The Effect of Humidity on Hydration Kinetics of Mixtures of Nitrofurantoin Anhydride and Diluents

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The effect of humidity on mixtures of nitrofurantoin and crystalline lactose or microcrystalline cellulose was investigated by X-ray diffraction analysis, water content measurement and thermogravimetry. The water content of 50% (w/w) mixture was measured after storage at 95 and 100% relative humidity (RH), 40 °C for 24 h. The hydration of the mixture containing microcrystalline cellulose at 95% RH was the slowest, and that containing lactose at 100% RH was the fastest. The hydration process of nitrofurantoin anhydride was analyzed based on the three-dimensional phase boundary theory. The hydration rate of the nitrofurantoin was accelerated by adding lactose, but not by microcrystalline cellulose. Since lactose had a critical relative humidity at around 95% RH, the hydration of the mixture occurred in the solution after the lactose rapidly dissolved by deliquescence. However, the hydration rates of the mixture with microcrystalline cellulose were much slower than those of the anhydride.

Keywords nitrofurantoin; anhydride; diluent; stability; hydration; kinetic analysis

The interaction of water with pharmaceuticals plays a fundamental role in many aspects of drug development, from synthetic design and dosage form to effective product packaging and drug bioavailability. The affinity that a substance has for sorbing water vapor is generally referred to as hygroscopicity. Since adsorption is not an entropically favored process, the water–solid interaction must provide a sufficient enthalpic driving force if such sorption is to occur. Zografi and his colleagues[1-5] reported the moisture sorption kinetics for pure and/or mixtures of water-soluble substances under conditions of high humidity. The U.S. Food and Drug Administration (FDA) reported that the *in vitro* dissolution rate of commercial carbamazepin preparations decreased up to one third of that of fresh when exposed to 97% relative humidity (RH) for 2 weeks.[6] Findings of the potentially harmful effects of high humidity may contribute to some of the "no drug effect" reports occasionally received by the FDA on the commercial tablets.[6]

On the other hand, nitrofurantoin is widely used as an urinary tract antibacterial drug,[7] however, it has bioavailability problems. Formulation factors of the drug preparation, mainly particle size,[8] affect the dissolution rate,[9] bioavailability in humans and the incidence of side-effects.[10] The USP XXII monograph for nitrofurantoin tablets requires not less than 25% of a labeled amount of drug to be dissolved within 60 min at a pH 7.2 in phosphate buffer. Gouda *et al.*[11] and Ebian *et al.*[12,13] 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 temperature. The *in vitro* dissolution rate of the tablets decreased specially dramatically after storage at 100% RH.[12] We characterized the anhydride and monohydrate forms of nitrofurantoin,[14] its dissolution behaviors,[14] and the phase transformation under a high humidity condition.[15] In this study, in order to clarify the stability of nitrofurantoin preparations following storage at relatively high humidity as reported by Gouda *et al.*[11] and Ebian *et al.*,[12,13] we analyzed the physicochemical stability of nitrofurantoin anhydrate containing two typical diluents, lactose and crystalline cellulose under high humidity conditions using kinetic methods.

Experimental

Materials A bulk powder (lot 11085) of nitrofurantoin was obtained from the Fukujyu Pharmaceutical Co., Ltd., Tokyo, Japan. The anhydride and the monohydrate were obtained by recrystallization in saturated acetone and distilled water as described previously.[15] α-Lactose monohydrate and microcrystalline cellulose (PH-101) were obtained from Nakalai Tesque Co. (Osaka, Japan) and Asahikasei Co. (Tokyo, Japan), respectively.

Preparation of Sample Powder Sample physical mixtures were obtained from 50% (w/w) nitrofurantoin and 50% (w/w) lactose monohydrate or microcrystalline cellulose by hand shaking in a plastic bag without mechanochemical effect.

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

Measurement of the Anhydride Content in Mixtures of Anhydride and Monohydrate Standard mixtures were obtained by physically mixing the anhydride and monohydrate of nitrofurantoin. After standard samples were mixed with 50% (w/w) α-lactose monohydrate or crystalline cellulose at various ratios in a mortar by a spatula, the X-ray diffraction profiles were measured. The calibration curve for measuring the monohydrate content was obtained based upon the peak height of X-ray diffraction intensities at $2\theta=14.4°$ due to the anhydride, and at $2\theta=13.9°$ due to monohydrate. The plots of the mixtures with lactose and crystalline cellulose showed good linear correlation, and the following regression equations were obtained:

$$Y_{14.4}=403-3.95\,X_{al} \quad (\gamma^2=0.998) \quad (1)$$
$$Y_{13.9}=0.29+2.92\,X_{ml} \quad (\gamma^2=0.995) \quad (2)$$
$$Y_{14.4}=319-3.11\,X_{ac} \quad (\gamma^2=0.995) \quad (3)$$
$$Y_{13.9}=2.24+3.45\,X_{mc} \quad (\gamma^2=1.00\ ) \quad (4)$$

where Eqs. 1 and 2 are applicable to the mixture with lactose, Eqs. 3 and 4 are applicable to the mixtures with the mixtures with crystalline cellulose, $Y_{14.4}$ and $Y_{13.9}$ are intensities due to the anhydrate and monohydrate, X_{ac} and X_{mc} are anhydrate and monohydrate contents in the mixture with crystalline cellulose, X_{al} and X_{ml} are the percent of anhydrate and monohydrate content in the mixture with lactose and γ is the correlation coefficient constant.

Hence, these two calibration curves attributable to the peak at $2\theta=13.9°$ and 14.4° were used to determine the monohydrate and

anhydride contents, and the amount transformed to the other crystal form was obtained from the calibration curves.

Thermal Analysis Thermogravimetry (TG) was performed using type DT-30 instruments (Shimadzu Co., Kyoto, Japan). The operating conditions in an open-pan system were as follows: sample weight, 5 mg; heating rate, 10 °C/min; and N_2 gas flow rate, 50 ml/min.

Water Content After an aluminum crimp cell for TG containing sample powder (10 mg) was stored at 40 °C at 89, 95 and 100% RH for 24 h, the TG curve was measured. The water content of sample was defined as the weight loss at 110 °C on the TG curve.

Storage Conditions The samples were stored in 150 ml of a plastic bottles with caps which also contained 40 ml of various kinds of saturated salt solutions and were kept at 40.0±0.5 °C.

Transformation of Anhydride to Monohydrate at Various Relative Humidities and Temperatures Samples (80 mg) were loaded in the glass holder of an X-ray diffractometer and stored under various conditions. The amount transformed was determined as described in the previous section. The computer program MULTI[16] was used for the nonlinear least-squares fit of the hydration kinetics shown in Eq. 5.[17,18] The kinetic parameters were calculated using the damping Gauss–Newton method after the initial values of the parameters were determined by the Simplex method. A weight of unity was used in this analysis.

$$x=\{1-(k(t-t_0))/3\}^3 \quad (5)$$

where x is the weight fraction of monohydrate, t is time, t_0 is the induction period and k is the hydration rate constant.

Results and Discussion

Change of X-Ray Diffraction Profiles of the Mixtures of Anhydrate with Diluents at High Relative Humidity Figure 1 shows the X-ray diffraction profiles of the mixtures of anhydride with microcrystalline cellulose or lactose at 95% RH, and at 40 °C. The two mixtures did not show any difference after storage at 0, 11, 32, 53, 62, 75 and 82% RH for 3 months. However, at 95—100% RH the peak at $2\theta=13.9°$ due to monohydrate increased, and that at $2\theta=14.4°$ due to anhydrate decreased with elapsed time. The increase of peak intensity at 13.9° of the mixture with lactose was much faster than that of the mixture with crystalline cellulose. This suggested that the crystalline transformation of nitrofurantoin at high humidity depended on the type of diluent, and that mixing with lactose accelerated the transformation.

Effects of Diluents on the Stability of Mixture of Nitrofurantoin and Diluents at Various Relative Humidity Levels Figure 2 shows the effect of relative humidity on the water content of nitrofurantoin anhydride, lactose and microcrystalline cellulose after storage at 40 °C for 24 h. As shown previously,[15] the anhydride without diluents did not transform at 0, 11, 32, 53, 62, 75 and 82% RH, did so partially at 89% RH, and was completely transformed at 95—100% RH after storage at 40 °C for 3 months. The water content of the microcrystalline cellulose increased with increasing RH. The lactose did not absorb the water vapor at less than 95% RH, but the water content at 100% was much higher than that at 95% RH, indicating that the critical relative humidity (CRH) of lactose was around 95% RH.

Figure 3 shows the effect of RH on the water content of a 50% (w/w) mixture of nitrofurantoin anhydride with lactose or microcrystalline cellulose after storage at 40 °C for 24 h. The water content of the mixture with microcrystalline cellulose was almost the same as that of pure microcrystalline cellulose. However, the X-ray diffraction profiles of those mixtures have small diffraction

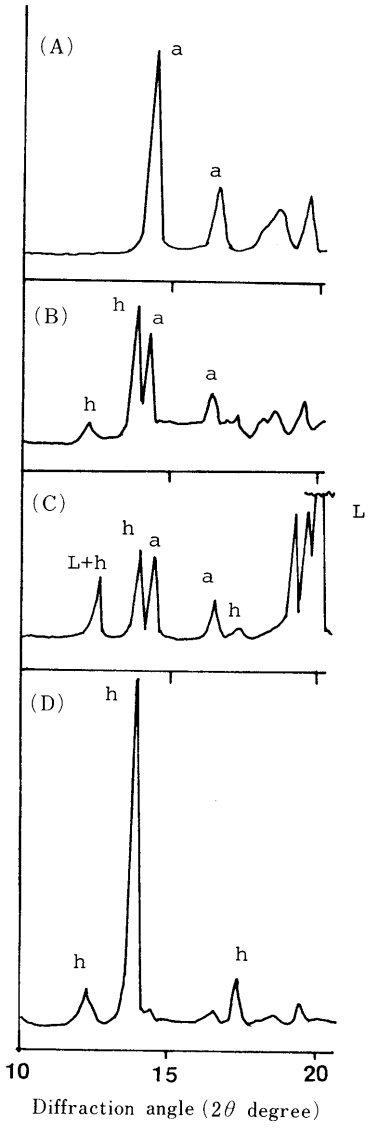

Fig. 1. X-Ray Diffraction Profiles of Mixtures of Nitrofurantoin and Diluents at Various Relative Humidities

(A), anhydrate; (B), the mixture with microcrystalline cellulose at 95% RH, 40 °C for 22 d; (C), the mixture with lactose at 95% RH, 40 °C for 15.5 h; (D), monohydrate. a, h and L in Fig. 1 represents the diffraction peaks attributable to anhydrate, monohydrate and lactose, respectively.

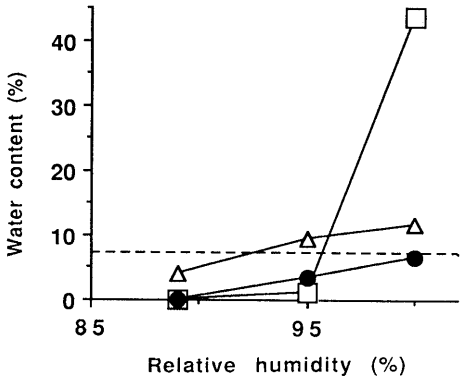

Fig. 2. Effect of Relative Humidity on Water Content of Nitrofurantoin, Lactose and Microcrystalline Cellulose

●, nitrofurantoin; □, lactose; △, microcrystalline cellulose. The dotted line represents the theoretical water content of nitrofurantoin monohydrate.

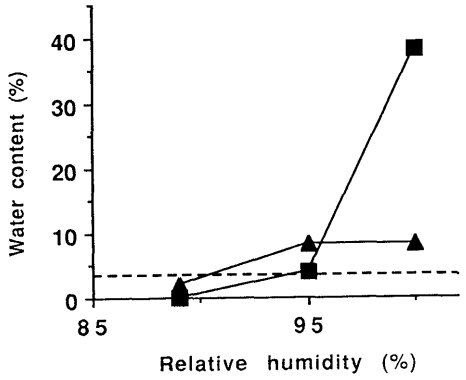

Fig. 3. Effect of Relative Humidity on Water Content of the Mixtures with Lactose or Microcrystalline Cellulose

■, lactose; ▲, microcrystalline cellulose. The dotted line represents the theoretical water content of nitrofurantoin monohydrate.

TABLE I. Hydration Kinetic Parameters of Mixtures of Nitrofurantoin Anhydride (NF) with Lactose (LA) or Microcrystalline Cellulose (MC) at Various Relative Humidity Levels at 40 °C

Storage conditions	T_{50}[a] (h)	K (S.D.) (h^{-1})	t_0[b] (S.D.) (h)	SS[c]
NF 95% RH	53.6	1.10×10^{-2} (1.26×10^{-3})	−2.66 (5.44)	3.44×10^{-2}
NF 100% RH	3.87	1.23×10^{-1} (4.26×10^{-3})	-1.10×10^{-1} (1.39×10^{-1})	1.65×10^{-3}
NF–LA 95% RH	17.5	7.27×10^{-2} (8.96×10^{-3})	6.26 (9.50×10^{-1})	4.06×10^{-2}
NF–LA 100% RH	4.33	1.57×10^{-1} (1.64×10^{-2})	3.89×10^{-1} (3.76×10^{-1})	2.76×10^{-2}
NF–MC 95% RH	403	1.55×10^{-3} (4.21×10^{-5})	4.09 (11.1)	2.33×10^{-3}
NF–MC 100% RH	186	3.68×10^{-3} (2.58×10^{-4})	1.76×10 (1.12×10)	2.24×10^{-2}

a) Time required for 50% hydration; b) the induction period; c) the residual sum of the square.

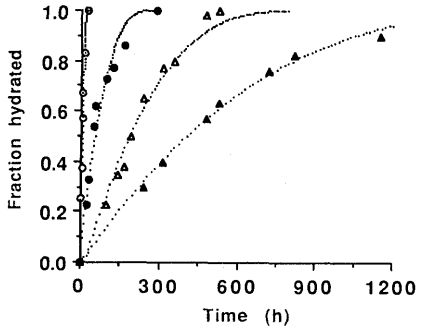

Fig. 4. Hydration Profiles of the Mixture of Nitrofurantoin with Microcrystalline Cellulose

○●, nitrofurantoin without diluent; ▲△, mixture containing microcrystalline cellulose. The open and closed symbols represent data at 100 and 95% RH, respectively. The dotted lines represent theoretical values.

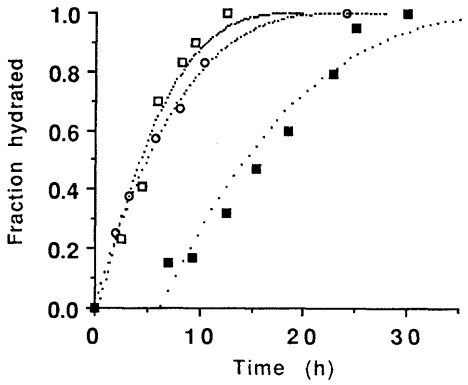

Fig. 5. Hydration Profiles of the Mixture of Nitrofurantoin with Lactose

○, nitrofurantoin without diluent at 100% RH; □■, mixture containing lactose. The open and closed symbols represent the data at 100 and 95% RH, respectively. The dotted lines represent the theoretical values.

peaks attributable to the monohydrate, indicating that most of the water was absorbed by the microcrystalline cellulose. The mixture containing lactose at less than 95% RH did not absorb the water vapor, but the water content of the mixture containing lactose at 95% RH was larger than that of pure lactose. The value was the same as that of nitrofurantoin monohydrate, and the X-ray diffraction profile was identical to that of the monohydrate, indicating that the anhydride transformed into the monohydrate at more than 95% RH.

Effect of Diluents on the Hydration Kinetics of Anhydride to Monohydrate Figures 4 and 5 show the hydration processes of a mixture of anhydride with microcrystalline cellulose or lactose at 95 and 100% RH, and at 40 °C. The time required for 50% hydration (T_{50}) are summarized in Table I. The hydration of the mixture with microcrystalline cellulose at 95% RH was the slowest, and that of the mixture with lactose at 100% RH was the fastest. To clearify the mechanism, the hydration process of nitrofurantoin anhydride was analyzed kinetically as previously described,[15,17,18] based upon the three-dimensional phase boundary theory (Eq. 5). The kinetic parameters obtained by nonlinear curve fitting are given in Table I. Results of the fitting index parameter (the residual sum of squares (SS)) supported the hypothesis that this equation is applicable to the present hydration system. The theoretical values (shown by dotted lines in Figs. 4 and 5) were in good agreement with the observed values under all storage conditions. These results suggest that the hydration process of the anhydride followed three-dimensional phase boundary kinetics.

The hydration rate of the mixture with lactose at 100% RH was almost the same as that of the anhydride, and at 95% RH that of the mixture with lactose was 6.6 times higher than that of the anhydride. Since lactose had a CRH at around 95% RH, the hydration of the mixture occurred in the aqueous solution after the lactose was rapidly dissolved by deliquescence.

On the contrary, the hydration rates of the mixture with microcrystalline cellulose at 95 and 100% RH were about 7 and 33 times slower than those of the anhydride. The hydration of the mixture at 95% RH containing lactose showed an induction period, but those of the mixtures with microcrystalline cellulose and/or the drug without diluent had no induction because these values were negligible. After the stability test, the sample powders of lactose mixtures were visually confirmed to have changed to the liquid state above the CRH, but the mixture of microcrystalline cellulose did not. These results

suggested that the cellulose had more hydrophilic nature than nitrofurantoin, because the microcrystalline cellulose absorbed water vapor into the hydrogen network between the cellulose in the crystalline structure, while lactose absorbed the water vapor and made the liquid in which the drug dissolved. This suggests that the effect of the atmospheric water vapor pressure on the hydration of nitrofurantoin differed depending on the physicochemical properties of diluents. Hydration can therefore be controlled by a formulation such as a type of diluent.

Conclusion

These results show that the crystallographic phase of a drug changes during storage at relatively high humidity and that it is affected by the diluent. Since commercial drug preparations have side effects caused by fluctuation in the dissolution rate affecting the bioavailability, the stability of diluent powders may be one of the most important factors in controlling the bioavailability of a preparation. This makes information about the physicochemical stability of these modifications useful in designing high quality drug preparations.

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