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Physicochemical characteristics of porous crystalline cellulose and formation of an amorphous state of ethenzamide by mixing

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Abstract

The physicochemical characteristics of porous crystalline cellulose (PCC) have been investigated. The specific surface area and pore size distribution curve of PCC were determined from nitrogen gas adsorption isotherms. The specific surface area and pore volume of PCC were decreased on grinding with a mortar and pestle or after storage at high relative humidities, which was attributed to the destruction of the porous structure of PCC. When a physical mixture of ethenzamide (EZ) and PCC was stored for 1 month under dry conditions, amorphization of EZ was observed. After heating the mixture of PCC and EZ at 100°C for 2 h, crystalline EZ changed to an amorphous state. In the stored or heated mixtures of PCC-EZ, EZ molecules would be adsorbed physically onto the pore surface of PCC. The heated mixture of PCC-EZ showed a high rate of dissolution of EZ in polar and nonpolar solvents. Nonporous microcrystalline cellulose was unable to transform crystalline EZ to the amorphous state.

Key words: Porous crystalline cellulose; Pore size distribution; Dissolution; Specific surface area; Grinding; Water vapor adsorption; Ethenzamide; Amorphism

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1. Introduction

The interactions between medicinal molecules and porous materials, such as controlled pore glass or activated carbon, have been investigated in a number of previous papers (Kannisto and Neuvonen, 1984; Nakai et al., 1984, 1985, 1989; Konno et al., 1986). In a mixture of a drug and porous materials, the drug molecules adsorbed onto the surface of the porous materials and were founds to exist in the amorphous state (Nakai et al., 1984; Nakagami, 1991). The physicochemical properties of drug molecules adsorbed onto porous materials have been reported to differ markedly from those in the crystalline state (McGinity and Lach, 1977; Yonemochi et al., 1989).

Microcrystalline cellulose (MCC) is known to be an excellent excipient for tablet preparation by the direct compression method. Porous crystalline cellulose (PCC), characterized by a porous structure, is derived from MCC through several

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physicochemical treatments. Since some porous materials such as controlled pore glass are known to improve the dissolution properties of drugs (Nakai et al., 1985), PCC is expected to be a superior excipient to MCC. In this study, the physicochemical characteristics of PCC, such as specific surface area and pore size distribution, were investigated. The changes in pore structure of PCC after grinding or storage at high relative humidities (RH) were also examined. The molecular state of ethenzamide (EZ) in the mixture with PCC was investigated by means of powder X-ray diffractometry and dissolution testing.

2. Materials and methods

2.1. Materials

PCC and MCC (PH-101) were obtained from Asahi Chemical Industrial Co. (Japan) and used after drying at 110°C for 3 h in vacuo. EZ (Iwaki Pharmaceutical Co., Ltd, Japan) was used as received from the supplier.

2.2. Preparation of ground and stored PCC samples

Ground samples of PCC were obtained by grinding PCC in a mortar and pestle for a given time and dried at 110°C for 3 h in vacuo. Stored samples of PCC were prepared by storing PCC in containers which were kept at constant relative humidities (RH) at 40°C for 1 week; these samples were then dried at 110°C for 3 h in vacuo.

2.3. Measurements of nitrogen gas adsorption

An adsorption apparatus was instrumented according to the specifications of the technical bulletin of the Mellon Institute of Industrial Research. Dead space was measured by using helium gas.

2.4. Powder X-ray diffractometry

A Rigaku Denki 2027 diffractometer (Japan) was used under the following conditions: target, Cu; filter, Ni; voltage, 30 kV; current, 5 mA; receiving slit, 0.15°; time constant, 0.5 s; scanning speed, 2°/min; chart speed, 40 mm/min.

2.5. Preparation of PCC-EZ and MCC-EZ mixtures

A physical mixture of EZ and PCC was prepared by simple blending. A heated mixture of PCC-EZ was obtained by heating the physical mixture of PCC-EZ at 100°C for 2 h. No variation in EZ content was observed during heating. A physical mixture of EZ and MCC was prepared by simple blending. A ground mixture of MCC-EZ was prepared by grinding the physical mixture of MCC-EZ for 10 min using a vibrational sample mill (Heiko Seisakusho Model TI-200, Japan).

2.6. Dissolution testing

A powder sample containing 5% EZ was introduced into a beaker containing 300 ml of distilled water or *n*-hexane thermostated at 37.0 ± 0.5°C. The sample weights were 200 mg for distilled water and 40 mg for *n*-hexane. 3-ml samples of the solution were pipetted at definite time intervals, and filtered through a membrane filter (Toyo Roshi, Japan, 0.22 μm). 3 ml of medium was added to the test solution after sample withdrawal. Determination of the EZ released from the samples was carried out with a Shimadzu UV-160 double-beam spectrophotometer (Japan) at 229 nm.

3. Results and discussion

3.1. Physicochemical characteristics of PCC

The specific surface area of PCC was determined as 130 m^2/g according to the BET equation (Brunauer et al., 1938) using a nitrogen gas adsorption isotherm. The effect of grinding on the specific surface area of PCC is shown in Fig. 1. The specific surface area decreased rapidly during the initial 5 min grinding period followed by a gradual decrease up to 30 min grinding.

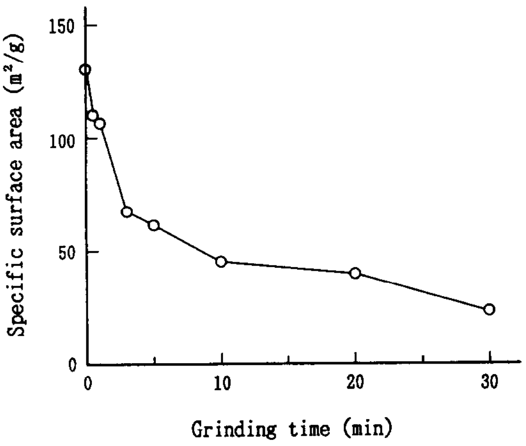

Fig. 1. Effect of grinding on the specific surface area of PCC.

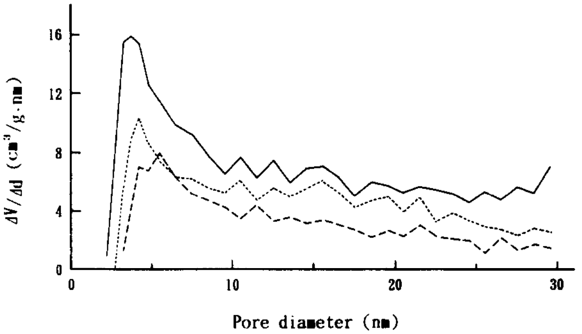

Fig. 3. Effect of grinding on pore size distribution of PCC. (———) Intact, (- - - - - -) ground for 3 min, (— — —) ground for 10 min.

After 30 min grinding with the mortar and pestle, the specific surface area of PCC was reduced to 23.5 m^2/g.

Fig. 2 depicts the pore size distribution curve of PCC as determined by the method of Cranston and Inkley (1957) using a nitrogen gas desorption isotherm. $\Delta V/\Delta d$ represents the volume of pores having a diameter between $(d - \Delta d/2)$ and $(d + \Delta d/2)$; Δd is very small compared with d. From the pore size distribution pattern of PCC, it was found that pores of about 4.0 nm were the most predominant. The effect of grinding on the pore size distribution of PCC is shown in Fig. 3. The pore volume of the ground samples was decreased by grinding over the entire range of pore sizes calculated. The total pore volumes of samples ground for 0, 3 and 10 min were 0.30, 0.20 and 0.13 cm^3/g, respectively. Consequently, the decrease in specific surface area was attributed to the destruction of the pore structure of PCC throughout the full range of pore diameters.

Fig. 4 demonstrates the effect of RH on the specific surface area of PCC. After allowing PCC to stand at definite RH values for 1 week, water molecules adsorbed onto the surface of PCC were evaporated by heating at 110°C for 3 h. Increasing RH led to a decrease in the specific surface area. Fig. 5 shows the effect of RH on the pore size distribution of PCC. As the RH was increased, the pore volume of the stored samples decreased, while no further reduction in pore volume was observed when the stored sample was kept again under the same conditions. In the case

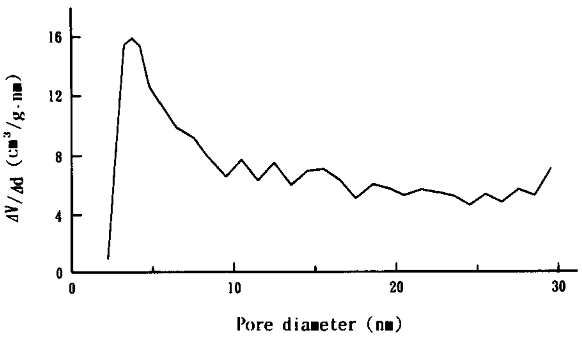

Fig. 2. Pore size distribution curve of PCC.

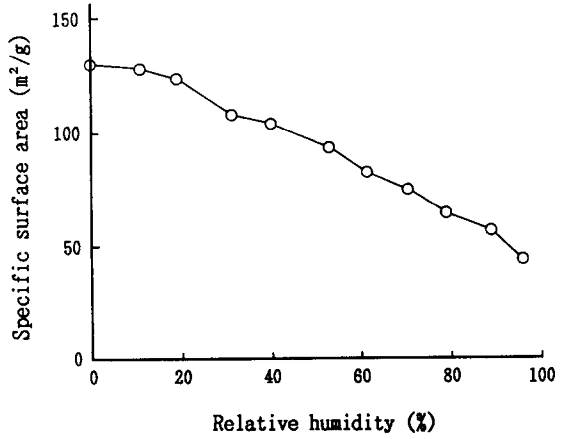

Fig. 4. Effect of relative humidity on the specific surface area of PCC after storage at 40°C for 1 week.

of 61.5% RH, the number of pores with diameters less than 7.0 nm was significantly decreased. At 89.0% RH, a decrease in pore volume was observed in the range of pore diameters less than 20 nm. As the amount of water adsorbed onto PCC increased with increasing RH, the decrease in pore volume of PCC after storage at high RH and subsequent drying was considered to be related to the adsorption and condensation of water molecules at a particular pore.

The maximum pore diameter of the condensed capillary is calculated from the Kelvin equation:

$$\ln\frac{P}{P_0} = -\frac{2\gamma V\cos\theta}{rRT}$$

where P is the relative vapor pressure, P_0 denotes saturated vapor pressure, γ is the surface tension, V represents the molar volume of liquid adsorbate, θ is the angle of contact, r denotes the pore radius, R is the gas constant and T represents the absolute temperature. The calculated maximum pore diameters of condensed capillaries at 61.5 and 89.0% RH were 4.0 and 17 nm, respectively. The calculated pore diameters were in good agreement with the greatest values of the pore diameters for decreasing pore volume after storage at 61.5 and 89.0% RH, as illustrated in Fig. 5. During the drying process, the desorption of water from PCC might induce destruction of the capillary structure. After storage at 19.2% RH, no reduction in pore volume of PCC was observed. This result can be explained in terms of calculation of the condensed pore diameter at 19.2% RH; at 19.2% RH, only pores with the diameter of less than 1.2 nm allowed for water condensation. Consequently, the decrease in pore volume observed in the stored samples was ascribed to the desorption of water molecules, followed by the destruction of small capillaries.

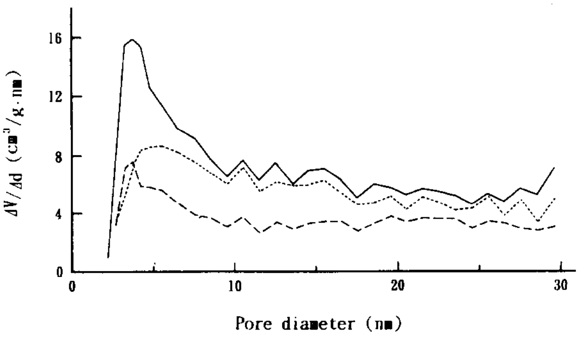

Fig. 5. Effect of relative humidity on pore size distribution curve of PCC after storage at 40°C for 1 week. (———) Intact, (- - - - -) 61.5% RH, (— — —) 89.0% RH.

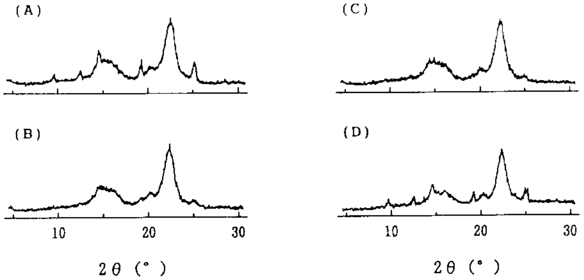

Fig. 6. Powder X-ray diffraction patterns of the mixtures of 10% EZ and 90% PCC after storage at 40°C for 1 month at various relative humidities. (A) Physical mixture, (B) 0% RH, (C) 40.0% RH, (D) 97.0% RH.

3.2. *Change in crystallinity of EZ in a PCC-10% EZ physical mixture*

Fig. 6 shows the powder X-ray diffraction patterns of PCC-10%EZ mixtures before and after storage of the mixtures for 1 month at 40°C and 0, 40.0 and 97.0% RH. In the physical mixture (A), X-ray diffraction peaks were observed at $2\theta = 14.5$, 19.3 and 25.3° attributable to EZ crystals. Following storage at 0 and 40.0% RH (represented by patterns B and C in Fig. 6), the X-ray diffraction peaks of EZ crystals disappeared. It was found that the mixing of EZ with PCC under dry conditions led to the transformation of crystalline EZ to the amorphous state. EZ molecules would be adsorbed physically onto the pore surface of PCC. In the case of 97.0% RH (Fig. 6D), X-ray diffraction peaks of EZ crystals were still observed; EZ remained in the crystalline state under this condition. Matsumura et al. (1985) reported that coexisting water vapor caused a decrease in the adsorption of organic molecules onto porous materials. At 97.0% RH, the maximum pore diameter for water condensation was calculated as 42 nm. All capillaries of PCC were filled with water at 97.0% RH, and molecules of EZ had little chance to adsorb onto the surface of PCC. These results indicated that the indispensable condition for amorphization of EZ by mixing with PCC was storage under dry conditions.

3.3. Effect of PCC on dissolution of EZ

Fig. 7 illustrates the powder X-ray diffraction patterns of 5% mixtures of EZ with PCC or MCC. In the physical mixtures (Fig. 7A,C), X-ray diffraction peaks of EZ crystals were observed at $2\theta = 14.5$, 19.3 and 25.3°. For the mixture with PCC, X-ray diffraction peaks of EZ crystals disappeared after heating at 100°C for 2 h (Fig. 7B). In the mixture with MCC, X-ray diffraction peaks of EZ crystals disappeared after grinding for 10 min (Fig. 7D). Thus, the transformation of EZ crystals to an amorphous state could be accomplished both by heating the PCC-EZ mixture and by grinding the MCC-EZ mixture. Since EZ crystals could not adopt an amorphous state after heating at 100°C for 2 h in the physical mixture of MCC-EZ it was considered that the mode of interaction between cellulose and EZ in the heated mixture of PCC-EZ differed from that in the ground mixture of MCC-EZ.

The dissolution patterns of EZ from three preparations in water at 37°C are shown in Fig. 8. The dissolution of EZ from the heated mixture of PCC-EZ and from the ground mixture of MCC-EZ was faster than that from the physical mixture of MCC-EZ. The greater dissolution rates in both systems were attributed to the amorphous state of EZ. In the heated mixture of PCC-EZ, EZ was completely released after 10 min. The rate of dissolution of EZ from the heated mixture of PCC-EZ was more rapid than that from the ground mixture of MCC-EZ. This result is indicative of different modes of interaction between crystalline cellulose and EZ in the heated mixture of PCC-EZ and in the ground mixture of MCC-EZ. Fig. 9 demonstrates the dissolution patterns of EZ from three preparations in *n*-hexane at

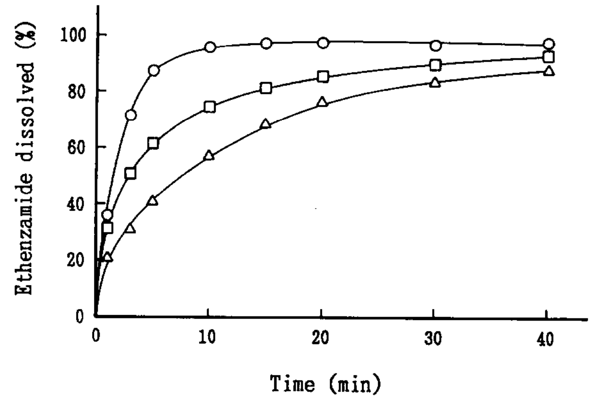

Fig. 8. Dissolution patterns of EZ in distilled water at 37°C. (○) PCC+5% EZ heated mixture; (□) MCC+5% EZ ground mixture; (△) MCC+5% EZ physical mixture.

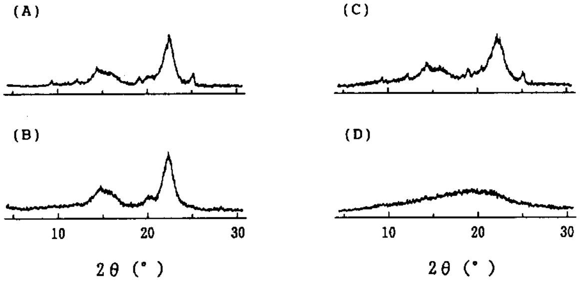

Fig. 7. Powder X-ray diffraction patterns of the mixtures of 5% EZ and 95% PCC or MCC. (A) PCC+5% EZ physical mixture, (B) PCC+5% EZ heated mixture, (C) MCC+5% EZ physical mixture, (D) MCC+5% EZ ground mixture.

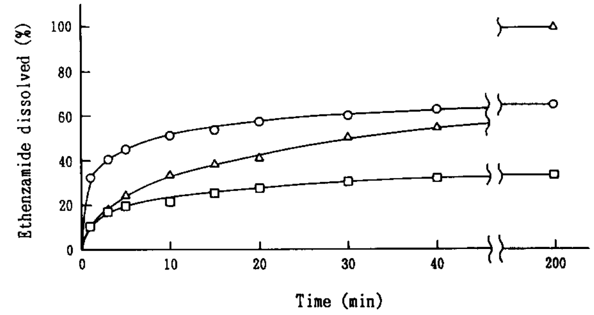

Fig. 9. Dissolution patterns of EZ in *n*-hexane at 37°C. (○) PCC+5% EZ heated mixture; (□) MCC+5% EZ ground mixture; (△) MCC+5% EZ physical mixture.

37°C. During the initial stage of dissolution, the heated mixture of PCC-EZ exhibited the greatest rate of dissolution among the three preparations. After 200 min, only 34% of EZ was released from the ground mixture of MCC-EZ, while 65% was released from the heated mixture of PCC-EZ. In the heated mixture of PCC-EZ, EZ molecules would be adsorbed physically onto the pore surface of PCC. On the other hand, in the ground mixture of MCC-EZ, EZ molecules were found in the network structure of the hydrogen bonding of cellulose molecules (Nakai et al., 1977). As *n*-hexane could scarcely destroy the hydrogen bonding network of cellulose because of its nonpolar nature, the release of EZ was suppressed from the ground mixture of MCC-EZ. In the heated mixture of PCC-EZ, EZ was not completely released. This appears to be due to air remaining in the PCC pore, resulting in insufficient permeation of *n*-hexane into the porous structure. While EZ molecules existed in the amorphous state in both the heated mixture of PCC-EZ and ground mixture of MCC-EZ, it was interesting to note that the modes of interaction between EZ and cellulose exerted a significant influence upon the dissolution behavior of EZ from the mixtures.

4. Conclusions

The specific surface area of PCC was determined to be 130 m^2/g and PCC was found to possess many pores with a diameter over the range of 3.0–30 nm. The specific surface area and pore volume of PCC were observed to decrease with grinding or storage at high RH and subsequent drying. Mixing of EZ with PCC under dry conditions led to the transformation of crystalline EZ into the amorphous state. A high dissolution rate of EZ was observed in both polar and nonpolar solvents in the heated mixtures of PCC-EZ. In the PCC-EZ mixtures, EZ molecules adsorbed onto the PCC surface, and these adsorbed and activated molecules contributed to the enhancement of dissolution. PCC appears to be a useful pharmaceutical additive, since it improves the dissolution properties of drugs.

Acknowledgments

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