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Physicochemical interactions of praziquantel, oxamniquine and tablet excipients

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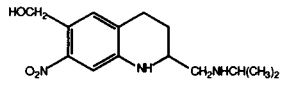
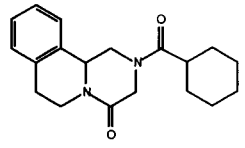
Abstract—A differential scanning calorimetry and infrared spectrophotometry study of potential interactions between oxamniquine and praziquantel, two synergistic anti-parasitic drugs, indicated that they did not interact on fusion. Mixtures of the two drugs with each of nine common pharmaceutical excipients (Ac-Di-Sol, Avicel, Crospovidone, calcium phosphate, magnesium stearate, starch, lactose, PEG 6000, stearic acid) appeared to interact only with stearic acid. These results suggested that a combination solid dosage form was feasible.

CHEMICAL STRUCTURES



Oxamniquine



Praziquantel

Parasitic diseases of man and animals include those produced by various *Schistosoma* spp. (flukes). Many drugs have been used in the treatment of schistosomal diseases (Roche et al 1989), of which two of the most recently introduced are oxamniquine (Vansil, Pfizer) and praziquantel (Biltricide, Miles). It has been shown that a combination of these two agents is synergistic when tested in mice infected with *S. mansoni* (Brammer & Shaw 1981; Shaw & Brammer 1983; Botros et al 1989). A 1:2 w/w combination was shown to be equi-active with 4- to 5-fold higher doses of oxamniquine alone or 8- to 10-fold higher doses of praziquantel alone (Brammer & Shaw 1981). This result may be of significance in using lower doses to reduce side-effects. As therapy with both drugs concommittantly would be more convenient with a combination tablet, it was of interest to study the possibility of interactions involving praziquantel, oxamniquine and excipients. Interactions could have deleterious effects on drug bioavailability from a solid dosage form. These results would be useful in designing a combination dosage form.

Thermal analysis of solid-liquid phase transitions is a rapid means of screening drug-excipient mixtures for possible interactions (Guillory et al 1969; Smith 1982; van Dooren 1983; Botha & Lötter 1989). The present study obtained differential scanning calorimetry (DSC) curves of oxamniquine or praziquantel alone or in combination; and 1:1 w/w mixtures of praziquantel/oxamniquine with excipients (Smith 1982). Infrared (IR) spectrophotometry was used to examine mixtures of oxamniquine and praziquantel.

Materials and methods

Chemicals. Praziquantel (Miles Pharmaceutical, West Haven, CT) (Embay 8440, 671936L), oxamniquine (Pfizer Inc, Groton, CT) (Lot No. 7M365-90QCS-03), starch, microcrystalline cellulose (Avicel, FMC Corp., Philadelphia, PA, USA), cross-linked sodium carboxymethylcellulose (Ac-Di-Sol, FMC Corp., Philadelphia, PA, USA), lactose (Mallinckrodt, St Louis, MO, USA), stearic acid (Fisher, Fair Lawn, NJ, USA), polyethylene glycol 6000 (PEG 6000, Fisher, Fair Lawn, NJ, USA), cross-linked polyvinylpyrrolidone (Crospovidone, Kollidon CL, BASF, Ludwigshafen, Germany), magnesium stearate (Cardinal Products, Durham, NC) and dibasic calcium phosphate (J. T. Baker, Phillipsburg, NJ, USA) were used as received.

Methods. 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 scan (2·0–10·0°C min^{-1}, 30 mL min^{-1} N_2 purge). IR spectrophotometry was performed with a 1420 Ratio Recording Infrared Spectrophotometer (Perkin-Elmer, Danbury, CT, USA). Samples (1 mg) in finely ground KBr (100 mg, Fisher IR grade) were compressed (10 000 psi), and the pellet scanned over the range 4000–1000 cm^{-1}.

Sample preparation. Mixtures were prepared by intimately grinding the materials with an agate mortar and pestle; heating the two drugs (oxamniquine, 0·3 mol ratio) in a vial until they just melted, then cooling the melt; or evaporation of methanol solutions of the drug mixture.

Results and discussion

Praziquantel and oxamniquine exhibited single endotherms (T_{onset} 137·8 and 145·9°C, respectively) (Fig. 1). Reported melting ranges are 136–138 and 147–149°C, respectively (Windholz 1983). Areas of the endotherms gave ΔH_f values of 32·3 and 60·0 kJ mol^{-1}. The smaller ΔH_f value for praziquantel reflects its lack of functional groups which would promote intermolecular hydrogen-bonded interactions. Scans of oxamniquine (mol ratio, 0·1 to 0·9) in praziquantel displayed either a single endotherm or two broad overlapping endotherms (Fig. 1). Scans of a 1:1 w/w mixture of the drugs (1:1 mol ratio) and the following excipients were superpositions of scans for the 1:1 mol ratio mixture and the excipient alone: Ac-Di-Sol; Avicel; Crospovidone; dibasic calcium phosphate; magnesium stearate and starch, while those for 1:1 w/w physical mixtures of the drugs (1:1 mol ratio) with lactose, PEG 6000 or stearic acid were not (see discussion). The IR spectrum of a physical mixture of the drugs (1:2 mol ratio), displayed all the major bands found in spectra of each component alone; no new bands were seen.

The use of solid-liquid phase diagrams relating thermal properties to composition for investigation of intermolecular interactions is well established (Sekiguchi et al 1963; Guillory et al 1969), although not always advocated (Smith 1982). Such diagrams permit clear separation of specific intermolecular interactions (due to chemical reactions such as salt formation, which may affect bioavailability or cause difficulties in material

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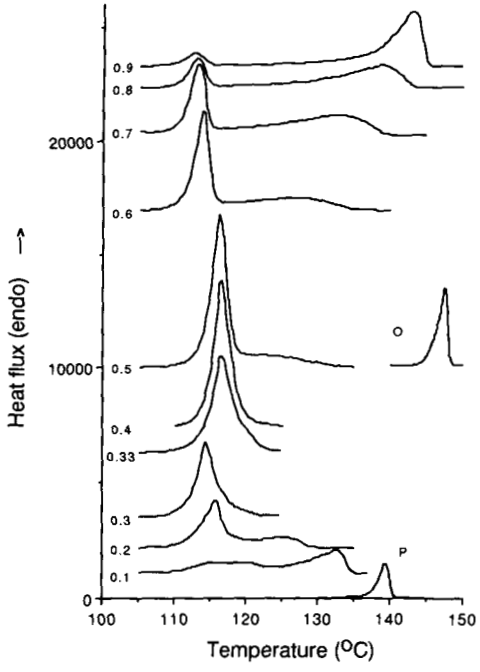

FIG. 1. DSC scans of oxamniquine and praziquantel and of their physical mixtures with the given mol ratio of oxamniquine.

processing) from physical interactions (e.g. eutectic formation, which could even enhance biopharmaceutical properties such as dissolution rate). The data in Fig. 1 were used to construct a phase diagram of the melting behaviour (solidus/liquidus temperature or ΔH_f for the eutectic peak as a function of mol ratio) of physical mixtures of the two drugs (Figs 2, 3). These are in good agremeent and show a eutectic point at 114–115°C with a composition of 0·33–0·40 mol ratio of oxamniquine. The phase diagram constructed from eutectic peak ΔH_f values is easier to construct, as it involves two linear plots which intersect at the eutectic composition (0·35–0·36 mol ratio of oxamniquine). The phase diagrams give no indication of specific interactions under the conditions studied.

The DSC curve of a solidified melt showed no phase transitions, suggesting that glass formation took place. Such a glass could have useful formulation properties, such as increased

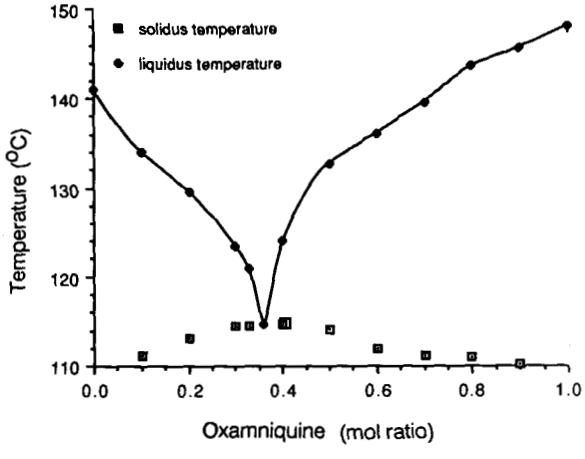

FIG. 2. Phase diagram for the oxamniquine-praziquantel system (solidus or liquidus temperatures as a function of oxamniquine mol ratio). The point at mol ratio 0·36 is extrapolated.

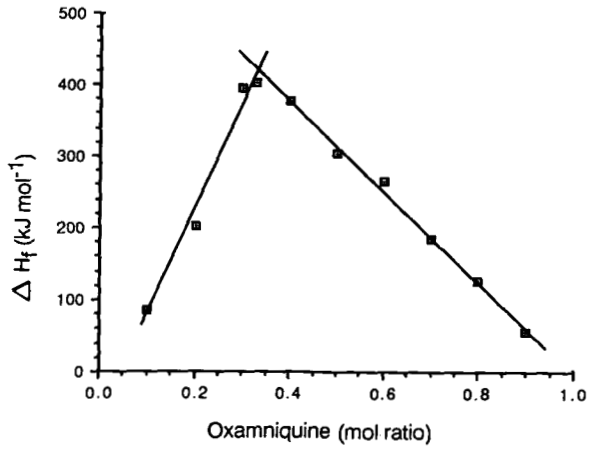

FIG. 3. Phase diagram for the oxamniquine-praziquantel system (enthalpy of fusion for the eutectic peak as a function of the oxamniquine mol ratio).

dissolution rate. Scans of mixtures obtained by evaporation of solutions (mol ratio of oxamniquine, 0·3 to 0·5) were similar to those for physical mixtures, except that the eutectic endotherms had a T_{onset} of 110°C. This is more consistent with the eutectic temperatures for physical mixtures with either high (>0·7) or low (<0·1) mol ratios of oxamniquine. It suggests that physical mixing may not always give a sufficiently intimate mixture for thermal equilibrium during the scan, depending on the heating rate. The IR spectra of pure drugs, and the mixture (0·33 mol ratio of oxamniquine) supported the absence of interactions during the physical mixing process.

Scans of drug mixtures with starch, Avicel, Ac-Di-Sol, Crospovidone or dibasic calcium phosphate were simple sums of scans of the drug mixture and the excipient separately. These results indicated that interactions were absent. For a mixture of oxamniquine with praziquantel in PEG 6000, melting of the excipient occurred with T_{onset} of 60·9°C, followed by a very broad endotherm with T_{onset} of 94·2°C. It is likely that the mixture of praziquantel and oxamniquine dissolved in the molten PEG 6000, although a small amount may have remained intact to melt near the eutectic temperature. For lactose (T_{onset} 146·1°C; ΔH_f 135 J g^{-1}), and endotherm corresponding to the eutectic was observed (T_{onset} 113°C) as well as a broad second endotherm (T_{onset} 141·7°C; ΔH_f 48·4 J g^{-1}, expected ΔH_f 67·5 J g^{-1}), corresponding to lactose. Comparison of the observed ΔH_f values suggests that about one-third of the lactose had dissolved in the melted drug mixture. In the cases of PEG 6000 and lactose, specific interactions between the excipient and the drug mixture were probably absent. For a mixture with stearic acid (T_{onset} 68·8°C), only two endotherms were observed, T_{onset} 63·7°C and T_{onset} 70·5°C. It is highly likely that a specific interaction took place with this mixture, probably involving reaction of the COOH group of stearic acid with the more basic of the amino groups of oxamniquine.

The interpretation of thermal analysis studies on drug-drug or drug-excipient interactions is often difficult, especially when only a single composition is examined. Several of the oxamniquine-praziquantel-excipient mixtures in this study exhibited DSC curves which were simple sums of those for the excipient and drug mixture alone and clearly involved no interactions, but this is often not the case. It would be much more difficult to distinguish between eutectic formation, dissolution of drug in a molten second component, or chemical (specific) interactions, based on thermal examination of a single composition mixture. Simple thermal analysis compatibility screening, as suggested elsewhere (Smith 1982) is rapid, but its value seems to be mainly

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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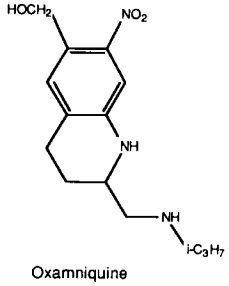
Abstract—New dissolution rate, chemical stability and thermal analysis data are reported for an anti-schistosomal drug, oxamniquine. A slow dissolution rate (40–70% in 1 h) was found, which may contribute to its erratic clinical response. The drug was found to be chemically stable in water for at least 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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