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Quantitative correlation between initial dissolution rate and heat of fusion of drug substance

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Abstract

The initial dissolution rates of amorphous, partial crystalline and crystalline samples of terfenadine polymorphs (forms I and II) were measured by the rotating disk method. The heats of fusion due to crystalline fraction of samples were obtained by the differential scanning calorimetry (DSC) data taking into account the heat of crystallization and the heat capacity change at glass transition during the heating process. The logarithms of initial dissolution rates of different crystallinity samples were linearly correlated with the corrected heats of fusion, irrespective of the crystal forms.

Keywords: Amorphous; Crystallinity; Differential scanning calorimeter (DSC); Dissolution rate; Polymorphism; Quality control

1. Introduction

In recent years, the quality of solid pharmaceutical substance is strictly controlled with appropriate analytical procedures (Byrn et al., 1995). The polymorphic forms and crystallinity of drug substances are the major physicochemical properties that affect drug dissolution, chemical stability, as well as drug bioavailability. Even a small amount of contamination of polymorphs and amorphous form may alter its physicochemical properties of the original drug substances (Ito et al., 1997; Yonemochi et al., 1997).

In the aspect of quality control of drug substances, these physicochemical properties should be controlled as one of the solid state specifications, because the metastable form and/or amorphous form are generally thermodynamically unstable, i.e. higher energetic state than the stable form and/or crystalline form. The metastable forms and amorphous forms are much more soluble and sometimes much more unstable than their crystalline counterparts. In a development of new drug substance, the meaning set of solid state specifications should be determined scientifically. There are cases where the polymorphs and amorphous forms are contaminated in the drug substances with batch to batch difference during the scale up process (Hendriksen, 1990). Therefore, there is an urgent need to estimate the dissolution behavior of the drug substance.

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The identification of polymorphic form is usually characterized by the powder X-ray diffraction measurement. However, the evaluation of the degree of crystallinity and the content of amorphous form by this method are not sensitive enough (Nakai et al., 1985). Differential scanning calorimeter (DSC) is a one of tools for the evaluation of polymorphs and amorphous state (Yonemochi et al., 1999), however, the disadvantage of this method is that physical state of sample could be transformed during the heating process. Therefore, the correction for the thermograms should be required for the quantitative analysis of the physical properties.

The aim of this study is to estimate the initial dissolution rate of drug substances by DSC and to qualify the possibility for application for the quality control of drugs, which might be possibly contaminated polymorphs and amorphous fraction in them.

2. Materials and methods

2.1. Materials

Terfenadin was supplied by Kyoto Pharmaceutical Industries (Kyoto, Japan). Other chemicals were of special reagent grade.

2.2. Preparation of samples

Polymorphic forms of I and II of terfenadine were prepared by the crystallization from n-butanol and ethyl acetate, respectively (Sheikh et al., 1996). The different crystallinity of terfenadine samples were prepared by grinding, using a CMT model TI 100 vibration mill (Tokyo, Japan). Quenched terfenadine was prepared by cooling the melt.

2.3. Powder X-ray diffraction measurement

The powder X-ray diffraction pattern was obtained from a RAD type diffractometer (Rigaku Denki, Tokyo, Japan) using a scintillation counter. The measurements were done as described previously (Yoshihashi et al., 1998).

2.4. Measurement of heat of fusion

Perkin–Elmer DSC7 was used for the determination of heat of fusion, heat of crystallization, heat of relaxation, glass transition temperature, and melting point. The DSC apparatus was calibrated with indium as the standard. Accurately weighed amount (4–6 mg) of sample was transferred to aluminum sample pans and the sides of the cover were crimped. Samples were run at a scanning rate of 5 K/min. The heat of fusion of sample was calculated according to the theory.

2.5. Initial dissolution rate measurement by rotating disk method

The initial dissolution rates were measured using rotating disk method. The disk was of 6 mm diameter and the powder was compacted at the force of 9.8×10^3 N/cm^2. The disk was rotated at 200 rpm at 25°C. The solvent for the dissolution test of sample was JP No.1 disintegration solution (pH 1.2). The released drug was determined spectroscopically.

2.6. Determination of the degree of crystallinity

The degree of crystallinity of sample was calculated by DSC using the following equation (Pikal et al., 1978).

$$\alpha = \frac{(\Delta H_s - \Delta H_a)}{(\Delta H_c - \Delta H_a)} \times 100(\%) \quad (1)$$

where ΔH_s, ΔH_a and ΔH_c are heats of solution of sample, amorphous standard (100% amorphous) and crystalline standard (100% crystalline), respectively. Crystalline standard was prepared by the slow crystallization from the solution. Amorphous standard was prepared by the rapid cooling of the melted sample.

3. Theory

If the transition of amorphous to crystalline state does not occur during the heating process, the heat of fusion is directly obtained from the melting enthalpy of crystalline region of solid.

However, if a part of amorphous region crystallizes during the heating, the heat of fusion should be overestimated and it is necessary to subtract the heats of crystallization and excess enthalpy of super cooled liquid. Therefore, the heat of fusion for the partially crystalline sample was corrected in the following manner.

The relationship between the free energy change (ΔG), the enthalpy change (ΔH) and the entropy change (ΔS) under the isothermal condition is given in the following equation.

$$\Delta G = \Delta H - T \cdot \Delta S \tag{2}$$

At the melting point of substance, the solid and the liquid are in equilibrium, hence $\Delta G = 0$.

$$\Delta G_m = \Delta H_m - T_m \cdot \Delta S_m = 0 \tag{3}$$

where ΔG_m is free energy change, ΔH_m is enthalpy change and ΔS_m is the entropy change at the melting point. Therefore,

$$\Delta S_m = \frac{\Delta H_m}{T_m} \tag{4}$$

Assuming a solid melts at a temperature (T_n) which is below the true melting point of the substance, the entropy change due to melting is approximately constant (Craig and Newton, 1991).

$$\frac{\Delta H_m}{T_m} = \frac{\Delta H_n}{T_n} \tag{5}$$

where ΔH_n is the enthalpy change at T_n. If a part of amorphous region crystallizes during the heating process, the crystallized amount should be subtracted as follows.

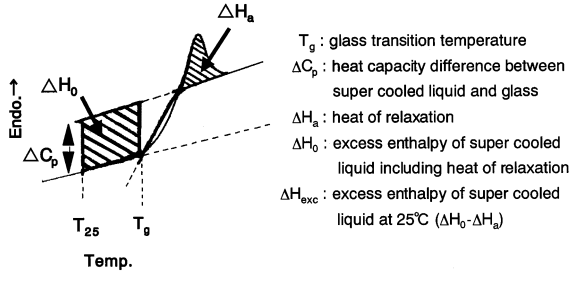

Fig. 1. Change in heat capacity around glass transition temperature.

$$\Delta H_x = \Delta H_m \cdot \frac{T_x}{T_m} - \Delta H_{cry} \tag{6}$$

where ΔH_x is the heat of fusion at the crystallization temperature (T_x), and ΔH_{cry} is the heat of crystallization. If the sample shows the glass transition, it should be necessary to consider the heat of relaxation and the excess enthalpy of supercooled liquid. The excess enthalpy of supercooled liquid at 25°C (ΔH_{exc}) would be obtained using Eq. (7) and Eq. (8) as indicated in Fig. 1 (Yoshida, 1986).

$$\Delta H_{exc} = \Delta H_0 - \Delta H_a \tag{7}$$

$$\Delta H_0 = \Delta C_p \cdot (T_g - T_{25}) \tag{8}$$

where ΔH_0 is excess enthalpy of supercooled liquid containing heat of relaxation, ΔH_a is heat of relaxation, ΔC_p is heat capacity difference between the supercooled liquid and the glass, and T_g and T_{25} are the temperatures at glass transition and 25°C, respectively.

Therefore, the heat of fusion extrapolated at 25°C (ΔH_{25}) taking into account of crystallization and glass transition could be obtained from Eq. (9).

$$\Delta H_{25} = \Delta H_x \cdot \frac{T_{25}}{T_x} - [\Delta C_p \cdot (T_g - T_{25}) - \Delta H_a] \tag{9}$$

4. Results and discussion

4.1. Heat of fusion extrapolated at 25°C (ΔH_{25}) of crystalline, partially crystalline and quenched glass samples of terfenadine

The powder X-ray diffraction patterns of crystalline and ground samples of terfenadine polymorphs are shown in Fig. 2. The intensities of the diffraction peaks due to terfenadine crystals (forms I and II) decreased with an elongation of the grinding time, halo patterns were observed after 60 min of grinding for form I and 30 min of grinding for form II, respectively. The crystallization and glass transition due to amorphous fraction was observed on the DSC trace of 30-min ground sample. The heats of fusion for crystalline, partially crystalline and quenched glass samples were calculated according to Eq. (9). Table 1

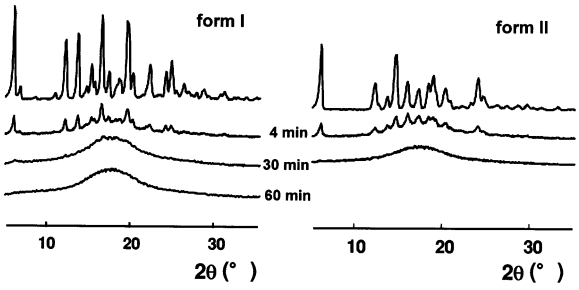

Fig. 2. Changes in powder X-ray diffraction patterns of terfenadine, (form I and form II) by grinding.

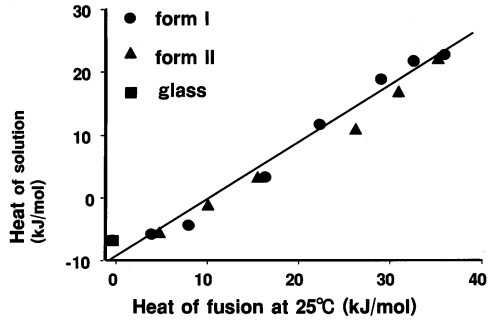

Fig. 3. Relationship between heat of fusion and heat of solution at 25°C.

shows the thermodynamic parameters of terfenadine form I for the determination of the heat of fusion at 25°C (ΔH_{25}).

4.2. Relationship between heat of fusion and heat of solution of terfenadine samples

The heat of solution represents the sum of the enthalpies of each stage of the dissolution process. As indicated in Born–Haber cycle (Atkins, 1986), the dissolution may consist of the dissociation of the solid-state bonding and the solvation of the solute molecules. Therefore, the heat of solution (ΔH_s) can be represented by the sum of the heat of fusion (ΔH_m) and the heat of mixing (ΔH_{mix}).

$$\Delta H_s = \Delta H_m + \Delta H_{mix} \quad (10)$$

In the separate paper (Terada et al., submitted), we have obtained the heat of solution of various crystallinity terfenadine samples by isothermal microcalorimetry. The heats of fusion of terfenadine samples were plotted against the heat of solution. As shown in Fig. 3, the linear correlation with a slope of about 1.0 was observed between the heat of solution and the heat of fusion. According to Eq. (10), the intersection with the coordinate axis is assumed to be the heat of mixing of supercooled liquid of terfenadine with the solvent. The heat of solution of quenched glass terfenadine was measured to be -6.89 kJ/mol and it was in good agreement with the intersection value. Since T_g of terfenadine is about 60°C, the quenched glass sample is present as a glassy state at 25°C, therefore, the intercept in Fig. 3 would not strictly be related to the heat of mixing of supercooled liquid. The T_g of quenched ethyl quininecarbonate is known to be 5°C (Fukuoka et al., 1989) and this drug forms stable supercooled liquid at 25°C. The heat of fusion of ethyl quininecarbonate was determined as 28.28 kJ/mol at 25°C and the heat of solution of the drug into *N*,*N*′-dimethyl formamide (DMF) was also determined as 26.99 kJ/mol. The heat of mixing for supercooled liquid was obtained to be -1.03 kJ/mol. The sum of the heat of fusion and the heat of mixing of ethyl

Table 1
Thermodynamic parameters of various terfenadine form I samples used for the evaluation of ΔH_{25}

Sample	T_x (°C)	ΔH_{cry} (kJ/mol)	T_m (°C)	ΔH_m (kJ/mol)	ΔC_p (kJ/mol)	T_g (°C)	ΔH_{25} (kJ/mol)
Crystal		0	148.7	50.99			36.03
1-min Ground	63.9	3.47	147.4	47.94			32.59
2-min Ground	67.6	9.19	146.8	45.99			29.00
4-min Ground	69.4	10.03	144.1	43.44			22.31
6-min Ground	68.9	16.76	144.9	13.49			16.40
30-min Ground	76.4	20.38	144.2	33.39	0.28	57.9	2.72
60-min Ground	83.9	71.34	142.4	43.44	0.46	61.2	0.45

quininecarbonate was calculated to be 27.31 kJ/mol, which was in good agreement with the heat of solution. Therefore, the heat of mixing obtained from the intercept in Fig. 3 could be considered to be the heat of mixing of terfenadine form I into DMF.

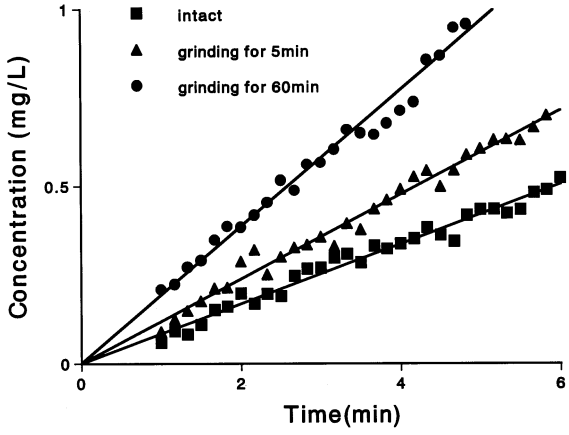

Fig. 4. Intrinsic dissolution rates of terfenadine in JP 1st fluid (pH 1.2).

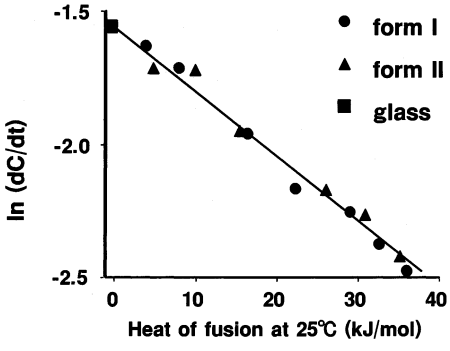

Fig. 5. Relationship between heat of fusion and logarithms of initial dissolution rate of terfenadine.

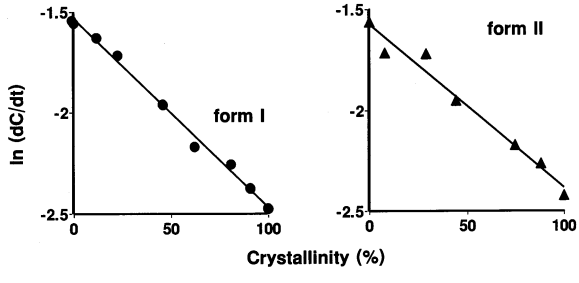

Fig. 6. Relationship between crystallinity evaluated by heat of fusion at 25°C and logarithms of initial dissolution rate.

4.3. Quantitative correlation between initial dissolution rates and heat of fusion of terfenadine samples

The initial dissolution rates of terfenadine samples under the constant surface area condition were measured. A linear relation was observed between the time and the amount dissolved, as shown in Fig. 4. The transition from amorphous to crystalline form was not observed during the dissolution study. The correlation between initial dissolution rates and the heat of fusion was illustrated in Fig. 5. The initial dissolution rates of ground samples increased as the heats of fusion decreased. A linear correlation was obtained between the logarithm of initial dissolution rate and the heat, irrespective of the difference of polymorphs, as estimated from the present theory. As shown in the separate paper (Terada et al., submitted), the heat of solution is also quantitatively related to the logarithms of initial dissolution rates. This result suggested that the initial dissolution rate could be estimated by DSC. Therefore, for the drug substance which does not decompose before melting, DSC would be more convenient to determine the initial dissolution rate compared to the microcalorimetry.

4.4. Evaluation of degree of crystallinity for terfenadine samples by DSC

The degree of crystallinity of terfenadine samples was evaluated by DSC using Eq. (1). Fig. 6 represents the correlation between the logarithms of initial dissolution rate and the degree of crystallinity of various terfenadine samples. The degree of crystallinity obtained from DSC was well correlated to the heat of fusion, and this relationship could be applied to the estimation of the dissolution rate of drug substance having a different crystallinity.

5. Conclusions

The heat of fusion extrapolated at 25°C (ΔH_{25}) was obtained taking into account of heat of crystallization, heat of relaxation and excess enthalpy of supercooled liquid. The initial dissolution rates of terfenadine samples, which were consisted of polymorphs and amorphous forms, were measured by the rotating disk method. The logarithms of the initial dissolution rate of samples was linearly correlated with the heats of fusion obtained by the DSC, and this relationship holds as independent of crystalline behavior. This result indicated that the initial dissolution rate could be estimate from the heat of fusion using DSC. This experimental technique involved would be comparatively easy to determine, and the relationship obtained would have the possibility to facilitate the quality control of drug substance which contains small amount of amorphous or polymorphs.

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