Physicochemical Stability of Nitrofurantoin Anhydrate and Monohydrate Under Various Temperature and Humidity Conditions

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INTRODUCTION

Nitrofurantoin is widely used as an urinary tract antibacterial drug (1); however, it has bioavailability problems. Formulation factors of the drug preparation, mainly particle size (2), affect the dissolution rate (3), bioavailability in humans, and incidence of side effects (4). The USP XXII monograph for nitrofurantoin tablets requires not less than 25% of the labeled amount of drug to be dissolved in 60 min in a pH 7.2 phosphate buffer. Gouda *et al.* (5) and Ebian *et al.* (6,7) reported that the dissolution rate and bioavailability of nitrofurantoin commercial tablets in humans decreased after 1–8 weeks of storage at different relative humidities at higher temperatures. They concluded that the dissolution rate decreased by the agglomeration of the mixture of powders in the preparation, but they did not provide experimental evidence of crystallographic transformation. Marshall and York (8) reported three modifications of nitrofurantoin (two anhydrates and a monohydrate) which were recrystallized from formic acid or aqueous solutions of formic acid and discussed the relation between the particle shape and the properties of recrystallization solvents. Previously, we characterized the anhydrate and monohydrate forms of the drug and their dissolution behaviors (9). The effects of humidity conditions on the phase transformation of nitrofurantoin modifications have not yet been reported. In order to clarify the decreased dissolution rate of nitrofurantoin preparations after storage under high-relative humidity conditions, reported by Gouda *et al.* (5) and Ebian *et al.* (6,7), we analyzed the physicochemical stability of the anhydrate and monohydrate under high- and low-humidity conditions using kinetic methods.

EXPERIMENTAL

Materials. A bulk powder (Lot 11085) of nitrofurantoin was obtained from Fukujyu Pharmaceutical Co. Ltd., Japan. The anhydrate (I) was obtained by recrystallization using hot saturated solutions of acetone. The saturated solutions were allowed to stand at room temperature, and the crystals were filtered and dried *in vacuo* at room temperature for 2 hr. The monohydrate (II) was obtained by recrystallization method from a saturated aqueous solution of the drug: the solution was allowed to stand at room temperature and then the separated crystals were filtered and dried *in vacuo* at room temperature for 2 hr. After preparation the sample powders were stored in 100-ml closed containers at room temperature.

X-Ray Powder Diffraction Analysis. X-ray powder diffraction profiles were taken at room temperature with an X-ray diffractometer (XD-3A, Shimadzu Co.). The operating conditions were as follows: target, Cu; filter, Ni; voltage, 20 kV; current, 5 mA; receiving slit, 0.1 mm; time constant, 1 sec; counting range, 1 kcps; scanning speed, 1° 2θ/min.

Measurement of the Content of II in the Mixtures of I and II. Known quantities of standard mixtures were obtained by physically mixing I and II at various ratios in a mortar. The calibration curve for measuring II content was obtained based on the peak height of X-ray diffraction intensities at 16.5° due to I and 21.5° due to II. The plots gave good linear correlations, as follows:

$$Y_a = -1.66\,C + 167 \qquad (r = 0.988)$$

$$Y_h = 4.33\,C - 3.77 \qquad (r = 0.994)$$

where C is the percentage content of II, Y_a is the peak intensity at $2\theta = 16.5°$, Y_h is the peak intensity at $2\theta = 21.5°$, and r is the correlation coefficient.

Hence, these two calibration curves were used to determine the II and I contents, and the amount transformed to the other crystal form was obtained from the calibration curves.

Thermal Analysis. Thermogravimetry (TG) were performed with Type DTA-TG instruments (Shimadzu Co.). The operating conditions in an open-pan system were as follows: sample weight, 5 mg; heating rate, 10°C/min; N_2 gas flow rate, 50 ml/min.

Transformation of I to II at Various Relative Humidities and Temperatures. Samples (80 mg) were loaded in a glass holder for the X-ray diffractometer, and then the holder was stored at various humidity levels (0–100% RH) at 25, 40, and 45°C. The amount transformed was determined according to the method described in the previous section. After the stability experiments at various humidity levels, II contents were measured by using DTA-TG analysis. The computer program MULTI (10) was used for the nonlinear least-squares analysis of the hydration kinetics shown in Eq. (1) (11,12). The kinetic parameters were calculated by using the damping Gauss–Newton method after the initial values of the parameters were determined by the Simplex method. A weight of unity was employed in this analysis.

$$x = [1 - (kt + C)/3]^3 \qquad (1)$$

where x is the weight fraction of II, t is time, k is the hydration rate constant, and C is a constant.

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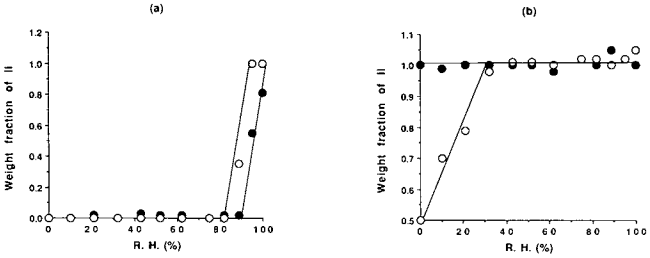

Fig. 1. Effect of relative humidity on I (a) and II (b) of nitrofurantoin at 25 and 40°C. (●) 25°C; (○) 45°C.

RESULTS AND DISCUSSION

Stability of I and II at Various Relative Humidity and Temperature Levels. Figure 1 shows the effect of relative humidity on the II content after storage at 25 and 40°C for 4 months. II partially transformed to I at 0–21% RH at 40°C. On the contrary, II did not transform to I at 0–21% RH at 25°C. I did not transform to II at 89% RH but it showed a tendency of transformation at 95–100% RH and 25°C. I did not transform at 0–82% RH at 40°C but partially transformed at 89% RH and 40°C and completely transformed at 95–100% RH and 40°C. These pseudoequilibrium results document the remarkable hysteresis in this sorption system. Tabibi and Hollenbeck (13) reported that isothermal desorption hysteresis of sugar was inevitable in any system of which dehydration requires elevated temperature. Therefore, these results indicated that II was apparently stable at 32–100% RH and 40°C and at 0–100% RH and 25°C, and I was stable at 0–82% RH and 40°C and at 0–89% RH and 25°C.

Hydration Kinetics of I to II. Figure 2 shows the hydration process of I and II at 89, 95, and 100% RH and at 40 and 45°C. The hydration rate of the anhydrate increased with increasing relative humidity but was barely affected by temperature. To clarify the hydration mechanism, the hydration

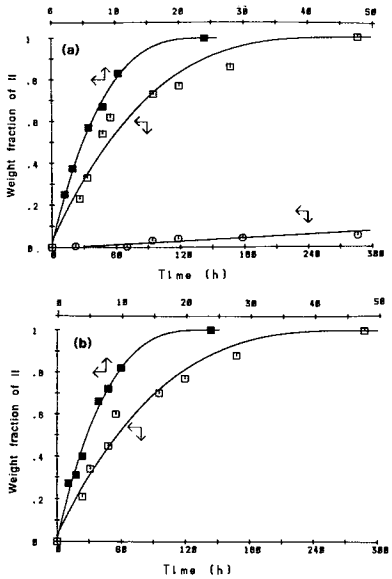

Fig. 2. Hydration process of I at various relative humidities and 40 and 45°C. (a) At 40°C; (b) at 45°C; (■) at 100% RH; (□) at 95% RH; (○) at 89% RH. The solid lines represent the theoretical curves.

Table I. Hydration Kinetic Parameters of I at Various Relative Humidity and Temperature Levels

Storage conditions	$T_{1/2}$ (hr)[a]	K (hr^{-1}) (SD)	C (SD)	SS[b] × 10^3
40°C, 100% RH	4.9	0.123 (0.004)	0.0135 (0.0150)	1.65
40°C, 95% RH	54.1	0.0110 (0.0013)	0.0295 (0.0572)	34.4
40°C, 89% RH	2014	3.12×10^{-4} (7.31×10^{-6})	−0.0102 (0.0050)	0.731
45°C, 100% RH	4.7	0.129 (0.0068)	0.0063 (0.0251)	1.65
45°C, 95% RH	56.5	0.0104 (0.0009)	0.0292 (0.0422)	20.2

[a] Time required for 50% hydration.
[b] The residual sum of squares.

process was analyzed by a kinetic method. Sekiguchi *et al.* (11) reported that the dehydration of sulfaguanidine monohydrate followed a three-dimensional phase boundary equation, which is suitable as a common kinetic equation for solid-state reaction (12) of cubic or sphere crystals. Since nitrofurantoin I consisted of polycrystals which formed fine cubic or plate crystals (9), the model equation [Eq. (1)] based on the three-dimensional phase boundary theory (11) was applied to the present transformation system. The kinetic parameters obtained by nonlinear curve fitting are given in Table I. The results of the fitting index parameter [the residual sum of squares (SS)] supported the hypothesis that this equation may be applicable to the present hydration system. The theoretical values (shown by solid lines in the figure) were in good agreement with the observed values under any storage condition. These results suggest that the hydration process of I followed a three-dimensional phase boundary kinetics and that the hydration proceeded three-dimensionally from the surface into the crystal entity. The hydration rate of I at 40°C and 100% RH was 11.2 times higher than that at the same temperature and 95% RH and 392 times higher than that at the same temperature and 89% RH. However, the hydration rates at 40 and 45°C and the same humidity were similar. This result suggests that the atmospheric water vapor pressure may be the main factor for the hydration of I. However, the crystallographic stabilities of I and II were remarkable at 25 and 40°C (Fig. 2).

Conclusion. Crystallographic phase changes of the drug can occur during the storage period at relatively high or low humidities. Whereas therapeutic side effects are associated with fluctuations of dissolution rate and hence bioavailability of commercial preparations, the crystallographic stability of nitrofurantoin bulk powder may be one of the most important factors for controlling bioavailability of the preparation. Therefore, information about the physicochemical stabilities of these modifications is useful for designing high-quality preparations of the drug.

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