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HABIT MODIFICATIONS OF NITROFURANTOIN CRYSTALLIZED FROM FORMIC ACID MIXTURES

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ABSTRACT

The crystal size and the length to width ratio of Nitrofurantoin, an anti-bacterial urinary tract drug, can be controlled using an appropriate mixture of solvents and suitable crystallization conditions.

Some solvents will form undesirable complexes with the drug (DMF) while with others no crystal structure modification or complexation was detected (HCO_2H).

The length (y) to width (x) ratio of the Nitrofurantoin varies from 2.5 to 1.5 when crystallized from pure formic acid or in a mixture with water or ethanol.

The y/x values correspond to the solvent interactions and supersaturation (S).

The crystal growth regularity is ascribed to the solvent power and thus when more regular crystals will precipitate bioavailability and solubilization of the drug will increase. Best results were obtained when mixture of formic acid-ethanol solution was used as crystallization media yielding large tabular crystals.

INTRODUCTION

Some organic chemists feel that once the molecular formula of a potential drug is established and understood, the compound is

ready for formulation and no further investigation is needed. Yet every year, numerous papers appear demonstrating that the performance of different drugs depends on, among other parameters, the habit and crystalline modification of the drug (1-6).

Crystal habit of an organic compound may tablet well while another may cause difficulties. One crystalline modification may show better solubility and bio-availability than another polymorph of the same drug (1). Those examples demonstrate only parts of the importance of knowing the polymorphism and habit modifications of each organic compound prepared in the laboratory and emphasizes the importance of having the capability to control the crystallization conditions.

The crystalline modifications, their structure and habit changes were reviewed by Haleblian (1) for some pharmaceutical important solids. Among the factors affecting the crystal habit of the drug, one can find the degree of supersaturation, the nature of crystallizing solvent and the presence of impurities in a form of cosolute, cosolvents and adsorbable foreign materials (1). In a number of papers it was also pointed out, that in some cases those factors can also affect the crystal structure of the drug and cause the formation of polymorphs (7, 8).

In the following study we tried to establish the role of those parameters on the habit and modification of an important drug manufactured in this country and in many others. N-(5-nitro-2-furfurylidene)-1-aminohydantoine known also as Nitrofurantoin (NFT) is prepared according to know-how incorporated in a series of international patents (9). It is known in pharmacology for many years as an internal antiseptic and mainly as an antibacterial chemotherapeutic agent for oral use useful for the treatment of urinary tract infections.

The purified product is reported to be recrystallized from several polar solvents and mainly from Dimethylformamide (DMF), Dimethylacetamide (DMA), Trichloracetaldehyde, acetic acid and a variety of acetic acids and water mixtures.

The pure product obtained from the manufacturer is a lemon-yellow fine powder with irregular shaped crystals in the range of 1-5μ. When the drug as such is tabletted and taken orally, side effects were detected with some patients. The drug partly dissolves in the oral tracts causing vomitting effect. Microencapsulation of large size crystals of that drug was shown to prevent this side effect (10).

Thus, the aim of this study is to search for suitable conditions for crystallization of the drug and to examine carefully the effect of each parameter on the crystal habit and structure of the drug. In order to evaluate critically the effect of the crystallization conditions on the crystal characteristics, the solubility curves of NFT in several solvents were determined. On the basis of this data the attainable supersaturation in these solvents was also measured.

EXPERIMENTAL

Materials - pure N-(5-nitro-2-furfurylidene)-1-aminohydantoine (NFT) was obtained from "Assia pahrmaceutical Industries, Israel" and its purity (>99.5%) was tested via known procedures and by repeated crystallizations. Its elemental analysis showed C 40.38% (40.35), H 2.83% (2.52) and N 23.48% (23.53) and m.p. was 269-271° (decomp.)

The solvents for crystallization were spectroscopic grade (>99%) formic acid and spectroscopic grade methanol, ethanol (99.5%) and dioxane from Malinkrodt or Baker.

Analytical Methods

Samples obtained from the crystallization bath were examined for their purity using simultaneous DTA, TG and DTG determinations on a Mettler Thermoanalyzer under controlled dry nitrogen flow of 5 l/h. Perkin Elmer, Great IR, Model 457 spectrometer was used to evaluate possible complexes with the solvent (see fig. 1) elemental analyses were carried out after every crystallization process. X-rays measurements were done on carefully grounded

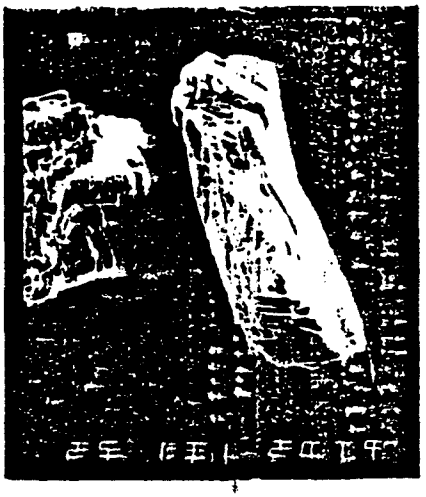

Figure 1: Nitrofurantoin crystals obtained from DMF solution. Magnitude of 130.

powder with Philips diffractometer using Cu radiation and Ni filter. Diffraction analyses were repeated several times using samples crystallized from various solvents at several conditions.

Observations on the crystal habit and determination of the length to width ratios as well as crystals size were done using a scanning electron microscope (SEM).

Crystallization Techniques

All the experiments were carried out in a thermostatic bath with controlled cooling profile.

Solubility curves were obtained according to procedures described elsewhere (11). Supersaturation determinations were carried out for equilibrium concentrations of 40°C and crystallization temperatures were in the range of 9 -40°C.

The cooling procedure was discontinued after the beginning of crystallization and the crystals were removed from the solution onto a slide glass and taken for inspection to the SEM.

RESULTS

Solubility Data

In patents describing the preparation of Nitrofurantoin, various polar organic solvents were used for crystallization and purification purposes. Among them one can find Dimethylformamide (DMF); Nitromethane; Dimethylacetamide (DMA) and some combinations of acetic acid and water (9). Several solvents were examined, in the present study, as crystallization media.

When DMF was used, big and regular shaped crystals of Nitrofurantoin were obtained (Fig. 1). Mixtures of DMF with a variety of other polar solvents such as water, ethanol, methanol, dioxane caused formation of tabular crystals and large enough for microencapsulation. However when submitted to elemental analysis, a complex of the solvent with the solute was detected, C 41.63 (40.38), H 4.03 (2.53), N 22.09 (23.42). DTA measurements, IR spectroscopy (Fig. 2) and X-ray diffractions (Fig. 3) confirmed those findings.

When acetic acid or formic acid were used no such complexation was observed (C 40.36, H 2.54, N 23.19) (Fig. 2-3) and thus formic acid was chosen as suitable crystallization solvent in several combinations with other polar solvents. X-rays diffractions and elemental analysis of all crystals obtained from formic acid confirmed an absence of complexation. (Figures 2-3)

Those results led us to believe that any of the above mixtures can be used for industrial processes in which the crop has to be crystallized.

The solubility curves of Nitrofurantoin in those mixtures were determined and are presented in Fig. 4.

It can be seen that pure formic acid is the most powerful solvent for this substance. (Fig. 1 curve 1). Addition of increasing amounts of water in the formic acid will cause a drastic decrease in the solubility of nitrofurantoin. (Fig. 4 curves 2, 6). By substituting the water with methanol, ethanol or dioxane an increase in the NFT solubility in the mixture can be achieved (Fig. 3 curves 3, 4, 5).

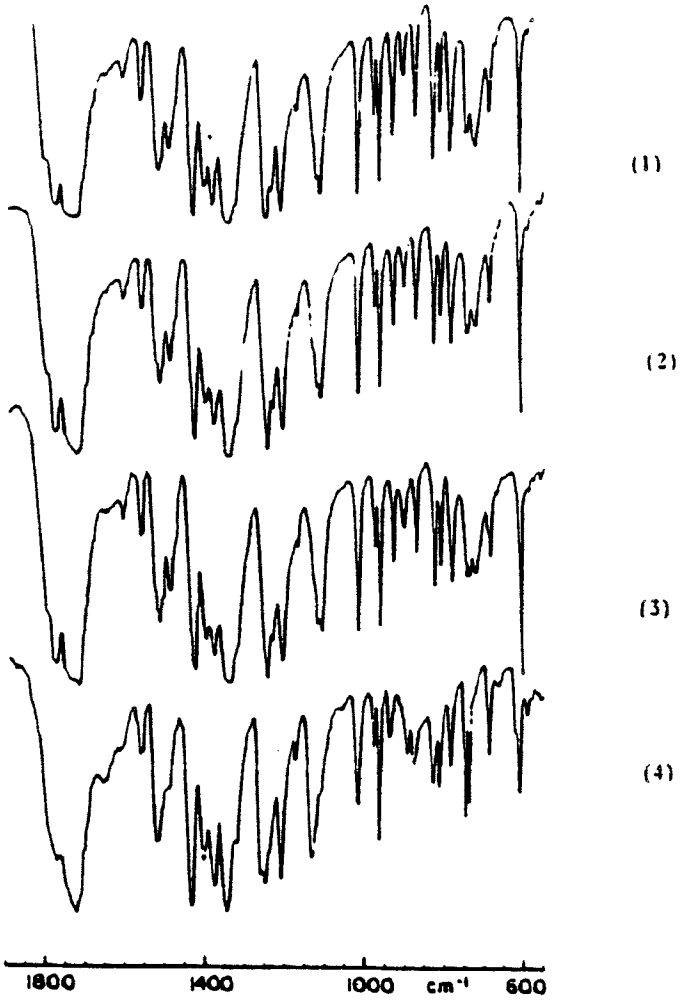

Figure 2: Infra-red spectra of NFT crystallized from (1) HCO_2H; (2) HCO_2H:EtOH; (3) HCO_2H: dioxane in comparison to NFT crystallized from DMF (4)

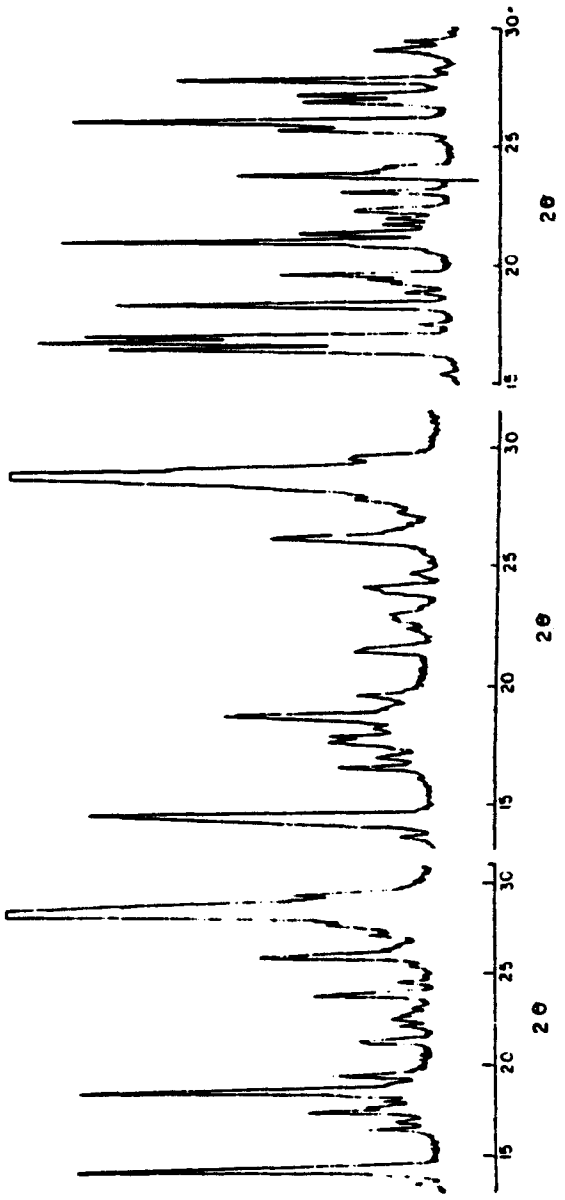

Figure 3: X-rays diffraction of NFT crystallized from (1) HCO_2H; (2) HCO_2H:EtOH; (3) DMF.

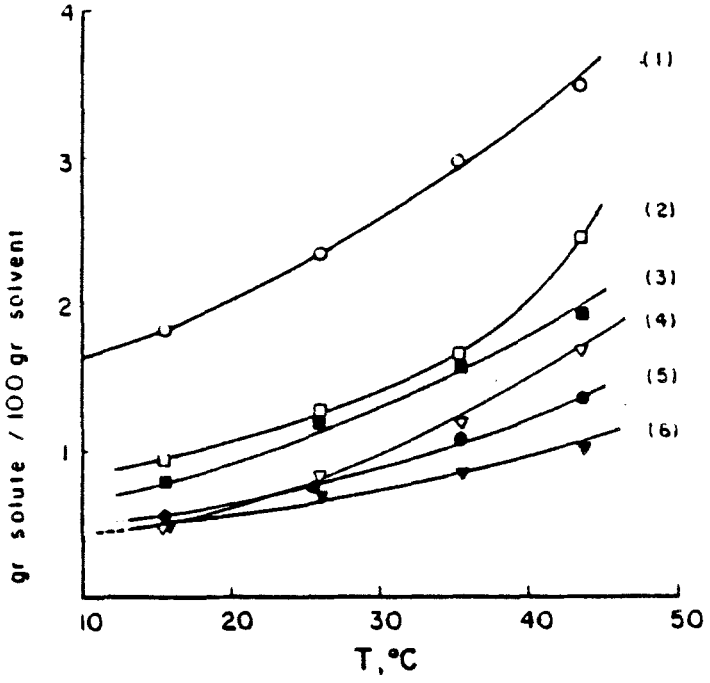

Figure 4: Solubility curves of Nitrofurantoin in (1) formic acid; (2) formic acid - H_2O (4:1) (3) formic acid-EtOH (2:1); (4) formic acid-dioxane (2:1); (5) formic acid - MeOH (2:1); (6) formic acid H_2O (2:1).

Supersaturation measurements

Based on the solubility curves measurements, the crystallization convenient temperatures were detected and the supersaturation values ($S=\frac{C}{C_s}$) were calculated and summarized in Table 1. The Tc, and S values demonstrate that when changing the flow regime of the system by shaking or stirring the solution, the supersaturation values will decrease markedly. This phenomenon was detected in each one of the systems investigated regardless of the composition of the solvent mixtures. The same phenomenon was also detectected in systems of cholesterol (12), fatty acids (13), 1,4-Di-t-butylbenzene (14) in previous studies.

TABLE 1

Exp.No.	Solvent	Crystallization conditions	$Tc_{(°C)}$ (1)	$S = \frac{C}{C^*}$
1	HCO_2H	quiescent	15	1.811
2	"	shaken	23	1.574
3	"	stirred	25	1.436
4	$HCO_2H:H_2O$(4:1)	quiescent	11	2.325
5	"	shaken	22	1.785
9	"	stirred	27	1.562
10	$HCO_2H:H_2O$(2:1)	quiescent	9	2.608
11	"	shaken	21	1.818
12	"	stirred	25	1.558
13	HCO_2H:MeOH(2:1)	quiescent	17	2.78
14	"	shaken	29	1.576
15	"	stirred	38	1.050
16	HCO_2H:EtOH(2:1)	quiescent	9	2.520
17	"	shaken	--	--
18	"	stirred	24	1.600
19	HCO_2H:dioxane	quiescent	15	1.892
20	"	shaken	19	1.692
21	"	stirred	26	1.543

The effect of solvent composition on the supersaturation values of nitrofurantoin solutions obtained in various flow regime at 0.03°C/min cooling rate.
(1) $Ts=40°C$

The comparison of the supersaturation data obtained for various solvents in quiescent systems shows an increase in the values with the decrease in the solubility power. Thus Nitrofurantoin will precipitate at 15°C (S=1.811) when crystallized from $HCO_2H:H_2O$(4:1) and at 9°C (S=2.608) when 2:1 $HCO_2H:H_2O$ was used. The same trend was detected for shaked and stirred solutions (see Table 1).

Observations of Crystal Habit

The crystal habit was not affected by the length of time which elaspsed from the beginning of the precipitation until the withdrawal of the sample. There was no detectable change either in habit or in size of crystals taken from any particular solvent withing periods of 10 sec to 30 min. after the onset of crystallization. The NFT obtained from the manufacturer without any treatment is shown in Fig. 5 from which it can be seen that the crystals are very small (0.5-1μ) and tabular with y/x ratio of ~2.5. When crystallization was performed in pure formic acid, in a quiescent system, cooled at 0.03°C/min, a tabular to needle-like crystal was obtained with y/x ratio of 8 (see Table 2). The crystals are larger in size (125-800μ). With the same solvent in stirred or shaken systems, when lower supersaturation values were measured, smaller but shorter crystals were obtained. (y/x = 6) as illustrated in Fig. 6 and Table 2.

When water was added to the crystallization solvent (HCO_2H: H_2O 4:1) the solubility decreased and the supersaturation values obtained for the various flow regime were larger than obtained in pure formic acid. The crystals are bigger in size and more plate-like with y/x ratio of 4 for stirred solution and y/x ratio of 9 for quiescent systems (Fig. 7, 8). Addition of more water to the formic acid decreased even more its solubility and increased the supersaturation values. The crystals are much smaller in size than when detained from pure formic acid and tabular to needle-like with y/x ratios of up to 26. (fig. 8, 10). On the other hand when ethanol was used in combination with formic acid very large and well-shaped crystals were obtained. The effect upon the supersaturation values was similar to that of water but less pronounced. The crystals obtained in shaken and stirred solutions were tabular to plate or cube like with y/x values close to 1.5 (Fig. 11, 12) and average size of 170-300μ. The mixtures of formic acid with dioxane yields similar habits but more twin-like, or conglomerates (Fig. 13, 14).

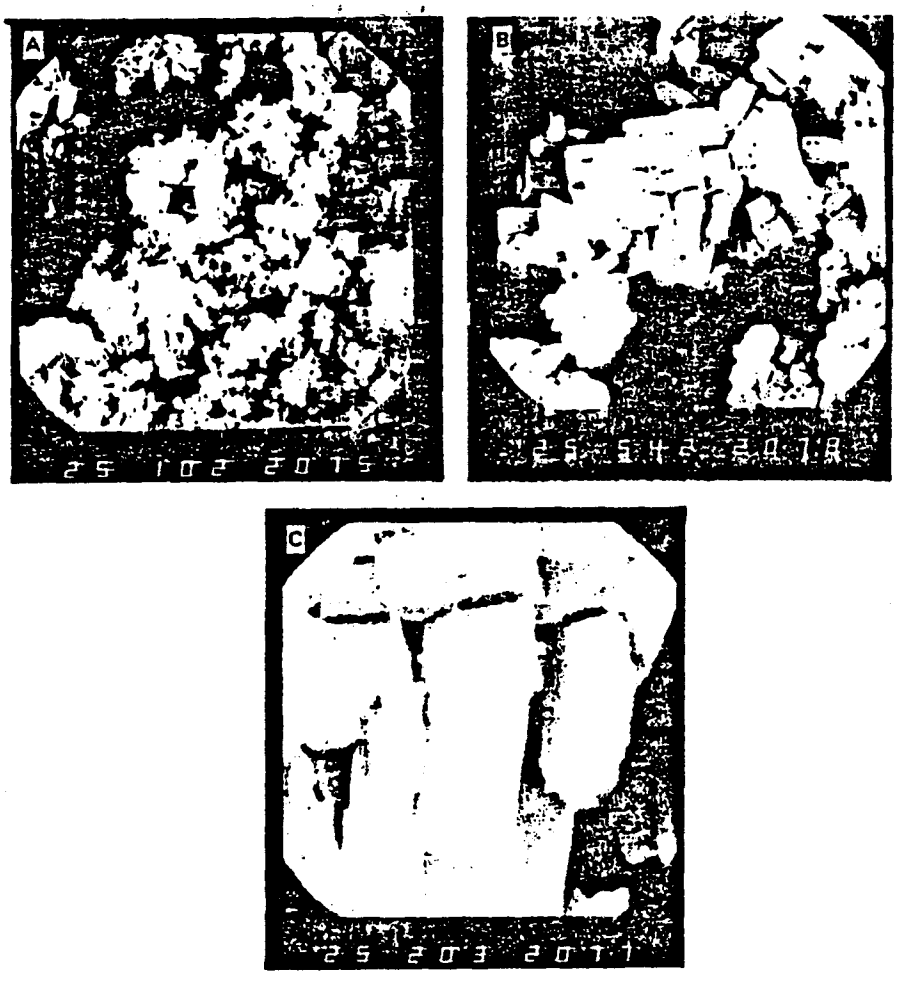

Figure 5: Nitrofurantoin crystals obtained from the Israeli manufacturer without further crystallization: a) Magn. x 1000, b) Magn. x 5400, c) Magn. x 20,000.

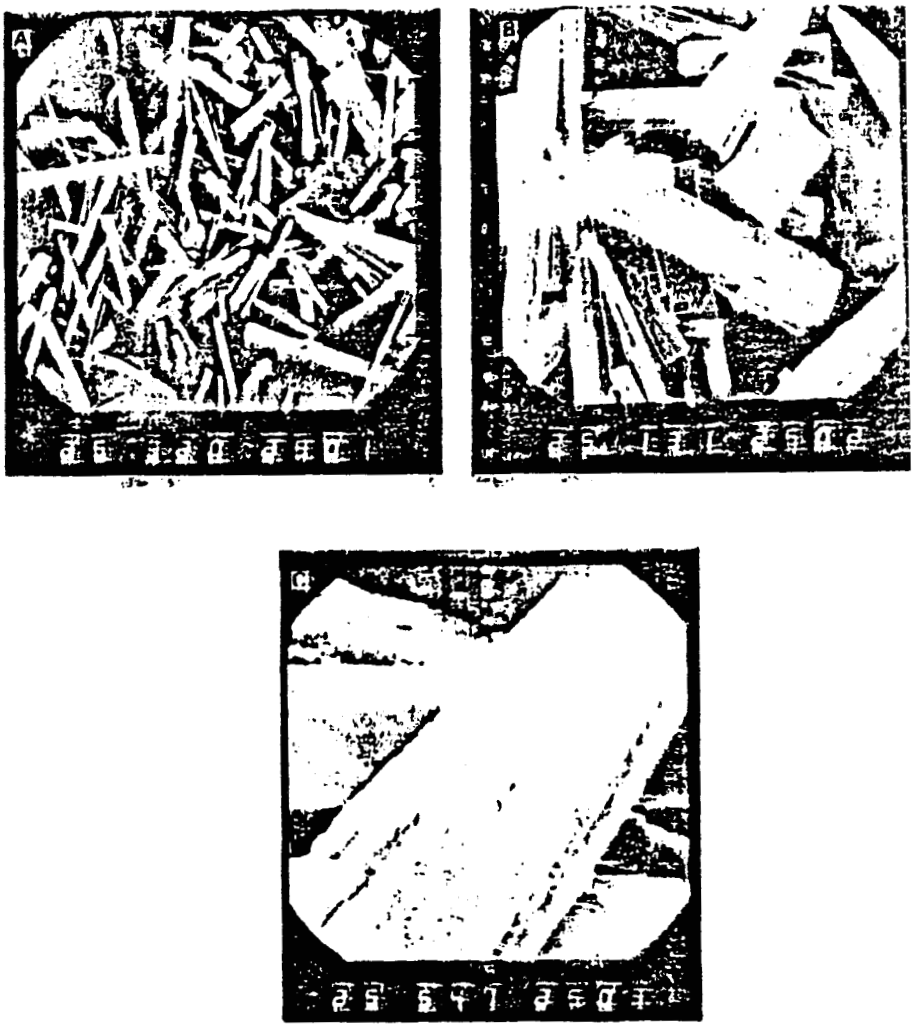

Figure 6: Nitrofurantoin crystals obtained from formic acid in stirred solution at 0.03°C/min cooling rate. a) Magn. x 32, b) Magn. x 130, c) Magn. x 540.

TABLE 2

Exp. No	Solvent	Crystallization conditions	Supersaturation (S)	Habit	Crystal dimensions (μ)	y/x (average)	Fig. No.
	--(1)	--	--	Acicular	0.65/1.5	2.5	5(a,b,c)
1	HCO_2H	quiescent	1.811	needles	100/800	8	--
3		stirred	1.436	tabular	45/300	6	6(a,b,c)
4	HCO_2H-H_2O (4:1)	quiescent	2.325	tabular	62/580	9	7
		stirred	1.562	plates	17/40	4	8
10	HCO_2H-H_2O (2:1)	quiescent	2.608	needles	30/600	20	9
12		stirred	1.538	needles	7/110	15	10
16	HCO_2H-EtOH (2:1)	quiescent	2.520	plates cubes	230/700	3	11
18		stirred	1.600	plates	200/300	1.5-2	12
19	HCO_2H-dioxane	stirred	1.543	twin plates	600/800	1.5	13

Crystal Habit, size and length to width ratio of NFT crystallized from various systems at 0.03°C/min.

NOTE: (1)Crystals obtained from manufacturer without further crystallization.

Figure 7: Nitrofurantoin crystals obtained from formic acid water (4:1) solution in quiescent system at 0.03°C/min cooling rate. Magn. x 32.

Figure 8: Nitrofurantoin crystals obtained from stirred formic acid-water (4:1) solution at 0.03°C/min cooling rate. Magn. x 32.

Figure 9: Nitrofurantoin crystallized from formic acid-water (2:1) solution at 0.03°C/min cooling rate. Magn. x 130.

Figure 10: Nitrofurantoin crystals obtained from stirred formic acid-water (2:1) solution at 0.03°C/min cooling rate. Magn. x 540.

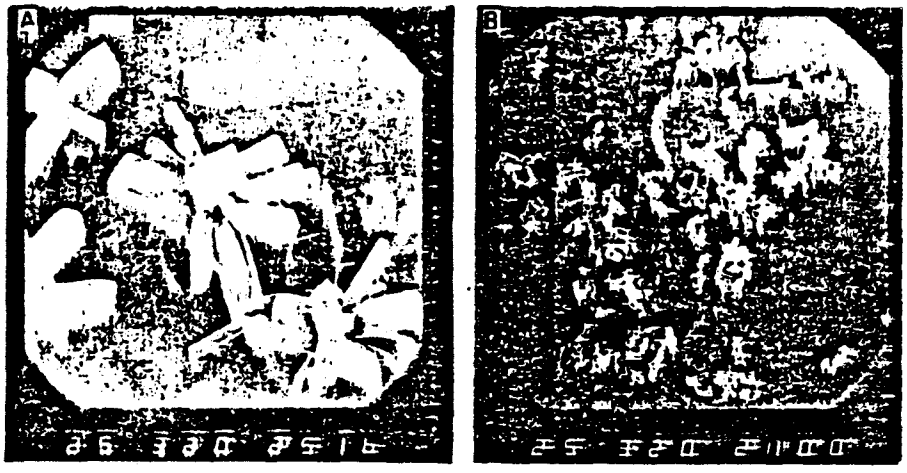

Figure 11: Nitrofurantoin crystals obtained from quiescent formic acid-ethanol (2:1) solution at a) 0.03°C/min cooling rate, b) 0.1°C/min cooling rate. Magn. x 32.

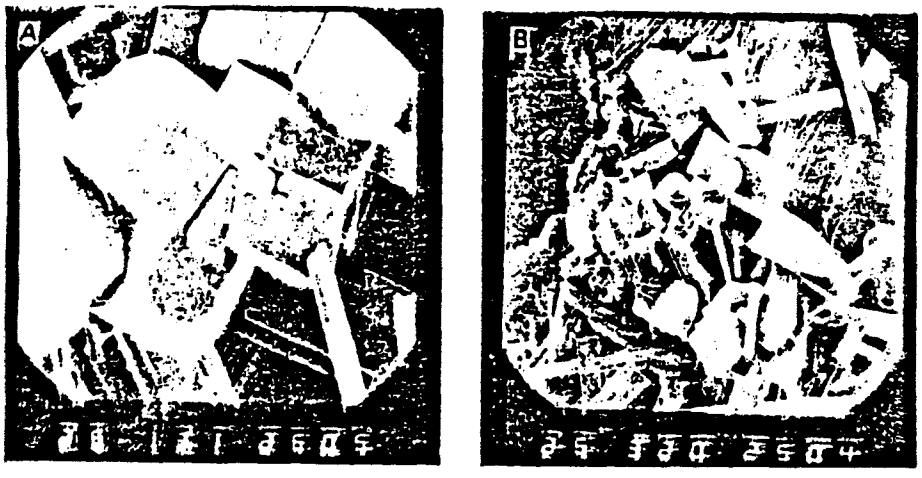

Figure 12: Crystallization of Nitrofurantoin from stirred formic acid-ethanol (2:1) solution at 0.03°C/min cooling rate a) Magn. x 130, b) Magn. x 32.

Figure 13: Nitrofurantoin crystals obtained from stirred formic acid-dioxane (2:1) solution at 0.03°C/min cooling rate. Magn. x 32.

The effect of cooling rate on the metastable zone widths was demonstrated in Table 3, from which it can be seen that when nitrofurantoin was crystallized in formic acid-ethanol (2:1) solution at a quiescent condition, the supersaturation values increased remarkedly with an increase in the cooling rate. Thus, values of 2.520 and 2.051 were obtained at 0.03°C/min and 1.0°C/min cooling rates respectively. The length to width values increased with the supersaturation and became more elongated. The crystal dimensions decreased considerably.

DISCUSSION

The use of solvents such as DMSO, DMF and DMA will result in crystals of regular shape and size but cannot serve as crystallization solvents since a complexation with the solute takes place and the poisonous solvent remains in the final product.

In a search for suitable solvents it was found that ethyl acetate, formic and acetic acids will not complex with the solute.

TABLE 3

Cooling rate °C/min	Tc(°C)	S	y/x	Crystals dimensions (μ)	Fig. No.
0.03	9-10	2.520	3	230/760	11a
0.1	8	2.745	5	100/800	11b
0.5	6	2.906	7	25/250	--
1.0	6	3.051	7	15/150	--

Effect of cooling rate on supersaturation values, length to width ratios and crystal habit and size of nitrofurantoin crystallized in a mixture of formic-ethanol (2:1) at a quiescent solution.

X-rays measurements, elemental analysis, infra-red spectra and differential thermal analysis proved that the crystal structure of the NFT did not change after the crystallization.

The results of this work demonstrate clearly that the crystal structure and habit of NFT can be governed by controlling the crystallization solvents and conditions in which the drug was precipitated. Thus, by choosing the appropriate cooling rate, flow regime and solvent mixtures it was found that cube-like crystals of significantly big size can be obtained.

Mixtures of formic acid with water, dioxane methanol and ethanol did not change the crystal structure but had a significant effect on the habit and the size of the NFT crystals. Regular shaped cubes crystals were obtained with an average size of 200-300 microns when mixture of 2:1 fromic acid-ethanol was used as crystallization solvent in stirred solutions cooled at 0.03°C/min.

The correlation between nucleation, crystal growth rates and supersaturation values has been shown in both inorganic and organic materials (15). $J=k_n \Delta C^n$, where J is the nucleation

rate and ΔC is the supersaturation value. Using an empirical equation it was also demonstrated that the length to width ratio of the crystals obtained is linearly related to the supersaturation values, $y/x=k_m \Delta C^n$ (16). Assuming both equations are valid in our system, it was reasonable to search for suitable solvent and crystallization conditions to gain low supersaturation values in order to decrease the ratio of length to width and obtain cubic or tabular crystals. On the other hand high supersaturations caused bigger crystals in size suitable for microencapsulation.

Nucleation can often be induced by external influences on the crystallization system. Agitation, mechanical shock, friction and extreme pressures within the solution were shown by early experiments to influence the supersolubility curve (15, 17, 18). In most studies it has been found generally that mechanical disturbance such as agitation can decrease supersaturation values and enhance nucleation and crystal growth (15). Thus, by shaking or stirring the crystallization system the supersaturation values for each solvent decrease and as a result the crystals obtained were smaller in size but less elongated than when quiescent system was used.

The effect of cooling rate was also examined and as expected, an increase in the cooling rate of the crystallization system caused an increase in the supersaturation values and more elongated, needle-like crystals were collected. Nyvlt (19) and Nielsen (20), using the classical nucleation relationship, demonstrated that there is a linear dependence between the cooling rate, log b, and the maximum allowable supersaturation, ΔC_{max}.

Those findings were proven again in the NFT solutions and thus in cooling rate of 1.0°C/min, the supersaturation values were remarkably larger than when the solution was cooled at 0.03°C/m (Table 3).

In conclusion, it can be seen that in order to obtain large cubical crystals one should examine possible solute-solvent in-

teractions, and the solubility power of the solvent. Then the crystallizer should be designed for low cooling rates, control of temperatures and appropriate agitation.

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