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SOME PROPERTIES OF DIAZEPAM-POLYETHYLENE GLYCOL 6000 SOLID DISPERSIONS AND THEIR MODIFICATION IN THE PRESENCE OF STEARIC ACID OR POLYSORBATE 80.

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ABSTRACT

Physical mixtures and melts of diazepam and polyethylene glycol 6000 (PEG 6000) have been studied by Differential Scanning Calorimetry (DSC) and Differential Thermal Analysis (DTA). Problems were encountered in determining the precise position of the eutectic which contained <30% diazepam. Melts contained amorphous diazepam and, immediately after preparation, an unstable form of PEG 6000 which transformed on storage to a more stable form, probably folded crystals. Dissolution rates were determined by constant surface area methodology and were greatest in melts containing 15% diazepam. The inclusion of 1 or 5% polysorbate 80 or 1% stearic acid into the melts slightly increased the dissolution rates from dispersions containing 5, 10 or 15% diazepam but especially from dispersions containing 20% diazepam.

A limited 4-week ageing study indicated that age-induced changes depended on both the storage temperature and diazepam concentration. The inclusion of either stearic acid or polysorbate 80 appeared not to protect dissolution rates against ageing.

INTRODUCTION

Sekiguchi & Obi[1] were the first authors to suggest that solid dispersions be used to increase the bioavailability of poorly water soluble drugs by reducing their particle size. A number of hypotheses have been put forward concerning the mechanisms of increased dissolution rates of solid-dispersed drugs, including solubilization effects associated with the carrier[2], a reduction in the aggregation of hydrophobic drugs[3], an increase in wettability[1] and the solidification of the drug in a readily soluble metastable form[4]. Solid dispersions can be prepared by several techniques including fusion of the drug with the carrier and co-precipitation or co-evaporation from a common solvent or following the addition of molten carrier to a drug already dissolved in a suitable organic solvent. The dissolution rates of poorly water soluble drugs have been satisfactorily improved by solid dispersion in water-soluble carriers such as polyethylene glycol (PEG) or polyvinylpyrrolidone; in particular PEGs of various molecular weights have been widely employed to produce solid dispersions by the fusion method[5-8].

Straight line relationships exist between the drug content of the dispersion at low drug concentrations and the dissolution rates obtained from constant surface area discs[9-15]. The limits of drug composition (from zero drug content to that providing the maximum dissolution rate) corresponding to this linearity is drug dependent and represents unhindered, i.e., carrier controlled, dissolution from the dispersion[2,10,16]. Examples of some drug concentrations which have provided maximum release rates are 15% paracetamol, 10% indomethacin, 5% phenacetin and as low as 2% for phenylbutazone[14].

This paper examines the properties of diazepam-PEG 6000 solid dispersions prepared by the fusion method using thermal analysis to establish the phase equilibrium of the system and using dissolution rates determined from constant surface area discs to determine the content that provides the maximum dissolution rate. Already a limited number of studies on solid dispersions of diazepam in PEG 4000 have been published[17-19].

This paper further examines the effects induced by including low levels of either the surfactant polysorbate 80 or stearic acid into dispersions containing 5-20% diazepam. Dispersions utilising surfactants such as polyoxyethylene 40 stearate[20] or poloxamers[21] as carriers are recognized as possessing high dissolution rates partly because of their surface activity. It seems not unreasonable that the incorporation of low levels of surfactant into a solid dispersion will further modify the dissolution rates.

Additionally dissolution rates from solid dispersions using PEG 6000 as carrier are very prone to age-induced changes[12,15,16]. The results of a limited 4-week ageing study are also presented in order to evaluate whether the addition of either stearic acid or polysorbate 80 to the dispersion significantly modified the response to ageing.

MATERIALS & METHODS

Materials

Diazepam B.P., polysorbate 80 (Polyoxyethylene [20] sorbitan mono-oleate [Tween 80], B.D.H., U.K.), stearic acid (Specially pure; B.D.H., U.K.) and PEG 6000 (B.D.H., U.K.) were used without further purification.

Thermal Analysis

Differential Scanning Calorimetry (DSC)

DSC was performed using a Perkin Elmer Differential Scanning Calorimeter (DSC 1B) using aluminium sample pans and lids. Samples weighing ≈5mg were heated from 300K at a rate of 8°C min^{-1}

Preparation of physical mixtures. Diazepam and PEG 6000 were weighed and mixed in proportions varying from 0 to 100% diazepam by trituration.

Preparation of Melts. Sample pans containing weighed physical mixtures were heated at 140°C for 20 sec, cooled and stored at room temperature for 1 hour.

Preparation of Annealed Melts. Sample pans containing weighed physical mixtures were heated at 140°C for 20 secs, cooled and stored at 37°C for 7 days.

Differential Thermal Analysis

Samples (≈20mg) of the physical mixtures were weighed into the aluminium sample pans, melted at 140°C for 20 secs and cooled immediately at ≈4°C on a steel plate for 60 secs before transferring for analysis to a Stanton Redcroft Model 671 Differential Thermal Analyzer whose head had been pre-cooled to ≈4°C. The head and sample was further cooled to -70°C using liquid nitrogen and scans were recorded at a heating rate of 10°C min^{-1}

Preparation of Solid Dispersions

Mixtures of diazepam and PEG 6000 containing 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 30, 40 or 50% diazepam in PEG 6000 were heated at 140°C to effect mixing, this being the lowest temperature that fusion of diazepam readily took place. Diazepam was miscible with PEG 6000 in the molten state. Dispersions containing 5, 10, 15, or 20% diazepam and either 1 or 5% of polysorbate 80 or stearic acid were similarly prepared. Samples intended for dissolution from constant surface area discs were poured immediately into upturned aluminium vial covers (2cm internal diameter) so that an excess existed[9]. Immediately before a dissolution rate measurement the excess was sliced away with a razor blade to produce a flat surface.

Constant Surface Area Dissolution Studies

One hour after the samples had been prepared, dissolution rate measurements were performed in duplicate by the method of

Dubois & Ford[14] using a modified USP dissolution apparatus with flow through facilities [Copley Computerized Dissolution System series 8000]. Dissolution rates were determined at least in duplicate for each composition. Diazepam levels were monitored at 260nm. Discs were placed 3cm from the bottom of the flask and rotated at 100rev min^{-1} in 1000ml distilled water at 37°C. Dissolution rates (mg min^{-1}) were calculated by linear regression from the data provided by the apparently linear segments of the dissolution profiles.

Ageing Studies

Selected solid dispersions were stored for 4 weeks at 4, 25 and 37°C to assess the stability of their dissolution rates to ageing.

RESULTS AND DISCUSSION

Thermal Analysis Studies

Fig 1 shows DSC scans of the physical mixtures. Throughout the whole composition range endotherms corresponding to the solidus (melting of PEG 6000) were present and characterized by an onset tempterature (T_o) and a peak melting temperature (T_m). The melting endotherms corresponding to excess diazepam, characterized only by their T_m, were apparently present in mixes containing only in excess of 30% diazepam indicating that the eutectic composition was <30% diazepam. Mixes containing 20 and 30% diazepam displayed shallow broad endotherms at ≈80° and ≈106°C respectively that may have represented diazepam fusion. Physical mixes are not ideal for determining phase equilibria because of a slowness of the individual components to mix. The apparent phase equilibria from physical mixes is shown in fig 2. The precise position of the eutectic cannot be determined although both the T_o and T_m due to PEG decreased as the diazepam content was increased from 0 to 10% which is indicative of solid solutions.

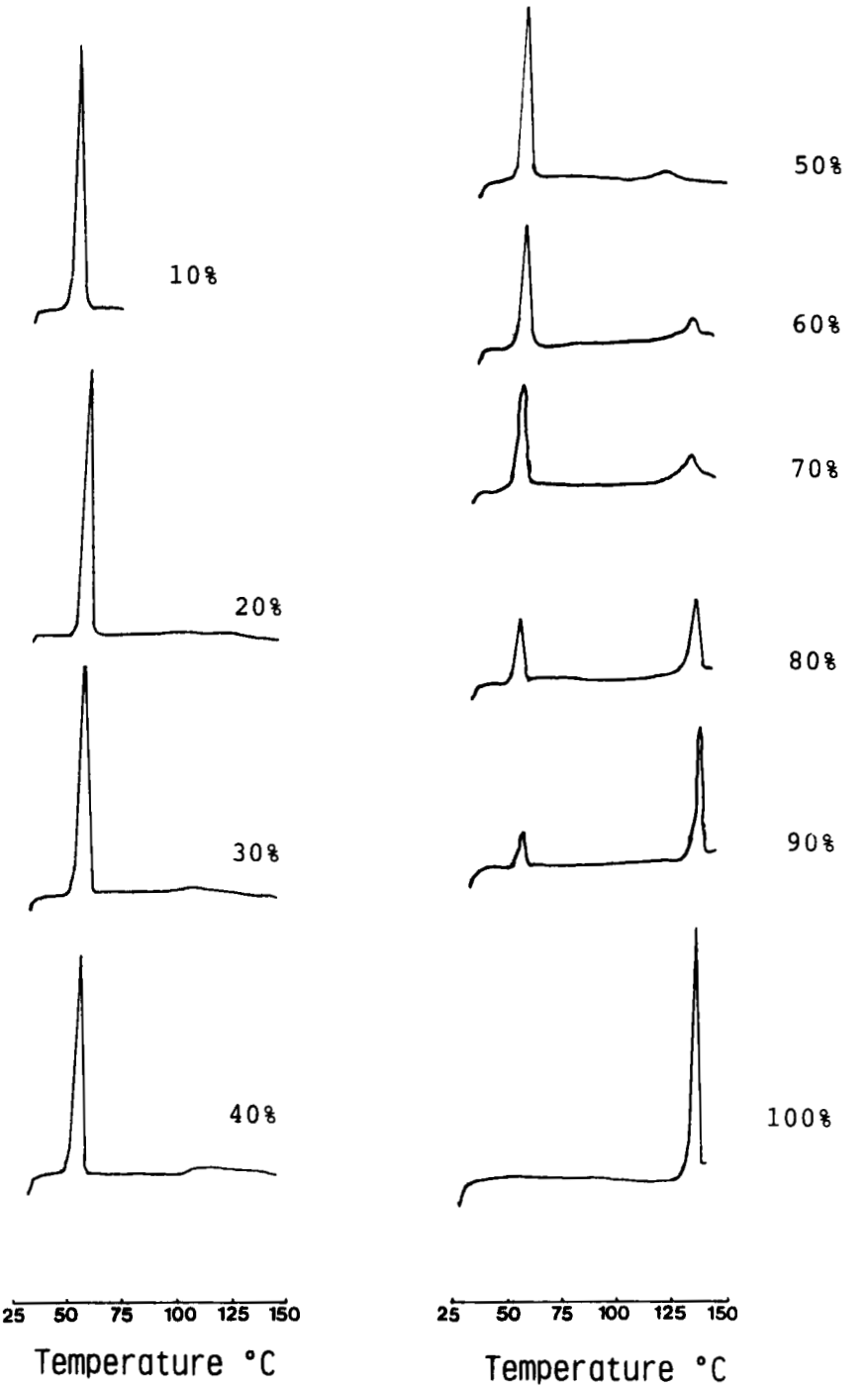

FIGURE 1. DSC scans of diazepam-PEG 6000 physical mixes obtained at 8° min^{-1}. (% refer to % diazepam)

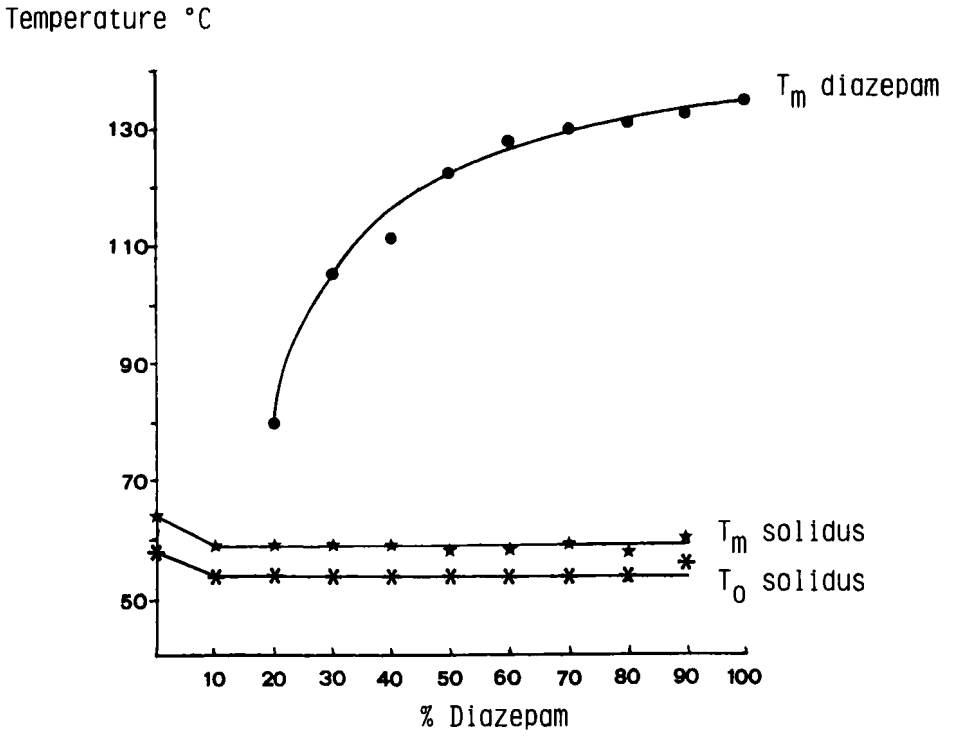

FIGURE 2. Phase diagram derived from D.S.C. scans of diazepam - PEG 6000 physical mixes obtained at 8° min^{-1}. (as Figure 1)

DSC of the fused samples produced scans (fig 3) somewhat different to those of physical mixes. The T_o of the solidus endotherm could not be detected when scanning commenced at 300K and is therefore omitted in fig 4. Fused PEG 6000 displayed a double melting endotherm with T_m at 57° and 62°C. Such phenomena have been recorded previously in studies using PEG 6000 as a carrier for glutethimide[13] and when freshly melted PEG was scanned at 5° but not 10°C min^{-1} [22]. The lower transition corresponds to the melting of fully extended-chain crystals and the higher transition to folded chain crystals[22,23]. Double melting points were detected in all melts containing from 0 to 50% diazepam

inclusive and endotherms corresponding to the solidus temperature in melts containing up to 80% diazepam. Indeed the lower peak developed at the expense of the higher melting peak indicating a preference for the immediate crystallization of the lower melting form at the expense of the higher melting form. As the diazepam content increased the size of the whole endothermic event associated with the melting of the PEG decreased in area to an extent greater than anticipated from the reduction in PEG content and its T_m gradually decreased (figs 3 & 4). Melting was inapparent in melts containing 90% diazepam. Fused and cooled diazepam displayed only a small endotherm with T_m at 134°C indicative of a high degree of amorphousness within its solidified melt. The phase diagram (fig 4) constructed from this DSC data therefore indicated that diazepam was probably present in the melts only as an amorphous form which did not recrystallize during warming at the heating rate employed. The decrease in T_m associated with the PEG moiety in the melts at low diazepam contents is associated with solid solution formation.

Because of the problems in establishing phase equilibria via thermal analysis of physical mixes due to slowness of mixing and of melts due to the amorphousness of diazepam, samples melted and subsequently annealed at 37°C, were also studied (fig 5). The lower melting point endotherm in PEG 6000 alone was reduced to a shoulder and the T_ms of the solidus endotherms in the presence of 10-90% diazepam were similar to those observed in physical mixes. A gradual exothermic drift was apparent which may have reflected some instability. Fusion of diazepam was inapparent in annealed melts containing <30% diazepam, barely recognizable in melts containing 30 and 40% diazepam and only readily apparent in melts containing ≥50% diazepam. Thus the phase diagram constructed from the annealed samples (fig 6) merely confirms that the eutectic occured at <30% diazepam. There was little evidence of solid solution formation and the similarity in melting data of the excess diazepam between figs 2 and 6 emphasizes a probable lack of polymorphic change.

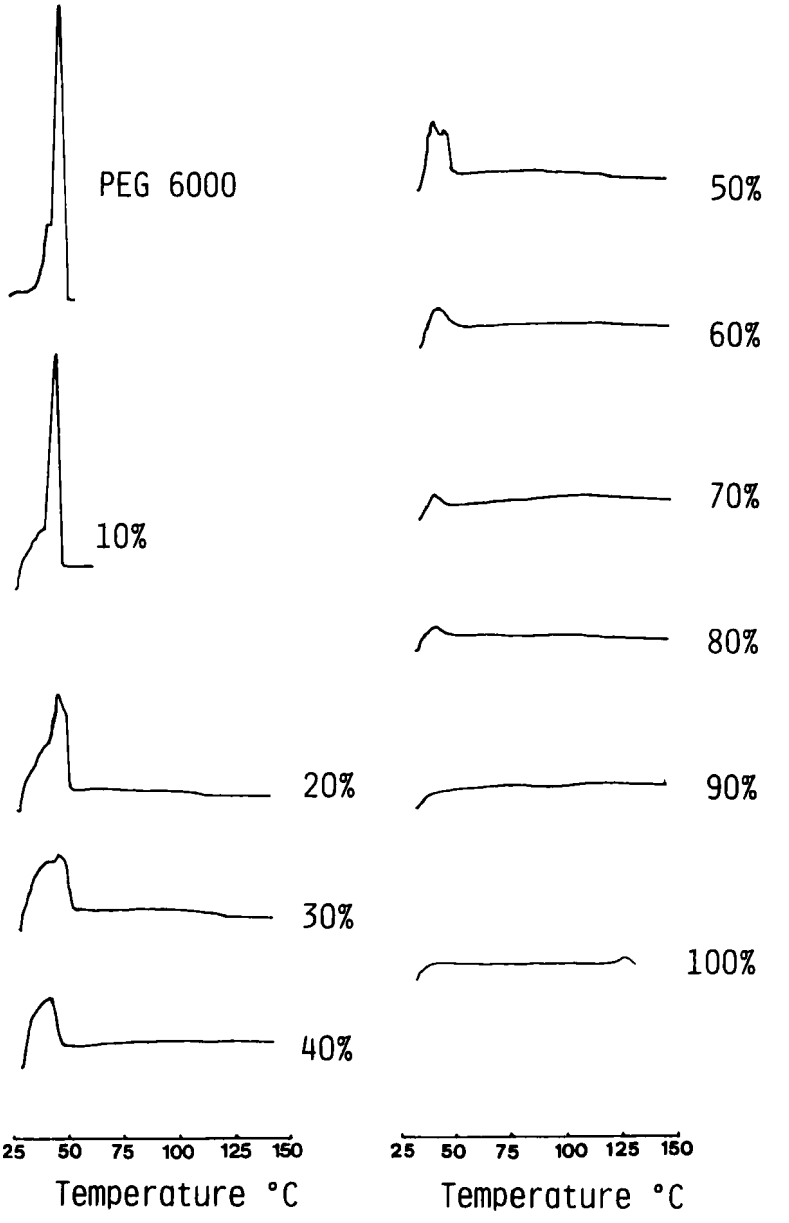

FIGURE 3. D.S.C. scans of diazepam - PEG 6000 melts following fusion at 140°C and storage at room temperature for 1 hour (% refer to % diazepam)

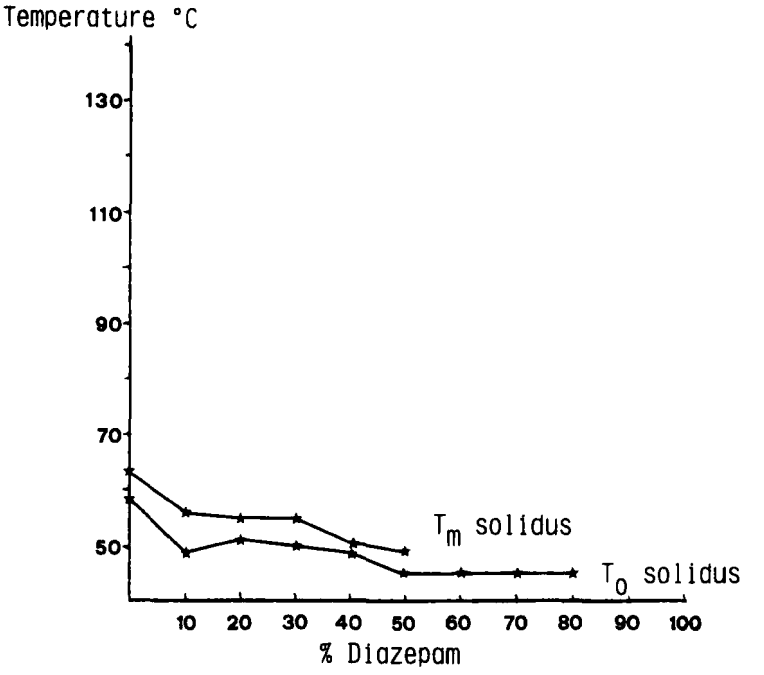

FIGURE 4. Phase diagram derived from D.S.C. scans of solidified diazepam - PEG 6000 melts obtained following fusion at 140°C and storage for 1 hour at room temperature (as Figure 3)

Sub-ambient DTA scans were used to assess the stability of the amorphous state by the predictive methods of Ford[22]. Problems were apparent in replicating scans containing high levels of diazepam possibly as a result of inconsistant nucleation. The DTA scans (fig 7) show that pure diazepam formed a physically unstable glass with a glass transition temperature of ≈25°C. The addition of 10% PEG 6000 somewhat stabilized the glass as evidenced by the lack of recrystallization exotherms. Small recrystallization exotherms were readilly apparent in melts containing 70-80% diazepam. At drug levels of ‹60% diazepam much recrystallization of PEG had occured before the samples were scanned although small

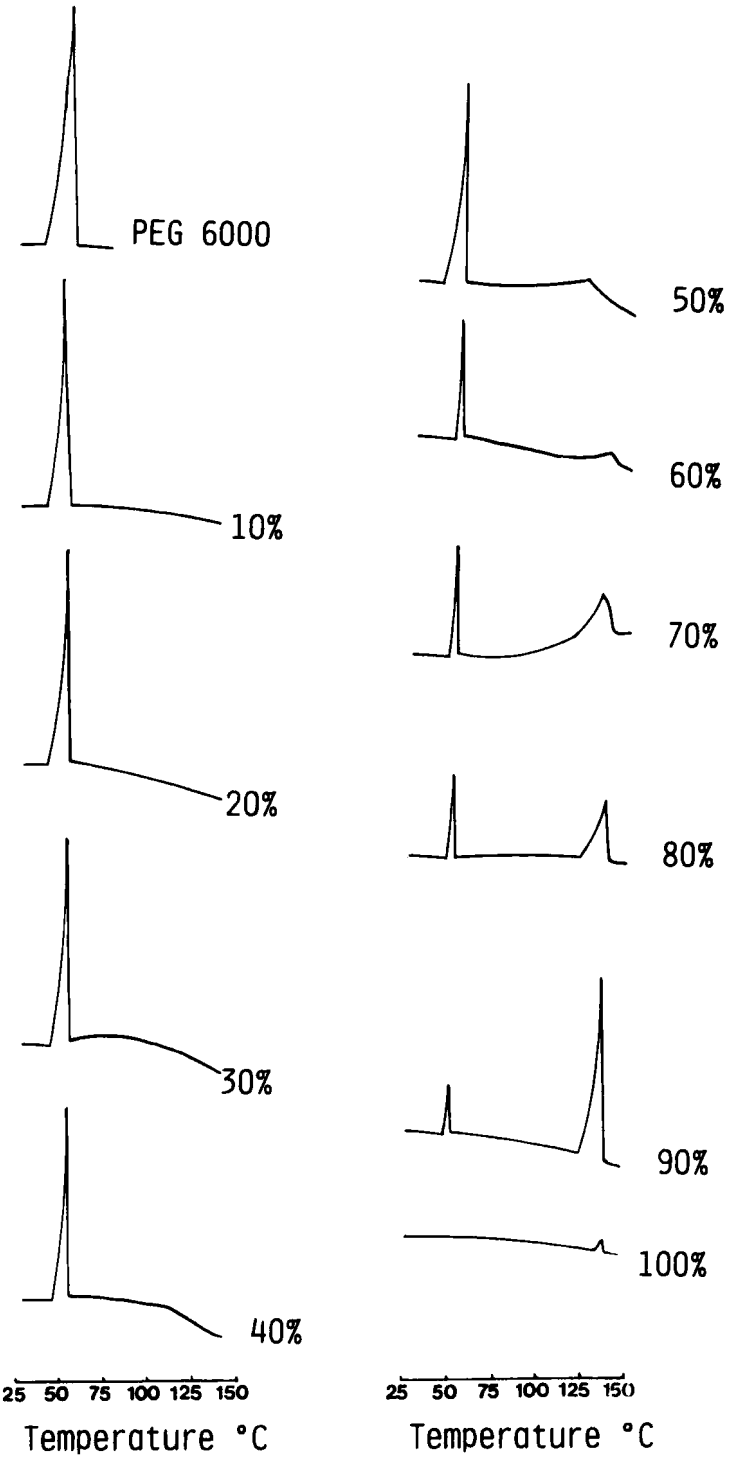

FIGURE 5. D.S.C. scans of diazepam - PEG 6000 melts following fusion at 140°C and annealing at 37°C for 7 days. (% refer to % diazepam)

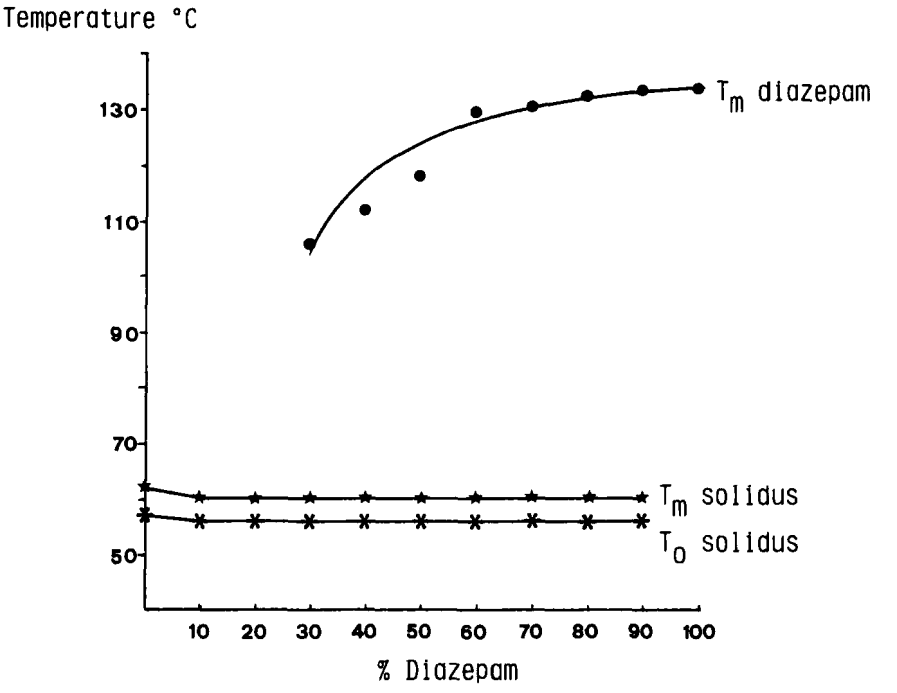

FIGURE 6. Phase diagram derived from D.S.C. scans of diazepam - PEG 6000 melts annealed at 37°C for 7 days (as Figure 5)

exotherms were apparent before the PEG endotherm in melts containing 40-60% diazepam. At low diazepam levels some secondary transitions occured prior to the melting of PEG as previously observed[22] in other PEG 6000 solid dispersions. Non-crystallinity, as measured in terms of either the crystallinity of the drug or that of the PEG, is a measure of potential for rapid dissolution. Ford[22] found that, following rapid chilling from the fusion temperature to 4°C, 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 occured over a limited range

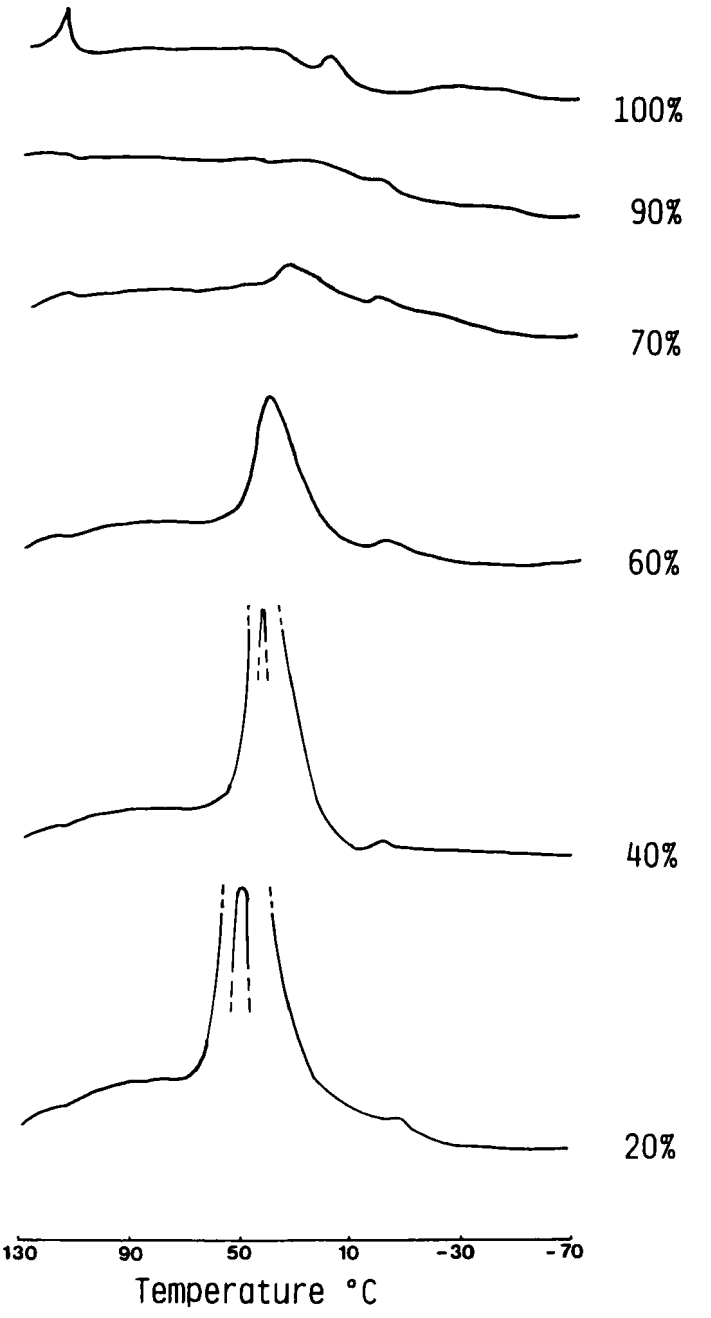

FIGURE 7. DTA scans of diazepam - PEG 6000 melts following fusion at 140°C, cooling to 4°C and then to -70°C obtained at 10°C. (% refer to % diazepam)

of low drug content. Lack of diazepam recrystallization in the diazepam-PEG 6000 system would therefore appear to favour its use as a solid dispersion system but evidence of metastable forms of PEG would indicate a potential problem with ageing. However since solid solution formation also may account for rapid release rates[3,10,16] there is a further potential for increased dissolution rates. Additionally the lack of any glass transition made impossible the prediction of ageing effects by predictive methods (22).

No precise value of the eutectic composition could be estimated because of lack of diazepam endotherms at <30% drug. Thus the eutectic was certainly <30% diazepam and may have been close to the value of 17% diazepam reported in the diazepam-PEG 4000 system[17,18]

Dissolution Rate Studies

The dissolution profiles (fig 8) were generally linear for melts containing ≤15% diazepam. The dispersion containing 15% diazepam had the fastest dissolution rate. Dispersions containing 5-15% diazepam were able to dissolve rapidly and form a supersaturated solution of the drug. Precipitation occured at ≈120mg ml^{-1}. As the diazepam content increased to >15% drug the profiles initially became biphasic (e.g., 20% diazepam; fig 8) and thereafter the dissolution rates considerably reduced. For instance, the dispersion containing 40% diazepam was less than a thirtieth that of the optimum at 15% (0.16 mg min^{-1} compared with 5.23 mg min^{-1}). The changes of dissolution rate with composition are indicated in fig 9, the dissolution rate-composition profile, which is similar to that obtained for other drug-PEG 6000 dispersions[10,13,14]. The initial, approximate straight line, relationship represents the range over which the PEG controlled the dissolution rates. The slope of this line was estimated as 0.476 (2.5 and 5% diazepam) and 0.397 mg min^{-1} $\%_{\langle drug \rangle}^{-1}$ (2.5, 5, and 7.5% diazepam) which compares with a weighted mean of 0.451 mg min^{-1} $\%_{\langle drug \rangle}^{-1}$ derived using the same experimental procedures

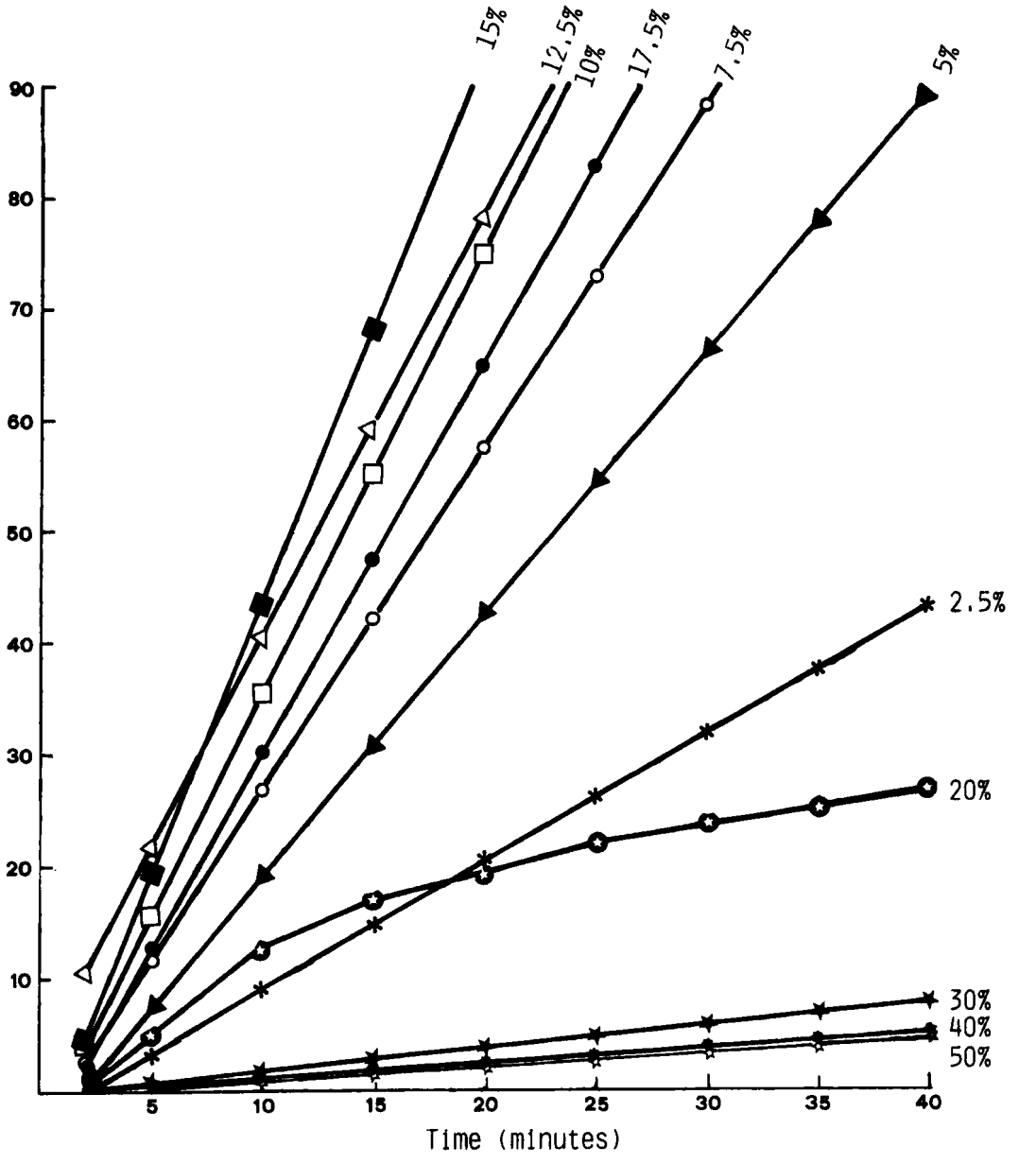

FIGURE 8. Dissolution profiles of some 1 hour old melts of diazepam-PEG 6000 into distilled water at 37°C (% refer to % diazepam)

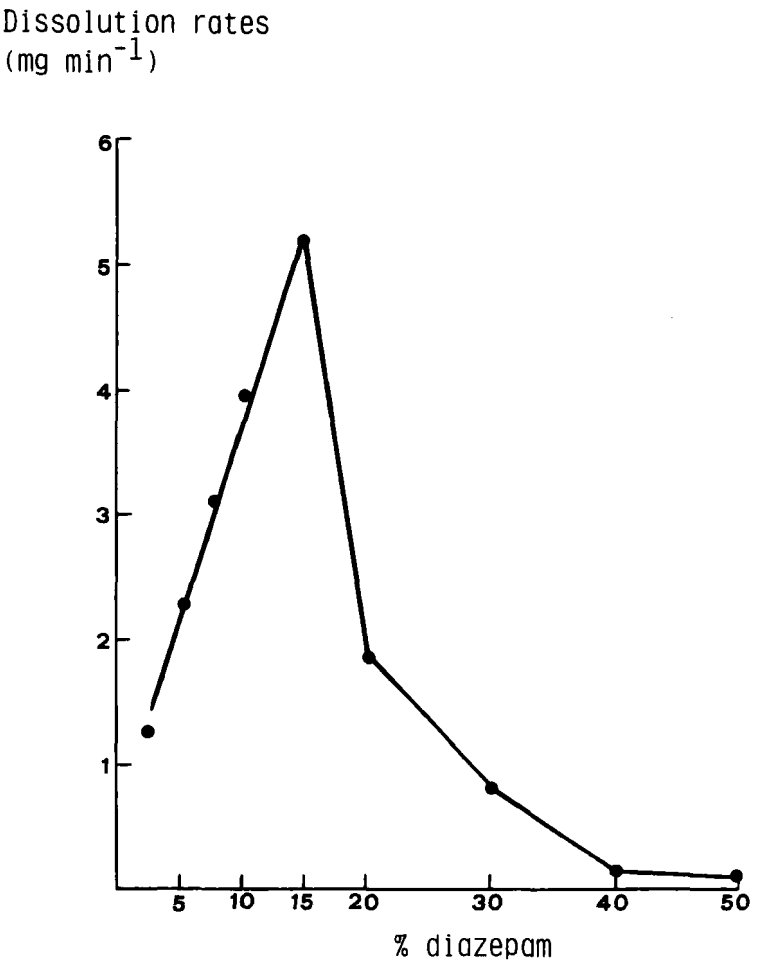

FIGURE 9. Dissolution rate-composition profile of diazepam-PEG 6000 resolidified melts showing the effect of composition (% diazepam) on the dissolution rates of diazepam (mg min^{-1})

from nine other drugs[14]. However it will be apparent from fig 9 that the relationship between dissolution rate and composition is only somewhat tenuously linear and that any calculated slopes are only approximations. This lack of linearity compared with other published systems may reflect a problem in adequately wetting the surface of the dissolving dispersion.

Results for diazepam-PEG 4000 dispersions[17] indicated that the dissolution rate of diazepam was increased following its solid dispersion in PEG 4000. Since dissolution of particulates was examined no estimate of the compostion giving the fastest dissolution rate was obtained. However the higher the proportion of PEG 4000 in the melt (90 and 95%) the greater the dissolution rate of diazepam[17]. The system containing 17% diazepam (the eutectic) did not display any great enhancement of dissolution[17].

Effect of added substances

In an attempt to extend the range over which unhindered dissolution from the dispersions occurs or to further increase dissolution rates low levels of either polysorbate 80 or stearic acid were incorporated into the dispersions. The rationale behind the use of stearic acid is that it will alter the crystalline structure of PEG 6000. Their eutectic composition contains <20% stearic acid which favored the existance of both melting forms of PEG[24]. This in turn might modify the dissolution rate of any solid dispersed drug. Polysorbate 80, as a surfactant, would obviously increase wetting of any released particles. Indeed Attia et al[19] found that the incorporation of either polysorbate 20 or polysorbate 80 into the dissolution media increased the dissolution rates of diazepam-PEG 4000 dispersions provided the surfactant was present above its critical micelle concentration. No differences were apparent beteween the DSC scans of the melts and physical mixes containg 1% or 5% polysorbate 80 and PEG alone.

Table 1 lists the dissolution rates obtained from solid dispersions containing polysorbate 80 or stearic acid. Linear dissolution profiles were obtained from dispersions containing 5-20% diazepam and 1 or 5% polysorbate 80. The surfactant increased the dissolution rates of dispersions containing 5, 10 and 15% diazepam somewhat marginally but large increases were noted in the dispersions containing 20% diazepam. The increases in rates probably reflect the wetting ability of polysorbate 80 and the vast increase achieved with the 20% dispersion reflects an

TABLE 1

The Effect of 1 or 5% Stearic Acid or 1 or 5% Polysorbate 80 on the Dissolution Rates of Various Diazepam- PEG 6000 Solid Dispersions.

% Diazepam	% Stearic Acid		% Polysorbate 80		No
	1%	5%	1%	5%	Additive
5%	2.00	0.67	2.30	2.48	2.35
10%	4.31	0.89	4.56	4.73	3.96
15%	7.66	1.40	7.08	6.84	5.23
20%	9.59	0.78	10.19	9.68	1.86

increase in the composition range over which dissolution is carrier-controlled. Fig 10, a dissolution rate-composition profile similar to fig 9, illustrates the influences of polysorbate 80 and stearic acid and emphasizes the extension of the range of carrier-controlled dissolution.

The two concentrations of polysorbate 80 gave very similar results. However differences were noted between the effects of 1% and 5% stearic acid on dissolution rates. At the lower concentration of 1%, stearic acid acted similarly to polysorbate 80. Whatever the mechanism therefore of this increased release following the incorporation of 1% stearic acid and, although still under investigation, some alteration in the PEG structure is at present favoured, it appears that only low levels of stearic acid are required to exert their effects.

The values of the slopes in fig 10 for melts containing 5-20% diazepam were 0.522, 0.523 and 0.473 mg min^{-1} $\%_{(drug)}^{-1}$ for dispersions containing 1% stearic acid, 1% polysorbate 80 and 5% polysorbate 80 respectively which compares with a weighted mean of 0.451 mg min^{-1} $\%_{(drug)}^{-1}$ derived previously[14]. This almost certainly corresponds to an improvemnt in the wetting of the dissolving dispersion.

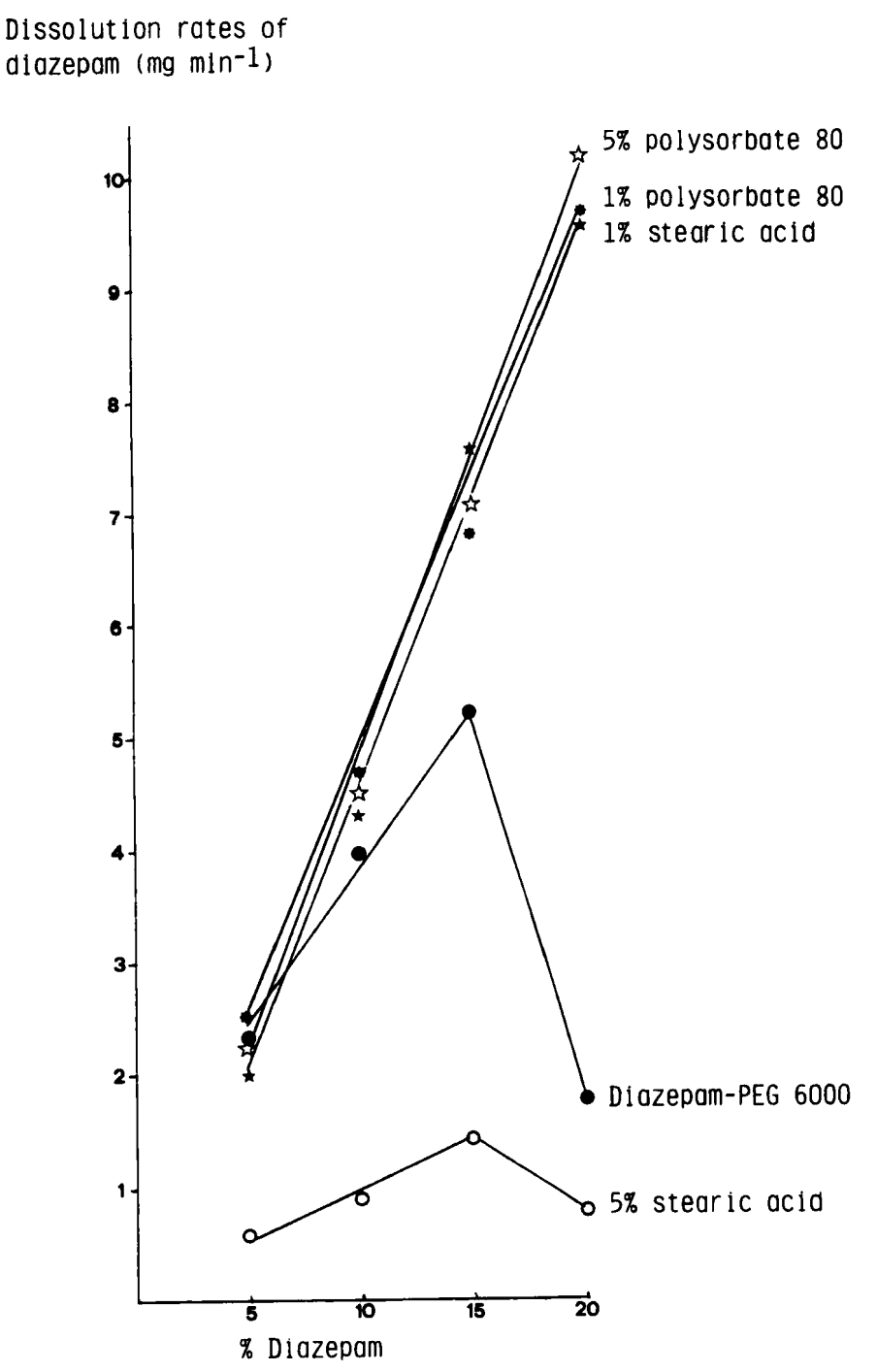

FIGURE 10. The effect of 1 or 5% polysorbate 80 and 1% or 5% stearic acid on the dissolution rate - composition profile of diazepam-PEG 6000 resolidified melts.

TABLE 2

The Effect of Storage on the Dissolution Rates (mg min^{-1}) of some Diazepam-PEG 6000 Solid Dispersions.

Solid dispersion Composition	Storage Temperature	DISSOLUTION RATES Unaged	1 day	7 days	14 days	28 days
5% diazepam	4°C	2.35	2.55	2.51	2.57	*
	5°C		2.46	2.31	2.31	*
	37°C		2.39	0.36	0.31	*
5% diazepam	4°C	2.00	2.54	2.35	2.40	*
1% stearic acid	25°C		1.97	1.41	2.20	*
	37°C		2.25	1.14	0.15	*
5% diazepam	4°C	2.30	2.41	2.38	2.39	*
1% polysorbate 80	25°C		2.47	2.34	2.00	*
	37°C		2.48	0.37	0.20	*
5% diazepam	4°C	2.48	2.59	2.63	2.50	*
5% polysorbate 80	5°C		2.54	2.49	2.36	*
	37°C		2.50	1.57	0.18	*
10% diazepam	4°C	3.96	4.15	5.04	4.10	4.17
	5°C		4.01	4.11	4.15	3.11
	37°C		3.92	0.17	0.50	0.35
10% diazepam	4°C	4.31	4.10	4.01	4.97	5.05
1% stearic acid	25°C		3.53	4.12	3.98	0.94
	37°C		3.44	0.12	0.48	0.28
10% diazepam	4°C	4.56	4.76	4.89	4.91	4.58
1% polysorbate 80	25°C		4.57	4.49	3.41	0.27
	37°C		3.96	0.18	0.77	0.25
10% diazepam	4°C	4.73	4.77	4.72	4.88	4.72
5% polysorbate 80	25°C		4.66	4.44	1.67	0.23
	37°C		3.51	0.21	0.32	0.27
20% diazepam	4°C	1.86	1.52	2.10	2.73	1.30
	25°C		0.91	0.90	1.05	1.92
	37°C		0.91	0.61	0.26	0.28
20% diazepam	4°C	9.59	8.92	3.87	7.10	8.17
1% stearic acid	25°C		4.52	4.17	6.07	0.51
	37°C		2.58	0.15	0.21	0.30
20% diazepam	4°C	10.19	10.65	8.96	9.99	10.72
1% polysorbate 80	25°C		10.05	8.96	7.87	1.33
	37°C		9.83	0.14	0.46	0.28
20% diazepam	4°C	9.68	9.03	9.10	9.38	9.31
5% polysorbate 80	25°C		8.77	6.75	1.90	0.30
	37°C		8.38	0.30	0.87	0.30

* Not studied.

At the higher concentration of 5%, stearic acid impeded dissolution, probably by forming a hydrophobic film about the other components. Similar effects were induced by aerosil (colloidal silicon dioxide) on the dissolution of griseofulvin dispersions based on PEG 3000[25]. Increased crystallinity was thought to be responsible for the low rates.

AGEING STUDIES

The dissolution rates measured after 4 weeks aging at 4, 25 or 37°C (table 2) suggest that the effects of ageing increase with both temperature and the proportion of the drug in the dispersion and are similar to those obtained with the indomethacin- PEG 6000 dispersion[12]. Thus in the limited ageing studies the severity of the observed changes ranked as 20% > 10% > 5% in terms of percentage diazepam in the discs or 37° > 25° > 4°C in terms of the temperatures of storage. Consequently dispersions containing 5% diazepam and stored at 4°C displayed little change in dissolution rates during storage. The results are at odds with reports that a dispersion containing 10% diazepam in PEG 4000 was more affected by aging at 4°C than at 37°C[17], though it is known that for some dispersions such as sulphaguanidine- PEG 6000[15], storage at 37°C protects against aging. However some variations in the general ageing trends in dissolution rates could be discerned, possibly due to inconsistant crystallization[13].

The presence of stearic acid or polysorbate 80 failed to provide adequate protection against aging. The dissolution rate of the dispersions containing either material underwent no significant change when stored at 4°C. Tremendous decreases in dissolution rates were apparent for dispersions containing 10 or 20% diazepam, especially at the latter concentration. In the unaged systems 20% diazepam corresponded to those dispersions which benefited most from the incorporation of polysorbate 80 or stearic acid. Although these materials provided dispersions which

possessed dissolution rates far above those obtained in their absence, they failed to exert any protective influence against the effects of ageing. Indeed following storage at 37°C (table 2) the dissolution rates of dispersions containing 20% diazepam and 1 or 5% polysorbate 80 or 1% stearic acid were <5% that of the unaged product following storage for 28 days.

CONCLUSIONS

PEG 6000increased the dissolution rate of diazepam significantly by solid dispersion methods. Further increases in the rates were accomplished by the additional inclusion of stearic acid (1%) or polysorbate 80 (1 or 5%) into the dispersions and especially at those diazepam-PEG ratios which marked the limit of carrier controlled dissolution. No significant protection aging was accomplished by the addition of either material.

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