Effect of Grinding on Dehydration of Crystal Water of Theophylline

Satit PUTTIPIPATKHACHORN, Etsuo YONEMOCHI, Toshio OGUCHI, Keiji YAMAMOTO, and Yoshinobu NAKAI*

Faculty of Pharmaceutical Sciences, Chiba University, 1–33 Yayoicho, Chiba 260, Japan. *Received February 2, 1990*

The effect of grinding on the dehydration of crystal water of theophylline has been studied. It was observed that the water content of theophylline hydrate decreased with increased grinding time. As the grinding time proceeded, the results of differential scanning calorimetry (DSC) indicated that crystal water of ground theophylline hydrate dehydrated in three steps at *ca.* 58, 44, and 17 °C, respectively. Powder X-ray diffraction study revealed that the crystal lattice of theophylline monohydrate collapsed by grinding, and part of the theophylline molecules subsequently rearranged the collapsed lattice to form theophylline anhydrate. The result of Fourier transformed infrared spectroscopy demonstrated that the hydrogen bonds between crystal water molecules and theophylline molecules were weakened or destroyed to some extent by grinding. It was supposed that crystal water in the ground theophylline hydrate might exist at least in three molecular states of different hydrogen-bonding. From DSC study, it was suggested that the ruptured hydrogen bonds of water molecules in the ground theophylline hydrate were strengthened after storage under 96.5% relative humidity at 30 °C.

Keywords theophylline hydrate; crystal water; grinding effect; dehydration; thermal analysis; powder X-ray diffraction; Fourier transformed infrared spectroscopy

Many organic drugs exist in a solid state as hydrates. It is known that the hydrate state of drugs affects solubility, stability and bioavailability of pharmaceutical formulations.[1,2] The hydrate–anhydrate transformation of drugs has often been observed during unit operation processes of pharmaceuticals, such as grinding and drying. Thus, the property of crystal water is one of the important factors that should be considered in pharmaceutical design.

The purpose of this work was to investigate the effect of grinding on the physical and chemical properties of medicinal hydrate in a solid state. Crystalline theophylline monohydrate was chosen since the crystal structure of the hydrate,[3] as well as that of the anhydrate,[4] have already been reported. Shefter *et al.*[5,6] have studied the dehydration kinetics of theophylline monohydrate by using the powder X-ray diffraction technique. Recently, the dehydration kinetics of theophylline monohydrate was also determined by Otsuka and Kaneniwa,[7] and Suzuki *et al.*[8] In the present study, the grinding effect on the dehydration behaviour of crystal water of theophylline was mainly examined by thermal analysis. Furthermore, the loss in water content, the crystalline transformation, and the change in Fourier transformed infrared (FT-IR) spectra were also investigated.

Experimental

Materials Theophylline monohydrate (water content 8.90%) was obtained by recrystallization from distilled water at 25 °C and subsequent drying at room temperature. Theophylline anhydrate was prepared by drying theophylline monohydrate at 100 °C for 1 h and storing it over P_2O_5 in a desiccator.

Preparation of Ground Samples A vibrational mill (Heiko Seisakusho TI-200) made of tungsten carbide was used. The volume of the mill was 140 cm^3 and the height of the rod was 55 mm. Three grams of theophylline monohydrate were ground for 5 s—10 min to obtain ground samples. In order to investigate the rehydration behaviour, the ground samples were stored in an atmosphere of 96.5% relative humidity (RH) at 30 °C for one week.

Determination of Water Content The water content of each sample was determined by the Karl–Fischer method using a Hiranuma AQ-3C aquacounter.

Differential Scanning Calorimetry (DSC) An open aluminum pan for the solid sample was used. Each sample weight was 2.0 mg. After the aluminum pan containing the sample was placed into the furnace, the furnace was cooled by liquid nitrogen. The measurements, using a DuPont TA 9900 thermal analysis system, were carried out from 0 °C under nitrogen gas flow (50 ml/min) at a heating rate of 4 °C/min.

Thermogravimetry (TG) A DuPont TA 9900 thermal analysis system was used. The sample weight was 8.0 mg. The measurements were done at a heating rate of 0.5 °C/min under nitrogen gas flow (50 ml/min).

Powder X-Ray Diffraction A Rigaku Denki 2027 diffractometer using a scintillation counter was used. The X-ray source was CuKα with a Ni filter (30 kV, 5 mA). The scanning speed was 4°/min.

FT-IR Spectroscopy FT-IR spectra were obtained by the Nujol method using a Nicolet 5ZDX FT-IR spectrometer.

Results and Discussion

As the grinding proceeded, the loss in water content of theophylline hydrate was observed as presented in Fig. 1. It was shown that the water content of the ground samples slightly decreased at an initial stage of the grinding and the gradual decrease in the water content was observed when the grinding time proceeded more than 3 min. The ground sample was found to be 6.4% of water content after grinding for 10 min. The loss of crystal water may be accelerated both by mechanical impact and by heat generated during grinding. The mechanical impact gives the crystal a damage which produces a dynamic effect on the dehydration rate and the nucleation of the dehydrated crystal.

In order to investigate the dehydration behaviour of the crystal water of theophylline, DSC and TG analyses were carried out. Figure 2 shows the grinding effect on DSC curves of dehydration of theophylline hydrate. In the case

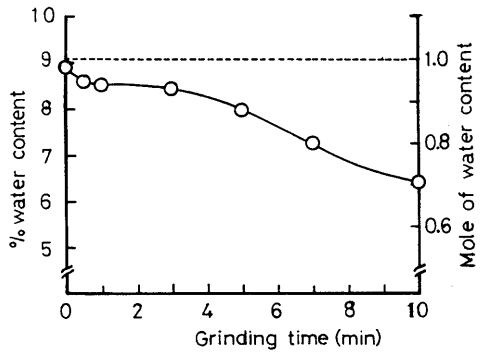

Fig. 1. Effect of Grinding Time on Water Content of Theophylline Hydrate

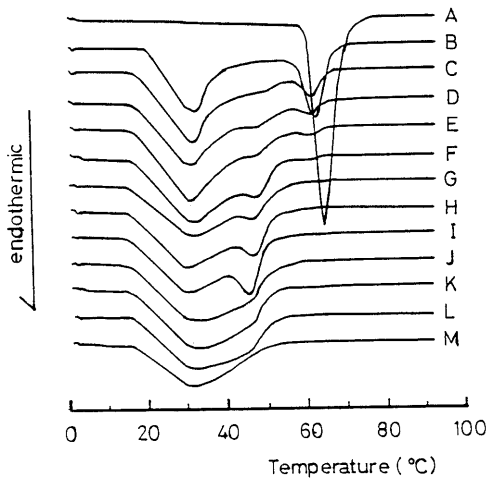

Fig. 2. Effect of Grinding Time on DSC Curves of Dehydration of Theophylline Hydrate

Grinding time: A, intact; B, 5 s; C, 10 s; D, 15 s; E, 20 s; F, 25 s; G, 30 s; H, 45 s; I, 1 min; J, 3 min; K, 5 min; L, 7 min; M, 10 min.

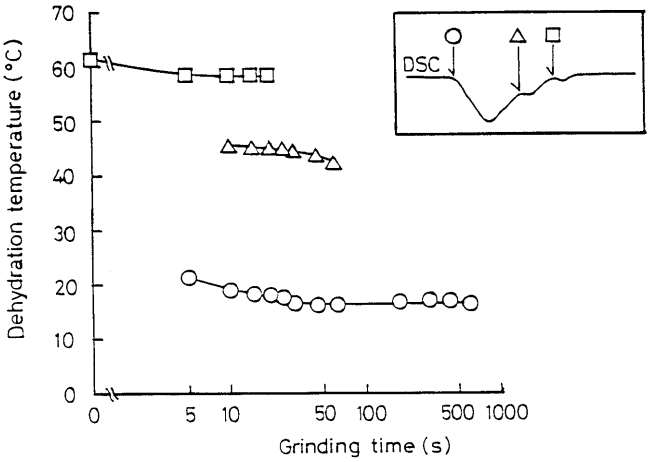

Fig. 3. Relationship between Grinding Time and Dehydration Temperatures of Theophylline Hydrate

○, lower temperature; △, intermediate temperature; □, higher temperature.

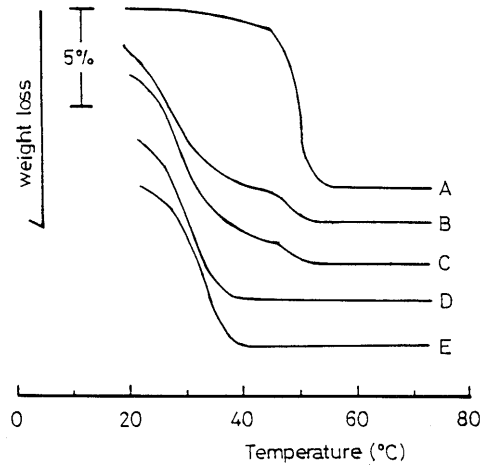

Fig. 4. Effect of Grinding Time on TG Curves of Theophylline Hydrate

Grinding time: A, intact; B, 5 s; C, 10 s; D, 30 s; E, 1 min.

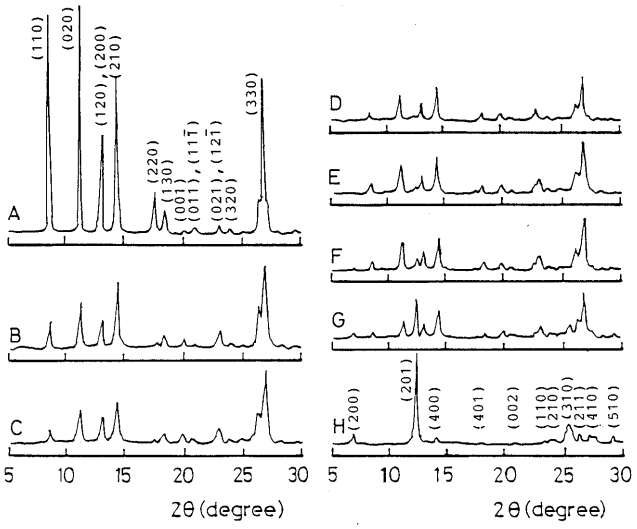

Fig. 5. Effect of Grinding Time on Powder X-Ray Diffraction Patterns of Theophylline Hydrate

Grinding time: A, intact; B, 5 s; C, 10 s; D, 30 s; E, 1 min; F, 5 min; G, 10 min; H, anhydrate. Miller indices of theophylline monohydrate and anhydrate were calculated according to refs. 3 and 4 respectively.

of the crystalline theophylline monohydrate, the dehydration curve showed a sharp endothermic peak of dehydration at 61 °C. As the grinding time increased, the dehydration temperature of crystal water of theophylline was found to shift to a lower temperature. When the grinding proceeded for 5 s the dehydration curve of theophylline hydrate appeared to be of two steps of dehydration, lower and higher temperatures, respectively. When the grinding time further proceeded to 10 s, theophylline hydrate dehydrated in three steps at lower, intermediate and higher temperatures, respectively. After grinding for 30 s, the dehydration peak of theophylline hydrate at the higher temperature disappeared. As the grinding further proceeded, an increase in peak intensity at the intermediate temperature was observed. Moreover, in the case of a 10 min ground sample of theophylline hydrate, only a broad dehydration peak at the lower temperature remained. The relationship between the onset temperatures of dehydration, obtained from DSC measurements, and the grinding time, is shown in Fig. 3. The dehydration temperatures of ground theophylline hydrate were found to be *ca.* 58, 44 and 17 °C, previously named the higher, intermediate and lower temperatures of dehydration, respectively. In addition, the effect of grinding on TG curves of theophylline hydrate is shown in Fig. 4. As the grinding time increased, the dehydration temperature of the crystal water of theophylline hydrate tended to shift to a lower temperature. This result indicated a good agreement with the result obtained by DSC study. The observation that the grinding affected the dehydration temperature of crystal water of theophylline hydrate by shifting it to a lower temperature was similar to the results found in sodium prasterone sulfate dihydrate,[9] ampicillin trihydrate,[10] and cefixime trihydrate.[11]

It was reported that the chains of water molecules which hydrogen-bonded with theophylline molecules existed along the plane parallel to the *c*-axis of the crystal.[3] Changes in crystalline characteristics of theophylline hydrate by grinding were observed as shown in Fig. 5. The intensity of diffraction peaks due to theophylline monohydrate, especially in the (*hk*0) projections, decreased to a large extent

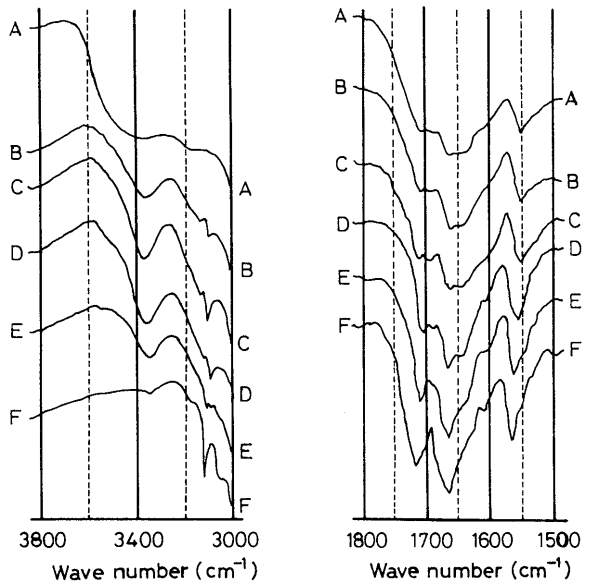

Fig. 6. Effect of Grinding Time on FT-IR Spectra of Theophylline Hydrate

Grinding time: A, intact; B, 5 s; C, 1 min; D, 5 min; E, 10 min; F, anhydrate.

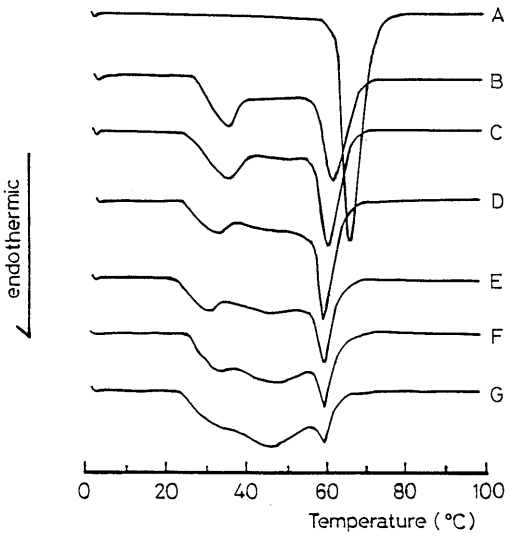

Fig. 7. DSC Curves of Dehydration of Ground Theophylline Hydrate Stored under 96.5% RH at 30 °C for One Week

Grinding time before storage: A, intact; B, 5 s; C, 10 s; D, 30 s; E, 1 min; F, 5 min; G, 10 min.

at an initial stage of grinding and slightly decreased when further grinding proceeded. In addition, the diffraction peak due to (201) plane ($2\theta = 12.6°$) of theophylline anhydrate appeared after grinding more than 30 s and the intensity of this diffraction peak gradually increased with further grinding time. The obtained results revealed that the crystal lattice of theophylline monohydrate collapsed by grinding and then a part of the theophylline molecules subsequently rearranged the collapsed lattice to form theophylline anhydrate, mostly along (20l) plane parallel to the *b*-axis. It was also indicated that theophylline existed in both hydrate and anhydrate states in the ground samples.

According to the report on the crystal structure of theophylline monohydrate by Sutor,[3] each theophylline molecule is linked to a water molecule by an O–H···N bond at the N atom of the imino (C=N) group, and each water molecule further forms two hydrogen bonds with adjacent water molecules.

As it was reported that hydrogen bonding of water molecules to the host organic molecules in the crystal lattice could play an important role in the dehydration of the organic hydrates,[12,13] further study on the molecular state of crystal water of theophylline was carried out by means of FT-IR spectroscopy. Figure 6 shows changes in the FT-IR spectra of theophylline hydrate as a function of grinding time in the regions of 3000—3800 and 1500—1800 cm^{-1}. In both regions of wave number, the FT-IR spectra of theophylline hydrate tended to change to that of theophylline anhydrate as the grinding time increased. The crystalline theophylline monohydrate showed a broad band around 3340 cm^{-1}. This band was assigned to the hydroxyl stretching vibration of water molecules which formed a hydrogen bond with theophylline molecules in addition to other water molecules. When the grinding time increased, the intensity of this band was found to decrease. This result was attributed to the loss in water content by grinding as well as the decrease in the number of hydrogen bonding of water molecules. Moreover, the FT-IR band of theophylline hydrate around 1650 cm^{-1} was attributed to the bending vibration of water molecules, as no FT-IR band around 1650 cm^{-1} appeared in theophylline anhydrate. This band intensity was found to decrease as the grinding time increased and only the shoulder of this band was observed after grinding for 10 min. This observation was also attributed to the loss in water content of theophylline hydrate by grinding. In addition, the FT-IR band of crystalline theophylline monohydrate at 1555 cm^{-1} was assigned to the imino stretching vibration.[14] In the case of theophylline anhydrate, the imino band was observed at 1567 cm^{-1}. The increase in grinding time resulted in the shift of the imino band to a higher wave number. It was suggested that the hydrogen bonds between crystal water molecules and theophylline molecules were weakened or destroyed to some extent by grinding.

The rehydration behaviour of the ground sample of theophylline hydrate was examined by exposing it to an atmosphere of 96.5% RH at 30 °C. By means of powder X-ray diffraction study and water content measurement, all of the ground samples were found to be monohydrate after storage for one week. The dehydration behaviour of each storage sample, studied by DSC measurements, are shown in Fig. 7. It was observed that the crystal water in the ground samples of theophylline hydrate recovered to dehydrate at a higher temperature after storage under 96.5% RH at 30 °C for one week. In addition, under this storage condition, all of the ground samples showed dehydration endothermic peaks around 57 °C which were assumed to be that of theophylline monohydrate. It was suggested that, after storage at high humidity, the crystal water molecules rearranged from a disordered state to a more ordered state and the ruptured hydrogen bonds between crystal water molecules and theophylline molecules were strengthened. However, the increase in grinding time resulted in the decrease in the intensity of the recovered dehydration peak at a higher temperature. This result indicated that the longer the grinding time, the more difficult is the recovery of crystal water of theophylline to dehydrate at the higher

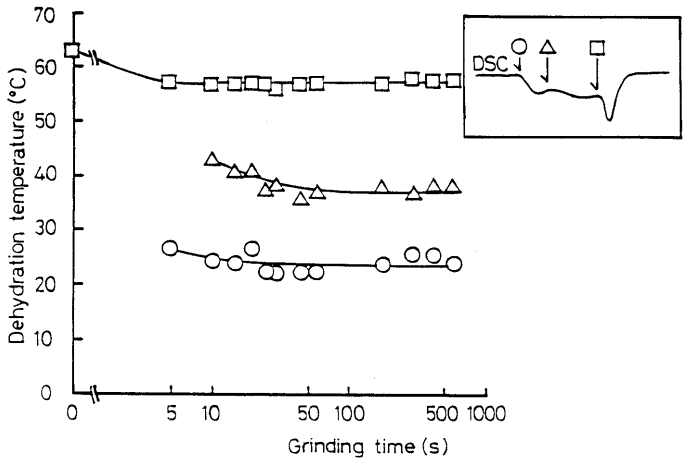

Fig. 8. Dehydration Temperatures of Ground Theophylline Hydrate Stored under 96.5% RH at 30 °C for One Week as a Function of Grinding Time before Storage

○, lower temperature; △, intermediate temperature; □, higher temperature.

temperature. In other words, it seemed to be difficult for water molecules of the longer-time ground samples to form stronger hydrogen bonds with theophylline molecules since the lattice defect was increased by grinding. The relationship between the onset temperatures of dehydration of theophylline hydrate, obtained from DSC curves in Fig. 7, and the grinding time was represented in Fig. 8. After storage under 96.5% RH at 30 °C for one week, there were three steps of dehydration of crystal water of the ground theophylline hydrate at respective temperatures in the same regions as those found in the ground samples before storage.

As the grinding reduces the particle size and changes the surface feature of the crystal, it seemed that these changes might affect the dehydration behaviour of the crystalline hydrate.[7,15,16] Besides the particle size and the surface feature, the change in the molecular state of water molecules in the crystal lattice, produced by crystal defect, has an important role in determining the dehydration behaviour. The results obtained in this study demonstrated that the hydrogen bonds between crystal water molecules and theophylline molecules were weakened or destroyed to some extent by grinding, resulting in three steps of dehydration as observed in Fig. 2. It was supposed that crystal water molecules in the ground samples of theophylline hydrate might exist in at least three molecular states of different hydrogen bonding.

Acknowledgement This work was supported in part by a grant from the Uehara Memorial Foundation.

References

1) J. K. Haleblian, *J. Pharm. Sci.*, **64**, 1269 (1975).
2) P. York, *Int. J. Pharmaceut.*, **14**, 1 (1983).
3) D. J. Sutor, *Acta Crystallogr.*, **11**, 83 (1958).
4) A. A. Naqvi and G. C. Bhattacharyya, *J. Appl. Crystallogr.*, **14**, 464 (1981).
5) E. Shefter and G. Kmack, *J. Pharm. Sci.*, **56**, 1028 (1967).
6) E. Shefter, H. Fung, and O. Mok, *J. Pharm. Sci.*, **62**, 791 (1973).
7) M. Otsuka and N. Kaneniwa, *Chem. Pharm. Bull.*, **36**, 4914 (1988).
8) E. Suzuki, K. Shimomura, and K. Sekiguchi, *Chem. Pharm. Bull.*, **37**, 493 (1989).
9) H. Nakagawa, Y. Takahashi, and I. Sugimoto, *Chem. Pharm. Bull.*, **30**, 242 (1982).
10) Y. Takahashi, K. Nakashima, H. Nakagawa, and I. Sugimoto, *Chem. Pharm. Bull.*, **32**, 4963 (1984).
11) S. Kitamura, A. Miyamae, S. Koda, and Y. Morimoto, *Int. J. Pharmaceut.*, **56**, 125 (1989).
12) P. R. Perrier and S. R. Byrn, *J. Org. Chem.*, **47**, 4671 (1982).
13) S. R. Byrn, "Solid-State Chemistry of Drugs," Academic Press, New York, 1982, pp. 149—188.
14) J. L. Cohen, *Anal. Profiles Drug Subst.*, **4**, 466 (1975).
15) K. Sekiguchi, K. Shirotani, O. Sakata, and E. Suzuki, *Chem. Pharm. Bull.*, **32**, 1558 (1984).
16) M. J. Pikal, J. E. Lang, and S. Shah, *Int. J. Pharmaceut.*, **17**, 237 (1983).