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Modification of adipic acid crystals. II. Influence of growth in the presence of oleic acid on crystal properties

K.Y. Chow, J. Go, Wang Zhongshan *, M. Mehdizadeh and D.J.W. Grant

Faculty of Pharmacy, University of Toronto, Toronto, Ont. M5S 1A1 (Canada)

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Summary

Adipic acid (AA) was crystallized under defined conditions from water containing 0–110 μmol · dm^{-3} oleic acid (OA). With increasing concentration of OA, the water content of the crystals was constant (0.047 ± 0.005 mole fraction), while the uptake of OA increased linearly, and the dissolution rate (DR) and specific surface area (SSA) of a defined sieve fraction decreased. The decrease in DR exceeded the decrease in SSA. Washing the crystals with chloroform removed an appreciable proportion of the poorly water-soluble OA from the surface of the crystals and produced a marked increase in DR. OA at 15 μmol · dm^{-3} caused a doubling of DR, whereas higher concentrations reduced DR of the washed crystals to the original value. Increasing incorporation of OA into the AA crystals reduced their density, indicating a decrease in crystallinity. Increasing incorporation of OA also reduced the melting point, T_m, the enthalpy of fusion, ΔH^f, and the enthalpy of solution, ΔH^s, of the crystals, indicating an increase in energy of the crystalline bulk, corresponding to an increase of lattice strain. Higher concentrations of OA reversed the energetic effects. The reduction in the entropy of fusion by small amounts of OA was greater than the increase in the sum of the ideal partial molar entropies of the components of the crystals by a factor approaching 1000. This indicates that OA greatly disrupts the order of the crystal lattice of AA.

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* *Permanent address*: Shanghai Institute of Drug Control, Shanghai, People's Republic of China.
Correspondence: D.J.W. Grant, Faculty of Pharmacy, University of Toronto, 19 Russell Street, Toronto, Ont. M5S 1A1, Canada.

Introduction

Growth of adipic acid crystals from water containing trace amounts of fatty acids and fatty alcohols modifies the crystal habit (Fairbrother and Grant, 1978, 1979). The uptake of fatty acids by the crystals also changes their density, enthalpy of fusion, enthalpy of solution, specific surface area and dissolution rate (Chow et al., 1984). Growth in the presence of oleic acid is found to exert a particularly pronounced effect on the habit and to influence the thermosonimetric properties of adipic acid crystals (Clark and Fairbrother, 1981).

The chemical synthesis and purification of drugs and excipients, though designed to yield materials of a reproducible high chemical purity, may not necessarily produce batches of product with equivalent pharmaceutical properties (Jones, 1981; York, 1983). Thus, trace concentrations of synthetic intermediates or degradation products in the liquors used for crystallization or precipitation can affect the surface and bulk properties of the particles produced. Examples are known for which certain physicochemical properties, such as melting point, solubility, and particle size distribution are hardly affected, whereas the physico-technical properties of the particles, such as strength, cohesiveness, compressibility and lubricity, are significantly altered. Such cases include grade variability or batch-to-batch variation in: (a) lubrication properties of magnesium stearate (Hanssen et al., 1970; Butcher and Jones, 1972; Müller, 1977; Miller et al., 1983); and (b) compaction behaviour or compression properties of a commercial brand of microfine cellulose, Elcema G250 (Rees and Rue, 1978) and of aspirin, barbitone and sulphathiazole (Summers et al., 1976).

Oleic acid ((Z)-9-octadecenoic acid) is a useful pharmaceutical excipient and solvent and is one of the most common naturally occurring fatty acids (Windholz et al., 1983). Since the oleic acid molecule is much larger than the molecules of adipic acid and of the fatty acids previously used as additives (Chow et al., 1984), we wished to ascertain whether significant amounts would be taken up by growing crystals and, if so, whether the thermodynamics, density, surface and dissolution rate of the crystals would be changed significantly.

Materials and Methods

Reagents and materials

The adipic acid used was the same as that described by Chow et al. (1984). The oleic acid was supplied by Sigma Chemicals, St. Louis, MO, as a highly pure analytical grade and was used as received. Water was distilled in an all-glass apparatus.

Batch crystallization from water

The process employed has been described by Chow et al. (1984).

Incorporation of oleic acid into growing crystals

The procedures have been described by Chow et al. (1984) using [9,10-^{3}H]oleic acid (New England Nuclear) as the radio-labelled additive and a commercial scintillation cocktail (Beckman Ready-Solv HP/b).

Determination of the water content of the crystals

The water content of 0.5 g samples of a defined sieve fraction (250–355 μm, 60–45 mesh) of adipic acid crystals was determined by Karl Fischer titration using Metrohm equipment (655 Dosimat, 614 Impulsomat, and 605 pH-meter). The Karl Fischer reagents (Eugen Scholz modification) and hydration standard, sodium tartrate dihydrate, were Hydranal grade, manufactured by Riedel-de Haën, Seelze, F.R.G. and supplied by Crescent Chemicals, Hauppauge, NY, U.S.A. Since the process of drying the crystals after harvesting effectively removes all adsorbed water, the water content being determined is that within the crystal lattice of adipic acid.

Microscopic methods, calorimetric techniques, X-ray powder diffraction and measurements of density, specific surface area and dissolution rate

The following techniques were carried out as described by Chow et al. (1984): optical microscopy, scanning electron microscopy (SEM), hot stage microscopy (HSM), X-ray powder diffraction, differential scanning calorimetry (DSC), solution calorimetry (SC), and measurements of density, specific surface area (SSA) and dissolution rate (DR). Using DSC, the melting point, T_m, and the enthalpy of fusion, ΔH^f, of the crystals were determined as previously described, while from SC, the enthalpy of solution, ΔH^s, of the crystals in water at 25°C was measured (Chow et al., 1984).

Results and Discussion

Influence of crystal size

Since crystal properties frequently depend on particle size, the extent of this effect was studied as previously described (Chow et al., 1984). Firstly, over 90% of the crystals, with and without various concentrations of oleic acid, were within the sieve fraction 150–850 μm, which, from a pharmaceutical point of view, is relatively large and certainly not small enough for a size-related increase in surface energy. Secondly, after growth in the absence of oleic acid, crystals of different sieve fractions ranging from < 75 μm to 850 μm gave essentially the same values of $T_m = 420.9 \pm 0.1$ K, $\Delta H^f = 34.34 \pm 0.20$ kJ $\cdot$ mol^{-1}, $\Delta H^s = 33.20 \pm 0.49$ kJ $\cdot$ mol^{-1}, and density $= 1.3510 \pm 0.0012$ g $\cdot$ cm^{-3}. Consequently, the effects of oleic acid, to be discussed, cannot be attributed to changes in the crystal size distribution and must therefore reflect a direct influence of oleic acid on the properties under consideration.

Additive incorporation and density

The mole fraction of oleic acid taken up by the crystals increased linearly with increasing concentration of oleic acid in solution (Table 1). Progressive dissolution

TABLE 1

INCORPORATION OF [^{3}H]-LABELLED OLEIC ACID BY ADIPIC ACID CRYSTALS [a], THE WATER CONTENT [b] OF THE CRYSTALS AND THEIR CRYSTALLINITY [c]

Initial concentration of oleic acid (μmol·dm^{-3})	Mole fraction of oleic acid in the crystals ($x_{ol} \times 10^4$)	Mole fraction of water in the crystals ($x_w \times 10^2$)	Crystallinity expressed as a percentage
0	0	4.67	90.2
15.7	0.386	5.93	88.0
31.5	0.698	4.90	86.2
47.2	1.01	4.37	84.4
62.9	1.32	4.45	82.7
78.7	1.63	4.45	80.9
94.4	1.95	4.52	79.1
110.1	2.26	4.52	–

[a] Crystallized from aqueous solutions containing an initial supersaturation of 0.308 mol·dm^{-3} adipic acid with various initial concentrations of oleic acid.

[b] Mean value ± standard error, $x_w = 0.047 \pm 0.005$.

[c] Calculated using Eqn. 4 and the smoothed densities from the solid line in Fig. 1.

of the crystals with chloroform or in water in the dissolution rate experiments indicates that oleic acid is distributed throughout the crystals with a slightly higher concentration near the surface. This corresponds to a solid solution of oleic acid in adipic acid with some adsorbed oleic acid.

The mole fraction of water, x_w, in the adipic acid crystals is remarkably constant at 0.047 ± 0.005 (Table 1), indicating that the uptake of oleic acid by growing adipic acid crystals does not alter the small concentration of water in the crystals. This behaviour contrasts sharply with the influence of *p*-acetoxyacetanilide in controlling the water content of acetaminophen crystals (Chow et al., 1985).

The uptake of oleic acid by the crystals decreases their density (Fig. 1) indicating appreciable lattice expansion. The density values calculated from the small amounts of oleic acid incorporated according to the various models of solid solution formation (Chow et al., 1984, Eqns. 1–9) indicate that simple 1 : 1 substitution (Eqn. 3, with $p = 1$) and the simple interstitial model (Eqn. 8) predict densities that are almost constant (Fig. 1). Although the experimental decreases in density show some variability on the highly expanded scale (Fig. 1), they show a satisfactory fit to Eqns. 5 and 6 in Chow et al. (1984) with $p = 65 \pm 10$. For the purpose of this estimation, the mole fraction of incorporated water was assumed to be constant (Table 1). The calculated value of p corresponds to the loss of 55–75 molecules of adipic acid for each oleic acid molecule incorporated substitutionally or interstitially into a given lattice volume. This large estimated displacement indicates that each oleic acid molecule incorporated causes considerable disruption of the crystal lattice and appears to be consistent with the great disparity in molecular size of oleic acid (an unsaturated C_{18} acid) and adipic acid (a C_6 dibasic acid). The double bond with a Z- or cis-configuration must reduce the flexibility of the oleic acid molecule and thereby

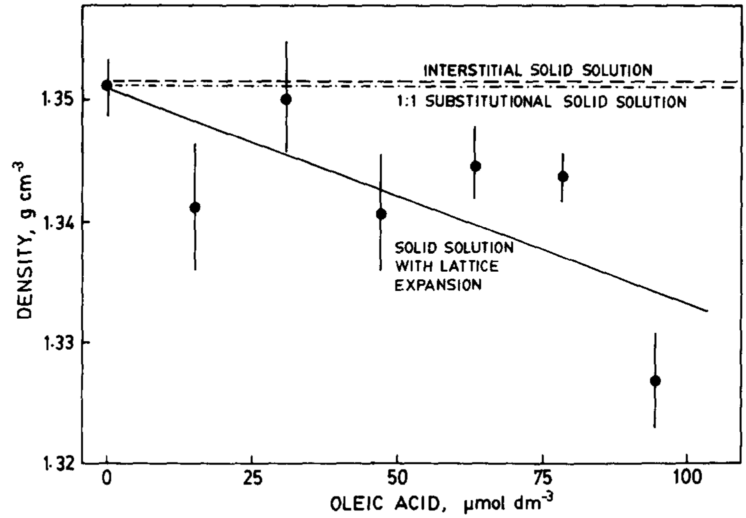

Fig. 1. Density at 25°C of adipic acid crystals grown in aqueous solutions containing an initial supersaturation of 0.308 mol·dm^{-3} adipic acid and various initial concentrations of oleic acid. The vertical bars indicate the standard errors. The horizontal and sloping lines represent the densities predicted (Chow et al., 1984) from x_{ol} (Table 1) assuming a simple 1 : 1 substitutional solid solution (–·–·–·–), a simple interstitial solid solution (– – – –), and a solid solution with lattice expansion (———). The line of best fit corresponds to the exclusion of 65 molecules of adipic acid for each molecule of oleic acid incorporated.

further disrupt the lattice and increase the mean lattice dimensions of the adipic acid crystals.

The maximum measured decrease in density brought about by the presence of oleic acid in the crystals was 1.2% (Fig. 1). If any possible crystal imperfections (defects and dislocations) are assumed to increase each linear dimension by about the same amount, the maximum increase in lattice spacing brought about by oleic acid in the adipic acid crystals under study would be by a factor of $(1.012)^{1/3} = 1.004$, i.e. by +0.4%. However, since the limit of detection of changes in lattice spacing by X-ray powder diffraction is 0.5% (Chow et al., 1984), the diffraction patterns of the adipic acid crystals failed to show any differences in lattice spacings between all the samples investigated. This negative result also confirms the absence of polymorphism and the lack of formation of stoichiometric hydrates.

Density is believed to decrease linearly with decreasing degree of crystallinity which itself decreases with increasing concentration of crystal imperfections (defects and dislocations) and therefore with increasing crystal disorder. Hüttenrauch (1978) has recommended the use of density measurements to estimate the degree of crystallinity using the crystallographic density, d_{100}, as the standard corresponding to 100% crystallinity calculated from

$$d_{100} = Mn/Nv \qquad (1)$$

where M = molecular weight of the substance, n = number of molecules per unit cell, N = Avogadro's constant, 6.022×10^{23} mol^{-1}, and v = volume of the unit cell from single crystal X-ray diffraction measurements.

As the standard corresponding to 0% crystallinity, Hüttenrauch (1978) has recommended the amorphous state of the substance. Unfortunately, the truly amorphous state without any regions of crystalline ordering is difficult to achieve for many substances. For example, the quenched melt may not be completely amorphous, but may contain regions of crystalline order. Furthermore, although prolonged milling may cause the density of a substance to fall to a constant minimum value, an equilibrium between processes of particle fracture and particle agglomeration may occur. In either case the crystallinity will not be zero, but finite. Accordingly, we suggest that 0% crystallinity may more appropriately correspond to the supercooled liquid state, whose density, d_0, can be estimated from group contributions, V_g, to the molar volume, V_m, of the liquid, thus:

$$d_0 = M/V_m \tag{2}$$

$$V_m = \Sigma V_g \tag{3}$$

The degree of crystallinity, expressed as a percentage, may be calculated from:

$$c = \frac{d - d_0}{d_{100} - d_0} \times 100 \tag{4}$$

where d is the measured density.

In the case of adipic acid in this and our previous work (Chow et al., 1984), $d_{100} = 1.366\ \mathrm{g \cdot cm^{-3}}$ from Eqn. 1 in which $n = 2$ and $v = 35.53$ Å^3 calculated from the unit cell dimensions of adipic acid crystallized from water (Housty and Hospital, 1965). For adipic acid $d_0 = 1.214\ \mathrm{g \cdot cm^{-3}}$, the mean of the values calculated using Eqn. 2 from the molar volume, 120.8 $\mathrm{cm^3 \cdot mol^{-1}}$ (from Exner, 1967) and 120.0 $\mathrm{cm^3 \cdot mol^{-1}}$ (from Rheineck and Lin, 1968), each calculated from group contributions using Eqn. 3.

The crystallinity values in Table 1 were calculated by means of Eqn. 4 using the calculated values of d_{100} and d_0 stated above and the smoothed densities represented by the full line in Fig. 1. According to the definition employed, the crystallinity of adipic acid grown in the absence of oleic acid is only 90%, suggesting that the conditions of crystallization (supersaturation 0.308 $\mathrm{g \cdot dm^{-3}}$, rapid crystallization over 1 h) introduces an appreciable concentration of crystal imperfections, which would not be apparent after a process of slow crystallization that is usually employed to provide the carefully selected single crystals for X-ray crystallography. This reduction of crystallinity by about 10% is probably associated with the water content of the crystals, $x_w \approx 0.05$ (Table 1). Growth of adipic acid crystals in the presence of oleic acid reduces the crystallinity by a further 2–11%, which represents an enormous decrease relative to the small content of oleic acid in the crystals ($x_{ol} \approx 4 \times 10^{-5}$ to 2×10^{-4}). The reductions in density and crystallinity, as a result of increasing concentration of oleic acid, parallel the decrease in acoustic emission in thermosonimetry (Clark and Fairbrother, 1981) and the disturbance to crystal growth as reflected by increasing pitting of the faces and loss of edge definition of the crystals. The common underlying origin of these effects is probably the increasing concentration of crystal imperfections (impurity defects and dislocations) caused by contamination with oleic acid.

Thermodynamic properties

Growth of adipic acid crystals in the presence of increasing concentrations of each fatty acid additive causes T_m (Fig. 2), ΔH^f and ΔH^s (Fig. 3) to decrease to minima, indicating an increase in lattice strain, and then to increase to values which approach those in the absence of additive, indicating a release of lattice strain. The lattice strain may arise from "impurity defects" and dislocations induced by the presence of the additive in the crystals (Hüttenrauch, 1978). The changes in ΔH^f (-1.9 to -9.2% in Fig. 3) are about 3–6 times larger than the changes in T_m (-0.7 to -1.6% in Fig. 2), so the entropy of fusion, ΔS^f, (Table 2) parallels ΔH^f fairly closely. Following the arguments presented by Chow et al. (1984), *decreases* in ΔH^f and ΔS^f correspond to *increases* in the enthalpy, internal energy and entropy of the crystal lattice, H_{solid}, U_{solid} and S_{solid}, respectively, according to the equations:

$$\Delta H^f = H_{liquid} - H_{solid}; \quad \Delta U^f = U_{liquid} - U_{solid}; \quad \Delta S^f = S_{liquid} - S_{solid} \qquad (5)$$

(The main assumption here is that the amounts of the additives in the molten crystals are sufficiently small that the enthalpy, internal energy and entropy of the relatively disordered liquid state, H_{liquid}, U_{liquid} and S_{liquid}, respectively, are virtually constant. In view of the small values of x_{ol} and the approximate constancy of x_w (Table 1), this assumption appears to be justified.)

From the analytical data presented in Table 1 the ideal partial molar entropy of

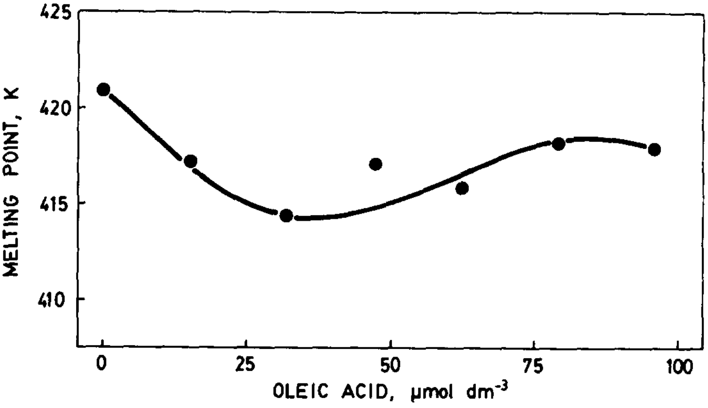

Fig. 2. DSC melting point, T_m, of adipic acid crystals grown in aqueous solutions containing an initial supersaturation of 0.308 mol·dm^{-3} adipic acid and various concentrations of oleic acid.

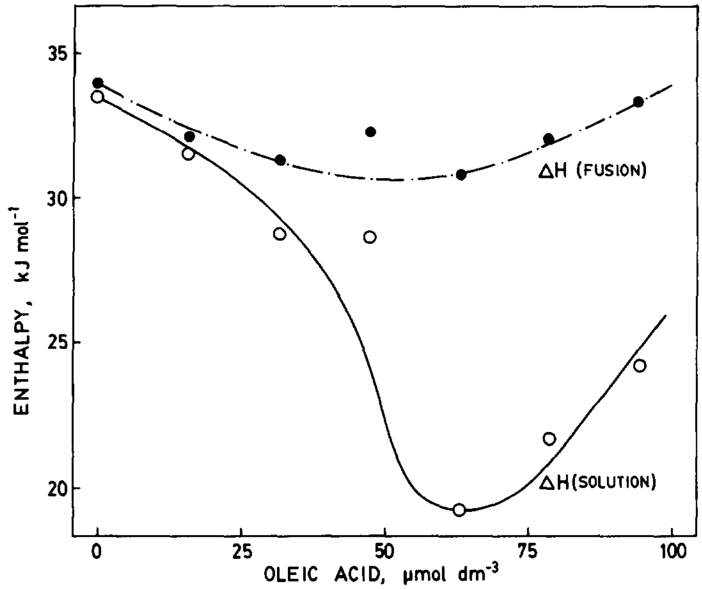

Fig. 3. Enthalpy of fusion, ΔH^f, (–·–●·–·–) at the melting point and enthalpy of solution, ΔH^s, (—○—) to 8.55 mmol·dm^{-3} in water at 298.15K for adipic acid crystals grown in aqueous solutions containing an initial supersaturation of 0.308 mol·dm^{-3} adipic acid and various initial concentrations of oleic acid.

adipic acid, $\bar{S}^{id}_{ad}$, oleic acid, $\bar{S}^{id}_{ol}$, and water, $\bar{S}^{id}_{w}$, in the crystals were calculated as follows:

$$\bar{S}^{id}_{ad} = -Rx_{ad} \ln x_{ad}; \quad \bar{S}^{id}_{ol} = -Rx_{ol} \ln x_{ol}; \quad \bar{S}^{id}_{w} = -Rx_{w} \ln x_{w} \tag{6}$$

where x_{ad}, x_{ol} and x_w are the mole fractions of adipic acid, oleic acid and water, respectively, in the crystals. The ideal molar entropy of mixing, ΔS^m_{ideal}, was calculated by summation, thus:

$$\Delta S^m_{ideal} = \bar{S}^{id}_{ad} + \bar{S}^{id}_{ol} + \bar{S}^{id}_{w} \tag{7}$$

In view of the very small changes in x_{ol} (Table 1), the progressive increase in $\bar{S}^{id}_{ol}$ is in danger of being swamped by the relatively large fluctuations in $\bar{S}^{id}_{w}$ resulting from the variability of x_w about its mean value, 0.047. Consequently, x_w was assumed to have this constant value, which leads to $\bar{S}^{id}_{w} = 1.199$ J · K^{-1} · mol^{-1} in Eqns. 6 and 7. Table 2 presents the calculated values of $\bar{S}^{id}_{ad}$, $\bar{S}^{id}_{ol}$ and ΔS^m_{ideal}. The changes in these values brought about by the presence of oleic acid are generally much smaller than the corresponding changes for acetaminophen crystals caused by the presence of *p*-acetoxyacetanilide (Chow et al., 1985).

The increase in S_{solid}, corresponding to a decrease in ΔS^f (Table 2) is about 1–7 J · K^{-1} · mol^{-1} which is of the order 10^3 or 10^2 times the changes in ΔS^m_{ideal}. This

TABLE 2

ENTROPY OF FUSION, $\Delta S^f = \Delta H^f/T_m$, IDEAL PARTIAL MOLAR ENTROPIES [a] OF ADIPIC ACID, $\bar{S}_{ad}^{id}$, OLEIC ACID, $\bar{S}_{ol}^{id}$, AND WATER [b] AND THE IDEAL MOLAR ENTROPY OF MIXING [c], ΔS_{ideal}^m, OF ALL THREE COMPONENTS OF ADIPIC ACID CRYSTALS [d]

Initial concentration of oleic acid (μmol·dm^{-3})	ΔS [f]	Change [e] in S_{solid}	Change [f] in $\bar{S}_{ad}^{id}$	$\bar{S}_{ol}^{id}$	Change [g] in ΔS_{ideal}^m
	(J. K^{-1}·mol^{-1})		(mJ·K^{-1}·mol^{-1})		
0	80.56	0	0	0	0
15.7	76.95	+3.60	+0.31	3.26	+3.57
31.5	75.49	+5.07	+0.55	5.56	+6.11
47.2	77.38	+3.17	+0.80	7.73	+8.52
62.9	74.04	+6.52	+1.05	9.82	+10.86
78.7	76.56	+4.00	+1.29	11.83	+13.13
94.4	79.62	+0.94	+1.54	13.84	+15.38
110.1	–	–	+1.79	15.80	+17.59

[a] Calculated from Eqn. 6.

[b] $\bar{S}_w^{id} = 1199$ mJ·K^{-1}·mol^{-1}.

[c] Calculated from Eqn. 7.

[d] Crystallized from aqueous solutions containing an initial supersaturation of 0.308 mol·dm^{-3} adipic acid with various initial concentrations of oleic acid.

[e] Calculated assuming S_{liquid} is constant in Eqn. 5.

[f] With respect to $\bar{S}_{ad}^{id} = 383.52$ mJ·K^{-1}·mol^{-1} for crystals grown in the absence of oleic acid.

[g] With respect to $\Delta S_{ideal}^m = 1582.83$ mJ·K^{-1}·mol^{-1} for crystals grown in the absence of oleic acid.

suggests that the much larger increases in the entropy of the solid are better attributed to the introduction of crystal imperfections (impurity defects and dislocations) brought about by the additives in the crystals, than to simple mixing or dilution effects in the crystals. The data for *n*-alkanoic acids as additives in adipic acid crystals lead to similar conclusions (Chow et al., 1984). A plot of ΔS^f against ΔS_{ideal}^m for the first 3 points of decreasing ΔS_{ideal}^m (increasing change in S_{solid}) has a correlation coefficient of -0.990, a ΔS^f intercept of 80.56 J·K^{-1}·mol^{-1}, and a slope of -841. The slope is about 100 times greater than that for acetaminophen doped with *p*-acetoxyacetanilide and water (Chow et al., 1985), suggesting that oleic acid exerts a very much greater disruptive influence on the crystal lattice of adipic acid. Although the presence of oleic acid (like the *n*-alkanoic acids) influences the density (Fig. 1), T_m (Fig. 2), ΔH^f (Fig. 3) and ΔS^f (Table 2), the effects are not mediated by the water content, unlike the effects of *p*-acetoxyacetanilide on the properties of acetaminophen crystals (Chow et al., 1985).

The enthalpy of solution, ΔH^s, of adipic acid crystals is also affected by growth in the presence of oleic acid (Fig. 3) and hence by the incorporated oleic acid. The trend is similar to that of ΔH^f, but the relative and absolute changes in ΔH^s are much larger. These differences probably arise: (a) from the fact that ΔH^s and ΔH^f were measured at different temperatures (298 K and $T_m \approx 420$K, respectively); and (b) from the effect of oleic acid on the molar heat capacity of the crystals, as proposed for *n*-alkanoic acids as additives (Chow et al., 1984).

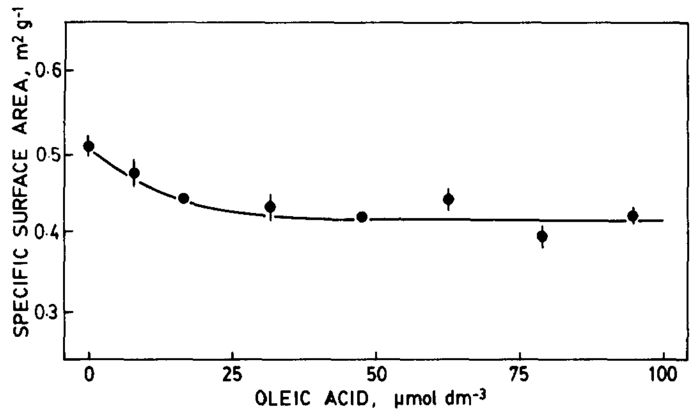

Fig. 4. Specific surface area of adipic acid crystals grown in aqueous solutions containing an initial supersaturation of 0.308 mol·dm^{-3} and various initial concentrations of oleic acid.

Crystal surfaces

The SSA of a collection of particles depends on the particle size distribution and on the surface features of individual particles. The crystal size distribution, determined by sieve analysis (Chow et al., 1984), was found to be independent of the concentration of oleic acid. The decrease of about 20%, caused by up to 15.6 μmol·dm^{-3} oleic acid, and the eventual levelling of SSA at higher concentrations (Fig. 4) are largely determined by differences in surface features. Adipic acid crystals grown in the absence of additive consist of hexagonal slabs (Fig. 5, upper left) with perceptible surface features on the micro-scale (Fig. 5, upper right), but when grown in the presence of oleic acid, the crystals are rounded (Fig. 5, lower left) with somewhat smoother features on the micro-scale (Fig. 5, lower right). The reduction in SSA brought about by oleic acid contrasts with the maxima in SSA caused by the lower *n*-alkanoic acids (Chow et al., 1984). Oleic acid, which consists of long molecular chains, is presumably adsorbed extensively by van der Waals forces on to the crystal surfaces where it obscures many of the surface irregularities that are more readily apparent in the presence of the lower fatty acids. Oleic acid does, however, produce some sharp irregularities resembling the "saw-teeth" produced by growth of adipic acid crystals in the presence of *n*-octanoic or *n*-undecanoic acid. Such features indicate the creation of new faces with higher Miller indices which are normally unstable and are outgrown in the absence of the additive to produce large, relatively flat faces. The small undulations (Fig. 5, upper right) on these large faces may reflect local concentration changes in the solution during rapid crystal growth. Oleic acid, perhaps by slowing down the growth of these faces, may reduce these concentration differences and thereby produce smoother planes. That the surface features are not artifacts of SEM was confirmed by optical microscopy.

Dissolution rate

As in previous studies with adipic acid (Chow et al., 1984), the dissolution–time profile of 1.00 g of crystals of a defined sieve fraction (425–850 μm; 20–35 mesh) in

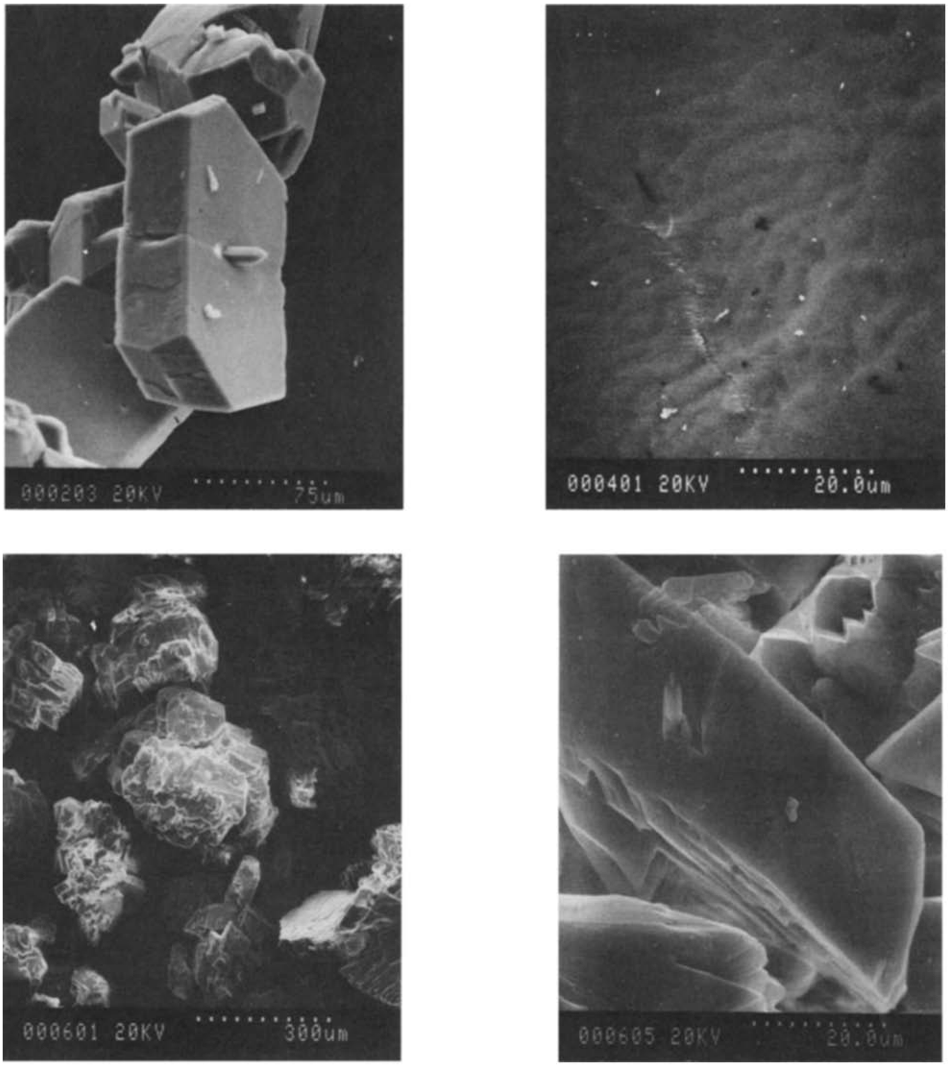

Fig. 5. Scanning electron micrographs of the surfaces of adipic acid crystallized from water in the absence of oleic acid (upper left and upper right) and in the presence of 31.5 μmol$\cdot$dm^{-3} oleic acid (lower left and lower right). The initial supersaturation of adipic acid was 0.308 mol$\cdot$dm^{-3} in each case.

750 cm^3 of distilled water was determined at 4°C. The initial dissolution rate of the crystals prepared as described (Chow et al., 1984) decreased progressively with increasing concentration of oleic acid (Fig. 6). This dissolution behaviour differs from that of crystals containing hexanoic acid or undecanoic acid, low concentrations of which accelerate dissolution (Chow et al., 1984). The decrease brought about by oleic acid was greater than the decrease in SSA (Fig. 4) determined by nitrogen adsorption. This behaviour might suggest a reduction in the dissolution rate per unit

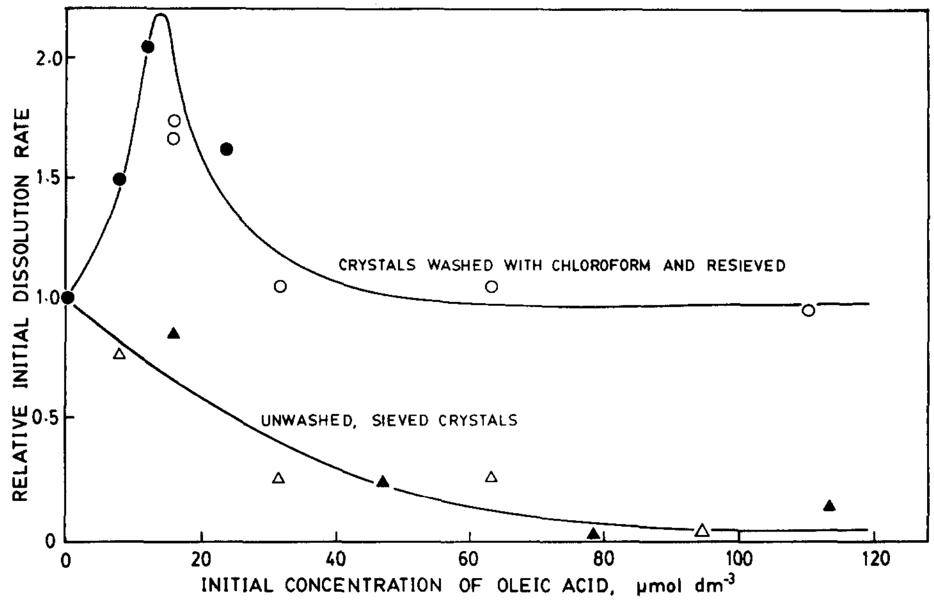

Fig. 6. Relative initial dissolution rate of adipic acid crystals (sieve fraction 425–850 μm) grown in aqueous solutions containing an initial supersaturation of 0.308 mol · dm^{-3} adipic acid and various initial concentrations of oleic acid: unwashed crystals (△, experiment 1; ▲, experiment 2); crystals washed with chloroform (○, experiment 1; ●, experiment 2).

surface area (intrinsic dissolution rate); if it is assumed that the crystal surface area exposed to the aqueous dissolution medium is proportional to that available to nitrogen adsorption. The dissolution behaviour might also suggest that the presence of oleic acid in the crystals reduces the wetted surface area by a greater proportion than the surface area available for nitrogen adsorption. In either case, the inhibitory influence of oleic acid on the dissolution rate of adipic acid probably results from the surface adsorption of poorly water-soluble oleic acid whose aqueous solubility ($<$ 1.8 mmol · dm^{-3} at 25°C, Seidell, 1941) is much lower than that of adipic acid (160 mmol · dm^{-3} at 25°C, Grant et al., 1984). A number of solvents were tested for their ability to dissolve oleic acid in preference to adipic acid. For this purpose the solvent of choice was chloroform, in which oleic acid is soluble in all proportions at temperatures at or above 20°C (Stephen and Stephen, 1963) and in which adipic acid is much less soluble (4.86 mmol · dm^{-3} at 40°C, Fairbrother, 1981; the estimated solubility at 25°C is 3 mmol · dm^{-3}).

Crystals of adipic acid (10 g), which had been grown in the presence or absence of oleic acid, were placed in a 60 cm^3 sintered glass Buchner funnel of coarse porosity. The crystals were washed by adding 25 cm^3 of chloroform, swirling, and aspirating the solvent under gentle suction over a 5-min period. After a second washing, the crystals were dried for 18 h under vacuum over paraffin wax and phosphorus pentoxide and were sieved as described for the dissolution study. No differences in the shape, size and surface appearance could be detected microscopically between the washed and unwashed crystals, suggesting that only a very thin layer of oleic acid has been adsorbed and removed. During sieving of adipic acid crystals, static electrification of the surface is usually observed. This effect was greatly reduced after washing with chloroform, suggesting that an insulated layer of a less polar material, presumably oleic acid, had been removed.

The overall shape of the dissolution profile showed a gradual decrease in dissolution rate with time (cf. Chow et al., 1984) and this qualitative behaviour was unchanged after washing with chloroform. With increasing content of oleic acid, the initial dissolution rate (and intrinsic dissolution rate) of the chloroform-washed crystals increased sharply to a maximum and then decreased less steeply to a constant value equal to that of the pure adipic acid crystals (Fig. 6). Washing of the crystals with chloroform followed by drying could result in some recrystallization of adipic acid on the crystal surfaces, thereby changing the surface energy and surface area. This effect will probably be negligible, identical from one sample of crystals to another and independent of the amount of oleic acid present, in view of the constant relative amounts of chloroform and crystals, the infinite solubility of oleic acid and the very low solubility of adipic acid in chloroform. Thus, it is unlikely that the maximum in the plot of dissolution rate against oleic acid concentration could be caused by recrystallization of adipic acid.

Since the increased dissolution rate occurred only when the oleic acid had been removed from the crystal surfaces, it appears that the oleic acid blocks the active sites of dissolution on the surface of the crystals and/or reduces their wetted surface area. Similar increases in the dissolution rate to a maximum are given by increasing concentrations of hexanoic acid or undecanoic acid, for which an increase of crystal energy has been suggested (Chow et al., 1984). However, with oleic acid the maximum in dissolution rate, reflecting a higher surface energy, occurs at a lower concentration of oleic acid (Fig. 6) than the maximum in the bulk energy of the crystals (minimum ΔH^f and ΔH^s, Fig. 3) suggesting that the dissolution rate is being influenced by other factors, such as the wetted surface area. Further studies are in progress.

Conclusions

Growth of adipic acid crystals in the presence of increasing concentrations of oleic acid causes small but linearly increasing incorporation of oleic acid and significant lattice expansion which may reflect considerable lattice disruption and reduced crystallinity. This is consistent with the great disparity in molecular size and shape between oleic acid and adipic acid. The water content of the crystals is virtually unaffected. Oleic acid appears to become concentrated at or near the crystal surface where it reduces the dissolution rate and specific surface area of untreated crystals. This may reflect the propensity of the long molecular chains of oleic acid to interact by van der Waals forces at the crystal surfaces.

Low concentrations (up to 16 μmol · dm^{-3}) of oleic acid increase the dissolution rate of chloroform-washed crystals, suggesting an increased surface energy. Higher concentrations of oleic acid cause the dissolution rate of chloroform-washed crystals to return to the original value, suggesting that the additive blocks the active sites of dissolution (cf. Tawashi and Piccolo, 1970; Piccolo and Tawashi, 1970, 1971a and b). Relatively low concentrations of oleic acid (up to 63 μmol · dm^{-3}) cause the bulk crystal energy to increase to a maximum (corresponding to minima in T_m, ΔH^f and ΔH^s), reflecting an increase of the bulk lattice strain to a maximum. The increase in the entropy of the solid is a factor approaching 1000 times that calculated assuming ideal mixing of the components of the crystals, suggesting very considerable lattice disruption of the crystal lattice of adipic acid by oleic acid. Higher concentrations ($>$ 63 μmol · dm^{-3}) of oleic acid cause the crystal energy to return to the original value suggesting a gradual release of lattice strain. This reversal may result from the reorganization of the incorporated molecules of oleic acid into environments of lower energy.

Although the above results show rough similarities to the patterns established for the doping of adipic acid with the lower fatty acids (Chow et al., 1984) and for the doping of acetaminophen with water and *p*-acetoxyacetanilide (Chow et al., 1985), there are important differences of detail. These differences underline the necessity of further research in understanding the influence of crystal additives on the pharmaceutical properties of drug crystals.

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