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Prediction of the induction period of crystallization of naproxen in solid dispersion using differential scanning calorimetry

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Abstract The induction period of crystallization of amorphous naproxen in solid dispersion was measured by DSC. Hydroxypropylmethylcellulose acetate succinate LG (HPMCAS-LG) was selected as a polymer of solid dispersion, because of the excellent inhibitory effect of crystallization. Naproxen was chosen as a model drug having poor water solubility and poor physical stability of glassy state. The prediction of crystallization of amorphous naproxen in solid dispersion at the desired storage temperature or the desired polymer content was carried out. If the storage condition satisfied the requirement that was either more than 90% of HPMCAS-LG content at 333 K or below storage temperature of 301 K for 50% HPMCAS-LG content, the induction period of crystallization of naproxen in solid dispersion would be more than 1 year. The storage period of amorphous drug in solid dispersion of desired storage temperature and desired drug content might be predictable from measurement data of induction period of crystallization.

Keywords Induction period · Physical stability · Crystallization · DSC · HPMCAS-LG · Naproxen · Solid dispersion

Introduction

Many drugs have the problem of being only poorly soluble in aqueous solution. This problem can lead to poor bioavailability and frequently results in variable dissolution rates. Improving dissolution properties is a major obstacle that must be overcome because many new drugs discovered by combinatorial chemistry and high-throughput screening are poorly water-soluble. So, it is important to improve the solubility and/or dissolution rate for poorly water-soluble drugs. Various techniques have been used to improve the solubility and dissolution rate of sparingly soluble drugs in water. Among them, the formation of a solid dispersion using a carrier is widely used to improve the dissolution rate of drugs. In solid dispersion systems, many drugs may exist as an amorphous form in polymeric carriers, and this may result in improved solubility and dissolution rates as compared with crystalline material, hence increases bioavailability [1–6]. However, amorphous drug tends to be less thermodynamically stable, as the molecules changes from their higher energy amorphous state to a lower energy crystalline state [7]. The process of crystallization consists of two major steps: nucleation and crystal growth. The nucleation rate is generally governed by the activation energy to develop stable nuclei and for molecule diffusion. The crystallization of amorphous drug in the solid dispersion influences the physical properties of the drug such as solubility, mechanical properties, and dissolution rate. Therefore, the prediction of their physical stability of amorphous drug in the solid dispersion is important.

Isothermal crystallization of amorphous drug is known as an exothermal process, and detectable by DSC measurement. The induction period of crystallization of amorphous drug in solid dispersion is determined by DSC. We have already reported the inhibitory effect of Polyvinylpyrrolidone on the crystallization of amorphous tolbutamide in the solid dispersion [8]. Hydroxypropylmethylcellulose acetate succinate LG (HPMCAS-LG) is known as a water-soluble polymer, used in technological processes as a film-forming agent or protective layer, and it is the excellent inhibitory

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effect of crystallization. Hence, HPMCAS-LG was chosen as a model polymer of solid dispersion. Naproxen was chosen as a model drug of solid dispersion, which was nonsteroidal anti-inflammatory drug derived from propionic acid and widely used as analgesic and antipyretic. The physicochemical properties of Naproxen were poor water solubility, low dissolution rate in water and poor glass forming property, that is, Naproxen glass was easily crystallized by cooling the melts [9]. The objective of this study was to predict the induction period of crystallization of amorphous drug by DSC and to estimate the physical stability of amorphous drug in the solid dispersion.

Experimental

Materials

Naproxen, ethanol, and dichloromethane were purchased from Wako Pure Chemical Industries, Ltd. and HPMCAS-LG was supplied by Shin-Etsu Chemical Co., Ltd. All the reagents were of analytical grade or JP XV grade and used as received.

Preparation of solid dispersions

Various ratios of naproxen and HPMCAS-LG were dissolved in solvent (ethanol:dichloromethane = 1:1), and the solvent was evaporated at about 333 K; then, the solid dispersions containing different ratios of naproxen and HPMCAS-LG were prepared. The prepared solid dispersions were then dried in vacuo over phosphorus pentoxide in a desiccator for several days.

DSC measurement

DSC measurements were carried out with a Perkin-Elmer DSC 7 (Perkin-Elmer, USA) under nitrogen flow. The DSC scan was calibrated with indium and distilled water as a standard. Solid dispersions containing drug of 2.0 mg were hermetically sealed in aluminum pans and placed in the DSC cell. For isothermal crystallization process, the samples were heated to 443 K at 20 °C/min 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 and remained isothermally until the crystallization was initiated. From the result of the DSC measurement, the melting point of naproxen was 429.9 K, but its glassy temperature (T_g) was not detected, since crystallization of the supercooled liquid of naproxen was very fast.

Solubility of naproxen in solid dispersions

Solubility of naproxen in solid dispersions was calculated by solubility parameter. For calculation of the solubility parameters of HPMCAS-LG, the group contribution method of Fedors was employed [10]. The partial solubility parameters of each structural group in HPMCAS-LG were taken into account, and the total for all the structural groups were summed up. Solubility parameter of naproxen was calculated by the method of Sakellariou et al. [11]. The calculated solubility parameters for HPMCAS-LG and naproxen were 29.2 and 21.9 $J^{1/2}$ $cm^{-3/2}$, respectively. The activity (a_2) of naproxen is estimated by following equation:

$$\ln(a_2) = -\frac{\Delta H_f}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right) \quad (1)$$

where ΔH_f, R, T_m, and T are the molar heat of fusion, gas constant, temperature of fusion of the crystalline compound, and measurement temperature, respectively. Solubility of naproxen in solid dispersions (X_2) is estimated by following equation [12]:

$$\ln(X_2) = \ln(a_2) - \frac{V_2\varphi_1^2(\delta_1 - \delta_2)^2}{RT} \quad (2)$$

where V_2, ϕ_1, δ_1, and δ_2 are the molar volume of naproxen, the volume fraction of HPMCAS-LG, solubility parameter of HPMCAS-LG, and solubility parameter of naproxen, respectively.

Results and discussion

Prediction of induction period of crystallization of naproxen in solid dispersion with HPMCAS-LG at 333 K

The isothermal crystallization DSC curve of solid dispersion of naproxen containing 3% HPMCAS-LG at 333 K is shown in Fig. 1.

The "t_i" in the figure means the induction period of crystallization from supercooled liquid of naproxen [8]. T_g of naproxen was not detected, but the crystallization of naproxen was controlled by adding HPMCAS-LG and understood that naproxen in polymer maintained supercooled liquid. Therefore, the influence of the polymer content on crystallization of naproxen in polymer was examined.

In order to determine t_i of naproxen at the various mixing ratios of HPMCAS-LG, the isothermal crystallization of those was measured. Effect of HPMCAS-LG contents on t_i for naproxen in solid dispersion at 333 K is

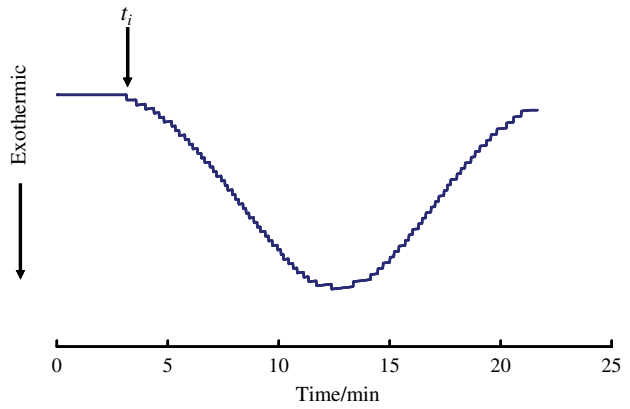

Fig. 1 DSC curve of the isothermal crystallization of naproxen solid dispersion containing 3% HPMCAS-LG at 333 K

shown in Fig. 2. From Fig. 2, it was found that on increasing the HPMCAS-LG content, the t_i also increased.

In general, a homogeneous nucleation rate (I) is shown in the following equation [13, 14]:

$$I = k_1 \cdot \exp\left(-\frac{16}{3}\pi\left(\frac{\sigma}{kT}\right)^3 \frac{v^2}{(\ln S)^2}\right) \quad (3)$$

where k_1, σ, k, T, v, and S are the frequency factor, the interfacial energy, Boltzmann constant, the experimental temperature, the molecular volume of naproxen and the supersaturation ratio defined as C/Cs. C and Cs are the concentration and solubility of naproxen in HPMCAS-LG., respectively.

The solubility of naproxen in HPMCAS-LG was estimated from Eq. 2 and the solubility was calculated to be 3.87×10^{-3} g g^{-1} at 333 K.

The induction time is inversely proportional to the nucleation rate as shown in the following equation [13]:

$$I = (1/V)(\mathrm{d}N/\mathrm{d}t) = (1/V)(N_i/t_i) \quad (4)$$

where N is the number of nuclei in a given volume V at $t = t$, N_i is that at $t = t_i$.

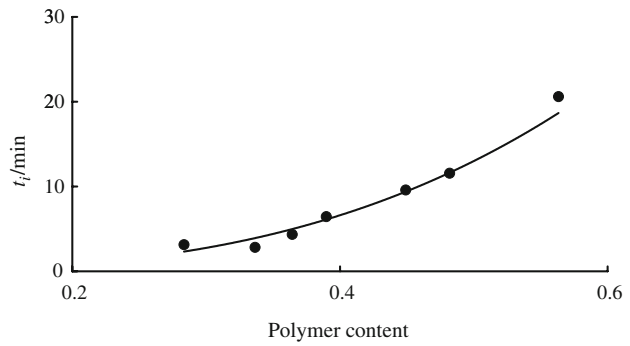

Fig. 2 Effect of HPMCAS-LG content on the isothermal crystallization of naproxen at 333 K

Combining Eqs. 3 and 4, the Eq. 5 is obtained as follows:

$$\ln(t_i V) = -\ln\left(\frac{k_1}{N_i}\right) + \frac{k_2}{(\ln(S))^2} = k_3 + \frac{k_2}{\left(\ln\left(\frac{C}{Cs}\right)\right)^2} \quad (5)$$

where k_2 ($k_2 = -16/3 \cdot \pi(\sigma/kT)^3 \cdot v^2$) and $k_3 \cdot (k_3 = -\ln(k_1/N_i))$ are constant.

From Eq. 5, the linear relationship would be obtained between $\ln(t_i V)$ and $(\ln(C/Cs))^{-2}$. The value of C used by the experiment is from 28.3×10^{-2} to 56.3×10^{-2} g g^{-1}. The $\ln(t_i V)$ was plotted against $(\ln(C/Cs))^{-2}$, and the linear relation was obtained as shown in Fig. 3.

The higher concentrations of t_i's were extrapolated from linear relation of Fig. 3. The predicted t_i of naproxen as a function of HPMCAS-LG concentration at 333 K was plotted as shown in Fig. 4.

From Fig. 4, induction period of crystallization of naproxen containing 90% of HPMCAS-LG at 333 K was estimated about 1 year. When the polymer contained 90% or more, induction period of crystallization of naproxen became long. Therefore, it was considered that prediction of induction period of crystallization of naproxen in solid dispersion containing various HPMCAS-LG contents at the constant temperature might be possible from these results.

Prediction of induction period of crystallization of naproxen in 50% HPMCAS-LG solid dispersion at desired temperature

The effect of the temperature on the induction period of crystallization of naproxen containing 50% HPMCAS-LG is shown in Fig. 5.

The curvature with the minimum value at 335–336 K was obtained. If homogeneous nucleation occurred in the solid dispersion at various temperatures, then the homogeneous

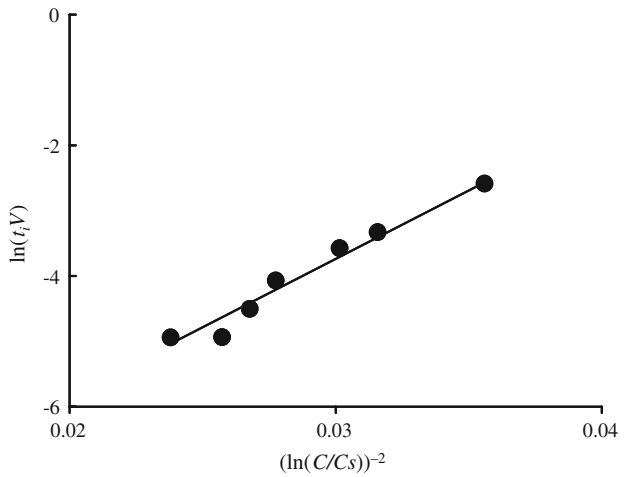

Fig. 3 Straight-line relationship between $\ln(t_i V)$ and $(\ln(C/Cs))^{-2}$ on the isothermal crystallization of naproxen at 333 K

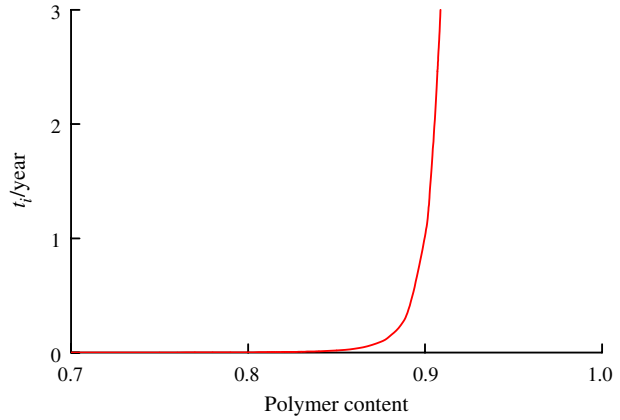

Fig. 4 Prediction curve of induction period of crystallization of naproxen in desired HPMCAS-LG content at 333 K

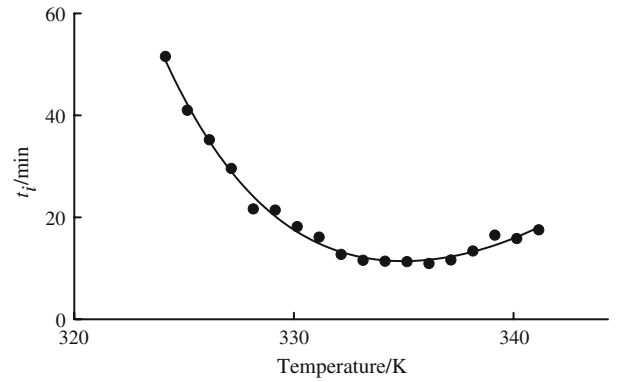

Fig. 5 Effect of the temperature on the induction period of crystallization of naproxen containing 50% HPMCAS-LG

nucleation rate is estimated [13–15]. We have previously reported that the induction time is inversely proportional to the nucleation rate as shown in the following equation [8].

$$1/t_i = A' \cdot \exp\left(-\frac{16\pi\sigma^3 T_m^2 V_m^2}{3(T_m - T)^2 \Delta H_f^2 kT}\right) \cdot \exp\left(-\frac{\Delta E}{kT}\right) \quad (6)$$

where A' is a constant; σ is the interfacial energy; V_m is the volume of crystal; ΔH_f is the enthalpy of fusion; ΔE is the activation energy for molecule diffusion.

The values of T_m, V_m, and ΔH_f were 430.1 K, 1.92×10^{-4} cm^3 mol^{-1}, and 29.6 kJ mol^{-1}, respectively. Using these values, the curve calculated from nonlinear least-squares method by substituting measurement temperature and t_i of naproxen containing 50% of HPMCAS-LG for Eq. 6 was shown in Fig. 6.

The obtained curve accorded with experimental data well, because the value of the chi-square was 4.1×10^{-5}. From the curve, desired t_i was obtained by substituting desired temperature value for Eq. 6 and prediction curve of t_i was obtained. The prediction curve was shown in Fig. 7.

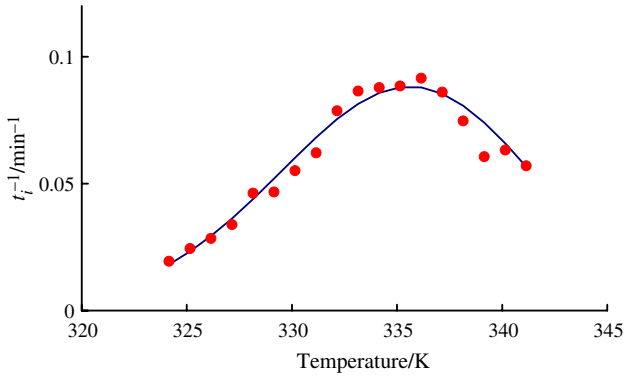

Fig. 6 Plot of the measured homogeneous nucleation rate data and curve applied the data to Eq. 6

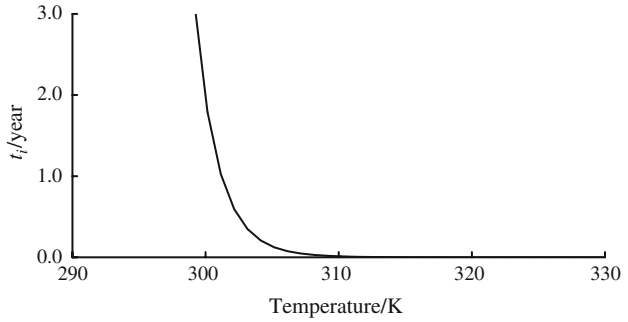

Fig. 7 Prediction curve of induction period of crystallization of naproxen in 50% HPMCAS-LG at desired temperature

From Fig. 7, at 301 K, the induction period of crystallization of naproxen containing 50% of HPMCAS-LG was about 1 year. When the storage condition satisfied the requirement that storage temperature became 301 K or less, the induction period of crystallization of naproxen rapidly became long. Therefore, it was considered that the prediction of induction period of crystallization of naproxen in solid dispersion containing 50% HPMCAS-LG content at the desired temperatures might be possible from these results.

Conclusions

Prediction of the induction period of crystallization of naproxen in solid dispersion in desired HPMCAS-LG content at 333 K and in 50% HPMCAS-LG solid dispersion at desired temperature could be carried out by DSC. When the HPMCAS-LG content was more than 90% at 333 K or the storage temperature was below 301 K in the 50% HPMCAS-LG solid dispersion, the induction period of crystallization of naproxen in solid dispersion would be more than 1 year.

The storage period of crystallization of amorphous drug in solid dispersion of desired temperature and drug content

might be predictable from measurement data of induction period of crystallization. In order to make sure the availability of proposed method, real time stability study should be necessary for real dosage forms.

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