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Physical Stability of Solid Dispersions Containing Triamterene or Temazepam in Polyethylene Glycols

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Abstract

The effect of storage on the physical stability of solid dispersions of triamterene or temazepam in polyethylene glycols was studied using differential scanning calorimetry (DSC), particle-size analysis and dissolution methods.

The enthalpies of fusion of the carriers, without included drug and previously fused and crystallized, increased on storage. Analysis of similarly treated solid dispersions, containing either 10% temazepam or 10% triamterene, showed that each drug influenced the morphology of the polyethylene glycol (PEG). The enthalpies and melting points of the solidus components of the dispersions' carriers were initially reduced after preparation, but on storage these increased. The particle sizes of the drugs dispersed in the PEGs increased on storage. The changes in dissolution after storage of triamterene or temazepam dispersions were smaller for dispersions in PEG 1500 than for dispersions in PEGs of higher molecular weight (PEG 2000, PEG 4000 or PEG 6000) in which the reduction in dissolution was particularly marked during the first month of storage. The rank order of changes in dissolution were PEG 1500 $\ll$ PEG 2000 $<$ PEG 4000 $\sim$ PEG 6000.

A solid dispersion is an homogeneous mixture of a drug in a physiologically inert carrier; it is prepared by intermediate action of heat, solvent or a combination of heat and solvent (Ford 1986). Solid dispersions increase the dissolution rates of poorly soluble drugs by increasing solubility and reducing particle size, with concomitant increases in surface area, changes in crystal form, and improved wetting, complexation, compound formation or microenvironmental solubilization (Ford 1986).

Despite the potential of formulating a drug as a solid dispersion, few commercial products exploit the technique. This might be because of difficulties encountered in processing the dispersion systems (Ford 1986) or that the dissolution of the drugs from solid dispersions reduce during storage (Vudatha & Rogers 1992).

The dissolution rates of triamterene or temazepam were increased after solid dispersion in polyethylene glycols (PEGs); the extent of the increase was dependent on the drug/carrier ratio or the molecular weight of the PEG (Dordunoo et al 1991). In addition, there were further increases in dissolution when these dispersions were prepared at higher fusion temperatures (Dordunoo et al 1992). Temazepam dissolved in the PEG at the higher temperatures whereas triamterene was still present as discrete particles (Dordunoo et al 1991). Particle-size analysis performed on the dispersions revealed slight reductions in the particle size of triamterene when the dispersions were prepared at 150°C. Dispersion of temazepam in PEG resulted in a pronounced reduction in its particle size (Dordunoo et al 1991). In addition, the crystallinities of the dispersions, as measured by the enthalpies of fusion, were lower than those of the carriers.

The aims of this study were to determine whether the dissolution of dispersions containing triamterene or temazepam were prone to ageing, the nature and mechanisms of any such ageing behaviour, and to predict, prevent or minimize the tendency of solid dispersions to age.

Materials and Methods

Chemicals

Triamterene was obtained from Secipharma, Italy; temazepam was supplied by Hoechst, Milton Keynes, UK. Polyethylene glycols were obtained from Hoechst. All materials were used as supplied. Each drug was of BP standard.

Thermal analysis

Differential-scanning calorimetry (DSC) was conducted using a Perkin-Elmer DSC 7 coupled to a TAC 7 and a liquid-nitrogen-cooling accessory; the instrument was calibrated with indium. Two samples were scanned for each storage condition.

Thermal analysis of polyethylene glycols. Samples (approximately 5 mg) of PEG 1500, PEG 2000, PEG 4000 or PEG 6000 were weighed into aluminium pans (Perkin-Elmer, 50 mL), crimped and heated at 10° min^{1} from 0 to 100°C to determine the onset temperature, peak temperature and enthalpy of fusion of the untreated polymers. Each sample was then rapidly cooled from 100 to 0°C at 200° min^{-1}. Samples were re-scanned from 0 to 100°C at 10° min^{-1}, after holding at 0°C for 5 min, to give the scans for freshly prepared melts. After fusion, samples were stored at room temperature and re-scanned after various times to determine any changes in the DSC scans.

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Thermal analysis of triamterene or temazepam. Triamterene samples (approximately 3 mg) in crimped aluminium pans with pin-holes in the lids were scanned from ambient to 340°C at 20° min^{-1} to determine the onset, peak temperatures and heats of fusion. Samples of triamterene were also heated to 325°C (before decomposition occurred) and subsequently cooled at 20° min^{-1} to 25°C to examine recrystallization. Samples were stored at room temperature and re-scanned at 20° min^{-1} from 200 to 340°C after storage for 24 h, 7 days or 6 months.

Temazepam samples (approximately 5 mg) were crimped in aluminium pans and scanned from ambient to 165°C at 10°C min^{-1}. Samples were subsequently cooled at 10° min^{-1} to 0°C and re-scanned after storage at room temperature for 0 or 24 h, 7 days or 6 months. A slower heating rate was used for temazepam because it is more stable near its melting point than is triamterene.

Thermal analysis of dispersions. Mixtures containing 10% triamterene or 10% temazepam in each of the PEGs were carefully weighed and triturated at a temperature 5° above the melting point of the polymer (i.e. 50°C for PEG 1500, 55°C for PEG 2000, 60°C for PEG 4000 and 65°C for PEG 6000) to ensure adequate mixing. Samples (approximately 5 mg) of each dispersion were crimped in aluminium sample pans and heated at 100°C for 5 min and subsequently cooled to 0°C at 200° min^{-1}. Thermal analysis, at a scanning rate of 10° min^{-1} from 0 to 100°C, was then performed on samples which had been stored at room temperature for periods up to 6 months.

Other samples (approximately 5 mg) of dispersions containing 10% triamterene were also prepared as above but were heated to 150°C for 5 min instead of 100°C, before cooling to 0°C, to determine the effect of the higher fusion temperature on the physical stability of the dispersions.

Particle-size analysis

Dispersions containing 10% triamterene or temazepam in PEG were prepared by heating weighed amounts of the drug and the carrier at 150°C for 30 min (triamterene) or 100°C for 10 min (temazepam). The dispersions were cooled to 60°C and introduced into hard gelatin capsules with Pasteur pipettes and left to cool to room temperature under natural draught. After approximately 1 h, approximately 1 mg of each dispersion was removed from the hard gelatin capsule and placed on a microscope slide. The cover slip was then pressed firmly on to the dispersion in order to spread it thinly. Dispersions in PEG 2000, PEG 4000 or PEG 6000, which could not be pressed directly, were softened by warming at the melting point of the carrier for about 5 s; the cover slip was then pressed on. The slides were analysed using image-shearing microscopic methods (Dordunoo et al 1991). Capsules containing the dispersions were stored for six or twelve months at room temperature and their contents similarly subjected to particle-size analysis.

Dissolution studies

Dispersions (100 g) containing 2, 5, 10, 20, 30 or 50% triamterene in PEG 1500, PEG 2000, PEG 4000 or PEG 6000 were prepared by heating at 150°C, with stirring, for 30 min. The resulting dispersions were introduced into hard gelatin capsules (Capsugel, size 2) by use of a Zanasi LZ64 capsule-filling machine modified to handle liquids; a temperature of 60°C was used for dispersions in PEG 1500 or PEG 2000 and 75°C for dispersions in PEG 4000 or PEG 6000. Samples of the filled capsules were stored at room temperature. Dissolution studies were conducted on the stored capsules using the methods described by Dordunoo et al (1991). Results are the means from six capsules.

Dispersions, 100 g, containing 2, 5, 10, 20, 30 or 50% temazepam in PEG 1500, PEG 2000, PEG 4000 or PEG 6000 were prepared by heating at 100°C (for dispersions containing 2, 5 or 10% temazepam), 130°C (20 or 30% temazepam) or 150°C (50% temazepam) for 5 min, with stirring. The resulting solutions were then liquid-filled, as described above, into hard gelatin capsules which were stored as for triamterene capsules and tested as previously described (Dordunoo et al 1991).

For both drugs, the amount (%) of drug dissolved after 30 min was used as the major indicator of dissolution performance.

Results

Thermal analysis of triamterene, temazepam and PEGs

DSC studies revealed that triamterene melted at 323°C but did not recrystallize until cooled to approximately 265°C at 20° min^{-1}. The DSC scans of triamterene fused, cooled and recrystallized and tested 24 h or more after melting were similar to those of untreated samples. The two values for the enthalpies of fusion were 212·7 and 216·5 J g^{-1} for the untreated samples and 210·5 and 215·1 J g^{-1} for samples 24 h after recrystallization.

The enthalpy of fusion of untreated temazepam was 87·4 and 90·0 J g^{-1} at 159°C but this drug did not recrystallize immediately after melting and subsequent cooling. When re-heated at 10°C min^{-1}, however, endothermic transitions were observed at approximately 70°C. Their enthalpies increased on storage from approximately 2·5 J g^{-1} after 24 h to 13·6 J g^{-1} after 3 months. Because the transitions were associated with an endothermic shift in baseline, they probably corresponded to a glass transition. The energy of the anomalous endothermic phenomenon might have reflected structural relaxation of the glass (Kerc et al 1991) which would explain the gradual increase in enthalpy on storage.

Fusion and recrystallization resulted in an increase in the number of endotherms for PEG 6000 and a reduction of the onset temperature of melting. During storage, the scans of PEG 6000 gradually reverted to that of the untreated polymer and, after storage for six months, the scans were identical with that of the untreated polymer. Such changes were also apparent with PEG 4000. These findings confirmed the production of at least two physical forms of PEG 4000 and PEG 6000 after fusion and recrystallization, as shown by the presence of the two endotherms; the lower-melting forms transformed to the higher-melting form on storage (Buckley & Kovacs 1976; Chatham 1989). Although neither PEG 1500 or PEG 2000 showed evidence of two forms after recrystallization, the enthalpies of fusion of each of the PEGs were reduced after fusion and recrystallization (Table 1) indicating that fusion increased the amorphousness of the polymers.

The scans of the PEGs stored for 24 h after fusion and recrystallization were similar to those of samples tested

Table 1. The enthalpies of fusion of PEG 1500, PEG 2000, PEG 4000 and PEG 6000.

Carrier	Enthalpy (J g^{-1})	
	Untreated	Treated
PEG 1500	177·7; 179·5	168·4; 171·0
PEG 2000	187·7; 190·7	174·9; 177·5
PEG 4000	190·4; 192·2	176·4; 180·2
PEG 6000	188·3; 191·5	176·9; 180·3

The enthalpies, obtained by DSC at 10° min^{-1}, were measured both for untreated PEG and for PEG treated by heating to 100°C and then rapidly cooling (200° min^{-1}) to 0°C and immediate re-scanning at 10° min^{-1}. Values are reported in duplicate.

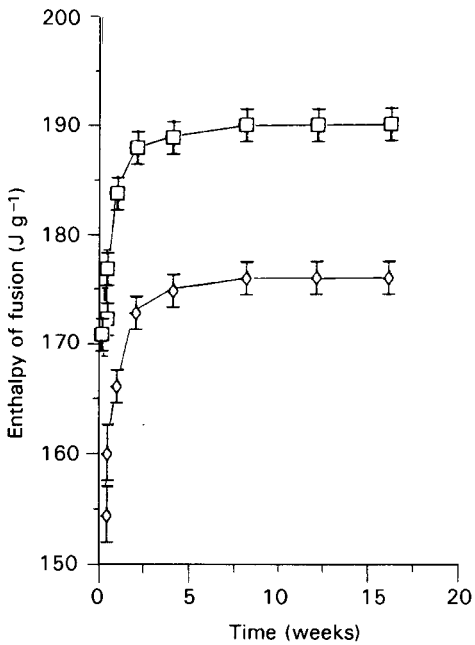

FIG. 1. The effect of storage at room temperature on the enthalpies of fusion of PEG 1500 (◇) and PEG 6000 (□). Values were obtained from DSC scans at 10° min^{-1}. Values are the means ± s.d. from two determinations.

immediately after recrystallization. As is evidenced by Fig. 1, however, there were progressive increases in enthalpy during storage. These predominantly occurred during the first month of storage. Such data clearly indicate that the polymers, in the absence of drug, solidified to an unstable form which changed to a more stable form on storage. Obviously, therefore, the inherent properties of the polymers might themselves contribute to any age-induced changes in the formulated solid dispersion.

Thermal analysis of dispersions containing 10% triamterene

The DSC scans of freshly prepared dispersions containing 10% triamterene in PEG 1500 or PEG 2000 and fused at 100 or 150°C were similar to those of the corresponding freshly melted PEGs. The scans of dispersions in PEG 4000 or PEG 6000, however, showed the absence of the first endotherm or a reduction in its size compared with scans of the unaged PEG 4000 or PEG 6000. Because triamterene is present as discrete particles in these dispersions (Dordunoo et al 1991), its presence seemed to have influenced the morphology of PEG 4000 or PEG 6000, favouring the formation of the crystalline form of higher melting point at the expense of that with the lower melting point.

The scans of the dispersions containing 10% triamterene in the carriers changed gradually on storage until after about six months they became similar to those of the untreated carrier samples. The enthalpies of fusion of dispersions containing 10% triamterene increased on storage (Table 2) and can be compared with expected values which were calculated as 90% of the values of the enthalpies of fusion of the untreated, pure polymers. Triamterene has very limited solid or liquid solubility in PEG (Dordunoo et al 1991) and should, therefore, not contribute to the fusion of the carrier. Indeed, the drug alone tended to recrystallize rapidly. Immediately after preparation the enthalpies of fusion of dispersions prepared at 150°C were lower than those of corresponding dispersions prepared at 100°C (Table 2). This indicates lower crystallinity of the dispersions prepared at 150°C compared with those prepared at 100°C. The enthalpies of fusion of the dispersions increased on storage in a manner similar to those observed with the PEGs alone.

Thermal analysis of dispersions containing 10% temazepam

The DSC scans of dispersions containing 10% temazepam in the PEGs were similar to the corresponding scans of the freshly prepared or aged samples of the pure polymers. The enthalpies of fusion of the dispersions (Table 3) increased on storage in a manner similar to those of the pure carriers or dispersions containing triamterene. The values were approximately

Table 2. The effect of molecular weight of PEG, fusion conditions and storage on the solidus enthalpies of fusion of dispersions containing 10% triamterene fused at 100°C or 150°C and stored at room temperature for six months.

Carrier	Fusion temperature				Calculated value*
	Freshly prepared		Stored for 6 months		
	100°C	150°C	100°C	150°C	
PEG 1500	146·5; 148·3	135·4; 138·4	157·8; 160·4	163·5; 166·1	160·7
PEG 2000	153·6; 156·2	143·6; 146·8	161·5; 164·9	188·9; 192·1	170·3
PEG 4000	156·6; 159·8	146·8; 148·8	173·3; 176·9	197·2; 201·2	172·2
PEG 6000	159·9; 162·9	146·7; 149·6	176·9; 180·5	201·5; 204·7	170·9

*The calculated values were determined by assuming that the drug did not contribute to the enthalpy at the solidus temperature because of its low solubility in PEG; the values are equivalent to 90% of the enthalpies of the untreated carrier in Table 1. Values are reported in duplicate.

Table 3. Effect of storage on the enthalpies of fusion of dispersions of 10% temazepam fused at 100°C and stored at room temperature for six months.

Carrier	Freshly prepared	Stored for 6 months	Calculated values*
PEG 1500	119·4; 123·2	145·8; 148·4	169·9
PEG 2000	143·5; 146·1	166·4; 169·4	178·9
PEG 4000	144·0; 147·2	169·6; 173·0	181·1
PEG 6000	143·9; 147·7	169·5; 172·3	179·8

*The calculated values were determined assuming the drug contributed to the enthalpy at the solidus temperature because of its solubility in PEG and are equivalent to 90% of the enthalpies of the untreated carrier in Table 1 and 10% of the enthalpy of the drug. Results are reported in duplicate.

35 J g^{-1} lower than the values expected from the values of the pure carriers and indicate that the temazepam dispersions were considerably more amorphous than the corresponding triamterene dispersions, even after storage. It should be remembered that temazepam itself under-cooled to form a non-crystalline solid.

Particle-size analysis

Previous studies (Dordunoo et al 1991) demonstrated that there were no changes in the particle size or size distribution of triamterene after its dispersion in PEGs when the dispersions were prepared at 70 or 100°C. Particle-size reduction and narrowing of the size distribution (Fig. 2) were, on the other hand, apparent in solid dispersions containing 10% triamterene heated at 150°C for 30 min. Slight increases in the particle size of triamterene occurred during subsequent storage (Fig. 2; Table 4).

Table 4. The effect of storage on the particle size of triamterene, temazepam or their dispersions prepared at 150°C for 30 min (triamterene) or 100°C for 5 min, and stored for 24 h or 6 months.

Sample	Mean size (μm)	
	24-hour sample	6-month sample
Triamterene	7·1 ± 0·9	7·1 ± 1·1
10% Triamterene-PEG 1500	4·9 ± 1·2	7·3 ± 1·3
10% Triamterene-PEG 6000	5·4 ± 0·7	6·9 ± 0·9
Temazepam	9·2 ± 1·4	9·2 ± 1·4
10% Temazepam-PEG 1500	1·9 ± 0·4	4·1 ± 1·1
10% Temazepam-PEG 6000	2·1 ± 0·7	4·6 ± 0·8

Results are the mean ± s.d. from two determinations.

No particles of temazepam were observed 1 h after preparation when dispersions containing 10% temazepam were prepared at 100°C. This was because of the relatively high solubility of this drug in the PEGs during the preparation of the dispersions (Dordunoo et al 1991). Particles of temazepam precipitated during initial storage for 24 h. The range of sizes of the deposited particles after storage for six months is shown in Fig. 3. Quite clearly an increase in the particle size of the temazepam occurred with a shift in the frequency of distribution and a loss of particles around the 2·5 μm size.

Dissolution studies

The dissolution of triamterene from dispersions prepared at 100°C did not change during storage, irrespective of the drug concentration or the molecular weight of the PEG. This contrasts with the behaviour of diazepam-PEG 6000 (Fernandez et al 1989) or indomethacin-PEG 6000 (Ford & Rubinstein

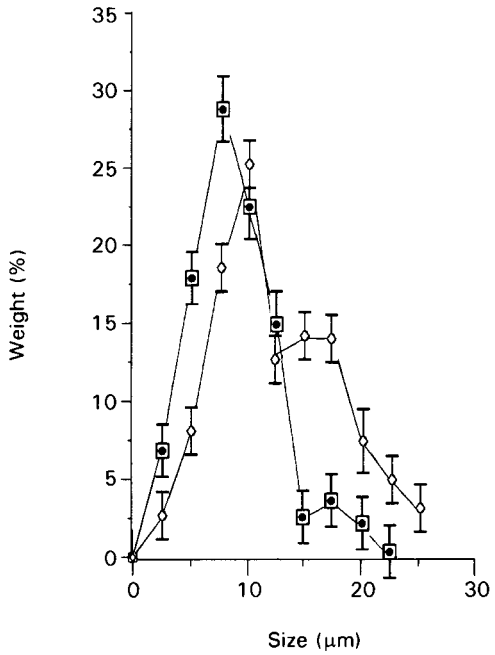

FIG. 2. The particle-size distribution of triamterene in dispersions of 10% triamterene in PEG 6000, fused at 150°C for 30 min and stored at room temperature for 1 h (⊡) or 12 months (◇). Values are the means ± s.d. from two determinations.

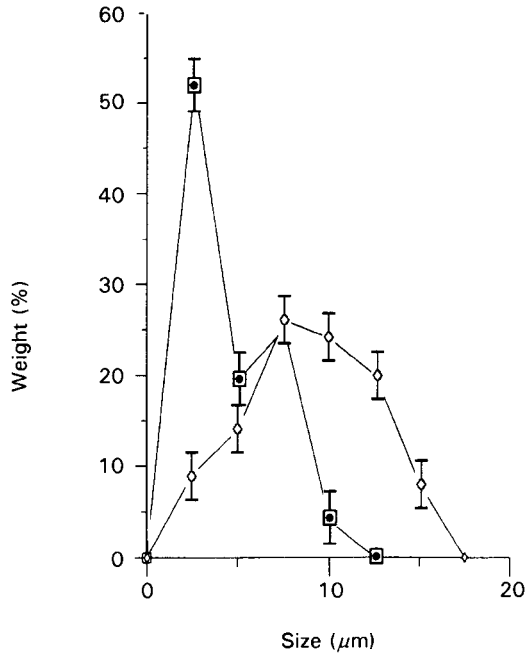

FIG. 3. The particle-size distribution of temazepam in dispersions of 10% temazepam in PEG 6000 fused at 100°C for 10 min and stored at room temperature for 24 h (⊡) or 6 months (◇). Values are the means ± s.d. from two determinations.

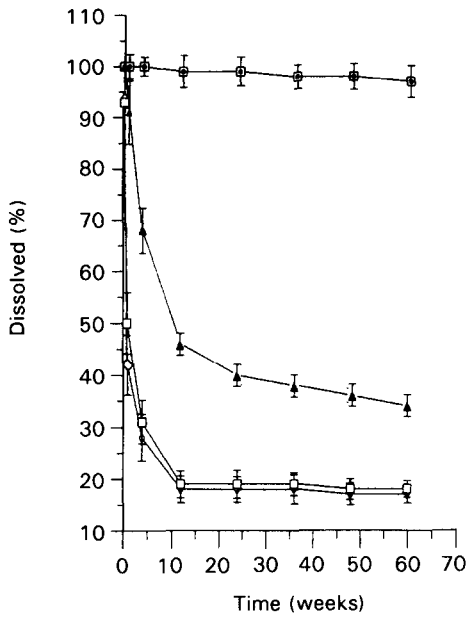

FIG. 4. Effect of storage time on the amount (%) of triamterene dissolved after 30 min from dispersions containing 10% triamterene in PEG 1500 (⊡), PEG 2000 (▲), PEG 4000 (◇) or PEG 6000 (□) prepared by fusion at 150°C for 30 min and stored at room temperature. Values are the means ± s.d. from six determinations.

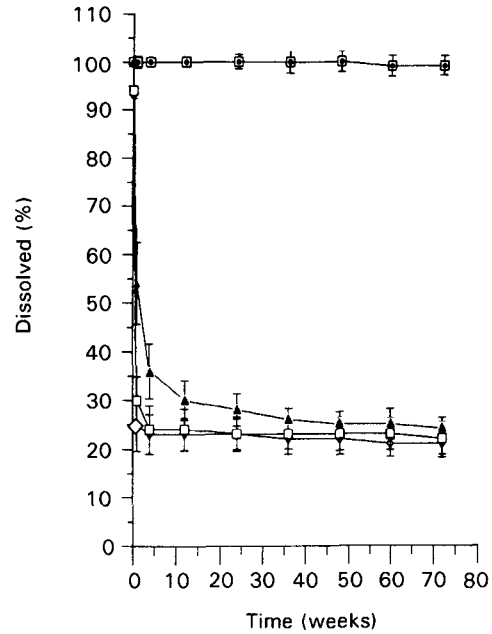

FIG. 5. Effect of storage time on the amount (%) of temazepam dissolved after 30 min from dispersions containing 10% temazepam in PEG 1500 (⊡), PEG 2000 (▲), PEG 4000 (◇) or PEG 6000 (□) prepared by fusion at 100°C for 10 min and stored at room temperature. Values are the means ± s.d. from six determinations.

1979); in these dispersions dissolution rates decreased on storage. The absence of ageing effects in dispersions containing triamterene prepared at 100°C might be because of the low solubility of this drug in the PEG at this temperature and the consequent small change in the particle size of triamterene after preparation (Dordunoo et al 1991). Interestingly, Saers et al (1993) reported that the rates of dissolution of PEG 3000 dispersions containing 10% griseofulvin were not changed after slow cooling, but decreased in preparations which had been rapidly cooled.

In contrast, the dissolution rates of dispersions of triamterene fused at 150°C or of dispersions of temazepam fused at 100°C decreased on storage to an extent which depended on the molecular weight of the PEG (Figs 4 and 5) and the drug/carrier ratio used (e.g. Figs 6 and 7). Dissolution from capsules containing dispersions of up to 50% triamterene or 50% temazepam in PEG 1500 did not change substantially on storage, irrespective of the fusion temperature. Figs 8 and 9 show the marginal changes that occurred for dissolution of triamterene and temezapam from their 10% dispersions in PEG 1500. For dispersions of 10% triamterene in PEG 2000, PEG 4000 or PEG 6000 prepared at 150°C for 30 min, however, dissolution was reduced on storage (Fig. 4); similarly prepared dispersions containing 2% triamterene aged much more slowly (Fig. 6). Similar results were obtained for dispersions of temazepam (Figs 5 and 7).

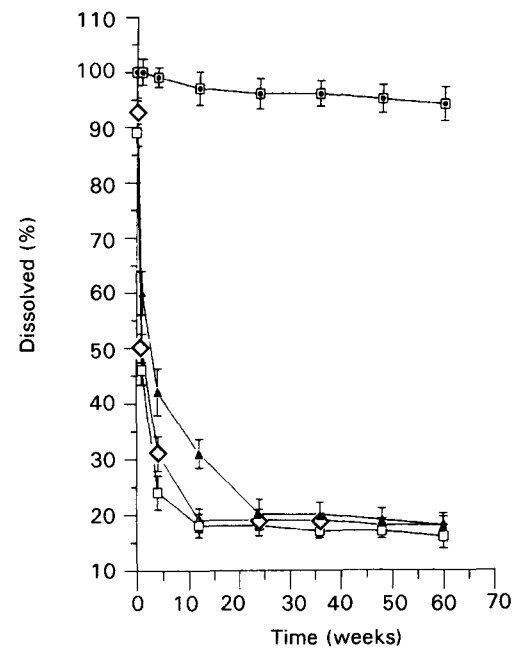

FIG. 6. Effect of storage time on the amount (%) of triamterene dissolved after 30 min from dispersions containing 2 (⊡), 5 (▲), 10 (◇) or 20% (□) triamterene in PEG 6000 prepared by fusion at 150°C for 30 min and stored at room temperature. Values are the means ± s.d. from six determinations.

Discussion

The crystallization of polymers from melts usually results in the formation of solids of varied crystallinity, the extent of which depends on, for example, the rate of cooling and previous thermal history (Chatham 1989; Craig & Newton 1991). The reductions in the melting points and enthalpies of fusion of recently recrystallized PEG samples reflect, therefore, a decrease in the amounts of crystalline regions in the polymers. The further reductions in the enthalpies observed for PEGs or their dispersions containing temazepam or triamterene prepared at 150°C indicate the development of further amorphousness in the melts. On storage, the observed increase in enthalpy is indicative of gradual conversion of the amorphous

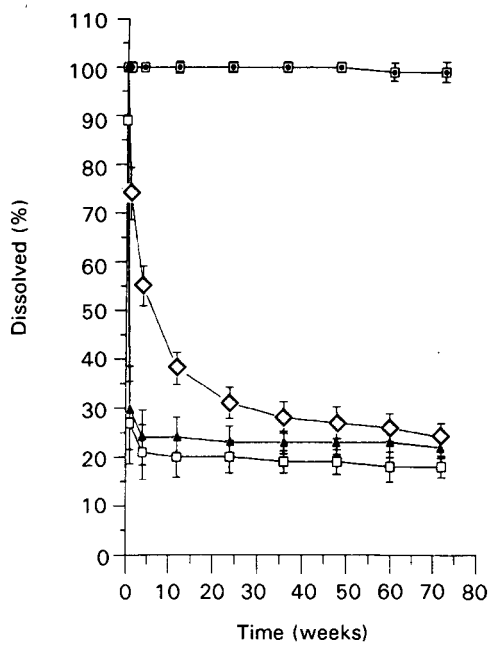

FIG. 7. Effect of storage time on the amount (%) of temazepam dissolved after 30 min from dispersions containing 2 (⊡), 5 (◇), 10 (▲) or 20% (□) temazepam in PEG 6000 prepared by fusion at 100°C for 10 min and stored at room temperature. Values are the means ± s.d. from six determinations.

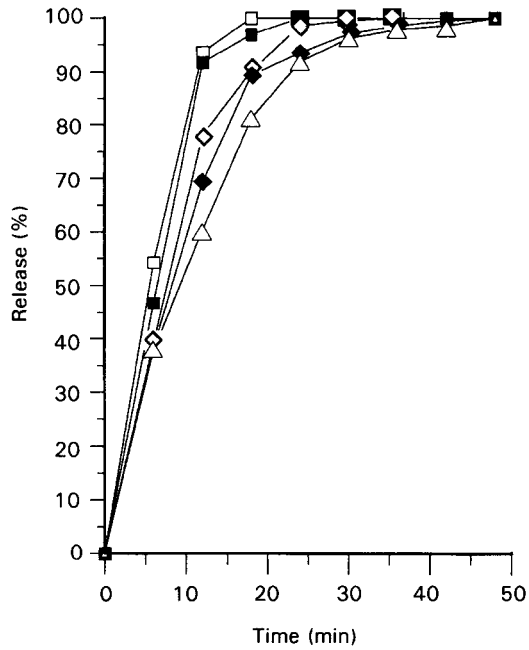

FIG. 8. Effect of storage for 24 h (□), 1 week (■), 12 weeks (◇), 24 weeks (◆) or 36 weeks (△) on the dissolution profiles of triamterene from dispersions of 10% triamterene in PEG 1500 prepared by fusion at 150°C for 30 min and stored at room temperature. Values are the means from six determinations.

forms into crystalline states. Saers et al (1993) reported that an increase in the heat of fusion of dispersions containing 10% griseofulvin in PEG 3000 occurred after storage at 25 and 35°C but not at 45°C. Polyethylene glycols exist as extended or folded forms (Craig & Newton 1991). Although it is unlikely that these different forms would have equal enthalpy values, the gradual changes in the shapes of the endotherms of

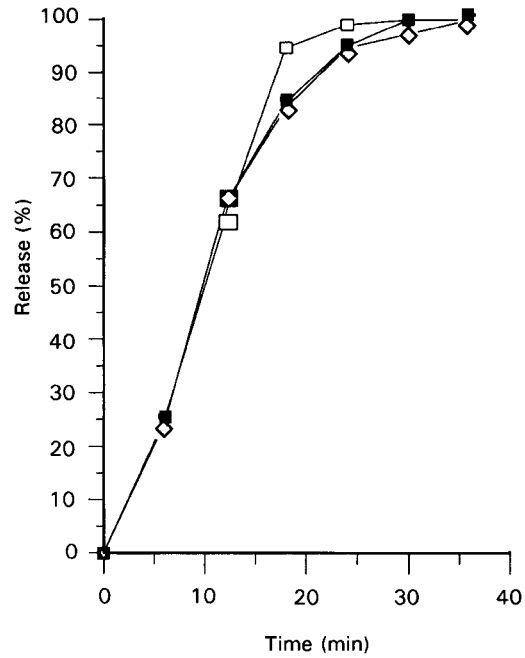

FIG. 9. Effect of storage for 24 h (□), 3 months (■) or 8 months (◇) on the dissolution profiles of temazepam from dispersions of 10% temazepam in PEG 1500 prepared by fusion at 100°C for 10 min and stored at room temperature. Values are the means from six determinations.

both the pure polymers and their dispersions clearly indicate a transition of one form of the polymer to another.

The molar fractions of the drug and the carriers seem to play a dominant role in moderating the effects of ageing. The approximate molar drug/PEG ratios for dispersions containing 10% triamterene or 10% temazepam, on the basis of the nominal molecular weights of the PEGs, are 1 : 1·6, 1 : 1·3, 1 : 0·6 and 1 : 0·4 for PEG 1500, PEG 2000, PEG 4000 and PEG 6000, respectively. Thus on a molecular weight basis the drugs were the minor components in dispersions in PEG 1500 and PEG 2000 but were the major components in dispersions in PEG 4000 or PEG 6000. This suggests that solid dispersions, in which the drug is present as the minor molar component, would show little change in dissolution with time. This assertion was supported by the observation that dispersions containing 2% triamterene or temazepam in PEG 6000 did not show any reduction in dissolution during storage (Figs 6 and 7).

The particle size of the drugs in the dispersions increased on storage. This might have resulted either from the deposition of the drug from its solid solution in PEG on to particles which had already formed, as would occur initially with triamterene, or from differences in the solubility of the micronized particles of the drug produced in the dispersion, the differences in solubility probably occurring with temazepam. When solid particles are dispersed in their own saturated or supersaturated solution there is a tendency for the smaller particles to dissolve and the solute to be deposited later on the larger particles (Knapp 1922). Smaller particles would therefore disappear and the larger particles would grow larger.

As is apparent from Tables 2 and 3, the enthalpies of the dispersions in PEG 1500 increased, suggesting that crystalline transformation had occurred during storage. There were, in

addition, increases in the particle sizes of both drugs dispersed in PEG 1500. These were not, however, reflected in a reduction of dissolution compared with the dispersions in the higher-molecular-weight PEGs. The data suggest that ageing and decreases in dissolution rate on storage are more complicated phenomena than suggested by Craig (1995) who considered that dissolution rate depended on the degree of crystallinity of PEG and that polymorphic transitions of the carrier or particle-size changes of the drug did not, therefore, reduce dissolution. The nature of the drug-carrier interactions should affect the ageing characteristics of the dispersions and might explain the role of temperature on ageing. Triamterene has a very limited solid or liquid state solubility in PEG, forming virtually a monotectic mixture with PEGs whereas temazepam formed a partial solid solution (Dordunoo et al 1991).

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