ELSEVIER

International Journal of Pharmaceutics 112 (1994) 65–78

international journal of pharmaceutics

The controlled crystallisation of a model powder: 1. The effects of altering the stirring rate and the supersaturation profile, and the incorporation of a surfactant (Poloxamer 188)

A.J. Mackellar [a], G. Buckton [a,*], J.M. Newton [a], B.Z. Chowdhry [b], C.A. Orr [c]

[a] *Centre for Materials Science, School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK*
[b] *School of Chemical and Biological Sciences, University of Greenwich, London SE18 6PF, UK*
[c] *SmithKline Beecham, Clarendon Road, Worthing, Sussex, UK*

Received 21 March 1994; modified version received 29 April 1994; accepted 30 May 1994

Abstract

A model drug (ethyl *p*-hydroxybenzoate) has been crystallised from propanol-water mixtures by the addition of water. The effects of rate of water addition, stirring speed and stirrer type have all been investigated. By consideration of the extent of turbulence and the degree of supersaturation, the process can be assumed to be driven by secondary nucleation mechanisms. A change in habit from plates to prismatic was observed with changes in the rate of addition of the crystallising fluid. The effect of addition of a surfactant (poloxamer 188) was investigated. It was found that the size and habit were altered by the presence of the surfactant, in a concentration-dependent manner. Differential scanning calorimetry (DSC) studies were interpreted to show that it was improbable that the surfactant was incorporated within the crystal lattice. By use of solution calorimetry, it was seen that a more favourable heat of solution was obtained in the presence of poloxamer. If the crystals were washed, however, there was no difference between the heat of solution for crystals which were prepared with or without added poloxamer. This was taken to show that the poloxamer was reversibly bound to the crystal surface. Contact angle measurements revealed that control crystals have a greater contact angle than those produced in the presence of poloxamer after washing of the crystals to remove reversibly adsorbed surfactant, thus the surface remained more hydrophilic if the crystal had been formed in the presence of poloxamer. Consequently, it is argued that the poloxamer is adsorbing and slowing the growth of hydrophilic surfaces of the crystal, thus making the final crystal more hydrophilic. For this to be true, there must be a deviation from the standard view of poloxamers adsorbing to hydrophobic surfaces in a largely irreversible manner. This view relates to adsorption from water, but in this work the adsorption is from a propanol-water mixture. High-sensitivity DSC of the solution showed that there were no phase transitions for the surfactant in the mixed solvent (whereas there are transitions in water). It is proposed that this reveals fundamental information about the conformation of the surfactant in this mixed solvent system, and that this conformational change is the reason for the change in the adsorption profile of the surfactant onto the solid.

Keywords: Poloxamer; Crystallization; Contact angle; Solution calorimetry; DSC; High-sensitivity DSC; Particle size; Crystal habit

* Corresponding author.

SSDI 0378-5173(94)00165-2

1. Introduction

It is well established that a powder's physicochemical form has a vital bearing on its performance during processing and on its clinical usefulness (e.g., York, 1983). Particle size and shape, surface nature and solid state form are all examples of fundamental properties that will define a powder's derived behaviour (Jones 1981). Although the importance of physicochemical form is clear it is not generally regarded as being of overriding importance in the primary production of powders where other criteria such as purity and yield are uppermost. However, there is a strong case for utilising the crystallisation process to optimise powder properties, and thus to ease dosage form production difficulties, or to optimise bioavailability.

Huttenrauch (1983) identifies a number of procedures that will affect a material's fundamental properties. These include milling and drying as well as crystallisation. He indicates that crystallisation will affect most of the fundamental properties and then in a cascade effect, the derived properties. It was the aim of this piece of work to manipulate the fundamental properties of a model drug via the crystallisation process. Specifically, the effect of altering the stirring rate and supersaturation under which crystallisation is carried out, are investigated, as is the effect of adding a surfactant during the process.

1.1. Crystallisation theory

The theory of crystallisation is complex and extensive and only a brief outline is given here to clarify the terms used. Although it is an oversimplification, crystallisation can be conveniently thought of as proceeding through three stages: the development of supersaturation, nucleation and then growth. Supersaturation is the vital factor in most expressions used to describe nucleation and growth and as such it is important to describe it precisely. There are various ways of describing it (Mullin, 1993) but the term relative supersaturation (σ) will be used in this work:

$$\sigma = (c - c_{eq})/c_{eq} \quad (1)$$

where c is the concentration, and c_{eq} denotes the equilibrium solubility of the solute in the solvent.

Nucleation is often described as primary or secondary. Primary nucleation can be further classified as homogeneous or heterogeneous. During homogeneous nucleation solute molecules aggregate around each other. It is an energetically unfavourable process and as such is only possible when supersaturation is high. Heterogeneous nucleation requires less supersaturation as solute molecules cluster around foreign particles or onto surfaces within the crystalliser. Although the precise mechanisms of secondary nucleation are unclear particles are thought to arise from an indistinct crystal/solution interface after a contact with another crystal or with a part of the crystalliser. The process can occur when supersaturation is very low. Crystal growth can occur by a variety of mechanisms according to the conditions during crystallisation and the substance being crystallised.

1.2. Stirring rate

The stirring rate (or power input) operating during a crystallisation procedure can have a profound effect on crystal product, particularly on the crystal size distribution (CSD). Changes in the CSD can be produced by an effect on several of the different parts of the crystallisation process.

The metastable region is the region of the solubility profile in which a solution is supersaturated but will not nucleate and its width can be significantly affected by the extent of agitation operating in the vessel (Nyvlt, 1971). In general the greater the agitation the narrower the metastable region and so the solution is more likely to nucleate and produce a smaller mean crystal size. Crystal growth is often thought of as a two step process of diffusion of solute molecules to crystal surfaces followed by integration of molecules into the crystal lattice. It has been shown that as stirring rates increase then so do crystal growth rates and this has been assumed to occur because of reduced diffusional resistance as stirring rates increase (Youngquist and Randolph, 1972). The relationship holds until a particular stirring rate is reached after which no increase occurs because solute diffusion is maximised. Integration at the crystal surface is then the rate-limiting step.

Secondary nucleation is critically dependent on stirring rates and it is well accepted that as stirring rates increase then so does the secondary nucleation frequency (Youngquist and Randolph, 1972). This phenomenon causes an apparent decrease in growth rates at rapid stirring rates caused in fact, by an increase in secondary nucleation rates.

1.3. Supersaturation profile

The supersaturation profile is the rate and extent of supersaturation development and depletion during crystallisation. There are several reports of the effect of changing the supersaturation profile on crystal product as a result of changing cooling rates. Jones and Mullin (1974) cooled saturated solutions at different rates in an attempt to limit nucleation and maximise growth onto seed particles. Natural cooling produced a surge of supersaturation causing nucleation to be significant and as a result median crystal size was reduced. Other cooling regimens attempted to hold the supersaturation developed, within the metastable region. In this way nucleation was limited (although not absent) and a larger median crystal size resulted.

1.4. The addition of surfactants

Davey (1982) reported that the effect of additives on crystal properties was most commonly due to changes in crystal growth. Additives most commonly adsorb at the crystal/liquid interface, thus altering the growth rate of that region. However, other studies have described how additives can affect nucleation processes (e.g., Mullin, 1993). Stefen (1988) reported that additives could be used to reduce the mean particle size of a crystal yield and suggested the effect was seen by influencing primary nucleation.

2. Materials and methods

2.1. Materials

Ethyl *p*-hydroxybenzoate (EHB, Nipa Laboratories, Pontypridd) was used as the model crystallising substance. Its solubility profile in a range of propan-2-ol (BDH)/water mixtures was determined. Water was double distilled in an all-glass still. Poloxamer 188 (Synperonic, ICI) was used as the surfactant. Poloxamers are a series of polyoxyethylene-polyoxypropylene ABA (POE-POP-POE) block co-polymer non-ionic surfactants whose properties vary significantly according to the molecular weights of the different polymer blocks and the overall molecular size of the surfactant. The final figure multiplied by 10 indicates the percentage of POE in the molecule whereas the first two multiplied by 100 approximates the molecular weight of the POP portion.

2.2. Methods

2.2.1. Solubility studies

An excess of solute was agitated with the different solvent mixtures. After filtering, solute concentration was determined by UV analysis at 259 nm. Equilibrium was assumed to be reached after 24 h as a further measurement at 48 h showed no change in concentration. The solubility profile is shown in Fig. 1.

2.2.2. Crystallisation procedure

As can be seen from Fig. 1, EHB solubility increases as the propan-2-ol mole fraction increases. Crystallisation was therefore carried out

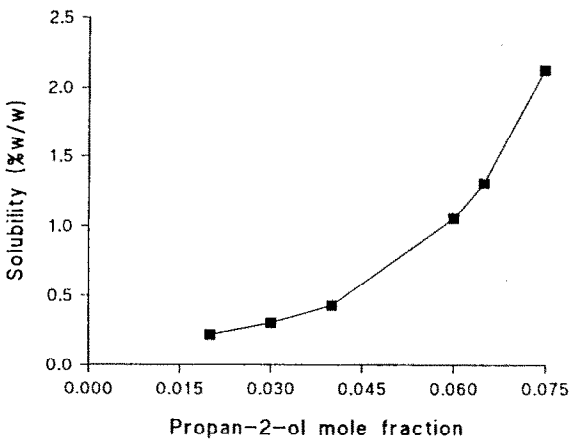

Fig. 1. Solubility profile of EHB in propan-2-ol/water mixtures.

by the dilution with water of a saturated solution of EHB in which the initial solvent mixture had a reasonably high propan-2-ol mole fraction. A solvent mixture having a propan-2-ol mole fraction of 0.065 was used to prepare a 1.29% w/w EHB solution at 55°C. Crystallisation took place in a 200 ml capacity screw topped vessel in which 48.3 g of solvent dissolved 0.63 g solute. The solution was then cooled to 30°C, producing a saturated solution. Crystallisation took place by the addition of 20 g water via a port in the vessel's lid. Supersaturation profiles were varied by changing the rate at which water was added to the vessel. It was either added rapidly using a pipette (40 g min^{-1}) or progressively more slowly using a peristaltic pump (Minipuls 3, Gilson). Details of the profiles are given in section 3. Unless otherwise specified in section 3, all experiments were carried out with the magnetic stirrer at 900 rpm, with precipitation fluid added at 40 g min^{-1}.

After the addition of water, stirring continued for 5 min after which the crystals were filtered using a Buchner apparatus. The crystals were dried in a vacuum oven (Heraeus, Geprufte Sicherheit) at 60°C 400 mmHg for 1 h. Crystals were stored over silica gel prior to analysis.

The study into the effect of surfactant on crystallisation was undertaken by crystallising EHB by diluting a mixed propan-2-ol/water EHB solution with an aqueous solution of poloxamer. According to the concentration of the added poloxamer solution a final range of poloxamer concentration within the crystalliser from 0.23 to 0.027% w/w was produced. The diluting solution was added rapidly (40 g min^{-1}) using a pipette and the solution was agitated using a magnetic stirrer operating at 900 rpm.

2.2.3. Supersaturation profiles

Two supersaturation profiles were produced, the first by adding the precipitating liquid (water) rapidly from a pipette, and the second by slow addition from a pump, these are shown in Fig. 2. The profile for the rapid addition was derived by filtering at various times after the addition of all the water (at which time crystallisation had not commenced) and from the yield of crystals recovered the concentration, and therefore supersaturation, at that time could be calculated. For the 0.49 g min^{-1} addition rate crystallisation commenced after 14 min and so relative supersaturations until this point could be calculated easily. The portion of this profile after the first appearance of crystals is an estimation although it seems a reasonable assumption that relative supersaturation will not increase when crystalline material is forming.

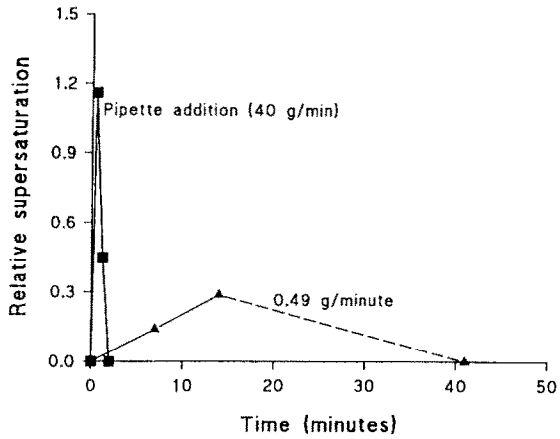

Fig. 2. Supersaturation profiles for crystallisation when water was added rapidly (40 g min^{-1}) from a pipette (■), and more slowly (0.49 g min^{-1}) using a peristaltic pump (▲).

2.2.4. Stirring rate studies

The crystallisation system described above was agitated using either a simple magnetic stirrer (Rank Brothers, Cambridge) or a propeller design of stirrer driven by a rotational motor (Lab-Plant, Huddersfield). The shaft of the propeller stirrer entered the vessel via a second port in the vessel's lid. The stirring rate of the magnetic stirrer was quantified using a transistor stroboscope (Dawe Instruments, London).

Three different stirring rates were used for each stirrer: 480, 900 and 1260 rpm for the magnetic stirrer and 500, 800 and 1300 rpm for the propeller stirrer. Reynold's numbers (Re) were calculated for the propeller stirrer using the following relationship (Coulson et al., 1990):

$$\mathrm{Re} = d^2 N \rho / \eta \qquad (2)$$

where d is the stirrer diameter, N represents the stirrer speed, ρ is the solution density and η

denotes the solution viscosity. Values of density and viscosity were taken from West (1933).

2.2.5. Size analysis

Crystals were initially assessed using light microscopy (Olympus BH-2). A camera attachment (Olympus OM2) allowed the production of photomicrographs. Particle size analysis was undertaken using laser diffractometry (Malvern 2600). Crystals were presented for measurement in a saturated solution of EHB in water to prevent any particle dissolution. To produce an adequate dispersion of crystal aggregates a drop of Span 85 (Koch Light) was added to the cell.

2.2.6. Shape analysis

Shape factors were derived using image analysis. A video camera was mounted on the top of the microscope and the image transferred to an IBM XT computer. After the creation of a binary image particles were selected individually and analysed to produce shape factors in terms of moments of inertia. The crystals were described in this work using the terms elongation and aspect ratio. Elongation is defined as the difference between the maximum and minimum moments of inertia, divided by the sum of the moments. The aspect ratio is the ratio of the square root of the maximum and minimum moments of inertia. At least 200 particles were selected for each batch under consideration.

2.2.7. DSC studies

A DSC (Perkin Elmer, 7 series) was used to investigate any changes in melting point, heat of fusion and also to estimate crystal purity. An initial rapid scan (10°C min^{-1}) from 50 to 130°C was followed by five replicates for each sample at a scanning rate of 2°C min^{-1}.

Solutions of poloxamer (0.09% w/v) in propan-2-ol-water mixtures were examined using high-sensitivity DSC (Microcal MC-2, from 10 to 70°C at 60 1°C min^{-1}).

2.2.8. Solution calorimetry

A Tronac 450 adiabatic calorimeter was used to determine heats of solution. The machine consists of a large volume water bath in which a silvered Dewar 50 ml capacity reaction vessel is immersed. The water bath was maintained very precisely at 30°C (±0.0003°C). Temperature inside the vessel is monitored using a thermocouple. The powder to be analysed was accurately weighed into a glass ampoule which was then sealed using a plastic cap and beeswax. The glass ampoule was then equilibrated in the calorimeter, under the surface of the test liquid, and then broken by activating a remote switch. This releases the contents of the ampoule into the liquid in which the heat of solution is being measured. Water was used in this work and the figures discussed in section 3 are an average of five replicates. Full details of the calculation of heat of solution are given by Craig and Newton (1991).

2.2.9. Contact angle studies

Contact angles were determined using the Wilhelmy gravitational method. Thin plates of the material being tested were made by compressing around 200 mg of powder in a Specac hand operated hydraulic press at 8.57 ton cm^{-2} for 2 min. The force exerted on this plate on immersion into a liquid of known surface tension was then measured and using the following relationship contact angles could be calculated:

$$\text{force} = p\gamma_{lv} \cos \theta \quad (3)$$

where p is the perimeter of the plate, γ_{lv} denotes the surface tension of the liquid, and θ is the contact angle. In this study water was used as the liquid of known surface tension (72.3 mN m^{-1}).

A commercial dynamic contact angle measuring device (Cahn) was used to measure the force acting on the plate.

3. Results and discussion

3.1. Stirring rate studies

Calculated values for Reynolds' numbers are listed in Table 1 and as can be seen they are high, indicating turbulent flow within the vessel. The assumptions inherent in Eq. 2 are not applicable to the case of the magnetic stirrer and so Reynolds' numbers were not calculated for this

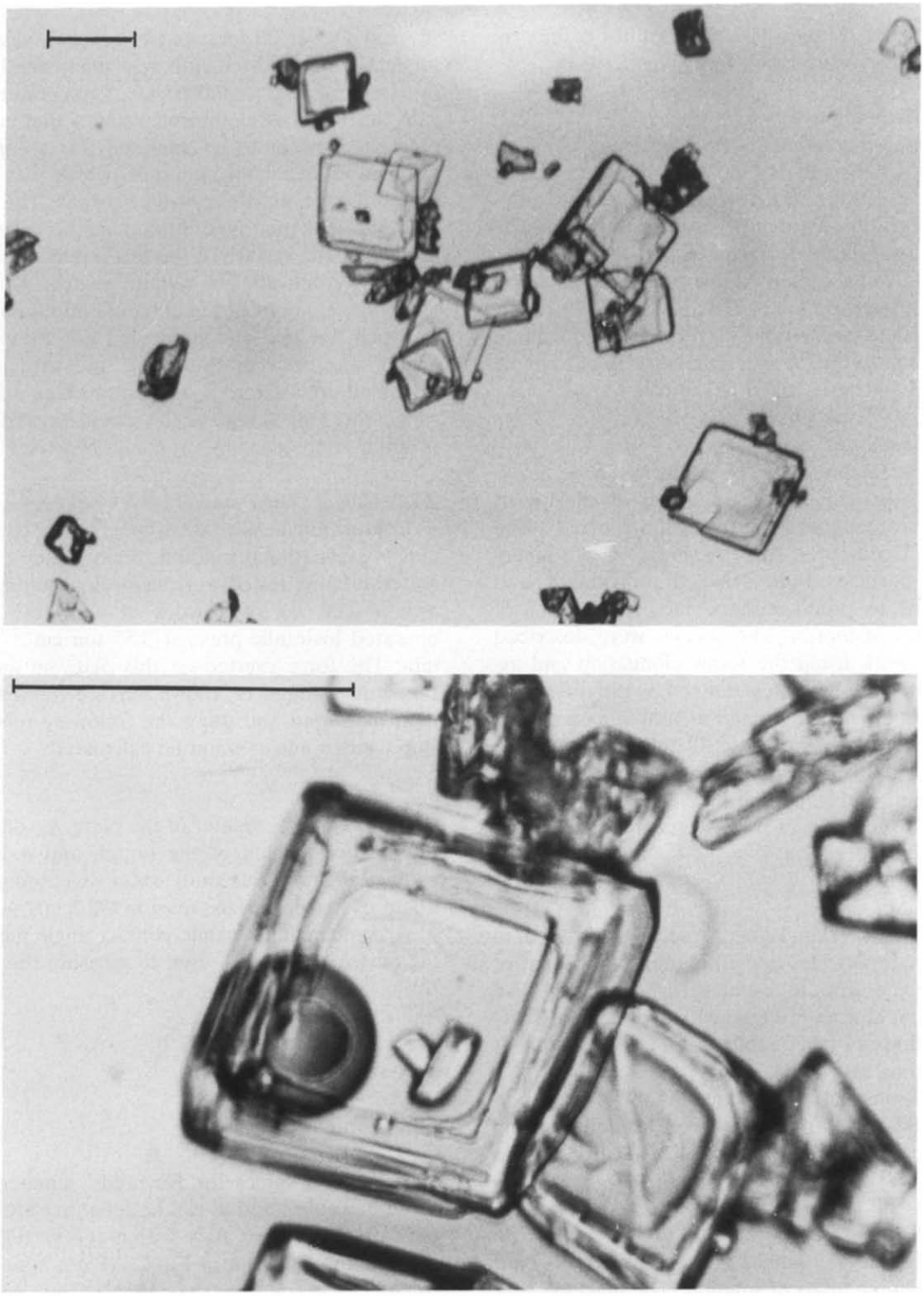

Fig. 3. Photomicrographs of crystals produced using the magnetic stirrer at 900 rpm.

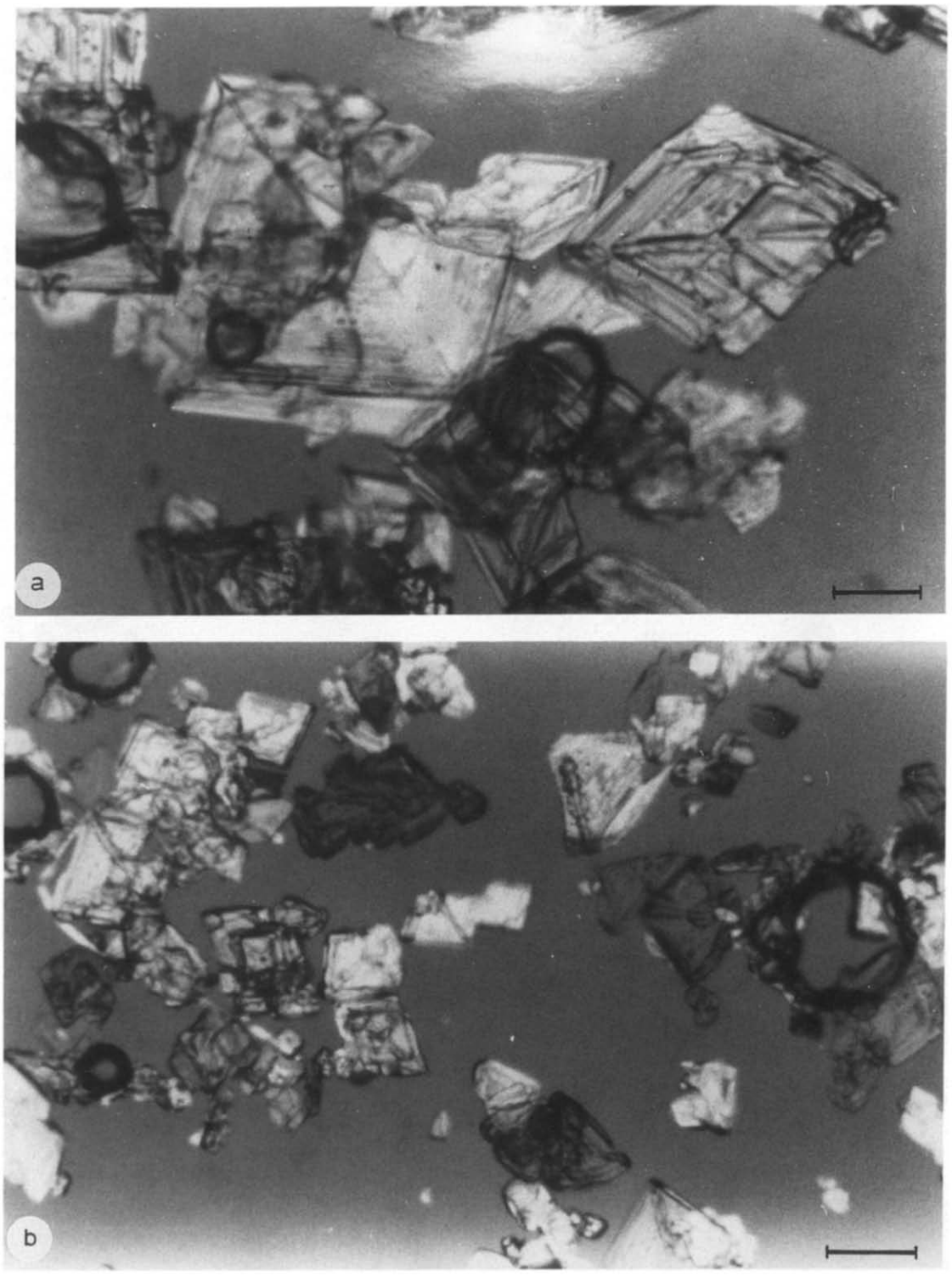

Fig. 4. Photomicrographs of crystals produced using the propeller stirrer at (a) 500 rpm and (b) 1300 rpm.

Table 1
Reynolds number (Re) values calculated for the stirring of the precipitated vessel with the propeller stirrer, and sizes for both stirrers as determined by the laser diffraction system

rpm	Reynolds number	90% undersize	50% undersize	10% undersize
Propeller stirrer				
500	6428	190.1±10.1	87.6±4.9	30.0±3.1
800	6669	175.1±12.3	80.7±5.3	28.1±2.9
1300	10838	165.8± 9.9	74.5±3.9	26.0±1.4
Magnetic stirrer				
480		139.8±7.8	72.7±1.3	25.7±1.6
900		119.2±8.8	66.2±4.2	24.6±2.6
1260		97.6±8.0	52.0±3.7	21.7±2.4

system. However, visually it was quite clear that this system was equally well agitated.

Particle sizes produced at different stirring rates are shown in Table 1. For these experiments, the precipitating fluid (water) was added via the pipette. It can be seen that as the stirring rate was increased then crystal size decreased. This was the case for both the propeller and magnetic stirrer. Photomicrographs of particles, produced at the different stirring rates using the magnetic stirrer and the propeller, are shown in Fig. 3 and 4, respectively. As can be seen from these pictures, particles produced when stirring was most vigorous appear quite broken which could account to some extent for the size reduction seen at the highest stirring rates. It appears, however, that crystals produced at intermediate stirring rates (i.e., 800 and 900 rpm) are distinctly formed crystals of smaller size. This would suggest that the increased stirring rate produces an increased nucleation rate.

As noted in section 1, stirring can affect both secondary and primary nucleation, however, the

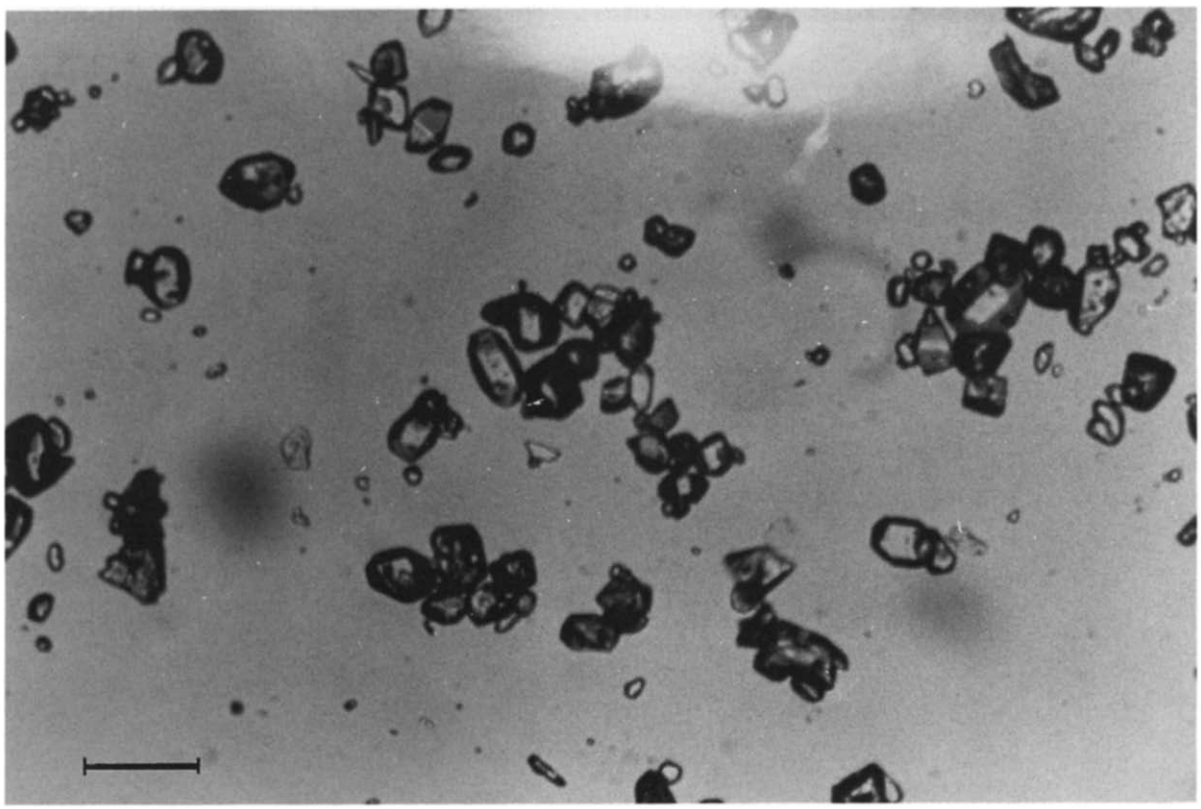

Fig. 5. Photomicrograph of crystals prepared by adding water at a slower rate, thus extending the supersaturation profile.

maximum relative supersaturation under which this crystallisation is carried out is relatively low and so it would be expected that primary nucleation would not be significant. The reduced crystal size seen as stirring rates increase is therefore likely to arise as a result of increased secondary nucleation.

The crystals obtained when using the paddle stirrer can also indicate that secondary nucleation is the dominant nucleation process in this crystallisation. Using the paddle stirrer, at a low stirring rate (80 rpm), the drowning procedure produced only a very few, large, flakey crystals which were not sufficient to classify. As the stirring rate increased a greater, though still small number, of smaller crystals were produced. These crystals were still too fragile and large to assess. This work leads to the conclusion that the addition of water to the saturated solution of EHB is not adequate to produce significant nucleation. Thus, only a few particles will form, probably via a heterogeneous mechanism after which vigorous stirring is necessary to produce secondary nuclei onto which growth can then occur.

3.2. Supersaturation profile

As can be seen from the results in Table 2, as the addition rate of the precipitating liquid decreases, the crystal size decreases. Photomicrographs of the crystals produced at the slower addition rate are shown in Fig. 5. It can be seen that a change in crystal habit has occurred when compared to the crystals produced by rapid liquid addition (Fig. 3). Crystals produced when water is added in an extended manner adopt an acicular habit. The results reported here are contrary to the findings of Jones and Mullin (1974), who reported that a more prolonged and less intense supersaturation should reduce nucleation and therefore increase crystal size. In the current study it has already been shown that the supersaturation is not sufficient to produce significant primary nucleation but that particles arise via a secondary nucleation mechanism. The supersaturation developed by the rapid dilution process is then adequate to allow these nuclei to grow into relatively large particles showing a platey habit. It appears that the lower levels of supersaturation produced by a gradual addition of water does not allow as much crystal growth and so smaller crystals are produced. This hypothesis requires that secondary nucleation can occur in conditions of low supersaturation in which rapid crystal growth is not favoured. Various studies have in fact shown that secondary nucleation will occur when supersaturation is very low and crystal growth is insignificant (e.g., Youngquist and Randolph, 1972).

The change in crystal habit arises presumably as a result of the reduced crystal growth rates. Crystal habit arises as a result of the relative growth rates of different faces. Fast growing faces grow out of existence and final crystal habit is dominated by the slowest growing faces (Mullin, 1993). As the crystal growth rates decrease because of the extended addition rate of water new faces appear which previously grew out of existence.

Table 2
Particle size data produced as a result of changing the rate of addition of water to the crystallisation vessel

Fluid addition rate ($g\ min^{-1}$)	90% undersize	50% undersize	10% undersize
40.00	119.2±8.8	66.2±4.2	24.6±1.6
3.61	122.1±9.7	66.9±5.0	24.4±2.1
1.72	88.1±5.9	50.4±3.8	23.9±1.6
0.49	79.4±4.4	47.2±1.9	19.7±1.6

3.3. Addition of surfactants

Results of the size analysis for crystals produced in the presence of surfactant are shown in Table 3. It can be seen that the poloxamer produced a significant and concentration-dependent size reduction.

It has been noted above, that a change in crystal habit from platey to prismatic occurs with changes in the rate of addition of the precipitating fluid. As can be seen by comparison of the photomicrographs in Fig. 3 of 'control' (i.e., the same protocol, but without surfactant) type crystals and Fig. 6 for crystals produced in the presence of poloxamer 188 at a concentration of 0.23% w/w, this change in habit is seen again.

Table 3
Particle size data of crystals produced in the presence of Poloxamer 188, of various concentrations (figures given below are the concentrations of surfactant in the solution that was added to initiate crystallisation, not the amount in the crystal; this notation is used throughout this paper)

Poloxamer concentration (% w/w)	90% undersize	50% undersize	10% undersize
0.230	52.2±3.8	32.2±3.0	14.6±2.8
0.150	71.7±2.3	40.3±2.6	17.2±0.9
0.130	74.3±4.8	38.7±1.7	17.3±0.4
0.090	74.8±3.3	38.4±1.3	15.7±1.3
0.061	73.8±1.8	41.7±2.7	19.4±3.0
0.046	98.8±4.0	53.7±1.9	23.0±1.7
0.027	92.6±2.2	50.7±2.1	21.3±1.6

It was also apparent that as the concentration of poloxamer increases the percentage of crystals of a prismatic habit also increases. This effect was quantified by microscopical examination of the crystals. At least 200 particles were observed and assigned to either shape category. The proportions of different shapes are shown in Fig. 7. The image analysis system also allowed shape factors for the different habits to be calculated. It can be seen that crystals of a prismatic habit are significantly more elongated and have greater aspect ratios than crystals of a platey habit.

It can be seen from Fig. 7 that the appearance of the smaller crystals of acicular habit follows that of the change in 50% undersize as poloxamer concentration increases. Fig. 8 shows the mixtures of crystal habit for crystals produced in the presence of poloxamer 188 at a concentration of 0.09% w/w.

Fairbrother and Grant (1978, 1979) suggested that the change in habit of adipic acid crystals came about as the result of incorporation of

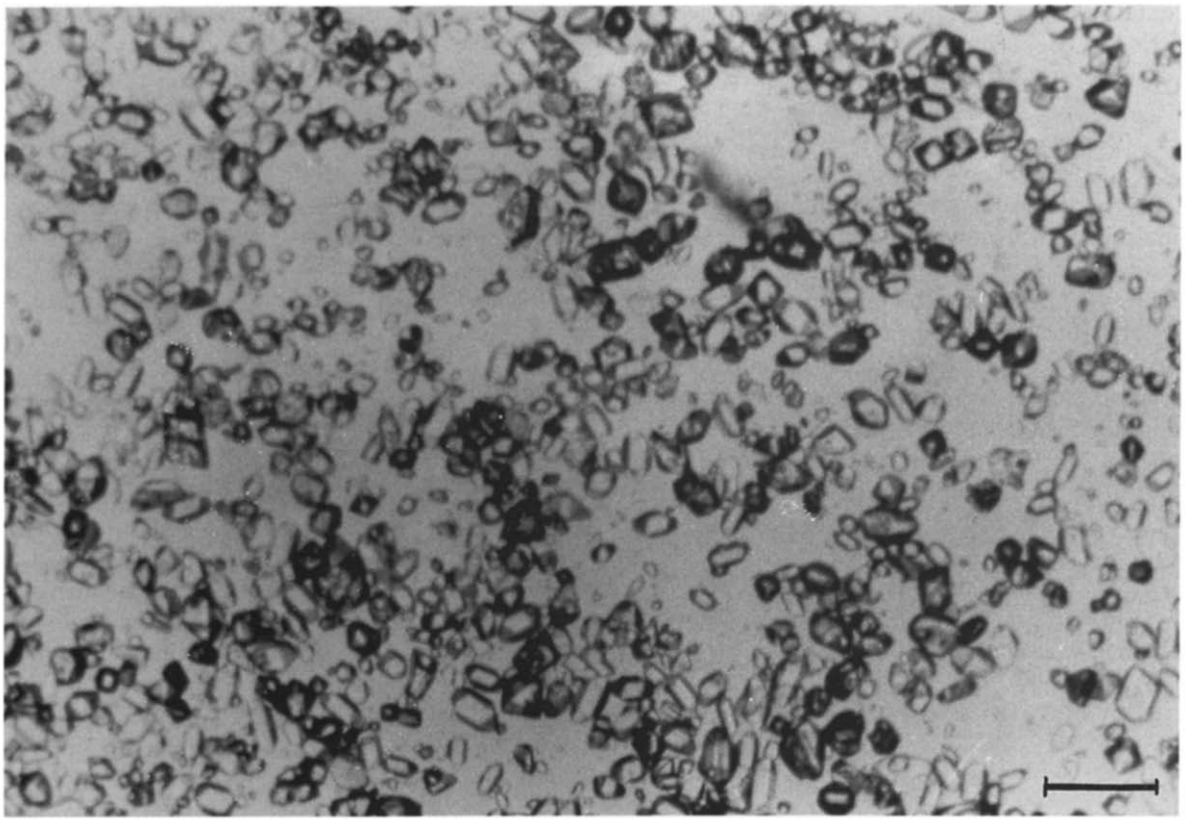

Fig. 6. Photomicrograph of crystals prepared in the presence of poloxamer at concentrations of 0.23% w/w.

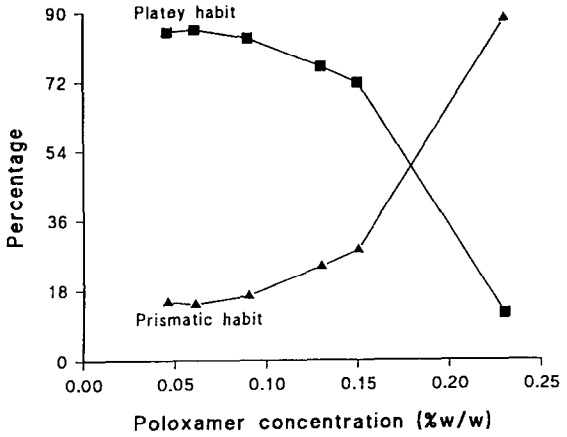

Fig. 7. Relative proportions of plate and prism habit produced following inclusion of surfactant during crystallisation.

additive molecules into the crystal lattice. In an extension of this work Chow et al. (1984) demonstrated the uptake of additive into the crystal lattice by radio labelling the *n*-alkanol or *n*-alkanoic acid. They suggested this incorporation caused the change seen in crystal habit and also showed that the inclusion of additive within the lattice caused changes in heats of fusion and melting point as indicated by DSC studies.

Table 4
Table of results obtained from DSC studies

Poloxamer concentration (% w/w)	Enthalpy of fusion (kJ mol^{-1})	% purity	Melting point (°C)
0.230	25.9	99.61	114.28
0.090	26.0	99.61	114.45
0.046	26.1	99.62	114.26
0 (control)	25.9	99.40	114.21

The results of DSC studies on various batches of EHB crystals are shown in Table 4 and as can be seen, there are no significant differences between crystals of different habits. It would appear therefore that the change in crystal habit does not come about as a result of additive incorpora-

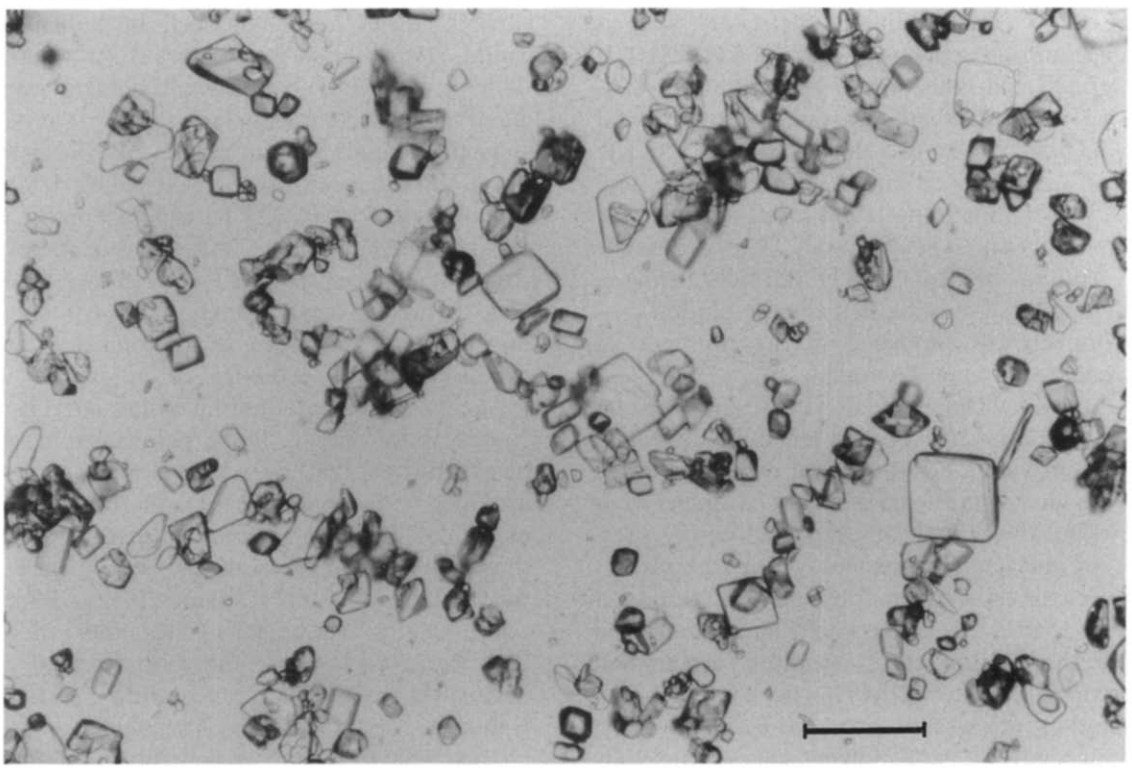

Fig. 8. Photomicrograph of crystals prepared in the presence of poloxamer at concentrations of 0.09% w/w.

Table 5
Measured heat of solution into water for samples of model drug prepared in different ways

Sample description	Heat of solution ($J\ g^{-1}$)
Crystallised in the presence of 0.23% solution of poloxamer 188	142.3 ± 6.9
Control	156.6 ± 8.7
Crystallised in the presence of poloxamer 188, then washed	157.8 ± 9.47

tion into the crystal lattice. This hypothesis is further strengthened when it is seen that purity, as detected by DSC analysis, is not changed by the presence of poloxamer during crystallisation. No events other than a melting endotherm were seen throughout this work suggesting that the change in crystal form is not seen as a result of the formation of a solvate or a polymorph.

Three different samples were analysed using solution calorimetry: crystals prepared when no poloxamer was present (I), crystals prepared in the presence of poloxamer 188 at a concentration of 0.23% w/w (II) and these same crystals washed with a saturated aqueous solution of EHB (III). It was hoped that this washing procedure would remove any adsorbed poloxamer from crystal faces. These results are shown in Table 5. The thermal event was an endothermic response and it can be seen that type II produced a lower heat of solution than type I crystals. This difference was seen to be significantly different using a Student's *t*-test showing that the dissolution process for crystals produced in the presence of poloxamer was more favourable.

A study by Chiou et al. (1976) showed that crystals produced in the presence of surfactant showed an increased dissolution rate. This effect was related to an increase in crystal defect density within the crystal lattice caused by the presence of surfactant molecules within the lattice. However, as demonstrated by the DSC results, it appears that in this case no poloxamer is retained within the crystal lattice. Another explanation offered by Chiou et al. (1976) for the change in dissolution rate was an increased ease of wetting of the crystals by the dissolving solvent caused by surface adhering surfactant molecules. It must also be remembered that the heat of solution is a composite response consisting of a number of thermal events, e.g., heat of wetting, breaking of solute/solute bonds, formation of solute/solvent bonds, etc. It seems likely therefore that the difference in heat of solution between samples I and II is seen as a result of an increased ease of wetting caused by adhering poloxamer molecules to the surfaces of EHB crystals. When the sample of crystals that were produced in the presence of poloxamer were washed to remove surfactant molecules the reduced heat of solution was no longer seen. A value similar to that of sample I crystals was produced. This implies that poloxamer molecules do in fact adsorb to crystal faces during crystallisation and so cause the differences seen in heat of solution. The results presented here indicate that the poloxamer has been washed off the surface. The ease of removal will depend very much on the conformation by which it has adsorbed. If the adsorption is by multiple contacts with one of the chains of the surfactant then the adsorption would be predicted to be non-reversible, as even though each individual bond would reversibly form and break, it would be unlikely that all the bonds would break at once to allow the surfactant to detach itself.

Contact angle measurements of crystals produced in the presence of poloxamer 188 at a concentration of 0.23% w/w and control type crystals were 34.1 ± 1.8 and $40.0 \pm 1.2°$, respectively. It can be seen that control type crystals have a higher contact angle than crystals produced in the presence of poloxamer. Crystals produced in the presence of poloxamer were washed to remove adhering poloxamer, as discussed above and so, if the poloxamer has truly been removed, the lower contact angle cannot be ascribed to the presence of adhering surfactant molecules. It appears therefore that crystals produced in the presence of poloxamer have distinctly different surface characteristics. To investigate whether washing had any other affect on the contact angle result, the control crystals were also washed with a saturated solution of EHB in water, dried, and assessed for contact angle. No change was seen for the control crystals before and after washing.

Using these three sets of results (DSC, heat of solution and contact angle) a mechanism can be proposed for the way in which poloxamers can change the size and habit of EHB crystals. From the DSC results and solution calorimetry it appears that poloxamer molecules are not built into the crystal lattice. The poloxamer adsorbs onto the crystal surface and inhibits the approach of solute molecules thereby slowing crystal growth rates and producing smaller crystals. In the examples discussed above (e.g., Fairbrother and Grant (1978, 1979) and Chow et al. (1984)), a change of crystal habit was seen after the incorporation of additives into the crystal lattice. Berkovitch-Yellin et al. (1985) showed that the inclusion of an additive within a crystal lattice is dependent on changes in bond strength between the additive and crystallising molecules. That is, the smaller the change in bond strength the greater is the inclusion of additive. They did, however, show that even molecules whose incorporation into the additive was insignificant could have a profound effect on crystal habit.

Crystal habit arises as a result of the relative growth rates of different faces. If the rate of growth of a particular face changes in relation to another then a change of habit will result (Mullin, 1993). The results presented here indicate that preferential adsorption of surfactant has occurred on certain faces of the growing crystal. The fact that the polarity of crystal surfaces changes after the poloxamer has been included, and then washed off, indicates that the preferential adsorption was such that hydrophilic faces were allowed to grow, whilst the more hydrophobic faces were inhibited. It is interesting to note that the change in surface polarity as indicated by contact angle determinations can not be detected by solution calorimetry. This suggests that the effect of altered polarity on heat of solution is obscured by the more significant components of the heat of solution response, i.e., bond breakage and formation.

The fact that the hydrophobic faces constitute a smaller part of the crystals produced in the presence of the surfactant implies that these were free to grow, in comparison to the hydrophilic faces which were restricted in their growth. This implies that the surfactant adsorbed to the hydrophilic faces, which would constitute an interaction between the polyoxyethylene portion of the poloxamer and the crystal. It is more likely that the attachment of the end of this chain would lead to reversibility of adsorption, than if the central polyoxypropylene were involved in adsorption, when it is known that dense loops adhere to hydrophobic materials in an almost irreversible manner.

The adsorption of poloxamers to solids by means of loops and chains, which results in irreversible adsorption (due to the multitude of individual contact points between each surfactant molecule and the surface, which will not all break simultaneously) has mostly been for the adsorption from water onto a hydrophobic surface. In water, the poloxamer will have a hydrophobe (i.e., the polyoxypropylene chain) which by itself is not soluble in water, and which is accommodated in the water structure only by the hydrophilic chains. The organisation of water molecules to facilitate this situation will be part of an entropic driving force that will encourage the adsorption to hydrophobic surfaces. This entropic arrangement of water is the basis of the 'hydrophobic effect'. The conformation of poloxamers in water can be probed by high sensitivity scanning calorimetry. It has been shown (Mitchard et al., 1990, 1992; Beezer et al., 1992) that poloxamer surfactants in dilute solution in water show a characteristic phase transition. This has been related to a dehydration of the hydrophobic core and is indicative of the instability of the hydrophobe in water. For the current study, the poloxamer dissolved in water/propan-2-ol mixtures was investigated. No thermal events were seen, which shows that a very different situation exists for this solvent system than exists for water. In the propan-2-ol/water mixture, the hydrophobe does not dehydrate, presumably because the polyoxypropylene is able to interact with the propan-2-ol. At the mole fractions used, the propan-2-ol is itself incorporated interstitially in the structure of water. The three component mixture will be extremely complex, especially with respect to changes in concentration of the three ingredients. The absence of the thermal event

means that the surfactant is in a different conformation in the presence of propan-2-ol, and it can be assumed that the driving force for polyoxypropylene adsorption to hydrophobic surfaces will consequently be much less than exists in the aqueous system. The absence of the thermal event provides fundamentally important information about the structure of poloxamer surfactants in complex liquid systems. This change in nature (compared with water) may well be the reason for the fact that the adsorption of poloxamer onto the model drug seems to be by way of polyoxyethylene adsorption, and also to be reversible.

Acknowledgements

Thanks are due to the SERC and SmithKline Beecham for the provision of a CASE award to A.J.M.

References

Beezer, A.E., Mitchard, N., Mitchell, J.C., Armstrong, J.K., Chowdhry, B.Z., Leharne, S.A. and Buckton, G., High-sensitivity differential scanning microcalorimetry of phase transitions in dilute solutions of poly (oxyethylene)+poly(oxypropylene)+poly(oxyethylene) block copolymers. *J. Chem. Res.*, (S) (1992), 236–237.

Berkovitch-Yellin, Z., Van Mil, J., Addadi, L., Idelson, M., Lahar, M. and Leiserowitz, L., (1985), Crystal morphology engineering by 'tailor made' inhibitors: a new probe to fine intermolecular interaction. *J. Am. Chem. Soc.*, 107 (1985) 3111–3122.

Chiou, W.L., Chen, S.J. and Athanikos, N., Enhancement of dissolution rates of poorly soluble drugs by crystallisation in aqueous surfactant solutions: I. Sulphathiazole, prednisolone and chloramphenical. *J. Pharm. Sci.*, 65 (1976) 1702–1704.

Chow, E.Y.J., Go, J., Mehdizadeh, M and Grant, D.J.W., Modification of adipic acid crystals: influence of growth in the presence of fatty acid additives on crystal properties. *Int. J. Pharm.*, 20 (1984) 3–24.

Coulson, J.M., Richardson, J.F., Backhurst, J.R. and Harker, J.H., *Chemical Engineering*, Vol. I, 4th Edn, Pergamon, Oxford, 1990.

Craig, D.Q.M. and Newton, J.M., Characterisation of polyethylene glycols using solution calorimetry. *Int. J. Pharm.*, 74 (1991) 43–48.

Davey, J.R., The role of additives in precipitation processes. In Jancic, S.J. and De Jong, E.S. (Eds), *Industrial Crystallisation*, North-Holland, Amsterdam, 1982, pp. 123–135.

Fairbrother, J.E. and Grant, D.J.W., Crystal engineering studies with an excipient material (adipic acid). *J. Pharm. Pharmacol.*, (Suppl.) 31 (1979) 27P.

Fairbrother, J.E. and Grant, D.J.W., The crystal habit modification of a tablet lubricant, adipic acid. *J. Pharm. Pharmacol.*, (Suppl.) 30 (1978) 19P.

Huttenrauch, R., Modification of starting materials to improve tabletting properties. *Pharm. Ind.*, 45 (1983) 435–440.

Jones, A.G. and Mullin, J.W., Programmed cooling crystallisation of potassium sulphate solutions. *Chem. Eng. Sci.*, 29 (1974) 105–118.

Jones, T.M., The physicochemical properties of starting materials used in tablet formulation. *Int. J. Pharm. Tech. Prod. Mfr.*, 2 (1981) 17–24.

Mitchard, N., Beezer, A.E., Mitchell, J.C., Armstrong, J.K., Chowdhry, B.Z., Leharne, S. and Buckton, G., Thermodynamic analysis of scanning calorimetric transitions observed for dilute aqueous solutions of ABA block copolymers. *J. Phys. Chem.*, 96 (1992) 9507–9512.

Mitchard, N., Beezer, A., Rees, N., Mitchell, J., Leharne, S., Chowdhry, B. and Buckton, G., Polyoxyethylene-polyoxypropylene block copolymers: a novel phase transition in aqueous solution of Pluronic F87 (poloxamer 237). *J. Chem. Soc., Chem. Commun.*, (1990) 900–901.

Mullin, J.W., *Crystallisation*, 3rd Edn, Butterworth, London, 1993.

Nyvlt, J., *Industrial Crystallisation From Solutions*, Butterworth, London, 1971.

Stefen, M., Controlled precipitation: a method to produce small drug particles and to increase bioavailability. *J. Galen. Saint-Remy-de-Provence*, 181 (1988) 45–53.

West, C.J., *International Critical Tables*, McGraw Hill, New York, 1933.

York, P., Solid state properties of powders in the formulation and processing of solid dosage forms. *Int. J. Pharm.*, 14 (1983) 1–28.

Youngquist, G.R. and Randolph, A.R., Secondary nucleation in a class II system: Amonium sulfate-water. *AIChE Symp. Ser.*, 18 (1972) 421–429.