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Note

Effect of hydroxypropylmethylcellulose (HPMC) on the release profiles and bioavailability of a poorly water-soluble drug from tablets prepared using macrogol and HPMC

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Abstract

The aim of the present study was to investigate the effect of hydroxypropylmethylcellulose (HPMC-2208), used as an excipient for controlled release of drug, on the release profiles and bioavailability of the poorly water-soluble nifedipine (NP) from a tablet prepared using macrogol 6000 (PEG) and HPMC. The crushing tolerance of the NP tablet prepared using PEG and HPMC (NP-PEG-HPMC tablet) was markedly increased with increasing compression force used during the preparation from 20 to 200 MPa. The values reached their maximal levels (approximately 13 kg for the NP-PEG-HPMC tablet and 8 kg for the PEG tablet) at the compression force of 100 MPa. Although NP is a poorly water-soluble drug, it was rapidly dissolved from the NP-PEG tablet (without HPMC) due to the improvement of its dissolution rate in the presence of PEG. NP dissolution was complete at the latest within 1 h. On the other hand, dissolution of NP from the NP-PEG-HPMC tablet was significantly delayed with an increase in the concentration of HPMC in the tablet. The dissolution of NP from the NP-PEG-HPMC tablet containing 50% HPMC-2208 was markedly delayed as the viscosity of HPMC also increased. Interestingly, the same peak plasma NP concentration (C_{max}) and the area under the plasma NP concentration–time curve (AUC_{0-10}) were observed for both the NP-PEG tablet and NP-PEG-HPMC tablets, however, the time to C_{max} (t_{max}) for the NP-PEG-HPMC tablet was significantly higher when the NP-PEG-HPMC tablet was orally administered to rabbits. We describe here a preparation method of a new sustained-release NP-PEG-HPMC tablet using a mixture of NP-PEG granules (prepared with PEG) and HPMC.

Keywords: Hydroxypropylmethylcellulose; Macrogol 6000; Sustained release tablet; Nifedipine

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1. Introduction

Hydroxypropylmethylcellulose (HPMC) is an attractive non-ionic ingredient of a water-soluble cellulose ether derivative (cellulose hydroxypropyl methyl ether) for use in controlled-release preparations. It is available in grades containing 16.5–30% of methoxy and 4.0–32.0% of hydroxypropoxy groups, with specified viscosities for specific concentrations (Der Marderosian, 1990). Wilson and George (1989) reported the preparation method of a matrix tablet containing isomazole, an orally active cardiotonic agent, with various concentrations of HPMC hydrogel. They observed that the HPMC concentration required to be within a narrow range in the matrix tablet to achieve sustained release of isomazole. Furthermore, Devi et al. (1989) reported that the zero-order release of oxprenolol hydrochloride, a β-adrenergic blocking agent, was obtained by controlling the swelling and erosion of the matrix using only a mixture of the drug, HPMC and sodium carboxymethylcellulose (Na CMC), and compressing the mixture directly into tablets. Recently, the release of atenolol from a hydrophilic matrix tablet (Vazequez et al., 1996) prepared using HPMC mixture as gelling agent and a sustained release tablet (Katzhendler et al., 1998) of carbamazepine have been investigated.

We often encounter the problem of low bioavailability following oral administration of drugs, such as nifedipine (NP) which is a potent Ca antagonist in clinical use, with the characteristics of very low solubility and dissolution rate in water. To overcome this problem, in our previous study (Watanabe et al., 1995), using NP as a model drug with the characteristic of poor water solubility, we developed a preparation method for the NP macrogol-matrix tablet prepared using macrogols (PEG-6000, -20 000, -50 000), a hydrophilic polymer. We found a significant increase in the dissolution rate and bioavailability of NP after oral administration of the prepared tablet in rabbits. In the present study, we investigated a new preparation method of the controlled release tablet of NP, using PEG-6000 to improve its dissolution (Watanabe et al., 1995) and HPMC for controlled release of the drug. Concerning NP preparations, various controlled release NP granules (Sugimoto et al., 1982; Kohri et al., 1986; Watanabe et al., 1993) and tablets (Avgerinos and Gorrod, 1990; Abrahamsson et al., 1998; Iglesias et al., 1998) have been investigated. However, to our knowledge, no experiment on the preparation of tablets containing NP, a poorly water-soluble drug, using macrogols in combination with HPMC has been reported.

Concerning the effect of the degree of substitution (DS) of methoxy and hydroxypropoxy groups in the chemical structure of HPMC (-2208, -2906 and -2910), Alderman (1984) reported that the fastest-hydrating of the polymers, namely HPMC-2208 (DS: methoxy, $0.19 \sim 0.24$; hydroxypropoxy, $0.04 \sim 0.12$) adequately provided for sustained release of a drug. On the other hand, HPMC-2906 (DS: methoxy, $0.27 \sim 0.30$; hydroxypropoxy, $0.04 \sim 0.075$) and HPMC-2910 (DS: methoxy, $0.28 \sim 0.30$; hydroxypropoxy, $0.07 \sim 0.12$) did not hydrate sufficiently fast to protect the tablet from rapid disintegration and dissolution. Therefore, we chose HPMC-2208 in this study. The effects of HPMC-2208 on the release profiles and bioavailability of NP from an NP-PEG-HPMC tablet prepared using a mixture of NP-PEG granules (prepared with PEG) and HPMC were studied. The dissolution behavior of NP in vitro and the plasma NP concentrations in rabbits after oral administration of the prepared tablet were evaluated.

2. Materials and methods

NP (JP XIII) was purchased from Nihon Baruku Yakuhin Co., Osaka, Japan. Macrogol 6000 (PEG) was purchased from Wako Pure Chemical Industries, Tokyo, Japan.

The HPMC (-2208, JP XIII) listed in Table 1 were kindly supplied by Shin-Etsu Chemical Co., Tokyo, Japan. All experiments were carried out in a dark room, in view of the high sensitivity of NP to light (Jakobsen et al., 1979; Sugimoto et al., 1982). A schematic illustration of the preparation method of the sustained-release NP tablet is shown in Fig. 1. In the first step, NP was added to PEG melted by heating at 80°C, and completely

Table 1
Physicochemical parameters of HPMC

Type	Viscosity[a] (mm^2/s)	DS[a]	
		Methoxy	Hydroxypropoxy
HPMC-2208			
400	390	0.24	0.07
4000	4040	0.24	0.08
15 000	16 800	0.23	0.07

[a] 2% solution, 20°C, reported by Shin-Etsu technical information.

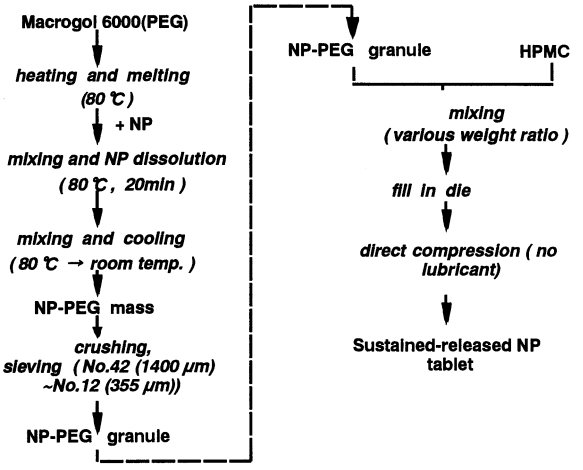

Fig. 1. Schematic illustration of the preparation of method for sustained release tablets (NP-PEG-HPMC tablet).

Table 2
Composition of tablet (200 mg)[a]

Preparation	NP (mg)	PEG (mg)	HPMC (mg)
NP-PEG tablet	10(5%)	190 (95%)	
NP-PEG HPMC tablet	10 (5%)	130 (65%)	60 (30%)
NP-PEG HPMC tablet	10 (5%)	110 (55%)	80 (40%)
NP-PEG HPMC tablet	10 (5%)	90 (45%)	100 (50%)

[a] The concentration (%) of each material in the tablet is described in parentheses.

dissolved. After cooling to room temperature, the solidified mass was crushed with a mill (HCM-510, Toshiba Co., Tokyo, Japan). The crushed mass was passed through a sieve (No. 12 (1400 μm) No.42 (355 μm)) to obtain NP-PEG granules (left panel in Fig. 1). In the second step, HPMC was mixed with the NP-PEG granules in various weight ratios (HPMC concentration, 0–50%). Then, 200 mg tablets (diameter, 9 mm; 14 R) containing 10 mg of NP were prepared by the compression method (right panel in Fig. 1). The composition of the prepared tablet is listed in Table 2. For the control experiment an NP-PEG tablet was prepared without HPMC.

The crushing tolerance (the stress required to break a tablet by compression) of the prepared tablets, was measured with a semiautomatic tablet hardness tester (TS-50N, Okada Seiko Co., Ltd., Tokyo, Japan). The dissolution behavior of the prepared tablets of NP was observed with a dissolution test apparatus (NTR-VS, Toyama Sangyo Co., Ltd., Osaka, Japan), using the paddle method (JP X III). As the dissolution mediums, the first fluid (pH 1.2) for the JP XIII disintegrating test was used, at a constant temperature (37 ± 0.1°C). The shaft rotation speed was set at 100 rpm. The medium (suspension) was immediately filtered through a nitrocellulose membrane filter (Dismic-25, pore size 0.8 μm, Toyoroshi, Tokyo, Japan) to remove the particles. The concentration of NP was determined spectrophotometrically at 340 mn.

For oral administration experiments, male rabbits (Japan White) weighing 2.8–3.1 kg were used. Prior to each oral administration, the rabbits were starved for 24 h according to the method of Maeda et al. (1979) with a slight modification, and were allowed free access to tap water only. They were housed individually in cages under environmentally controlled conditions (23 ± 2°C; 55 ± 5% relative humidity, 12 h light/dark cycle). To facilitate oral administration of preparations by gastric intubation, 400 mg capsule-shaped tablet (caplet; minor axis, 6 mm; major axis, 16 mm) containing 10 mg of NP was prepared instead of the disk-shaped tablet described above; however no difference in the dissolution profile between the caplet and the disk-shaped tablet was

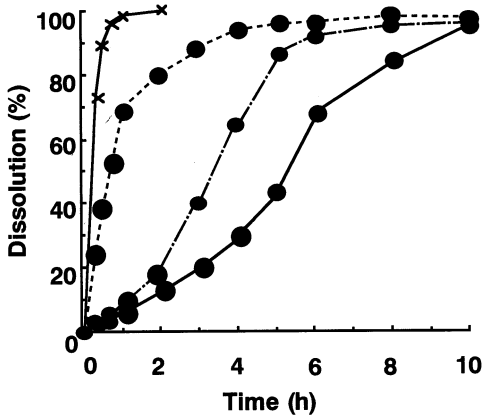

Fig. 2. Drug-release profiles of tablets prepared with 10 mg of NP and various concentrations of HPMC-2208 (4000). Dissolution medium: JP XIII 1st medium (pH 1.2). HPMC concentration: —×—, 0%; – –●– –, 30%; –·–●–·– 40%; —●—, 50%. Each point represent the mean of six experiments.

observed. A caplet was set on the tip of a gastric intubation tube made of silicone rubber, then this caplet was administered into the stomach of rabbits by gastric intubation of the rubber tube. The plasma concentration of NP was assayed by high-performance liquid chromatography (HPLC), as reported by Miyazaki et al. (1984). The peak NP concentration (C_{max}) and the time to C_{max} (t_{max}) were obtained from the individual plasma NP concentration–time curves, and the area under the concentration–time curves from 0 to 10 h after administration (AUC_{0-10}) was calculated using the trapezoidal rule. For statistical analyses, one-way analysis of variance and Dunnett's test were used. A P value of < 0.05 was considered to denote a significant difference.

3. Results and discussion

In preliminary experiments, the crushing tolerance of the prepared tablet was significantly increased with increasing compression force from 20 to 200 MPa. These values reached their maximal levels (approximately 13 and 8 kg for the NP-PEG-HPMC tablet and the PEG tablet, respectively) at the compression force of 100 MPa. It seemed that the prepared tablets had sufficient hardness for practical use. Therefore, the compression force was set at 100 MPa in this study.

Fig. 2 shows the in vitro dissolution profile of NP from the prepared tablet containing NP-PEG granules (for contents, see Table 2) and HPMC-2208 at various concentrations (0, 30, 40 and 50%). Although NP is a poorly water-soluble drug, it was rapidly dissolved from the NP-PEG tablet (without HPMC) due to improvement of dissolution rate owing to presence of PEG. NP dissolution was complete at the latest within 1 h. On the other hand, dissolution of NP from the NP-PEG-HPMC tablet was significantly delayed with increasing HPMC-2208 concentration in the tablet. The prepared tablet did not disintegrate; however, a gel layer was formed on the surface of the tablet due to swelling of HPMC in the presence of water. Consequently, NP was gradually released from the tablet. In the case of the NP-PEG-HPMC tablet containing the maximum concentration of HPMC (50%), the dissolution percentage was approximately 50% by the end of 5 h. The differences in the NP dissolution profile in the presence of various concentrations of HPMC-2208 may be due to the differences in the thickness of the HPMC gel layer formed on the surface of the tablets (Ju et al., 1995).

In subsequent studies, we evaluated the tablets prepared using HPMC of various viscosities (Table 1). The concentration of each type of HPMC-2208 (400, 4000 and 15 000) was set at 50% since the maximum effect of HPMC on sustained release of NP from the tablet was achieved at this concentration (results mentioned above). As shown in Fig. 3, the dissolution of NP from the NP-PEG-HPMC tablet prepared using 50% HPMC (2208) was markedly delayed with increasing viscosity of HPMC (400, 390 mm^2/s; 4000, 4040 mm^2/s; 15 000, 16 800 mm^2/s). However, the differences in the NP dissolution profile were not significant, when the concentration of HPMC used was 30%. It is presumed that the gel layer formed on the surface of tablet is relatively thicker when a higher concentration (50%) of HPMC is used. In this case, a higher viscosity of the gel layer formed is more effective for sustained release of NP from the prepared tablet. On the other hand, the gel layer formed on the surface of

the tablet is relatively thinner when a lower concentration (30%) of HPMC is used; therefore, the effect of viscosity of the gel layer formed would be marginal. This may explain the observed absence of any significant differences in the NP dissolution profile in the case of tablets prepared using 30% HPMC.

To elucidate the absorption behavior of NP from the NP-PEG-HPMC tablet, three NP preparations, namely, NP powder (capsule), NP-PEG tablet and NP-PEG-HPMC tablet, were orally administered to rabbits. For the NP-PEG-HPMC tablet, HPMC-2208 was used at the concentration of 50%, at which the maximum effect on the sustained release of NP was observed. Fig. 4 shows the plasma NP concentration–time curves plotted after oral administration of these preparations, and the pharmacokinetic parameters of NP are summarized in Table 3. The plasma NP concentration obtained after administration of NP in powder form was low, since the dissolution rate of NP is very low. However, the plasma NP concentration was significantly higher following the administration of the NP-PEG tablets due to the improvement of NP dissolution rate in the gastrointestinal fluid owing to the presence of PEG, a hydrophilic polymer. The AUC_{0-10} of NP increased approximately 5-fold.

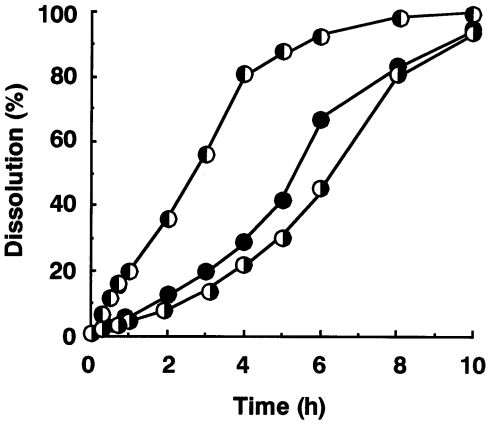

Fig. 3. Drug-release profiles of tablets prepared with 10 mg of NP and various degrees of polymerization of HPMC-2208 (400, 4000 and 15000). Dissolution medium: JP XIII 1st medium (pH 1.2). Key: ◐, 400; ●, 4000; ◑, 15000. Each point represent the mean of six experiments.

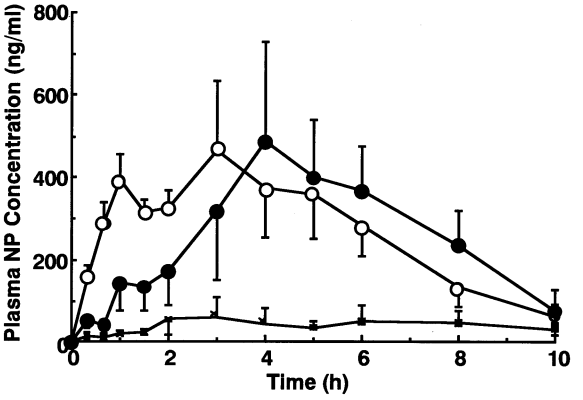

Fig. 4. Plasma NP concentration–time curves in rabbits after oral administration of the prepared tablets. Each point represents the mean ± S.E. of three to five rabbits. Key: X, powder (gelatin capsule); ○, NP-PEG tablet; ●, NP-PEG-HPMC tablet (HPMC-2208 (4000), conc. 50%).

Table 3
Pharmacokinetic parameters of NP after oral administration[a]

Preparation	C_{max} (ng/ml)	t_{max} (h)	$AUC_{0\rightarrow10}$ (h · ng/ml)
Powder	63 ± 43	2.8 ± 1.4	412 ± 249
NP-PEG tablet	614 ± 132[c]	2.5 ± 0.6	2870 ± 499[c]
NP-PEG-HPMC tablet[b]	611 ± 154[c]	5.2 ± 1.0[d]	2602 ± 557[c]

[a] Each value represents the means ± S.E. of 3–5 rabbits.
[b] HPMC 2208–4000, conc. 50%.
[c] Statistically significant differences: $P<0.05$ in NP-PEG or NP-PEG-HPMC tablet vs. powder.
[d] Statistically significant differences: $P<0.05$ in NP-PEG-HPMC tablet vs. NP-PEG tablet.

Interestingly, the same values of C_{max} and AUC_{0-10} were observed for NP-PEG as well as NP-PEG-HPMC tablets; however, the t_{max} value following oral administration in rabbits was significantly ($P < 0.05$) increased for the NP-PEG-HPMC tablet (Table 3). The t_{max} value for the NP-PEG-HPMC tablet was approximately 5 h. These results suggest that HPMC in the tablet does not have any influence on the NP bioavailability, but it does influence the rate of release of NP, consequently, the rate of absorption changes. The NP concentration–time curve indicating delayed NP release following the ad-

ministration of the NP-PEG-HPMC tablet to the rabbits is in general agreement with the release profile of NP obtained for the same tablet in vitro. In conclusion, we have demonstrated a preparation method for a new sustained release NP tablet (NP-PEG-HPMC tablet), using a mixture of NP-PEG granules and HPMC. This method increased the NP bioavailability and conferred a characteristic of sustained release, as compared with the powdered form of the drug. These NP-PEG-HPMC tablets prevent abrupt increase in plasma NP concentrations without decrease of NP bioavailability as compared with the NP-PEG tablets.

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