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Influence of compaction on the intrinsic dissolution rate of modified acetaminophen and adipic acid crystals

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Summary

Previous work has shown that aqueous crystallization of acetaminophen in the presence of *p*-acetoxyacetanilide or adipic acid in the presence of *n*-alkanoic acids (carbon number ≥ 6) modifies the dissolution rate of free floating crystals per unit surface area in the USP Apparatus 2 (crystal intrinsic dissolution rate, i.e., crystal-IDR). The present work measures and compares the corresponding dissolution rates of compacted discs per unit surface area of disc (disc intrinsic dissolution rate, i.e., disc-IDR). The differences between the crystal IDRs (by factors of 1–2.4) of the acetaminophen samples almost disappeared with the disc-IDRs. This result confirms that crystal habit is the major factor which determines the intrinsic dissolution rate of acetaminophen crystals, rather than crystal energetics. On the other hand, differences between the crystal-IDRs of the adipic acid samples persisted, although somewhat reduced, among the disc-IDRs. This result confirms that the crystal energetics is the major factor which determines the intrinsic dissolution rate of adipic acid crystals. Significant changes in the dissolution behavior after compaction of the adipic acid samples suggest that compaction alters the nature, concentration and/or profile of the crystal defects that determine the crystal energetics. Implications in using the disc method for intrinsic dissolution rate measurement are discussed.

Introduction

The physical properties of crystals which affect the dissolution behavior of solids in liquids have been reviewed recently (e.g. Burt and Mitchell, 1980, 1981; Chow and Grant, 1989). In addition to polymorphism, these physical factors include crystal habit, crystal imperfections (defects and impurities) and solvation (both stoichiometric and non-stoichiometric), as summarized in Table 1. Furthermore, Chow A.H.-L. et al. (1985) and Chow K.Y. et al. (1984, 1985) showed that growth of crystals of acetaminophen and adipic acid, respectively, in aqueous solutions containing small amounts of specific additives produces modifications to the crystal properties, such as the habit, energy and entropy, density, thermal expansivity, dissolution rate and intrinsic dissolution rate (IDR). The dissolution rate of the crystals was measured by means of the beaker-stirrer method employing Apparatus 2 of the USP XXI (1985).

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TABLE 1

Physical properties of crystals which influence their intrinsic dissolution rate (polymorphism excluded)

(a) Crystal habit of the crystals
(i) Crystal anisotropy: different polarity of various crystal faces results in difference in affinity for water, i.e. wettability
(ii) Habit-related hydrodynamics: needle-shaped particles favor streamlined flow of dissolution medium over the particles
(b) Solvation within the crystals Stoichiometric or nonstoichiometric solvates, including hydrates. Dissolution rates: (i) solvate > non-solvate; (ii) anhydrate > hydrate
(c) Crystal defects (imperfections) Increasing density of defects (dislocations and other imperfections) corresponds to increases in the internal energy, enthalpy, entropy and free energy, and hence to increases in the thermodynamic activity and dissolution rate

This technique provides constant average hydrodynamic conditions of solvent flow around the intact crystals without prior mechanical manipulation. Division of the dissolution rate so determined by the surface area of the crystals (specific surface area multiplied by the mass) affords the intrinsic dissolution rate of the intact crystals (crystal-IDR). The dissolution rate of the solid so determined is found to correlate with some of the other physical properties.

The additives mentioned above are incorporated into the crystal lattice, forming a solid solution and/or are adsorbed onto the crystal surfaces during crystallization. For adipic acid, crystal energy and surface area are suggested as the factors controlling the dissolution rates of different crystal modifications, i.e. crystal-IDR depends on the crystal energy. For acetaminophen crystals, on the other hand, crystal habit appears to be the major factor controlling crystal-IDR (Chow and Grant, 1989). The relative importance of the various physical properties of the crystals in controlling the dissolution rate may be differentiated by also measuring the intrinsic dissolution rate of a compacted disc of a drug (dissolution rate per unit surface of the disc). Since the habit will be destroyed when the crystals are crushed and compressed to form a compact of constant surface area, both the effects due to the habit and the surface area of the individual crystals are eliminated.

The intrinsic dissolution rate, i.e. the mass flux J, may be described by the well-known Noyes-Whitney equation,

$$J = \frac{dm}{dt} \cdot \frac{1}{A} = k(C_s - C) \quad (1)$$

where dm/dt = rate of increase of the mass of solute released per unit time t, k = mass transfer coefficient, A = surface area of the sample, C_s = intrinsic solubility at the sample surface, and C = concentration of solute dissolved at time t. Under sink conditions, $C_s \gg C$,

$$J = \frac{dm}{dt} \cdot \frac{1}{A} = kC_s \quad (2)$$

If crystal habit controls crystal-IDR, habit destruction due to compaction should result in a constancy in J for the compacted discs (i.e. disc-IDR). In contrast, if the crystal energetics (defects and/or solvation) control crystal-IDR, the differences in J for the original crystals (i.e. crystal-IDR) may still exist for disc-IDR, since it is probable that the crystal energetics will be preserved after compaction. The last assumption may be violated, depending on the behavior of the crystal under compression.

The aim of the present study is to measure disc-IDR of various modified solid samples of acetaminophen and adipic acid and to compare the results obtained with the previous results for crystal-IDR, in order to confirm whether crystal habit or crystal energetics (defects and/or solvation) control the dissolution rate of the drugs under study. As before, crystal modification was achieved by growing the crystals of acetaminophen or adipic acid from aqueous solution containing defined concentrations of *p*-acetoxyacetanilide or an *n*-alkanoic acid (carbon number $\geqslant 6$), respectively, under conditions previously defined (Chow A.H.-L. et al., 1985, Chow K.Y. et al., 1984, 1985). We wish to provide a greater understanding of the relationship between the dissolution rate of drugs and the physical properties of their crystals.

Materials and Methods

Reagents and materials

The source of the adipic acid was the same as that described by Chow K.Y. et al. (1984). The alkanoic acids were supplied as highly pure analytical grades and were used as received: hexanoic acid and octanoic acid (99.5 + %, Gold Label, Aldrich, Milwaukee, WI); undecanoic acid (99 + %, Sigma, St. Louis, MO); oleic acid (99 + %, Aldrich). Chloroform was spectrophotometric grade (99 + %, Gold Label, Aldrich). Sodium hydroxide was AR grade (Mallinckrodt). Brij 30 (polyoxyethylene 4-lauryl ether) was supplied by Sigma. The sources of samples of acetaminophen (P) and *p*-acetoxyacetanilide (A) were the same as those employed and described by Chow A.H.-L. et al. (1985). Water was distilled and stored in an all-glass apparatus (Glenwood, Minneapolis, MN).

Batch crystallization from water

Defined batches of crystals of P were prepared according to the procedure reported by Chow A.H.-L. et al. (1985) with the following specifications: P (9 g) was crystallized from water (390 g) containing 0, 600*, or 1500 mg dm^{-3} A at a constant stirring speed of 240 ± 1 rpm. The crystals of adipic acid were obtained using the process which has been described by Chow K.Y. et al. (1984, 1985) with the following specifications: adipic acid (18 g) was crystallized from water (400 g): (i) without additives, (ii) containing hexanoic acid (C_6) at 250* or 500 mg dm^{-3}, (iii) octanoic acid (C_8) at 15* or 7.5 mg dm^{-3}, (iv) undecanoic acid (C_{11}) at 2.5* or 5.0 mg dm^{-3}, and (v) oleic acid (C_{18}) at 3.3* or 6.6 mg dm^{-3}. In the initial experiments the crystals were doped at that optimum additive concentration (marked with an asterisk) which gave the maximum effect on the dissolution rate of the crystals measured using Apparatus 2 of the USP XXI (1985). Crystals prepared at twice or half these optimum additive concentrations were also employed. C_{11}- and C_{18}-doped crystals, and the single surface of a compact made from them, were washed with chloroform to remove the surface-adsorbed additives as described by Chow K.Y. et al. (1985).

Intrinsic dissolution rate

A compacted disc dissolution apparatus, designed to minimize variations of rotating speed and shaft wobbling, was employed which was similar to that of Doherty and York (1987) modified from the apparatus of Collett et al. (1972). The dissolution cell consisted of a poly(methyl methacrylate) beaker, a top cover with an outlet for sampling, and a stainless steel sample holder for the compact. In the holder, powder samples (unsieved, 300 ± 1 mg) were compressed directly by a hydraulic press (1 metric ton, 60 s, Carver Laboratory Press, model C, Menomonee, WI) to form the compact (1 cm diameter). The same compression pressure was applied to all the samples because it has been shown that the dissolution rate may slightly decrease with increasing pressure (Doherty, 1986). The sample holder with the in-situ compact was screwed into the center of the cell base so that the single face of the compact was exposed to the dissolution medium (distilled water, 900 g, outgassed and pre-equilibrated at 37 ± 0.2° C). Since the compact remains intact in the holder and is not removed from it, interference to the compact due to handling was thus minimized. This arrangement also eliminated capping and lamination which often occur during ejection of acetaminophen discs from the die cavity after compression. After transferring the dissolution medium to the vessel which was also pre-equilibrated at 37° C ± 0.2° C, samples (10 g) were taken at fixed times for 60 min, and the mass of acetaminophen or adipic acid dissolved was calculated from the concentration after correcting for the change in volume of the dissolution medium. Samples of the dissolution medium were removed at a point halfway up the beaker beneath the liquid surface to minimize error due to possible variation in concentration of the solute within the vessel. The samples were diluted and assayed for acetaminophen by UV spectrophotometry on a spectrophotometer (Beckman DU-50) using a determined calibration curve which was found to be rectilinear in the concentration range 1.1–17.0 μg/g [absorbance = -9.9474×10^{-4} + 0.06306 × concentration (μg/g), $\lambda_{max} = 243$ nm, $r^2 = 0.9999$, $n = 8$]. In a preliminary study, the sample solutions were analyzed both before

and after filtration by passing through a syringe-millipore assembly (Milliport GS, 0.22 μm, 13 mm diameter) to detect any undissolved solid particle dislodged from the compact. The compacts of both acetaminophen and adipic acid were found to dissolve steadily without particle loss or disintegration, since the results for the filtered and unfiltered samples were almost identical (variation < 1.0%). Subsequently, no filtration of the sample solution was necessary. For adipic acid samples, the amounts dissolved were determined by titration with 0.01 or 0.001 N NaOH to pH 8.00 using a combination pH electrode with calomel reference (Fisher Scientific) connected to a pH meter (Accumet, model 620, Fisher Scientific). The choice of the pH value 8.00 was based on calculations for solutions containing a diacidic weak base (Martin et al., 1972),

$$[H_3O^+] = \frac{K_2 K_w}{C_b} \quad (3)$$

$$pH = -\log \frac{K_2 K_w}{C_b} \quad (4)$$

where K_2 is the second ionization constant of the conjugate acid (for adipic acid, $K_2 = 5.29 \times 10^{-6}$ at 25 °C), K_w is the ionic product of water ($K_w = 1 \times 10^{-14}$ at 25 °C) and C_b is the concentration of the diacidic weak base solution which is the sodium salt of adipic acid after titration. For the dissolution of adipic acid compact, C_b was found to range from 10 to 200 mg/900 g solution in 5–60 min. The end-point pH of the titration thus ranged from pH 7.53 to 8.23 by calculation using Eqn. 4 and 8.00 was chosen as a realistic intermediate value. In order to obtain the calibration plot for the titration of adipic acid vs NaOH, the titration curves were first constructed by titrating adipic acid solutions of known concentration against the standard NaOH solutions, using distilled water as the control. The weight of each NaOH solution required to bring the adipic acid solution to pH 8.00 was read directly from the titration curve. After subtracting the value for pure water as the control, these amounts were plotted against the concentration of adipic acid to yield the calibration plot.

X-ray powder diffraction

Although there is no known polymorphism of adipic acid (Fairbrother, 1981), acetaminophen has been reported to exist in two polymorphic forms, monoclinic and orthorhombic (Haisa et al., 1974, 1976). To detect possible polymorphic transformation during compression of the crystals, X-ray powder diffraction was carried out on acetaminophen and adipic acid samples, both before and after compaction, using an X-ray generator (Rigaku 4011) at 15 mA, 25 kV with CuKα radiation and a goniometer (Rigaku 2171) with 2θ increasing at $\frac{1}{2}$ or 2 degree/min. The X-ray powder diffraction patterns of the two substances did not change, indicating that compaction did not induce polymorphic changes.

Results and Discussion

Acetaminophen

For acetaminophen, the linearity of the dissolution plot (Fig. 1) confirms that dissolution takes place under sink condition, which is expected in view of the relatively small size of the sample (300 mg) and large volume of the dissolution medium (900 ml) in comparison with the solubility of acetaminophen (19.3 g dm^{-3} at 37 °C; Grant et

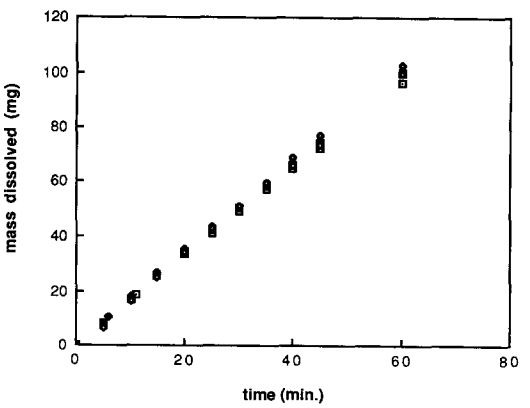

Fig. 1. Dissolution profiles of compacted discs of acetaminophen: raw material before recrystallization (⊡), recrystallized from water (◆), recrystallized from aqueous solutions in the presence of 600 mg dm^{-3} (□) and 1500 mg dm^{-3} (◇) of *p*-acetoxyacetanilide; linear regression analysis: $r^2 > 0.999$, $n = 10$ for each run.

TABLE 2

Intrinsic dissolution rates of compact discs (disc-IDR) of acetaminophen crystallized from water containing p-acetoxyacetanilide (A)

Crystallization medium	Concentration A (mg dm^{-3})	Disc-IDR (mg $min^{-1} cm^{-2}$)
Water	0	2.09 ± 0.00 [a]
None (raw material)	0	2.07 ± 0.04
Water	600	2.13 ± 0.02
Water	1500	2.20 [b]

[a] Mean ± uncertainty range in two experiments.
[b] Single determination due to low yield of crystallized product.

al., 1984). Except for the compact prepared from the heavily doped sample (crystallized in the presence of 1500 mg dm^{-3} A), all the acetaminophen compacts were almost indistinguishable in their dissolution rates (Table 2). This behavior indicates that disc-IDR is virtually constant and is in sharp contrast to the diverse rates of crystal-IDR reported previously for the corresponding untreated powder samples (Chow, A.H.-L., 1985). These contrasting results show that crystal habit which is destroyed during compaction is the most important factor affecting the intrinsic dissolution rate of acetaminophen crystals. This finding agrees well with the recent multiple linear regression analysis for acetaminophen crystallized under a variety of conditions (Chow and Grant, 1989). That analysis shows a fairly high correlation ($r^2 = 0.67$, $n = 29$) between the crystal habit elongation (length/width) ratio and the crystal-IDR. The present results thus confirm the superior importance of crystal habit, including anisotropy and habit-related hydrodynamics, in influencing the aqueous dissolution rate of acetaminophen crystals.

Adipic acid

For adipic acid, the titration curves and the derived calibration plot are shown in Figs. 2 and 3, respectively. The excellent sensitivity in the concentration range 12.5–200 mg in 900 g solution justifies the titration method for assay. The crystal-IDRs are summarized in Table 3. Representative dissolution plots are shown in Fig. 4.

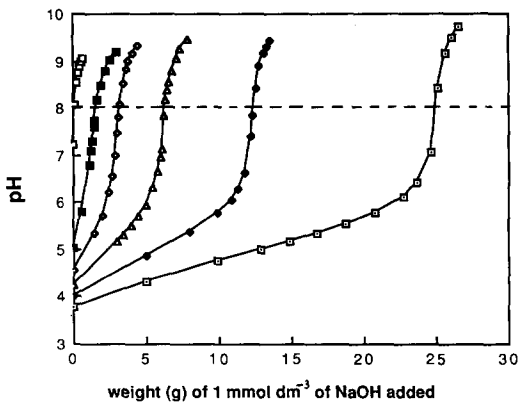

Fig. 2. Titration curve of solutions of adipic acid (10 g accurately weighed) with standard NaOH solution. Acid concentration (in mg dm^{-3}): 201.52 (⊡), 99.66 (◆), 50.44 (△), 25.16 (◇) 12.57 (■) and distilled water as blank (□). The broken line corresponds to the endpoint at pH 8.0.

The coefficient of determination, r^2, of the linear regression analysis of mass released against time was > 0.99, except where stated in footnotes g and h in Table 3. In contrast to the almost superimposible dissolution profiles of acetaminophen discs, adipic acid samples show a large variation in disc-IDR, as illustrated in Fig. 4. In comparison with the samples recrystallized from water in the absence of additives, the dissolution behavior of doped samples is divided into the following three

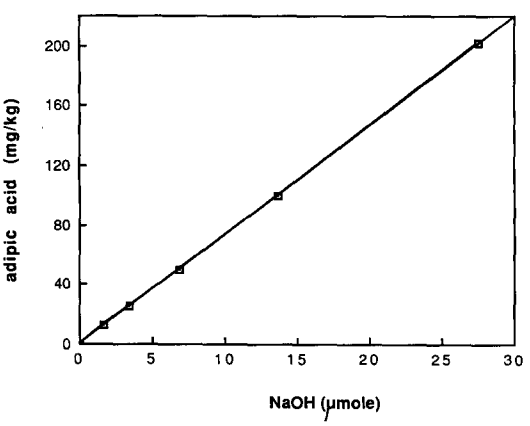

Fig. 3. Calibration plot for the titrimetric assay of adipic acid. Linear regression equation: adipic acid concentration (mg kg^{-1}) = 0.2483 + 7.2894 × amount of NaOH (μmol), r^2 = 0.9999, $n = 5$.

TABLE 3

Intrinsic dissolution rates of various compacted samples (disc-IDR) of adipic acid in water 37 °C

Crystallization medium	Concentrations of additive (mg dm^{-3})		Disc-IDR (mg min^{-1} cm^{-2}) of sample doped at			% difference of disc-IDR with reference to the undoped control crystals		
	Optimum concn.	Higher concn. [a]	Optimum concn.		Higher concn. [a]	Optimum concn.		Higher concn.
			Run 1	Run 2		Run 1	Run 2	
None (raw material)	–	–	3.97	3.79	–	+27	+20	–
Water	–	–	3.21	3.12	–	0 ± 2		–
+ hexanoic acid	250	500	3.48	–	3.41	+10	–	+8
+ octanoic acid	15	7.5 [b]	3.41	3.39	3.25 washed [d]	+8	+7	+3 [b]
+ undecanoic acid	2.5	5.0	1.90(20–60) [c]	–	1.78(20–60)	−40	–	−44
			2.26(5–20)	–	1.90(5–20) [g] washed [d]	−29	–	−40
+ oleic acid	3.3	6.6	1.75(15–60)	1.74(25–61) [e]	1.77(20–60)	−45	−45	−44
			2.18(5–20) washed [d]	2.17(5–15) [e,g] washed [d]	1.81(5–20)	−31	−32	−43
			1.93(15–60)	2.07(25–61) [e]	–	−39	−35	–
			2.89(5–15) [g] washed [f]	2.28(5–15) [e]	–	−9	−28	–
			1.77(20–60)	–	–	−44	–	–
			2.21(5–15) [h]	–	–	−30	–	–

[a] Twice the optimum concentration for doping, see under Batch crystallization from water.
[b] Half the optimum concentration for doping, see under Batch crystallization from water.
[c] Values in brackets indicate the time interval (in min); for samples doped with undecanoic acid or oleic acid, 2 intervals were used due to the non-linearity of the data plot of mass released vs. time.
[d] Crystals before compression and the compact after compression were both washed with chloroform.
[e] Dissolution medium contained Brij 30 (10 mg dm^{-3}) dissolved in distilled water.
[f] Only the crystals before compression were washed with chloroform.
[g] $r^2 = 0.98$.
[h] $r^2 = 0.94$.
For the remainder $r^2 > 0.99$.

groups: (A) uncrystallized raw material, having an appreciably higher disc-IDR (by 23%); (B) samples doped with hexanoic acid (C_6) or octanoic acid (C_8), showing a significantly higher disc-IDR (by 7–10%); and (C) samples doped with undecanoic acid (C_{11}) and oleic acid (C_{18}), having a significantly lower disc-IDR (by about 30%).

Since compaction of the crystals standardizes the crystal habit and the surface area, the higher disc-IDR of Type A is most readily attributable to the higher energy state of the raw material which presumably contains a greater density of crystal defects, such as impurity defects and dislocations, which result from the manufacturer's processing treatment. If this hypothesis is correct, it should be possible to lower the defect content and hence the mean crystal energy and therefore disc-IDR by recrystallization. Indeed, this hypothesis was confirmed by the smaller disc-IDR of the reference crystals recrystallized from distilled water in the absence of additives. For C_6-doped crystals of Type B, the small increase in disc-IDR can be explained by the incorporation of the additive molecules which introduce impurity defects and

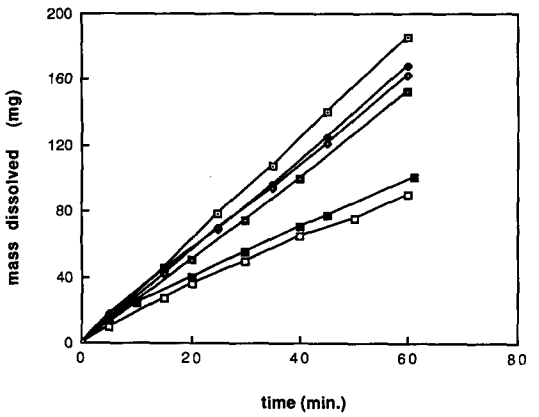

Fig. 4. Dissolution profiles of compacted discs of adipic acid: raw material before recrystallization (⊡), recrystallized from water (■), recrystallized from aqueous solutions in the presence of hexanoic acid (250 mg dm^{-3}) (◆), octanoic acid (15 mg dm^{-3}) (◇), undecanoic acid (2.5 mg dm^{-3}) (■), and oleic acid (3.3 mg dm^{-3}) (□).

attendant dislocations into the crystal lattice of adipic acid (Chow K.Y. et al., 1984, 1985). However, the percentage increase in disc-IDR is not as high as that of crystal-IDR. Presumably, compression, which causes plastic deformation of the crystals, induces stepwise migration of the lattice defects through the crystal until they emerge at the crystal faces and disappear (Hüttenrauch, 1978). However, the slight increase in disc-IDR for the C_8-doped samples contrasts with the decrease of crystal-IDR (Chow, K.Y. et al., 1984). In explanation, compaction is such a drastic process that it may change the actual nature of the crystal defects, as well as their concentration in the sample. In general, the dissolution data correspond well with the measured decreases in melting point (m.p.), enthalpy of fusion (ΔH^f), and enthalpy of solution (ΔH^s) induced by the various additives in the crystals (Chow, K.Y. et al., 1984, 1985), and consequently correspond with increases in the concentrations of crystal defects. This explanation is further supported by a smaller increase in disc-IDR following a smaller doping concentration of C_8 (Table 3) and is also associated with smaller decreases in m.p., ΔH^f and ΔH^s (Chow, K.Y. et al., 1984, 1985).

The additives giving Type C behavior, i.e. undecanoic and oleic acid, have low aqueous solubilities, 0.56 and < 1.8 mmol dm^{-3}, respectively, at 25 °C (Singleton, 1960; Seidell, 1941). In these cases, the observed decreases in disc-IDR may be ascribed to reductions in the wettability of the solid surface and to the poisoning of the active site for aqueous dissolution at the surface and within the lattice by the hydrophobic additives (Piccolo and Tawashi, 1970, 1971a, b; Chow, K.Y. et al., 1985).

This hypothesis is supported by previous studies of crystal-IDR, in which washing the C_{18}-doped crystals with chloroform effectively removed the surface-adsorbed C_{18} and resulted in an increase in crystal-IDR (Chow, K.Y. et al., 1985; Go and Grant, 1987). However, chloroform washing of the discs prepared by compacting crystals doped with C_{18} did not increase disc-IDR (Table 3 under 'washed'). This negative result could not be attributed to the use of Brij 30 in the dissolution medium for the crystals (Chow, K.Y. et al., 1985), since Table 3 (footnote e) shows no improvement on disc-IDR when Brij 30 was added to the dissolution medium. This inhibitory behavior may be ascribed to the thorough dispersion of C_{18} throughout the disc during compaction of the doped crystals. Since adipic acid has a very low solubility in chloroform, subsequent washing of the disc with this solvent will not remove the hydrophobic C_{18} molecules just beneath the surface, so the disc-IDR will be permanently reduced below that of the disc prepared from crystals free of C_{18}.

The effects of crystal additives on disc-IDR are generally smaller than the corresponding effects of crystal-IDR. These differences may be attributed to a compaction stress-induced reduction in the concentration and effectiveness of the higher energy crystal defects which had previously been created by doping of the crystals.

Compaction of a solid, in a crystalline and/or powder form, for the preparation of a disc or tablet may change the nature of the solid state. An implication of the present results to dissolution studies is that, when using the compacted disc method for measuring the intrinsic dissolution rate, caution must be exercised in interpreting the effect

of compaction on the dissolution behavior of the samples. When crystal habit controls the intrinsic dissolution rate, compaction of the solid to form a disc will destroy the habit of individual particles and render meaningless any comparison of their disc-IDRs. On the other hand, if crystal energetics control the dissolution rate, the differences in the crystal-IDR may still be apparent in the disc-IDRs, but could be attenuated to different extents depending on the crystallization conditions including the nature and concentration of the additive.

Conclusions

The results confirm the importance of crystal habit in controlling the dissolution rate of acetaminophen, and crystal energetics (i.e. defects) in controlling the dissolution rate of adipic acid. Furthermore, crystal engineering could be a practical approach for modifying the dissolution rate of pharmaceuticals. During the preparation of a disc or tablet, compaction of the solid drug particles will destroy their habit and may also alter the densities of the various crystal defects, hence the disc-IDR may be very different from crystal-IDR due to the effects of compaction.

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