International Journal of Pharmaceutics, 55 (1989) 257–263
Elsevier

IJP 01879

Crystallisation solvent induced solid-state and particulate modifications of nitrofurantoin

P.V. Marshall * and P. York

School of Pharmacy, Pharmaceutical Technology, University of Bradford, Bradford (U.K.)

(Received 29 March 1989)
(Accepted 27 April 1989)

Key words: Nitrofurantoin; Crystallisation solvent; Crystal structure; Habit modification; Crystal/solvent interaction; Thermal analysis; Particle shape analysis

Summary

Nitrofurantoin has been batch crystallised from both formic acid and formic acid/water (2 : 1). Powder X-ray analyses indicated different crystal structures. Thermal analysis (DSC and TGA) data showed that this was due to the formation of a monohydrate in the sample crystallised from the binary solvent. Production of the monohydrate was attributed to changes in the interactions between nitrofurantoin and the solvent systems during crystallisation. On drying the monohydrate, a stable anhydrous form was obtained. Marked differences in crystal habit of the two samples, as shown by scanning electron microscopy and image analysis, were maintained. The sample crystallised from formic acid had tabular crystal habit whilst that from formic acid/water was needle-like. This habit modification was thought to be associated with preferential adsorption of the water molecules by polar crystal faces, thus inhibiting their growth.

Introduction

The process of crystallisation from solution is commonly used in the final stage of the synthesis of drug substances to obtain materials with a high chemical purity. However, it has been demonstrated that a change of the crystallisation solvent can lead to alterations of the crystals produced, particularly the crystal habit (Mullin, 1972; Davey, 1982).

As a consequence, several attempts have been made to change the properties of drug crystals by the use of alternative solvents to produce powders with preferred processing properties. Drug substances that have been examined include nitrofurantoin (Garti and Tibika, 1980), ibuprofen (Gordon and Amin, 1984) and hexymethylmelamine (Gonda et al., 1985). In the present investigation, the study of Garti and Tibika (1980) is extended with nitrofurantoin crystallised from two solvents and possible mechanisms for the resulting modifications in both the solid-state and particulate properties of the crystals discussed.

Materials and Methods

Materials

Nitrofurantoin (Sigma Chemical Co., Poole, U.K.) and formic acid (BDH Chemicals, Poole,

* *Present address*: Pfizer Central Research, Sandwich, Kent, U.K.

Correspondence: P. York, School of Pharmacy, Pharmaceutical Technology, University of Bradford, Bradford BD7 1DP, U.K.

TABLE 1

Samples of nitrofurantoin crystallised from various solvents at an initial relative supersaturation of 1.62 at 22 °C.

Sample code	Solvent	Weight of nitrofurantoin (g)
NFI	Formic acid	532.50
NFII	Formic acid/water (2:1)	136.24

U.K.), of the highest purity commercially available, were used without further purification. Water was deionised and double distilled.

Preparation of crystals

The weights of nitrofurantoin reported in Table 1 (corresponding to an initial relative supersaturation of 1.62 at 22 °C) and 8 litres of either formic acid, for the preparation of NFI, or formic acid/water (2:1) for NFII, were placed in a 12 litre round-bottomed flask immersed in a thermostatically controlled water bath at 60 ± 0.1 °C. Supersaturated solutions were prepared by stirring with an 8 cm diameter 4-bladed metal paddle at 170 rpm for 2 h. These solutions were cooled to 22 °C by means of a cooling coil in the water bath and adjusting the thermostat to this temperature. After a further 9 h stirring, the crystals produced were harvested on a sintered glass funnel (no. 3) with the aid of vacuum. They were then dried at 60 °C for 12 h, with a further 24 h storage over molecular sieve (type 5A) under vacuum and stored at 20 °C, 40 ± 5% relative humidity, protected from light, prior to use. Sample NFIII was prepared by drying NFII at 125 °C for 2 h. The 125–250 μm sieve fraction of the crystals was used for all further investigations.

X-ray powder diffraction (XPD)

X-Ray diffraction spectra of powder samples were obtained using an X-ray diffractometer (PW1120/00, Phillips, The Netherlands) with a proportional detector probe. Copper K_α (alpha) radiation with a wavelength of 0.1541 nm was used. A scanning rate of $1° \cdot 2\theta$/min over the range 4 to $30° \cdot 2\theta$ was used to produce the spectra on a recorder.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed using a differential scanning calorimeter (Model 910, Dupont Instruments, Stevenage, U.K.) and thermal analyser (Model 1090, Dupont Instruments, Stevenage, U.K.). The system was calibrated with a high purity sample of indium. Samples weighing between 1 and 10 mg were heated at 10 °C/min in a crimped aluminium pan.

Thermogravimetric analysis (TGA)

Thermogravimetric analysis (Model 951 Thermogravimetric Analyzer, Dupont Instruments, Stevenage, U.K. with a Model 1090 Thermal Analyzer, Dupont Instruments, Stevenage, U.K.) was carried out on powder samples of between 4 and 10 mg at a heating rate of 10 °C/min.

Scanning electron microscopy (SEM)

Photomicrographs of powder samples were obtained using a scanning electron microscope (Stereoscan 600, Cambridge Scientific Instruments, Cambridge, U.K.) fitted with a back-scattered electron detector (K.E. Developments, Cambridge, U.K.). Specimens were mounted on a metal stub with adhesive tape and coated under vacuum with gold prior to observation.

Particle shape and size

The particle shape and size distribution of powder samples were determined using an image analyser (Magiscan 2, Joyce-Lobel, Gateshead, U.K.). The system was calibrated in terms of microns per pixel (picture points) using a linear graticule. The crystals were mounted on glass microscope slides using a solution containing 3 drops of a photographic wetting agent (Fotoflo, Kodak/Ilford, U.K.) in 100 ml of water. Owing to the cohesive nature of the crystals, manual editing with a light pen of the images produced was necessary in order that individual particles could be measured.

The following parameters were measured for the samples analysed, for at least 100 crystals:

(a) detected area;
(b) length;
(c) breadth;
(d) perimeter.

Using these parameters, two shape factors, namely aspect ratio and roundness, were calculated for each particle measured. These shape factors were defined by the following equations:

$$\text{Aspect ratio} = \frac{\text{Length}}{\text{Breadth}} \quad (1)$$

$$\text{Roundness} = \frac{\text{Perimeter}^2}{4 \cdot \pi \cdot \text{Area}} \quad (2)$$

The size of each particle measured was described by its projected diameter, calculated as follows:

$$\text{Projected diameter} = \sqrt{\frac{4 \cdot \text{Area}}{\pi}} \quad (3)$$

Mean values of aspect ratio, roundness and projected diameter were also calculated for each sample.

True density

The true density of powder samples was determined using an air comparison pycnometer (Model 930, Beckman Instruments, Fife, U.K.).

Results and Discussion

Representative DSC traces obtained for NFI, NFII and NFIII are illustrated in Fig. 1. All the samples exhibited melting endotherms at 267 °C. Following the melting of these samples, a rapid exothermic heat flow occurred due to the decomposition of the samples and thus it was not possible to calculate heat of fusion. NFII displayed an additional endotherm at 114 °C which was not observed after drying at 125 °C for 2 h. This additional endotherm was attributed to the loss of solvent retained by the nitrofurantoin.

TGA also revealed the weight loss that occurred during heating of NFII (Fig. 2). The irreversible nature of this process was demonstrated by an absence of weight loss during the analysis of NFIII. The weight loss of NFII, 6.08% w/v, occurred between 89 and 122 °C, the same temperature range of the additional endotherm obtained during the DSC analysis of this material.

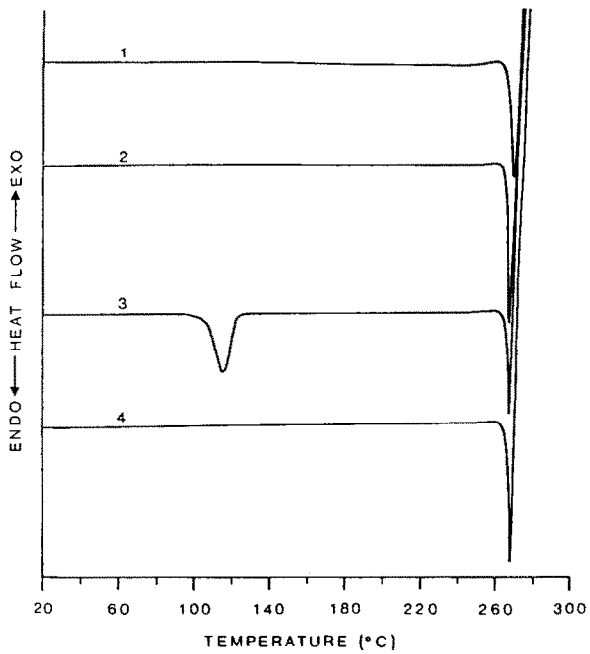

Fig. 1. Representative DSC thermograms of nitrofurantoin samples: (1) as supplied; (2) NFI; (3) NFII; (4) NFIII.

Thermal analysis of NFII thus indicated the retention of a solvent of crystallisation in some manner by the crystals. The relatively sharp form of the additional endotherm on the DSC thermogram and the shape of the TGA trace suggested a discrete loss of the solvent that has been bound to the crystals in the form of a solvate. From a consideration of the molecular weights of

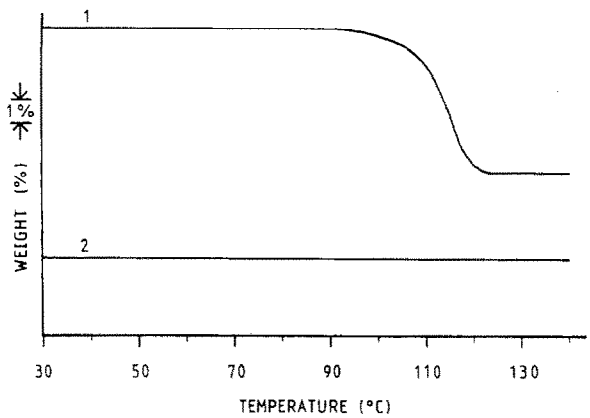

Fig. 2. Representative TGA thermograms of nitrofurantoin samples: (1) NFII; (2) NFIII.

TABLE 2

Solubility parameters (Hildebrand units) of solvents investigated

Solvent	Total solubility parameter	Dispersion component	Polarity component	Hydrogen bonding component
Formic acid	12.2	7.0	5.8	8.1
Formic acid/water (2 : 1)	15.7	7.2	6.5	12.3
Water	23.4	7.6	7.8	20.7

nitrofurantoin, formic acid and water and the possible production of a stoichiometric 1 : 1 solvate, the theoretical solvent content of a formic acid solvate and a hydrate of nitrofurantoin are 16.19 and 7.03% w/w, respectively. The weight loss determined from thermal analysis thus strongly indicated the formation of a monohydrate as opposed to a formic acid solvate. In addition, integration of the additional endotherm on the DSC thermogram for NFII indicated a loss of 7.25% w/w water, using a value of 40.66 kJ/mol for the vaporisation of water at 100 °C (Eisenberg and Kauzmann, 1969).

The production of the monohydrate on crystallising nitrofurantoin from formic acid/water (2 : 1) rather than formic acid was attributed to differences in the interactions between nitrofurantoin and formic acid and water molecules during crystallisation. In an attempt to assess the properties of the two solvents, solubility parameters were used. These parameters were subdivided into their dispersion, polar and hydrogen bonding components and the values, according to those reported by Hansen and Beerbower (1971), are reported in Table 2. (The value for the mixture of formic acid and water (2 : 1) was calculated by summing the values for the two solvents multiplied by their volume fractions.) Although it is not known which particular property of the solvent is responsible for the formation of the monohydrate, the total solubility parameters and their various components of formic acid and water are different, particularly the polarity and hydrogen bonding components. Whilst solubility parameters are not available for nitrofurantoin, the molecule possesses some polar regions. As a result, the interaction of water molecules with nitrofurantoin would be expected to be greater than with formic acid. Thus, water molecules associated with nitrofurantoin molecules in solution could have been retained at the active sites of crystal growth, possibly leading to incorporation into the crystal lattice, while desolvation of formic acid molecules could have occurred more readily. Garti and Tibika (1980) detected the formation of complexes of different crystal structures of nitrofurantoin with dimethylformamide but not with mixtures of formic acid and water.

The different crystal structure of NFII compared to NFI and NFIII and the commercially available sample is clearly demonstrated by the XPD spectra (Fig. 3). However, although NFI, NFIII and the commercially available sample exhibited spectra with identical 2θ values, the relative intensities of these peaks were modified, particularly for NFI compared to the other two samples. It is likely that the crystals exhibited preferred orientations when introduced into the metal sample-holder used to obtain spectra due to their markedly different crystal habits. As a consequence the relative abundance of the planes exposed to the X-ray source would have been altered producing the variations in the relative intensities of the peaks. The 4% difference in true density for NFI and NFIII (Table 3) was attributed to expansion of the crystal lattice of NFII during the additional drying leading to the expulsion of the water of crystallisation.

The large differences in the crystal habits of NFI and NFIII are revealed by the scanning electron photomicrographs (Fig. 4) and the values of the two shape factors (Table 3) obtained for these two samples. Although a quantitative assessment of the particle shape of NFII was not carried

TABLE 3

Properties of samples NFI and NFIII

Figures in brackets are standard deviations.

Sample	True density ($g \cdot cm^{-3}$)	Aspect ratio	Roundness	Projected diameter (μm)	
				Arithmetic mean	Median
NFI	1.646 (3.95×10^{-3})	1.29 (0.31)	1.23 (0.13)	97.27 (48.52)	78.90
NFIII	1.574 (2.85×10^{-3})	7.09 (2.85)	3.29 (1.11)	93.19 (31.72)	88.55

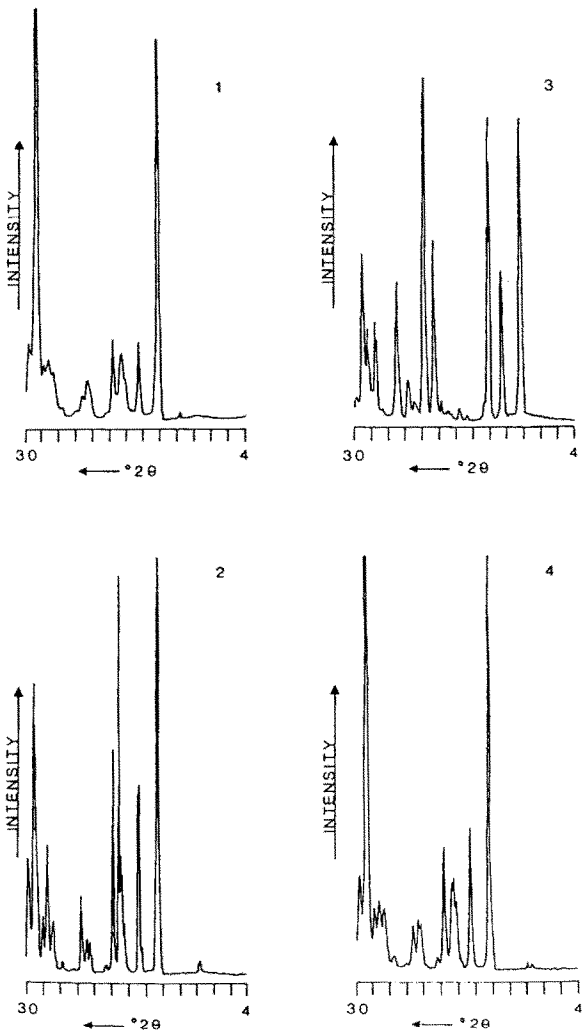

Fig. 3. XPD spectra of nitrofurantoin samples: (1) as supplied; (2) NFI; (3) NFII; (4) NFIII.

out, the photomicrographs in Fig. 4 demonstrate that the removal of the water of crystallisation did not alter the shape of the crystals. NFI displayed a tabular crystal habit with correspondingly low values for both aspect ratio and roundness. The crystal habit of NFIII was needle-like, with a number of the crystals exhibiting extensive elongation producing the relatively high standard deviation for both the aspect ratio and roundness. The acicular shape of NFIII is further demonstrated by the high roundness value which is characteristic of a particle far removed from a spherical shape.

A review of the literature relating to solvent induced habit modifications reveals the importance of the interactions between solute and solvent molecules at the various crystal/solution interfaces (e.g. Wells, 1946; Hartman, 1963; Bourne and Davey, 1976a and b; Davey et al., 1982). Owing to these interactions, the roughness of the interfaces may be altered, producing a change in the growth kinetics of the crystal, with an enhancement of the growth rate of the faces that interact strongly with the solvent (e.g. Davey, 1982). Alternatively, the solvent molecules may be preferentially adsorbed by certain crystal faces due to stronger interactions and thus inhibit the growth of these faces (e.g. Berkovitch-Yellin, 1985). Whilst it is possible that the growth kinetics of the crystal faces of nitrofurantoin in the two crystallisation solutions were altered, a detailed examination is beyond the slope of this study. Thus, the habit modifications will be discussed in terms of preferential adsorption of the solvent molecules.

As discussed earlier, water and formic acid

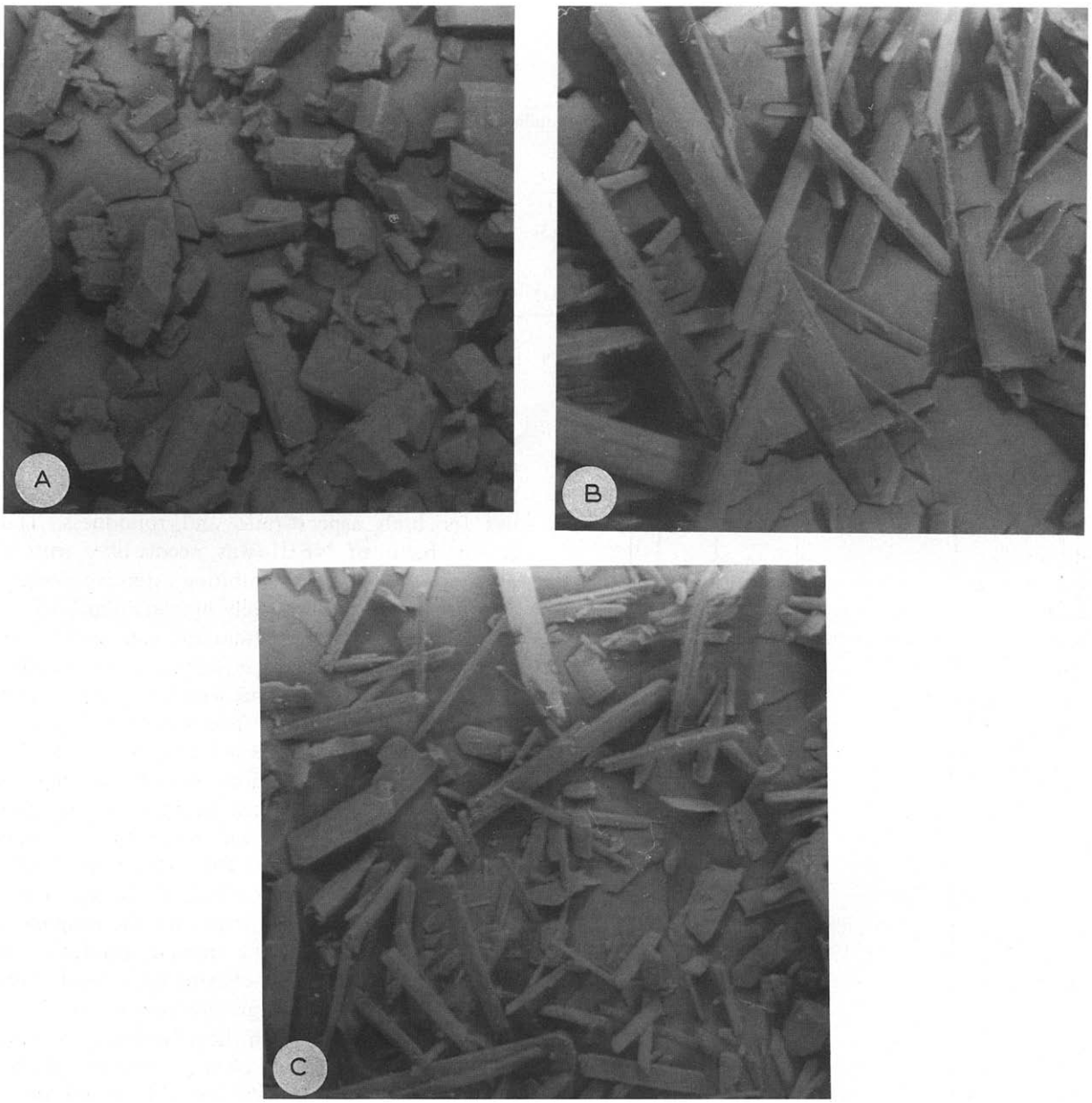

Fig. 4. SEM photomicrographs of nitrofurantoin samples: (A) NFI; (B) NFII; (C) NFIII. Magnification: ×75.

possess different properties, particularly in terms of their polarity and hydrogen bonding components of the solubility parameters. Berkovitch-Yellin (1985) proposed that the polarity of the solvent was the critical factor in determining the habit of the crystals produced. The dissimilar properties of formic acid and water would appear to support this hypothesis. Thus, the more polar water molecules would be preferentially adsorbed by the polar crystal faces with inhibition of the growth of these faces, leading to the observed habit modification.

Whilst the arithmetic mean values of the projected diameters of NFI and NFIII were similar (Table 3), the standard deviation and median values revealed a different particle size distribution for the two samples. This would arise from the altered growth rates of the various crystal faces as described above.

Conclusions

Crystallisation of nitrofurantoin from formic acid and formic acid/water (2 : 1) produced samples with different crystal structures as demonstrated by XPD. The sample crystallised from the binary solvent was indicated by thermal analysis to be a monohydrate, thought to be formed due to stronger interactions between water and nitrofurantoin molecules during crystallisation. Additional drying of the monohydrate at 125 °C produced a stable anhydrous form. Scanning electron microscopy and image analysis revealed widely different crystal habits for the two samples. This was also thought to be due to the preferential adsorption of the more polar water molecules by polar crystal faces.

Acknowledgements

One of us (P.V.M.) thanks the SERC for a CASE award and The Boots Company plc., the collaborating body. We also thank Victor Hawkins (University of Leeds) for helpful discussions and the use of an image analyzer.

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