Comparison of Crystallinity of Cefditoren Pivoxil Determined by X-Ray, Differential Scanning Calorimetry and Microcalorimetry

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The heat of crystallization and heat of solution of cefditoren pivoxil of different crystallinities were determined by differential scanning calorimetry and isothermal microcalorimetry, respectively. The heat of crystallization and heat of solution of ground cefditoren pivoxil showed good linear correlation with the degree of crystallinity determined by Ruland's method by powder X-ray diffractogram. The changes in crystallinity of amorphous cefditoren pivoxil by adsorption of alcohol vapor could be evaluated for small amounts of sample by use of heat of crystallization. Since the apparent dissolution rate of cefditoren pivoxil of various crystallinities correlated with the heat of solution, microcalorimetry was found to be useful for prediction of dissolution behavior.

Key words crystallinity; cefditoren pivoxil; amorphous; grinding; heat of crystallization; heat of solution

The crystallinity of drug substances and additives is one of the fundamental physicochemical properties in formulation design because it affects the pharmaceutical properties such as dissolution behavior,[1] hygroscopicity,[2] chemical stability[3] and bioavailability[4] of oral solid dosage forms. Several methodologies are available to determine the degree of crystallinity, such as X-ray diffraction,[5,6] differential scanning calorimetry (DSC),[7] infrared spectroscopy[8] and solution calorimetry.[9,10] Yonemochi *et al*. reported that a linear correlation was observed between the heat of crystallization and heat of solution, which were evaluated for ground or spray-dried ursodeoxycholic acid by DSC and solution calorimetry, respectively.[11,12] Thompson *et al*. reported that the heat of solution, determined for mixtures of an amorphous and crystalline beta-lactam antibiotic by solution calorimetry, showed a good correlation with the mixing ratio.[13]

Cefditoren pivoxil is a new oral cephalosporin antibiotic. We have already reported that the degree of crystallinity of cefditoren pivoxil, which was determined according to Ruland's method using a powder X-ray diffractogram, decreased through the process of grinding.[14] In this study, we evaluated the crystallinity of cefditoren pivoxil by heat of crystallization and heat of solution. These results were compared with the crystallinity calculated according to Ruland's method. Further, the heat of crystallization was applied to evaluate changes in crystallinity of amorphous cefditoren pivoxil under the saturated vapor of alcohols. The relationship between the heat of solution and the dissolution behavior of cefditoren pivoxil with various crystallinities is also discussed.

Experimental

Materials Cefditoren pivoxil was synthesized at Meiji Seika Kaisha, Ltd. (Japan). Organic solvents, sodium chloride and hydrochloric acid were of analytical reagent grade.

Preparation of Amorphous Solid Three grams of cefditoren pivoxil was ground by a vibration mill (model TI-200, CMT, Tochigi, Japan) for 1 to 30 min. The grinding cell was made of aluminum oxide.

Thermal Analysis A differential scanning calorimeter (DSC, model DSC3100, MAC Science, Yokohama, Japan) and a thermogravimetry apparatus (TG, model TG-DTA2000, MAC Science) were used under a nitrogen gas flow (60 ml/min) at a heating rate of 10 °C/min. For the calibration of enthalpy determination, indium of 99.99% purity was used.

Crystallization of Amorphous Solid One hundred and fifty mg of 30 min ground cefditoren pivoxil powder was exposed to saturated vapors of methanol, ethanol, 1-propanol, 1-butanol and 1-pentanol in a desiccator at 40 °C.

Determination of Apparent Solubility in Alcohols Ten grams of intact cefditoren pivoxil powder was suspended in 10 ml of methanol, ethanol, 1-propanol, 1-butanol and 1-pentanol at 25 °C, respectively. The suspensions were shaken for 30 s per 5 min and shaking was repeated 6 times. The aliquots were filtered through a Millipore filter (0.45 μm). The concentrations of cefditoren pivoxil were determined by HPLC as described previously.[14]

Solution Calorimetry The heats of solution of intact and ground cefditoren pivoxil powders were determined using an isothermal heat-conduction twin type microcalorimeter (model MPC-11, Tokyo Riko Co., Ltd., Tokyo, Japan). Before measurement, cefditoren pivoxil powder was dried over phosphorus pentoxide under reduced pressure at 25 °C for 12 h. The water contents in dried samples ranged from 0.11 to 0.22% after measurement using a Karl-Fischer titrator (model AQ-6, Hiranuma Sangyo, Ibaraki, Japan). Therefore, it was assumed that the difference in water content between dried samples hardly affected the value of the heat of solution. Two hundred mg of cefditoren pivoxil powder was dissolved in 20 ml of dimethyl sulfoxide (*ca*. 0.2% water content) at 25.0 °C. The dissolution medium was stirred at 50 rpm by a paddle.

Dissolution Study Fifty mg (potency) of cefditoren pivoxil powder was suspended in 500 ml of the 1st fluid (pH 1.2) for the disintegration test in the 13th edition of Japanese Pharmacopoeia in a dissolution apparatus (model NTR-6100, Toyama Sangyo, Osaka, Japan) at 37 °C. The suspensions were stirred at 50 rpm by the paddle. Aliquots were filtered through a G-4 filter (Toyama Sangyo). The amount of dissolved cefditoren pivoxil was determined by an ultraviolet spectrophotometer (model UV-160, Shimadzu, Kyoto, Japan) at 272 nm.

Results and Discussion

Evaluation of Crystallinity by Heat of Crystallization The DSC curves of the intact and ground cefditoren pivoxil are shown in Fig. 1. An endothermic event at 210 °C followed by an exothermic peak was observed for the intact cefditoren pivoxil. The endothermic peak at 210 °C was confirmed to be due to fusion from the observation with the melting point apparatus, and the exothermic peak was due to decomposition from the results of TG measurement. For ground samples, on the other hand, an exothermic peak in the range 133—142 °C, an endothermic peak in the range 195—202 °C and the following exothermic peak were observed; they were concluded to be due to recrystallization, fusion and decomposition, respectively. The position of exothermic

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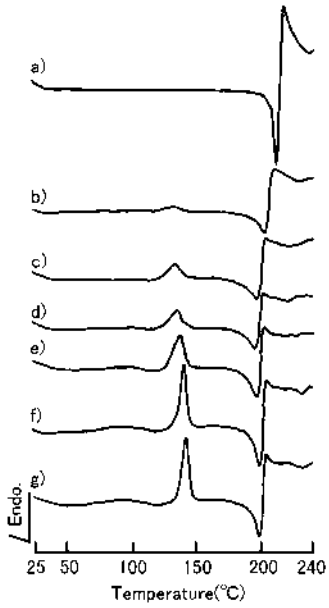

Fig. 1. DSC Curves of Intact and Ground Cefditoren Pivoxil
Grinding time; a) 0 min, b) 1 min, c) 3 min, d) 5 min, e) 10 min, f) 20 min, g) 30 min.

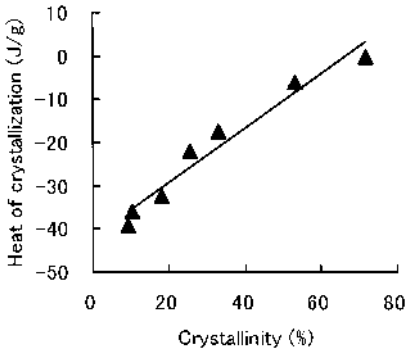

Fig. 2. Relationship between Crystallinity and Heat of Crystallization of Cefditoren Pivoxil

peaks due to recrystallization was shifted to higher temperature with the extension of grinding time. The progress of amorphization could cause the higher temperature peak shift, as Yamaguchi *et al*. observed that the temperature of exothermic peaks due to recrystallization shifted higher with changes in the spray-drying conditions.[15] As the exothermic peaks became greater with the extension of grinding time, the heats of crystallization were determined from the area of the exothermic peaks. The relationship between the heat of crystallization of the ground cefditoren pivoxil and the crystallinity determined according to Ruland's method by X-ray diffractogram, is shown in Fig. 2. A good linear correlation was found between the two values with a correlation coefficient of 0.978. This indicates that the two parameters are equally useful for the evaluation of crystallinity.

Based on the above results, the physicochemical stability of amorphous cefditoren pivoxil was evaluated using the heat of crystallization as an index to represent the crystallinity. The changes in the heat of crystallization of 30 min ground cefditoren pivoxil stored in the saturated vapor of several alcohols at 40 °C are shown in Fig. 3. Rapid crystallization was observed, when the samples were stored in the vapor of alcohol of lower molecular weight. The amorphous state, however, was maintained for 180 min under the saturated vapor of 1-pentanol. As the vapor pressure of methanol, ethanol, 1-propanol, 1-butanol and 1-pentanol was 266, 134, 52, 18 and 7 mmHg at 40 °C, respectively,[16] it was presumed that the adsorption of methanol or ethanol was more favorable than the other alcohols. Further, the apparent solubility of the intact cefditoren pivoxil in methanol, ethanol, 1-propanol, 1-butanol and 1-pentanol was found to be 12.2, 1.7, 1.6, 1.1 and 0.8 mg/ml at 25 °C, respectively. This also suggested that the more rapid crystallization under methanol vapor could be attributed to the greater solubility in methanol. From the above results, it was concluded that DSC was useful to evaluate the changes in crystallinity using a small amount of amorphous solid.

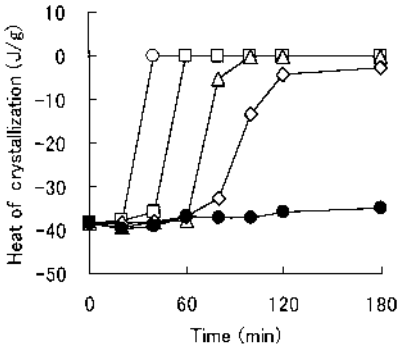

Fig. 3. Changes in Heat of Crystallization of 30 min Ground Cefditoren Pivoxil after Storage under Saturated Vapor of Various Alcohols at 40 °C
Vapor; ○, methanol; □, ethanol; △, 1-propanol; ◇, 1-butanol; ●, 1-pentanol.

Prediction of Dissolution Behavior by Heat of Solution

Thermograms for the dissolution of intact and ground cefditoren pivoxil into 20 ml of dimethyl sulfoxide are shown in Fig. 4. We used dimethyl sulfoxide as a dissolution medium, since intact cefditoren pivoxil was insoluble in water and only slightly soluble in ethanol. All heats of solution observed were exothermic, and the absolute value of heat of solution increased with extension of the grinding time. The relationship between degree of crystallinity and heat of solution of the ground cefditoren pivoxil is shown in Fig. 5. A good linear correlation was found between the two values with a correlation coefficient of 0.980. The evaluation of crystallinity from the heat of solution appears to be a reasonable and predictable method compared to other methods such as X-ray and DSC.

The dissolution process of a solid can be divided into two steps, liberation as a single molecule from the solid state and solvation of the molecule. The heat of solution, ΔH_{soln}, can be expressed as the sum of the heat of liberation of the molecule from solid state, ΔH_{lib}, and the heat of solvation, ΔH_{solv}, as shown in Eq. 1.

$$\Delta H_{soln} = \Delta H_{lib} + \Delta H_{solv} \quad (1)$$

Generally, ΔH_{lib} shows a positive value and ΔH_{solv} shows a negative value, and ΔH_{soln} is decided by this balance.[11] As ΔH_{solv} should be a constant value in this study, the increment in exothermic ΔH_{soln} reflects by the decrease in ΔH_{lib} with decreasing crystallinity of cefditoren pivoxil. In other words, it was shown that less enthalpy sufficed for liberation of a single molecule from the amorphous solid, compared with

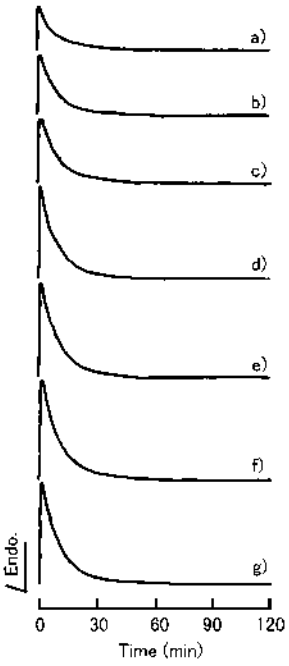

Fig. 4. Thermograms for Dissolution of Intact and Ground Cefditoren Pivoxil into Dimethyl Sulfoxide at 25 °C

Grinding time; a) 0 min, b) 1 min, c) 3 min, d) 5 min, e) 10 min, f) 20 min, g) 30 min.

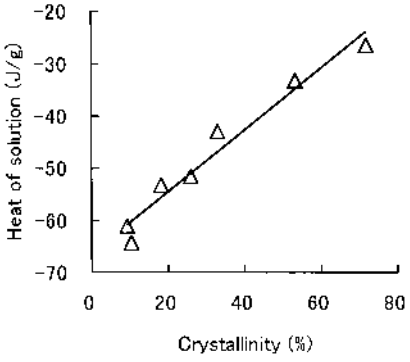

Fig. 5. Relationship between Crystallinity and Heat of Solution of Cefditoren Pivoxil

the crystal, since the polymorph of cefditoren pivoxil has not been observed.

The dissolution patterns of intact and ground cefditoren pivoxil in the 500 ml of 1st fluid (pH 1.2, JP13) at 37 °C are shown in Fig. 6. Dissolution was enhanced with the decrease in crystallinity. As the slope from 0 to 2 min could be used as an index to represent the apparent dissolution rate, the obtained values are plotted against the heat of solution as an index to express the crystallinity. A good linear correlation was found between the slope and the heat of solution with a correlation coefficient of −0.972. It was shown that the dissolution behavior of cefditoren pivoxil with different crystallinities could be predicted from the heat of solution.

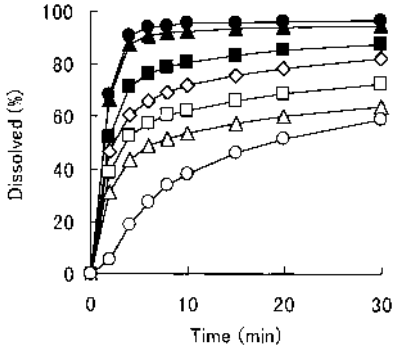

Fig. 6. Dissolution Patterns of Intact and Ground Cefditoren Pivoxil in the 1st Fluid (pH 1.2, JP13) at 37 °C

Grinding time; ○, 0 min; △, 1 min; □, 3 min; ◇, 5 min; ■, 10 min; ▲, 20 min; ●, 30 min.

Conclusions

The heat of crystallization determined by DSC, and the heat of solution determined by isothermal microcalorimetry, were closely correlated with the crystallinity of cefditoren pivoxil. When amorphous cefditoren pivoxil was stored in the vapor of alcohols, the rate of recrystallization could be evaluated using a small amount of sample by determining the heat of crystallization. Since the apparent dissolution rate of cefditoren pivoxil with various crystallinity was found to be associated with the heat of solution, microcalorimetry was available to predict the dissolution behavior.

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