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Study of the Interaction of Dithranol with Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin in Solution and in the Solid State

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Abstract

The interaction between dithranol and heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TMBCyD) has been investigated in aqueous solution containing isoascorbic acid (0·2% w/v) as antioxidant and in the solid state. The interaction in the solid state was studied by differential scanning calorimetry (DSC), infrared spectroscopy (IR), X-ray powder diffractometry (XPD) and a dissolution-rate method.

The extent of complexation between the two substances was poor, as indicated by the low value of the slope of the linear part of the solubility curve. A phase diagram was constructed by measuring the thermal behaviour of various re-solidified physical mixtures of dithranol and of TMBCyD previously subjected to heating until melting of the TMBCyD. The loss of dithranol, owing to sublimation and degradation caused by the thermal treatment used, was less than 10%. In keeping with XPD and IR data, the phase diagram indicated that a complex was formed containing 13·7% dithranol (molar ratio 1:1) which had a congruent melting point at 164°C. The drug dissolution rate from the 1:1 complex was measurable, unlike that of the corresponding physical mixture, and was significantly increased when the complex was dispersed in the glassy matrix of TMBCyD, as it was in re-solidified mixtures containing 2–7% dithranol.

The results show that the solubility of dithranol is increased significantly as a consequence of its interaction with TMBCyD, despite the low extent of complexation between the two substances.

Dithranol is widely used for the first line of treatment of psoriasis. Owing to its insolubility in water, conventional treatment entails topical application of ointments or pastes containing 0·1–1% dithranol for a few hours. The stability of dithranol in ointments, creams, pomades and pastes is dependent on the excipients used and on the concentration of the drug. Low-strength formulations are the least stable, and give rise to the final oxidation products danthron and the dimer dianthrone (Hiller et al 1995), both of which cause irritation and staining of the skin (Mustakallio 1981).

Attempts to increase both the stability and bioavailability of dithranol have produced several types of formulation, chief among which are liposomal formulations (Gehring et al 1995), ointment formulations containing ascorbyl palmitate as an antioxidant (Weller et al 1990), formulations in which dithranol is microencapsulated by crystalline monoglycerides (August 1989) and a dithranol-polyvinylpyrrolidone co-evaporate (Delneuville et al 1996). Penetration-enhancement of dithranol has been noted with liposomal formulations (Gehring et al 1992).

Cyclodextrins (CyDs) are cyclic oligosaccharides known to form inclusion complexes with many substances; their use as solubilizing and stabilizing agents in pharmaceutical development has recently been reported (Loftsson & Brewster 1996). Penetration-enhancing activity has been demonstrated for CyDs with several drugs (Loftsson et al 1994; Preiss et al 1994; Vollmer et al 1994) and, more recently, chemically modified CyDs have received considerable attention because of their complexing abilities and improved solubility in water and, in

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some instances, in organic solvents. Among methylated CyDs, heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TMBCyD) has, in addition to its advantageous features of solubility in both water and organic solvents, useful thermal behaviour (Nakai et al 1984); it has been shown that inclusion complexes can be formed by heating physical mixtures of this CyD with drugs (Nakai et al 1987; Abdel Rahman et al 1993).

We have studied the complexation of dithranol with several CyDs, both in solution and in the solid state, to investigate whether such interactions are useful for drug solubilization and stabilization (which in turn could prove expedient for the preparation of topical formulations with enhanced drug-penetration properties).

Herein we report our findings from experiments with TMBCyD and illustrate the physicochemical properties of solid dispersions obtained by heating physical mixtures of dithranol with this CyD.

Materials and Methods

Materials

Dithranol (1,8-dihydroxy-9[10*H*]-anthracenone), danthron (1,8-dihydroxyanthraquinone), heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TMBCyD) and D-isoascorbic acid (D-*erythro*-hex-2-enoic acid γ-lactone) were obtained from Sigma-Aldrich (Milan, Italy). Dianthrone (1,8,1′,8′-tetrahydroxy-10,10′-dianthrone) was synthesized by procedures described elsewhere (Segal et al 1971). All solvents were of analytical grade or high-performance liquid chromatography (HPLC)-grade. Water was purified by means of Milli-Q Plus system (Millipore, USA).

Assay

The HPLC method used for assay of dithranol and its degradation products danthron and dianthrone was a modification of that described by Cheah et al (1989). The instrument used was a Perkin-Elmer (USA) Series 4 HPLC pump equipped with a Rheodyne (Cotati, USA) 7125-075 valve (with 100-μL loop) and a Hewlett-Packard (HP; USA) 1040 M series II diode-array detector managed by an HP 98572A Chem-Station. Reversed-phase chromatography was performed at room temperature (20–24°C) on a chemically bonded stationary phase, 5 μm LiChrospher 100 RP-18, packed into a 250 mm × 4 mm i.d. LiChroCART cartridge; the column was protected with a LiChroCART 25-4 precolumn containing 5 μm LiChrosorb RP-8 (Merck, Darmstadt, Germany). The mobile phase (helium-degassed) was 72:28 (v/v) acetonitrile–water containing 5% (v/v) glacial acetic acid; the flow rate was 1 mL min^{-1}. The aqueous component of the mobile phase was filtered through a Sartorius SM 16249 apparatus (Sartorius, Goettingen, Germany); cellulose acetate filtering membranes, pore size 0·45 μm, were used for filtration of mobile phase and samples.

The acquisition wavelengths used for detection of dithranol, danthron and dianthrone were 353, 433 and 369 nm, respectively, the absorption maxima of the three compounds; the bandwidth was 4 nm. The reference wavelength used was 550 nm (bandwidth 20 nm). Recording of the chromatograms was performed in 'all spectra' mode within the wavelength range 250–600 nm (step = 4 nm).

The modified method was validated by use of standard solutions of each compound in 1,4-dioxane (containing isoascorbic acid 0·2% w/v), diluted 1:1 with water before injection into the chromatograph. This procedure enabled direct HPLC analysis of aqueous samples from the study of phase solubility and from the dissolution test, after dilution 1:1 with 1,4-dioxane containing the antioxidant (unless this was already present in the sample).

Solubility study

The phase–solubility study was performed according to the method of Higuchi & Connors (1965). Excess dithranol (0·4 mg) was added to glass vessels (50 mm × 10 mm i.d.) containing aqueous solutions (1·0 mL) of TMBCyD (various concentrations) and isoascorbic acid (0·2% w/v). The containers were closed and the suspensions obtained were stirred magnetically (12 mm × 4·5 mm stirring bar) at 400 rev min^{-1} on a water-bath maintained at constant temperature (25·0 ± 0·5°C) by use of a RCS6 Lauda (Germany) thermostat. Equilibrium was reached after 24 h and each sample was filtered (membrane filter, 0·45 μm pore size) and the filtrate (0·5 mL) was then diluted with an equal volume of 1,4-dioxane and assayed by HPLC. The study was conducted in duplicate.

Preparation of simple and ground physical mixtures

An MM 2 type mixer mill (Retsch, Germany) was used to prepare ground mixtures from simple physical mixtures. Each grinding jar (stainless steel; volume 1·5 mL) contained one grinding ball (stainless steel; 5 mm diameter). The total sample weight was approximately 150 mg. The grinding time was 15 min and the oscillating frequency was 500 min^{-1}. The same apparatus, without the grinding ball, was used for preparation of simple physical mixtures (mixing time 15 min, oscillating frequency 500 min^{-1}).

Preparation of solid dispersions (heating method)
The physical mixture (approx. 150 mg) was transferred to a Pyrex vial (3 mL; covered with an aluminium-foil cap) and put in the oven of a gas chromatograph (Perkin-Elmer model 8310) at 50°C; the temperature was then increased at 30° min^{-1} to 165°C and maintained at this value for 5 min. Soon thereafter the vial was removed from the oven and left to cool to room temperature. The product was then gently ground (oscillating frequency 150 min^{-1}, grinding time 2 min).

Evaluation of sample degradation
The sample (approx. 1 mg, accurately weighed) was dissolved in 1,4-dioxane (0·500 mL) containing isoascorbic acid (0·2% w/v). An equal volume of water was added and, after stirring, the resulting solution was analysed by HPLC.

Differential-scanning calorimetry (DSC)
The Perkin-Elmer DSC-7 (previously calibrated with indium and zinc; running the Perkin-Elmer PC series thermal analysis system software, DSC-7 standard program) was operated with crimped aluminium sample pans at a scanning speed of 10° min^{-1}, under nitrogen, between 50 and 200°C. The sample weight was 2–3 mg.

The extrapolated onset temperature was used to describe peaks in DSC curves, because, unlike the peak temperature, it is not influenced by variations in sample size.

The same temperature was measured for glass transitions, which are generally considered more significant (Ford & Timmins 1989).

Hot-stage microscopy (HSM)
Observations were made by use of an FP 82 HT hot-stage (Mettler Toledo, Switzerland) and an Alphaphot-2 YS2-H polarizing microscope (Nikkon Corporation, Japan).

Infrared absorption spectroscopy (IR)
IR measurements were made with a Perkin-Elmer 1310 spectrophotometer, using the KBr disc method.

X-ray powder diffraction (XPD)
A Philips (The Netherlands) powder diffractometer with Bragg-Brentano geometry was used. Measuring conditions were: target Cu, filter Ni, voltage 45 kV, current 35 mA, time-constant 3 s. Samples obtained by the heating method were compared with the corresponding physical mixtures whose components had previously been separately subjected to the same thermal treatment.

Dissolution studies
Samples were sieved by means of an Erweka (Heusenstamm, Germany) sieve set type VS. Drug dissolution from the samples was determined according to the dispersed-amount method of Nogami et al (1969). An amount of sample (particle size $< 0·3$ mm) equivalent to 0·3 mg dithranol was placed in the dissolution vessel (round-bottomed flask; 50 mL) containing water (10·0 mL) maintained at $25·0 \pm 0·5$°C and magnetically stirred at 400 rev min^{-1} (20 mm × 6 mm stirring bar). At appropriate intervals a sample of suspension (1·0 mL) was withdrawn and filtered through a 0·45-μm membrane filter; the filtrate (0·5 mL) was diluted 1:1 with 1,4-dioxane containing isoascorbic acid (0·2% w/v) and 100 μL of the final solution assayed by HPLC. Each sample withdrawn was immediately replaced by an equal volume of water (Wurster & Taylor 1965). Each study was performed at least in duplicate.

Dissolution curves were characterized by dissolution efficiency obtained with time (t) equal to 30 min (Khan 1975) and results were evaluated by analysis of variance and the least significant difference test ($P < 0·05$ was considered as indicative of significance).

Results and Discussion

In a typical chromatogram the retention times of dithranol, danthron and dianthrone were 8, 7·5 and 13·5 min, respectively. 1,4-Dioxane was chosen as solvent for standard solutions because of its miscibility with water, its high boiling point and the high stability of dithranol in this solvent (Cavey et al 1982).

Interaction in aqueous solution
The phase-solubility study was performed in the presence of an antioxidant (isoascorbic acid) to prevent, or at least reduce, degradation of dithranol. Preliminary experiments enabled verification of equilibrium solubility within 24 h. Under the experimental conditions used the level of degradation, in terms of relative danthron and dianthrone content, was 2–5% w/w of the solute at TMBCyD concentrations > 100 mg mL^{-1}.

The solubility isotherm of dithranol in the presence of TMBCyD is depicted in Figure 1. It showed a marked initial curvature then a linear trend for TMBCyD concentrations $> 0·05$ M, characterized by a slope with a 95% confidence interval of $0·0078 \pm 0·0008$. This might indicate that complexation of a superior order occurred in TMBCyD; the extent of complex formation was, however, poor, because the resulting slope value

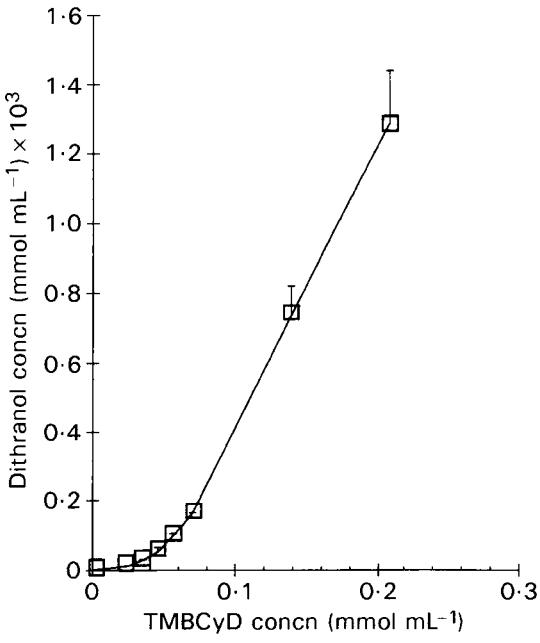

Figure 1. Phase-solubility diagram of dithranol in the presence of TMBCyD in aqueous solution containing isoascorbic acid (0·2% w/v) at 25°C. Each point represents the mean value from duplicate analyses; vertical bars indicate s.d.

was similar to that observed, for example, for the weak tetracycline-β-CyD system, and considerably smaller than that seen for pharmaceutical compounds that interact strongly (Lach & Cohen 1963).

It must be noted that, in the absence of TMBCyD, no appreciable amount of dithranol could be detected in an aqueous solution of 0·2% w/v isoascorbic acid. For this reason it was not possible to calculate the values of the apparent formation constants of 1:1 or superior order complexes for the examined system.

Interaction in the solid state

Figure 2 illustrates some DSC scans obtained from simple physical mixtures of dithranol and TMBCyD. Interaction caused by heating during scanning was evinced by the appearance of new endotherms different from those of the single components (curves B–L). In particular, the endotherm at approximately 165°C, the intensity of which initially rose then decreased with increasing dithranol concentration (curves F–L), was indicative of the melting of a new compound. This phenomenon was even more marked for physical mixtures previously subjected to grinding (Figure 2, curves B′–L′). The constancy of transition temperatures at approximately 150 and 155°C implied the presence of eutectic mixtures, whereas the melting endotherm of a dithranol-TMBCyD complex became more intense at approximately 165°C. The exotherm extending from 85 to 100°C in curve A′ was attributed to crystallization of cyclodextrin, which trituration had made partially amorphous; for the ground mixture containing 4% dithranol (see below) the effect of this process was also confirmed by XPD. The exotherms present in the subsequent curves (B′–L′) were presumably a consequence of crystallization of the components for which trituration had resulted in loss of crystallinity (Kaneniwa et al 1978); their position appeared to be dependent on the composition of the mixture, as revealed by the slight shift towards lower temperatures, probably because of the mutual influence of the components on the grinding effects.

The thermal treatment described in the Materials and Methods section was designed on the basis of information yielded by DSC. Samples were analysed to verify the possible loss of dithranol as a result of sublimation and degradation. The recovery of dithranol ranged from 91 to 102% w/w, and increased with the amount of drug in the sample; the mean loss of dithranol in the heated samples, owing to formation of danthron and dianthrone, was $2{\cdot}0 \pm 0{\cdot}4\%$ w/w ($n = 14$, 95% confidence interval). These data indicate that dithranol loss was limited and was essentially a result of sublimation during the heating process.

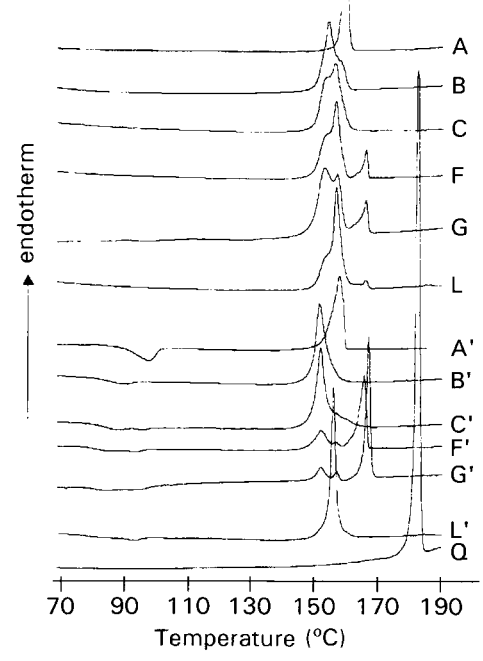

Figure 2. DSC scans obtained from pure components, simple physical mixtures (pm) and ground mixtures (gm) of dithranol and TMBCyD containing different amounts of dithranol: A, pure TMBCyD; B, pm 4% dithranol; C, pm 6% dithranol; F, pm 11% dithranol; G, pm 13·7% dithranol; L, pm 30% dithranol; A′, ground pure TMBCyD; B′, gm 4% dithranol; C′, gm 6% dithranol; F′, gm 11% dithranol; G′, gm 13·7% dithranol; L′, gm 30% dithranol; Q, pure dithranol.

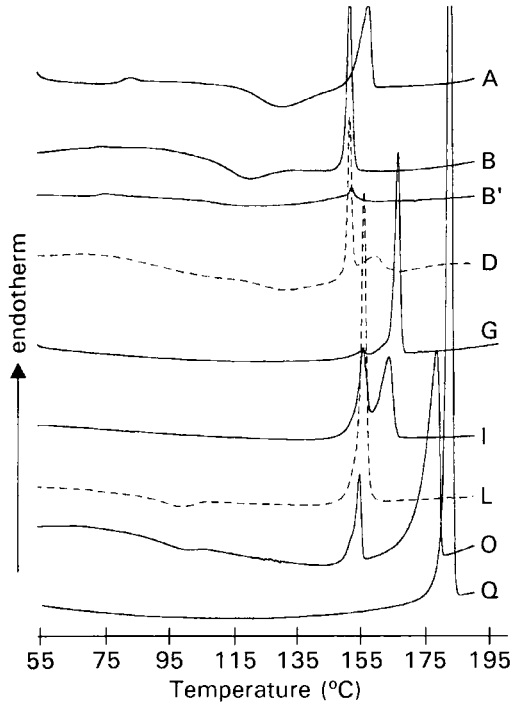

Figure 3. DSC scans obtained from heated components and from solid dispersions of dithranol and TMBCyD containing different amounts of dithranol: A, pure TMBCyD; B, 4% dithranol; B′, 4% dithranol—as glassy mass; D, 7·3% dithranol; G, 13·7% dithranol; I, 20% dithranol; L, 30% dithranol; O, 80% dithranol; Q, pure dithranol.

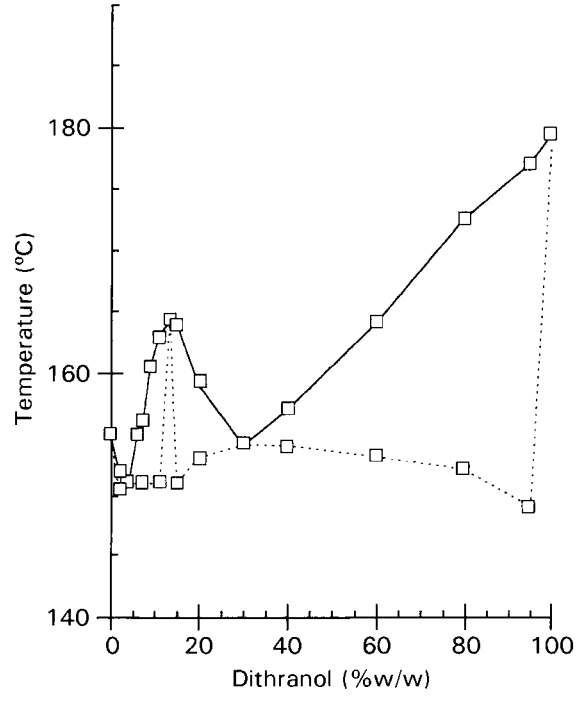

Figure 4. Phase diagram of the dithranol-TMBCyD system, constructed from DSC data obtained from solid dispersions.

The phase diagram constructed by use of the DSC scans obtained from solid dispersions, some of which are reported in Figure 3, is depicted in Figure 4. This showed two eutectic systems and a maximum corresponding to 1:1 molar composition (13·7% dithranol) representing a dithranol-TMBCyD complex with a congruent melting point at 164°C, between those of the pure components. The signals in its X-ray diffractogram (D, Figure 5) were significantly different from those of the 1:1 physical mixture of the heated components (C, Figure 5) and from those of the 1:1 physical mixture of the untreated components (E, Figure 5). This pattern substantiates the existence of a new crystalline phase. The IR spectra of the complex and of the corresponding physical mixture obtained from the thermally-treated components are presented in Figure 6. Spectral differences, possibly as a result of inclusion of dithranol in the cavity of TMBCyD, could be seen in the out-of-plane bending region of the aromatic C–H bond (800–700 cm^{-1}), in the C=C stretching aromatic region, between 1600 and 1450 cm^{-1}, and in the methyl symmetric bending region (at approximately 1375 cm^{-1}).

Under the experimental conditions used, the pure re-solidified TMBCyD was obtained in a glassy state, as an easily pulverizible mass. Its X-ray diffractogram (B, Figure 5) appeared as a halo pattern, typical of the amorphous state, according to the signals in the corresponding DSC scan (A, Figure 3). Here, the marked exotherm, followed by the melting endotherm, suggested that a crystallization

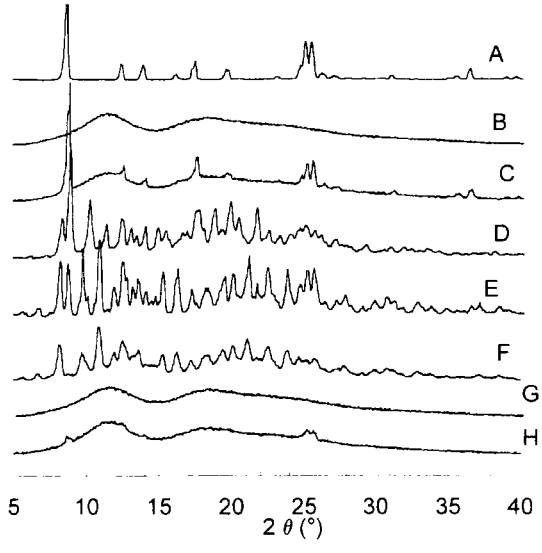

Figure 5. X-ray diffractograms of individual components and dithranol-TMBCyD mixtures of different molar ratios: A, dithranol after thermal treatment; B, TMBCyD after thermal treatment; C, 1:1 physical mixture of the heated components (13·7% dithranol); D, 1:1 complex; E, 1:1 physical mixture; F, 1:4 ground mixture (4% dithranol); G, 1:4 solid dispersion (eutectic); H, 1:4 physical mixture of the heated components.

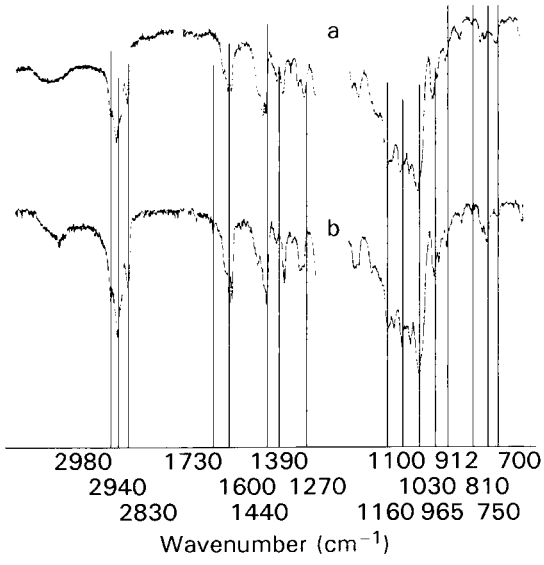

Figure 6. IR spectra of 1:1 molar ratio dithranol-TMBCyD mixtures: a, physical mixture of the heated components (13·7% dithranol); b, complex.

process occurred during scanning; a small endothermic peak at 80°C, as a result of a glass transition, was also evident. HSM observation showed that crystallization was preceded by complete transition from a glassy state to a liquid state.

Solid dispersions containing a low dithranol content maintained the appearance of glassy mass, a feature that enables very rapid drug dissolution (Ford 1986; Chiou & Riegelman 1971).

The eutectic systems of the phase diagram corresponded to dithranol/TMBCyD molar ratios of 1:4 (4% dithranol) and 2·6:1 (30% dithranol); the eutectic temperatures were 151°C and 154°C, respectively. Of the two systems, that containing 4% dithranol was obtained as a transparent glassy solid. The sharp fusion peak in its DSC scan (B, Figure 3), which appeared only after gentle grinding of the sample before DSC analysis, was preceded by a broad exotherm extending from 100 to 130°C, indicative of a re-crystallization process favoured by heating during scanning. The sample, if analysed directly as it was recovered from the vial, i.e. as a glassy mass, had a melting endotherm that was seemingly strongly reduced, as shown in DSC scan B′ in Figure 3; a baseline shift arising from a glass transition at 72°C was also noticeable. HSM observation of the unground sample enabled detection of the initial presence of a few small crystalline masses dispersed in a glass matrix and subsequently the slow transition to a liquid phase accompanied by the slow formation of crystals which melted at 148–154°C.

These observations, and the fact that little evidence of solid solution formation could be drawn from the phase diagram, might lead to the conclusion that the complex was initially dissolved to a great extent in the glass matrix of the carrier and that as a result of grinding further crystallization occurred, probably of a simple eutectic mixture of the complex and of TMBCyD. In any case, the X-ray diffractogram (G, Figure 5) of the re-solidified, gently ground mixture of eutectic composition (4% dithranol) contained no signals (although such signals were, in contrast, visible in the diffractogram of the corresponding physical mixture of the heated components, H). This finding is consistent with the presence of either an amorphous state or extremely fine crystallites.

Dissolution studies

Figure 7 shows the dissolution profiles of several systems. It is apparent that, in contrast with the corresponding physical mixture, for which no dithranol was detectable in solution, the complex enabled delineation of a dithranol dissolution profile (dissolution efficiency 3%). A significantly better result was obtained from the solid dispersion of the complex in TMBCyD of eutectic composition (4% dithranol), which showed a remarkable increase in dissolution efficiency (47%). The cor-

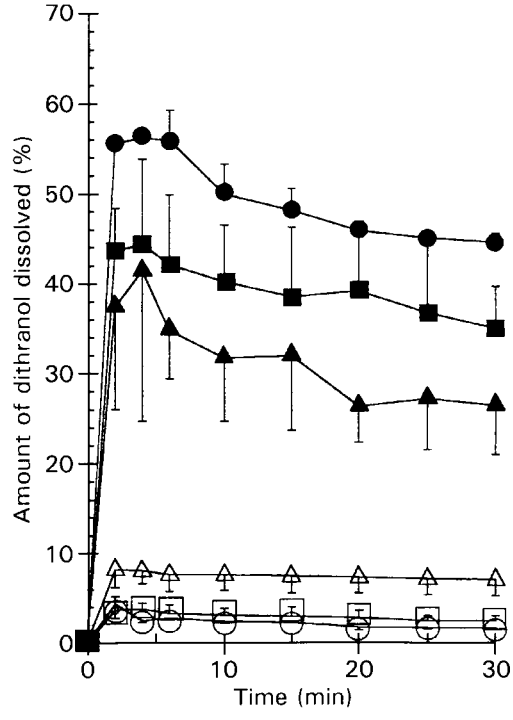

Figure 7. Dissolution profiles of dithranol-TMBCyD mixtures: ●, solid dispersion of eutectic composition (4% dithranol); ■, solid dispersion at 2% dithranol (n = 3); ▲, solid dispersion at 7·3% dithranol; △, ground mixture at 4% dithranol; □, 1:1 complex (13·7% dithranol); ○, complex-TMBCyD physical mixture (4% dithranol). Each point is the mean of results from at least two replicate analyses; vertical bars represent s.e.m.

responding simple physical mixture released no detectable amount of dithranol in solution, in keeping with the phase-solubility study (Figure 1) because the concentration of TMBCyD in the dissolution medium was very low ($< 0{\cdot}001$ M). In contrast, a dissolution profile comparable with that yielded by the complex was obtained from the corresponding ground mixture (dissolution efficiency 7%). In this case, drug dissolution might be explained by the partial loss of crystallinity of the system as a result of grinding, and by an increase in the wettability of dithranol because of its more intimate contact with TMBCyD, which has surfactant properties (Nakai et al 1977; Kaneniwa et al 1978). The drug signals were indistinguishable in the X-ray diffractogram of this ground mixture (F, Figure 5); only those of TMBCyD were evident, but these were less intense and rather broadened, indicating that grinding induced a reduction of TMBCyD crystallinity. However, an interaction between dithranol and TMBCyD as a result of the mechanical treatment cannot be excluded; as has already been discussed, this is also suggested by the DSC scans of the ground mixtures. The dissolution efficiency (2%) of the physical mixture complex-TMBCyD containing 4% dithranol indicated that simple mixing of the components did not enhance dissolution. Therefore, the dissolution achieved with the solid dispersion of eutectic composition can be explained by the rapid release of the complex already dissolved in the water-soluble glass-forming carrier. This might also account for the phenomenon of slight supersaturation observed during the initial stage of dissolution (Chiou & Riegelman 1971).

The dependence of dissolution on the drug/carrier ratio within the range 0–14% dithranol can be evaluated by comparing the dissolution profiles from solid dispersions of the complex containing 2%, 4% (eutectic composition) and 7·3% drug in TMBCyD. The dissolution efficiency values (38% and 47%, respectively) of dispersions of 2% and 4% dithranol were not significantly different, whereas the dissolution efficiency (30%) of dispersion of 7·3% dithranol was significantly lower than that of the eutectic composition. This trend of dissolution behaviour was not unexpected, because the increase of the relative amount and, consequently, of the crystalline fraction of the complex could promote aggregation and agglomeration among fine crystallites of this less hydrophilic component, thus hindering the dissolution of the drug (Chiou & Riegelman 1971).

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