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Bioavailability and Stability of Nifedipine-Enteric Coating Agent Solid Dispersion¹⁾

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The absorption behavior and stability of nifedipine-enteric coating agent solid dispersions were studied using hydroxypropylmethylcellulosephthalate (HP-55) and methacrylic acid-methacrylic acid methyl ester copolymer (Eudragit L) as carriers. In the rat *in situ* absorption study, the dissolution behavior of HP-55 solid dispersion in the gastrointestinal tract was confirmed to be pH-dependent. After oral administration of these solid dispersions in beagle dog, area under the blood concentration curve (AUC) values were equivalent to that of polyvinylpyrrolidone solid dispersion, which showed remarkably improved dissolution behavior and bioavailability as compared with nifedipine alone. These systems were stable chemically and physically at 40 °C and 40 °C/80% R.H. during 6 months, and could be useful sustained absorption dosage forms with good bioavailability.

Keywords—nifedipine; solid dispersion; coprecipitate; stability; bioavailability; enteric coating agent

We have reported²⁾ a solid dispersion system or coprecipitate obtained from nifedipine and enteric coating agent (hydroxypropylmethylcellulosephthalate 200731 (HP-55), or methacrylic acid-methacrylic acid methyl ester copolymer (Eudragit L)) by a solvent method. Nifedipine in these solid dispersions was amorphous and was practically insoluble in JP X 1st fluid (pH 1.2). However, it dissolved rapidly in JP X 2nd fluid (pH 6.8) and showed a supersaturation phenomenon. These results suggested that these solid dispersion systems might be useful for bioavailability enhancement and development of a sustained-release preparation of nifedipine. In this report, the absorption behavior of nifedipine from these systems in rat or beagle dog was investigated. Further, the stability of these systems at 40 °C and 40 °C/80% R.H. was studied.

Experimental

All experimental methods except for the *in situ* absorption study were the same as those reported previously.^{2,3)} Solid dispersion systems were prepared by the solvent method. Nifedipine (3 g) and a polymer (9 g) were dissolved in about 90 ml of mixed solvent (ethanol: dichloromethane = 1:1) and then the solvent was evaporated off under reduced pressure. The residual solid was pulverized and the 32-80 mesh fraction was used in all experiments.

In Situ Absorption Study—Male Wistar rats weighing 180-210 g were fasted for one night prior to the experiment, but water was allowed freely. The rats were anesthetized with 20% urethan solution and the intestine was exposed by a mid-line abdominal incision. A sample containing 2.5 mg of nifedipine was packed into a capsule (Minicapsule, Japan Elanco Co., Ltd.) and administered.

a) Gastric Absorption of Nifedipine from Solid Dispersion: The pylorus was ligated and 2 ml of 0.1 N HCl was injected into the stomach. After these operations, a capsule was administered orally using a catheter.

b) Intestinal Absorption of Nifedipine from Solid Dispersion: A capsule was inserted into the intestine from 1 cm beyond the bile duct. After ligation of the intestine at the point of insertion, 1 ml of water was injected into the intestine.

In both experiments, 300 μ l aliquots of blood were collected at approximate times from the jugular vein. Nifedipine was assayed by using a gas chromatograph equipped with an electron-capture detector according to a reported procedure.⁴⁾ All experiments were carried out in triplicate.

Results and Discussion

Absorption Behavior of Nifedipine from Solid Dispersion

1. Rat *in Situ* Absorption Study—The dissolution behavior of nifedipine from a solid dispersion was previously found to be pH-dependent, and the dissolution curve of nifedipine showed supersaturation in JP X 2nd fluid.²⁾ Thus, it may be assumed that the dissolution behavior of nifedipine from the solid dispersion in the gastrointestinal tract varies with the progress of transport through the gastrointestinal tract. The time course of the blood levels of nifedipine when HP-55–nifedipine (3:1) solid dispersion was administered into the stomach or small intestine is shown in Fig. 1, together with the results for polyvinylpyrrolidone (PVP)–nifedipine (3:1) solid dispersion and the crystalline form of nifedipine.

It was reported³⁾ that PVP–nifedipine solid dispersion could improve the drug bioavailability as a result of supersaturation following rapid dissolution of nifedipine. The absorption behavior of nifedipine from HP-55 solid dispersion was similar to that from PVP solid dispersion in the small intestine, and the bioavailability of solid dispersion was remarkably increased as compared with that of the crystalline form of nifedipine. However, the amount of nifedipine absorbed from HP-55 solid dispersion was very low in the stomach. The absorption study showed that the dissolution rate of HP-55 solid dispersion in the stomach is slower than that of the crystalline form of nifedipine. The results obtained in this absorption study are consistent with those of an *in vitro* dissolution study.²⁾ That is, the

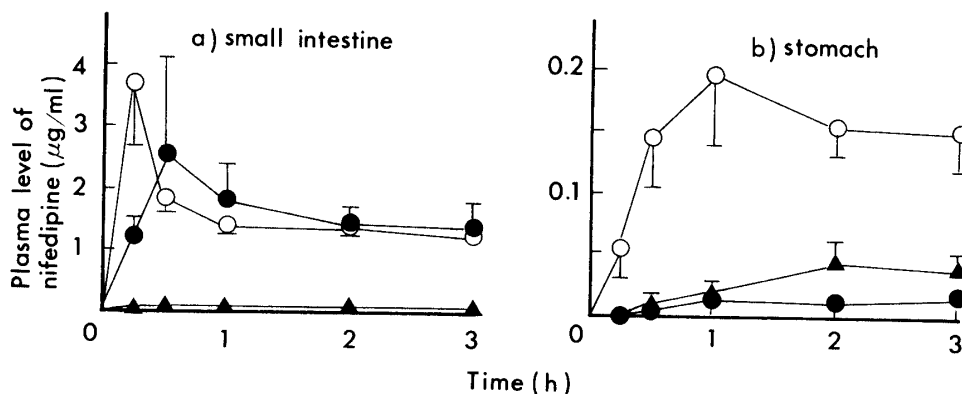


Fig. 1. *In Situ* Absorption of Nifedipine from Different Sites of Rat Gastrointestinal Tract after Administration of Solid Dispersion (Equivalent to 2.5 mg of Nifedipine)

●, HP-55–nifedipine (3:1) solid dispersion; ○, PVP–nifedipine (3:1) solid dispersion; ▲, nifedipine crystals.
Each point represents the average \pm S.E. of three determinations.

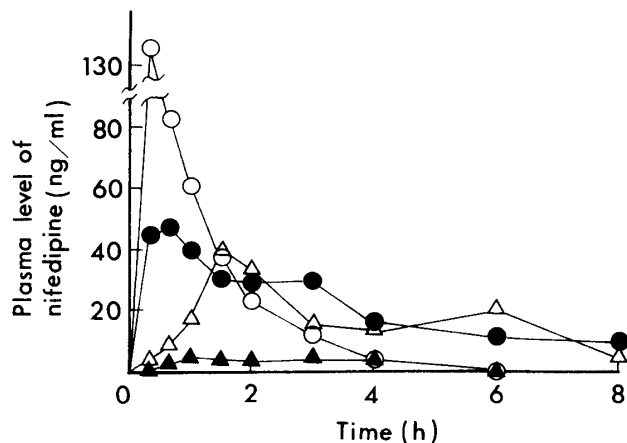


Fig. 2. Average Plasma Nifedipine Levels after Oral Administration of Solid Dispersion (Equivalent to 10 mg of Nifedipine)

●, HP-55–nifedipine (3:1) solid dispersion; △, Eudragit L–nifedipine (3:1) solid dispersion; ○, PVP–nifedipine (3:1) solid dispersion; ▲, nifedipine crystals.
Each point represents the average of three determinations.

pH-dependency of the dissolution behavior of HP-55 solid dispersion in the gastrointestinal tract was confirmed.

2. In Vivo Absorption Study in Beagle Dog—In order to ascertain the absorption behavior of nifedipine from solid dispersion systems, the samples were orally administered to beagle dogs. The gastrointestinal absorption of nifedipine from HP-55 or Eudragit L solid dispersion was compared with that from PVP solid dispersion or the crystalline form of nifedipine. Mean plasma levels of nifedipine after oral administration of the samples (equivalent to 10 mg of nifedipine) to three dogs are shown in Fig. 2.

It was found that nifedipine from HP-55 or Eudragit L solid dispersion was absorbed slowly. AUC_{0-8h} values of HP-55, Eudragit L and PVP solid dispersions were 168.1, 135.1, 154.8 ng·h/ml respectively, and were much higher than that of the crystalline nifedipine (23.5 ng·h/ml). It was concluded that the solid dispersion system using an enteric coating agent might be useful as a sustained absorption dosage form.

Stability of Solid Dispersions

Storage of PVP solid dispersion system under humid conditions resulted in a decrease of nifedipine dissolution, and it was confirmed that this was due to the crystallization of nifedipine, which was initially dispersed in the PVP matrix in a nearly amorphous form.³⁾ In this report, solid dispersions using enteric coating agent were stored at 40°C and 40°C/80% R.H. for 6 months, and their dissolution and X-ray diffraction properties were studied. Moreover, the residual nifedipine in the solid dispersion after storage was also investigated. As reported earlier,²⁾ nifedipine was present as an amorphous form in enteric coating agent matrix before storage.

1. Dissolution and X-Ray Diffraction Properties of the Solid Dispersion—In the dissolution study, solid dispersion containing the equivalent of 50 mg of nifedipine was dispersed in 500 ml of dissolution medium at 37°C. Figure 3 shows the effect of storage on the dissolution behavior of the samples in JP X 2nd fluid.

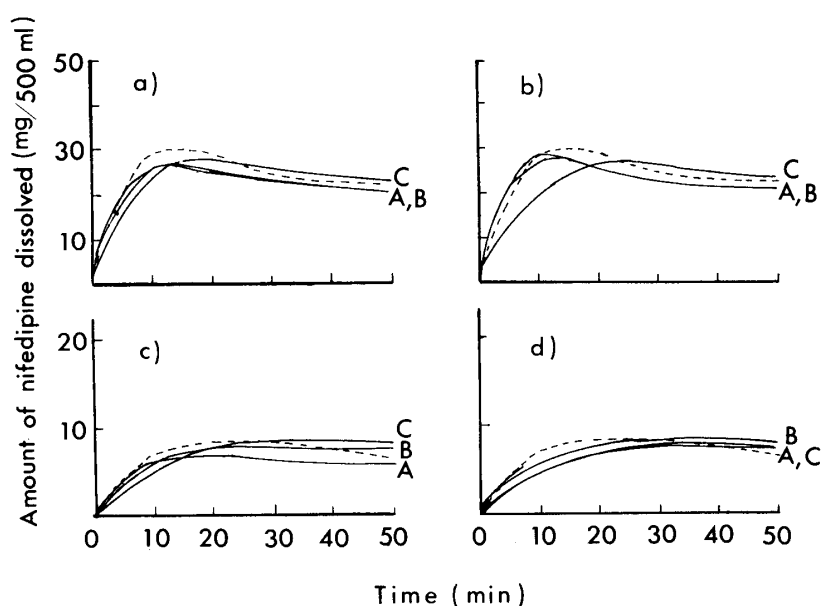


Fig. 3. The Effect of Storage on the Dissolution Behavior of Nifedipine from Solid Dispersion in JP X 2nd Fluid (pH 6.8)

Storage conditions: HP-55-nifedipine (3:1) solid dispersion was stored at 40°C (a) and 40°C/80% R.H. (b). Eudragit L-nifedipine (3:1) solid dispersion was stored at 40°C (c) and 40°C/80% R.H. (d).

Storage period: A, 2 months; B, 4 months; C, 6 months.

The dotted line shows the dissolution curve before storage.

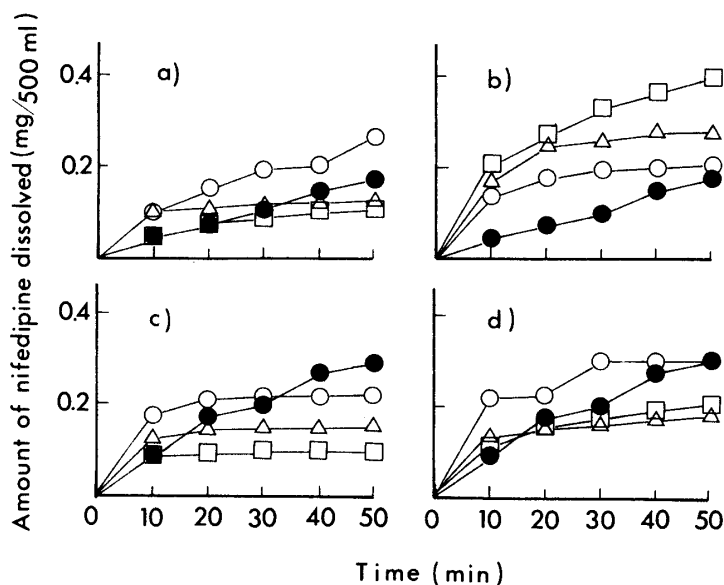


Fig. 4. The Effect of Storage on the Dissolution Behavior of Nifedipine from Solid Dispersion in JP X 1st Fluid (pH 1.2)

Storage conditions: HP-55-nifedipine (3:1) solid dispersion was stored at 40 °C (a) and 40 °C/80% R.H. (b). Eudragit L-nifedipine (3:1) solid dispersion was stored at 40 °C (c) and 40 °C/80% R.H. (d).

Storage period: ●, initial; ○, 2 months; △, 4 months; □, 6 months.

The dissolution behavior of HP-55 and Eudragit L solid dispersions did not change during storage. The dissolution behavior in JP X 1st fluid did not change much (Fig. 4).

The X-ray diffraction data also supported these results, since the diffraction patterns of the stored samples did not show any sharp peak attributable to nifedipine crystals. It was concluded that the physicochemical state of both HP-55 and Eudragit L solid dispersions did not change under the test conditions. In the case of PVP matrix, nifedipine gradually became crystalline under high R.H. conditions, depending on the aging period. As PVP is hygroscopic, and the system absorbs water vapor from the atmosphere during storage,^{3a)} it can be assumed that nifedipine acquired molecular mobility in the matrix when the sample absorbed water vapor.^{3a,5)} On the other hand, HP-55 and Eudragit L were not hygroscopic, and the amount of water vapor adsorption was less than 5% in all stored samples after 6 months. Therefore the physicochemical state of solid dispersion should be stable.

2. Chemical Stability—Nifedipine contents in the stored samples were periodically determined by high performance liquid chromatography (HPLC) and ultraviolet (UV) methods. No significant decrease of nifedipine content after storage was observed in solid dispersions using HP-55 and Eudragit L. The HPLC and thin layer chromatography (TLC) chromatograms of the samples did not reveal the formation of any decomposition product during storage. Thus, it was confirmed that solid dispersion systems using HP-55 or Eudragit L as a carrier were chemically and physically stable over a long period at 40 °C and 40 °C/80% R.H.

References and Notes

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