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Research paper

Understanding the solid-state behaviour of triglyceride solid lipid extrudates and its influence on dissolution

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ABSTRACT

Three monoacid triglycerides differing in their fatty acid chain lengths were extruded below their melting temperatures. Physical characterization was conducted on the powders as well as the extrudates with a combination of DSC, XRPD and vibrational spectroscopy to get a deeper insight into the complex solid-state behaviour of lipids and solid lipid extrudates during processing and storage. The combination of extrusion temperature and friction was a key factor for the lipid polymorphic behaviour after extrusion. Polymorphic transitions had a strong influence on the dissolution behaviour due to crystallization of the stable β-form from the unstable α-form on the surface of the extrudate. These correlations help to understand the solid-state behaviour of lipids and to avoid process conditions which lead to unstable dosage forms. Tailor-made dissolution profiles for a model drug could be achieved using triglycerides of different fatty acid chain lengths as the dissolution rate is chain-length dependent. The solid-state form of the drug was unchanged after storage in accelerated conditions over 10 months. These studies demonstrate that although triglycerides are a promising basis for oral dosage forms, a good understanding and monitoring of the solid-state behaviour is mandatory to obtain reliable and reproducible dosage forms.

1. Introduction

Lipids are a group of excipients that have recently generated substantial interest for the production of oral dosage forms. They show a high variability in their physico-chemical properties which offer various possibilities for different types of pharmaceutical formulations. In particular, they have shown a high potential for the development of controlled release systems. On the one hand, lipids can be used for prolonged release [1]. In addition, they are able to enhance the solubility and permeability of drugs with poor oral bioavailability [2], a fact that is increasingly important since a large proportion of the newly developed APIs have low solubility and permeability (Bioclassification System Class 4). Furthermore, taste masking is also feasible with the help of lipids [3]. In addition, a specific advantage of lipids is that they are biodegradable and physiologically nontoxic.

Various preparation techniques have been used to produce lipid-based oral dosage forms. The most common approach involves melting the lipid and then resolidification with the solid API to form a matrix [4–7]. One relatively new technique is solid lipid extrusion [8,9]. Using this technique, glycerides which are available as pharmaceutical excipients in powdered form such as Dynasan® for instance are blended with a specific amount of an API and extruded through an extruder below their melting temperatures avoiding melting of the whole lipid mass. The resulting extrudates are spheronized to pellets or cut into cylinders of suitable size, depending on the applicable dosage form. Although the lipid pellet or extrudate provides a lot of advantages, the formulation is quite difficult.

Due to their chemical and physical structures, lipids exhibit complex solid-state behaviour including melting, crystallization and physical modifications during processing and even storage [10]. They usually exhibit three different polymorphic forms (α, β′ and β). The relationship is monotropic in most cases: the α-form is the least thermodynamically stable form, β′ is metastable and β is stable, exhibiting the densest packing mode for a lipid [11,12]. Since the polymorphic behaviour is typically monotropic, each polymorph has its unique melting point. The lipid polymorphic behaviour is quite difficult to predict. Thus, for example, a dosage form produced with a metastable lipid modification and the desired properties may subsequently transform to a more stable one [13,14]. The result is usually a deterioration of the product's quality and its desired properties including drug release profiles. Moreover, the physical "ageing" effects during storage must be well understood to avoid any further drug release alteration during storage [15].

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At present, there is a lack of understanding of the physico-chemical behaviour at the core and on the surface of solid lipid extrudates during processing and storage. The aim of this study was to better understand the solid-state behaviour of triglycerides during solid lipid extrusion and relate this to the drug-dissolution behaviour from the extrudates. This should allow the production of stable dosage forms with reproducible and advantageous performance characteristics (e.g. dissolution). Three pure monoacid triglycerides differing only in their fatty acid chain lengths were extruded below their melting temperature. Physical characterization was conducted on the powders as well as on the extrudates with a combination of DSC, XRPD and vibrational spectroscopy [16]. Dissolution tests and storage experiments were also performed and the results interpreted in light of the physical characterization results.

2. Materials and methods

2.1. Materials

The pure powdered monoacid triglycerides trilaurin (Dynasan 112®), tripalmitin (Dynasan 116®) and tristearin (Dynasan 118®) provided by Sasol (Witten, Germany) were used as received. The model drug theophylline anhydrate (BASF, Ludwigshafen, Germany) was used in powdered form as supplied. Theophylline monohydrate was prepared by recrystallization of theophylline anhydrate from purified water. All crystal forms were verified by X-ray powder diffraction and compared to the theoretical patterns available from the Cambridge Structural Database (Cambridge Crystallographic Data Centre (CCDC), Cambridge, United Kingdom), using the associated Mercury software (v. 1.5). The reference codes for the crystal structures used were: BAPLOT01 (theophylline anhydrate), THEOPH01 (theophylline monohydrate), BTRILA05 (trilaurin β-form), SUWMAY (tripalmitin β-form), and QOYKIY (tristearin β-form). Resolidified melts for variable X-ray powder diffraction measurements were produced by heating the powdered lipids up above their individual melting temperature and holding the melt for at least 3 min to erase structural memory. The melts were poured into the X-ray diffraction sample holders, resolidified rapidly on ice and measured directly afterwards.

2.2. Methods

2.2.1. Extrusion

The powdered glycerides were used in pure form or were weighed in a 1:1 ratio with theophylline anhydrate and then blended in a laboratory mixer (LM20 Bohle, Ennigerloh, Germany) for 15 min at 25 rpm. The powders were fed from a gravimetric dosing device (KT20K-Tron Soder, Lenzhard, Switzerland) into the barrel of a co-rotating twin-screw extruder (Mikro 27GL-28D, Leistritz, Nürnberg, Germany) and extruded with a constant screw speed of 30 rpm and a feeding rate of 40 g min^{-1}. The processing temperature was individually chosen depending on the melting temperature of the lipid. The extruder die plate contained 23 holes of 1 mm diameter and 2.5 mm length.

2.2.2. Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed using a DSC 821e calorimeter (Mettler-Toledo, Gießen, Germany). The samples were heated from 20 to 300 °C with a heating rate of 10 °C min^{-1}. All experiments were conducted twice using hermetically sealed aluminium pans (40 μl) containing approximately 5 mg of sample.

2.2.3. X-ray powder diffraction (XRPD)

The samples were measured using a theta–theta X-ray powder diffractometer (D8 Advance, Bruker AXS GmbH, Karlsruhe, Germany). Measurements were done in symmetrical reflection mode with CuKα radiation (λ = 1.54 Å) using Göbel mirror bent multilayer optics. The angular range measured was 5–40° (2θ), with a step size of 0.05° (2θ). The measuring time was 1 s per step. The samples were put in the sample holder and gently compressed to smooth the surface. All experiments were conducted in triplicate. Variable temperature measurements were also done with the same diffractometer with resolidified melts of the lipids (see above) in the temperature range of 25 °C up to the individual melting temperatures of the lipids.

2.2.4. Attenuated total reflectance infrared (ATR-IR) spectroscopy

Samples were measured using an FTIR spectrometer (Bruker FTIR Vertex 70, Bruker, Ettlingen, Germany) with an ATR accessory fitted with a single reflection diamond/ZnSe crystal plate (MIRacle ATR, PIKE Technologies, Madison, WI, USA). The samples were placed in the ATR device without any preparation and measured using 64 scans for each spectrum. Spectra were collected between 4000 and 650 cm^{-1}. All experiments were conducted in triplicate.

2.2.5. Near infrared (NIR) spectroscopy

For NIR measurements, a NIR spectrometer (NIR-256L-2.2T2, Control Development Inc., South Bend, IN, USA) with a thermoelectrically cooled 256 element InGaAs array detector, tungsten light source and a fiber optic reflectance probe (six illuminating optical fibers around one signal collecting fiber) was used. A reference spectrum was recorded with a Teflon background. The spectra were collected from 1100 to 2200 nm with 30 ms integration time and 500 scans per spectrum. All experiments were conducted in triplicate.

2.2.6. Dissolution

Dissolution studies were performed according to the USP29 Method 2 with a paddle apparatus (Sotax AT7 smart, Sotax, Lörrach, Germany). Extrudates were cut to lengths of approximately 1 cm, and a sample size of 140 mg was used in each vessel. Experiments were conducted in purified water containing 0.001% polysorbate 20 at 37 ± 0.5 °C with a stirring speed of 50 rpm. The absorption of the medium was measured at 5 min intervals using a UV–vis spectrometer with an absorption wavelength of 242 nm (Lambda 40, Perkin-Elmer, Rodgau-Juegesheim, Germany) in a continuous flow-through cuvette. The experiments were conducted in triplicate taking the mean for the dissolution curve. The standard deviation was below 3% in all cases.

2.2.7. Storage

Samples were stored for 10 months in a climate chamber (KBF 240, Binder, Tuttlingen, Germany). The extrudates were placed in open Petri dishes and exposed to accelerated and constant climatic conditions (40 °C/75% RH).

2.2.8. Scanning electron microscopy (SEM)

SEM micrographs were recorded on samples mounted on aluminium stubs using double-sided carbon tape and sputter coated with platinum for 20 s. They were viewed using a DSM 962 scanning electron microscope (Carl Zeiss, Oberkochen, Germany).

3. Results and discussion

3.1. Obtaining extrudates with acceptable external appearance

During extrusion the equipment variables as well as the process variables can be modified. In these experiments all equipment variables, e.g. the screw configuration and the design of the die plate, were kept constant so that different runs were comparable.

Among the process variables one can distinguish between screw speed, feed rate and temperature. The screw speed and the feed rate were adjusted to obtain a continuous product flow and then retained unchanged for all the experiments. The only parameter which was chosen individually for each powder mixture was the barrel temperature.

The lipids used differ in their melting temperature depending on the chain length of the fatty acids esterified with the glycerol molecule. The aim of the extrusion experiments was to obtain reproducible cylindrical extrudates with a smooth surface and a high mechanical stability. Experiments were performed at different temperatures that were below the melting point of each lipid but sufficiently high to form intact extrudates. The best results were achieved at extrusion temperatures just a few degrees below the melting temperature of the individual lipid. In trilaurin, the glycerol molecule is esterified with three relatively short fatty acids (12 C atoms). The melting point in the literature is 46 °C [17]. The most suitable extrudates for formulation were obtained with a processing temperature of 40 °C. Elongating the fatty acid chain lengths with four C atoms each (compared to trilaurin) to form tripalmitin leads to a higher melting point of 66 °C [17]. It was possible to produce good extrudates at 55 °C and at 60 °C. The smoothest extrudates were obtained with a processing temperature of 60 °C. In the tristearin molecule, glycerol is esterified with three stearic acids (18 C atoms). The melting point is 73 °C [17]. Suitable extrudates could be obtained with processing temperatures of 55 and 65 °C.

The external appearance of all triglyceride extrudates was similar for the best processing temperatures for each individual lipid mentioned above. Fig. 1 shows two SEM images of two representative extrudate surfaces: pure tripalmitin (Fig. 1a) and a combination of tripalmitin and theophylline (50% w/w lipid/drug) (Fig. 1b). Both extrudates show a continuous and rather smooth surface. The mixture of lipid and drug results in a rougher surface than the pure lipid due to the fact that the lipid partly melts on the surface during processing, whereas the drug remains completely solid.

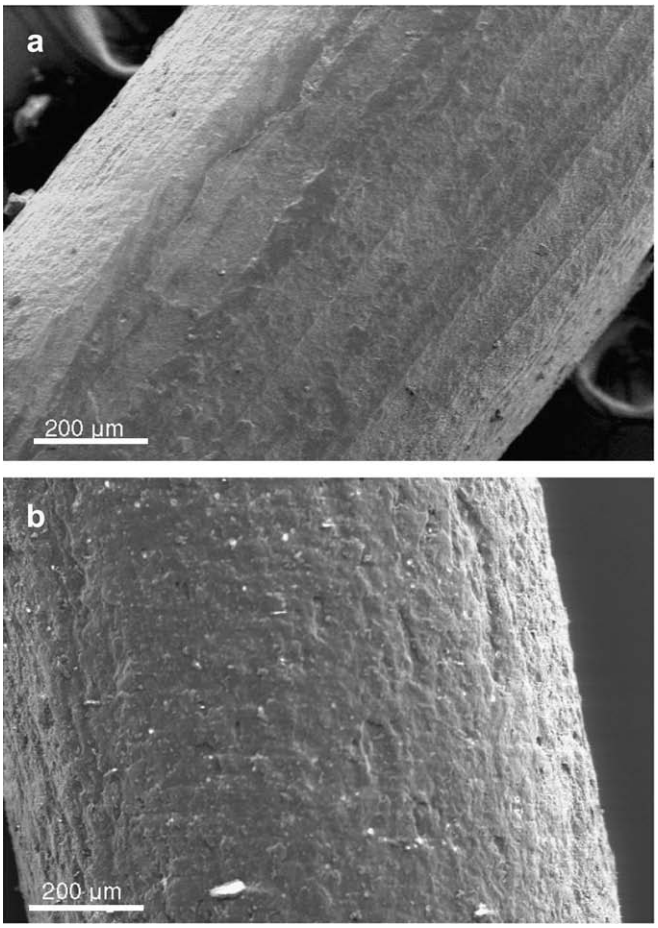

Fig. 1. SEM images of extrudate surfaces (a) 100% tripalmitin and (b) 50% tripalmitin/50% theophylline (w/w).

3.2. Solid-state structure analysis of extrudates

As previously stated, lipids can exhibit quite complex polymorphic behaviour during processing and storage. Monitoring the pure triglycerides individually should show the influence of the lipid structure in combination with temperature on the solid-state behaviour of the extrudates. Using DSC, XRPD and ATR-IR spectroscopy as complementary methods the powders of the different substances, the pure lipid extrudates and the mixed extrudates of 50% lipid/drug (w/w) were examined.

3.2.1. Trilaurin

The results of the physical characterization of this triglyceride with the shortest fatty acid chains (12 C atoms) of the processed lipids are shown in Fig. 2. The DSC thermograms of powder, extrudate (100% lipid) and extrudate with drug (50% w/w lipid/drug) (Fig. 2a) do not show significant changes in the onset of the lipid melting peaks. The stable β-form can be identified in each thermogram by its melting peak with an onset at 45 °C [17]. There is no evidence of an interaction between lipid and drug, since theophylline shows a sharp melting peak onset at 270.8 °C (the melting temperature of the stable anhydrate form of theophylline in the literature is 275.8 °C [18]) and there are no other thermal events. In addition, in the XRPD patterns (Fig. 2b) the trilaurin β-form is indicated by three strong reflections at 19.4° (2θ), 23.1° (2θ) and 24.05° (2θ) [19] in the lipid powder and extrudate. The peak positions of the drug, for example, at 7.1° (2θ) and 12.6° (2θ), are the same as those for the powder indicating that no polymorphic change has occurred in the drug. In addition, no solid-state changes or interactions were observed using ATR-IR spectra, with the peak positions and relative intensities of trilaurin and theophylline unchanged (Fig. 2c). For trilaurin the following peaks can be identified: CH_2 scissoring (1473 cm^{-1}), C=O stretch (1735 cm^{-1}), CH_2 symmetric stretch (2851 cm^{-1}) and CH_2 antisymmetric stretch (2919 cm^{-1}) [20,21]. Theophylline anhydrate shows specific peaks like C=O stretches (1665 and 1713 cm^{-1}) and the CH stretch (3122 cm^{-1}) [22]. In summary, none of the analytical methods used in this context was able to detect any solid-state changes of the glyceride or interactions with the drug before and after processing. Trilaurin remained in its stable β-form, and the crystal structure of theophylline anhydrate was unchanged.

3.2.2. Tripalmitin

Tripalmitin contains the intermediate fatty acid chains length in these studies (16 C atoms). Extrudates produced at 55 °C and at 60 °C did not exhibit differences according to the solid-state analysis, so only the 60 °C results are shown. Analysis using DSC, XRPD and ATR-IR spectroscopy revealed the lipid remained crystalline in the most stable β-form after processing (Fig. 3). No interactions between drug and lipid could be observed. The DSC thermograms (Fig. 3a) depict clearly separated melting peaks of lipid (onset 63.6 °C) and drug (onset 270.7 °C) [17,18], and the peak positions in the XRPD patterns (Fig. 3b) [19,23] and ATR-IR (Fig. 3c) spectra remain unchanged after extrusion [20,21].

3.2.3. Tristearin

Tristearin is the triglyceride with the longest fatty acids used in these studies (18 C atoms). Extrudates were produced at 55 °C and at 65 °C, and in this case obvious differences can be observed be-

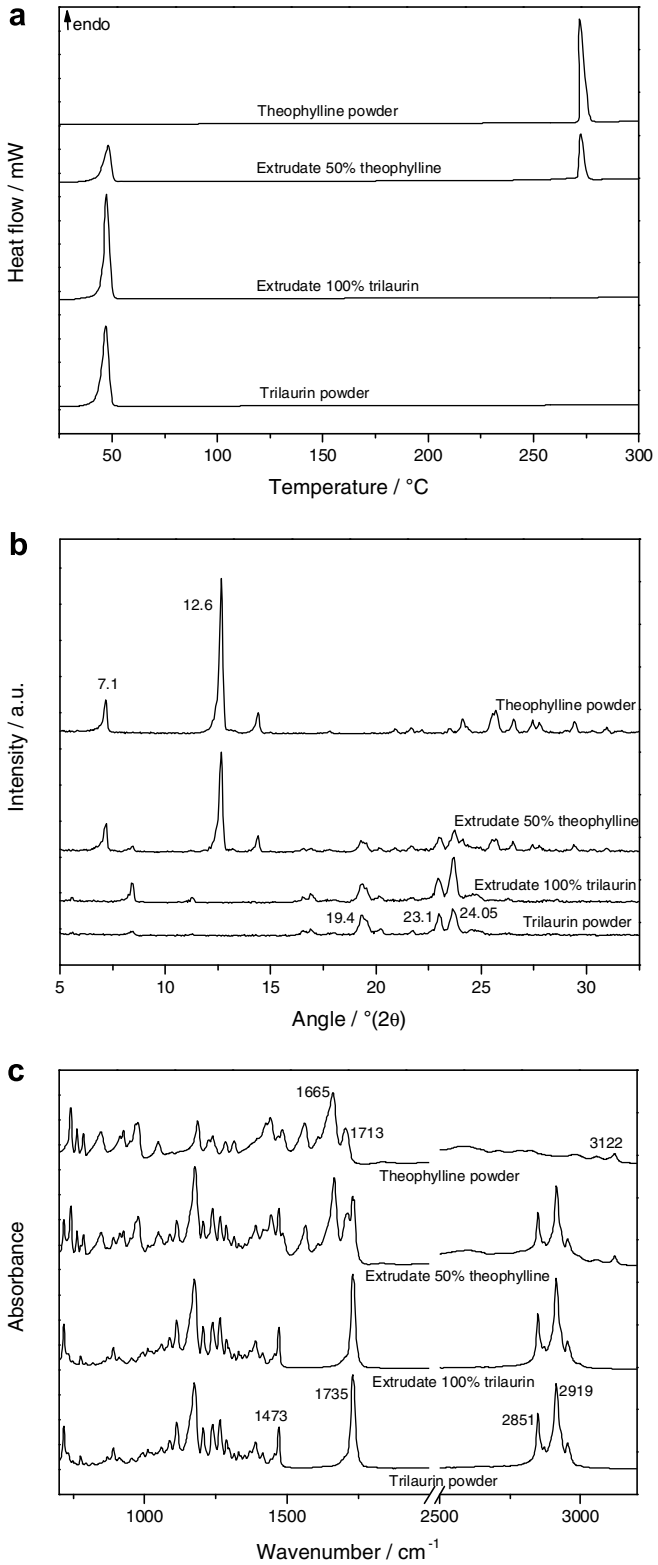

Fig. 2. Physical characterization of trilaurin and theophylline powders and extrudates (a) DSC thermograms, (b) XRPD patterns and (c) ATR-IR spectra.

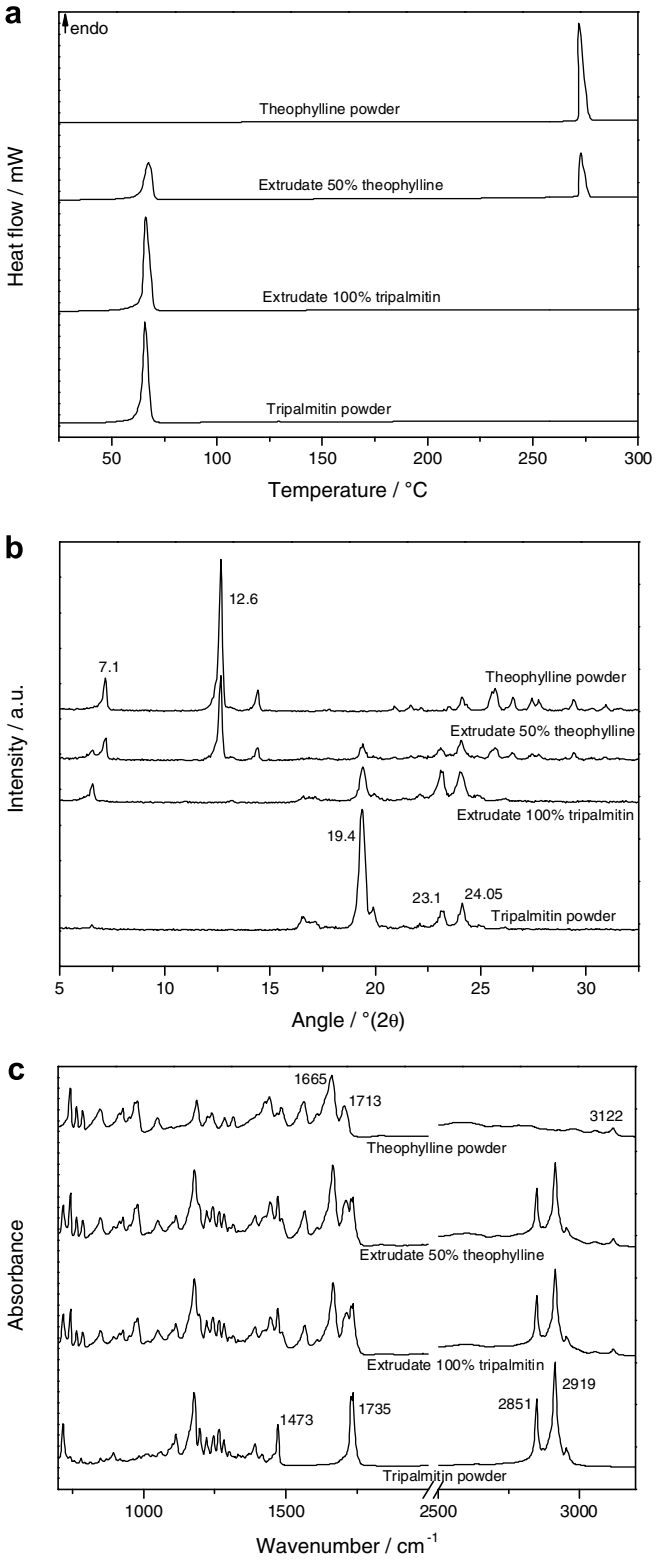

Fig. 3. Physical characterization of tripalmitin and theophylline powders and extrudates (a) DSC thermograms, (b) XRPD patterns and (c) ATR-IR spectra.

tween extrudates produced at the two temperatures. The thermograms collected from these samples give an interesting insight into the solid-state behaviour of tristearin. For the DSC measurements, pure tristearin powder shows a clear melting endotherm of the lipid β-form with an onset temperature of 70.7 °C (Fig. 4a). The extrudate (100% lipid) produced at 55 °C showed a small amount of α-form (small endotherm with an onset of 50.2 °C), whereas the extrudate (100% lipid) produced at 65 °C results in a thermogram representing, like the powder, only the β-form [17,24]. Therefore, the extrusion temperature has a distinct influence on the solid-state structure of the lipid in the extrudate. With regard to the extrudates containing the model drug theophylline anhydrate,

Fig. 4a reveals the same behaviour as that seen for the 100% lipid extrudates. The extrudate produced at 55 °C shows the presence of a small amount of the α-form, while the extrudate produced at 65 °C shows the same thermal events as the pure lipid powder with the additional drug-melting peak (onset 271.1 °C).

ATR-IR spectra of the lipid powder (pure β-form) and the pure lipid extrudates produced at different temperatures corroborate these observations (Fig. 4b). In the region around 1300–1400 cm^{-1} (highlighted), the differences in the peak shape between the 100% tristearin extrudate produced at 55 °C and the powder and the extrudate produced at 65 °C (pure β-form) can be observed [20,21]. Diffractograms were taken of powders, extrudate (100% lipid) and extrudate with drug (50% w/w lipid/drug). The temperature dependant behaviour revealed with DSC measurements (see above) can also be monitored with XRPD (Fig. 5). The pure lipid extrudates produced at different temperatures were compared to the pure powders in the different polymorphic forms (Fig. 5a). In the region around 20.0–23.0° (2θ) (highlighted), the extrudate produced at 55 °C shows some α-form with the characteristic peak at 21.4° (2θ), whereas extrudates produced at 65 °C only show β-form indicated by the peaks at 19.4° (2θ), 23.1° (2θ) and 24.05° (2θ) as the powder [19,24]. Addition of the model drug does not change the solid-state behaviour of the lipid (Fig. 5b). Extrudates produced at 55 °C contain the α-form (21.4° (2θ)), while extrudates produced at 65 °C do not.

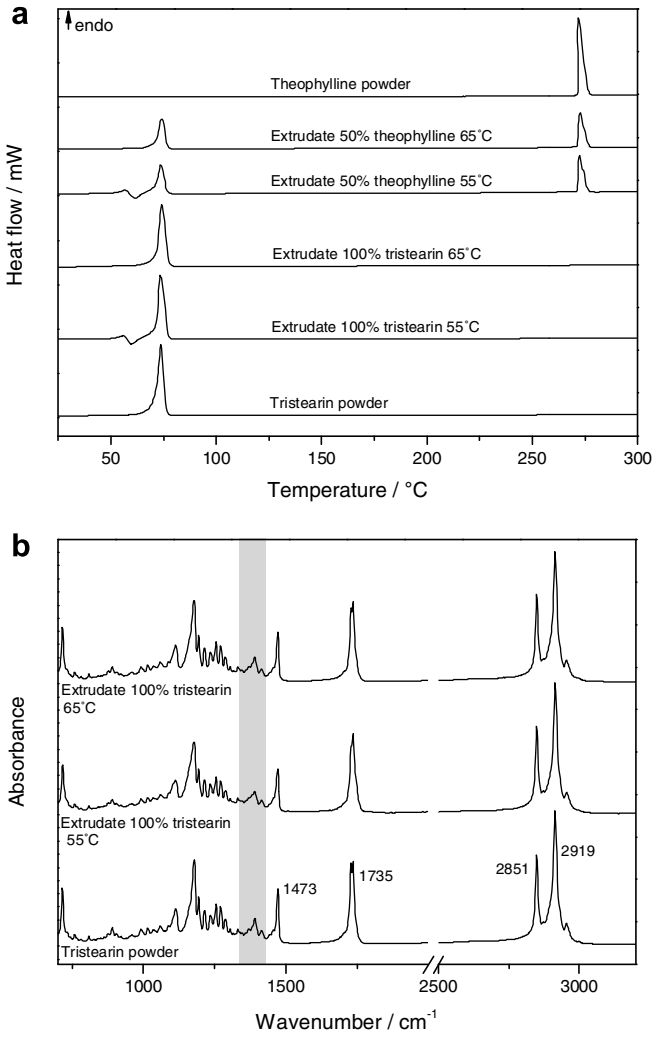

Fig. 4. Physical characterization of tristearin (a) DSC thermograms and (b) ATR-IR spectra.

3.3. Interpreting the solid-state behaviour of the triglycerides during extrusion

To further understand the solid-state behaviour of tristearin, diffractograms of the powder were also taken while heating the

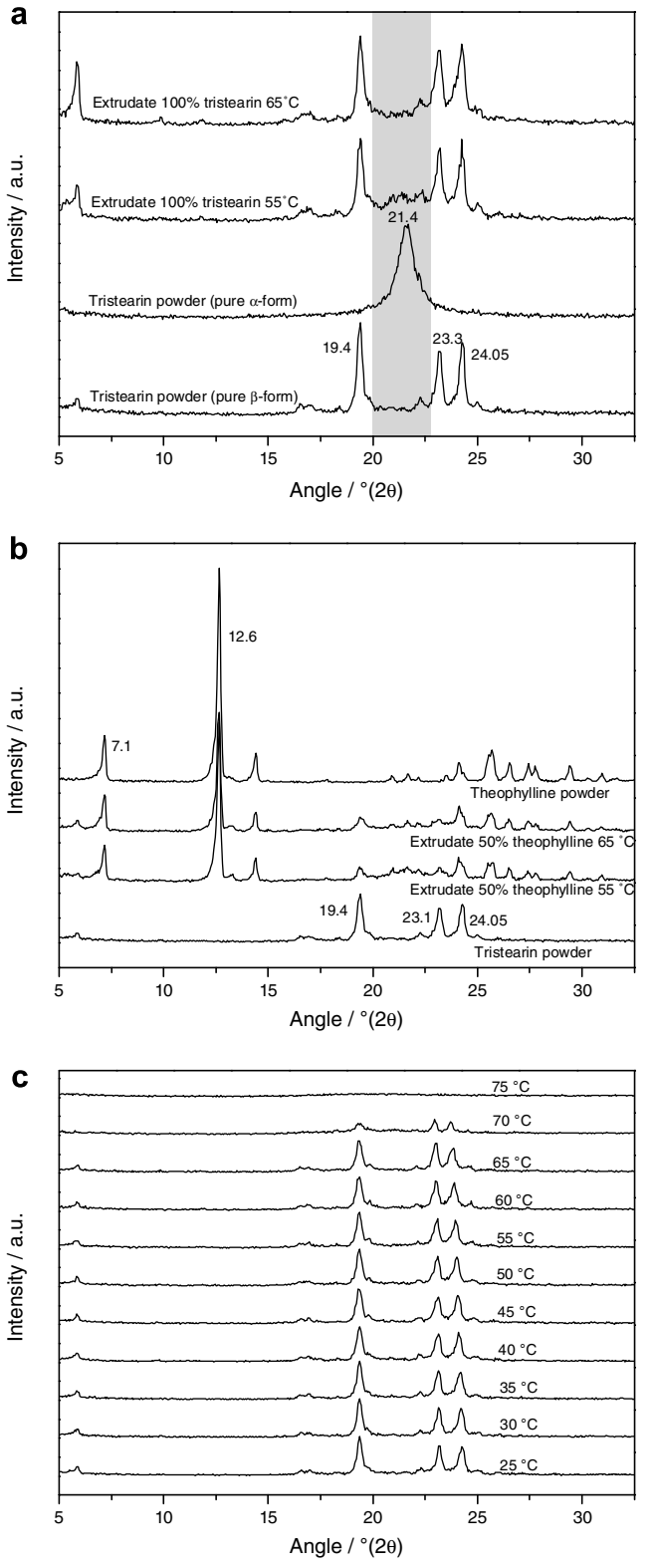

Fig. 5. XRPD patterns of (a) tristearin powder and extrudates, (b) tristearin and theophylline powders and extrudates and (c) variable temperature XRPD patterns of tristearin powder.

sample from 25 to 75 °C in 5 °C steps (Fig. 5c). Interestingly, there was no incidence of any structural changes until melting. This is in agreement with the monotropic relationship between the three polymorphs of the triglycerides, and thus the observed α-form must be created via the melt [11,12]. Therefore, the α-form monitored in the extrudates produced at 55 °C cannot exclusively be attributed to the influence of the processing temperature.

The phase behaviour of monoacid triglycerides at different pressures has been studied [25]. The pressure was found to have an influence on the lipid polymorphic transition behaviour depending on the pressure range which is applied to the lipids. During extrusion, the pressure was monitored simultaneously never exceeding 0.7 MPa. According to the study, this pressure is below that required to have an influence on the lipid transition behaviour.

A combination of temperature and friction during extrusion seems to be the factor influencing the solid-state structure of tristearin during extrusion. Friction causes the temperature to rise and some melting at the edges of the lipid mass is induced inside the extruder barrel. This happens at both extrusion temperatures. The difference in the polymorphic form which can be found in the extrudate after processing is due to the temperature at which the extrudate mass leaves the extruder. After leaving the die plate hole, the molten portion of the lipid at the surface directly solidifies. The α-form is supposed to crystallize after melting up to the temperature of 54.5 °C, according to a study by MacNaughtan et al. [26] using DSC. Hence, at an extrusion temperature of 55 °C the molten part of the extrudate mass appears to partly crystallize in α-form.

The temperature at which the extrudate leaves the die plate seems to be a key factor determining the crystallization behaviour from the molten component of the extruded lipid. To prove this hypothesis variable temperature XRPD measurements were done with the lipid powders. They were completely melted and resolidified again. Tripalmitin and tristearin resolidified in the α-form, while trilaurin only crystallized into the β-form as the α-form is unstable at room temperature due to its low melting point of 14 °C [17]. The resolidified samples were heated up in the X-ray diffractometer to monitor the physical structure at each temperature step. The results of these measurements were in agreement with the extrusion results (Fig. 6). Trilaurin (Fig. 6a) forms the stable β-form before melting at 45 °C [17]. Tripalmitin (Fig. 6b) exhibits pure α-form in the lower temperature region (up to 40 °C). Around the melting point of the α-form (46 °C) [17] and above the transformation the more stable β-form can be observed. At the extrusion temperatures of these experiments (55 and 60 °C), only β-form can be observed. Tristearin (Fig. 6c) shows in general the same solid-state behaviour, but at slightly different temperatures. Up to 55 °C, pure α-form can be monitored exclusively as the melting point of the α-form for tristearin is 55 °C [17], and above this temperature the β-form crystallizes. So as seen in the extrusion experiments, partial α-form is obtained at 55 °C while at 65 °C only the β-form appears.

3.4. Storage stability

All extrudates in stable β-form were stored for 10 months in accelerated conditions (40 °C/75% RH). Physical characterization was performed using XRPD and NIR spectroscopy to detect water absorption. There was no evidence of any solid-state changes in the lipid or the drug (tripalmitin extrudates are shown in Fig. 7 as an example). For all triglycerides, the β-form is thermodynamically stable at 40 °C as evidenced by the XRPD patterns in Fig. 7a, and increased water activity is likely to have a minimal effect on the thermodynamically stable form since the lipids are hydrophobic. Despite there being some evidence that theophylline monohydrate is the thermodynamically stable form in these conditions

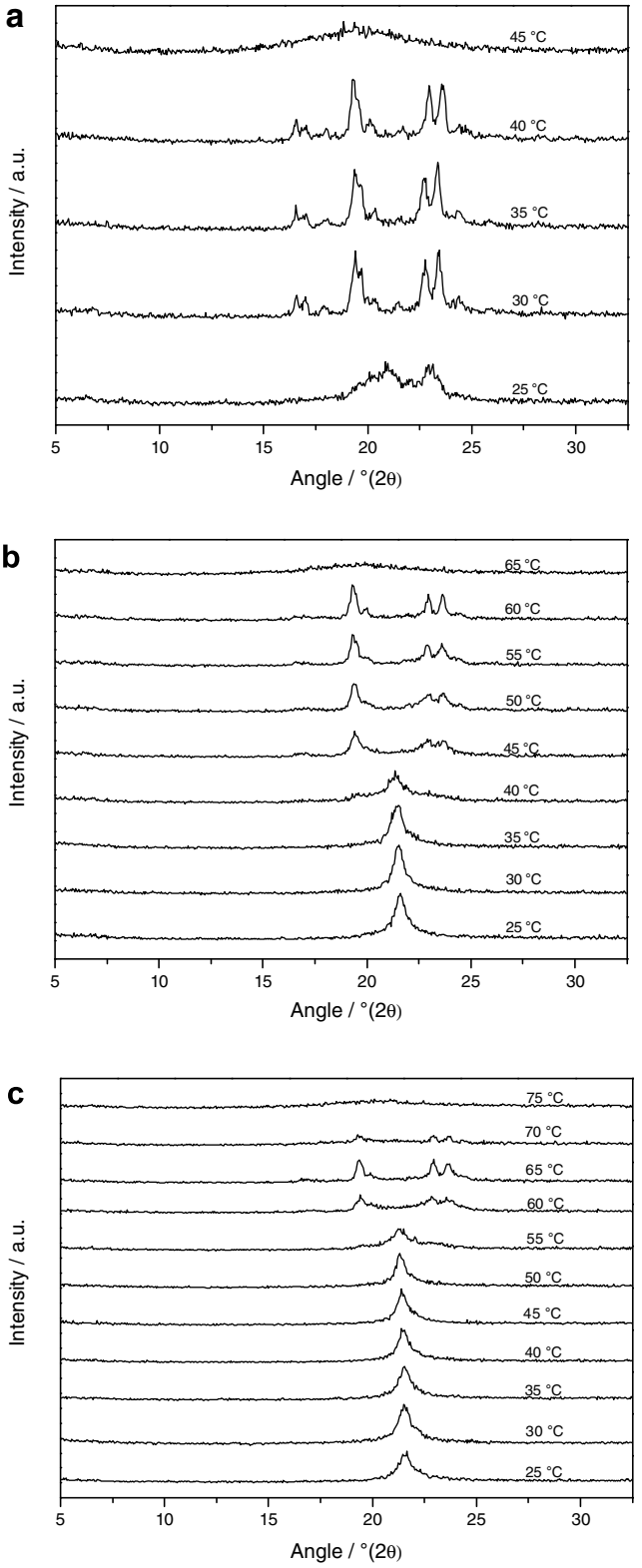

Fig. 6. Variable temperature XRPD patterns of resolidified melts of (a) trilaurin, (b) tripalmitin and (c) tristearin.

[27], the drug remained in the anhydrate form as the XRPD patterns depict. NIR spectra in Fig. 7b support these results as the main peaks for the monohydrate form, specifically the OH overtone (1490 cm^{-1}) and the OH combination (1970 cm^{-1}) bands associated with water, are not observed for the extrudates. The lack of

transformation of theophylline anhydrate to the monohydrate is likely to be due to two factors: an intrinsically slow transformation rate and the hydrophobic barrier provided by the lipid matrix.

3.5. Dissolution from triglyceride matrices

Dissolution from triglyceride matrices is completely diffusion controlled since the matrix stays intact after the release of the drug. Comparison of the three triglycerides revealed a chain-length dependent dissolution behaviour: the longer the fatty acid chains the slower the dissolution of the drug (Fig. 8a).

Fig. 8b depicts how polymorphism of a lipid during processing can influence the dissolution rate of the dosage form after storage. Tristearin extrudates produced at 55 °C exhibited a slower release of the drug than tristearin extrudates produced at 65 °C. This observation is unintuitive at first glance because the dissolution is purely diffusion controlled. A less dense packing mode of the matrix due to formation of the less ordered α-form in case of the extrudate produced at 55 °C as stated before should lead to an equal or higher dissolution rate. The explanation for this apparent anomaly can be found with a closer look at the surface of the extrudates. The surface of a tristearin extrudate produced at 65 °C consists of a rather smooth structure (Fig. 9a), while the surface of an extrudate produced at 55 °C is covered by sharp fractal structures (Fig. 9b). The presence of these sharp fractal structures has been described in the literature and is known as the "blooming effect" [28]. When the extrudate leaves the extruder die plate and the molten parts of the lipid recrystallize as the unstable α-form, a transformation to the stable β-form results. The formation of β-form results in the flowery fractal structures on the surface of the extrudate. The fractal structures increase the contact angle to water [29], which would be expected to decrease wetting, and hence the dissolution rate of the drug in the dissolution medium.

4. Conclusions

The solid-state behaviour of triglyceride solid lipid extrudates is influenced by different factors during processing and has to be well understood and monitored to obtain reproducible dosage forms of high quality. The combination of temperature and friction was found to be a key point for the lipid polymorphic composition after extrusion. As some lipid melting always occurs while extruding triglycerides, the temperature of the extruder die plate should always be above the melting point of the unstable α-form of the extruded triglyceride to avoid subsequent alteration of the product which could be shown to strongly affect the dissolution rate. Tailor-made dissolution profiles can be achieved using triglycerides of different fatty acid chain lengths as the dissolution rate is chain-length

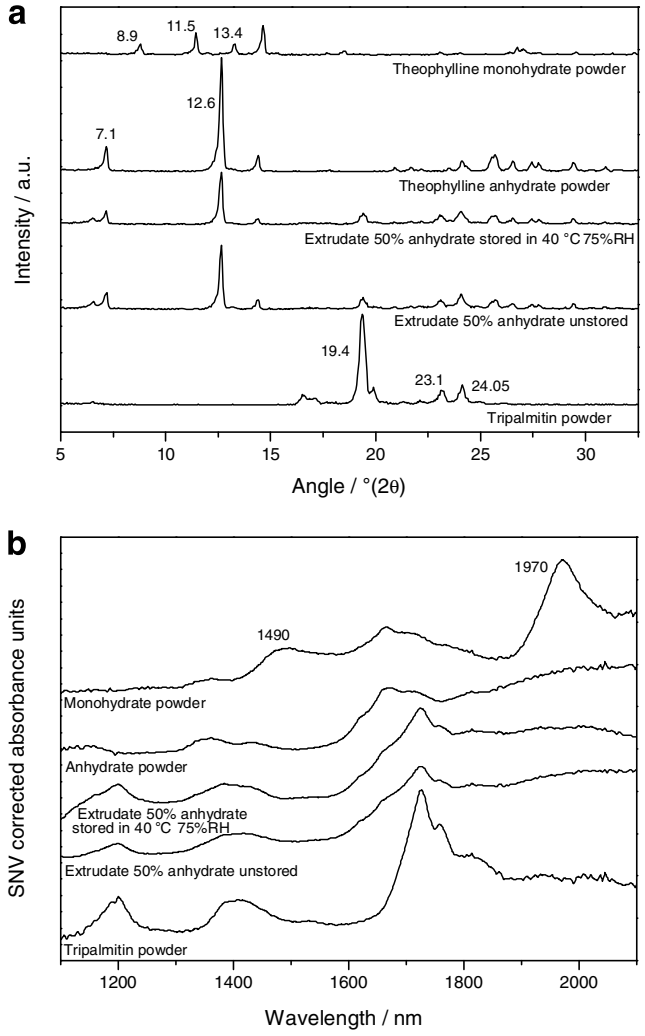

Fig. 7. Storage of tripalmitin extrudates for 10 months (a) XRPD patterns and (b) NIR spectra.

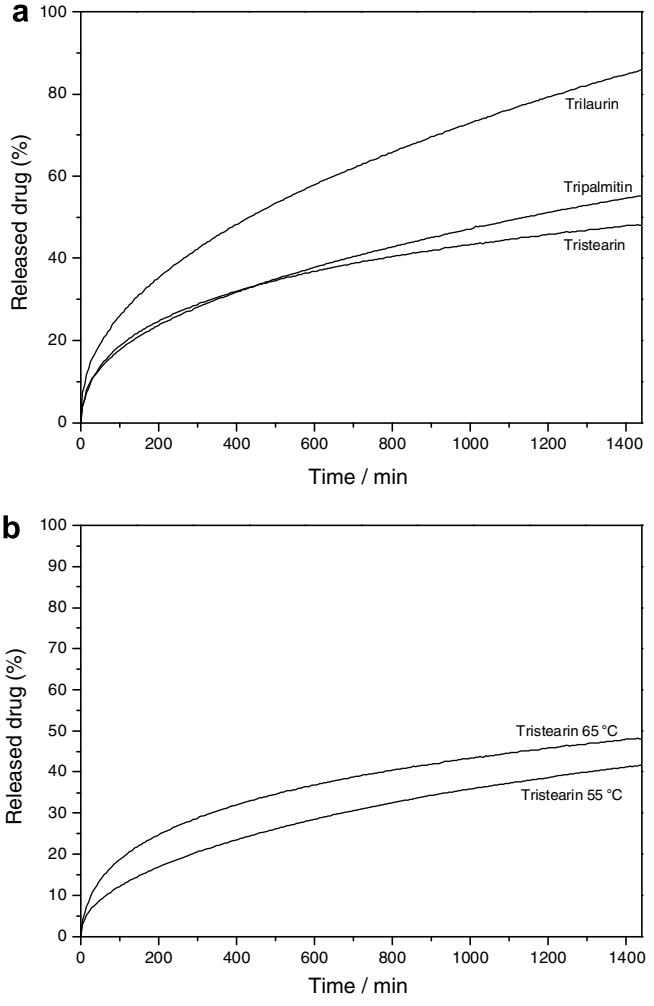

Fig. 8. Dissolution curves of triglyceride extrudates (a) comparison of different triglycerides and (b) comparison of tristearin extrudates produced at different temperatures ($n = 3$, mean, cv < 3% not shown).

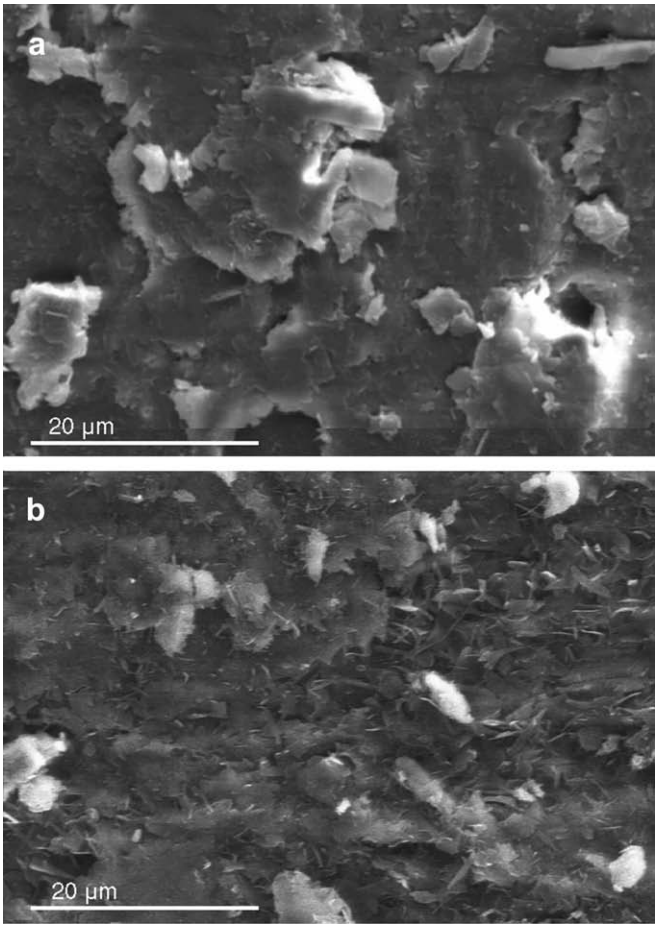

Fig. 9. SEM images of the surface of tristearin extrudates produced at (a) 65 °C and (b) 55 °C.

dependent. Storage experiments in accelerated conditions also suggested that the anhydrate form of the drug was stable over 10 months with the hydrophobic barrier of the lipid helping to protect the drug against any hydrate formation. The understanding of polymorphic behaviour of triglyceride solid lipid extrudates and its effect on dissolution will help in the development of solid lipid extrudates with desired and predictable dissolution behaviour.

Acknowledgements

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