CHARACTERIZATION OF NITROFURANTOIN ANHYDRATE AND MONOHYDRATE, AND THEIR DISSOLUTION BEHAVIORS

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The anhydrate and monohydrate of nitrofurantoin were characterized by X-ray powder diffraction analysis, infrared spectroscopy and thermal analysis. The solubility of the anhydrate was 1.44 times that of the monohydrate at pH 6.8 (JP XI, 2nd. fluid), 37°C .

KEYWORDS nitrofurantoin; anhydrate; monohydrate; solubility; X-ray powder diffractometry; thermal behavior; pseudopolymorphism

Nitrofurantoin is widely used as a urinary tract antibacterial drug, but it has bioavailability problems. Formulation factors of the drug preparation, mainly particle size,[1] affect the dissolution rate, bioavailability in humans and the incidence of side-effects.[2] The USP XX monograph for nitrofurantoin tablets requires not less than 25% of the labeled amount of drug to dissolve it in 60 min in a pH 7.2 phosphate buffer. Gouda et al.[3] and Ebian et al.[4,5] reported that the dissolution rate of nitrofurantoin tablets and the bioavailability in humans decreased after the tablets were stored for 1 - 8 weeks at higher relative humidities and temperatures. On the other hand, it has been suggested in a personal communication[6] that nitrofurantoin can exist in two crystalline forms (anhydrate and monohydrate), but detailed description of the physicochemical properties of the forms is less qualitative. There are many pharmaceutical problems in the preparation of nitrofurantoin, but no report about the effect of the crystalline state of a bulk powder on dissolution rate has been published yet.

Anhydrate was obtained by recrystallizing from an acetone solution of the drug, and drying in vacuo. Monohydrate was obtained by recrystallizing from aqueous solution, and drying in vacuo. Figure 1 shows the X-ray powder diffraction profiles of anhydrate and monohydrate nitrofurantoin. The main diffraction peaks of the anhydrate were at 14.4 and 28.8° (2θ), and those of the monohydrate were at 10.1, 12.3, 13.9 and 27.2°. These diffraction patterns were thus significantly different from each other. The results of elemental analyses and proton NMR indicated that the monohydrate and anhydrate contained no impurities, but had different crystalline structures. The infrared (IR) spectrum of the anhydrate showed the following absorption bands: a band at 3325 cm^{-1} was attributed to the NH group,[6] bands at 1828, 1803 and 1750 cm^{-1} were attributed to the C=O group in the hydantoin[6] ring, and bands at 1580 and 1540 cm^{-1} were attributed to the α-nitrofuran ring.[6] The monohydrate exhibited absorption peaks at 3600 - 3450 cm^{-1} attributed to the hydroxyl group. A band at 3170 cm^{-1} was attributed to the NH group, bands at 1798 and 1743 cm^{-1} were attributed to the C=O group in the hydantoin ring, and bands at 1580 and 1540 cm^{-1} were attributed to the α-nitrofuran ring. The differential thermal analysis (DTA) curve of the anhydrate had an endothermic peak at 272°C and a subsequent exothermic peak at 276°C with loss of weight in thermogravimetry (TG) curve. These endo-exothermic peaks were due to decomposition after melting. The DTA curve of the monohydrate had an endothermic peak at 120 -

128°C with 7.05% loss of weight in the TG curve, a second endothermic peak at 273°C, and a subsequent exothermic peak at 276°C with loss of weight. This suggested that the first endothermic peak was caused by the dehydration of 1 mol/mol of crystal water (calcd. 7.03%), and that the second endo-exothermic peaks were due to decomposition after melting. After heat treatment of the monohydrate at 150°C for 10 min, the X-ray diffraction pattern was identified as that of the anhydrate. This suggested that the monohydrate was transformed to anhydrate by dehydration.

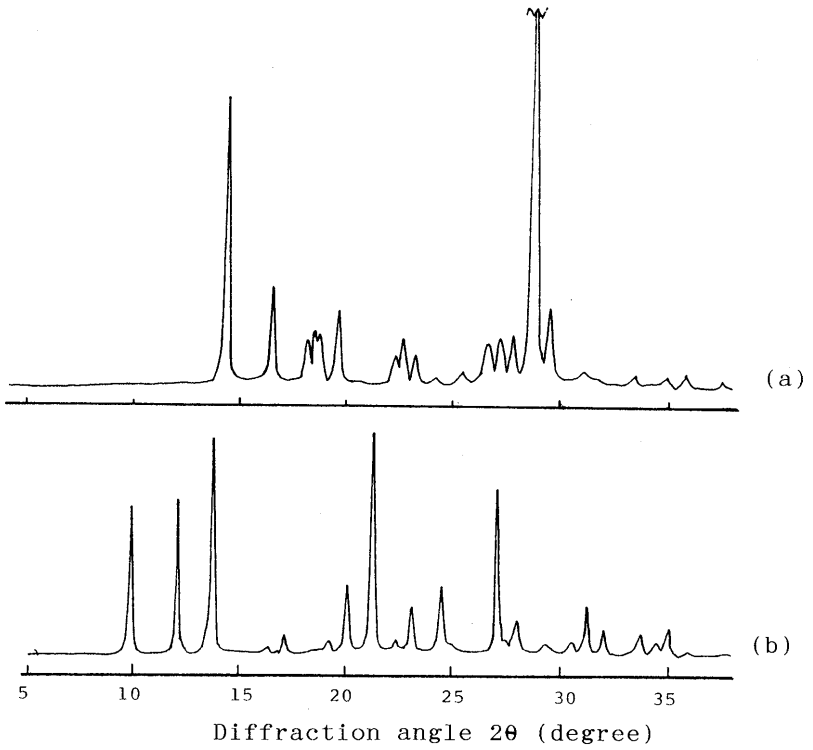

Fig. 1 X-Ray Powder Diffraction Profiles of Nitrofurantoin Anhydrate and Monohydrate
(a) anhydrate, (b) monohydrate; (target Cu, K_α, filter Ni).

Figure 2 shows the dissolution profiles of nitrofurantoin anhydrate and monohydrate in JP XI, 2nd fluid (pH = 6.8) at 37 ± 0.5°C. The anhydrate showed a characteristic convex dissolution profile with a maximal solubility. The monohydrate had a normal dissolution profile. The dissolution profile of the anhydrate obtained by the dispersed powder method was similar to that of theophylline involving a crystallization process together with a phase change from anhydrate to monohydrate.[7] After the dissolution experiment with the anhydrate, the precipitate had the same X-ray diffraction pattern as the monohydrate. Apparently the dissolution behavior of the anhydrate involves a crystallization process together with a phase change from anhydrate to monohydrate. The solubility of anhydrate (39.3 mg/100 ml) was 1.44 times that of the monohydrate (27.4 mg/100 ml).

It seems that the crystalline phase difference of nitrofurantoin is a very important factor because the bioavailability of its preparations are affected by the solubility the of bulk powder. More detailed information on the characterization and stability of the anhydrate and monohydrate will be reported elsewhere.

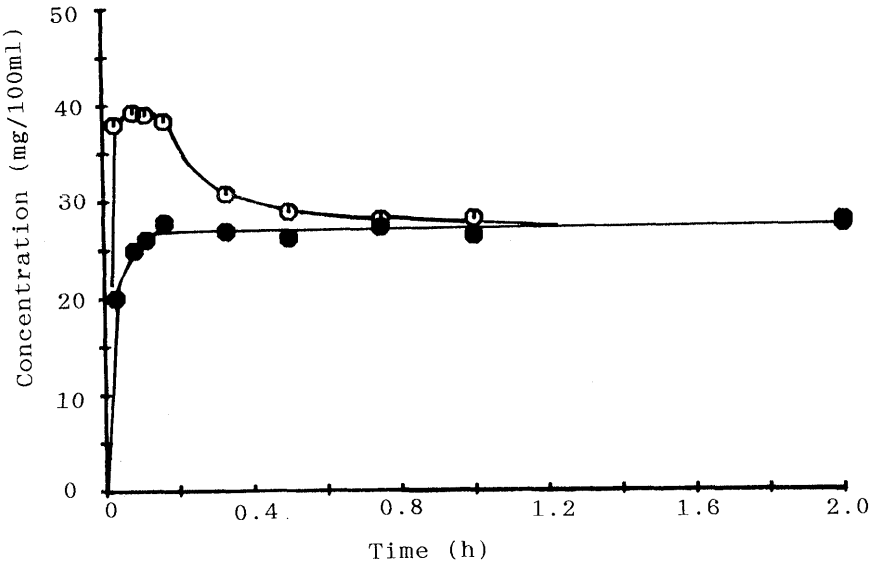

Fig. 2. Dissolution Profiles of Nitrofurantoin Anhydrate and Monohydrate at pH 6.8 (JP XI, 2nd. Fluid) at 37°C
○, anhydrate; ●, monohydrate.

REFERENCES

1) H. E. Paul, K. J. Hayes, M. F. Paul and A. R. Borgmann, J. Pharm. Sci., 56, 882 (1967).
2) D. E. Cadwallader, T. R. Bates, and A. H. Rosenberg, J. Pharm. Sci., 63, 643 (1975)
3) H. W. Gouda, M. A. Moustafa and H. I. Al-Shora, Int. J. Pharmaceut., 18, 213 (1984)
4) A. E. A. R. Ebian, R. M. A. Moustafa and E. B. Abul-Enin, Egypt. J. Pharm. Sci., 26, 287 (1985).
5) A. E. A. R. Ebian, H. T. Fikrat, R. M. A. Moustafa and E. B. Abul-Enin, Egypt. J. Pharm. Sci., 27, 347 (1986).
6) D. E. Cadwallader and H. W. Jun, Analytical Profiles of Drug Substances, 3,, 346 (1976).
7) E. Shefter and T. Higuchi, J. Pharm. Sci.,52, 781 (1963).

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