Kinetic Study of the Transformation from Tetrahydrate to Monohydrate of a New Antiallergic, Sodium 5-(4-oxo-phenoxy-4H-quinolizine-3-carboxamide)-tetrazolate

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Two hydrates (tetrahydrate, I, and monohydrate, II) of a new antiallergic, sodium 5-(4-oxo-phenoxy-4H-quinolizine-3-carboxamide)-tetrazolate (FR71021), were prepared and characterized by means of infrared spectrometry, thermal analysis, and power X-ray diffraction spectrometry. While I was confirmed to dehydrate readily resulting in an anhydrate form (noncrystalline form) below its critical relative humidity for dehydration, I was also transformed into II under humid conditions. The transformation kinetics from I to II were investigated under varying temperature and humidity conditions by a powder X-ray diffraction technique. The transformation mechanism followed a zero-order reaction, and the apparent transformation rate constant (k) could be described as a function of water vapor pressure (P), temperature (T), and the interaction orders between water vapor pressure and the samples (s): $k = A \cdot \exp(-E_a/\mathrm{RT}) \cdot P^s$, where E_a is the activation energy and R is the gas constant.

KEY WORDS: antiallergic; hydrate form; crystalline water; powder X-ray diffraction; transformation kinetics; water vapor pressure.

INTRODUCTION

It is difficult to predict drug stability in solid dosage forms because the reaction in the solid state is affected by many variables, and the decomposition mechanisms involved are not fully understood. Further, there are problems in predicting solid–solid transformation of polymorphs or dehydration of drug hydrates during storage or pharmaceutical processing such as grinding, drying, and compressing. It is important to know the mechanism of solid-state phase transformation of the active ingredient in a dosage form, because polymorphic changes of desolvation of drugs dramatically alter the pharmaceutical properties of the preparation (1,2). We suggested previously that environmental moisture and temperature affect the crystalline transition between tetrahydrate and monohydrate of a new antiallergic sodium, 5-(4-oxo-phenoxy-4H-quinolizine-3-carboxamide)-tetrazolate (FR71021) (3). In the present study we analyzed the kinetics of the transformation process of the drug hydrates under varying humidity and temperature.

MATERIALS AND METHODS

Sodium 5-(4-oxo-phenoxy-4H-quinolizine-3-carboxamide)-tetrazolate, FR71021, was synthesized by Fujisawa Pharmaceutical Co., Ltd., and its tetrahydrate, I (water content, 16.1%; calcd, 16.3%), and monohydrate, II (water content, 5.0%; calcd, 4.6%), were prepared by recrystalization from the solutions of ethanol/water (2:1) and isopropanol/water (2:1), respectively. The water contents of I and II were measured by the Karl Fischer method. Compounds I and II used in this study were ground in a mortar and sieved (63 μm) in order to obtain good reproducibility in the intensities of powder X-ray diffraction. All other reagents were of reagent grade.

Powder X-Ray Diffraction Analysis

Powder X-ray diffraction was measured at room temperature (25°C) with a powder X-ray diffractometer (Rigaku Denki). The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 35 kV; current, 20 mA; time constant, 1 sec; slit, 0.04; counting time, 0.5 sec.

Thermal Analysis

A thermogravimetric analyzer (Model TG/DTA 200, Seiko Denshi Kogyo) was used to confirm the dehydration of I and II by heating 5 mg of the sample at a heating rate of 10°C/min in an open pan under the flow of nitrogen (100 ml/min).

Measurement of the Contents of I and II in the Solid-State Mixture

Physical standard mixtures were obtained by mixing two hydrates. Lithium fluoride (LiF) (25%, w/w) was mixed in the standard sample as an internal standard material. Five replicate analyses of X-ray diffraction patterns were performed, and the mean values were used in the study for transformation kinetics. The calibration curves for measuring the contents of I and II were based on the diffraction peak height ratio of the standard mixture and LiF. In this study, samples stored under various conditions were assumed to represent a homogeneous system and the contents of two hydrates in samples were calculated from the calibration curves.

Storage of Samples for Kinetic Study

Kinetic studies were carried out by weighing 0.3 g of I into glass dishes (15 × 5 mm), each of which was placed in reaction vessels containing a saturated solution of inorganic salts (NaCl, KCl, or KNO_3). In this study, the relative humidity in the vessel containing water was regarded as 100% RH. The reaction vessels were placed in a thermostated oven (Mini Jet Oven, Toyama, Sangyo). The relative humidities were 74.7% at 50°C, 74.7% at 45°C, 74.7% at 40°C, and 74.8% at 35°C for saturated NaCl solution, 81.3% at 50°C, 81.7% at 45°C, 82.3% at 40°C, and 82.9% at 35°C for saturated KCl solution, and 84.8% at 50°C, 87.0% at 45°C, 89.0% at 40°C, and 90.8% at 35°C for saturated KNO_3 solution (4). The samples were removed at appropriate intervals and analyzed by powder X-ray diffraction method to determine the contents of I and II. Compound I was confirmed to be chem-

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ically stable at 40°C and 75% RH for 3 months by checking the remaining amount of FR71021 and the breakdown products using HPLC.

RESULTS AND DISCUSSION

Identification of I and II

The X-ray diffraction profiles of I and II are shown in Fig. 1. They distinctly differ from each other, as I shows a characteristic peak at $2\theta = 7.6°$ and II at $2\theta = 5.7°$, respectively.

Determination of the Content of Two Hydrates

Crystal structure analysis of I revealed four crystallographically independent water molecules; one of them coordinates to Na^+, and the other three water molecules are in a channel structure linked by hydrogen bonds to each other (3). These four crystalline water molecules could be differentiated with the use of thermal analysis (TG/DTA), which indicated that three water molecules are removed at 50–100°C and the remaining one at 100–150°C.

Although the Karl Fischer method or thermal analysis is useful for quantifying water content, it cannot distinguish between physically bound and crystalline water, which is easily removed at relatively low temperature. On the other hand, the powder X-ray technique is suitable for determining the relative amounts of solid-state forms, such as present in a mixture of hydrate and anhydrate (5,6).

In the case of FR71021, it was possible to determine the content of I and II because the diffraction peak at $2\theta = 7.6°$ of I and the peak at $2\theta = 5.7°$ of II did not overlap with each other. Therefore, the internal standard method reported by Otsuka *et al.* (7) was used to determine the contents of these two forms. As the calibration curves obtained for determining the weight percentage of I, α'I, and that of II, α'II, were both straight lines, α'I and α'II were estimated by the least-squares method as follows:

$$\alpha'\text{I} = 39.952 \cdot A(\text{I}) - 1.846 \qquad (r = 0.998) \tag{1}$$

$$\alpha'\text{II} = 32.258 \cdot A(\text{II}) + 1.419 \qquad (r = 0.997) \tag{2}$$

where $\alpha'\text{I} = 100 \cdot WI/(WI + WII)$, $\alpha'\text{II} = 100 \cdot WII/(WI + WII)$, WI = weight of I, WII = weight of II, $A(\text{I})$ = intensity ratio of I versus LiF, and $A(\text{II})$ = intensity ratio of II versus LiF. In this transformation process from I to II, however, weight loss as a result of dehydration should be considered. Thus, the mole percentages of these hydrates were corrected using the following equations.

$$\alpha\text{I} = \frac{\alpha'\text{I} \cdot M(\text{II})}{100 \cdot M(\text{I}) - 54.0 \cdot \alpha'\text{I}} \times 100 \tag{3}$$

$$\alpha\text{II} = \frac{(100 - \alpha'\text{I}) \cdot M(\text{I})}{100 \cdot M(\text{II}) + 54.0 \cdot \alpha'\text{II}} \times 100 \tag{4}$$

where αI = mole percentage of I, αII = mole percentage of II, M(I) = molecular weight of I (442.3), M(II) = molecular weight of II (388.3), and 54.0 = molecular weight of 3 mol of water.

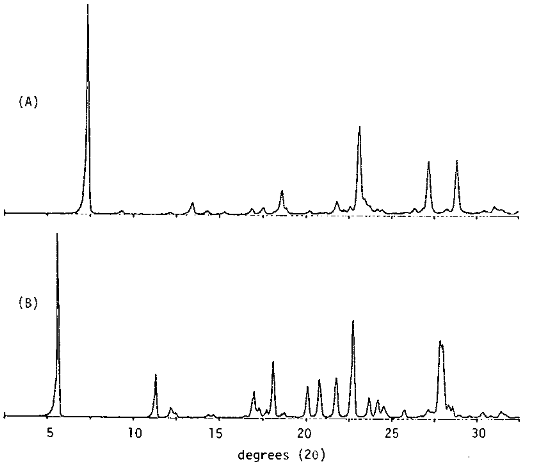

Fig. 1. Powder X-ray diffraction profiles of (A) I and (B) II.

Kinetic Study

Figure 2 shows the typical changes with time in the X-ray diffraction profile during the isothermal transformation from I to II at 50°C and 75% RH. The intensity of the diffraction peak at $2\theta = 7.6°$ (attributed to I) decreased, while that at $2\theta = 5.7°$ (attributed to II) increased with increasing storage time. Further, a halo pattern attributable to a noncrystalline form was not observed in any sample stored under various temperature and humidity. Since only the

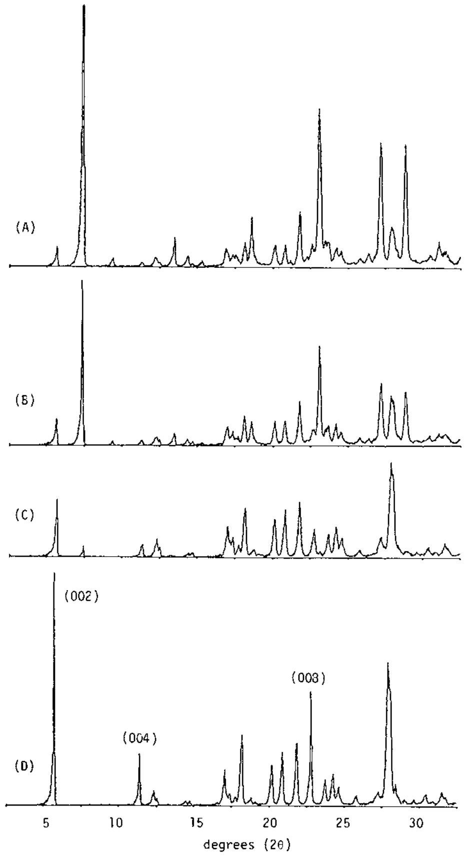

Fig. 2. Changes with time in the powder X-ray diffraction profiles of I at 50°C and 75% RH: (A) 10 min; (B) 20 min; (C) 60 min; (D) intact phase of II.

characteristic peaks of I and II were observed in these X-ray profiles, the transformation from I to II may be the only process occurring.

Figures 3 and 4 show the fraction (mol%) of I and II stored at various temperature and 75% RH, and different humidities at 40°C, respectively.

In a previous paper (3), we have reported that I easily lost four molecules of crystalline water by heating during storage in an open system and that the resultant dehydrated form, which was confirmed to be an amorphous state, rapidly restored via a hydration process in a reversible manner. On the other hand, it also became clear that I transformed to II under high temperature and humidity such as 60°C and 75% RH (3). The present study shown in Figs. 3 and 4 further suggests that environmental moisture as well as temperature plays an important role in the transformation process from I to II.

From a stoichiometric point of view, it was expected that the sum of I and II at each storage period should be 100%. However, the amount of II did not attain 100% even if I completely disappeared after storage for 2 days at 50°C and 75% RH (Fig. 3). Further, the intensities of some peaks, especially 2θ = 5.7, 11.3, and 22.8° of II obtained by the transformation from I, were considerably weaker than those of II obtained by crystallization from isopropanol/water (2:1) solution (Fig. 2). However, the intensities of the peaks of II that appeared during the transformation process, except those above the characteristic peaks, did not show a disproportionate decrease in their intensities. A similar result was reported for two types of theophylline anhydrate (8); the intensities of (h00) reflections of theophylline anhydrate crystallized from water at 95°C were much stronger than those obtained by drying the monohydrate at 100°C. In the case of II, single-crystal X-ray structural analysis revealed that the above diffraction peaks, 2θ = 5.7, 11.3, and 22.8°, could be assigned (002), (004), and (008) reflections, respectively. The single crystal X-ray structural analysis for II also revealed that a hydrogen bond as well as a coordinate bond between water molecules and Na^+ was observed on the a–b plane, and a van der Waals force among drug molecules was observed only along the c-axis (3). These results indicate that the crystal structure of II obtained by transformation process showed considerable disorder in the direction of c-axis. Therefore, in this study, only the kinetics of crystal transformation from I to II were investigated, because the peak at 2θ = 5.7° was unsuitable for determining the content of II.

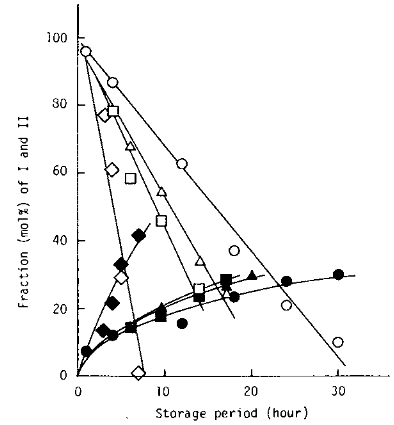

Fig. 4. Residual fraction of I and fraction formed of II during the transformation process at 40°C under various humidities. Residual fraction of I: (○) 75% RH; (△) 84% RH; (□) 93% RH; (◇) 100% RH. Formation fraction of II: (●) 75% RH; (▲) 84% RH; (■) 93% RH; (◆) 100% RH.

The mechanism of polymorphic transformation of pharmaceutical solids has been interpreted on the basis of the theoretical models proposed by Prout and Tompkins, phase boundary reaction, dimensional diffusion model, or nucleation model (9,10). However, attempts have failed thus far to combine the effects of both temperature and humidity (water content) on the solid-state transformation process. Therefore, we included the content change of I during storage under various conditions in the quantitative evaluation of theoretical models. Further, the influence of temperature and humidity on the transformation of FR71021 was estimated concomitantly.

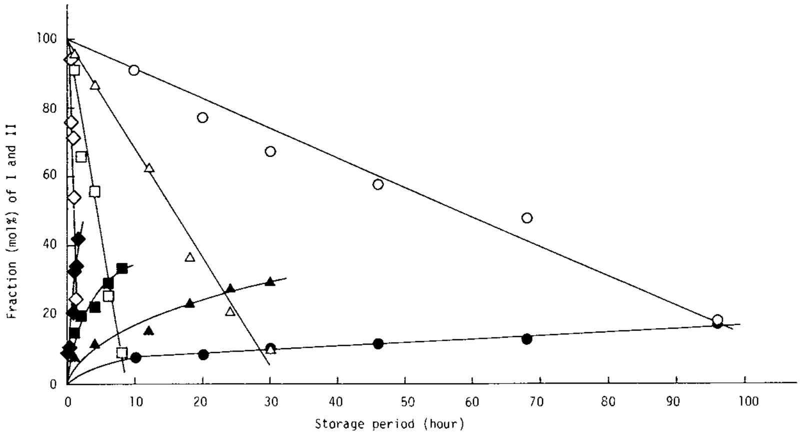

Fig. 3. Residual fraction of I and fraction formed of II during the transformation process at various temperatures and 75% RH. Residual fraction of I: (○) 35°C; (△) 40°C; (□) 45°C; (◇) 50°C. Formation fraction of II: (●) 35°C; (▲) 40°C; (■) 45°C; (◆) 50°C.

Plotting αI against storage period, t on the abscissa gave a straight line as shown in Figs. 3 and 4, which suggests that this transformation process follows a pseudo-zero-order reaction. In order to describe the transformation rate of I, the following hypothesis was applied, which was proposed for the mechanism of solid-state hydrolysis of propantheline bromide with respect to the effect of temperature and water vapor pressure (11). The apparent transformation rate constant, k, is assumed to be expressed in terms of water vapor and temperature as shown in the following equation:

$$k = k' \cdot P^s$$

or

$$\ln k = \ln k' + s \cdot \ln P \tag{5}$$

where k denotes the apparent rate constant, k' the rate constant, P the water vapor pressure, and s the interaction order between water vapor pressure and the sample. The value of k' can be expressed as the Arrhenius equation,

$$k' = A \cdot \exp(-E_a/\mathrm{RT}) \tag{6}$$

where E_a is the activation energy, and R is the gas constant. A plot of ln$k$ against ln$P$ at a constant temperature and various water vapor pressures should provide a straight line, the slope of which represents the s value. One should then be able to estimate the s value by the least-squares method from the data obtained at various levels of RH at constant temperature. The relationship between ln$k$ and ln$P$ at 40°C is linear (Fig. 5), except at 40°C and 100% RH. Therefore, the environmental humidity has significant influence on the transformation mechanism from I to II; that is, below the critical relative humidity for dehydration, I was transformed into the anhydrate form (noncrystalline form) spontaneously as mentioned in the previous report (3). Where moderate amounts of water exist in the surrounding, in contrast, water molecules are expected to act as a plasticizer to increase the movement of solid-state molecules by reducing hydrogen bonding between adjoining molecules. As a result, the crystalline changes are triggered by these freely movable water molecules. In the case of 100% RH, however, deviation from linearity as presented in Fig. 5 may be caused by the higher mobility of the adsorbed water, which is more movable than that of crystalline water molecules in the crystal lattice of I.

Once the value of s is known, the value of k' can be calculated by substituting the values of k and P at various temperatures into Eq. (5), on the assumption that s is constant throughout the studied temperatures. In this case, 3.17 was used as the s value which was obtained from the slope in Fig. 5. The relationship between lnk' against $1/T$ is shown in Fig. 6, and a good linearity was observed between lnk' and $1/T$. From the above relation, E_a was estimated to be 22.8 kcal/mol. Therefore, the transformation rate at various temperatures under 70–90% RH at 35–50°C can be predicted by Eq. (5), where s has been estimated as mentioned above, and k can be calculated according to Eq. (5) on the basis of the estimated values of E_a, s, and k'. By using these estimated values of E_a, s, and k', the apparent transformation rate at various temperature and humidity can be shown by Eq. (7).

$$k = 2.13 \times 10^9 \cdot \exp(-22800/\mathrm{RT}) \cdot P^{3.17} \tag{7}$$

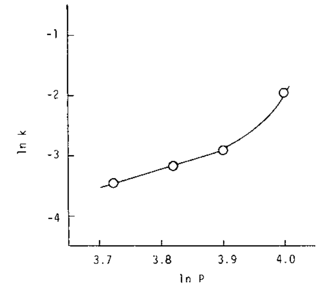

Fig. 5. Effect of water vapor pressure on the apparent rate constant for the transformation from I to II.

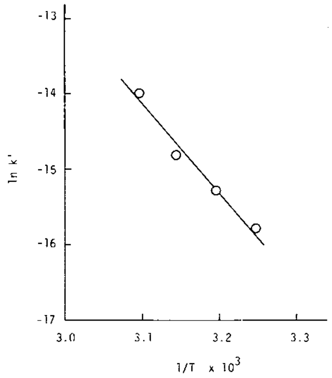

Fig. 6. Arrhenius plots of the rate constant for the transformation of I to II.

The kinetic study described here will prove useful for estimating crystalline changes of solid-state drugs that exist as polymorphs or various hydrate forms.

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