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An investigation into the effect of preparation conditions on the structure and mechanical properties of pharmaceutical glyceride bases

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Abstract

The structures of a range of pharmaceutical glycerides (Gelucires 43/01, 50/02, 54/02, 50/13 and 55/18) have been studied using polarized light microscopy fitted with a hot-stage facility and differential scanning calorimetry (DSC). In particular, the effects of preparation conditions on the structure and melting behaviour of the samples have been examined using protocols involving solvent crystallisation and solidification from the melt using different cooling rates. Despite the chemical complexity of these systems, the Gelucires crystallised into distinct regions which could be differentiated using polarized light microscopy. Hot-stage microscopy studies showed that the solvent and slow melt crystallisation processes generally resulted in a greater proportion of material in the higher melting point forms. DSC produced a series of broad peaks which yielded melting data which was in reasonable agreement with those obtained using the microscopy studies. A greater dependence on preparation conditions was found for Gelucires with a higher glyceride content. The tensile strengths of tablets moulded from the various Gelucires were examined and were shown to be dependent on the preparation conditions used.

Key words: DSC; Gelucire; Glyceride; Hot-stage microscopy; Polarized light microscopy; Polymorphism; Tensile strength

1. Introduction

Glycerides are fatty acid esters of glycerol which may be used as bases for a number of dosage forms, notably controlled release systems and suppositories. A persistent problem associated with their use is that commercial glycerides and glyceride-based products are invariably chemically complex and may exist in a variety of crystal forms, many of which are metastable (Vaughen, 1979; Sato and Kuroda, 1987; Precht, 1988). These alterations in structure have been associated with corresponding alterations in product performance. For example, changes in the crystal structure of glyceride suppositories have been related to changes in the in vitro and in vivo drug release properties (Taylor and Simp-

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kins, 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., 1981) or the change from the amorphous to the crystalline state of the fat bases (Coben and Lordi, 1980; Laine et al., 1988).

Studies have also been conducted on pure glycerides in an attempt to relate the simpler behaviour of these samples to that of complex commercial materials (Precht, 1988). Three polymorphic forms, α, β and β', have been described for tripalmitin and tristearin polycrystalline aggregates grown from the melt phase, the form obtained being dependent on the thermal history of the sample (Hoerr, 1960; Hernqvist, 1988). However, when dealing with commercial materials, the possibility of solid solution and eutectic formation, fractionation, polymorphism of the individual glyceride components and the existence of mixed amorphous regions within the solid renders any comparisons with pure glycerides difficult.

Gelucires are a group of glyceride-based excipients which have been widely studied as controlled release matrices (Dennis et al., 1990; Prapaitrakul et al., 1991; Remunan et al., 1992). These materials are composed of mixes of mono-, di- and triglycerides with polyethylene glycol esters of fatty acids and are classified by two numbers, the first referring to the approximate melting point of the base and the second to the HLB value. The latter may range from 1 to 18, depending on the composition of the base, particularly the ratio of glycerides to the more polar polyethylene glycol esters. These materials may be used as bases for liquid-filled hard gelatin capsules (De Barochez et al., 1989; Bodmeier et al., 1990), tablets produced by melt (Vila Jato et al., 1990; Llabres and Farina, 1991; Remunan et al., 1992) or solvent (Saraiya and Bolton, 1990) granulation processes, or as retardant coatings for granules or beads containing drugs (Magron et al., 1987; Laghoueg et al., 1989; Delgado et al., 1991). In all cases, the manufacturing process involves transforming the solid Gelucire base into a liquid form, followed by some method of solidification.

Given the propensity of glycerides to exhibit complex crystallisation behaviour, it is reasonable to suggest that the manufacturing conditions used in the preparation of the Gelucire dosage forms may have an effect on the physical structure of the bases which may in turn effect product performance. In this study, the structure of Gelucire systems has been investigated using DSC and polarized light microscopy, firstly to assess the usefulness of these techniques in the study of such complex systems and secondly to investigate the effect of preparation conditions on the structure of the Gelucire bases. The tensile strengths of tablets moulded from the various bases will then be assessed in order to examine the effects of preparation conditions on their mechanical properties. It is well known that different cooling rates will result in changes to the mechanical properties of fats. Mulder (1953) explained this effect in terms of the rapid cooling protocols resulting in the formation of mixed crystals of glycerides. This was later demonstrated in milk fat by DeMan (1961a,b). There is therefore an association between structure and mechanical properties of glycerides, thus there may be a relationship between the thermal behaviour of Gelucire samples and their tensile strengths.

2. Materials and methods

2.1. Description of Gelucires used in the study

Five Gelucires (Gattefosse, St. Priest) were used throughout the study, these being 43/01, 50/02, 50/13, 54/02 and 55/18. Gelucire 43/01 is a mixture of triglycerides, obtained from interesterification of hydrogenated palm and palm-kernel oils. Gelucire 54/02 or Precirol or glyceryl palmitostearate is a mixture of di- and triglycerides and contains 8–17% of monoglycerides. Gelucires 43/01 and 54/02 do not contain PEG esters. It should be noted that Gelucire 43/01 has a wide range of fatty acid chains, ranging from C12 to C18 while Gelucire 54/02 contains mainly C16 and C18. Gelucires 50/02 and 50/13 are waxy solids and are mixtures of glycerides and PEG esters of fatty acids. They have the same melting points but 50/13 has a higher HLB value

owing to a higher proportion of PEG esters. 50/02 has a wider range of fatty acid compositions, ranging from C12 to C18, while 50/13 is composed principally of palmitate (C16) and stearate (C18) esters and also contains free PEGs. The PEGs used in the manufacturing of these Gelucires are PEG 1500. Gelucire 55/18 is polyoxyethylene glycol 6000 dipalmitostearate and does not contain glyceride species. It is obtained from direct esterification of fatty acids with PEG 6000.

2.2. Sample preparation

Three methods of preparation were used for polarized light microscopy. Method A (solvent crystallisation) involved the preparation of a solution containing 10% w/v Gelucire in chloroform. The solution was dropped on a microscopic slide and the solvent allowed to evaporate under ambient conditions. At the first sign of crystallisation a cover slip was placed to retard solvent evaporation so that the crystallisation occurred slowly and the resultant crystals were large enough for clear observation. The sample was allowed to dry in a desiccator at room temperature for 24–48 h and then placed in an oven and dried under vacuum (200 mbar) at room temperature for a further 24–48 h.

In method B (slow cooling) approx. 2–3 mg of Gelucire were placed on a microscope slide and covered with a cover slip. The samples were 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. The temperature was maintained at 75°C for 1 h, after which the oven was automatically cooled at 0.17°C/min (10°C/h) to 30°C. Method C (fast cooling) involved the same heating cycle but the samples were flash cooled in liquid nitrogen. The above heating protocol was selected in order to remove the thermal history of the samples, as well as to represent extremes of cooling behaviour.

For the DSC studies using method A (solvent crystallisation), 100 mg of 10% w/w Gelucire in chloroform solution was poured into a petri dish (diameter = 9.2 cm, height = 0.8 cm). The solvent was allowed to evaporate at room temperature until the first sign of crystallisation was seen, after which the cover was placed on the dish to retard solvent evaporation. After 24 h, when the bottom of the petri dish was covered with thin plate of crystallised fat, a spatula was then used to gently break up the aggregates, and hence further facilitated solvent evaporation. The crystallised sample was then allowed to dry under vacuum (200 mbar) at room temperature for a further 48 h. For methods B and C (slow and fast cooling), a sample of Gelucire (5–7 mg) was accurately weighed to 0.01 mg in an aluminium DSC pan which was then covered and crimped. Each sample pan was then placed in a small glass bottle, placed in a programmable oven and subjected to thermal treatment described earlier.

In addition to the methods described above, a further cooling protocol (method D) was used for the DSC studies whereby the sample was allowed to solidify under ambient conditions in order to mimic the situation likely to be encountered in practice. 40 g of sample was put in a 250 ml beaker, placed in a programmable oven and heated at 3°C/min to 75°C. The temperature was held for 1 h at 75°C before the beaker was taken out of the oven. Approx. 5 g of the molten sample was immediately poured into a glass bottle (diameter = 2.0 cm, height = 3.2 cm), which had been previously left at room temperature, and allowed to cool. By inserting a temperature probe into the bottle, it was found that the melt was cooled from 75 to 25°C in 2–5 min depending on the type of Gelucires used. The cooling was non-linear fashion, being faster at higher temperature, thus the cooling rate could not be calculated.

For the tensile strength studies, the bases were fabricated into cylinder-shaped tablets by pouring molten Gelucires into an aluminium mould (4 × 9 holes of diameter 1.25 cm and 0.68 cm deep) to overflow. After solidification, the tablets were pushed out and a sharp blade was used to cut away excess fat on the top of the tablets. The tablets obtained after cutting 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. Methods B–D (slow cooled, fast cooled and ambiently cooled) were used to prepare the tablets. Tablets were also prepared in brass moulds of the same dimensions for comparison.

2.3. Optical examination and melting point determination

An Olympus BH-2 polarizing microscope (Olympus Ltd, London) fitted with an OM2 35 mm camera system and hot-stage apparatus (Mettler Model FP52) was used to examine the appearances and to determine the melting points of the crystallised Gelucires. The melting points were recorded as the temperature at which crystals completely melted (T_m). Under polarised light, T_m is the temperature at which birefringent or interference colours disappear. A red filter was placed between the analyser and the eyepiece to increase the contrast between background and crystals so that the determination of T_m could be more accurate. In addition, contrast and visibility could be enhanced by the phase contrast technique, which was of particular use in the observation of detail of small crystals. A heating rate of 2°C/min was used unless otherwise stated and the equipment standardised using indium (melting point 156.6°C). Melting point determinations were undertaken in triplicate.

2.4. DSC

A Perkin-Elmer DSC-7 connected to a DEC 325c personal workstation (Perkin Elmer Ltd) was used throughout. The CCA7 controlled cooling accessory, which employed liquid nitrogen as a coolant, was always turned on to control the temperature of the DSC block, which acted as a temperature sink (in which the sample holder was buried), at −40°C at all times during operation. The instrument was operated under nitrogen purge gas at a rate of 25–30 ml/min, unless otherwise stated. Indium and zinc standards (Perkin Elmer, Beaconsfield) were used for temperature and area (heat of transition) calibration.

It is generally accepted that the scanning speed, particle size distribution of the samples and sample size should be standardised if accurate or meaningful results are to be obtained from the DSC data. In the present study, these factors were standardised as in the following manners. The sample sizes commonly used in DSC investigation of fats range from 3 to 20 mg (e.g., Liversidge et al., 1981; Coben and Lordi, 1980). In this study, it was found that 3–4 mg of samples were needed to cover the whole bottom of the sample pan without leaving any hole while more than 12 mg of samples would require a high compression force to crimp the sample pans, which could lead to leakage of the molten samples. In addition, to minimise a thermal gradient in the sample near the top and the bottom of the pan due to low thermal conductivity of fats, the samples should be as thin as possible. Consequently, a sample size of 5–7 mg was considered to be optimal and was used throughout. Preliminary studies indicated that there was no difference in response between samples containing different particle sizes, probably because the crimping process caused all samples to become compressed into a thin sheet within the pan. A heating rate of 2°C/min was used throughout as no evidence for recrystallisation into higher melting point forms was seen on using slower rates.

2.5. Tensile strength measurements

A diametral compression test (Fell and Newton, 1968, 1970) was used to evaluate the mechanical strength of the moulded tablets. Each tablet was weighed to ±0.0001 g and its diameter and thickness measured to ±0.002 cm. The maximum load at which the tablet collapsed or broke between two parallel platens of the diametral compression tester (CT40 Engineering Systems, Nottingham) was recorded as P and the tensile strength calculated according to Eq. 1:

$$\sigma = 2P/\pi Dt \quad (1)$$

where σ is the tensile strength (kg cm^{-2}), P denotes the load in kg, D is the tablet diameter (cm) and t represents the tablet thickness (cm).

To ensure that the tablets fractured in tension and that the strength calculated from Eq. 1 represented tensile strength, only tablets that broke

into two halves along the diameter were recorded. Six to 12 tablets were evaluated for each sample. One-way analysis of variance was used for comparison between samples.

3. Results and discussion

3.1. Microscopy studies

3.1.1. Solvent crystallisation studies

Solvent crystallisation studies were conducted in order to identify the morphologies and the T_m values of the stable polymorphic forms. Theoretically, solvent crystallisation leads to the formation of the most stable glyceride polymorphs (Sato and Kuroda, 1987), although how this may be reflected in the complex systems under study here is less certain. The T_m values are shown in Table 1 for all five Gelucire samples under examination, while photomicrographs and a more detailed discussion of the melting behaviour are provided below for Gelucires 43/01, 54/02 and 55/18.

Fig. 1–3 are representative photomicrographs of solvent crystallised 43/01, 54/02 and 55/18. In the following discussion, crystals which have the same shape and T_m values are described as the same form which was numbered I, II, III, etc., in order of increasing T_m values. It should be emphasised that these forms of crystals were not of any particular pure components, but are more likely to comprise complex mixtures of different crystal forms and different chemical entities.

A typical appearance of Gelucire 43/01 crystallised from chloroform is shown in Fig. 1 using polarized light. Three distinct morphologies could be identified and described as forms I–III in order of increasing melting ranges, these ranges being given in Table 2. Observations under phase contrast indicated that form II consisted of needle-shaped crystals which formed spherulitic structures, while form III was composed of plate-shaped crystals which formed larger, less well-defined aggregates. Form I was considered to be any material which was not within the structures ascribed to forms II and III. On heating the sample at 0.2°C/min to 38–40°C, transition of form I to forms II and III could be seen, although no transition from form II to form III was observed.

Table 1
A comparison between the values of T_m [a] obtained from hot-stage microscopy and T_b [b] from DSC curves and the temperature at the last peak maximum from DSC curves of gelucire samples

Sample	T_m (°C)	T_b (°C)	Temperature at the last peak (°)
A43/01	57.1	49.0	41.1
B43/01	50.4	47.0	39.1
C43/01	47.7	46.9	34.2
A50/02	60.4	58.9	51.6
B50/02	49.8	49.6	46.9
C50/02	47.6	47.6	45.3
A54/02	66.4	65.5	62.4
B54/02	59.3	59.5	56.5
C54/02	55.9	57.1	56.5
A55/18	55.3	55.5	54.9
B55/18	51.7	57.2	53.3
C55/18	53.0	53.7	53.3
A50/13	66.5	65.7	60.5
B50/13	61.2	60.1	50.1
C50/13	59.1	58.2	55.0

[a] Temperature at which crystals completely melt as seen on hot-stage microscopy.
[b] Temperature at which an endotherm in a DSC thermogram returns to the baseline.

The structure of Gelucire 54/02 is shown in Fig. 2, taken under polarized light. Four crystal types were observed under phase contrast whose melting behaviour corresponded to the ranges given in Table 2. No transformations between the crystal types were observed using slower heating rates.

Solvent crystallisation of Gelucire 55/18 produced a solid with a poorly defined structure (form I). Small numbers of spherulites were also found but were present in such low proportions that the value of T_m given in Table 1 is that of form I. The melting range Gelucire 55/18 was relatively sharp, occurring within 3°C. This is to be expected, as this Gelucire comprises only PEG diesters of palmitic and stearic acids. No polymorphic transformation was observed in C55/18 on heating at slower rates.

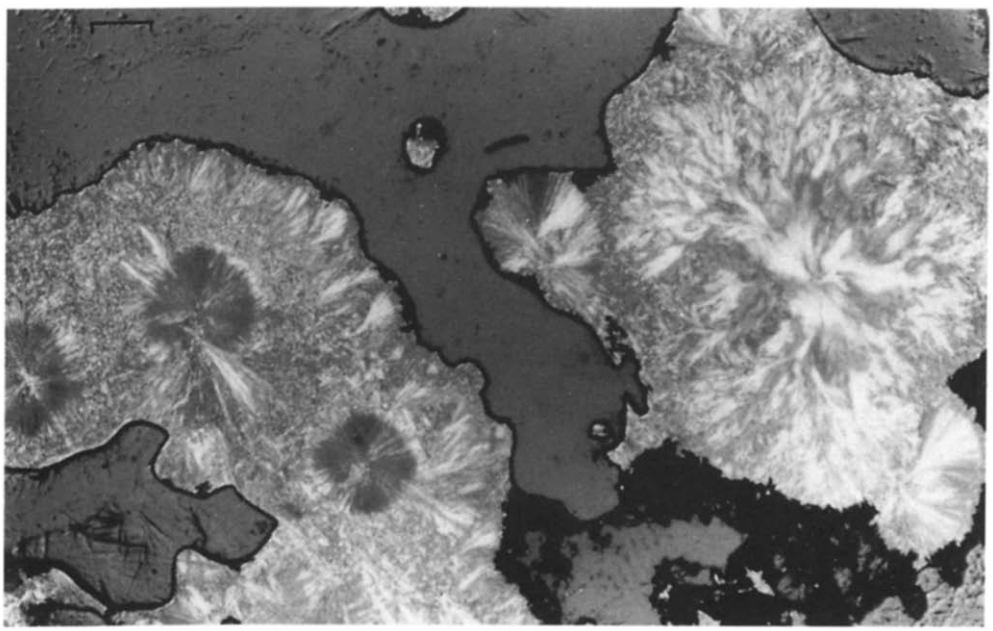

Fig. 1. Photomicrograph of Gelucire 43/01 crystallised from chloroform (scale represents 50 μm) taken under polarized light using a red filter. The large aggregate on the right is composed of form III while the spherulites on the left are form II.

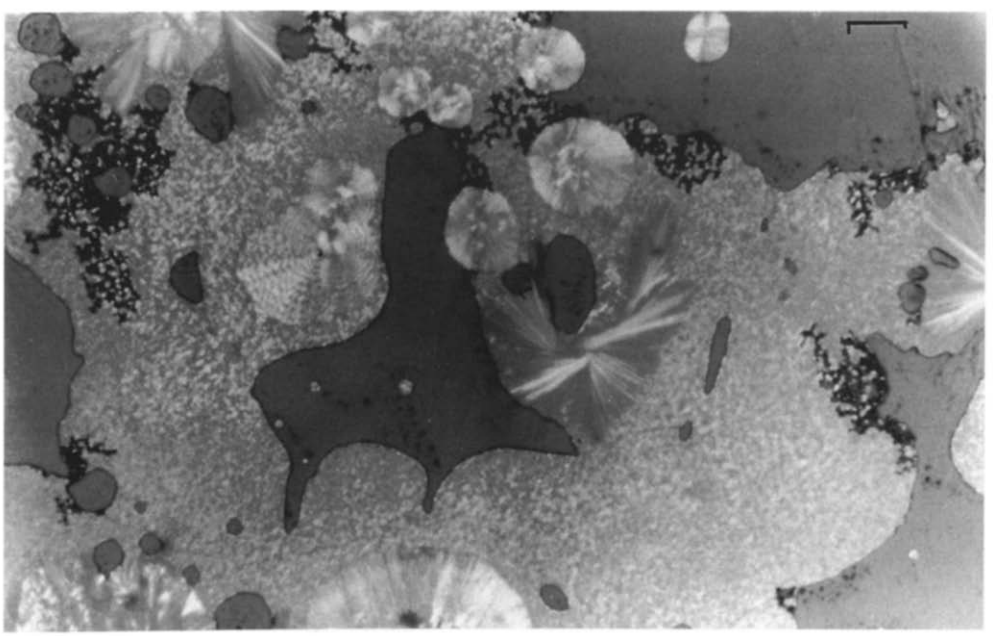

Fig. 2. Photomicrograph of Gelucire 54/02 crystallised from chloroform (scale represents 50 μm, polarized light, red filter).

Table 2
Melting ranges of various crystal forms found in Gelucire samples crystallised from chloroform

Sample/form	Melting range (°C)
43/01	
I	< 35–40
II	42–50
III	47–57
54/02	
I	> 45–57
II	> 52–64
III	54–67
IV	56–67
55/18	
I	53–55.5
II	> 72

3.1.2. Melt crystallisation studies

In comparison with the solvent crystallised samples (method A), the melt crystallised samples (methods B and C) had lower melting points (T_m). The differences in T_m values range from 2.3°C between A55/18 and C55/18 to 12.8°C between A50/02 and C50/02. Moreover, the differences were greater in Gelucires which contain large proportions of glycerides, i.e., > 6°C in 43/01, 50/02 and 54/02, thus indicating that the observed changes in structure are at least partially a function of the crystal form of the glycerides. Some of the higher melting forms which were observed after solvent crystallisation were not seen on crystallisation from the melt, hence the latter samples may contain a higher proportion of metastable forms of glycerides. In Gelucires which are high in PEG ester contents, e.g., 50/13 and 55/18, the differences between T_m values of solvent and melt crystallised samples were less pronounced, i.e., ≤ 3.6°C. Table 1 shows that the slowly cooled samples (method B) were a few degrees higher than those prepared by fast cooling (method C), indicating that fast cooling resulted in the solidification of a large proportion of samples in metastable or lower melting forms. Slow cooling also produced considerably larger spherulites, as shown for Gelucire 43/01 in Fig. 4a and b.

3.2. DSC

3.2.1. Comparison with polarized light microscopy studies

Interpretation of the DSC data involves two principle difficulties. Firstly, the DSC curves obtained from Gelucire samples were usually broad

Fig. 3. Photomicrograph of Gelucire 55/18 crystallised from chloroform (scale represents 20 μm, polarized light, red filter).

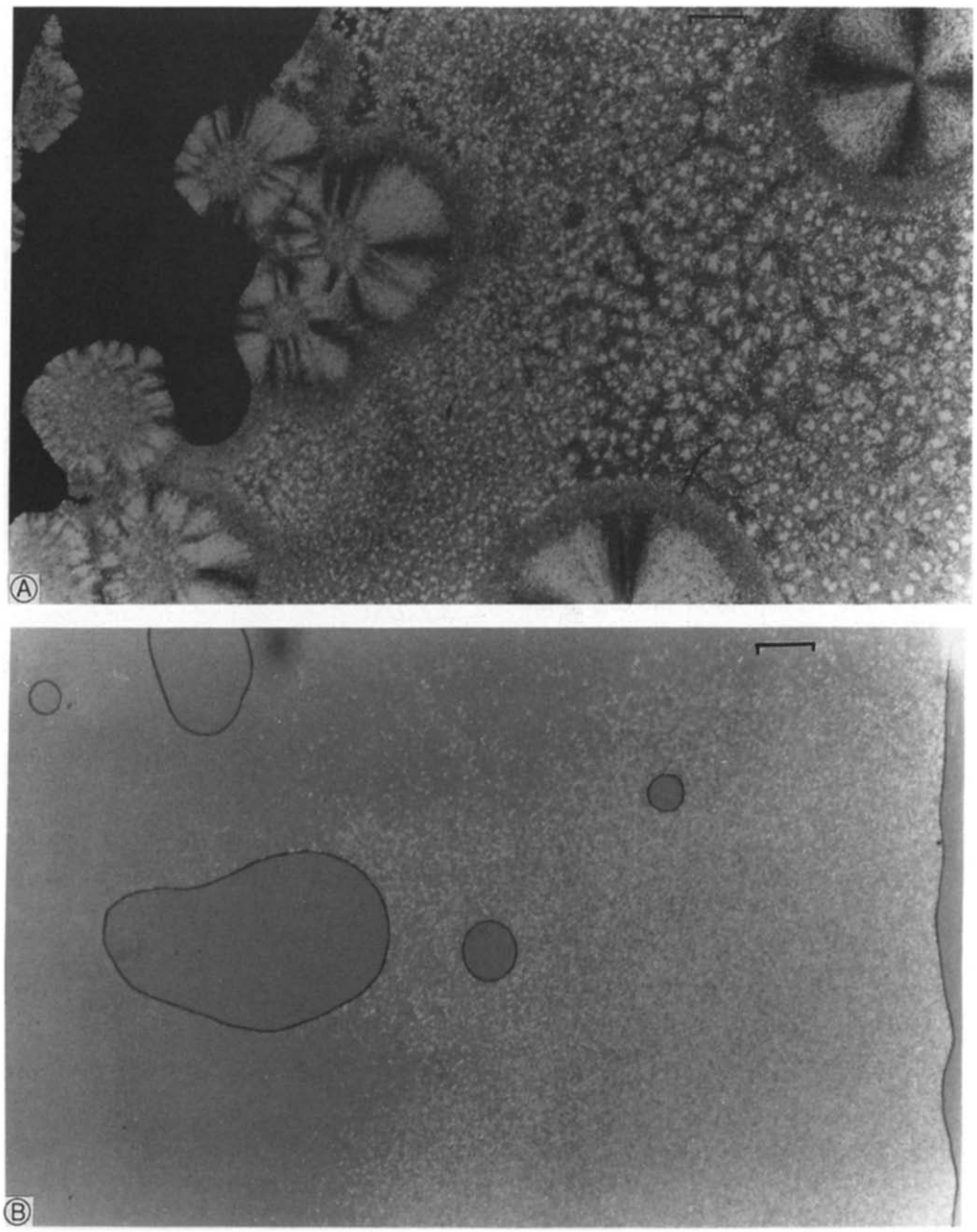

Fig. 4. Photomicrograph of Gelucire 43/01 a) slow cooled and b) fast cooled from the melt (scale represents 50 μm, polarized light, red filter).

and, in most cases, composed of more than one peak. Secondly, it is not possible to ascribe the various peaks to any particular crystal form for such complex samples. However, it is nevertheless useful to compare the data obtained from the DSC studies to those from microscopy. Liversidge et al. (1981) were able to relate the melting point of the highest melting component of suppository

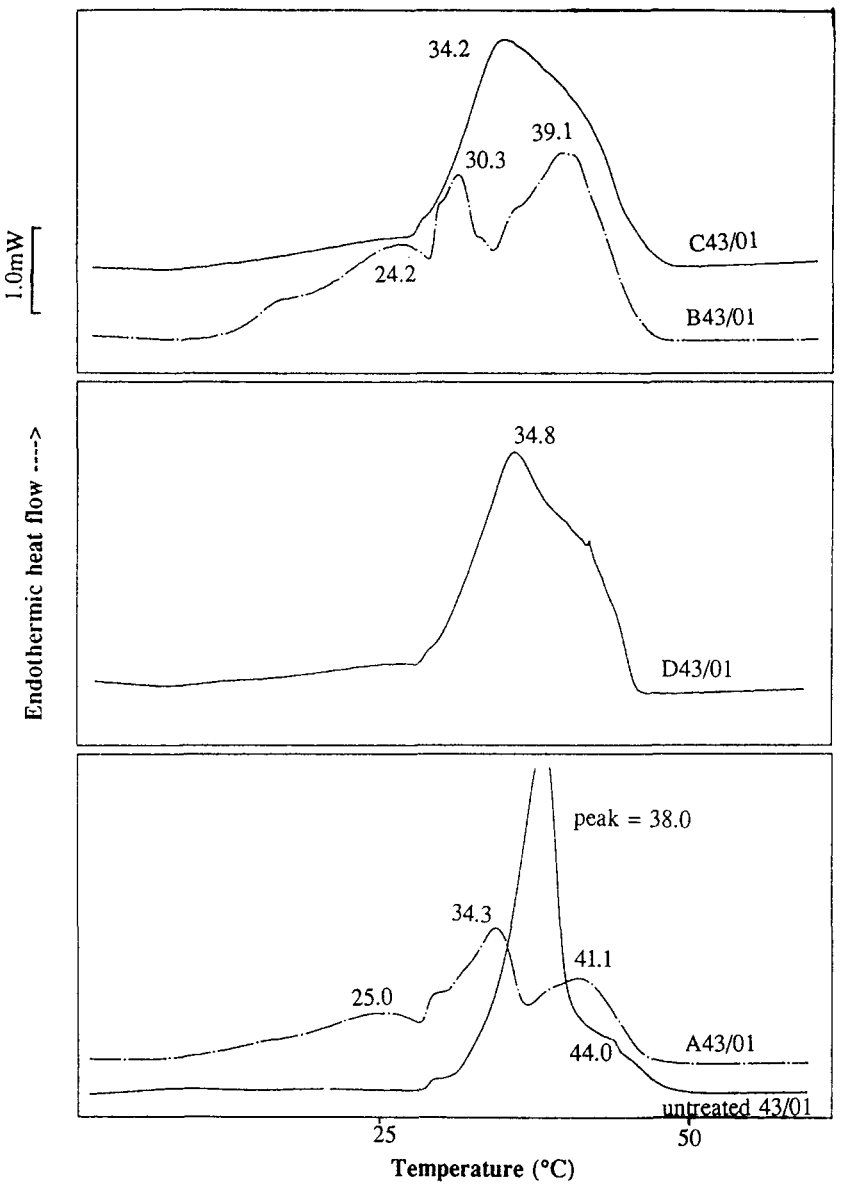

Fig. 5. DSC curves of Gelucire 43/01: A, solvent crystallized; B, slowly cooled; C, fast cooled; D, ambiently cooled.

bases under hot-stage microscopy to the temperature at the last peak maximum under DSC. These two temperatures agreed within ± 1°C and were taken as the melting points of those bases. Some investigators, however, did not find such a relationship for samples of paracetamol-phenazone mixtures (Grant et al., 1980) or synthetic suppository bases (Fabregas, 1991). Grant et al. (1980) suggested that the differences lay in the nature of the measuring method, as hot-stage microscopy is observing the behaviour of a few individual crystals, while DSC is essentially averaging the behaviour of all the species which melt at any particular temperature. A further possible explanation for the differences between the two methods may lie in the sample preparation techniques,

as a sample in a crimped aluminium pan under nitrogen will experience a different heat flux from one which is exposed to the atmosphere on a glass slide.

The temperatures at the last peak of the DSC profiles are given in Table 1, along with the T_m values obtained from hot-stage microscopy. There appears to be little relationship between the two, other than that the DSC results tend to be higher in most cases. There appears to be a better relationship with the temperature at which the endotherm returns to the baseline (T_b). This may be expected, as the apex of the peak represents the temperature at which the heat flux into the sample is proceeding at the greatest rate, rather than necessarily when the melting process is com-

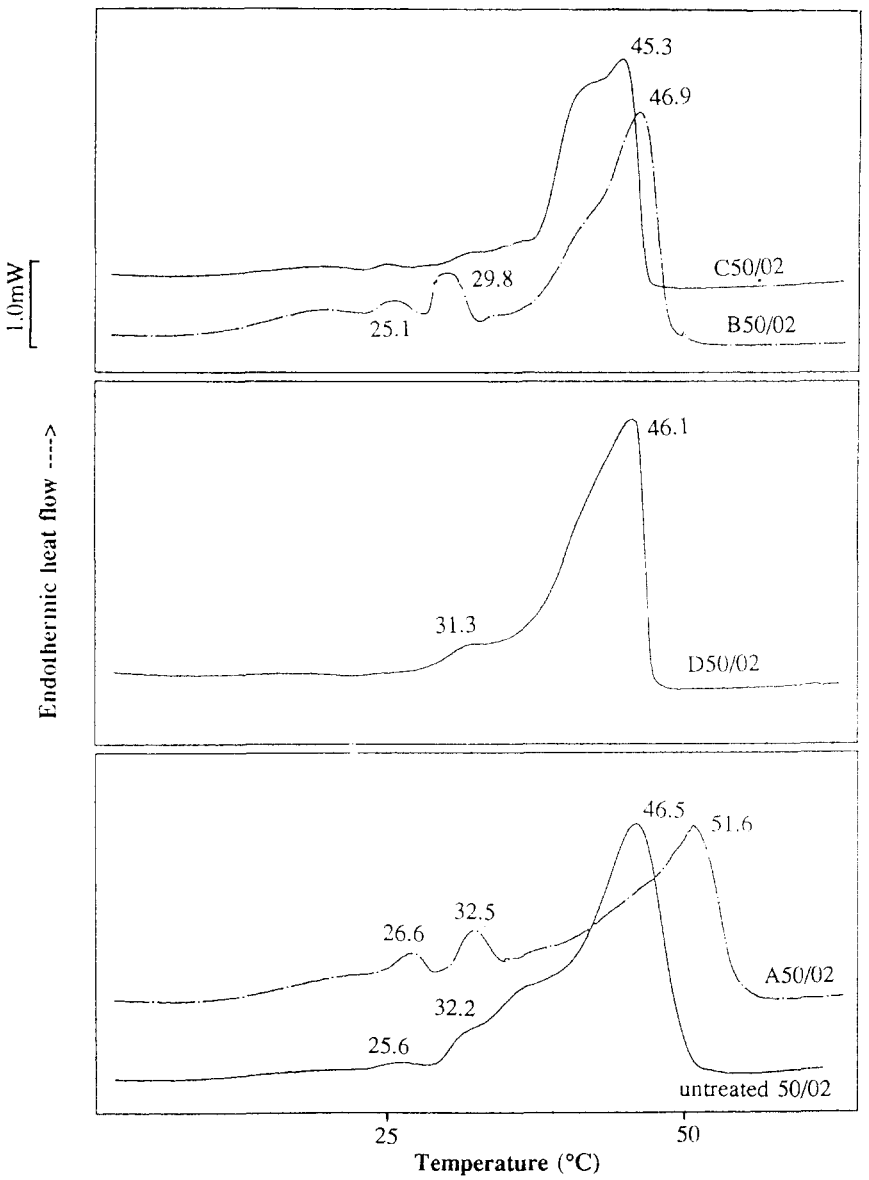

Fig. 6. DSC curves of Gelucire 50/02: A, solvent crystallized; B, slowly cooled; C, fast cooled; D, ambiently cooled.

pleted, which is in turn given by the point at which the endotherm returns to the baseline.

3.2.2. Thermal behaviour of Gelucires prepared by different methods

Fig. 5–9 illustrate the DSC curves of the Gelucires prepared using the various methods. Table 3 shows the calculated values of ΔH_f of these samples. The DSC curves and ΔH_f values of untreated samples are also provided for comparison. As was found for the hot-stage microscopy studies, the T_b values or temperature at the last peak (T_p) of slowly cooled samples were higher than those of fast cooled samples and usually less than those of untreated samples, while the values for the solvent crystallised samples were higher than for the melt crystallised samples. On exam-

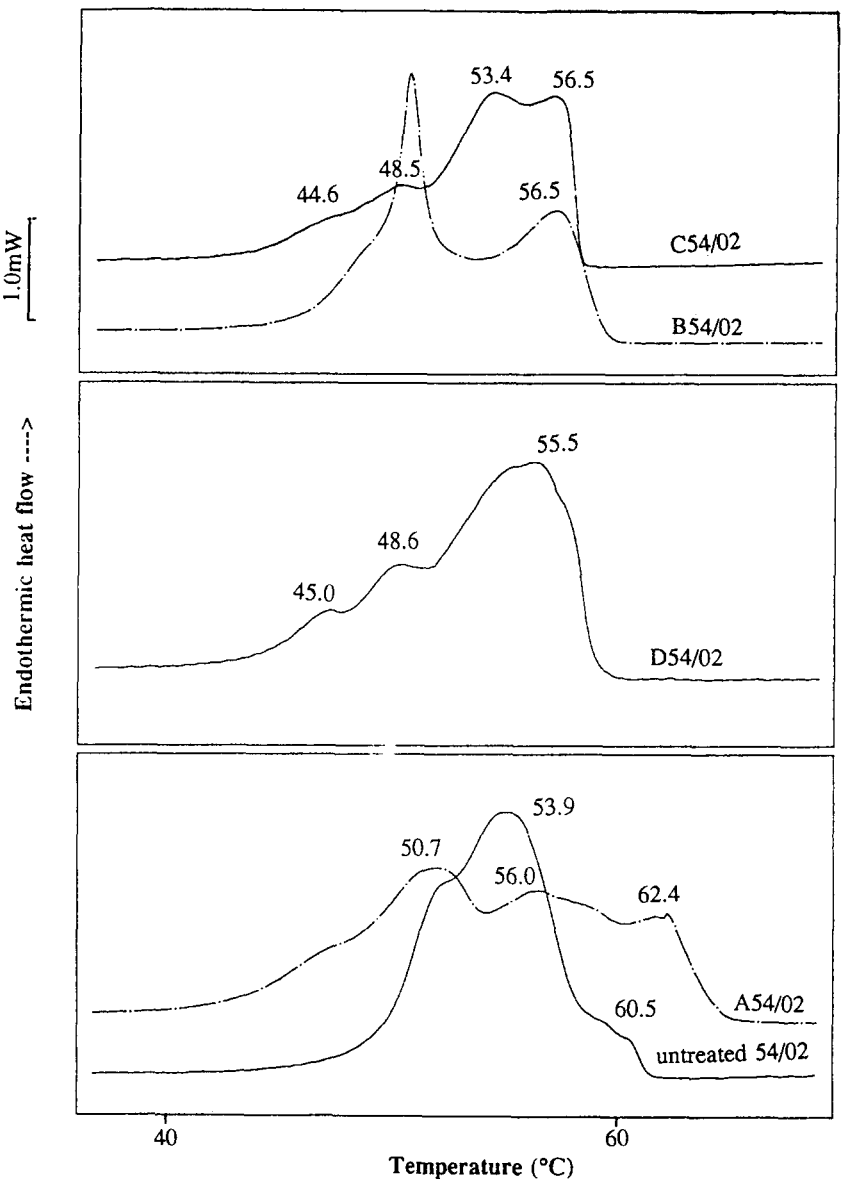

Fig. 7. DSC curves of Gelucire 54/02: A, solvent crystallized; B, slowly cooled; C, fast cooled; D, ambiently cooled.

ining the individual profiles, the samples composed largely of glycerides produced broad peaks which showed considerable dependence on preparation conditions. Fast cooled Gelucire 43/01 (Fig. 5) showed a broad and largely featureless profile while the slowly cooled sample showed three peaks, as did the solvent crystallised sample. While this corresponds with the observation of there being three forms observed using hot-stage microscopy, the temperature ranges show little correlation. Gelucire 50/02 (Fig. 6) showed a marked increase in the main peak melting point on crystallisation from chloroform compared to the melt crystallised samples, while Gelucire 54/02 (Fig. 7) showed broad endotherms for fast cooled and solvent crystallised

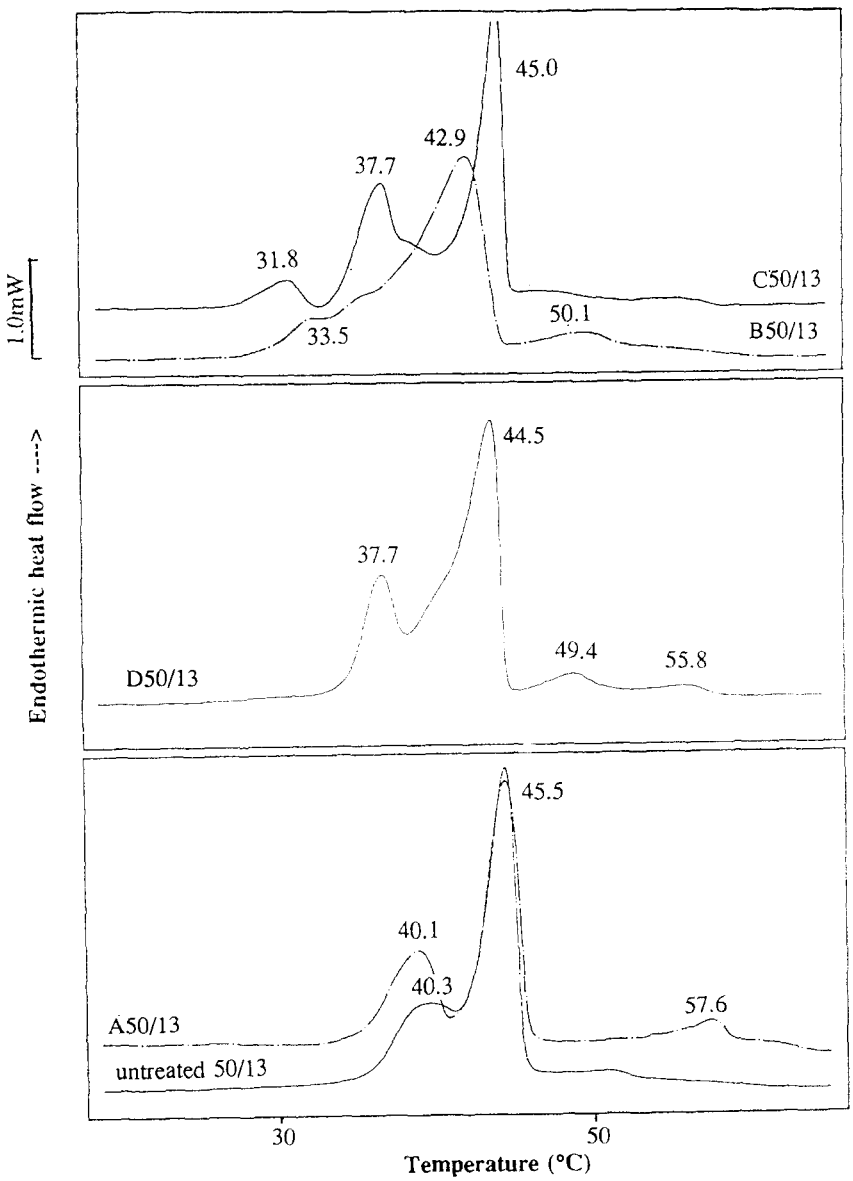

Fig. 8. DSC curves of Gelucire 50/13: A, solvent crystallized; B, slowly cooled; C, fast cooled; D, ambiently cooled.

samples, although two distinct peaks are seen for slowly cooled samples.

The samples containing higher quantities of PEG esters showed more well-defined endotherms (Fig. 8 and 9), with Gelucire 55/18 showing a relatively sharp endotherm which showed considerably less dependence on preparation conditions than did the other materials. It is interesting to note that the melting point of the untreated Gelucire 55/18 is higher than that of the solvent crystallised materials, which is in contrast to the behaviour observed for the other Gelucires. This material has not been previously studied in terms of polymorphic behaviour, although polyethylene glycols are known to exist in different chain-folded forms which are struc-

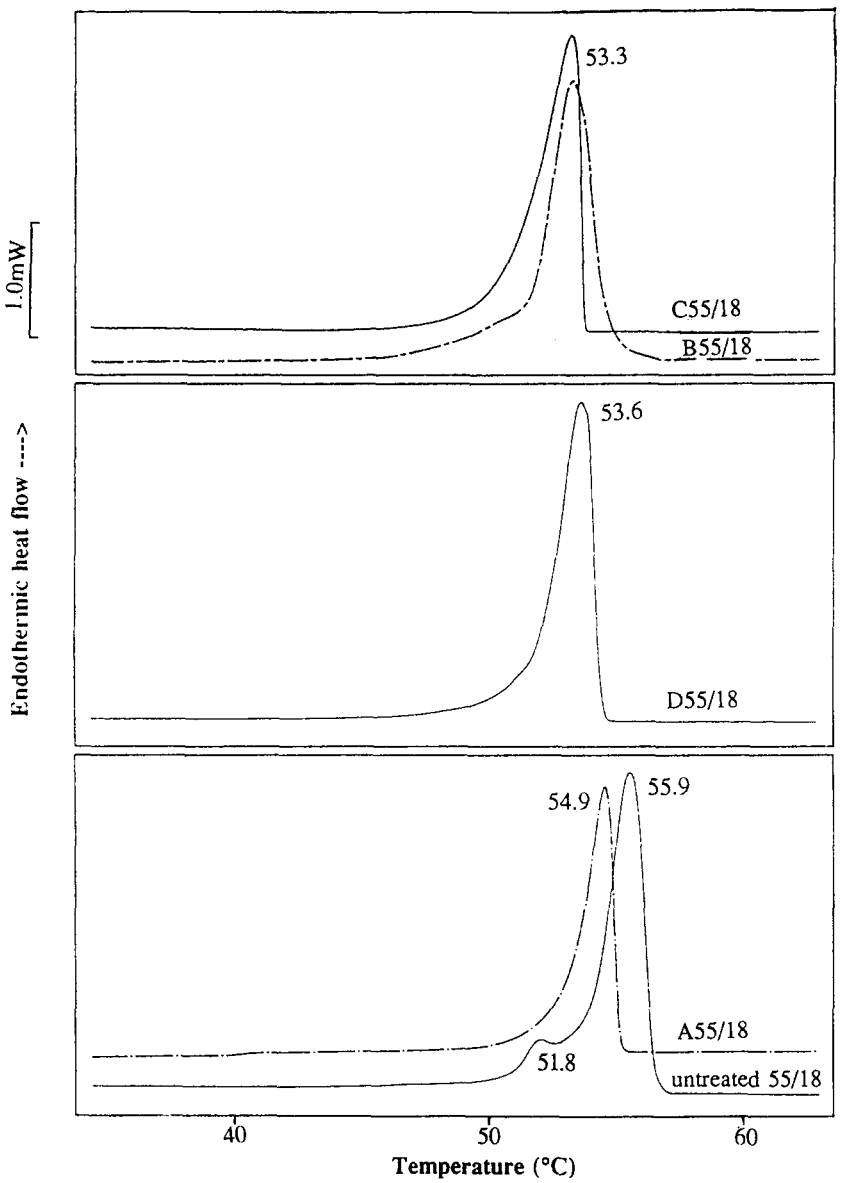

Fig. 9. DSC curves of Gelucire 55/18: A, solvent crystallized; B, slowly cooled; C, fast cooled; D, ambiently cooled.

Table 3
ΔH_f values (J/g) of Gelucires prepared by different methods

Gelucire	Method of preparation			
	A	B	C	untreated
43/01	128.5	128.2	119.1	137.1
50/02	125.3	118.3	105.6	123.5
54/02	170.2	133.5	121.5	155.0
50/13	142.5	135.2	123.6	147.3
55/18	156.8	146.8	132.5	159.2

turally dependent on the thermal history of the sample (Craig and Newton, 1991). It is possible that similar behaviour is present for these PEG stearates. In general, the ambiently cooled samples (method D) gave similar profiles to those seen for fast cooled samples.

The values of ΔH_f of slowly cooled samples were invariably higher than those of fast cooled but lower than those of untreated samples and solvent crystallised materials with the exception of 43/01, for which the values for the slowly cooled and solvent crystallised samples were not significantly different (see Table 3).

3.3. Tensile strength measurements

Most of the moulded Gelucire tablets subjected to the diametral compression test broke into two halves along the diameter. This indicated the normal tensile fracture of the specimen and thus the value calculated using Eq. 1 was valid as a measure of tensile strength (σ) (Fell and Newton, 1970). The exception was the failure that occurred in Gelucire 43/01. Only half of the B43/01 and D43/01 tablets subjected to the test had normal tensile fracture. The rest failed to break, presumably because the base was too soft and simply deformed under stress. The use of filter paper (0.03 mm thick) to cushion at the point of contact of tablet and the metal platen, as used by Fell and Newton (1970), did not improve the outcome. Therefore, in the B43/01 and D43/01, only the loads that caused tensile failure were recorded and used in calculation.

Initial studies involved the use of brass moulds. It was noted that some of the tablets revealed a light blue colour, especially those prepared via method B. Since brass is a composite metal containing copper which is a strong prooxidant of glycerides, it was thought that Gelucires which were cast in brass moulds might undergo oxidation. Therefore, experiments were conducted to compare the tensile strength of tablets cast in brass with those cast in an aluminium mould.

Table 4
Tensile strengths of various Gelucire moulded tablets (kg cm^{-2}) cast in brass and aluminium moulds (slowly cooled)

Sample	Mould used	
	Brass	Aluminium
43/01	2.51 ± 0.33	3.27 ± 0.25
54/02	5.49 ± 0.63	7.41 ± 1.17
50/02	3.34 ± 0.33	4.21 ± 0.41

Table 4 lists the σ values of tablets cast in brass and aluminium moulds. It is clear that in Gelucire 43/01, 50/02 and 54/02, which contain glycerides, the σ values of the tablets cast in brass mould were lower than those casted in aluminium mould ($p < 0.001$ in all cases). The σ values of Gelucire 55/18 tablets were not affected by the type of mould used. The results suggest that oxidation of glycerides occurred in the bases that were cast in brass mould leading to lower σ values of tablets. Further investigations of σ values in this work, therefore, were performed on tablets cast in aluminium mould. As copper cups have been used to prepare Gelucire tablets for dissolution studies in previous investigations, the presence of this interaction is noteworthy.

Table 5 lists the tensile strength of moulded tablets made by cooling Gelucire bases at different rates. Because of the exceptionally fast rate

Table 5
Tensile strength of tablets (kg cm^{-2}) made using different cooling rates

Gelucire	Method of cooling		
	B	C	D
43/01	3.27 ± 0.25	3.80 ± 0.70	3.93 ± 0.49
54/02	7.41 ± 1.17	5.60 ± 0.78	5.44 ± 0.59
50/02	4.21 ± 0.41	4.43 ± 1.06	4.02 ± 0.26
50/13	8.19 ± 1.28	–	6.65 ± 0.85
55/18	3.91 ± 0.65	1.94 ± 0.34	4.04 ± 0.31

of cooling used in method C, 55/18 developed some cracks, which led to the unusually low σ values, and hence was excluded from discussion. There were significant differences between σ values of tablets produced from different cooling rates for Gelucires 43/01, 54/02 and 50/13, i.e., D,C > B in 43/01 ($p < 0.01$); B > C,D in 54/02 and 50/13 ($p < 0.001$). There was no significant difference between σ values of tablets produced from different cooling rates in 55/18 (B and D) and 50/02, despite the differences in morphologies and thermal properties found earlier.

Comparison with the data obtained from the thermal studies indicates that for Gelucire 43/01, the endotherms for the fast and ambiently cooled (C and D) samples were similar, while the photomicrographs showed that the slowly cooled samples had a population of large spherulties which was absent in the fast cooled samples. As spherulites, especially large ones, reduce the strength and toughness of polymers and tend to make them brittle (Schott, 1983), the difference in tensile properties may be at least partially a function of the spherulite size. However, slow cooling did not result in a lower strength for all the Gelucires, despite this method resulting in larger spherulites, hence other factors, such as degree of crystallinity or the nature of the mixed crystals present in the solid samples might be more important in determining the σ values of Gelucires. In addition, for any cooling method, there is no trend of strength with Gelucire composition. The results therefore demonstrate that while the preparation conditions may effect the tensile strength of Gelucires, it is difficult at this stage to identify the critical factors determining the strength of these materials with certainty.

4. Conclusions

The study has examined the use of polarized light microscopy in conjunction with DSC in order to characterise the solid structures of a range of Gelucires. The samples have been shown to be sensitive to preparation conditions, which may in turn be of importance not only to the immediate product perfomrance but, if metastable forms are being generated by a particular manufacturing process, may also result in physical instability of the samples. It is therefore necessary to have methods of assessing the solid structure in order to control such parameters. In general, the two techniques gave results which were broadly in agreement and suggested that despite the physical and chemical complexity of the samples, certain reasonably well defined crystal forms were produced using the different manufacturing techniques. Clearly, it is inappropriate to describe these forms in terms of specific polymorphic forms, however, the results indicate that it is possible to broadly categorise these structures according to their melting point ranges. It is also interesting to note that the correlation between the nominal and experimental melting points for each Gelucire is tenuous.

In terms of the use of polarised light microscopy and DSC, the results present a strong case for the use of these techniques in conjunction, as the benefits and weaknesses of the techniques are complementary. Polarised light microscopy allowed the operator to see the solid structure directly and was an effective method of differentiating between different crystal populations in a sample, both under ambient conditions and using the hot-stage microscopy facility. The technique was also used to detect recrystallisation into a more stable crystal form, as seen in this study for Gelucire 43/01. However, the results obtained will inevitably be operator dependent and the difficulty in maintaining thermal equilibrium across the hot stage precludes the use of the technique as a highly accurate thermal method, at least compared to DSC. The latter technique allowed a more objective quantification of melting point ranges and also provides data regarding the energy associated with the various transitions. However, this study has shown that DSC may be inferior to the microscopic technique in terms of distinguishing between different crystal forms, especially if the melting ranges of these forms tend to overlap. Use of the two techniques together therefore surmounts most of the difficulties seen for the individual methods.

Measurement of the tensile strength of the Gelucire tablets has indicated that different cool-

ing conditions may result in differences in strength. While there is some evidence for a relationship between spherulite size and mechanical properties seen for Gelucire 43/01, this was contradicted by observations made for the other bases. A number of additional factors may therefore be determining the physical properties of the Gelucires and more studies are required in order to identify them. In general, however, the study has shown that the preparation conditions used in the manufacture of Gelucire systems may have an effect on the structure and mechanical properties of the bases, hence care must be taken in order to control these variables when examining the properties of Gelucire dosage forms.

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