in the conservative nature of the results. Careful assessment of endotherm areas (as in the lactose example, above) may help interpretation of studies of a single composition.

The use of IR in the study of potential drug-drug and drug-excipient interactions has been discussed previously (French & Morrison 1965). In this study, the IR spectra of praziquantel, oxamniquine and a binary mixture containing 0·33 mol ratio of oxamniquine confirmed the absence of interactions in this system during the physical mixing process. This result is not unexpected, as the only functional groups in the praziquantel molecule are two tertiary amide moieties. These would only be expected to form weak dipolar interactions with other molecules. This interpretation is supported by the smaller value of ΔH_f for praziquantel (32·3 kJ mol^{-1}).

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Physicochemical properties of oxamniquine indicate a new polymorphic form

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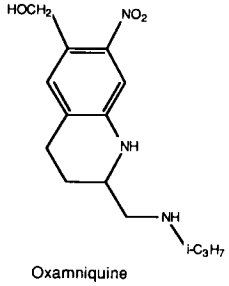
Abstract—New dissolution rate, chemical stability and thermal analysis data are reported for an anti-schistosomal drug, oxamniquine. A slow dissolution rate (40–70% in 1 h) was found, which may contribute to its erratic clinical response. The drug was found to be chemically stable in water for at least 21 days at 37°C. Dissolution rate and thermal analysis evidence is presented for a previously unreported polymorph (Form III). This form appears to be intermediate in physical stability between the known Forms I and II.

Oxamniquine (I, Vansil) has been used for about 15 years in the treatment of schistosomal diseases of man and animals (Roche et al 1989). A high degree of inter-subject variability has been noted in serum concentrations of orally administered oxamniquine in man (Kaye 1978), which may be one reason for its reported erratic clinical response (Foster 1987). Variability has also been reported for some pharmacokinetic parameters (area under the plasma-time curve, peak plasma concentration, time to peak) in healthy volunteers (Kokwaro & Taylor 1985). Data supporting a hypothesis for the clinical behaviour (and, by inference, the pharmacokinetic behaviour) based on variable gut wall drug metabolism has been obtained from in-vivo and in-vitro studies (Kaye & Roberts 1980). However, other factors could also contribute to the erratic behaviour, such as low dissolution rates. It has been shown that a combination of oxamniquine with praziquantel (II, Biltricide, Miles) has a synergistic effect when tested as an oral suspension in mice infected with *S. mansoni* (Brammer & Shaw 1981; Shaw & Brammer 1983; Botros et al 1989). A recent study indicated that these two agents did not seem to interact with each other, or with several common formulation excipients, in the solid state (Prankerd & Ahmed 1992). It was concluded from these results that a combination tablet dosage form of the two drugs was feasible.



Oxamniquine

Aqueous solubility, partition coefficient and pK_a values at 25°C have been previously reported (Kofitsekpo 1980). The intrinsic solubility has been found to be $7{\cdot}89 \times 10^{-5}$ M (22·0 μg mL^{-1}). The log P value (octanol/water) for the neutral species was reported to be $2{\cdot}245 \pm 0{\cdot}064$. The drug has two protonation

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sites with $pK_{a1} = 3{\cdot}28 \pm 0{\cdot}07$ (ring nitrogen) and $pK_{a2} = 9{\cdot}53$ (side-chain nitrogen). Two polymorphic modifications of I were recently demonstrated by differential scanning calorimetry (DSC), with melting ranges 117–118°C (Form II) and 146–148°C (Form I) (Kuhnert-Brandstätter & Völlenklee 1987). Form II was shown to be physically less stable. IR spectra and DSC data were recently obtained for I alone or in combination with II (Prankerd & Ahmed 1992). These data suggested a lack of interactions during physical mixing and melting processes. Melting of a physical mixture resulted in a eutectic mixture (1·8 mol of II to 1 mol of I). The enthalpy change for fusion of I ($\Delta H_f = 60{\cdot}0$ kJ mol^{-1}) is large (Prankerd & Ahmed 1992), accounting in part for its low aqueous solubility reported by Kofitsekpo (1980).

The present study was undertaken to characterize the physicochemical properties of oxamniquine and to seek possible physicochemical explanations for the erratic pharmacokinetic behaviour.

Materials and methods

Deionized water was redistilled from an all-glass still. Reagents were American Chemical Society Reagent grade and solvents were HPLC grade from Fisher (Fairlawn, NJ, USA). Oxamniquine (Pfizer Inc, Groton, CT, USA; Lot 7M365-90QCS-03) was recrystallized from the following solvents: methanol, acetone, methanol-acetone (1:1, v/v), methanol-water (2:1, v/v), acetone-water (2:1, v/v) and ethyl acetate.

Ultraviolet-visible (UV-VIS) spectra were obtained in Spectrosil cuvettes with an HP8451A diode-array spectrophotometer (Hewlett-Packard, Corvallis, Oregon, USA). Saturated solubility measurements were obtained by equilibrating the drug with distilled water in sealed vials attached to a shaft rotating at about 60 rev min^{-1} in a bath (Haake NK 22) at $37{\cdot}0 \pm 0{\cdot}05$°C. Samples were taken periodically, filtered (0·45 μm membrane filter) and analysed by UV. The stability of oxamniquine in aqueous solutions stored at $37{\cdot}0 \pm 0{\cdot}1$°C for 21 days was monitored by UV. Dissolution rates under sink conditions were obtained in a modified USP paddle apparatus (100 rev min^{-1}) at $37{\cdot}0 \pm 0{\cdot}1$°C. Finely powdered samples (100 μm sieve; 20 mg) were wetted with a few drops of dissolution medium (0·001%, w/v Tween 80 in water or 0·1 M HCl), then transferred to a dissolution beaker containing 1000 mL of the medium. The medium was passed through a flow cell by a peristaltic pump, and the absorbance monitored (247 nm) over 2 h. Six runs were performed on untreated oxamniquine and two runs on each recrystallized sample. DSC was performed with a Perkin-Elmer DSC-7 (Perkin-Elmer, Danbury, Connecticut, USA) calibrated with indium and zinc standards. Samples (1·5–3 mg) of the powdered drug or mixture were weighed into aluminum sample pans and an empty sample pan was used as a reference. A blank baseline, recorded at the same heating rate, was subtracted from each thermal scan (usually 20·0°C min^{-1}, 30 mL min^{-1} N_2 purge).

Results and discussion

No changes were observed in the UV-visible spectra of oxamniquine in aqueous solutions after 21 days, indicating that equilibration times of 6–7 days for saturated solubility measurements would not be compromised by chemical degradation. The saturated solubility in water was found to be $8{\cdot}77 \times 10^{-4}$ M (245 μg mL^{-1}) at 37·0°C. Dissolution of oxamniquine in 0·1 M HCl was complete in about 2 min, but in water was only about 80–85% complete in 2 h at 37·0°C (Fig. 1). Oxamniquine which had been recrystallized from various solvents exhibited dissolution

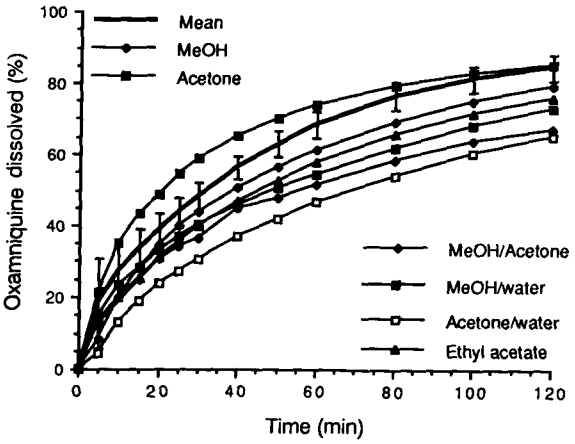

FIG. 1. Dissolution of oxamniquine in aqueous 0·001% w/v Tween 80. "Mean" is the arithmetic mean of 6 runs for untreated oxamniquine and error bars are the maximum deviations from the mean. The remaining plots are for the means of duplicate runs.

profiles which were similar in appearance to those from untreated material. However, the extent of dissolution at specified time intervals was usually less than that from untreated oxamniquine (Fig. 1). DSC of oxamniquine recrystallized from acetone, methanol-acetone and methanol-water gave virtually the same melting endotherms as untreated oxamniquine (T_{onset} 146–148°C), although ΔH_f ranged from 50·3–55·9 kJ mol^{-1} (Form I). However, material recrystallized from ethylacetate, methanol or acetone-water gave scans which had a discontinuity with a lower onset temperature (T_{onset} 142–144°C) on the leading edge of the Form I melting endotherm (Fig. 3).

Dissolution rate experiments were performed in an unbuffered aqueous medium containing 0·0010% w/v Tween 80. The non-ionic surfactant (at less than the critical micelle concentration, 0·0014%) (Wan & Lee 1974) was needed as oxamniquine is very difficult to wet. Preliminary experiments without Tween 80 gave highly erratic dissolution rate profiles, as the drug floated on the surface of the medium.

The well separated pK_a values ($pK_{a1} = 3{\cdot}28$; $pK_{a2} = 9{\cdot}53$) (Kofitsekpo 1980) suggest that the predominant species in the unbuffered dissolution medium was the monoanion. Although oxamniquine dissolved rapidly in 0·1 M HCl, very little would be absorbed from the stomach in-vivo, as it is doubly protonated. Oxamniquine which dissolves in the stomach is likely to reprecipitate on transport into the higher pH of the ileum. Slow dissolution of the reprecipitated drug may contribute to the erratic pharmacokinetic profile (Kokwaro & Taylor 1985) of oxamniquine, as well as the reported metabolic effects (Kaye & Woolhouse 1976; Kaye & Roberts 1980). At pH ~ 7, the highest pH usually found in the small intestine, the apparent log P of oxamniquine will be < 0 (Kofitsekpo 1980), due to the positively charged monocation. Absorption may be retarded by the low log P value and may vary with small changes in ileal pH.

Fig. 1 shows the dissolution profiles of oxamniquine when recrystallized from different solvents. All samples, except that recrystallized from acetone, dissolved more slowly than the untreated material. Fig. 2 is a plot of the times to reach 50% dissolution (T50) as a function of ΔH_f for each sample. The points in Fig. 2 fall into two groups: (i) untreated, acetone-, methanol-acetone- and methanol-water-recrystallized material, for which there is a linear relationship between T50 and ΔH_f; and (ii) ethylacetate-, methanol- and acetone-water-recrystallized material, for which there is no relationship. The variation in dissolution rates with ΔH_f probably resulted from differences in

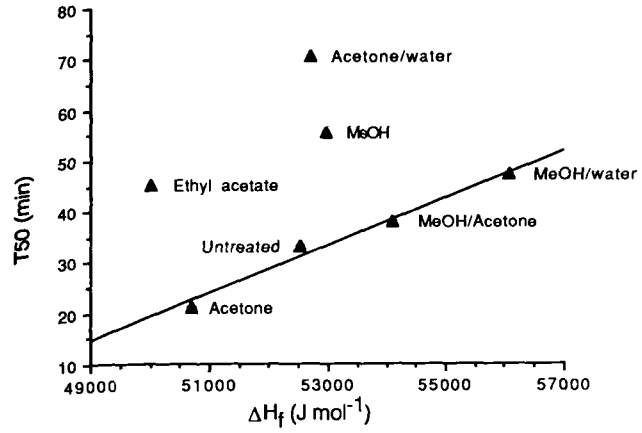

FIG. 2. Relationship between T50 and ΔH_f for oxamniquine after recrystallization from different solvents. The straight line is the line of best fit for the four samples lacking DSC evidence for Form III (group i).

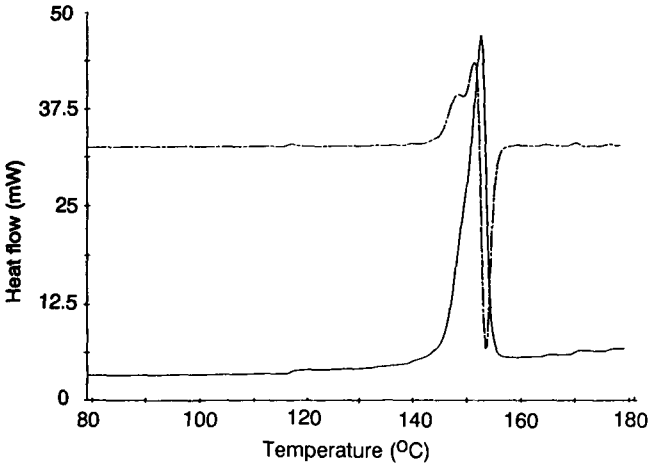

FIG. 3. DSC scan (——) and its first derivative (– – –) for a sample of oxamniquine which had been recrystallized from acetone-water.

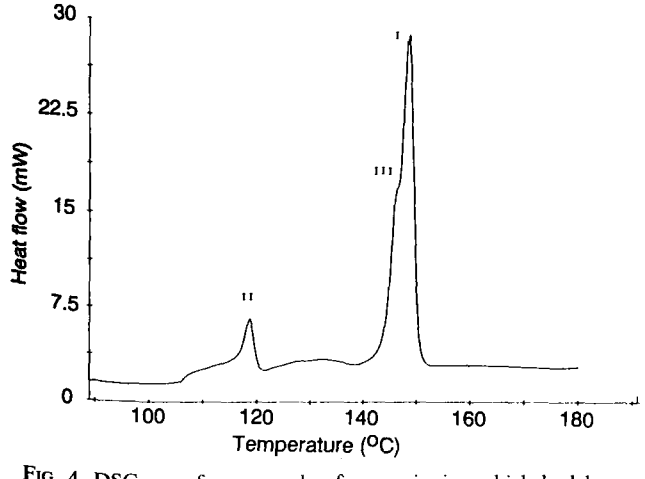

FIG. 4. DSC scan for a sample of oxamniquine which had been melted, then cooled.

the percent crystallinity of these samples. The dissolution rates are expected to be proportional to measures of crystal lattice energy, such as ΔH_f, as in group i. Oxamniquine recrystallized from acetone had the lowest ΔH_f and a dissolution rate which was faster than untreated oxamniquine.

Preparation of polymorphs of oxamniquine was attempted by recrystallization from solvents of different polarity or by fusion, then rapid cooling. DSC scans of the group ii samples displayed, to a greater or lesser extent, a discontinuity in the Form I melting endotherm (Fig. 3). This is demonstrated clearly by the first derivative of the scan. It was inferred that this discontinuity was a partly obscured endotherm for a previously unreported polymorphic form. The inference of the new form, Form III, is supported by the dissolution rate data for group ii, which did not conform to the linear relationship of group i (Fig. 2). Rapid cooling of melted oxamniquine gave a sample which more clearly displayed a DSC transition corresponding to the postulated Form III, as well as the previously reported Forms I and II (Fig. 4). DSC scans at 2, 5, 10, 20 and 40°C min^{-1} of oxamniquine recrystallized from acetone-water showed that the endotherm for Form III became more prominent as heating rate was increased, suggesting that this form is less stable than Form I. Thermal events relating to the previously described Form II (Kuhnert-Brandstätter & Völlenklee 1987) were scarcely apparent in the scans of oxamniquine after recrystallization from ethyl acetate, methanol or acetone-water (group ii), suggesting that Form II is less stable than Form III.

Thus, erratic clinical behaviour of oxamniquine may result from poor absorption, due to slow dissolution in neutral or mildly basic intestinal fluids Form I was stable in aqueous solution for at least 21 days at 37°C. Dissolution rates and DSC analysis suggest that oxamniquine can exist as a previously unreported polymorph, Form III, which appears to be intermediate in physical stability between Forms I and II.

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