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Evaluation of a floating dosage form of nicardipine hydrochloride and hydroxypropylmethylcellulose acetate succinate prepared using a twin-screw extruder

Kouichi Nakamichi *, Hiroyuki Yasuura, Hiroshi Fukui, Masaaki Oka, Syougo Izumi

Pharmaceutics Research Laboratory, Nippon Shinyaku Co., Ltd., 14 Nishinosyou-Monguti-cho, Kisshoin, Minami-ku, Kyoto 601-8500, Japan

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Abstract

A floating dosage form composed of nicardipine hydrochloride (NH) and hydroxypropylmethylcellulose acetate succinate (enteric polymer) was prepared using a twin-screw extruder. By adjusting the position of the high-pressure screw elements in the immediate vicinity of die outlet, and by controlling the barrel temperature, we were able to prepare a puffed dosage form with very small and uniform pores. It was found that the porosity and pore diameter could be controlled by the varying amount of calcium phosphate dihydrate. In the shaking test, the puffed dosage form was found to have excellent floating ability and mechanical strength in acid solution (JP First Fluid, pH 1.2). The dissolution profile of NH was controlled by the amount of wheat starch. In the dissolution test using JP Second Fluid (pH 6.8), rapid dissolution of NH and loss of buoyancy were observed. It was shown that the puffed dosage form, consisting of enteric polymer prepared using the twin-screw extruder, was very useful as a floating dosage form that was retained for a long period in the stomach.

Keywords: Twin-screw extruder; Nicardipine hydrochloride; Hydroxypropylmethylcellulose acetate succinate; Floating dosage form; Dissolution; Buoyancy

1. Introduction

The twin-screw extruder is a type of mixer that continuously carries out process operations such as kneading, shearing, heating, compressing, melting and cooling (Mueller et al., 1992; Follonier et al., 1994, 1995; Nakamichi et al., 1996; Zhang and McGinity, 1999). The puff ability is one of the mechanical options offered by this machine. In the field of food manufacture, the twin-screw extruder has been used to produce puffed products such as snack foods with improved texture (Mercier and Feillet, 1975; Faubion et al., 1982;

* Corresponding author. Tel.: +81-75-3219124; fax: +81-75-3219038.

E-mail address: k.nakamichi@po.nippon-shinyaku.co.jp (K. Nakamichi).

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Peri et al., 1983; Gomez and Aguilera, 1984; Kirby et al., 1988; Munakata et al., 1989; Chinnaswamy, 1993; Sokhey et al., 1994; Fan et al., 1996).

To control the transport of dosage forms in the digestive tract, several floating systems have been investigated by pharmaceutical researchers (Sheth and Tossounian, 1984; Ushimaru et al., 1985; Stockwell, et al., 1986; Ingani et al., 1987; Mazer et al., 1988; Timmermans and Moes, 1990; Kawashima et al., 1991; Hilton and Deasy, 1992). For example, foaming polystyrene or puffed rice coated with pharmacologically active substances (Watanabe et al., 1980) and foaming microcapsules (Ichikawa et al., 1991a) have been developed.

Floating dosage forms are useful for drugs that are expected to act directly on the upper digestive tract (Hofmann et al., 1983) or are intended to be absorbed only from this part of the tract. These dosage forms are also considered to prolong drug release in the gut (Ichikawa et al., 1991b).

To achieve the presented aims, it is very important to select appropriate starting materials. As far as the ideal floating dosage form is concerned, it should have a high buoyancy, adequate mechanical strength, excellent acid resistance and a high drug-releasing capacity in the stomach.

In the present study, we used the puff ability of the twin-screw extruder as one of the physical methods to prepare a floating dosage form. We chose nicardipine hydrochloride (NH) as a model drug and an enteric polymer, hydroxypropylmethylcellulose acetate succinate (HPMCAS), as the main excipient. The buoyancy, acid-resistance and drug-releasing properties of the puffed dosage form were evaluated.

2. Materials and methods

2.1. Materials

HPMCAS (AQOAT-MF®; Shin-Etsu Chemical Co., Ltd.) was chosen as the enteric polymer and NH (Japanese 13th Pharmacopoeia, Fuji Chemical Co., Ltd.) was selected as the model drug. Calcium phosphate dihydrate (CP) (Kyowa Kagaku Kogyo Co., Ltd.), dried aluminum hydroxide gel (Kyowa Chemical Industry Co., Ltd.), talc (Fuji Talc Industrial Co., Ltd.), light anhydrous silicic acid (Nippon Aerosil Co., Ltd.) and magnesium stearate (Taihei Chemical Industrial Co., Ltd.) met the requirements of the Japanese Pharmacopoeia. Hydrated silicon dioxide (Shionogi Co., Ltd.) and wheat starch (WS) (Yuka Sangyo Co., Ltd.) met the requirement for Japanese Pharmaceutical excipients. All other reagents were commercially available, and of guaranteed quality.

2.2. Preparation of floating dosage form

According to the formulation shown in Tables 1 and 2, the floating dosage forms were prepared on a laboratory scale (500 g each). Each ingredient was weighed and mixed by hand in a polyethylene bag for 3 min. This mixture underwent processing in the twin-screw extruder (Model KEX-30, co-rotating type; Kurimoto,

Table 1
Formulation of puffed NH–HPMCAS with the twin-screw extruder (%)

	Rp. 1	Rp. 2	Rp. 3	Rp. 4	Rp. 5	Rp. 6	Rp. 7	Rp. 8	Rp. 9
Nicardipine hydrochloride (NH)	–	10	30	9.3	9.3	9.3	9.3	9.3	9.3
HFMCAS	100	90	70	83.3	83.3	83.3	83.3	83.3	83.3
Calcium phosphate dihydrate (CP)	–	–	–	7.4	–	–	–	–	–
Dried aluminum hydroxide gel	–	–	–	–	7.4	–	–	–	–
Talc	–	–	–	–	–	7.4	–	–	–
Light anhydrous silicic acid	–	–	–	–	–	–	7.4	–	–
Hydrated silicon dieoxide	–	–	–	–	–	–	–	7.4	–
Magnesium stearate	–	–	–	–	–	–	–	–	7.4

Table 2
Formulation of puffed NH–HPMCAS with the twin-screw extruder (%)

	Rp. 10	Rp. 11	Rp. 12	Rp. 13	Rp. 14	Rp. 15
Nicardipine hydrochloride (NH)	10	10	10	10	10	10
HPMCAS	86	82	78	72	67	62
Calcium phosphate dihydrate (CP)	4	8	12	8	8	8
Wheat starch (WS)	–	–	–	10	15	20

Co., Ltd.). The operating conditions were as shown in Table 3.

The product was then cut into pieces of about 100 mm in length and dried in a hot-air circulating oven (Model GF-100; ALP Co., Ltd.) for 3 h at 50°C. To measure the pore volume, buoyancy and dissolution rate, the samples were cut into pieces 8–12, 20 and 2 mm long, respectively and dried for 2 h at 50°C.

2.3. Evaluation of the physicochemical properties and buoyancy of the floating dosage form

2.3.1. Appearance

The appearance of the floating dosage form was monitored visually and by scanning electron microscopy (Model S-2100, Hitachi Scanning Electron Microscope; Hitachi Co., Ltd.) to evaluate its shape. The outer diameter of the floating dosage form was measured with slide calipers (Model SR-44; Mitutoyo Co., Ltd.)

2.3.2. Measurement of porosity, pore size distribution and average pore diameter

The pore volume of the floating dosage form was measured with a pore sizer (Pore Sizer Model 9320; Shimadzu Corp.). The porosity, pore distribution and average pore diameter were calculated using the computing software supplied with the instrument. The porosity, however, is an apparent value that does not contain dead pores, because mercury in the equipment cannot fill pores perfectly. In this paper, it was shown as a relative index.

2.3.3. Measurement of buoyancy

According to a previous patent (Ushimaru et al., 1985), the buoyancy of the floating dosage form was measured as follows.

1. Three hundred milliliters of JP first fluid (pH 1.2) for the disintegration test was transferred to a brown glass bottle (volume, 500 ml; mouth diameter, 24 mm; bottom diameter, 74 mm; height, 183 mm).
2. Two portions of the floating dosage form (20 mm) were placed in the brown glass bottle, which was then capped tightly.

Table 3
Operating conditions

Screw pattern (from hopper side)	
Conveying screw	16 mm; pitch (P) length, 48 mm ×2 12 mm; P length, 48 mm ×2 9.6 mm; P length, 48 mm ×2 8 mm; P length, 48 mm ×6 8 mm; P length, 24 mm ×1
Mixing and kneading paddle	Reverse with twisting angle of 30°; length, 24 mm ×1
Rotating speed of screw	100 r.p.m.
Set temperature of barrel	100–130°C
Die diameter	1 mm ∅ × 5 holes
Extruding pressure	100–150 kg/cm^2
Powder feeding speed	30 g/min
Infusion speed of water from liquid additive feeding barrel	2 ml/min
Amount processed	490 g

3. The brown glass bottle was placed in a shaker (Shaker Model SA-31; Yamato Scientific Co., Ltd.) and shaken horizontally at a frequency of 300 times per minute, using a shaking amplitude of 5 cm.
4. At predetermined times, samples were transferred to a 1000 ml glass beaker containing 900 ml JP first fluid.
5. A microload transducer (UL-2GR; Shinkoh Minebea Co., Ltd.) was used and this was fitted with a holder to keep the floating dosage form submerged in the center of the beaker, 20 mm from the surface. A blank test was performed to allow correction of the 0 point.
6. The floating dosage form was fixed to the holder and the upward force was measured electrically (Amplifier, TA-353; Sogokeiso Co., Ltd.) to determine the buoyancy.
7. After measuring the buoyancy, the sample was returned to the glass bottle. Procedures (3)–(6) were repeated three times to measure the buoyancy electrically (Amplifier, TA-353; Sogokeiso Co., Ltd.) to determine the overall buoyancy.

2.3.4. Dissolution test

The dissolution test was carried out according to Method 2 (paddle method, Dissolution Test, 13JP). Either 900 ml JP first fluid or JP second fluid was warmed at 37 ± 0.5°C.

A 2 mm section of floating dosage form containing 20 mg NH was placed in a sinker and the paddle rotated at 100 r.p.m. A 5-ml aliquot of the dissolved solution was collected at scheduled times then filtrated through a membrane filter with a pore size of 0.22 μm (MILEX-GS; Japan Millipore Ltd.). The amount of NH was determined by high-performance liquid chromatography (SLC-10A; UV detector, SPD-10A; Shimadzu Corp.).

The operating conditions were as follows: column, Cosmosil (4.6 mm × 150 mm); mobile phase, a mixture of 0.05 M potassium dihydrogen phosphate and acetonitrile (60:40, v/v); flow rate, 1.0 ml/min; column temperature, 40°C; and wavelength, 237 nm.

Since NH is unstable in normal light, the dissolution test was conducted under light provided by a pure yellow fluorescence lamp (National Colored Rapid Start, FLR40S•Y-F/M, 40 W).

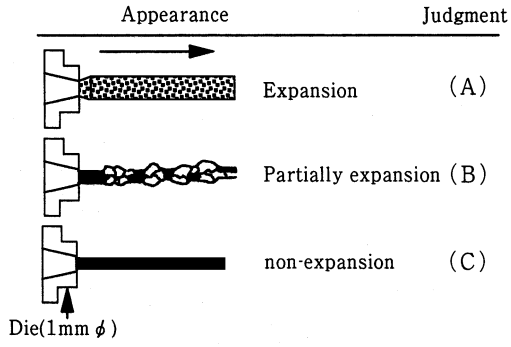

Fig. 1. Appearance of puffed NH–HPMCAS prepared with the twin-screw extruder.

3. Results and discussion

3.1. Appearance of the floating dosage forms

The appearance of the puffed dosage form in the vicinity of the die outlet was classified as one of three types (A, B and C) as shown in Fig. 1. The samples prepared from only HPMCAS (Rp. 1) and from two components of HPMCAS and NH (Rp. 2 and 3) were classified as B-type appearance (partial expansion), and the shape of the puff was not uniform. The samples that had CP, dried aluminum hydroxide gel and talc added to a mixture of NH and HPMCAS (Rp. 4, 5 and 6) were classified as A type. These samples had an outer diameter of 1.4–1.5 mm and relatively uniform pores. The samples to which light anhydrous silicic acid and hydrated silicon dioxide (Rp. 7 and 8) were added were classified as B type. The sample prepared by adding magnesium stearate (Rp. 9) were classified as C type. The scanning electron microphotographs of these types are shown in Fig. 2. The A type was associated with relatively uniform pores, while the B type had the network structure of HPMCAS and could be made into a film in the expanded part. The C-type forms had no pores and took the form of a hard fused mixture.

Since CP is generally used for pharmaceutical products, we selected it as the excipient to prepare the buoyant dosage forms in the present study.

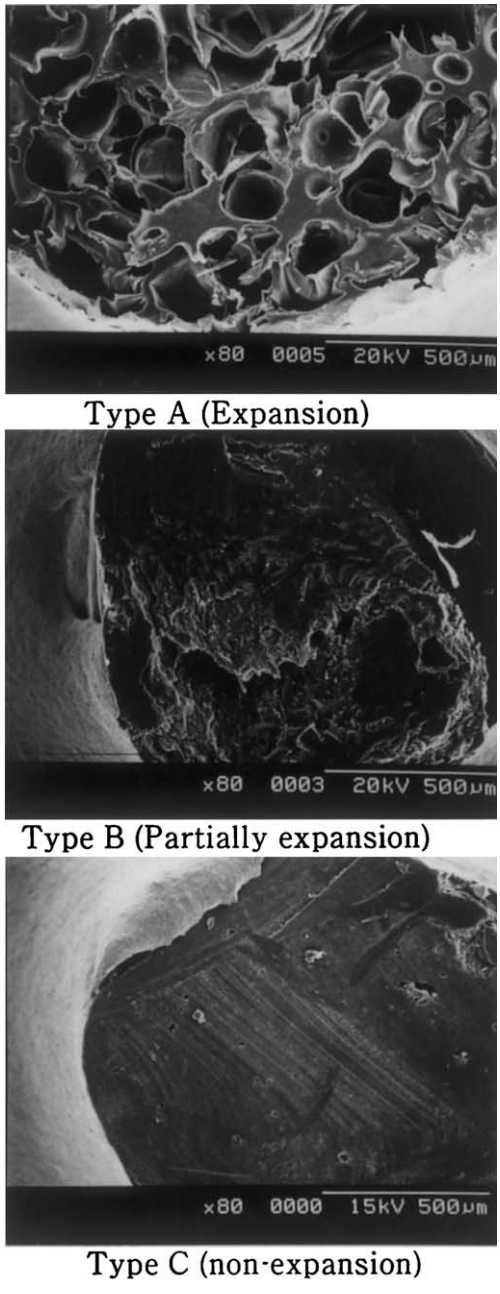

Fig. 2. Scanning electron microphotographs of puffed NH–HPMCAS.

3.2. Measurement of the porosity, pore size distribution and average pore diameter of the floating dosage forms

The effect of CP on the porosity of the floating dosage forms is presented in Table 4. The porosity of the floating dosage forms increased directly in proportion to the amount of added CP.

The changes in the pore size distribution of the floating dosage forms are shown in Fig. 3. In the sample without CP, the pores with a diameter less than 1 μm occupied about 70% of the all pores and the average pore diameter was 0.02 μm. The pore distribution of 10–50 μm was increased by the addition of CP. When the CP content was 4, 8 and 12%, the corresponding pore distribution was 40, 50 and 78%, respectively, while the average pore diameters were 13.2, 11.0 and 19.5 μm, respectively.

The phenomenon of expansion is due to the increased volume induced by the rapid fall from a high pressure to the normal pressure (Yano, 1991). The twin-screw extruder provides both heat and pressure to the materials simultaneously. The release of pressure takes place exclusively at the die outlet. The materials supplied continuously to the extruder from the hopper are softened and melted by heat from the barrel until the die outlet is reached. At the same time, the materials are compressed by the conveying screw and the mixing paddle. The pressure at the fifth barrel, located just before the die, was found to be about 100–150 kg/cm^2 in the present study. By extruding the materials through the 1 mm ∅ die into a region of normal pressure, we obtained a floating dosage form consisting mainly of NH–HPMCAS. Kurokawa (1987) reported that puffed corn starch was too hard and its texture was unsuitable because of large and non-uniform air bubbles when only corn starch was used. However, the addition of a small amount (0.5–5%) of pulverized eggshell (Calhope) to this formulation resulted in the production of uniform bubbles, giving a soft texture. They described how pulverized eggshell served as boiling stones when the materials were extruded under high temperature and from a high-pressure region into one of normal pressure (Kurokawa, 1987).

The addition of CP to NH–HPMCAS improved the uniformity of the average pore diameter and

Table 4
Effect of CP on porosity and average pore diameter

	Rp. 2	Rp. 10	Rp. 11	Rp. 12
CP (%)	0	4	8	12
Porosity (%)	5	19	61	72
Average pore diameter (μm)	0.02	13.2	11.0	19.5

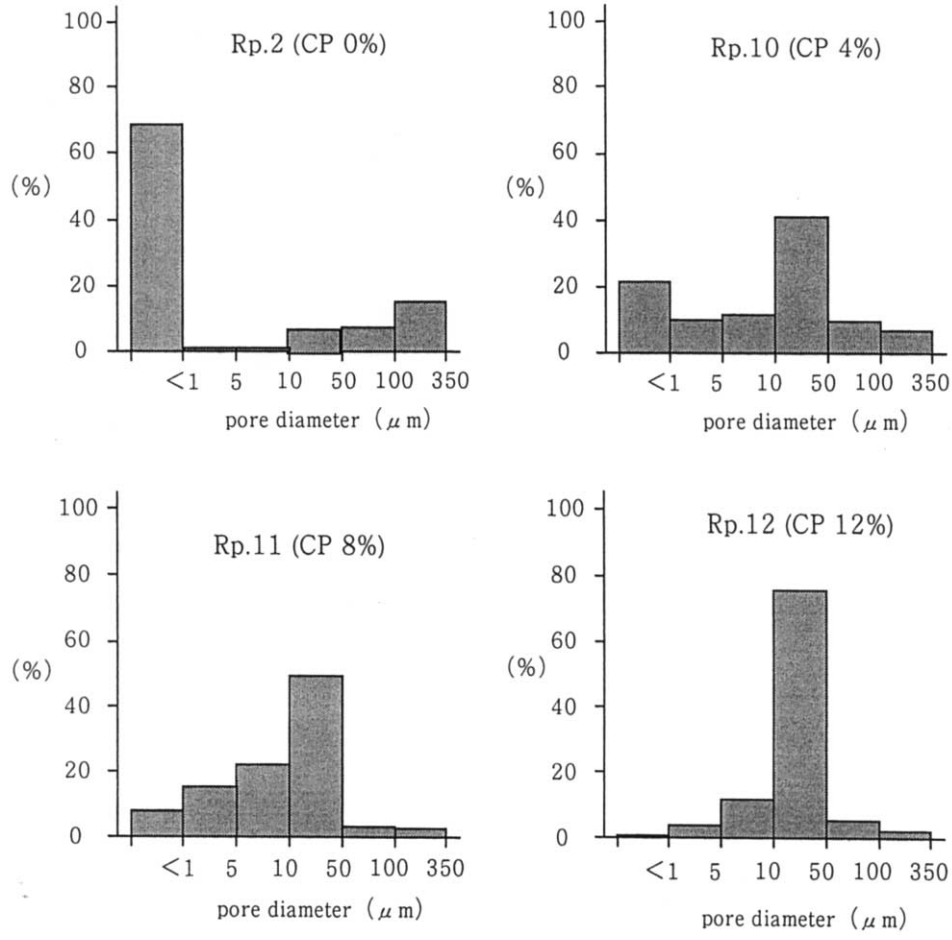

Fig. 3. Effect of CP content on pore size distribution.

increased the porosity in direct proportion to the amount of added CP. Although the detailed mechanism is still unknown, CP and other porous agents may assist expansion, i.e. they could act as boiling stones like the micronized eggshell powder.

Thus, it has been shown that CP is a useful agent to assist expansion when preparing floating NH–HPMCAS using the twin-screw extruder, and the porosity and pore diameter can be controlled by the amount of CP.

3.3. Buoyancy of the floating dosage forms

The buoyancy of the floating dosage forms is shown in Fig. 4. Just before shaking (the external destructive power was zero), the buoyancy was proportional to the amount of CP added, i.e. it was about 10 dyne at 4% of CP, about 80 dyne at 8% of CP, and about 130 dyne at 12% of CP. Therefore, the initial buoyancy depends on the porosity.

The buoyancy decreased with time after imposing external destructive power. The CP 4% dosage form lost its buoyancy and precipitated at 1 h, although it maintained its original appearance.

Therefore, it was considered that the loss of buoyancy was caused by penetration of water into the pores of this product, leading to an increased specific gravity.

The CP 12% dosage form showed the highest initial buoyancy, but had disintegrated 2 h after shaking, and the buoyancy fell very rapidly thereafter. Since the porosity of this dosage form was high (72%, Table 4) and CP is soluble in JP first fluid, it appears that water infiltrates the sample more rapidly than other samples, leading to dissolution of the network structure. In contrast, the CP 8% dosage form remained floating for a period of at least 6 h.

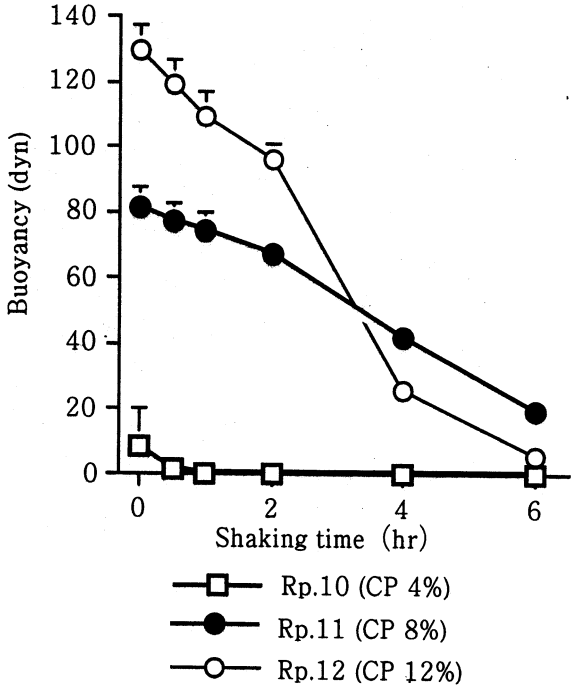

Fig. 4. Effect of CP content on buoyancy (mean ± S.D., $n = 3$). □, Rp. 10 (CP 4%); ●, Rp. 11 (CP 8%); ○, Rp. 12 (CP 12%).

It was shown that the floating dosage forms of NH–HPMCAS prepared using the twin-screw extruder have a high acid resistance and their buoyancy is controlled by the amount of CP.

3.4. Dissolution of NH from the floating dosage forms

The dissolution profiles of NH from the floating dosage forms using JP first fluid are shown in Fig. 5. The dissolution of the samples prepared with NH, HPMCAS and CP was less than 10%, even at 3 h, irrespective of the amount of CP. These low values were considered to be due to the acid resistance of HPMCAS.

WS can be easily expanded and converted to a water-soluble pregelatinized starch using the twin-screw extruder. Thus, WS was added to the formulation containing 8% CP (Rp. 11), which exhibited an excellent buoyancy as shown in Fig. 4. The amount of added WS was 10, 15 and 20% (Rp. 13, 14 and 15). The dissolution rates of NH from floating NH–HPMCAS increased directly in proportion to the amount of added WS. These WS-containing preparations exhibited a high floating ability as well as the WS-free preparation (Rp. 11), and their buoyancy values in JP first fluid were 50.3 ± 3.1 dyn (Rp.13), 47.5 ± 3.5 dyn (Rp.14) and 44.8 ± 3.0 dyn (Rp.15), respectively, 3 h after starting the test (mean ± S.D., $n = 3$). In this fluid, the drug release from the preparations should be sustained for 6 h during the flotation. Also, the preparations containing more than 20% WS would be meaningless as the sustained release dosage forms because the release becomes more rapid.

The results of the dissolution test using JP second fluid are shown in Fig. 6. The dissolution of NH from the floating dosage forms was rapid, and about 60–80% had dissolved 0.5 h after starting the test in the case of all samples. There-

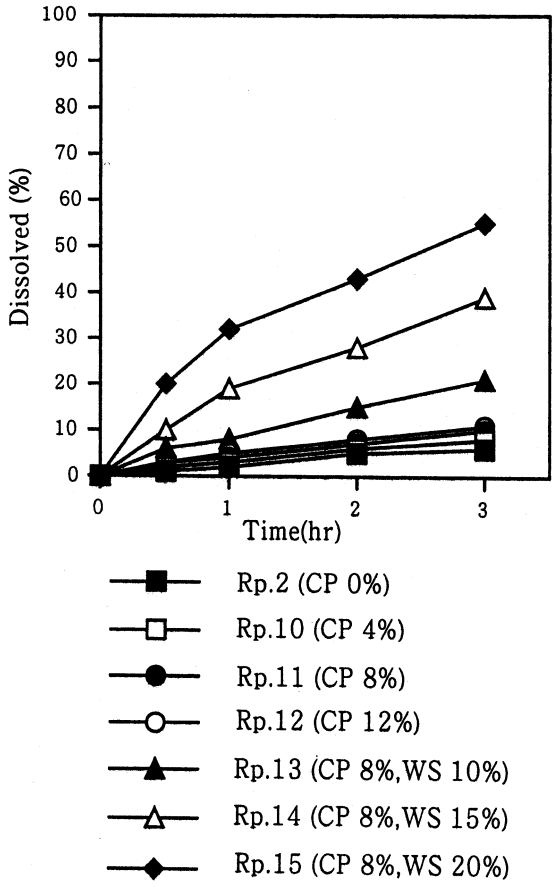

Fig. 5. Dissolution profiles of NH from puffed NH–HPMCAS in JP first fluid (pH 1.2) at 37°C. ■, Rp. 2 (CP 0%); □, Rp. 10 (CP 4%); ●, Rp. 11 (CP 8%); ○, Rp. 12 (CP 12%); ▲, Rp. 13 (CP 8%, WS 10%); △, Rp. 14 (CP 8%, WS 15%); ◆, Rp. 15 (CP 8%, WS 20%).

fore, processing using the twin-screw extruder does not change the enteric nature of HPMCAS.

These results show that the expansion after addition of WS controls the release of NH without any loss of buoyancy.

4. Conclusion

To obtain a gastric floating dosage form, we prepared floating dosage forms consisting mainly of enteric polymer (HPMCAS) using the puff ability of the twin-screw extruder and came to the following results.

1. It is easy to prepare floating dosage forms, consisting mainly of NH–HPMCAS, using the twin-screw extruder.
2. CP serves as the auxiliary substance in manufacturing floating dosage forms of NH–HPMCAS. The porosity and pore diameter of the floating dosage forms can be controlled by the amount of CP added.
3. The floating dosage forms consisting mainly of NH–HPMCAS remained buoyant in JP first fluid for a long period, and had excellent acid resistance and mechanical strength.
4. The degree of dissolution of NH from floating dosage forms can be controlled by the amount of wheat starch.
5. Processing using the twin-screw extruder does not change the nature of the enteric dissolution of the puffed HPMCAS.

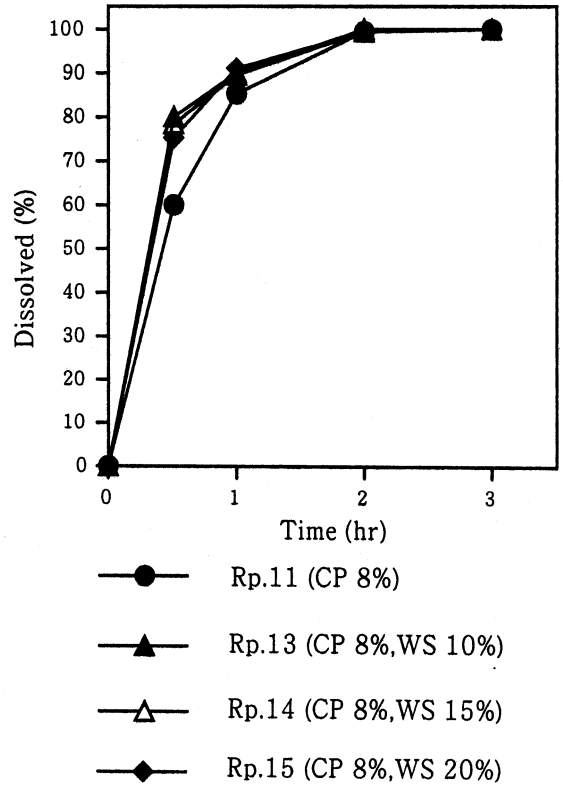

Fig. 6. Dissolution profiles of NH from puffed NH–HPMCAS in JP second fluid (pH 6.8) at 37°C. ●, Rp. 11 (CP 8%); ▲ Rp. 13 (CP 8%, WS 10%); △, Rp. 14 (CP 8%, WS 15%); ◆, Rp. 15 (CP 8%, WS 20%).

These results showed that the puffed dosage form of HPMCAS prepared using the twin-screw extruder is useful for achieving a long intragastric retention, and the puff ability of the twin-screw extruder is useful for manufacturing floating dosage forms.

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