Effect of 2-Hydroxypropyl-β-cyclodextrin on Crystallization and Polymorphic Transition of Nifedipine in Solid State

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The glassy state of nifedipine (NP) was prepared in the absence and presence of 2-hydroxypropyl-β-cyclodextrin (HP-β-CyD), and its crystallization and polymorphic transition behavior was investigated by differential scanning calorimetry (DSC) and powder X-ray diffractometry. In DSC thermograms, the glassy NP exhibited an endothermic peak at 48°C representing the glass transition of NP, an exothermic peak at 105°C for the crystallization to a metastable form of NP (Form B), an exothermic peak at 125°C for the polymorphic transition of Form B to a stable form of NP (Form A), and an endothermic peak at 171°C for the melting of Form A. The powder X-ray diffractogram of Form B was apparently different from that of Form A. In the presence of HP-β-CyD, the exothermic peak at 125°C for the Form B to A transition disappeared and a new endothermic peak appeared at 163°C. This new peak was ascribed to the melting of Form B, and the conversion of Form B to Form A was significantly suppressed in HP-β-CyD matrix. Upon storage at 60°C, the glassy NP was converted to Form A with an activation energy of 18 kcal/mol. The apparent dissolution rate of the NP/HP-β-CyD (molar ratio 1:1) increased in the order of glassy NP < Form A < Form B, because the glassy NP was readily converted to Form A upon contact with water, resulting in a lower dissolution rate. The present data suggest that HP-β-CyD is useful for the preparation of a fast dissolving form of metastable NP through glassy NP.

KEY WORDS: nifedipine; 2-hydroxypropyl-β-cyclodextrin; crystallization; polymorphic transition; dissolution.

INTRODUCTION

Many solid compounds exist in different crystalline modifications such as amorphous, crystalline or solvated forms, affecting solubility, dissolution rate, stability and bioavailability of the drugs. Therefore, it is important to control the crystallization and polymorphic transition of solid drugs (1–3). The multi-functional characteristics of cyclodextrins (CyDs) can improve pharmaceutical properties of drug molecules, as drug carriers (4–6). 2-Hydroxypropyl-β-CyD (HP-β-CyD) has superior properties (a highly water-soluble, amorphous powder with no detectable oral toxicity) as a pharmaceutical additive (7–9). Crystalline nifedipine (NP), a calcium channel antagonist, is converted to an amorphous state by spray-drying with HP-β-CyD, and the bioavailability of NP is improved by oral administration of the spray-dried product in dogs (10,11). In the course of the study, we found that a metastable form of NP occurs at an early stage of the crystallization of NP from the spray-dried HP-β-CyD complex. This metastable NP resembled one (Form II) of NP modifications reported by Eckert & Müller (12) in thermal behavior. However, the crystallization and polymorphic transition behavior of NP modifications is poorly understood because of their lability. In this study, glassy NP was prepared by using HP-β-CyD matrix and its crystallization and polymorphic transition behavior was investigated in detail.

MATERIALS AND METHODS

Materials

NP and HP-β-CyD with an average degree of substitution of 5.8 were donated by Bayer Yakuhin Ltd. (Osaka, Japan) and Nippon Shokuhin Kako Co. (Tokyo), respectively. Other materials and solvents were of analytical reagent grade. All experiments were carried out under light-protected conditions to prevent the photodecomposition of NP.

Preparation of Glassy NP

NP crystals (size < 5 μm) or its physical mixture with HP-β-CyD (molar ratio of 1:1, about 300 mg) were wrapped with aluminium foil and heated to 200°C at a heating rate of 5–10°C/min in an oven and the NP melt or the solid samples containing NP melt were immediately cooled down to 0°C. No degradation of NP under these experimental conditions was confirmed by gas-chromatography (13).

Powder X-ray Diffractometry and Differential Scanning Calorimetry (DSC)

The X-ray diffraction profiles were measured using a Rigaku Rint-2500 (voltage 60 kV and current 300 mA, Tokyo) or a Rigaku CN4037A1 (voltage 30 kV and current 20 mA) diffractometer with Ni-filtered Cu-Kα radiation. Because the glassy NP was readily transformed to the stable form of NP by mechanical stresses such as grinding, the sample was carefully mounted on a glass plate. DSC measurements were carried out by a Rigaku Denki TAS 100 thermal analyzer with a data analysis system. The sample (3.0 mg) was heated at a scanning rate of 10°C/min over the temperature range of 25–200°C. The heat of fusion was calibrated with using indium (purity: 99.999%, melting point: 156.4°C, ΔH: 6.80 mcal/mg, heating rate: 10°C/min) (14), and was determined from an average of three measurements, which was within 3% of each other.

Ageing Studies in Isothermal Condition

The test powders (5 mg) were placed in DSC cells, in desiccators at constant relative humidities, and then stored at constant temperatures. At appropriate time intervals the samples were withdrawn and subjected to DSC measurements. In the case of higher humidities, the samples were dried for 2 h over P_2O_5 before DSC measurements.

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Dissolution Studies

The dissolution behavior of NP was examined according to the dispersed amount method (15). An excess amount of sample powder (equivalent to 5.0 mg NP) was added to water (900 ml), and the dissolution medium was stirred at 37°C and 100 rev min^{-1}. At appropriate time intervals, a 5.0 ml of solution was sampled by a pipet with a cotton plug and diluted with water and NP was assayed spectrophotometrically at 254 nm. No degradation of NP under the dissolution test was confirmed by gas-chromatography (13).

RESULTS AND DISCUSSION

Transition Behavior of Glassy NP

A glassy state of NP was prepared by the chilling method, and its transition behavior was investigated. The chilled NP showed a halo-pattern in the powder X-ray diffractogram and four endo- or exo-thermic peaks at 48°C, 105°C, 125°C and 171°C were observed in the thermogram. These results suggested that the chilled NP may be in glassy state and changes to other forms during the non-isothermal heating. The endo- and exo-thermic peaks were assigned as follows: (1) The small endothermic peak at 48°C is due to a glass transition of NP, because of the increase in heat capacity of NP, and this transition temperature was similar to that of felodipine, a nifidipine derivative (16). The ratio of the glass transition temperature and melting point (171°C as described later) of NP was 0.72 (= 321/444) and within the range (0.69–0.85) so far reported for other glassy compounds (17). (2) The exothermic peak at 105°C is due to the crystallization to a metastable NP (defined as Form B), because the preheated chilled NP to 110°C resulted in only a polymorphic transition to a stable NP (defined as Form A) at 125°C. The powder X-ray diffractogram of the preheated NP was apparently different from those of glassy NP and Form A, as described later. (3) The small exothermic peak at 125°C is due to the polymorphic transition of Form B to Form A, because the preheated chilled NP to 130°C showed only an endothermic peak at 171°C due to the melting of Form A, and its diffraction pattern coincided with that of Form A. (4) The endothermic peak at 171°C is due to the melting of Form A.

The powder X-ray diffraction pattern of several NP forms was compared to assess the internal structure of Form B (Fig. 1). The diffraction pattern of the ground stable NP crystals (Fig. 1b) coincided in both reflection angle (2 θ) and intensity with those of the computer-simulated pattern (Fig. 1a) drawn on the basis of single crystal data of NP (18). In the case of the unground stable NP crystals and Form A crystals grown from the glassy NP (Figs. 1c and 1d), the diffraction intensities were apparently different from the theoretical one, although the 2 θ angle coincided with the theoretical one, suggesting an anisotropically developed crystal plane. For example, the peaks at 2 θ = 8.06°, 16.19° and 24.37° assigned to the crystal planes of Miller indices (100), (200) and (300 or 221), respectively, were much stronger than other peaks, suggesting a well-developed (h00) plane. On the other hand, the diffraction pattern of Form B (Fig. 1e) was apparently different in both 2 θ and intensity from stable NP crystals, two new peaks being observed at 2 θ = 7.14° and 23.93°, indicating that Form B is a polymorph of NP. Since NP molecules in the Form A crystal are hydrogen-bonded to each other to form a molecular layer in the bc plane which then stacks along a-axis (18), this stacking seems to be irregular (19) in the Form B crystal. If the peak of Form B at 7.14° is assumed to be the reflection from the (100) plane, the a-axis (12.37 Å) is longer by about 1.4 Å than that (10.97 Å, 2 θ = 8.06°) of Form A, although the crystal system of Form B is unknown. The loosely stacked layer structure of NP molecules in the a-axis direction can be postulated as a possible packing mode for the metastable NP crystal.

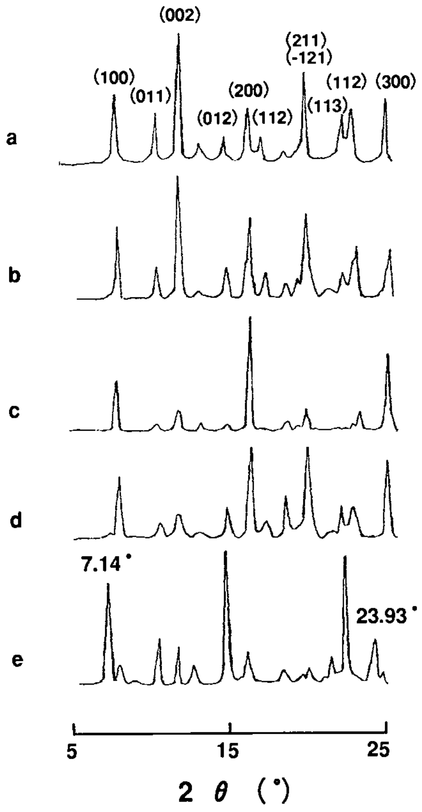

Fig. 1. Powder X-ray diffractograms of NP crystals prepared various methods. (a) computer-simulated pattern of NP; (b) Form A recrystallized from methanol (ground); (c) Form A recrystallized from methanol (unground); (d) Form A prepared by heating glassy NP to 130°C; (e) Form B prepared by heating glassy NP to 110°C.

Non-isothermal Transition Behavior of Glassy NP in the Presence of HP-β-CyD

Fig. 2 shows DSC thermograms of the chilled NP/HP-β-CyD in various molar ratios. With increasing amount of HP-β-CyD, the exothermic peak (125°C) of the Form B to Form A transition and the endothermic peak (171°C) of the melting of Form A disappeared, while a new endothermic peak appeared at 163°C. This new endothermic peak could be assigned to the melting of Form B, because the heated sample (up to about 130°C) of the chilled NP/HP-β-CyD exhibited powder X-ray diffraction peaks at 2θ = 7.1° and 23.9° characteristic of Form B. The area of the 163°C-peak was constant above the 1:1 (NP/HP-β-CyD) molar ratio, thus the 1:1 mixture was used in the following study. The glassy NP

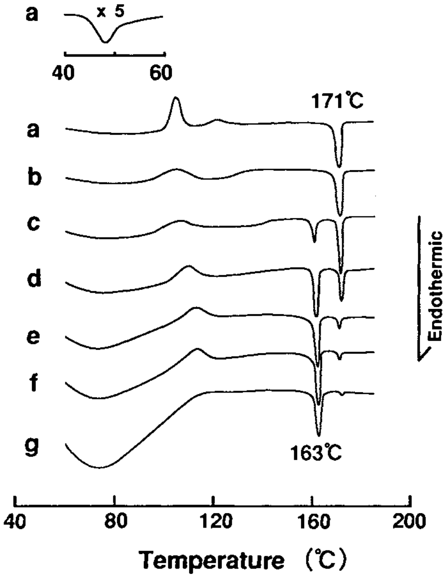

Fig. 2. DSC thermograms of chilled NP/HP-β-CyD mixtures in various molar ratios (content of NP: 0.6 mg). NP/HP-β-CyD: (a) 1:0.0 (NP alone); (b) 1:0.25; (c) 1:0.5; (d) 1:0.75; (e) 1:1; (f) 1:1.5; (g) 1:2.

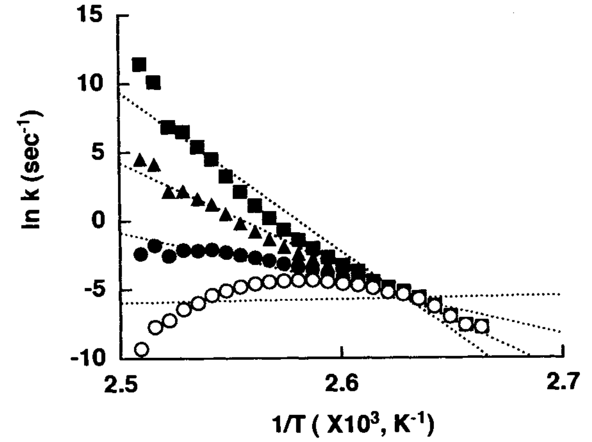

Fig. 3. Arrhenius plots for conversion of glassy NP to Form B in HP-β-CyD matrix, assuming various reaction orders (n). (○) n = 0 (correlation coefficient (r) = 0.084; (●) n = 1, r = 0.956; (▲) n = 2, r = 0.993; (■) n = 3, r = 0.975.

in HP-β-CyD matrix was easily converted to Form A by physical impacts; for example, the 3 min-grinding caused the conversion of glassy NP to Form A. However, the endothermic area of 171°C accounted for 75% of total NP amount in the matrix, when the NP amount was calculated using the known heat of fusion (6.8 kcal/mol) of Form A. The residual NP (25%) may exist as an amorphous inclusion complex with HP-β-CyD which was stable to the grinding and heating. The heat of fusion of Form B at 163°C was calculated to be 5.7 kcal/mol. The crystallizing behavior of glassy NP to Form B in HP-β-CyD matrix during DSC heating was investigated by analyzing the exothermic peak of about 105–115°C according to Eq. (1) reported by Torfs et al. (20):

$$k = (dH/dt)/[\Delta H_{total}(\Delta H_{rest}/\Delta H_{total})^n] \qquad (1)$$

where n is reaction order, and dH/dt, ΔH_{total} and ΔH_{rest} are heat flow, total heat and residual heat above T_i, respectively, which were calculated from areas of the peak (20). Then, the crystallization rate constant (k) was calculated at various T_i, and the Arrhenius plots assuming n = 0 to 3 are shown in Fig. 3. The plot gave a good straight line when n = 2, suggesting the second order crystallization, and the activation energy assuming the second order crystallization was 153.4 kcal/mol.

The transition of Form B to Form A in HP-β-CyD matrix was carried out in a DSC cell at 145°C, i.e., the chilled mixture was heated (10°C/min) to 145°C to convert glassy NP to Form B, and maintained at 145°C for constant periods, and then DSC was measured up to 200°C. The amounts of Form A and Form B were calculated from the endothermic area of 171°C and 163°C, respectively, using their heats of fusion. Fig. 4 shows the time course for the conversion of Form B to Form A in HP-β-CyD matrix at 145°C, where the amount of Form B decreased with increase in that of Form A. The Hancock-Sharp plot (Eq. (2)) (21–23) for the conversion gave a straight line with a slope (m) of 0.95 as shown in Fig. 4B. In Eq. 2, α is the fraction of

$$\ln[-\ln(1-\alpha)] = \ln B + m \cdot \ln t \qquad (2)$$

transition, B is a constant, t is the time interval to be kept at 145°C, m is an intrinsic value depending upon reaction mechanism. The m value of 0.95 indicated that the transition of Form B to Form A in HP-β-CyD matrix proceeds according

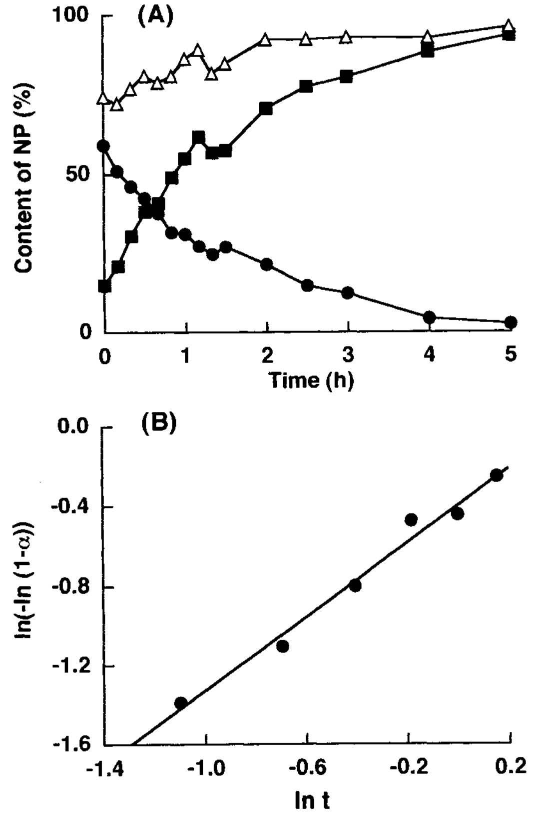

Fig. 4. Time courses (A) and Hancock-Sharp plot (B) for conversion of Form B to Form A in HP-β-CyD matrix at 145°C. (■) Form A; (●) Form B; (△) Form A + Form B.

to the first-order mechanism. Unfortunately, detailed analysis could not be undertaken because NP (25%) in the amorphous complex was simultaneously converted to Form A at the high temperature (see the change in total content of NP in Fig. 4).

Isothermal Transition Behavior of Glassy NP in the Presence of HP-β-CyD

The chilled NP/HP-β-CyD mixture was stored at 60°C, a temperature below the crystallization, and over P_2O_5 to avoid the effect of humidity. Upon the storage, the exothermic peak at about 105–115°C and the endothermic peak at 163°C decreased, while the endothermic peak at 171°C increased, suggesting that the glassy NP was converted to Form A in the HP-β-CyD matrix. Fig. 5A shows the time course of the conversion of glassy NP to Form A at 50–80°C, where contents of the glassy NP and Form A were calculated from the exothermic area at about 105–115°C (glassy NP to Form B) or the endothermic area at 163°C (melting of Form B) and the endothermic area at 171°C (melting of Form A), respectively. The content of Form A increased with time, with concomitant decrease of glassy NP (data were not shown here). The amount of (glassy NP + Form A) was about 75% of total NP in HP-β-CyD matrix, thus the remaining 25% of NP would be thermally stable complex under these experimental conditions. Since the Hancock-Sharp plots (Eq. 2) gave m = 1.95, the time courses were analyzed according to the Avrami-Erofeev equation (Eq. (3)) (21) to obtain rate constants (k) of the crystallization.

$$[-\ln(1 - \alpha)]^{1/2} = kt \qquad (3)$$

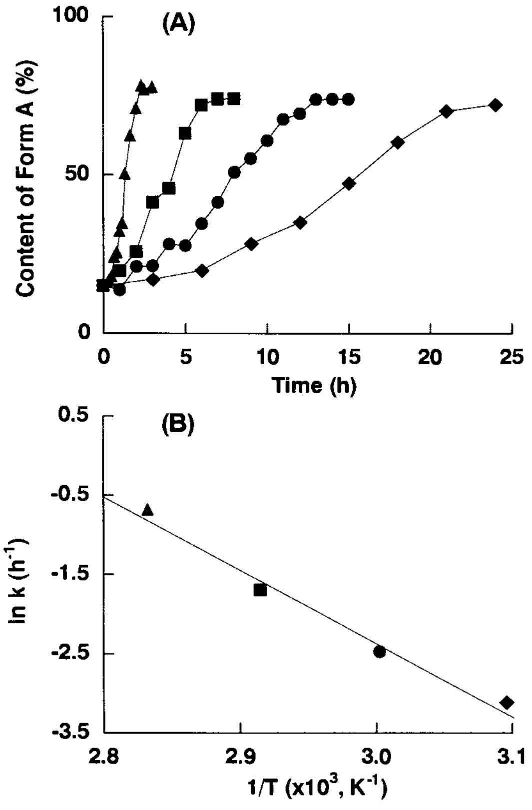

Fig. 5. Time courses (A) and Arrhenius plot (B) for formation of Form A from glassy NP in HP-β-CyD matrix, during storage over P_2O_5 and at various temperatures. (◆) 50°C; (●) 60°C; (■) 70°C; (▲) 80°C.

The activation energy for the crystallization of the glassy NP to Form A in HP-β-CyD matrix was calculated from the Arrhenius plot (Fig. 5B) and was 18.0 kcal/mol. Fig. 6 shows the effect of humidity on the crystallization of the glassy NP to Form A in HP-β-CyD matrix at 60°C. The crystallization rate of the glassy NP increased with increasing humidity, and all NP in HP-β-CyD matrix was converted to Form A. In contrast to the case of storage over P_2O_5, the sample powders stored at higher humidities may adsorb sufficient moisture to form supersaturated liquid phase on surface of particles, in which the nucleation and crystallization of the glassy NP (75%) including the amorphous form (25%) may occur. The rapid conversion of the glassy NP to Form A upon contact with water was observed in the dissolution studies as described below.

Dissolution Behavior of NP in HP-β-CyD Matrix

Fig. 7 shows the dissolution profiles of the glassy NP, Form B and Form A in HP-β-CyD matrix. The apparent dissolution rate of NP increased in the order of glassy NP < Form A < Form B, although the initial rate was Form A < Form B = glassy NP. The rate deceleration of the glassy NP may be due to the rapid conversion to stable NP crystals with larger size, after contact with water, as expected from Fig. 6. Indeed, Form A having crystal size more than 0.3 mm precipitated from the dissolution medium during the measurements.

CONCLUSION

The glassy NP in HP-β-CyD matrix was converted to the metastable form of NP, Form B, in the non-isothermal heating, whereas it was converted to Form A when stored below the crystallization and transition temperatures. The Arrhenius plots for conversions of the glassy NP to Form A (activation energy: 18.0 kcal/mol) and to Form B (153.4 kcal/mol) intersected at about 105°C. This roughly coincided with the polymorphic transition temperature of 125°C (Form B to

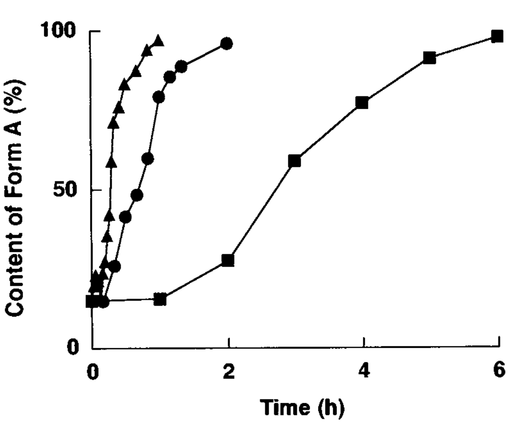

Fig. 6. Time courses for formation of Form A from glassy NP in HP-β-CyD matrix, during storage at 60°C and various relative humidities (R.H.). (■) 22% R.H.; (●) 50% R.H.; (▲) 75% R.H.

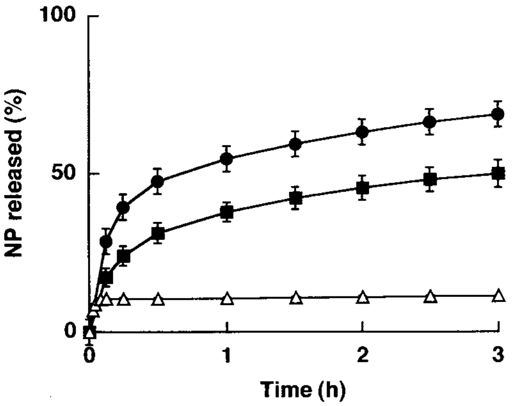

Fig. 7. Dissolution behavior of glassy NP (△), Form A (■) and Form B (●) in HP-β-CyD matrix, measured by dispersed amount method (medium: water at 25°C).

Form A), although a different analytical treatment and temperature range were employed. Therefore, the transition of glassy NP to Form A in HP-β-CyD matrix may precede that to Form B at lower temperature, whereas the latter route precedes at higher temperature. The present data suggest that HP-β-CyD is useful for the selective preparation of Form B as a fast dissolving form of NP, and will provide a rational basis for design of formulation and storage condition in the solid dosage forms of NP.

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