ELSEVIER

International Journal of Pharmaceutics 226 (2001) 163–179

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Preparation and characterisation of a range of diclofenac salts

Karen M. O'Connor, Owen I. Corrigan *

Department of Pharmaceutics and Pharmaceutical Technology, School of Pharmacy, University of Dublin, Trinity College, Dublin 2, Ireland

Received 16 March 2001; received in revised form 4 July 2001; accepted 4 July 2001

Abstract

Physicochemical properties of diclofenac salts prepared using eight different counterions and including five novel salts, obtained with the bases 2-amino-2-methyl-1,3-propanediol, 2-amino-2-methylpropanol, *tert*-butylamine, benzylamine and deanol, were compared. Four of the bases used to prepare these salts were related in their chemical structure, differing only in the number of hydroxy groups. Characterisation techniques included X-ray diffraction, differential scanning calorimetry, thermogravimetric analysis, thermomicroscopy, Karl Fischer titration, FT-IR spectroscopy and elemental analysis. In the case of salts prepared from 2-amino-2-methylpropanol and benzylamine, two polymorphic forms of each salt were identified. For the 2-amino-2-methyl-1,3-propanediol salt, a pseudopolymorphic form was identified. The aqueous solubilities of the salts studied ranged from 3.95 mM (tris(hydroxymethyl)aminomethane salt) to 446 mM (deanol salt), corresponding to a 113-fold difference in solubility. The solubility of diclofenac deanol was higher than the solubilities for diclofenac salts reported earlier. Correlation was found between the inverse of the salt melting point and the logarithm of salt solubility. A log–log relationship was observed between salt solubility and hydrogen ion concentration in the salt solution. Relationships between the properties of the salt-forming agents and those of the resulting diclofenac salts were explored. Reasonable correlation was found between the free base melting point and the salt melting point.

Keywords: Salts; Diclofenac; Tris(hydroxymethyl)aminomethane; 2-Amino-2-methyl-1,3-propanediol; 2-Amino-2-methylpropanol; *tert*-Butylamine; Benzylamine

1. Introduction

Salt formation is a simple means of modifying the properties of a drug having ionisable functional groups in order to overcome some undesirable feature of the parent drug (Anderson and Conradi, 1985). The physicochemical characteristics and resultant biological performance of a drug can be dramatically altered by conversion to a salt form (Berge et al., 1977; Bighley et al., 1996).

* Corresponding author. Tel.: +353-1-608-2782; fax: +353-1-608-2783.

E-mail address: ocorrign@tcd.ie (O.I. Corrigan).

0378-5173/01/$ - see front matter
PII: S0378-5173(01)00800-6

Salt-forming agents are often chosen empirically. The preferred salt form is selected after considering the practical issues such as cost of raw materials, ease of crystallisation and percent yield and other basic considerations such as stability, hygroscopicity and flowability of the resulting salt form (Berge et al., 1977).

Ideally, it would be useful to be able to predict the salt properties from the properties of the counterion used. Several studies have described the dependence of salt properties on the nature of the counterion used (Chowhan, 1978; Gould, 1986; Pandit et al., 1989; Forbes et al., 1995). In addition, studies have been carried out to investigate quantitative relationships between counterion characteristics and properties of the resulting salt form (Anderson and Conradi, 1985; Gould, 1986; Rubino, 1989; Thomas and Rubino, 1996). Unfortunately, no reliable way of predicting the influence of a salt-forming agent on the behaviour of the parent compound has been reported. Only qualitative 'rules of thumb' are generally found. For example, increasing the hydrophilicity of the counterion has been proposed as a means of increasing the water solubility of the resultant salt, as reported for a series of erythromycin salts (Jones et al., 1969). However, these qualitative rules may not be very reliable (Anderson and Flora, 1996). Therefore, selection of an appropriate counterion to produce a salt with the desired combination of properties is still being carried out on an empirical basis.

Diclofenac, 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid (D), is a potent non-steroidal anti-inflammatory drug, therapeutically used in inflammatory and painful conditions of rheumatic and non-rheumatic origin. It is an acidic compound (pK_a 3.80 at 25 °C) with very low aqueous solubility (6×10^{-5} M at 25 °C) in the unionised form (Chiarini et al., 1984). Many studies have been carried out on the modification of the solubility and dissolution rate of diclofenac by the preparation of salts from a variety of inorganic and organic bases (Fini et al., 1991a,b, 1993a,b, 1994a. 1995a, 1996). However, no trends have been established between counterion characteristics and the properties of the resultant salt forms.

In order to advance our understanding of diclofenac salts, a range of salts was prepared and examined. Six basic organic compounds were selected for salt formation. These are listed, with the abbreviations used and the chemical structures, in Table 1.

The study included four primary amines, each having four carbons and zero, one, two or three hydroxyl group(s), respectively: *tert*-butylamine (*t*BA), 2-amino-2-methylpropanol (AMP), 2-amino-2-methyl-1,3-propanediol (AMPD) and tris(hydroxymethyl)-aminomethane (TRIS). In addition, salts of the four-carbon, tertiary amine, deanol (DNL), and the aromatic primary amine, benzylamine (BA), were included in the study.

Tris(hydroxymethyl)aminomethane is used as an alkalising agent in the treatment of metabolic acidosis (Martindale, 1999). It is a commonly used base in the preparation of salts (Roseman and Yalkowsky, 1973; Gu and Strickley, 1987; Wang and Chowhan, 1990; Gabr and Borg, 1999), including some commercially marketed salts (Berge et al., 1977). It has been used earlier to prepare a salt with diclofenac (Fini et al., 1996). The four-carbon primary amines selected (*t*BA, AMP, AMPD and TRIS) were used by Anderson and Conradi (1985) in a study involving the preparation of a series of salts of the non-steroidal anti-inflammatory drug, flurbiprofen. The study investigated possible relationships between the solubilities of the salts and their melting points and cation hydrophilicities. Deanol and benzylamine were used previously by Hirsch et al. (1978) to form salts with fenoprofen in an attempt to increase the stability of the drug.

Relevant physical properties of the six bases selected are outlined in Table 2. The salts formed using these counterions were characterised by differential scanning calorimetry (DSC), thermogravimetric analysis (TG), thermomicroscopy, X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR) and elemental analysis.

2. Materials and methods

2.1. Materials

Salts were prepared from diclofenac acid (AMSA) and the following bases: AMP (Sigma), AMPD (Sigma), DNL (Sigma), BA (Sigma), TRIS (Aldrich) and *t*BA (Aldrich). The solvents used for salt preparation were acetone (BDH), methanol (Riedel-de Haën) and ethyl acetate (Riedel-de Haën).

2.2. Preparation of diclofenac salts

Salts were prepared by dissolving diclofenac acid in an appropriate solvent and mixing in an equimolar amount of base dissolved in the solvent. Initial attempts to prepare each salt were carried out using acetone. If acetone was found to be inappropriate, preparation was carried out using methanol or ethyl acetate. The resulting product was recovered by filtration under vacuum in cases where a precipitate resulted. If no precip-

Table 1
Bases selected for the preparation of diclofenac salts

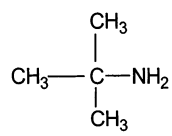
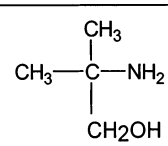
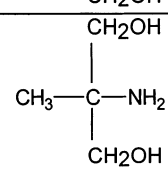
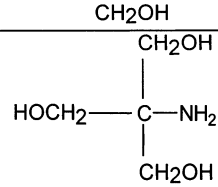
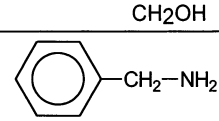
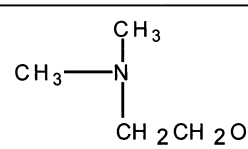
Name	*Abbreviation*	*Chemical Structure*	*log P*
tert-butylamine	tBA		1.19
2-amino-2-methylpropanol	AMP		1.04
2-amino-2-methyl-1,3-propanediol	AMPD		0.89
tris(hydroxymethyl)aminomethane	TRIS		0.74
benzylamine	BA		1.69
2-(dimethylamino)ethanol *or* deanol	DNL		0.92

Table 2
Properties of bases selected for the preparation of diclofenac salts

Base	Molecular weight	pK_a	Melting point (°C)	Boiling point (°C)	Solubility/miscibility [a]
*t*BA	73.14	10.69 [b]	−66.9 [c]	44 [c]	Miscible with alcohol
AMP	89.14	9.69 [b]	25.5 [c]	165.5 [c]	Miscible with water; soluble in alcohols
AMPD	105.14	8.80 [b]	109–111 [a]	151–152 [a]	250 g dissolved in 100 ml water at 20 °C; soluble in alcohols
TRIS	121.14	8.30 [a]	171.5 [c]	219–220 [c]	Solubility in water: 550 mg/ml at 25 °C; soluble in alcohol, acetone, methanol
BA	107.2	9.35 [b]	10 [b]	185 [c]	Miscible with water, alcohol, ether
DNL	89.14	9.26 [b]	−59°C [c]	134 [c]	Miscible with water, alcohol, ether
DEA	73.14	10.84 [d]	−49.8 [c]	55.5 [c]	Miscible with water, alcohol
HEP	115.18	9.72 [e]	< −60 [f]	79–81 [g]	–

[a] From Merck Index (1996).
[b] From Dean (1987).
[c] From CRC Handbook of Chemistry and Physics (1995).
[d] From Albert and Serjeant (1984).
[e] From Fini et al. (1994a).
[f] Information obtained by DSC: temperature reduced to −60 °C (2 °C/min), no thermal events observed.
[g] Supplier's catalogue.

itate was formed, the product was recovered by removing excess solvent using a Büchi Rotavapor apparatus linked to a Büchi vacuum system. All products were allowed to dry by exposure to ambient conditions for 48 h. Salt formation was confirmed by powder X-ray diffraction, differential scanning calorimetry, infrared spectroscopy and elemental analysis.

2.3. Powder X-ray diffraction

Powder X-ray diffraction measurements were carried out on a Siemens D500 X-ray powder diffractometer. Powdered samples were mounted in conventional cavity mounts; compressed discs were mounted in a holder with a 13 mm diameter aperture. Samples were scanned in the 2θ range of 5–35° at a rate of 3°/min.

2.4. Differential scanning calorimetry

Differential scanning calorimetry was performed on powdered samples ($n = 3$) using a Mettler Toledo DSC 821^e, with Mettler Toledo STAR^e software version 5.1. Unless otherwise specified, each sample (5–10 mg) was run in sealed aluminium pans with three vent holes pierced in the lid. Each run was carried out under nitrogen purge at a heating rate of 10 °C/min (unless otherwise specified). The onset temperature and enthalpy change for each thermal event was calculated.

2.5. Thermogravimetric analysis

Thermogravimetric (TG) analysis was carried out on powdered samples (5–10 mg) using a Mettler TG 50 linked to a Mettler MT5 balance. Data was processed using Mettler Toledo STAR^e software version 5.1.

2.6. Thermomicroscopy

Thermomicroscopy was carried out on a Reichert hot stage with and without crossed polarising filters. Samples were mounted in air or in silicone oil (to detect desolvation).

2.7. Karl Fischer titration

Karl Fischer titrations (KFT), for the determination of water content, were carried out on powdered samples using Metrohm 701 KF Titrino linked to a Metrohm 703 Ti stand. All analyses were performed in triplicate.

2.8. Elemental analysis

Elemental analysis (C, H, N) was carried out on powdered samples (~ 2 mg) using an Exetor Analytical CE440.

2.9. Fourier transform infrared spectroscopy

FT-IR spectra were obtained from 32 scans over the range of 4000–400 cm^{-1} (Nicolet 205). KBr discs were prepared by grinding 5–10 mg sample with 100 mg KBr.

2.10. UV assay for the determination of diclofenac concentration

Diclofenac was assayed by measurement of UV absorbance at $\lambda = 276$ nm (Adeyeye and Li, 1990) using a Hewlett–Packard 8452A diode array spectrophotometer.

2.11. Solubility studies

Equilibrium solubilities were determined using a modification of the sealed ampoule method of Mooney et al. (1981). Excess solid (approximately 2–3 times the estimated solubility) was placed in 5 ml deionised water in a 10 ml glass ampoule, which was then heat-sealed. Ampoules were placed in a shaker water bath (Precision Scientific) at 25 °C and agitated at 150 cycles/min. At 24, 48 and 72 h, samples were withdrawn from the ampoules, filtered through a 0.45 μm filter (Gelman Sciences), diluted appropriately and assayed for the drug content. The pH of the filtered solution was determined using an Orion Model 520A pH meter. Solubility determinations were carried out in triplicate. Where relevant, at the end of a solubility determination, the solid was recovered for powder XRD analysis, to ascertain any possible phase changes.

2.12. Intrinsic dissolution rate determination

Intrinsic dissolution rate (IDR) studies were performed using the USP 24 paddle method (United States Pharmacopeia, 2000). Discs were prepared by compressing 200 mg of powder in a Perkin–Elmer hydraulic press, for 5 min under 8 ton of pressure, using a 13 mm punch and die set. Analysis of the compressed discs by XRD confirmed that the crystal form of the original powder was retained following the compression procedure. Paraffin wax was used to mount the discs in stainless steel disc holders, leaving one face exposed (surface area, 1.327 cm^2). The dissolution runs were carried out at 25 °C in 900 ml deionised water at 50 rpm (Sotax AT7 dissolution bath). Aliquots (5 ml) were withdrawn at 5, 10, 15, 20 and 25 min intervals, filtered through a 0.45 μm filter (Gelman Sciences), diluted if necessary and assayed for drug content. The withdrawn sample was replaced with 5 ml of deionised water. All dissolution runs were carried out in triplicate, in sink conditions. The initial linear portion of each dissolution profile (0–15 min) was used to derive the intrinsic dissolution rate.

3. Results and discussion

3.1. Characterisation of salt forms prepared

The XRD traces and DSC scans for the salt products are presented in Figs. 1 and 2, respectively. Using FT-IR, salt formation could be established by: (a) the absence of the carboxylic acid peak at 1684 cm^{-1} (Silverstein and Webster, 1998; Palomo et al., 1999); (b) the presence of bands characteristic of carboxylic acid salts, at 1650–1550 and 1440–1335 cm^{-1} (Socrates, 1994); and (c) absorption at 3350–3150 cm^{-1}, attributable to NH_3^+ stretching of solid amine salts (Socrates, 1994). The FT-IR spectra for each of the products were consistent with salt formation.

3.1.1. Diclofenac tert-butylamine (DtBA)

The DSC scan for D*t*BA, the salt formed between diclofenac acid and *t*BA from acetone, displayed an endothermic peak with an onset temperature of 153 °C, followed by a larger endothermic peak over the temperature range of

160–200 °C. The TG trace showed a marked increase in the rate of weight loss at a temperature corresponding to the onset of the second endotherm. Examination of the sample by thermomicroscopy revealed complete melting of the sample in the temperature range of 145–155 °C, corresponding to the first endotherm in the DSC scan. No further events were observed. The broad nature of the trace for the second endotherm and the sharp increase in the rate of weight loss suggested the occurrence of degradation at that temperature. Therefore, the two endotherms in the DSC scan (onset temperatures, 153 and ~160 °C) may result from melting of the salt, followed by degradation. The onset value of the first endotherm, 153 °C, was considered to be the melting point of D*t*BA.

3.1.2. Diclofenac 2-amino-2-methylpropanol (DAMP)

When the salt preparation procedure was carried out using AMP as the basic counterion, two different products were identified, DAMP-I and DAMP-II, prepared using 35 and 7.5% w/v of drug in acetone, respectively. The XRD patterns (Fig. 1) were found to differ in their peak position and relative intensities. The DSC trace for DAMP-I showed a melting peak with an onset value of 182 °C, followed by the broad volatilisation–decomposition peak characteristic of diclofenac salts (Fig. 2). The TG trace revealed an increase in the rate of weight loss from ~180 °C. The DSC scan for DAMP-II displayed subtle differences relative to that of DAMP-I. The peak temperature of the endotherm was close to that of

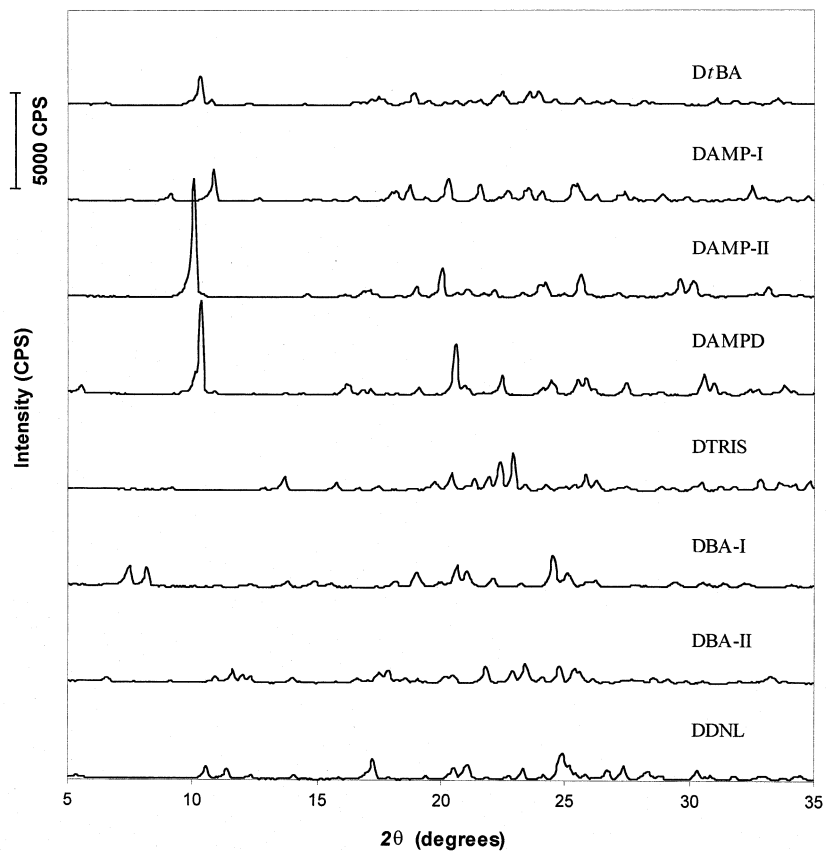


Fig. 1. XRD traces of the diclofenac salts prepared.

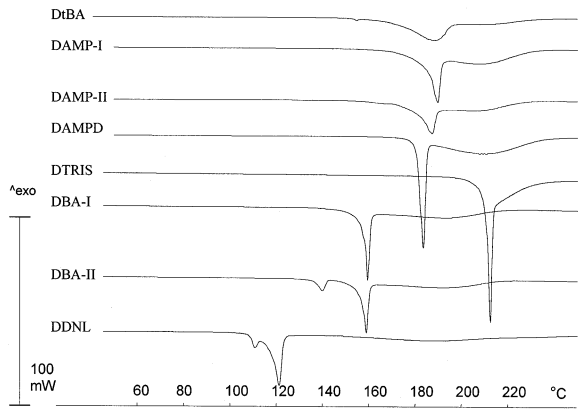


Fig. 2. DSC traces for the diclofenac salts prepared.

the endotherm in the DAMP-I DSC scan (188 °C). The onset value of 161 °C was considerably lower than that for DAMP-I. Further investigation of the thermal properties of DAMP-II was required to explain the presence of what appears to be two overlapping peaks. Altering the sample size or heating rate of DAMP-II resulted in no greater resolution of the two peaks. A sample of DAMP-II, when examined by thermomicroscopy, displayed melting from 130 °C, a temperature approximately corresponding to the onset of the endotherm in the DSC scan, followed by re-crystallisation and subsequent re-melting. Further investigation by DSC involved heating the sample to 170 °C, cooling the sample to 25 °C and re-heating the sample to 250 °C (a) after 10 min and (b) after 4 days. In each case, the DSC and XRD traces obtained were identical to those of DAMP-I. This suggests the existence of two forms of DAMP: DAMP-I, which melts at 182 °C; and DAMP-II, which converts on heating to DAMP-I.

3.1.3. Diclofenac 2-amino-2-methyl-1,3-propandiol (DAMPD)

The DSC scan for DAMPD, the salt formed from diclofenac acid and AMPD in methanol, displayed a sharp endotherm with an onset value of 180 °C (Fig. 2). Thermomicroscopic examination of the sample confirmed that this endotherm was attributable to the melting of the salt form. The broad endotherm from ~185 °C in the DSC scan and the corresponding weight loss in the TG trace was consistent with decomposition and/or volatilisation of the molten drug.

Attempts to prepare a salt with diclofenac acid and AMPD using acetone or acetone with different quantities of methanol as the solvent resulted in products that differed from DAMPD, the 1:1 salt described above. Analysis by XRD, DSC, TG, thermomicroscopy, elemental analysis and KFT revealed the presence of water of crystallisation in varying proportions in the products. Recrystallisation from water, by allowing slow evaporation of water from a saturated aqueous solution at room temperature, resulted in a new form of DAMPD. This form was characterised using XRD, DSC, TG, FT-IR, elemental analysis and KFT and identified as DAMPD monohydrate (DAMPD-MH). The XRD trace and DSC scan for the monohydrate are presented in Figs. 3 and 4, respectively.

3.1.4. Diclofenac tris(hydroxymethyl)aminomethane (DTRIS)

The DSC scan for DTRIS, the salt formed from diclofenac acid and TRIS in methanol, revealed an endotherm with an onset value of 209 °C (Fig. 2). Thermomicroscopy confirmed that this endotherm was attributable to melting of the salt. This value differed from the melting point of 194–196 °C reported earlier for DTRIS (Fini et al., 1996). However, no XRD data was given in the latter study.

3.1.5. Diclofenac benzylamine (DBA)

Attempts to prepare a salt from diclofenac acid and benzylamine by precipitation from acetone were unsuccessful. Combination of solutions of diclofenac acid and benzylamine in methanol resulted in the formation of a product after the evaporation of the solvent. However, two products were identified when the procedure was carried out in ethyl acetate: DBA-I or DBA-II (the different products resulted from slight changes in preparation conditions). DBA-II was identical to the product prepared from methanol. The XRD patterns for the two forms (Fig. 1) were found to differ in their peak position and relative intensities. The DSC trace for DBA-I (Fig. 2) showed an

endothermic peak with an onset value of 157 °C, followed by the broad volatilisation–decomposition peak characteristic of diclofenac salts. Thermomicroscopy confirmed that the endotherm at 157 °C was due to melting of the salt. The TG trace revealed an increase in the rate of weight loss from a temperature corresponding to the onset of the endothermic event in the DSC scan. This may be attributed to the volatilisation of the sample as it melted. The DSC scan for DBA-II (Fig. 2) differed from that of DBA-I by the presence of a second endothermic peak with an onset value of 137 °C. The TG trace obtained was similar to that for DBA-I. Thermomicroscopy, displayed melting at a temperature corresponding to the onset of the first endotherm in the DSC scan, followed by re-crystallisation into acicular crystals. These crystals melted at ~160 °C, a temperature corresponding to the onset of the second endotherm in the DSC scan. Further investigation by DSC involved heating the sample to 143 °C (past the first endotherm), cooling to 25 °C and re-heating the sample to 250 °C (a) after 10 min and (b) after 2 days. In each case, the DSC and XRD traces obtained were identical to those of DBA-I. This suggests the existence of two forms of DBA: DBA-I, which melts at 157 °C; and DBA-II, which converts on heating to DBA-I. This thermal behaviour is consistent with a Type 2 polymorphic transition (Giron, 1995).

3.1.6. Diclofenac deanol (DDNL)

The DSC scan for DDNL, the salt formed with diclofenac acid and DNL from acetone, showed two overlapping endotherms, the onset temperature of the first endotherm being 105 °C (Fig. 2). Thermomicroscopy revealed melting from ~105 °C, followed by crystallisation of crystals from the melt and subsequent re-melting. This crystallisation and melting of the newly formed crystals explained the presence of the second endotherm (peak temperature, 120 °C) in the DSC scan. An exothermic re-crystallisation peak may be masked because of the occurrence of the two melting endotherms close together. The TG trace showed an increase in the rate of weight loss from 110 °C, resulting in a step corresponding to a weight loss of ~6% w/w. Analysis by KFT excluded the possibility of water being present in the sample. The weight loss may be because of the volatilisation of deanol (b.p. 135 °C) from the melt. In conclusion, two forms of DDNL were shown to exist; one converted to the other on heating.

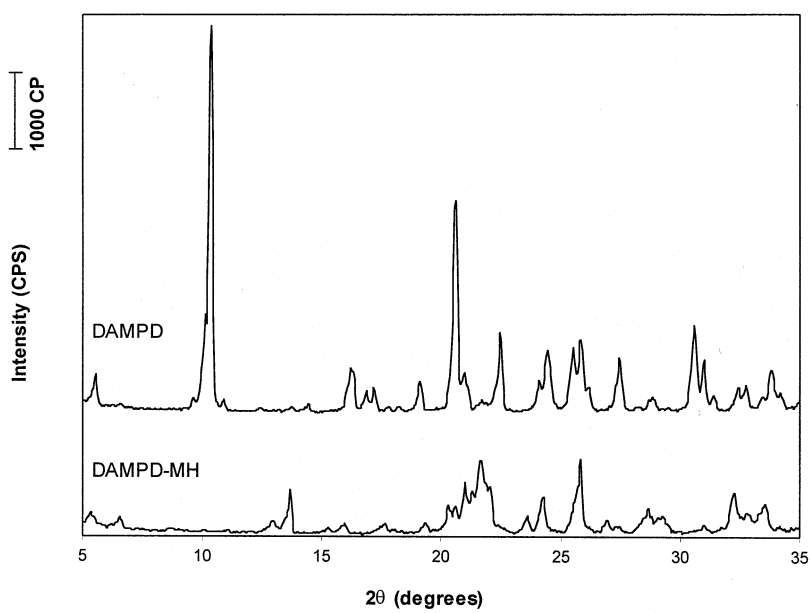


Fig. 3. XRD traces of DAMPD and DAMPD monohydrate (DAMPD-MH).

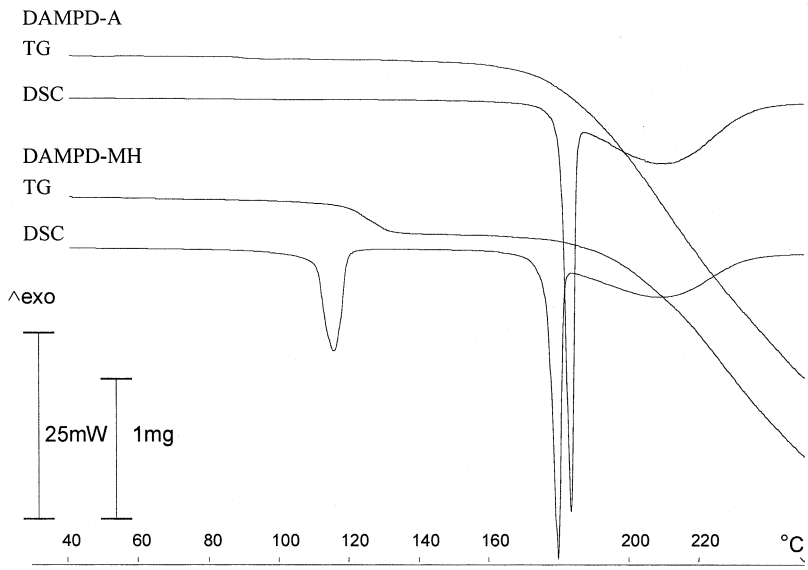


Fig. 4. DSC and TG scans for DAMPD and DAMPD monohydrate (DAMPD-MH).

3.2. Solubility and intrinsic dissolution rate studies of the diclofenac salts prepared

Of the two forms of DAMP, DAMP-I was selected for the investigation of solubility and dissolution rate because of: (a) its single melting endotherm in the DSC scan; and (b) its easiness in preparation relative to DAMP-II. For these same reasons, DBA-I was selected over DBA-II for the investigation of solubility and intrinsic dissolution rate.

Of the diclofenac salts studied, DBA was the only one for which a different XRD pattern, relative to a powder sample, was obtained following compression. An extra peak was observed at $2\theta = 9.45°$ in the XRD trace for the disc. This extra peak suggested a change in the solid-state form of the salt due to the compression procedure. Despite the existence of an additional peak in the XRD trace, DSC analysis of disc re-ground after compression at 8 ton for 5 min did not reveal any change in the thermal behaviour of the salt. However, when the compression time was increased to 10 min, an additional endotherm was observed at ~ 110 °C in the DSC scan of the re-ground disc. This endotherm was observed to increase in magnitude with an increasing compression time, e.g. the ΔH values for the endotherms after 10 min and 12 h compression were 5.51 and 10.37 J/g, respectively. The changes in the solid-state properties of DBA-I following compression could not be accounted for by the conversion to DBA-II. The additional peak in the XRD trace following compression did not correspond to a peak characteristic of DBA-II. The extra endotherm in the DSC scan for the reground discs occurred at a temperature (onset 110 °C) lower than that of the first endotherm in the DSC scan for DBA-II, which had an onset value of 137 °C. Due to the effect of compression, the intrinsic dissolution rate study performed on discs prepared from DBA-I yielded a result ($4.57 \times 10^{-4} \pm 0.15 \times 10^{-4}$ mmol/min/cm^2) which did not relate to the salt in its original solid state.

The solubility and intrinsic dissolution rate values determined for the salts prepared are presented in Table 3. The solubility and intrinsic dissolution rate values for diclofenac diethylamine (DDEA) (O'Connor and Corrigan 2001) and diclofenac *N*-(2-hydroxyethyl)pyrrolidine (DHEP) (Ledwidge and Corrigan, 1998) reported earlier are also included in the table.

Using anhydrous DAMPD as the starting material, a solubility value of 6.77 ± 0.03 mM at 25 °C was obtained. The XRD trace of the solid in equilibrium with the saturated solution after 24 h (the first sampling time) was consistent with that of the monohydrate form of the salt. Therefore, the solubility of the salt is limited to that of its monohydrate form, which forms in a solution of the anhydrate. The intrinsic dissolution rate of the salt in water at 25 °C was determined as $4.51 \times 10^{-4} \pm 0.07 \times 10^{-4}$ mmol/min/cm^2. XRD analysis of a disc after 5 min dissolution generated a trace consistent with the monohydrate form of the salt, indicating that the conversion of the anhydrate to the monohydrate had occurred. The intrinsic dissolution rate determined therefore related to the DAMPD monohydrate. Almost instantaneous hydration of the solid on the surface of discs upon immersion in water has been reported earlier (Rubino 1989). The latter author reported no differences in the dissolution rates determined for the anhydrous, sesquihydrate and 4.6 hydrated forms of sodium sulfathiazole due to hydration of the anhydrate and sesquihydrate forms to the most hydrated form.

The measured solubility of DTRIS in water at 25 °C (3.89 mM) compared well with the value of 4.00 mM reported by Fini et al. (1996). The solubility of DDNL in water at 25 °C (446.65 mM) was found to be considerably higher than the solubilities determined for the other salts examined. This salt also showed a superior aqueous solubility to DHEP (273 mM, Ledwidge and Corrigan, 1998), the most soluble salt form of diclofenac available in pharmaceutical products.

Several studies have reported a direct relationship between solubilities and intrinsic dissolution rates for a large variety of substances (Parrott et al., 1955; Hamlin et al., 1965; Higuchi et al., 1965; Nelson and Shah, 1975; Shah and Nelson, 1975; Tsuji et al., 1978; Nicklasson et al., 1981, 1982; Sjökvist Saers and Craig, 1992; Forbes et al., 1995). This solubility–dissolution rate relationships can be used to estimate solubilities where limited amounts of material were available (Nicklasson and Nyqvist, 1983) and to aid salt selection (Forbes et al., 1995).

According to the Noyes–Whitney equation (Noyes and Whitney, 1897), under sink conditions the following relationship should apply

$$G = KC_S \quad (1)$$

where G is the intrinsic dissolution rate, C_S is the solubility and K is the dissolution rate constant. When the solubilities are plotted against the intrinsic dissolution rates on a log–log scale, a linear relationship with a slope of 1.0 is expected, in accordance with the following derivation of the Noyes–Whitney equation

$$\log G = \log K + \log C_S \quad (2)$$

Table 3
Melting points, solubility and intrinsic dissolution rates for diclofenac salts in water at 25 °C

Salt	Melting point (°C)	Solubility (mM)	PH of saturated solution	Intrinsic dissolution rate $\times 10^4$ (mmol/min/cm^2)
D*t*BA	152.37 ± 0.29	5.46 ± 0.05	7.45	3.86 ± 0.09
DAMP	183.21 ± 2.14	21.8 ± 0.3	7.62	13.8 ± 0.3
DAMPD	179.19 ± 0.70	6.77 ± 0.03	7.24	4.51 ± 0.07
DTRIS	208.92 ± 0.10	3.95 ± 0.04	7.13	2.45 ± 0.06
DBA	156.25 ± 0.58	4.16 ± 0.04	7.21	4.57 ± 0.15 [a]
DDNL	108.46 ± 0.35	447 ± 15	8.57	167 ± 3
DDEA	124.65 ± 0.35 [b]	35.0 ± 0.7 [b]	8.19 [b]	18.7 ± 0.4 [b]
DHEP	101.95 ± 0.07	273 [c]	8.21 [d]	36.2 [d]

[a] This value does not relate to the original solid form of the salt.
[b] From O'Connor and Corrigan (2001).
[c] From Ledwidge and Corrigan (1998).
[d] From Ledwidge et al. (1996).

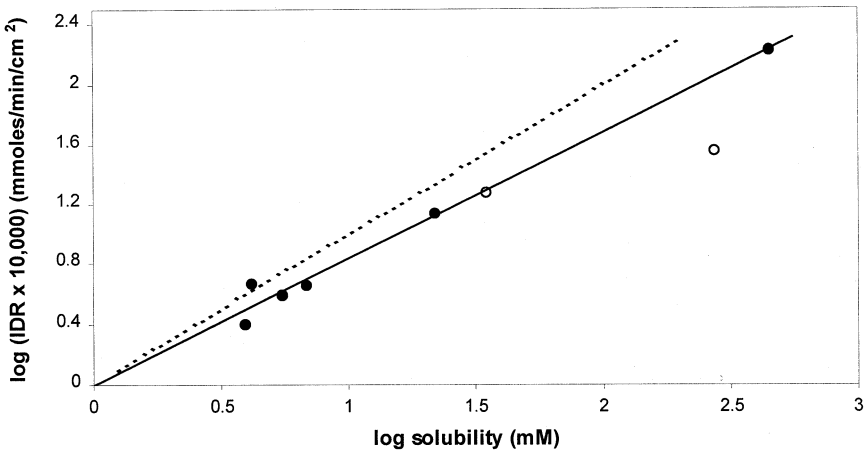


Fig. 5. Plot of log solubility (mM) vs. log (intrinsic dissolution rate $\times 10^4$) (mmoles/min/cm^2) for the diclofenac salts studied (●) and DDEA and DHEP (○). The dashed line represents the theoretical relationship of slope unity.

The log–log plot of solubility against intrinsic dissolution rate for the diclofenac salts is presented in Fig. 5. Also included in the graph are the DDEA and DHEP data. The line of best fit ($R^2 = 0.985$, $n = 6$) was found to have a slope of 0.84 ± 0.05. Deviation from the theoretical line with a slope of unity (indicated by the dashed line in Fig. 5) indicates lower dissolution rates than expected for salts with higher solubilities. This may be due to high viscosities of solutions of the higher solubility salts or micelle formation, resulting in a reduction in their diffusion coefficients. According to the Stokes–Einstein equation (Flynn et al., 1974), the diffusion coefficient is inversely related to the viscosity of the medium. The influence of the viscosity of a salt solution on diffusion through the aqueous boundary layer has been reported earlier (Nelson, 1957; Morozowich et al., 1962; Serajuddin and Jarowski, 1985a).

Previous studies have reported linear relationships between log solubility and log dissolution rate, with slopes of unity or close to unity: 1.02 ± 0.04 (Nicklasson et al., 1981), 1.00 ± 0.06 (Nicklasson et al., 1982) and 1.06 (Forbes et al., 1995). Nelson and Shah (1975) and Shah and Nelson (1975) reported slopes of 0.939 and 0.978, respectively, for a plot of log C_S versus log G for a series of alkyl esters of p-aminobenzoic acid. The authors proposed that a small change in diffusivity over the ester series might have contributed to the reduced slope.

3.3. Relationships between salt melting point and solubility for the diclofenac salts studied

Thomas and Rubino (1996) reported an inverse linear relationship between the salt melting point and the logarithm of salt solubility for a series of secondary amine hydrochloride salts ($n = 8$). Ledwidge (1997) reported a similar relationship for a series of salts of an experimental basic drug CEL50 ($n = 7$). Gould (1986), on examination of data obtained from a range of salts of a basic anti-malarial drug (Agharkar et al., 1976), reported a direct relationship between the inverse of the melting point and the logarithm of the solubility ($n = 4$). Anderson and Conradi (1985) reported a non-linear relationship between the salt melting point and log K_{SP} for a series of flurbiprofen salts ($n = 6$). Conversely, Gu and Strickley (1987) concluded that no simple solubility–melting point relationship could be established for tris(hydroxymethyl)aminomethane salts of four anti-inflammatory salts.

The melting point values for the diclofenac salts studied, including DDEA and DHEP, are listed in Table 3. A trend was observed between the salt melting point and the logarithm of the solubility

($R^2 = 0.6651$, $n = 8$) and between the inverse of the melting point and the logarithm of the solubility ($R^2 = 0.7780$, $n = 8$).

3.4. Exploration of relationships between properties of the salt-forming agent and those of the resulting salt form

In accordance with the linear relationship between the conjugate acid and the salt melting points reported for a series of salts of UK47880 (Gould, 1986), examination of the data for the diclofenac salts revealed reasonable correlation ($R^2 = 0.7518$, $n = 7$) between the base and salt melting points (Fig. 6). However, no correlation was observed between the base melting point and salt solubility. This lack of correlation is in accordance with the results obtained by Ledwidge (1997) for a series of CEL50 salts.

No correlation was found between base pK_a and salt solubility for the diclofenac salts, in accordance with the reported poor correlation between counter-acid pK_a and salt solubility for a series of CEL50 salts (Ledwidge, 1997).

Examination of the data obtained for the diclofenac salts revealed a linear log–log relationship between $[H^+]$ and salt solubility ($R^2 = 0.8957$, $n = 8$). The pH of the saturated solution is plotted against the logarithm of salt concentration in Fig. 7. This trend is consistent with the linear relationship between the final solution hydrogen ion concentration, $[H^+]$, and salt solubility reported by Ledwidge (1997).

The solubility and saturated solution pH values obtained for each of the salts is plotted in relation to the theoretical pH–solubility curves in Fig. 8. The theoretical curves were derived from Eq. (3) (Chowhan, 1978), using values of 0.037 mM and 5.02 for intrinsic solubility and pK'_a, respectively (Ledwidge and Corrigan, 1998).

$$C_S = [HA]_S + [A^-] = [HA]_S\left(1 + \frac{K'_a}{[H_3O^+]}\right) \quad (3)$$

Whereas the data points for most of the salts are consistent with the expected pH–solubility relationship, the solubility values for DDNL and DHEP are considerably higher than expected given the pH of their saturated solutions. Similar deviations from theoretical pH–solubility profiles have been reported for the salts of acidic (Roseman and Yalkowsky, 1973; Chowhan, 1978; Serajuddin and Jarowski, 1985a) and basic (Serajuddin and Rosoff, 1984; Serajuddin and Jarowski, 1985b; Serajuddin and Mufson, 1985) compounds. As a result of these deviations, estimation of the apparent pK_a from the pH–solubility data would result in a lower (in the case of an acidic compound) or higher (for a basic compound) value

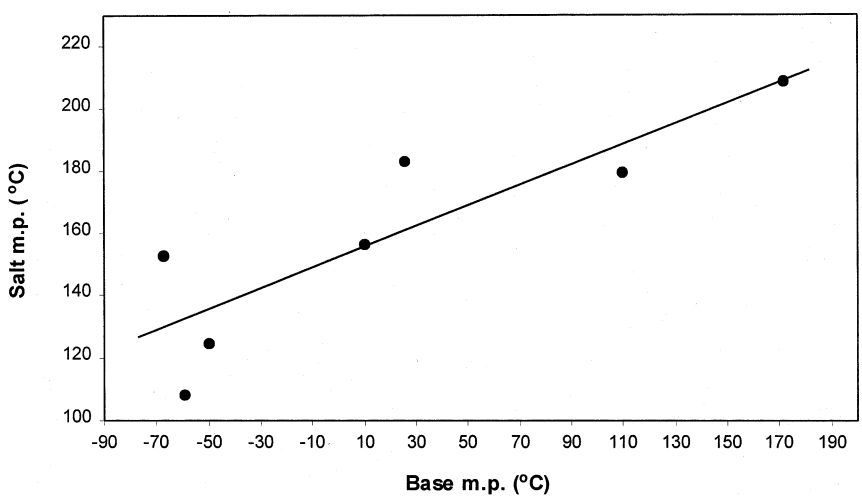


Fig. 6. Base melting point vs. salt melting point for the diclofenac salts studied.

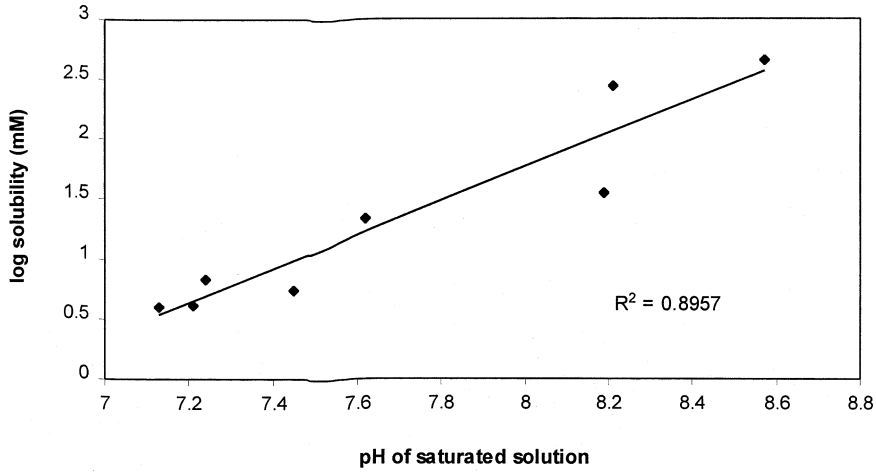


Fig. 7. pH of the saturated solution vs. solubility of the salt for the diclofenac salts studied.

than the potentiometrically determined value for the pK_a of the acid or base.

In line with the previous findings, deviation of the data points for DHEP and DDNL from the theoretical line (Fig. 8) indicated an apparent pK_a value lower than 5.02. Eq. (3) was used to fit a pH–solubility curve to the DDNL and DHEP data. The value for intrinsic solubility was fixed at 0.037 mM (Ledwidge and Corrigan, 1998); a value of 4.47 ± 0.04 was obtained for the pK'_a.

Roseman and Yalkowsky (1973) investigated the pH–solubility behaviour of the tromethamine salt of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and observed that at pH values above 5, there was a marked increase in solubility, significantly greater than what would be expected from the ionisation constant of the acid. This behaviour was attributed to the formation of micelles that solubilise the drug once critical concentration and pH values are reached.

In the current study and the previous studies (Roseman and Yalkowsky, 1973; Chowhan, 1978; Serajuddin and Jarowski, 1985a), the apparent reduction in the pK'_a value observed in the pH–solubility profiles can be attributed to the technique used in estimating the pK'_a and consideration of the equilibrium involved. The apparent dissociation constant, K'_a, is given by

$$K'_a = \frac{[H_3O^+][A^-]}{[HA]} \quad (4)$$

where [X] denotes the concentration of species X. The association of the ionised molecules, $[A^-]$, into micelles resulted in the solubilisation of the protonated acid, HA, causing an increase in the effective concentration of HA. The method used in this study to estimate pK'_a involved the application of Eq. (3), which describes the pH–solubility relationship for a weak acid at pH values less than the pH_{max}. This equation assumes that the solubility of the free acid is limiting and that the increase in solubility with an increasing pH is due to the increasing $[A^-]$. Solubilisation of HA due to micelle formation resulted in an overestimation of the contribution of $[A^-]$ to the total solubility, C_S, and an exaggerated value for the ratio of ionised to unionised forms of the acid, $[A^-]/[HA]$, was obtained. From Eq. (4), it can be seen that the calculated K'_a value is therefore an overestimation, resulting in an observed pK'_a value lower than the true value.

The octanol–water partition coefficient (log P) of each base, an indicator of base hydrophilicity, was estimated using fragment constants (Hansch and Leo, 1979) and is presented in Table 1. No correlation was found between the diclofenac salt solubility and counterion hydrophilicity. This is in

accordance with the results of the study by Anderson and Conradi (1985) on a series of flurbiprofen salts.

As can be observed from the data in Tables 2 and 3 for the salts prepared from the series of four-carbon primary amines, *t*BA, AMP, AMPD and TRIS, no general trends exist between counterion properties, hydrophilicity, melting point and pK_a, and salt solubility.

The rank order of diclofenac salt solubilities was found to be AMP > AMPD > *t*BA > TRIS. Anderson and Conradi (1985) prepared flurbiprofen salts using the same series of bases and reported a rank order of AMPD > TRIS ≅ AMP > *t*BA for their solubilities.

The most hydrophilic counterion within the series, TRIS, resulted in the salt of lowest solubility. This is contrary to the expected trend of an increase in water solubility with an increasing hydroxylation, or hydrophilicity, of the base. However, the hypothesis that greater hydrophilicity of the counterion results in greater water solubility of the resulting salt neglects the possibility of stronger interactions in the crystal due to increased polarity of the counterion. DTRIS has the highest melting point (209 °C) within the series. Therefore, its low water solubility can be attributed to its strong crystal lattice. The strength of the crystal lattice can be attributed to the symmetry of the counterion (Gould, 1986; Anderson and Flora, 1996) and hydrogen bonding within the crystal. Fini et al. (1995a) studied the solubility of a range of diclofenac salts, including salts prepared using monoethanolamine, diethanolamine, triethanolamine and TRIS. They reported that the presence of hydroxyl groups in the ethanolamine cations did not result in an improvement in salt solubility. Furthermore, the increase in hydroxyl group number within the group was not reflected in an increase in solubil-

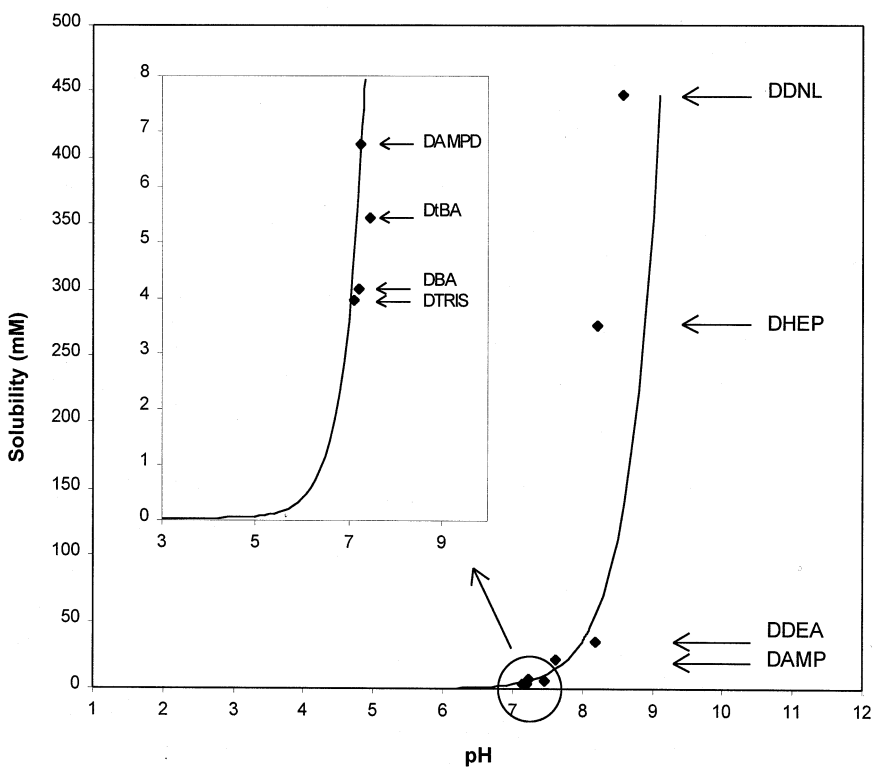


Fig. 8. pH of the saturated solution vs. solubility for each of the diclofenac salts. The lines represent the theoretical pH–solubility profiles.

ity. TRIS, with three hydroxyl groups, resulted in the salt of lowest solubility within the group. These observations were attributed to intermolecular hydrogen bond interactions existing in the solid state. Also, in the case of diclofenac salts, the influence of intramolecular hydrogen bonding needs to be considered (Fini et al., 1996). In a previous study, Dhanaraj and Vijayan (1987) examined the crystal structure of the meclofenamic acid–ethanolamine 1:1 salt in the solid state and reported that the hydroxyl group of the cation interacted via a hydrogen bond with the carboxylate group of the anion. Since meclofenamic acid closely resembles diclofenac acid in molecular structure, it was not surprising that this type of hydrogen bond was found to exist in salts of diclofenac containing cations carrying the hydroxyethyl moiety (Castellari and Sabatino, 1994). Therefore, the overall hydrophilicity of the salts was masked by internal interactions and their affinity for polar solvents was reduced.

The salt displaying the highest water solubility within the series (21.76 mM) is that of AMP, the base with one hydroxyl group. The melting point determined for DAMP (183 °C) is the second highest of the four salts. Therefore, the high aqueous solubility of the salt cannot be attributed to either the hydrophilicity of the base or weak crystal lattice forces in the salt.

The pK_a of TRIS (8.30) is the lowest in the series and the pH of a saturated solution of DTRIS (7.13) is lower than the values obtained for the other salts in the series. The low solubility of DTRIS is therefore consistent with the linear relationship between the pH of the saturated solution and the logarithm of the solubility of the salt (Fig. 7). In accordance with this trend, the pH of a saturated solution of DAMP, the most soluble salt, is higher than the pH of the solutions of the other salts in the series, despite the pK_a of AMP being one unit lower than that of *t*BA.

In summary, the solubility of the salts of diclofenac and the four-carbon primary amines was not shown to be dependent on any one parameter, but on a combination of factors such as salt crystal lattice strength and the pH of the saturated salt solution.

Acknowledgements

The authors are grateful to Microanalytical Laboratory, Department of Chemistry, University College Dublin for carrying out the elemental analysis and Enterprise Ireland for the financial support to K.O'C.

References

Adeyeye, C.M., Li, P.K., 1990. In: Florey, K. (Ed.), Analytical Profiles of Drug Substances. Academic Press, San Diego, pp. 123–144.

Agharkar, S., Lindenbaum, S., Higuchi, T., 1976. Enhancement of solubility of drug salts by hydrophilic counterions: properties of organic salts of an antimalarial drug. J. Pharm. Sci. 65 (5), 747–749.

Albert, A., Serjeant, E.P., 1984. The Determination of Ionisation Constants, 3rd ed. Chapman and Hall, New York.

Anderson, B.D., Conradi, R.A., 1985. Predictive relationships in the water solubility of salts of a nonsteroidal anti-inflammatory drug. J. Pharm. Sci. 74 (8), 815–820.

Anderson, B.D., Flora K.P., 1996. Preparation of water-soluble compounds through salt formation. The Practice of Medicinal Chemistry, Academic Press, London, pp. 739–754.

Berge, S.M., Bighley, L.D., Monkhouse, D.C., 1977. Pharmaceutical salts. J. Pharm. Sci. 66 (1), 1–19.

Bighley, L.D., Berge, S.M., Monkhouse, D.C., 1996. Salt forms of drugs and absorption. In: Swarbrick, J., Boylan, J.C. (Eds.), Encyclopedia of Pharmaceutical Technology, vol. 13. Marcel Dekker, pp, New York, pp. 453–499.

Castellari, C., Sabatino, P., 1994. Anti-inflammatory drugs: 1-(2-hydroxyethyl)-pyrrolidinium salt of diclofenac. Acta Crystallogr. C 50, 1723–1726.

Chiarini, A., Tartarini, A., Fini, A., 1984. pH–solubility relationship and partition coefficients for some anti-inflammatory arylaliphatic acids. Arch. Pharm. (Weinheim, Ger.) 317, 268–273.

Chowhan, Z.T., 1978. pH–solubility profiles of organic carboxylic acids and their salts. J. Pharm. Sci. 67 (9), 1257–1260.

CRC Handbook of Chemistry and Physics, 76th ed. CRC Press, Boca Raton, USA, 1995.

Dean, J.A., 1987. Handbook of Organic Chemistry. McGraw-Hill, New York.

Dhanaraj, V., Vijayan, M., 1987. Crystal structures of 1:1 complexes of meclofenamic acid with choline and ethanolamine. Biochim. Biophys. Acta 924, 135–146.

Fini, A., Fazio, G., Rabasco, A.M., 1993a. 1-Octanol–water partitioning of diclofenac salts. Acta Technol. Legis Medicamenti IV (1), 33–44.

Fini, A., Fazio, G., Rapaport, I., 1993b. Diclofenac/*N*-(2-hydroxyethyl) pyrrolidine: a new salt for an old drug. Drug Exp. Clin. Res. 19 (3), 81–88.

Fini, A., Fazio, G., Fernández-Hervás, M.J., Holgado, M.A., Rabasco, A.M., 1996. Factors governing the dissolution of diclofenac salts. Eur. J. Pharm. Sci. 4, 231–238.

Fini, A., Fazio, G., Orienti, I., Bertasi, V., Zecchi, V., Rapaport, I., 1991a. Self-association and release of diclofenac/*N*-(2-hydroxyethyl)pyrrolidine salt (DHEP). Proc. 10th Pharm. Tech. Conf., Bologna, Italy, pp. 48–64.

Fini, A., Fazio, G., Orienti, I., Zecchi, V., Rapaport, I., 1991b. Chemical properties-dissolution relationship. IV. Behaviour in solution of the diclofenac/*N*-(2-hydroxyethyl)pyrrolidine salt (DHEP). Pharm. Acta. Helv. 66 (7), 201–203.

Fini, A., Fazio, G., Rabasco, A.M., Fernández-Hervás, M.J., Holgado, M.A., 1995a. Pre-formulation study of diclofenac salts. Proc. 14th Pharm. Tech. Cong., Barcelona, Spain, pp. 82–90.

Fini, A., Fazio, G., Rabasco, A.M., Holgado-Villafuerte, M.A., Fernández-Hervás, M.J., 1994a. Influence of the chemical form in the solution behaviour of diclofenac salts. Proc. 13th Pharm. Tech. Conf., Strasbourg, France, pp. 793–801.

Flynn, G.L., Yalkowsky, S.H., Roseman, T.J., 1974. Mass transport phenomena and models: theoretical concepts. J. Pharm. Sci. 63 (4), 479–510.

Forbes, R.T., York, P., Davidson, J.R., 1995. Dissolution kinetics and solubilities of *p*-aminosalicylic acid and its salts. Int. J. Pharm. 126, 199–208.

Gabr, K.E., Borg, M.E., 1999. Characterisation of hydrochlorothiazide–trometamol mixtures. Pharm. Ind. 61 (3), 281–285.

Giron, D., Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, Thermochemica Acta, 249(1995)1–59.

Gould, P.L., 1986. Salt selection for basic drugs. Int. J. Pharm. 33, 201–217.

Gu, L., Strickley, R.G., 1987. Preformulation salt selection. Physical property comparisons of the tris(hydroxymethyl)aminomethane (THAM) salts of four analgesic/anti-inflammatory agents with the sodium salts and the free acids. Pharm. Res. 4 (3), 255–257.

Hamlin, W.E., Northam, J.I., Wagner, J.G., 1965. Relationship between in vitro dissolution rates and solubilities of numerous compounds representative of various chemical species. J. Pharm. Sci. 54 (11), 1651–1653.

Hansch, C., Leo, A., 1979. Substituent Constants for Correlation Analysis in Chemistry and Biology. Wiley, New York.

Higuchi, W.I., Mir, N.A., Parker, A.P., Hamlin, W.E., 1965. Dissolution kinetics of a weak acid, 1,1-hexamethylene *p*-tolylsulfonylsemicarbazide, and its sodium salt. J. Pharm. Sci. 54 (1), 8–11.

Hirsch, C.A., Messenger, R.J., Brannon, J.L., 1978. Fenoprofen: drug form selection and preformulation stability studies. J. Pharm. Sci. 67 (2), 231–236.

Jones, P.H., Rowley, E.K., Weiss, A.L., Bishop, D.L., Chun, A.H.C., 1969. Insoluble erythromycin salts. J. Pharm. Sci. 58 (3), 337–339.

Ledwidge, M.T., Draper, S.M., Wilcock, D.J. and Corrigan, O.I., Physiochemical characterisation of diclofenac N-(2-hydroxyethyl)pyrrolidine: anhydrate and dihydrate crystalline forms. J. Pharm. Sci., 85, 1 (1996) 16–21.

Ledwidge, M.T., Corrigan, O.I., 1998. Effects of surface active characteristics and solid state forms on the pH solubility profiles of drug-salt systems. Int. J. Pharm. 17, 187–200.

Ledwidge, M.T., 1997. The effects of pH, crystalline phase and salt formation on the solubility of ionisable drugs. PhD Thesis, University of Dublin.

Martindale, The Extra Pharmacopoeia, 32nd ed. Pharmaceutical Press, London, 1999.

Merck Index, 12th ed. Merck & Co., New Jersey, 1996.

Mooney, K.G., Mintun, M.A., Himmelstein, K.J., Stella, V.J., 1981. Dissolution kinetics of carboxylic acids. I. Effect of pH under unbuffered conditions. J. Pharm. Sci. 70 (1), 13–22.

Morozowich, W., Chulski, T., Hamlin, W.E., Jones, P.M., Northam, J.I., Purmalis, A., Wagner, J.G., 1962. Relationship between in vitro dissolution rates, solubilities, and LT_{50}'s in mice of some salts of benzphetamine and etryptamine. J. Pharm. Sci. 51 (10), 993–996.

Nelson, E., 1957. Solution rate of theophylline salts and effects from oral administration. J. Am. Pharm. Assoc. Sci. Ed. 46 (10), 607–614.

Nelson, K.G., Shah, A.C., 1975. Convective diffusion model for a transport-controlled dissolution rate process. J. Pharm. Sci. 64 (4), 610–614.

Nicklasson, M., Nyqvist, H., 1983. Studies on the relationship between intrinsic dissolution rates and rates of water adsorption. Acta Pharm. Suec. 20 (5), 321–330.

Nicklasson, M., Brodin, A., Nyqvist, H., 1981. Studies on the relationship between solubility and intrinsic rate of dissolution as a function of pH. Acta Pharm. Suec. 18, 119–128.

Nicklasson, M., Brodin, A., Stenlander, C., 1982. The dependence of intrinsic rates of dissolution on hydrodynamic conditions using a thermodynamic approach. Acta Pharm. Suec. 19, 25–36.

Noyes, A.A., Whitney, W., 1897. The rate of solution of substances in their own solutions. J. Am. Chem. Soc. 19, 930–936.

O'Connor, K.M., Corrigan, O.I., 2001. Comparison of the physicochemical characteristics of the *N*-(2-hydroxyethyl)pyrrolidine, diethylamine and sodium salt forms of diclofenac. Int. J. Pharm., 222, 281–293.

Palomo, M.E., Ballesteros, M.P., Frutos, P., 1999. Analysis of diclofenac sodium and derivatives. J. Pharm. Biomed. Anal. 21, 83–94.

Pandit, N.K., Strykowski, J.M., Shtohryn, L., 1989. The effect of salts on the distribution and solubility of an acidic drug. Int. J. Pharm. 50, 7–13.

Parrott, E.L., Wurster, D.E., Higuchi, T., 1955. Investigation of drug release from solids. I. Some factors influencing the dissolution rate. J. Am. Pharm. Assoc. Sci. Ed. 44 (5), 269–273.

Roseman, T.J., Yalkowsky, S.H., 1973. Physicochemical properties of prostaglandin $F_{2\alpha}$ (tromethamine salt): solubility

behaviour, surface properties and ionisation constants. J. Pharm. Sci. 62 (10), 1680–1685.

Rubino, J.T., 1989. Solubilities and solid state properties of the sodium salts of drugs. J. Pharm. Sci. 78 (6), 485–489.

Serajuddin, A.T.M., Jarowski, C.I., 1985a. Effect of diffusion layer pH and solubility on the dissolution rate of pharmaceutical acids and their sodium salts. II. Salicylic acid, theophylline and benzoic acid. J. Pharm. Sci. 74 (2), 148–154.

Serajuddin, A.T.M., Jarowski, C.I., 1985b. Effect of diffusion layer pH and solubility on the dissolution rate of pharmaceutical bases and their hydrochloride salts. I. Phenazopyridine. J. Pharm. Sci. 74 (2), 142–147.

Serajuddin, A.T.M., Mufson, D., 1985. pH–solubility profiles of organic bases and their hydrochloride salts. Pharm. Res. 2, 65–68.

Serajuddin, A.T.M., Rosoff, M., 1984. pH–solubility profile of papaverine hydrochloride and its relationship to the dissolution rate of sustained-release pellets. J. Pharm. Sci. 73 (9), 1203–1208.

Shah, A.C., Nelson, K.G., 1975. Evaluation of a convective diffusion drug dissolution rate model. J. Pharm. Sci. 64 (9), 1518–1520.

Silverstein, R.M., Webster, F.X., 1998. Spectrometric Identification of Organic Compounds, 6th ed. Wiley, New York.

Sjökvist Saers, E., Craig, D.Q.M., 1992. An investigation into the mechanism of dissolution of alkyl *para*-aminobenzoates from polyethylene glycol solid dispersions. Int. J. Pharm. 83, 211–219.

Socrates, G., 1994. Infrared Characteristic Group Frequencies, 2nd ed. Wiley, New York.

Thomas, E., Rubino, J., 1996. Solubility, melting point and salting-out relationships in a group of secondary amine hydrochloride salts. Int. J. Pharm. 130, 179–185.

Tsuji, A., Nakashima, E., Hamano, S., Yamana, T., 1978. Physicochemical properties of amphoteric β-lactam antibiotics. I. Stability, solubility and dissolution behaviour of amino penicillins as a function of pH. J. Pharm. Sci. 67 (8), 1059–1066.

United States Pharmacopeia 24. United States Pharmacopeial Convention, Rockville, Maryland, 2000.

Wang, L.H., Chowhan, Z.T., 1990. Drug-excipient interactions resulting from powder mixing. V. Role of sodium lauryl sulphate. Int. J. Pharm. 60, 61–78.