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The use of dielectric analysis as a means of characterising the effects of moisture uptake by pharmaceutical glyceride bases

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Abstract

The effects of storing Gelucires 43/01, 50/02, 50/13 and 55/18 under dry conditions (5% RH) and conditions of elevated humidity (80% RH) have been investigated using differential scanning calorimetry (DSC), viscosity measurements, low frequency dielectric spectroscopy and dissolution studies. DSC investigations indicated that Gelucires containing a high proportion of polyethylene glycol (PEG) stearates showed more marked changes when stored at elevated humidities than did those containing a higher proportion of glycerides. Similarly, Gelucire 55/18, which contains only PEG stearates, showed evidence of degradation on storage at high humidities. Dielectric studies indicated that samples containing a higher proportion of PEG stearates demonstrated an increase in response after storage at elevated humidities compared to freshly prepared samples, while those stored under dry conditions generally showed a decrease. Dissolution studies indicated that while the rate of theophylline release from Gelucire 50/02 samples decreased on storage at elevated humidities, the dissolution rate from Gelucire 50/13 samples increased. This may be a reflection of the different mechanisms of drug release from the two bases.

Keywords: Dielectric; Differential scanning calorimetry; Dissolution; Glyceride; Hydration; Viscosity

1. Introduction

Gelucires are a family of glyceride-based excipients which may be used in the manufacture of controlled release dosage forms. These materials consist of mixes of mono-, di- and triglycerides with polyethylene glycol (PEG) stearates, the nature and proportion of these components determining the hydrophobicity and drug release properties of the corresponding dosage forms (Craig, 1995). Each Gelucire is described by two numbers, the first referring to the melting point of the base and the second to the HLB number, hence the nomenclature adopted for these materials gives some indication as to their physical properties.

Due to the chemical and physical complexity of these systems, it has proved difficult to develop

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effective means of monitoring and hence controlling the quality of Gelucire products. Previous studies have used thermal methods (e.g. Sutananta et al., 1994a,b), particularly differential scanning calorimetry (DSC), which allows examination of the various physical structures that may be adopted by the bases. However, the method is invasive and requires the operator to relate the melting behaviour at elevated temperatures to the structure at room temperature. As an alternative approach, low frequency dielectric analysis has been used (Sutananta et al., 1995a). This method involves the application of an alternating field to a sample and the measurement of the response over a range of frequencies. The response is expressed in terms of the capacitance (C), which is related to the energy stored by the system, and the dielectric loss G/ω, where G is the conductance of the system and ω is the frequency in radians. By monitoring both the absolute values of these two parameters and the shape of the spectrum obtained over a range of frequencies, it is possible to obtain information regarding the structure of the sample. In an earlier study (Sutananta et al., 1995a), it was suggested that the dielectric response is related to the degree of segregation shown by the sample, i.e. the extent to which various components of the Gelucires crystallise into distinct regions. As these measurements may be obtained isothermally at any temperature, the introduction of the technique represents a potentially useful new approach to the study of these materials and indeed to pharmaceutical solids in general.

A further, important consideration in the development of Gelucires as dosage forms is the effects of humidity on the structure and drug release properties of the bases. While glycerides are not in themselves hygroscopic, the presence of the PEG stearates may facilitate an interaction with water, hence it is logical to suggest that the chemical composition of the Gelucires may determine the behaviour of the base on storage at elevated humidities. Furthermore, previous studies (Lievens et al., 1990) have indicated that dielectric analysis may be used to detect the presence of residual solvents in solid materials, hence it is of interest to study the effects of moisture on the dielectric response. In this study, therefore, a range of Gelucire samples have been examined after storage under low or high humidities using DSC, viscosity measurements and dielectric spectroscopy. The effects of storage conditions on the drug release rate have also been noted. In this way, it is intended that not only will the effects of moisture uptake on Gelucire structure be characterised but the use of dielectric analysis in the study of solid samples of pharmaceutical interest will be further developed.

2. Materials and methods

Gelucires 43/01, 50/02, 50/13 and 55/18 (Gattefosse s.a.) and anhydrous theophylline (Sigma) were used as received. Gelucire 43/01 is composed of triglycerides while Gelucires 50/02 and 50/13 contain a mixture a mono-, di- and triglycerides and PEG esters, with Gelucire 50/13 containing a higher proportion of the hydrophillic PEG stearates. Gelucire 55/18 contains only PEG stearates with no glycerides (Sutananta et al., 1994b).

Samples were stored at 21°C over silica gel (referred to henceforth as 5% RH, as in practice an RH of 0–10% was measured) or over a saturated solution of sodium chloride (79–82% RH, henceforth referred to as 80% RH). The various samples were stored up to a maximum of 220 days, although measurements were made at different time intervals, depending on the method of analysis, due to the different sensitivities of the various techniques to moisture uptake. Moisture uptake studies were performed on moulded tablets (1.25 × 0.65–0.68 cm), previously cooled under ambient conditions from 75°C. The tablets were stored at 80% RH for 30 days, with no corresponding uptake being detected for samples stored at 5% RH.

For the DSC studies, approximately 5 g of the ambiently cooled samples were placed in glass bottles and stored as described above. DSC measurements were conducted using a Perkin Elmer DSC-7 (Perkin Elmer Ltd.) (Sutananta et al., 1994a,b). A scanning speed of 4°C/min. was used throughout the study. Viscosity measurements

were performed as previously described (Sutananta et al., 1995c) using a Carrimed CSL 500 Controlled Stress Rheometer (TA Instruments Ltd.), using continuous shear flow measurements. All samples showed Newtonian behaviour, thus enabling a single viscosity value to be quoted. Samples of Gelucire 50/13 and 55/18 were prepared by heating the samples to 75°C for 1 h, then cooling under ambient conditions. Samples were then stored at 5% or 80% relative humidity for 220 days.

Dielectric measurements were performed using a Dielectric Spectrometer (Dielectric Instrumentation Ltd., Worcs., UK) as previously described (Sutananta et al., 1995a). An alternating field was applied using a voltage of 1 V r.m.s. for Gelucires 43/01 and 50/02 and 0.1 V r.m.s. for Gelucires 50/13 and 55/18 over a frequency range of 10^{-3} Hz to 10^{6}Hz. Samples were moulded into flat faced tablets of diameter 1.25 cm and thickness 0.40–0.42 cm (Sutananta et al., 1995a), with the material being cooled from the melt under ambient conditions. The temperature and humidity of measurement were controlled by placing the sample (and the measuring box) in a humidity controlled oven. Samples were measured at 20°C after 60 days storage at 5% or 80% RH.

Dissolution studies were performed as described previously (Sutananta et al., 1995b,c). Moulded tablets of Gelucires 50/02 and 50/13 containing 30% theophylline were prepared and cooled under ambient conditions. The tablets were then left for up to 60 days at either 5% or 80% RH prior to testing.

3. Results and discussion

3.1. Moisture uptake studies

The amount of moisture taken up by the various Gelucire samples is shown in Table 1. While samples containing PEG esters showed greater moisture uptake than did Gelucire 43/01, which contains only glycerides, it was noted that Gelucire 50/13 showed a greater uptake than did Gelucire 55/18, despite the latter containing only PEG esters with no glycerides. It was also noted in a previous study (Sutananta et al., 1995a) that Gelucire 50/13 showed a stronger dielectric response than did Gelucire 55/18, this response being associated with the polarity of the sample. It is therefore possible that the two observations are related.

3.2. Differential scanning calorimetry

Fig. 1a–d compares the DSC curves of ambiently cooled samples aged for 220 days under relative humidities of 5% and 80% RH. It may be seen that the endotherms of Gelucires 50/13 and 55/18 showed marked differences, depending on the relative humidity of storage, while Gelucire 50/02 showed an additional peak on storage at 80% RH. The DSC curves were essentially unchanged for Gelucire 43/01. It was also observed that no differences were seen between samples stored at 5% and 80% RH up to 90 days of storage for any of the Gelucires.

It is likely that the changes in endotherm shape noted for certain Gelucires is at least partially a function of the presence of the PEG esters, although mono- and diglycerides may also hydrogen bond with water to some extent. A number of hypotheses have been proposed concerning the interaction of PEG chains and water, including trihydrate and monohydrate complex formation through the ether group of the polymer chains (Graham et al., 1989; Graham, 1992). In addition, the DSC curve of the Gelucire 50/13 sample stored at 80% RH was very similar to that of freshly prepared slow cooled Gelucire 50/13 (Sutananta et al., 1994a). It has been suggested (Sutananta et al., 1994a) that slow cooling facilitates fractional crystallisation of the Gelucires, i.e. crys-

Table 1
Moisture uptake by various Gelucire samples after storage for 30 days at 80% relative humidity

Gelucire	Water absorbed (% w/w of dry bases)
43/01	<0.02
50/02	0.52
50/13	1.12
55/18	0.65

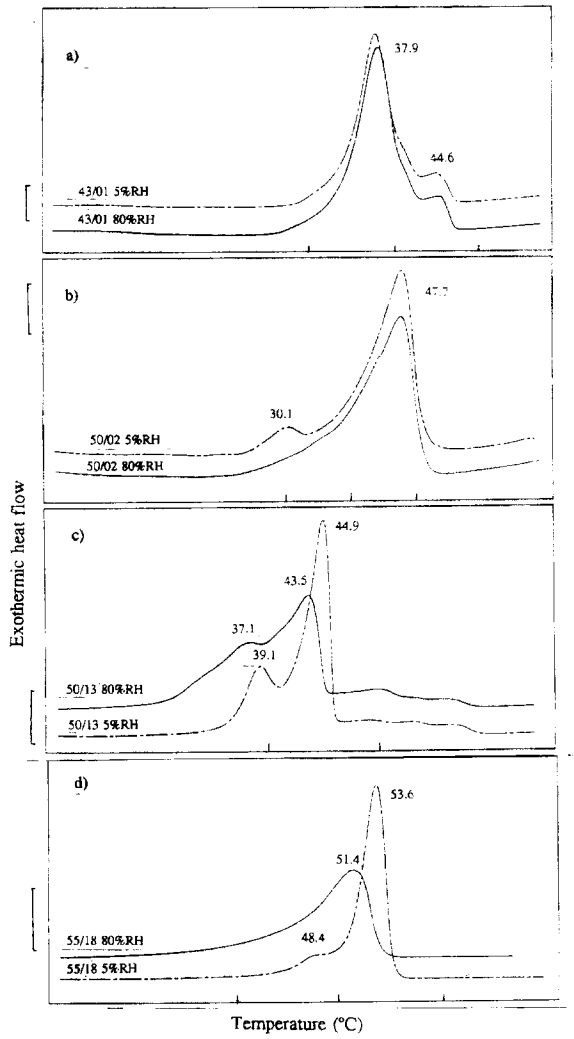

Fig. 1. DSC traces of Gelucires (a) 43/01, (b) 50/02, (c) 50/13 and (d) 55/18 after storage for 220 days under conditions of 5% and 80% RH. Bar indicates 1.0 mW.

tallisation of the components into segregated regions. It is therefore possible that the presence of moisture is facilitating this segregation process, resulting in the similarity between the endotherms of slow cooled Gelucire 50/13 and the ambiently cooled base stored under high humidity conditions.

3.3. Viscosity studies

Previous studies have indicated that storage of heat-treated Gelucire 55/18 in the solid state results in a decrease in the viscosity upon melting compared to fresh samples (Sutananta et al., 1995c). This decrease was ascribed to degradation of the sample, hence it is of interest to assess the corresponding effects of storage under different humidities and remelted. Table 2 shows the viscosities of Gelucires 50/13 and 55/18 stored for 220 days under low or high relative humidities. Storage under high humidity conditions did not effect the viscosity of molten Gelucire 50/13, even though the DSC traces of solid Gelucire 50/13 samples showed marked differences between high and low humidity storage conditions. In contrast, the viscosity of 55/18 samples stored under high humidities was less than half the value of those stored under dry conditions, suggesting that moisture may accelerate the degradation of Gelucire 55/18. The viscosity of samples stored under low humidity conditions was slightly less than the fresh samples, hence these samples also degraded but to a much lesser extent than in the presence of high levels of moisture.

3.4. Dielectric analysis

Preliminary studies indicated that while measurement of the 80% RH samples under corresponding humidity conditions would theoretically reduce errors due to water evaporation during measurement, a layer of water was found to form on the outside surface of the tablet which led to the establishment of a conduction pathway between the electrodes, thereby giving artificially

Table 2
Viscosities (Pa.s) of molten Gelucires 55/18 and 50/13 stored for 220 days under different humidity conditions

Sample	Relative humidity (%)	
	5	80
Gelucire 55/18		
60°C (1.822 Pa.s)[a]	1.503	0.726
70°C (1.355 Pa.s)	1.164	0.519
Gelucire 50/13		
65°C (0.062 Pa.s)	0.059	0.060
70°C (0.054 Pa.s)	0.052	0.052

[a]The viscosity shown in parentheses is the viscosity at 0 days.

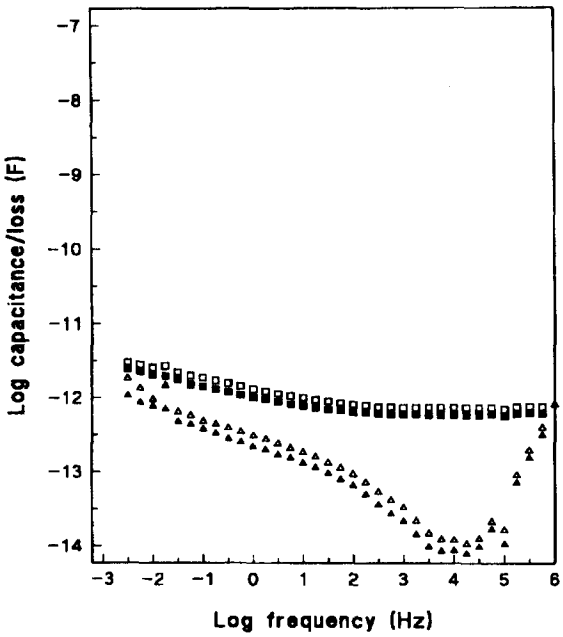

Fig. 2. Dielectric response of Gelucire 43/01 on storage for 60 days. Keys: □, △ capacitance and loss of sample stored at 80% RH; ■, ▲ capacitance and loss of sample stored at 5% RH.

high responses. It was therefore decided that samples would be measured at 5% RH, as preliminary studies showed that repeat measurements on the same 80% RH sample showed identical responses, hence the effects of water desorption during measurement were found to be negligible.

The dielectric responses of Gelucire samples aged for 60 days at 5% and 80% RH are shown in Fig. 2 to Fig. 5. The values associated with the response can be found in Table 3. Generally, samples stored at 80% RH for 60 days had greater responses in terms of the values of capacitance and loss than those stored at 5% RH for the same periods of time over the range of frequencies studied. The values of capacitance and loss of aged samples stored at 5% RH were usually slightly lower than those of freshly prepared samples while those stored at 80% RH were much higher. In addition, the crossover frequencies of the samples stored at 80% RH shifted towards the higher frequencies while those stored at 5% RH remained unchanged in this respect. The decrease seen on storage under dry conditions is of interest, as in a previous study (Sutananta et al., 1995a) it was suggested that samples previously slow cooled from the melt gave higher dielectric responses than fast cooled materials due to the former process resulting in segregation of the components of the sample. Examination of the DSC curves for aged Gelucire samples (Sutananta et al., 1995b) indicated a tendency for the Gelucires to show a smaller number of peaks on storage, implying that the segregation is reduced. The decrease in dielectric response seen here is consistent with these findings in that a lower response was found for the less segregated system, thereby lending support to the hypothesis that the dielectric response is associated with component segregation.

Fig. 2 shows the response of Gelucire 43/01, which indicates only a small increase in response on storage at 80% RH. This material is composed almost entirely of triglycerides (Sutananta et al., 1994b), hence it would not be expected to exhibit extensive water uptake, as was found to be the case (Table 1). The other Gelucire samples, how-

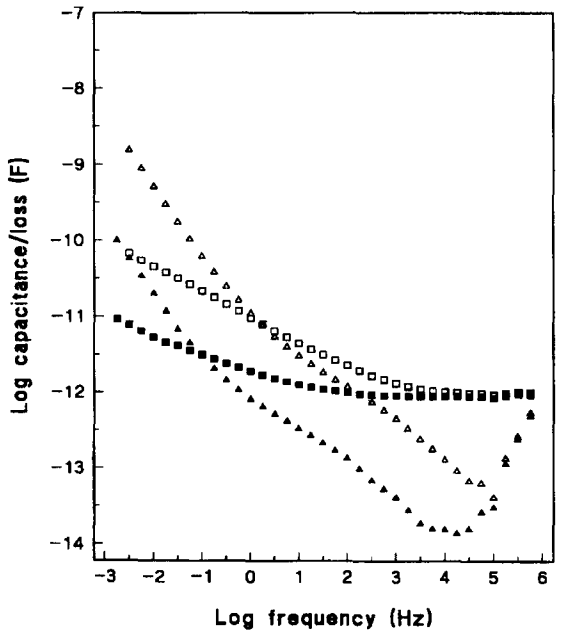

Fig. 3. Dielectric response of Gelucire 50/02 on storage for 60 days. Keys: □, △ capacitance and loss of sample stored at 80% RH; ■, ▲ capacitance and loss of sample stored at 5% RH.

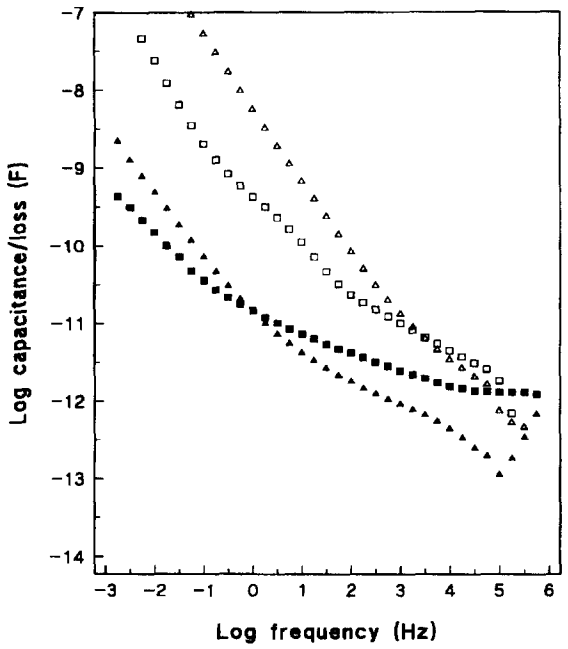

Fig. 4. Dielectric response of Gelucire 50/13 on storage for 60 days. Keys: □, △ capacitance and loss of sample stored at 80% RH; ■, ▲ capacitance and loss of sample stored at 5% RH.

ever, showed more substantial increases in response (Figs. 3–5). The increase seen for Gelucire 50/02 reflects an increase in the conductance of the system due (directly or indirectly) to the presence of the water. There is no evidence for the involvement of a different dielectric mechanism for the two stored samples, as indicated by the similarity of slopes for the capacitance and loss. The response of Gelucire 50/13 samples, however, shows a change in the log/log capacitance slope below approximately 1 Hz to give a value similar to that of the loss. Parallel capacitance and loss log/log curves are characteristic of quasi-d.c. conductivity, whereby charges move through the system by means of a "hopping' process. This involves the movement of charges between specific sites within the sample, rather than by continuous movement through the system (d.c conductivity) (Dissado and Hill, 1984). Ramdeen et al. (1984) have suggested that quasi-d.c. conductivity in humidified samples may be a reflection of charge movement between water molecules adsorbed at specific sites within the sample, hence a similar mechanism may be present in the systems under investigation here.

Gelucire 55/18 samples again show a change in spectral shape after storage under high humidities, over and above the changes in absolute values (Fig. 5). The abrupt change in slope of the capacitance at approximately 0.1 Hz may be due to the establishment of a barrier layer at the electrode surface (Hill and Pickup, 1985), although the spectra does not extend sufficiently far down in frequency in order to see this effect in its entirety. It should be noted, however, that in all cases the observed changes may be due either to alterations in the structure of the Gelucire or to the presence of moisture in the sample. Both effects may be of relevance, as the changes seen in the samples stored under low humidity conditions (which, interestingly, were not detected using DSC over the same time period) are unlikely to be due to changes in moisture content, while the presence of water in samples stored at 80% RH is almost certain to contribute to the observed increase in response.

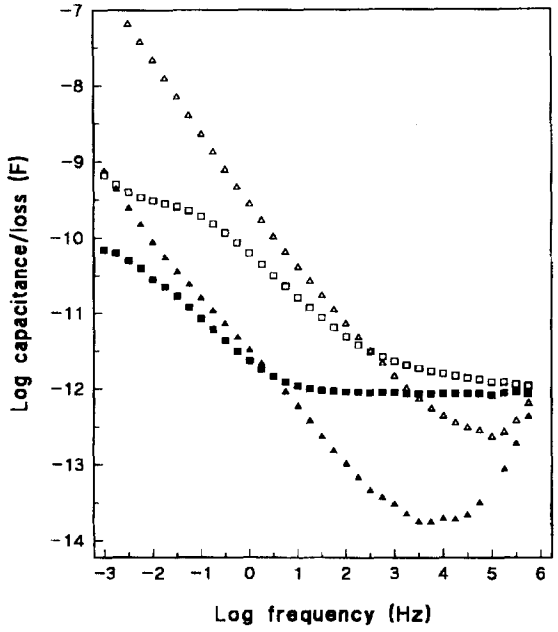

Fig. 5. Dielectric response of Gelucire 55/18 on storage for 60 days. Keys: □, △ capacitance and loss of sample stored at 80% RH; ■, ▲ capacitance and loss of sample stored at 5% RH.

Table 3
Characteristic parameters associated with the dielectric response of Gelucire bases on storage at different humidities. A, fresh sample; B, stored for 60 days at 5% RH; C, stored for 60 days at 80% RH

Sample	C(F × 10^{-12}) at 10 kHz	C(F × 10^{-12}) at 0.1 Hz	G(Mho × 10^{-9}) at 10 kHz	Slope of log G/ω against log ω < 1 Hz[a]
A43/01	0.79	1.45	0.63	-
B43/01	0.59	1.41	0.55	-
C43/01	0.74	1.86	0.75	-
A50/02	0.91	3.02	1.20	0.99
B50/02	0.89	3.16	0.97	0.96
C50/02	1.02	21.3	8.11	0.97
A50/13	1.48	40.7	30.11	0.91
B50/13	1.55	36.3	27.47	0.92
C50/13	4.47	2060	213.08	0.99
A55/18	0.96	40.7	3.38	0.96
B55/18	0.87	8.51	1.23	0.92
C55/18	15.8	193	27.47	0.96

[a]Slope calculated (where possible) from linear portion of log G/ω against log ω graph at lowest frequencies studied

3.5. Dissolution studies

The effect of moisture on the rate of release of drug from Gelucires 50/02 and 50/13 matrices stored under different relative humidity conditions was studied and the results are shown in Fig. 6 and Fig. 7, respectively. The release profile from Gelucire 50/02 matrices stored under dry conditions did not change markedly from that of freshly prepared samples, while samples stored at 80% RH yielded slower profiles. However, the Gelucire 50/13 matrices stored for 60 days at 80% RH released the drug faster than did those stored at low humidity conditions (Fig. 7), being almost complete in 10 h. As previously noted (Sutananta et al., 1995c), storage under dry conditions led to an increase in dissolution rate. For freshly prepared samples, slow cooling from the melt resulted in an increase in dissolution rate compared to ambiently cooled samples (Sutananta et al., 1995b), hence the increase in dissolution rate noted here for Gelucire 50/13 stored under high humidity conditions is consistent with the suggestion that storage in the presence of moisture produces a structure similar to that of freshly prepared slow cooled Gelucire 50/13.

Storage under elevated moisture conditions has therefore resulted in opposite effects on the release from Gelucire 50/02 and 50/13 matrices. This may be a reflection of the different mechanisms of drug release from the two matrices, as release from Gelucire 50/13 is erosion controlled whereas that from 50/02 is diffusion controlled (Sutananta et

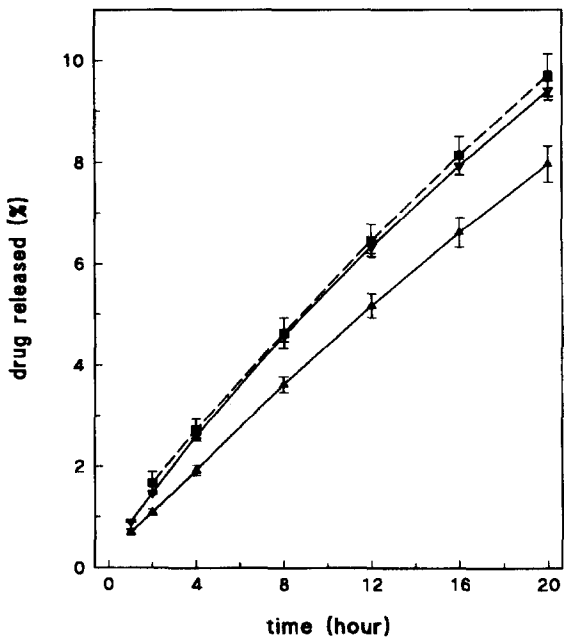

Fig. 6. The effect of moisture on the release of theophylline from Gelucire 50/02 matrices containing 30% drug. Keys: ■ (broken line) 1 day, ▽ kept 60 days at 5% RH, ▲ kept 60 days at 80% RH.

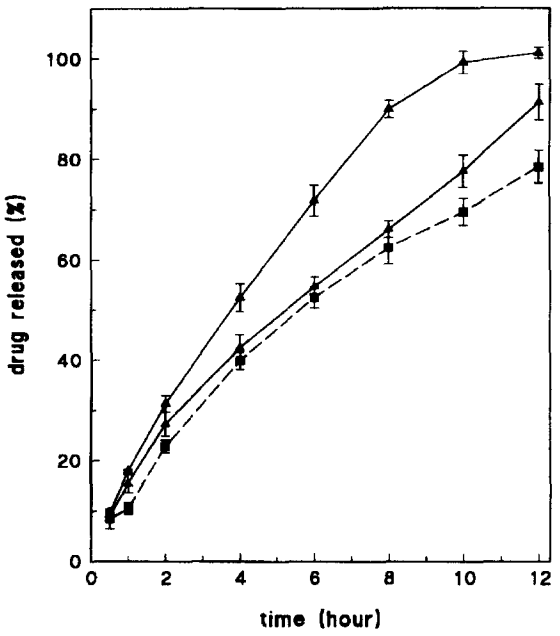

Fig. 7. The effect of moisture on the release of theophylline from Gelucire 50/13 matrices containing 30% drug. Keys: ■ 1 day, ▲ kept 60 days at 5% RH, △ kept 60 days at 80% RH.

al., 1995b). However, as comparatively little is known regarding these processes in the context of Gelucire structure, it is not possible at this stage to provide a more fundamental explanation for the observed changes.

4. Conclusions

The study has demonstrated that Gelucires will undergo structural alterations on exposure to high humidities, the extent of the changes being highly dependent on the chemical composition of the base. Both DSC and dielectric analysis indicated that samples with a high PEG stearate content will undergo more marked changes in structure, although dissolution studies indicated that the effect of these changes on drug release behaviour are not, at this stage, easily predictable. The study has also highlighted the use of dielectric analysis as a means of characterising solid materials, both in terms of structural changes and the detection of moisture.

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