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PREFORMULATION STUDIES ON SOLID DISPERSIONS CONTAINING TRIAMTERENE OR TEMAZEPAM IN POLYETHYLENE GLYCOLS OR GELUCIRE 44/14 FOR LIQUID FILLING OF HARD GELATIN CAPSULES.

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ABSTRACT

Solid dispersions of triamterene or temazepam in polyethylene glycols or gelucire 44/14 have been investigated. The phase equilibria of the drugs and carriers were determined by Differential Thermal Analysis and Hot Stage Microscopy. Particle Size Analysis was carried out using double image microscopy, whilst phase solubility techniques and dissolution methods were used to study solubility, dissolution and ageing.

It has been shown that triamterene forms monotectics with polyethylene glycols and gelucire 44/14 and temzepam shows partial solubility. The effect of the carriers on particle size depends on the solubility of the drug in the carrier and size reduction is observed where the drug is soluble in the carrier.

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The aqueous solubilities of both drugs are increased by PEGs and gelucire 44/14 with the latter producing greater increases. The carriers, PEG 1000, PEG 1500 and gelucire 44/14 also increased dissolution rates of both drugs giving three- to four-fold increases compared with the higher molecular weight PEGs.

Ageing effects observed for temazepam-PEG solid dispersions were found to be reduced by the use of lower molecular weight PEGs or gelucire 44/14.

INTRODUCTION

Solid dispersion techniques are used to increase the solubility, rates of dissolution and bioavailability of poorly water soluble drugs[1,2,3,4]. These systems are formed by incorporating the drug(s) into one or more, water-soluble, inert carriers by melting (fusion), solvent or both fusion-solvent methods. Technologically, the fusion method is the least difficult provided the drug and the carrier are completely miscible in the molten state[5]. However, thermal instability can preclude the use of this method. The solvent method is unsuitable for liquid filling except when combined with the fusion method. Processing solid dispersions into tablets has presented difficulties due the waxy nature of the formulations[4,6] and Ford[4] suggested that the filling of hard gelatin capsules is a means of circumventing these processing problems.

Several carriers have been used in solid dispersions but, for liquid filling of hard gelatin capsules, a low melting point of the fill is desirable. Polyethylene glycols (PEGs) and Gelucires have been used in the liquid filling of hard gelatin capsules[6,7,8] Polyethylene glycols are water-soluble and have low melting points (34-65^{o}C), but solid dispersions based on

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PEGs are prone to ageing; there is a reduction of dissolution rate on storage[9]. The performance of polyethylene glycol matrices, viz. increased solubility, increased dissolution rates and ageing are also known to be influenced by the molecular weight of the PEG and the weight fraction of the carrier[10]. Gelucires are low-melting (33-62 °C), hydrogenated natural fats and oils to which PEGs and esters thereof are added to vary the HLB value from 1 to 14 with Gelucire 44/14 being water dispersible[11].

Triamterene is a synthetic, potassium-sparing diuretic which shows the existence of different crystal forms[12]. It has an aqueous solubility of 45μg/ml[13] which marks it out as a drug whose absorption may be dissolution-rate limited with consequent potential bioavailability problems. Bioavailabilities, as low as 30% with wide intersubject variation, have been reported[14]. These studies suggest that triamterene could benefit by formulation as a solid dispersion.

Temazepam, 3-hydroxydiazepam, is a benzodiazepine with limited aqueous solubility and similarly should benefit from formulation as a solid dispersion.

This study reports the phase diagrams, solubilities, particle size analyses and dissolution rates of dispersions of triamterene or temazepam in polyethylene glycols [PEG 1000, PEG 1500, PEG 4000, PEG 6000 and PEG 10,000] and gelucire 44/14 as a preformulation study for their ultimate incorporation as liquid-filled hard gelatin capsules.

MATERIALS

Triamterene USP, temazepam USP, polyethylene glycol 1000, 1500, 4000, 6000 and 10,000 (British Drug Houses, U.K.), Gelucire 44/14 (Gattefosse, France) and

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polysorbate 80 (British Drug Houses, U.K.) were used without further purification.

METHODS.

Differential Thermal Analysis (DTA).

Various drug-carrier compositions were accurately weighed and heated at 5 °C above the melting points of the carriers, to facilitate mixing, and stirred until the mass solidified. Approximately 5mg of each sample was then crimped in aluminium pans and examined using a Stanton Redcroft Differential Thermal Analyser Model 671.

Samples containing triamterene were, prior to analysis, heated at 10°C min^{-1} from ambient to, and maintained at, 70 or 100°C for 30 minutes to establish equilibria within the samples. Samples were examined following storage at room temperature for one hour. Scans [at 10°C min^{-1}] were initially obtained from 20 to 330 °C, but once decomposition of samples had been established the upper temperature was reduced to 170°C.

For temazepam-carrier blends, prior to analysis, samples were heated at 10 °C min^{-1} from ambient temperature to 160 °C and cooled rapidly with liquid nitrogen to 0°C. Scans were then obtained at a heating rate of 10°C min^{-1} from 20 to 160°C for samples which had been stored at room temperature for one hour.

Hot Stage Microscopy (HSM).

Accurately weighed quantities of the drugs and the carriers in the desired ratios were blended by trituration at 5 °C above the melting point of the carrier and allowed to set at room temperature. About

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1mg of each blend was heated to 150°C on a microscope slide, covered by a cover slip, and allowed to cool to room temperature. The slides were subsequently stored at room temperature for 24 hours and analysed using a Mettler FP82 Hot Stage and FP80 Central Processor, heating at 5 °C min^{-1} from 25 to 330 °C for samples containing triamterene and from 25 to 160°C for samples containing temazepam to determine the solidus and liquidus temperatures for each sample.

Particle Size Analysis.

The particle size distributions of the dispersions were determined using a Particle Size Micrometer and Analyser Type 526 (Fleming Instruments Ltd), counting at least 625 particles for each blend. Samples were analysed after storage at room temperature for two hours or 30 days.

The required drug-carrier blends were prepared by trituration at 5 °C above the melting point of the carrier and allowed to set at room temperature. Samples were then placed on a microscope slide and heated on a Mettler FP82 Hot Stage. For triamterene-carrier blends, the slides were maintained at either 70 °C or 100°C for 30 minutes, before cooling either rapidly to 0 C in a stream of liquid nitrogen (which took about one minute) or by cooling under natural convection to room temperature. Temazepam-carrier blends were heated at 5°C min^{-1} to a temperature 5 °C above the liquidus temperature of the particular blend. Samples were then cooled similarly to the triamterene-carrier blends.

Solubility Studies.

The solubilities of the drugs in solutions of the carriers were determined by mixing 20 mg of the drug in

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10 ml each of solutions containing 5, 10, 15 or 20% w/v of PEG 1000, PEG 4000, PEG 6000, PEG 10,000 or Gelucire 44/14 for 24 hours at 37°C. Triamterene was examined in 0.1M HCl solutions and temazepam in aqueous solutions. The solutions were filtered through 0.2um cellulose nitrate filters (Whatman), diluted appropriately with distilled water and the solubilities determined from absorbances measured using a Cecil CE272 UV Spectrophotometer at 237 nm for temazepam and 360nm for triamterene.

Encapsulation and Dissolution Testing.

Triamterene-carrier blends were heated at 100°C for 15 minutes before being cooled with stirring to 70 °C, prior to filling into hard gelatin capsules, size 1 (Elanco Lok-cap) with pipettes. Initially capsules were filled to contain 12.5% triamterene (30mg) dispersed in PEG 1000, PEG 1500, PEG 4000, PEG 6000, PEG 10,000 or Gelucire 44/14. The effects of variation of the triamterene-carrier ratio on dissolution rates were examined using dispersions containing 2, 5, 10, 15, 20, 30 or 50% tiamterene dispersed in PEG 1500, PEG 6000 or Gelucire 44/14. Because the volume of the dispersions was too great for the size of the capsules, drug contents of 8 and 20 mg were used for dispersions containing 2 and 5% triamterene respectively.
Additionally capsules were prepared to contain 10% triamterene (30mg), 2 or 5% polysorbate 80, in PEG 1500 or PEG 6000.

Dispersions containing temazepam were heated at 5°C above their liquidus temperature for 15 minutes before cooling, with stirring to 70 °C, prior to filling into size 1, hard gelatin capsules with pipettes. Initially capsules were filled to contain 10% temazepam (20mg)

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dispersed in PEG 1000, PEG 1500, PEG 4000, PEG 6000, PEG 10,000 or Gelucire 44/14. The effects of variation of the temazepam-carrier ratio on dissolution rates were examined using dispersions containing 2, 5, 10, 15, 20, 30 or 50% drug dispersed in PEG 1500, PEG 6000 or Gelucire 44/14. Capsules containing 2% temazepam only contained 8 mg drug. Additionally capsules were prepared to contain 10% temazepam (20mg), and up to 20% polysorbate 80 in PEG 6000.

Dissolution studies were performed, in quadruplicate, using a Copley Dissolution tester, Series 8000, on capsules stored at room temperature for one hour, 24 hours, 48 hours, 7 days and 3 months. The USP XXII Apparatus 1 (Basket Method) was used at stirring rates of 50 and 100 revolutions per minute respectively for temazepam and triamterene into 1000 ml of 0.1N HCl at 37 ^{o}C. Temazepam and triamterene were assayed spectrophotometrically at 237nm and 360nm respectively.

RESULTS AND DISCUSSION

Thermal Analysis.

Differential thermal analysis indicated that the PEGs and gelucire 44/14 were unstable on heating to temperatures above 170 ^{o}C as shown by broad exotherms which commenced at about 170 ^{o}C (figure 1). A single endotherm was apparent with each of the PEGs, although Ford[15] reported that PEG 6000 displayed a double melting endotherm at a scan rate of 5 ^{o}C min^{-1}, but only one endotherm when drugs were dispersed in it by fusion. A complex melting endotherm was apparent with gelucire 44/14 (figure 1).

The melting points of the pure drugs, as determined from the temperatures of the DTA endotherm peaks, were

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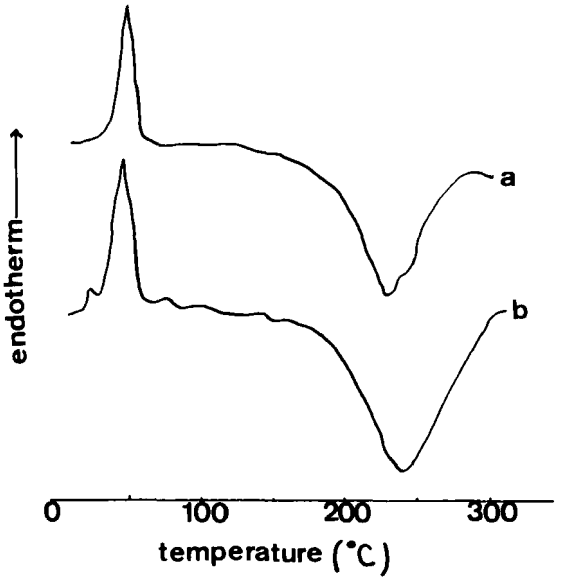

FIGURE 1.
DTA scans of (a) PEG 1500 and (b) gelucire 44/14 obtained at 10 C min^{-1}.

327 °C and 157 °C for triamterene and temazepam respectively (figure 2). Pure triamterene, during HSM using a microscope slide without a cover slip, underwent sublimation at 310 °C while covered samples melted at 327-329 °C. The endothermic increase in the DTA baseline (figure 2) may therefore represent sublimation of the drug. Temazepam displayed a decompostion exotherm at 220 °C (figure 2).

Differential thermal analysis of dispersions of triamterene in the PEGs or gelucire 44/14 (examples are shown in figure 3) showed no peaks for triamterene irrespective of the weight fraction of the drug, probably due to the melting endotherm of the drug coinciding with the decomposition of the carriers.

However, HSM studies showed that dispersions containing 0.1% triamterene in PEG 1500 and PEG 6000

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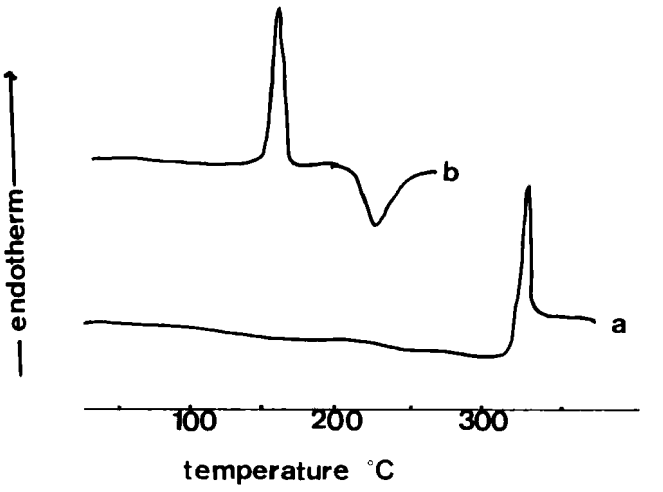

FIGURE 2.
DTA scans of (a) triamterene and (b) temazepam obtained at 10 C min^{-1}.

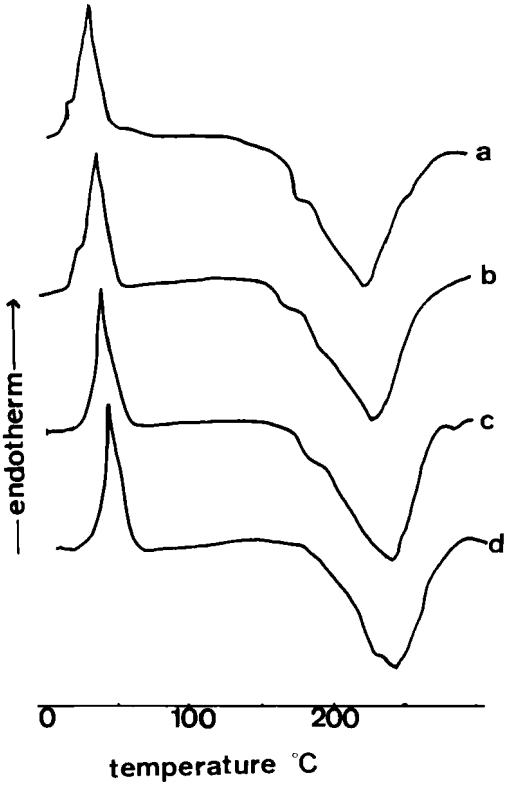

FIGURE 3.
DTA scans of triamterene-PEG 6000 and triamterene-gelucire 44/14 solid dispersions obtained at 10 C min^{-1}. KEY: (a) 10% triamterene in gelucire 44/14; (b) 30% triamterene in gelucire 44/14; (c) 10% triamterene in PEG 1500 and (d) 30% triamterene in PEG 1500.

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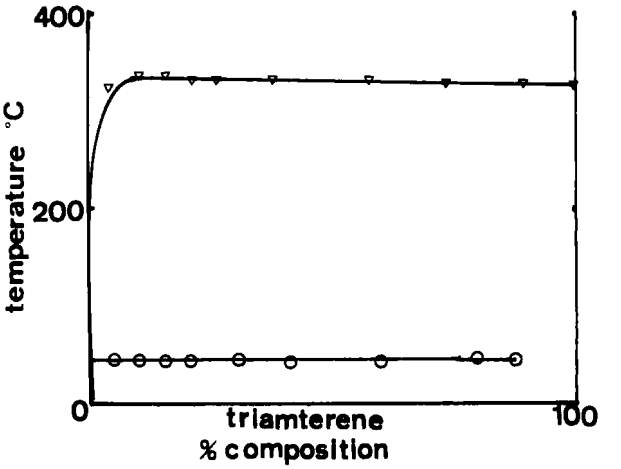

FIGURE 4.
Phase diagram of triamterene-PEG 1500 solid dispersion.
KEY: O solidus temperature; ▽ liquidus temperature.

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each displayed a liquidus temperature of 120 °C, corresponding to the melting of excess triamterene indicating a very limited solubility of triamterene in PEG in the solid state. At drug composition of 0.2% and above in PEG or Gelucire 44/14, HSM showed that the decomposition of the carrier occurred at about 170°C and that the drug melted at about 327°C.

The incorporation of triamterene into the carriers resulted in no change in either the onset (T_o) or peak (T_m) temperatures of the endotherms displayed by the carriers. Representative examples of the phase diagrams are indicated (triamterene in PEG 1500, figure 4; triamterene in gelucire 44/14, figure 5); all were monotectics. Solidus temperatures were determined by DTA and liquidus temperatures by HSM. Although common in metallurgy, few monotectics have been described in pharmaceutical systems e.g., griseofulvin-PEG 2000[16],

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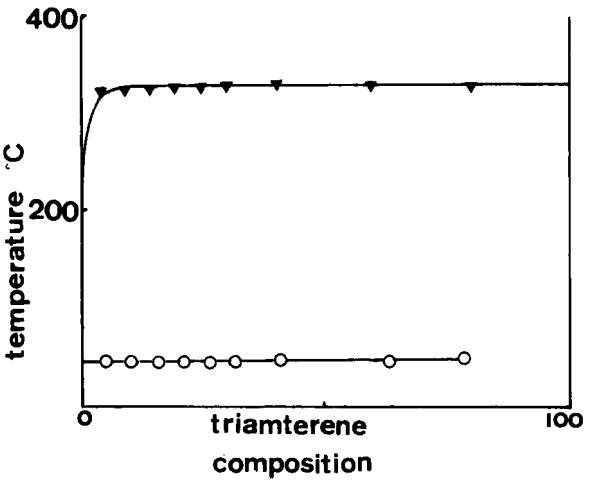

FIGURE 5.
Phase diagram of triamterene-gelucire 44/14 solid dispersion. KEY: O solidus temperature; ▼ liquidus temperature.

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tolbutamide-PEG 2000[16], trimethoprim-PEG 4000[17] and nortriptyline hydrochloride in various PEGs[18].

During DTA of the various temazepam-PEG or gelucire 44/14 systems no endotherms corresponding to the melting of excess temazepam were apparent in compositions containing up to and including 30% drug (figures 6 & 7). Above this composition broad endotherms, which corresponded to the melting of temazepam, were apparent. It can be deduced therefore that temazepam dispersed in PEG or gelucire 44/14 was at least partly amorphous, similar to reports for diazepam dispersed in PEG 6000[10].

The phase diagrams of the solid dispersions containing temazepam were determined from the onset temperatures for the melting of the solidus (T_o) and peak temperatures of the solidus (T_m), each by DTA, and the liquidus temperature (T_l) from HSM[19]. Representative phase diagrams are given for temazepam-PEG 1500 (figure

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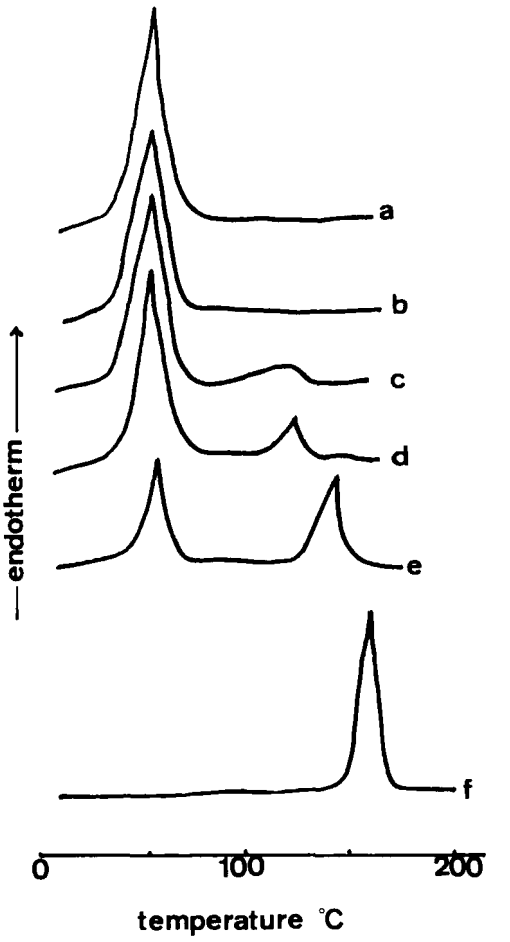

FIGURE 6.
DTA scans of temazepam-PEG 6000 solid dispersions obtained at 10 C min^{-1}. KEY (% temazepam): a: 0, b: 10, c: 30, d: 60 and e: 100.

8) and temazepam-gelucire 44/14 (figure 9). The incorporation of temazepam into the PEGs and the gelucire 44/14 resulted in an approximate $5^{O}C$ depression in the (T_o) of the solidus, irrespective of the composition and carrier. At drug contents less than 2% in the PEGs, no crystallites were observed in the solid state by microscopy indicative of the formation of a

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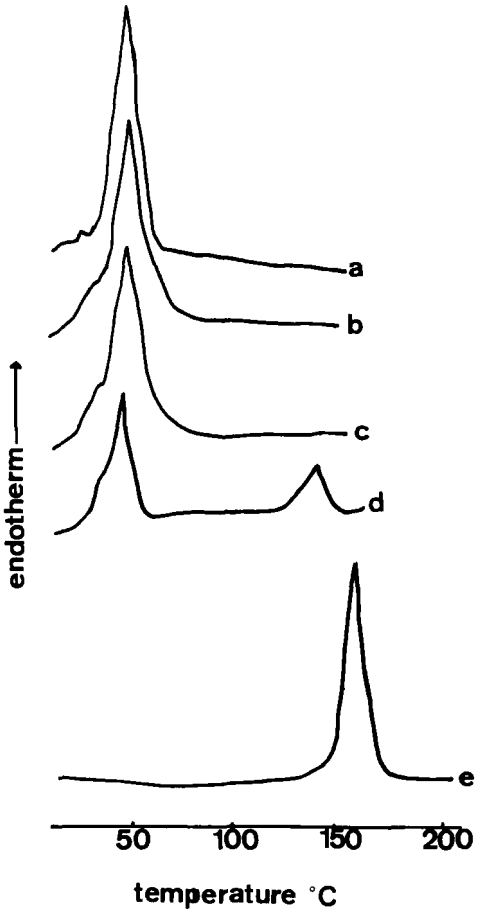

FIGURE 7.
DTA scans of temazepam-gelucire 44/14 solid dispersions obtained at 10 C min^{-1}. KEY (% temazepam): a: 0, b: 10, c: 30, d: 60 and e: 100.

solid solution of temazepam in the PEG. The T_m of the solidus reached a minimum in temazepam-PEG 6000 dispersions containing about 5% drug. The liquidus temperatures of the PEG dispersions, at compositions containing less than 15% temazepam, decreased as the molecular weight of PEG decreased, reflecting differences in the melting point of the pure PEGs. These differences in the liquidus points gradually were

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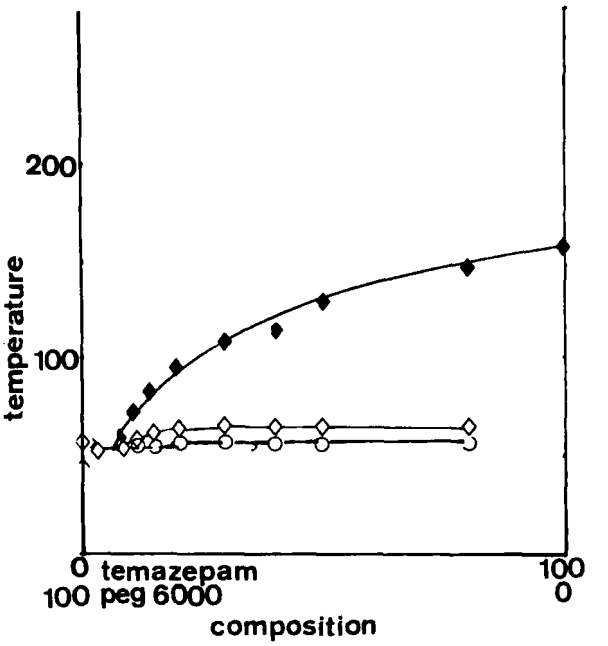

FIGURE 8.
Phase diagram of temazepam-PEG 6000 solid dispersion. KEY: ○ onset temperature; ◇ peak temperature, ◆ liquidus temperature.

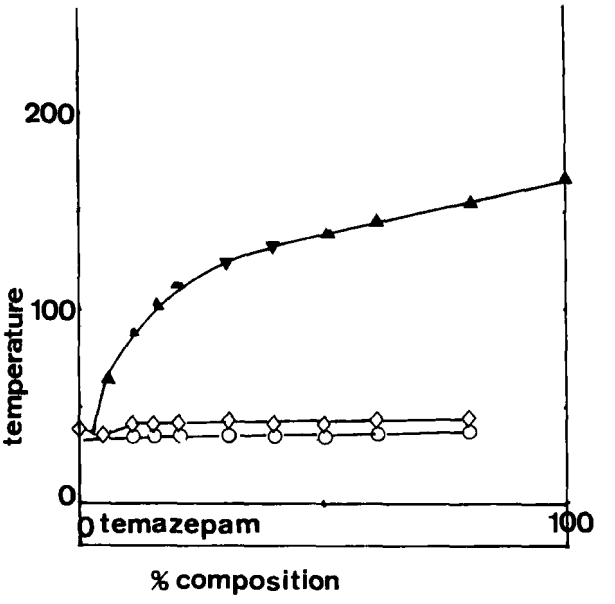

FIGURE 9.
Phase diagram of temazepam-gelucire 44/14 solid dispersion. KEY: ○ onset temperature; △ peak temperature ▼ liquidus temperature

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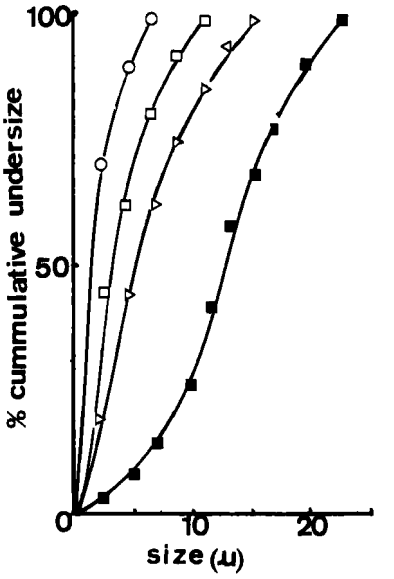

FIGURE 10.
Effect of drug content on the particle size distribution of temazepam in temazepam-PEG 1500 solid dispersions. KEY (% temazepam): ○ 5; □ 10; ▽ 20; ■ 100.

insignificant in dispersions containing in excess of 15% temazepam.

For temazepam-gelucire 44/14 dispersions the composition with the minimum T_m was about 2% drug. The phase diagram for temazepam-gelucire 44/14 (figure 9) showed higher liquidus temperatures than for the dispersions in PEG which had the same comparable melting point, i.e. PEG 1500, for dispersions containing up to 80% temazepam. This, coupled with the lower temazepam-gelucire 44/14 content (2% as compared with 5% for PEG 1500) giving the minimum T_m, indicates a lower solubility of temazepam in gelucire 44/14 than in PEG 1500.

Particle size analysis.

There was no change in the particle size or size distribution of triamterene following its dispersion in

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TABLE 1: Effect of Drug Content on the Particle Size Distribution of Temazepam in Temazepam-PEG 1500 Solid Dispersions.

Drug content (%)	% under size			
	2.5µm	5µm	7.5µm	10µm
5	71	92	100	-
10	45	63	74	90
20	20	45	63	75
100	1	8	18	40

either the PEGs or gelucire 44/14 and preparation at 70 or 100°C. All samples, including the pure triamterene, gave 10% under 5µm with a mass median size of approximately 20µm. This lack of change was presumably due to triamterene being virtually insoluble in the carriers at these temperatures as evidenced from the phase diagrams (e.g., figures 4 & 5). However, a dispersion of 0.1% triamterene in PEG 1500 prepared at 130 °C, (10°C above the liquidus temperature), showed profound particle size reduction with all particles being less than 5µm. The drug dissolved at the elevated temperature and subsequently precipitated on cooling. Such low solubility would indicate that in a dispersion containing 5% drug, less than one fiftieth of the particles would have dissolved at 100 °C thereby accounting for the apparent lack of change in either particle size or its distribution.

In contrast, there was a pronounced reduction in the particle size of temazepam following its dispersion in either the PEGs or gelucire 44/14 (e.g., see figure 10). This was because temazepam dissolved in the carriers at the temperatures employed to prepare the dispersion and the particle size measured would be that of the resultant precipitate. The extent of this reduction

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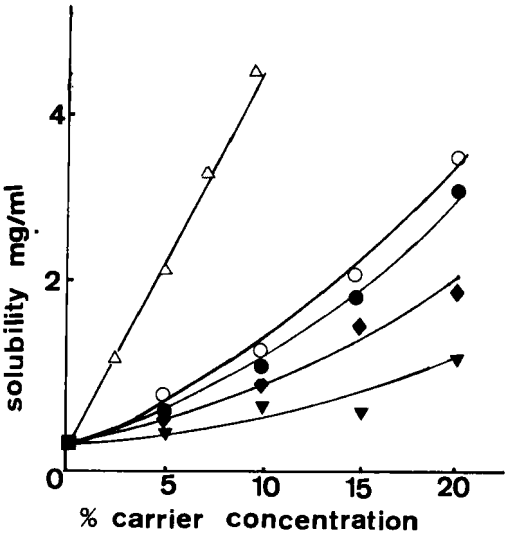

FIGURE 11.
Effects of PEGs and gelucire 44/14 on aqueous solubility of triamterene at 37 C. KEY: ○ PEG 1000; ▼ PEG 4000; ● PEG 6000; ◆ PEG 10,000 and △ gelucire 44/14.

depended on the drug-carrier ratio and the cooling conditions used to prepare the dispersion. The variation of particle size with drug content is indicated by the data presented in table 1.

Particle aggregation and agglomeration increased with an increase in drug content which largely accounted for the increase in particle size described in table 1. Rapid cooling, utilizing liquid nitrogen, further reduced particle size and particle aggregation and agglomeration. For example, rapid cooling using liquid nitrogen of dispersions containing 10% temazepam in any of the PEGs resulted in all particles being less than 2.5μm, whereas cooling to room temperature resulted in approximately 40% of particles being less than 2.5μm.

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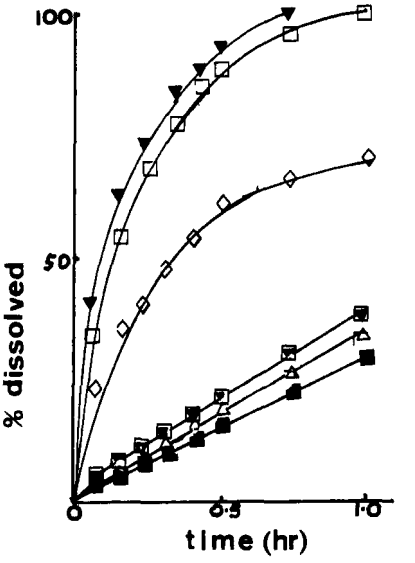

FIGURE 12.
Effects of carriers on the dissolution of triamterene from capsules containing solid dispersions of 12.5% triamterene in PEGs or gelucire 44/14.
KEY: ▼ PEG 1000; ◇ PEG 1500; △ PEG 4000; ◪ PEG 6000; □ gelucire 44/14; ■ pure triamterene.

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Solubility and dissolution.

The solubility of triamterene was found to be 321µg/ml in 0.1M HCl at 37 °C. The solubility was increased by the presence of PEGs and gelucire 44/14 with PEG 1000 and gelucire 44/14 apparently producing the greatest increases in solubility (figure 11).

The rates of dissolution of triamterene from capsules liquid-filled with solid dispersions in PEG matrices, depended on the molecular weight of the PEG and the ratio of drug:carrier in the capsules. Figure 12 illustrates the variation of dissolution induced by the molecular weight of PEG for dispersions containing 12.5% triamterene. Polyethylene glycols 4000 and 6000

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increased the dissolution of triamterene only slightly while PEG 1000 and PEG 1500 produced substantial increases in dissolution. For example, the percentage of drug released after 1 hour was 95, 66, 36, 38, and 36 for PEG 1000, PEG 1500, PEG 4000, PEG 6000 and pure triamterene respectively.

The observation that more complete or more rapid dissolution occurs with lower molecular weight PEGs has previously been reported[20 21]. In this study visual examination of the capsules following dissolution showed that the contents remained as wet plugs after the gelatin capsule had dissolved. The behaviour of the plugs depended on the molecular weight of the PEG. For example was accompanied by the rapid dissolution of both components as previously reported for glutethimide-Renex 650 solid dispersions[22]. Although lower molecular weight PEGs dissolve faster than their higher molecular weight conterparts[23], the melting range of PEG 1000 containing 12.5% triamterene was 30-34 C (HSM data) which is lower than the temperature of the dissolution fluid and would thus exert a greater influence on the release of triamterene from PEG 1000 matrices.

Capsules containing 12.5% triamterene in PEG 1500 showed an initial rapid drug release which slowed down condisiderably after 20 minutes. It is postulated that the initial rapid release might be due to the dissolution of PEG 1500 solubilizing the drug. After about 20 minutes the surface of the plug would become richer in the hydrophobic triamterene which would retard dissolution. In the cases of capsules containing 12.5% triamterene in PEG 4000 and PEG 6000 the plug formed retained the shape of the original gelatin shell. The linear dissolution profile obtained may be consistent with triamterene release being predominately drug controlled.

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TABLE 2: Effect of Molecular Weight of Polyethylene Glycols and Drug Content on $T_{80\%}$ of Capsules containing Triamterene-PEG solid dispersions.

DRUG CONTENT (%).	$T_{80\%}$ (minutes)		
	PEG 1000	PEG 1500	PEG 6000
2%	< 10	12	20
5%	-	45	>120
10%	25	120	-

(-) not determined

This is undoubtedly a problem in dispersions where the drug has a very limited solubility in the carrier, does not dissolve in it during preparation and thereby does not allow the rapid release of drugs afforded by those dispersions where the drug is soluble in the carrier[4].

Table 2 summarises the effect of the molecular weight of PEG on release of triamterene from its dispersions in PEG. Plug formation resulted in dissolution that depended on the drug:carrier ratio in the dispersion. At low drug levels (2%) complete dissolution was achieved within 20 minutes. Figure 13 shows the effect of drug levels on the dissolution of triamterene from capsules filled with dispersions of triamterene in PEG 6000. The rate of dissolution decreased and became triamterene controlled when the drug content was increased to 5% and above due to the formation of plugs.

Incorporation of polysorbate 80 into 10% triamterene-PEG dispersions caused substantial increases in the dissolution rates of triamterene from these systems. These results compare well with previous studies[10] where polysorbate 80 increased the dissolution of diazepam in PEG 6000 dispersions.

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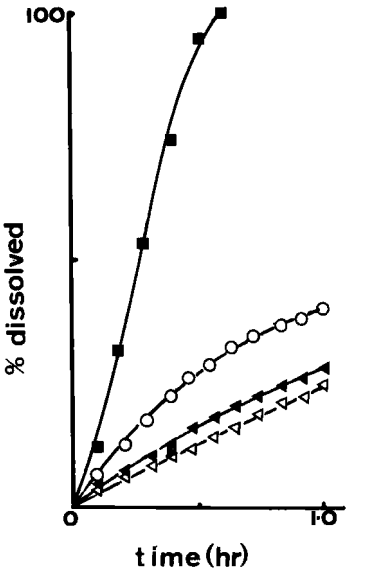

FIGURE 13.
Effects of drug:carrier weight ratio on dissolution of triamterene from capsules filled with dispersions prepared using PEG 6000. KEY (% triamterene): ■ 2; ○ 5; ▼ 10 and ▽ 20.

Figure 14 illustrates the effect of addition of 2 or 5% polysorbate 80 to dispersions in PEG 1500 or PEG 6000 containing 10% triamterene. The results show that the amount of polysorbate required to achieve $t_{80\%}$ of less than one hour depended on the molecular weight of PEG. The increases in dissolution of triamterene was probably due to better wetting of the drug crystals in the dispersion by polysorbate 80.

The aqueous solubility of temazepam was 175μg ml-1 and PEGs and Gelucire 44/14 increased its solubility (figure 15), gelucire apparently giving the greatest increase in solubility.

The dissolution of solid dispersions of temazepam in PEGs depended on the molecular weight of the PEG. The

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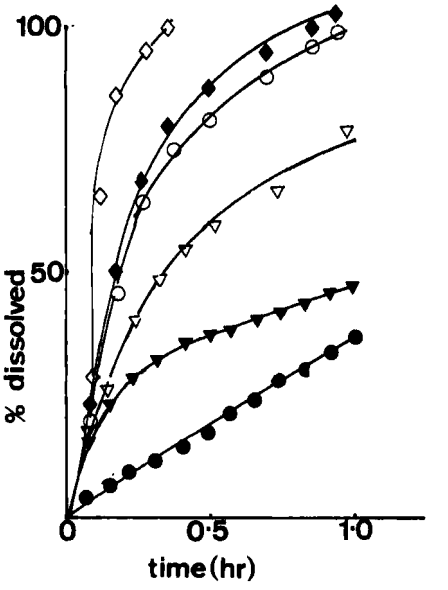

FIGURE 14.
Effect of polysorbate 80 on dissolution of triamterene from capsules containing 10% triamterene. KEY: ○ 2% polysorbate 80/PEG 1500; ◇ 5% polysorbate 80/PEG 1500; ▼ 2% polysorbate 80/PEG6000; ◆ 5% polysorbate/ PEG 6000; ▽ PEG 1500 and ● PEG 6000.

dissolution rates for the PEG-based solid dispersions containing 10% temazepam decreased as the molecular weight of PEG increased, with PEG 1000 providing the greatest increase in dissolution (figure 16). The increases in dissolution rates could be attributed to the reduction in particle size of temazepam that occurred on preparation of the dispersion (figure 10).

Drug release from the temazepam-PEG dispersions (figure 17) depended also on the drug:carrier ratio as had been reported for diazepam-PEG 6000 dispersions[10]. The dissolution rates decreased as drug content increased presumably because temazepam release became increasingly drug controlled. Dissolution from

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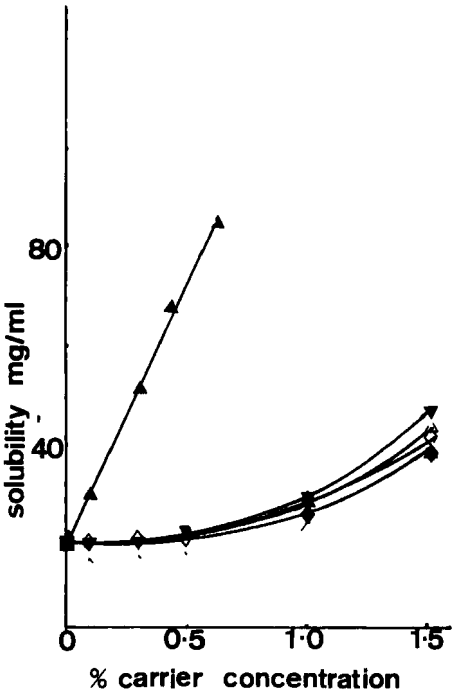

FIGURE 15.
Effects of PEGs and gelucire 44/14 on aqueous solubility of temazepam at 37 C. KEY: ▼ PEG 1000; ◆ PEG 4000; △ PEG 6000; ◇ PEG 10,000 and ▲ gelucire 44/14.

temazepam-gelucire 44/14 dispersions showed profiles similar to temazepam-PEG 1500 solid dispersions with the rate decreasing with an increase in drug content. No plugs, analagous to those seen in the triamterene systems, were observed in unaged samples.

Ageing of dispersions.

The dissolution of triamterene from its dispersions in the PEGs or gelucire 44/14 did not alter with storage, irrespective of drug concentration and molecular weight of the PEG. This is in contrast with

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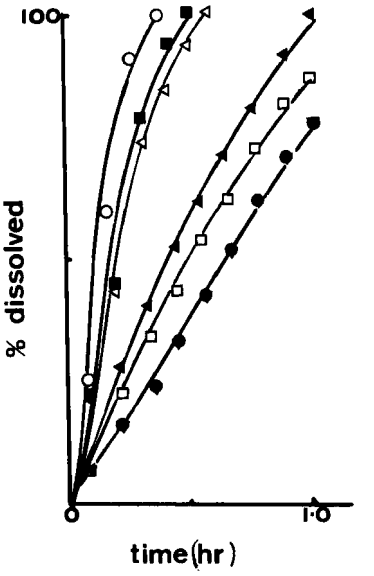

FIGURE 16.
Effects of carriers on dissolution of temazepam from capsules filled with dispersions containing 10% temazepam in PEGs or gelucire 44/14.
KEY: ○ temazepam-PEG 1000; ■ temazepam-PEG 1500; ● temazepam-PEG 4000; ▲ temazepam-PEG 6000; □ temazepam-PEG 10,000, △ temazepam-gelucire 44/14.

diazepam-PEG 6000[10] and indomethacin-PEG 6000[9] which showed ageing effects that depended on the drug:carrier ratio. The absence of ageing effects in the triamterene dispersions may be due to the drug remaining as crystals over the range of temperature used to prepare the samples with little effect on the particle size of triamterene.

However the dispersions containing polysorbate 80 showed ageing which depended on the amount of polysorbate 80 added and on the molecular weight of PEG used in the dispersion. For example, the incorporation of 2% polysorbate 80 into PEG 1500 dispersions containing 10% triamterene gave a $t_{80\%}$ of less than 30

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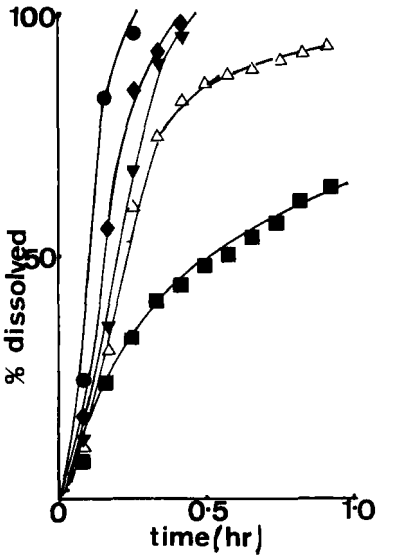

FIGURE 17.
Effects of drug:carrier weight ratios on dissolution of temazepam from capsules filled with dispersion prepared using PEGs or gelucire 44/14. KEY (% temazepam): ● 5; ◆ 10; ▼ 15; △ 20 and ■ 100.

minutes when tested after 24 hours but this increased to in excess of one hour following room temperature storage for 7 days. In similar samples but containing 5% polysorbate 80 in PEG 1500 the surfactant appeared to protect against age induced changes, since storage at room temperature for four months gave a t80% of less than 18 minutes, equivalent to that of the 24 hour-old sample.

In dispersions containing 10% triamterene and 5% polysorbate 80 in PEG 6000 the $t_{80\%}$ was about 25 minutes for 24 hour-old capsules, but on storage for 4 months the $t_{80\%}$ increased to more than 120 minutes. Thus although the incorporation of 5% polysorbate appeared to prevent ageing in dispersions containing 10% triamterene and PEG 1500, it did not in capsules containing PEG 6000.

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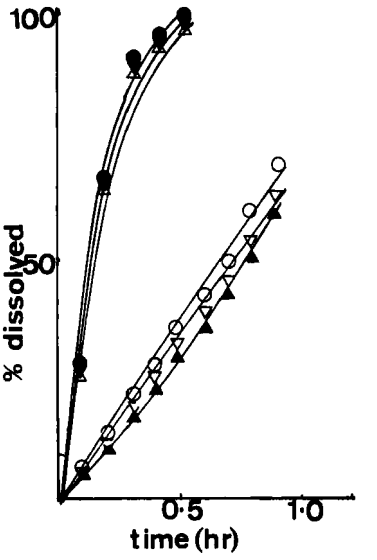

FIGURE 18.
Effect of ageing on dissolution of temazepam from capsules containing 10% temazepam in PEGs.
KEY: △ 24hr-PEG 4000; ▼ 24hr-PEG 6000; ● 24hr-PEG 10,000; ▲ 7 day-PEG 4000;▽7 day-PEG 6000 and ○ 7day-PEG 10,000.

The dissolution from capsules containing up to 30% temazepam dispersed in gelucire did not show any changes in dissolution during storage. In contrast capsules containing temazepam-PEG solid dispersions showed changes which depended on the molecular weight of the PEG. Although temazepam-PEG 1500 capsules containing up to 20% drug did not age when stored at room temperature for 2 months, ageing was apparent in dispersions containing 10% temazepam in PEG 4000, PEG 6000 and PEG 10,000 (figure 18).

The dissolution from aged capsules containing PEG 6000 was rather erratic as shown by greater standard deviations (coefficient of variation of 37%) in drug release for 24 hour- and 48 hour-old capsules compared

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to those containing PEG 4000 and PEG 10,000 (coefficient of variation of less than 5%). Erratic dissolution has been similarly shown for glutethimide-PEG dispersions[21].

Generally capsules prepared with PEG 1000 showed leakage from the gap between the cap and body of the hard gelatin shell on storage at room temperature. Furthermore, capsules containing 12.5% triamterene in PEG 1000 capsules cracked at the curvature of the cap which could be due the hygroscopicity of the PEG 1000 and the nature of the drug since cracking was not observed in capsules containing 10% temazepam.

CONCLUSIONS

This study indicates that preparing solid dispersions of triamterene or temazepam in PEGs or gelucire 44/14 improves the in vitro release rates of the drugs. The magnitutude of the increases depends on the molecular weight of the PEG, the drug:carrier ratio and the phase interaction between the drug and the carrier. For temazepam, which showed liquid state solubility in the carriers, increased dissolution was attributed to a reduction in particle size. Triamterene formed monotectics with PEG and gelucire 44/14 and the increased dissolution may be attributed to increased wetting. Gelucire 44/14 and the lower molecular weight PEGs (PEG 1000 and PEG 1500) gave faster release which decreased when drug levels were increased for both triamterene and temazepam and showed no effects of ageing. Polyethylene glycol 1000 may not be suitable for liquid-filling of hard gelatin capsules on account of its low melting point which makes dispersions prepared with this polymer likely to leak from the gelatin capsules. The results further suggest that for both triamterene and temazepam, gelucire 44/14 and PEG 1500

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are better carriers than the higher molecular weight PEGs because the capsules prepared with gelucire 44/14 and PEG 1500 increased dissolution of the drugs by four and three times respectively when compared with the higher molecular weight PEGs. In addition, the capsules remained stable with respect to dissolution and did not show signs of leakage on storage.

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