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THE USE OF THERMAL ANALYSIS IN THE STUDY OF SOLID DISPERSIONS

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ABSTRACT

Differential thermal analysis (DTA) has been used to study the properties of seven drug-polyethylene glycol 6000 solid dispersions immediatley after preparation by rapid cooling. PEG 6000 displayed a melting point of 64°C but other, second order transitions occurred at 29 to 40°C and at ~ -50°C. Melts of chloramphenicol, glutethimide, griseofulvin, indomethacin and paracetamol solidifed to glasses, but phenacetin and phenylbutazone recrystallised. By examining the dispersions at various drug:PEG 6000 ratios, ranges were estimated which corresponded to PEG recrystallisation, PEG fusion, drug recrystallisation and drug fusion. It was predicted that systems which displayed PEG melting endotherms at drug contents of 0 to $>$ 70% drug and drug melting endotherms at contents in excess of 50% drug, made unsuitable solid dispersions because increases in dissolution rate occurred over a limited range of low drug content. Graphs of reciprocal glass transition temperatures (T_g) and dispersion content

indicated a transition temperature for PEG 6000 at -71°C. Using this value and the observed T_g values of the drugs, estimates of T_g values were compared with observed values throughout the drug:PEG 6000 phase diagrams. Systems where the observed T_g values were higher than calculated T_g values (paracetamol or chloramphenicol) were less prone to age-mediated dissolution changes than those systems where the calculated T_g values exceeded the observed values (glutethimide, griseofulvin or indomethacin).

INTRODUCTION

The use of water-soluble carriers in enhancing the dissolution rates of poorly water-soluble drugs by solid dispersion technology is well recognized. The mechanisms of transport have been reviewed[1,2] and drug entrapment by the carrier should be in as near to the molecular state as possible to provide rapid dissolution rates. The carrier molecular size should therefore be considerably greater than that of the drug[3] and consequently polymers such as polyethylene glycol (PEG) or polyvinylpyrrolidone are commonly used. PEG (molecular weight 1000-20,000) favours the formation of interstitial solid solutions with drugs and their viscous properties at temperatures just above their freezing points retard crystallisation and favour supercooling[3].

A typical paper, detailing a solid dispersion, gives information on the phase diagram, constructed from differential thermal analytical data, on the influence of carrier on drug solubility and on dissolution rates. Examples include studies on indomethacin-PEG 6000[4], phenacetin-PEG 6000[5] and paracetamol-PEG 20,000[6]. These studies are often supplemented by analytical techniques such as X-ray diffraction[7] or diffuse reflectance IR spectroscopy[8]. Usually these studies are completed on dispersions which have been prematurely aged or devitrified[7] and consequently

information on drug-carrier interactions or crystallisation characteristics is lost. Dubois and Ford[9] recently reported gross similarities in the release of ten drugs solid dispersed in PEG 6000 and subsequently examined[10] the age-induced dissolution changes in eight of these systems. This paper examines the thermal analysis of several of these drug-PEG 6000 dispersions in an attempt to identify the importance of crystallisation temperatures (T_c), melting temperature (T_m) and glass transition temperatures (T_g) as indicators of the dissolution performance and potential ageing problems of these systems. Since PEG is a highly crystalline polymer[11] differential thermal analysis (DTA) was completed on dispersions freshly prepared by the melt method and rapidly cooled.

MATERIALS AND METHODS

Seven drugs (all BP grade except phenylbutazone, Sigma Chemicals, U.S.A.) were used without further purification. PEG 6000 (B.D.H., U.K.) was the same batch as previously used[8-10].

Solid Dispersion Preparation

Drug-PEG blends were prepared by trituration. Samples (10-25 mg) were accurately weighed into aluminium sample pans and fused for 20 secs on a Reichert-Koffler hot stage microscope stage. Fusion temperatures are given in table 1. Immediately after fusion the samples were chilled rapidly on a stainless steel plate at 4°C for 15 secs.

Differential Thermal Analysis

After chilling, samples were transferred for analysis to a Stanton Redcroft Model 671 Differential Thermal Analyzer whose head had been cooled to 4°C. Liquid nitrogen purged the apparatus to -120°C and the samples analysed at a heating rate of

TABLE 1

Derived melting points (T_m) and fusion temperatures used to prepare solid dispersions

Drug	T_m (°C)	Fusion temp (°C)
Chloramphenicol	152	160
Glutethimide	88	120
Griseofulvin	222	230
Indomethacin	158	180
Paracetamol	169	180
Phenacetin	138	160
Phenylbutazone	107	120

10°C min^{-1}. Where crystallisation had occurred prior to heating (as evidenced by a fusion endotherm corresponding to PEG but with no prior crystallisation exotherm) samples were analysed by transferring, immediately following chilling at 4°C, to the analyser head which had been precooled to -120°C and heating at 10°C min^{-1}. The former method was the one of choice since the latter allowed ingress of water vapour which condensed to ice and made interpretation of DTA traces in the range -10°C to +30°C difficult. (Figures showing DTA traces have base line changes due to moisture, the artefacts are labelled by 'A'.) However the rapid cooling method was necessitated for dispersions with high PEG content. This method did not, however, prevent the spontaneous crystallisation of all dispersions containing 10% drug. Where mentioned in the text some dispersions were also examined at a heating rate of 5°C min^{-1}. Melting and crystallisation temperatures were taken as peak temperatures; glass transition temperatures as the midpoint in the endothermic step[12].

Additionally the untreated drugs were examined to ascertain their T_m values and re-examined following fusion as table 1 and

chilling, by heating at 10°C min^{-1}. PEG 6000 was similarly studied following 30 secs fusion at 75, 115 or 140°C.

Hot Stage Microscopy (HSM)

Collaboration of the DTA traces was made by examining the various drug-PEG systems using a Reichert-Koffler hot stage microscope.

RESULTS AND DISCUSSION

Drugs and PEG 6000

Each of the drugs analysed prior to treatment displayed only one endotherm giving the melting points stated in table 1. No polymorphic modifications were apparent at heating rates of either 10°C or 5°C min^{-1}.

Untreated PEG 6000 gave a weak endothermic change in baseline at ~ -50°C and another endothermic baseline change at 29 to 40°C, before fusion at 63 to 64°C. The trace was identical when obtained at 5°C or 10°C min^{-1} (figure 1). Transition temperatures below the T_m have been reported for PEG in the ranges -83 to -33°C and -10 to +40°C, corresponding to a glass transition (T_g) and to rotational or oscillatory movements of the molecules in crystalline regions about their helical axis[13]. Indeed, Lange et al[13] demonstrated two T_g values at -83 to -73°C and above -40°C designated as $T_{g(L)}$ and $T_{g(U)}$ respectively arising from amorphous phases free from restraints and under restraint by crystallites. The second order transition at ~ -50°C may therefore represent a T_g value. However the transition at 29° to 40°C may represent a T_α transition or an initial stage in melting of PEG which takes place over a 30°C range and may consist of three melting endotherms[13]. The lowest melting peak (T_{m_I}) is generally interpreted as a melting of a crystalline fraction formed by less stereo-regular fractions which had been rejected during primary

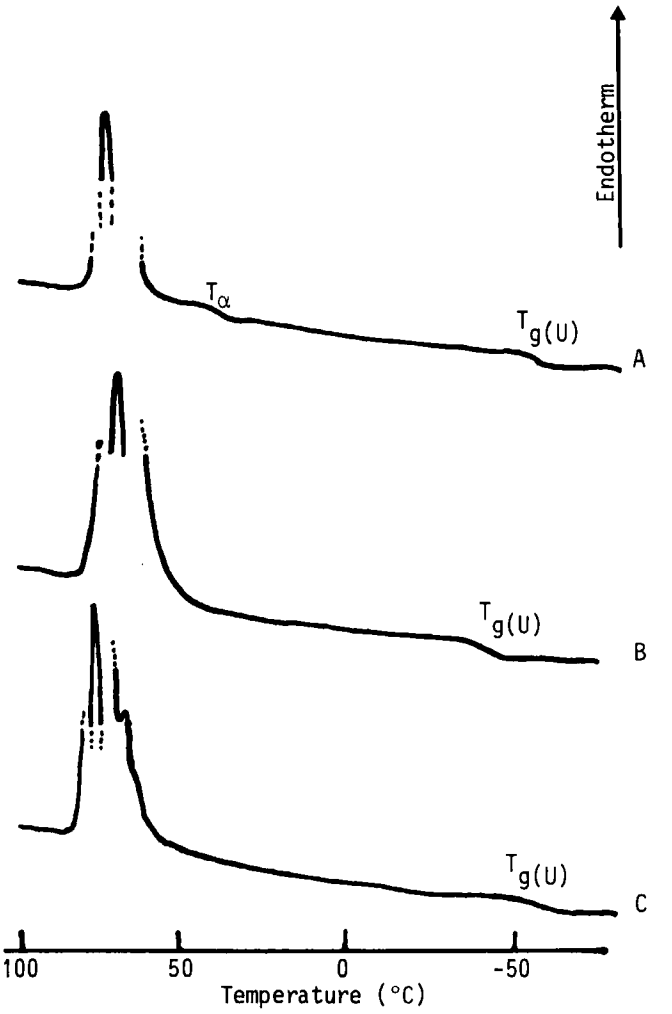


FIGURE 1

DTA Scans of PEG 6000

A. Untreated, 10° min^{-1}

B. 30 sec at 140°C, 10° min^{-1}

C. 30 sec at 115°C, 5° min^{-1}

crystallisation and formed defect crystals exhibiting a lower melting temperature. In this paper this endothermic change is described as a T_α transition. The final melting point of the polymer (64°C) probably corresponds to the third melting endotherm ($T_{m_{III}}$) corresponding to fusion of folded chain crystals[13]. The melting point for the perfectly crystalline polymer with fully linear (non-folded chains) has been estimated to be 75 ± 3°C[14] but at a molecular weight of 6000, PEG cystallises as folded polymer chains[15] resulting in the lower final melting point.

Fusion of PEG 6000 altered the appearance of the DTA scan although differences caused by the variation in the fusion temperature were negligible. The second order transition in the range -50 to -28°C apparently increased in strength (figure 1). This increase in $T_{g(U)}$ implies that fusion reduced the crystallinity of the polymer[13], the rapid crystallisation of the sample at 4°C probably leaving residual, amorphous non-crystalline PEG. The melting endotherm of the sample peaked at 64°C, although a broadening of the melting range occurred making the demarcation of the T_α transition impossible. However at the slower heating rate of 5°C min^{-1} a second endothermic peak at 57°C was also apparent (figure 1). This corresponds to the $T_{m_{II}}$ transition. Although the $T_{m_{II}}$ and $T_{m_{III}}$ transitions were shown[13] to correspond to melting of the fully extended-chain crystal and folded-chain crystal respectively the opposite interpretation has also been cited[15]. Nonetheless a heating rate of 5°C min^{-1} distinguished two separate PEG 6000 melting endotherms, only in the recently fused samples. No equivalent double melting was found in any of the solid-dispersion samples when scanned at 5°C min^{-1}.

Chloramphenicol-PEG 6000 Dispersions

Glassy chloramphenicol displayed T_g, T_c and T_m values respectively at 28, 76 and 152°C (figure 2). HSM showed that chloramphenicol recrystallised to broad plates. Melts containing

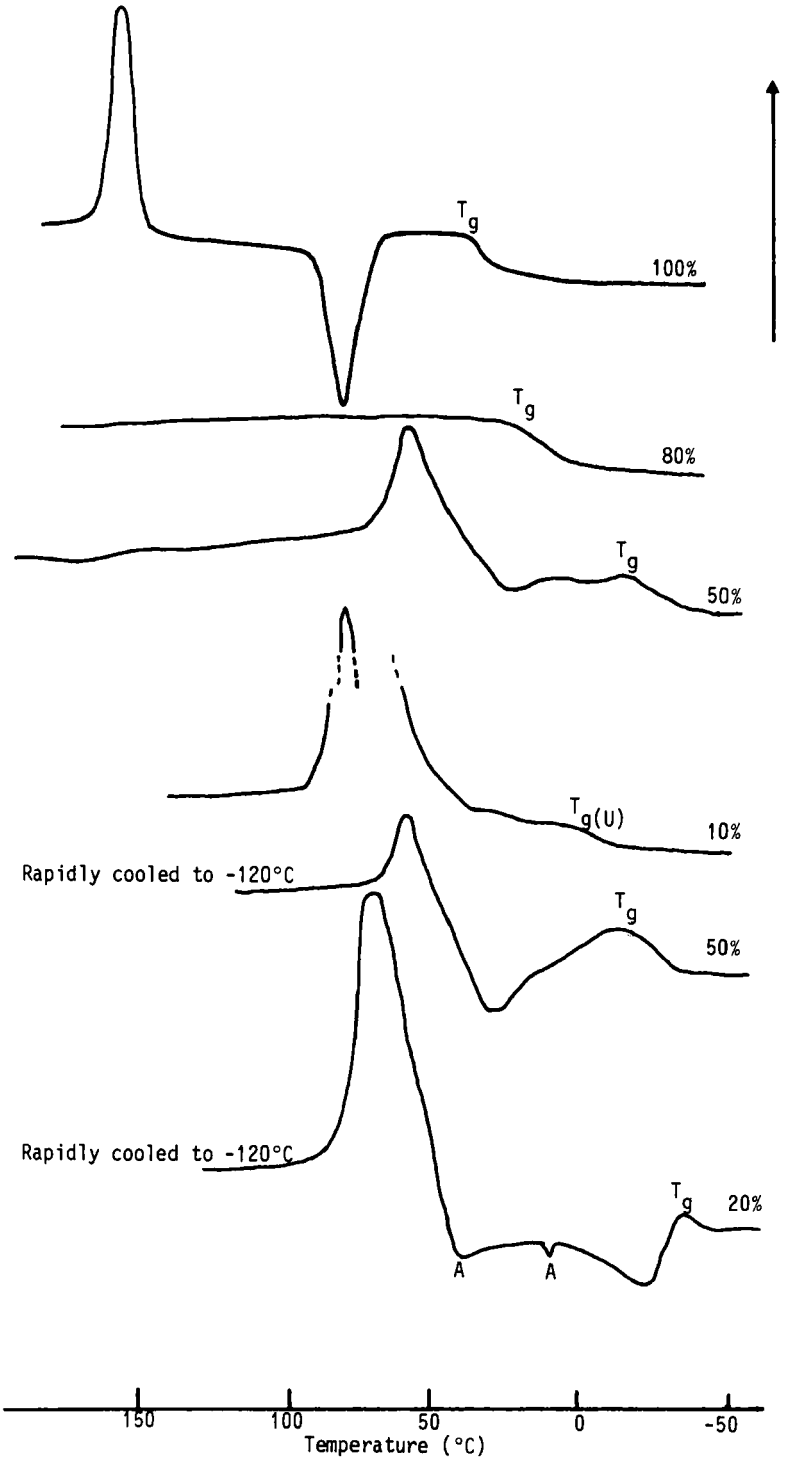


FIGURE 2

DTA Scans of Chloramphenicol-PEG 6000

(% = % drug, all 10° min^{-1})

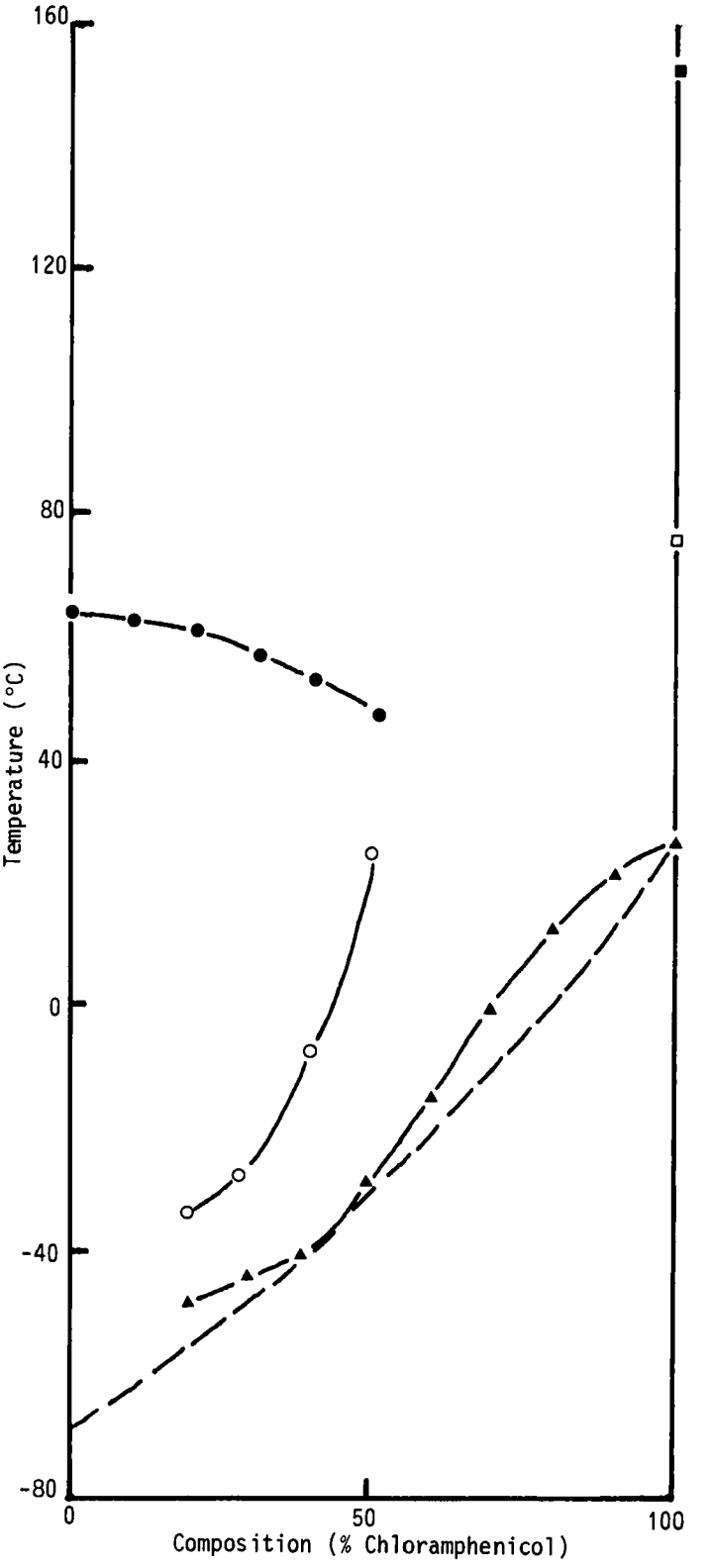
60-90% chloramphenicol solidified to glasses which had well-defined T_g values, but no other transitions. Melts containing $\leqslant$ 50 chloramphenicol displayed endotherms corresponding to the solidus line of a phase diagram (equivalent to PEG or eutectic component fusion) but were at least partially crystalline before analysis. Indeed samples containing 20 to 50% chloramphenicol displayed small exotherms before the melting endotherm. Samples containing 10-30% chloramphenicol displayed some evidence of a $T_{g(U)}$ value in the range -30 to -10°C.

Rapid cooling to -120°C enabled T_g determination in samples containing 20-60% chloramphenicol (figure 2). Crystallisation exotherms and PEG fusion endotherms were also apparent. The temperature differences between T_g and T_c values became less as the PEG content increased (figure 3). Thus for melts containing 50, 40 and 20% chloramphenicol these differences were 53, 32 and 14°C respectively. A heating rate of 5°C min^{-1} little altered the DTA scans.

The phase diagram (figure 3) provided no evidence of the eutectic composition. The lack of a melting curve corresponding to chloramphenicol indicated that PEG 6000 successfully prevented crystallisation of the drug, and the lack of a T_m (PEG) curve at compositions > 50% chloramphenicol indicated that the drug retarded PEG crystallisation. Indeed in preparations examined microscopically no drug crystallites were apparent at any composition.

Glutethimide-PEG 6000

Glassy glutethimide displayed only one transition corresponding to a T_g of 0°C (figure 4). T_g values were obtained in samples cooled to 4°C and containing 50 to 90% glutethimide. The presence of recrystallisation exotherms in the range 50-80% glutethimide and fusion endotherms corresponding to T_m (PEG) in the range 10-80% glutethimide implies a failure of glutethimide to



retard the crystallisation of PEG. Endothermic baseline drifts at ~ -25°C occurred in melts containing < 40% glutethimide and were attributed to $T_{g(U)}$ transitions.

Prior cooling to -120°C allowed determination of T_g values in samples containing 30-90% glutethimide and T_c (PEG) values in samples containing 30-70% drug (figures 4,5). A heating rate of 5°C min^{-1} little changed the DTA traces. The phase diagram (figure 5) showed no eutectic. However, Ford[16] has shown that the eutectic contained 32% glutethimide and that PEG 6000 generally showed a double melting endotherm across the phase diagram. However the sample was 24 hours old compared with the freshly-prepared samples in this study. This confirms the importance of the age of PEG samples in DTA interpretation[17] and shows that ageing/annealing may produce two crystal forms of PEG 6000.

Griseofulvin-PEG 6000

Glassy griseofulvin showed DTA transitions corresponding to a T_g at 89°C, a T_c at 149°C and a T_m at 222°C at a heating rate of 10°C min^{-1}. T_g values were observed in melts containing 40-100% griseofulvin when cooled to 4°C. Additionally crystallisation of griseofulvin was apparent with a T_c of 97-115°C in melts

FIGURE 3

Phase Diagram of Chloramphenicol-PEG 6000

KEY

● : PEG fusion endotherm

○ : PEG recrystallisation exotherm

■ : Drug fusion endotherm

□ : Drug recrystallisation exotherm

▲ : T_g values

Broken line: predicted T_g values

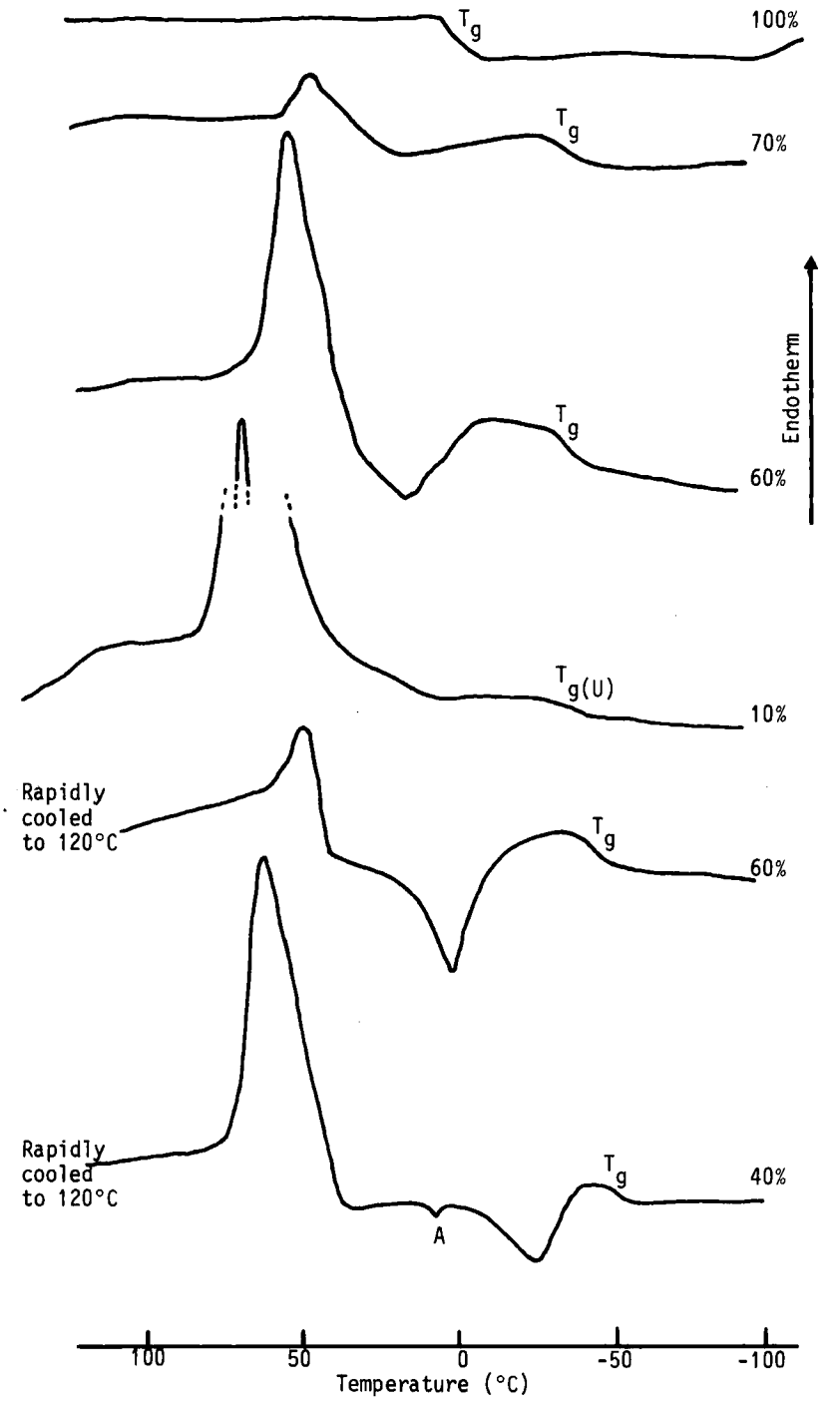


FIGURE 4

DTA Scans of Glutethimide-PEG 6000

(% = % drug, all 10° min^{-1})

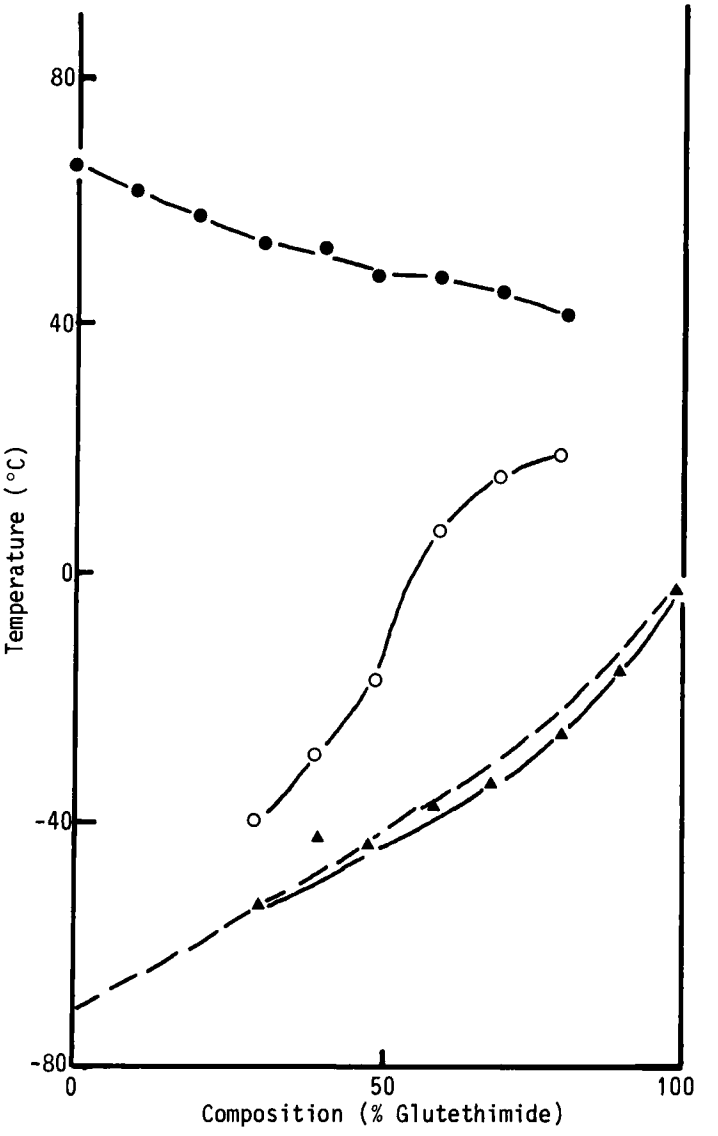


FIGURE 5

Phase Diagram of Glutethimide-PEG 6000

(Key: As Figure 3)

containing 40 to 90% drug. Further recrystallisation, evidenced by a second exotherm, appeared at 172-183°C before the T_m (drug) was obtained (figures 6,7). HSM studies revealed that at the lower recrystallisation temperature small crystal rosettes formed at nucleation sites and gradually formed small needles and plates. At temperatures in excess of ~ 120°C slow complete transformation to broad plates and needles occurred indicating polymorphic conversion. DTA scans revealed that PEG recrystallisation occurred in melts containing 40-60% drug, prior to drug recrystallisation. Melts containing < 40% griseofulvin had at least partially recrystallised before analysis and melts containing ⩽ 50% griseofulvin showed endotherms equivalent to PEG fusion.

Rapid cooling to -120°C allowed determination of T_g values in the range 20-90% griseofulvin (figure 7). PEG recrystallisation occurred in melts in the range 20-60% griseofulvin. A heating rate of 5°C min^{-1} little altered the DTA traces.

The phase diagram (figure 7) indicates that PEG poorly prevented the recrystallisation of griseofulvin. However, the drug retarded PEG crystallisation since no PEG endotherms were apparent at drug concentrations in excess of 60%. Chiou[7] used X-ray diffraction to analyse griseofulvin-PEG 6000 dispersions and reported that DTA of this system indeed displayed an exothermic transition peak below the melting point.

Indomethacin-PEG 6000

The DSC characteristics of this system have been established[18] showing a phase diagram with a eutectic containing 13% indomethacin with evidence of a solid solution of indomethacin in PEG 6000. No T_g values were reported although the system was glassy at high drug levels. DTA revealed that a T_g for indomethacin existed at 41°C although no subsequent transitions were apparent. At 10°C min^{-1} hearing rate T_g values were obtained

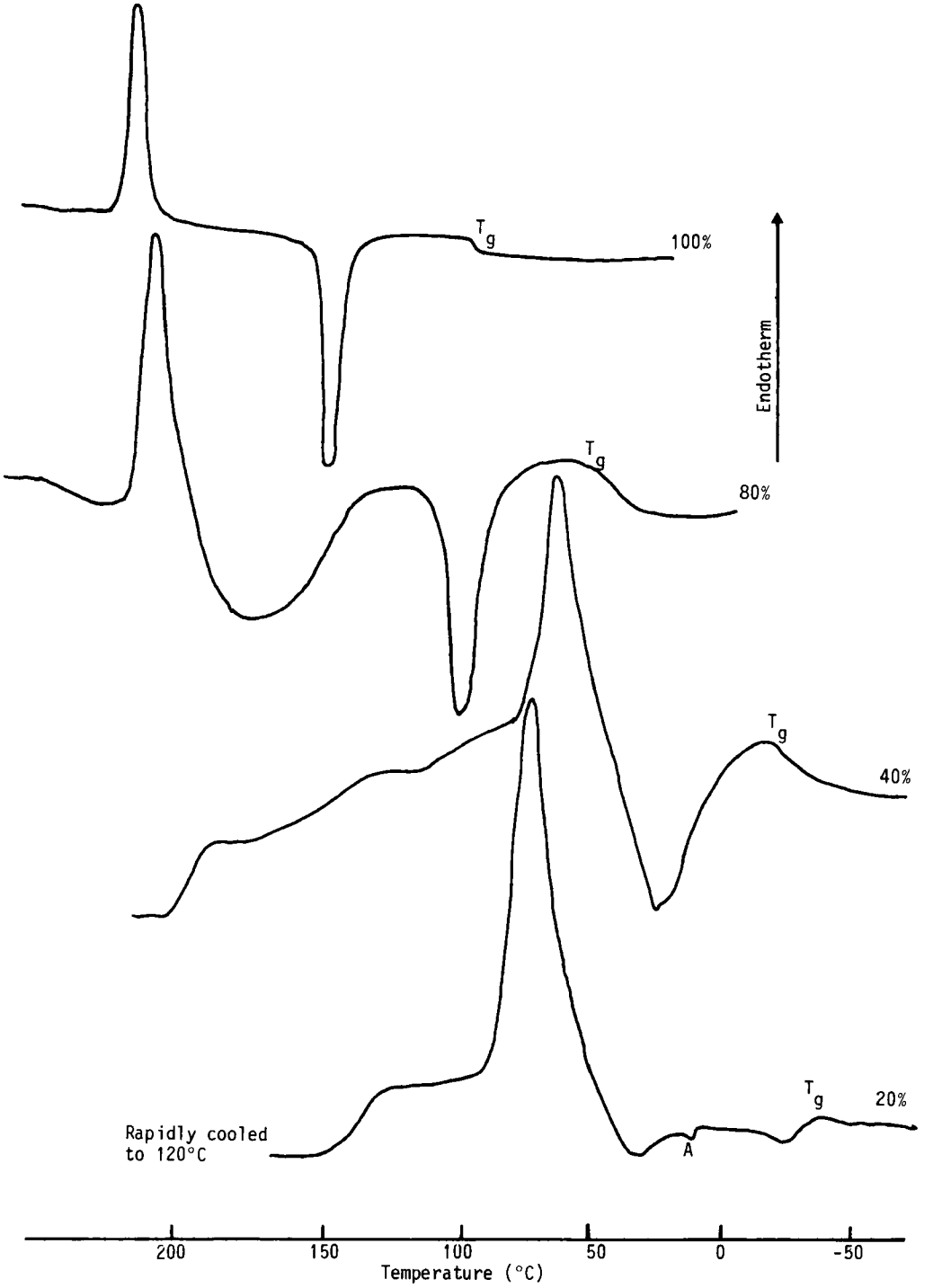


FIGURE 6

DTA Scans of Griseofulvin-PEG 6000

(% = & drug, all 10° min^{-1})

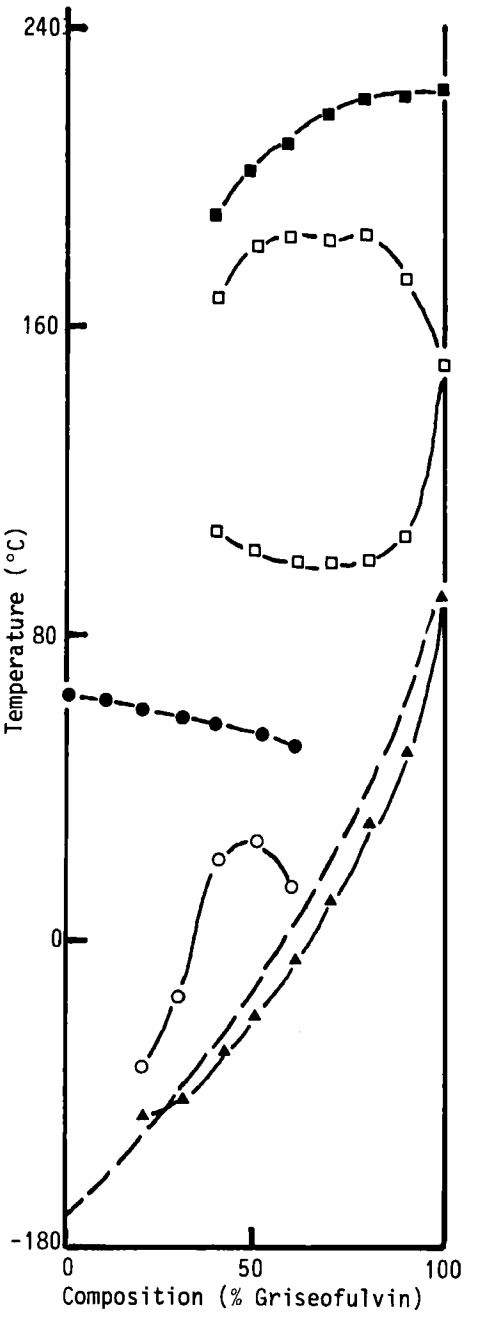


FIGURE 7

Phase Diagram of Griseofulvin-PEG 6000

(Key: As Figure 3)

in the range 40-100% indomethacin. Some PEG recrystallisation occurred in melts 50-60% indomethacin and PEG fusion endotherms occurred in melts containing ⩽ 60% indomethacin. Melts of composition ⩽ 40% indomethacin had recrystallised. Following rapid cooling to -120°C, T_g values were determined in melts (⩾ 20% indomethacin) (figures 8,9). Transitions (T_α) were apparent in melts containing 0-30% and cooled to 4°C. PEG appeared to inhibit indomethacin recrystallisation.

Heating at 5°C min^{-1} produced different DTA scan characteristics. For glassy indomethacin a T_g value at 43°C was followed by recrystallisation at 135°C and by two melting endotherms at 152 and 156°C. Indomethacin recrystallisation and fusion were apparent in melts containing 60-90% drug but only one fusion endotherm was noted. Glass transitions occurred in melts containing ⩾ 30% indomethacin and T_m (PEG) values in melts containing ⩽ 70% drug.

Paracetamol-PEG 6000

Glassy paracetamol displayed T_g, T_c and T_m values at 24, 74 and 171°C respectively (figure 10). T_g values were apparent in melts containing ⩾ 40% paracetamol. Some PEG recrystallisation occurred in the range 30 to 60% paracetamol, although melts containing ⩽ 40% paracetamol had at least partially crystallised before analysis. PEG fusion endotherms occurred in the range 0 to 60% paracetamol. Exotherms corresponding to T_c (paracetamol) and T_m (paracetamol) endotherms were present in melts containing ⩾ 60% paracetamol. Second order transitions, corresponding to $T_{g(U)}$, were apparent in recrystallised melts containing 10-30% drug at ~ -15°C. Rapid cooling to -120°C allowed T_g determination in melts containing ⩾ 20% paracetamol.

At a heating rate of 5°C min^{-1} paracetamol displayed T_g, T_c and T_m values at 26, 62 and 169°C. Melts containing ⩾ 50% paracetamol displayed exotherms corresponding to paracetamol

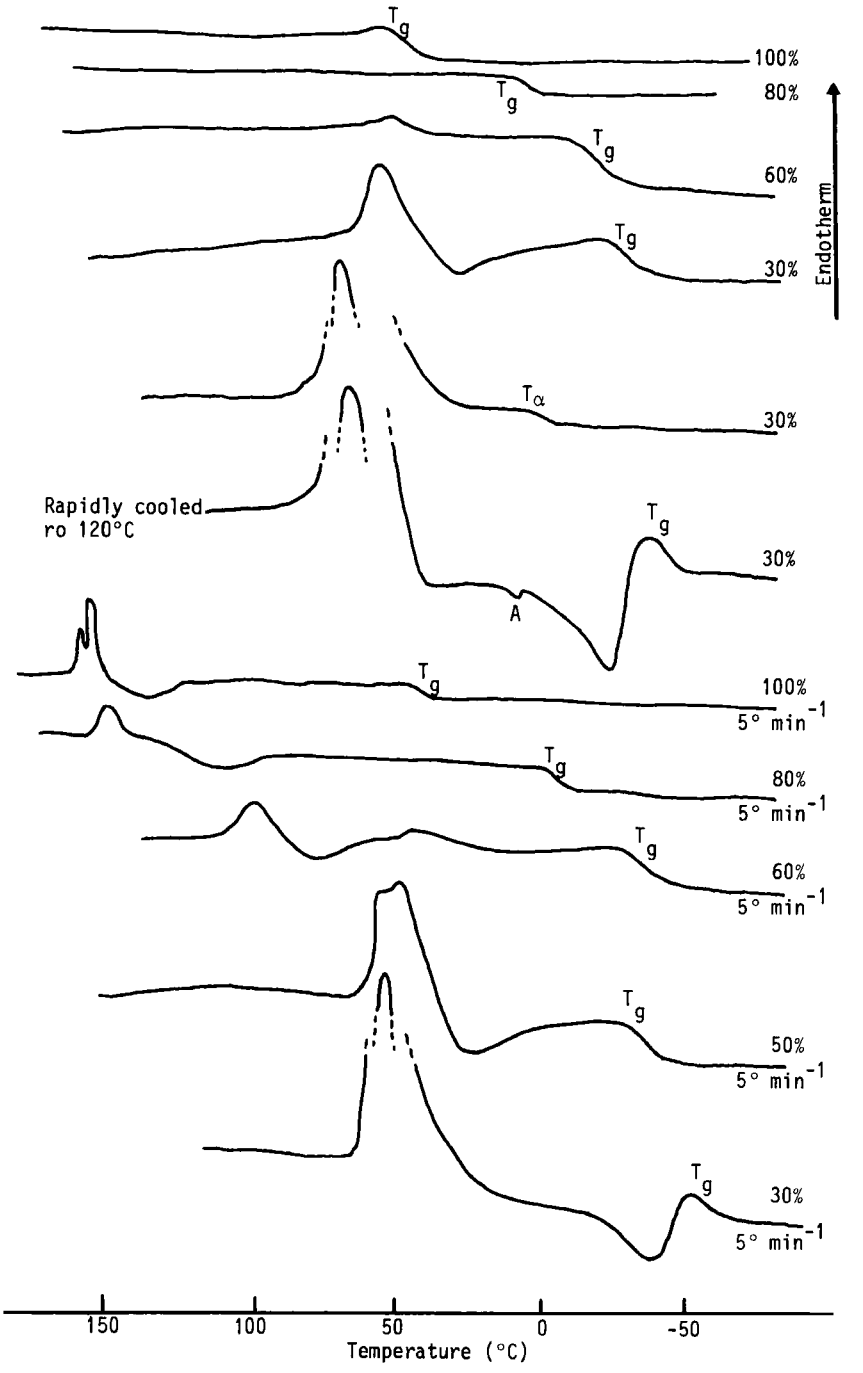


FIGURE 8

DTA Scans of Indomethacin-PEG 6000
(% = % drug, all 10° min^{-1} except
where stated.)

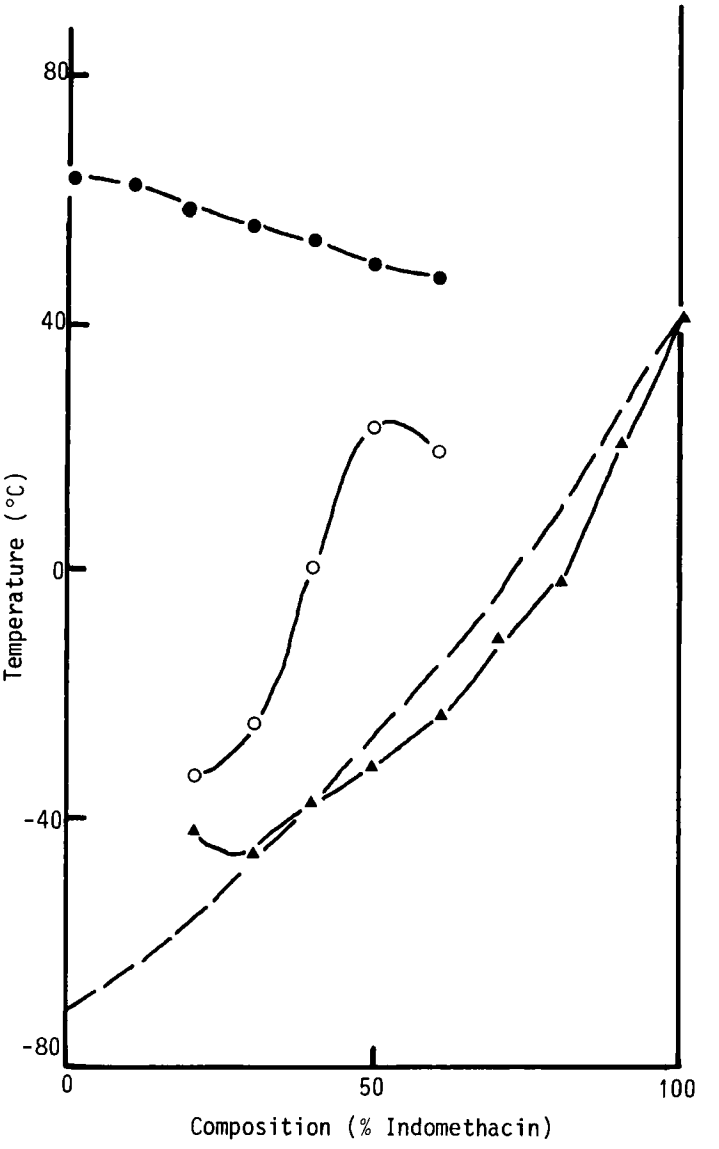


FIGURE 9

Phase Diagram of Indomethacin-PEG 6000

(Key: As Figure 3)

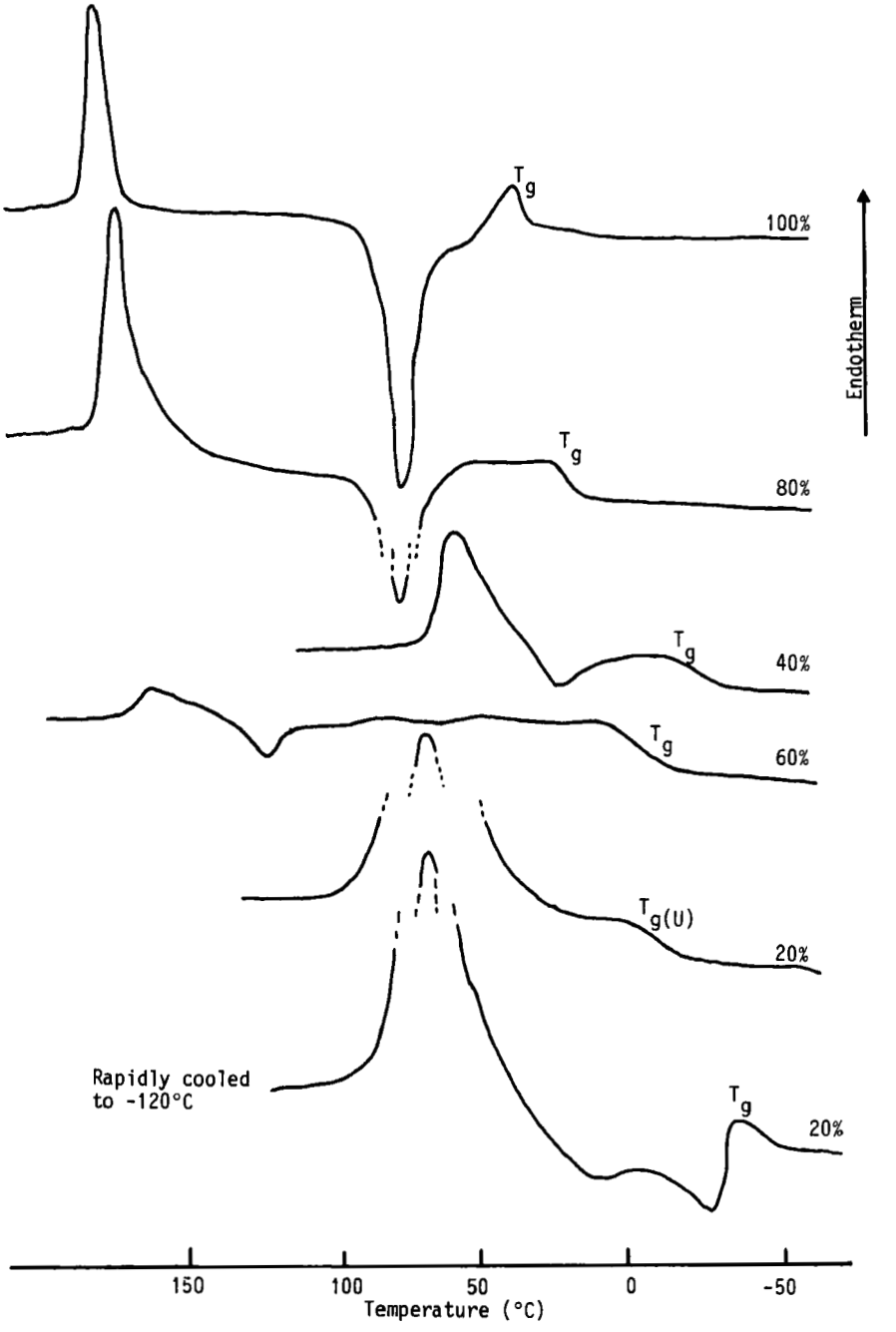


FIGURE 10
DTA Scans of Paracetamol-PEG 6000
(% = % drug; all 10° min^{-1})

recrystallisation. T_c values at this heating rate were 10-15°C lower than at 10°C min^{-1}.

The phase diagram (figure 11) indicated an intersection of the T_m (paracetamol) curve and T_c (paracetamol) curve at ~ 50% paracetamol. Similarly the T_g curve and the T_c (PEG) curve intersected at about 15% paracetamol. The inhibition of crystallisation of paracetamol by PEG was therefore not as great as displayed by indomethacin or glutethimide.

Phenacetin-PEG 6000

Phenacetin did not congeal to a glassy solid and therefore no T_g or T_c values were obtained. None of the phenacetin-PEG 6000 melts displayed a glass transition (figure 12). Endotherms in melts containing 0-90% phenacetin corresponding to PEG fusion and in melts containing 20-100% phenacetin corresponding to drug fusion were observed. Extrapolation of the liquidus line to the PEG (T_m) line (figure 13) gave an estimate of eutectic composition of ~ 8% phenacetin, compared to a literature value of 5%[5]. Melts containing up to 30% phenacetin displayed minor endothermic drifts at ~ 35°C and at -40 to -20°C (figure 12). These probably corresponded to T_α and $T_{g(U)}$ transitions respectively.

Phenylbutazone-PEG 6000

Although phenylbutazone did not display a T_g, the incorporation of PEG 6000 produced well defined glass transitions for melts containing 30-90% phenylbutazone and rapidly cooled to -120°C: therefore, the DTA scans showed considerable interference due to moisture making determination of $T_{g(U)}$ and T_α values impossible. Since phenylbutazone-PEG 6000 rapidly crystallised to a very hard solid[8] this system was not examined in melts cooled to 4°C. Strong recrystallisation exotherms were also apparent in the 30-90% phenylbutazone range, corresponding to PEG crystallisation, their peak temperatures reducing as the PEG content increased

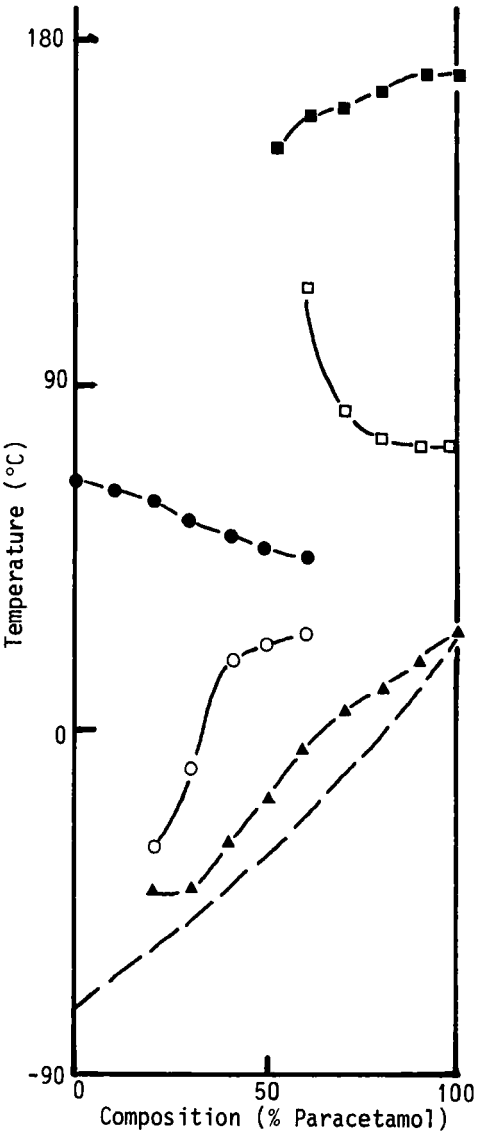


FIGURE 11

Phase Diagram of Paracetamol-PEG 6000

(Key: as Figure 3)

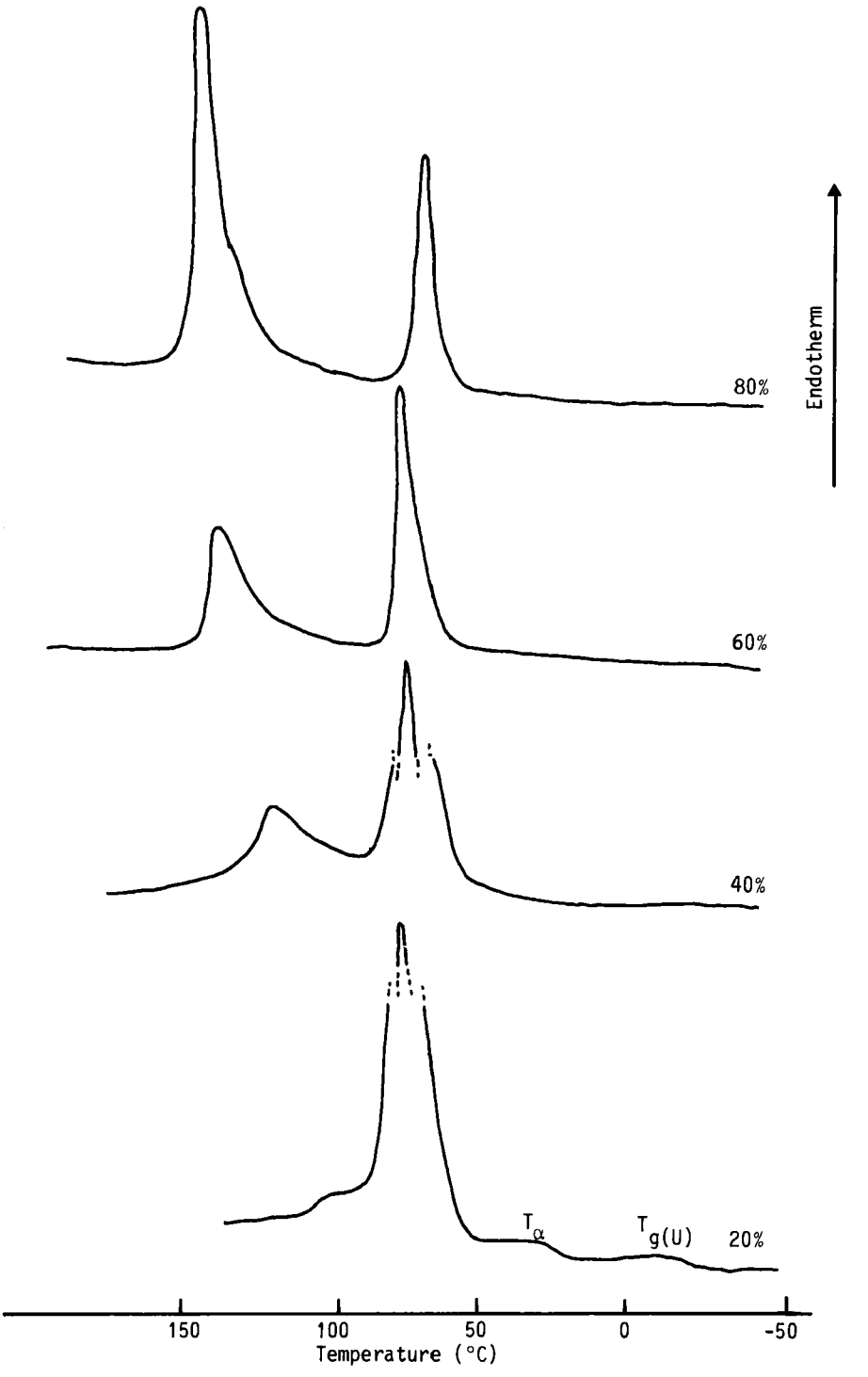


FIGURE 12

DTA Scans of Phenacetin-PEG 6000

(% = % drug, all 10° min^{-1})

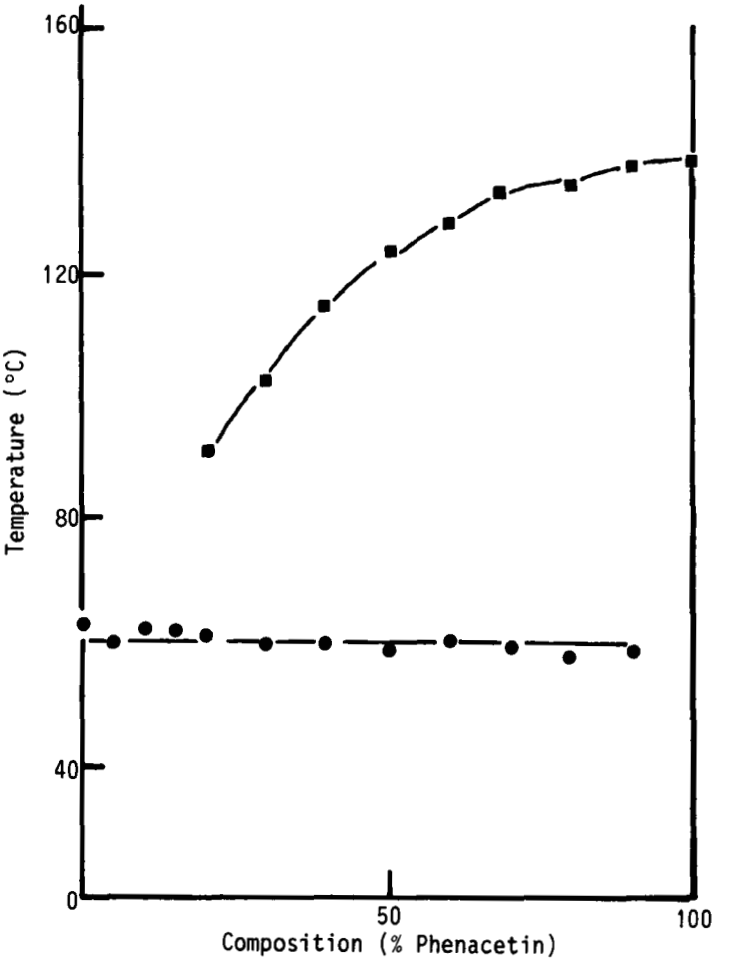


FIGURE 13
Phase Diagram of Phenacetin-PEG 6000
(Key: As Figure 3)

(figures 14,15). Additionally, exotherms at around 40°C, in the range 20-80% drug, probably corresponded to phenylbutazone recrystallisation. However, melts containing ⩽ 60% phenylbutazone had at least partially crystallised before analysis, despite the low cooling temperature. PEG endotherms were apparent in melts

containing 0 to 90% PEG 6000. Phenylbutazone, previously fused, displayed endotherms of approximately equal height, with peak temperatures of 98 and 108°C. A recrystallisation exotherm was not apparent between the two peaks (figure 14). For melts containing 10 and 20% PEG 6000 the peak heights were again approximately equal, but with 30% PEG present the second peak was considerably smaller and had vanished in the presence of 40% PEG. Melts containing $\leqslant$ 40% phenylbutazone did not display an endotherm equivalent to drug melting. HSM studies indicated that needle crystals formed at temperatures in excess of PEG fusion and that, on melting, they transformed to plate crystals. Hoelgaard and Moller[19] found that melting endotherms due to phenylbutazone were not apparent on DSC analysis of phenylbutazone-PEG 6000 melts in the range 30-50% phenylbutazone.

At a heating rate of 5°C min^{-1} similar values of T_g and T_m (PEG) were obtained. The T_c (PEG) values were some 6-8°C lower than those obtained at 10°C min^{-1}. Major differences occurred around the phenylbutazone fusion complex (figure 14). The value of the initial endotherm was ~ 8°C lower and followed by an exotherm obviously corresponding to recrystallisation before the second fusion endotherm. In melts containing 50% phenylbutazone the higher melting endotherm was small but as the phenylbutazone content increased, this endotherm became larger than the lower melting point peak. Obviously the faster heating rate did not allow nucleation and conversion to the higher melting form.

Previous studies have demonstrated that a eutectic exists containing 28% phenylbutazone[19] and that the system is highly crystalline[8]. Similar reports outling polymorphic conversion by different heating rates[20] and fusion[21] have been published.

General Discussion

The phase diagrams were, whenever possible, constructed from samples which were not crystalline before analysis. Thus at low

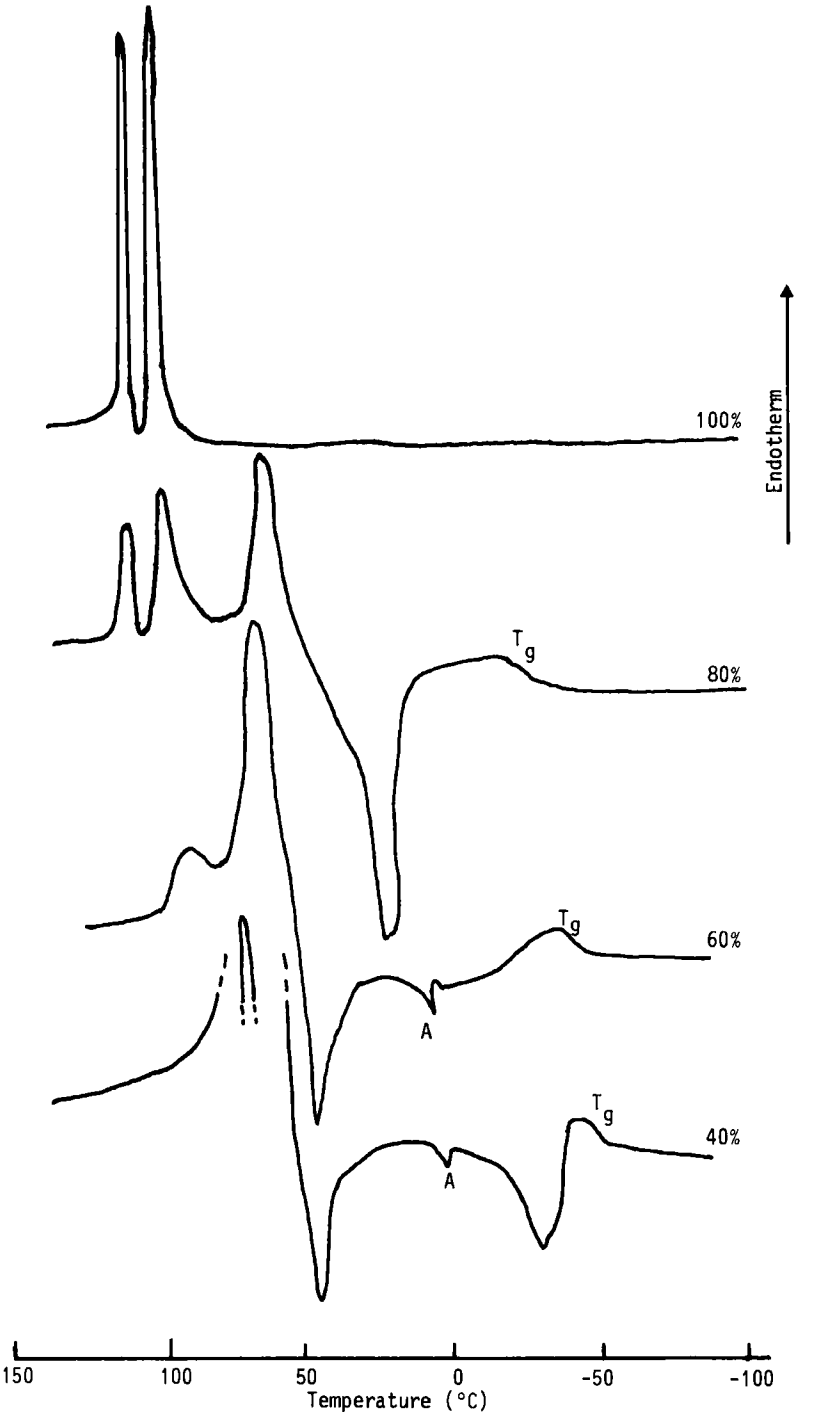


FIGURE 14A

DTA Scans of Phenylbutzone-PEG 6000
(% = % drug; all 10° min^{-1} and rapidly cooled to -120°C)

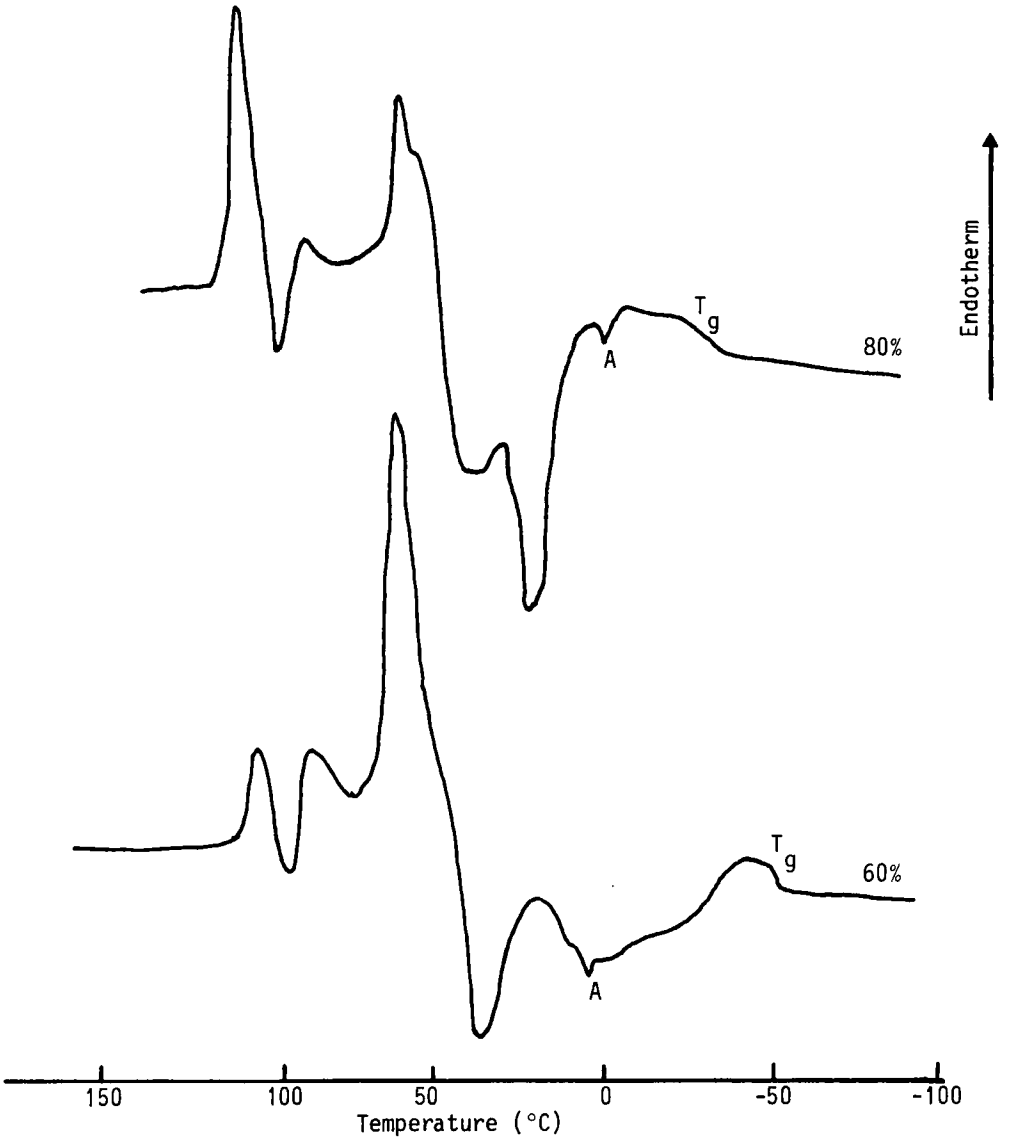


FIGURE 14B

DTA Scans of Phenylbutazone-PEG 6000

(% = % drug; all 5° min^{-1} and rapidly cooled to -120°C)

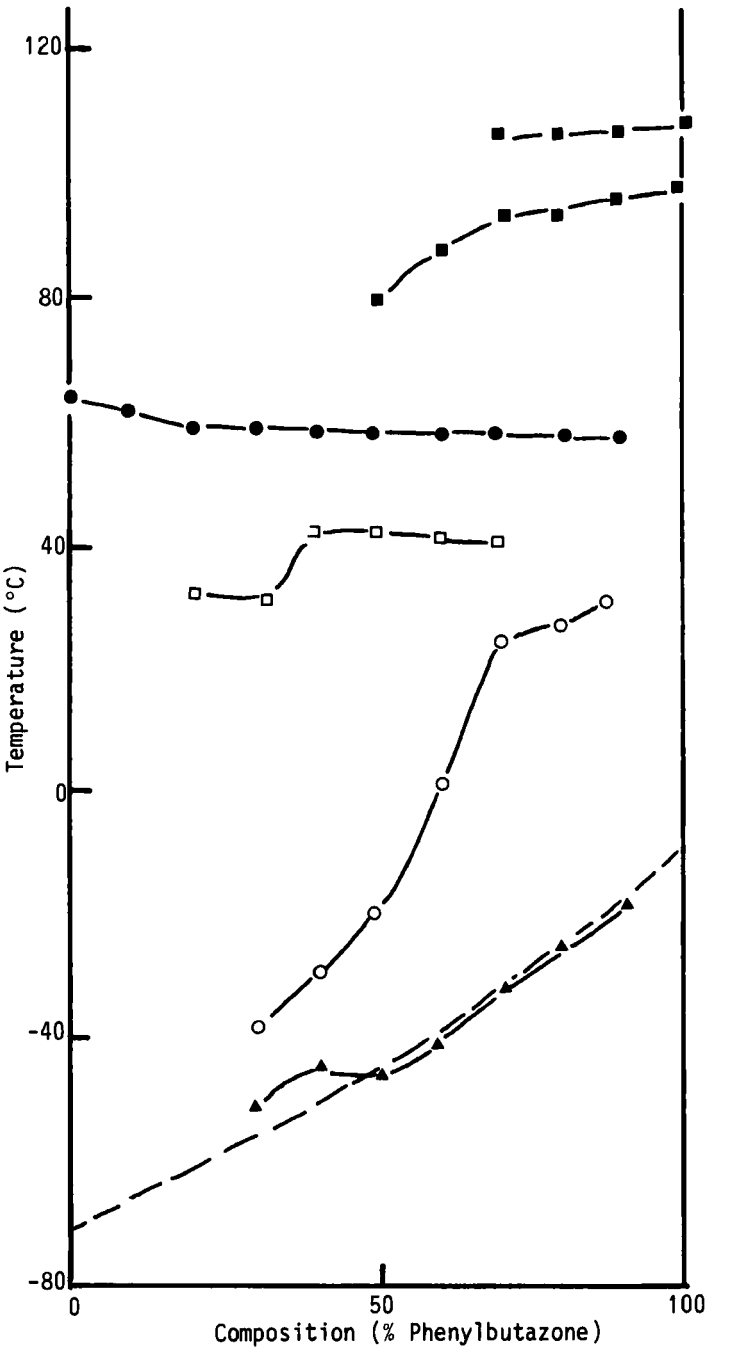


FIGURE 15
Phase Diagram of Phenylbutazone-PEG 6000
(Key: As Figure 3)

drug levels data from samples rapidly cooled to -120°C were used. The diagrams provide several indications of the dissolution potential of solid dispersions and possible ageing problems. Such criteria include (a) the composition range over which PEG endotherms are apparent, with or without being superceded by PEG recrystallisation exotherms, (b) the composition range over which drug melting endotherms are apparent, with or without prior drug crystallisation exotherms and (c) the position and extent of the range over which the glass transition temperatures occurred. The mechanisms of increased dissolution rates from solid dispersions have been discussed[1] and related to conventional phase diagrams. Thus systems which display eutectic formation with concomitant particle size reduction of the drug, solid solutions and amorphous or glassy solids possess the potential for increased dissolution rates. Thus fast release is regarded as occurring from systems which entrap the drug in a molecular state[1] and ageing may be regarded as resulting from self association of the drugs and carriers in the solid state[22].

Loss of crystallinity in a system on preparation is therefore a measure of its potential to provide fast release and can be measured either as a function of drug or PEG crystallinity. On the basis of the absence of drug endotherms indomethacin and glutethimide would seem prime candidates for fast release systems because of their intrinsic ability to form glassy solids. Chloramphenicol (figure 2) formed a glass which was unstable to heat treatment. However, incorporation of PEG 6000 produced a stable glass which did not allow drug recrystallisation. Given that drug endotherms reflect an instability of amorphous structure and the greater the composition range over which drug fusion occurs, the poorer the stability of the amorphous state then approximate rankings would be indomethacin = glutethimide > chloramphenicol > phenylbutazone = paracetamol > griseofulvin > phenacetin. This ranking however bears little correlation to drug

dissolution rates[9] where phenylbutazone was a poor performer having an optimum dissolution rate in dispersions containing 2% drug whereas paracetamol showed an optimum composition at > 15%.

More realistically the phase diagrams may be examined also for drug crystallisation exotherms prior to drug melting endotherms. On this basis glutethimide and indomethacin systems rank best since neither recrystallisation nor drug fusion was apparent (figures 5,9). Equally because the phenacetin system had already recrystallised before analysis it ranked poorly. The phenylbutazone system must rank lowly because drug recrystallisation occurred in the exotherms prior to PEG recrystallisation (figures 14,15). Given that the smaller the range over which drug recrystallisation occurs, the greater the protection exerted by PEG against drug recrystallisation the remaining systems from table 2 would rank (in order of protection and ideally dissolution rates) as chloramphenicol > paracetamol > griseofulvin. In comparison with previous results both phenylbutazone and phenacetin had relatively low optima at 2 and 5% drug content respectively[9] and indomethacin a high optima at near 15%[4,9]. However the optimum for glutethimide is difficult to predict due to irreproducible dissolution rates for this system at drug contents > 10%[9,16]. The results however based on recrystallisation of drugs do not fully explain the high optimum of the paracetamol-PEG 6000 system[9].

It is assumed that for a solid dispersion to provide fast release over a large composition range retardation of carrier crystallinity must also occur[8]. Thus table 2 may also be used to examine PEG fusion when ideally endotherms should occur only at high PEG content to indicate a potentially good dispersion. Using these criteria the systems rank as chloramphenicol > griseofulvin = indomethacin = paracetamol > glutethimide > phenacetin = phenylbutazone. Thus this classification predicts the low optima of phenylbutazone and phenacetin and the relatively high optimum

TABLE 2

Composition ranges of solid dispersions throughout which drug fusion, drug recrystallisation, PEG fusion, PEG recrystallisation and glass transition temperatures were recorded.

	Composition Ranges (% Drug)				
Drug	Drug Fusion (Endotherm)	Drug Recrystallisation (Exotherm)	PEG Fusion	PEG recrystallisation	Glass Transition Temperature (T_g)
Chloramphenicol	100	100	0-50	20-50	20-100
Glutethimide	-	-	0-80	30-80	30-100
Griseofulvin	40-100	40-100	0-60	20-60	20-100
Indomethacin	-	-	0-60	20-60	20-100
Paracetamol	50-100	60-100	0-60	20-60	20-100
Phenacetin	20-100	-	0-90	-	-
Phenylbutazone	50-100	-	0-90	30-90	30-90

of chloramphenicol, but not the high optima of paracetamol and indomethacin.

Similarly the recrystallisation ranges for PEG merely re-emphasise that the phenacetin system (figures 12,13) had crystallised prior to analysis and that the recrystallisation of PEG was not protected by either phenylbutazone or glutethimide. The others systems performed equivalently.

This technique of examining quench-cooled dispersions only predicts those dispersions which will provide increases in dissolution over a small range near to the 100% PEG level. Unsuitable drug candidates can therefore be predicted on the basis of the appearance of drug endotherms and exotherms at levels above and including 50% drug and by the presence of PEG endotherms throughout most of the phase diagram e.g. 0-80% for glutethimide and 0-90% for phenacetin and phenylbutazone.

There remains however the usefulness of these diagrams in the prediction of ageing problems for solid dispersions. Merckle[22] implied that ageing is due to self association of the drug and/or carrier within a dispersion. Some idea of the exent to which this interaction can occur may be studied from a knowledge of glass transitions throughout the composition range.

In polymeric systems, the T_g of a mixture of two miscible glass forming materials is given by the equation[12]:

$$\frac{1}{T_g} = \frac{W_a}{T_{g_a}} + \frac{W_b}{T_{g_b}} \qquad \text{——— equation 1}$$

where for this study W_a and W_b are the weight fractions of drug and PEG respectively and T_{g_a} and T_{g_b} are the T_g of drug and PEG respectively. This equation has been used to study the glass transition temperatures of citric acid mixtures with either benzoic acid or phenobarbitone[23]. The equation can be arranged to

$$\frac{1}{T_g} = \frac{W_a(T_{g_b} - T_{g_a})}{T_{g_a} T_{g_b}} + \frac{1}{T_{g_b}} \qquad \text{——— equation 2}$$

which predicts a straight line relationship between $\frac{1}{T_g}$ and W_a[12]. Figure 16 shows the relationships of reciprocal T_g and drug content for the six drugs which displayed glass transitions. The straight line relationship did not hold for the whole of the plots. T_g values of the pure drugs generally were lower than predicted. Linear regression of the straight line portions

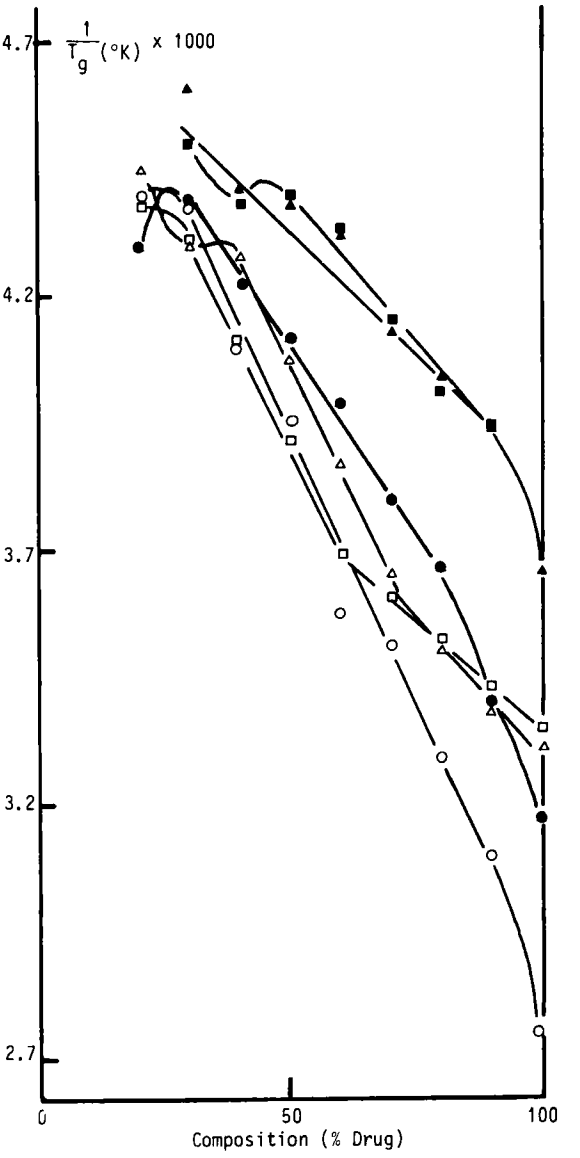


FIGURE 16

Graph Showing The Relationship Between Reciprocal T_g and Composition For Melts of PEG and

△ : Chloramphenicol

▲ : Glutethimide

○ : Griseofulvin

● : Indomethacin

□ : Paracetamol

■ : Phenylbutazone

predicted the value of T_g when W_a = 0, i.e. the value of T_{gb}, the glass transition of PEG. Estimates varied from -77.2°C to -65°C and gave a mean value of -70.6 ± 4.4°C. As indicated earlier in this paper PEG displays 2 or 3 glass transition temperatures. However the value corresponds to estimated values of -83 to -33°C[13] and to -60°C[24].

The T_g value of PEG 6000 was taken as -71°C and used with the T_g values of the drugs, by substitution into equation 1, to predict the influence of drug composition on T_g values. The value of phenylbutazone was not determined experimentally but was estimated from figure 15 to be -10°C. These estimated values of T_g are included in the phase diagrams and may be compared with the determined values. Determination of T_g values was impossible in systems containing 10% drug and difficult in those containing 20 or 30% due to rapid crystallisation of PEG, a phenomenon noted for PEG 4000[11]. Nonetheless comparison of the phase diagrams indicates four possible effects:

(a) No glass transition temperatures were determined (phenacetin-PEG 6000 (figure 13).

(b) The predicted transitions approximately overlapped the observed transitions (figures 15, phenylbutazone-PEG 6000).

(c) The predicted glass transitions were higher than the experimentally observed values. This occurred for griseofulvin-PEG 6000 (figure 7), indomethacin-PEG 6000 (figure 9) and glutethimide-PEG 6000 (figure 5).

(d) The observed glass transitions were higher than the predicted values. This corresponds to the phase diagrams incorporating chloramphenicol (figure 3) or paracetamol (figure 11).

Timko and Lordi[23] studied the phenobarbitone-citric acid system and their observed T_g values were lower than predicted. This was because the bonding between citric acid and phenobarbitone molecules was less than that between either citric

or phenobarbitone molecules alone. Summers[25] derived theoretical T_g values for various barbiturate-citric acid systems using the Gordon-Taylor equation[26] and showed that experimentally derived values were higher than predicted values due again to a stronger interaction between the two components than the arithmetic mean or the bond strengths of the individual components.

The ageing characteristics of several of the systems examined in this paper have been published elsewhere[10]. These can be summarised by quoting the % decrease in dissolution rate of dispersions containing 10% drug and stored at 25°C for 12 weeks. These decreases were 35% (chloramphenicol), 94% (glutethimide), 99% (griseofulvin), 97% (indomethacin), 12% (paracetamol) and 67% (phenacetin). Phenylbutazone ageing was not studied because the release rate for this system was only 1% of that predicted[9].

The severity of ageing can be related to the relationship between the estimated and observed values of T_g. The least affected systems contained paracetamol or chloramphenicol. Their phase diagrams showed that the observed T_g values were higher than anticipated, and indicates that the strength of interaction between the two components was stronger than the mean of the bond strengths in PEG, paracetamol or chloramphenicol alone. Such interactions would seem to protect the systems against ageing, possibly by retarding drug association[22]. Those systems which were greatly affected by age were indomethacin, griseofulvin and glutethimide. Their observed T_g values were lower than the predicted values. This indicates a greater attraction of the molecules for their own species rather than each other because the bonding between PEG and the drug molecules was less than that between PEG or the drugs alone. This would suggest an increase in self association of the drugs or PEG consequently making the system sensitive to age. The rapid crystallisation of the phenacetin-PEG 6000 and phenylbutazone-PEG systems probably lead to the intermediate ageing characteristics of the phenacetin

system[10] and low dissolution rates of the phenylbutazone-PEG 6000 dispersion[8,9].

CONCLUSIONS

Thermal analysis of freshly prepared, quench cooled PEG-6000-solid dispersions may be used to predict dispersions which are suitable for use as fast release systems. Crystallisation of PEG 6000 to produce PEG melting endotherms throughout the major part of the phase diagram (0 to > 70% drug) coupled with drug fusion endotherms in systems containing ⩾ 50% drug, indicates that the dissolution rate optimum will occur in dispersions at only low drug levels ($< \sim 5\%$). Ageing problems can be predicted from a knowledge of glass transition temperatures. Using the derived value for a T_g of PEG 6000 at -71°C, predicted T_g values were determined across the phase diagram and compared with experimentally observed values. When predicted T_g values are higher than the observed T_g values the system is expected to display ageing problems. Conversely when observed T_g values are higher than the predicted T_g values the system is anticipated to be less prone to ageing. The influence of ageing on $T_{g(U)}$, $T_{g(L)}$ and T_α transitions of PEG 6000 dispersions at low drug levels is currently under investigation.

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