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RESEARCH PAPER

Moisture Uptake of Polyoxyethylene Glycol Glycerides Used as Matrices for Drug Delivery: Kinetic Modelling and Practical Implications

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ABSTRACT

Purpose Gelucire 50/13, a polyoxyethylene glycol glyceride mixture, has been widely used in drug delivery, but its moisture uptake behaviour is still poorly understood. In this study, the effects of relative humidity, temperature, and drug incorporation on the moisture uptake of Gelucire are reported in relation to their practical implications for preparation of solid dispersions using this material.

Methods DVS combined with kinetics modelling was used as the main experimental method to study the moisture uptake behaviour of Gelucire. Thermal and microscopic methods were employed to investigate the effect of moisture uptake on the physical properties of the material and drug loaded solid dispersions.

Results The moisture uptake by Gelucire 50/13 is temperature and relative humidity dependent. At low temperatures and low relative humidities, moisture sorption follows a GAB model. The model fitting indicated that at high relative humidities the sorption is a complex process, potentially involving PEG being dissolved and the PEG solution acting as solvent to dissolve other components.

Conclusion Careful control of the storage and processing environmental conditions are required when using Gelucire 50/13. The incorporation of model drugs not only influences the moisture uptake capacity of Gelucire 50/13 but also the solidification behaviour.

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INTRODUCTION

Water miscible, amphiphilic excipients and polymers have been widely used for forming solid dispersions for improving the dissolution of poorly soluble drugs (1–3). Amphiphilic excipients, such as polyoxyethylene glycol glycerides (Gelucires®), have demonstrated the ability to improve the dissolution as well as the absorption of poorly water-soluble drugs (4–7). Gelucires are a family of amphiphilic materials derived from mixtures of mono-, di-, and triglycerides and polyethylene glycol (PEG) esters of fatty acids with hydrophilic-lipophilic balance values (HLB) from 1 to 18 and melting points from 40 to 60°C (5–7). For oral delivery, different grades of Gelucires have been widely used to produce solid dispersions for immediate and sustained release formulations (4–10). Despite the promising *in vivo* performance of these formulations, concerns over the physical stability of these excipients have slowed the development of solid dispersion products using these excipients as matrix materials. The crystallisation of Gelucires and the effects of aging on polymorphic transformation and formulation performance have been studied extensively (4,8,9,11–14). The uptake of liquid water (as bulk water) into Gelucires can also lead to the formation of different liquid crystalline phases depending on the water content (4,15). This tendency to interact with water is a result of the amphiphilic nature of the materials. However, there is little information in literature on how these materials interact with environmental moisture at different temperatures and relative humidities. A clear understanding of the moisture uptake behaviour of these materials is extremely important for providing guidance for the processing and storage of solid and semi-solid formulations prepared using Gelucires.

Gelucire 50/13 (stearoyl macrogol-32 glycerides, EP) is composed of approximately 8% (*w*/*w*) free PEG 1500, 20% (*w*/*w*) mono-, di, and tri-glycerides of hydrogenated palm oil (mainly stearic and palmitic acid), and 72% (*w*/*w*) monoacyl- (MPEG) and diacyl- (DPEG) derivatives of PEG 1500 (14). It has been traditionally used as a sustained release matrix material (7,16–18), but has also been found to have applications for the immediate release of poorly water-soluble drugs through formation of spray-chilled microspheres (4). The molecular conformation of crystalline Gelucire 50/13 has been well established through the combined use of thermal, small angle X-ray scattering (SAXS) and FT-IR spectroscopic methods (14). There are three major lamellar phases with different long spacings present in the solid Gelucire 50/13 (without any additional thermal treatment) at room temperature (14). The thermal transition at approximately 35–42°C was suggested to be associated with the melting process between the first two lamellar phases that are believed to be linked with the present of MPEG and DPEG (14). The final lamellar phase melts at approximately 54°C. These transition temperatures may vary slightly depending on the heating rate (14). The physical stability of dry Gelucire 50/13 has been reported to be highly dependent on the thermal history of the sample (11,12,14).

Whilst dry Geluicre 50/13 is reasonably well characterised, little is known about its moisture uptake and the effects this has on formulation performance. A clear understanding of the environmental moisture uptake behaviour of this material will assist the development of sustained and immediate release solid dispersion applications of this material for drug delivery. In this paper we examine moisture uptake by Gelucire 50/13 solids and Gelucire 50/13 based solid dispersions containing model drugs with different solid solubilities in Gelucire 50/13. The work was conducted with a particular focus to providing a better understanding of moisture absorption kinetics of Gelucire 50/13 using mathematical models as an indicator of the general type of behaviour to be expected from these types of excipients and to identify the possible factors that can affect moisture uptake and formulation performance.

Mathematical Modelling of Moisture Sorption Process

For many amphiphilic materials, moisture uptake is a complex process, typically consisting of two stages, an adsorption stage (where the moisture covers the surface of the material) and the absorption stage (where the moisture penetrates into the material, causing hydration and swelling). Different mathematical models have been used to describe these two different processes. Fitting experimental data using these models can provide an indication of the mechanisms of moisture uptake. The equilibrium water vapour uptake capacity of a material can be described by a variety of isotherms (19,20). The typical sigmoidal shape often seen with water sorption is described as type II Brunauer-Emmett-Teller (BET) of the fitting of the original two parameter BET equations (21). For complex materials, such as food products in a water activity range of 0–0.85, the semi-empirical Guggenheim-Anderson-de Boer (GAB) model shows to be the most versatile model for fitting water sorption data (22). The GAB model is in the form as Eq. 1,

$$\frac{w}{w_m} = \frac{Cka_w}{(1 - ka_w)(1 - ka_w + Cka_w)} \tag{1}$$

where w is the moisture content (%), w_m is the moisture content corresponding to monolayer moisture adsorption, C is the Guggenheim constant, k is the compensating constant for multiplayer moisture adsorption, and a_w is the water activity expressed as relative humidity (22). As Gelucire is a complex mixture like many foods, such a model is likely to be appropriate for use to describe its equilibrium, adsorption behaviour.

At a fixed relative humidity, the moisture uptake of a material often is a combination of adsorption and absorption processes. For porous materials, such as porous silicon, activated carbons, and woods, adsorption dominates the moisture uptake process and the dynamics of the moisture adsorption process can be described using nested models based on a double stretched exponential (DSE) model (19–23) as shown in Eq. 2.

$$\frac{M_t}{M_e} = A_1\left(1 - e^{-(k_1 t)^{\beta_1}}\right) + (1 - A_1)\left(1 - e^{-(k_2 t)^{\beta_2}}\right) \tag{2}$$

where M_t is the accumulative moisture uptake at time t, M_e is the equilibrium uptake, k_1 and k_2 are adsorption rate constants, β_1 and β_2 are the exponents, and A_1 and $(1\text{-}A_1)$ are the fractional contributions of the different adsorption processes that are related to the adsorption rate constants k_1 and k_2 respectively. In the cases that $\beta_1=\beta_2=1$, the DSE model can be converted into double exponential (DE) model (19–23) as shown in Eq. 3.

$$\frac{M_t}{M_e} = A_1\left(1 - e^{-(k_1 t)}\right) + (1 - A_1)\left(1 - e^{-(k_2 t)}\right) \tag{3}$$

For materials such as amorphous glass and polymers, the moisture uptake is mainly dominated by diffusion, either as classical Fickian diffusion or Case II diffusion (24–28). In Fickian diffusion, the concentration gradient of water gradually builds up over time as the water adsorbs to the surface, and the water moves into the material through across a diffusion gradient. For homogenous spheres, the isothermal diffusion of moisture into the spheres can be described using Eq. 4.

$$\frac{M_t}{M_e} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\left(\frac{1}{n^2}\right) exp\left(\frac{-Dn^2\pi^2 t}{a^2}\right) \tag{4}$$

where M_t is the moisture uptake at time t, M_e is moisture uptake at equilibrium, D is the diffusion coefficient, a is the radius of the solid spheres, and n is a numerical index.

For Case II diffusion, a high surface water concentration quickly builds up at the adsorption stage and the boundary of this water shell outer layer slowly moves inwards to the centre of the material (Peleg model). It has been widely used for describing the moisture uptake of many agricultural and food materials (29).

$$M_t = M_0 + \frac{t}{A_1 + A_2 \cdot t} \quad (5)$$

In the Peleg model (Eq. 5), M_t is the moisture uptake at time t, M_0 is initial moisture content at time 0, A_1 is the Peleg rate constant, and A_2 is the Peleg capacity constant. These models described above are used later in this paper to fit the experimental moisture sorption data of Gelucire 50/13, in order to help interpret the underlying mechanisms of moisture uptake by this material.

MATERIALS AND METHODS

Materials

Gelucire 50/13 was obtained from Gattefossé S.A.S. St Priest (France) as a gift, with a melting point of ~50°C and a HLB value of 13. The Gelucire pellets were gently ground using pestle and mortal and particles in the size range 106–153 μm were used for all tests. Paracetamol, caffeine anhydrous, ibuprofen, indomethacin, and PEG 1500 were all obtained from Sigma (Gillingham, Dorset, UK).

Methods

Preparation of Solid Dispersions

Solid dispersions were prepared by adding approximately 5% *w/w* of the model drug (Paracetamol, Ibuprofen, Caffeine, Indomethacin) to molten Gelucire 50/13 at approximately 65–70°C. The molten mixtures were continuously mixed using a magnetic stirrer to ensure the uniform mixing of the drug in the lipid. The samples were then removed from the heat and left at room temperature to cool and solidify for up to 4 h, at which point they were ready for further analysis. The uniformity of the drug distribution in the resultant solid dispersions were tested using PL-HSM. All samples for the DVS tests were ground using a pestle and mortar and particles in the size range 106–153 μm were obtained by sieving. In order to study the physical stability of the solid dispersions under humid conditions, the samples were exposed to either ambient conditions (22°C/40%RH) or 25°C/75%RH created by a saturated salt (NaCl) solution. The physicochemical properties of these dispersions were evaluated after 10 weeks storage under the different conditions.

Dynamic Vapour Sorption (DVS)

The DVS studies were conducted using a TGA Q5000 (TA Instruments, New Castel, USA). Samples of 5–10 mg of milled Gelucire 50/13 or solid dispersions were loaded into the instrument. On each experimental run, an initial drying process was performed by holding the chamber temperature at 25°C and the relative humidity at 0% for 60 min. Four different types of DVS experiments were performed. Sorption isotherm runs were performed at 25°C and at 37°C with stepwise increases in relative humidity from 0 to 90%RH in 10%RH increments. Either a change of less than 0.01% in weight over a 30-min period or a maximum time period of 180mins per step was allowed for equilibration. The adsorption-desorption isotherm was performed at 25°C with the adsorption being as described above and then immediately followed by desorption isotherms from 90 to 0%RH. The temperature ramp adsorption runs were conducted at 75%RH with increasing temperatures stepwise (20, 30, 37, 45, and 55°C) from 20 to 55°C. Each isothermal step was held for 120mins. Finally, isohumic experiments were performed at temperatures from 20 to 50°C at 75%RH and a minimum of 4 h were allowed equilibrium to be reached. The kinetic model fitting of the isotherm adsorption data were performed using Table Curve® 2D version 5.01 (SYSTAT Software Inc., CA, USA). For the normalised data profiles, the model selection criteria are 99% residual being below ±2% and with least number of variables in the fitted model.

Differential Scanning Calorimetry (DSC)

The DSC experiments were carried out using a TA MDSC Q1000 (TA Instruments, New Castel, USA). A heating/cooling rate of 10°C/min was used up to a temperature of 80°C before re-cooling to −10°C at the same rate. A purge gas of nitrogen was used at a flow rate of 50 ml/min. DSC pans were prepared using TA instruments standard aluminium crimped pans, and circa 2–3 mg sample sizes were used for each measurement. Temperature calibration performed using three calibrates and heat capacity calibration using sapphire was performed prior to sample measurements.

Polarised Light Hot Stage Microscopy (PL-HSM)

The melting of Gelucire 50/13 was studied using polarised light, hot-stage microscopy (PL-HSM). A Leica DM LS2 polarised light microscope (Wetzlar GmbH, Germany) connected to a video capture system was equipped with a Mettler Toledo FP82HT hot stage (Beaumont Leys Leicester, UK) controlled by a Mettler Toledo FP 90 central processor (Beaumont Leys Leicester, UK). A small quantity of Gelucire 50/13 or the drug loaded solid dispersions was

placed between a sample and cover slide. The sample stage was heated up to 65°C at 10°C/min. The videos of the melting process of the tested solids were recorded and analysed.

RESULTS

Moisture Sorption Isotherm of Un-treated Gelucire 50/13

The results for the sorption isotherms at 25°C and 37°C of the powdered Gelucire 50/13 without additional treatment are shown in Fig. 1a and b. It can be seen clearly that the moisture sorption is temperature and relative environmental humidity dependent. Below 60% RH, the sorption of moisture by Gelucire 50/13 is below 1 mmol/g for both 25°C and 37°C when equilibrium was reached. At both 25 and 37°C, the moisture uptake is dramatically increased when the relative humidity is above 70%RH. The moisture uptake between 70 and 90%RH is slightly higher at 25°C (17.3 mmol/g) than 37°C (12.6 mmol/g). Despite the differences within the region of 70–90%RH, the total amount moisture uptake by Gelucire 50/13 after 2 h at 90%RH is very similar (15–17 mmol/g) at both temperatures. This indicates that the maximum moisture storage capacity of Gelucire 50/13 is around 15–17 mmol/g which is equivalent to 27–32% (*w*/*w*) water sorption (in comparison to the initial dry weight of the material).

At 25°C and 0–70%RH, the moisture adsorption exhibits a pattern similar to many complex food materials, where multiple stages of adsorption can be identified. As seen in Fig. 1a, at 25°C and low relative humidities (0–20% RH), there is a steady increase in water content with RH, which is likely to be saturating the surfaces of the material with a single layer of moisture (stage A). With increasing relative humidity (20–50% RH), the rate of moisture adsorption slightly reduces as this is in the period of multiple layers of moisture adsorbing onto the surface (stage B). With further increases in relative humidity (50–70% RH), the moisture diffuses into the material and builds up interconnected layers of adsorbed moisture (stage C). The data within 0–70% RH was fitted using the GAB model and the values of w_m, C, and k were found to be 0.146, 2.54, and 0.012, respectively. The significance of these parameters is not certain as there is some evidence that they are not entirely orthogonal in the fitting process (22) and different sets of these values can give very similar sorption isotherms. However the fact that the general shape is similar to those observed in complex systems such as foods suggests that a combination of mechanisms may be at work. At 37°C, the isotherm adsorption pattern within 0–70% RH also can be fitted using the GAB model and the values of w_m, C, and k were found to be 22.04, 0.014, and 0.011, respectively. The increase in monolayer adsorption (w_m) indicates more rapid surface adsorption

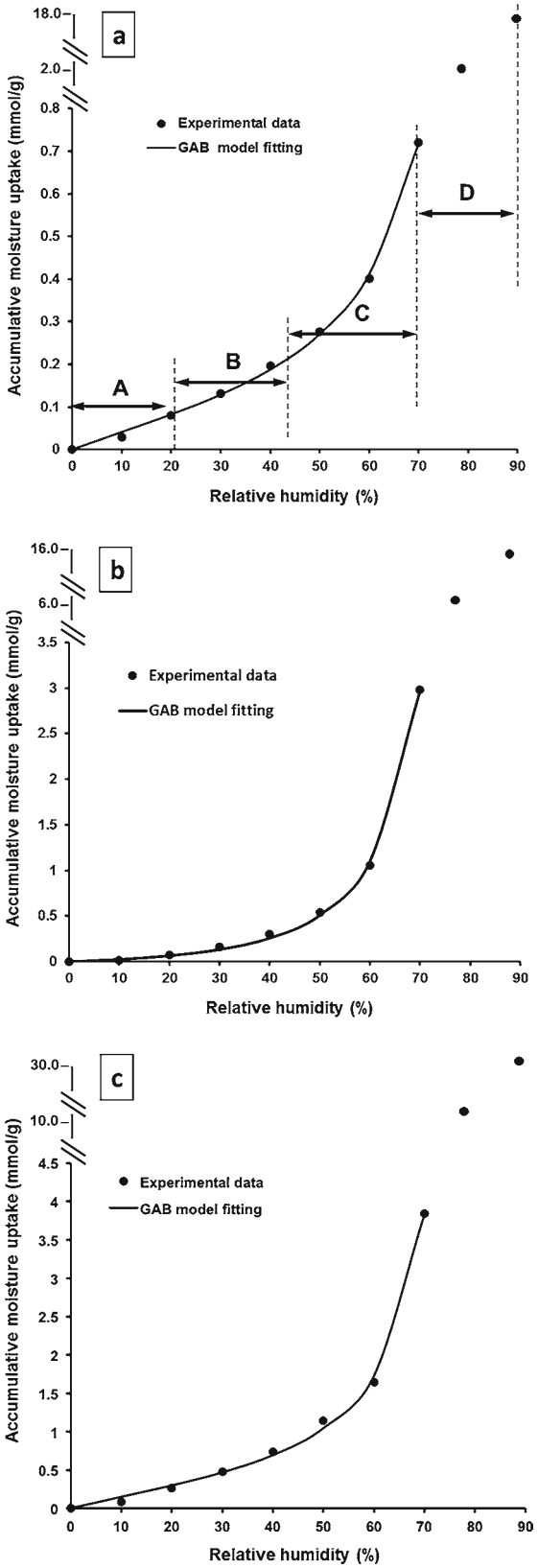

Fig. 1 Sorption isotherms of (**a**) untreated Gelucire 50/13 at 25°C with identified different sorption regiments of A-single layer adsorption, B-multiple layers adsorption, C-interconnected layers adsorption, and D- water absorption; (**b**) untreated Gelucire 50/13 at 37°C; and (**c**) PEG 1500 at 25°C for comparison.

with increasing the temperature from 25°C to 37°C. Despite the fit to the GAB isotherm there is a strong resemblance to the Flory Huggins (BET type III isotherm) for the 37°C data. This isotherm has been associated with water sorption on rubbery polymers (30) and plasticised polymers (21).

For both temperatures, the GAB model cannot be used to describe the behaviour at high relative humidities. 70–75%RH is the critical humidity range of the acceleration of moisture uptake of Gelucire 50/13. A similar finding was also reported for Gelucire 44/14 (15). In the case of Gelucire 44/14 study, this was attributed to the swelling and dissolution of the PEG 33 component of the material. It is possible that similar behaviour occurs in Gelucire 50/13 as it contains PEG 1500, which is swellable and soluble in water. At this stage possibly the dissolution of PEG 1500 requires rapid moisture uptake and it acts as a as solvent to further dissolve other components such as glycerides and PEG esters in Gelucire 50/13 (stage D).

In order to explore this mechanism, this behaviour was compared with the pure PEG 1500. As seen in Fig. 1c, the sorption isotherm of PEG 1500 at 25°C showed relative humidity dependent sorption. Less than 2 mmol/g uptake was observed at relative humidities below 60%RH. Significant increases in the uptake were observed at 70–90%RH. This rapid uptake may be associated with the swelling and dissolution of free PEG 1500. However, in the case of Gelcuire 50/13 other mechanisms must also be involved; the total sorption of Gelucire 50/13 at 25°C would be below 4.2 mmol/g if PEG 1500 was the sole contributor to this effect as there is only approximately 8% (*w*/*w*) free PEG 1500 in Gelucire 50/13.

Temperature Effect on Isohumic Moisture Sorption of Gelucire 50/13

The temperature effect on the moisture uptake of Gelucire 50/13 was further explored using isohumic tests at fixed 75%RH covering a series of chosen temperatures. The reason for choosing 75%RH is that according to the sorption isotherm results, 70–75%RH is the critical humidity before the dramatic increase in moisture uptake of Gelucire 50/13. In addition it is a common stress condition used for pharmaceutical stability testing. As Gelucire 50/13 has a relatively low melting temperature of approximately 50°C, it is important to first understand the behaviour of the material under dry conditions. The melting and solidification process of Gelucire 50/13 has been studied and the structural identifications at different temperatures are summarised in Table I. As seen in Fig. 2, the melting of Gelucire 50/13 can be divided into three major stages. From the onset at 35°C up to 38°C there is a broad shallow endothermic peak which has been attributed to the equilibrium of two different lamellar confirmations within the crystalline structures of Gelucire 50/13 according to the SAXS data

Table I Comparison of Temperature ramp Isohumic DVS Results with the Molecular Structural Confirmation of Gelucire 50/13 Detected by Thermal and Spectroscopic Methods

		20–35°C	35–42°C	42–50°C	50–55°C
Melting	SAXS (14)	3 lamellar phases	Equilibrium between 2 of the lamellar phases, no changes with the 3rd phase	Melting of one of the lamellar phase with longer spacing (121 Å, 90 Å)	Melting of another lamellar phase (49.5 Å)
	DSC	No changes	Long stretched onset of the main melting	Main melting	Second melting as shoulder peak
	DVS	Constant increase in equilibrium moisture uptake with increasing temperature	Reduction on equilibrium moisture uptake after reaching maximum at 37°C	Further reduction on equilibrium moisture uptake with increasing temperature	
Cooling	SAXS (14)	Simultaneous crystallisation of two lamellar phase (121 and 90 Å) at 29°C		Crystallisation of the other lamellar phase (49.5 Å) at 47°C	
	DSC	Exothermic peak at 28°C		Exothermic peak at 44°C	
	DVS	Slow increase in moisture uptake between 45 and 20°C		Reduction on the moisture uptake with reducing temperature from 55 to 45°C	

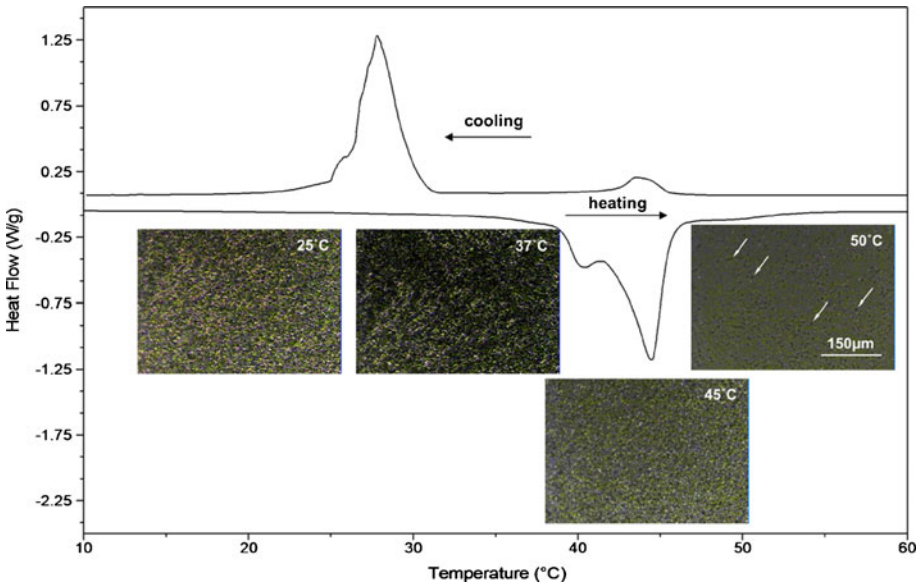

Fig. 2 Multi-component nature of dry Gelucire 50/13 demonstrated by DSC and corresponding PL-HSM results during melting and cooling of the material.

reported previously (14). These two lamellar structures melt at approximately 42°C. A large proportion of the crystalline component with a relatively longer spacing melts between 42 and 50°C, and the small proportion of short spacing lamellar phase that is evenly distributed in the material melts at 50–54°C (14). This correlates with the PL-HSM data, which show different components melting at different temperatures as seen in Fig. 2. The size of the domains with different compositions can be roughly estimated according to the PL-HSM results. It seems that the small proportion of components with the highest melting temperature have dimensions of of 5–7 μm. On cooling the molten Gelucire 50/13, two exothermic transitions at 28 and 44°C can be seen. They are associated with crystallisation of different lamellar phases of the material (14).

Based on an understanding of the response of dry Gelucire 50/13 to heating and cooling, five different temperatures were selected for the temperature ramp isohumic tests, two below the melting of the lipid (20 and 30°C) and three at and above the onset of melting at, 37 (also reflects body temperature), 45, and 55°C. Two experiments were performed using these conditions, heating from 20 to 55°C to achieve the melting of the material and cooling from 55 to 20°C (pre-melted at 55°C/0%RH) to lead to the solidification of Gelucire 50/13. During the isohumic heating experiment at 75%RH, it can be seen in Fig. 3 that at temperatures up to 30°C the total water uptake is limited to within 2% (*w*/*w*). The accumulated moisture uptake reaches 9% when the temperature is increased to 37°C. With further increase in temperature to 45°C, the profile turns into desorption, as water loss is evident, 1.6% and 1.4% water loss are observed for the 45°C and 55°C isohumic stages, respectively. As shown in Fig. 2 that the first melting of dry Gelucire 50/13 occurs between 42 and 50°C, it is possible that once Gelucire 50/13 starts to melt the miscibility with

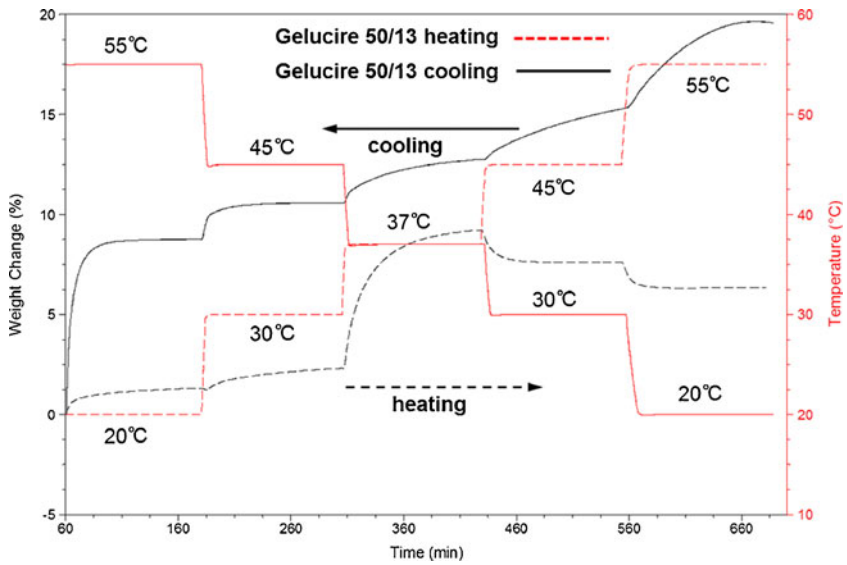

Fig. 3 Temperature ramp isohumic (at 75%RH) profiles of Gelucire 50/13 powders during heating (*dash line*) and cooling (*solid line*).

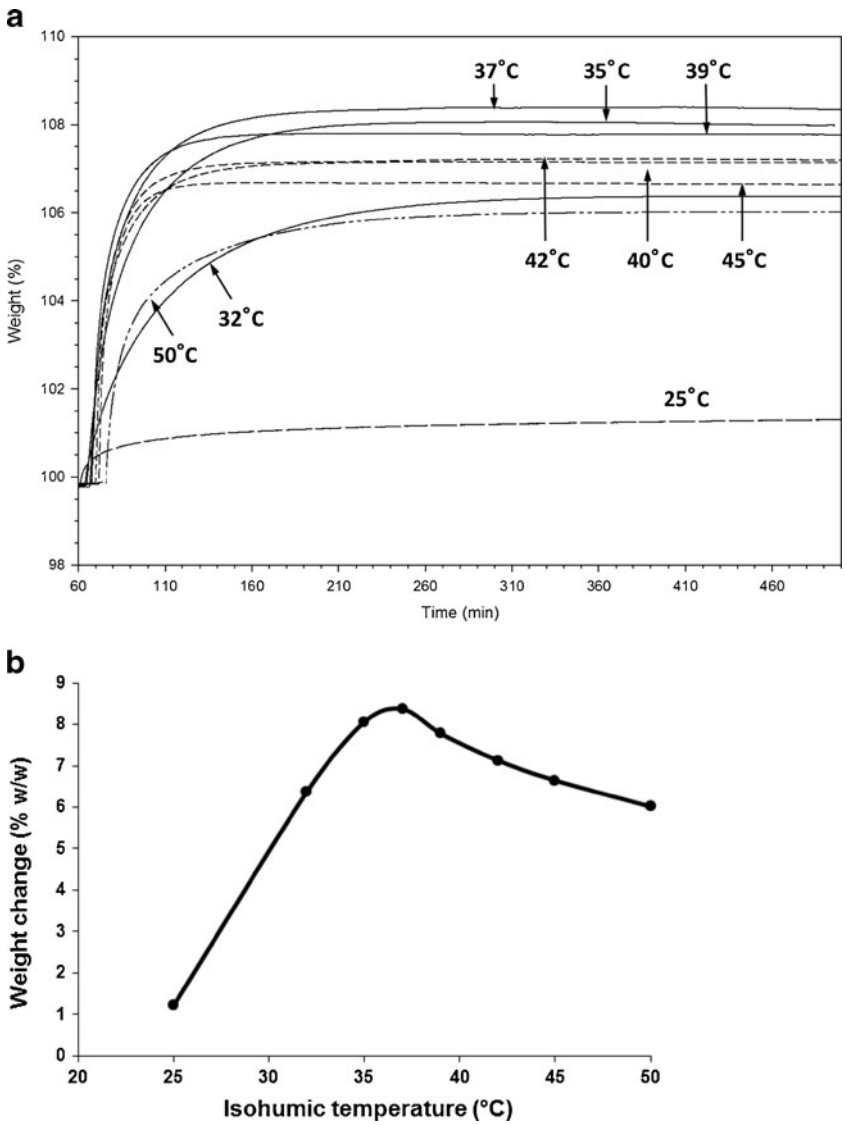

Fig. 4 (**a**) Isohumic (at 75%RH) profiles of Gelucire 50/13 powder at temperatures between 25 and 50°C; (**b**) the plot of equilibrium mositure sorption (plateau value) against temperature.

water reduces. This effect may contribute to the observed weight loss at 45 and 55°C in the DVS results.

Following melting of Gelucire 50/13 at 55°C/0%RH, the isohumic sorption profile (Fig. 3) at 75% RH shows some interesting features during the solidification of the material. It is noted that the moisture uptake of dry molten Gelucire 50/13 at 75% RH/55°C is 8% when the plateau is reached. The moisture sorption further continues with decreasing the temperature. Between 45 and 30°C the water uptake is similar at each isohumic stage (between 2 and 2.7%). At 20°C, the water uptake increases to 4.2% within 2 h. In total, the material takes up approximately 13% (*w*/*w*) more moisture during cooling than it does during the melting process. There is no obvious correlation between the recrystallisation behaviour of dry Gelucire 50/13 (DSC data) and the variable temperature isohumic results. This is expected as in the isohumic experiments, Gelucire 50/13 continuously takes up moisture during the cooling and swells which can delay/

Table II DE Model Fitting Parameters of Isohumic Results at 25, 32, 37, 42, 50°C

Fitting parameters	25°C	32°C	37°C	42°C	50°C
A_1	22.7%	16.8%	75.7%	58.3%	68.4%
Fast rate constant k_1 (s^{-1})	0.107	0.071	0.041	0.065	0.021
Slow rate constant k_2 (s^{-1})	0.014	0.017	0.202	0.548	0.161
Fitting R^2	0.998	0.9999	0.9999	0.9992	0.9992
Fitting error	0.0019	0.0007	0.0009	0.0045	0.0013

prevent the solidification of the material. Due to the moisture uptake during cooling in this experiment, the material is likely to remain semi-solid instead of completely crystallising with consequent solidification.

In order to eliminate the heating ramp effect and obtain kinetic information, moisture sorption at 75%RH at different temperatures were performed. All tests were carried out for at least 8 h in order to ensure the samples had reached equilibrium. Figure 4a demonstrates the effect of temperature on isothermal moisture uptake. As seen in Fig. 4b, with increasing the temperature the equilibrium sorption capacity reaches a maximum of 8.6% at 37°C. It is also noted that the time required to reach equilibrium sorption is shorter at the temperatures between 37 and 45°C and significantly reduced after the complete melting of Gelucire at 50°C.

The sorption data of Gelucire 50/13 at 75%RH and different temperatures were fitted using different type of exponential models and diffusion (Fickian and Peleg) models discussed earlier. In the cases of exponential models, the difference between DSE and DE is that in DSE, the two processes have a distribution of relaxation times for each process, whereas in the DE model there are only two single relaxation times for each process. Models such as DE and SE can be difficult to distinguish due to their similarities in curve shape. Therefore, the selecting criteria of the suitable model fitting is that 99% of residual of the normalised data being within ±2% with the least number of variables. Across the temperature range from 25 to 50°C, the DE model provides the best fitting with the residual being below ±1% for the temperatures of 32, 37, 42, and 50°C (Table II). The excellent fitting to a DE model suggests that the sorption behaviour at these temperatures is dominated by a two-process mechanism with two different relaxation times. Through the model fitting, the proportion (A_1) of the process with the faster rate constant (k_1) and slower rate constant (k_2) can be obtained, as seen in Table II. The proportion (A_1) of the process with the faster rate constant (k_1) appears to reach a maximum at 37°C. This may help to explain the highest equilibrium sorption capacity reached at 37°C.

The sorption data collected at 35, 39, and 45°C showed similarly good fitting with either the Peleg or Fickian diffusion models, which were better than the fittings obtained with the DE/DSE model. This suggests that at these temperatures the moisture sorption may be largely dominated by diffusion of moisture into the material. For the data collected at 25°C/75%RH, the fitting R^2 for the DE model (0.9985) and diffusion model (0.9991) are extremely close, but the DE model provides a better fit of the data at the initial stage of sorption and the Fickian diffusion model gives a better fit of data generated later in the experiment. This is demonstrated by the residual data shown in Fig. 5a and b. This suggests that there are different dominating uptake mechanisms at different stages of moisture sorption, with adsorption dominating at early stages and sorption by diffusion at later stages of the process. Overall, it is clear that several sorption models can be fitted to the experimental data. However it is not convincing that the model can be used to truly reflect the physical process of the sorption, but more a good way to parameterise the results.

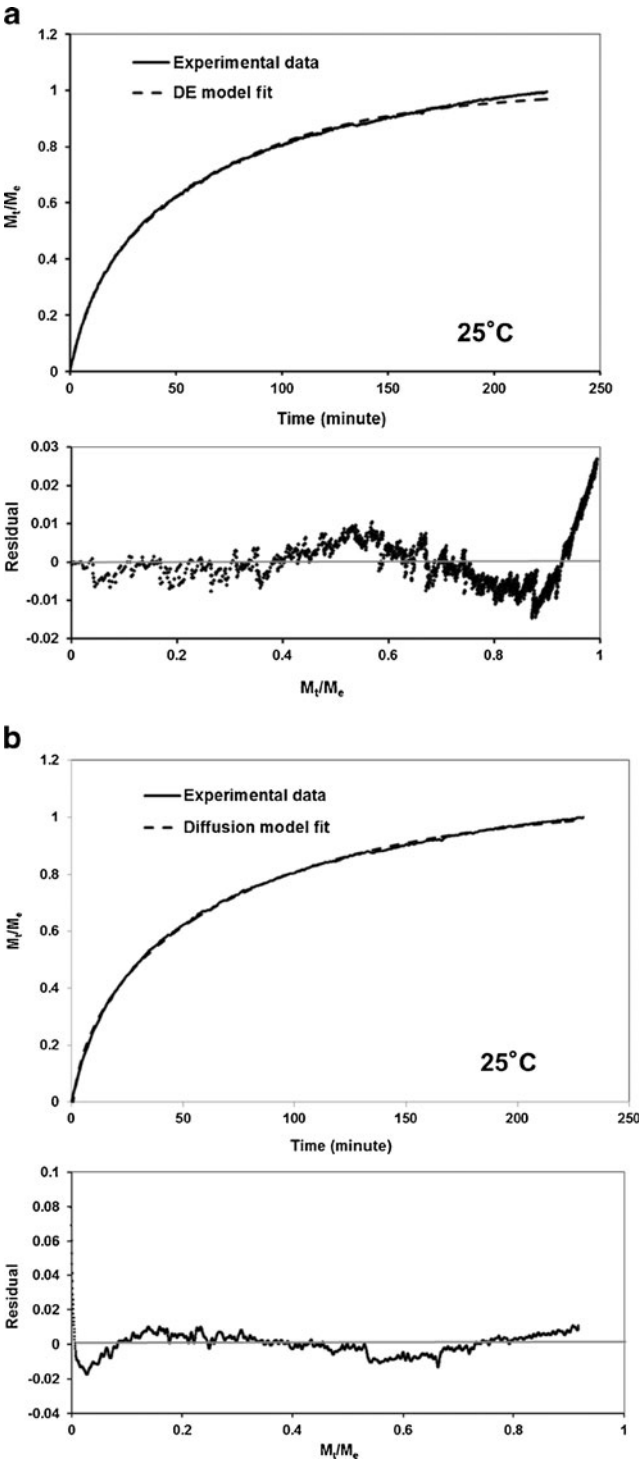

Fig. 5 Example kinetic model fitting and fitting residual of the moisture sorption behaviour of Gelucire 50/13 using (**a**) DE model at 25°C, (**b**) Fickian diffusion model at 25°C and (**c**) DE model at 32°C.

Effect of Drug Incorporation on Moisture Sorption of Gelucire 50/13

After drug incorporation, the solid dispersions containing 5% (*w*/*w*) of the model drug were tested using the isohumic experiment with a temperature ramp. It can be seen in Fig. 6 that the water-soluble model drug, caffeine, which has little interaction/dissolution in the lipid during the preparation of the solid dispersion, shows little effect on the moisture sorption behaviour of Gelcuire 50/13. Two poorly water-soluble model drugs, indomethacin and ibuprofen, which were partially and completely dissolved in Gelucire 50/13, respectively during preparation. However, presumably because of an increased overall hydrophobicity of the solid dispersion particles, the addition of these drugs reduced the moisture uptake of the systems in comparison to the lipid alone and the caffeine system. Paracetamol, which has a higher aqueous solubility than indomethacin and ibuprofen is completely dissolved in Gelucire 50/13 during preparation. The paracetamol containing solid dispersions showed the highest total moisture uptake capacity among the tested systems. Although the underpinning mechanism of this observation is not clear, it is possible paracetamol is molecularly dispersed in Gelucire 50/13 and deliquesces along with free PEG and promotes further moisture uptake. It is also noted that at 75%RH, all drug loaded dispersions except paracetamol dispersions show their highest moisture uptake at the 37°C isotherm step, followed by moisture loss at 45°C. In terms of the total moisture uptake, the incorporation of indomethacin and ibuprofen reduced the total moisture uptake. For paracetamol loaded dispersions, the highest moisture uptake occurred at 30°C. This is unique to paracetamol-loaded systems and may be associated with the different thermal behaviour of the dispersions as seen in Fig. 7d.

Moisture uptake can alter the packing and nanostructure of the solid dispersions during aging, which may influence the physical performance of the formulations including processibility. Therefore, the impact of moisture uptake on the melting and solidification behaviour of the aged solid dispersions was further investigated. As seen in Fig. 7a, exposure to 75%RH shows a more obvious effect on the solidification process than on the melting behaviour of Gelucire 50/13. The complete solidification was shifted by more than 5°C below the original solidification temperature after exposure to 75%RH. Considering the melting process may have released most of the moisture content in the sample (as the experiments were performed in crimped DSC pans under constant nitrogen flow), the decrease in solidification temperature may be a result of a small amount of residual moisture remaining in the sample, as well as the change in the polymorphic form of the lipid. For the drug-loaded systems, storage at different humidities has little impact on the melting and solidification of solid dispersions containing caffeine and indomethacin. However, after storage at 75% RH the solid dispersions containing paracetamol and ibuprofen both are semi-solid (instead of solid) and show significant reductions in the solidification temperatures of the material to below 0°C (which is likely to be the ice formation of entrapped moisture). As discussed earlier, these two systems are molecular dispersions of drug in the lipid. The drug may be structurally involved during the moisture uptake. The results indicate that permanent structural alternation occurs after exposure to humidity.

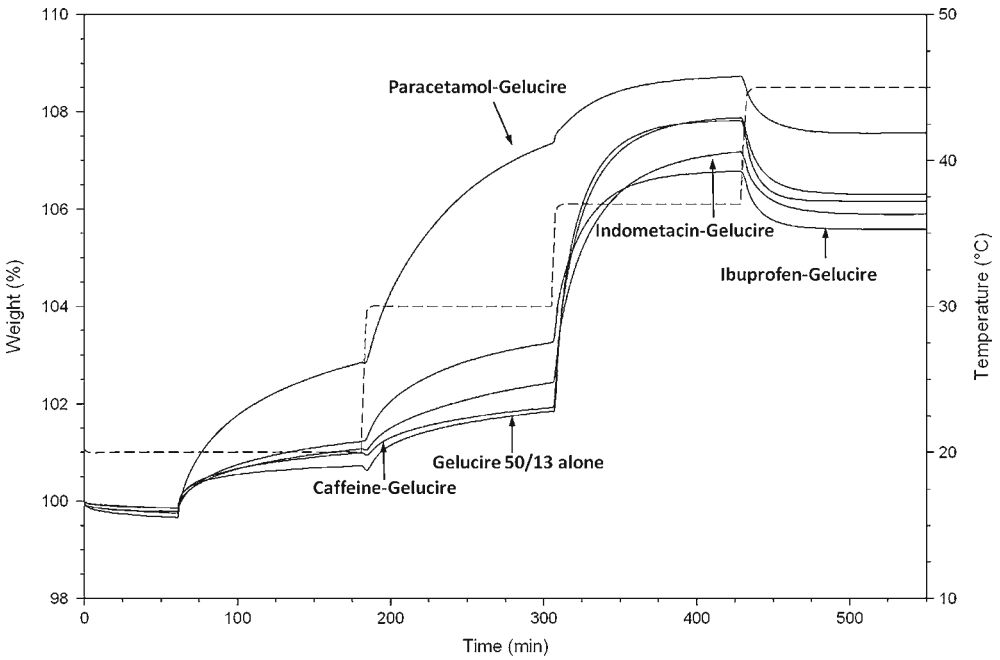

Fig. 6 Temperature ramp (20–45°C) isohumic (at 75%RH) profiles of Gelucire 50/13-drug solid dispersions.

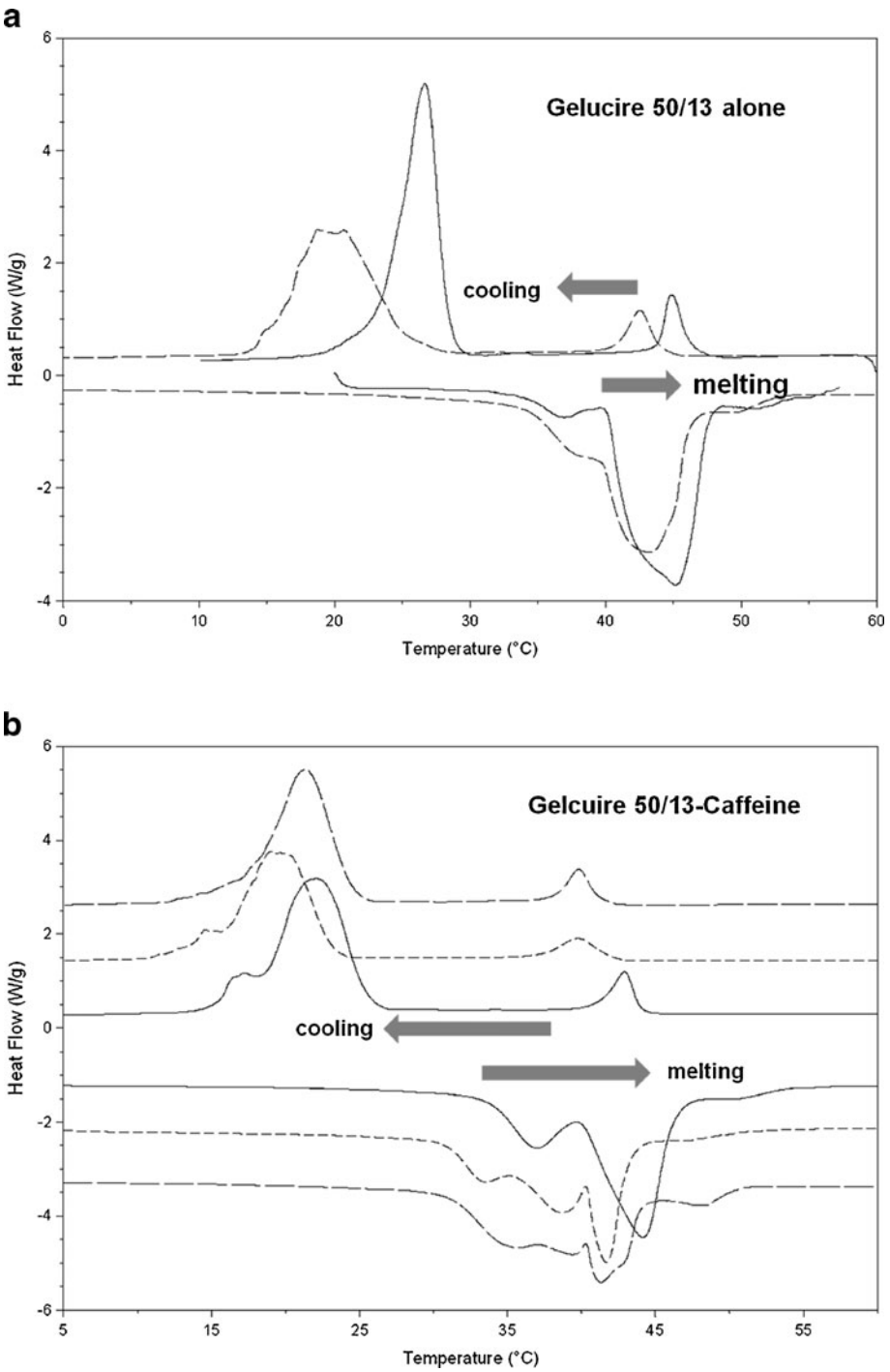

Fig. 7 DSC thermal graphs of Gelucire 50/13-drug dispersions before (*solid line*) and after aging under 40% (*short dash line*) and 75%RH (*long dash line*) for 1 month. (**a**) Gelucire 50/13 alone (in powder form); (**b**) Gelucire 50/13-Caffiene dispersions; (**c**) Gelucire 50/13-Indomethacine dispersions; (**d**) Gelucire 50/13-Paracetamol dispersions; (**e**) Gelucire 50/13-Ibuprofen dispersions.

DISCUSSION

This study investigated the moisture uptake behaviour of the amphiphilic material, Gelcuire 50/13 with the key motivation being to understand how Gelucire 50/13 response to environmental moisture and the likely significance of this on the processibility of the material. Gelucire 50/13 is a common material for forming solid dispersion formulations *via* fusion to enhance drug dissolution and absorption (4–9). Environmental moisture uptake by the material during the melt-cool process as well as over storage could have a significant impact on the

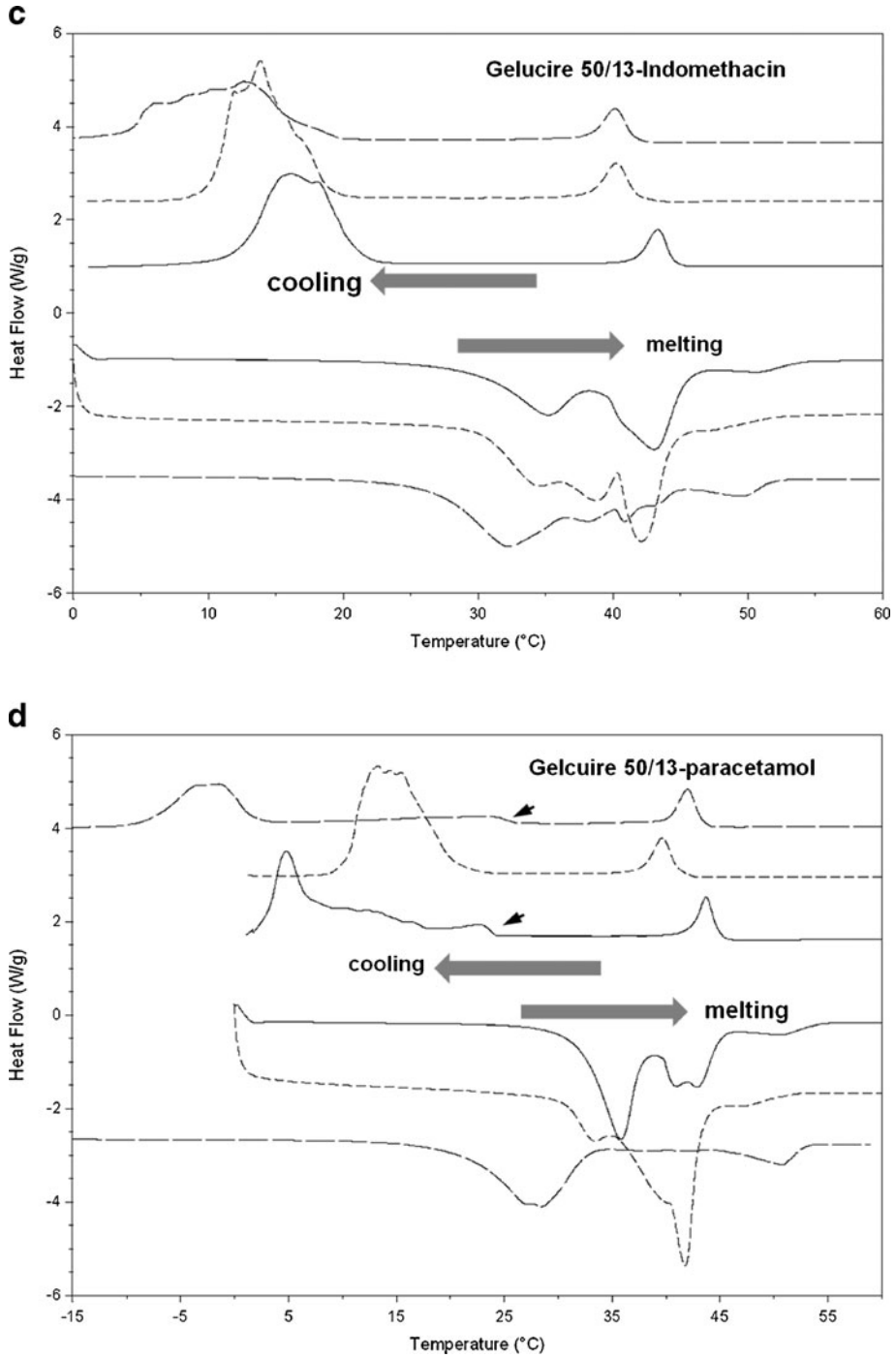

Fig. 7 (continued)

physical properties of the formulation. In this study, three key findings are reported. Firstly, the moisture uptake is significantly affected by the environmental humidity. At 25°C below 70% RH, the moisture uptake of Gelucire 50/13 is below 2% and follows a sorption dominated GAB model. A relative humidity of 70–75% is the critical point and above 75% RH the moisture sorption is dramatically increased. Secondly, environmental temperature can also have a significant impact on the moisture uptake of Gelucire 50/13. At temperatures above the onset of the melting of Gelcuire 50/13, the moisture uptake significantly increases and reaches a maximum of total moisture uptake at 37°C. Thirdly, the incorporation of a drug can also have profound impact on moisture uptake as well as the solidification behaviour of Gelucire 50/13.

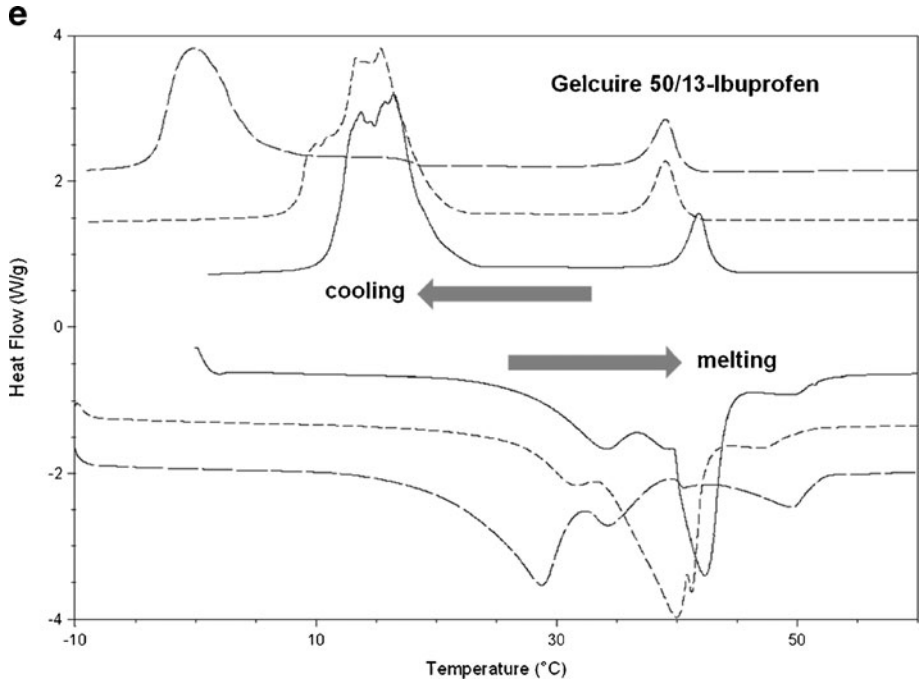

Fig. 7 (continued)

Factors Affect Moisture Uptake by Gelucire 50/13

A few recent studies have suggested that the environmental moisture uptake capacity of Gelucire 44/14 alters dramatically with relative humidity (15). This observed change in moisture uptake behaviour was mainly attributed to the swelling and dissolution of the hydrophilic components in Gelucire 44/14 (such as glycerol and PEG 33) under different humidity conditions (15). It is noted that at ambient temperature with relative humidity below 70%, the sorption isotherm of Gelucire 50/13 can be fitted well with the GAB model, which is typical for the moisture sorption of complex multi-component systems. At high environmental humidity (above 75%), Gelucire 50/13 can rapidly take up as much as 15–30% original weight of the material depending on the environmental temperature. Similar behaviour was observed in PEG 1500. The sorption isotherm of PEG 1500 showed sharp acceleration of moisture uptake above 70%RH. Although this is not classical deliquescence behaviour (31), it shares some similarities. Thus this may indicate that the critical RH (70%) is close to the vapour pressure of the saturated solution of PEG 1500. We speculate that this may also be the case for Gelcuire 50/13. At 37°C a proportion of PEG1500 may start to dissolve and form a solution in the absorbed moisture. The PEG 1500 solution may act as a solvent to dissolve other components in the material. According to a previous study of the bulk water uptake of Gelucire 50/13, this amount of moisture uptake can transfer the material into semi-solid liquid crystals and these micro-structural changes can impact on drug release from the solid dispersions (4).

As the uptake is highly relative humidity and temperature dependent, understanding the boundary conditions of the water uptake and the water sorption/desorption behaviour of Gelucire 50/13 can have significant practical implications for formulating and understanding the physical stability of formulations on storage containing this lipid excipient. For example, at room temperature it is safe to handle Gelucire 50/13 at ambient humidity. However if the ambient temperature is increased to above 35°C, Gelucire 50/13 should be handled under controlled humidity (below 60%RH) to avoid any excess amount of moisture uptake.

The incorporation of drugs into Gelucire 50/13 demonstrated significant impacts on the physical properties of the material. Although this has been reported before (8,11–13), this study has a particular focus with respect to the solidification of Gelucire 50/13 in the drug-loaded dispersions after aging under high relative humidity (above 75%RH). A series of drugs with different affinitities for dissolving into Gelucire 50/13 on melting were investigated. A low drug loading of 5% (*w*/*w*) was used in order to ensure the uniform distribution of the drug and minimise complications in data interpretation from over saturating Gelucire 50/13 with drug. Despite the similar melting properties of Gelucire loaded with paracetamol, indomethacin, and ibuprofen, the moisture uptake was increased at 30°C for the paracetamol loaded dispersion, and decreased at 37°C for the indomethacin and ibuprofen loaded dispersions compared to the Gelucire alone. This effect of paracetamol is likely to be mainly associated with the dissolution of molecularly dispersed paracetamol in dissolved PEG1500. After

exposure to moisture the drug loaded Gelucire solidification steps were shifted to lower temperatures with the paracetamol loaded dispersion having the most significant alteration in the solidification temperature. In all cases, the second exothermic peak showed more pronounced shifts. It was reported previously that the two exothermic transitions are associated with the crystallisation of lamellar phases in Gelcuire 50/13 with different spacings (14). Thus this indicates alteration of the micro-structure of Gelucire after exposure to moisture and formation of solid dispersions with drugs.

Practical Implications

There are two important practical aspects obtained from this study associated with the handling and storage of Gelucire 50/13 and Gelucire 50/13 based drug dispersion formulations. As the moisture uptake capacity of Gelcuire 50/13 changes with temperature in a different manner during melting and cooling, it is extremely important to control the environmental humidity being below 40% during sample preparation if melting and cooling of Gelucire 50/13 is involved. The material only starts to take up significant amounts of moisture at temperatures above 32°C even after exposure to 75%RH. The effect of relative humidity on the moisture uptake is limited unless the humidity reaches above 70–75% RH. Therefore, in terms of storage, temperature control below 35°C should be a priority.

CONCLUSION

This study investigated in detail the moisture uptake and storage behaviour of an amphiphilic formulation excipient, Gelucire 50/13 that is used commonly for forming solid dispersions. From the results, it is clear that environmental temperature and humidity are both critical factors for the equilibrium moisture uptake of the material. Under ambient conditions (25°C, 40–75% RH), little moisture sorption was observed in Gelucire 50/13. This can dramatically increase to nearly 30% *w/w* if the relative humidity is increased to 90% RH. This fast moisture sorption process at high RH is likely to be attributed to the dissolution of free PEG and glycerides and the swelling of PEG esters. On increasing the temperature, a significant increase in moisture uptake was observed at 37°C. Therefore, caution should be taken during processing of the material when formulating solid dispersions. Although model fitting is useful to parameterise the moisture sorption data, for complex materials, such as Gelucire 50/13, drawing conclusions on the actual physical process of the sorption based on model fitting should be done with caution. Finally, the effect of drugs on the moisture uptake and solidification process of the material is highly dependent on the interaction of the lipid with the drug. Exposure to high humidity (75% RH) can introduce significant changes in the molecular configuration of the Gelucire 50/13 such that they melt at lower temperatures and leads to an even lower complete solidification temperature.

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