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The effects of ageing on the thermal behaviour and mechanical properties of pharmaceutical glycerides

W. Sutananta [1], D.Q.M. Craig *, J.M. Newton

Centre for Materials Science, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK

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Abstract

The thermal behaviour of stored Gelucires 43/01, 50/02, 54/02, 50/13 and 55/18 has been studied, particularly with a view to examining the relationship between preparation conditions and physical stability. The endotherms of Gelucire 43/01 samples were found to approach an equilibrium shape on storage, with samples which had been fast cooled from the melt adopting this shape over the shortest period of time. Tempering of these materials at elevated temperatures resulted in alterations in the distribution of endotherms and represents a possible method of accelerating the transition to the equilibrium form. Ageing of Gelucires which contain mixes of glycerides and polyethylene glycol (PEG) esters resulted in changes in the endotherm shape but no evidence for an equilibrium profile was obtained. Studies on Gelucire 55/18, which contains only PEG esters, showed that the main endothermic peak exhibited little evidence for ageing effects, although a lower temperature shoulder was observed on storage. Tensile strength (σ) measurements indicated that the strength of the Gelucires also changed on storage. It was noted that materials containing either glycerides or PEG esters tended to show an increase in σ on storage, while Gelucires containing a mixture of the two components showed a decrease in strength.

Key words: Glyceride; Gelucire; Triglyceride; DSC; Tablet; Tensile strength; Stability

1. Introduction

Glycerides are a group of materials derived from natural products which have a wide variety of applications within pharmaceutical formulation. In particular, glycerides which are solid or semi-solid at room temperature are used as suppository bases and, more recently, as controlled release matrices (Howard and Gould, 1987; Kopcha et al., 1990, 1991). Gelucires are examples of commercially available glyceride bases which may be used for controlled release purposes, these materials comprising mixtures of glycerides with fatty acid esters of polyethylene glycol (PEG). Gelucires may exhibit complex morphological features, thus necessitating the development of techniques which may characterise the structures of these materials. In a recent study, Sutananta et al. (1994) studied the thermal and mechanical properties of these systems, demonstrating that both the melting behaviour

* Corresponding author.

[1] Present address: Faculty of Pharmacy, Silpakorn University, Sanamchan Palace, Nakornpathom 73000, Thailand.

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and the tensile properties of Gelucires are dependent on the preparation conditions. In particular, it was suggested that fast cooling produced systems whereby the various chemical components are combined into homogeneous structures, while slower cooling leads to fractionation of the Gelucire components into different regions on a microscopic scale.

It is well established that glyceride-based products may exhibit ageing effects, whereby a range of physical properties may change on storage of the bases. In particular, physical properties of glyceride suppositories such as melting point, softening time and hardness tend to increase with time (e.g., De Blaey and Rutten-Kingma, 1976; Moes and Jaminet, 1976; Coben and Lordi, 1980; Liversidge et al., 1981; Yoshino et al., 1981) and are sometimes accompanied by changes in the in vitro and in vivo release of drug from the dosage form (Kanto, 1975; Taylor and Simpkins, 1981; Kahela et al., 1987). The mechanism responsible for these changes has been attributed to either the conversion of triglycerides to more stable polymorphic forms (Liversidge et al., 1979, 1981; Yoshino et al., 1981, 1984; Pryce-Jones et al., 1989) or conversion from the amorphous to the crystalline state of the fat bases (Coben and Lordi, 1980; Laine et al., 1988). However, commercial glycerides are invariably highly chemically (and therefore physically) complex, hence polymorphic changes must be considered alongside phenomena such as eutectic or solid solution formation and segregation of components on a microsocopic scale.

A number of studies have also indicated that Gelucire products may exhibit ageing effects. Remunan et al. (1992a,b) noted a decrease in the dissolution rate of nifedipine from tablets containing nifedipine-PVP complex (90%) and Gelucire 53/10 (10%) during storage from 3 to 6 months. In contrast, Dennis et al. (1990) found that the time for 50% ketoprofen release from mixture of Gelucire 50/13 and 50/02 in vitro was reduced from 253 min directly after manufacture to 161 min after 28 days storage at 30°C. Nonetheless, no statistically significant changes were observed in vivo. Other studies have showed no changes in properties with time. For example, the dissolution of triamterene and temazepam from their dispersions in Gelucire 44/14 did not alter with storage up to 3 months (Dordunoo et al., 1991). The relationship between the storage of Gelucire dosage forms and changes in product performance is therefore poorly understood.

Given the observation that changes in the structure of Gelcuires may be detected using differential scanning calorimetry (DSC) (Sutananta et al., 1994), it is logical to suggest that ageing effects may also be detected and therefore more thoroughly understood using this method. Indeed, previous studies by Dennis (1988) demonstrated an increase in the melting points of a number of Gelucires (33/01, 46/07, 50/02, 50/13) on storage, although there was no clear correlation with drug release rate. A further complication lies in the chemical complexity of the Gelucire bases, which is summarised in Table 1. The bases may contain pure glycerides, glycerides and PEG esters in varying proportions or, in the case of Gelucire 55/18, pure polyethylene glycol esters with no glycerides present. There is no direct information on the way in which PEG esters of fatty acids solidify. However, it has been shown that thermal history affects the crystal structure and the dissolution rate of PEGs themselves and of drugs dispersed in solid dispersion with PEG as a carrier (Chatham, 1985; Craig and Newton, 1991), hence it is possible that the same will apply to the PEG esters.

In this study, a systematic investigation into the effects of storage conditions on a range of Gelucire samples, prepared under controlled conditions, has been performed and those changes related to alterations in the mechanical properties of the bases. In this way, it is intended that deconvolution of the factors determining the extent of ageing may be possible, along with an assessment of the effects of such processes on the physical properties of the Gelucire samples.

2. Materials and methods

2.1. Materials

Gelucires 43/01, 50/02, 54/02, 50/13 and 55/18 (Gattefosse s.a., St Priest) were used

throughout the study. The batches used here are the same as those described in a previous investigation (Sutananta et al., 1994).

2.2. Sample preparation

2.2.1. DSC

Slow and fast cooled samples were prepared for DSC studies by accurately weighing 5–7 mg into an aluminium DSC pan which was then covered and crimped. Each sample pan was then placed in a small glass bottle and heated in an LTE G150 Oven fitted with a Newtronic Micro 96 Digital Programmer (Laboratory Thermal Equipment, Oldham) at 3°C/min to a maximum temperature of 75°C, at which the samples were held for 1 h. For slow cooled samples, the oven was automatically cooled at 0.17°C/min (10°C/h) to 30°C. Fast cooled samples were prepared by flash cooling in liquid nitrogen. Samples were stored over silica gel at room temperature ($\approx$ 18–24°C). The relative humidity in the cabinets was found to be 0–10%.

2.2.2. Tensile strength studies

The method used for tensile strength studies was the same as that described in a previous investigation (Sutananta et al., 1994). Molten Gelucires were poured into an aluminium mould (4×9 holes of diameter 1.25 cm and 0.68 cm deep). The tablets obtained after cutting away excess solid were flat-faced cylinders whose diameter and thickness were accurately measured to 0.002 cm with a micrometer. Tablets were kept in a desiccator at room temperature over silica gel for 12–24 h before being subjected to any evaluation. Slow cooled samples were prepared as described above. However, previous studies (Sutananta et al., 1994) have indicated that very fast cooling may result in cracks in the moulded tablets, hence instead of immersing the samples in liquid nitrogen the molten materials were allowed to cool to room temperature under ambient conditions.

2.3. DSC investigations

A Perkin-Elmer DSC-7 connected to a DEC 325c personal workstation (Perkin Elmer Ltd) was used throughout, as described previously (Sutananta et al., 1994). Tempering studies were conducted on Gelucire 43/01. Fast cooled Gelucire 43/01 samples were annealed (or tempered) in an oven (TC 1900 Temperature Controller, ICI

Table 1
Approximate chemical composition (% w/w) of Gelucire samples studied (information supplied by Gattefosse s.a.)

Sample	Glycerides			PEG esters		FA composition (%)
	Mono-	Di-	Tri-	Mono-	Di-	
43/01	–	–	100	–	–	C8 (3); C10 (2); C12 (29); C14 (11); C16 (17); C18 (36)
54/02	8–17	50–52	31–34	–	–	C14 (2); C16 (49) C18 (47)
50/02 [a]	5	30	45	–	20	C12 (10); C14 (7) C16 (40); C18 (40)
50/13 [b]	5	8	8	29	43	C16 (46); C18 (51) C12, C14 (3)
55/18	–	–	–	15.2	84.1	C16 and C18

[a] 50/02 contains < 1% of free PEG and < 0.5% of free glycerol.
[b] 50/13 contains 5–8% of free PEG and < 1.5% of free glycerol.

Australia) at 29 or 36°C for 1–3 days, after which they were allowed to cool to room temperature prior to measurement. The coefficents of variation for peak temperatures and heats of fusion were $< 1\%$ and $< 1.5\%$, respectively.

2.4. Tensile strength measurements

A diametral-compression test (Fell and Newton, 1968, 1970) was used to evaluate the mechanical strength of the moulded tablets, as described previously (Sutananta et al., 1994) using a tensile testing apparatus (CT40 Engineering Systems, Nottingham). Six to 12 tablets were evaluated for each sample.

3. Results and discussion

3.1. Ageing of Gelucire 43/01

Fig. 1a and b illustrates the DSC thermograms of samples of Gelucire 43/01, slow cooled and fast cooled from the melt after ageing up to 280 days, with the ΔH_f values being given in Table 2. The sample underwent dramatic changes as reflected by the shape of the DSC curves and increase in ΔH_f values. Distinct melting regions were observed for the slow cooled samples, possibly due to segregation of the low and the high melting point glyceride components into different microscopic regions within the sample, as suggested in a previous study (Sutananta et al., 1994). Fast cooling, however, did not result in any segregation into different melting regions, as indicated by the broad, featureless peak shown in Fig. 1b.

On storage, the melting behaviour indicated that the slow cooled samples exhibited fewer but sharper peaks, while the fast cooled sample showed more narrow, well defined endotherms than did the freshly prepared material. All the aged traces resembled each other after 280 days, as did that of the untreated sample taken from the batch as received. Furthermore, the ΔH_f values of the fast and slow cooled samples were similar on ageing (Table 2). These observations imply that the aged DSC traces represent an equilibrium structure of the sample, whereby instead of segregation of the material into different melting fractions, a greater degree of homogeneity has been generated within the sample. Furthermore, changes in the slow cooled DSC peaks occurred very slowly in comparison with the fast cooled sample. These slow rates of change may be a result of the segregation in the slow cooled material rendering recombination into the more homogeneous form difficult. The fast cooled material, however, showed little evidence of such segregation, thereby allowing a more rapid reorganisation into the equilibrium form.

The DSC data may also be presented in terms of the solid fat content, whereby the proportion of the endotherm that has melted at any particular temperature may be plotted against temperature. This is shown for slow and fast cooled Gelucire 43/01 in Fig. 2. Presentation of the data in this manner allows the operator to estimate the proportion of the material which has melted at any particular temperature, assuming that the endotherm area is directly proportional to the solid content. It may be seen from Fig. 2, for example, that a high proportion of the slow cooled sample will be in the molten state at the temperature of storage, hence this may contribute to the transformation from the segregated to the homogeneous microstructure on storage. Such changes have been previously suggested for fat products (Lovegren et al., 1976).

If the changes observed in the DSC traces are associated with alterations in the distribution of material within different melting fractions, then it is logical to suggest that by tempering the sample at a temperature immediately below that of the main equilibrium peak, it should be possible to form the equilibrium structure at a rapid rate, irrespective of the previous cooling rate. The results from the tempering study conducted at 36°C are shown in Fig. 3a. A large proportion of the material crystallised into the fraction which corresponded to the high temperature shoulder seen for the aged samples. On storage of this material, a proportion of this high temperature melting material had converted back into the lower temperature peak (Fig. 3b), hence although a higher melting point form had been obtained, this did not appear to be stable. On tempering the sample at 29°C, however, conversion to the peak seen for the aged samples was observed

(Fig. 3c). These studies therefore suggest that in order to obtain the equilibrium profile, it is advisable to temper at a temperaure approximately 9°C below the desired peak or to fast cool the sample, in which case a more unstable structure will be formed which rapidly converts to the stable form.

Gelucire 54/02, which also contains only glycerides, did not reach an equilibrium structure after 280 days, with the slow and fast cooled and

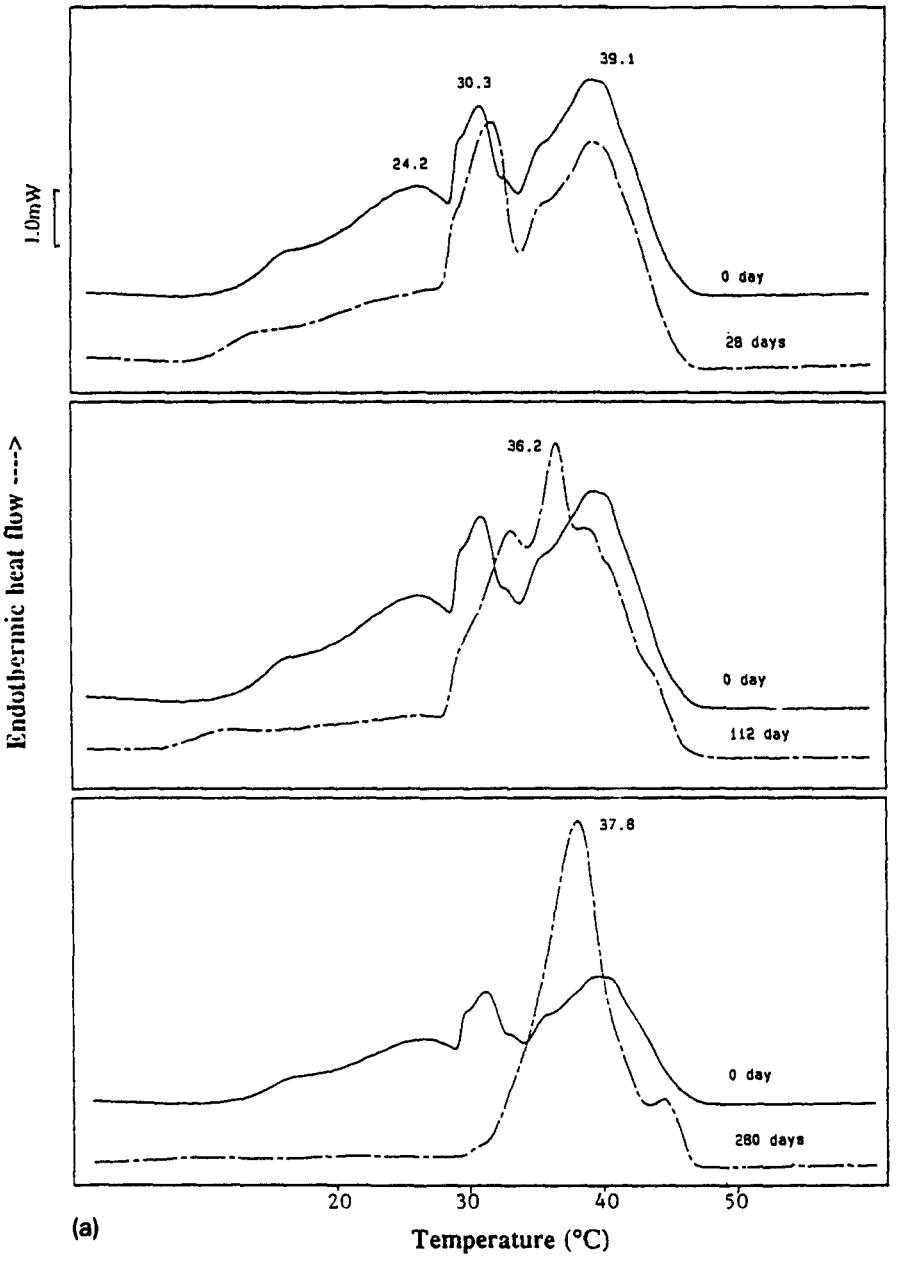

Fig. 1. DSC traces of stored (a) slow cooled and (b) fast cooled Gelucire 43/01.e

untreated samples showing greater differences in endotherm shape than was noted for Gelucire 43/01. This may be due to the greater chemical diversity within this sample rendering the recombination noted for Gelucire 43/01 difficult.

3.2. Ageing of Gelucire 50/02 and 50/13

While Gelucires 43/01 and 54/02 consist entirely of glycerides, other Gelucires are composed of mixes of glycerides and PEG esters, hence

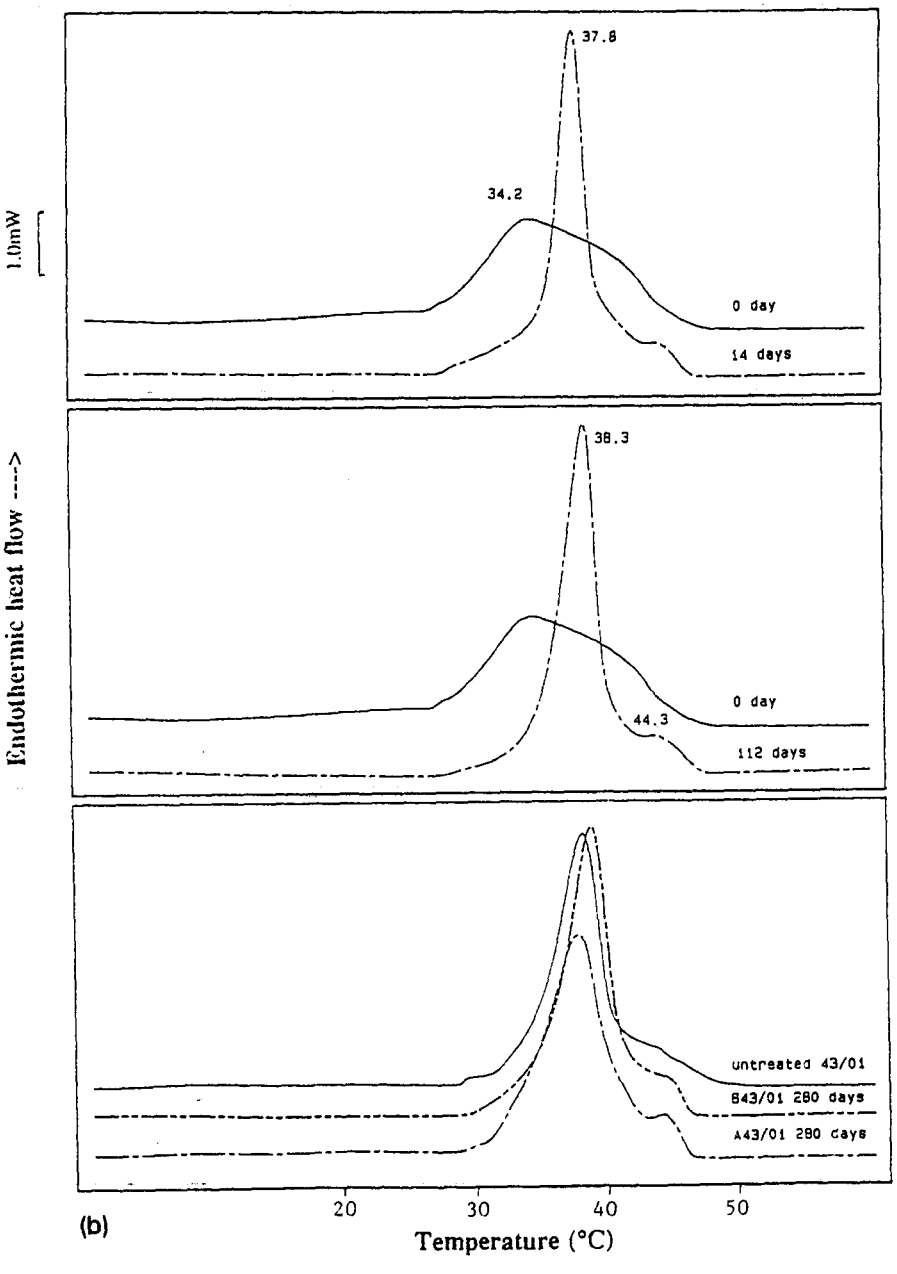

Fig. 1 (continued).

Table 2
ΔH_f values (J/g) of various Gelucire samples during storage up to 280 days (A, slow cooled; B, fast cooled)

Sample	Storage time (days)			
	0	14	112	280
A43/01	128.2	127.5	131.8	137.4
B43/01	118.9	125.7	133.9	134.6
A54/02	133.5	136.1	139.2	151.4
B54/02	121.5	134.5	136.7	149.7
A50/02	118.3	123.9	133.1	133.3
B50/02	105.6	123.9	132.9	134.4
A50/13	135.2	141.9	144.9	142.2
B50/13	123.6	141.9	143.3	143.4
A55/18	146.8	150.0	147.9	148.5
B55/18	132.5	138.4	147.5	146.0

their stability may differ from that outlined above. Upon ageing of Gelucire 50/02, the curves of the slow and fast cooled samples (given in Sutananta et al., 1994) became reasonably similar to that of the untreated sample, as noted for Gelucire 43/01. Similarly, the ΔH_f values were very similar on storage (Table 2). For Gelucire 50/13, the thermograms of 280 day aged slowly cooled and fast cooled samples showed much greater differences (Fig. 4). As Gelucire 50/13 contains various components with markedly different properties (i.e., glycerides and PEG esters), segregation of the components into different melting fractions will be extensive, particularly on slow cooling from the melt, with the recombination noted for Gelucire 43/01 being unlikely due to the larger chemical differences of the components in this sample. Preliminary studies have shown that molten Gelucire 50/13 did not completely mix with molten Gelcuires 43/01 or 54/02 but formed two separate phases. This indicates the limitation of solubility between glycerides and the PEG ester components of this sample.

3.3. Ageing of Gelucire 55 / 18

Gelucire 55/18 contains PEG esters of fatty acids and does not contain any glycerides, hence it is useful to consider the ageing behaviour of this sample in the context of the other Gelucires. The material is manufactured by a direct esterification reaction between fatty acids and PEG 6000. The molecule consists of a PEG backbone (Mol. Wt = 6000) and one or two fatty acid end groups (Mol. Wt ≈ 300) depending on whether one or two hydroxyl end groups of PEGs have been esterified. Fig. 5 shows DSC curves of slow and

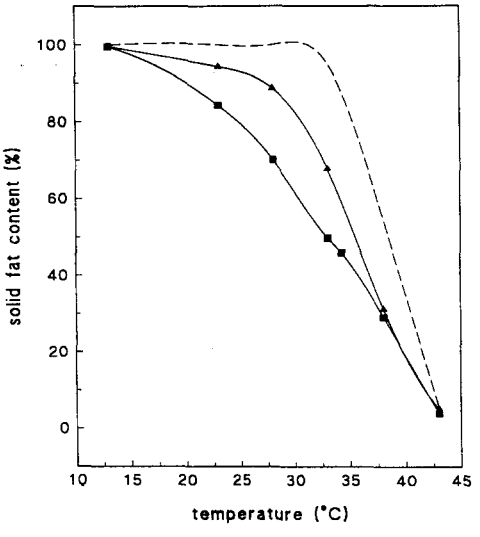

Fig. 2. Solid fat content as a function of temperature of Gelucire 43/01: (■) slowly cooled sample (0 day), (▲) fast cooled sample (0 day), (broken line) untreated sample.

fast cooled samples after ageing. Little change in the endotherms was observed, other than the appearance of a small low temperature shoulder. Previous studies using pure PEGs (Chatham, 1985; Craig and Newton, 1991) have indicated that such shoulders are a result of chain folding and it is possible that a similar phenomenon is being observed here, although such folded systems tend to be metastable with respect to the extended chains and hence may not be expected

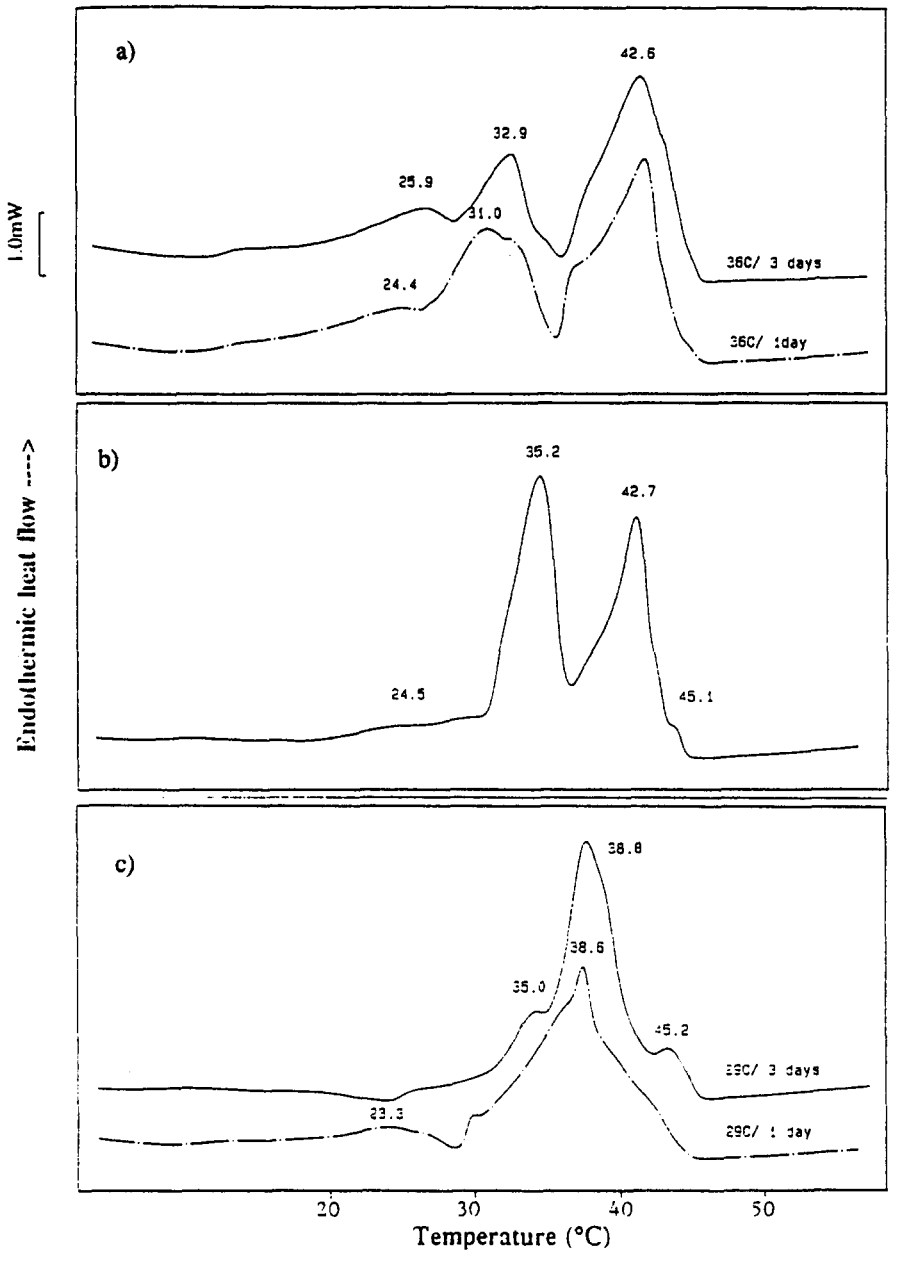

Fig. 3. Effect of tempering on the DSC curves of fast cooled Gelucire 43/01: (a) tempered at 36°C, (b) stored for 150 days after tempering at 36°C for 1 or 3 days, (c) tempered at 29°C.

to form spontaneously. The ΔH_f value of the fast cooled sample also increased compared to that of the slow cooled materials on storage.

Clearly, therefore, changes in the DSC traces of Gelucire products are associated with alterations in either the crystal structure of the glyceride components or changes in the microdistribution of the glyceride or PEG ester components

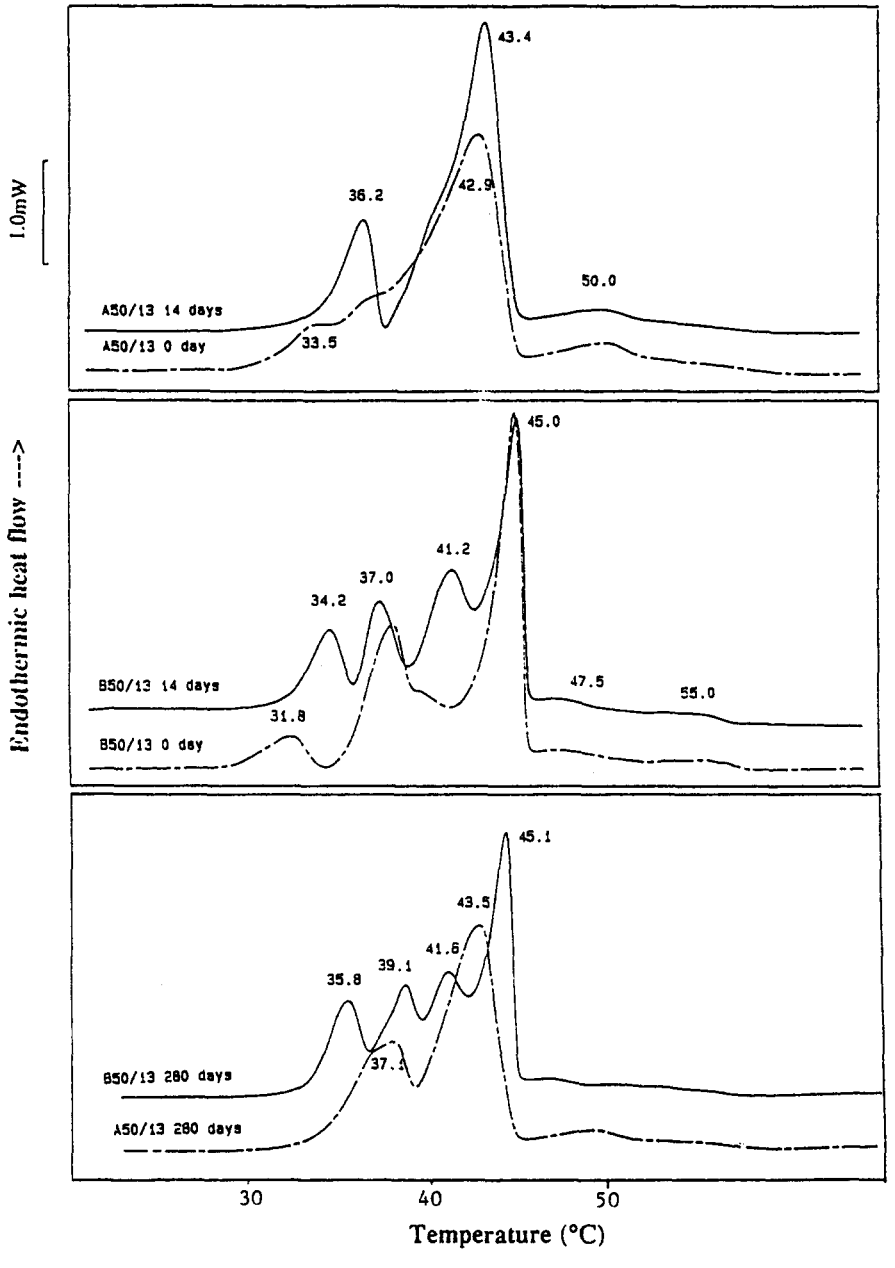

Fig. 4. DSC traces of stored slow (A) and fast (B) cooled Gelucire 50/13.

within the sample. The DSC curves of the PEG esters themselves do not appear to show a marked dependence on either the preparation conditions or storage time.

3.4. Tensile strength of aged tablets

Table 3 shows tensile strength (σ) values of tablets after ageing for various periods of time.

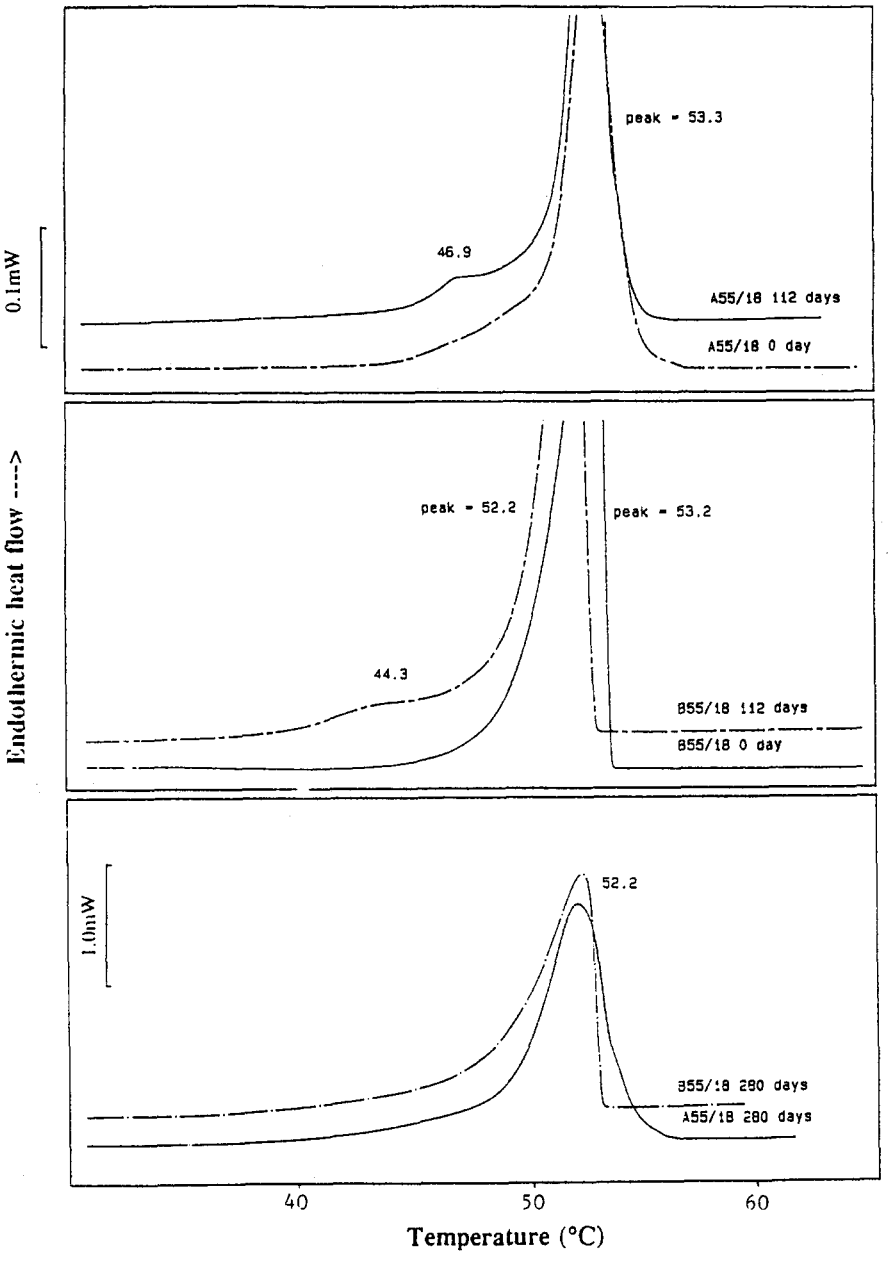

Fig. 5. DSC traces of stored slow (A) and fast (B) cooled Gelucire 55/18.

Table 3
Tensile strength of Gelucire moulded tablets (kg cm^{-2}, ±S.D.) after ageing for different periods of time (A, slow cooled; D, ambient cooling)

Sample	Storage time (days)			
	0	30	90	135
A43/01	3.27±0.25	3.08±0.20	4.20±0.40	4.77±0.37
D43/01	3.93±0.49	3.49±0.27	4.72±0.61	6.05±0.52
A54/02	7.41±1.17	8.65±0.64	8.35±1.44	7.94±1.25
D54/02	5.44±0.59	6.83±0.71	6.71±0.60	7.96±0.62
A50/02	4.21±0.41	4.30±0.13	3.33±0.34	3.61±0.15
D50/02	4.02±0.26	5.20±0.64	3.81±0.45	3.78±0.35
A50/13	8.19±1.28	7.03±1.70	6.71±1.16	5.91±1.67
D50/13	6.65±0.91	5.68±0.90	5.67±0.98	5.08±1.05
A55/18	3.91±0.65	4.22±0.58	4.55±0.55	4.08±0.40
D55/18	4.04±0.31	4.89±0.73	5.39±0.31	5.07±0.70

The σ values of tablets were found to increase, remain constant or decrease during ageing, depending on the composition and preparation conditions used. The σ value of both slow and ambiently cooled Gelucire 43/01 increased on storage ($p < 10^{-6}$) but their σ values were not equal even after 135 days. Gelucire 54/02 showed much smaller changes, with an increase in σ values being found in the ambiently cooled sample ($p < 0.0001$) but not in slow cooled. The two samples had equivalent σ values after 135 days. The increase in σ values in Gelcuires 43/01 and 54/02 showed a similar trend to the increase in ΔH_f noted in Table 2, implying that the crystal form may play a role in the increase of σ of the bases during storage.

The results therefore indicate that Gelucires containing a high proportion of glycerides demonstrate increases in σ values on storage. Furthermore, the σ values of aged ambiently cooled Gelucire 55/18 increased ($p < 0.005$) while that of slow cooled 55/18 remained essentially constant. However, a decrease in σ values was found in Gelucires which are mixtures of glycerides and PEG esters, i.e., Gelucires 50/02 and 50/13. There is therefore some correlation between chemical structure and changes in tensile strength, although clearly the mechanisms involved are complex. It is, however, of note that the changes in structure noted using the DSC studies are reflected by changes in the tensile strength of the samples.

4. Conclusions

The study has attempted to provide a systematic investigation into the factors which effect ageing processes in Gelucires. It is suggested that changes in DSC traces observed on storage are associated with the segregation or recombination of the Gelucire components into different microscopic regions within the sample, rather than simple polymorphic changes as such. The method of preparation is clearly important in determining the stability of the system, particularly for Gelcuire 43/01, as a highly unstable structure may be formed which rapidly converts to the more stable form. Furthemore, tempering has been shown to be of use in controlling the structure of this material, although it is clearly important to choose the appropriate temperature for the process. The other Gelcuires under investigation also showed changes in their DSC traces, with Gelucire 55/18 showing only small changes in response which may correspond to chain folding phenomena. The tensile strengths of Gelucire moulded tablets also showed alterations on storage. While more work is required to identify the mechanisms involved, there appeared to be an increase in strength for systems containing only glycerides but a decrease for glyceride/PEG ester mixes. There was an increase in strength seen for Gelucire 55/18, which contains only PEG esters, hence the decrease seen for the mixtures may be associated with changes in the distribution of the two components with respect to each other rather than to changes in tensile strength of either the glyceride or PEG ester components in themselves. These studies therefore have implications not only for the development of thermal analysis as a means of characterising Gelucires but also in the understanding of how processing

variables may affect the structure, stability and mechanical strength of Gelucire products.

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