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International Journal of Pharmaceutics 174 (1998) 187–200

international journal of pharmaceutics

Effects of surface active characteristics and solid state forms on the pH solubility profiles of drug–salt systems

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Received 11 May 1998; received in revised form 29 July 1998; accepted 30 July 1998

Abstract

The pH solubility profiles of five drug–salt systems (diclofenac sodium, diclofenac *N*-(2-hydroxyethyl)pyrrolidine, CEL50 phosphate, theophylline sodium and phenazopyridine hydrochloride) were examined. With the exception of the diclofenac sodium (Na) system supersaturation was observed at the theoretical pH of maximum solubility (pH_{max}) in all profiles. Characterisation of the solid phases involved indicated that inhibition of nucleation of the final solid form is responsible for the formation of supersaturated solutions at the pH_{max}. The surface active characteristics of the drug–salts were investigated and a general relationship between supersaturation at the pH_{max} and self-association of the drug–salts was observed. It is proposed that self-association of the drug in the region of the pH_{max} reduces the rate of nucleation of the final salt. Furthermore higher levels of supersaturation are observed when the free drug is used as the starting material indicating the key role of the solid phase employed in determining the level of supersaturation obtained. Possible pharmaceutical applications of supersaturation at the pH_{max} are discussed.

Keywords: Drugs; pH solubility profiles; Surface activity; Supersaturation; Self-association

1. Introduction

Supersaturated solutions contain more dissolved solute than a saturated solution at a given temperature and solvent volume or solvent composition. Widely accepted ways of creating supersaturated solutions are via cooling a saturated solution, evaporation of solvent, reaction of two or more components to produce a new and less soluble compound and addition of a component which reduces saturation solubility. The effects of supersaturated solutions on drug delivery have been investigated for such drugs as chlorothiazide (O'Driscoll and Corrigan, 1982), nifedepine (Kondo et al., 1987), hydrocortisone acetate (Davis and Hadgraft, 1991) and bupranol (Kemken et al., 1992). All demonstrate that super-

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0378-5173/98/$ - see front matter
PII S0378-5173(98)00257-9

saturation can offer advantages to drug-delivery by enhancing drug flux across biological membranes.

The solubilities of organic acids and bases, which comprise the majority of drugs, are very dependent on pH. Hence Dittert et al. (1964) described a phase solubility method for assessing pH solubility profiles, using appropriate acids and bases to adjust the pH. Theoretical equations were developed to describe the pH solubility profile of drug–salt systems above and below the pH_{max}, the pH of maximum theoretical solubility where free drug and salt are inter-converted (Kramer and Flynn, 1972; Streng et al., 1984).

Several studies have investigated the pH solubility profiles of drug–salt systems and reported the existence of significant areas of supersaturation and deviation from the theoretical profiles at the pH_{max} (Bogardus and Blackwood, 1979; Serajuddin and Rosoff, 1984; Serajuddin and Jarowski, 1985a,b; Serajuddin and Mufson, 1985; Serajuddin and Jarowski, 1993; Shah and Maniar, 1993). The levels of supersaturation reported were significant (for example, more than four times the salt saturation solubility in the case of the theophylline Na salt system). Most reports suggest that supersaturation at the pH_{max} is due to self-association of the drug. The purpose of this work was to examine the pH solubility profiles of diclofenac Na, diclofenac *N*-(2-hydroxyethyl)pyrrolidine (HEP), CEL50 phosphate, theophylline sodium (Na) and phenazopyridine hydrochloride (HCl) and to clarify the relationship between pH solubility profiles (including supersaturation at the pH_{max}), solid phases in equilibrium with the solutions and their surface activity properties.

1.1. Theoretical treatment of pH solubility profiles

Theoretical pH solubility profiles can be generated from equations describing the relationship between pK_a, pH and solubility for weak acids and weak bases developed by Kramer and Flynn (1972). The overall profile is a combination of two individual profiles in which either the free drug or the appropriate salt is solubility limiting. It is non-uniformly continuous at the juncture of these two profiles. The juncture is the point at which the ionised and unionised species are simultaneously saturated and is designated the pH_{max}. For weak organic acids, at pH values above and below the pH_{max}, the following relationships apply (Chowhan, 1978):

$$S_{T,\,(pH > pH_{max})} = [A^-]\left(1 + \frac{[H_3O^+]}{K'_a}\right) \quad (1)$$

$$S_{T,\,(pH < pH_{max})} = [HA]\left(1 + \frac{K'_a}{[H_3O^+]}\right) \quad (2)$$

where S_T is the saturation solubility, $[H_3O^+]$ is the hydrogen ion concentration, K'_a is the apparent dissociation constant, $[A^-]$ is the saturation solubility of the salt, and [HA] is the intrinsic solubility of the acid. Similar equations were developed for weak organic bases.

2. Materials and methods

2.1. Preparation of solids

Anhydrous theophylline (Sigma), phenazopyridine HCl (Sigma), CEL50 monohydrate (Elan) and diclofenac Na (Elan) were used as received. Other salt forms were prepared by mixing equimolar amounts of free drug with the appropriate acid or base (*o*-phosphoric acid, Riedel de Haen; NaOH, Riedel de Haen; *N*-2-(hydroxyethyl)pyrrolidine, Aldrich) and precipitating the salt form from appropriate solvents. Free drug forms were obtained by pH adjustment using HCl (for diclofenac Na) or NaOH (for phenazopyridine HCl) and washing the precipitated free drug with deionised water. All solids (including polymorphs and pseudopolymorphs encountered) were characterised by powder X-ray diffraction (PXRD), thermal analysis (TA), Karl Fischer titration analysis (KFT) using methods described previously (Ledwidge et al., 1996) and by elemental analysis.

2.2. pK'_a determination and pH solubility profiles

Estimates of [HA] (acid intrinsic solubility) were saturation solubilities at $pH < 2$ (theophylline and diclofenac). Estimates of [B] (base intrinsic solubility) were taken from solubility measurements made at $pH > 11$ (phenazopyridine and CEL50). Apparent pK_a values (pK'_a) were calculated from pH solubility data fitted to the appropriate equations for acids and bases (Kramer and Flynn, 1972) using the MINSQ nonlinear curve fitting computer program, MicroMath®, 1991. Available literature pK'_a estimates were: theophylline, 8.4 at 37°C (Serajuddin and Jarowski, 1985b); diclofenac, 4 (temperature not given), (Adeyeye and Li, 1990); phenazopyridine, 5.2 at 37°C (Serajuddin and Jarowski, 1985a).

The pH solubility studies were determined using a modification of the phase solubility technique of Dittert et al. (1964). Saturated solutions of the acids, bases and salts were made by dissolving an excess of solid in deionised water. The solutions were maintained at either 25°C (diclofenac Na, diclofenac HEP and CEL50 phosphate) or 37°C (theophylline Na, phenazopyridine HCl) by means of jacketed water vessels linked to a temperature controlled water bath (Heto). A temperature of 37°C was used for theophylline and phenazopyridine systems to allow comparison with previous reports (Serajuddin and Jarowski, 1985a,b). Solutions were agitated constantly by overhead stirrers (Heidolph). pH adjustment of solutions at values above and below those of the saturated solutions was obtained by dropwise addition of solutions of the appropriate base (or NaOH) and acid (or HCl).

Supersaturated solutions are thermodynamically unstable and nuclei formation/crystal growth are kinetic processes. Thus the design of pH solubility profile experiments, specifically the time allowed for equilibration of solutions, will have an effect on the supersaturations, if any, achieved. The sampling procedure used here was based on the method of Serajuddin and Rosoff (1984). At 1-h intervals an aliquot was withdrawn and filtered through a 0.45 μm filter (the syringe, needle and filter were previously heated to the temperature of experiment). The filtrate was diluted appropriately and analysed spectrophotometrically (Hewlett Packard 8452A diode array spectrophotometer) using the following absorbance characteristics, which were previously determined: theophylline Na monohydrate $A_1^1 = 563$ at $\lambda = 272$ nm in water; phenazopyridine HCl $A_1^1 = 977$ at $\lambda = 392$ nm in acidified ethanol (1:9 1 M HCl:ethanol); CEL50 phosphate trihydrate $A_1^1 = 304$ at $\lambda = 276$ nm in water; diclofenac Na $A_1^1 = 309$ at $\lambda = 276$ nm in water; diclofenac HEP dihydrate $A_1^1 = 213$ at $\lambda = 276$ nm in water. The excess undissolved solid was retained at each sampling interval for analysis by PXRD. Any new solid phases, as determined by PXRD, were characterised fully by TA, KFT and elemental analysis. The solution pH was determined directly using an Orion Model 520A pH meter.

2.3. Surface tension measurements

The surface activity properties of the salt systems were investigated initially by surface tension measurements using a DuNouy Tensiometer (Cambridge). Replicate readings of surface tension obtained at 25°C were plotted against concentration. The critical aggregation concentration (CAC, Kriwet and Muller-Goymann, 1993) or critical micelle concentration (CMC) was determined from a change in the concentration dependence of surface activity. The CAC and CMC terms are applied to non-micellar and micellar methods of aggregation, respectively.

2.4. Conductivity measurements

A conductivity study was carried out using a modification of the method of Streng et al. (1996). Conductivity measurements were carried out using a Radiometer conductivity apparatus (CDM 2d conductivity meter with CDC 304 conductivity cell) which was calibrated using a 0.1 M solution of KCl at 25°C. A 30 ml solution of the appropriate salt in deionised water, at a concentration below saturation at 25°C, was placed in a jacketed vessel (50 ml) and maintained at 25°C using a temperature controlled water bath (Heto). The solution was agitated by an overhead stirrer (Heidolph) and at 10 min intervals the bulk solution

conductivity was measured. A 2.0 or 3.0 ml aliquot was withdrawn and replaced with an identical amount of deionised water. Successive conductivity measurements and dilutions were carried out until the concentration of the last diluted solution was well below the CAC/CMC as determined by surface tension measurements.

2.5. Solubilisation determinations

A solubilisation study using the water insoluble fluorescent compound *N*-phenyl-1-naphthylamine (NPN) was also carried out at 25°C (Rui et al., 1986). A range of aqueous solutions with varying drug concentration was made. Approximately 1 mg/10 ml of NPN was added to the solutions which were agitated at 25°C for 24 h using a temperature controlled shaker-waterbath (Gallencamp). A 4 ml aliquot of the solution was withdrawn and filtered through a 0.45 μm filter to remove excess solid NPN. The solutions were then analysed for fluorescence of NPN using a Perkin Elmer 204-A fluorescence spectrofluorimeter using an excitation wavelength (λ) of 356 nm and an emission λ of 410 nm. CMC determination was made from a plot of relative fluorescence intensity versus drug concentration. The solubilisation studies were carried out on all salts except phenazopyridine HCl which absorbs in the region of 410 nm and would thus interfere with the NPN fluorescence emission.

3. Results and discussion

3.1. pH solubility profile of diclofenac salts

The pH solubility profile of diclofenac Na is presented in Fig. 1. Anhydrous diclofenac Na dissolved in water at 25°C forming the tetrahydrate salt with a solution of solubility ≈ 65 mM at pH 7.89 (point a). Addition of NaOH to this suspension caused the solubility to be lowered as the pH exceeded 11, consistent with common-ion effects which have been reported for other drug–salt systems (Bogardus and Blackwood, 1979; Bogardus, 1982; Streng et al., 1984; Serajuddin and Jarowski, 1985b). Lowering the pH of a suspension of the salt (point a) with HCl caused a slight increase in solubility ($\approx 3\%$) followed by precipitation of the free acid and a drop in solubility. Diclofenac acid has a solubility of 0.241 mM at a pH of 5.47 in water (point b) and reduction of the pH of this suspension using HCl to < 2 gave an estimate of 0.037 mM for the intrinsic solubility. Addition of NaOH to the suspension caused the solubility to increase to a maximum of ≈ 67 mM at pH 8.03 as solid diclofenac Na tetrahydrate was formed in the solid phase. When the solid phase consisted completely of the Na salt tetrahydrate the solution pH increased on further addition of NaOH. A value of 5.02 at 25°C was obtained for pK'_a using non-linear curve fitting. The theoretical pH solubility profile was generated from Eqs. (1) and (2) as indicated in Fig. 1. No significant supersaturation is evident in the pH_{max} (7.9) region of the profile.

The pH solubility profile of diclofenac HEP is presented in Fig. 2. The solubility of the salt in water at 25°C is 273 mM at pH 9.12 (point a). The solid state form in equilibrium with this solution is diclofenac HEP dihydrate as previ-

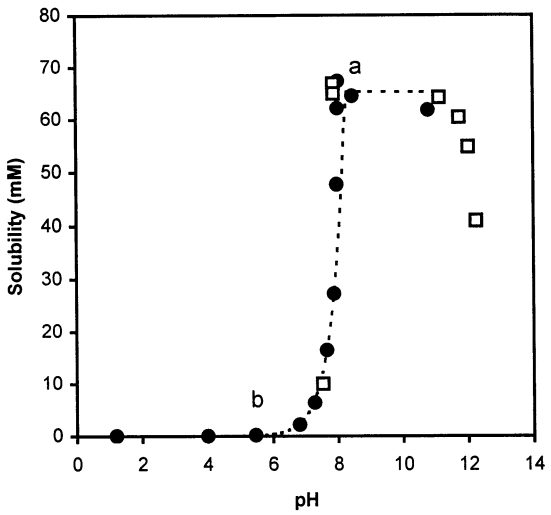

Fig. 1. pH solubility profile of diclofenac Na at 25°C using the free acid (circles) and sodium salt (squares) as starting materials. Points a and b represent the saturation states of the sodium salt tetrahydrate and the free acid respectively. The theoretical curves (dotted lines) were fitted using Eqs. (1) and (2) and the following physicochemical data: [HA] = 0.037 mM, $[A^-] = 65$ mM, $pK'_a = 5.02$.

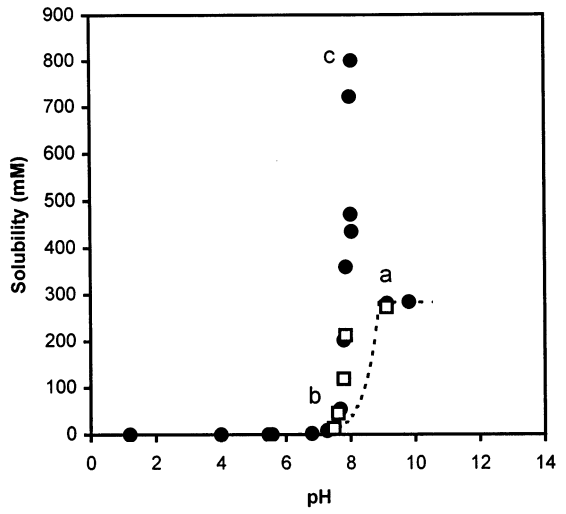

Fig. 2. pH solubility profile of diclofenac HEP at 25°C using the free acid (circles) and HEP salt (squares) as starting materials. Point a represents the saturation state of the HEP salt dihydrate. Point b (pH 7.69, 53 mM) represents the point of deviation from the theoretical profile. Point c represents a supersaturated solution in metastable equilibrium with an intermediate crystalline form. The theoretical curves (dotted lines) were fitted using Eqs. (1) and (2) and the following physicochemical data: [HA] = 0.037 mM, [A^-] = 273 mM, $pK'_a = 5.00$.

ously characterised (Ledwidge et al., 1996). Lowering the suspension pH using HCl caused conversion of the salt to the free acid and a reduction in solubility. The estimates for pK'_a and intrinsic solubility of diclofenac acid reported above were used in constructing the theoretical pH solubility profile indicated by the broken line in Fig. 2. The pH_{max} was 8.9. Adjusting the pH of a suspension of the acid using HEP caused a sharp increase in solubility that deviated significantly from the theoretical pH solubility profile at the point representing pH 7.69 and solubility 53 mM (point b). Analysis of the solid phase at pH 8.05 and solubility 335 mM showed conversion of the solid phase to an intermediate crystalline form. Characterisation of this crystalline form suggested that it is a monohydrate based on two diclofenac anions and one HEP cation (i.e. $(diclofenac)_2$ HEP monohydrate). Elemental analysis results for (diclofenac)2 HEP monohydrate were as follows: C 55.09% w/w, H 5.12% w/w, N 5.70% w/w (theory: C 54.92% w/w, H 5.30% w/w, N 5.65% w/w). Further addition of HEP caused the solubility to increase to above 800 mM at pH 8.06 (point c). Above this point, since the viscous and paste-like solution was difficult to filter accurately, no further solubility determinations were made, but the point of maximum supersaturation apparently had not been reached. In their investigation of the papaverine HCl and tiaramide HCl systems (Serajuddin and Mufson, 1985) the authors describe cooling or seeding the supersaturated solution at the pH_{max}, formed using the free drug as the starting material, in order to reduce the solubility to the level of the saturated salt. Addition of a few seed crystals of diclofenac HEP dihydrate caused the supersaturated solution at the pH_{max} to precipitate the salt dihydrate and the solubility reduced to 281 mM at pH 9.10, which is the approximate composition of a saturated solution of diclofenac HEP dihydrate. The diclofenac HEP system showed the most significant levels of supersaturation of all drug–salt systems studied and was the only one which required seeding with salt crystals to obtain the stable saturated salt solution from a supersaturated solution at the pH_{max}.

3.2. pH solubility profile of CEL50 phosphate

The pH solubility profile of the experimental drug–salt CEL50 phosphate, at 25°C is presented in Fig. 3. CEL50 phosphate trihydrate has an aqueous solubility of 4.13 mM at pH 3.70 and 25°C (point a). Increasing pH with NaOH causes a slight increase in solubility initially (4.43 mM) followed by a reduction in solubility and precipitation of CEL50 monohydrate Form II, the lower melting polymorph (transition $\approx$ 115°C). CEL50 monohydrate Form I has a melting point of $\approx$ 138°C. Lowering the pH of a suspension of CEL50 phosphate trihydrate using dropwise addition of phosphoric acid caused a reduction of the solubility of the salt, probably due to common-ion effects. CEL50 monohydrate Form I dissolves in water to form a 0.017 mM solution at pH 6.52 (point b). Increasing the pH by addition of NaOH to 11.87, gives an estimate of 0.012 mM for the intrinsic solubility. The estimate of pK'_a for

CEL50 using solubility data was 6.15 at 25°C. Reducing the pH of a suspension of the base (Form I) by addition of phosphoric acid solution caused an increase in solubility to a level of 7.45 mM at pH 3.41 (point c). As can be seen from the theoretical pH solubility profile this represents supersaturation in the region of the pH_{max} (3.7). The solid phase remained CEL50 monohydrate Form I. Further addition of phosphoric acid solution caused a lowering of the solubility of the solution, a reduction in pH and conversion of the solid phase to CEL50 phosphate trihydrate.

3.3. pH solubility profile of theophylline sodium

The pH solubility profile of theophylline sodium at 37°C is shown in Fig. 4. The salt (theophylline Na monohydrate) dissolved to form a solution of pH 11.37 and solubility 325 mM (point a). Using the salt as starting material, the solubility increases as pH is adjusted towards the pH_{max} (8.9) until pH 9.3 and a solubility of 660 mM is reached (point b). PXRD analysis of the solid phase confirms the presence of theophylline Na monohydrate only. Below the pH_{max}, the solubility is reduced and PXRD analysis confirms the presence of precipitated theophylline monohydrate. Using theophylline anhydrate as the starting material, the system equilibrates at pH 6.0 and a solubility of 58 mM with theophylline monohydrate as the solid phase (point c). Reduction of the pH with HCl gives an estimate of 56 mM for the intrinsic solubility of theophylline. At pH values below 2 the solubility begins to increase again due to ionisation of the basic function on this amphoteric molecule. However since this work is concerned with the acidic function of theophylline only, the pH solubility profile was not investigated below pH 1.50. Addition of NaOH to a suspension of theophylline caused an increase in solubility up to 940 mM in the region of the pH_{max} (point d). The solid phase detected at all points along this profile by PXRD was theophylline monohydrate. Further addition of

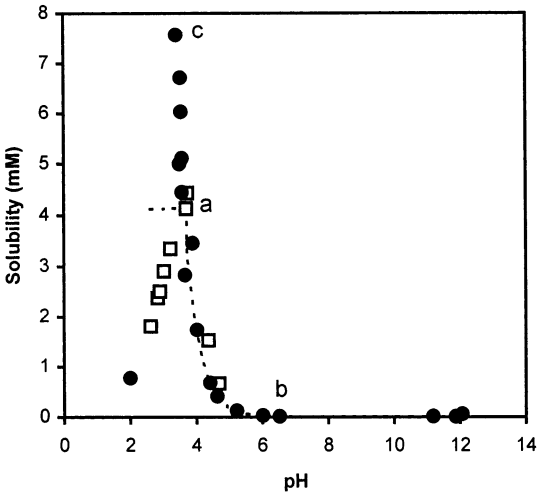

Fig. 3. pH solubility profile of CEL50 phosphate at 25°C using the free base (circles) and phosphate salt (squares) as starting materials. Points a and b represent the saturation states of the phosphate salt trihydrate and the free base monohydrate form I respectively. Point c represents a supersaturated solution in metastable equilibrium with the free base monohydrate. The theoretical curves (dotted lines) were fitted using the following physicochemical data: [B] = 0.012 mM, $[BH^+]$ = 4.130 mM, pK'_a = 6.15.

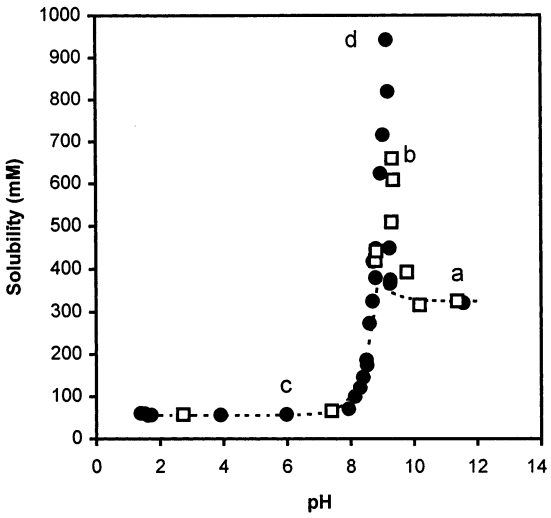

Fig. 4. pH solubility profile of theophylline Na at 37°C using the free drug (circles) and Na salt (squares) as starting materials. Points a and c represent the saturation states of theophylline Na monohydrate and the theophylline monohydrate respectively. Points b and d represent supersaturated solutions in metastable equilibrium with the Na salt monohydrate and theophylline monohydrate respectively. The theoretical curves (dotted lines) were fitted using Eqs. (1) and (2) and the following physicochemical data: [HA] = 56 mM, $[A^-]$ = 325 mM, pK'_a = 8.11.

NaOH caused a lowering of the solubility and precipitation of theophylline Na monohydrate. The pK'_a was estimated as 8.11. The theoretical pH solubility profile of the theophylline Na salt system is indicated by the broken line in Fig. 4. As reported by Serajuddin and Jarowski (1985b), the pH solubility curves of the free drug and the salt are identical except for the region of the pH_{max} where significant levels of supersaturation are observed. The level of supersaturation achieved using the free drug is greater than that of the salt.

3.4. pH solubility profile of phenazopyridine HCl

The pH solubility profile of phenazopyridine at 37°C is presented in Fig. 5. A saturated solution of the hydrochloride in water had a pH of 3.16 and a solubility of 19.90 mM (point a). Addition of NaOH caused a slight increase in solubility (20.66 mM) before the solubility reduced as phenazopyridine base (monohydrate) was precipitated. Using the anhydrous phenazopyridine as the starting material the stable form was the monohydrate giving a solubility of 0.20 mM and a pH of 6.02 (point b). Raising the pH to 11.2 resulted in an estimate of 0.13 mM for the intrinsic solubility of the base. Decreasing the pH of a suspension of the base caused a solubility increase to ≈ 55 mM at a pH of 3.13 (point c). Up to this point no precipitation of hydrochloride salt was observed by PXRD analysis. Further addition of HCl resulted in formation of phenazopyridine HCl and solubility lowering to 9.13 mM at pH 1.67. The theoretical pH solubility profile is indicated by the dotted line using a pK'_a of 5.15 at 37°C and there are two regions of deviation from the theoretical profile. The first region is the reduction of HCl salt solubility at pH values below 3, which may be explained by common-ion effects. In addition, supersaturation at the pH_{max} region of the profile (pH 3.1) was observed which, like the other systems investigated, was most significant when the free drug was used as the starting material. At the point of highest recorded solubility (point c) the composition of the solid phase was phenazopyridine monohydrate.

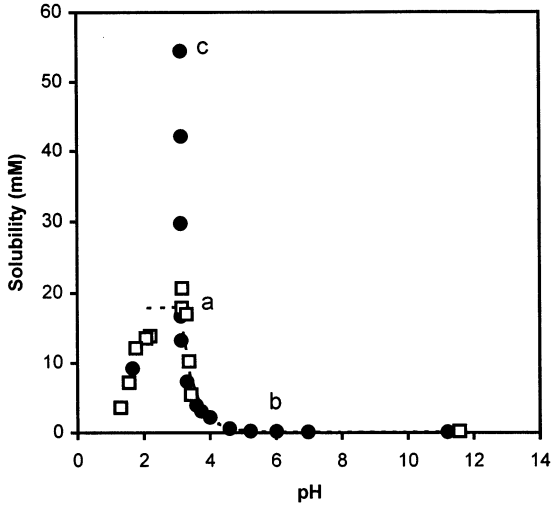

Fig. 5. pH solubility profile of phenazopyridine HCl at 37°C using the free base (circles) and HCl salt (squares) as starting materials. Points a and b represent the saturation states of the HCl salt and free base monohydrate form I. Point c represents a supersaturated solution in metastable equilibrium with the free base monohydrate. The theoretical curves (dotted lines) were fitted using the following physicochemical data: $[B] = 0.13$ mM, $[BH^+] = 19.90$ mM, $pK'_a = 5.15$.

3.5. Surface activity and self-association properties of drug–salt systems

The surface activity properties of diclofenac Na and diclofenac HEP are evaluated in Figs. 6–8. The surface tension plots (Fig. 6) show CAC/CMC values for the Na and HEP salts of 25 and 20 mM respectively. Solubilisation of NPN is only seen by solutions of the HEP salt at and above concentrations of 30 mM (Fig. 7), yielding a CMC of approximately 35 mM, as determined by the method of Rui et al. (1986). Conductivity experiments on diclofenac (Fig. 8) demonstrate an inflexion in the plot of molar conductivity versus square root of concentration for the HEP salt only (at approximately 35 mM). The difference between estimates of CMC obtained from the surface tension and conductivity/solubilisation properties of surfactant solutions is because the former is a function of the monomer concentration and the latter may be functions of aggregates (micelles) formed. It is generally found that micellisation does not simply occur at a single concen-

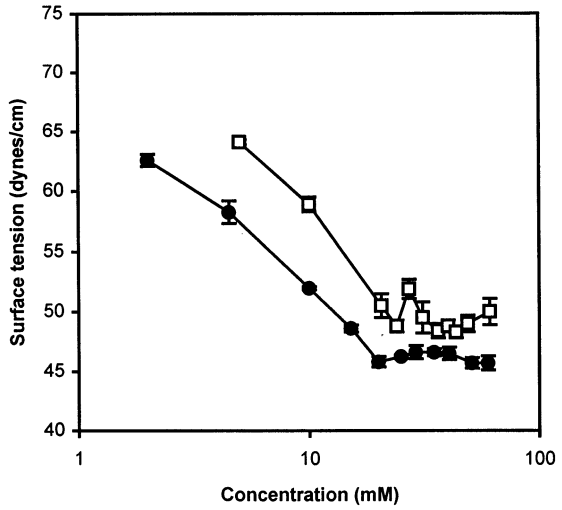

Fig. 6. Plot of surface tension versus concentration ($n = 3$) for diclofenac HEP (circles) and diclofenac Na (squares). The CMCs for diclofenac HEP and Na are 20 and 25 mM respectively.

tration, but over a range of concentrations (Florence and Attwood, 1988). These results demonstrate that diclofenac HEP and Na are surface active but that only the HEP salt shows micelle formation. These results agree with previous reports of micellisation behaviour of diclofenac

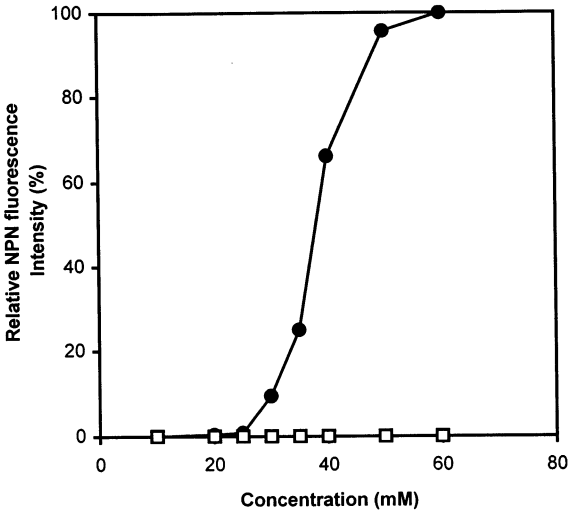

Fig. 7. Solubilisation plot of NPN by diclofenac HEP (circles) and diclofenac Na (squares). Diclofenac HEP shows a CMC at 35 mM.

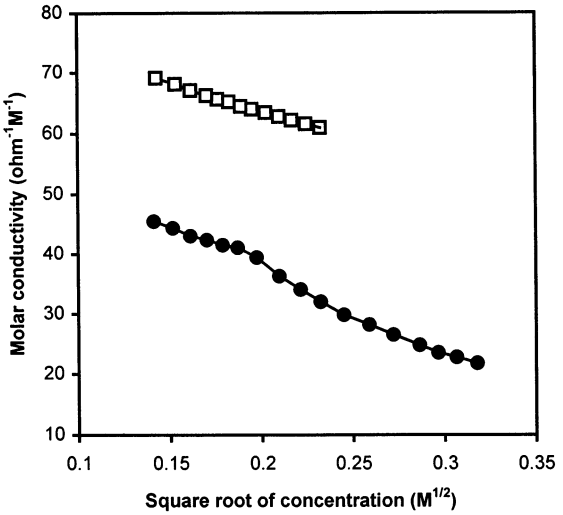

Fig. 8. Plot molar conductivity versus square root of concentration for diclofenac HEP (circles) and diclofenac Na (squares). Diclofenac HEP shows a CMC at 35 mM.

HEP (Fini and Fazio, 1991; Fini et al., 1995). However, we attribute the lack of comparable micelle formation in diclofenac Na to the effect of the counterion change (Na versus HEP), rather than solubility considerations. This conclusion is supported by observations of several workers on the influence of counter-ion on micellisation behaviour (Attwood and Florence, 1983).

Fig. 9 shows the results of the surface tension investigations of CEL50 phospate, theophylline Na and phenazopyridine HCl. The plot shows a significant decrease in surface tension as concentration is increased in the cases of all three salts indicating that they are surface active. CEL50 phosphate shows a CAC/CMC at 0.7 mM. No solubilisation of NPN was observed, nor was any inflexion observed in a plot of molar conductivity versus square root of concentration. These results suggest that the aggregation evident in the surface tension experiments was not micellar. The surface tension versus concentration plot for theophylline Na shows a CAC/CMC at 70 mM (Fig. 9). NPN solubilisation showed an insignificant increase in fluorescence intensity from 50 to 150 mM. However, there was a very pronounced inflexion in the conductivity plot at 100–110 mM which indicates micelle formation. The surface activity properties

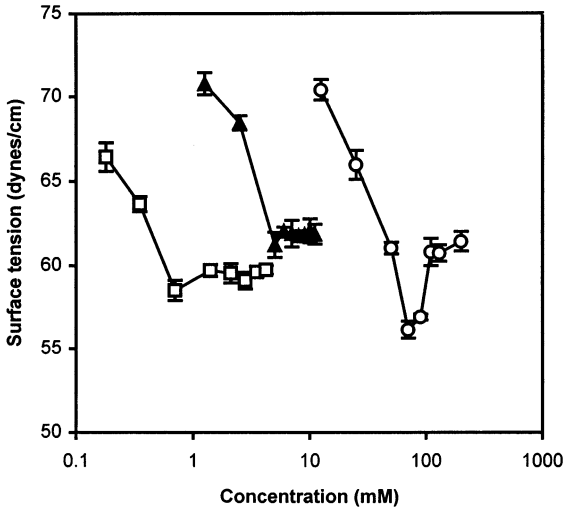

Fig. 9. Plot of surface tension vs concentration ($n=3$) for CEL50 phosphate (squares), phenazopyridine HCl (triangles) and theophylline Na (circles).

of phenazopyridine HCl were confirmed by surface tension measurements which showed a CAC/CMC at 5 mM (Fig. 9). Furthermore a plot of molar conductivity versus square root of concentration yields an inflexion at approximately 8 mM suggesting that the aggregates formed may be micellar.

For the drug–salt systems studied in the present work that demonstrated common-ion effects (diclofenac Na, CEL50 phosphate and phenazopyridine HCl) apparent solubility product (K'_{sp}) calculations were carried out and are presented in Tables 1–3. The K'_{sp} values were calculated from pH solubility data according to the method of Serajuddin and Mufson (1985). Bogardus and Blackwood (1979), Serajuddin and Mufson (1985) used K'_{sp} calculations taken from pH solubility data to demonstrate self-association in drug solutions. Increasing K'_{sp} values as drug concentrations increase are explained by a lowering of the drug activity coefficient due to possible formation of self-association complexes (Serajuddin and Mufson, 1985). The data presented here (Table 3) suggest that the K'_{sp} values for phenazopyridine HCl are not constant in the region of the pH solubility profile where common-ion effects are observed. That the K'_{sp} values for phenazopyridine HCl increase as the pH and solubility is increased suggests self-association of the drug in agreement with the surface tension and conductivity data. Similar patterns of change in the K'_{sp} values for CEL50 phosphate were observed (Table 2), again suggesting self-association of the drug in solution. Small increases in K'_{sp} for diclofenac Na, suggesting insignificant self-association compared to phenazopyridine HCl and CEL50 phosphate, were in agreement with the

Table 1
K'_{sp} estimates from pH solubility data for diclofenac Na

pH	$[Na^+]$ (M)	S_T (M)	K'_{sp}
7.88	6.68×10^{-2}	6.68×10^{-2}	4.467×10^{-3}
7.89	6.50×10^{-2}	6.49×10^{-2}	4.219×10^{-3}
11.13	6.55×10^{-2}	6.42×10^{-2}	4.204×10^{-3}
11.74	6.59×10^{-2}	6.04×10^{-2}	3.977×10^{-3}
12.02	6.52×10^{-2}	5.48×10^{-2}	3.574×10^{-3}

$[Na^+]$ was calculated by adding the molar concentrations of diclofenac Na (S_T) and hydroxyl ion.

Table 2
K'_{sp} estimates from pH solubility data for CEL50 phosphate

pH	$[PO_4^{3-}]$ (M)	S_T (M)	K'_{sp}
2.62	0.002604	0.001804	4.77×10^{-6}
2.84	0.002854	0.002372	6.77×10^{-6}
2.91	0.002913	0.002503	7.29×10^{-6}
3.03	0.003215	0.002904	9.34×10^{-6}
3.22	0.003548	0.003347	11.90×10^{-6}

$[PO_4^{3-}]$ was calculated by adding the molar concentration of CEL50 phosphate (S_T) and a third the molar concentration of the hydrogen ion.

Table 3
K'_{sp} estimates from pH solubility data for phenazopyridine HCl

pH	$[Cl^-]$ (M)	S_T (M)	K'_{sp}
1.3	0.053703	0.003585	1.93×10^{-4}
1.56	0.034743	0.0072	2.50×10^{-4}
1.76	0.02752	0.010142	2.79×10^{-4}
2.07	0.022067	0.013556	2.99×10^{-4}
3.16	0.018585	0.017894	3.33×10^{-4}

$[Cl^-]$ was calculated by adding the molar concentrations of phenazopyridine HCl (S_T) and hydrogen ion.

relative lack of surface activity detected from surface tension and conductivity experiments.

3.6. Solid phases and supersaturation in the pH_{max} regions

It is important to note that, from the PXRD patterns of solid phases, up to the highest levels of supersaturation in the pH_{max} region the final solid form is not present. For example, in the cases of CEL50 phosphate, theophylline Na and phenazopyridine HCl, when the starting material was free drug, the compositions of the solid phases at the highest level of supersaturation were pure free drug as determined by PXRD. This suggests that when the free drug is used as the starting material significant supersaturation occurs because of 'barrier(s)', at the pH_{max}, to the formation of the appropriate stable salt form. This agrees with the observation by Serajuddin and Rosoff (1984) that supersaturation of a solution in equilibrium with papaverine base at the pH_{max} is 'released' by nucleation of the final solid form (hydrochloride salt). In the absence of salt formation, the excess acid or base added to the solution of the free drug appears to cause an increase in the solubility above that of the saturated salt, limited only by the pH solubility profile of the free drug.

Diclofenac HEP is the only salt system studied which demonstrated conversion of the solid phase to another crystalline form in the pH_{max} region. Self-solubilisation and/or conversion of the acid into $(diclofenac)_2$ HEP monohydrate at the pH_{max} may be partly responsible for the observed supersaturation. However, adding seed crystals of the salt dihydrate causes the supersaturated solution around the pH_{max} to precipitate out the HEP salt dihydrate and the solution returns to saturation solubility. A similar effect is observed if a supersaturated solution is left for 24 h. Thus $(diclofenac)_2$ HEP is a metastable form when high levels of apparent supersaturation are achieved at the pH_{max} and the system will eventually precipitate out the stable diclofenac HEP dihydrate. Since the supersaturated state is metastable and can precipitate with time it is considered that the 'barrier(s)' to precipitation of the stable solid form are 'kinetic barrier(s)'.

3.7. Supersaturation and self-association in the pH_{max} regions

A summary of the solubility and surface activity properties of the drug–salt systems studied is presented in Table 4. In this table we define apparent supersaturation as solubility achieved at the pH_{max} relative to a saturated solution. According to this definition the level of supersaturation achieved in the diclofenac HEP system was greater than 3. However, since supersaturation begins significantly below the pH_{max}, the actual supersaturation achieved, relative to the theoretical profile, is greater than 18. It has previously been proposed that self-association may be responsible for supersaturation at the pH_{max} (Bogardus and Blackwood, 1979; Serajuddin and Jarowski, 1985a,b) in drug–salt systems. Several studies used K'_{sp} data to demonstrate drug self-association (Bogardus and Blackwood, 1979; Serajuddin and Jarowski, 1985a; Serajuddin and Mufson, 1985). However Serajuddin and Jarowski (1985a) found that the relative constancy of K'_{sp} values for phenazopyridine precluded any major self-association. Despite this, the authors suggest that self-association complexes may be formed in the region of the pH_{max}. The results of K'_{sp} calculations in the present work, including those for phenazopyridine HCl, are consistent with other investigations into surface activity of the drug–salt systems. From the results presented in Table 4 it appears that there is a general trend of supersaturation occurring at the pH_{max} in drug–salt systems where aggregates may be formed. Diclofenac HEP, theophylline Na and phenazopyridine HCl show micelle formation below the salt saturation solubility and significant supersaturation at the pH_{max}. CEL50 phosphate, although not micelle forming, is very surface active (a concentration of only 0.5–0.6 mM is required for an aqueous surface tension reduction of 10 dynes/cm) and demonstrates a lower level of supersaturation at the pH_{max} than the micelle forming systems. Finally, diclofenac Na, which appears to be the least surface active of all the systems investigated, does not demonstrate any appreciable supersaturation in the pH solubility profile.

Table 4
Details of levels of apparent supersaturation at the pH_{max} and surface active properties for the drug–salt systems studied

Salt system	Solubility (mM)	pH_{max}	Apparent supersaturation at the pH_{max}	Surface tension CAC or CMC (mM)	Inflexion in conductivity plot	Solubilisation of NPN
Diclofenac HEP	273	8.9	>3[a]	20	Yes	Yes
Theophylline Na	325[b]	8.9	2.9	70	Yes	No
Phenazopyridine HCl	20[b]	3.1	2.8	5	Yes	No
CEL50 phosphate	4.1	3.7	1.7	0.7	No	No
Diclofenac Na	65	7.9	<1.05	25	No	No

[a] The actual level of supersaturation achieved (relative to the theoretical pH solubility profile) is greater than 18 for diclofenac HEP.
[b] These results were obtained at 37°C.

As discussed above, 'kinetic barriers' to the precipitation of new solid phases could account for supersaturation observed in drug–salt systems. To understand the possible physicochemical basis for this and the link with surface activity of the drug–salt systems, it is necessary to consider the theory of crystal growth.

Current theories of crystallisation describe a three stage process, namely: supersaturation, nucleation and crystal growth. Primary nuclei may be homogenous (formed from solutions without any solid particles) or heterogenous (formed from solutions with foreign particles present). At supersaturation levels below Δc_{meta} (designated the metastable region) nuclei are not readily formed but crystals can grow. The $\Delta c_{meta.het}$ value for primary heterogenous nuclei is the level of supersaturation which allows foreign particles in solution to grow as nuclei and trigger off nucleation. It is greater than the level of supersaturation required to begin secondary nucleation ($\Delta c_{meta.sec}$) which occurs in the presence of solute crystals (Mullin, 1993). This accounts for the observation that precipitation of the stable salt form was facilitated by the addition of 'seed' crystals of diclofenac HEP dihydrate to a suspension supersaturated at the pH_{max}.

The $\Delta c_{meta.het}$ values are of interest in the context of the present work since throughout the pH solubility experiments there is a solid phase in contact with the supersaturated solutions. For non-ideal solutions it is more correct to use activities instead of concentrations. Thus, the required activity for nuclei formation in the pH solubility experiments can be defined as $\Delta a_{meta.het}$. A lowering of the activity coefficient of a drug, as concentrations increase, may occur due to self-association (Serajuddin and Mufson, 1985). Since activity is the product of the activity coefficient and concentration, this could maintain the solution activity below $\Delta a_{meta.het}$ and thereby retard nucleation.

The highest levels of apparent supersaturation at the pH_{max} were observed with the diclofenac HEP system (>3 at the pH_{max}, 8.9). Diclofenac HEP also demonstrates the most significant self-association of all the systems studied in that the aggregation complexes formed at 20 mM become micelles which can solubilise NPN. Furthermore, unlike any other salt system studied here, diclofenac HEP demonstrated appreciable levels of supersaturation at pH values significantly below the pH_{max}. In fact at all points above a solubility greater than the CMC (≈ 35 mM) there is deviation from the theoretical pH solubility profile. This may be due to self-solubilisation of diclofenac acid and $(diclofenac)_2$ HEP, in addition to the possible effects of a reduction of activity coefficient on the nucleation of the HEP salt.

Diclofenac Na does not demonstrate the micelle formation ability of the HEP salt probably due to the effects of the counterion. The pH solubility profile of diclofenac Na does not deviate appreciably from the theoretical profile in the pH_{max} region. This suggests that the critical factor in the supersaturation of the diclofenac HEP system is its self-association and micelle formation.

Phenazopyridine HCl and theophylline Na self associate to form micelles. Although CEL50 phosphate does not form micelles, because it is very surface active and because K'_{sp} estimates increase as drug concentration approaches saturation solubility (Table 2), the formation of other association complexes is not excluded. All three systems demonstrate supersaturation in the pH_{max} region which may be related to their surface properties. A reduction in the rate of nucleation of the final solid form may be caused by a reduction in activity coefficient (due to self-association) which maintains the solution activity below $\Delta a_{meta.het}$. Higher levels of supersaturation, possibly caused by greater reductions in activity coefficient due to micelle formation, are observed for the phenazopyridine and theophylline systems compared to the CEL50 phosphate system.

The increase in self-association for the drug–salt systems studied is in rank order with the increase in apparent supersaturation, i.e. diclofenac Na < CEL50 phosphate < phenazopyridine HCl < theophylline Na < diclofenac HEP.

It is observed in the drug–salt systems studied here, and in other systems for which pH solubility data on free drug and salt are available, that the most significant levels of supersaturation occur when the free drug is used as the starting material. According to the explanation discussed above the

supersaturation achieved is with respect to the solid form to be precipitated from solution. Thus, when the starting material is salt and pH is adjusted to form free drug, the supersaturation levels achieved are with respect to the free drug form. Since the saturation solubility of the free drug form is lower than that of the salt, levels of apparent supersaturation will be higher when the starting material is salt.

The phenomenon of supersaturation at the pH_{max} may have applications in enhancing drug flux across biological membranes as mentioned above. As with all supersaturated solutions, since they are thermodynamically unstable, attention to preserving physical stability would be required. Rates of aqueous dissolution of poorly soluble drugs which demonstrate supersaturation at the pH_{max} may also be enhanced. For example, the intrinsic dissolution rate of phenazopyridine free base into aqueous media (pH 1.1) was almost 14 times greater than the maximum rate achieved with the salt at any pH (Serajuddin and Jarowski, 1985a). It was demonstrated that in an acidic environment the base has a self-buffering action, keeping the pH at that of the pH_{max}. Thus supersaturation at the pH_{max} for phenazopyridine in the diffusion layer of the dissolving solid appears to be causing an exceptionally high rate of dissolution. Similarly, for poorly soluble drugs that demonstrate supersaturation at the pH_{max}, formulation of the free drug form with counter acids or bases could maintain the microenvironment pH of the diffusion layer at the pH_{max}. In turn, this could cause supersaturation in the diffusion layer and consequent enhancement of dissolution rates. Because of the observation that the free drug form gives a higher level of supersaturation, rates of dissolution greater than those possible using the corresponding salts could be achieved.

Acknowledgements

The authors wish to acknowledge Elan Corp. who provided funding to support this work.

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