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ESTIMATION OF PHYSICAL STABILITY OF AMORPHOUS SOLID DISPERSION USING DIFFERENTIAL SCANNING CALORIMETRY

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The physical stability of amorphous drug in solid dispersion was estimated using differential scanning calorimetry (DSC). Tolbutamide (TB) and flurbiprofen (FBP) were selected as insoluble drugs in water. Polyvinylpyrrolidone (PVP) was selected as a polymer for solid dispersion. Solid dispersions of various ratios of TB or FBP and PVP-K25 were prepared by solvent evaporation method and the induction period of crystallization from amorphous drug in solid dispersion was measured by DSC. Compared with FBP, the induction period of crystallization from TB was delayed by an addition of PVP. The improvement of the physical stability by the addition of PVP-K25 was estimated from the activation energy of diffusion of drug molecules and the interfacial free energy between drug crystal and supercooled liquid of drug in solid dispersion. From thses results, the hindrance of the diffusivity of the drug molecule might be mainly affected the delay of the induction period of crystallization of TB and FBP.

Keywords: *amorphous, DSC, flurbiprofen, nucleation, physical stability, polyvinylpyrrolidone, solid dispersion, tolbutamide*

Introduction

For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution of the drug in the gastrointestinal tract. Various techniques have been used to improve the dissolution rate of sparingly soluble drugs in water. Among them, the solid dispersion technique is widely used to obtain the amorphous state of drug and improves the dissolution rate of drugs, hence increases bioavailability [1–6]. However, amorphous drug is generally unstable and easily crystallized [7].

The main objective of this study was to estimate the physical stability of amorphous drug and clarify the effect of polymer on crystallization of amorphous drug in solid dispersion. The physical stability of amorphous drug was evaluated by the following three factors: the activation energy of diffusion of drug molecules, the interfacial free energy between drug crystal and supercooled liquid of amorphous drug in solid dispersion, and interaction of drug and polymer. The effect of polymer on crystallization of amorphous drug in solid dispersion was evaluated by the induction period of the crystallization of drug in solid dispersion under various isothermal conditions. TB and FBP were selected as insoluble drugs in water. In solid dispersion, PVP has been widely employed for high water solubility, low cost and low toxicity. Therefore, PVP was selected as a polymer of solid dispersion.

Experimental

Materials

Tolbutamide (Sigma Chemical Co., Ltd.), flurbiprofen (Sigma Chemical Co., Ltd.), PVP K-25 (Nacalai Tesque, Inc.) and ethanol (Wako Pure Chemical Industries, Ltd.) were purchased and used as received. All reagents were of analytical grade or JP XIV grade.

Preparation of solid dispersions

Various ratios of TB or FBP and PVP K25 were dissolved in ethanol and the solvent was evaporated with evaporator at about 40°C, and then the solid dispersions containing different ratios of TB or FBP and PVP K25 were prepared. The prepared solid dispersions were then dried in vacuo over phosphorus pentoxide in a desiccator for several days.

Methods

Differential scanning calorimetry

DSC measurements were carried out with a Perkin-Elmer DSC 7 differential scanning calorimeter (Perkin-Elmer, USA) under nitrogen flow. Samples containing drug of 2.0 mg were hermetically sealed in aluminum DSC pans and placed in the DSC cell. The DSC scan was calibrated with indium as a standard.

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For isothermal crystallization process, the samples were heated to 150°C for TB and 140°C for FBP at 20°C min^{-1} and kept at this temperature for 5 min to eliminate the residual crystals. Then they were cooled to the various crystallization temperatures at a rapid cooling rate of 200°C min^{-1} and remained isothermal until the crystallization was initiated. DSC measurements were performed in triplicate.

FTIR spectroscopy

Fourier transform infrared (FTIR) spectra of drug, PVP K-25 and solid dispersions were recorded using FTIR spectrometer (JASCO FT-IR-7300) equipped with a heating apparatus (HC-500/H model). The scanning wavelength of infrared was 4000–400 cm^{-1} at a resolution of 2 cm^{-1} with an average of 36 scans for each spectrum. The samples were sandwiched between KBr plates. They were heated to 150°C for TB samples and 140°C for FBP samples with the heating apparatus and were cooled to the room temperature under nitrogen flow. Then FTIR spectra were obtained.

Results and discussion

The isothermal crystallization DSC curves of FBP and solid dispersion of FBP containing 10% PVP are shown in Fig. 1.

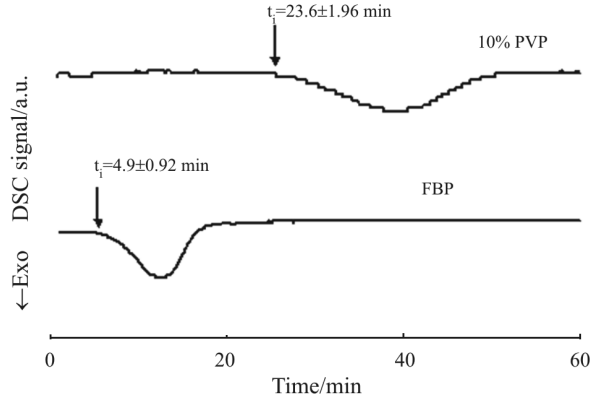

Fig. 1 Effect of PVP on the isothermal crystallization of flurbiprofen at 40°C

The 't_i' in the figure means the induction period of crystallization from supercooled liquid of FBP. The induction period of crystallization from FBP was delayed with an addition of PVP. That of TB was delayed with an addition of PVP as well as FBP.

Relationship between the induction period of crystallization from FBP or TB and PVP contents are shown in Figs 2 and 3.

The induction period of crystallization from amorphous drug was gradually delayed with increasing amounts of PVP. As the isothermal crystallization temperature became higher, the induction period of crystallization from amorphous drugs became faster. From these results, by substituting the equation of homogeneous nucleation rate for the induction period of the crystallization, the activation energy of diffusion of drug molecules and the interfacial free energy between drug crystal and supercooled liquid of drug in solid dispersion were calculated. In general, the equation of homogeneous nucleation rate is shown as follows [8, 9]

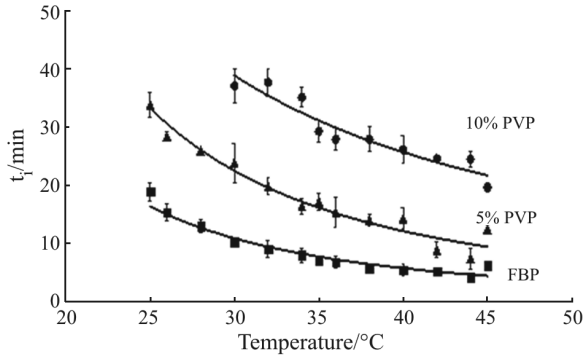

Fig. 2 Effect of storage temperature on the crystallization of FBP in solid dispersion of FBP and PVP

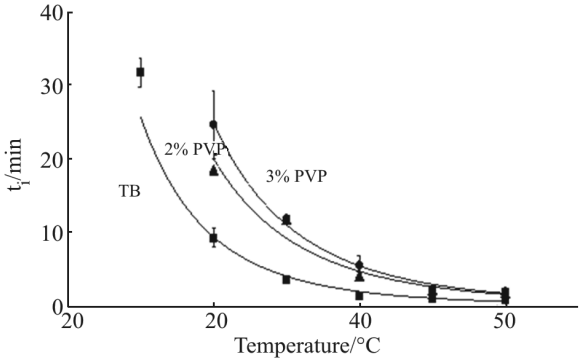

Fig. 3 Effect of storage temperature on the crystallization of TB in solid dispersion of TB and PVP

$$I = A\exp\left(-\frac{16\pi\sigma^3 T_m^2 V_m^2}{3(T_m - T)^2 \Delta H_f^2 kT}\right)\exp\left(-\frac{\Delta E}{kT}\right) \quad (1)$$

where I is the rate of nucleation, A is constant, σ is the interfacial energy, T_m is the melting point, V_m is the volume of crystal, T is the experimental temperature, ΔH_f is the enthalpy of fusion, ΔE is the activation energy for atomic diffusion.

This assumes that the induction time is inversely proportional to the nucleation rate as shown in the following Equation [10]

$$I = K/t_i \quad (2)$$

where K is a constant.

From Eqs (1) and (2), the following Eq. (3) is obtained.

$$1/t_i = A'\exp\left(-\frac{16\pi\sigma^3 T_m^2 V_m^2}{3(T_m - T)^2 \Delta H_f^2 kT}\right)\exp\left(-\frac{\Delta E}{kT}\right) \quad (3)$$

where A' is a constant.

Effect of temperature on the nucleation rate of FBP and TB is shown in Figs 4 and 5.

From Figs 4 and 5, the induction period of the crystallization fitted well for Eq. [3]. The effect of temperature on the nucleation rate of FBP and TB was examined. As the isothermal crystallization temperature increased, $1/t_i$ became greater. And $1/t_i$ decreased with increasing the PVP contents in both drugs. ΔE and σ were calculated by putting the induction period of the crystallization of drug into the Eq. (3). The influence of the PVP contents on ΔE and σ is shown in Figs 6 and 7.

σ was not influenced in each drug by the increasing amounts of PVP. ΔE of TB was increased rapidly as the amounts of PVP increase, but the no change for ΔE of FBP was observed. From those results, as the drug of FBP was dispersed in PVP, the delay of the induction period of crystallization of FBP was observed. On the other hand, as the hindrance of diffu-

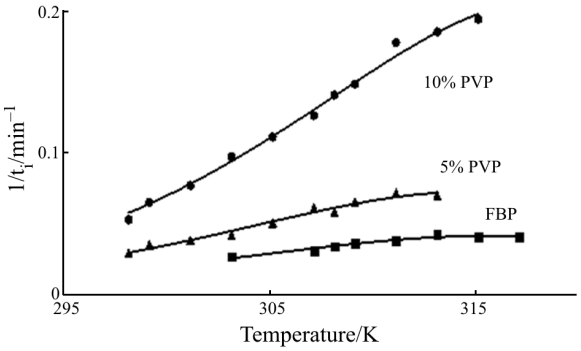

Fig. 4 Effect of temperature on the nucleation rate of FBP in solid dispersion

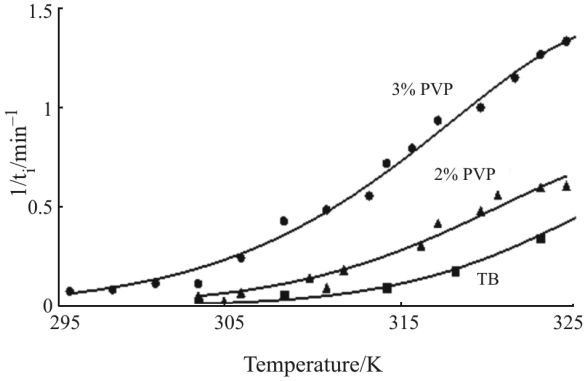

Fig. 5 Effect of temperature on the nucleation rate of TB in solid dispersion

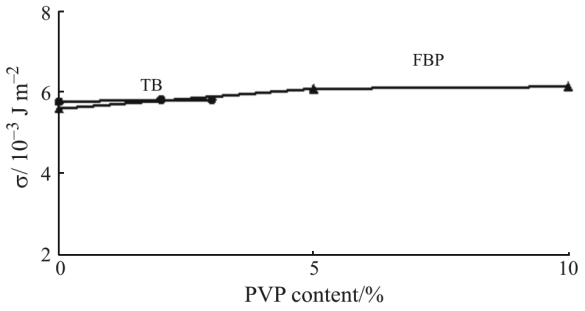

Fig. 6 Effect of PVP contents on σ value for the nucleation of FBP and TB

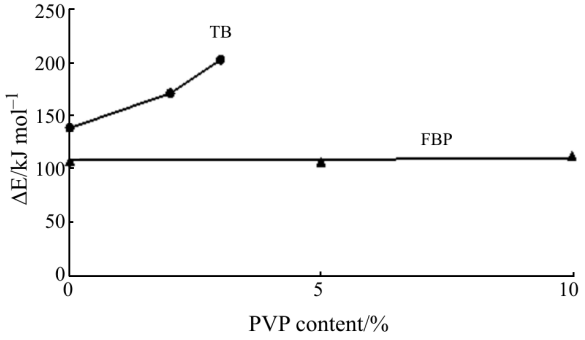

Fig. 7 Effect of PVP contents on ΔE value for the nucleation of FBP and TB

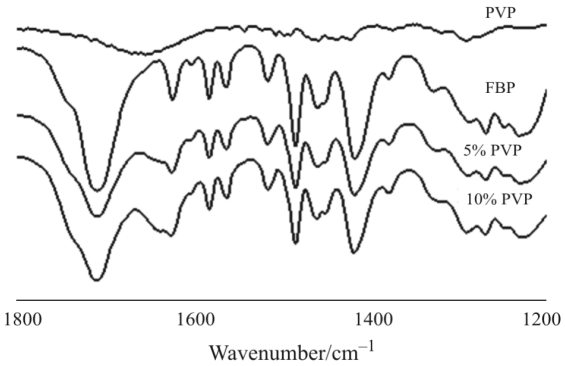

Fig. 8 IR spectra of solid dispersion of FBP and PVP

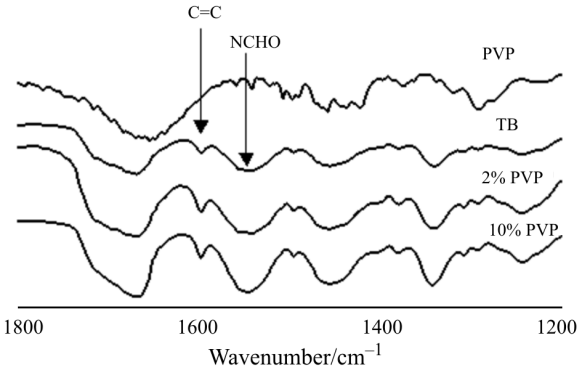

Fig. 9 IR spectra of solid dispersion of TB and PVP

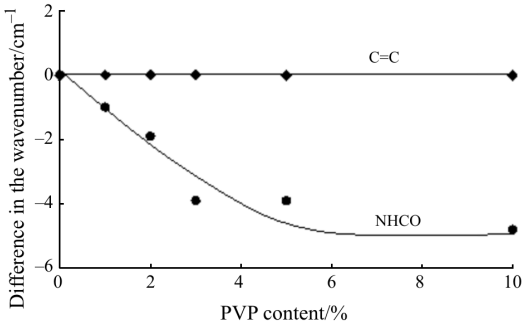

Fig. 10 Effect of PVP contents on the IR bands of TB

sion of TB molecule distributed into PVP occurred, the delay of the induction period of TB was larger than that of FBP. To confirm this, the interaction of TB-PVP and FBP-PVP was examined with FTIR. Figures 8 and 9 show the FTIR spectra of the drug, the polymer and the solid dispersions.

A remarkable interaction was not observed between FBP and PVP, however, the interaction between TB and PVP was observed. It was confirmed that 1546 cm^{-1} peaks assigned to amino group of TB shifted to the lower frequency with an increase in amounts of PVP. Therefore, it was considered that the diffusion of TB molecule might be restricted by the interaction of TB molecule and PVP.

Conclusions

The induction period of crystallization from supercooled liquid of TB and FBP in solid dispersion was delayed with an increase of PVP. Compared with FBP, the induction period of TB was significantly delayed with an increase of PVP. From the results of the change of ΔE of TB and the interaction of TB-PVP, it may be concluded that the diffusivity of TB molecule in PVP is larger than that of FBP in PVP. Therefore, the difference of the diffusivity might be mainly affected the delay of the induction period of crystallization of TB and FBP.

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