International Journal of Pharmaceutics, 60 (1990) 243–252
Elsevier

IJP 02050

Characterization of calcium fenoprofen

1. Powder dissolution rate and degree of crystallinity

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(Received 16 August 1989)
(Modified version received 18 November 1989)
(Accepted 21 November 1989)

Key words: Powder dissolution; Heat of solution; Calcium fenoprofen; Crystallinity; Crystal engineering; Characterization

Summary

Samples of calcium fenoprofen crystals have been prepared on laboratory, pilot and production scales, some by conventional aqueous precipitation, others under conditions designed to increase or decrease the degree of crystallinity. They were characterized by X-ray powder diffraction, scanning electron microscopy, Fourier transform infrared spectroscopy, surface area by nitrogen sorption, agglomerate size by Coulter counter, true density, sodium content, powder dissolution rates and heats of solution. No evidence of polymorphic variation was found. Most precipitation conditions gave partially fused agglomerates of primary crystals. Relative degrees of crystallinity were assessed from heats of solution. The more perfectly crystalline samples gave relatively high endothermic heats of solution coupled with low powder dissolution rates. Lattices with high levels of disruption, or low crystallinity, gave lower heats of solution coupled with enhanced powder dissolution rates. Heats of solution make a significant contribution to the overall characterization and to understanding batch-to-batch variation, and they relate well to the observed powder dissolution rates.

Introduction

There is increasing awareness of the need to characterise adequately solid pharmaceutical substances physically, particularly from the point of view of their solid-state and surface properties (York, 1983). Such properties include the habit and polymorphic form, the surface energy and the degree to which the lattice deviates from the perfectly crystalline.

Manufacturing procedures such as crystallization, precipitation, milling and granulation influence crystal bulk (Yamamoto et al., 1977) and surface (Buckton et al., 1988) properties, and these properties can in turn influence further procedures such as mixing, flow, filtration and compression (Cham, 1987; Dansereau and Peck, 1987), and also vital properties of the final formulation like chemical stability (Pikal et al., 1978) and dissolution rate (Kim et al., 1985).

Variations are often found between batches or between sources of the same chemical substance.

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In seeking explanations for such variations, experimenters have traditionally used chemical analysis for impurities or hydration level, but more recently awareness of possible habit or polymorphic differences (Haleblian and McCrone, 1969) has led to these phenomena being more frequently studied. However, it is only in more recent years that the more subtle differences in crystal order have been studied quantitatively, and invoked as causes of variation between samples.

Some workers have sought to introduce defects and impurities into crystals in a controlled manner, with the consequential variations in crystal properties being studied systematically (Hiestand et al., 1981; Wong and Aulton, 1987; Chow and Grant, 1988). Frequently this engineering of crystals leads to significantly higher dissolution rates (Al-Meshal et al., 1985). Among the quantitative approaches employed have been the degree of crystallinity (Pikal et al., 1978), the disruption index (Grant and York, 1986a), and the entropy of processing (Grant and York, 1986b).

In the present work, variations between batches of calcium fenoprofen dihydrate have been systematically examined. In some cases the variations were unplanned (samples from production lines) while in other instances the levels of defects and impurities, and thus the degree of crystallinity, were increased or reduced on a laboratory or pilot scale. The authors referred to above have employed methods based on enthalpy and entropy of fusion or solution processes. The former cannot be used here as calcium fenoprofen dihydrate decomposes before it melts, and accordingly the present work is based on heats of solution. The samples were characterized by several techniques, and correlations sought between the pharmaceutically important property of dissolution rate, and the solid-state properties of the samples.

Materials and Methods

Materials

Laboratory samples

Precipitation Two volumes of sodium fenoprofen solution (1.235 M) were metered by peristaltic pump into one volume of calcium chloride solution (1.349 M) with constant magnetic stirring in a water bath at 25 °C. The resulting crystals were filtered and air-dried over a period of 1–3 days to constant weight. The scale of operations was typically 35 g product. All laboratory precipitated samples are prefixed with the letter L. A control sample made as above was designated L1, but there were many variations on the procedure, as follows.

Small quantities of ethyl acetate were added to the calcium chloride solution prior to the metering in of the sodium fenoprofen. The total amount (by volume, as % of total final volume) was 0.17, 0.66 and 2.60% for samples L2, L3 and L4, respectively.

Sodium chloride was added to the calcium chloride solution such that the concentration there was 0.2 and 1.349 M, for samples L5 and L6, respectively. It should be remembered that sodium chloride is in any case formed in the reaction, but in these situations much more was present, especially in the early stages of the reaction.

Two samples were made under conditions of very low supersaturation, i.e. at high dilution. Sample L7 was made at 30-times the normal dilution (pH 10.7) and L8 at 50-times the normal dilution (pH 10.0). Under these conditions, crystallization was very slow, 24 h being allowed before the usual filtration and drying steps.

In view of interest in the concentration of Na^+ during the precipitation, one sample was made by adding only one tenth of the theoretically required amount of sodium fenoprofen to the calcium chloride. The resultant precipitate, sample L10, was thus made in an environment of very low Na^+ concentration, in contrast to the control and marked contrast to samples L5 and L6.

A sample was prepared (L11) with the normal order of addition reversed, thus giving a sample precipitated in a very high Na^+ environment in the early stages.

Recrystallization Calcium fenoprofen from a production line batch was recrystallized either from 50% aqueous ethanol (L9, L9′) or from water-saturated ethyl acetate (L12, L12′), followed by air-drying to constant weight.

Scaled-up samples

Samples were prepared broadly as above but on a scale of 4 kg. They are denoted by the prefix S. The control was S1; that made with 0.7% ethyl acetate was S2, with 1.349 M sodium chloride S3, and that made at 1/30 normal dilution at pH 10 was S4.

Production samples

On a production scale samples are made by precipitation substantially as described above. Several samples were selected from production lines in two countries, and represented several years' production experience. They are prefixed with the letter P. Two batches (P1 and P7) were known to have been poor in dissolution (see Results).

Buffer solution

A phosphate buffer of pH 7.4 was prepared from Na_2HPO_4 (0.0304 M) and KH_2PO_4 (0.0087 M), with 0.1% w/v of a nonionic surfactant (Berol 08, fatty alcohol ethoxylate) to assist wetting.

Sieving

Powdered samples were sieves in a nest of standard sieves to give a variety of fractions; the most commonly used fractions were 210-250, 150-210 and below 150 μm. Some samples could not realistically be sieved on account of their needle shape. In some cases static charges reduced the efficiency of sieving.

Methods

Powder dissolutions

The method was similar to that used by others (Stagner and Guillory, 1979; Lotter et al., 1983). Dissolutions were carried out using a six-vessel paddle stirred dissolution bath (Hanson Research Corp) equipped with six 1-l flat-bottomed dissolution beakers, each containing 1 l of phosphate buffer solution, and stirred at a constant speed of 150 pm. The contents of the dissolution beakers were thermostatted at 4°C. The vessel contents were withdrawn continuously by peristaltic pump through a glass wool filter, and passed through a 1-cm glass cuvette in an ultraviolet spectrophotometer (Uvicon 810). The absorbance was monitored every 30 s at 240 nm, and the cuvette flow was returned to the relevant beaker.

In a typical run, a weighed sample was rapidly tipped from a glass vial onto the surface of the stirred dissolution medium; within less than 30 s it had wetted and was dispersed throughout the bulk. The absorbance values were plotted vs time, and the initial dissolution rate determined. In most cases there was only a short period of linearity, particularly for the rapidly dissolving samples, in contrast to the data reported by Kaneniwa and Watari (1974). Normally three to six determinations were averaged except when availability of material precluded this. Means and standard deviations are reported in the relevant tables.

Scanning electron microscopy

SEM photographs were taken with a Cambridge Instruments Stereoscan S250. In addition, an optical microscope was used for routine examination of batches as they were made.

X-ray powder diffraction

These were run using Cu radiation at 35 kV and 25 mA, and were given 4 h exposure.

Sodium analysis

Na^+ contents were determined with a Perkin Elmer 1100B Atomic Absorption Emission spectrometer in emission mode.

Surface area determinations

Samples were outgassed at ambient temperature under vacuum for 24 h, and the surface areas determined on a Quantasorb by a single-point chromatographic technique.

Geometric surface area calculation

Samples were sized with a Coulter counter model TAII using a 400 μm tube and an electrolyte solution of sodium chloride (0.75%) saturated with calcium fenoprofen (approx. 0.25%). Areas were calculated on the assumption that the particles were spheres having a density of 1.1 g/ml; only the top 95% of the weight was counted towards the surface areas to reduce potential distortions by large numbers of very small particles.

Only the two smaller sieve fractions could be evaluated in this way. Samples were evaluated in triplicate; means and standard deviations are reported.

Heats of solution

Data were obtained using a Guild Corp. Model 400 solution calorimeter (Pikal et al., 1978). Samples were equilibrated in an atmosphere at 12% R.H. prior to being dissolved in a solvent blend of 59.5% ethanol, 39.5% acetone, and 1% water at 25.0 °C. This blend was chosen because it dissolved the sample rapidly, in less than 15 s. Preliminary tests showed the heat of solution was a nonlinear function of final concentration in the range 2-11 mM, so instead of the more usual correction to infinite dilution, heats of solution in this work were corrected to a final concentration of 7 mM. All samples were run in triplicate using three different weights, each separately corrected to the reference concentration.

True densities

True densities were determined by Helium pycnometry at ambient temperature, on a Micromeritics Autopycnometer 1320.

I.R. spectroscopy

Samples were incorporated into KBr discs and the spectra run on a Brucker 1FS 48 FT-IR in the range 400–3600 cm^{-1}.

Results

Samples from production lines

Dissolution rates of sieved fractions of active ingredient from production lines are shown on a weight basis in Table 1. Rates understandably decline as sieve size increases, qualitatively in line with the expected decline in area.

The ranking order is not identical in each sieve faction, but overall samples P3 and P8 are the fastest, and samples P5 and P7 are slowest, the differences between these groups being significant in spite of the generally high variability of the dissolution data. It should be noted that samples P1 and P7 are known to have given tablets with poor dissolution properties.

TABLE 1

Powder dissolution rates by sieve fraction, unit weight basis, production samples

Ref.	Dissolution rate (mg/min) (±SD)			
	−150 μm	+150 μm	+210 μm	Unsieved
P1	129±13	87±19	72±22	
P2	139±28	94± 0	63±11	
P3	218±36	136±27	90±18	
P4	155±21	126± 6	70±12	
P5	105±25	87±17	51± 3	
P6	134±21	122±11	102± 9	130±24
P7	105±12			104± 6
P8	222±36	125±13	91±12	

In seeking an explanation for the variation between samples, surface areas were determined by nitrogen sorption, and it was thus shown (Table 2) that the areas varied significantly between samples. Surprisingly the areas of larger sieve sizes were only slightly lower than the finest fraction, and not at all in the ratios expected on geometric considerations. The dissolution rates expressed on a unit surface area basis can also be placed in a ranking order which varies slightly between sieve fractions, but overall P3 and P4 are fastest, and P1 and P2 are slowest. The variation within the group is no less than when expressed on a weight basis, suggesting that there is no general correlation between dissolution rate and nitrogen surface area.

It could be argued that the nitrogen surface areas are not realistic in the context of dissolution rates in water. Gaseous nitrogen would be expected to penetrate pores and interstices in a short time period while water could dissolve the sample before it had time to penetrate. Accordingly, geometric surface areas were calculated from the Coulter counter data, and these are also shown in Table 2. There is no correllation between such calculated areas and the nitrogen surface areas, and the former are about 80-times smaller.

Dissolution rates may be recalculated on the basis of these geometric surface areas; a ranking order can again be observed, with P3 and P8 generally faster than others, in agreement with the weight-based data. The overall spread of results is

TABLE 2

Surface areas of production samples by nitrogen sorption and calculated by geometric method

Ref.	Surface areas by nitrogen sorption (units: m^2/g)			Calculated geometric surface areas (units: cm^2/g ($\pm$SD)	
	$-150\ \mu m$	$+150\ \mu m$	$+210\ \mu m$	$-150\ \mu m$	$+150\ \mu m$
P1	4.02	3.75		595 ± 35	261 ± 3
P2	3.7	3.68		530 ± 93	263 ± 11
P3	3.52	3.18	3.09	552 ± 19	305 ± 11
P4	2.91	2.8		668 ± 86	265 ± 13
P5	2.76	2.71		482 ± 64	239 ± 2
P6	3.63	3.58	3.5	572 ± 76	586 ± 117
P7				482 ± 64	252 ± 3
P8	4.29	3.7	3.69	498 ± 45	260 ± 3

just as variable as before, suggesting that calculated geometric surface areas cannot explain the observed differences.

Scanning electron micrographs show that differences between samples are not great; at low magnifications all samples appear granular, but fast P3 is rougher than slow P1. At higher magnifications the individual crystallites become visible, fused together to varying degrees, with P3 less fused and comprised of smaller crystallites than P1.

True densities of these samples by helium pycnometry are always in the range 1.303–1.305 g/ml, too close to provide a meaningful distinction between them. X-ray powder diffraction photographs were visually identical. Both of these approaches suggest consistency of crystal form throughout these samples. The results obtained from heats of solution determinations will be presented in a later section.

Samples made on laboratory and pilot scales

Powder dissolution rates are given on a weight basis in Table 3. The two control samples (L1 and S1) are much faster in dissolution than typical production samples in Table 1, and apart from L7 and S4, treated samples are even more markedly different. The two control samples differ in spite of identical methods of preparation other than scale. Comparison of different treatments will be referred to the relevant control in order to allow for this possible effect of scale. Differences are more pronounced in the smallest fraction, which tends to predominate, so the observations below tend to be weighted towards this smallest fraction.

Ethyl acetate at a moderate level (L3 and S2) gives considerable improvement over controls. The highest level (L4) causes a slight decline. Sodium chloride at a moderate level (L6 and S3) also gives considerable improvement over controls, about equal to the improvement caused by ethyl acetate at its optimal level. Calcium fenoprofen precipitated at high dilution (L7 and S4) is considerably slower than controls; the degree of supersatura-

TABLE 3

Powder dissolution rates by sieve fraction, on unit weight basis, laboratory and scaleup samples

Ref.	Dissolution rates (mg/min) ($\pm$SD)			Brief description
	$-150\ \mu m$	$+150\ \mu m$	$+210\ \mu m$	
L1	301 ± 68	250 ± 13	227 ± 41	laboratory control
L2	358 ± 37	223 ± 2	155 ± 11	low ethyl acetate
L3	402 ± 24	280 ± 17	297 ± 10	medium ethyl acetate
L4	361 ± 12	269 ± 13	224 ± 55	high ethyl acetate
L5	314 ± 45	231 ± 13	160 ± 16	low NaCl
L6	421 ± 27	269 ± 36	245 ± 73	high NaCl
L7	122 ± 4			very dilute
S1	206 ± 25	183 ± 25	157 ± 15	PP control
S2	363 ± 84	269 ± 37	269 ± 13	medium ethyl acetate
S3	348 ± 40	291 ± 38	237 ± 40	high NaCl
S4	173	90		very dilute

TABLE 4

Surface areas of laboratory and scaleup samples by nitrogen sorption and calculated by geometric method

Ref.	Specific surface area				
	By nitrogen sorption (m^2/g)			Calculated geometrically (cm^2/g) (±SD)	
	−150 μm	+150 μm	+210 μm	−150 μm	+150 μm
L1	3.43			1068 ± 109	350 ± 50
L2	3.65			557 ± 22	303 ± 2
L3	4.29			675 ± 36	320 ± 3
L4	5.47			550 ± 14	326 ± 10
L5	2.86			551 ± 22	299 ± 2
L6	2.44			561 ± 21	325 ± 9
L7	1.06				
S1	5.6	5.28	5.12	829 ± 7	558 ± 112
S2	6.29	5.73	5.58	805 ± 25	558 ± 22
S3	4.26	4.56	4.68	968 ± 76	331 ± 4
S4				1065 ± 129	811 ± 272

tion at which crystallization occurs is known to influence defect density and thus dissolution rate (Chow and Grant, 1988).

Surface areas of many of these samples have been determined both by nitrogen sorption and the geometric method, and these are presented in Table 4. As before, these methods give widely different results, and show no correlation with each other.

Increasing quantities of ethyl acetate give progressively higher nitrogen surface areas compared to relevant controls, which is also surprising as comparisons are between sieve fractions nominally the same. Equally surprisingly, sodium chloride gives progressively smaller areas. The very low area of the dilute sample (L7) is in line with its physical appearance of relatively large crystals.

The dissolution rates may be recalculated on a unit area basis, using either estimate of the area. The nitrogen-based results do not always agree well with the weight-based data, but the geometrically based data appear to be reasonably in line.

Examined under the scanning electron microscope at low magnification, the control samples comprise particles smaller, less spherical and rougher than production samples. Higher magnifications again show crystallites loosely fused together into an agglomerated structure but more open than production samples, thereby possibly explaining their faster dissolution rates.

Samples treated with ethyl acetate contain a significant minority of crystallites which are physically bent, but it is not clear how small quantities of dissolved ethyl acetate can cause such an effect upon crystal morphology. Samples treated with sodium chloride have zones of high crystallinity, with crystals that appear to grow in a fan-shape from a central point, and to have many cracks. However, there is no obvious visible reason for their excellent dissolution rates. Samples precipitated at high dilution are very clearly different from all others. At low magnification they are well formed large crystals; their low nitrogen surface areas and low dissolution rates are not surprising in view of their general appearance. X-ray powder diffraction patterns of the above samples are visibly identical, suggesting that the crystal form is the same in each case.

Sodium contents of several samples were determined; only sample L6 appears to have imbibed any sodium (0.46%); the control (L1) had 0.16%, and several others were close to this. The mole fractions, assuming the counterion to be only fenoprofen, were 0.038 and 0.106 for L1 and L6 respectively.

Samples crystallized from organic solvents

Samples crystallized from hot 50% aqueous ethanol (L9, L9′) give large long crystals which appear coloured under a microscope using polarized light. Hot ethyl acetate saturated with 4% water gives very small needles (L12, L12′), with less colour. Other solvents give crystals visually comparable to one of these types. Both forms differ from each other and also from all other samples described in this report, however when the infrared spectra of both samples were compared to that of the control sample (L1), all peaks for each of the three samples were identical in every respect. X-ray powder diffraction patterns were similarly run and were identical.

Due to the crystals being needle-shaped, sieving these samples is not very successful. Most of each sample is retained on a 500 μm sieve, and this 'fraction' was used in powder dissolution testing.

TABLE 5

Dissolution rates and nitrogen areas of organically crystallised samples

Ref.	Dissolution rates on unit weight basis (mg/min) (±SD)	Nitrogen surface area (m^2/g)
L9	166 ±21	2.63
L9′	20.3± 5.4	
L12	20.9± 1.1	7.74
L12′	75	

The nitrogen surface areas were also determined; the results are listed in Table 5. Clearly, different batches of material vary enormously in their dissolution properties, rendering such measurements almost useless in this instance. In any case, comparisons with the more usual spherical agglomerates would be difficult in view of the different shapes involved. The high nitrogen area of L12 is consistent with its physical appearance.

Heats of solution

All heats of solution are endothermic (positive) and refer to the enthalpy change associated with the transition from solid form to 7 mM solution. Heat terms associated with partial dilution and any possible solvation or desolvation reactions are automatically included, and the heats tabulated below (Table 6) are thus only meaningful comparatively. Considered comparatively they estimate enthalpy difference between samples in the solid state having different lattice energies.

As heats of solution relate to a bulk process rather than a surface process, it is appropriate to consider them in relation to weight-basis dissolution data. When placed in ranking order of heat of solution, the samples fall into four groups, as follows.

(1) Sample L9 has the highest heat of solution.

(2) All six production samples (P1–P6) have heats of solution up to about 0.9 kJ/mol less than L9.

(3) The laboratory control (L1) and the low-Na^+ sample (L5) have intermediate heats of solution, about 1.3–1.6 kJ/mol less than L9.

TABLE 6

Heats of solution, enthalpy differences and 'processing values' of laboratory and production samples

Sample ref.	Enthalpy of solution (kJ/mol)		Enthalpy difference taking sample L9 as zero	Processing value (see text) (J/mol per K)	
	Average	Error		Average	Error
L9	17.99	0.07	0.00	0.00	0.24
P1	17.74	0.29	0.25	0.84	0.97
P2	17.61	0.44	0.38	1.26	1.46
P5	17.53	0.17	0.46	1.54	0.56
P4	17.36	0.11	0.63	2.11	0.37
P3	17.32	0.36	0.67	2.25	1.19
P6	17.07	0.08	0.92	3.09	0.25
L5	16.74	0.15	1.26	4.21	0.49
L1	16.36	0.26	1.63	5.48	0.87
L2	15.94	0.39	2.05	6.88	1.31
L3	15,77	0.20	2.22	7.44	0.66
L6	15.69	0.26	2.30	7.72	0.88
L4	15.35	0.30	2.64	8.85	1.01

(4) The most significantly modified laboratory samples (high NaCl and all levels of ethyl acetate) have the lowest heats of solution of all, in the approximate range 2.0–2.6 kJ/mol less than L9.

Fig. 1 shows the apparent relationship between heats of solution and dissolution data for +150 μm sieved material. The correlation coefficient here is fair (0.89) and is similar to that obtained with −150 μm sieved material (0.87).

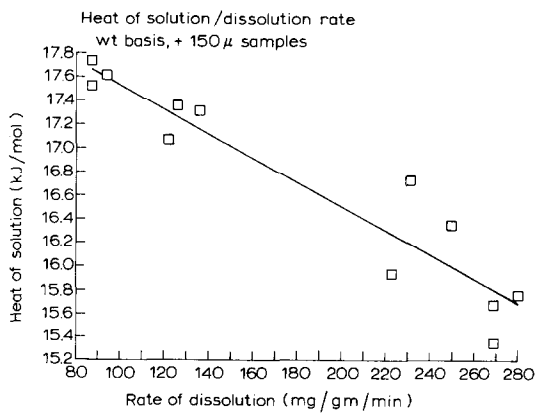

Fig. 1. Relationship between heats of solution and dissolution data for +150 μm sieved material.

Clearly, there is a general trend between heat of solution and dissolution data. Sample L9 is omitted from Fig. 1 because of the uncertainty in its dissolution rate (see above), but of the other samples the most significantly modified lab samples have the highest dissolution rates coupled with the least endothermic heats of solution

Discussion

Crystals from organic solvents differ significantly from each other in appearance. Both types of crystals as well as a precipitated control gave infrared spectra and X-ray powder diffraction patterns identical in every peak, strongly suggesting equivalent crystal forms. The differences in appearance are thus attributed to habit modification rather than to polymorphism.

Precipitated calcium fenoprofen samples differ considerably among themselves, especially in dissolution rate. Such samples when examined by scanning electron microscopy appear to be composed of small crystallites fused together in varying degrees to form relatively large agglomerates. This is consistent with the nitrogen surface areas of different sieve fractions differing only slightly from each other: a similar result has been reported for phenobarbitone (Buckton and Beezer, 1987). Nitrogen areas can be converted to equivalent sphere diameters of primary particles; most samples in the present work thus have primary particles in the range 0.7–2.0 μm, consistent with the scanning electron micrographs, but very small in comparison with the agglomerate sizes which vary up to 250 μm.

Agglomerate sizes can be directly measured by the Coulter counter technique, and these are consistent with the sieve sizes from which the samples were drawn. Dissolution rates should more meaningfully be related to agglomerate size (geometric surface area) than to primary crystallite size (nitrogen surface area) on the grounds that in a dissolution test, water must rapidly interact with the most readily available surface, the outer surface of an agglomerate, prior to dissolving it (Kaneniwa and Watari, 1974; Kouchiwa et al., 1985). Dissolution rates based on geometric area come closer to consistency with the weight-basis data than those based on nitrogen surface area, which supports the agglomerated crystallite model proposed.

Other workers have considered the degree of crystallinity of solid pharmaceuticals, and have related this to measurable parameters such as the heat of fusion (York and Grant, 1985) or the heat of solution (Pikal et al., 1978; Grant and York, 1986a) and thereby to the entropy of processing (Grant and York, 1986b). In the present work, fusion cannot be used as calcium fenoprofen does not melt without decomposition. However, heats of solution can be determined without difficulty as described earlier, and in principle one can derive the entropy of solution from a combination of enthalpy and free energy terms for the process. An alternative approach has been made, based on the ratio $\Delta H_{solution}/T$, as used by Grant and York (1986b) to reinterpret the data of Pikal (1978). This ratio has the units of entropy. They took the sample in any given series with the highest endothermic heat of solution as the most nearly perfect in crystallinity, and considered differences between the heats of solution of this sample and those of all other samples as a measure of the enthalpy of processing, $\Delta H_{processing}$. These are tabulated (Table 6) for the present samples, along with the ratio $\Delta H_{processing}/T$, which will be referred to as the 'processing value' in the ensuing discussion.

All production samples have low processing values (0.8–3.1 J/mol per K); the most significantly modified laboratory samples were highest (6.9–8.9 J/mol per K). The relationship between heats of solution and dissolution rates has been referred to already; clearly, the same comments apply to these derived processing values.

The sample that is apparently the most crystalline on the above basis is L9, which also looks the most crystalline under the optical microscope. This is not to suggest that crystallinity is necessarily high in an absolute sense. Production samples as a group are noncrystalline in appearance until the magnification is sufficient to see the crystallites from which the agglomerates are made. The solution heats confirm a relatively high degree of crystallinity not immediately obvious from appearances.

Ethyl acetate, when present during aqueous precipitation, causes considerable disruption to crystallinity, leading to the highest processing value (L4) in the present studies. The role of ethyl acetate is hard to identify. As heats of solution refer to a bulk rather than to a surface process, it would appear that the change induced by ethyl acetate is, at least predominantly, a bulk change. There is evidence from scanning electron microscopy that at least some crystallites are 'bent' and therefore presumably more strained and more defective than the norm.

The higher level of sodium chloride also gives a relatively high processing value (L6). Sodium assays confirm that Na^+ is present in the control sample (0.16%), but much more (0.46%) in this treated sample. The pseudo-disruption index proposed by Grant and York (1986a) is here calculated as only 1.53, which is very low compared to adipic acid doped with fatty acids (540–2383), suggesting a very low potential for lattice disruption, here compensated by a high additive concentration. Assuming the counter ion to be entirely fenoprofen, the present samples correspond to Ca : Na atomic ratios of 25.2 to 1 and 8.4 to 1 respectively, remarkably high levels and qualitatively suggesting a fair level of disruption. However, these ions have similar ionic radius (for Ca^{2+}, 9.9 nm; for Na^+, 9.7 nm) but of course a difference in valency.

Heats of solution of numerous samples of several antibiotics were determined by Pikal et al. (1978). When these results are expressed as processing units, the differences between least and most crystalline were much larger than in the present work, usually around 80 J/mol per K, rising to 185 J/mol per K in the case of cefazolin sodium. However, inspection of the list of samples employed reveals in many cases diversity in polymorphic form and/or hydration state, neither of which were factors in the present work. Also many of these samples were spray or freeze dried, processes known to give highly amorphous samples, and not employed in the present work. If such samples are neglected in the interests of comparing like with like, then the intra-substance variation declines to 30, 9.8 and 6.0 J/mol per K for cefazolin sodium, cephalothin sodium and cefamandole nafate, respectively. These are more closely similar to the variation found in the present work, 8.9 J/mol per K, for calcium fenoprofen, a substance of similar molecular weight and similarly possessing an organic anion.

Summary

Heats of solution provide a numeric characterization of the crystallographic states of the present samples consistent with their scanning electron micrographs, sodium contents, and above all powder dissolution rates. The crystallographic form appears not to vary within the samples studied, as demonstrated by their infrared spectra, X-ray powder diffractographs, and true densities. Correlations between powder dissolution rates and the intrinsic dissolution rates from rotating discs and with formulated tablets will be reported separately.

Acknowledgement

The author is very grateful to Dr. M.J. Pikal for the determinations of the heats of solution.

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