

## Release Characteristics of Nifedipine from 2-Hydroxypropyl- $\beta$ -cyclodextrin Complex during Storage and Its Modification of Hybridizing Polyvinylpyrrolidone K-30

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Amorphous nifedipine powders were prepared by spray-drying with 2-hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CyD) or polyvinylpyrrolidone K-30 (PVP). Upon storage of the products at a high temperature and humidity, nifedipine crystallized in matrices, yielding both bigger crystals ( $> 50 \mu\text{m}$ ) in a PVP matrix and smaller crystals (about  $5 \mu\text{m}$ ) in a HP- $\beta$ -CyD matrix. The release of nifedipine from tablets containing the HP- $\beta$ -CyD complex was accelerated upon storage, whereas that from the PVP solid dispersion was decelerated. The deceleration of the release rate was attributable to the growth of nifedipine crystals with a larger size in the PVP matrix. The release of nifedipine from the HP- $\beta$ -CyD complex at the early stage of storage was rather slow due to the low wettability and high compressibility of the tablets. However, over a longer period of storage, the inhibitory effect of HP- $\beta$ -CyD on the crystal growth of nifedipine took effect, leading to the release acceleration. To maintain the improved release of nifedipine over a long period of storage, a possible combination of HP- $\beta$ -CyD and PVP was investigated to act as a hybridizing drug carrier. Among various compositions, the 1:3:1 (nifedipine:PVP:HP- $\beta$ -CyD, weight ratio) product gave the most appropriate release profile without any decreased release of nifedipine at the early and late stages of storage.

**Keywords** nifedipine; 2-hydroxypropyl- $\beta$ -cyclodextrin; polyvinylpyrrolidone K-30; crystal growth; release control; storage

The oral bioavailability of nifedipine, a calcium channel antagonist, is known to be low because of its poor solubility and the slow dissolution of nifedipine crystals in water.<sup>1)</sup> Various pharmaceutical preparations such as polyvinylpyrrolidone<sup>1)</sup> and polyethylene glycol<sup>2)</sup> dispersions and fine granules<sup>3)</sup> have been developed to improve the oral bioavailability of nifedipine. However, amorphous nifedipine in these matrices gradually crystallizes during storage at high temperature and humidity, deteriorating its rapid dissolution characteristics. In previous papers,<sup>4,5)</sup> we reported that crystalline nifedipine can be converted to an amorphous form by spray-drying with 2-hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CyD), and the bioavailability of nifedipine was increased by oral administration as a HP- $\beta$ -CyD complex to dogs. In the course of the study, we found that the dissolution of nifedipine from a HP- $\beta$ -CyD complex in water tended to be accelerated upon storage, whereas that of the nifedipine/polyvinylpyrrolidone (PVP) solid dispersion was decelerated. In this study, therefore, an attempt was made to elucidate the anomalous release behavior of nifedipine in the HP- $\beta$ -CyD and PVP systems during storage. Furthermore, an optimal formulation of

HP- $\beta$ -CyD and PVP which would maintain the enhanced dissolution of nifedipine for a long period was surveyed by changing the combination ratios of each component.

### Experimental

**Materials** Nifedipine and HP- $\beta$ -CyD with an average degree of substitution of 5.8 were donated by Bayer Yakuin, Ltd. (Osaka, Japan) and Nippon Shokuhin Kako Co. (Tokyo, Japan), respectively. PVP K-30 (average molecular weight of 40000) was from Nakalai Tesque, Inc. (Kyoto, Japan). Other materials and solvents were of analytical reagent grade. All experiments were carried out under light-protected conditions to prevent the photodecomposition of nifedipine.

**Preparation of Amorphous Nifedipine Powder** Nifedipine powders were prepared according to the spray-drying method.<sup>6)</sup> Nifedipine and HP- $\beta$ -CyD or PVP in a 1:4 weight ratio were dissolved in the mixed solvent of ethanol-dichloromethane (1:1, v/v) and the solution was subjected to spray-drying, using a Pulvis GA32 Yamato spray-dryer (Tokyo, Japan). The drying conditions were the same as those reported previously.<sup>4)</sup>

**Measurements of Crystal-Growth Behavior** The test powders (150 mg,  $< 150$  mesh) were put in glass containers in desiccators at 75% relative humidity (r.h.) and then stored in incubators at  $60^\circ\text{C}$ . At appropriate time intervals, samples were withdrawn and used in further studies. The X-ray diffraction profiles were measured using a Rigaku Denki CN 4037A1 diffractometer (Tokyo, Japan) with Ni-filtered  $\text{CuK}_\alpha$  radiation. The

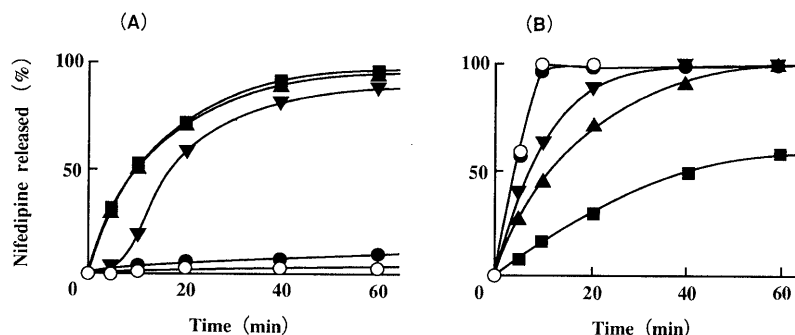


Fig. 1. Release Profiles of Nifedipine from Tablets Containing Its HP- $\beta$ -CyD Complex or PVP Solid Dispersion (Equivalent to 5 mg of the Drug) in Water at  $37^\circ\text{C}$ , Measured by the Paddle Method (100 rpm)

The samples were stored at  $60^\circ\text{C}$  and 75% r.h. for 0 d (○), 1 d (●), 3 d (▼), 7 d (▲) and 14 d (■). (A), HP- $\beta$ -CyD complex; (B), PVP solid dispersion.

apparent crystallinity of nifedipine in the physical mixture was taken as 100%, and the initial amorphous materials were considered to have 0% crystallinity. The X-ray diffraction peaks of the internal standard sample ( $S_i$ ) were measured and plots were made of the ratio of the peak height at  $2\theta = 11.8^\circ$  due to nifedipine crystals and at  $28.4^\circ$  due to  $S_i$ , then the fractional crystallization ( $\alpha$ ) of the sample was obtained by the use of calibration plots. Microscopic observations of nifedipine crystals were performed using an Olympus BH-2 microscope (Tokyo, Japan) after the removal of water-soluble ingredients by a 3-min suspension of the sample in water; no appreciable change in crystal size was observed during this wash. The average diameter and distribution of crystal size were measured using a Galai CIS-1 laser scan particle-size analyzer (Migdal Ha-Emek, Israel), after dissolving water-soluble ingredients in 0.01% (w/v) CMC solution, and were determined from particle volumes.

**Dissolution Studies** The dissolution test was essentially performed according to the paddle method in JP XII, using an automatic dissolution

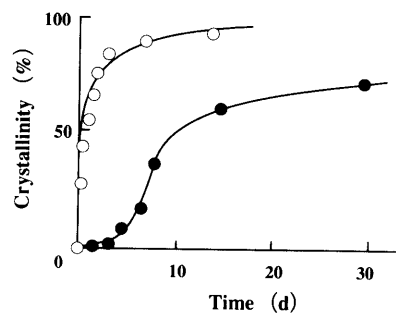


Fig. 2. Change in Apparent Crystallinity of Nifedipine in HP-β-CyD (○) or PVP (●) Matrices during Storage (60 °C and 75% r.h.)

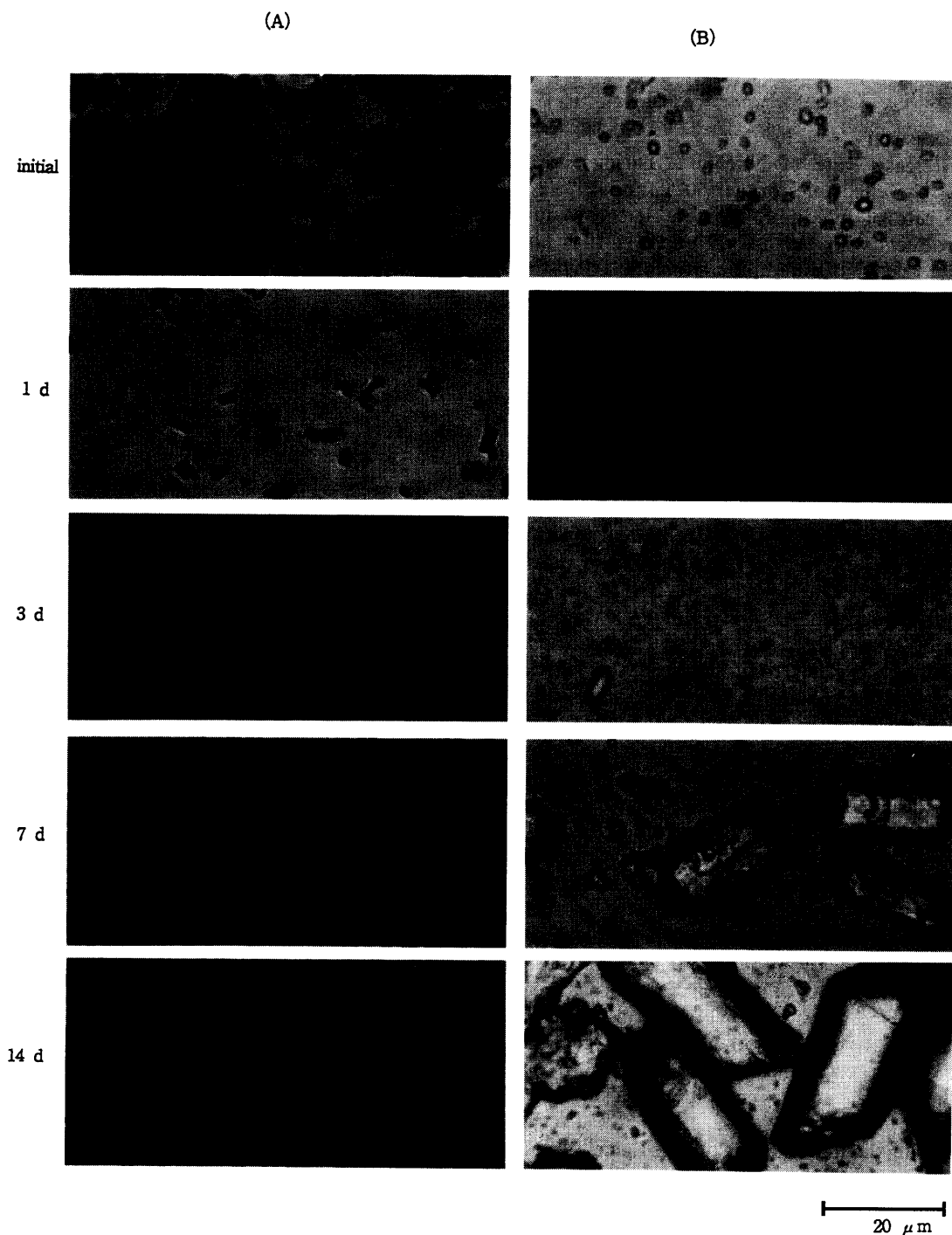


Fig. 3. Microphotographs of Nifedipine Crystals Grown in HP-β-CyD (A) or PVP (B) Matrices during Storage (60 °C and 75% r.h.)

testing apparatus.<sup>7)</sup> Deionized double-distilled water was used as a dissolution medium. Other conditions were as follows: tablet, 4 mm diameter containing 5 mg nifedipine; dissolution medium, 900 ml water; stirring speed, 100 rpm; temperature, 37°C. After storage, the test powder was dried under reduced pressure for 1 d, and compressed into tablets under a pressure of 50 kg cm<sup>-2</sup> in a hydraulic press, using a model R-303 (Riken Seiki, Tokyo, Japan).

**Measurements of Physicochemical Properties of Tablets** Water penetration rates into the tablets were measured by the same apparatus described previously,<sup>8)</sup> *i.e.*, the water uptake rate was read from a calibrated capillary tube,<sup>9)</sup> and the lag time of water-uptake was determined by plotting the rates according to the Washburn equation<sup>10)</sup> and by reading the point of intersection on the x-axis. The contact angles were measured by placing a drop of water on tablets and taking a picture.<sup>11)</sup> The hardness of the tablets was measured using a hardness tester (Kiya Seisakusho, Ltd., Tokyo, Japan). The disintegration time of the tablets was measured according to the method described in JP XII. The above parameters were determined by at least 6 repetitions. The tablet surface before and after storage was observed by a scanning electron microscope (Hitachi-Akashi S-501, Tokyo, Japan). The samples were coated with gold using a direct current sputter technique.

## Results and Discussion

### Change in Release Rate of Nifedipine during Storage

Figure 1 shows the effect of storage (60°C and 75% r.h.) on the release rate of nifedipine from tablets containing spray-dried products with HP-β-CyD or PVP. It is noteworthy that the release of nifedipine from the HP-β-CyD product in water was accelerated upon storage, whereas that from the PVP product was decelerated. The deceleration of the PVP product may be attributable to the crystal-growth of nifedipine in the matrix during storage, because the dissolution of nifedipine is known to be significantly affected by change in crystal size.<sup>2)</sup> Thus, to gain insight into the change in the release rate of nifedipine, some physicochemical properties, such as the crystallinity and crystal size of nifedipine in the HP-β-CyD complex and the PVP solid dispersion, were investigated. Figure 2 shows the change in apparent crystallinity of nifedipine in the matrices during storage at 60°C and 75% r.h. The spray-dried products of nifedipine with HP-β-CyD or PVP were in an amorphous form, but on storage at higher temperature and humidity, nifedipine crystals took shape in the matrices. The conversion rate of nifedipine from an amorphous to crystalline state was faster in the HP-β-CyD matrix than in the PVP matrix. On the other hand, the crystal size of nifedipine grown in the PVP matrix was much bigger than that grown in the HP-β-CyD matrix, as shown in Fig. 3. Figure 4 shows the change in crystal size of nifedipine grown in the matrices during storage. Nifedipine crystals grown in the PVP matrix had a mean diameter of about 50 μm (after storage of 28 d) and tended to increase on further storage, whereas the diameter of the crystals in the HP-β-CyD matrix was below about 5 μm. These results may indicate that a small number of nifedipine nuclei are created in the PVP matrix and grow up slowly to form big crystals. In the HP-β-CyD matrix, on the other hand, a large number of nifedipine nuclei crystallize rather quickly to small crystals and the crystallization is completed in a short period of time.

**Factors Affecting the Release Rate of Nifedipine** In order to gain insight into the change in release rate of nifedipine from amorphous products during storage, some properties of the tablets were investigated. Figure 5 shows the wettability of the tablets, measured according to the lag

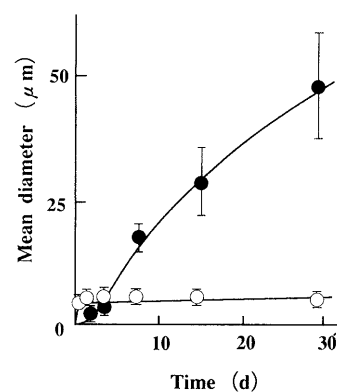


Fig. 4. Change in Mean Diameter of Nifedipine Crystals Grown in HP-β-CyD (○) or PVP (●) Matrices during Storage (60°C and 75% r.h.)

The bar represents the S.D. of the mean diameter.

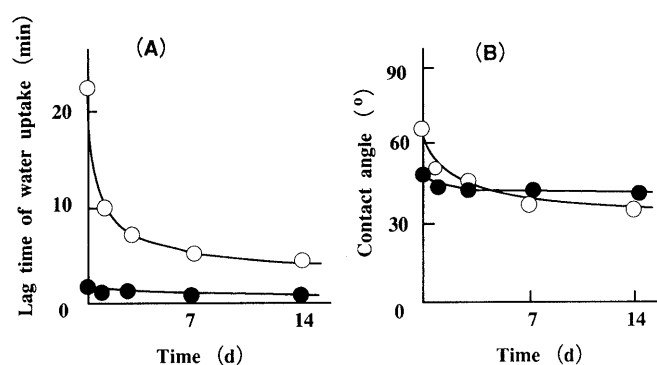


Fig. 5. Wettability of Tablets Containing HP-β-CyD Complex (○) or PVP Solid Dispersion (●), Measured by Changes in Lag Time of Water Uptake (A) and Contact Angle (B)

The samples were stored at 60°C and 75% r.h.

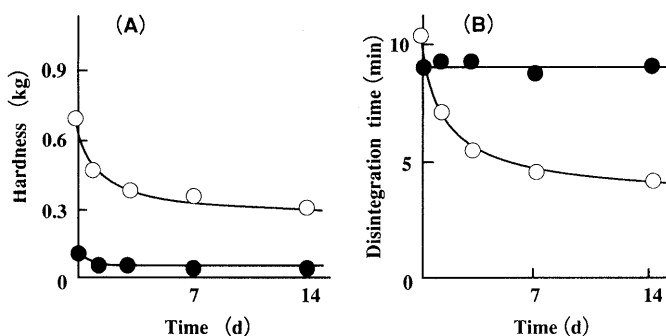


Fig. 6. Changes in Hardness (A) and Disintegration Time (B) of Tablets Containing HP-β-CyD Complex (○) or PVP Solid Dispersion (●) during Storage (60°C and 75% r.h.)

time of water-uptake and the contact angle. The wettability of the HP-β-CyD complex was low at the early stage but increased upon storage, whereas that of the PVP product remained almost constant. Figure 6 shows the hardness and disintegration time of tablets containing the HP-β-CyD complex or the PVP solid dispersion. It is obvious that both parameters of the HP-β-CyD complex decreased with an elapse of time, whereas those of the PVP solid dispersion were little changed. The longer disintegration time of the PVP product, in spite of the lower hardness, may result from the binding action of PVP. The tablet surface of the HP-β-CyD product was significantly changed upon storage,

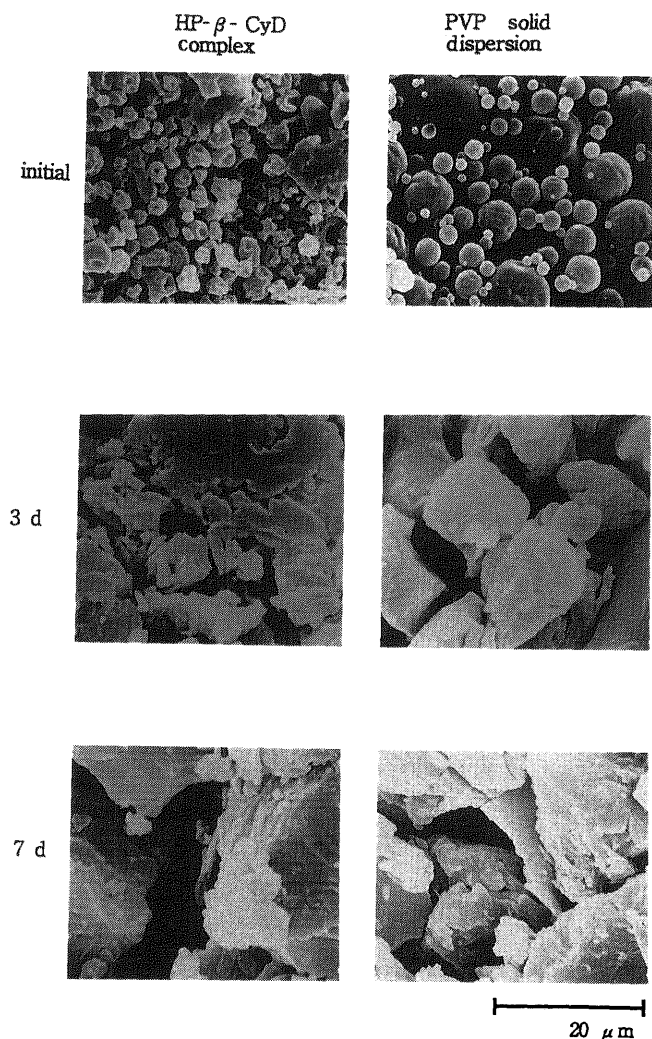


Fig. 7. Scanning Electron Micrographs of Surface of Tablets Containing HP-β-CyD Complex or PVP Solid Dispersion, Stored at 60°C and 75% r.h.

as is apparent from the photograph shown in Fig. 7. In the initial state, small particles of the HP-β-CyD complex were closely packed in the tablets, whereas on storage, a number of large pores were created on the surface and became progressively larger. In the case of the PVP product, the surface was little changed from about 1 d, although the surface immediately after spray-drying was slightly more closely packed. These changes in solid characteristics may be ascribed to the difference in moisture sorption behavior between HP-β-CyD and PVP, because the moisture sorption of the latter was about twice as high as that of the former, as shown in Fig. 8. The above results suggest that the inferior dissolution of the nifedipine/PVP solid dispersion upon storage is attributable to the formation of larger nifedipine crystals, since there was little change in its solid characteristics, such as wettability and compressibility. On the other hand, the rapid release property of the amorphous nifedipine-HP-β-CyD complex at the early stage of storage may be counteracted by the above described solid-characteristics of the complex, and after a long period of storage, the inhibitory effect of HP-β-CyD on the crystal growth of nifedipine may overwhelm the solid characteristics.

**Modified Release of Nifedipine by Hybridizing HP-β-CyD**

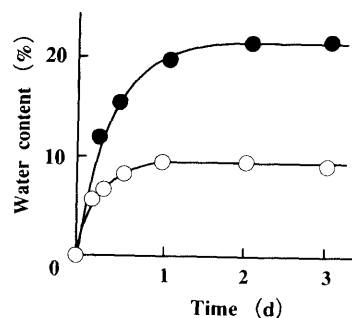


Fig. 8. Moisture Sorption Curves of HP-β-CyD Complex (○) or PVP Solid Dispersion (●), Stored at 60°C and 75% r.h.

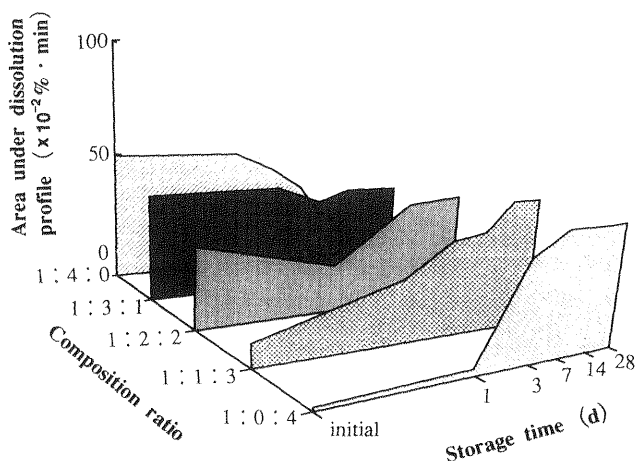


Fig. 9. Plots of Area under Release Profiles against Composition (Nifedipine: PVP: HP-β-CyD, Weight Ratio) and Period of Storage (60°C and 75% r.h.).

**and PVP** As mentioned above, opposite release characteristics, *i.e.*, acceleration and deceleration upon storage, respectively, of HP-β-CyD and PVP were observed. This led us to design a combined formulation of both components in order to maintain an improved release of nifedipine over a long period of storage. Figure 9 shows the change in the release behavior of nifedipine from tablets containing both the HP-β-CyD and PVP products in various ratios. In Fig. 9, the areas under the release profiles were plotted against the composition ratio and storage time, since there was little change in the release pattern of the products during storage. It is apparent that the release rate of nifedipine from the HP-β-CyD product at the early stage of storage increased with increasing amounts of the PVP product, and that the release rate can be controlled by combining HP-β-CyD and PVP in various ratios. Among these compositions, the 1:3:1 (nifedipine:PVP:HP-β-CyD) ratio seemed to be the most appropriate from a viewpoint of quality assurance, because this product resulted in a fast and constant release of nifedipine over a long period of time under the accelerated storage condition (60°C and 75% r.h.).

The present results suggest that the physicochemical properties of a spray-dried HP-β-CyD complex, such as wettability and compressibility, are significantly affected by humidity, resulting in changes in release rate; thus attention should be given to the storage conditions of the complexes. A combination of HP-β-CyD and PVP can serve as a better drug-carrier for maintaining the superior release characteris-

tics of nifedipine combined with a good tolerance for storage. Furthermore, this formulation may be particularly useful in solving the bioavailability problems encountered by the storage of amorphous nifedipine in solid dosage forms.

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