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# Solidification Studies of Polyethylene Glycols, Gelucire 44/14 or their Dispersions with Triamterene or Temazepam

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## Abstract

The solidification of polyethylene glycols (PEG 1500, PEG 2000, PEG 4000, PEG 6000), gelucire 44/14 or their dispersions containing triamterene or temazepam were studied to assess the feasibility of using these dispersions to liquid-fill hard gelatin capsules.

Solidification from melts, investigated by differential scanning calorimetry using cooling cycles, showed a tendency of the drugs, carriers or their dispersions to supercool. The degree of supercooling depended on the rate of cooling, the drug content and, for the PEGs, on the molecular weight. PEG 1500 and PEG 2000 gave one morphological form, irrespective of cooling rate; PEG 4000 and PEG 6000 solidified into at least two forms, depending on the cooling rate. Incorporation of drugs affected the morphology of the PEGs during solidification. The rate of crystal growth was, furthermore, influenced by the fusion temperature, molecular weight and the degree of supercooling. The degree of crystallinity, as measured by the enthalpies of solidification, decreased with increasing cooling rate.

The results show that reducing the rate of solidification could lead to incomplete solidification, giving products that are liable to change on storage.

Hard gelatin capsules are traditionally used to contain drugs in the form of powders or pellets. Walker (1980) and McTaggart et al (1984) utilized modified encapsulation machinery to prepare capsules filled with molten formulations of drug substances which solidify on cooling. Typical carriers used for such systems are polyethylene glycols of various molecular weights and macrogol esters such as the gelucires. Typically these carriers melt at, or below, approximately 70°C. Liquid-filling machines operate by holding the drug-carrier suspension or solution in a reservoir under agitation in the molten state and pumping it through a delivery orifice directly into the capsules. Whereas the reservoir and orifice are usually operated at controlled temperatures, the stage of the encapsulating machine operates at ambient conditions and may function as a heat sink leading to the rapid loss of heat from the capsules and their contents.

The aim of this study was to examine the solidification of polyethylene glycols and gelucire 44/14, by differential scanning calorimetry (DSC), to assess the potential problems induced by uncontrolled cooling during the liquid filling of hard gelatin capsules.

## Materials and Methods

Triamterene USP, temazepam USP, polyethylene glycol 1500, 2000, 4000, and 6000 (BDH, UK) and gelucire 44/14 (Gattefosse, France) were used as supplied. Because some amorphousness was apparent in the carriers or dispersions, the term 'solidification' is used throughout to describe the transition from liquid to solid state. Solidification of the carriers or their dispersions was studied using a Perkin-Elmer DSC7 differential scanning calorimeter, controlled by a Perkin-Elmer TAC/PC instrument controller and a cooling accessory. Liquid nitrogen was used as coolant to maintain the TAC system at − 70°C and dry, oxygen-free nitrogen was used as the purge gas. The DSC was calibrated with indium and zinc.

*Solidification of carriers*

Samples (approximately 5 mg) of PEG 1500, PEG 2000, PEG 4000, PEG 6000 or gelucire 44/14 were weighed into aluminium pans (Perkin-Elmer 50 μL), and the lids were crimped in position. Each sample was initially heated at 200°C $min^{-1}$ to 100°C and maintained at 100°C for 5 min to obliterate its previous history. The samples were subsequently scanned from 100 to 0°C at cooling rates of 2, 5, 10, 20, 30 or 40°C $min^{-1}$ to determine the effect of cooling rate on the DSC scans. The onset and peak temperatures and the enthalpies of solidification were determined in duplicate for each system. The differences in the onset or peak temperatures between the two determinations were less than 0·3°C; the differences in enthalpies were less than 2 J $g^{-1}$. The effect of fusion temperature on the solidification of the pure carriers was determined by heating the samples to 70, 100 or 150°C at 200° $min^{-1}$, holding at the fusion temperature for 5 min to obliterate previous thermal history, and then scanning from the fusion temperature to 0°C at 10°C $min^{-1}$. To determine the effect of holding times on the solidification of carriers, samples were heated to 100°C and kept at this temperature for 2, 5, 10, 20 or 30 min and scanned from 100 to 0°C at 10°C $min^{-1}$.

*Solidification of dispersions containing triamterene*

Mixtures of triamterene (10%) in each of the carriers were carefully weighed and triturated at 50°C (PEG 1500, PEG 2000 and gelucire 44/14) or 60°C (PEG 4000 and PEG 6000)

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to ensure adequate mixing. Samples (approximately 5 mg) of each drug-carrier mixture were then accurately weighed into sample pans which were crimped and, using the DSC7, heated to 100°C which was maintained for 5 min. The samples were subsequently scanned from 100 to 0°C at 5, 10, 20, 30 or 40°C $min^{-1}$. Other dispersions containing 2, 5, 10, 20 or 30% triamterene in PEG 1500 or PEG 6000 were similarly prepared and their samples scanned at 10°C $min^{-1}$ to determine the effect of drug : carrier ratio on the solidification of these carriers. The effect of fusion temperature on the solidification of dispersions containing 10% triamterene was determined by heating the samples to a maximum temperature of 70, 100 or 150°C at 200°C $min^{-1}$, holding at the fusion temperature for 5 min, and then scanning to 0°C at 10°C $min^{-1}$.

*Solidification of dispersions containing temazepam*

Dispersions containing 10% temazepam in the carriers were prepared at 100°C and analysed as described above for triamterene dispersions. These dispersions melted homogeneously at the preparation temperature. Other dispersions containing 2, 5, 10, 20, 30 or 50% temazepam were also prepared. Because temazepam dissolved in the carriers at higher temperatures, samples of these dispersions were crimped in aluminium pans and heated to a temperature which was 5°C above their liquidus temperatures (Dordunoo et al 1991). Scans were subsequently obtained from the fusion temperature to 0°C at 10°C $min^{-1}$. The effects of fusion temperature on the solidification of dispersions containing 10% temazepam were examined using dispersions in PEG 6000 which were prepared at 60°C for 5 min. Samples were taken and scanned to 0°C at 10°C $min^{-1}$ after heating to 70 or 100°C and being maintained at this temperature for 5 min.

## Results and Discussion

*Solidification of carriers*

Figs 1 and 2 show typical DSC scans of the PEGs during cooling. For PEG 1500 (Fig. 1), two exotherms were observed; the position of the smaller exotherm was not reduced to the same extent as the major exotherm as the cooling rate increased. The presence of two exotherms for PEG 1500 might be predicted because this molecular weight PEG is frequently a blend of equal parts of PEG 1540 and PEG 300 (Handbook of Pharmaceutical Excipients 1986).

There was one exotherm only for PEG 2000 during solidification, irrespective of the cooling rate, indicating the formation of one crystalline form of the polymer. For PEG 4000 and PEG 6000 however (Fig. 2), two exotherms were observed at cooling rates of 2, 5 or 10°C $min^{-1}$; these were presumably a result of the formation of two crystalline forms (Craig & Newton 1991a). In addition, the derivative DSC curve of the 20°C $min^{-1}$ scan indicated the presence of two events in the solidification exotherm. The relative sizes of the two exotherms depended on the cooling rate. For instance, PEG 6000 cooled at 2°C $min^{-1}$ produced a major exotherm which preceded the minor one. At cooling rates of 5 and 10°C $min^{-1}$ these two exotherms were of approximately equal size. Only one exotherm was apparent at cooling rates greater than 20°C $min^{-1}$.

Generally, the onset and peak temperatures were reduced as the rate of cooling was increased (Fig. 3), as has previously been observed by Buckley & Kovacs (1976). The reason for this trend may be inhibition of nucleation of the melt at the higher cooling rates and, consequently, lower solidification temperatures were observed (Jackson et al 1967).

Table 1 shows the variation of the enthalpies of solidification of PEG 1500 and PEG 6000 with cooling rate. Similar trends were observed with the other PEGs. The enthalpies decreased as the cooling rate was increased, indicating a reduction in the degree of crystallinity. The results in Table 1 may be compared with those previously reported. Craig & Newton (1991a, b) showed that for PEG 3400 and PEG 6000 the heats of fusion obtained at a scanning rate of 2°C $min^{-1}$ were 96 and 91%, respectively, of the values obtained at 8°C $min^{-1}$. Thus, although on heating the apparent enthalpies increased when the heating rate was increased, the heats of solidification decreased as the cooling rate was increased, indicating a greater degree of amorphousness within the sample as the cooling rate was increased. This implies that rapid cooling may lead to incomplete recrystallization.

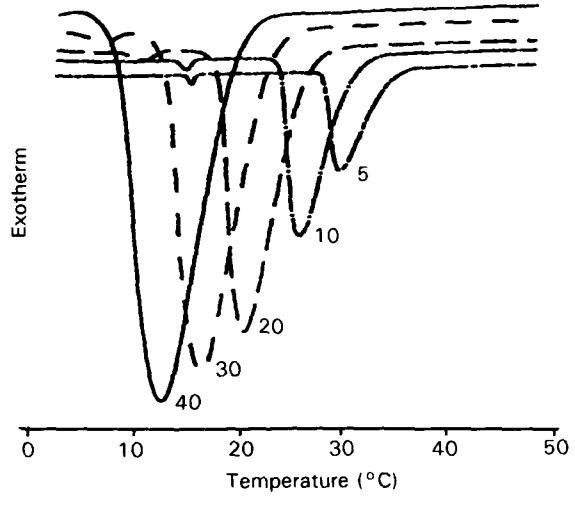


FIG. 1. The influence of cooling rates on the DSC scans of PEG 1500 after fusion at 100°C and during cooling at 5, 10, 20, 30 or 40°C $min^{-1}$.

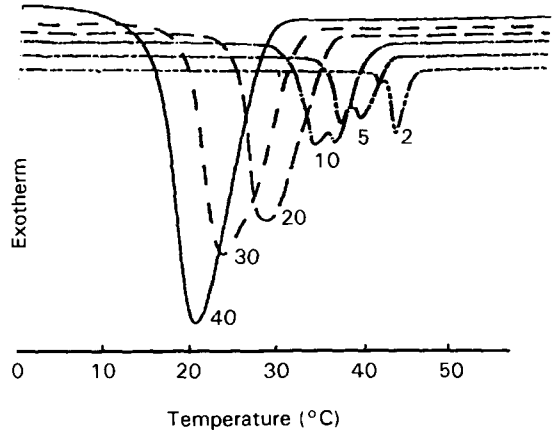


FIG. 2. The influence of cooling rates on the DSC scans of PEG 6000 after fusion at 100°C and during cooling at 2, 5, 10, 20, 30 or 40°C $min^{-1}$.

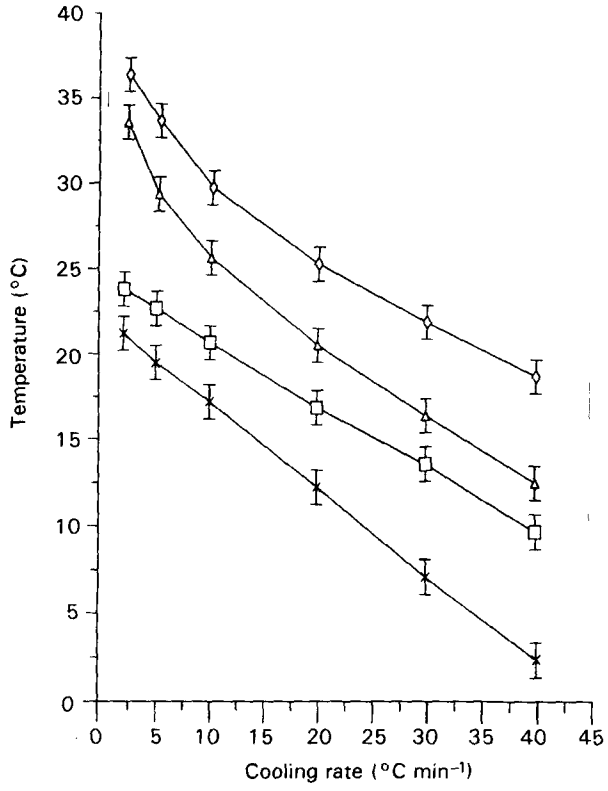


FIG. 3. The influence of cooling rates on the onset (◇, □) and peak temperatures (△, X) of solidification of PEG 1500 (◇, △) or gelucire 44/14 (□, X) previously melted at 100°C for 5 min.

Uncontrolled cooling in machines used for the liquid filling of gelatin capsules may, therefore, lead to systems with a potential to reorganize their solid structure on storage. The results from this study confirm that the cooling rate, by controlling the solidification temperature, influenced the morphology (as shown by the number of exotherms) or amorphousness (as indicated by the enthalpies of solidification) of the polyethylene glycols.

The onset and peak temperatures changed essentially with the molecular weight of the polyethylene glycol at the same rate of cooling (see Table 2). Comparison of solidification rates for the different molecular-weight materials would be possible only for equal extents of supercooling instead of at equal rates of cooling or equal values of temperature (Godovsky et al 1972). The solidification rates of the polymers were determined using equations 1 and 2. The half-lives ($t\frac{1}{2}$) of the solidification processes were determined using equation 1

Table 1. Effect of cooling rates on the enthalpy of solidification of PEG 1500 and PEG 6000, previously heated at 100°C for 5 min (values are the means of two determinations).

| Cooling rate (°C min$^{-1}$) | Enthalpy of solidification (J g$^{-1}$) | |
|---|---|---|
| | PEG 1500 | PEG 6000 |
| 2 | 151·1 ± 1·1 | 176·1 ± 1·4 |
| 5 | 148·4 ± 1·5 | 173·2 ± 1·1 |
| 10 | 144·5 ± 1·1 | 171·8 ± 1·1 |
| 20 | 141·4 ± 1·3 | 165·1 ± 0·9 |
| 30 | 139·1 ± 1·2 | 162·8 ± 1·2 |
| 40 | 135·2 ± 1·7 | 157·4 ± 1·3 |

Table 2. Effect of molecular weight on the onset and peak solidification temperatures of PEG 1500, PEG 2000, PEG 4000 and PEG 6000 obtained at a cooling rate of 20°C min$^{-1}$ (values are the means of two determinations).

| PEG | Onset temperature (°C) | Peak temperature (°C) |
|---|---|---|
| 1500 | 25·4 ± 0·2 | 20·6 ± 0·1 |
| 2000 | 29·6 ± 0·1 | 25·2 ± 0·1 |
| 4000 | 31·5 ± 0·2 | 27·9 ± 0·1 |
| 6000 | 36·4 ± 0·1 | 31·0 ± 0·1 |

(Kissinger 1957).

$$t\tfrac{1}{2} = (T_o - T_m)/\phi \quad (1)$$

where $\phi$ is the cooling rate in °C min$^{-1}$, and $T_o$ and $T_m$ are, respectively, the onset and peak temperatures in °C (where there was more than one exotherm the temperature taken was that of the first exotherm). Assuming that the solidification occurred by first-order reaction kinetics (Godovsky et al 1972), the half-life would be related to the solidification rate constant, k, by equation 2.

$$k = 0.693/t\tfrac{1}{2} \quad (2)$$

The extents of supercooling were determined by subtracting the onset temperature of solidification from the melting point of the PEG determined at equivalent heating rate. The variations of the solidification growth rate constants, k, with degree of supercooling and the nominal molecular weight of PEG are

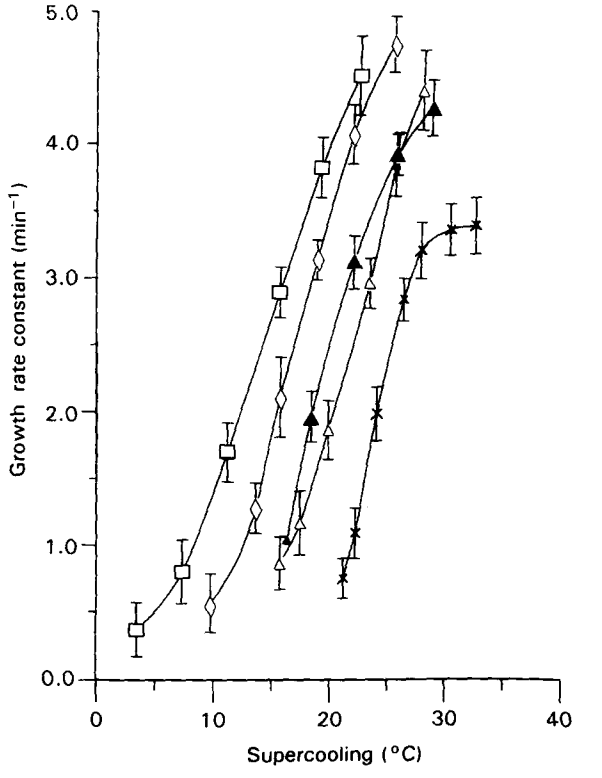


FIG. 4. The influence of supercooling on the solidification rate constants during recrystallization of PEG 1500 (□), PEG 2000 (◇), PEG 4000 (△), PEG 6000 (▲) or gelucire 44/14 (X) obtained at various cooling rates.

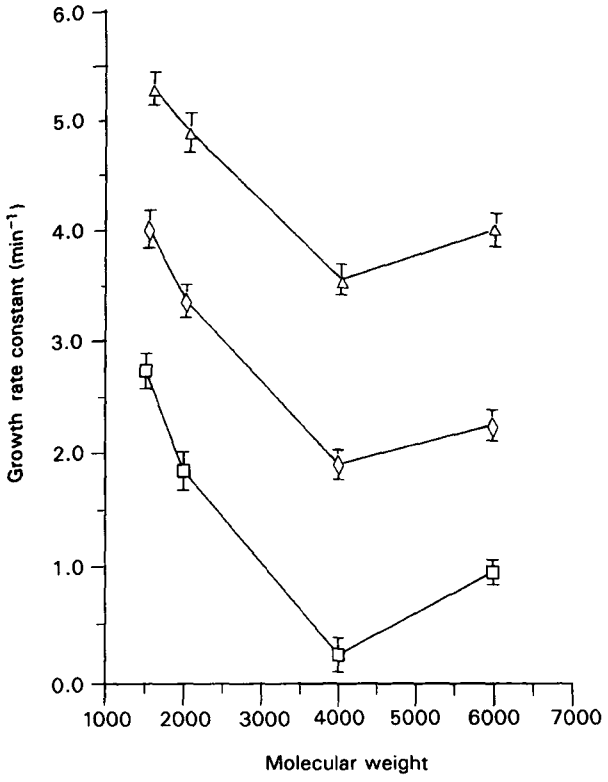


FIG. 5. The influence of molecular weight of PEG on the solidification growth rate constants at 15 (□), 20 (◇) or 25°C (△) of supercooling.

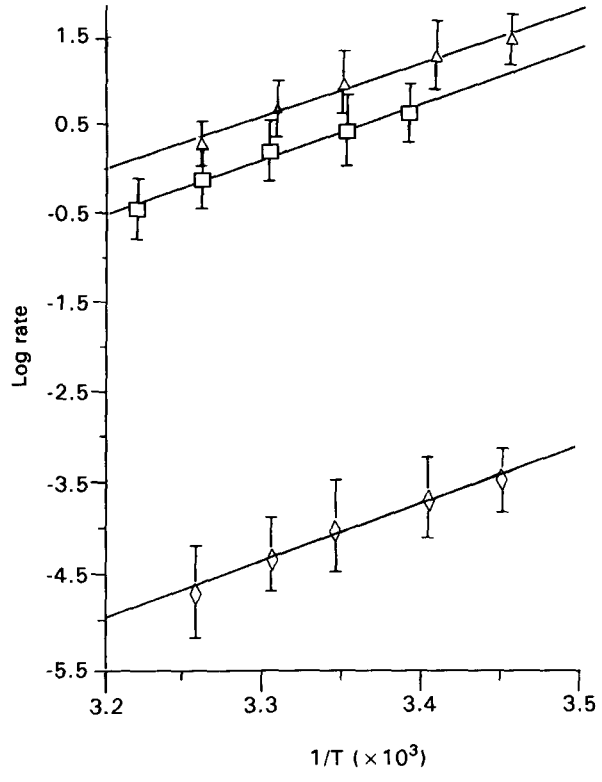


FIG. 6. Representative plots for PEG 1500 of log $k$ against $1/T_o$ (□), log $\phi$ against $1/T_m$ (△) and log $(\phi/T_m^2)$ against $1/T_m$ (◇).

shown in Figs 4 and 5, respectively. The solidification rate constants in Fig. 4 were determined at 15, 20 and 25°C of supercooling and are plotted in Fig. 5. The solidification rate constants were ranked in the order PEG 1500 > PEG 2000 > PEG 6000 > PEG 4000. Godovsky et al (1972), in a non-isothermal study of polyethylene oxides, observed a similar slowing down of crystallization rate with increasing molecular weight. They attributed a deep minimum in the rates in the region of molecular weight 4000 to a transition from completely extended chain crystallization to fold-chain crystallization. Godovsky et al (1972) also reported that the ability to fold during crystallization was followed by a simultaneous sharp increase in the crystallization rate at molecular weights greater than 4000 and by a change of morphology.

The differences in solidification rates between the PEGs narrowed as the degree of supersaturation increased, as is shown by the progressive flattening of the curves as the degree of supercooling was increased (Fig. 5). This may be ascribed to the preponderance of the inhibition of molecular transport over morphological changes (Godovsky et al 1972). The sigmoidal shape of some of the curves in Fig. 4 is probably a consequence of thermal inertia at low supercooling, and high melt viscosity at high degrees of supercooling (Jackson et al 1967).

In addition to the solidification rates, three methods were used to derive Arrhenius constants for the solidification processes. Using the Arrhenius relationship, a plot of log k against $1/T_o$ should give a slope equivalent to E/2·303R where E is the activation energy of solidification and R is the gas constant. Secondly, when log $\phi$ is plotted against $1/T_m$ (Duswalt 1974) the activation energy, E, may be derived by multiplying the slope by 2·19R. Thirdly, a plot of log $(\phi/T^2_m)$ against $1/T_m$ (Osawa 1970) may be used to determine E, because this equates to 2·303R multiplied by the slope of the plot.

Each of the three data treatments showed excellent correlation. For example, in Fig. 6 each of the three plots (log k against $1/T_o$, log $\phi$ against $1/T_m$ and log $(\phi/T_m^2)$ against $1/T_m$) gave correlation coefficients > 0·99 for PEG 1500. The three methods of determining the activation energies of solidification gave comparable values (Table 3), although the Osawa (1970) method consistently gave slightly higher values. The activation energies followed a pattern which was the reverse of that of the growth rate curves in that the activation energy of solidification was highest for PEG 4000.

When the carriers were fused at higher temperatures (e.g., Fig. 7 for PEG 6000 where a number of solidification events became apparent) or were held for longer holding times, at a particular fusion temperature (Table 4), there was a reduction of the solidification temperature and its associated enthalpies.

Table 3. The activation energies of the solidification process of the carriers derived from plots of (A) log $\phi$ against $1/T_m$ (after Duswalt (1974)); (B) log $(\phi/T_m^2)$ against $1/T_m$ (after Osawa 1970)) and (C) log k against $1/T_o$ (values are the means of two determinations).

| Carrier | Activation energy (kJ mol$^{-1}$) | | |
|---|---|---|---|
| | A | B | C |
| PEG 1500 | 95·9 ± 2·9 | 105·8 ± 4·3 | 99·0 ± 3·2 |
| PEG 2000 | 119·4 ± 3·2 | 127·6 ± 2·5 | 119·8 ± 4·3 |
| PEG 4000 | 121·8 ± 4·4 | 131·4 ± 2·1 | 122·5 ± 4·1 |
| PEG 6000 | 105·4 ± 3·8 | 116·0 ± 2·9 | 114·9 ± 3·6 |
| Gelucire 44/14 | 134·3 ± 4·2 | 138·2 ± 3·3 | 136·7 ± 2·5 |

This may be explained by the structured theory of liquids which stipulates that there is a limited three-dimensional structure of the molecules in liquids (Shinoda 1977), which would form centres for crystallization, or nuclei, during cooling. The proportion of these centres of crystallization would be expected to decrease when temperature is increased because any thermal energy supplied would be converted into kinetic energy of the molecules, in line with the kinetic theory of matter. The relative motion of the molecules would thereby increase, leading to greater disorder in the structure, or entropy, of the liquid. A gradual breakdown of these structures with increasing temperature or with longer holding times is, therefore, expected, leading to inhibition of solidification.

The solidification of gelucire 44/14 from its melts is shown in Fig. 8. The onset or the peak solidification temperatures of gelucire 44/14 followed a straight-line relationship with cooling rate in comparison to PEGs where curvilinear relationships were obtained (Fig. 3). Unlike PEGs, however, the enthalpy of solidification of gelucire 44/14 was unaffected by cooling rate; values were 102·4, 102·1, 101·9, 102·0 and 101·8 J $g^{-1}$ at cooling rates of 5, 10, 20, 30 and 40°C $min^{-1}$, respectively. The apparent lack of change in the enthalpy at different cooling rates would indicate the formation of one crystalline form on cooling. The activation energies of solidification of gelucire 44/14 were slightly higher than for the PEGs (Table 3). The rate constants for solidification of gelucire 44/14 were lower than those of the PEGs (see Fig. 4).

*Solidification of dispersions containing triamterene*

Fig. 9 gives examples of scans of dispersions containing 10% triamterene prepared at 100°C for 5 min. There was only one major exotherm for each of the dispersions in the PEGs

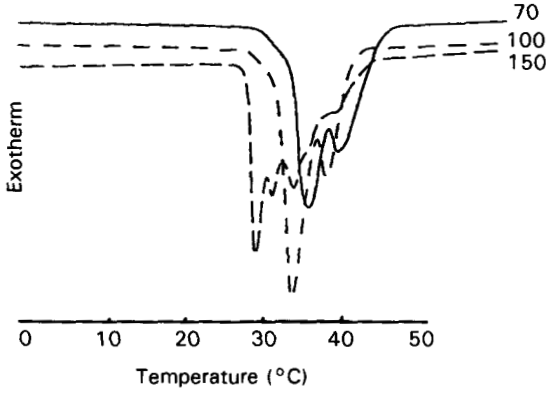


FIG. 7. The effect of holding at 70, 100 or 150°C for 2 min on the DSC scans of PEG 6000 obtained at a cooling rate of 10°C $min^{-1}$.

Table 4. Effect of holding times at 100°C on the solidification temperature ($T_o$) and enthalpy of solidification of PEG 6000 cooled at 10°C $min^{-1}$ (means of two determinations).

| Holding times (min) | Solidification temperature (°C) | Enthalpy of solidification (J $g^{-1}$) |
|---|---|---|
| 0 | 40·6 ± 0·2 | 178·7 ± 1·4 |
| 5 | 39·8 ± 0·1 | 173·0 ± 1·3 |
| 10 | 39·4 ± 0·2 | 170·9 ± 1·8 |
| 20 | 37·3 ± 0·1 | 169·1 ± 1·1 |
| 30 | 35·2 ± 0·2 | 165·8 ± 1·3 |

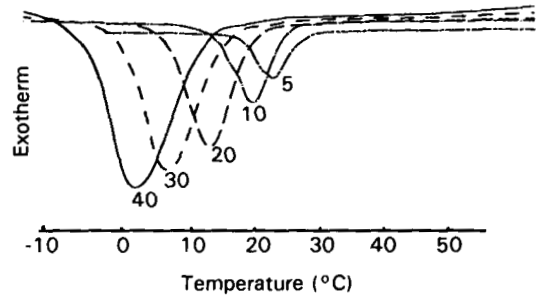


FIG. 8. The influence of cooling rates on the DSC scans of gelucire 44/14 after fusion at 100°C and during cooling at 5, 10, 20, 30 or 40°C $min^{-1}$.

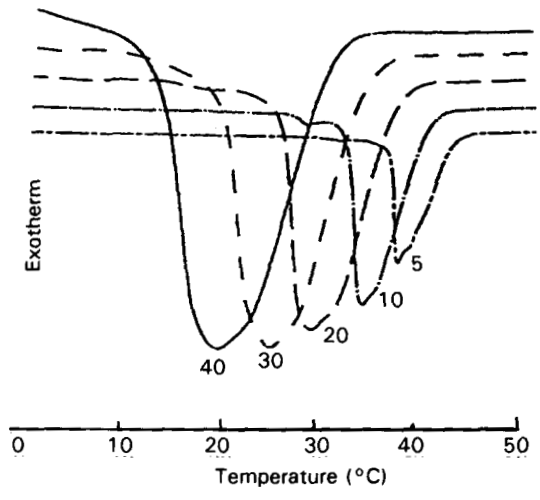


FIG. 9. The influence of cooling rates on the DSC scans of dispersions containing 10% triamterene in PEG 6000 during cooling at 5, 10, 20, 30 or 40°C $min^{-1}$.

showing that the presence of the triamterene particles had influenced the DSC scans and, therefore, the solidification process of the PEG. This was particularly apparent with dispersions of triamterene in PEG 4000 and PEG 6000 where the pure carriers displayed two separate exotherms when cooled at 2, 5 or 10°C $min^{-1}$ (Fig. 2).

The solidification temperatures of the dispersions containing triamterene decreased with higher cooling rates, as observed for the pure carriers. The temperatures of solidification obtained from scans of dispersions containing 2, 5, 10, 20 or 30% triamterene in the PEGs, which were fused at 100°C for 5 min, did not differ from those of the pure carriers, showing that the solidification temperatures of these dispersions were unaffected by the drug : carrier ratio. Heating of these dispersions to 150°C, however, resulted in slight reductions of the solidification temperatures (Table 5). The higher fusion temperature appeared to have inhibited the solidification of the dispersions, as observed with the pure carriers.

Because triamterene had negligible solubility in the carriers when the dispersions were prepared at 100°C (Dordunoo et al 1991), the observed values of enthalpy were compared with the expected values for the carrier alone (Table 6). The expected values were determined using equation 3.

$$\Delta H_{exp} = \Delta H^{\circ}.P/100 \quad (3)$$

Table 5. Effect of fusion temperature and cooling rate on the onset temperature of solidification of PEG 6000 or dispersions containing 10% triamterene in PEG 6000 heated to 100 or 150°C for 5 min (results are the means of two determinations).

| Cooling rate (°C min$^{-1}$) | Fusion temperature PEG 6000 | | 10% Triamterene PEG 6000 | |
|---|---|---|---|---|
| | 100°C | 150°C | 100°C | 150°C |
| 2 | 43·2 ± 0·2 | 40·2 ± 0·2 | 44·3 ± 0·1 | 35·7 ± 0·2 |
| 5 | 42·1 ± 0·1 | 39·6 ± 0·2 | 42·6 ± 0·2 | 34·5 ± 0·1 |
| 10 | 40·0 ± 0·1 | 36·9 ± 0·1 | 41·2 ± 0·2 | 31·9 ± 0·1 |
| 20 | 36·4 ± 0·2 | 34·1 ± 0·1 | 37·8 ± 0·2 | 28·0 ± 0·2 |
| 30 | 32·6 ± 0·2 | 30·8 ± 0·2 | 33·2 ± 0·1 | 24·9 ± 0·1 |
| 40 | 29·2 ± 0·2 | 27·6 ± 0·1 | 30·7 ± 0·2 | 21·7 ± 0·1 |

where $\Delta H°$ and $\Delta H_{exp}$ are the enthalpy of the pure carrier and the expected enthalpy of the dispersion, and P is the percentage of the carrier in the dispersion. There were no major differences between the experimentally derived values of the enthalpies of solidification of the dispersions prepared at 100°C, and the expected values. This similarity confirmed the lack of interaction between triamterene and the carriers when fused at 100°C. When fused at 150°C, however, dispersions containing 10% triamterene in the carriers possessed lowered enthalpies of fusion compared with fusion at 100°C, indicating an introduction of amorphousness into dispersions prepared at the higher temperatures.

Incorporation of triamterene into the PEGs reduced the activation energies of solidification. For example, in Table 7, the addition of 10% triamterene reduced the activation energy of crystallization of all PEGs by about 10–15%, as calculated by the method of Duswalt (1974). The growth rate constants of dispersions containing 10% triamterene in PEG 1500, at equal degrees of supercooling, increased, marginally, compared with the pure PEG 1500 (Fig. 10). The growth rate constants for dispersions using the other PEGs were, however, reduced (Fig. 11). The solidification rate constants of dispersions containing triamterene in gelucire 44/14 (Fig. 12) were lower than those observed for that carrier alone.

*Solidification of dispersions containing temazepam*

The presence of 10% temazepam in the carriers reduced the number of exotherms (Fig. 13) as observed with dispersions containing triamterene. The solidification temperatures of

Table 7. The activation energy of solidification of carriers and their dispersions containing 10% temazepam or 10% triamterene derived using the method of Duswalt (1974) (results are the means of two determinations).

| Carrier | Activation energy (kJ mol$^{-1}$) 10% Triamterene | 10% Temazepam |
|---|---|---|
| PEG 1500 | 81·8 ± 2·9 | 90·7 ± 2·7 |
| PEG 2000 | 93·7 ± 1·8 | 113·8 ± 1·3 |
| PEG 4000 | 113·9 ± 2·3 | 116·3 ± 1·9 |
| PEG 6000 | 96·5 ± 3·1 | 113·9 ± 2·9 |
| Gelucire 44/14 | 117·2 ± 3·7 | 132·6 ± 4·6 |

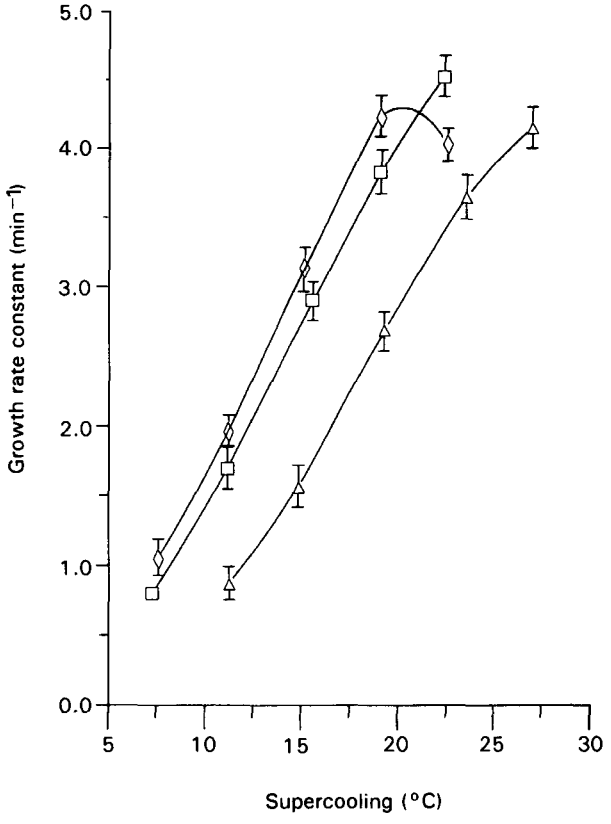


FIG. 10. The effect of degree of supercooling on the solidification rate constants of PEG 1500 (□) and its dispersions containing 10% triamterene (◇) or 10% temazepam (△) obtained at various cooling rates.

Table 6. Effect of drug on the enthalpies of solidification of dispersions containing 10% triamterene in PEG 1500, PEG 2000, PEG 4000, PEG 6000 or gelucire 44/14 previously heated to 100 or 150°C for 5 min, or containing 10% temazepam in PEGs or gelucire 44/14 previously heated at 100°C for 10 min. Dispersions were cooled at 10°C min$^{-1}$ (means of two determinations).

| Carrier | Enthalpy of solidification (J g$^{-1}$) | | | |
|---|---|---|---|---|
| | Calculated | 10% Triamterene fused at: | | 10% Temazepam |
| | | 100°C | 150°C | |
| PEG 1500 | 136·0 | 136·9 ± 0·9 | 109·5 ± 1·2 | 121·7 ± 1·2 |
| PEG 2000 | 144·0 | 142·3 ± 1·2 | 118·0 ± 1·4 | 134·4 ± 1·4 |
| PEG 4000 | 146·7 | 144·9 ± 0·8 | 127·7 ± 1·3 | 139·9 ± 1·1 |
| PEG 6000 | 152·1 | 147·1 ± 1·3 | 128·3 ± 1·2 | 141·1 ± 0·8 |
| Gelucire 44/14 | 91·9 | 88·8 ± 1·2 | 82·3 ± 0·9 | 86·0 ± 1·1 |

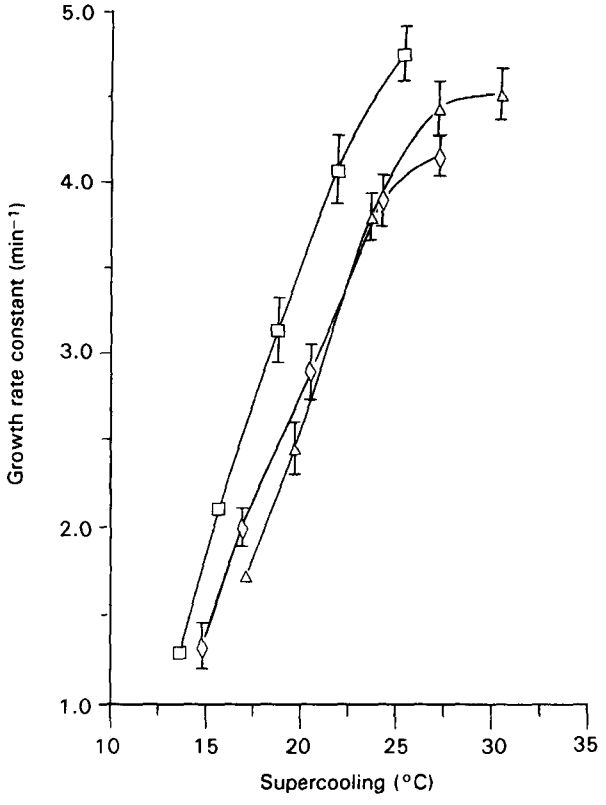


FIG. 11. The effect of degree of supercooling on the solidification rate constants of PEG 2000 (□) and its dispersions containing 10% triamterene (◇) or 10% temazepam (△) obtained at various cooling rates.

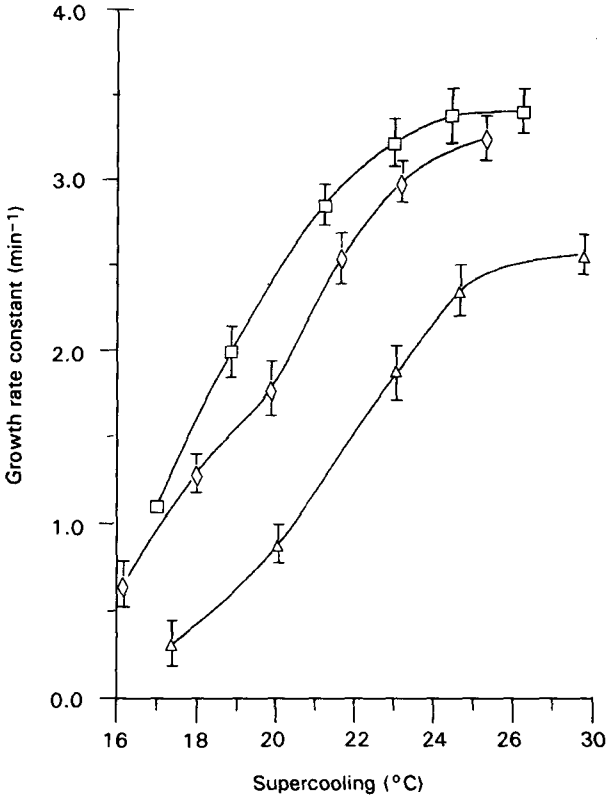


FIG. 12. The effect of degree of supercooling on the solidification rate constants of gelucire 44/14 (□) and its dispersions containing 10% triamterene (◇) or 10% temazepam (△) at various cooling rates.

dispersions containing temazepam were also reduced as the cooling rate was increased, as was observed for the carriers and dispersions containing 10% triamterene.

The solidification temperatures of dispersions containing temazepam, unlike those containing triamterene, depended on the drug : carrier ratio (Table 8) and were reduced as the temazepam content of the PEGs was increased (i.e. the degree of supercooling increased). The reductions became more pronounced as the dispersions contained increased quantities of the drug.

The enthalpies of solidification of dispersions of 10% temazepam in the carriers were lower than calculated (Table 6) showing that increased amorphous character was introduced into the dispersions by temazepam. Compared with dispersions containing the same proportion of triamterene and heated at 100°C, dispersions containing temazepam gave lower values of the enthalpy of solidification. These decreased with higher cooling rates (see PEG 2000 dispersions in Table 9). Similar effects were observed for the pure carriers and for dispersions containing 10% triamterene.

Figs 10–12 show examples of the influence of supercooling on the solidification rate constants of the carriers or their dispersions. The solidification rate constants of dispersions containing 10% temazepam were lower than those obtained for pure carriers or dispersions containing the equivalent amount of triamterene. This might have been because of the increased viscosity or glass-forming tendency of the dispersions containing temazepam, or both (Dordunoo et al 1991). Further

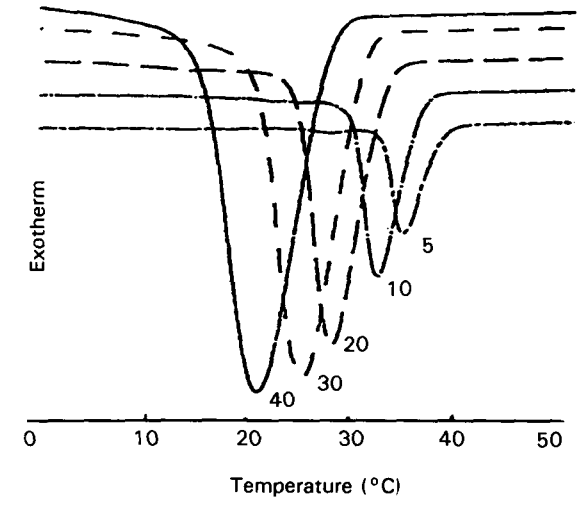


FIG. 13. The influence of cooling rates on the DSC scans of dispersions containing 10% temazepam in PEG 6000 during cooling at 5, 10, 20, 30 or 40°C $min^{-1}$.

confirmation of the reduced tendency of dispersions containing temazepam to solidify could be seen in the studies with various proportions of temazepam; these showed that there was an approximately 5°C reduction in the onset temperature for every 10% increase in proportion of temazepam in PEG 6000 (Table 8).

Addition of temazepam to PEGs slightly reduced the activation energies of the carriers but the reduction was less than

Table 8. Influence of drug : carrier ratios on the onset temperature of solidification of dispersions containing 2, 10, 20, 30 or 50% temazepam in PEG 6000 cooled at 10°C $min^{-1}$ (results are the means of two determinations).

| Dispersion | $T_o$ (°C) |
|---|---|
| PEG 6000 | 40·0 ± 0·1 |
| 2% temazepam-PEG 6000 | 39·3 ± 0·2 |
| 10% temazepam-PEG 6000 | 37·1 ± 0·1 |
| 20% temazepam-PEG 6000 | 31·1 ± 0·2 |
| 30% temazepam-PEG 6000 | 27·4 ± 0·2 |
| 50% temazepam-PEG 6000 | 15·3 ± 0·2 |

Table 9. Influence of cooling rates on the enthalpies of solidification of dispersions containing 10% temazepam in PEG 2000 previously heated at 100°C for 10 min (results are the means of two determinations).

| Cooling rate (°C $min^{-1}$) | Enthalpy (J $g^{-1}$) |
|---|---|
| 2 | 141·2 ± 1·2 |
| 5 | 138·4 ± 0·9 |
| 10 | 137·4 ± 1·1 |
| 20 | 136·6 ± 0·7 |
| 30 | 134·7 ± 1·0 |
| 40 | 132·2 ± 1·2 |

was observed for corresponding dispersions containing triamterene (Table 8). The effects of temazepam on the crystallization of gelucire 44/14 were similar to those of the corresponding dispersions using PEGs.

## Conclusions

The solidification of melts consists of three processes: achievement of supercooling; nucleation; and crystal growth. This study confirms that the degree of supercooling increased with increasing cooling rate.

Crystal growth rates are normally influenced by supercooling in exactly the same way as nucleation. The solidification rate would therefore decrease at high degrees of supercooling as observed for the higher molecular weight PEGs. Because faster cooling results in a greater degree of supercooling, solidification of PEGs at higher cooling rates would, furthermore, result in lower growth rates, as was observed for PEG 6000 at a cooling rate of 40°C $min^{-1}$. The cooling of dispersions on filling capsules during liquid filling can only be speculated on. The data suggest, however, that rapid cooling will leave material that is not fully solidified and is liable to change on storage. Ideally, such machines should have a heat-controlling mechanism. The storage of the melt at elevated temperatures and for a considerable period of time before filling of the reservoir would also strongly influence the properties of the contents of the capsule. Obviously the time that a melt is stored in the filling hopper before filling of the capsules will alter the amorphousness of the contents.

Higher fusion temperatures reduced the solidification temperature, probably by destroying the molecular structures in the melts which would have acted as centres for crystallization. The presence of triamterene particles in the melts did not promote the solidification process, especially in the dispersions containing the higher molecular weight PEGs. Solidification was inhibited by the presence of temazepam in all the carrier studies; the higher proportions of temazepam produced the greater degree of inhibition.

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