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Original Article

Effects of 2-Hydroxypropyl-β-cyclodextrin on Polymorphic Transition of Chlorpropamide in Various Conditions: Temperature, Humidity and Moulding Pressure

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Abstract

The amorphous complex of 2-hydroxypropyl-β-cyclodextrin (HP-β-CyD) with an oral hypoglycemic agent, chlorpropamide (CPM), in a molar ratio of 1:1 was prepared by the spray-drying method. The effects of storage (temperature and humidity) and moulding pressure on the polymorphic transition of CPM in HP-β-CyD matrix were investigated, in comparison with those of the CPM polymorphs, Form A (stable form) and Form C (metastable form). The formation of an amorphous complex of CPM with HP-β-CyD was confirmed by powder X-ray diffractometry and differential scanning calorimetry. During storage at various temperature and humidity conditions, the metastable Form C of CPM converted to the stable Form A, where the conversion proceeded according to the Jander equation with an activation energy of 51 kJ/mol (25–60 °C) and a reaction-order of 1.55 with respect to water content (relative humidity (RH) 20–75%). No polymorphic transition of Form A crystals was observed under the experimental conditions. In the case of the amorphous HP-β-CyD complex, Form C crystals were slowly produced, but the further conversion of the resulting Form C to Form A was markedly suppressed in HP-β-CyD matrix. Upon compression (2000 kg/cm^2), Forms A and C were converted to amorphous CPM in a major portion and Forms C and A, respectively, in a minor portion. The polymorphic transition behavior was clearly reflected in the dissolution rate of CPM, i.e., (1) the dissolution rate was in the order of HP-β-CyD complex > Form C > Form A, and (2) the dissolution rate of Forms A and C after the compression increased because of the conversion to amorphous state, while the complex maintained the fast dissolving property even after the compression. The results indicated that HP-β-CyD is useful not only for converting crystalline CPM to an amorphous substance, but also for maintaining the metastable form with fast dissolution rate, Form C, over a long period.

Introduction

The phenomenon in which a solid compound crystallizes into different forms, is expressed as polymorphism. Pharmaceutical properties of different polymorphs can vary significantly; for example, solubility, dissolution rate, stability and bioavailability, etc., of drugs [1, 2]. As a consequence, the rational control of crystal growth, habit and polymorphic transition, using pharmaceutical additives, becomes an attractive and intriguing area of drug research and development. Cyclodextrins (CyDs), cyclic oligosaccharides consisting of 6–8 glucose units linked through α-1,4 glycosidic bonds, form inclusion complexes with various drug molecules in solution and in solid state and have been utilized successfully to improve certain properties such as the solubility, stability and bioavailability of drugs [3, 4]. Many reports have shown that crystalline drugs can be converted to amorphous forms by complexation with amorphous CyDs such as 2-hydroxypropyl-β-CyD (HP-β-CyD), and their aqueous solubility and dissolution rates thus markedly increased [5–7]. However, the effects of storage and pressure during compression on pharmaceutical properties of amorphous CyD complexes, such as crystallization, dissolution and absorption behavior, etc., have not fully been elucidated. In previous papers [8, 9], we reported that an oral hypoglycemic agent, tolbutamide, forms an amorphous inclusion complex with HP-β-CyD, in which matrix the polymorphic transition of the drug is inhibited. In the present study, we looked at the effects of moulding pressure during tableting and storage

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Figure 1. Chemical structure of chlorpropamide (CPM).

conditions (temperature and humidity) on the crystallization of an oral hypoglycemic agent, chlorpropamide (CPM, Figure 1), from its HP-β-CyD complex, in comparison with those of CPM polymorphs. CPM was chosen because it has low solubility in water (7.5×10^{-4} M at 25 °C) and has several polymorphic forms, such as a stable form (Form A) and a metastable form (Form C), which are subject to polymorphic transition through compression during tableting, although the detailed mechanism of the pressure-induced transition is not fully elucidated [10, 11].

Experimental

Materials

Chlorpropamide (CPM) was purchased from Tokyo Kasei Co., Ltd. (Tokyo, Japan). HP-β-CyD (DS 4.8, average molecular weight 1414) was supplied from Nihon Shokuhin Kako Co. (Tokyo, Japan). Other chemicals and solvents were of analytical reagent grade, and deionized double-distilled water was used throughout the study.

Apparatus

Powder X-ray diffractograms were measured using a Rigaku Rint-2500 diffractometer under the following conditions: Ni-filtered CuK_α radiation (1.542 Å), a voltage of 40 kV, a current of 40 mA, a divergent slit of 1.74 mm (1°), a scattering slit of 0.94 mm (1°), a receiving slit of 0.15 mm, and a goniometer angular increment of 1°/min. The differential scanning calorimetry (DSC) analyses were carried out using a Perkin-Elmer DSC-7 thermal analyzer (Norwalk, CT) with a data analysis system (DEC station 325 computer, U.S.A.), operated with sample weights of 5 mg and a scanning rate of 10 °C/min under nitrogen atmosphere.

Preparation of CPM/HP-β-CyD complex

The solid CPM/HP-β-CyD complex in a molar ratio of 1:1 was obtained by dissolving the components (CMP 0.273 and 1.414 g HP-β-CyD) in a mixed solvent of ethanol/dichloromethane (1:1 v/v, 200 mL), followed by spray-drying under the following conditions: a Pulvis GA32 Yamato spray-drier (Tokyo, Japan), an air flow rate of 0.4 m^3/min, an air pressure of 1.0 kg f/cm^3, and inlet and outlet temperatures of 85 and 55 °C, respectively.

Ageing studies

The test powder (3–5 g, <100 mesh) was placed in glass containers in desiccators at various temperatures (25, 40 and 60 °C) and relative humidity (RH. 20, 30, 45 and 75%) adjusted by solutions saturated with potassium acetate, magnesium bromide, magnesium nitrate and sodium chloride in water [12]. At appropriate time intervals, samples were withdrawn, dried under reduced pressure for about 1 day at room temperature, and subjected to powder X-ray diffractometry. The content of CPM polymorphs (Form A and Form C) in matrices was calculated from areas of the diffraction peaks at $2\theta = 6.7°$ and 15.2° characteristic of the former and the latter crystals, respectively, in comparison with the peak area of an internal standard, silicone ($2\theta = 28.6°$). The standard calibration curve was made by mixing the polymorphs and HP-β-CyD in appropriate ratios and measuring the areas of above diffraction peaks.

Preparation of tablets

The test powder (100 mg, <100 mesh) was compressed into a cylindrical tablet (diameter 7 mm) at 2000 kg/cm^3 for different periods of time (0.1–7 min), using a RIKEN IR compressing machine (Tokyo, Japan). This process was repeated several times (1–15 times) to study effects of the number of times of compression, i.e., the compressed tablet was grounded by a motor and the sieved powder (<100 mesh) was again compressed. The content of CPM polymorphs was calculated by the method outlined above, and that of amorphous CPM was estimated by subtracting the amount of Forms A and C from the total amount of CPM.

Dissolution studies

The dissolution rate was measured according to the dispersed amount method [13]. A fixed amount (equivalent to CPM 300 mg, <100 mesh) of test powder was put into 50 mL of Japanese Pharmacopoeia XIV (JP XIV) first fluid (pH 1.2) and stirred at 100 rpm at 37 °C. At appropriate intervals, an aliquot (1.0 mL) was withdrawn with a cotton-plugged pipette, diluted with water, and analyzed spectrophotometrically for CPM at 230 nm. A constant volume of dissolution medium was maintained by adding an equal volume of the original medium.

Results and discussion

Effects of storage (temperature and humidity)

The solubility method and various spectroscopic studies (UV, CD and NMR) indicated that CPM forms inclusion complexes with α-CyD, β-CyD and HP-β-CyD in a molar ratio of 1:1 in aqueous solution, which will be

reported elsewhere. Therefore, the 1:1 solid of CPM/HP-β-CyD complex was prepared by the spray-drying method, and the effect of storage conditions on the polymorphic transition of CPM was investigated. Figure 2 shows the changes in powder X-ray diffraction pattern of the metastable Form C of CPM and CPM/HP-β-CyD complex during storage at 40 °C, 75% RH. Form A (stable form of CPM) and Form C gave X-ray diffraction peaks characteristic of the former and the latter crystals at 6.7° and 15.2°, respectively, and these peaks were employed for monitoring of the polymorphic transition. On the other hand, the CPM/HP-β-CyD complex gave a halo-pattern (Figure 2B), and the endothermic peaks due to the melting of Form A (128 °C) and Form C (131 °C) completely disappeared in DSC curves (data not shown), indicating that CPM forms an amorphous complex with HP-β-CyD in the solid state. As shown in Figure 2A, a large portion (>70%) of Form C was converted to the stable Form A crystals after 4 days when stored at 40 °C, 75% R.H., under which condition the polymorphic transition of Form A was not observed. In the case of the amorphous complex (Figure 2B), the peak of Form C slowly appeared, and the transition of the resulting Form C to Form A was not observed under these experimental conditions. Figure 3 shows time courses of the transition

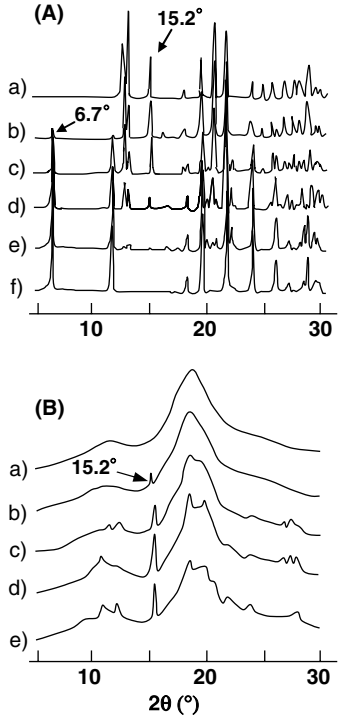


Figure 2. Changes in powder X-ray diffraction patterns of Form C and CPM/HP-β-CyD complex during storage at 40 °C, 75% RH. (A) Conversion of Form C to Form A: (a) intact Form C, (b) after 12 h, (c) after 1 day, (d) after 2 days, (e) after 4 days, (f) intact Form A. (B) Crystallization of Form C from CPM/HP-β-CyD complex: (a) intact CPM/HP-β-CyD complex, (b) after 1 day, (c) after 2 days, (d) after 7 days, (e) after 10 days.

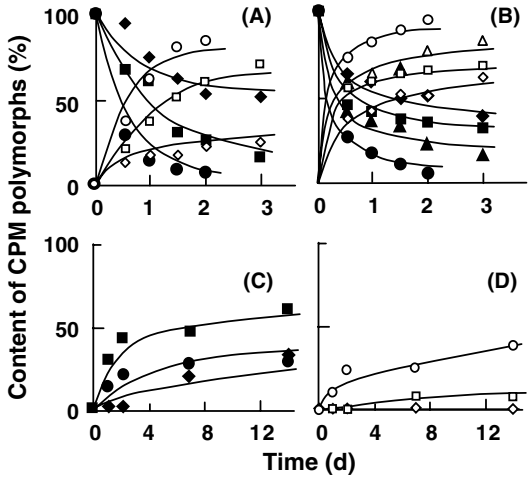


Figure 3. Time courses for contents of CPM polymorphs (Form A (open symbols) and Form C (closed symbols)) during storage at different temperature and humidity conditions. (A) Conversion of Form C to Form A at 75% RH: 25 °C (◇, ◆), 40 °C (□, ■), 60 °C (○, ●). (B) Conversion of Form C to Form A at 60 °C: 20% RH (◇, ◆), 30% RH (□, ■), 45% RH (△, ▲), 75%R.H.(○, ●). (C) Crystallization of Form C from CPM/HP-β-CyD complex at 75% RH: 25 °C (◆), 40 °C (■), 60 °C (●). (D) Crystallization of the resulting Form C to Form A in HP-β-CyD matrix at 75% RH: 25 °C (◇), 40 °C (□), 60 °C (○).

of Form C and CPM/HP-β-CyD complex during the storage. Form C was easily converted to Form A crystals, where the conversion increased as temperature and humidity increased. These transition-time profiles of Form C were analyzed according to the Hancock and Sharp equation (Equation (1) [14]):

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

where α stands for the fraction converted in time (t) and B is a constant. The plots according to Equation (1) gave a straight line (correlation coefficient (r) > 0.96) with m value of 0.55, indicating that the polymorphic transition of Form C to Form A proceeds in the three-dimensional diffusion mechanism, i.e., Jander equation shown by Equation (2) [14]:

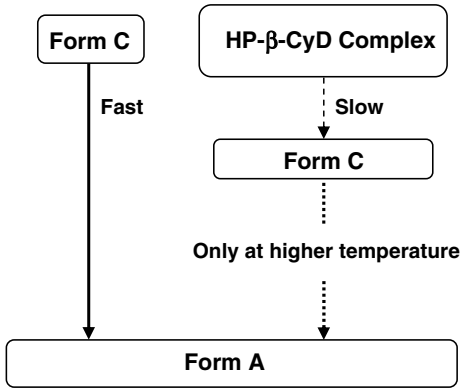
$$[1-(1-\alpha)^{1/3}]^2 = k \cdot t. \qquad (2)$$

Therefore, the conversion profiles of Figure 3 were analyzed by Equation (2) to obtain the rate constants for the transition of Form C to Form A. The plots of the left-hand side of Equation (2) *versus* time gave straight lines (r > 0.96), from whose gradients the following constants were obtained: At 75% RH (Figure 3A), k (25 °C) = 8.0×10^{-4} h^{-1}, k (40 °C) = 3.4×10^{-3} h^{-1} and k (60 °C) = 7.9×10^{-3} h^{-1}, and at 60 °C (Figure 3B), k (20% RH) = 1.0×10^{-3} h^{-1}, k (30% RH) = 1.6×10^{-3} h^{-1}, k (45% RH) = 2.6×10^{-3} h^{-1} and k (75% RH) = 7.9×10^{-3} h^{-1}. The linear Arrhenius plot gave an activation energy of 51 kJ/mol for the Form C to Form A conversion at 75% RH. Similar

activation energy of 44 kJ/mol was reported for the polymorphic transition of tolbutamide Form IV to Form II [15]. The transition rate of CPM Form C to Form A augmented as RH increased (Figure 3B). The conversion rate k in the presence of water (concentration C_{H_2O}) in the solid state is expressed in Equation (3) [16]:

$$\log k = \alpha \log(C_{H_2O}) + \log k', \qquad (3)$$

where k' and α are a second rate constant and a reaction-order with respect to water concentration. If C_{H_2O} is assumed to be equal to RH, the plot of log k *versus* log (RH) gives a straight line. In this CPM system, the α value of 1.55 was obtained from a straight line ($r = 0.97$) of the plot of log k *versus* log (RH). In the case of the CPM/HP-β-CyD complex (Figure 3C and D), Form C crystals slowly appeared, where the rate increased as temperature increased. The transition of the resulting Form C to Form A in HP-β-CyD matrix was negligible at 25 and 40 °C, whereas at higher temperature (60 °C) Form C converted to Form A. The result that the content of Form C at 60 °C is lower than that at 40 °C may be due to the consecutive conversion of Form C to Form A at a higher temperature. The crystallization of Form C from the HP-β-CyD complex was negligible at lower RH (20–45% RH). The polymorphic transition behavior of Form C and the HP-β-CyD complex was illustrated in Scheme 1. The metastable Form C of CPM is easily converted to the stable Form A, whereas in the HP-β-CyD complex Form C slowly crystallizes and the further conversion of the resulting Form C to Form A is markedly suppressed in HP-β-CyD matrix. It is well known that polymorphic transition proceeds *via* metastable forms to a stable form, according to the Ostwald's rule [7]. However, it is usually difficult to detect a metastable form, because of its labile property to convert to a stable form. Therefore, HP-β-CyD can work as a matrix for stabilization and detection of the resulting labile metastable forms.



Scheme 1. Proposed scheme for crystallization and polymorphic transition of CPM polymorphs and CPM/HP-β-CyD complex.

Compressing effects and dissolution behavior

Figure 4 shows the effects of compression during tableting, i.e., compression time and number of compression stroke, on the polymorphic transition of Forms A and C and CPM/HP-β-CyD complex. As shown in Figure 4 (upper), Forms A and C converted largely to amorphous form and slightly to their counterparts within about 1 min of the compression. Form C was more easily converted to amorphous state than Form A. When the compression was repeated (Figure 4 (lower panels)), the amount of amorphous form increased as the compressing cycle increased, and reached more than 50%, whereas the resulting counterparts were less than 20%. On the other hand, the HP-β-CyD complex exhibited no crystallization and polymorphic transition

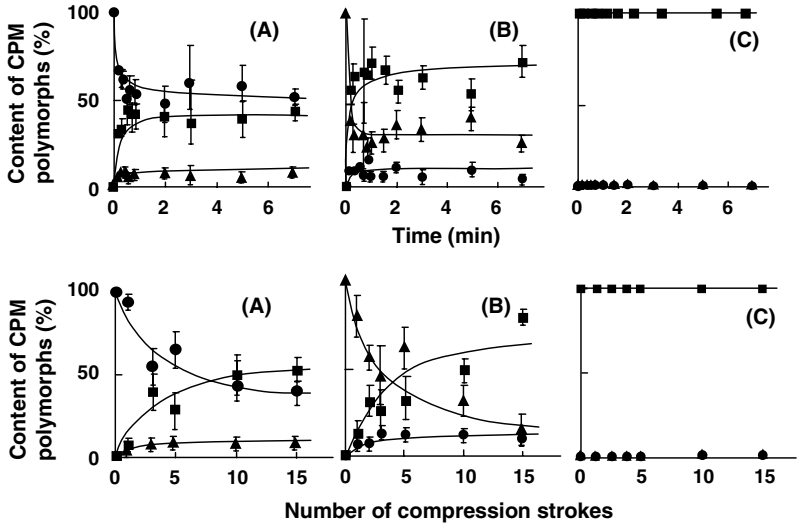


Figure 4. Changes in contents of CPM polymorphs after compression at 2000 kg/cm^2. The upper panels show the effect of compression time and the lower panels show the effect of number of compression strokes. (A) Compression of Form A, (B) Compression of Form C, (C) Compression of (A) CPM/HP-β-CyD complex. (●) Form A, (▲) Form C, (■) amorphous form.

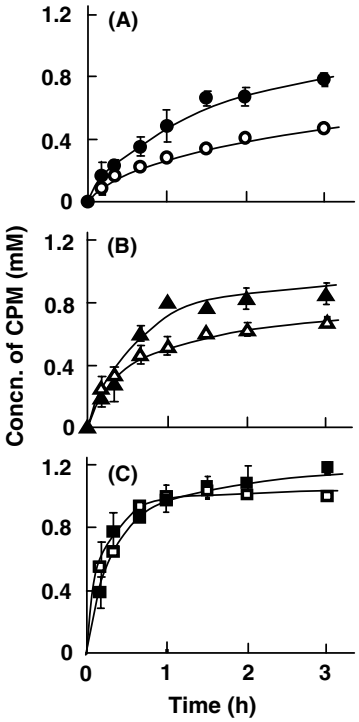


Figure 5. Dissolution profiles of Form A (A), Form C (B) and CPM/HP-β-CyD complex (C) before (open symbols) and after (closed symbols) compression in JP XIV first fluid (pH 1.2) at 37 °C.

under these compression conditions, keeping the stable amorphous state.

Figure 5 shows dissolution profiles of CPM/HP-β-CyD complex and Forms A and C before and after the compression (2000 kg/cm^2, 15 strokes of the compression). The dissolution rate of CPM before the compression was in the order of HP-β-CyD complex > Form C > Form A. After the compression, the dissolution rate of Forms A and C increased, because of the increase in amount of the amorphous part (Figure 4 (lower panels)). On the other hand, CPM/HP-β-CyD complex showed insignificant change in the dissolution rate and maintained the fast dissolving property, reflecting the stable amorphous state of the complex.

The present results suggest that HP-β-CyD is useful not only for converting crystalline CPM to an amorphous substance, but also for maintaining the fast dissolution rate of the drug even after the compression during tableting. Furthermore, HP-β-CyD can work as a matrix for stabilization and solubilization of the resulting labile metastable forms.

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