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The use of solution calorimetry with micellar solvent systems for the detection of polymorphism

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Abstract

The presence of multiple polymorphic forms in seven batches of raw material of a model compound having poor wettability properties (cimetidine) was studied by solution calorimetry. Due to the large number of polymorphic forms described in the literature ('Gazz. Chim. Ital., 109 (1979) 535'; 'J. Pharm. Sci., 73 (1983) 1436'; 'J. Pharm. Biomed. Anal., 3 (1985) 303') and its poor wettability characteristics, cimetidine was chosen as a model compound to illustrate the possible use of solution calorimetry in the detection of polymorphism using surfactant systems as solvents for dissolution. Due to the closeness of the melting points of the different polymorphic forms of cimetidine, DSC was not the best investigational tool. As initially suspected, the measurement of enthalpy of solution values in water of the cimetidine batches was not possible. However, the use of sodium dodecyl sulfate (SDS) and polysorbate 20 (Tween 20®) at concentrations above their respective cmc values permitted the detection of significant differences in enthalpy of solution among several batches. The presence of different polymorphic forms was confirmed by microscopy, X-ray powder diffractometry, and Fourier transform infrared spectroscopy.

Keywords: Polymorphism; Solution calorimetry; Surfactants

1. Introduction

Not only characterizing but also controlling the physical properties of pharmaceutical solids during manufacturing and subsequent storage and handling is of great importance to meet product specifications as well as insure adequate reproducibility of the pharmaceutical elegance, stability (Macek, 1965; Byrn, 1976), and bioavailability of the product. Numerous examples of significant bioavailability differences have been reported to originate from differences in the solid state of compounds (Haleblian and McCrone, 1969). In the case of a crystalline material, the possibility of encountering different crystal structures is known as polymorphism (Brittain and Byrn, 1999; Grant, 1999). Different polymorphic forms are characterized by different internal energy levels, with one form being the most stable and the other forms being metastable. Thus, studying the polymor-

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phism of a drug and the stability of all polymorphic forms relative to one another is a critical part of preformulation and should be addressed as early as possible in product development. Despite their chemical identity, different crystal structures of a given chemical entity often have quite different physical characteristics (i.e. melting point, heat of fusion, solubility, dissolution rate, vapor pressure, X-ray pattern, density, hygroscopicity, infrared spectrum, NMR spectrum, and enthalpy of solution). Isoperibol calorimetry has been used in a wide range of pharmaceutical applications, including the study of polymorphism (Guillory and Erb, 1985; Lindenbaum and McGraw, 1985; Nguyen et al., 1994; Thompson et al., 2001), crystallinity of drugs (Pikal et al., 1978; Suryanarayanan and Mitchell, 1984, 1985; Grant and York, 1986; Hendriksen, 1990; Gao and Rytting, 1997), and pharmaceutical formulations (Craig and Newton, 1991a,b). Indeed, polymorphic forms are usually characterized by different enthalpy of solution values in a given solvent. The differentiation of various polymorphic forms is based on differences in the lattice energy. However, in order to obtain accurate enthalpy of solution measurements, the dissolution process must be fast and not limited by saturation. In the case of poorly wettable drugs, the dissolution process in water is often not fast enough to permit accurate enthalpy of solution measurements. The use of an organic solvent is often required to permit polymorphic differentiation. The use of two different micellar solvent systems is illustrated in this study.

2. Materials and methods

2.1. Materials

Seven different batches of bulk cimetidine or *N″*-cyano-*N*-methyl-*N′*-{2-{[(5-methyl-1H-imidazol-4-yl) methyl]thio}ethyl}guanidine were provided by Invamed, Inc, North Dayton, NJ, and were used without further treatment or purification. Cimetidine is a specific histamine H_2 antagonist used for its inhibition of the histamine-stimulated production of gastric acid (Burland et al., 1975; Pounder et al., 1976). Cimetidine exists as numerous polymorphic forms which differ in their bioavailability properties principally due to their differences in dissolution rates (Kamiya et al., 1985; Funaki et al. 1986; Kokubo et al. 1987). Several papers have been published on the polymorphism of cimetidine (Prodic-Kojic et al., 1979; Shibata et al., 1983; Hegedüs and Görög, 1985; Tudor et al., 1991; Bueno and Sobrinho, 1995; Bauer-Brandl, 1996). However, the lack of consistency in the nomenclature of the different polymorphic forms of cimetidine among the different publications makes the gathering of information somewhat confusing. A. Brauer-Brandl (Bauer-Brandl, 1996) summarized the information published on the most significant polymorphic forms using the nomenclature by B. Hegedüs et al. (Hegedüs and Görög, 1985). This nomenclature will be used throughout this article.

SDS and polysorbate 20 were of the highest grade available from Sigma (St Louis, MO) and used without further purification. SDS and Tween 20® are characterized by cmc values at 25 °C of 0.2% weight by weight (Preston, 1948; Behn, 1994) and 0.006% weight by volume at 25 °C (Becher, 1967; Wan and Lee, 1974), respectively.

2.2. Methods

2.2.1. Isoperibol calorimetry

All enthalpy of solution measurements were determined using a Hart Scientific isoperibol calorimeter (Model 4285). The temperature of the reaction vessel was monitored as a function of time during dissolution of the cimetidine samples, allowing for the calculation of the enthalpies of solution. The accuracy of the measurements was verified by determining the enthalpy of solution of KCl in water at 25 °C. All measurements were performed at 25 °C in aqueous solutions containing either 95% ethanol, 1% sodium dodecyl sulfate, or 3% Tween 20®. Samples of about 10 mg of cimetidine were directly weighed into the batch assembly. The batch assembly was then placed in the reaction vessel containing 25 ml of solvent. Correct stirring was provided to optimize the

temperature uniformity of the solvent in the reaction vessel. The temperature was recorded every 2 s. Four measurements on each batch were performed in 95% ethanol. Measurements in 1% SDS and 3% Tween 20® were performed in triplicate.

2.3. Differential scanning calorimetry

All measurements were performed on a Perkin-Elmer DSC-4. The sample weights were about 5–6 mg. The calorimeter was calibrated for temperature and heat flow accuracy using the melting of pure indium (MP: 156.6 °C and ΔH_{fusion}: 28.45 J g^{-1}). The temperature range was from 30 to 200 °C and the heating rate was 5 °C min^{-1}. Disposable aluminum open pans were used. The thermograms were obtained in duplicate.

2.4. Thermal gravimetric analysis

All measurements were performed on a Perkin-Elmer TGA-2. The sample weights were about 5–6 mg. The temperature range was from 30 to 160 °C. The heating rate was 5 °C min^{-1}. One determination was performed on all batches.

2.5. Microscopy/thermomicroscopy

Microscopic observations were performed on all batches using a Bausch & Lomb microscope equipped with a polarized light system at a magnification of 70. The samples were dispersed in a drop of silicone oil on a microscope slide with a cover glass. The samples were then heated from 70 °C to complete melting at an approximate rate of 5 °C min^{-1} while maintaining constant microscopic observation of the samples.

2.6. X-ray diffractometry

Powder X-ray diffraction was performed on a Philips diffractometer instrumented with a Databox collection system. Patterns were acquired at room temperature.

2.7. Fourier transform infrared spectroscopy

Fourier transform infrared spectra were obtained using a Nicolet spectrometer over the range 400–4000 cm^{-1} with a resolution of 4 cm^{-1}. Dry potassium bromide (50 mg) was finely ground in an agate mortar and samples of cimetidine (1–2 mg) were subsequently added and gently mixed (in order to avoid trituration of the crystals). A manual press was used to form the pellets. Bauer-Brandl (Bauer-Brandl, 1996) reported that, although some polymorphic forms of cimetidine were very sensitive to grinding and milling, no polymorphic transition could be detected for any of the forms during compression (even at high pressure).

3. Results and discussion

3.1. Tests on material as received

The DSC thermograms of all batches were obtained in duplicate. Two of the batches (# D512730 & # D512731) presented higher melting points at approximately 143 °C than those of the five other batches at approximately 141 °C (Table 1). All cimetidine batches presented identical enthalpies of fusion (approximately 163 J g^{-1}). The absence of hydrates in all batches could be concluded based on the absence of any transition temperature at about 82 °C. However, the difference in melting temperature among batches was not sufficient to conclude the presence of polymorphism. Thermogravimetric

Table 1
Melting temperature and enthalpies of fusion of cimetidine batches

Batch #	Melting temperature (°C)	ΔH_{fusion} (J g^{-1})
DS96-65	141.96 (0.06)	167.78 (4.14)
DS96-66	141.59 (0.21)	161.80 (5.52)
DS96-67	141.78 (0.10)	164.51 (1.80)
D312363	141.38 (0.11)	166.31 (1.67)
D602205	141.75 (0.07)	161.13 (0.25)
D512730	143.68 (0.22)	166.69 (2.05)
D512731	143.04 (0.42)	165.98 (2.76)

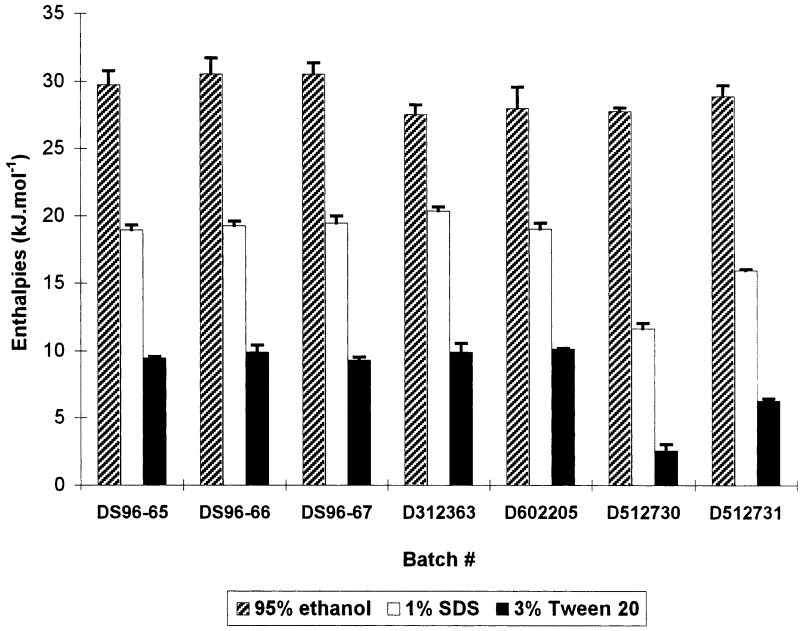

Fig. 1. Enthalpies of solution of cimetidine batches in different solvents.

analysis performed on all batches (data not shown) confirmed the absence of hydrate forms.

The experimental values of enthalpy of solution of cimetidine using water as solvent for dissolution could not be determined. Significant amounts of cimetidine were still undissolved at the end of the experiments. This could be the result of (i) insufficient solubility of cimetidine in water, and/or (ii) the insufficient rate of dissolution of cimetidine in water. Indeed, the dissolution process of the sample in the solvent chosen must be very rapid (10–20 s) to permit a reliable enthalpy measurement. Using solvents in which the solubility and/or the rate of dissolution of cimetidine were significantly increased was thus necessary to measure the enthalpies of solution of cimetidine.

The enthalpies of solution were measured in 95% ethanol (Fig. 1). Ethanol was chosen as a solvent for dissolution due to a significant increase of solubility of cimetidine (as compared with its solubility in water). Although the rate of dissolution of cimetidine in 95% ethanol was not optimum, the dissolution was complete by the end of each measurement. The enthalpy values were endothermic and ranged from 27.51 ± 0.71 (batch # D312363) to 30.54 ± 1.17 kJ mol^{-1} (batch # DS96-66). No significant differences in the enthalpy values could be detected among all batches despite the small within-batch variations (less than 5%). Statistical analyses were performed using an analysis of variance (ANOVA) test with α equal to 0.05. The enthalpy values in 95% ethanol of the two batches (# D512730 & # D512731) with lower melting point were not significantly different from those of all other batches.

Sodium dodecyl sulfate (SDS) solutions of different concentrations were subsequently tested as solvents for dissolution. Enthalpies of solution in SDS solutions at concentrations lower than the cmc (0.05 and 0.1%) could not be determined due to the presence of undissolved material in the isoperibol batch assembly. However, using SDS at a concentration of 1% weight by weight (significantly above its cmc) allowed for the measurement of the enthalpies of solution for all cimetidine batches (Fig. 1). The enthalpy values were endothermic and ranged from 11.67 ± 0.38 (batch # D512730) to 20.38 ± 0.29 kJ mol^{-1} (batch # D312363). A statistical analysis (ANOVA test with α equal to 0.05) showed a

significant difference between batches, with the enthalpy values of batches # D512730 and # D512731 significantly lower than those of all other batches. To confirm the significant batch-to-batch differences observed in 1% SDS, the enthalpies of solution were measured using a non-ionic surfactant solution. The presence of undissolved cimetidine was observed when Tween 20® was used at concentrations of 0.1 and 1.5%. Reliable measurements of enthalpy values were obtained at a concentration of 3% weight by weight (Fig. 1). Despite the fact that non-ionic surfactants have usually lower cmc values than ionic surfactants (Bury and Browning, 1953), a concentration of Tween 20® significantly higher than that of SDS needed to be used to permit accurate and reliable measurements of the enthalpies of solution. This need for increased surfactant concentration could be explained by the possibility of stronger specific interactions between cimetidine and the SDS micelles than between cimetidine and the Tween 20® micelles. The enthalpy values were endothermic and ranged from 2.59 ± 0.46 (batch # D512730) to 10.17 ± 0.04 kJ mol^{-1} (batch # D602205). A statistical analysis (ANOVA test with α equal to 0.05) showed a significant difference between batches; the enthalpy values of batches # D512730 and # D512731 were significantly lower than all other batches.

Based on the Noyes–Whitney equation, an increase in dissolution rate should be expected as the surfactant concentration increases due to the increase of the substrate solubility. Surfactants used below their cmc usually significantly increase the rate of dissolution of the substrate by improving its wettability without significantly changing the substrate solubility (Chiou et al., 1976; Florence, 1981; Veiga and Alvarez de Eulate, 1994). The Noyes–Whitney equation does not directly take into account the wettability factor. However, the surface area term considers the wettability indirectly; a well-wetted surface has a larger area of contact than a poorly wetted surface (Mall et al., 1996). On the other hand, when surfactants are used above their cmc, the substrate solubility is significantly increased while the dissolution rate increases at a slower rate than expected or even decreases (Veiga and Alvarez de Eulate, 1994). Short et al. (Short et al., 1972) reported a maximum of the dissolution rate constant of hydrocortisone at the cmc concentration of a non-ionic surfactant. Braun et al. (Braun and Parrott, 1972) reported that despite a linear increase of benzoic acid solubility with increasing concentration of polysorbate 80, the dissolution rate reached a maximum and then decreased due to an increase in the viscosity of the solution as well as an increase of the diffusion coefficient.

In the current study, when either of the surfactants was used at a concentration below its cmc value, some undissolved cimetidine was observed inside the batch assembly. Therefore, improving not only the dissolution rate of cimetidine but also its solubility by using concentrations above the cmc values, were necessary in order to perform the enthalpy measurements. Simply improving the wettability of cimetidine was not enough to permit accurate and reliable measurements of enthalpies of solution.

(Higuchi et al. (1963) showed that the solubility ratios of two forms of methylprednisolone were independent of the solvent and they determined the thermodynamics of transition by applying the Van't Hoff equation after having studied their solubilities at different temperatures. The determination of the transition temperature was also determined based on the fact that, at that a particular temperature, both forms have the same solubility. If two polymorphic forms (form I and form II) of a given drug, which only differ in their crystal morphology, are characterized by different enthalpy of solution values in solvent a ($\Delta H_{I,a}$ and $\Delta H_{II,a}$, respectively) and in solvent b ($\Delta H_{I,b}$ and $\Delta H_{II,b}$, respectively), the differences between the enthalpy of solution values of the two polymorphic forms measured in the same solvent ($\Delta H_{T,a} = \Delta H_{I,a} - \Delta H_{II,a}$ and $\Delta H_{T,b} = \Delta H_{I,b} - \Delta H_{II,b}$) should be identical and independent of the solvents used. The presence of pseudopolymorphs or different degrees of purity between the different polymorphic forms would most likely result in significant differences in the enthalpies of transition in different solvents.

Studying the solubility of polymorphs at different temperatures and then using the Van't Hoff

equation to extrapolate the thermodynamics of dissolution is tedious and can lead to systematic errors. Lindenbaum et al. (Lindenbaum and McGraw, 1985) showed that the thermodynamics of dissolution of polymorphic forms could be directly measured at the temperature of interest by solution calorimetry in a more accurate and convenient way. As long as the solvents chosen permit a rapid dissolution of the drug in the calorimeter, enthalpies of transition independent of the solvents should be observed. The authors studied the dissolution thermodynamics of two forms of sodium sulfathiazole in acetone and dimethylformamide (DMF). While the enthalpies of solution for the two forms in acetone and DMF were respectively exothermic and endothermic, the enthalpies of transition were independent of the solvent. The same observation was obtained for two forms of sulfathiazole when solubilized in methanol and acetone, except that the enthalpies of solution were endothermic in both solvents (Pakula et al., 1977).

In the case of cimetidine, where seven different batches had to be compared in three different solvents, plotting the enthalpy values measured in one solvent versus the values measured in another solvent should have theoretically led to a linear relationship if the batch-to-batch differences were independent of the solvent used. The enthalpy values of the seven batches measured in the different solvents (95% ethanol, 1% SDS, and 3% Tween 20®) were plotted against each other (Fig. 2). No linear relationships were observed when the enthalpy values measured in 95% ethanol were plotted versus the values obtained in 1% SDS (Fig. 2a) or versus the values in Tween 20® (Fig. 2b). However, a linear relationship was observed when the enthalpy values measured in 1% SDS were plotted versus the values in 3% Tween 20® (Fig. 2c). The linear relationship observed between the data sets obtained with the two micellar solvent systems indicated a good batch-to-batch correlation when the same dissolution process was involved, despite the difference in the surfactant type. The cluster of five data points in Fig. 2c was due to the fact that five batches had similar enthalpy values in 1% SDS and 3% Tween 20®. The fact that 95% ethanol did not permit any batch-to-batch differentiation could be explained by a relatively slow dissolution process in that particular solvent.

To confirm the presence of different polymorphic forms in batches # D512730 & # D512731 several techniques, including microscopy, X-ray powder diffractometry, and Fourier transform infrared spectroscopy were further used.

A microscopic observation using polarized light was performed on all batches No amorphous particles were detected using the polarized light microscope. The two batches with low values of enthalpies of solution in 1% SDS (# D512730 &

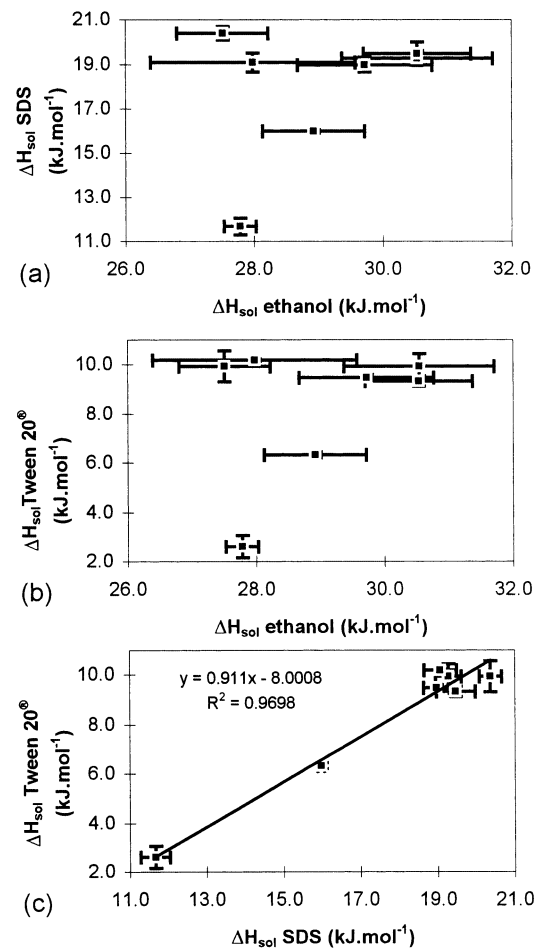

Fig. 2. Correlations between enthalpies of solution of cimetidine batches in different solvents. (a) SDS/ethanol. (b) Tween 20®/ethanol. (c) Tween 20®/SDS.

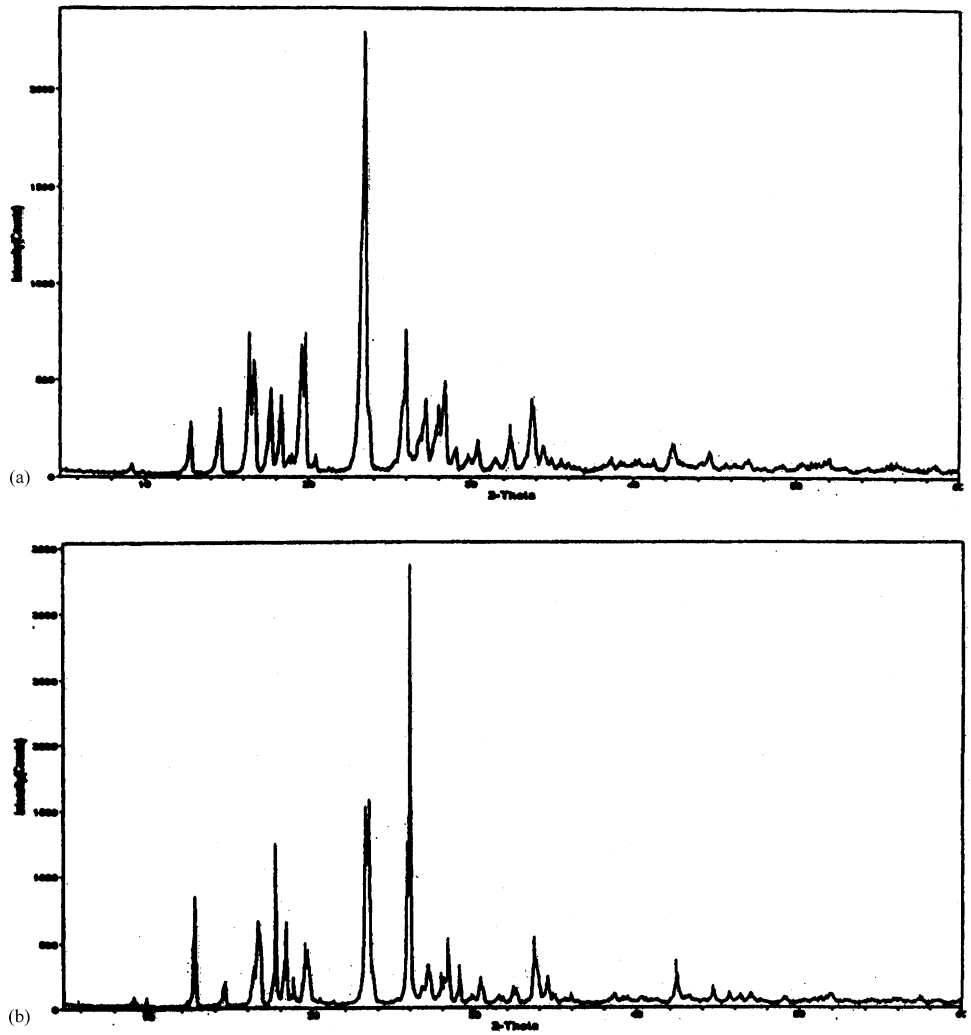

Fig. 3. X-ray powder diffraction patterns of two cimetidine batches. (a) # DS96-65. (b) # D512730.

D512731) contained two apparent crystal populations; large crystals were associated with small crystals, with both types of crystal interacting statically.

X-ray diffraction patterns were obtained for two different batches: one batch with a low enthalpy value in 1% SDS (# D512730) and one batch with a high enthalpy value in 1% SDS (# DS96-65). The x-ray pattern (Fig. 3) as well as the d-spacing values obtained for the batch with a high enthalpy of solution value (# DS96-65) could be matched with data previously obtained by Shibata et al. (Shibata et al., 1983) and by Bauer-Brandl (Bauer-Brandl, 1996) for the form A of cimetidine. The presence of pure form A was concluded in batch # DS 96-65. Based on the similarities of (i) enthalpy values in 1% SDS and 3% Tween 20®, (ii) melting temperatures, and (iii) microscopic observations with those obtained for batch # DS96-65, the presence of pure form A of cimetidine was concluded in batches # DS96-66, # DS96-67, # D312363, and # D602205. On the other hand, the X-ray pattern (Fig. 3) obtained for the batch with a low enthalpy value

(# D512730) could not be matched with any published scans. However, peaks from the X-ray pattern of batch # DS96-65 were present on the pattern of batch # D512730. Additional peaks and differences in intensities of the common peaks indicated the presence of other form(s) of cimetidine in addition to form A. The presence of form A as well as other polymorphic form(s) was concluded. Based on the similarities of (i) melting temperatures, and (ii) microscopic observations with those obtained for batch # D512730, the presence of form A of cimetidine associated with other polymorphic form(s) was concluded in batch # D512731. The difference in enthalpy values between batches # D512730 and # D512731 in 1% SDS and 3% Tween 20® could be explained by differences in the ratio of form A to the other form(s) of cimetidine.

An FTIR spectrum determination on all cimetidine batches was performed to confirm the presence of form A in all batches with high initial enthalpy of solution values in 1% SDS (# DS96-65, # DS96-66, # DS96-67, # D312363, and # D602705) and to evaluate the presence of other polymorphic form(s) in addition to form A in both batches with lower enthalpy of solution values (# D512730 and # D512731). The presence of the most significant IR bands of form A (1204, 1156, 1077, and 954 cm^{-1}) was clearly detected in the spectra of all batches. More complex spectra were obtained for both batches containing the two crystal populations. Although the presence of form A in these two batches could be detected, it was not clear (from the spectra published), which other polymorphic form(s) were also present. This could be explained by the fact that the large crystals were statically coated by the small ones (form A), which interfered with the identification of extra IR bands.

3.2. Tests on material after sieving

The microscopic observation of the seven batches of cimetidine revealed the presence of two crystal populations in batches # D512730 and # D512731: large crystals associated with smaller ones. All other batches were only composed of the small crystal population. Sieving was performed to try to separate the two crystal populations observed in batch # D512730 and # D512731. Sieving on a 90 mm gauge sieve allowed for the separation of the two crystal populations. However, due to static interactions between the two types of particles and despite a very thorough sieving using a metallic spatula, the presence of small particles surrounding the large crystals could still be microscopically observed. No particles were retained by the sieve for batches only composed of the small crystal population. Due to the correlation between the results obtained in 1% SDS and in 3% Tween 20®, further measurements of enthalpy of solution necessary to the study were only performed in 1% SDS. Moreover, due to the larger amplitude of the enthalpy values obtained in 1% SDS, more accurate results were obtained.

Enthalpies of solution of the two crystal populations separated by sieving from batches # D512730 and # D512731 were measured in 1% SDS (Fig. 4). Significant differences in the enthalpy values were obtained for the large crystal populations and the fine ones, with the large crystal populations having much smaller enthalpy values. The enthalpy values of the small crystals were not significantly different from the values obtained for the batches with high initial enthalpy values (form A of cimetidine).

Infrared spectra were obtained for the populations of crystals separated after sieving of batches # D512730 and # D512731 to evaluate the presence of different polymorphic forms between the different fractions. The spectra of the large crystal populations showed the presence of form A, probably due to the presence of the fine crystals attached to the large ones (despite the sieving process).

3.3. Tests on material after trituration

Trituration of the sample was performed to study the influence of trituration stress on cimetidine and to try to confirm the eventual polymorphic transition upon sieving of batches # D512730 and # D512731. The spontaneous transformation of a metastable polymorphic form of a compound to a more stable form might occur very slowly or even not occur in a realistic time frame depending on the magnitude of the energy

of activation of the transition process. However, slow transitions under normal storage conditions can be induced by mechanical stress such as trituration, milling, or compression (Chan and Doelker, 1985; Takahashi et al., 1985; Matsumoto et al., 1991; Ghan and Lalla, 1992; Otsuka and Matsuda, 1993; Otsuka et al., 1994). H.G. Ibrahim et al. (Ibrahim et al., 1977) showed that metastable forms of phenylbutazone underwent a polymorphic transition to a more stable form upon grinding and compressing the samples. J. Pirttimäki et al. (Pirttimäki et al., 1993) indicated that the metastable form I of anhydrous caffeine was converted to the stable form II upon grinding the sample for only 1 min. Bauer-Brandl (Bauer-Brandl, 1996) indicated that form C of cimetidine readily transformed to form B upon trituration using a mortar and pestle for less than 2 min. To insure complete conversion (if any) of the large crystals contained in batches # D512730 and # D512731, trituration of these two batches was performed in an agate mortar and pestle for about 3–5 min. Batches # DS96-65 and # D312363, which contained only form A, were also triturated to be used as negative controls.

The enthalpies of solution of the four triturated cimetidine batches were measured in 1% SDS. Two of the batches with high initial enthalpy values (# DS96-65 & # D312363) and two with low initial enthalpy values (# D512730 & # D512731) were triturated. A significant increase in the enthalpy of solution values upon triturating the samples was observed for both batches with low initial enthalpy values, whereas no significant changes were observed for both batches with high initial enthalpy values (Fig. 5). No significant differences in the enthalpy values obtained for the four triturated batches could be detected. A statistical analysis was performed using an analysis of variance (ANOVA) test with α equal to 0.05. The changes in enthalpy values observed for batches # D512730 and # D512731 upon triturating the samples could be explained by a (i) partial or total polymorphic transition, (ii) partial amorphization, or (iii) significant influence of the particle size on the enthalpy measurements. Partial amorphization of the samples did not seem to occur. Due to the loss of crystal structure during the amorphization process, less endothermic values should have been measured; however, in this case, more en-

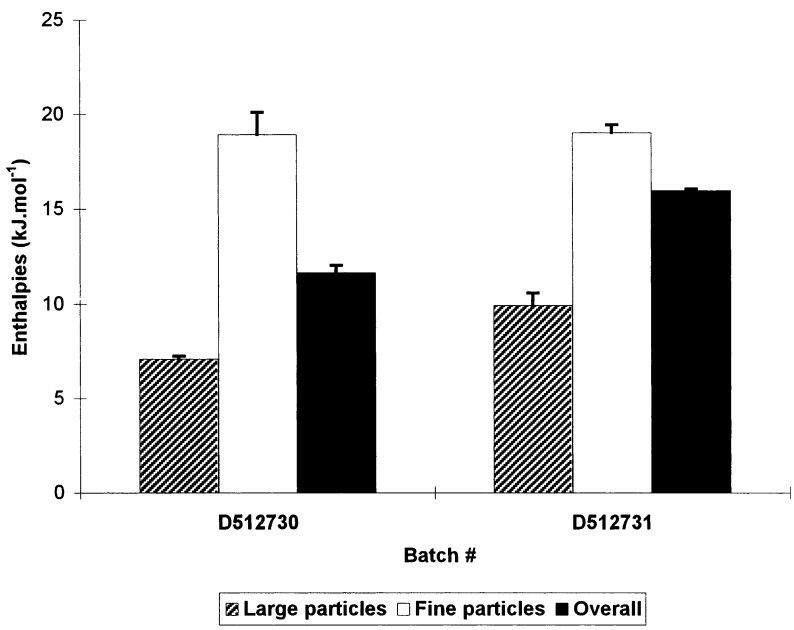

Fig. 4. Enthalpies of solution of cimetidine in 1% SDS after sieving.

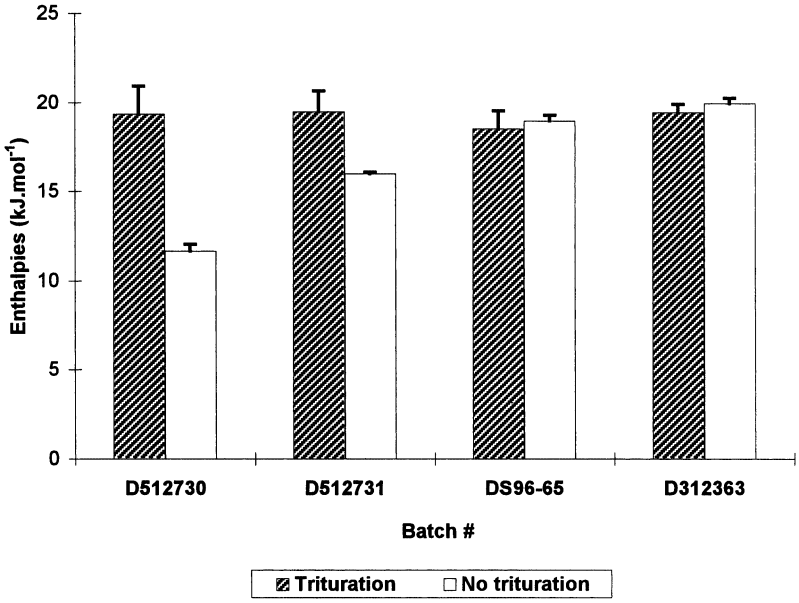

Fig. 5. Enthalpies of solution of cimetidine in 1% SDS after trituration.

dothermic enthalpy values were observed. Moreover, amorphization of any cimetidine forms was only reported after very long periods of mechanical treatment (Bauer-Brandl, 1996). The fact that no significant changes in the enthalpy values were observed in the two batches with high initial values (containing form A of cimetidine) seemed to indicate the absence of influence of particle size on the enthalpy measurements. The decrease of the particle size of batches # DS96-65 and # D312363 did not lead to an increase in the enthalpy values. The increase in the enthalpy values for batches # D512730 and # D512731 suggested a partial or total polymorphic transition. It was shown earlier that these two batches contained form A (small crystals) and another form of cimetidine (probably form C). Due to the fact that no significant changes in enthalpy values after trituration were observed for either of the two batches containing only the small crystals (form A), the large crystal population was more likely the one that underwent the polymorphic transition.

4. Conclusions

The utility of solution calorimetry with micellar solvent systems as an alternative method for the detection of polymorphism of poorly wettable compounds was demonstrated. The presence of different polymorphic forms of cimetidine was detected using solution calorimetry with 1% SDS, and 3% Tween 20®. Differential scanning calorimetry, microscopic observation, X-ray powder diffraction, and FTIR were used to confirm the solution calorimetric results. Form A of cimetidine was found to have a more endothermic enthalpy of solution than other forms of cimetidine, consistent with the fact that form A is the most stable form. The use of solution calorimetry was very useful in the detection of polymorphism of cimetidine, whereas the more conventional calorimetric methods (DSC and thermomicroscopy) failed due to the closeness of the melting points and the enthalpies of fusion of the different polymorphic forms.

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