Quantitative Correlation Between Initial Dissolution Rate and Heat of Solution of Drug

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Purpose. The aim of this study is to estimate the initial dissolution rate of drug substances by isothermal microcalorimetry. A theory was presented on the basis of Gibbs free energy and the Noyes–Whitney equation.

Methods. Polymorphic forms and quenched glass of indomethacin, and some different crystallinity samples of terfenadine were used. The heats of solution of samples were measured by isothermal microcalorimetry. The initial dissolution rates of samples were measured by rotating disk method at 25°C.

Results. Each drug showed a linear correlation between the heats of solution and the logarithms of initial dissolution rate, irrespective of their different crystal structure, such as polymorphic forms and crystallinity. The logarithms of initial dissolution rates were well correlated with the degree of crystallinity obtained by the isothermal microcalorimetry.

Conclusions. The initial dissolution rates of drug substances could be estimated quantitatively from the heats of solution as estimated from the present theory. Isothermal microcalorimetry was extremely useful for the estimation of the initial dissolution rates of polymorphs and of partially crystalline samples.

KEY WORDS: microcalorimetry; heat of solution; dissolution rate; polymorphism; amorphous; crystallinity.

INTRODUCTION

There is an increasing awareness that the solid pharmaceutical substances should be controlled in the physicochemical point of view (1). The polymorphic forms, crystallinity of drug substances are the major physicochemical properties that affect drug dissolution, chemical stability, as well as drug bioavailability (2,3). Even a small amount of contamination of polymorphs or amorphous may alter its physicochemical properties of original drug substances (4).

In the aspect of quality control of drug substances, these physicochemical properties should be controlled as one of the physicochemical specifications, because the metastable form and/or amorphous form are generally thermodynamically unstable, i.e. higher energy than the stable form and/or crystalline form. The metastable form and amorphous form are usually much more soluble and sometimes much more unstable than their crystalline counterparts. So, there are cases where the polymorphs and amorphous forms are contained with batch to batch difference during the production process of drug substances, and this difference may affect the dissolution behavior of drug. Therefore, there is an urgent need to estimate the dissolution behavior of the drug substance.

It is known that the degree of crystallinity is determined by powder X-ray diffraction (5), IR spectroscopy (6), and thermal analysis (7,8). The precision of obtained crystallinity and the detection limits for amorphous contents are dependent on the analytical methods (9). Isothermal microcalorimetry is a one of useful tools for the evaluation of crystallinity with potentially more precise and more definitive results.

The aim of this research is to clarify the quantitative relation between the initial dissolution rates and the heats of solution of drug substances. It would be applicable for the quality control of drug substances, which have polymorphic forms and/or contain amorphous fraction in them.

MATERIALS AND METHODS

Materials

Indomethacin and brucine were of JPXIII grade, supplied by Tokyo Kasei Co., Ltd. (Tokyo Japan). Terfenadine was supplied by Kyoto Pharmaceutical Industries, Ltd. (Kyoto Japan). Other chemicals were of special reagent grade.

Preparation of Samples

Polymorphic forms of indomethacin were prepared as described in the paper (10). Polymorphic forms of terfenadine were recrystallized from n-butanol and ethyl acetate, respectively (11). The quenched glasses of indomethacin, brucine and terfenadine were prepared by cooling the melted samples to the room temperature. The different crystallinity levels of terfenadine samples were prepared by grinding, using a Heiko Seisakusyo model TI 100 vibration mill.

Powder X-ray Diffraction Measurement

The powder X-ray diffraction pattern was measured by a RAD type diffractometer (Rigaku Denki, Tokyo Japan) using a scintillation counter. The measurements were done as described previously (12).

Measurement of Heat of Solution

The heats of solution of samples were determined by using an isothermal heat-conduction microcalorimeter (MMC-5111, Tokyo Riko) at 25°C, as described previously (13). About 0.2 g of each sample was dissolved in 25 ml of N, N′-dimethyl formamide and the heat of solution was measured. The calibration data was obtained using KCl solution.

Determination of Initial Dissolution Rate

The initial dissolution rates were measured using rotating disk method. The disk was of 6 mm diameter and the powder were compacted at the force of 9.8×10^3 N/cm^2. The disk was rotated at 200 rpm at 25°C. The solvents for the dissolution test for indomethacin, brucine and terfenadine were 200 ml of phosphate buffer (pH7.0), ethanol and JP No. 1 disintegration solution (pH 1.2), respectively. The drug release was determined spectrophotometrically.

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Determination of Crystallinity

The degree of crystallinity was obtained by the following equation (17).

$$\alpha(\%) = (\Delta Hs - \Delta Ha)/(\Delta Hc - \Delta Ha) \times 100 \quad (1)$$

where ΔHs, ΔHa and ΔHc are heats of solution of sample, amorphous standard (100% amorphous) and crystalline standard (100% crystalline), respectively. Crystalline standard was obtained by the slow crystallization from solution using the solvent cited at the sample preparation. Amorphous standard was obtained by the rapid cooling of the melted sample.

THEORETICAL SECTION

In general, the dissolution of solute into solvent may be accompanied by the Gibbs free energy changes (ΔG) as follows.

$$\Delta G = -RT \ln K = -RT \ln \gamma (X_1/(X_1 + X_2)) \quad (2)$$

where γ is activity coefficient; R is gas constant; T is absolute temperature; K is equilibrium constant. X_1 and X_2 are the molar fraction of solute and solvent, respectively. If the solid has a low solubility, $X_1 << X_2$, γ is approximated to 1, then, Eq. (2) may be rewritten to Eq. (3).

$$\Delta G = -RT \ln(X_1/X_2) = -RT \ln a \cdot Cs \quad (3)$$

where Cs is the equilibrium solubility of the solute and a is a constant.

According to the diffusion layer theory, the dissolution rate of solid is directly proportional to its solubility as shown in Noyes-Whitney equation (14).

$$dC/dt = k \cdot (Cs - C) \quad (4)$$

where k is apparent dissolution rate constant. C is dissolved concentration of the solute. Under the sink conditions, Cs >> C, equation (4) simplifies to

$$dC/dt = k \cdot Cs \quad (5)$$

Combining the Eq. (3) and (5), the following equation is obtained.

$$\Delta G = -RT \ln(dC/dt) - RT \ln (a/k) \quad (6)$$

Introducing enthalpy-entropy compensation (15), the following relation is obtained.

$$\Delta G = \Delta H - T \cdot \Delta S = \Delta H(1 - T/A) \quad (7)$$

where ΔH and ΔS are the enthalpy and entropy change at temperature T and A is constant.

From Eq. (6) and (7), the following equation could be obtained.

$$-RT \ln(dC/dt) - RT \ln(a/k) = \Delta H \cdot (1 - T/A) \quad (8)$$

For the dissolution study, Eq. (8) is written as

$$-RT \ln(dC/dt) - RT \ln(a/k) = \Delta H_{dis} \cdot (1 - T/A) \quad (9)$$

where ΔH_{dis} is the enthalpy obtained from dissolution study, and ΔH_{dis} can be expressed by Eq(10).

$$\Delta H_{dis} = \Delta H_{cal} + \Delta H_{dif} \quad (10)$$

where ΔH_{cal} is the heat of solution obtained by microcalorimetry and ΔH_{dif} is the difference in the heat of mixing between the heats obtained from the dissolution study and the microcalorimetry. Using Eq. (10), following equation is obtained.

$$-RT\ln(dC/dt) = \Delta H_{cal} \cdot (1 - T/A) + \Delta H_{dif} \cdot (1 - T/A) + RT \ln(a/k) \quad (11)$$

At a constant temperature, Eq. (11) is introduced into Eq. (12).

$$\ln (dC/dt) = -\Delta H_{cal} \cdot (1 - T/A)/RT + c \quad (12)$$

where c is $-\Delta H_{dif} \cdot (1 - T/A)/RT - \ln(a/k)$ and could be a constant.

If we perform the dissolution study using the weak electrolyte, the pH of the solution may strongly affect the solubility of weak electrolyte. Using the Henderson-Hasselbalch equation, the solubility of the acidic drug and basic drug should be represented as follows.

Solubility of weak acidic drug:

$$Cs = C_0 \cdot (1 + Ka/[H_3O^+]) \quad (13)$$

Solubility of weak basic drug:

$$Cs = C_0 \cdot (1 + [H_3O^+]/Ka) \quad (14)$$

where C_0 is a concentration of the molecular form of drug, Ka is a dissociation constant and $[H_3O^+]$ is a hydrogen ion concentration of solution. Therefore, the respective dissolution rates of weak acidic drug and weak basic drug at the sink condition are depicted as follows.

Dissolution rate of weak acidic drug:

$$dC/dt = k \cdot Cs = k \cdot C_0 \cdot (1 + Ka/[H_3O^+]) \quad (15)$$

Dissolution rate of weak basic drug:

$$dC/dt = k \cdot Cs = k \cdot C_0 \cdot (1 + [H_3O^+]/Ka) \quad (16)$$

In this research, $[H_3O^+]$ is maintained at constant through the experiment, equation (12) is available through the dissolution study irrespective of thenature of drug.

RESULTS AND DISCUSSION

Relation Between Initial Dissolution Rate and Heat of Solution of Polymorphs and Quenched Glass Sample

α-Form, γ-form and quenched glass of indomethacin were prepared and each form was identified by the powder X-ray diffraction. The initial dissolution rates of them are shown in Fig. 1. A linear dissolution was observed against the time. The initial dissolution rates of samples were in the order of quenched glass > α-form > γ-form. The obtained rates were plotted against the heat of solution and are shown in Fig. 2. As estimated from the theory, a linear correlation was observed between the logarithms of initial dissolution rate and the heats of solution of indomethacin samples having different physicochemical properties. Figure 3 shows Arrhenius plots of the samples. A linear relation was observed between the initial dissolution rate and inverse of absolute temperature for α-, γ- and glassy indomethacin. In order to examine the effect of activation energy on the initial dissolution rate of the samples, the activation

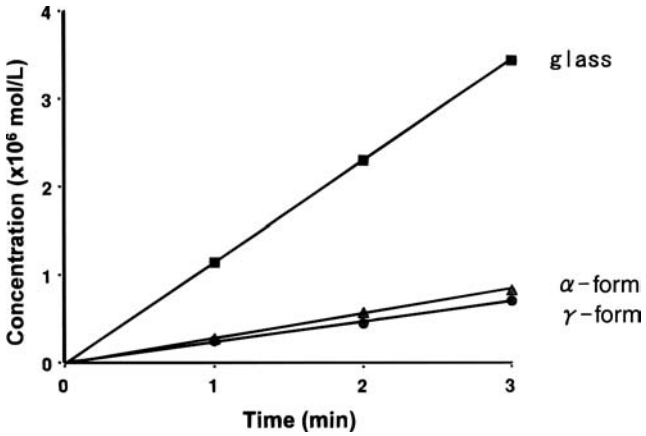

Fig. 1. Initial dissolution rate of indomethacin polymorphs and glass at 25°C in phosphate buffer (pH 7.0).

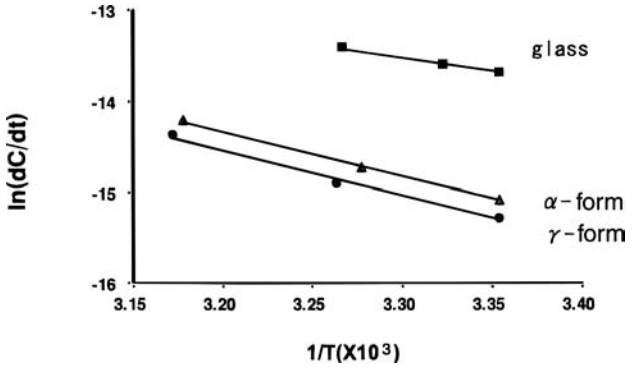

Fig. 3. Arrhenius plots of initial dissolution rate of indometacin polymorphs and glass.

energy for the dissolution were plotted against the logarithms of initial dissolution rates of samples. A good linear correlation was observed as shown in Fig. 4. The activation energy evaluated from the dissolution rate should be the sum of the heats of solution and dissociation and the activation energy of the solute diffusion into solvent (16). From the detailed comparison of Fig.2 and 4, both plots gave similar correlation with ln(dC/dt),therefore, the activation energy for the dissolution could be equivalent to the heat of solution (ΔH_{cal}).

Relationship Between Initial Dissolution Rate and Heat of Solution for Different Crystallinity Samples

The effect of crystallinity on the initial dissolution rate was also investigated. Terfenadine was used as a model compound because it has polymorphs and it is easy to obtain different crystallinity samples.

The powder X-ray diffraction patterns of ground samples of terfenadine (form I and form II) are shown in Fig. 5. The peak intensities of both polymorphs decreased with increasing the grinding time, and halo patterns were observed after 60min of grinding for form I and 30min of grinding for form II, respectively. The heats of solution of samples were changed from endotherm to exotherm with an increase in grinding time. The heats of solution of forms I and II of crystalline were 22.83 kJ/mol and 21.94 kJ/mol, respectively. 60 min of grinding for form I or 30min grinding for form II make terfenadine crystalline to amorphous, and the heats of solution were −5.85 kJ/mol for form I and −5.83 kJ/mol for form II, respectively.

The initial dissolution rates of terfenadine (form I and form II) with different levels of crystallinity samples were measured. A linear dissolution behavior was observed for all samples. The phase transition from amorphous to crystalline was not occurred during the dissolution study. For both polymorphs, the initial dissolution rate was increased as the crystallinity was decreased. It should be intuitively more likely that changes in lattice energy would be the major contribution to the dissolution rate of drug substance.

The correlation between initial dissolution rates and the heats of solution for terfenadine samples was illustrated in Fig 6. Irrespective of the presence of polymorphs and crystallinity difference, a linear correlation was obtained between them, as estimated from Eq. (12). We also examined this relationship for brucine having different crystallinity, the same linear correlation was obtained. These results indicated that the batch to batch variations of initial dissolution rate of drug substance could be estimated from the heat of solution data determined by the isothermal microcalorimetry.

Evaluation of the Initial Dissolution Data of Terfenadine from Crystallinity Data

The crystallinity of terfenadine samples was evaluated by isothermal microcalorimetry using Eq. (1). The degree of

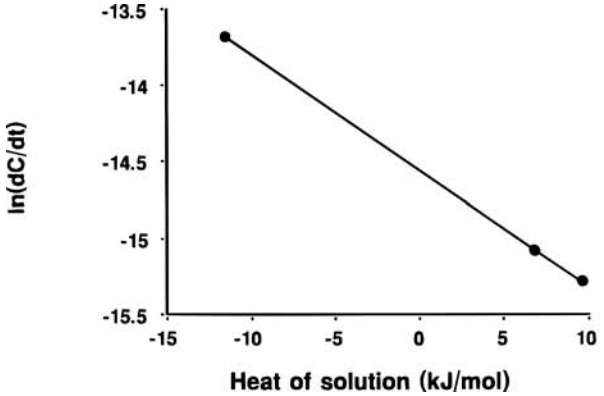

Fig. 2. Relationship between heat of solution and logarithm of initial dissolution rate of indometacin polymorphs and glass at 25°C.

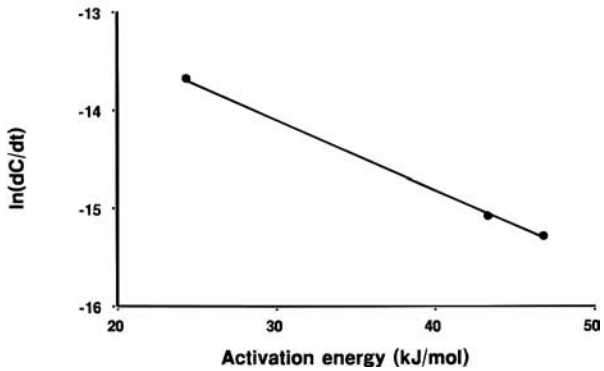

Fig. 4. Relationship between activation energy and ln(dC/dt) for dissolution of indometacin polymorphs and glass at 25°C.

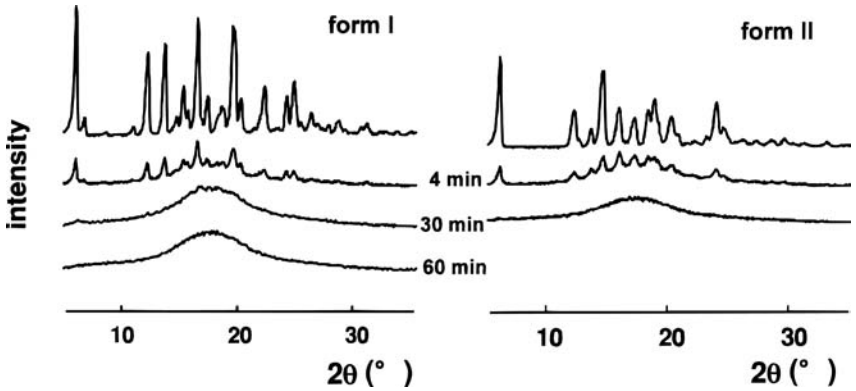

Fig. 5. Change in powder X-ray diffraction patterns of terfenadine (form I and form II) by grinding.

crystallinity was well correlated with the heat of solution, therefore, the plot of the calculated crystallinities against the logarithms of initial dissolution rate could be linear. As we would expect, a linear correlation (not shown) was obtained. Therefore, the crystallinity obtained by the microcalorimetry would be seems to make a significant contribution to evaluate the initial dissolution rate of the drug substance, in the case of the drug substance produced with batch to batch variable crystallinity.

CONCLUSIONS

A theory to correlate the dissolution rate and the heat of solution was presented on the basis of Gibbs free energy and Noyes-Whitney equation. Indomethacin, terfenadine and brucine having polymorphs and several levels of partially amorphous were used as a model of drug substances. The logarithms of initial dissolution rates of them were well correlated with the heats of solution obtained by the isothermal microcalorimetry, and this relationship was independent of the crystal behavior of them. In the case of partially amorphous samples, the logarithms of initial dissolution rates were well correlated with the degree of crystallinity as well as the heat of solution.

From these results, it is concluded that the initial dissolution rates of drug substances would be accurately predictable from the heats of solution as well as degree of crystallinity obtained by the isothermal microcalorimetry. This study could be applicable to the quality control for the drug substances which tends to lead batch to batch variations.

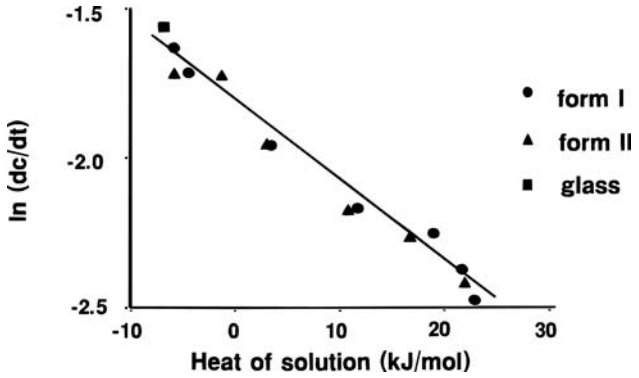

Fig. 6. Relationship between heat of solution and logarithm of initial dissolution rate of terfenadine.

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