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RESEARCH PAPER

Water Vapor Adsorption Properties of Amorphous Cefditoren Pivoxil Evaluated by Adsorption Isotherms and Microcalorimetry

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ABSTRACT

Water vapor adsorption of ground cefditoren pivoxil was studied. The amount of water adsorbed increased with a decrease in the crystallinity of cefditoren pivoxil. It was found from the microcalorimetric measurements that the differential heat of water vapor adsorption at 1.5% adsorbed water increased with decreasing crystallinity of cefditoren pivoxil, suggesting that hygroscopicity of cefditoren pivoxil was enhanced by grinding. These results indicated that hydrophilic adsorption sites in cefditoren pivoxil increased through the grinding process. The results of infrared (IR) spectra examination suggested that the increment of hydrophilic adsorption sites through the grinding process resulted from the change of the environment of the carbonyl groups in two esters and amide.

Key Words: *Amorphous; Cefditoren pivoxil; Grinding; Heat of adsorption; Microcalorimetry; Water vapor adsorption isotherm.*

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INTRODUCTION

Studies of the hygroscopicity of amorphous drugs are invaluable in the pharmaceutical fields. Ueno et al. described that decreasing crystallinity of spray-dried ursodeoxycholic acid caused an increase in the amount of water adsorbed (1). Similar results were also reported for lactose (2), raffinose (3), and sucrose (4) in the mixture of amorphous and crystalline materials.

Since recrystallization (5,6) and decomposition (7) of an amorphous drug are accelerated by uptake of water, it is very important to estimate the hygroscopic properties for prediction of physical and chemical stability of drugs. Heat of adsorption can be determined indirectly through the Clausius-Clapeyron equation (8) or an Arrhenius equation analogue (9) from an adsorption isotherm. As these methodologies require specific conditions and some assumptions, the direct determination of the heat of adsorption using a calorimeter seems to be more essential for precise measurement of the heat of adsorption (9).

We have already reported that the degree of crystallinity of cefditoren pivoxil, a new oral cephalosporin antibiotic, decreased with an increase in the grinding time (10). In this study, the water vapor adsorption isotherm and the heat of water vapor adsorption for cefditoren pivoxil in different crystallinities were measured, and the influence of crystallinity on hygroscopicity of cefditoren pivoxil was investigated. Further, the changes of molecular state through the grinding process are discussed from the infrared (IR) spectrum.

MATERIALS AND METHODS

Materials

Cefditoren pivoxil was synthesized at Meiji Seika Kaisha Limited (Gifu, Japan). Sodium chloride and potassium nitrate were analytical reagent grade.

Preparation of Amorphous Solid

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

Determination of Crystallinity

The crystallinity of cefditoren pivoxil was determined according to Ruland's method (11) using the powder X-ray diffraction patterns obtained on an X-ray diffractometer (model RINT 2000, Rigaku, Tokyo, Japan) with a scintillation counter, CuK_α radiation (40 kV, 40 mA), and a symmetrical reflection goniometer at 2°/min scanning between $2\theta = 5°$ and 140°.

Water Vapor Adsorption Analysis

A microbalance system (model MB300G, VTI, FL) was used for determination of water vapor adsorption isotherms at 20°C. Cefditoren pivoxil samples (ca. 100 mg) were placed on the microbalance pan, surrounded by a thermal jacket used for controlled isothermal scanning. Before the measurements, all samples were dried under a vacuum at 30°C until equilibrium was reached (i.e., the weight change for 5 min was less than 5 μg). Water vapor was then introduced to the sample at increments of 5% relative humidity (RH) up to 95% RH. A moisture level was maintained until the sample was equilibrated gravimetrically as described above. The measurements were performed in duplicate. The specific surface area was calculated from the water vapor adsorption isotherm below 50% RH using the method reported by Teng et al. (12).

Measurement of Specific Surface Area

A Microtrac Beta Sorb (model 4200, Nikkiso Co., Ltd., Tokyo, Japan) was used to determine the specific surface area. The BET equation was applied to the nitrogen gas adsorption isotherm.

Measurement of Mean Particle Diameter

A Microtrac HRA (model 9320-X100, Nikkiso Co.) was used to determine the mean particle diameter by a laser diffraction analysis. Sample powder was supplied from a Dry-sampler (model CDS-1, Nikkiso Co.).

Adsorption Microcalorimetry

The differential heat of water vapor adsorption q_d of the intact and the ground cefditoren pivoxil powders was determined by an isothermal heat-conduction-type twin microcalorimeter (model MPC-11, Tokyo Riko Co., Ltd., Tokyo, Japan) at 25.0°C. The adsorption assembly and the operating procedure reported by Kim et al. were used (13). The adsorption assembly was constructed of a glass tube, adsorption vessels, glass stopcocks, and a glass bottle. At first, 200 mg of cefditoren pivoxil powder were placed on the sample vessel, while the reference vessel was empty. The vessels were connected to the glass tube and evacuated for 12 hr at 25°C. The amount of water

adsorbed to cefditoren pivoxil was adjusted by choosing saturated salt aqueous solution, which has different water vapor pressure, and closing the stopcock at the appropriate time. Saturated solution of sodium chloride or potassium nitrate (10 ml) was put in the glass bottle, and then the glass bottle was connected to the glass tube and evacuated for 1 min. The amount of water adsorbed was determined by measuring the water content in cefditoren pivoxil before and after the calorimetric experiment. The water content was measured using a Karl-Fischer titrator (model AQ-6, Hiranuma Sangyo, Ibaraki, Japan).

Infrared Spectroscopy

A Fourier transformed IR spectrophotometer (model FT/IR-230, Jasco, Tokyo, Japan) was used. Measurements were carried out by the KBr disk method.

RESULTS AND DISCUSSION

Changes of Amount of Water Adsorbed by Grinding

The water vapor adsorption isotherms of the intact and the ground cefditoren pivoxil at 20°C are shown in Fig. 1. The intact cefditoren pivoxil slightly adsorbed water vapor, while the ground cefditoren pivoxil adsorbed much water vapor. Hysteresis between adsorption and desorption processes was found, and the area enclosed between adsorption and desorption events became greater as the crystallinity of cefditoren pivoxil decreased. This phenomenon might be caused by the capillary condensation in the amorphous portion of the cefditoren pivoxil. The relationship between the crystallinity of cefditoren pivoxil and the amount of water adsorbed at 95% RH is shown in Fig. 2. The amount of water adsorbed increased with the decrease in crystallinity of cefditoren pivoxil. A good linear correlation was observed between two parameters, with a correlation coefficient of −.992. This indicated that the water vapor adsorption analysis could be used to evaluate the crystallinity of cefditoren pivoxil.

The relationship between the crystallinity and the specific surface area of cefditoren pivoxil is shown in Fig. 3. The specific surface areas calculated from nitrogen gas adsorption isotherms were smaller than the values estimated from water vapor adsorption isotherms, and the difference between both values became greater with decreasing crystallinity of cefditoren pivoxil. Hancock and Zografi described that the amount of water taken up by amorphous solids was greater than that taken up by the crystalline form of the same chemical entity, which can

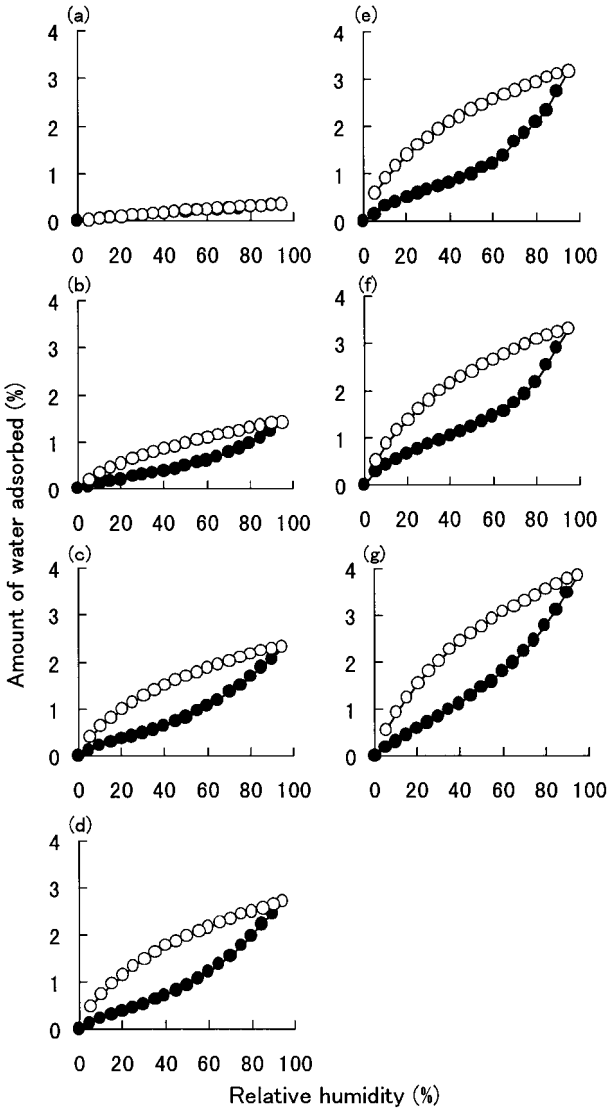

Figure 1. Water vapor adsorption isotherms of intact and ground cefditoren pivoxil at 20°C: ●, adsorption; ○, desorption. Grinding time: (a) 0 min; (b) 1 min; (c) 3 min; (d) 5 min; (e) 10 min; (f) 20 min; (g) 30 min.

be accounted for by the surface adsorption because water was absorbed into the bulk of the amorphous solids (14). As the sorption isotherm of the ground cefditoren pivoxil shown in Fig. 1 was a typical absorption isotherm for an amorphous solid (14), this phenomenon would be attributed to the absorption of water molecules into the ground cefditoren pivoxil particles.

On the other hand, the relationship between the crystallinity and the mean particle diameter of cefditoren pivoxil is shown in Fig. 4. Generally, as the mean particle

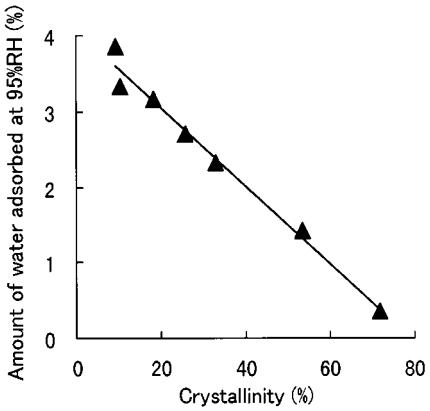

Figure 2. Relationship between crystallinity and amount of water adsorbed at 95% RH.

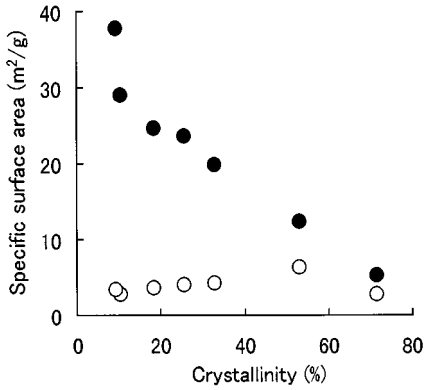

Figure 3. Relationship between crystallinity and specific surface area: ●, calculated from water vapor adsoption; ○, calculated from nitrogen gas adsorption.

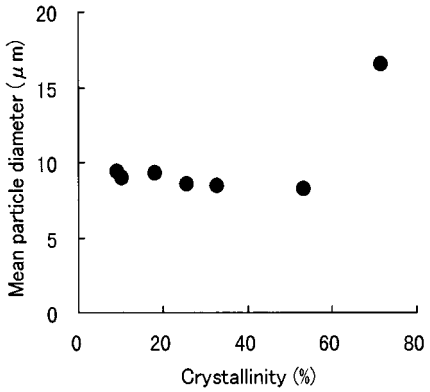

Figure 4. Relationship between crystallinity and mean particle diameter.

diameter of powders became small, the specific surface area increased. Since the specific surface areas calculated from nitrogen gas adsorption shown in Fig. 3 changed in inverse proportion to the mean particle diameter, the specific surface area calculated from nitrogen gas adsorption could be regarded as the actual value. However, Nakai et al. demonstrated that the increment of the amorphous portion in microcrystalline cellulose by grinding provided adsorption sites available for water vapor, while unavailable for nitrogen gas (15). Therefore, it could be also explained that the surface of ground cefditoren pivoxil was the adsorption sites available for water vapor in the wide sense. In this respect, the specific surface area calculated from water vapor adsorption might represent the true value if the hydrogen bonding between water molecules on the surface was taken into consideration. Moreover, the gradual increase in mean particle diameter of samples with crystallinity lower than 55.3% with decreasing crystallinity might result from aggregation of cefditoren pivoxil powder through the grinding process.

Changes of Hygroscopicity by Grinding

Hygroscopicity of the intact and the ground cefditoren pivoxil was also investigated from the determination of

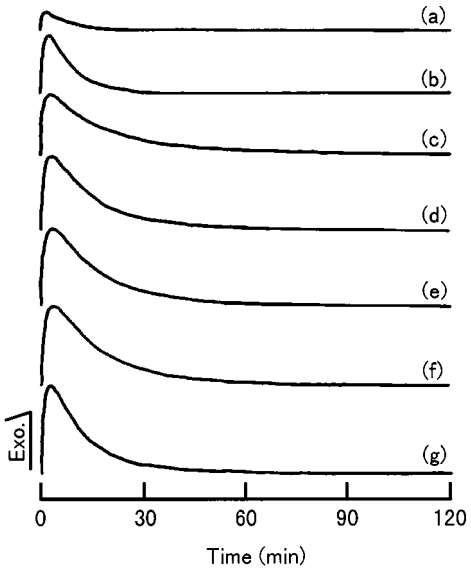

Figure 5. Thermograms for water vapor adsorption of intact and ground cefditoren pivoxil under 92% RH for 120 min at 25.0°C (amounts of water adsorbed are designated in parentheses). Grinding time: (a) 0 min (0.15%); (b) 1 min (1.00%); (c) 3 min (1.99%); (d) 5 min (2.26%); (e) 10 min (2.50%); (f) 20 min (2.67%); (g) 30 min (3.01%).

heat of water vapor adsorption. The typical thermograms of water vapor adsorption for the intact and the ground cefditoren pivoxil at 92% RH and for 120 min are shown in Fig. 5. The exothermic peaks became greater with increasing grinding time. The integral heat of adsorption q_{int} estimated from the area under the curve is plotted against the amount of water adsorbed in Fig. 6. The differential heat of adsorption q_d of water on cefditoren pivoxil with different crystallinities as a function of the amount of water adsorbed is shown in Fig. 7. The differential heat of adsorption q_d was calculated from the slope of the continuous three plotted points of q_{int} in Fig. 6, and the amount of water at the center point among three plotted points was used as the corresponding amount of water adsorbed. The dotted lines in Fig. 7 represent the value of 44 kJ/mol, which corresponded to latent heat of liquefaction of water at 25°C. The values of q_d came closer to 44 kJ/mol with the increase in the amount of water adsorbed, suggesting that the state of water molecules approached the progressive buildup of multilayers of wa-

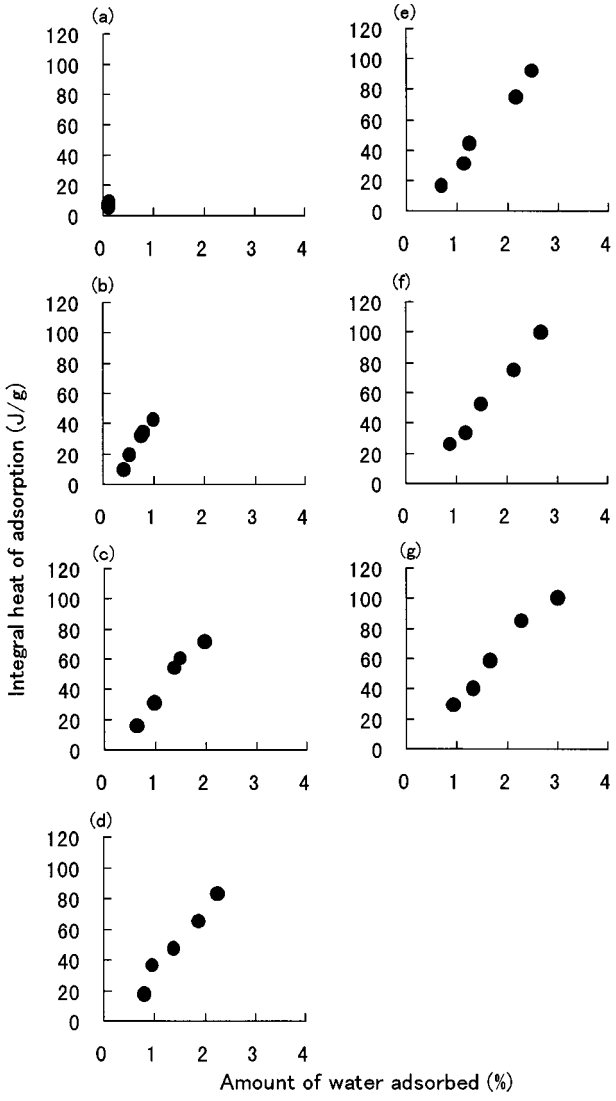

Figure 6. Relationship between amount of water adsorbed and integral heat of adsorption at 25.0°C. Grinding time: (a) 0 min; (b) 1 min; (c) 3 min; (d) 5 min; (e) 10 min; (f) 20 min; (g) 30 min.

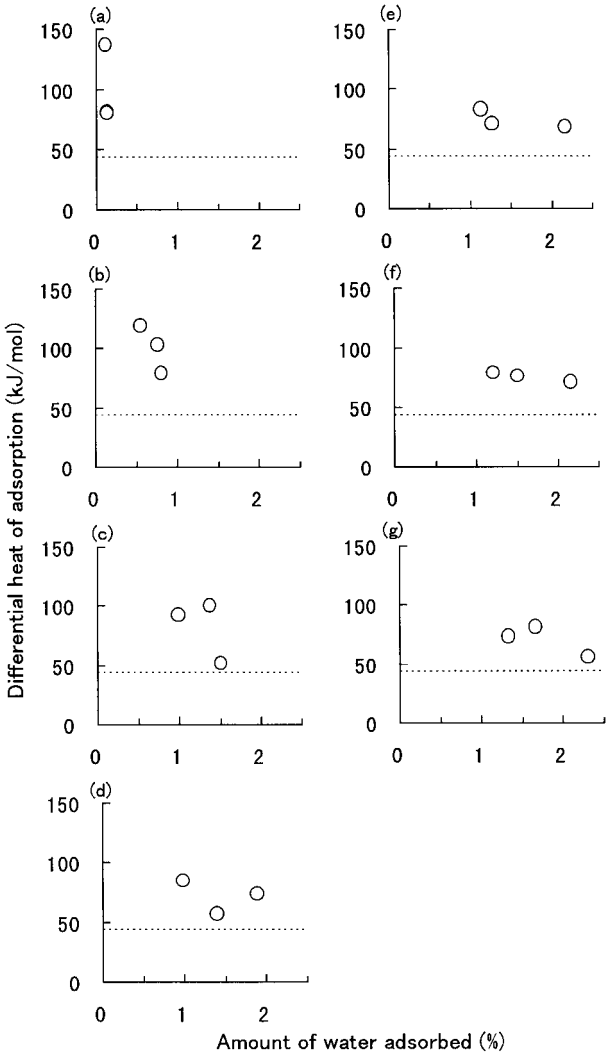

Figure 7. Relationship between amount of water adsorbed and differential heat of adsorption at 25.0°C. Grinding time: (a) 0 min; (b) 1 min; (c) 3 min; (d) 5 min; (e) 10 min; (f) 20 min; (g) 30 min.

ter adsorbed. The relationship between the crystallinity and q_d at 1.5% adsorbed water is shown in Fig. 8 for the samples for which crystallinity was less than 33.1%. The q_d at 1.5% adsorbed water increased with decrease in crystallinity of cefditoren pivoxil, suggesting that the hygroscopicity of cefditoren pivoxil was enhanced by the grinding. This result indicated that hydrophilic adsorption sites in cefditoren pivoxil increased through the grinding process.

Effects of Grinding on IR Spectrum

The IR spectra of the intact and the ground cefditoren pivoxil are shown in Fig. 9. The IR spectrum of the intact cefditoren pivoxil showed four carbonyl stretching bands due to β-lactam, two esters and amide at 1786 cm^{-1}, 1724 cm^{-1}, 1737cm^{-1}, and 1687 cm^{-1}, respectively. Among these carbonyl stretching bands, the intensities of two carbonyl stretching bands at 1724 cm^{-1} and 1737 cm^{-1} became small with the progress of grinding, and finally these peaks disappeared after grinding for 20 min. On the other hand, a new peak at 1750–1752 cm^{-1} appeared after 5 min of grinding, and this peak became stronger with the elongation of grinding. Moreover, the carbonyl stretching band at 1687 cm^{-1} became broad and shifted to a lower wavenumber with an increase in the grinding time. The carbonyl stretching bands at 1786 cm^{-1} showed no variation due to the grinding. These results suggested that the increment of hydrophilic adsorption sites through the grinding process resulted from the change of the environment of the hydrophilic groups, such as the carbonyl groups in two esters and amide.

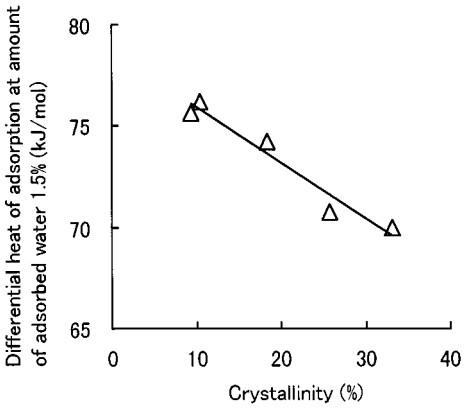

Figure 8. Relationship between crystallinity and differential heat of adsorption at 1.5% adsorbed water.

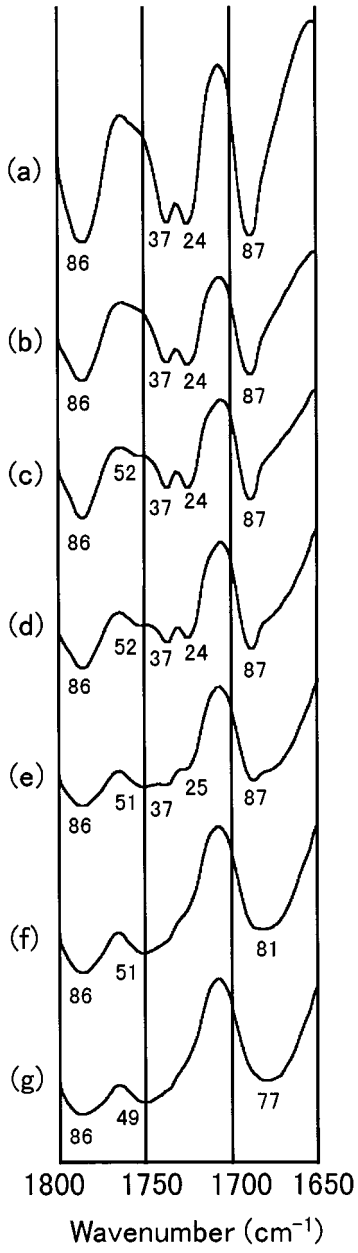

Figure 9. IR spectra of intact and ground cefditoren pivoxil. Grinding time: (a) 0 min; (b) 1 min; (c) 3 min; (d) 5 min; (e) 10 min; (f) 20 min; (g) 30 min.

CONCLUSIONS

Bolis et al. described that the differential heat of adsorption q_d of water with a solid could be used to define the degree of the interaction of the surface toward water (16). Namely, as the q_d of water with a solid became

greater than 44 kJ/mol, the surface could be defined as hydrophilic. Therefore, our results would reflect not only the increase in the hydrophilic adsorption sites in cefditoren pivoxil by the grinding, but also the increase in the affinity of the surface toward water. It could be supposed that the q_d of water was useful as an index to express simultaneously the number of the hydrophilic adsorption site and the degree of the interaction energy toward water of cefditoren pivoxil.

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