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RESEARCH PAPER

Naproxen Particle Design Using Porous Starch

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ABSTRACT

Naproxen (Nap) was embedded in porous starch by preferential grinding, and we examined the physicochemical properties of these particles, including pore diameter, pore volume, and dissolution of naproxen. Porous starch (PS) particles made by preferential grinding with a Mechanofusion system had a higher content of naproxen than those made using the Mechanomill as determined using a mercury porosimeter. Neither sample showed any significant changes in crystallization state of naproxen in particles as determined by powder X-ray diffraction and differential scanning calorimetry (DSC). No interactions occurred between naproxen and porous starch due to preferential grinding as determined by powder X-ray diffraction and DSC. The dissolution rate of drug from particles prepared by preferential grinding was faster than that from physical mixtures.

KEY WORDS: *Dissolution rate; Naproxen; Porous starch.*

INTRODUCTION

Many porous materials are used as excipients of drug formation. Active carbon has been used in medicine for a long time (for example, for absorption of gas within the body and as an antidote for absorption of poison). Montmorillonite has been used for sustained drug release (1,2). Yonemachi et al. (3) reported that drug molecules adsorbed onto porous materials differ markedly from those in the crystalline state.

The interactions between drug molecules and porous materials have been investigated in a number of previous studies (4–10). Nakai et al. (6) and Liao and Jarowski (7) reported that some porous materials, such as controlled pore glass, improved the dissolution properties of drugs. Matsumoto et al. (10) reported that ethenzamide formed an amorphous mass on mixing with porous crystalline cellulose. Porous crystalline cellulose, characterized by a porous structure, is derived from microcrystalline cellulose through several physicochemical

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treatments. Although some porous materials, such as controlled pore glass (11) and porous crystalline cellulose, are known to improve the dissolution properties of drugs, there have been few reports of controlled dissolution of drugs using porous starch (12).

In this study, particle design was carried out using naproxen and porous starch. The resulting particles were evaluated by the dissolution test, and their physicochemical properties were examined. The crystalline state of naproxen in mixtures with porous starch was also investigated by means of powder X-ray diffractometry and differential scanning calorimetry (DSC). In addition, the dissolution phenomenon of naproxen as a model drug from porous starch particles was also examined.

EXPERIMENTAL

Materials

Naproxen JP23 and porous starch obtained from San-Ei Sucrochemical Company, Limited were used as the test drug and carrier, respectively. Porous starch was prepared by adding amylase to a starch suspension in water at pH 4–5 and a temperature of 40°C. Other materials and solvents were analytical reagent grade.

Preparation of Naproxen in Porous Starch

Mechanomill Embedding Experiment

Naproxen was crushed at 1000 rpm using a Mechanomill (Okada Seiko Co., Ltd., Tokyo, Japan) for 2 h to produce particles of several micrometers. This naproxen was mixed with porous starch at a ratio of 1 : 5 at 1000 rpm for 30 min using a Mechanomill, sprayed with acetone every 2 min, and dried at 40°C for 24 h as shown in Fig. 1a.

Mechanofusion System Embedding Experiments

Embedding was performed using the Mechanofusion system. Briefly, a 1 : 5 mixture of naproxen and 1200 ml of crushed porous starch was mixed for 10 min in this apparatus (Fig. 1b). The clearance of stator and scraper between the inner surface of the revolution vessel were adjusted to 2.0 mm and 1.0 mm, respectively.

Schematic diagrams of the Mechanomill and Mechanofusion systems used are shown in Fig. 2.

Preparation of Physical Mixture

The physical mixture was prepared by mixing the drug and carrier with a test tube mixer (Scientific Industries,

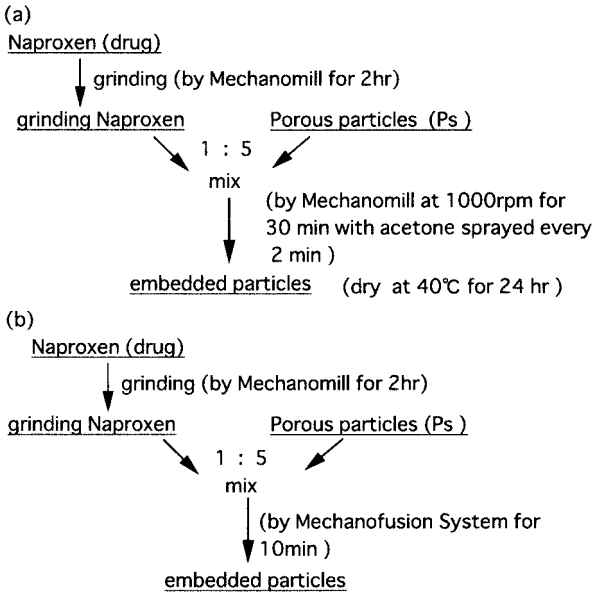

Figure 1. Preparation of embedded particles by Mechanomill and Mechanofusion system for Nap/Ps: (a) Mechanomill; (b) Mechanofusion system.

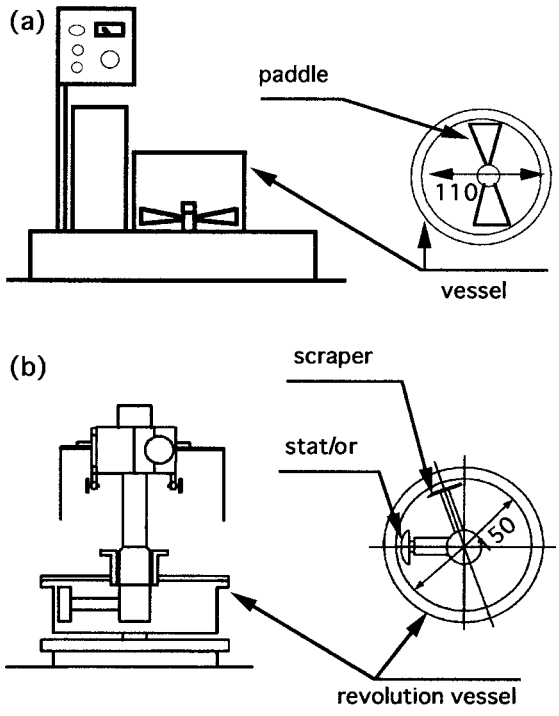

Figure 2. Schematic diagram of embedding: (a) schematic diagram of Mechanomill; (b) schematic diagram of Mechanofusion system.

Vortex-Genie 2, Tokyo, Japan) for 10 min at a constant amplitude and rate. These samples were passed through a 45-μm sieve and placed on a 30-μm sieve prior to use.

Confirmation of the Drug-Embedded Particle Formation by Scanning Electron Microscopy

The vapor deposition of gold was performed by ion sputtering (type JFC-110, JEOL Co., Ltd.), and embedding of the drug in the porous particles was confirmed using a scanning electron microscope (SEM) (JEOL type JSM-T-20).

Measurement of Pore Volume, Pore Diameter, and Quantity of Embedded Drug by Mercury Porosimetry

Pore volume and pore diameter were measured by mercury porosimetry (Poresizer 9305, Shimadzu, Kyoto, Japan). The quantity of the embedded drug was also determined using the same equipment.

The DSC was carried out with a type 3100 instrument (MAC Science Co., Ltd., Tokyo, Japan). The operating conditions in the open pan system were 10 mg sample weight, heating rate 10°C/min.

Powder X-Ray Diffraction Powder

X-ray diffraction analysis was performed with a Rigaku Geiger-Flex diffractometer (RAD-2VC) using nickel-filtered CuK_α radiation at 40 kV and 20-mA current. The scanning rate was 5°/min over a 2° range of 2°–60° with a sampling interval of 0.02°.

Table 1

High-Performance Liquid Chromatography Apparatus and Measurement Conditions

Integrator	C-R6A (Shimadzu)
Column	Cosmosil 5C18-AR (Nacalai Tesque Co., Ltd.)
Pump	LC-10AD (Shimadzu)
Detector	SPD-10A (Shimadzu)
Monitoring wavelength	272 nm
Mobile phase	Methanol:0.2% phosphoric acid = 7:3
Flow rate	1.0 ml/min

Release Studies

Release tests were performed according to the JP23 paddle method with the first fluid (pH 1.2) at 37°C ± 0.1°C, using sample powders that included 50 mg of naproxen. The rotation speed of the paddle was 100 rpm. The quantity of naproxen was assayed by HPLC at 272 nm under the conditions shown in Table 1.

RESULTS AND DISCUSSION

Confirmation of Embedding of Naproxen in Porous Starch Particles

An SEM photograph of the original particles of naproxen used as a model drug is shown in Fig. 3a. Mean particle size was about 50 μm, as determined using image analysis equipment (type Luzex-FS, Nireco Co., Ltd., Osaka, Japan). When naproxen was ground in the Mechanomill, the mean particle size was about 5–20 μm (Fig.

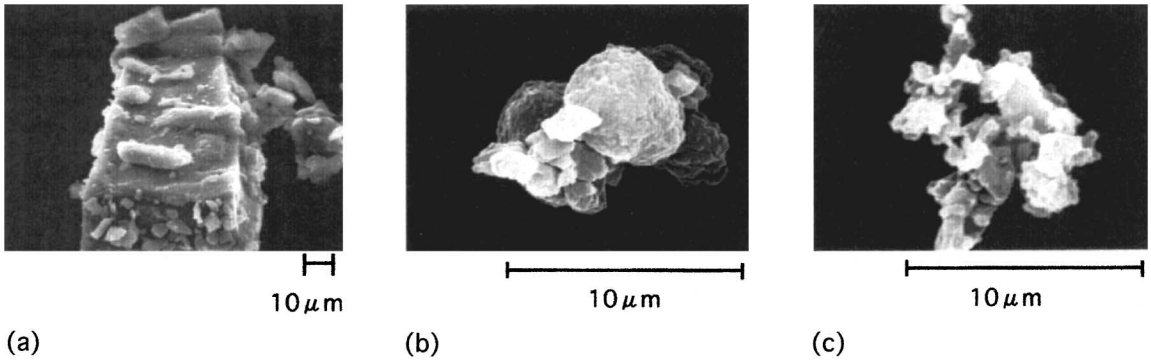

Figure 3. SEM photographs of naproxen particles: (a) original; (b) ground with a Mechanomill; (c) ground with the Mechanofusion system.

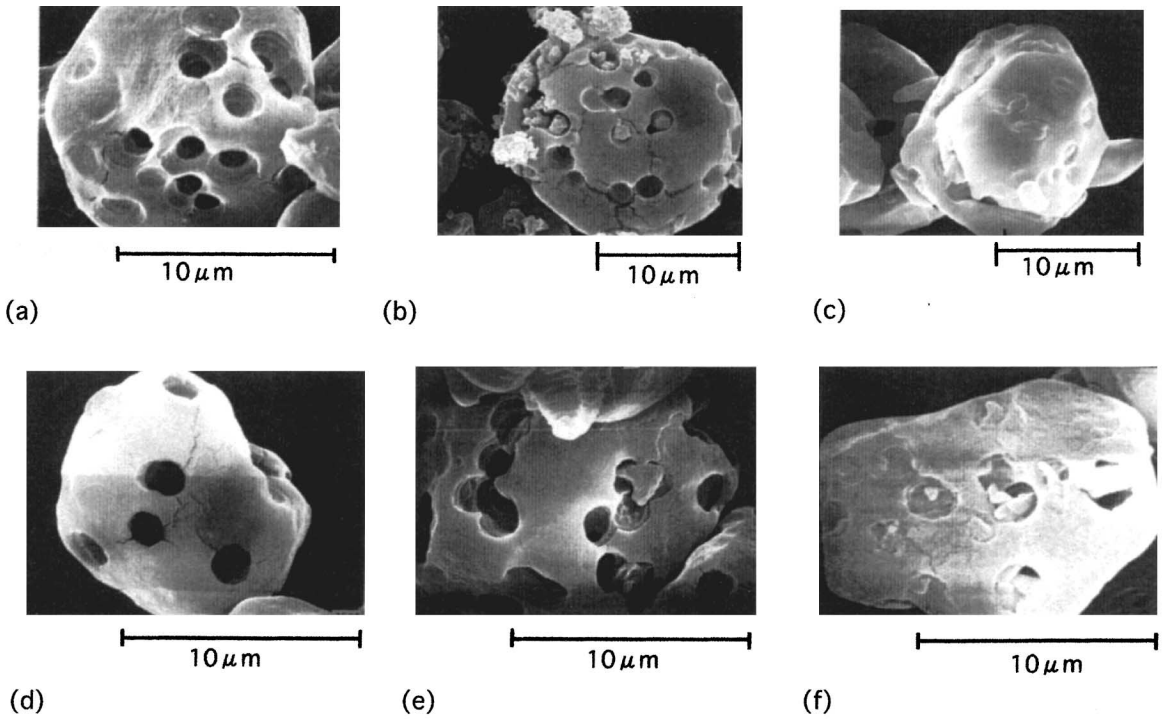

Figure 4. SEM photographs of porous starch and embedded particles: (a) original porous starch; (b) physical mixture (Nap/Ps = 1/5) Nap ground with a Mechanomill; (c) embedded particles (Nap/Ps = 1/5) ground with a Mechanomill; (d) porous starch ground with a Mechanofusion system; (e) physical mixture (Nap/Ps = 1/5) Ps and Nap ground with a Mechanofusion system; (f) embedded particles (Nap/Ps = 1/5) ground with a Mechanofusion system.

3b). On the other hand, as shown in Fig. 3c, about 40% of the particles were between 1.2 and 2.0 μm when grinding was performed using the Mechanofusion system. The agglomerated particles were dispersed in the water and carefully dried, then the particle size was measured with the image analyzer.

Figure 4a shows an SEM photograph of porous starch. Particle size of the porous starch was between 12 μm and 20 μm; the particles contained many pores. Figure 4b shows an SEM photograph of the physical mixture of naproxen and porous starch. Figure 4c shows an SEM photograph of samples of naproxen in porous starch prepared using the Mechanomill. Naproxen was shown to be embedded in the pores of the porous starch sprayed with acetone because the mean particle diameter of naproxen may be larger than the mean pore diameter of porous starch.

The results of the embedding experiment using the Mechanofusion system are shown in Figs. 4d to 4f. In these particles, it was clear that naproxen was embedded in the pores of the porous starch (Fig. 4f).

Pore Distribution of Porous Starch and Examination of Drug Quantity in the Pores by Mercury Porosimetry

Figures 5a and 5b show the pore diameter and volume and the embedding state of naproxen within the pores of particles produced using the Mechanomill. About 60% of the pores contained the drug (Fig. 5b). However, naproxen was also present in the interparticle space. Therefore, we tried to remove naproxen from the void by (1) dissolving naproxen using solvent in the void and (2) jet air sieving at 10–45 μm.

The results of the first method suggested that the pore volume of porous starch after washing was greater than that of unwashed porous starch. Thus, this method removed not only the naproxen between the particles, but also the naproxen in the pores (Fig. 6). The second method removed the naproxen between the particles, while that in the pores was retained (Fig. 7). This method was useful for removal of the drug in the interparticle space. Therefore, samples prepared by method 2 were used in the dissolution tests.

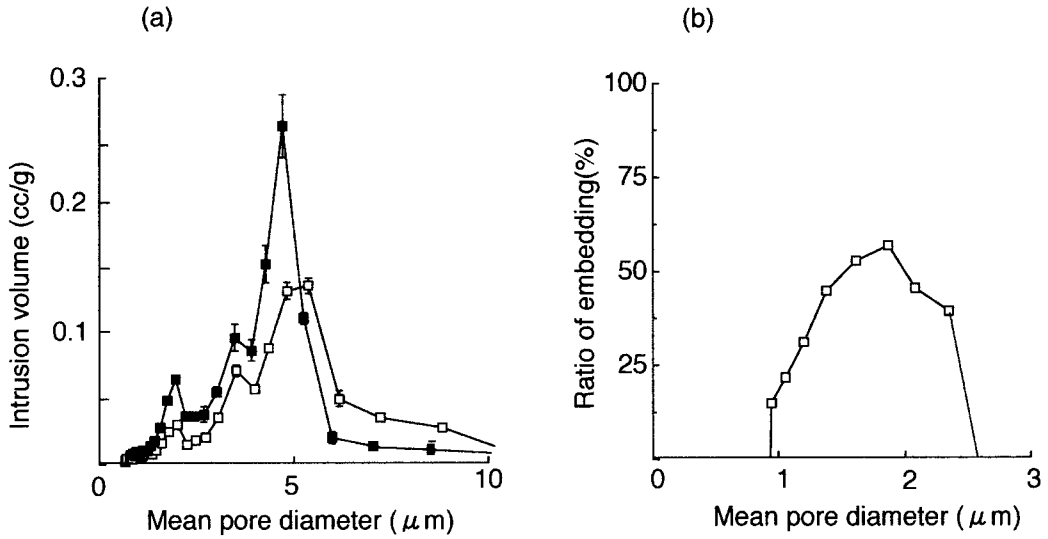

Figure 5. Relationship between mean pore diameter and intrusion volume, ■ original porous starch, □ embedded particles of Nap/Ps (= 1/5) prepared with a Mechanomill; (b) ratio of embedding to pore volume of porous starch.

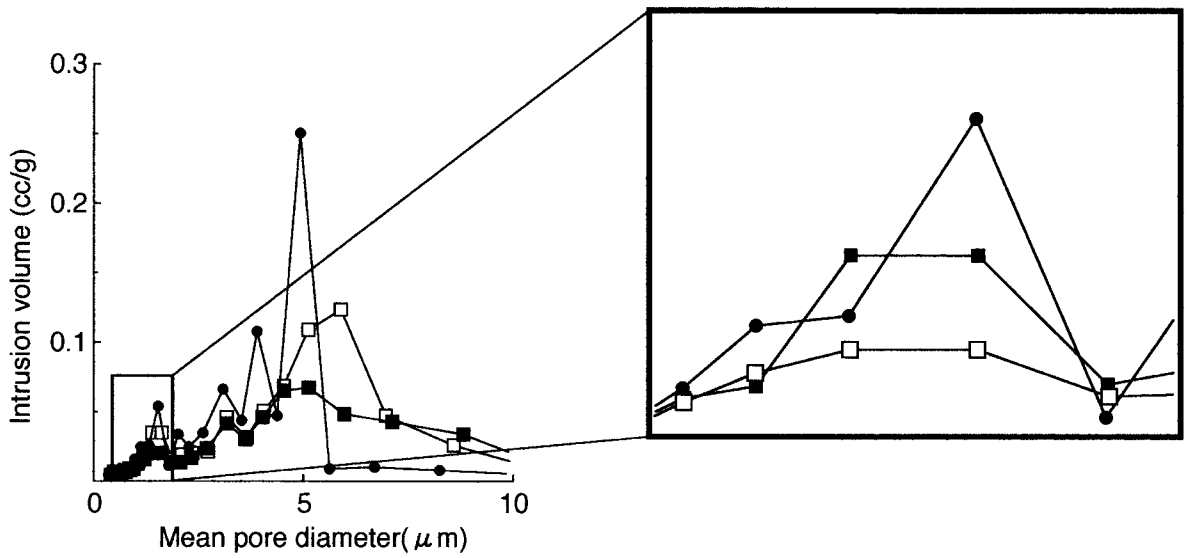

Figure 6. Relationship between mean pore diameter and intrusion volume: ● original porous starch, □ embedded particles of Nap/Ps (= 1/5) prepared with a Mechanomill, ■ embedded particles of Nap/Ps (= 1/5) prepared with a Mechanomill and washed with acetone.

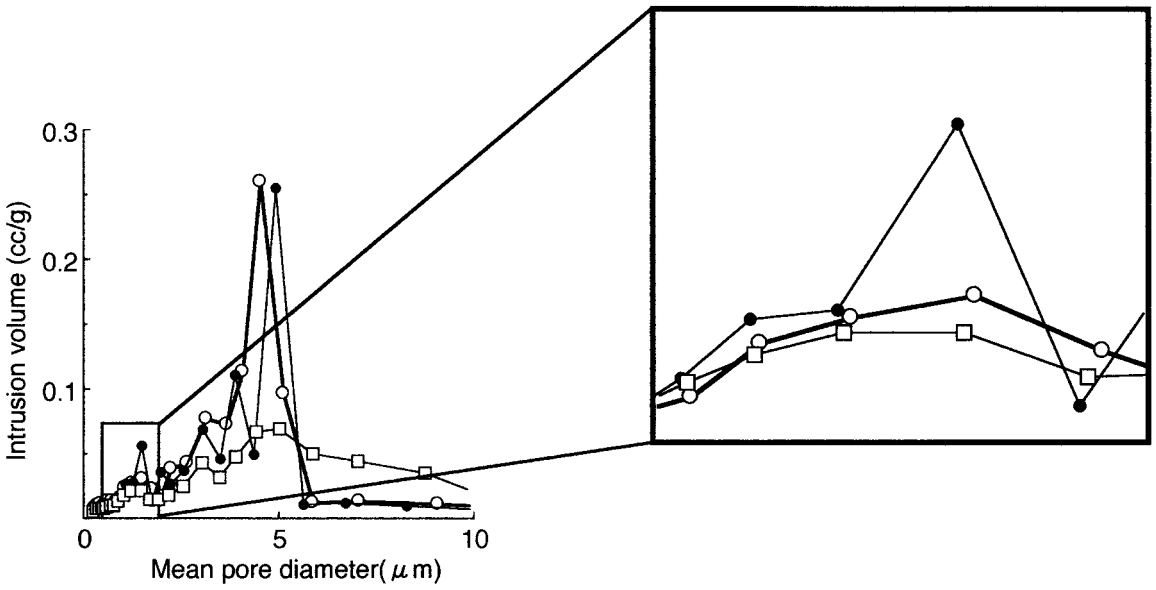

Figure 7. Relationship between mean pore diameter and intrusion volume: ● original porous starch, □ embedded particles of Nap/Ps (= 1/5) prepared with a Mechanomill, ○ embedded particles of Nap/Ps (= 1/5) prepared with a Mechanomill divided in a mortar.

The pore distribution of samples prepared using the Mechanofusion system is shown in Fig. 8. The drug was embedded in about 80% of the pore volume when the Mechanofusion system was used.

The differences in the embedding proportions between these two systems were also related to the differences in the particle size of naproxen. The drug is considered to be embedded in the pores by the action of frictional force and mechanical shock caused by mixing with the Mechanomill and gradual reduction in drug particle size due to spraying with acetone. However, porous starch scatters when mixed in the paddle of the Mechanomill since its particle size is small, and this results in a decrease in drug content since the frictional force and mechanical shock are weakened. On the other hand, in the Mechanofusion system, the particles are compressed by centrifugal force since the revolution vessel (shown in Fig. 2b) rotates at a high speed, and this increases the quantity of the embedded drug due to the compression and shear forces.

Confirmation of Crystallinity of Naproxen Embedded in the Porous Starch by Powder X-Ray Diffraction

The results of powder X-ray diffraction analysis of the naproxen/porous starch systems are shown in Fig. 9. The diffraction intensity of porous starch was small (Fig. 9a), suggesting that the crystallinity of porous starch was low. On the other hand, a sharp diffraction peak was observed for naproxen (Fig. 9b), indicating that the drug was highly crystalline. The diffraction peak indicated little change in the crystallinity in the samples prepared using the Mechanomill (Figs. 9c and 9d).

Samples prepared using the Mechanofusion system showed similar profiles on X-ray diffraction analysis (Figs. 9e and 9f). These observations indicated that the crystallinity of the drug did not change even when the drug was embedded in the pores of porous starch using the Mechanomill or Mechanofusion system.

Differential Scanning Calorimetry Confirmation of Crystallinity of Naproxen Embedded in the Porous Starch

Figure 10 shows the results of DSC analysis of physical mixtures and particles prepared using the Mechanomill and Mechanofusion systems. An endothermic peak by fusion of naproxen was observed at about 160°C. In the physical mixture and particles, the endothermic peaks (Figs. 10c–10f) were also observed at about 160°C. These results are in agreement with those of powder X-ray diffraction analysis.

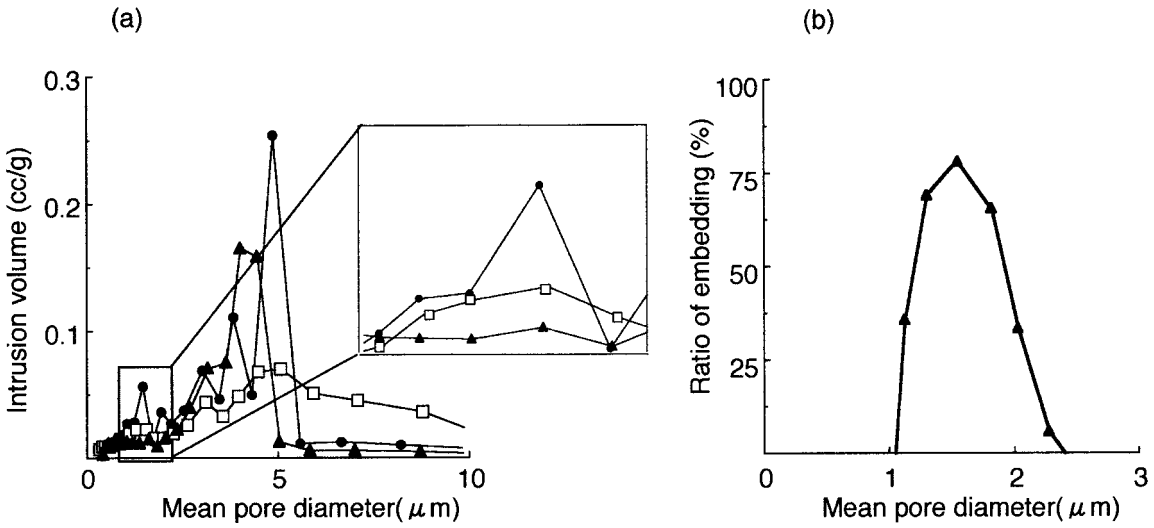

Figure 8. (a) Relationship between mean pore diameter and intrusion volume, ● original porous starch, □ embedded particles of Nap/Ps (= 1/5) prepared with a Mechanomill, ▲ embedded particles of Nap/Ps (= 1/5) prepared with a Mechanofusion system; (b) ratio of embedding to pore volume of porous starch.

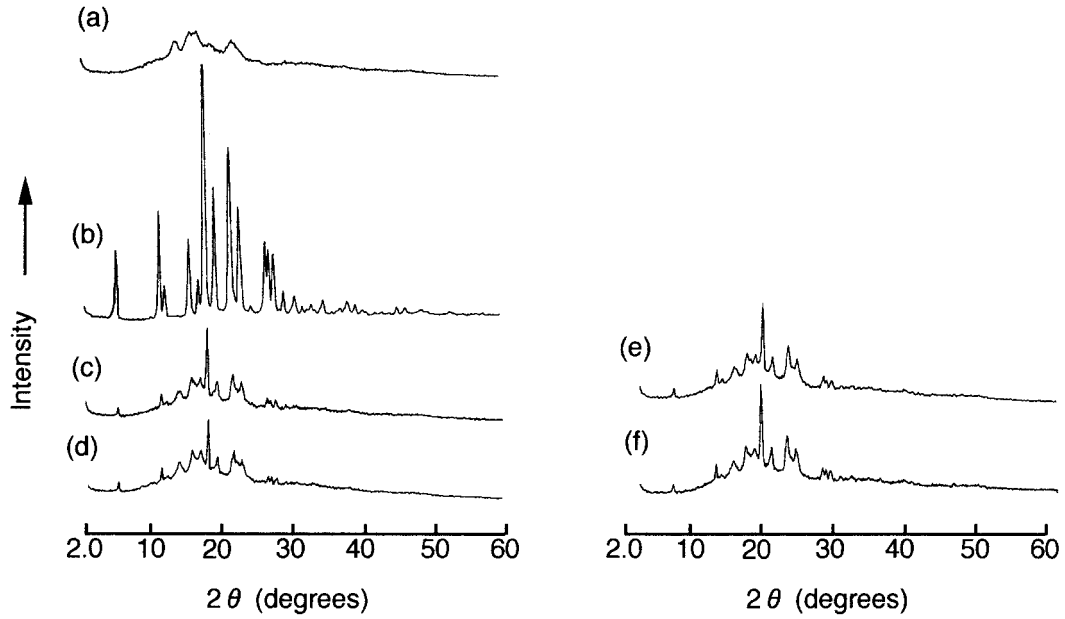

Figure 9. Powder X-ray diffraction pattern of Nap/Ps (= 1/5): (a) porous starch; (b) naproxen; (c) physical mixture ground with a Mechanomill; (d) embedded particles (preferentially ground with a Mechanomill); (e) physical mixture (naproxen and porous starch ground with a Mechanofusion system); (f) embedded particles (preferentially ground with a Mechanofusion system).

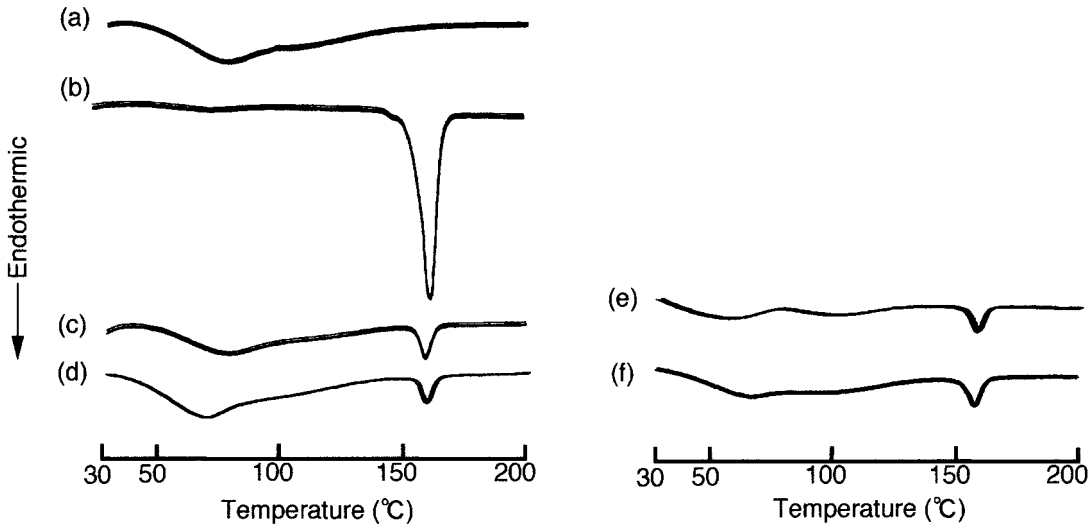

Figure 10. DSC thermograms for the Nap/Ps system: (a) porous starch; (b) naproxen; (c) physical mixture ground with a Mechanomill; (d) embedded particles prepared with a Mechanomill; (e) physical mixture prepared with a Mechanofusion system; (f) embedded particles prepared with a Mechanofusion system.

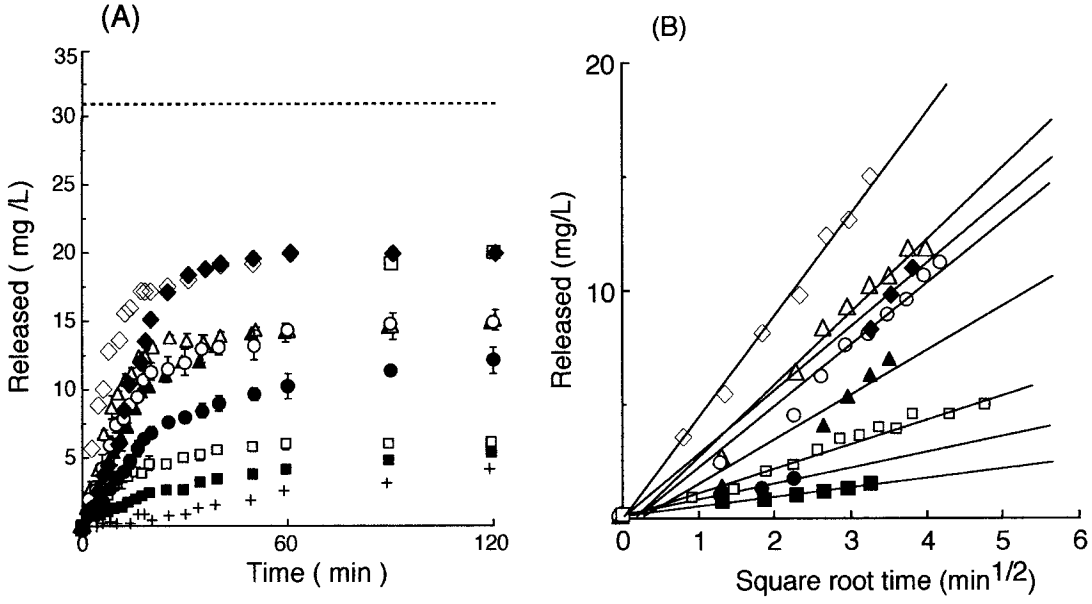

Figure 11. (a) Dissolution profiles and (b) square root time plots for dissolution for the Nap/Ps system with a Mechanomill. Physical mixture: ■, 0.1g; ●, 0.3g; ▲, 0.5g; ◆, 0.7g. Embedded particles: □, 0.1g; ○, 0.3g; △, 0.5g; ◇, 0.7g; + naproxen only. The dotted line shows the solubility of naproxen, and each point is the mean of three determinations.

The heats of fusion calculated from the above caloric measurements showed the same value of 12 J/g for physical mixtures and particles. These results indicate that naproxen was not amorphous. However, there were slight differences between particle samples, possibly due to the quantity of embedded drug because of the differences in pore number between the porous materials.

Dissolution of Naproxen Embedded in Porous Starch

The results of dissolution experiments of naproxen from porous starch particles prepared using the Mechanomill are shown in Fig. 11A. The dissolution rate of the drug from the particles was faster than that of the physical mixtures. Using these results, the results of plotting according to the Higuchi equation are shown in Fig. 11B:

$$Q = kt^{1/2} \quad (1)$$

where Q is the concentration of released drug, k is the apparent release rate constant, and t is the release time.

In the initial dissolution stage, a good straight line was obtained. The apparent release rate constants calculated from the slope of the straight line are listed in Table 2. For the first fluid used, the apparent release rate constant

Table 2

Apparent Release Rate Constant k *of Naproxen/Porous Starch System*

	k (mg per liter/min$^{1/2}$)	
Sample Amount (g)	Naproxen/Porous Starch PM	Naproxen/Porous Starch EP
Prepared using the Mechanomill		
0.1	0.41	1.08
0.3	0.23	0.90
0.5	0.45	0.64
0.7	0.40	0.64
Prepared using the Mechanofusion system		
0.1	1.10	1.46
0.3	1.01	1.45

EP, embedded particles; PM, physical mixture.

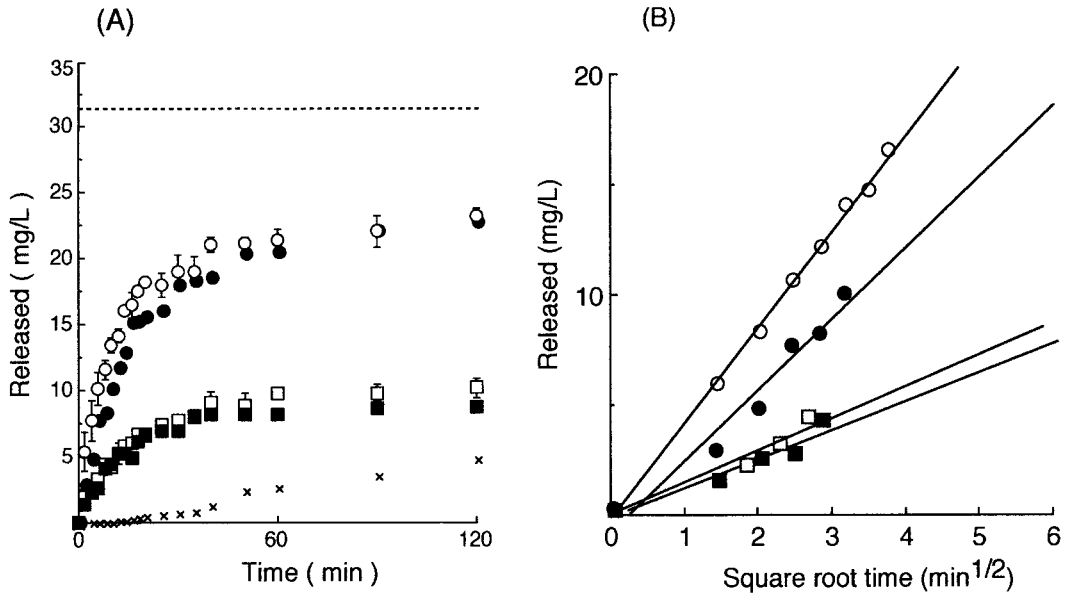

Figure 12. (a) Dissolution profiles and (b) square root time plots for dissolution for the Nap/Ps system with a Mechanofusion System. Physical mixture: ■, 0.1g; ●, 0.3g. Embedded particles: □, 0.1g; ○, 0.3 g; + naproxen only. The dotted line shows solubility of naproxen, and each point is the mean of three determinations.

of embedded particles with sample weight of 3.0 g was about 2.5-fold higher than that of the physical mixture.

The dissolution of the drug from particles formed using the Mechanofusion system is shown in Fig. 12A. Good linearity was obtained in the initial stage (Fig. 12B). The values of gradient k of these straight lines are shown in Table 2. The value of the apparent dissolution rate constant k of the drug-embedded particles was higher than that of the physical mixture, indicating that the dissolution was good. Comparison of the results of the Mechanofusion system and Mechanomill indicated that the dissolution rate was faster for the former. This is because the Mechanofusion system decreased the particle size of naproxen compared to the Mechanomill.

CONCLUSIONS

1. Porous starch was shown to be useful for preparation of drug-embedded particles. However, for efficient drug embedding, it was necessary for the porous material to contain abundant large pores.
2. We confirmed that no interaction occurred between drug and porous particles produced by the present method.
3. Embedding of the drug using the Mechanofusion system was more effective than using the Mechanomill.
4. The dissolution rate of drug with low water solubility was improved using hydrophilic porous particles.

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