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## Research Papers

# Modification of adipic acid crystals: influence of growth in the presence of fatty acid additives on crystal properties

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### Summary

When adipic acid is crystallized from water in the presence of a low concentration of an *n*-alkanoic acid, the additive is incorporated into the crystals and the crystal habit is changed. The following properties of harvested crystals grown in the presence of various concentrations of hexanoic ( $C_6$ ), octanoic ( $C_8$ ) or undecanoic acid ( $C_{11}$ ) were studied: dissolution rate (DR) and enthalpy of solution ( $\Delta H^s$ ) in water, enthalpy of fusion ( $\Delta H^f$ ), melting point ( $T_m$ ), density (d), specific surface area (A) and scanning electron microscopy (SEM). Increasing concentrations of  $C_6$  ( $0-5380 \mu\text{mol} \cdot \text{dm}^{-3}$ ) or  $C_{11}$  ( $0-67.1 \mu\text{mol} \cdot \text{dm}^{-3}$ ) caused increasing uptake of additive and pitting of the crystal surface under SEM, while DR and A of a defined sieve fraction increased and then decreased, whereas  $\Delta H^s$  and  $\Delta H^f$  decreased to minima and then increased. In general, the changes in  $T_m$  and entropy of fusion ( $\Delta S^f$ ) paralleled the changes in  $\Delta H^f$ .  $C_6$  caused negligible changes in d, whereas  $C_{11}$  significantly reduced d suggesting lattice expansion ( $0-0.8\%$ ). Various sieve fractions covering the range  $< 75 \mu\text{m}$  to  $850 \mu\text{m}$  showed negligible differences in  $\Delta H^f$ ,  $\Delta H^s$ ,  $T_m$  and d.  $C_8$  ( $0-139 \mu\text{mol} \cdot \text{dm}^{-3}$ ) elicited behaviour similar to that produced by  $C_6$  and  $C_{11}$ , except that it reduced DR and increased d ( $< 0.8\%$ ). X-Ray powder diffraction of all crystalline samples failed to detect any changes in lattice dimensions ( $< 0.5\%$ ). Overall, DR did not exactly parallel A or SEM on the one hand nor  $\Delta H^f$ ,  $\Delta H^s$ ,  $T_m$  or d on the other hand, implying that DR depends on both the surface and bulk properties of the modified crystals. The results suggest that growth of drug crystals in the presence of low concentrations of non-toxic additives can be used to control dissolution rate and crystal energy.

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## Introduction

Growth of adipic acid crystals from water containing trace amounts of *n*-alkanoic acids or *n*-alkanols produces modifications to the crystal habit (Fairbrother and Grant, 1978) and arises through the uptake of the additive by the growing crystals (Fairbrother and Grant, 1979). This co-crystallization phenomenon implies that the additives are present in solid solution at very low concentrations. The question arises as to what extent the presence of the additives is changing other pharmaceutically related properties, such as crystal structure (reviewed by Halebian, 1975), crystal energy (reviewed by Hüttenrauch, 1978) and dissolution rate. The purpose of the present work is to study these possibilities and explore any links between them. The introduction of a second component into a crystal may be expected to introduce imperfections into the more or less imperfect crystalline structure which, as well as accounting for the observed effects, may provide a useful means of controlling the pharmaceutical properties of solid drugs.

Lattice imperfections have themselves been shown to play significant roles in pharmaceutical technology (Hüttenrauch, 1978). Actual crystals contain numerous imperfections, i.e. defects and dislocations, in the ordered regularly repeating 3-dimensional lattice associated with the perfect crystalline state. Additional disorder is created by the crystal surface. The presence of ions or molecules of an additive or impurity introduces further imperfections, often known as impurity defects, and is expected to increase the entropy of the crystalline state and to create regions of misfit with unbalanced intermolecular forces, thereby also increasing the internal energy and enthalpy of the crystals. For certain concentrations of imperfections or incorporated additives, the effect on the  $\Delta H$  term may well be greater than that on the  $T\Delta S$  term, in which case the free energy of the crystals, in the bulk or at the surface, will be increased. Certain crystal imperfections therefore increase the dissolution rate, e.g. of potassium perchlorate (Burt and Mitchell, 1981) and chemical reactivity, such as the rate of oxidation, hydrolysis or decomposition, of the crystals (Boldyrev et al., 1979; Byrn, 1982), and their hygroscopicity, wettability and mechanical compressibility (Hüttenrauch, 1978). The concentration of lattice defects can also be increased by drying, e.g. lactose monohydrate, by mechanical stress, e.g. potassium perchlorate (Friesen et al., 1981), or by milling, e.g. digoxin (Florence et al., 1974) and lactose (Hüttenrauch, 1978), thus accounting for possible batch-to-batch variations in pharmaceutical raw materials. The presence of minute traces of impurities in the crystals could well have similar consequences which are worthy of exploration.

The model substance chosen for our present and previous work is adipic acid, since this substance is not subject to polymorphism or solvate (hydrate) formation. This has been confirmed by X-ray powder diffraction in the present work and is important because polymorphism or solvate formation is normally the first interpretation given for differences in physical and chemical properties of any solid compound. Adipic acid is also a neglected pharmaceutical excipient that has been used as a tablet lubricant (Hoss, 1970, 1971a), as an acidulant in effervescent tablets (Hoss, 1971b; Baker 1971; Andersen, 1972) and as a constituent of tablet coating

films (Ikegami et al., 1973; Fulger, 1973; Korshunova et al., 1978). Adipic acid is comparable to citric, malic, succinic and tartaric acids as a safe food additive (Horn et al., 1957) and is used as a constituent of table salt of low sodium content.

## Materials and Methods

### *Reagents and materials*

Adipic acid was a certified grade supplied by Fisher Scientific (Don Mills, Ontario). The sample was the purest available and gave the same behaviour in differential thermal analysis, hot stage microscopy and crystallization experiments (Fairbrother and Grant, 1978, 1979) as samples supplied by B.D.H. Chemicals, Poole, Dorset, U.K. and by I.C.I. Nylon Works, Wilton, U.K.

Hexanoic acid (BDH Chemicals, Toronto, Ont.) was purified by distillation in an all-glass apparatus, collecting the middle fraction boiling at 205°C. Octanoic (BDH Chemicals) and undecanoic acid (Sigma Chemicals, St. Louis, MO) were highly pure analytical grades and were used as received. Water was distilled in an all-glass apparatus.

### *Batch crystallization from water*

Adipic acid (18 g) was dissolved in 400 cm<sup>3</sup> of distilled water at 45°C and the additive was added to form a clear solution. The solution was transferred to a 500 cm<sup>3</sup> three-necked, round-bottomed flask immersed in a thermostatic water bath at 34.0 ± 0.1°C. The contents of the flask were stirred at 238 rpm by means of a glass or teflon paddle. After 1 h, unless otherwise stated, crystallization was almost complete. The crystals were then rapidly filtered off, spread on a glass Petri dish, air-dried overnight and further dried over phosphorus pentoxide in a vacuum desiccator for 3 days before use.

### *Incorporation of additives by growing crystals*

Uptake of each additive was determined by measuring the loss of [<sup>14</sup>C]-labelled additive from the aqueous solution at the same time as the loss of adipic acid, monitored by titration with alkali, during crystallization. This method was found to be more accurate and reliable than the alternative of monitoring the incorporation of the label into the crystals themselves (Narang et al., 1978), since it avoids the consequences of surface contamination by the mother liquor. For our purposes *n*-[1-<sup>14</sup>C]hexanoic acid, *n*-[1-<sup>14</sup>C]octanoic acid, sodium salt (Amersham) and *n*-[1-<sup>14</sup>C]undecanoic acid (Faculty of Medicine, University of Toronto) were employed.

Samples of the mother liquor were removed by a pipette fitted with a filter and 1 cm<sup>3</sup> aliquots were transferred to 10 cm<sup>3</sup> of the following scintillation cocktail: toluene (scintillation grade) 2 dm<sup>3</sup>, isoctylphenoxypolyethoxyethanol (Triton X-100 scintillation grade) 1 dm<sup>3</sup>, 2,5-diphenyloxazole (PPO) 15 g and 1,4-bis 2-(4-methyl-5-phenyloxazolyl)benzene 300 mg. Using a Beckman LS 7500 microprocessor-controlled liquid scintillation counter, the counting rate, from the mean of duplicate 10 min counts, was corrected for quenching by Compton edge and for the blank and expressed as the disintegration rate.

Plots of concentration of additive in solution against concentration of dissolved adipic acid were linear and readily enabled the mole fraction of each additive in the crystals to be evaluated at each additive concentration as shown in Table 1.

#### *Optical microscopy*

About 1 mg of sample was placed on a microscope slide and examined under a Hughes-Owens Microscope fitted with Norman Objectives, attachments for polarized light and a camera (Carl Zeiss, Oberkochen, Germany).

#### *Scanning electron microscopy (SEM)*

The crystals were coated with graphite under vacuum and examined in a Hitachi S-520 scanning electron microscope.

#### *Hot-stage microscopy (HSM)*

Less than 1 mg of sample was placed between a microscope slide and a cover slide and heated at 1–5°C/min under a Kofler hot-stage microscope (Reichert, Austria) fitted with polarizers. The onset of melting was characterized by the first appearance of the liquid and the completion of melting was taken to be the final disappearance of the solid.

TABLE 1

INCORPORATION OF [<sup>14</sup>C]LABELLED *n*-ALKANOIC ACID ADDITIVES BY ADIPIC ACID CRYSTALS GROWN IN AQUEOUS SOLUTIONS CONTAINING AN INITIAL SUPERSATURATION OF 0.308 mol·dm<sup>-3</sup> ADIPIC ACID AND VARIOUS INITIAL CONCENTRATIONS OF ADDITIVE.

Additive	Initial concentration (μmol·dm <sup>-3</sup> )	Mole fraction, $x_2$ , of additive in the crystal ( $\times 10^3$ )
Hexanoic acid	1076 <sup>a</sup>	0.826
	2150 <sup>b</sup>	5.16
	3230	7.32
	4300	7.32
	5380	7.32
Octanoic acid	34.7 <sup>a</sup>	0.238
	69.3	0.669
	104.0 <sup>b</sup>	0.821
	138.7	1.112
Undecanoic acid	13.4 <sup>a,b</sup>	0.219
	26.8	0.494
	40.3	0.841
	53.7	1.187
	67.1	1.532

<sup>a</sup> Concentration corresponding to minimum  $\Delta H^*$  and threshold of habit change.

<sup>b</sup> Concentration corresponding to minimum  $\Delta H^f$  and appreciable habit change.

### *X-ray powder diffraction*

X-ray diffraction patterns of powder samples were determined using copper  $K_{\alpha}$  (nickel filter) and iron  $K_{\beta}$  (manganese filter) radiation from a Siemens X-ray generator with a Siemens diffractometer. A fine sieve fraction ( $< 75 \mu\text{m}$ ) of the original crystalline material was used without further treatment, whenever possible, to avoid introducing further crystal imperfections. If the sample was so coarse that unsatisfactory diffraction patterns were obtained, the sample was ground with an agate pestle and mortar.

Growth of adipic acid in the presence of the highest and the lowest concentration of each additive gave undetectable changes ( $< 0.5\%$ ) in lattice spacings even with the X-radiation of longer wavelength. The changes in lattice spacing were also undetectable even after grinding the adipic acid crystals. This confirms the absence of polymorphism or hydrate formation.

The limit of detection of possible changes in lattice spacing is about  $\pm 0.5\%$ . If any possible imperfections are assumed to change each linear dimension by about the same amount, the corresponding limit of detection of the possible changes in volume or density is by a factor of about  $(1.000 \pm 0.005)^3$ , i.e.  $\pm 1.5\%$ . By means of the appropriate technique, density changes of this order may be detectable, even though changes in lattice spacing were found not to be detectable by X-ray diffraction measurements.

### *Density measurements*

The density of adipic acid crystals was determined using a liquid pycnometer at a room temperature of  $25^{\circ}\text{C}$  taking the usual precautions (Bauer, 1949; Bauer and Lewin, 1972). In this method the volume of an accurately weighed amount of solid (1 g) was found by determining the changes in weight when the pycnometer ( $10 \text{ cm}^3$ ) was successively filled with a liquid of known density, solid plus air, and solid plus liquid. The liquid used was isooctane (99 mol percent from Fisher Scientific, Don Mills, Ont.) which had previously been saturated with adipic acid at  $25^{\circ}\text{C}$  (solubility  $24.2 \text{ mg} \cdot \text{dm}^{-3}$ ). The density of this solution at  $25^{\circ}\text{C}$  was determined by pycnometry to be equal to that of pure iso-octane within experimental error ( $0.6878 \pm 0.0001 \text{ g} \cdot \text{cm}^{-3}$ ). Before adding the final amount of liquid, any trapped air surrounding the solid was removed by placing the open pycnometer under a bell jar at a reduced pressure of 60 mm Hg for 30 min. The mass of solid deposited by the resulting evaporation of the isooctane was well within the weighing error ( $< 0.15 \text{ mg}$ ). After a further 30 min the liquid was added to the mark. Weighing of the closed pycnometer was carried out after equilibration for a further 30 min. The major source of errors (S.E.M. =  $0.001 \text{ g} \cdot \text{cm}^{-3}$ ) is probably temperature variation in the liquid ( $24\text{--}25^{\circ}\text{C}$ ) and in the laboratory ( $23\text{--}26^{\circ}\text{C}$ ).

### *Differential scanning calorimetry (DSC)*

The enthalpy of fusion,  $\Delta H^f$ , of adipic acid crystals was determined by heating 3–5 mg of crystals encapsulated in aluminium at a rate of  $10^{\circ}\text{C}/\text{min}$  (range  $10 \text{ mcal} \cdot \text{s}^{-1}$ ) in a Perkin-Elmer DSC-2C differential scanning calorimeter using helium as the gas phase and 3.5 mg of indium as the calorimetric standard.

The DSC melting point,  $T_m$ , was taken to be the temperature at the point of intersection of the leading line of steepest slope and the base line. The DSC freezing point,  $T_f$ , was characterized by the point of intersection of the lagging line of steepest slope and the base line. The so-called DSC peak temperature,  $T_p$ , was taken to be the temperature at the point of intersection of both lines of steepest slope and was indistinguishable from the temperature of the summit of the peak.

#### *Solution calorimetry*

The enthalpy of solution,  $\Delta H^s$ , of adipic acid crystals (5 mg) in water (4 cm<sup>3</sup>) was measured by means of an LKB-10700-2 batch rotating microcalorimeter. The heat changes were corrected for frictional heat evolved by the process of rotation of the calorimeter. Three rotations were sufficient to ensure complete dissolution and total heat change. The concentration of adipic acid after complete dissolution (8.55 mmol · dm<sup>-3</sup>) is sufficiently low for the solution to be considered infinitely dilute (Pikal et al., 1978).

#### *Specific surface area (SAA)*

The specific surface area of adipic acid crystals was determined by absorption of nitrogen at 0.1, 0.2 and 0.3 mole percent in helium using the BET adsorption isotherm (Lowell, 1979) and a Quantasorb Surface Area Analyzer (Quantachrome Corporation, Syosset, NY). Samples (ca. 0.5 g) were outgassed under nitrogen at 1 atm at 40°C for 1 h.

#### *Dissolution rate*

The dry adipic acid crystals were sieved and 1.0 g of the fraction 425–850  $\mu\text{m}$  (20–35 mesh) was added at zero time to 750 cm<sup>3</sup> of aqueous dissolution medium. The USPXX/NFXV (1982) dissolution test using Apparatus 2 with paddle stirring at 50 rpm was employed in an automated dissolution apparatus (Dissoette, Hansen Corporation, Northridge, CA). Samples of 5 cm<sup>3</sup> were withdrawn every 2 min and the mass of adipic acid dissolved was calculated from the concentration after correcting for the change in volume of the dissolution medium. The concentration of dissolved adipic acid was determined by titration with standard sodium hydroxide to pH 9.55 using a Sargent recording pH stat (Sargent-Welch Scientific, Skokie, IL). At least 3 dissolution tests were carried out on each sample and the mean value was taken.

Using pure water or dilute hydrochloric acid, some crystals tended to float on the surface of the liquid, perhaps on account of the air trapped in the surface irregularities. To improve the wettability several concentrations of various surface active agents were tested. For the dissolution tests polyoxyethylene (4) lauryl ether (Brij 30, Atlas, ICI Americas) at 10 mg · dm<sup>-3</sup> was added to the dissolution medium, since this caused the crystals to be wetted and to sink immediately after they were added. Hydrochloric acid at 1–1000 mmol · dm<sup>-3</sup> did not affect the dissolution profile of adipic acid crystals and was therefore omitted. This lack of influence of low pH values suggests that the first trace of adipic acid ( $\text{p}K_a$  4.43, 5.41) in solution quickly reduces the pH value to below 4 at which the ionization of the adipic acid is suppressed.

In order to reduce the dissolution rate of adipic acid crystals sufficiently to enable the initial dissolution rate to be determined from the initial slope of the dissolution-time curve, the temperature of the thermostic water bath was reduced to 4.0°C by means of a “cold-finger” cooler (Lauda IC-6, Brinkman Instruments).

## Results and Discussion

### *Density and additive incorporation*

Growth of adipic acid crystals in the presence of an additive causes the additive to be incorporated into the crystals and influences their density. The relationship between the mole fraction of a given additive in the crystals and the density of the crystals may provide information about the nature of the incorporation of the additive. Incorporation may cause an expansion or contraction of the lattice which is equivalent to the loss or gain of molecules from a given volume. This volume may conveniently be defined as the molar volume,  $V_m$ , of the pure crystal lattice of adipic acid whose density,  $d_0$ , is given by

$$d_0 = M_1/V_m \quad (1)$$

where  $M_1$  is the molecular weight of adipic acid. For crystals containing the additive at a mole fraction,  $x_2$ , the adipic acid is present at a mole fraction,  $x_1 = 1 - x_2$ , since the drying procedure ensures that water is essentially absent. The density,  $d$ , of these crystals can be expressed as a function of additive content according to various models, where  $M_2$  is the molecular weight of the additive.

#### (1) Substitutional solid solution

(a) If, for every molecule of additive incorporated,  $p$  molecules of adipic acid are lost, as a result of substitution and/or lattice expansion, then:

$$d = \frac{M_1}{V_m} (1 - px_2) + \frac{M_2}{V_m} x_2 \quad (2)$$

Eliminating  $V_m$  using Eqn. 1, we obtain

$$d = d_0(1 - px_2 + x_2M_2/M_1) \quad (3)$$

or

$$\frac{d_0 - d}{d_0} = x_2 \left( p - \frac{M_2}{M_1} \right) \quad (4)$$

A plot of  $(d_0 - d)/d_0$  against  $x_2$  is then linear passing through the origin and  $p$  may be calculated from the slope. For a simple 1 : 1 substitutional solid solution with no change of lattice dimensions,  $p$  is unity.

(b) If for every molecule of additive incorporated,  $q$  molecules of adipic acid are also gained, perhaps as a result of lattice contraction, then

$$d = d_0(1 + qx_2 + x_2M_2/M_1) \quad (5)$$

or

$$\frac{d - d_0}{d_0} = x_2 \left( q + \frac{M_2}{M_1} \right) \quad (6)$$

A linear plot of  $(d - d_0)/d_0$  against  $x_2$  enables  $q$  to be calculated.

## (2) Interstitial solid solution

(a) In a simple interstitial solid solution with no change of lattice dimensions, each additive molecule occupies a hitherto vacant site in an interstice, so that

$$d = \frac{M_1}{V_m} + \frac{M_2}{V_m} \frac{x_2}{x_1} \quad (7)$$

Eliminating  $V_m$  using Eqn. 1 as before affords

$$d = d_0(1 + x_2M_2/x_1M_1) \quad (8)$$

$$= d_0(1 + m_2/m_1) \quad (9)$$

where  $(m_2/m_1)$  is the ratio of additive mass to adipic acid mass in the crystals. In the present examples, and perhaps also in other organic solid solutions,  $x_2$  is sufficiently small ( $< 0.01$ ) that  $x_1$  can be assumed to equal unity with negligible error.

(b) If each additive molecule present in an interstitial position causes the loss of  $p$  molecules of adipic acid, as a result of steric displacement and/or lattice expansion, Eqn. 7 can be modified to forms analogous to Eqns. 2–4 which may be treated in a similar way.

(c) If each additive molecule present in an interstitial position causes the gain of  $q$  molecules of adipic acid, perhaps as a result of lattice contraction, Eqn. 7 can be modified to forms analogous to Eqns. 5 and 6 which may be similarly treated.

## (3) Data analysis

The incorporation of hexanoic acid into adipic acid crystals (Table 1) leads to density changes which are negligible within experimental error (Fig. 1a). The density data correspond to simple 1:1 substitution according to Eqn. 3 with  $p = 1$ , while the simple interstitial model, according to Eqn. 9 predicts densities that are too high (Fig. 1a).

The uptake of octanoic acid by growing adipic acid crystals (Table 1) increases the density (Fig. 1b), whereas simple 1:1 substitution (Eqn. 3, with  $p = 1$ ) or the



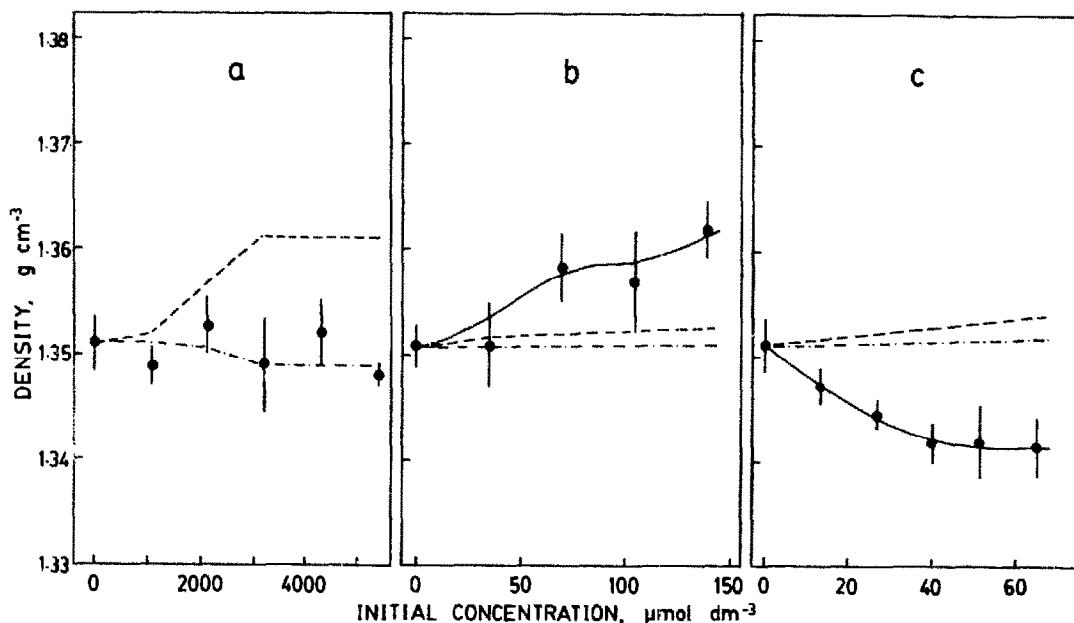


Fig. 1. Density at 25°C of adipic acid crystals grown in aqueous solutions containing an initial supersaturation of  $0.308 \text{ mol} \cdot \text{dm}^{-3}$  adipic acid and various initial concentrations of: (a) hexanoic acid; (b) octanoic acid; and (c) undecanoic acid. The vertical bars indicate the standard errors. - - - - , densities predicted from  $x_2$  (Table 1) and Eqn. 3 with  $p=1$ , corresponding to a simple substitutional solid solution. - · - · - · , densities predicted from  $x_2$  (Table 1) and Eqn. 8 corresponding to a simple interstitial solid solution. (b) ———, line of best fit to Eqn. 5, corresponding to  $q=6$ . (c) ———, line of best fit to Eqn. 3, corresponding to  $p=13$ .

simple interstitial model (Eqn. 8) predict densities that are too low and almost constant. The density data accord well with Eqns. 5 and 6 with  $q=6 \pm 1$ . This corresponds to the gain of 5 to 7 adipic acid molecules for each octanoic acid molecule incorporated into a given volume of lattice either by a substitutional or by an interstitial mechanism.

The incorporation of undecanoic acid (Table 1) at first reduces the density of adipic acid crystals until a plateau is reached (Fig. 1c). Simple 1:1 substitution (Eqn. 3, with  $p=1$ ) and the simple interstitial model (Eqn. 8), respectively, predict negligible and small increases in density. The decreasing density measurements agree well with Eqns. 3 and 4 with  $p=13 \pm 2$ . This corresponds to the loss of 11 to 15 adipic acid molecules for each undecanoic acid molecule incorporated either substitutionally or interstitially into a given lattice volume. The levelling of the density at higher concentrations of incorporated additive implies a limit to lattice expansion.

Although the crystal size (sieve fraction) slightly influences the density of the crystals (Table 3), the particle size distribution of the samples were so similar (Table 3) that the variations in density shown in Fig. 1 cannot be attributed to differences of crystal size.

#### *Thermodynamic properties*

Crystal energies frequently depend on particle size. For example, the surface free energy of particles tends to increase with decreasing particle size according to the Kelvin equation (Shaw, 1970), but the effect only becomes significant for diameters

TABLE 2

ENTROPIES OF FUSION,  $\Delta S^f = \Delta H^f/T_m$ , OF ADIPIC ACID CRYSTALS GROWN IN AQUEOUS SOLUTIONS CONTAINING AN INITIAL SUPERSATURATION OF  $0.308 \text{ mol} \cdot \text{dm}^{-3}$  ADIPIC ACID AND VARIOUS CONCENTRATIONS OF FATTY ACID ADDITIVES

Additive	Initial concentration ( $\mu\text{mol} \cdot \text{dm}^{-3}$ )	$\Delta S^f$ ( $\text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$ )	$\Delta S_{\text{ideal}}^m$ ( $\text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$ )
None	0	78.5	0
Hexanoic acid	1076	74.9	0.0556
	2150	71.3	0.269
	3230	80.7	0.360
	4300	79.5	0.360
	5380	79.8	0.360
Octanoic acid	34.7	76.0	0.0185
	69.3	75.0	0.0462
	104.0	70.1	0.0553
	138.7	75.4	0.0721
Undecanoic acid	13.4	77.2	0.0172
	26.8	74.8	0.0354
	40.3	66.7	0.0565
	53.7	68.7	0.0763
	67.1	74.2	0.0953

much less than  $1 \mu\text{m}$ . Differences of particle size can appreciably affect the peak parameters in quantitative DCS on account of a reduced rate of heat transfer through a bed of larger particles (van Dooren, 1980; van Dooren and Müller, 1981). However, in the present work various sieve fractions of adipic acid, which had been crystallized from water, gave values of DSC melting point,  $\Delta H^f$  and  $\Delta H^s$  which were essentially constant within experimental error (Table 3). This indicates that the relatively large changes in melting point (Fig. 2),  $\Delta H^f$  (Fig. 3) and  $\Delta H^s$  (Fig. 4) cannot be attributed to the changes in the relative proportions of crystals of various sizes and must result from the presence of fatty acids in the crystals. In fact, the vast majority of the crystals are relatively large, falling within a relatively restricted size range,  $75\text{--}850 \mu\text{m}$ , corresponding to particles that are relatively large from a pharmaceutical viewpoint.

Growth of adipic acid crystals in the presence of increasing concentrations of each fatty acid additive causes the absolute DSC melting point,  $T_m$  (Fig. 2), and the enthalpy of fusion,  $\Delta H^f$  (Fig. 3), to decrease to minima, indicating an increase in lattice strain, and then to increase to values which approach or exceed those in the absence of additive, indicating a release of lattice strain. The lattice strain may arise from the "impurity defects" and dislocations induced by the presence of the additive in the crystals (Hüttenrauch, 1978). Crystal growth in the presence of higher concentrations of hexanoic acid ( $> 3 \text{ mmol} \cdot \text{dm}^{-3}$ ) causes levellings in the concentration of incorporated additive (Table 1), in  $T_m$  (Fig. 2a) and in  $\Delta H^f$  (Fig. 3a).

TABLE 3  
 PERCENT (w/w), DSC MELTING POINTS,  $T_m$ , ENTHALPIES OF FUSION,  $\Delta H^f$ , ENTHALPIES OF SOLUTION,  $\Delta H^s$ , AND DENSITIES,  $d$ , OF  
 VARIOUS SIEVE FRACTIONS OF PURE ADIPIC ACID CRYSTALS HARVESTED FROM AQUEOUS SOLUTION AND DRIED IN AIR

Mesh size ( $\mu\text{m}$ )	% (w/w)		$T_m$ (K)		$\Delta H^f$ (kJ·mol <sup>-1</sup> )		$\Delta H^s$ (kJ·mol <sup>-1</sup> )		1000 d (g·cm <sup>-3</sup> )	
	mean <sup>a</sup>	S.E. <sup>b</sup>	mean <sup>c</sup>	S.E. <sup>b</sup>	mean <sup>c</sup>	S.E. <sup>b</sup>	mean <sup>c</sup>	S.E. <sup>b</sup>	mean	S.E. <sup>b</sup>
< 75	1.0	0.4	421.2	0.18	33.57	0.59	33.65	0.22	1346.8	1.55
75-90	1.1	0.3	420.9	- <sup>e</sup>	33.84	- <sup>e</sup>	-	-	-	-
90-125	4.3	0.5	421.0	0.05	34.29	0.98	33.27	0.58	-	-
125-150	3.1	0.5	420.9	0.03	35.00	0.24	33.56	0.47	1349.8 <sup>c</sup>	0.38
150-180	6.8	0.7	421.0	- <sup>e</sup>	34.02	- <sup>e</sup>	-	-	-	-
180-250	20.8	1.5	420.9	- <sup>e</sup>	34.38	- <sup>e</sup>	31.95	0.93	1352.4 <sup>c</sup>	2.62
250-425	57.1	3.2	421.0	0.06	34.15	0.20	33.57	0.62	1355.1 <sup>d</sup>	1.01
> 425	5.8	1.2	420.2	0.28	34.93	0.26	-	-	-	-
Mean <sup>f</sup>	-	-	420.9	0.09	34.34	0.20	33.20	0.47 <sup>g</sup>	1351.0	1.21
Desiccated <sup>g</sup>	-	-	419.3	0.25	34.08	0.34	33.42	0.32	-	-

<sup>a</sup> 21 samples; "doped" crystals gave essentially the same distribution.

<sup>b</sup> Standard error of the mean.

<sup>c</sup> 3 samples.

<sup>d</sup> 4 samples.

<sup>e</sup> Only one measurement.

<sup>f</sup> Calculated over all mesh sizes.

<sup>g</sup> Over phosphorus pentoxide.

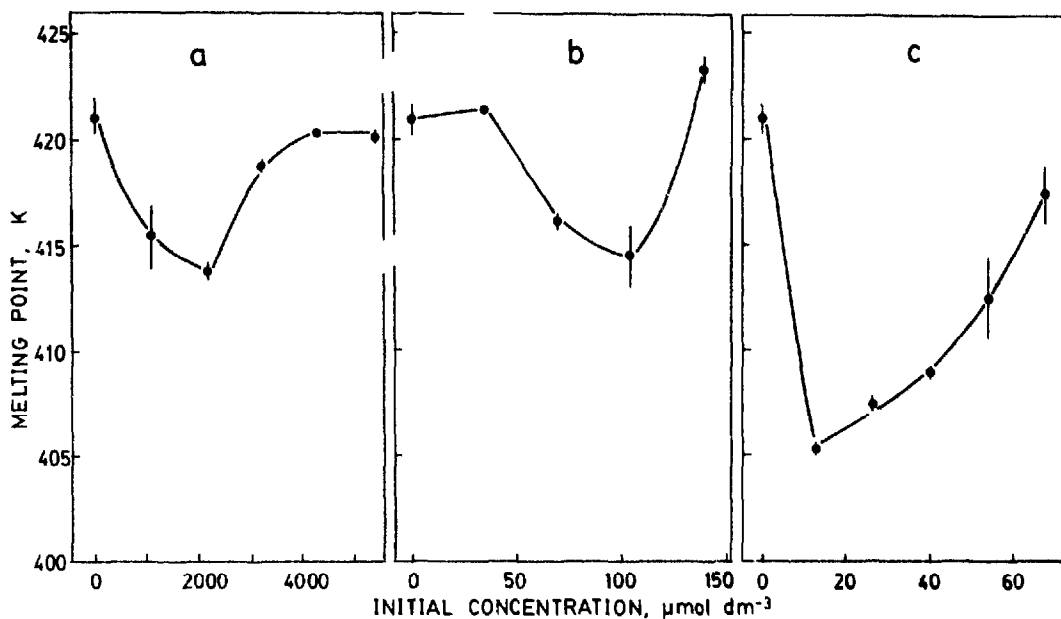


Fig. 2. DSC melting points,  $T_m$ , of adipic acid crystals grown in aqueous solutions containing an initial supersaturation of  $0.308 \text{ mol} \cdot \text{dm}^{-3}$  adipic acid and various initial concentrations of: (a) hexanoic acid; (b) octanoic acid; and (c) undecanoic acid. The vertical bars indicate the standard errors. The individual values were confirmed by hot-stage microscopy.

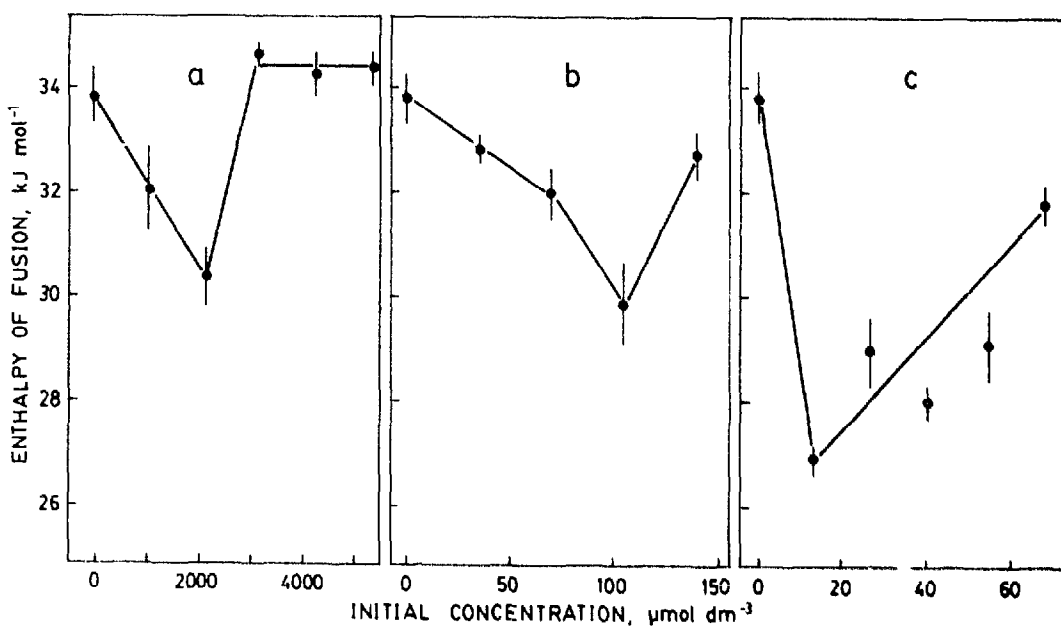


Fig. 3. Enthalpies of fusion,  $\Delta H^f$ , at the melting point of adipic acid crystals grown in aqueous solutions containing an initial supersaturation of  $0.308 \text{ mol} \cdot \text{dm}^{-3}$  adipic acid and various initial concentrations of: (a) hexanoic acid; (b) octanoic acid; and (c) undecanoic acid. The vertical bars indicate the standard errors.

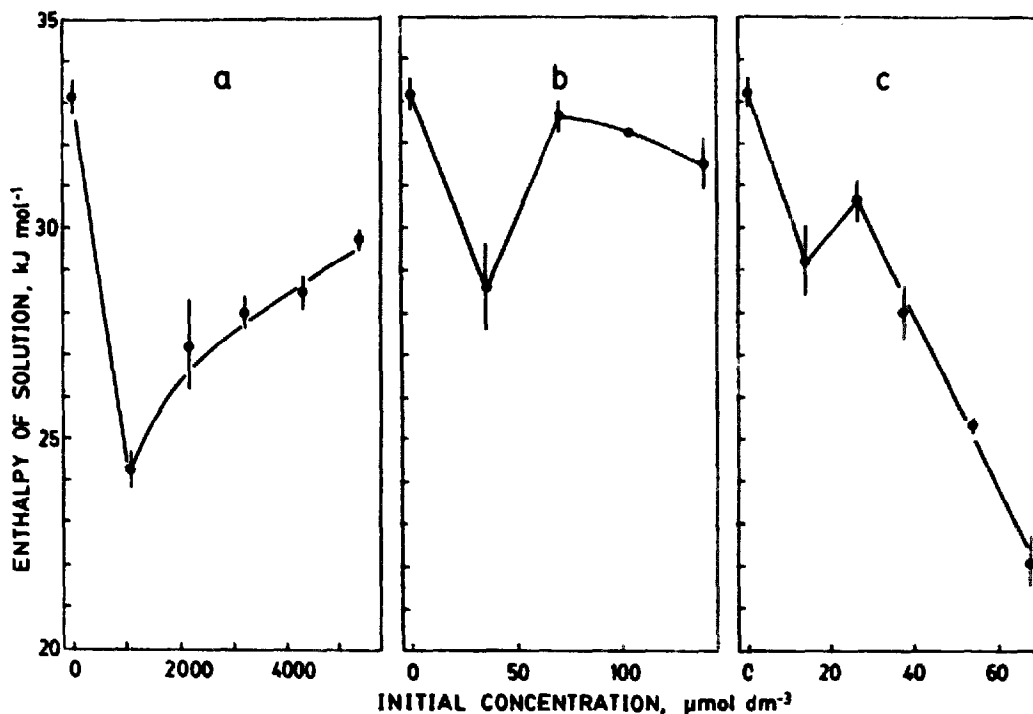


Fig. 4. Enthalpies of solution,  $\Delta H^\circ$ , to  $8.55 \text{ mmol} \cdot \text{dm}^{-3}$  at 298.15 K. of adipic acid crystals grown in aqueous solutions containing an initial supersaturation of  $0.308 \text{ mol} \cdot \text{dm}^{-3}$  of adipic acid and various initial concentrations of: (a) hexanoic acid; (b) octanoic acid; and (c) undecanoic acid. The vertical bars indicate the standard errors.

This emphasizes the dependence of these thermodynamic properties on the presence and concentration of additive in the crystals.

The changes in  $\Delta H^f$  ( $-7.7$  to  $-20.7\%$  in Fig. 3) are about 6 times larger than the changes in  $T_m$  ( $-1.5$  to  $-2.8\%$  in Fig. 2), so the entropy of fusion,  $\Delta S^f$  (Table 2) parallels  $\Delta H^f$  fairly closely. A reduction of  $\Delta S^f$  accords with a build-up of lattice strain and an increase in  $\Delta S^f$  with strain release. These concepts follow from and are extended by the following thermodynamic arguments. The molar thermodynamic quantities for the fusion process at constant atmospheric pressure,  $p$ , are related as follows:

$$\Delta H^f = \Delta U^f + p\Delta V^f = \Delta S^f/T_m \quad (10)$$

where

$$\Delta H^f = H_{\text{liquid}} - H_{\text{solid}} \quad (11)$$

$$\Delta U^f = U_{\text{liquid}} - U_{\text{solid}} \quad (12)$$

$$\Delta V^f = V_{\text{liquid}} - V_{\text{solid}} \quad (13)$$

$$\Delta S^f = S_{\text{liquid}} - S_{\text{solid}} \quad (14)$$

and the other quantities are defined above. Since the mole fractions of additives in the system are  $< 0.01$ , then  $H_{\text{liquid}}$ ,  $U_{\text{liquid}}$ ,  $V_{\text{liquid}}$  and  $S_{\text{liquid}}$  are probably changed negligibly by the additives used. Consequently, the decreases in  $\Delta H^f$  (Fig. 3) and  $\Delta S^f$  (Table 2) brought about by the additives correspond to increases in  $H_{\text{solid}}$  and  $S_{\text{solid}}$ . Since the changes in density (Fig. 1) are proportionately much less (by factors of about 10) than the changes in  $\Delta H^f$ , then  $V_{\text{solid}}$  and  $\Delta V^f$  in Eqns. 10 and 13 may be considered virtually constant. A change in enthalpy of the crystals therefore directly reflects a change in internal energy. Thus, the presence of small concentrations of additive in the crystals increases  $U_{\text{solid}}$  and  $S_{\text{solid}}$ , while larger concentrations decrease these thermodynamic quantities.

The increase in  $S_{\text{solid}}$ , corresponding to the decrease  $\Delta S^f$  (Table 2), is of the order  $1\text{--}12 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$  which is several orders of magnitude larger than the ideal molar entropy of mixing, which is given by

$$\Delta S_{\text{ideal}}^m = -R(x_1 \ln x_1 + x_2 \ln x_2) \quad (15)$$

where  $R$  is the molar gas constant,  $8.3143 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$ , and  $x_1$  and  $x_2$  are the mole fractions of the respective components in the mixture.  $\Delta S_{\text{ideal}}^m$  probably corresponds quite closely to the entropy of mixing of the additive with the adipic acid in the molten state, since both components are chemically similar, being carboxylic acids. The much larger increase in the entropy of the solid (deduced above) is therefore better attributed to the introduction of impurity defects and dislocations brought about by the presence of the additives in the crystals, albeit in minute amounts (Table 1), than to simple mixing or dilution effects in the crystals.

The enthalpy of solution,  $\Delta H^s$ , of the crystals is also affected by growth in the presence of the fatty acid additives (Fig. 4). Low concentrations of each additive produce an initial decrease in  $\Delta H^s$ , which is followed by an increase at a slightly higher concentration. This increase persists in the presence of higher concentrations of hexanoic acid (Fig. 4a) but is followed by a decrease in  $\Delta H^s$  with octanoic acid (Fig. 4b) or undecanoic acid (Fig. 4c). Higher concentrations of undecanoic acid produce a large decrease. The initial decrease in  $\Delta H^s$  occurs at lower concentrations than that of  $\Delta H^f$  (Fig. 3) and the final decreases in  $\Delta H^s$  at higher concentrations are not seen with  $\Delta H^f$ .

The differences in behaviour of  $\Delta H^s$  and  $\Delta H^f$  of the crystals following incorporation of additives probably arise: (a) from the fact that these quantities were measured at different temperatures ( $298 \text{ K}$  and  $T_m \approx 420 \text{ K}$ , respectively); and (b) from the effects of the additives on the molar heat capacity of the crystals,  $C_{p(\text{solid})}$  according to the following thermodynamic arguments. At room temperature,

$$\Delta H_{298 \text{ K}}^s = \Delta H_{298 \text{ K}}^m + \Delta H_{298 \text{ K}}^f \quad (16)$$

where  $\Delta H_{298 \text{ K}}^m$  is the enthalpy of mixing of supercooled molten crystals with water. Since the crystals contain only minute amounts of additives ( $x_2 < 0.01$ ) and since the

additives are chemically similar to adipic acid, the  $\Delta H^m$  term will be virtually unaffected by the presence of the additives.  $\Delta H^s$  is therefore directly dependent on  $\Delta H^f$  at room temperature,  $\Delta H^f_{298\text{ K}}$ , which differs from the  $\Delta H^f$  value measured at the melting point,  $\Delta H^f(T_m)$ , thus:

$$\Delta H^f_{298\text{ K}} = \Delta H^f(T_m) - \int_{298\text{ K}}^{T_m} \Delta C_p \cdot dT \quad (17)$$

where

$$\Delta C_p = C_{p(\text{liquid})} - C_{p(\text{solid})} \quad (18)$$

If the temperature is below  $T_m$ , the liquid will be in a hypothetical supercooled state. The heat capacity of the liquid state, like the other thermodynamic properties of this state, is probably changed to a negligible extent by the additives, so  $\Delta C_p$  is largely controlled by the effects of the additive on  $C_{p(\text{solid})}$ .  $\Delta C_p$  is often assumed to be relatively independent of temperature. Then, combining Eqns. 16, 17 and 18, we obtain

$$\Delta H^s_{298\text{ K}} = \Delta H^m_{298\text{ K}} + \Delta H^f(T_m) + (T_m - 298\text{ K})[C_{p(\text{solid})} - C_{p(\text{liquid})}] \quad (19)$$

where  $\Delta H^m_{298\text{ K}}$  and  $C_{p(\text{liquid})}$  are only slightly influenced by additives and may be assumed to be constants. Thus,  $\Delta H^s_{298\text{ K}}$  is essentially a function of  $C_{p(\text{solid})}$  as well as  $\Delta H^f(T_m)$  and the differences between the corresponding curves in Fig. 3 and 4 may be ascribed to the influence of the additive on  $C_{p(\text{solid})}$ . For the present system the heat capacity-entropy equation may be applied to the crystals at constant pressure, thus:

$$S(\text{solid}) = \int_0^T \frac{C_{p(\text{solid})}}{T} \cdot dT \quad (20)$$

Values of  $C_{p(\text{solid})}$  could not be determined with sufficient accuracy by DSC to enable the influence of the additives to be properly assessed, since the heat capacity is a "second-order" quantity on which the additives themselves exert relatively small effects. The trends in  $C_{p(\text{solid})}$  can, however, be predicted from Eqn. 20.

The incorporation of small quantities of each additive (Table 1) increases  $S_{\text{solid}}$ , as deduced from the reduction in  $\Delta S^f$  (Table 2), and therefore also increases  $C_{p(\text{solid})}$  according to Eqn. 20. The additive is probably introducing defects and dislocations into the crystal lattice, thereby increasing its disorder (higher entropy) and also making more energy levels available for the absorption of heat by the lattice (higher heat capacity). The incorporation of larger amounts of octanoic or undecanoic acid (Table 1) then reduces  $S_{\text{solid}}$ , as deduced from the later increase in  $\Delta S^f$  (Table 2). According to Eqn. 20 this corresponds to a reduction of  $\Delta C_{p(\text{solid})}$ , which, according to Eqn. 19, exerts a negative effect on  $\Delta H^s$  (Fig. 4b and c), even though  $\Delta H^f$  may still be increasing (Fig. 3b and c). The reduction in  $S_{\text{solid}}$  caused by higher concentra-

tions of octanoic or undecanoic acid indicates a progressive ordering of the impurity defects or dislocations which may be associated with the release of lattice strain indicated by the increases in  $T_m$  (Fig. 2) and  $\Delta H^f$  (Fig. 3). The incorporation of higher concentrations of hexanoic acid produces a plateau of  $\Delta H^f$  (Fig. 3a) and  $\Delta S^f$  (Table 2) perhaps with a slightly negative slope which may be consistent with the gradual rise in  $S_{\text{solid}}$ ,  $C_{\text{p(solid)}}$  and  $\Delta H^s$  (Fig. 4a).

### Crystal surfaces

The specific surface area (SAA) of a collection of particles depends on the particle size distribution. The crystal size distribution, determined by sieve analysis and shown in Table 3, was found to be independent of the nature or concentration of the three fatty acid additives used. The differences in the SAA of representative batches of crystals shown in Fig. 5, is therefore largely determined by differences in the surface features. Fig. 5 shows that crystal growth in the presence of each additive, corresponding to increasing incorporation, causes an increase and then a decrease in the SAA. The increase in SAA is reflected in changes in the scanning electron micrographs (Fig. 6 and 7) of the tabular, hexagon-shaped crystals of adipic acid. Hexanoic acid produces rounded surface irregularities, resembling "brain convolutions", on the tabular crystals (Fig. 6 upper right, Fig. 7 upper left), while octanoic and undecanoic acid produce sharper irregularities resembling "saw teeth" (Fig. 6 lower right and left, Fig. 7 upper right and lower left). Higher concentrations, e.g.  $67.1 \mu\text{mol} \cdot \text{dm}^{-3}$ , of undecanoic acid (Fig. 7 lower right) produce numerous surface striations resembling the cleavage planes of slate, while octanoic acid produces a constriction or "waist" in the crystal (Fig. 6 lower left). Such features indicate the

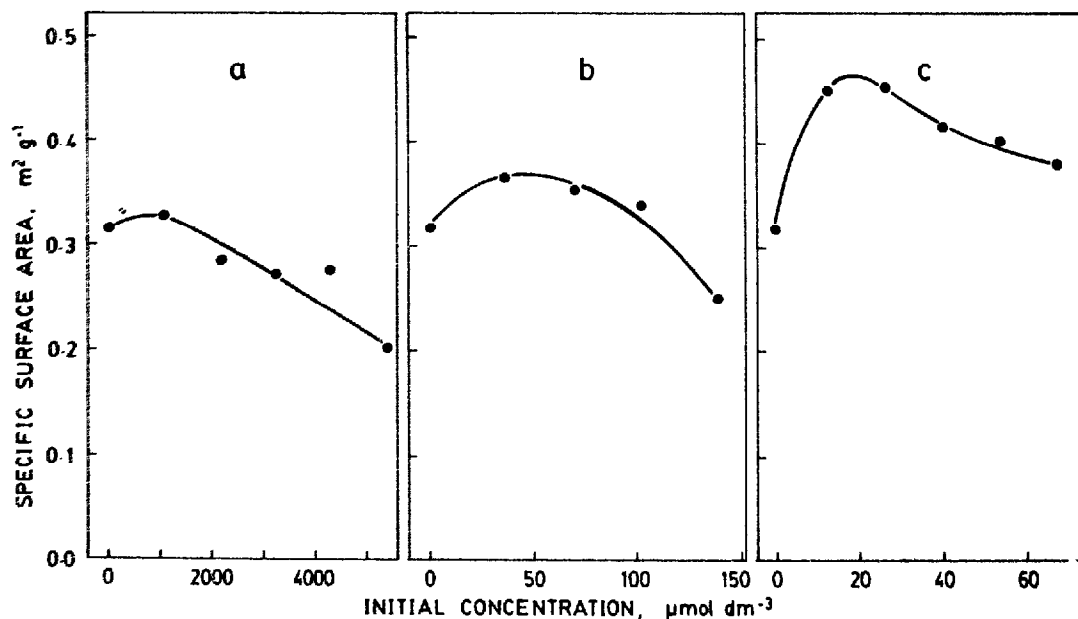
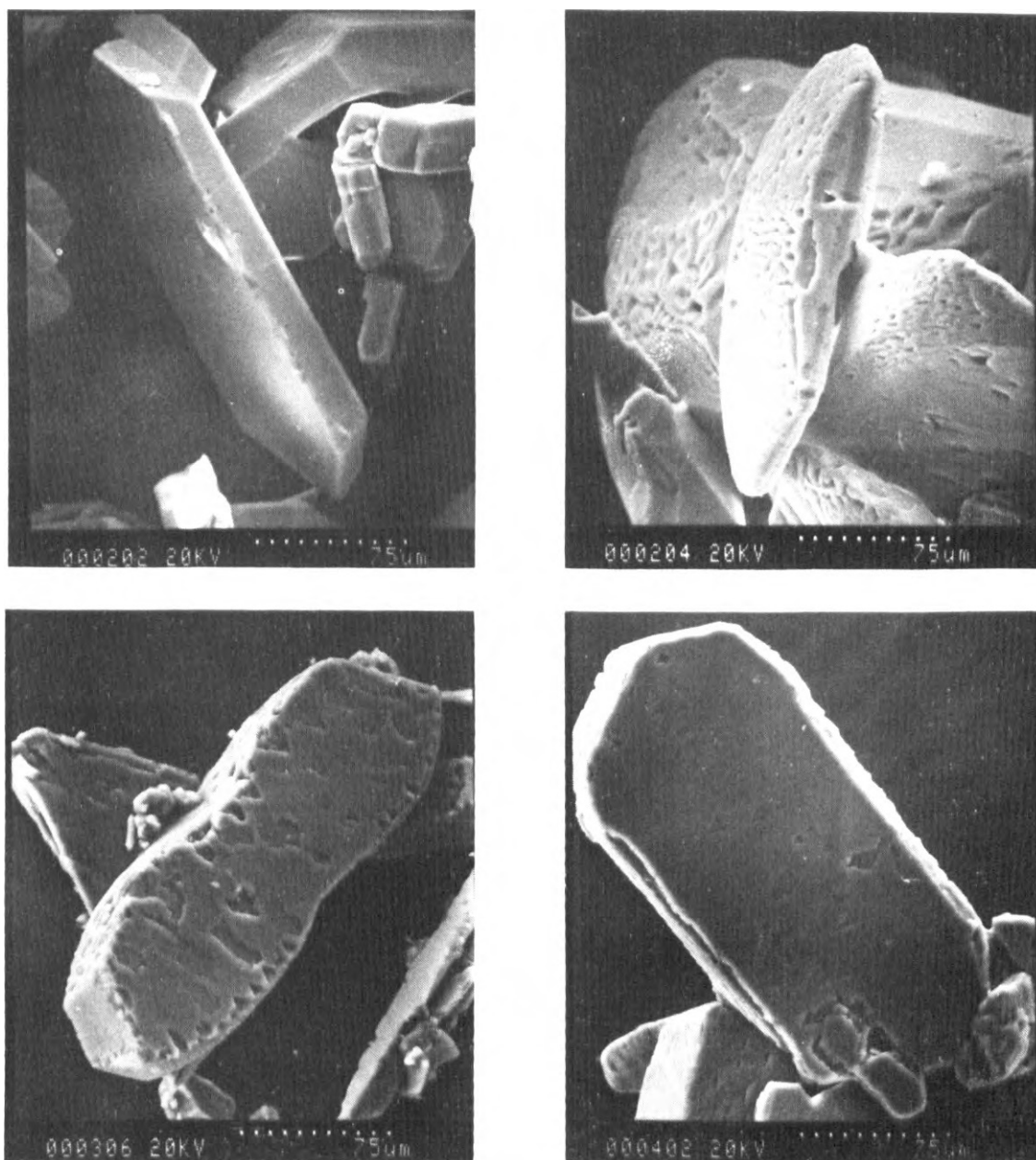


Fig. 5. Specific surface area of adipic acid crystals grown in aqueous solutions containing an initial supersaturation of  $0.308 \text{ mol} \cdot \text{dm}^{-3}$  and various initial concentrations of: (a) hexanoic acid; (b) octanoic acid; and (c) undecanoic acid.





**Fig. 6.** Scanning electron micrographs of the surfaces of adipic acid crystallized from water containing the following additives: upper left, pure water; upper right,  $2150 \mu\text{mol}\cdot\text{dm}^{-3}$  hexanoic acid; lower left,  $104.0 \mu\text{mol}\cdot\text{dm}^{-3}$  octanoic acid; lower right,  $13.4 \mu\text{mol}\cdot\text{dm}^{-3}$  undecanoic acid.

creation of new faces with high Miller indices that are normally unstable and are outgrown in the absence of additive producing flat, regular faces (Fig. 6 upper left). That the surface irregularities are not artifacts of SEM was confirmed by optical microscopy. These irregularities were apparent at all concentrations of each additive that were employed (Table 1) and suggest that the additives inhibit or interrupt the growth of certain crystal planes. The reduction in the SAA at high concentrations of

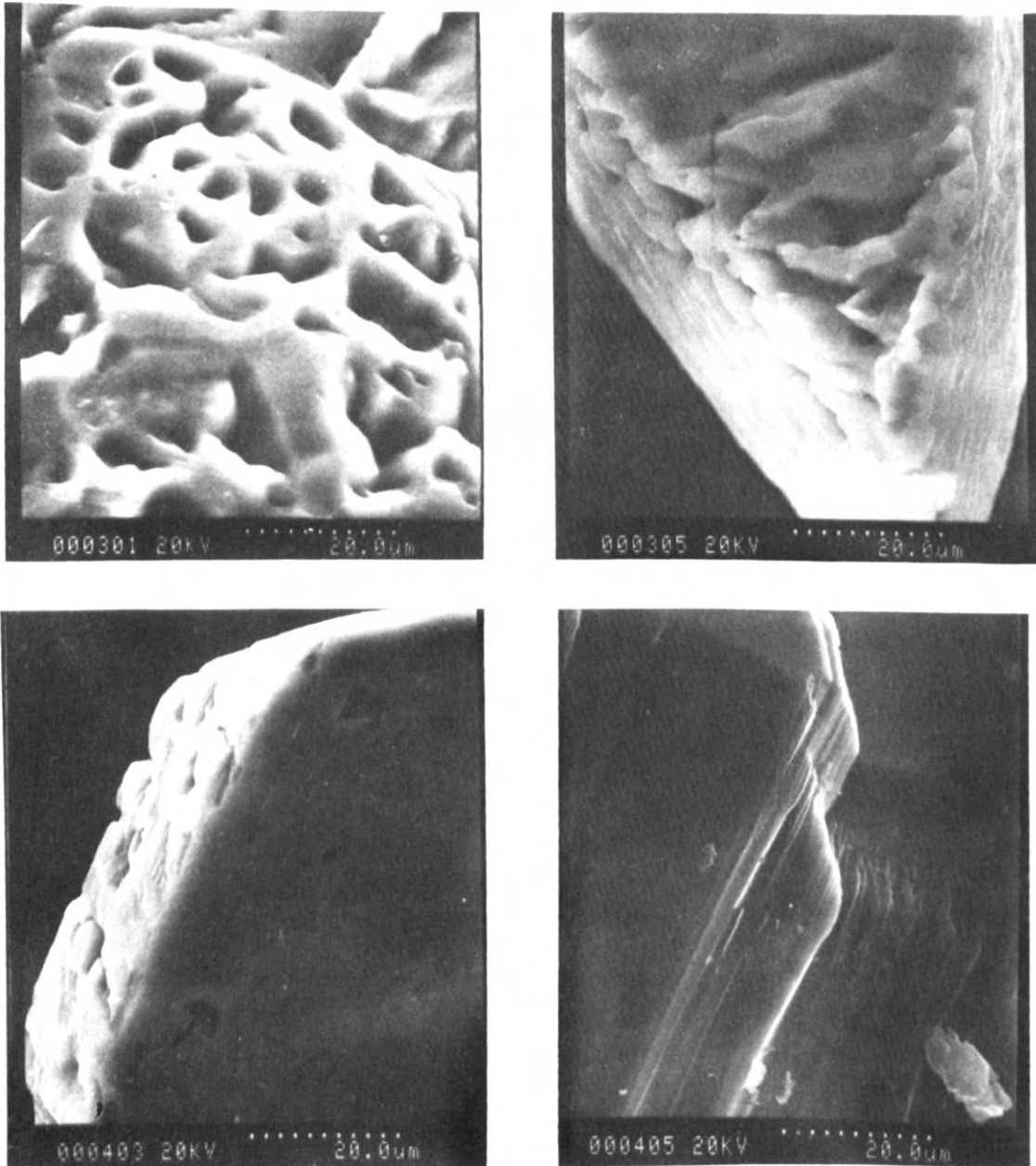


Fig. 7. Scanning electron micrographs of the surfaces of adipic acid crystallized from water containing the following additives: upper left,  $2150 \mu\text{mol}\cdot\text{dm}^{-3}$  hexanoic acid; upper right,  $104.0 \mu\text{mol}\cdot\text{dm}^{-3}$  octanoic acid; lower left,  $13.4 \mu\text{mol}\cdot\text{dm}^{-3}$  undecanoic acid; lower right,  $67.1 \mu\text{mol}\cdot\text{dm}^{-3}$  undecanoic acid.

additive (Fig. 5) is difficult to explain and might be attributable to decreases in the number and/or surface area of the micropores (cf. the influence of  $13.4$  and  $67.1 \mu\text{mol}\cdot\text{dm}^{-3}$  undecanoic acid in the lower half of Fig. 7).

#### *Dissolution rate*

As expected, the dissolution rate of  $1 \text{ g}$  of crystals decreased with increasing

particle size and was about 3.1 times greater for the 180–425  $\mu\text{m}$  (35–80 mesh) sieve fraction than for the 425–850  $\mu\text{m}$  (20–35 mesh) sieve fraction. The larger of these size ranges was selected for dissolution studies, since it gave more reproducible dissolution rates for control crystals grown in the absence of additives.

Fig. 8 shows typical dissolution profiles of adipic acid crystals of the defined sieve fraction, grown in the absence and presence of various concentrations of one of the additives. From such plots the initial dissolution rate was calculated.

Growth in the presence of increasing concentrations of hexanoic and undecanoic acid, corresponding to increasing incorporation into the crystals, caused the dissolution rate to increase to a maximum about twice that in the absence of additive and then to decrease (Fig. 9). These changes are greater than the corresponding changes in specific surface area (Fig. 5) and parallel quite closely the changes in enthalpy of fusion (Fig. 3) which is closely related to the thermodynamic activity of the solid (Hildebrand and Scott, 1950) with respect to the liquid solute. Thus, the dissolution rate of crystals doped with hexanoic or undecanoic acid appears to parallel the energy of the crystals. The parallelism between dissolution rate (Fig. 9) and  $\Delta H^f$  (Fig. 4) is less close and may reflect the fact that the dissolution conditions are so far removed from equilibrium that the usual concepts of equilibrium thermodynamics (Katchalsky and Curran, 1965) do not apply.

The presence of octanoic acid in the crystals actually reduces the dissolution rate (Fig. 9) even though it produces surface irregularities (Fig. 6 and 7) and increases the specific surface area (Fig. 5), and the crystal energy (lower  $\Delta H^f$ , Fig. 3, and lower

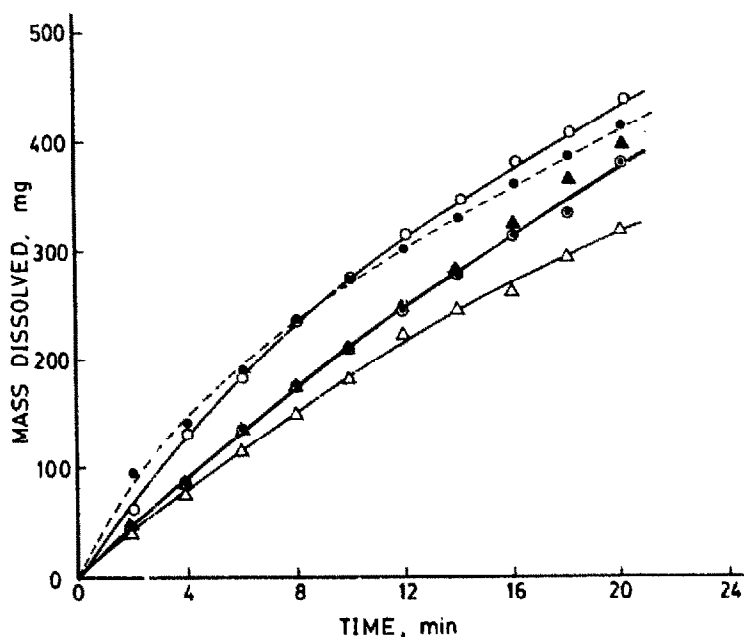


Fig. 8. Dissolution-time profiles of adipic acid crystals grown in aqueous solutions containing an initial supersaturation of  $0.308 \text{ mol}\cdot\text{dm}^{-3}$  adipic acid and various initial concentrations of hexanoic acid:  $\circ$  —  $\circ$ , 0;  $\circ$  —  $\circ$ ,  $1076 \mu\text{mol}\cdot\text{dm}^{-3}$ ;  $\bullet$  —  $\bullet$ ,  $2150 \mu\text{mol}\cdot\text{dm}^{-3}$ ;  $\Delta$  —  $\Delta$ ,  $3230 \mu\text{mol}\cdot\text{dm}^{-3}$ ;  $\blacktriangle$  —  $\blacktriangle$ ,  $4300 \mu\text{mol}\cdot\text{dm}^{-3}$ .

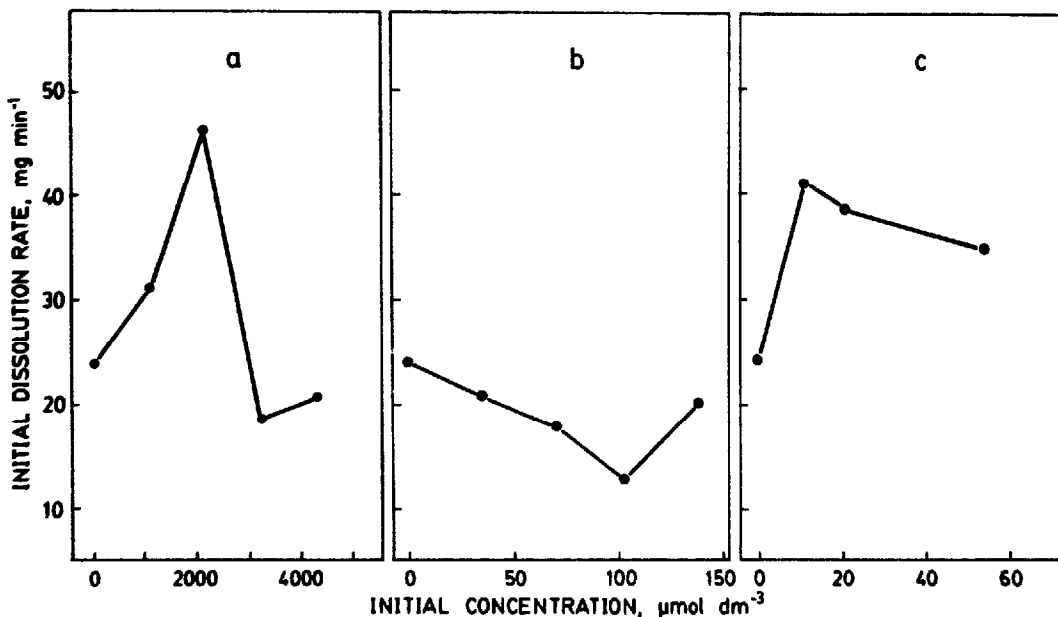


Fig. 9. Initial dissolution rate of adipic acid crystals grown in aqueous solutions containing an initial supersaturation of  $0.308 \text{ mol} \cdot \text{dm}^{-3}$  adipic acid and various initial concentrations of: (a) hexanoic acid; (b) octanoic acid; and (c) undecanoic acid.

$\Delta H^\ddagger$ , Fig. 4). A possible reason for this difference from hexanoic and undecanoic acids may be the different arrangement of the molecules of the additive, octanoic acid, in the crystal lattice, which may be reflected in the fact that octanoic acid causes the density to increase (Fig. 1b), corresponding to lattice contraction, unlike hexanoic or undecanoic acids (Fig. 1a and c). The octanoic acid molecules may be so positioned that they are acting as inhibitors or poisons of the higher energy sites from which dissolution preferentially occurs. In support of this suggestion, certain dyes retard the dissolution of drugs, such as sulphonamides and phenobarbital by adsorption at the active sites of dissolution (Tawashi and Piccolo, 1970; Piccolo and Tawashi, 1970, 1971a and b).

## Conclusions

The incorporation of hexanoic acid does not change the density of adipic acid crystals suggesting substitution, but low concentrations increase the crystal energy, specific surface area and dissolution rate and produce marked surface irregularities. Undecanoic acid behaves similarly but low concentrations reduce the density to a plateau suggesting lattice expansion up to a certain extent. Octanoic acid differs in that it not only increases the density, suggesting lattice contraction, but also reduces the dissolution rate. The effects on dissolution rate cannot be explained in terms of the surface area and the energy of the crystals alone, but imply a combination of influences.

The concentrations in the crystallization medium required to produce equivalent

effects decrease in the order: hexanoic acid, octanoic acid, undecanoic acid, corresponding to increasing crystal modification. An analogous rank order is found in the effects of the additives on crystal habit (Fairbrother and Grant, 1978, 1979).

The results indicate that the incorporation of small amounts of structurally similar additives can increase the energy of pharmaceutical crystals and increase or decrease their dissolution rate. These principles may not only offer considerable potential and scope in pharmaceutical formulation but may account for hitherto unexplained examples of batch to batch variation in pharmaceutical materials.

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