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Stability of Nifedipine-Polyvinylpyrrolidone Coprecipitate[1)]

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The chemical and physicochemical stability of nifedipine in nifedipine-polyvinylpyrrolidone (PVP) coprecipitate systems was studied. It was found that nifedipine in the coprecipitate systems was chemically stable to heat and humidity. Storage of the coprecipitate systems under humid conditions was found to influence the dissolution behavior. The X-ray diffraction pattern of coprecipitate which had been stored under very humid conditions showed many sharp peaks attributable to nifedipine crystals. It is suggested that the inferior dissolution of the humidly stored coprecipitate systems resulted from the partial crystallization of amorphous nifedipine in the PVP matrix. Correlations between the *in vitro* dissolution behavior and the *in vivo* bioavailability parameters following oral administration to dogs were studied to confirm the effect of storage on the bioavailability. It was concluded that coprecipitate systems of nifedipine with PVP should be stored in such a way that they are not exposed to humidity so as to avoid a decrease of drug bioavailability.

Keywords——nifedipine; polyvinylpyrrolidone; coprecipitate; stability; aging; dissolution behavior; bioavailability; crystallization

Nifedipine is a poorly water-soluble drug whose bioavailability is low when it is administered orally in the crystalline form. The nifedipine-polyvinylpyrrolidone(PVP) coprecipitate system was shown to have a rapid dissolution rate and good bioavailability in the previous paper.[2)] It was also confirmed that nifedipine was probably present in its amorphous form in the PVP matrix.

The amorphous form may crystallize upon aging over a long period of time, especially at high relative humidity (R.H.), resulting in a decrease in the dissolution rate of nifedipine.

There are a few reports concerning stability during the preparation of solid dispersed or coprecipitate systems,[3)] but little work has been done regarding the effect of aging on the dissolution rate and on the chemical stability of these systems. Allen *et al.*[3a)] reported that a corticosteroid-sugar glass dispersion sample after storage at 25° for 30 days showed no decrease in the dissolution rate, but this storage term is rather short. Frömming *et al.*[4)] studied the dissolution rate of salicylic acid in PEG 6000, and reported that the dissolution rates of solidified melts with amorphous salicylic acid were stable during storage for one year. However, they did not study the effect of heat or humidity during storage on the dissolution rate. El-Banna *et al.*[5)] studied the degradation rate of aspirin in solid dispersion systems, and concluded that the polar and hygroscopic nature of urea and PVP tend to allow aspirin to degrade when incorporated into this type of carrier as coprecipitates.

Therefore the present study was undertaken to evaluate the chemical stability and the dissolution rate of nifedipine, especially in its dosage form, fine granules, in the nifedipine-PVP coprecipitate system. The relationship between the *in vitro* dissolution behavior of various nifedipine preparations and the *in vivo* bioavailability parameters in dogs was also studied to confirm the effect of the physicochemical stability of the coprecipitate on its bioavailability.

Experimental

Materials——Nifedipine, mp 171—172°, presently on the market was used without further purification. The nifedipine powder was pulverized in a vibrating sample mill (Heiko, TI-100) to a fine powder; the particle

size determined by an air permeability method using a specific surface area meter (Shimadzu Seisakusho, SS-100) was about 9.6 μm. Polyvinylpyrrolidone K-30 (PVP, average molecular weight 40000, Gokyo Trading Co., Ltd.), whose particle size as determined by an air permeability method was about 24 μm, and 80 mesh crystalline lactose (DMV) were used as received. 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.[6]

Table I. Formulation of the Test Sample

Sample	Nifedipine[a] (g)	PVP-K30 (g)	Crystalline lactose (g)
"Coprecipitate"	10	30	—
Physical mixture	10	30	—
Reference	10	30	—
Coprecipitated fine granules	10	30	120
Plain granules	10	30	120

a) The particle size of nifedipine as determined by an air permeability method was about 9.6 μm.

Sample Preparation——The chemical composition of each sample is shown in Table I. The binary coprecipitate system, which is referred to the "coprecipitate," was prepared by the solvent method from an ethanol solution as reported in a previous paper,[2] and particles of 60—100 mesh size were used. The physical mixture was prepared by thoroughly mixing the fine nifedipine powder with PVP in a mortar with a spatula. The reference sample for X-ray diffractometry was prepared by evaporation of a PVP aqueous suspension of the fine nifedipine powder. The coprecipitated fine granule is a model preparation of a practical dosage form using a coprecipitate system. The coprecipitated fine granules were prepared by means of a fluid-bed spray granulator. Granules of 80 mesh crystalline lactose, suspended in a fluidized-bed, were coated with a nifedipine-PVP ethanol solution. The particle size distribution of the coprecipitated fine granules was adapted to that of the fine granules in J.P. IX.[7] The plain granules for *in vivo* administration experiments were prepared by a wet-granulation method. A mixture of the fine nifedipine powder, crystalline lactose and PVP was kneaded with 50% ethanol aqueous solution, and the damp mass was forced through 20 mesh screen by hand. After being dried on a tray, the granules were sieved to comply with the particle size distribution test described in J.P. IX[7] by using 16 and 48 mesh screens. The disintegration time of these granules by the J.P. IX method was 1 min.

Storage Conditions——In order to study the stability, the "coprecipitate," the physical mixture and the coprecipitated fine granules were stored in air-tight glass containers at 21° or 40°, or kept in desiccators at various relative humidities (R.H.) and 21°. The high R.H. conditions (75%, 84% and 98%) were attained by using saturated solutions of sodium chloride, potassium bromide and disodium phosphate, respectively, at 21°. In order to correct for the weight change caused by absorption of moisture during storage, the stored samples were dried under reduced pressure (0.2 mmHg) at room temperature for 6 hr in a phosphorous pentoxide desiccator before every experiment. Under these drying conditions, sample weights became constant. The amounts of water vapor adsorption of samples stored under the high R.H. conditions are represented in tables and captions of figures as percentages of the sample weights. The water vapor adsorptions by the samples which were stored at 21° and 40° in air-tight glass containes were negligible.

Chemical Stability——Nifedipine contents in the stored samples were assayed by a high-performance liquid chromatography (HPLC) method 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 the previous paper.[2]

Dissolution Study——A simple beaker-stirrer dissolution method reported in the previous paper[2] was employed. As the sample was agglomerated after storage under humid conditions, it was pulverized and sieved, and then the same mesh size fractions as the initial ones were used. All dissolution experiments were carried out in duplicate or triplicate and were highly reproducible. Thus, only mean values are reported.

X-ray Diffraction and Small-Angle Scattering——An X-ray diffractometer (Geigerflex 2027, Rigaku Denki, Ltd.) was used to study the wide-angle ($5° \leqq 2\theta \leqq 30°$) diffraction and the small-angle ($0.3° \leqq 2\theta \leqq 1.5°$) scattering. Powdered samples (sub 200 mesh sieve) were mounted on a sample holder, and the X-ray diffraction or scattering patterns were determined using Cu K_α radiation (40 kV, 20 mA).

***In Vivo* Methodology**——Beagle dogs, 8—12 kg, fasted for 24 hr, 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 a time interval of one week. Plasma samples were assayed for nifedipine by means of a gas chromatograph equipped with an electron-capture detector.[8]

Results and Discussion

Chemical Stability of Nifedipine in Coprecipitate Systems

The coprecipitated fine granules were prepared by coating the surface of crystalline lactose with a film of the coprecipitate. The thickness of the coprecipitate layer of the coprecipitated fine granules is less than that of the "coprecipitate," so a difference in stability between the coprecipitated fine granules and the "coprecipitate" may occur. In order to compare the stability, the coprecipitated fine granules, the "coprecipitate" and a physical mixture of nifedipine with PVP were stored at 21°, 40° or 21° at 75% R.H. for 6 months.

Table II. Residual Nifedipine in the Various Stored Samples

Sample	Storage condition	Period, month 1	2	3	4	6
"Coprecipitate"	21°	100.0±1.9		97.2±1.8		96.3±1.2
	40°	100.8±2.9		97.9±2.9		100.3±0.6
	75% R.H., 21°	102.8±4.9 (12.5%)		99.2±3.9 (17.0%)		97.8±4.0 (17.3%)
Physical mixture	21°	100.0±1.8		99.0±1.7		101.8±2.0
	40°	100.2±3.0		99.6±3.1		97.9±1.7
	75% R.H., 21°	99.0±3.7 (15.7%)		98.1±3.7 (24.7%)		100.1±2.9 (23.3%)
Coprecipitated fine granules	21°		100.0±4.8		95.6±1.3	97.6±8.1
	40°		100.9±2.5		97.1±1.8	102.9±3.2
	75% R.H., 21°		101.3±0.8 (4.1%)		100.4±5.6 (5.1%)	98.8±6.2 (5.5%)

Average data for 4 experiments are given with the standard deviations. Water vapor adsorption (%) of samples which had been stored at 75% R.H. and 21° are also given in parentheses.

No decomposition product was found by TLC in any of the samples during storage. At appropriate time intervals, nifedipine contents in the stored samples were also determined by HPLC (see Table II). No significant decreases of nifedipine contents after storage under these conditions were observed in any system, and HPLC chromatograms did not show any decomposition product. These results indicate that nifedipine involved in the two coprecipitate systems is as chemically stable to heat and humidity as in the physical mixture.

El-Banna *et al.*[5] reported the degradation of aspirin in the binary coprecipitate of aspirin and PVP. The results showed that coprecipitated aspirin decomposed rapidly under high humidity, although crystalline aspirin was very stable. They concluded that the polar and perhaps the hygroscopic nature of PVP tended to enhance the degradation of aspirin when it was incorporated into PVP as a coprecipitate. Further, the aspirin-PVP system exhibited lower degradation rates than those for the aspirin-urea system. They postulated from this result that the partial decomposition of urea to ammonia increased the pH of the residual water and thus increased the rate of decomposition of aspirin.

As shown in Table II, nifedipine included in the coprecipitate system was very stable at 75% R.H. and 21° for 6 months, indicating that nifedipine is not hydrolyzed under conditions of high humidity. Generally, a carboxylic acid ester is easily hydrolyzed under weak alkaline conditions. If urea is used as a matrix for a nifedipine solid dispersion system, nifedipine may be hydrolyzed by the urea decomposition product, ammonia, during prolonged aging. For this reason, PVP is a good matrix for a nifedipine coprecipitate system.

Physicochemical Stability of Nifedipine in Coprecipitate Systems

The dissolution and X-ray diffraction properties of the "coprecipitate" and the coprecipitated fine granules, after storage under various conditions, were studied to investigate their

physicochemical states. Both coprecipitate samples were stored at 40° or at 21° and 75% R.H.

(i) **Dissolution Behavior of the "Coprecipitate"**——Before storage, a "coprecipitate" sample containing the equivalent of 50 mg of nifedipine was dissolved rapidly in 500 ml of water. The concentration of nifedipine in the medium quickly reached about 60 mg/l, in spite of its low solubility (about 11 mg/l) in water. This supersaturated concentration was maintained for over half an hour, and then decreased gradually to the normal solubility (Fig. 1, A). Although the exact physical nature of these coprecipitate systems was not investigated in this study, it is believed that nifedipine lacks crystallinity in these systems.[2] Supersaturation following rapid dissolutions like this has been reported for a solid dispersion system[3c] and a coprecipitate system.[9]

Storage at 40° did not have any effect on the dissolution behavior of the "coprecipitate" (Fig. 1-a). On the other hand, storage under humid conditions (75% R.H. at 21°) resulted in a marked change of dissolution behavior (Fig. 1-b). In the case of the sample stored at 75% R.H. and 21°, supersaturation was also observed following a rapid dissolution, but this supersaturation was not maintained for a long period. This rapid recrystallization of nifedipine

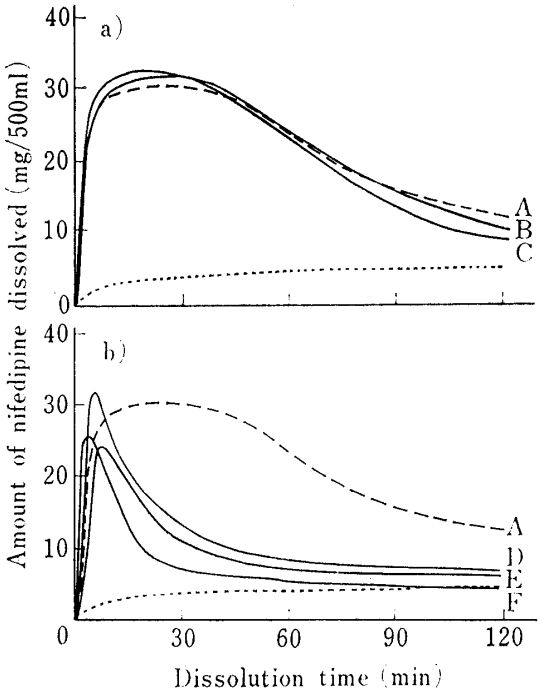

Fig. 1. The Effect of Storage on the Dissolution Behavior of Nifedipine-PVP "Coprecipitate" (Amount Equivalent to 50 mg of Nifedipine) in 500 ml of Water at 37°

Storage conditions: (a) 40° and (b) 75% R.H., 21°. Storage period (water vapor adsorption): (A) initial, (B) 3.5 months, (C) 6 months, (D) 0.5 month (14.7%), (E) 1.5 months (13.4%), and (F) 4 months (13.6%). Nifedipine-PVP physical mixture is represented by a dotted line for comparison.

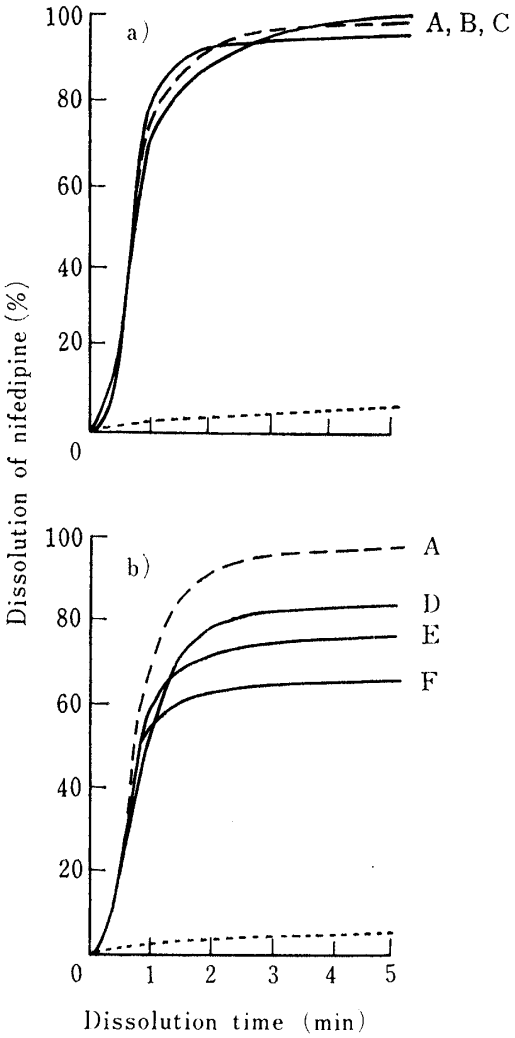

Fig. 2. The Effect of Storage on the Dissolution Behavior of Nifedipine-PVP "Coprecipitate" (Amount Equivalent to 10 mg of Nifedipine) in 500 ml of Water at 37°

Storage conditions and period: see Fig. 1.

in the medium may be a result of the formation of very fine nifedipine crystals in the PVP matrix during storage under humid conditions. Such very fine nifedipine crystals in the system may act as nuclei for recrystallization in the dissolution medium.

In order to confirm this, a dissolution study was also carried out so that the coprecipitate system could completely dissolve. The initial "coprecipitate" samples containing the equivalent of 10 mg of nifedipine dissolved completely in 500 ml of water in a few minutes (Fig. 2, A). This complete dissolution results in a supersaturation of nifedipine (20 mg/l), but recrystallization was not observed until 10 min. Storage of samples under humid conditions (75% R.H. at 21°) resulted in decreases of the dissolution (Fig. 2-b), although storage at 40° did not affect the dissolution behavior (Fig. 2-a).

This incomplete dissolution of the humidly stored samples also suggests the formation of very fine nifedipine crystals during storage. Therefore X-ray diffractions of the samples were measured to examine the presence of nifedipine crystals.

(ii) X-ray Diffraction Patterns of the "Coprecipitate"——X-ray diffraction patterns of the nifedipine-PVP coprecipitates (before and after storage at 75% R.H. and 21°) and references are shown in Fig. 3. The diffraction pattern of PVP did not show any sharp peak. In the case of a reference sample in which nifedipine crystals had been dispersed, many sharp diffraction peaks were observed. These sharp peaks are attributed to nifedipine crystals. The diffraction pattern of the initial "coprecipitate" did not show any sharp peak attributable to nifedipine crystals, and it was very similar to that of PVP. This result suggests that nifedipine is dispersed in the PVP matrix in a nearly amorphous form. After storage at 75% R.H. and 21° for 4 months, the "coprecipitate" showed inferior dissolution behavior, as shown in Figs. 1 and 2, and a slight change of the diffraction pattern was observed. However, no sharp and strong peak attributable to nifedipine crystals was observed.

The samples were stored at a higher R.H. to discover whether these amorphous systems in the coprecipitate crystallize upon aging under humid conditions. Aging at 84% R.H. and 21° for 4 days or at 98% R.H. and 21° for 2 days influenced the dissolution behavior

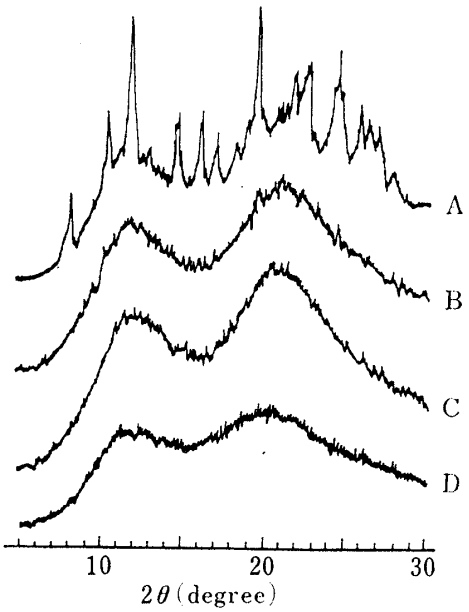

Fig. 3. X-ray Diffraction Patterns of Various Nifedipine-PVP Preparations

Key: (A) dispersed nifedipine crystals in PVP, (B) nifedipine-PVP "coprecipitate" after storage at 75% R.H., 21° for 4 months (water vapor adsorption: 13.6%), (C) initial "coprecipitate", and (D) PVP alone.

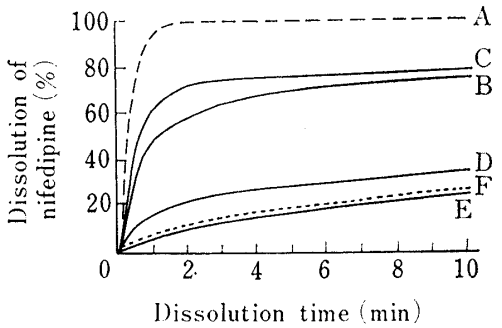

Fig. 4. The Effect of Storage on the Dissolution Behavior of Nifedipine-PVP "Coprecipitate" (Amount Equivalent to 10 mg of Nifedipine) in 500 ml of Water at 37°

Storage conditions: (B) 84% R.H., 21° and (C—E) 98% R.H., 21°. Storage period (water vapor adsorption): (A) initial, (B) 4 days (19.5%), (C) 2 days (35.6%), (D) 4 days (38.6%), and (E) 6 days (37.4%). Dispersed nifedipine crystals in PVP are represented by a dotted line (F) for comparison.

(Fig. 4, B or C) and X-ray diffraction patterns (Fig. 5, B or C) of the "coprecipitate." These aging effects were very similar to the aging effects of storage at 75% R.H. and 21° for 4 months (Fig. 2-b, F and Fig. 3, B).

However, after storage for a longer period at 98% R.H. and 21°, the dissolution curves approached that of the reference sample in which nifedipine crystals had been dispersed in a PVP matrix (Fig. 4, D, E and F). X-ray diffraction peaks attributable to nifedipine crystals became noticeable after 4 and 6 days at 98% R.H. and 21° (Fig. 5, D and E). As well as the dissolution curve, the diffraction pattern of the 98% R.H. aged sample approached that of the reference sample, depending on the aging period.

These results suggested that the inferior dissolution behavior of the "coprecipitate" after storage under humid conditions was due to the crystallization of nifedipine which was initially dispersed in the PVP matrix as a nearly amorphous form. However, X-ray diffractometry can barely detect particles whose sizes are smaller than about 100 Å.[10]

Therefore small-angle X-ray scattering measurements were carried out to measure the size of microcrystalline nifedipine particles in the humidly stored samples whose wide-angle diffraction patterns did not show sharp peaks and whose dissolution was impaired.

The scattering pattern of the "coprecipitate" was nearly identical with that of PVP. No difference in the scattering pattern of the "coprecipitate" before and after storage was

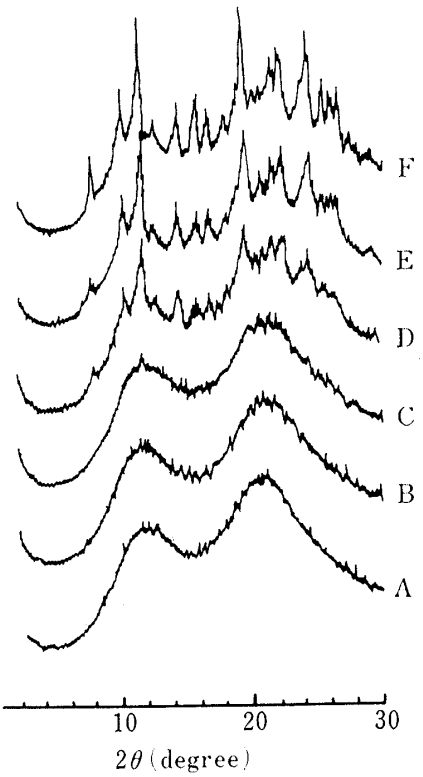

Fig. 5. The Effect of Storage on X-ray Patterns of the "Coprecipitate"

Storage conditions and period: see Fig. 4.

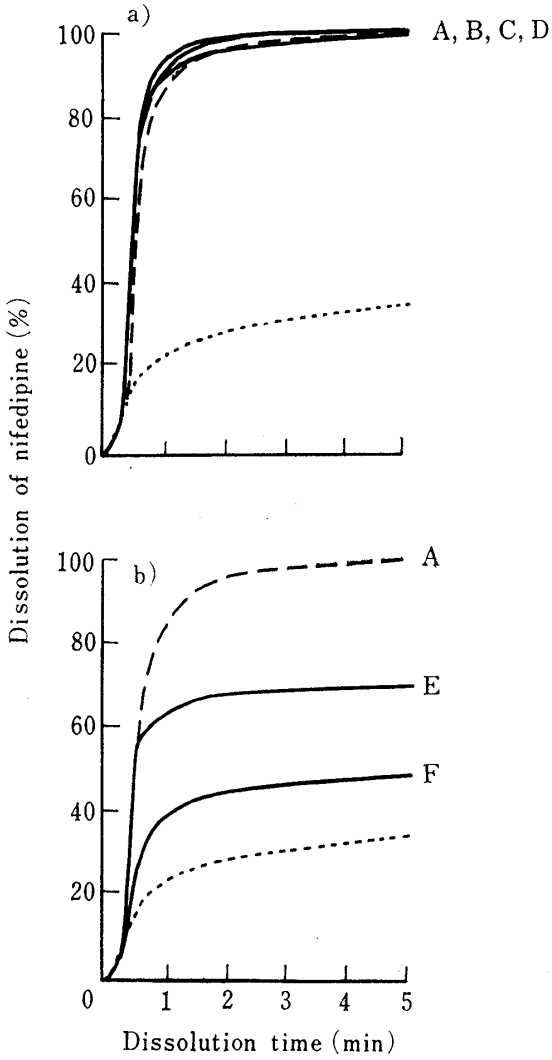

Fig. 6. The Effect of Storage on the Dissolution Behavior of the Coprecipitated Fine Granules (Amount Equivalent to 10 mg of Nifedipine) in 500 ml of Water at 37°

Storage conditions: (a) 40° and (b) 75% R.H., 21°. Storage period (water vapor adsorption): (A) initial, (B) 1 month, (C) 2 months, (D) 6 months, (E) 1 month (3.6%), and (F) 2 months (4.1%).

The plain granules are represented by a dotted line for comparison.

observed. It was impossible to correlate quantitatively the crystallinity of nifedipine in the sample to its dissolution behavior, because the crystallinity could not be determined sensitively.

(iii) Aging Effects on the Coprecipitated Fine Granules——The coprecipitated fine granules were also influenced by aging under humid conditions. When the initial coprecipitated fine granules containing the equivalent of 10 mg of nifedipine were dissolved into 500 ml of water, a complete dissolution was observed within a few minutes (Fig. 6, A) and the attainment of supersaturation (20 mg/l) was similar to what was observed in the case of the "coprecipitate" shown in Fig. 2, A.

Aging at 40° over 6 months did not have any effect on the dissolution behavior of the coprecipitated fine granules (Fig. 6-a), although aging under humid conditions (75% R.H. at 21°) resulted in a marked decrease of the dissolution (Fig. 6-b).

The aging effect of humidity on the dissolution behavior of the coprecipitated fine granules was more obvious than on that of the "coprecipitate."

However, the aging effect on the X-ray diffraction pattern was not obvious. Because many diffraction peaks attributable to the crystalline lactose used as a carrier of the granules overlap with peaks of nifedipine crystals, and because the composition ratio of nifedipine in the coprecipitated fine granules was very small (6.3%), diffraction peaks attributable to nifedipine crystals could hardly be distinguished even in a sample stored for a long time under high R.H. conditions.

It was found that the dissolution of both the "coprecipitate" and the coprecipitated fine granules was decreased after storage under humid conditions. These decreases may be due to crystallization of the amorphous nifedipine in the matrix, although sharp X-ray diffraction peaks attributable to nifedipine crystals could not be detected in every case.

Nakai *et al.*[11] suggested that the crystallization of amorphous *d*-camphor or naphthalene in ground mixtures with microcrystalline cellulose was caused by the enhancement of molecular movement in the matrix when the sample absorbed water vapor. A similar mechanism can be assumed for the crystallization of nifedipine in coprecipitate systems after storage under humid conditions. That is, the matrix of coprecipitate systems, PVP, is hygroscopic,[12] so the coprecipitate system absorbs water vapor from the atmosphere during storage under high R.H. conditions. Consequently, nifedipine acquires molecular mobility in the matrix, and then gradually crystallizes.

TABLE III. Comparison of the Bioavailability Parameters of the Coprecipitated Fine Granules and Plain Granules

Parameter	Preparation		
	Coprecipitated fine granules	Coprecipitated fine granules[a]	Plain granules
C_{max}, ng/ml	177.0±22.2	102.4±6.9	83.4±8.9
		$p<0.01$	$p<0.025$
	$p<0.005$		
T_{max}, min	20±0	20±0	27±4
		NS[b]	NS[b]
	NS[b]		
$AUC_{0-240\ min}$, μg·min/ml	10.9±1.2	9.3±0.9	8.2±1.4
		NS[b]	NS[b]
	NS[b]		

Average data for 6 dogs are given with the standard errors of the mean.
a) Sample stored at 75% R.H. and 21° for 1 months (water vapor adsorption: 3.6%).
b) No significance.

The coprecipitate might dissolve in absorbed water to form a supersaturated solution of nifedipine which might form nuclei for crystallization. Imaizumi *et al.* suggested that a supersaturation phenomenon to form nuclei for crystallization might be involved in the transition of amorphous indomethacin to the crystalline form at high R.H.[13]

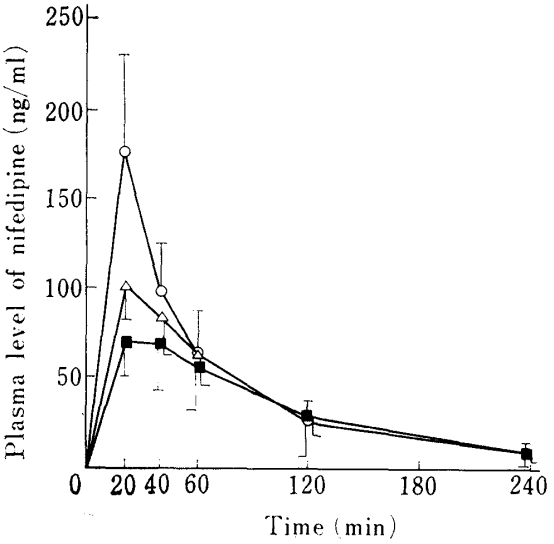

Fig. 7. Average Plasma Nifedipine Levels after Oral Administration of the Coprecipitated Fine Granules or Plain Granules (Amount Equivalent to 10 mg of Nifedipine)

Key: (○) initial coprecipitated fine granules, (△) coprecipitated fine granules after storage at 75% R.H., 21° for 1 month (water vapor adsorption: 3.6%), and (■) plain granules.
Each point represents the average ± SD of six dogs.

Relationships between Dissolution Behavior and Bioavailability

As mentioned before, storage under highly humid conditions was found to influence the dissolution behavior of coprecipitate systems. It is well known that the bioavailability of a drug is influenced by the dissolution behavior of the preparation. Thus, three nifedipine preparations whose chemical compositions are identical (nifedipine: PVP: lactose 1:3:12) were studied to determine the relationship between dissolution behavior and bioavailability after oral administration to beagle dogs. The dissolution properties of these preparations were quite different from each other, and significant differences were observed in dissolution (%) at 10 min.

Mean plasma levels of nifedipine after oral administrations of 160 mg of the test preparations (equivalent to 10 mg of nifedipine) to six dogs are shown in Fig. 7 and Table III. Three variables were examined in a bioavailability assesment using the plasma level data. These included: area under the time-plasma level curve (AUC) from 0 to 240 min, maximum

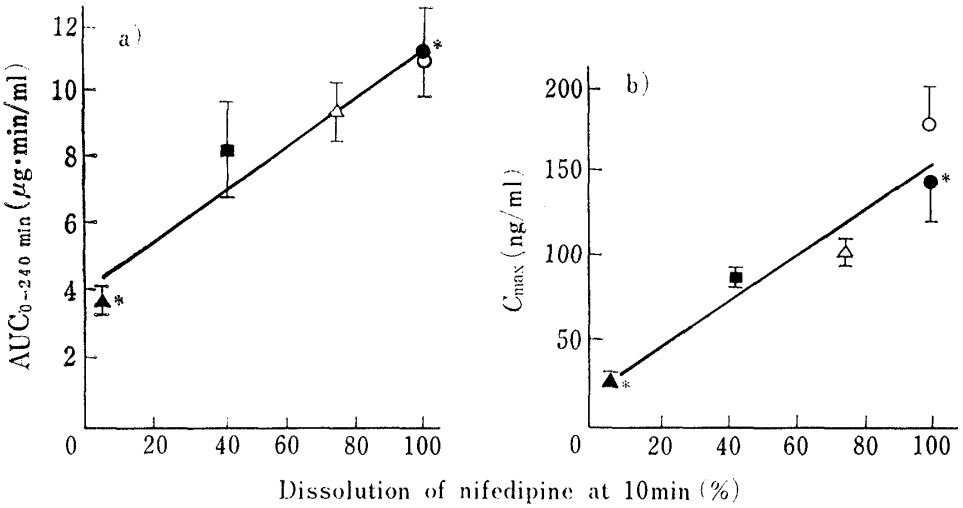

Fig. 8. Relationships between the *in Vitro* Measurement of Dissolution (%) of Nifedipine at 10 min and the *in Vivo* Measurement of $AUC_{0-240\ min}$ (a) or C_{max} (b)

Correlation coefficient: (a) 0.97 ($p<0.01$), and (b) 0.96 ($p<0.01$).
Key: see Fig. 7 and (●*) nifedipine-PVP "coprecipitate," and (▲*) physical mixture. The data with asterisks are cited from our previous paper.[2]

observed concentration (C_{max}) and time required to attain maximum observed concentration (T_{max}).

Nifedipine was rapidly absorbed after oral administrations of the coprecipitated fine granules (T_{max}=20 min, C_{max}=177 ng/ml). In the case of the coprecipitated fine granules stored under humid conditions (dissolution at 10 min, about 75%), T_{max} did not change but C_{max} decreased to 102 ng/ml. In the case of the plain granules (dissolution at 10 min, only about 40%), C_{max} found to be the lowest (83 ng/ml) and T_{max} was delayed (27 min). The value of AUC decreased in parallel with the decrease of the dissolution at 10 min.

Relationships between dissolution behavior and bioavailability (expressed as dissolution percentage *versus* AUC or C_{max}) are shown in Fig. 8. They include the data on the "coprecipitate" and the physical mixture, which were reported in a previous paper.[2] Linear correlations exist between the amount of nifedipine dissolved in 10 min and the variables of bioavailability. The correlation coefficients are 0.97 (AUC) and 0.96 (C_{max}). These good *in vitro-in vivo* correlations suggest that the dissolution process is the rate-limiting step in the absorption of nifedipine from the gastrointestinal tract.

The present investigation reconfirmed that the coprecipitate system effectively improves the bioavailability of nifedipine. It is also concluded that coprecipitate systems of nifedipine with PVP should be stored with protection from humidity so as to avoid a decrease of the bioavailability.

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References and Notes

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