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INFLUENCE OF FATTY ACID ADDITIVES ON THE DISSOLUTION BEHAVIOR OF ADIPIC ACID CRYSTALS

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ABSTRACT

Adipic acid crystallized from water containing various concentrations of hexanoic, octanoic or undecanoic acid was examined using differential scanning calorimetry (DSC), density measurements and dissolution rates. Parallel decreases (and increases) in the enthalpy of fusion (ΔH^f), entropy of fusion (ΔS^f) and melting point (T_m) were observed; these changes correspond to increases (and decreases) of both the crystal energy and the concentration of crystal imperfections, resulting from the presence of additives in the crystals. When the crystals were well wetted, the rate of dissolution was inversely related to ΔH^f, T_m and ΔS^f in agreement with the usual assumption that "impurity" defects increase the energy and consequently enhance the dissolution rate of the crystals. The initial dissolution rate of the crystals, however, decreased with decreasing ΔH^f, T_m and ΔS^f, suggesting a reduction of wettability which may be caused by an associated increase in the concentration of surface irregularities. DSC appears to be a more sensitive indicator of crystal imperfection than density for doped adipic acid crystals.

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INTRODUCTION

Crystal imperfections, i.e. point defects and dislocations, are present in all crystals and may influence many pharmaceutical properties of drugs and excipients (1,2,3), such as the wettability (1), mechanical compressibility (1,4) and rate of dissolution (5) of drugs and excipients. Moreover, the crystallinity or the concentration of crystal imperfections can easily be altered [a] by normal pharmaceutical processing, such as drying (1,6), e.g. of lactose monohydrate (6), and milling, e.g. of digoxin (7) and lactose (1), and [b] by crystallization in the presence of additives (8) or under different growth conditions (9,10). Variations in the nature and concentration of crystal imperfections may account for possible batch-to-batch differences, bio-inequivalences and difficulties in the manufacture of pharmaceutical formulations.

This study continues our investigations of the influence of trace additives in solid solution on the pharmaceutical properties of crystals of adipic acid, a pharmaceutical excipient (8). The crystallinity of adipic acid crystals was modified by crystallization in the presence of various concentrations of a fatty acid additive (hexanoic, octanoic or undecanoic acid). The influence of each additive was then quantified by DSC and density measurements and the results obtained were compared with those derived from dissolution studies. The objective of this study is to explore the relationship between the crystal thermodynamics and the dissolution rate of a pharmaceutical solid (adipic acid), doped with structurally-related additives (n-alkanoic acids).

MATERIALS AND METHODS

Materials

Adipic acid was of certified grade (Fisher #A44) and its properties have been described previously (8). The fatty acids were the purest available or were purified by distillation (8). Water was distilled in an all-glass apparatus.

Batch Crystallization from Water

Relatively large quantities of crystals were required for determinations of densities and dissolution rates. This necessitated a new, scaled-up version of an earlier batch crystallization process (8). The U.S.P. XX (1980) Dissolution Apparatus II (the Automated Dissoette, Hanson Corporation, Northbridge, California) was used as the batch crystallizer. This apparatus allowed up to 6 simultaneous crystallizations to take place, each in a 1 liter dissolution vessel, inside a thermostatically controlled water bath. In each dissolution vessel, 80 g of adipic acid and 2 ml of ethanol, containing a defined amount of the fatty acid additive, were dissolved in 800 ml of distilled water at 60°C. The solutions were gang-stirred at 100 r.p.m., equilibrated at 60°C for at least 1 hour and allowed to crystallize for 18 hr by permitting the entire 25 liter water bath to cool spontaneously to 25°C. The conditions of crystallization were further defined by this decrease in temperature during crystallization which was of the first order, the rate constant being 3.23×10^{-3} min^{-1} over the 18 hr period.

The crystals thus obtained were harvested by rapid filtration through a Whatman #1 filter paper on a Buchner funnel using moderate suction, air-dried overnight, sieved, further dried over phosphorus pentoxide under vacuum, and stored in air-tight amber glass jars for further experiments. To avoid any influence of particle size on the experimental findings, sieve fractions of 425-850 μm (20-35 mesh) were used in all experiments.

Differential Scanning Calorimetry (DSC)

Samples of 3 to 5 mg of adipic acid crystals were heated (from 320 K to 450 K) in aluminum pans for volatile samples at a rate of 10°C/min in a Perkin-Elmer DSC-2C differential scanning calorimeter (DSC) with a Perkin-Elmer 56 dual pen recorder. Nitrogen (20 psi) was used as the purge gas and 5 mg of pure indium as the calorimetric standard. The order of scanning in each set of samples was randomized to avoid systematic errors and the performance, as well as the calibration of the calorimeter, were checked every fifth scan using an indium standard. All weights were determined using an electronic microbalance (Perkin-Elmer AD-22 Autobalance). Each batch of crystals was examined in triplicate.

The enthalpy of fusion (ΔH^f) was determined by comparing the area under the thermograms of the samples and the indium standard. The thermograms were traced repeatedly (3 times) on chart-recorder paper and the average areas under the curves were determined by cutting and weighing. Since a relatively sharp fusion peak was observed from the DSC thermogram of each sample, the fusion process could be considered as a first order isothermal transition. Hence, the melting point (T_m) of the sample was taken as the temperature at the point of intersection of the leading line of steepest slope and the base line of the thermogram (11). Since the change in free energy during melting was zero, the entropy of fusion (ΔS^f) of each sample was calculated by dividing ΔH^f by T_m of the crystals.

Density Measurements

The density of adipic acid crystals was determined by liquid displacement pycnometry as previously described (8).

Dissolution Rate Determination

The dissolution profile of the adipic acid crystals was determined using the method and conditions previously described (8). As shown in Fig. 1, the dissolution profile of adipic acid crystals grown in the absence of fatty acid additives displays a typical reduction in dissolution rate with time (Fig. 1, upper curve), whereas that of crystals grown in the presence of a fatty acid displays, in certain cases, an increase in dissolution rate with time (Fig. 1, lower curve). In view of the biphasic dissolution profiles produced by the fatty acids, the "initial dissolution rate" was calculated from the initial slope of the dissolution-time curve (from 0 to 6 min). The subsequent dissolution rate was estimated from the slope between 6 and 12 min and was later corrected for the reduction in crystalline surface area, which was calculated from the mass of the crystals already dissolved, to provide the "apparent intrinsic dissolution rate", as described in a subsequent section entitled Dissolution Studies.

RESULTS AND DISCUSSION

Thermal Analysis using DSC

Parallel decreases (and increases) in ΔH^f, ΔS^f and T_m of the adipic acid crystals were observed with increasing concentration of each additive present during crystallization. The percentage changes in absolute T_m were smaller than the percentage changes in ΔH^f and ΔS^f and were, therefore, sometimes less apparent (Fig. 2-4, Table 1).

Decreases in ΔH^f, ΔS^f and T_m indicate increases in crystal energy and disorder (12) and probably reflect an increase in the concentration of lattice imperfections. The converse also applies. This relationship between

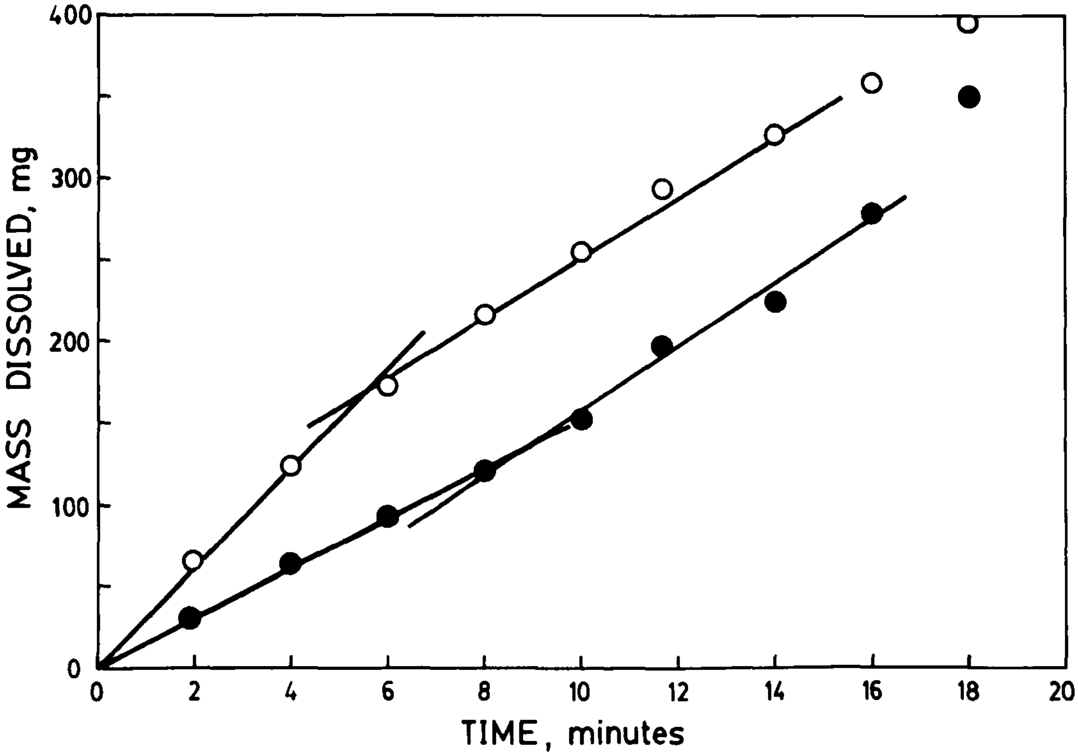

FIGURE 1

Dissolution profile of adipic acid crystals grown in the absence (O, upper curve) and in the presence of 15 μg/ml of octanoic acid (●, lower curve).

the thermodynamic properties of melting and the crystal energy and entropy has been described and explained in a previous publication (8).

The difference in thermodynamic properties among the crystal samples are unlikely to be caused by changes of particle size, since a defined sieve fraction were used in all experiments. Furthermore, previous work indicated negligible influences of particle size (8). Moreover, the changes of thermodynamic properties could not have arisen from the presence of stoichiometric hydrates or polymorphs, since no desolvation or polymorphic

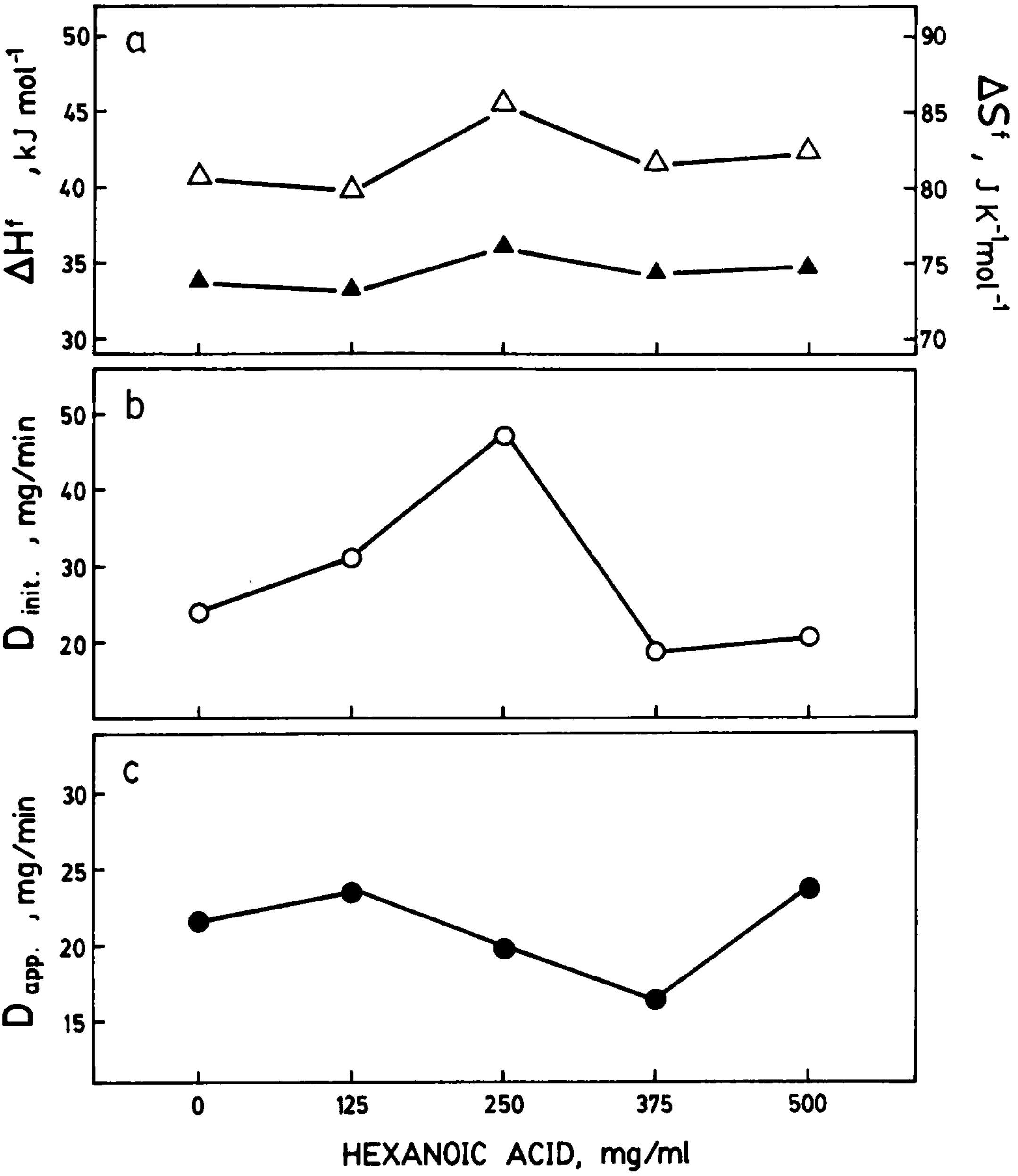

FIGURE 2

[a] Entropy of fusion, ΔS^f,(△) and enthalpy of fusion, ΔH^f,(▲), [b] initial dissolution rate, D_{init} (O), and [c] apparent intrinsic dissolution rate, D_{app}, (●) of adipic acid crystals grown in the presence and absence of various concentrations of hexanoic acid.

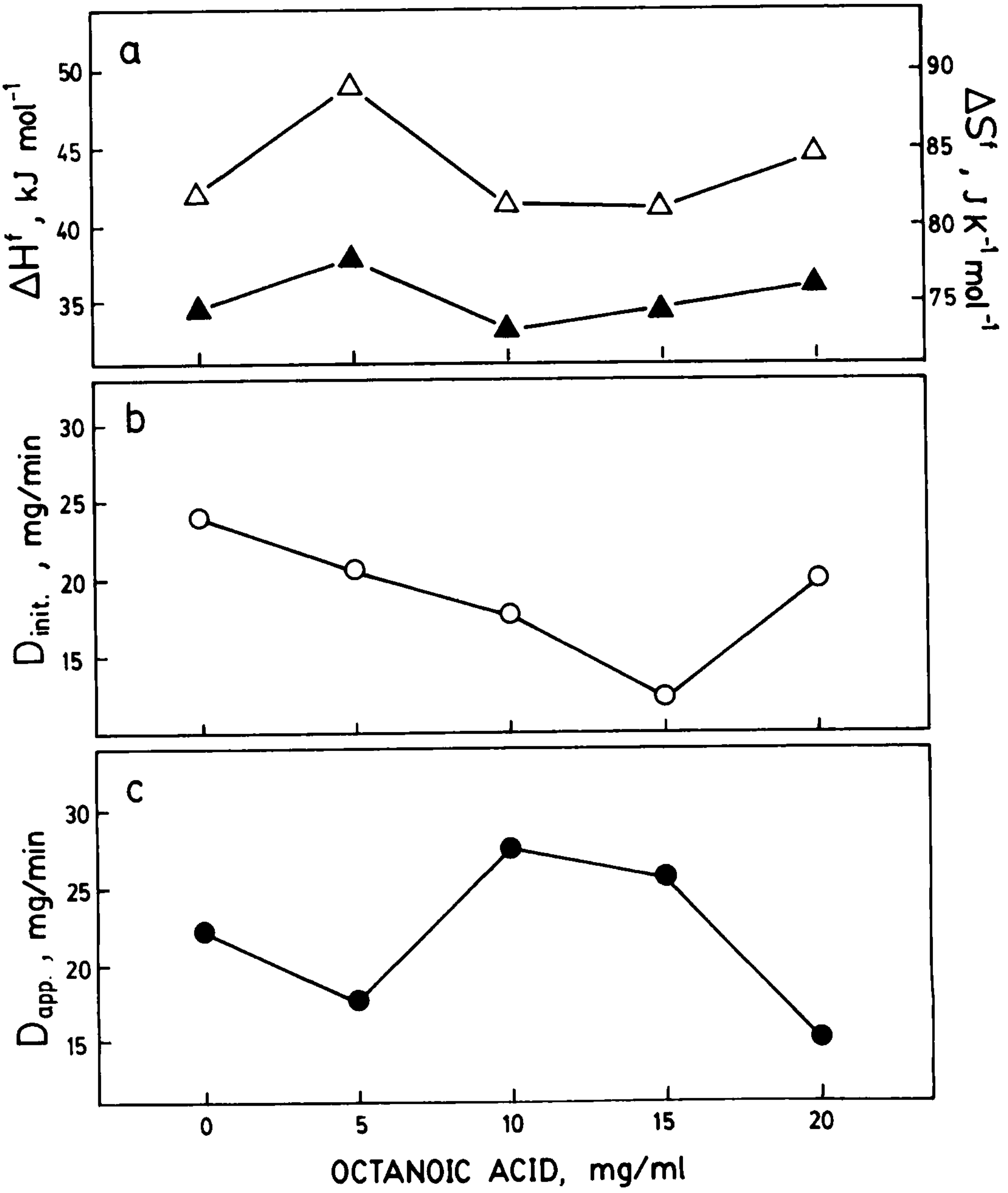

FIGURE 3

[a] Entropy of fusion, ΔS^f,(△) and enthalpy of fusion, ΔH^f,(▲), [b] initial dissolution rate, D_{init}, (O), and [c] apparent intrinsic dissolution rate, D_{app}, (●) of adipic acid crystals grown in the presence and absence of various concentrations of octanoic acid.

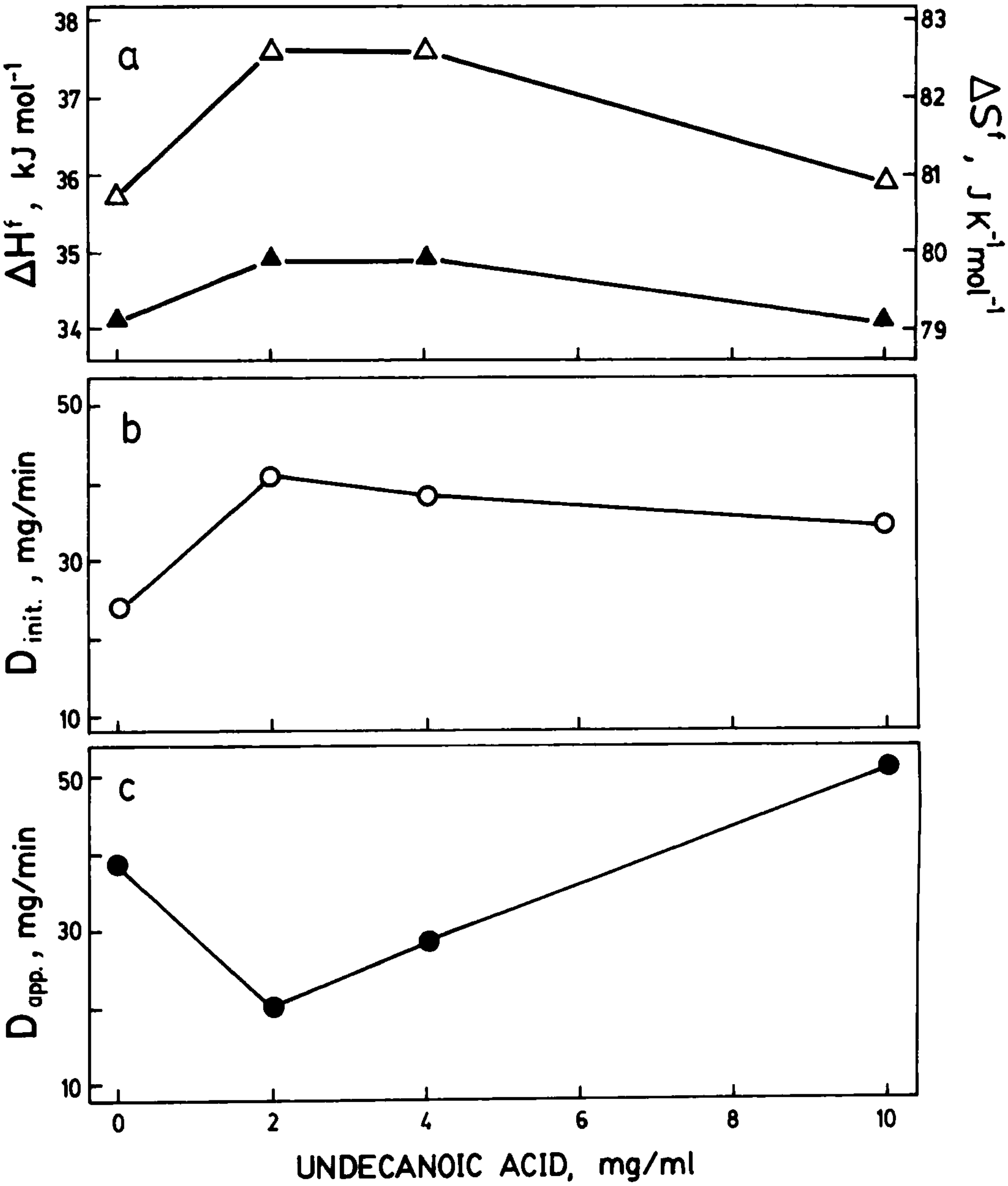

FIGURE 4

[a] Entropy of fusion, ΔS^f, (△) and enthalpy of fusion, ΔH^f, (▲), [b] initial dissolution rate, D_{init}, (O), and [c] apparent intrinsic dissolution rate, D_{app}, (●) of adipic acid crystals grown in the presence and absence of various concentrations of undecanoic acid.

TABLE 1

DSC Melting Point and Density of Adipic Acid Crystals Grown in Aqueous Solution Containing Fatty Acid Additives

Additive	Additive Concentration (μg/ml)	Melting point[a] (K)	Density[a] (g cm^{-3})
Hexanoic acid	0	421.4 (0.7)	1.362 (0.001)
	125	418.3 (1.1)	1.358 b
	250	423.0 (1.6)	1.359 (0.001)
	375	421.0 (3.2)	1.361 (0.002)
	500	421.2 (1.6)	1.362 (0.005)
Octanoic acid	0	422.5 (2.2)	1.359 (0.002)
	5	424.0 (0.3)	1.367 (0.007)
	10	421.7 (4.1)	1.365 (0.004)
	15	420.3 (0.8)	1.361 (0.002)
	20	425.1 (0.8)	1.360 (0.002)
Undecanoic acid	0	423.2 (1.8)	1.358 (0.001)
	2	422.7 (2.3)	1.358 (0.005)
	4	422.8 (3.1)	1.359 (0.002)
	10	421.7 (2.6)	1.356 (0.002)

a The standard deviation of 3 samples is given in parentheses.

b Number of samples = 2

transition was detected using DSC. In fact, no hydrates or polymorphs of adipic acid have been reported in the literature over the range of temperatures under consideration. Furthermore, it has also been shown that the presence of fatty acids in the crystallization of adipic acid did not affect the uptake of water into the lattice (13). Thus, the thermodynamic properties of the adipic acid crystals are most likely influenced by an alteration of the concentration of crystal imperfections caused by the presence of additives in the bulk or on the surface of the crystals.

Density Determinations

The density of crystals is reported by several investigators to be related to the concentration of crystal defects and the degree of crystallinity (1,8,14,15). However, the samples of adipic acid crystals which showed smaller variations in $\Delta H^f, \Delta S^f$ and T_m than those previously reported did not given any detectable differences in true density within experimental error (Table 1). This suggests that the procedure for density measurement may not be sufficiently sensitive to detect smaller, but pharmaceutically significant, changes of crystal imperfections which are detectable by DSC and dissolution studies. Thus, more sensitive properties or improved techniques of density measurement may be preferable for quantifying the crystallinity of pharmaceutical solids.

Dissolution Studies

The usual decrease in dissolution rate of pure (undoped) crystals (Fig. 1, upper curve) indicates a decrease in the crystalline surface area as the solid in the surface irregularities dissolves. The unusual increase in dissolution rate with time for adipic acid crystals grown in the presence of fatty acid additives (Fig. 1, lower curve) suggests that the slower initial dissolution rate is controlled by the surface properties, such as wettability, whereas the faster final dissolution rate is controlled by the bulk properties. Both the surface and the bulk properties are influenced by the presence of fatty acid additives in the crystals (8).

The initial dissolution rate, D_{init}, of adipic acid crystals was found to be positively related to the corresponding ΔH^f, T_m and ΔS^f values (Fig. 2-4, Table 1). An opposite relationship is expected from the following thermodynamic equation which predicts the thermodynamic activity, a, of the bulk crystals (16):

$$\ln a = -(\Delta H^f/R) \cdot (1/T - 1/T_m) \qquad \text{(Eqn 1)}$$

$$= -\Delta S^f \cdot (1/R) \cdot (T_m/T - 1) \qquad \text{(Eqn 2)}$$

Here the standard state of unit activity is the pure supercooled liquid, T is the absolute temperature, R is the gas constant and the other quantities have been defined above. According to Eqn. 1, ΔH^f, (or ΔS^f and T_m) are inversely related to a of the crystals. The rate of dissolution of the crystals under sink condition is proportional to a of the crystals which is approximately proportional to their solubility, s, in the Noyes-Witney equation, thus:

$$dm/dt = k' \; A \; a \qquad \text{(Eqn 3)}$$

$$dm/dt = k \; A \; s \qquad \text{(Eqn 4)}$$

where m is the mass dissolved, t is the time and k' (or k) is the dissolution rate constant which depends on the definition of a (or s). Accordingly, the initial rate of dissolution should also be inversely related to ΔH^f (or ΔS^f and T_m), which directly reflect the energy or entropy of the crystals and hence the concentration of imperfections in the crystals. Eqns. 1-3 assume [a] that ΔH^f is relatively insensitive to temperature (i.e. ΔC_p is ignored), [b] that the interaction of the supercooled liquid with water is constant, independent of the small concentration of the additive and [c] that the intrinsic dissolution rate of the crystals in water is proportional to a. It is extremely unlikely that the relative directions of the changes predicted by Eqns. 1-4 will be modified by the lack of exactness of these assumptions.

The accelerating dissolution rate (Fig. 1, lower curve), may be caused by initially imperfect wetting of the crystal surfaces. The surface irregularities, previously demonstrated using the scanning electron microscope (8), probably reduce the wettability of the crystals as a result of the entrapment of air in the crevices of the surface even though the specific surface area may actually have increased (8). These surface irregularities must result from increases of the concentration of crystal imperfections, introduced by the presence of the additive. Hence, an increase in the concentration of crystal imperfections, which corresponds to decreases in ΔH^f, ΔS^f and T_m, brings about an increase of surface irregularities and a decrease of the wettability leading to the observed decrease in the initial dissolution rate of the crystals. Another possibility is that the dissolution is hindered by the adsorption of the additives on to the surface of the adipic acid crystals as in the case of the more hydrophobic additive, oleic acid (13). However, the additives employed in this study are shorter chain fatty acids which are relatively hydrophilic. Furthermore, it has been shown by Fairbrother and Grant (17) that the additives employed in this study are located inside, rather than on the surface of, the adipic acid crystals. Hence it is likely that the initial dissolution rate is retarded by the surface irregularities resulting from an increased density of crystal imperfections.

Since dissolution is initially controlled by the surface properties, the two stages (Fig. 1, lower curve) may readily be explained. The first stage is controlled initially by the wetting process, as described, while the second stage, which is represented by the intrinsic dissolution rate, is governed by the bulk structure of the crystals and is, therefore, related positively to the concentration of crystal imperfections. The two-stage dissolution observed in this study is characterized by analogous changes in the dissolution profile of each "doped" crystalline sample. In fact, some pairs of dissolution-time curves intersect each other (Fig. 1), suggesting that the dissolution does not follow the cube-root law (18) but is controlled by the surface and bulk properties of the crystals.

If the two-stage dissolution correctly describes the dissolution profile of the adipic acid crystals, the final dissolution rate should increase with increasing crystal energy and be inversely related to the ΔH^f, ΔS^f and T_m. This was indeed found to be the case, but, since it could have been an artifact of the change in mass and area of the remaining crystals, a correction was applied to enable the intrinsic dissolution rate to be estimated more accurately. To test the hypothesis more appropriately, a simple procedure for estimating the intrinsic dissolution rate of the crystals was derived as follows.

Since sieved crystals were used for the dissolution studies, they may be considered to be essentially monodispersed. If the crystals are assumed to approximate to spheres of initial radius r_o, the initial mass, M_o, available for dissolution is given by:

$$M_o = (4/3)\,\pi\,N\,d\,r_o^3 \qquad \text{(Eqn 5)}$$

where N is the number and d is the density of the crystals. After time t, the mass becomes:

$$M = (4/3)\,\pi\,N\,d\,r^3 \qquad \text{(Eqn 6)}$$

where r is the radius of the crystals of mass M at time t.

Hence $M/M_o = (r/r_o)^3$ (Eqn 7)

The surface area, A, at time t can now be calculated as follows:

$$A = 4\pi r^2 N = 4\pi r_o^2 N \; (M/M_o)^{2/3} \qquad \text{(Eqn 8)}$$

Substituting Eqn. 8 into the Noyes-Witney equation (Eqns. 3 and 4) under sink conditions, the intrinsic dissolution rate of the crystals at time t is given by:

$$(dm/dt).1/A = (4\pi N r_o^2 (M/M_o)^{2/3})^{-1} \, dm/dt = k'a = ks \qquad \text{(Eqn 9)}$$

Since N, r_o and s are constant in the dissolution experiment, the intrinsic dissolution rate may be expressed as:

$$(dm/dt).\ 1/A = K' (M/M_o)^{-2/3} \, dm/dt = K'D_{app} \qquad \text{(Eqn 10)}$$

where $(M/M_o)^{-2/3}(dm/dt) = D_{app}$ (Eqn 11)

and $K' = 1/(4\pi N r_o^2) = \text{constant}$ (Eqn 12)

Here dm/dt is the rate of dissolution, M is the mass remaining at time t and D_{app} is the apparent intrinsic dissolution rate, which is directly proportional to the intrinsic dissolution rate and is experimentally accessible. Using Eqns. 10 and 11, the relative value of the intrinsic dissolution rate at time t, i.e. D_{app}, can be calculated from M and dm/dt, provided that the dissolution medium is still under sink conditions. The mass, M, remaining at time t can be calculated using the following equation:

$$M = M_o - m \qquad \text{(Eqn 13)}$$

where M_o is the initial mass, and m is the mass of adipic acid dissolved, which was measured by titration.

The rate of dissolution, dm/dt, at time t was calculated from the slope of the dissolution curve between 6 and 12 min (e.g. in Fig. 1). The optimal time of 6 to 12 min was chosen because [a] the crystals were apparently well wetted, and because [b] the concentration of adipic acid in the dissolution media was still less than 10% of the solubility, which is normally accepted as the sink condition for dissolution (19).

This method of estimating the relative value of the intrinsic dissolution rate assumes [i] that the crystals are monodispersed throughout dissolution, [ii] that the sink condtion still holds at time t = 12 min, [iii] that all the crystals are well wetted at time t, [iv] that the rate of dissolution is independent of the distance from the center of the crystals, and [v] that the number of particles is constant throughout the initial stages of the dissolution process, which is true only if the crystals are of the same size and dissolve at the same rate.

D_{app} is inversely related to ΔH^f, ΔS^f and T_m of the crystals (Fig. 2-4). This agrees with the hypothesis that the presence of the additive in the crystals increases (or decreases) the concentration of imperfections, the crystal energy, and crystal disorder (as reflected by decreases or increases in ΔH^f, ΔS^f and T_m) and therefore increases (or decreases) $\underline{a}$ (Eqns. 1 and 2) and D_{app} (Eqns. 9 and 11). Moreover, this further supports the suggestion that D_{init} is controlled by a different mechanism than is D_{app}, namely, by the wettability of the crystals.

The fact that a few of the calculated D_{app} values do not fall into the predicted patterns, draws attention to the limitations of the dissolution model described. Some of the discrepancies of the correlation may be explained [a] by an oversimplification of the processes involved, [b] by differences between the bulk and the surface imperfections of the crystals and [c] by incomplete wetting of the crystals during the estimation of the intrinsic dissolution rate.

CONCLUSIONS

The results of the present work suggest that differential scanning calorimetry is a more sensitive technique than density measurements for estimating small differences in the concentrations of imperfections in organic crystals. The dissolution data also indicate that both the surface and the bulk properties of the crystals may be markedly affected by variations of crystal imperfections, caused by the presence of incorporated fatty acid additives. A better understanding of the influence of traces of additives, impurities and crystal imperfections on the pharmaceutical properties of drugs and excipients may help to improve the manufacture and the quality control of formulations.

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