[Chem. Pharm. Bull. 33(4)1615—1619(1985)]

Application of Solid Dispersions of Nifedipine with Enteric Coating Agent to Prepare a Sustained-Release Dosage Form[1)]

AKIHIKO HASEGAWA,* HIROSHI NAKAGAWA, and ISAO SUGIMOTO

Pharmaceuticals Research Center, Kanebo, Ltd., 1–5–90, Tomobuchi-cho, Miyakojima-ku, Osaka 534, Japan

(Received June 14, 1984)

Pre-formulation studies were carried out to develop a sustained-release dosage form of nifedipine with good bioavailability. Granules were prepared by spray-coating nifedipine-enteric coating agent solid dispersions on an inert core material. Typical enteric coating agents, hydroxypropylmethylcellulose phthalate and methacrylic acid–methacrylic acid methyl ester copolymer, were used as carriers of the solid dispersions. Dissolution of nifedipine from granules coated with solid dispersions was practically nil in JPX 1st fluid, but a supersaturation phenomenon was observed in JPX 2nd fluid. These granules resulted in prolonged absorption of the drug with good bioavailability in beagle dogs and human volunteers. This absorption characteristic arises from the pH dependency of the dissolution behavior of these solid dispersions. That is, dissolution of nifedipine was suppressed in acidic medium and showed supersaturation in comparatively neutral medium. It was confirmed that the granules were transported through the gastrointestinal tract and showed prolonged drug release behavior with good bioavailability.

Keywords——nifedipine; solid dispersion; enteric coating agent; formulation study; sustained-release dosage form

Nifedipine is a poorly water-soluble drug whose bioavailability is low when it is orally administered in crystalline form. Solid dispersions using water-soluble polymers, polyvinylpyrrolidone and hydroxypropylmethylcellulose, are useful dosage forms,[2)] since rapid absorption of nifedipine is attained with good bioavailability by the oral administration of these systems. That is, nifedipine is rapidly dissolved and shows a supersaturation phenomenon from these systems in water. However, prolonged absorption of nifedipine is necessary for the treatment of hypertension for the following two reasons: 1) nifedipine is eliminated rapidly from the plasma compartment[3)] and its antihypertensive effect lasts only for a few hours,[4)] 2) frequent drug administration may reduce patient compliance and the therapeutic efficacy.

An enteric dosage form is one of the ways available for sustaining drug absorption. The possibility of delaying absorption is dependent on the rate of transport of the dosage form through the gastrointestinal tract in the case of enteric dosage forms, and so the rate of gastric emptying is an important factor.[5)] Many investigations on the transport of enteric dosage forms through the gastrointestinal tract have been reported,[6)] and it was demonstrated that a multiple-unit type dosage form such as granules is superior to a single-unit type, because the granules would be successively transported through the gastrointestinal tract after oral administration and produce a delayed absorption pattern and a more reproducible absorption behavior as compared with a single-unit enteric dosage form.

We have reported[7a)] the solid dispersions or coprecipitate obtained from nifedipine and enteric coating agents (hydroxypropylmethylcellulose phthalate and methacrylic acid–methacrylic acid methyl ester copolymer) by a solvent method. Nifedipine in these solid dispersions was amorphous and was practically insoluble in JPX 1st fluid (pH 1.2). However, it dissolved rapidly in JPX 2nd fluid (pH 6.8) and showed a supersaturation phenomenon. These solid dispersions provided sustained absorption of nifedipine in beagle

dogs with good bioavailability after oral administration.[7b] Moreover, they were stable chemically and physically for 6 months under hot and humid conditions.[7b]

In this paper, we report pre-formulation studies of granules coated with solid dispersions, aimed at developing a sustained-release dosage form, and we describe the *in vitro* dissolution behavior and *in vivo* absorption properties.

Experimental

Materials——Nifedipine, mp 171—172 °C was prepared in our plant and pulverized to a fine powder. The particle size determined by an air permeability method was about 3 μm. Hydroxypropylmethylcellulose phthalate 200731 (HP-55, JPX grade, Shin-Etsu Chemical Ind., Co., Ltd.), methacrylic acid–methacrylic acid methyl ester copolymer (Eudragit L, Röhm Pharma GmbH, W. Germany), and hydroxypropylcellulose (HPC-L, Nippon Soda Co., Ltd.) were used as received. Sucrose (Non Pareil 103, Freund Ind., Co., Ltd.) was used as an inert core material. Rapidly soluble fine granules containing 10 mg of nifedipine[8] (Sepamit®, Kanebo, Ltd., Japan) and sustained-release tablets containing 20 mg of nifedipine (Adalat® retard, Bayer AG, Zürich) were obtained on the Japanese and European markets, respectively. Other chemicals were of reagent or JPX grade.

Methods——All experiments were carried out in a dark room in view of the high sensitivity of nifedipine to light.[9]

Preparation of Granules——Nifedipine (60 g) and polymer (180 g) were dissolved in 2200 ml of mixed solvent (ethanol : dichloromethane = 1 : 1) and the solution was spray-coated on the surface of 510 g of Non Pareil 103 using a CF-granulator (Model CF-360, Freund Ind., Co., Ltd.). That is, solid dispersions were formed on the surface of the sucrose core. The granules obtained were dried overnight at 40 °C. The nifedipine content of these granules was about 7%. CF-granulator is a newly developed powder-coating system utilizing a centrifugal-fluidizing drive.[10] Nifedipine powder-coated granules were also prepared as a control for dissolution and administration studies with the CF-granulator: 1500 g of Non Pareil 103 was coated with mixed powder of 300 g of nifedipine and 1170 g of corn starch using 400 ml of 7.5% aqueous solution of HPC-L as a binder.

Dissolution Study——A simple beaker-stirrer dissolution method reported in the previous paper[11] was employed. The test solution was filtered (Millipore, 0.22 μm pore size) and assayed by spectrophotometry (325 nm). All dissolution experiments were carried out in duplicate and the results were highly reproducible. Thus, only mean values are reported.

Absorption Behavior in Beagle Dog——Male beagle dogs (11—13 kg), which had been fasted for 24 h but allowed free access to water, were orally given test preparations equivalent to 10 mg of nifedipine with 80 ml of water. Plasma samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6 and 8 h after the administration. Doses were administered by the cross-over arrangement with an interval of one week. Plasma samples were assayed for nifedipine by means of a gas chromatograph equipped with an electron capture detector as previously reported by us.[12]

Absorption in Man——This study was conducted under medical supervision at Kanebo Health Insurance Center. Healthy male volunteers aged between 29 and 44 years (mean age: 33 years) participated in this study. Each subject gave his informed consent in writing. The mean weight of the subjects was 63.8 kg (range: 50—86 kg). A medical history and complete physical examination and laboratory screen (hematology, urinalysis and blood chemistry) were performed on each subject before drug administration. They were all in excellent health and were not taking any medication at the time of the study. At the beginning of the study, the subjects were randomly assigned to treatment groups. Each group received Sepamit®, Adalat® retard, or test preparation of HP-55 containing 10 mg of nifedipine at 9 a.m. after a 14 h fast, and meals were served at 12 a.m. on study days. During each treatment period, 4 ml aliquots of blood were collected at appropriate times after dosing. Plasma samples were assayed for nifedipine.[12]

Results and Discussion

Dissolution Behavior of Granules Coated with Solid Dispersions

The dissolution properties of nifedipine from granules in JPX 1st fluid and 2nd fluid are shown in Fig. 1.

In this case, test preparations containing 50 mg of nifedipine were dispersed in 500 ml of dissolution medium at 37 °C. The dissolution curve of nifedipine from the control granules containing the nifedipine powder rapidly reached the solubility of nifedipine in both JPX 1st and 2nd fluids, but did not show supersaturation. However, the dissolution rate of nifedipine from granules coated with solid dispersions was remarkably suppressed compared with that of control granules in JPX 1st fluid, and showed supersaturation in JPX 2nd fluid. HP-55

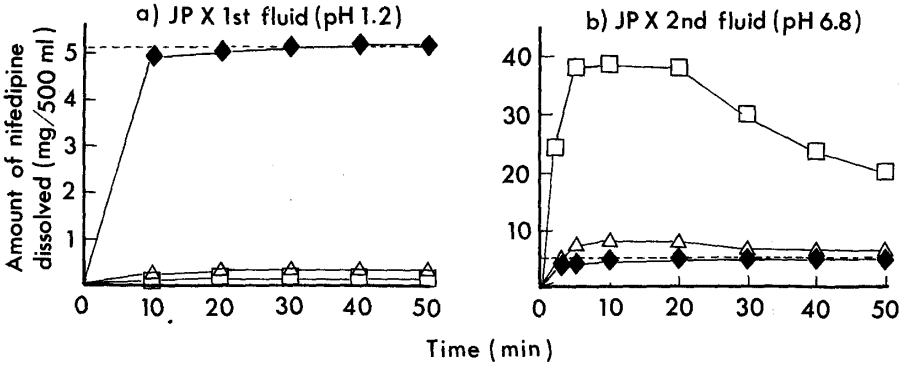

Fig. 1. Dissolution Behavior of Nifedipine from Granules Coated with Solid Dispersions in JP X 1st Fluid and 2nd Fluid

(◆), control granules (□), HP-55–nifedipine (3 : 1); (△), Eudragit L–nifedipine (3 : 1). The dotted line shows the solubility of nifedipine in JP X 1st or 2nd fluid.

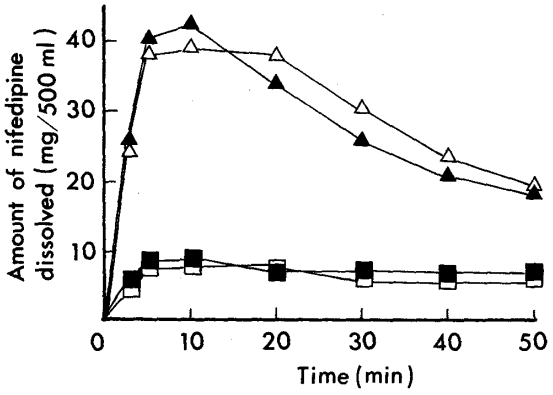

Fig. 2. Dissolution Behavior of Nifedipine from Granules Coated with Solid Dispersions in JP X 2nd Fluid after Pre-treatment with JP X 1st Fluid for 2 h

HP-55–nifedipine (3 : 1): (△), untreated; (▲), pre-treated with JP X 1st fluid. Eudragit L–nifedipine (3 : 1): (□), untreated; (■), pre-treated with JP X 1st fluid.

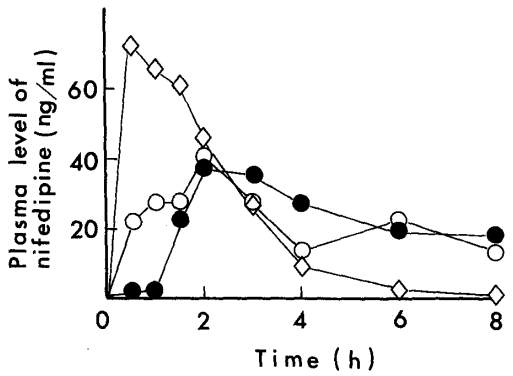

Fig. 3. Mean Plasma Nifedipine Levels of Beagle Dogs after Oral Administration of Granules Coated with Solid Dispersions

(◇), control granules; (○), granules coated with nifedipine–HP-55 (1 : 3) solid dispersions; (●), granules coated with nifedipine–Eudragit L (1 : 3) solid dispersions.

granules showed higher supersaturation than Eudragit L granules. These results are similar to those for solid dispersions previously reported.[7a)]

Figure 2 shows the dissolution behavior of nifedipine from the granules coated with solid dispersions in JP X 2nd fluid after pre-treatment with JP X 1st fluid. That is, the dissolution behavior of these granules in JP X 2nd fluid was studied following incubation of the granules in JP X 1st fluid for 2 h at 37 °C. If the dissolution behavior of granules in JP X 2nd fluid was influenced by the pre-treatment with JP X 1st fluid, these granules would not be a useful dosage form, since it is likely that these systems would stay in the stomach for a few hours after oral administration. In the case of both HP-55 and Eudragit L granules, the dissolution behavior in JP X 2nd fluid was not affected by the pre-treatment with JP X 1st fluid (Fig. 2). Therefore, these systems should be useful for providing sustained drug absorption because of their gastric resistance after oral administration.

Absorption Behavior in Beagle Dog

Mean plasma concentrations of nifedipine after oral administration of the test preparations containing 10 mg nifedipine to three dogs are shown in Fig. 3.

It was evident that the granules coated with nifedipine–HP-55 and nifedipine–Eudragit L

solid dispersions were both superior sustained absorption dosage forms compared to the control granules. $AUC_{(0-8\,h)}$ values of control granules, HP-55 granules and Eudragit L granules were 181.8, 176.3, 175.1 ng·h/ml, respectively. That is, the absorbed amount of nifedipine from these granules coated with solid dispersions was nearly the same as that of the control granules. Delayed absorption patterns were obtained, and higher plasma levels were maintained even at 8 h, though the control granules gave an undetectable plasma nifedipine level at 8 h.

Absorption in Man

As it was found that the granules coated with solid dispersions might be useful as a sustained-release dosage form with good bioavailability in the beagle dog study, an absorption study in man was performed. HP-55 was used as a carrier of the solid dispersions. Plasma nifedipine concentration data after administration of HP-55 granules were compared with those of rapidly soluble nifedipine fine granules[8] (Sepamit®) and sustained-release nifedipine tablet (Adalat® retard) (Fig. 4).

Although the content of nifedipine in HP-55 granules was 10 mg, the absorption behavior of nifedipine from HP-55 granules was similar to that from the sustained-release tablet containing 20 mg of nifedipine. The administration of HP-55 granules resulted in maintenance of a therapeutic plasma concentration for a longer period of time than after the same dose given as rapidly soluble fine granules (it was reported that the lowest therapeutically effective level of nifedipine might be in the range from 20 to 30 ng/ml).[13] Thus, granules coated with solid dispersions should produce a much more sustained antihypertensive action. Therefore, it appears that the administration of these granules containing 10 mg of nifedipine will be sufficiently effective if the granules are given twice daily in the treatment of hypertension.

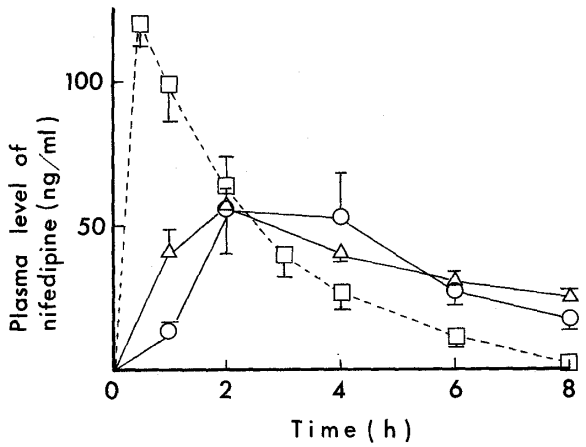

Fig. 4. Comparison of Mean Plasma Nifedipine Levels after Oral Administration of Granules Coated with Nifedipine–HP-55 Solid Dispersions (—○—), Fine Granules (—□—) and Sustained-Release Tablet (—△—)

TABLE I. Comparison of the Bioavailability Parameters

Sample	Nifedipine content (mg)	Number of subjects	T_{max} (h)	C_{max} (ng/ml)	$AUC_{(0-8\,h)}$ (ng·h/ml)
HP-55 granules[a]	10	3	2.7±1.2	74.9± 3.5	277.5± 43.9
Fine granules[b]	10	6	0.5±0.0	120.2±19.7	303.2±115.2
Sustained-release tablet[c]	20	8	2.0±0.9	61.4±15.0	300.7± 57.4

Each value represents the average±S.D. *a*) Granules coated with nifedipine and HP-55 solid dispersions. *b*) Sepamit®. *c*) Adalat® retard.

Table I shows the bioavailability parameters of each dosage form of nifedipine. This study did not follow a complete cross-over design because it was simply a pre-treatment study to develop the sustained-release dosage form. Thus, statistical analysis could not be performed. The $AUC_{(0-8\,h)}$ value of HP-55 granules containing 10 mg nifedipine was 92% of that of rapidly soluble fine granules and showed nearly the same value as a 20 mg sustained-release tablet presently on the market. Therefore, it was confirmed that these granules provide a useful prolonged absorption dosage form with remarkably good bioavailability. C_{max} of rapidly soluble fine granules was 120.2 ng/ml, while C_{max} of HP-55 granules was only 62% of this value. In the administration study of HP-55 granules, volunteers experienced mild side effects, such as headaches and facial flushing, as compared with those in the case of the rapidly soluble fine granules. This might be caused by the lower C_{max} of HP-55 granules.

Conclusion

The present results indicate that the spray-coating of a solid dispersion of a poorly-water soluble drug and an enteric coating agent onto an inert core material may provide an effective sustained-release dosage form with good bioavailability.

Acknowledgement The authors are grateful to Mr. A. Yamagata for his assistance in preparing the granules.

References and Notes

1) A part of this work was presented at the 104th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, March, 1984.
2) I. Sugimoto, A. Kuchiki, and H. Nakagawa, *Chem. Pharm. Bull.*, **29**, 1715 (1981); I. Sugimoto, K. Sasaki, A. Kuchiki, T. Ishihara, and H. Nakagawa, *ibid.*, **30**, 4479 (1982).
3) T. S. Foster, S. R. Hamann, V. R. Richards, P. J. Bryant, D. A. Graves, and R. G. McAllister, *J. Clin. Pharmacol.*, **23**, 161 (1983).
4) M. Thibonnier, F. Bonnet, and P. Corvol, *Eur. J. Clin. Pharmacol.*, **17**, 161 (1980).
5) C. Bogentoft, *Pharmacy International*, **3**, 366 (1982).
6) H. Maekawa, Y. Takagishi, and Y. Doi, *Yakuzaigaku*, **30**, 102 (1970); E. Hunter, J. T. Fell, and H. Sharma, *Drug Dev. Ind. Pharm.*, **8**, 751 (1982); T. Hovi, K. Josefsson, and O. V. Renkonen, *Eur. J. Clin. Pharmacol.*, **25**, 271 (1983); H. Ogata, *Seiyaku Kojo*, **3**, 477 (1983).
7) *a*) A. Hasegawa, H. Nakagawa, and I. Sugimoto, *Yakugaku Zasshi*, **104**, 485 (1984); *b*) A. Hasegawa, H. Nakagawa, and I. Sugimoto, *Chem. Pharm. Bull.*, **33**, 388 (1985).
8) I. Sugimoto, H. Nakagawa, A. Kuchiki, S. Kondo, K. Tohgo, K. Sasaki, K. Takahashi, A. Yamagata, and I. Utsumi, *Kiso to Rinsho*, **13**, 1643 (1979).
9) S. Ebel, H. Schutz, and A. Hornitscheck, *Arzneim.-Forsch.*, **28**, 2188 (1978); A. Kudo, J. Sakai, H. Kono, F. Sueshige, and K. Kamiyama, *Kiso to Rinsho*, **6**, 259 (1972).
10) Y. Funakoshi, M. Yamamoto, Y. Matsumura, and H. Komeda, *Powder Technology*, **27**, 13 (1980).
11) I. Sugimoto, A. Kuchiki, H. Nakagawa, K. Tohgo, S. Kondo, I. Iwane, and K. Takahashi, *Drug Dev. Ind. Pharm.*, **6**, 137 (1980).
12) S. Kondo, A. Kuchiki, K. Yamamoto, K. Akimoto, K. Takahashi, N. Awata, and I. Sugimoto, *Chem. Pharm. Bull.*, **28**, 1 (1980).
13) K. Aoki, K. Sato, Y. Kawaguchi, and M. Yamamoto, *Eur. J. Clin. Pharmacol.*, **23**, 197 (1982).