Physicochemical Characterization and Drug Release Studies of Naproxen Solid Dispersions Using Lactose as a Carrier[1)]

Noriyuki HIRASAWA, Kazumi DANJO,* Mitsumasa HARUNA, and Akinobu OTSUKA

Faculty of Pharmacy, Meijo University, 150 Yagotoyama Tempaku-ku, Nagoya 468–8503, Japan.
Received December 8, 1997; accepted February 23, 1998

Naproxen solid dispersions were prepared by melting and rapid cooling with liquid nitrogen using lactose as a carrier. The physical characterisitics of these solid dispersions were investigated by powder X-ray diffraction, differential scanning calorimetry and dissolution rate analyses. The degree of crystallinity of naproxen in solid dispersions decreased with decreases in the molar ratio of naproxen to lactose. Fourier-transform infrared (FT-IR) analysis demonstrated the presence of intermolecular hydrogen bonds between naproxen and lactose in solid dispersions. Dissolution studies indicated that the dissolution rate was markedly increased in solid dispersions compared with physical mixtures and pure drugs. These results indicated that lactose is useful as a carrier for production of solid dispersions.

Key words naproxen; lactose; solid dispersion; dissolution; hydrogen bonding

Poorly water-soluble drugs often show low absorption and weak bioavailability, and their uses are limited by their dissolution rates. Therefore, improvements in dissolution rate and/or solubility are important for development of drugs. The solid dispersion method for improving the dissolution rate of poorly water-soluble drugs was first proposed by Sekiguchi and Obi,[2)] and the technique has been widely used to prepare both fast release and sustained release drugs by melting (fusion), solvent or melting-solvent methods.[3)] It is occasionally difficult to apply these methods, however, thermal instability of the drug during melting is often a significant problem, as is selecting the solvent and residual solvent for use in the solvent method.[4,5)] Several water-soluble polymer carrier systems, for example, PEG, PVP and HPC,[6–10)] have been used for fast release preparations. The mechanisms of interaction between drug and carrier in solid dispersions have been studied.[11–13)] However, there have been few studies of solid dispersions using low molecular weight substances as carriers.[14–16)]

In this study, naproxen was used as a model poorly water-soluble drug, and lactose, which has low molecular weight, was used as the carrier. Naproxen–lactose solid dispersion was prepared by the melting method to improve dissolution of naproxen. Fourier-transform infrared (FT-IR) was used to examine the interaction between drug and carrier in the solid dispersion.

Experimental

Materials Naproxen JPXIII and lactose obtained from De Melkindustrie Veghel bv (DMV, Pharmatose, 80M) were used as the test drug and carrier, respectively. Other materials and solvents were of analytical reagent grade.

Preparation of Solid Dispersion Solid dispersions of naproxen/lactose were prepared by the melting method. Mixtures of drug and carrier in molar ratios of 1/1, 1/5, and 1/10 were heated at 220 °C (melting point of lactose), with constant stirring with a spatula, until a homogeneous melt was obtained, and this melt was dropped into liquid nitrogen for solidification (rapid quench cooling method). The solid samples were ground with an agate mortar and pestle, passed through a 212 μm sieve and placed on a 106 μm sieve prior to use.

Preparation of Physical Mixture The physical mixture was prepared by mixing the drug and carrier with a test tube mixer (Scientific Industries, Vortex-Genie 2) for 5 min at constant amplitude and rate. These samples were passed through a 212 μm sieve and placed on a 106 μm sieve prior to use.

Powder X-Ray Diffraction Powder X-ray diffraction analysis was performed with a Rigaku Geiger–Flex diffractometer (RAD-2VC) using Ni-filter, Cu$K\alpha$ radiation, a voltage of 40 kV, and a current of 20 mA. The scanning rate was 5°/min over a 2θ range of 2—60° and with a sampling interval of 0.02°.

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

Infrared Spectra FT-IR spectra were obtained with a type FT-200 instrument (HORIBA) using transformation of 100 scans by the KBr disk method.

Dissolution Test Dissolution tests were performed according to the JPXIII paddle method, using sample powders (106—212 μm) including 50 mg of naproxen and 500 ml of dissolution medium JPXIII 1st fluid (pH 1.2) or 2nd fluid (pH 6.8) at 37±0.1 °C. The rotation speed of the paddle was 100 rpm. The quantity of naproxen was assayed by HPLC at 272 nm.

Results and Discussion

Degree of Crystallinity of Naproxen in Solid Dispersion

Powder X-ray diffraction patterns for lactose, naproxen, their physical mixtures and samples prepared by the melting method are shown in Fig. 1. Many sharp peaks were observed in the diffraction patterns of lactose and naproxen. The diffraction patterns of naproxen in all physical mixtures were similar to those of naproxen alone, indicating that crystallinity of the drug did not change in the physical mixtures. In the diffraction patterns of the melted and cooled samples, on the other hand, the characteristic diffraction peak for naproxen gradually decreased with increasing lactose content, and a change to a halo pattern was observed in the mixture at drug/carrier ratios of 1/5 or 1/10. This indicated that the crystallinity of naproxen decreased as it dispersed in lactose. Therefore, it is believed that the drug could be dispersed homogeneously in an amorphous state or dissolved in the carrier.[6)]

DSC thermograms for lactose, naproxen, their physical mixtures and samples prepared by the melting method are shown in Fig. 2. Lactose showed an endothermic peak at about 148 °C which may have been caused by the dissociation of water of crystallization from α-lactose

* To whom correspondence should be addressed.

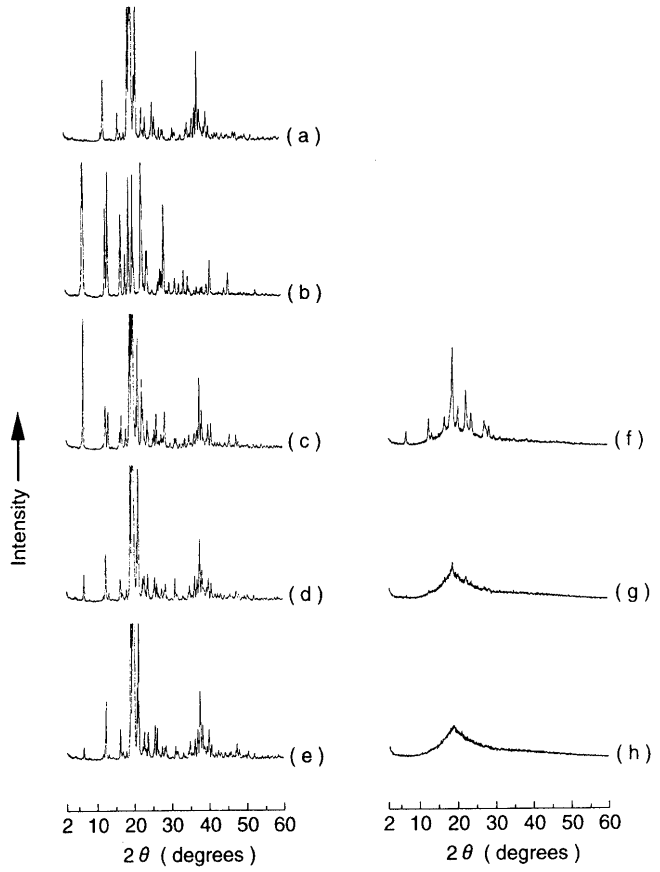

Fig. 1. Powder X-Ray Diffraction Patterns

(a), lactose; (b), naproxen; (c), naproxen/lactose = 1/1 physical mixture; (d), naproxen/lactose = 1/5 physical mixture; (e), naproxen/lactose = 1/10 physical mixture; (f), naproxen/lactose = 1/1 solid dispersion; (g), naproxen/lactose = 1/5 solid dispersion; (h), naproxen/lactose = 1/10 solid dispersion.

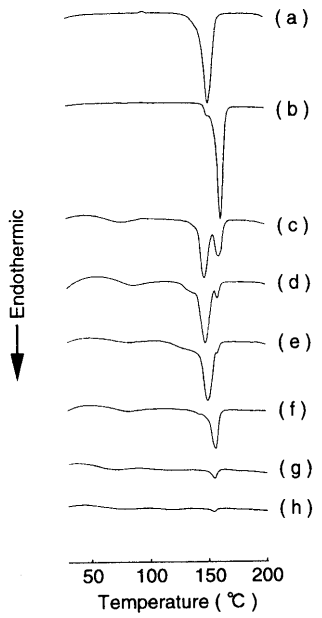

Fig. 2. DSC Thermograms

(a), lactose; (b), naproxen; (c), naproxen/lactose = 1/1 physical mixture; (d), naproxen/lactose = 1/5 physical mixture; (e), naproxen/lactose = 1/10 physical mixture; (f), naproxen/lactose = 1/1 solid dispersion; (g), naproxen/lactose = 1/5 solid dispersion; (h), naproxen/lactose = 1/10 solid dispersion.

monohydrate. Naproxen showed an endothermic peak at about 158 °C, corresponding to the melting of naproxen. The heat of fusion of naproxen (ΔH) was calculated,[17]

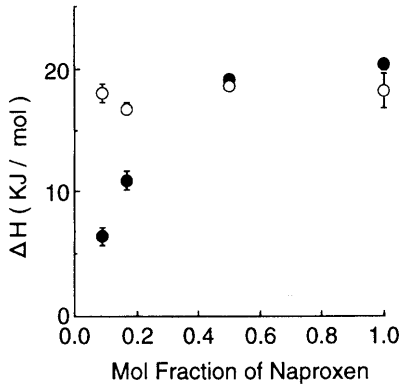

Fig. 3. Relationship between Heat of Fusion (ΔH) and Mol Fraction of Naproxen

○, physical mixture; ●, solid dispersion.

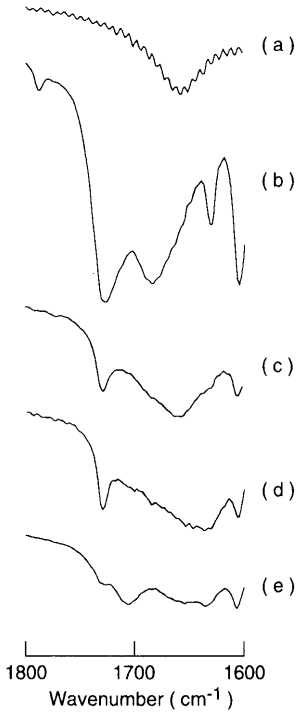

Fig. 4. FT-IR Spectra

(a), lactose; (b), naproxen; (c), naproxen/lactose = 1/10 Physical mixture; (d), naproxen/lactose = 1/5 solid dispersion; (e), naproxen/lactose = 1/10 solid dispersion.

and the relationship between heat of fusion (ΔH) and mol fraction of naproxen is shown in Fig. 3. For the physical mixtures, the ratio of naproxen to lactose did not affect ΔH value. For samples prepared by the melting method, however, the ΔH values decreased as the ratio of naproxen to lactose decreased.

These X-ray diffraction studies and DSC measurements suggested that although naproxen and lactose could not form solid dispersions by physical mixing, when the mixtures were melted and quenched solid dispersions could be obtained. The degree of crystallinity of naproxen in the solid dispersions was dependent on the molar ratio of naproxen to lactose.

Mechanism of Interaction between Drug and Carrier

FT-IR spectra for lactose, naproxen, physical mixture and solid dispersions are shown in Fig. 4. Naproxen showed carbonyl stretching vibration ($\nu_{C=O}$) bands at 1728 and

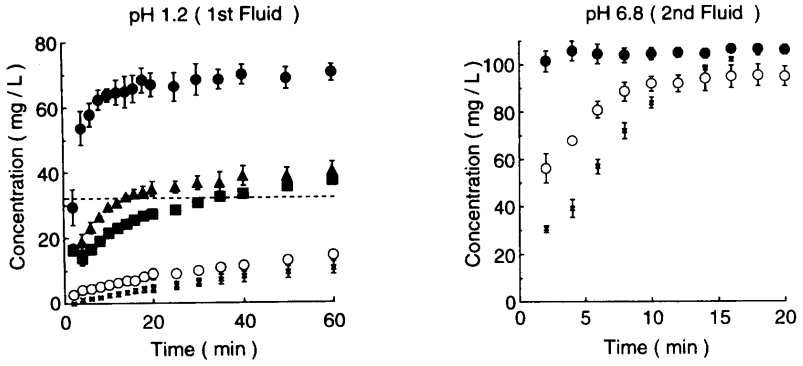

Fig. 5. Dissolution Profiles of Naproxen–Lactose System

×, naproxen; ○, naproxen/lactose = 1/10 physical mixture; ■, naproxen/lactose = 1/1 solid dispersion; ▲, naproxen/lactose = 1/5 solid dispersion; ●, naproxen/lactose = 1/10 solid dispersion. Each point represents the average and S.D. ($n = 3$). The dotted line shows solubility of naproxen.

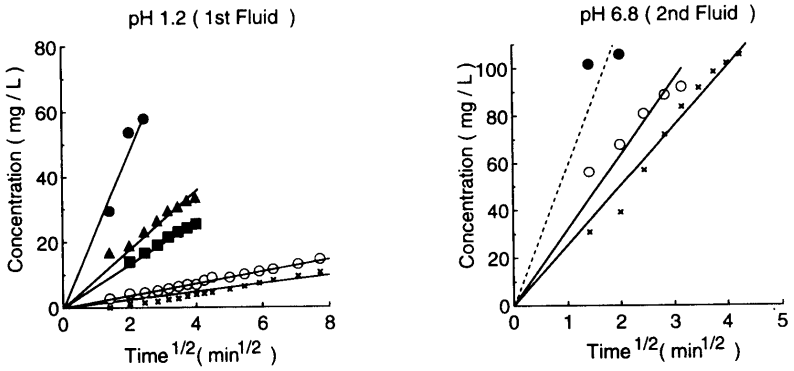

Fig. 6. Square Root Time Plots for Dissolution of Naproxen–Lactose System

×, naproxen; ○, naproxen/lactose = 1/10 physical mixture; ■, naproxen/lactose = 1/1 solid dispersion; ▲, naproxen/lactose = 1/5 solid dispersion; ●, naproxen/lactose = 1/10 solid dispersion. Each point represents the average ($n = 3$).

Table 1. Apparent Dissolution Rate Constants (mg/l·min$^{1/2}$)

	pH 1.2	pH 6.8
Nap	1.205	25.266
Nap : Lac = 1 : 10 PM	1.818	31.786
Nap : Lac = 1 : 1 SD	6.625	—
Nap : Lac = 1 : 5 SD	8.945	—
Nap : Lac = 1 : 10 SD	24.25	59.199

Table 2. Apparent Dissolution Rate Constants, K (mg/l$^{1/2}$)

	pH 1.2	pH 6.8
Nap	1.205	25.266
Nap/Lac = 1/10 PM	1.818	31.786
Nap/Lac = 1/1 SD	6.625	—
Nap/Lac = 1/5 SD	8.945	—
Nap/Lac = 1/10 SD	24.25	59.199

1680 cm^{-1}; the former was assigned to the free carboxyl group and the latter to the dimeric structure formed by hydrogen bonding of the carboxyl groups. Naproxen and lactose physical mixture also showed a carbonyl stretching band due to carboxylic C=O stretching at 1728 cm^{-1}, but the dimer carbonyl stretching vibration band at 1680 cm^{-1} changed to a broad strong band. This suggested that there was no interaction between naproxen and lactose in the physical mixture. Solid dispersions with a drug/carrier ratio of 1/5 showed a very broad band at 1680 cm^{-1} due to dimer carboxylic C=O stretching. However, for solid dispersions with a drug/carrier ratio of 1/10, the carbonyl stretching band due to carboxylic C=O stretching was very broad and shifted from 1728 to 1707 cm^{-1}, *i.e.*, to a lower wave number, indicating the presence of intermolecular hydrogen bonds between naproxen and lactose.[18]

Release Rate of Naproxen from Naproxen–Lactose Solid Dispersions The dissolution profiles of naproxen, physical mixture and solid dispersions are shown in Fig. 5. Naproxen underwent dissolution from solid dispersions at pH 1.2; not only fast dissolution in the initial stage but supersaturation was observed. We considered that the reason why the supersaturation state was maintained for a long period was because lactose acted as a dissolution aid and inhibited recrystallization of the drug. Also, at pH 6.8 naproxen dissolution was faster from solid dispersion than from physical mixtures or the pure drug. Figure 6 shows the dissolution concentration of naproxen plotted against the square root of time. In the initial dissolution stage, a good straight line was obtained. In the case of naproxen/lactose = 1/10, however, dissolution of naproxen reached 100% in the early stage; this is shown by a dashed line. The dissolution rate constants calculated from the slope of the straight line are listed in Table 1. At pH 1.2, the apparent dissolution rate constant of solid dispersion with a drug/carrier ratio of 1/10 was about 20-fold higher than that of pure naproxen. The relationship

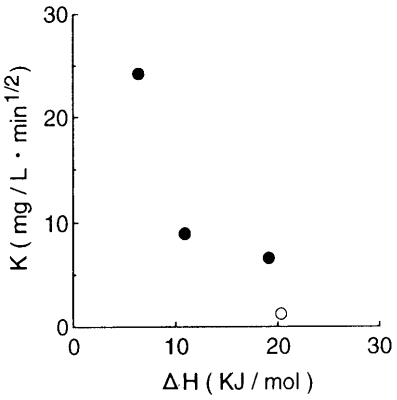

Fig. 7. Relationship between Heat of Fusion (ΔH) and Apparent Dissolution Rate Constant (K) for pH 1.2

○, naproxen; ●, solid dispersion.

between the apparent dissolution rate constant (K) and heat of fusion of naproxen (ΔH) is shown in Fig. 7. K became larger as the ΔH value decreased (*i.e.*, as crystallinity of naproxen decreased).

This was due to formation of the high energy amorphous form. Yuasa *et al.*[19] suggested that release rate of drug (Flurbiprofen) was nearly proportional to the ratio of hydrogen bonding with carrier (HPC). In the solid dispersions of naproxen/lactose ratio of 1/5 and 1/10, which had low crystallinity of naproxen, the strongest intermolecular hydrogen bonding between the naproxen and lactose could be assumed and hence the largest dissolution rate was obtained.

Conclusion

Naproxen formed solid dispersions with lactose when drug and carrier were melted completely and then solidified by the rapid quenching cooling method. The degree of crystallinity of naproxen in solid dispersions, however, differed greatly with the ratio of these components in the mixture. Intermolecular hydrogen bonds between drug and carrier in the solid dispersion were analyzed by FT-IR spectroscopy. The dissolution of naproxen, which is poorly soluble in water, was markedly improved using solid dispersions with drug and carrier at a molar ratio of 1/10.

References and Notes

1) Part of this work was presented at the 117th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, March 1997, Abstracts of Papers, Vol. 4, p. 42.
2) Sekiguchi K., Obi N., *Chem. Pharm. Bull.*, **9**, 886—872 (1961).
3) Chiou W. L., Riegelman S., *J. Pharm. Sci.*, **60**, 1281—1302 (1971).
4) Bloch D. W., Speiser P. P., *Pharm. Acta Helv.*, **62**, 23—27 (1987).
5) Nakamichi K., *Pharm. Tech. Japan*, **11**, 737—742 (1995).
6) Law S. L., Lo W. Y., Lin F. M., Chaing C. H., *Int. J. Pharm.*, **84**, 161—166 (1992).
7) Mura P., Manderioli A., Bramanti G., Ceccarelli L., *Drug Develop. Ind. Pharm.*, **22**, 909—916 (1996).
8) Tantishaiyakul V., Kaewnopparat N., Ingkatawornwong S., *Int. J. Pharm.*, **143**, 59—66 (1996).
9) Yagi N., Terashima Y., Kenmotsu H., Sekikawa H., Takada M., *Chem. Pharm. Bull.*, **44**, 241—244 (1996).
10) Yuasa H., Takahashi H., Ozeki T., Kanaya Y., Ueno M., *Chem. Pharm. Bull.*, **41**, 397—399 (1993).
11) Sekizaki H., Danjo K., Eguchi H., Yonezawa Y., Sunada H., Otsuka A., *Chem. Pharm. Bull.*, **43**, 988—993 (1995).
12) El-Hinnawi M. A., Najib N. M., *Int. J. Pharm.*, **37**, 175—177 (1987).
13) Doherty C., York P., *J. Pharm. Sci.*, **76**, 731—737 (1987).
14) Allen L. V., Yanchick V. A., Maness D. D., *J. Pharm. Sci.*, **66**, 494—497 (1977).
15) Ghanem A., Meshali M., Ibraheem Y., *J. Pharm. Pharmacol.*, **32**, 675—677 (1980).
16) Danjo K., Nakata T., Otsuka A., *Chem. Pharm. Bull.*, **45**, 1840—1844 (1997); Ford J. L., *Pharm. Acta Helv.*, **61**, 69—88 (1986).
17) Ford J. L.., Timmis P., "Pharmaceutical Thermal Analysis", Ellis Horwood Limited, New York, p. 73, 1989.
18) Bettinetti G. P., Mura P., Liguori A., Bramanti G., *Il Farmaco Ed. Pr.*, **43**, 331—343 (1988) (in Italian).
19) Yuasa H., Ozeki T., Takahashi H.,Kanaya Y., Ueno M., *Chem. Pharm. Bull.*, **42**, 354—358 (1994).