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Stability and Bioavailability of Nifedipine in Fine Granules[1)]

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In order to develop preparations of nifedipine with good bioavailability and stability, especially in relation to humidity, various fine granules were prepared by coating lactose surfaces with a dispersion system of nifedipine and water-soluble polymer. The system using polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose (HPMC) showed good dissolution properties and bioavailability of nifedipine. It was found that nifedipine in these preparations was chemically stable for 3 months at 75% relative humidity and 40°C. An X-ray diffraction study suggested that nifedipine was present in its amorphous form in the preparations using HPMC or PVP. Amorphous nifedipine in fine granules using HPMC was found to be stable under humid conditions, although crystallization occurred in the granules using PVP. The fine granules using HPMC and PVP both showed good bioavailabilities after oral administrations in dogs, and no significant difference was observed in bioavailability parameters between the fine granules using HPMC and PVP. Preparation of fine granules using HPMC may be a useful means to improve the bioavailabilities and stabilities of poorly water-soluble drugs.

Keywords——nifedipine; dispersion system; hydroxypropylmethylcellulose; polyvinylpyrrolidone; stability; bioavailability

Nifedipine is a poorly water-soluble drug whose bioavailability is very low when it is orally administered in crystalline form. The preparation of a nifedipine-polyvinylpyrrolidone (PVP) dispersion system by a coprecipitation method improved the dissolution properties and bioavailability of nifedipine,[2a)] but it was very difficult to prepare dosage forms based on this dispersion system because of handling difficulties.

We prepared fine granules by coating an inert core, such as crystalline lactose, with nifedipine.[2b)] The fine granules should have a large surface area, and were expected to show rapid drug dissolution and good bioavailability. The dissolution properties and the drug stability of the fine granules were maintained over 6 months at 40°C in an air-tight container, but at high humidity, the amorphous form of nifedipine in the PVP matrix changed to the crystalline form by absorbing water, with the result that the dissolution rate and the bioavailability decreased.

The purpose of this study was to develop nifedipine-containing fine granules with both good bioavailability and stability to humidity.

Experimental

Materials——Nifedipine, mp 171—172°C, was prepared in this research center. The nifedipine powder was pulverized to a fine powder in a fluid energy mill; the perticle size determined by an air permeability method using a specific surface area meter (Shimadzu Seisakusho, SS-100) was about 2 μm. Polyvinylpyrrolidone (PVP, PVP-K30, GAF Co.), hydroxypropylmethylcellulose 2910 (HPMC, Shin-Etsu Chemical Industry, Co., Ltd.), methylcellulose (MC, Shin-Etsu Chemical Industry, Co., Ltd.), hydroxypropylcellulose (HPC, HPC-L, Nippon Soda, Co., Ltd.), macrogol 4000 (PEG 4000, Sanyo Chemical Industries, Ltd.), ethylcellulose (EC, Ethocel Standard 10, Dow Chemical International Inc.), polyoxyl 40 stearate (POS, Nikkol MYS-40, Nikko Chemicals, Co., Ltd.), and crystalline lactose (80 mesh crystalline lactose, DMV) were used as received. Four grades of HPMC (TC5-E, TC5-R, TC5-S and Metolose 60SH-50, with designated viscosities as 2% aqueous solutions of 3, 6, 15 and 50 cP, respectively) and two grades of MC (Metolose SM-15 and SM-400, with designated viscosities as 2% aqueous solutions of 15 and 400 cP, respectively) were used. Other chemicals were of reagent grade.

Method——All experiments were carried out in a dark room in view of the high sensitivity of nifedipine to light.[3]

Preparations of the Fine Granules——Nifedipine (1 g) and a polymer (0—7 g) were dissolved in about 50 ml of mixed solvent (ethanol: dichloromethane = 1: 1), then 92—99 g of 80 mesh crystalline lactose was added. The resultant slurries were dried with a hand dryer until the smell of the solvent disappeared, then pulverized by hand. The resultant granules were dried on a tray in a vacuum oven (0.2 mmHg, 50°C, 3 h). After being pulverized in a mortar and pestle, dried granules were screened through a 32 mesh screen to obtain fine granules. The weight ratio of nifedipine to polymer was confirmed to be 1: 3 unless otherwise stated. In the case of the fine granules containing 5% nifedipine, used as samples for an X-ray diffraction study, 5 g of nifedipine and 15 g of polymer were dissolved in a solvent, then 80 g of 80 mesh crystalline lactose was added. The resultant slurries were taken through the same procedures as the slurries for the fine granules containing 1% nifedipine.

Dissolution Study——a) Dispersed Amount Method: Following previous papers,[2] a sample of fine granules containing 50 mg of nifedipine was dispersed in 500 ml of water maintained at 37°C. The solution was pumped at a rate of 50 ml/min through a glass filter (40—50 μm pore size) into a 0.5 cm flow cell and then backed into the reservoir. The absorbance of the solution was monitored with a recording spectrophotometer (Type 156, Hitachi, Ltd.) at 325 nm.

b) Rotating Disk Method: Disks of 1.5 g and 1.6 cm diameter were prepared by compression of fine granules at 300 kg/cm^2 for 10 min in a compression punch and die (Yuatsu Power, Riken Seiki Co., Ltd.). Each disk was fixed with a water-insoluble adhesive (Konishi, Ltd.) on the bottom of the shaft used in the dissolution test, method 1, described in JP X. Each disk was mounted with paraffin wax so that only one face remained exposed. The shaft was then immersed in 150 ml of water maintained at 37°C and rotated at 200 rpm. Analytical procedures were the same as for the dispersed amount method. All dissolution experiments were carried out in duplicate or triplicate and the results were highly reproducible. Thus, only mean values are reported.

Solubility Study——A tightly capped 100 ml flask, containing 50 ml of the polymer or surfactant solution (0—5%) and 50 mg of nifedipine fine powder, was shaken horizontally in a water bath maintained at 37°C for 14 h, then centrifuged. The absorbance of the supernatant was measured at 350 nm. The supernatant of the polymer or surfactant solution after ultracentrifugation was used as a control solution.

Storage Conditions——In order to study the drug stability, the fine granules were kept in desiccators maintained at 75% relative humidity (R.H.) and 40°C. For the X-ray diffraction study, the fine granules were kept in desiccators maintained at 84% R.H. and 21°C. The high R.H. conditions (75% and 84% R.H.) were attained by using saturated solutions of sodium chloride and potassium bromide, respectively.

Chemical Stability Study——Nifedipine contents in the stored samples were assayed by high-performance liquid chromatography (HPLC) using a model 440 liquid chromatograph equipped with a μBondapak C_{18} column (Waters Associates, Inc.). Thin-layer chromatography (TLC) was also used to check decomposition products. The conditions of HPLC and TLC were the same as those reported in previous papers.[2] Nifedipine contents were also assayed by ultraviolet (UV) spectrophotometry (model 100-60, Hitachi, Ltd.). Six hundred mg of stored sample (which was equivalent to 6 mg of nifedipine) was dissolved in 200 ml of ethanol. After centrifugation of the sample solution, the absorbance of the supernatant was measured at 350 nm using ethanol as a reference solution.

X-Ray Diffraction Study——The fine granules containing 5% nifedipine before and after storage were powdered to below 74 μm. The powdered samples were mounted on a sample holder, and the X-ray diffraction patterns were determined using an X-ray diffractometer (Geigerflex 2027, Rigaku Denki, Ltd.; Cu$K\alpha$; 40 kV; 20 mA).

***In Vivo* Methodology**——Beagle dogs (8—12 kg), which had been fasted for 24 h, but allowed free access to water, were orally administered the test preparation equivalent to 10 mg of nifedipine with 100 ml of water. Plasma samples were collected at 20, 40, 60, 120 and 240 min after the administration. Doses were administered by the crossover arrangement after an interval of one week. Plasma samples were assayed for nifedipine by means of a gas chromatograph equipped with an electron capture detector.[4]

Results and Discussion

Selection of Polymers for the Fine Granules

Fine granules containing 1% nifedipine were prepared using various water-soluble polymers listed in JP X. In order to compare the dissolution rates, fine granules using an insoluble polymer, ethylcellulose (EC), or using no polymer were also prepared. Dissolution curves of nifedipine from various preparations containing the equivalent of 50 mg of nifedipine dissolved in 500 ml of water at 37°C are shown in Fig. 1. The dissolution curve of nifedipine from the fine granules using no polymer (broken line) did not show supersaturation (sol-

ubility in water at 37°C: *ca.* 5.5 mg/500 ml). It appeared that insoluble polymer retarded the dissolution of nifedipine from the fine granules. On the other hand, the dissolution of nifedipine from the fine granules using any of the water-soluble polymers was improved, as compared to that using no polymer. Supersaturation of nifedipine in the medium was observed following the dissolutions of the fine granules using water-soluble polymers. The effects of polymers on the drug dissolution varied widely. In particular, the effects of polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose (HPMC) and methylcellulose (MC) were remarkable. In the case of the fine granules using PVP, the concentration of nifedipine in the medium quickly reached about 60 mg/l and then decreased gradually. In the case of the fine granules using water-soluble polymers other than PVP, supersaturated levels of nifedipine were maintained for over 15 min.

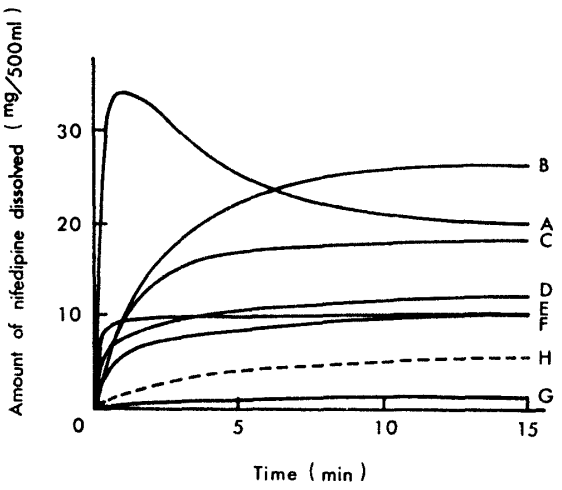

Fig. 1. Dissolution Behavior of Fine Granules containing 50 mg of Nifedipine and 150 mg of Various Polymers in 500 ml of Water at 37°C

(A) PVP, (B) HPMC, (C) MC, (D) HPC, (E) POS (F) PEG 4000, (G) EC. Fine granules using no polymer are represented by a broken line (H).

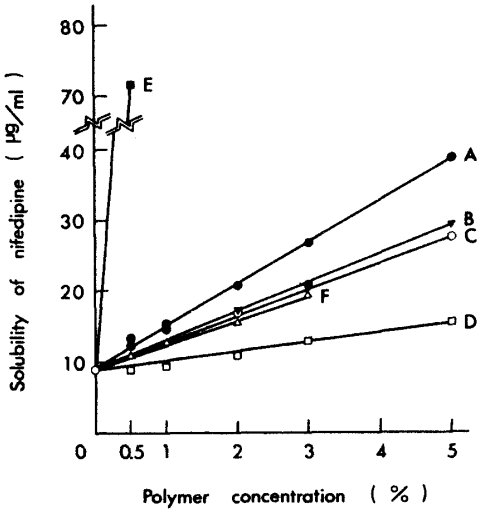

Fig. 2. The Effect of Polymer on the Solubility of Nifedipine

Key: see Fig. 1.

In order to find the reason for the differences among the fine granules, the effects of the polymers on nifedipine solubility were investigated. All of the water-soluble polymers showed a solubilizing effect. Polyoxyl 40 stearate (POS) was the most effective. In the case of other polymers, the solubilizing effects were not so strong, but appreciable effects were observed at high polymer concentration (Fig. 2).

Because the polymer concentration in the dissolution medium became only 0.03 % (w/v) under the experimental conditions given in Fig. 1, the improvements of dissolution rates could not be due only to solubilization. Other factors which may contribute to the dissolution behavior of nifedipine from the fine granules are: 1) the wettability, or affinity for water of the drug is improved, 2) the drug crystals dispersed on the surface of the fine granules are extremely small, or the drug may be wholly or partly in the amorphous state, 3) very high concentrations of polymer are formed in the vicinity of the granule surface, so the solubility of nifedipine at the surface is increased, improving the apparent dissolution rate, 4) recrystallization of nifedipine in the supersaturated solution is retarded by polymer molecules in the medium.

Lerk *et al.* reported that hexobarbital, a hydrophobic drug, when dispersed with MC or hydroxyethylcellullose, showed improved dissolution in water.[5] Thus, improvement of wettability might enormously affect the dissolution of nifedipine. Further, in the case of

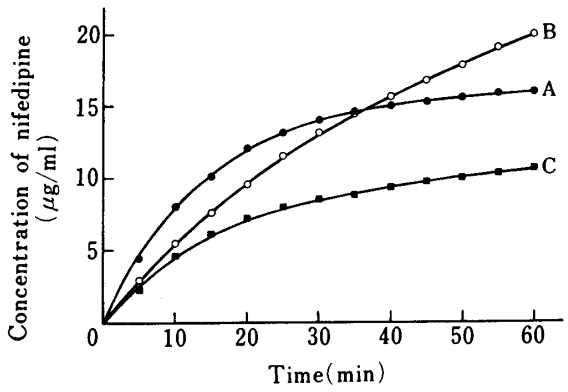

Fig. 3. Dissolution Behavior of Fine Granules containing Various Polymers as determined by the Rotating Disk Method

(A) PVP, (B) HPMC, (C) POS.
Each point is the mean of three determinations and each curve is computed from Eq. 1.

fine granules using PVP, it was reported that nifedipine in the film of coprecipitate on the fine granule surfaces might be in an amorphous state.[2b] Sekikawa *et al.* proposed as a dissolution mechanism for drug–PVP coprecipitate that high concentrations of both drug and PVP coacervated in the vicinity of the coprecipitate.[6] PVP has been shown to inhibit or retard the crystallization of some drugs in solution.[7]

Nogami *et al.* analyzed the dissolution phenomena involving simultaneous phase changes with *p*-hydroxybenzoic acid and phenobarbital, which change to the respective hydrates during dissolution.[8] Takayama *et al.* applied the equation (Eq. 1) proposed by Nogami *et al.* to the analysis of the dissolution patterns of coprecipitates by the rotating disk method.[9]

$$dC/dt = k_t[C_{SM}\cdot\exp(-k_r t) + C_{SO}\{1-\exp(-k_r t)\} - C] \qquad \text{Eq. (1)}$$

where C is the concentration at time t in the bulk solution; C_{SM} or C_{SO} is the saturated concentration before and after the crystallization, respectively; k_t is the dissolution rate constant; k_r is the crystallization rate constant.

Table I. Dissolution Parameters obtained by Calculation using Eq. 1 from the Dissolution Data (Rotating Disk Method)

Sample	$k_t \times 10^2$ (min^{-1})	C_{SM} (μg/ml)	C_{SO} (μg/ml)	$k_r \times 10^2$ (min^{-1})
PVP	1.09	102.7	17.4	7.27
HPMC	1.17	53.3	34.0	5.00
POS	1.27	48.3	13.7	7.50

The dissolution parameters in Eq. 1 were calculated from the dissolution data obtained here by the rotating disk method. The values of k_t, k_r, C_{SM} and C_{SO} in Eq. 1 were computed by the non-linear least-squares method[10] using the dissolution data from Fig. 3; the results are summarized in Table I. Samples which showed good dissolution behavior in Fig. 1 were chosen for the dissolution study by the rotating disk method. Although the sample using POS showed inferior dissolution, it was also tested because of the great solubilizing effect of POS. In the case of the sample using MC, disintegration of the disk occurred immediately after the start of the dissolution test. Thus, it was excluded from computation of the dissolution parameters because the dissolution surface area could not have remained constant.

Quite a good fit to the data was obtained by the use of Eq. 1. The values of k_t for all samples were almost the same, and it appears that the diffusivity of nifedipine was not affected by the various polymers. C_{SM} is thought to be a parameter indicating the degree of amorphous nature of nifedipine and/or the solubilizing effect of polymer. The value of C_{SM} for the sample using PVP was greater than others. The value of k_r for the sample using HPMC was smaller than for those using PVP and POS. The values of C_{SO} computed were appreciably greater than the value of solubility of nifedipine in water (*ca.* 11 μg/ml). Because C_{SO} is the saturated concentration after supersaturation, it seems to be affected by the crystal-

lization rate of nifedipine in the medium. One reason why the values of C_{SO} were larger than the usual solubility may be the inhidition of crystallization by polymer molecules. The values of C_{SO} differed considerably among the samples. In the case of the fine granules using PVP, the larger value of C_{SM} is thought to contribute to the fast dissolution rate and the supersaturation at the initial stage in Fig. 1, and a large difference of the values between C_{SM} and C_{SO} might result in fast recrystallization in the medium. On the other hand, in the case of the fine granules using HPMC, the initial dissolution rate was inferior to that in the case using PVP, but the small difference between C_{SM} and C_{SO} might result in a high supersaturated concentration for a long time. In the case of the fine granules using POS, the small value of C_{SM} and the small difference between C_{SM} and C_{SO} seemed to be the reason for the inferior dissolution behavior. The reason why the value of C_{SO} in the case of POS was small despite the large solubilizing effect is not clear. The contribution of k_r to the dissolution behavior might not be negligible.

It was reported that the dissolution behavior of fine granules using PVP was affected by the degree of polymerization of PVP and the weight ratio of PVP to nifedipine.[2a] Also, in the case of both HPMC and MC, various grades are available on the market. Because those grades are different in average degree of polymerization, the aqueous solutions show various viscosities. Therefore, fine granules using various grades of HPMC or MC were prepared and the dissolution properties were compared (Fig. 4). There was no obvious difference among the dissolution properties of the fine granules using different grades of each polymer. Therefore, the lowest polymerization grade of each polymer was chosen to prepare the fine granules, because a low-viscocity polymer solution is more convenient for practical use.

Fine granules using various weight ratios of each polymer to nifedipine were prepared and their dissolution properties are shown in Fig. 5. The larger the ratio of polymer to nifedipine became, the more the dissolution of the fine granules using HPMC or MC was

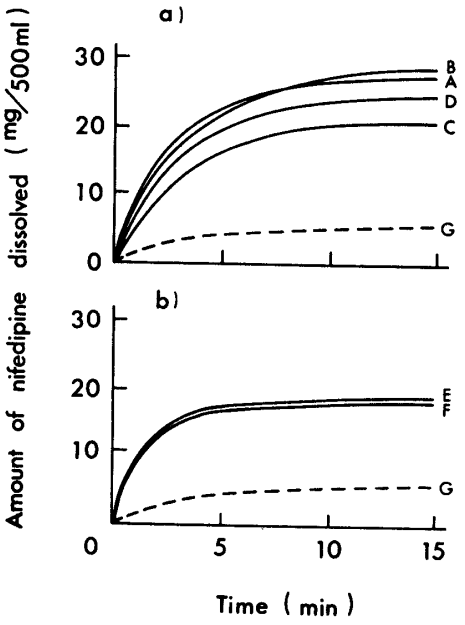

Fig. 4. Dissolution Behavior of Fine Granules containing 50 mg of Nifedipine and 150 mg of Various Grades of HPMC (a) or MC (b) in 500 ml of Water at 37°C

Polymer grade: (A) 3 cP, (B) 6 cP, (C) 15 cP, (D) 50 cP, (E) 15cP, and (F) 400 cP.
The fine granules using no polymer are represented by a broken line (G) for comparison.

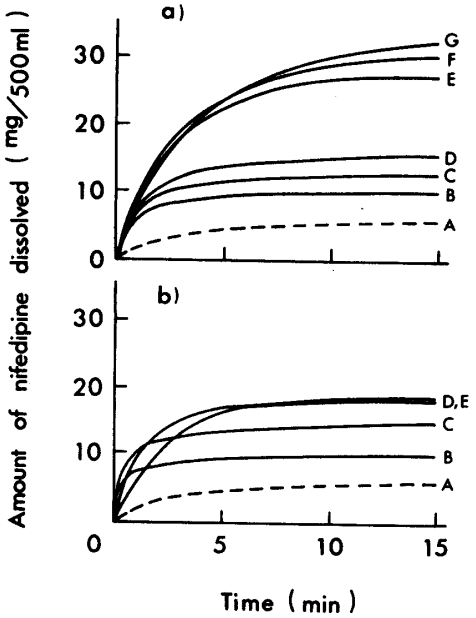

Fig. 5. Dissolution Behavior of Fine Granules containing 50 mg of Nifedipine and Various Weights of HPMC (a) or MC (b) in 500 ml of Water at 37°C

Weight ratio (nifedipine: polymer): (A) 1: 0, (B) 1: 0.2, (C) 1: 0.5, (D) 1 : 1, (E) 1 : 3, (F) 1 : 5, and (G)1: 7.

improved. However, in the case of HPMC, the dissolution was not much improved over the ratio of 1 : 3 . In the case of MC, the effect of the weight ratio on dissolution behavior was not as great as that in the case of HPMC. No difference was found in dissolution behavior of fine granules using MC between the ratios of 1 : 1 and 1 : 3.

Therefore, fine granules for studies of stability ane bioavailability were prepared using the lowest polymerization grade of each polymer at the weight ratio of 1 : 3.

Stability of the Fine Granules

(i) **Chemical Stability**——The fine granules using PVP were reported to be stable on storage under three conditions, 21°C ,40°C, and 75% R.H. at 21°C, in the previous paper.[2b] In this study, fine granules using PVP, HPMC and MC were stored at 75% R.H. and 40°C for 3 months. Nifedipine contents in the stored samples were periodically determined by HPLC and UV methods. No significant decrease of nifedipine content after storage was observed in the fine graunles using any of the polymers (see Table II). The HPLC and TLC chromatograms of the samples did not show any decomposition product during storage.

Table II. Effect of Polymer on the Residual Amount (%) of Nifedipine in Samples stored at 75% R.H. and 40°C

Sample	Assay method	Storage period (month)			
		Initial	1	2	3
PVP	UV	100.0	98.4	98.3	98.5
	HPLC	100.0	99.2	102.0	99.0
HPMC	UV	100.0	106.7	99.9	100.0
	HPLC	100.0	96.8	97.9	98.3
MC	UV	100.0	109.0	100.2	99.5
	HPLC	100.0	105.2	104.3	105.6

No decomposition product was found by HPLC and TLC of any sample.

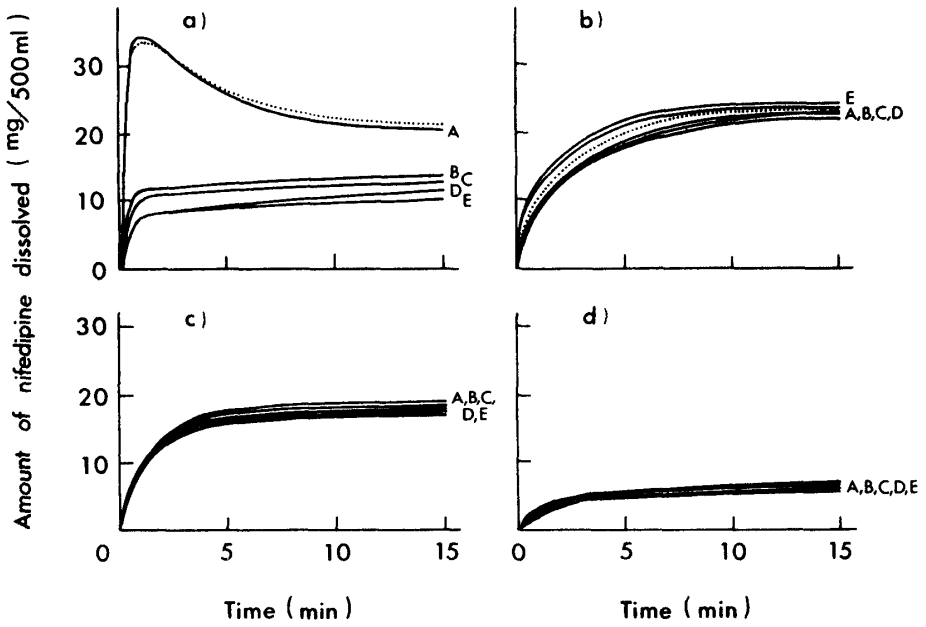

Fig. 6. Effect of Storage at 75% R.H. and 40°C on the Dissolution Behavior of Fine Granules using PVP (a), HPMC (b), MC (c), or No Polymer (d)

Storage period: (A) initial, (B) 1 week, (C) 2 weeks, (D) 4 weeks, and (E) 6 weeks.

These results indicate that nifedipine in the fine granules using weter-soluble polymers is stable to heat and humidity. It was suggested that the kind of polymer used did not affect the chemical stability of nifedipine in the fine granules.

(ii) Dissolution Behavior of Stored Samples——In order to compare the physicochemical stability of nifedipine in the fine granules, the dissolution properties of stored samples were studied. The effects of storage on the dissolution behavior of the fine granules varied considerably, as shown in Fig. 6. In the case of the fine granules using PVP, the dissolution behavior changed after storage and approached that in the case using no polymer. On the other hand, the dissolution behavior of the fine granules using HPMC, MC and no polymer did not change during storage. The dissolution behavior of the samples stored at 40°C in air-tight containers is also represented as dotted lines in Fig. 6. Whichever polymer was used, the dissolution behavior of the samples stored at 40°C was identical with that of the corresponding sample before storage. Since heat alone did not affect the dissolution behavior, humidity is presumed to be the reason for the poorer dissolution of the fine granules using PVP after storage at 75% R.H. and 40°C. The fine granules using HPMC and MC differed from those using PVP in physicochemical stability to humidity.

(iii) X-Ray Diffraction Patterns——In order to investigate the reason for the differences in aging effect, the X-ray diffraction patterns of the fine granules were measured to examine the crystallinity of nifedipine. However, it was difficult to distinguish the X-ray diffraction peaks attributable to nifedipine crystals from peaks attributable to lactose crystals because the nifedipine content in the fine granules was only 1%. Therefore, fine granules containing 5% nifedipine were prepared by the same procedures as the fine granules containing 1% nifedipine; in all cases, the dissolution behavior of the fine granules containing 5% nifedipine was essentially the same as that of the fine granules containing 1% nifedipine. The aging effects (84% R.H., 21°C) on the dissolution behavior were also the same as those of the fine granules containing 1% nifedipine shown in Fig. 6. Only in the case of PVP was the dissolution less effective. This suggests that the fine granules containing 1% and 5% nifedipine are essentially identical.

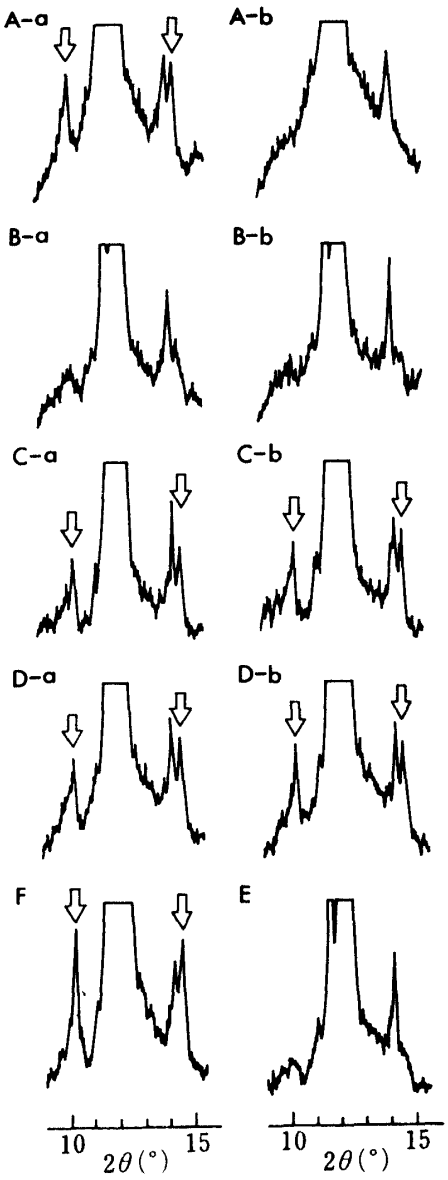

Fig. 7. Comparison of the X-Ray Diffraction Patterns of Fine Granules using Various Polymers after (a) and before (b) Storage at 84% R.H. and 21°C for 10 d

(A) PVP, (B) HPMC, (C) MC, and (D) no polymer.
Diffraction patterns of the crystalline lactose alone (E) and the physical mixture (F) of nifedipine fine powder and crystalline lactose are represented for comparison.

X-Ray diffraction patterns of the fine granules before and after storage (84% R.H., 21°C) are shown in Fig. 7. The diffraction patterns of crystalline lactose alone and a physical

mixture of nifedipine fine powder and crystalline lactose are shown in Fig. 7 for reference. Sharp diffraction peaks attributable to nifedipine crystals at $2\theta=10.3°$ and 14.6° were distinguishable from peaks attributable to crystalline lactose.

First, the diffraction patterns of the samples before storage were compared with those of the physical mixture. The diffraction patterns of the fine granules using PVP and HPMC did not show sharp diffraction peaks attributable to nifedipine crystals. This result suggessts that nifedipine is present as the amorphous form. On the other hand, in the diffraction pattern of the fine granules using MC or no polymer, sharp peaks attributable to nifedipine crystals were observed. This means that nifedipine is present in its crystalline form, in contrast to the granules using HPMC or PVP. The weaker intensities of the diffraction peaks of the fine granules using MC or no polymer as compared to those of the physical mixture suggests some decrease of crystallinity of nifedipine. However, the evident difference between the dissolution properties of samples using MC and no polymer (Fig. 1) is not explicable in terms of a difference in the crystallinity of nifedipine in the samples; some other factor presumably contributed to the improved dissolution from granules using MC.

Secondly, the diffraction patterns of fine granules stored under humid conditions were compared with those before storage. Except in the case using PVP, no difference was observed between the patterns before and after storage. The appearances of sharp diffraction peaks in the stored granules using PVP suggest that crystallization of nifedipine had occurred. However, in the case using HPMC, the diffraction patterns of samples before and after storage lacked sharp peaks attributable to nifedipine crystals. This result suggests that amorphous nifedipine in the fine granules using HPMC is stable humidity.

The water vapor adsorption of the stored granules using HPMC was almostly equal to that of granules using no polymer and was about seven times less than that of granules using PVP (see Table III). The significant difference of water vapor adsorption is presumably due to the difference of hygroscopicity between the polymers, which must account for the marked difference in stability of nifedipine.

Table III. The Effect of Polymers on Water Vapor Adsorption by the Fine Granules after Storage[a)]

Sample	PVP	HPMC	MC	No polymer
Adsorption (%)	4.6	0.7	0.9	0.5

a) 84% R.H., 21°C, 10 d.

Bioavailability of the Fine Granules

It was reported that there was a good relationship between dissolution behavior and bioavailability of various nifedipine preparations.[2)] The fine granules using PVP, HPMC and MC, which showed good dissolution, and the fine granules using no polymer were studied to compare their bioavailabilities. Mean plasma concentrations of nifedipine after oral administra-

Table IV. Comparison of the Bioavailability Parameters of the Fine Granules

Sample	AUC (μg·min/ml)	C_{max} (ng/ml)	T_{max} (min)
PVP	12.4±0.7 a, d, e	190.2±7.9 g, j, k	20±0 m
HPMC	11.5±3.1 b, d, f	161.9±22.7 h, j l	20±0 n
MC	10.4±0.6 c, e, f	120.3±16.2 i, k, l	20±0 o
No polymer	6.6±1.0 a, b, c	46.5±7.8 g, h, i	53±12 m, n, o

Significance level; a, b, c, g, h, i, k, m, n, o: $p<0.01$; e: $p<0.05$; d, f, j, l: no significance.

tion of 1 g of test preparations (equivalent to 10 mg of nifedipine) to three dogs are shown in Fig. 8. Three parameters were examined to assess bioavailability from the plasma concentration data (Table IV). These were maximum observed concentration (C_{max}), time required to attain C_{max} (T_{max}) and area under the time-plasma concentration curve (AUC) from 0 to 240 min.

Bioavailability parameters of the fine granules using no polymer were found to be inferior (C_{max}=46.5 ng/ml, T_{max}=53 min and AUC=6.6 μg min/ml) to those of granules using water-soluble polymers. T_{max} of any sample using polymer was fast (20 min) regardless of the polymer species. C_{max} values of samples using polymers were about 3-fold to 4-fold higher and AUC values were 1.5-fold to 2-fold larger than those of granules using no polymer. Statistically significant differences in all bioavailability parameters were found between the sample using no polymer and samples using any polymer ($p<0.01$). Therefore, the bioavailability of fine granules containing 1% nifedipine is improved by using polymers.

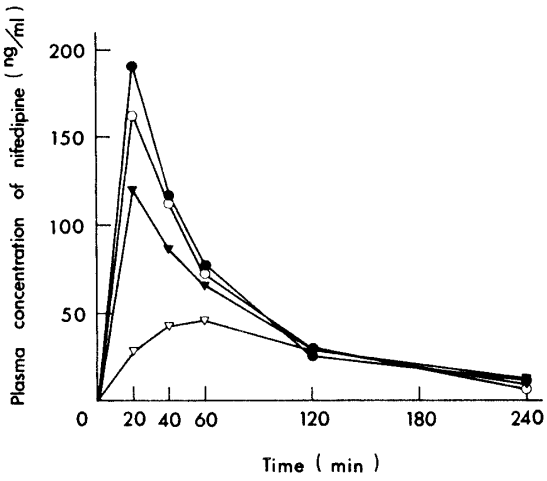

Fig. 8. Average Plasma Concentration of Nifedipine after Oral Administration of Fine Granules Containing 10 mg of Nifedipine and 30 mg of Various Polymers

(●) PVP, (○) HPMC, (▼) MC, and (▽) no polymer.

The T_{max} values of granules using all the polymers were identical, 20 min. C_{max} and AUC values were in the order PVP> HPMC>MC. However, the only statistically significant differences were those between the granules using PVP and MC (C_{max}, $p<0.01$; AUC, $p<0.05$).

Thus, although the bioavailability of the fine granules using MC was better than that of granules using no polymer, it was inferior to that of granules using PVP. Since the differences in bioavailability parameters between the fine granules using PVP and HPMC were not statistically significant, fine granules using PVP or HPMC appear to be bioequivalent.

Conclusion

The fine granules obtained by coating lactose surfaces with nifedipine and HPMC showed good drug dissolution behavior and bioavailability in dogs, as did those using PVP instead of HPMC. An X-ray diffraction study suggested that nifedipine in the fine granules using HPMC or PVP was in an amorphous state. Amorphous nifedipine in the fine granules using HPMC was shown to be stable to humidity, in contrast to the case of granules using PVP. Preparations of fine granules using HPMC may therefore provide a useful approach to obtain good bioavailability and stability of poorly water-soluble drugs.

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References and Notes

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2) *a*) I. Sugimoto, A. Kuchiki, H. Nakagawa, K. Tohgo, S. Kondo, I. Iwane, and K. Takahashi, *Drug Dev. Ind. Pharm.*, **6**, 137 (1980); *b*) I. Sugimoto, A. Kuchiki, and H. Nakagawa, *Chem. Pharm. Bull.*, **29**, 1715 (1981).

3) S. Ebel, H. Schütz, 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).
4) S. Kondo, A. Kuchiki, K. Yamamoto, K. Akimoto, K. Takahashi, N. Awata, and I. Sugimoto, *Chem. Pharm. Bull.*, **28**, 1 (1980).
5) C.F. Lerk, M. Lagas, J.T. Fell, and P. Nauta, *J. Pharm. Sci.*, **67**, 935 (1978).
6) H. Sekikawa, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **27**, 1223 (1979).
7) H. Sekikawa, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **26**, 118 (1978); A.P. Simonelli, S.C. Mehta, and W.I. Higuchi, *J. Pharm. Sci.*, **59**, 633 (1970).
8) H. Nogami, T. Nagai, and T. Yotsuyanagi, *Chem. Pharm. Bull.*, **17**, 499 (1969).
9) K. Takayama, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **28**, 3304 (1980).
10) K. Yamaoka, Y. Tanigawa, T. Nakagawa, and T. Uno, *J. Pharm. Dyn.*, **4**, 879 (1981).