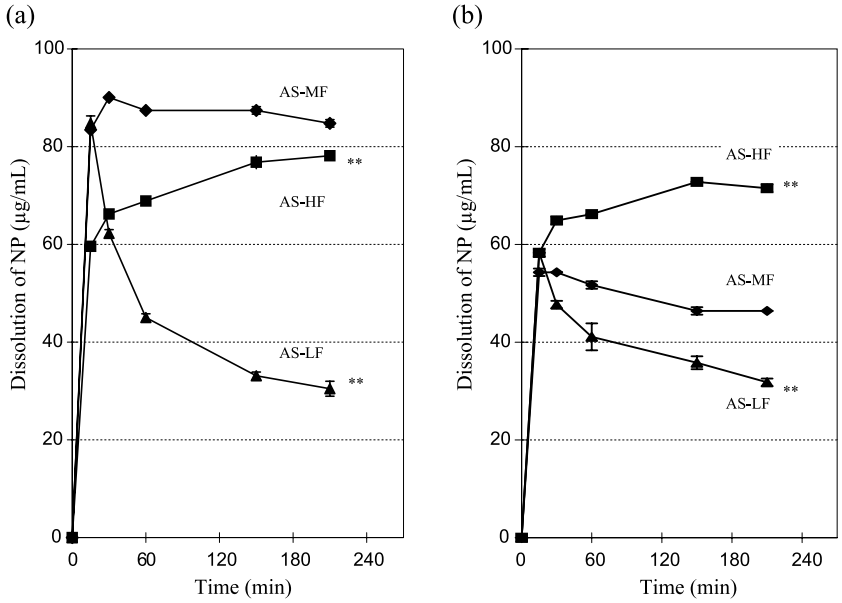

Figure 7. Effect of substitution type on dissolution of NP from NP–HPMCAS solid dispersions: a) NP:HPMCAS = 1:2; b) NP:HPMCAS = 1:1. Each point represents the mean ± SD (n = 3). Where a bar is not shown, the SD lies within the symbol. **Significantly different from AS-MF ($P < 0.01$).

Table 2. Substitution patterns of HPMCAS used for solid dispersions.

Type	Content of substituents (%)				Soluble at pH of
	Succinoyl	Acetyl	Methoxyl	Hydroxypropoxyl	
AS-LF	14.8	7.3	7.1	22.7	5.5 and higher
AS-MF	11.0	9.3	7.4	23.0	6.0 and higher
AS-HF	7.8	11.1	7.4	23.5	6.5 and higher

Three kinds of NP–HPMCAS solid dispersions were prepared using AS-LF, AS-MF, and AS-HF, respectively, and the dissolution profiles in the test fluid of pH 6.8 were evaluated. The NP–HPMCAS solid dispersions were prepared at the weight ratio of 1:1 or 1:2 (NP: HPMCAS), respectively. The two different weight ratios showed no peak of NP crystals in X-ray diffraction analysis, and it was found that the minimum polymer ratio required to make a complete amorphous drug was 1:1, which was the same for all substitution types. Figure 7 shows the dissolution profiles. Pure HPMCAS of the three types adequately dissolved in the test fluid of pH 6.8. All solid dispersions dissolved completely in the test fluid and improved the dissolution of NP in the initial stage, but the dissolution rate and the recrystallization behavior were different. The AS-HF showed slower release of NP and the highest and most stable drug release of the three. Significant recrystallization was found when using AS-LF. However, when the amount of polymer was increased, the highest release was found with AS-MF. There were no significant differences in the IR spectra of the three types. The reasons for these dissolution differences are not clear. However, it does appear that the substituents have an important influence on the drug release. It may be necessary to determine the optimum substituent ratio for each active ingredient.

CONCLUSIONS

Our results indicate that HPMCAS can be a useful polymer as a carrier in a solid dispersion. The polymer suppressed recrystallization of the test drug more efficiently than did the other polymers tested. Further studies using other drugs are in progress.

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