International Journal of Pharmaceutics, 5 (1980) 239–251
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EFFECT OF HABIT MODIFICATION ON DISSOLUTION RATE

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(Received December 21st, 1979)
(Revised version received and accepted March 4th, 1980)

SUMMARY

The effect of habit modification on the dissolution rate of $NiSO_4\alpha 6\ H_2O$ in 60% ethanol was studied using a rotating basket method. Bipyramidal crystals were grown in a fluidized-bed crystallizer and platy crystals were recrystallized from supersaturated solutions of nickel sulfate containing small amounts of gelatin. Acicular crystals were prepared by the topotactic dehydration of acicular crystals of $NiSO_4 \cdot 7\ H_2O$, grown from solution at room temperature. X-ray diffraction powder patterns for the 3 habits were identical and characteristic of $NiSO_4\alpha 6\ H_2O$. DSC thermograms of platy and acicular habits were similar but differed from the bipyramidal habit. Solubilities of all habits in the dissolution medium were identical.

The observed dissolution rate constant, K'_{obs}, for the bipyramidal crystals was greater than for the platy crystals at both low and high rotation rates but the difference was less pronounced at the lower rotation rate. At the high rotation speed, dissolution was under mixed surface–transport control. K'_{obs} for the acicular crystals was similar to the bipyramidal habit and greater than the platy habit. The difference in K'_{obs} must be due to different values of the overall surface energy of the crystals. Intrinsic dissolution rates for the 3 habits, determined by a rotating disc method, were similar confirming that differences in K'_{obs} were due to habit modification.

INTRODUCTION

Fuhrer (1978) believes that most of the unsolved problems concerning the dissolution properties of a drug which arise during the preparation and storage of solid dosage forms are due to crystallographic changes. These changes include polymorphic transitions, changes in the surface characteristics and habit modifications. Carstensen (1973) has

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stated that 'since dissolution rates differ for different habits this aspect is of great pharmaceutical significance' and 'crystals of different habits may exhibit biological differences'. However, there is little experimental evidence to support these statements concerning the effect of crystal habit on dissolution.

Habit modifications normally arise when the environment of a growing crystal affects its external shape without changing its internal structure. These modifications include variations in size, the relative development of certain faces and the kind and number of faces present.

Using a single crystal dissolution method, Burt and Mitchell (1979) demonstrated dissolution anisotropy in nickel sulfate α-hexahydrate crystals and predicted that where different faces of the same crystal dissolve at different rates, then modification of crystal habit should affect the bulk dissolution rate. In general, differences in dissolution rate, expressed as an observed rate constant (see Eqn. 1), both for the dissolution of single faces, K_{obs}, and for the bulk dissolution of different habits, K'_{obs}, will depend on: (a) the nature of the rate-controlling step in the dissolution reaction: and (b) whether the crystals are isotropic or anisotropic.

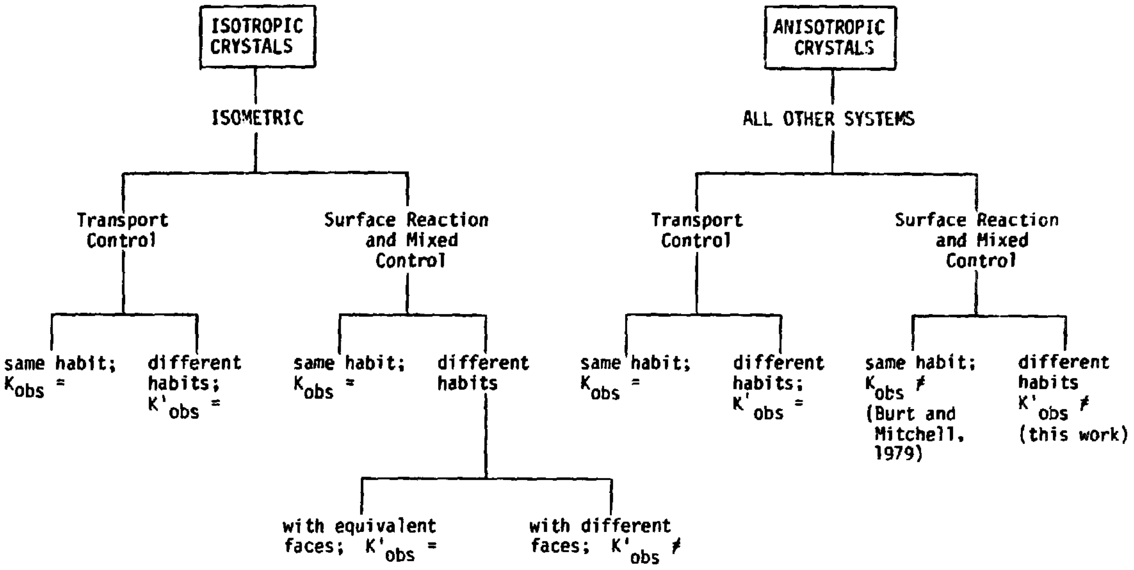
Depending on such variables as the degree of agitation, temperature or the dissolution medium, the dissolution reaction may be transport controlled, surface controlled or mixed transport–surface controlled (Burt and Mitchell, 1979). Where dissolution is purely transport controlled, then, for both isotropic and anisotropic crystals, K_{obs} should have the same value for each face of a given crystal, and K'_{obs} for bulk dissolution should be independent of crystal habit. Where the reaction is under surface control or mixed transport–surface control, it is expected that, in most cases, K'_{obs} will depend on crystal habit. However, the relationship between habit and K'_{obs} will depend on whether the crystals are isotropic or anisotropic. For isotropic crystals, K_{obs} will be the same for each face and where different habits have equivalent crystallographic faces then K'_{obs} should be independent of crystal habit. However, where different habits have different crystallographic faces then K'_{obs} for the bulk dissolution of isotropic crystals will be different. For anisotropic crystals, K_{obs} will differ for each crystallographic face and different habits will exhibit different values of K'_{obs}.

The above predictions are summarized in Scheme 1 but there is little confirmatory evidence in the literature.

Sodium chloride, an isotropic crystal belonging to the isometric system, normally forms cubic crystals but when grown in a solution containing 10% urea forms octahedral crystals. The atomic arrangement on all faces of each habit is identical but the cubic faces consist of alternating Na^+ and Cl^- ions whereas the octahedral faces consist of all ions of like charge (Bunn, 1961). Van Hook (1961) reviewed early work on the two habits of NaCl. Although somewhat contradictory, the results show that the octahedral faces dissolve faster than the cubic faces and that this relationship is reversed in the presence of urea.

Single crystal studies of anisotropic crystals of $MgSO_4 \cdot 6\,H_2O$ have shown that dissolution rates along two crystallographic axes are equal when dissolution is transport-controlled (Treivus, 1964). Similarly Karshin and Grigoryan (1970) found no difference in the dissolution rate of two crystallographic planes of gypsum single crystals when the reaction was under transport control but under surface control there was a 3-fold differ-

Scheme 1. Predicted behavior of crystalline Faces and Habits on Dissolution Rate.



K_{obs} = observed rate constant for the dissolution of different faces on a given crystal

K'_{obs} = observed rate constant for bulk dissolution

ence in dissolution rates. Burt and Mitchell (1979) found that two different faces of $NiSO_4\alpha6\ H_2O$ dissolved at different rates under both mixed and surface controlled conditions.

Although there have been few systematic studies of the effect of habit modification on bulk dissolution, the limited data available from single crystal studies suggests that the effects of habit modification will become apparent only when dissolution is under surface or mixed control. Chakrabarti et al. (1977) studied the effect of cubic and needle-shaped habits of phenytoin on dissolution rate. Different size fractions of the two habits were obtained by sieving and the dissolution rates of the various fractions compared. Small differences were found for the larger size range material. However, size classification by sieving does not permit an accurate comparison of the surface area of the two habits and dissolution rate. In addition, the nature of the rate-controlling step was not considered.

We believe that there are two main reasons for the dearth of information on any relationship between crystal habit and dissolution, and especially so, in the pharmaceutical literature: (a) difficulties in the choice of a suitable crystalline material; and (b) difficulties in methodology.

It is often very difficult to produce well-formed crystals of organic compounds. Large, complex molecules have difficulty in forming crystals, especially when they have a special arrangement of points of attraction (Bunn, 1964). The crystals when formed tend to be small, fragile and of widely differing size and shape.

Apart from single crystal methods, methods for measuring the dissolution rate fall into two categories, namely constant surface methods and multiparticulate bulk dissolution methods. In constant surface methods the solid is usually ground to form small particles which are then compressed into a disc. Size reduction and compression probably obliterate any effect due to the original habit. In the bulk dissolution method evaluation for any effect due to different habits is difficult or impossible because of differences in size and shape.

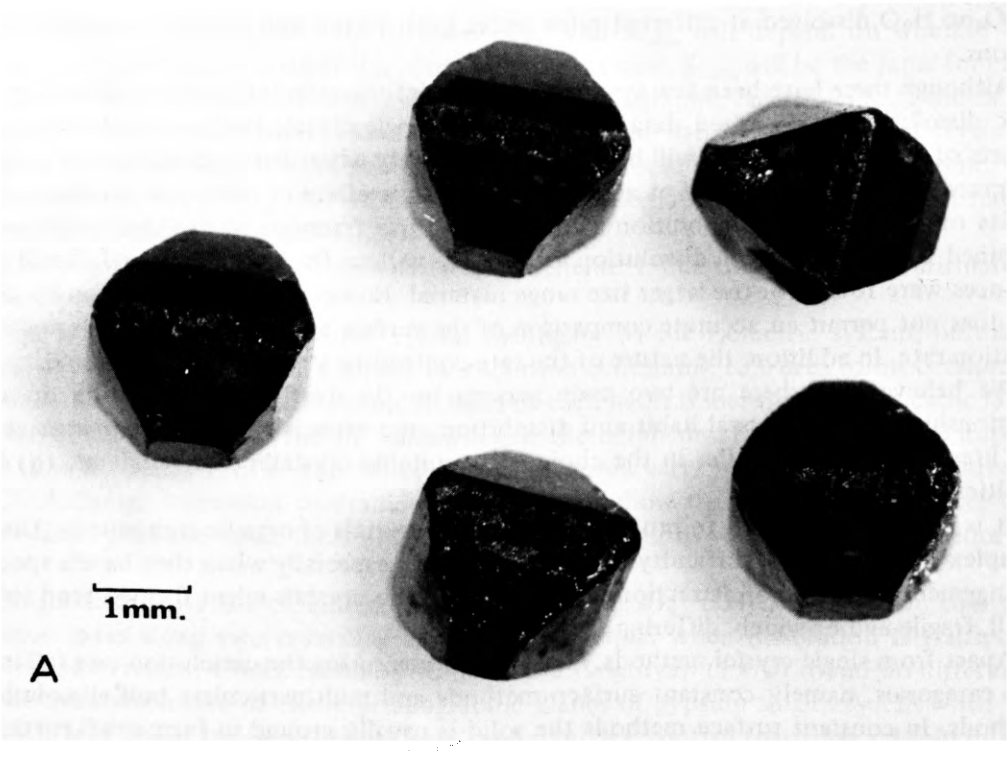
The method used in this work permits determination of the dissolution rates of 3 habits of $NiSO_4\alpha 6\ H_2O$ of measurable surface area with no alteration of surface characteristics. $NiSO_4\alpha 6\ H_2O$ was chosen as a model crystalline material since the 3 habits could be grown as large, well-formed crystals and the dissolution anisotropy of one of the habits has been reported (Burt and Mitchell, 1979).

MATERIALS AND METHODS

Crystal habits

Bipyramidal habit. The crystals were grown in a fluidized-bed crystallizer under carefully controlled conditions of temperature and supersaturation by Phillips and Epstein (1974). Crystals selected for the dissolution studies were between 2.1–2.4 mm in width and 2.4–2.8 mm in length.

Platy habit. A supersaturated solution of $NiSO_4 \cdot 6\ H_2O$ (certified A.C.S., Fisher Scientific) in distilled water was prepared at 48°C and a small amount (approximately $0.2\ mg \cdot ml^{-1}$) of gelatin B.P. (British Drug Houses) in distilled water was added. The very high concentration of soluble electrolyte (nickel sulfate) resulted in the 'salting out' of



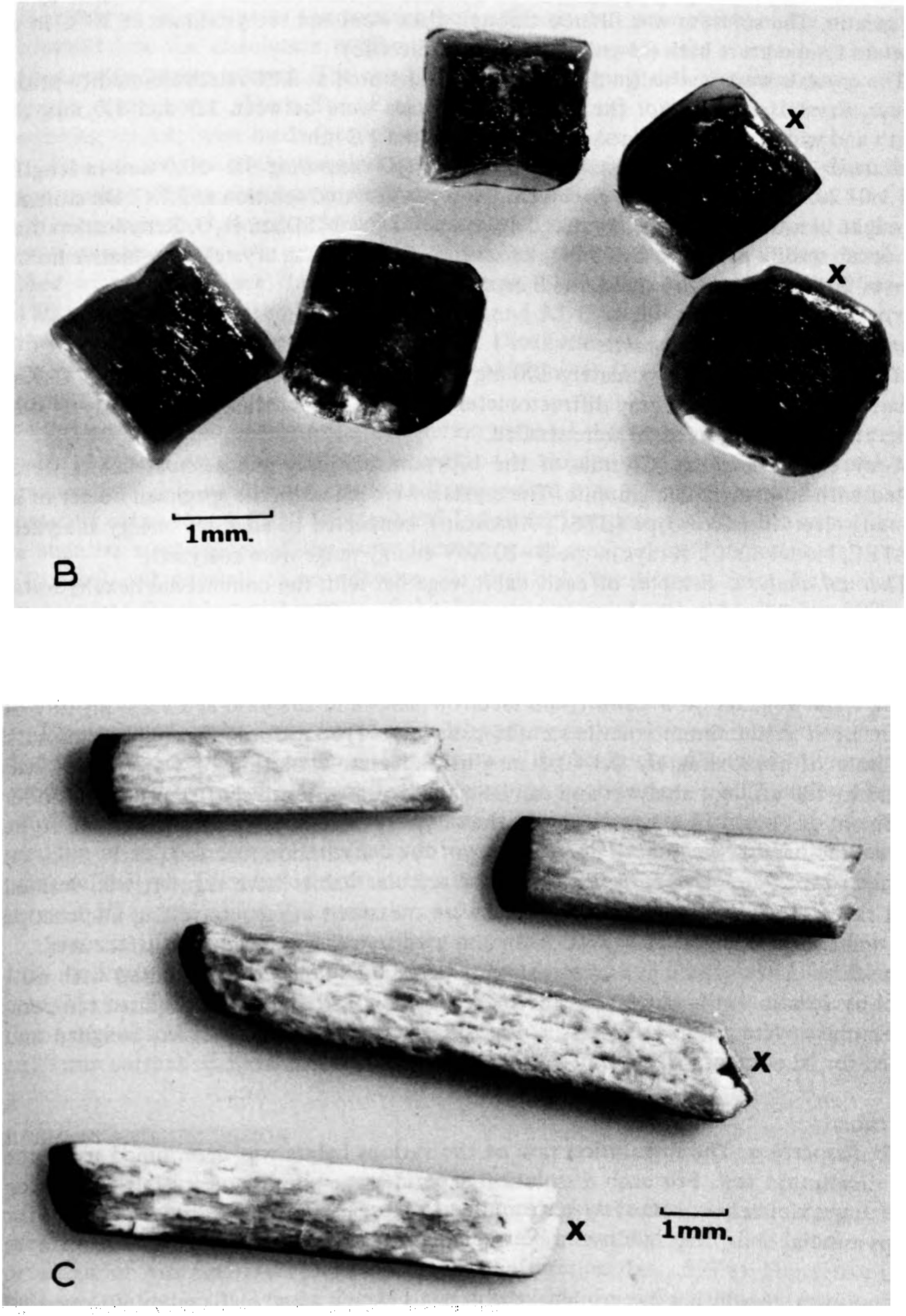


Fig. 1. Habit modifications of $NiSO_4\alpha 6\ H_2O$. A: bipyramidal habit. B: platy habit. C: acicular habit. X, after dissolution.

the gelatin. The solution was filtered through glass wool and recrystallized at 38°C in a constant temperature bath (Magni Whirl, Blue M Electric).

The crystals were washed in distilled water and stored at 84% relative humidity prior to use. Crystals selected for the dissolution studies were between 1.7 and 3.0 mm in length and width with a thickness of between 0.6 and 1.2 mm.

Acicular habit. Acicular crystals of $NiSO_4 \cdot 7\ H_2O$ measuring 6.0–10.0 mm in length and 1.0–2.0 mm in width were grown from a supersaturated solution at 22°C. On storage overnight in a desiccator, the crystals dehydrated to give $NiSO_4\alpha 6\ H_2O$. Rehydration did not occur readily as shown by storage of several of the acicular crystals at a relative humidity of 90% (25°C). Fig. 1 shows the 3 crystalline habits.

Characterization of crystal habits

X-ray diffraction. Approximately 300 mg of the ground samples was exposed to $CuK\alpha$ radiation in a wide angle X-ray diffractometer (Philips). The location and intensity of the peaks at different values of 2θ were studied.

X-ray energy analysis. Crystals of the bipyramidal, platy and acicular habits were coated with spectrographic graphite. The crystals were placed in the specimen holder of a scanning electron microscope (ETEC, Autoscan), connected to an X-ray energy analyzer (ORTEC, Model 6200). X-rays in the 0–20 KeV energy range were analyzed.

Thermal analysis. Samples of each habit, together with the commercial hexahydrate and the crystallized heptahydrate were analyzed using a differential scanning calorimeter (Perkin Elmer DSC-1B) with a thermal conductivity effluent analyzer. Samples of 1–5 mg were weighed on a Cahn Gram electrobalance and analyzed at a scanning rate of 10°/min both in aluminum volatile sample pans (closed) and in volatile sample pans with a pin hole of approximately 0.1–0.2 mm in diameter. Evolution of water vapor was detected by the effluent analyzer and can be estimated quantitatively from the area under the effluent gas peak. However, weighing the sample pan after each peak was found to be more satisfactory for the quantitative analysis of the dehydration reaction.

Surface area. The bipyramidal, platy and acicular habits have regular, well-defined crystal faces. The dimensions of each face were measured using a travelling microscope (Swift and Son) reading to $\pm 5.0 \times 10^{-4}$ cm and used to calculate the total surface area.

Solubility. After grinding, excess amounts of each habit were equilibrated with 60% ethanol by rotation in a water bath thermostatically controlled at the required temperature. Samples were filtered using a syringe fitted with a Millipore filter, weighed and analyzed for Ni content using atomic absorption spectrophotometry.

Dissolution

Bulk dissolution. The dissolution rate of the various habits was determined using the U.S.P. dissolution test. For each dissolution experiment, a number of crystals were taken to give approximately constant weights and surface areas. Between 9 and 15 crystals for the bipyramidal and platy habits and between 3 and 7 crystals for the acicular habit were used.

Before each dissolution experiment, the crystals were washed in 10 ml of 60% ethanol for 1 min to remove surface particulate matter and then dried and weighed. 900 ml of 60% ethanol was placed in a covered, 1000 ml glass vessel and equilibrated at the desired temperature in a constant temperature bath. The crystals were placed in the wire basket, lowered into the dissolution medium and rotated by means of a constant speed motor (Fisher Stedispeed stirrer). The rotating velocity (in rpm) was measured using an electronic stroboscope (Flash Tac, Electronic Applications) and constant checks on the rotating velocity were made throughout the dissolution trial.

One ml samples of the dissolution medium were removed from a point 4–5 cm below the surface of the dissolution medium at suitable time intervals, made up to 5 ml with distilled water and stored in airtight, borosilicate glass vials prior to analysis. At the end of each experiment, the crystals were reweighed and the weight loss during dissolution used as a mass balance check. Dissolution was followed at rotation speeds of between 150 and 750 rpm at temperatures of 9.9, 22 and 30°C for 50–90 min during which time there was negligible change in surface area. Dissolution occurred under sink conditions since at no time did the concentration of $NiSO_4\alpha 6\ H_2O$ exceed 1.8% of its saturation solubility.

Intrinsic dissolution. Intrinsic dissolution rates of the bipyramidal and platy crystals were measured using the rotating disc method of Nogami et al. (1966). The crystals were ground in a glass mortar and pestle and compressed into 1.3 cm diameter discs at 5 tons pressure using a press (C 30 Research and Industrial Instruments). The disc was affixed to a stainless steel holder of the same diameter using non-perfumed, colorless nail enamel (Rimmel nail enamel) as an adhesive. So that only the bottom face of the disc was exposed to the solvent, the edges of the disc were covered with the adhesive. 500 ml of 60% ethanol was placed in a 600 ml jacketed glass beaker connected to a constant temperature circulator (Haake FE) and fitted with a cover to minimize solvent evaporation.

The jacketed beaker was placed on a laboratory jack which was raised to immerse the disc to a fixed depth (2 cm from the bottom of the beaker) and rotated by means of the constant speed motor checked with the electronic stroboscope. 1 ml samples of the dissolution medium were removed from a point 6–7 cm below the surface of the dissolution medium at suitable time intervals, made up to 5 ml in distilled water and stored as above prior to analysis. Dissolution was carried out at a rotation speed of 300 rpm at temperatures of 30 and 45°C for 120 min.

Analysis of dissolution medium. The samples were analyzed for their Ni content using a Ni hollow cathode lamp (Varian Techtron) and an atomic absorption spectrophotometer (Varian Techtron Model 5). The samples were vaporized in an air–acetylene mixture flame and absorbances measured at a wavelength of 232.2 nm with a slit width of 50 μm and lamp current of 5 mA.

RESULTS AND DISCUSSION

X-ray diffraction powder patterns for the bipyramidal, platy and acicular habits were identical with each other and with ACS nickel sulfate hexahydrate; all d-values were characteristic of $NiSO_4\alpha 6\ H_2O$ (Selected Powder Diffraction data, 1974). Successive powder patterns of the heptahydrate showed rapid dehydration with d-values corresponding to the initial formation of the $\beta 6\ H_2O$ polymorphic form (Selected Powder Diffraction data, 1974) and transition to $\alpha 6\ H_2O$ within 1 h. The acicular habit used in this work therefore forms spontaneously at room temperature from the topotactic reaction:

$$\underset{\text{translucent, emerald green}}{NiSO_4 \cdot 7\ H_2O} \rightarrow \beta 6\ H_2O \rightarrow \underset{\text{opaque, greenish-white}}{\alpha 6\ H_2O}$$

In a topotactic dehydration of this type, there is no change in the external form of the crystal (Glasser et al., 1962). Comparison of the X-ray peak heights and widths of the acicular habit with those of the other two habits revealed no differences in crystallinity.

X-ray energy spectra were obtained for the 3 crystal habits to check for purity of the crystals. In addition to the energy peaks characteristic for nickel sulfate, the bipyramidal crystals contained a very small amount of potassium and a trace amount of bromine. The platy crystals contained only a trace of potassium and the acicular crystals showed no additional peaks.

Thermal analysis results are given in Table 1. Each temperature is the mean value of the peak maximum obtained from several scans. Since the desolvation of solvates is highly dependent on the experimental conditions, the sequence of peaks is of more significance than the actual temperature. The total water loss obtained on heating each sample to about 500°C confirmed that each habit was the hexahydrate. Columns 1 and 2 show peaks without an accompanying water loss and are interpreted to be internal transitions. The

TABLE 1

THERMAL ANALYSIS AND X-RAY DIFFRACTION

A, closed pan; B, pan with pinhole.

Habit	Temperature of transition or dehydration (mol H_2O vaporized/mol $NiSO_4 \cdot 6\ H_2O$) [a]						X-ray
	1	2	3	4	5	6	
A.C.S. A	90	–	119				
B	96 [b]	103	113(2)	–	173	>400(6)	$\alpha 6\ H_2O$
Bipyramidal A	97	–	118				
B	98 [b]	103	118(2)	–	174(5)	>400(6)	$\alpha 6\ H_2O$
Platy A	–	106	118 [c]	128			
B	96	108	118 [c]	128(2)	159(5)	>400(6)	$\alpha 6\ H_2O$
Acicular A	–	107	–	126			
B	96	110	120 [c]	128(2)	162(5)	>400(6)	$\alpha 6\ H_2O$
Heptahydrate B	97	107	122	131	160	>400	$7\ H_2O \rightarrow \beta 6\ H_2O \downarrow \alpha 6\ H_2O$

[a] Values in parentheses are to the nearest stoichiometric ratio.

[b] Very small peak.

[c] Shoulder.

peaks in columns 3 and 4 include dehydration and simultaneous vaporization since the peaks occurred both using closed pans, which prevent water loss, and using pans with a pin-hole. Peaks 5 and 6 are also the result of simultaneous dehydration and vaporization but it was not possible to demonstrate the dehydration in a closed pan since the pressure exerted by vaporizing water distorted or even exploded the pan.

The DSC scan of the bipyramidal habit agrees with that of the original ACS material. Thermograms of the platy and acicular crystals are almost identical with each other but differ in several respects from the bipyramidal habit. Thus, in closed pans, transition peak 1 is characteristic of the bipyramidal habit while peak 2 is characteristic of the platy and acicular habits.

The endothermic reactions for the bipyramidal habit between 113 and 119°C (peak 3) include:

$$NiSO_4 \cdot 6\,H_2O(s) \rightarrow NiSO_4 \cdot 4\,H_2O(s) + 2\,H_2O(l)$$

$$2\,H_2O(l) \rightarrow 2\,H_2O(g)$$

whereas the corresponding reactions for the platy and acicular crystals occur mainly between 126 and 128°C with only a slight shoulder indicating some dehydration and vaporization at about 118°C.

Dehydration reactions can be affected by changes in the ratio between the surface and volume of the crystals i.e. modification of crystal habit (Boldyrev, 1975a) and this may provide an explanation for the dissimilar DSC scans. Further details of the thermal analysis of the three habits and other crystal modifications will be given elsewhere.

The DSC scan for the heptahydrate corresponds to that of the platy and acicular habits. Both DSC and X-ray require the sample to be ground before analysis. A rapid weight loss after grinding and the subsequent DSC scan and X-ray diffraction pattern indicate that the heptahydrate dehydrates very rapidly and that the thermogram is actually that of $NiSO_4\alpha 6\,H_2O$.

The overall bulk dissolution rate of the 3 habits may be described by:

$$\text{rate} = S \cdot K'_{obs}(Cs - C) \qquad (1)$$

where S is the total surface area of the crystals, Cs is the equilibrium solubility in the diffusion layer at the solid–liquid interface, C is the concentration in the bulk solution at time t and K'_{obs} is an observed rate constant. When Cs >> C and S is constant, the overall dissolution rate is proportional to K'_{obs}. Fig. 2 shows typical plots of concentration change with time for the bipyramidal crystals at different rotation velocities. The slopes ($mg \cdot cm^{-3} \cdot s^{-1}$) were determined using linear regression analysis * and were used to calculate K'_{obs} ($cm \cdot s^{-1}$) from the relationship:

$$K'_{obs} = \frac{\text{slope}}{Cs} \cdot \frac{V}{S} \qquad (2)$$

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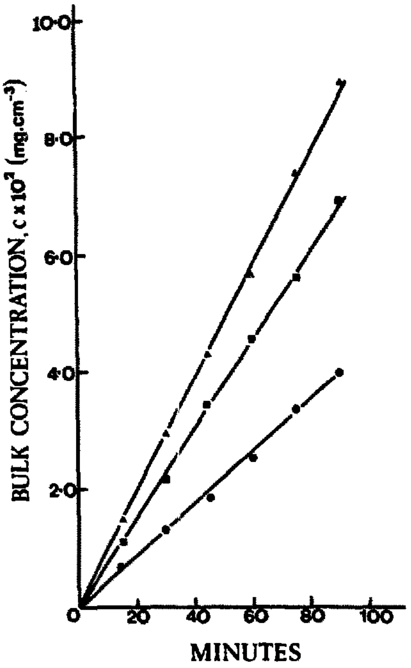
* Using a Wang 600 programmable calculator.



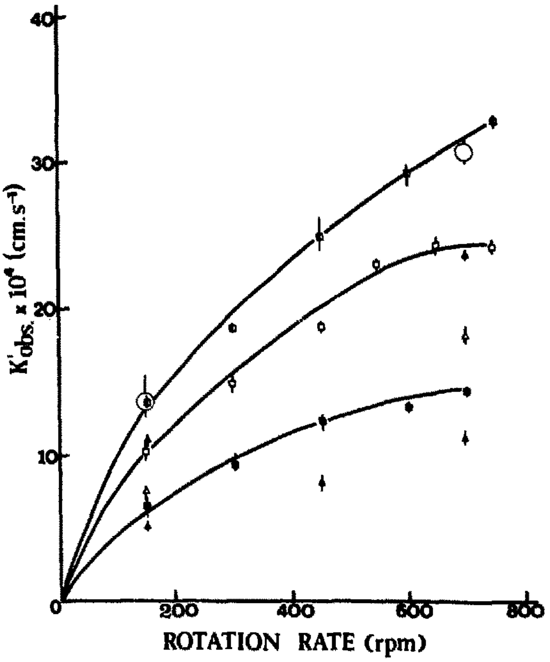


Fig. 2. Plot of the change in bulk concentration as a function of time for the bipyramidal crystals at 22°C. Rotation rates: 150 rpm, ●; 450 rpm, ■; 650 rpm, ▲.

Fig. 3. Plot of K'_{obs} as a function of the rotation rate for the 3 habits. Temperatures: 9.9°C, bipyramidal ■, platy ▲; 22°C, bipyramidal □, platy △; 30°, bipyramidal ◨, platy ◭, acicular ○. Each point represents the mean of 3 determinations. Bars indicate the range of K'_{obs}.

where V is the volume of dissolution medium.

Values of Cs at different temperatures and S are given in Table 2. From Van't Hoff plots of the solubility data the heat of solution, ΔHs, was found to be +5.84 kcal · mol^{-1} (+24.4 kJ · mol^{-1}). Due to the very narrow size range of the bipyramidal crystals, the total surface area was the same for each determination. However, the platy and acicular habits possessed greater size differences and the total surface area for different dissolution experiments varied between the ranges given in Table 2.

Fig. 3 shows a plot of K'_{obs} as a function of rotation rate for the bipyramidal habit.

TABLE 2

SOLUBILITIES AND SURFACE AREAS

Habit	C_S (mg · cm^{-3})			S (cm^2)
	9.9°C	22°C	30°C	
Bipyramidal	1.64	2.56	3.26	2.4 (15) [a]
Platy	1.64	2.56	3.22	2.2–2.8 (9–13) [a]
Acicular	1.64	2.56	3.26	1.6–2.5 (3–7) [a]

[a] Number of crystals for each experiment.

K'_{obs} for the platy and acicular habits are given at 150 rpm and 700 rpm. Reproducibility for the bipyramidal and platy crystals was good as indicated by the range of K'_{obs}. The acicular crystals were less well formed than the other habits making the surface area determination less reliable and the reproducibility was not as good at the lower rotation rate.

The observed rate constants for the bipyramidal and platy crystal habits are significantly different. The difference increases with rotation rate as expected for a mixed transport–surface reaction controlled dissolution reaction (Burt and Mitchell, 1979).

It is well documented that the different faces of an anisotropic crystal have different values of the surface free energy. Different habits will vary in the relative proportion of the various faces. Therefore, it seems likely that the accompanying change in overall surface energy is responsible for the differences in K'_{obs}. It is postulated that the surface energy of the platy crystals was lower than that of the bipyramidal crystals, although determination of the surface energies would be necessary to confirm this. Fig. 3 shows that K'_{obs} for the acicular habit was of equal magnitude to the bipyramidal habit but greater than for the platy habit. Since the acicular habit was formed so readily by dehydration of $NiSO_4 \cdot 7\ H_2O$, it might be expected that rehydration would occur during dissolution. However, there was no change in the slope of the concentration vs time curves for either bulk or intrinsic dissolution (see below) as would be expected if rehydration took place (Nogami et al., 1969). In addition, the solubility of the acicular crystals in 60% ethanol was identical to that of the other two habits (Table 2) indicating that, over a period of 60 h, there was no reversion to $NiSO_4 \cdot 7\ H_2O$. Although by definition, the acicular crystals are a true habit modification, their method of preparation differed markedly from the conventional technique of altering the environment of the growing crystal, used in the preparation of the other two habits. The mechanism of the topotactic reaction might be expected to affect the characteristics of the crystal surface (Boldyrev, 1975b). It is of interest therefore that the bipyramidal and acicular habits have similar values for K'_{obs} but differ in their thermograms, while the thermograms of the acicular and platy habits are similar but not their values of K'_{obs}.

X-ray powder diffraction and DSC are amongst the techniques most widely used to characterize solids prior to dissolution studies. Since all 3 habits have identical X-ray powder diffraction patterns it is apparent that neither powder diffraction patterns nor DSC thermograms can be correlated in a simple way with bulk dissolution rates.

It was necessary to show that the observed differences in K'_{obs} for the bipyramidal, platy and acicular crystals were due to the effect of habit modification and not to differences in intrinsic dissolution rates, resulting, for example, from crystal poisoning by impurities. The results in Table 3 show that there is no significant difference in the intrinsic dissolution rates for each habit and that the trace impurities detected by X-ray energy analysis did not affect the intrinsic dissolution rates. Furthermore the lower K'_{obs} value for the platy crystals was unlikely to be due to crystal poisoning since X-ray energy analysis showed that this habit contained fewer trace impurities than the bipyramidal crystals. An experiment was also carried out in which 2 $\mu g \cdot ml^{-1}$ gelatin was added to the dissolution medium and the dissolution rate of the bipyramidal crystals determined. K'_{obs} was the same in the presence or absence of the added gelatin, thus showing that trace amounts of gelatin (such as might be present in the platy crystals) added to the dissolution me-

TABLE 3

INTRINSIC DISSOLUTION RATES

Temp. (°C)	Habit	Intrinsic dissolution rate × 10^5 (mg · cm^{-3} s^{-1})
30	Bipyramidal	1.06
	Platy	1.08
	Acicular	1.05
45	Bipyramidal	2.77
	Platy	2.58
	Acicular	2.62

dium do not result in inhibition of dissolution. These experiments support the conclusion that the marked differences between K'_{obs} for the bipyramidal and acicular habits and K'_{obs} for the platy habit were due to habit modification and not to differences in intrinsic dissolution rate.

Activation energies for dissolution of the bipyramidal and platy crystals at rotation speeds of 150 and 700 rpm obtained from Arrhenius plots are given in Table 4. Values of K'_{obs} for the bipyramidal crystals at 700 rpm were determined by interpolation. At the lower rotation speed the activation energies for the two habits are similar and are within the range usually accepted for transport-controlled processes i.e. 2.8–7.0 kcal · mol^{-1} (11.7–29.3 kJ · mol^{-1}). At the rotation speed of 700 rpm the activation energies, although showing a small increase, are not significantly different from the values at 150 rpm.

CONCLUSIONS

(1) The three crystal habits of $NiSO_4\alpha 6\ H_2O$ show identical X-ray diffraction patterns and therefore have the same crystal structure.

(2) The DSC thermogram for the bipyramidal habit differs significantly from the platy and acicular habits.

TABLE 4

ACTIVATION ENERGIES OF DISSOLUTION FOR THE BIPYRAMIDAL AND PLATY HABITS

Rotation rate (rpm)	E_a (kcal · mol^{-1}) [a]	
	Bipyramidal habit	Platy habit
150	6.2 (5.2–6.7)	6.1 (6.0–6.3)
700	6.4	6.6 (6.5–6.8)

[a] Values in parentheses are the range of E_a.

(3) In this simple anisotropic, inorganic model system, modification of crystal habit has an effect on bulk dissolution rate under conditions where the surface reaction contributes to the overall dissolution process.

(4) The difference in K'_{obs} for the bipyramidal and platy habits increased with rotation rate as expected for a mixed transport–surface reaction controlled dissolution reaction.

(5) K'_{obs} for the acicular habit was similar to the bipyramidal habit although its preparation by means of dehydration of $NiSO_4 \cdot 7\ H_2O$ might have been expected to affect the properties of the crystal surface and therefore the dissolution reaction.

(6) Similarities in X-ray diffraction powder patterns and DSC thermograms for the different habit modifications do not indicate that the bulk dissolution of these habits will necessarily be the same. On the other hand, differences in DSC thermograms do not necessarily indicate that the bulk dissolution of the various habits will be different.

(7) Intrinsic dissolution rates for the 3 habits were similar confirming that the differences in K'_{obs} were due to habit modification.

The extension of this study into pharmaceutical systems is of considerable importance.

ACKNOWLEDGEMENTS

The authors thank Dr. R. Phillips and Dr. N. Epstein, Department of Chemical Engineering, University of British Columbia, for the fluidized-bed-grown nickel sulfate crystals, Mrs. R. Butters and Mr. A. Lacis (Department of Metallurgy) for X-ray diffraction and X-ray energy analysis and Mr. M. Friesen for technical help.

This investigation was supported by a research grant from the Medical Research Council of Canada.

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