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Research Article

Investigating the Principles of Recrystallization from Glyceride Melts

Maike Windbergs,[1,2,3] Clare J. Strachan,[2,4] and Peter Kleinebudde[1,5]

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Abstract. Different lipids were melted and resolidified as model systems to gain deeper insight into the principles of recrystallization processes in lipid-based dosage forms. Solid-state characterization was performed on the samples with differential scanning calorimetry and X-ray powder diffraction. Several recrystallization processes could be identified during storage of the lipid layers. Pure triglycerides that generally crystallize to the metastable α-form from the melt followed by a recrystallization process to the stable β-form with time showed a chain-length-dependent behavior during storage. With increasing chain length, the recrystallization to the stable β-form was decelerated. Partial glycerides exhibited a more complex recrystallization behavior due to the fact that these substances are less homogenous. Mixtures of a long-chain triglyceride and a partial glyceride showed evidence of some interaction between the two components as the partial glyceride hindered the recrystallization of the triglyceride to the stable β-form. In addition, the extent of this phenomenon depended on the amount of partial glyceride in the mixture. Based on these results, changes in solid dosage forms based on glycerides during processing and storage can be better understood.

KEY WORDS: lipids; partial glycerides; polymorphism; recrystallization; triglycerides.

INTRODUCTION

During the last decade, there has been increased interest in lipids for the formulation of pharmaceutical dosage forms (1). The high variability in their structure and therefore versatile physicochemical properties offer various possibilities for the production of different dosage forms. Several systems for the delivery of drugs have already been introduced into the market, with their characteristics depending on both the choice of lipid and processing technique. As one of the first attempts, capsules were filled with liquid or semi-solid lipid formulations in which the active pharmaceutical ingredient (API) is either suspended or dissolved (2,3). Solid particles can be produced with a variety of different methods including melt extrusion (4), melt granulation (5,6), spray cooling (7), or spray drying (8). The resulting particles can either be processed into tablets or filled into capsules. Additional established systems are solid lipid nanoparticles (9) and nanostructured lipid carriers (10) which can be produced by different techniques. In general, each of the techniques mentioned above involves complete or almost complete melting of the lipid followed by resolidification in most cases. There is also a relatively new approach for the formulation of lipid-based dosage forms called solid lipid extrusion in which the lipid remains mostly solid during processing (11–13).

The advantages of lipid-based formulations include the possibility of prolonged release (14) as well as enhancement of solubility and permeability for APIs exhibiting poor bioavailability (15,16). As the majority of newly developed chemical entities have poor solubility and permeability (17), bioavailability enhancement is increasingly important. Furthermore, taste masking and protection of sensitive APIs is possible with the help of lipids as excipients (18). In addition, lipids are biodegradable and physiologically nontoxic.

Lipid-based dosage forms can exhibit stability problems associated with complex solid-state behavior (19). In general, three polymorphic forms are characteristic for lipids in which the fatty acid chains exhibit different packing modes and consequent thermodynamic energies (20). The α-form is the highest energy polymorph, the β′-form is intermediate, and the β-form is the lowest energy and hence thermodynamically stable form (21). Furthermore, for some lipids, an additional form called the sub-α-form is known. The relationship between the different forms is monotropic, and thus, transformations to more stable forms over time are likely to happen. However, the resulting polymorphic form and transformation rate are influenced by the temperature of the system (22).

As previously mentioned, most processing approaches involve the melting of the lipid with the potential for an unstable polymorphic form to crystallize during resolidification. Therefore, the processing of dosage forms is often accompanied by undesired solid-state changes (23,24). In addition, the polymorphic form of the lipid after processing

[1] Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Universitaetsstr. 1, 40225 Düsseldorf, Germany.
[2] Centre for Drug Research, University of Helsinki, Helsinki, Finland.
[3] Division of Pharmaceutical Technology, Faculty of Pharmacy, Helsinki, Finland.
[4] School of Pharmacy, University of Otago, Dunedin, New Zealand.
[5] To whom correspondence should be addressed. (e-mail: kleinebudde@uni-duesseldorf.de)

might undergo a change to another form during storage, often referred to as "aging" in the literature (25). These changes can lead to alteration of the dissolution characteristics of the drug and possibly bioavailability of the drug in human body (12,26).

At present, there is a lack of understanding of the underlying principles of such transformations during the manufacturing of pharmaceutical dosage forms, and hence, the formulation of lipid-based dosage forms is often performed based on empirical knowledge. However, for reliable and reproducible dosage forms, an understanding of the physicochemical behavior is mandatory to prevent potential stability problems.

In previous studies, different triglycerides which were processed to solid lipid extrudates were found to exhibit different polymorphic forms after manufacturing depending on their structure and the extrusion temperature (12). In addition, interactions between triglycerides and partial glycerides were revealed during extrusion, which subsequently affected the release of the drug (27). Based on these experiences, a systematic investigation of the influence of chain length, storage temperature, substitution, and interactions between different lipids was performed. Therefore, different powdered glycerides were melted above their melting points and resolidified in Teflon molds as thin lipid layers in order to investigate their recrystallization behavior. Storage experiments were performed using different climatic conditions (room temperature and 40°C) to examine the influence of temperature on the crystallization processes. In addition, mixtures of different lipid powders were prepared and subjected to the same experiments as the pure powders to eludicate possible interactions between the lipids which might affect the recrystallization behavior. Based on these studies with the lipid layers serving as model systems, a better understanding of the processes determining the solid-state behavior of lipid-based dosage forms should be provided in order to ensure reproducible and stable lipid-based dosage forms.

MATERIALS AND METHODS

Materials

The pure powdered monoacid triglycerides trilaurin (Dynasan 112®), tripalmitin (Dynasan 116®), and tristearin (Dynasan 118®), as well as the partial glycerides glyceryl monostearate (Inwitor 491®) and glyceryl stearate (Imwitor 900P®), were provided by Sasol (Witten, Germany) and used as received. The crystal structure of the powders was verified with X-ray powder diffraction before use.

Methods

Preparation of Melts

The powdered lipids were completely melted 20°C above their melting points. Each melt was held for 3 min before they were poured into purpose-built Teflon molds. The melts resolidified in thin lipid layers (2 mm) in ambient conditions.

Storage

The lipid layers were stored at either room temperature or in a climate chamber at 40°C (Ehret, Emmendingen, Germany).

Sampling

At certain time points, samples of appropriate size of the lipid layer surface were removed with a medical scalpel and investigated. Analysis was performed on the freshly resolidified sample and after 24 and 48 h. Afterwards, measurements were conducted in a 2-day interval up to 16 days. The following measurements were accomplished after 24, 36, 48, and 60 days.

Differential Scanning Calorimetry

Thermal analysis was performed on the lipids using a DSC 821e calorimeter (Mettler-Toledo, Gießen, Germany). Samples (approximately 5 mg) were weighed into 40-µl aluminum pans which were hermetically sealed. The apparatus was heated from 20°C to 100°C with a heating rate of $10°C min^{-1}$. All experiments were conducted twice.

X-Ray Powder Diffraction

Diffractograms were recorded with a theta–theta X-ray diffractometer (D8 Advance, Bruker AXS GmbH, Karlsruhe, Germany). Measurements were performed in symmetrical reflection mode with CuKα radiation (λ=1.54 Å) with Göbel mirror bent multilayer optics in the angular range of 5–40° (2θ). The step size was 0.05° (2θ), and the measuring time was of 1 s per step. Each experiment was conducted in triplicate compressing the samples into the sample holder, hence providing a smooth surface.

Hot-Stage Microscopy

Thermomicroscopic investigations were performed with a hot-stage FP 900 (Mettler-Toledo, Gießen, Germany) in combination with an optical microscope M 76 (Leica, Wetzlar, Germany). The powdered lipids were heated up to 10°C above their melting points, and the melt was held for at least 3 min at this temperature before monitoring the resolidification at room temperature.

RESULTS AND DISCUSSION

Monoacid Triglycerides and the Influence of Fatty Acid Chain Length

Three monoacid triglycerides differing in their fatty acid chain length were investigated with respect to their recrystallization behavior from the corresponding melts. The resolidified melts were stored either at room temperature or 40°C and investigated after certain time intervals with a combination of differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) measurements.

Trilaurin, a monoacid triglyceride containing 12 C-atoms for each fatty acid esterified with the glycerol molecule, exhibits two melting endotherms for the freshly solidified sample (Fig. 1a, b) with the onsets at 34°C and at 44°C

(Fig. 1a, b). The first endotherm is due to the melting of the unstable β′-form, whereas the second endotherm indicates the melting of the stable β-form of trilaurin. Both onsets are in good agreement with the reported melting points of the two forms (28). As thermal events observed using DSC are associated with physical and/or chemical changes which have not been present in the original sample, XRPD patterns were recorded as complimentary data (Fig. 2a, b). The freshly resolidified sample of trilaurin exhibits several peaks which can be related to different polymorphic forms. Peaks at 19.4° and 23.1° are due to the β-form, whereas the peak at 21.1° corresponds to the β′-form (29). After 24 h of storage at room temperature, only the stable β-form can be detected using both DSC and XRPD (Figs. 1a and 2a). The same result is obtained for those samples stored at 40°C (Figs. 1b and 2b). The unstable α-form is not observed in these studies due to the fact that its reported melting point of 14°C is below room temperature (28). In conclusion, for trilaurin, the storage temperature of the resolidified melt is of minor importance as the samples stored at different temperatures exhibit the same thermal behavior irrespective of storage conditions. The recrystallization from the melt was visualized by hot-stage microscopy (Fig. 3a). The appearance of the β-form is associated with a flower-like morphology.

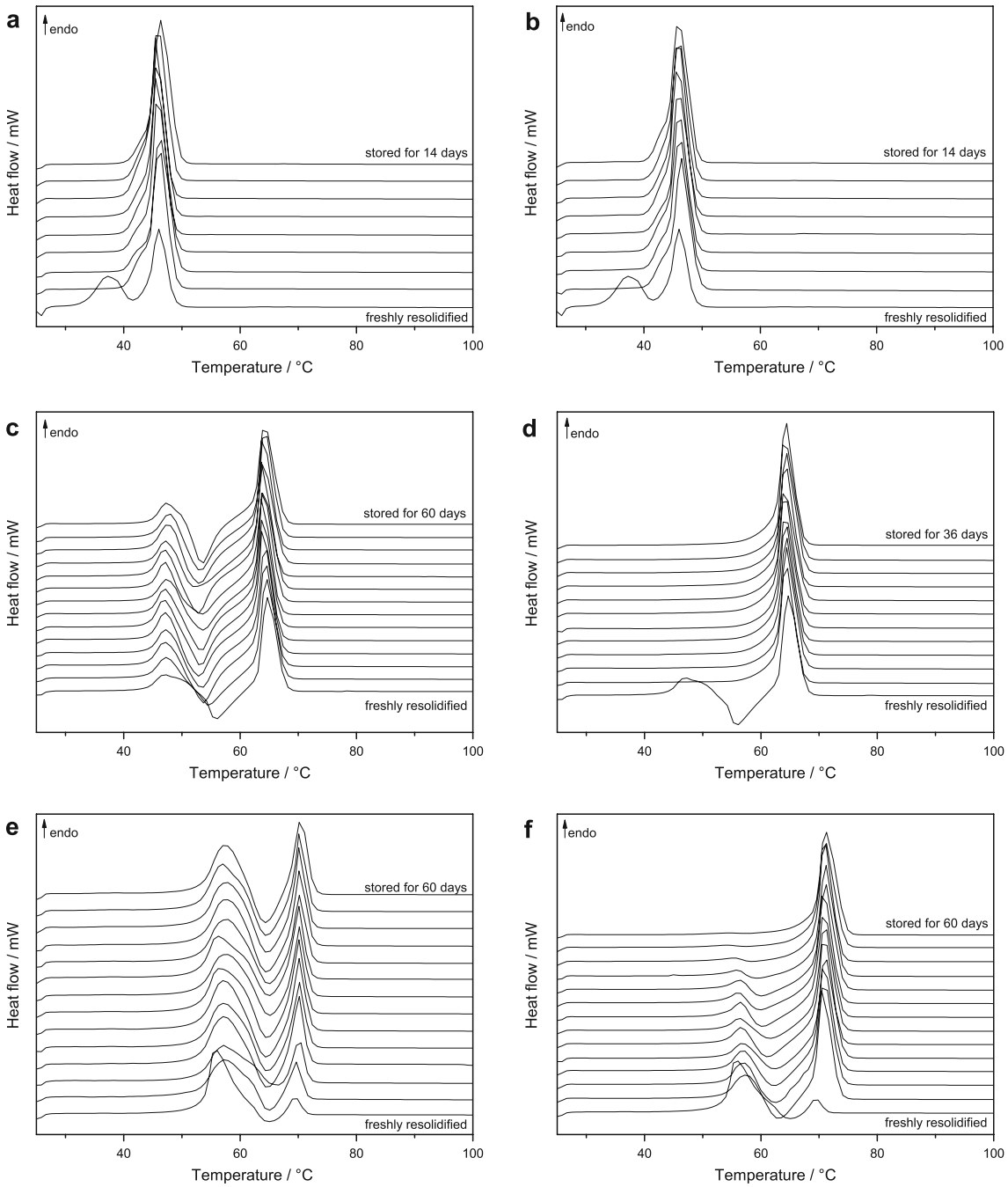

Fig. 1. DSC thermograms of resolidified triglycerides during storage. Trilaurin **a** at room conditions, **b** at 40°C, tripalmitin **c** at room conditions, **d** at 40°C, tristearin **e** at room conditions and **f** at 40°C

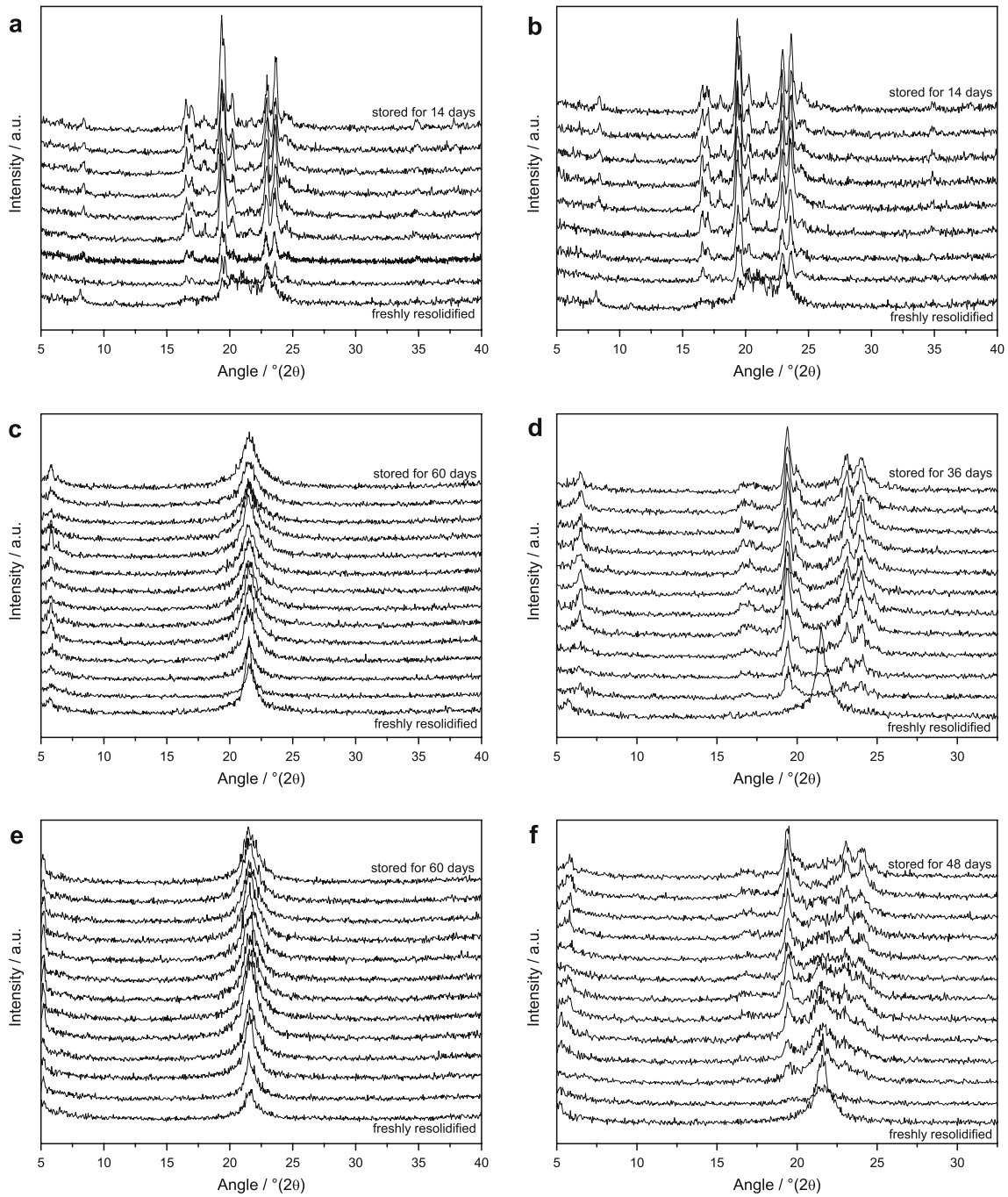

Fig. 2. XRPD patterns of resolidified triglycerides during storage. Trilaurin **a** at room conditions, **b** at 40°C, tripalmitin **c** at room conditions, **d** at 40°C, tristearin **e** at room conditions and **f** at 40°C

Tripalmitin is a triglyceride with the fatty acids each containing 16 C-atoms. The corresponding thermograms are depicted in Fig. 1c, d. Different polymorphic forms as can be identified in the figures for the freshly resolidified sample. The endothermic melting peak of the unstable α-form is depicted with its onset at 44°C directly followed by the recrystallization exotherm of the metastable β′-form (onset 51°C) (28). This peak is formed through the resolidification of the molten α-form during DSC measurement. The stable β-form can be identified by its melting endotherm (onset 63°C). The melting points in the literature are in good agreement with those in this study (28). The XRPD patterns of the sample samples are depicted in Fig. 2c, d. The freshly resolidified sample exhibits only the pure α-form, as indicated by the peak at 21.4° (29). During the storage at room temperature (Fig. 2c), the α-form of the triglyceride remains the only polymorphic form which can be detected. DSC measurements exhibit some shortcomings in this context as the sample which had originally been in the α-form is able to recrystallize in other polymorphic forms after less stable forms melt during the measurements. This example shows the importance of choosing suitable analytical methods as DSC must be complemented by a method such as XRPD to defintively determine the crystal form(s) of the sample. The

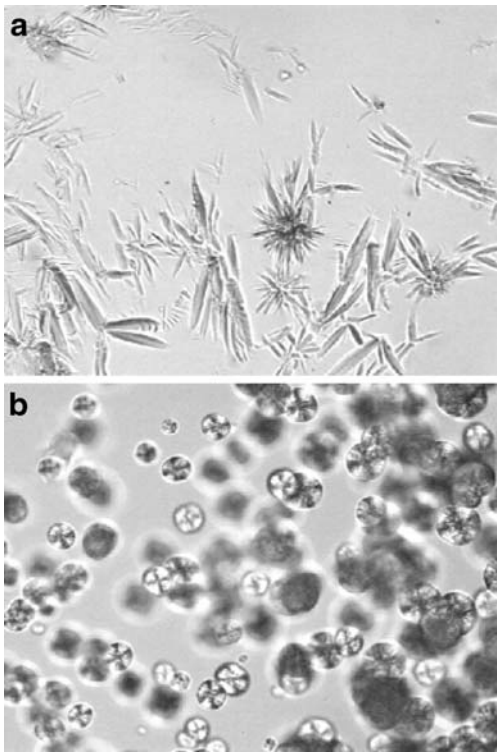

Fig. 3. Recrystallization of triglycerides from the melt. **a** Trilaurin and **b** tripalmitin

same solid-state behavior was observed with both DSC (Fig. 1d) and XRPD (Fig. 2d) for the sample stored at 40°C. After 24 h of storage, only the β-form of the lipid can be detected. Interestingly, the β′-form cannot be detected, a fact which is in accordance with the literature (29). Two reasons have been proposed for this: on the one hand, the melting of the β′-form is strongly suppressed by the recrystallization of the β-form which hinders its detection, and on the other hand, there is evidence that the α-form can directly transform to the β-form.

In conclusion, tripalmitin crystallizes in its α-form after melting. During storage, the temperature plays an important role and affects the rate of recrystallization to a more stable form. During storage at 40°C, the stable β-form was obtained after 24 h, whereas at room temperature, no recrystallization had occurred after 60 days. The crystallization of the α-form from the melt could be visualized with hot-stage microscopy (Fig. 3b).

Tristearin is the triglyceride with the longest fatty acids (chain length 18 C-atoms) and hence the highest melting point. It also showed different solid-state behavior in different storage conditions. The freshly resolidified samples (Fig. 1e, f) exhibit the following thermal events during DSC measurements: a melting endotherm of the unstable α-form (onset 54°C), a recrystallization exotherm of the metastable β′-form (onset 63°C), and a melting endotherm of the stable β-form (onset 69°C) (28). Tristearin samples stored at room temperature exhibit all three forms in the DSC thermograms during the investigation period of 60 days (Fig. 1e). With respect to the storage at 40°C, the effect of temperature on the recrystallization is clearly visible (Fig. 1f). Already after 1 day of storage, the α-form melting endotherm has decreased in intensity, while the β-form melting endotherm peak has increased in intensity. After 48 days, the α- and β′-forms cannot be detected in the thermogram. Therefore, the recrystallization to the stable β-form was complete.

The data recorded with DSC and XRPD revealed a behavior that was similar to that of tripalmitin. The XRPD patterns of tristearin are depicted in Fig. 2e, f. The freshly resolidified sample exhibited only the α-form of the lipid, as indicated by the sole peak at 21.4° (29). The same results could be found for the samples stored at room temperature over 48 days. Samples stored at 40°C exhibited solid-state transformations during storage. As for tripalmitin, no peaks indicating the β′-form (peaks at 21.1° and 23.3°) can be observed as discussed above (29). After 4 days of storage, peaks indicating the β-form appear (19.4° and 23.1°). The DSC thermograms and XRPD patterns are in good accordance with respect to when only the β-form is observed for the tristearin samples. Both methods suggest that the α-form is not present after 48 days of storage. Prior to this, a mixture of peaks correlating to α- and β-form can be found.

The influence of chain length on recrystallization rate was evident upon comparison of tripalmitin and tristearin, with tristearin, which consists of longer fatty acids, exhibiting a slower recrystallization to the stable form. This fact should be interpreted in light of the temperature difference between the storage and melting temperatures of the β-form of the two lipids. For tristearin, this difference is 33°C, while for tripalmitin, it is 26°C.

In conclusion, fatty acid chain length, storage temperature, and storage time were found to affect the recrystallization behavior of lipids from resolidified melts. The chain length of the fatty acids which are esterfied with glycerol in a triglyceride molecule affected the recrystallization as the transformation rate from unstable to stable polymorphic forms decreased with increasing chain length at the temperatures used for storage experiments in this study. The second variable, storage temperature, had a pronounced effect on recrystallization to more stable polymorphic forms. Increasing the temperature greatly accelerated the recrystallization to the stable form.

Partial Glycerides and the Influence of Degree of Esterification

In contrast to the triglycerides in which each moiety of the glycerol molecule is esterified with a fatty acid, partial glycerides contain only one or two esterified glycerol moieties. In this study, a monoglyceride and a mixed partial glyceride consisting of approximately equal proportions of monoglycerides and diglycerides containing stearic acid were investigated.

The DSC thermograms of the monogylceride glyceryl monostearate are depicted in Fig. 4a, b. The freshly resolidified sample exhibits two endothermic melting peaks with onsets at 37°C and 71°C. The lower melting endotherm could be identified as the sub-α-form of the partial glyceride (28). The endotherm with the onset at 71°C is due to the melting of the α-form (28). The XRPD diffractograms (Fig. 5a, b) show a significant peak for the α-form at 21.3° (30). The sub-α-form could not be identified with this method in this study. During storage at room temperature, the sub-α-form can be detected up to 36 days with DSC. The α-form

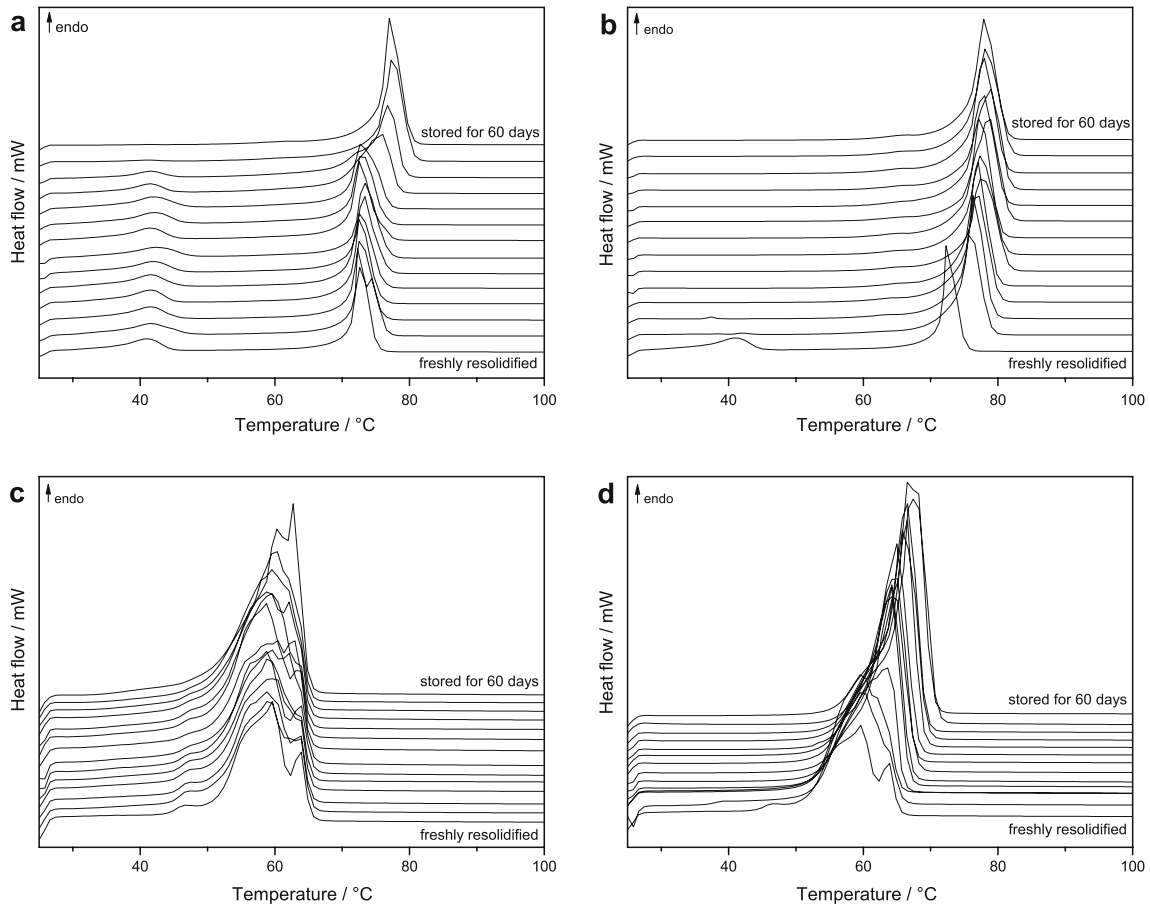

Fig. 4. DSC thermograms of resolidified partial glycerides during storage. Glyceryl monostearate **a** at room conditions, **b** at 40°C, glyceryl stearate **c** at room conditions and **d** at 40°C

can be monitored up to 16 days. Subsequently, the peak shifts slightly toward higher temperatures to reach a melting endotherm with an onset of 75°C after 36 days of storage. This peak corresponds to the stable β-form of the lipid (30). The results are in good agreement with the XRPD patterns (Fig. 5a) as they also show evidence of the β-form after 24 days of storage (19.5° and 22.5°) (30). After 36 days of storage, the peak indicating the α-form disappears. In comparison, the samples stored at 40°C only exhibit the sub-α-form for the freshly resolidified sample (onset 37°C) as well as the α-form (onset 71°C; Fig. 4b) (28). After 24 h of storage, these peaks can no longer be detected. With respect to other polymorphic forms, the peak with an onset of 75°C indicating the stable β-form is observed after 1 day of storage at 40°C. These findings correspond to the data obtained by XRPD (Fig. 5b).

The results for the second partial glyceride glyceryl stearate which was investigated are depicted in Figs. 4c, d and 5c, d. As the substance is rather chemically inhomogeneous, the assignment of melting or crystallization events in the thermograms is very difficult (28), with the different thermal events overlapping. It can thus only be stated that the melting endotherm during storage at room temperature shifts to higher temperatures over time, indicating transformations to more stable and less energetic forms. During storage at 40°C, this shift occurs faster and the peaks are more defined as the higher temperature facilitates such transformations. The peak at 22° in the XRPD pattern (Fig. 5c, d) suggests the α-form of the glycerides for the freshly resolidified sample (Fig. 5c) (28). During storage at room temperature, a broader pattern occurs which cannot be definitively assigned. In comparison, at 40°C storage, the peaks become more resolved (Fig. 5d).

In conclusion, the peak assignment in the case of the partial glycerides is more complex than for triglycerides. Temperature plays an important role during storage as increased temperature increases the velocity of recrystallization.

Mixtures of a Triglyceride and a Partial Glyceride and the Impact of Interactions

Two different mixtures of tristearin and glyceryl monostearate powders were prepared to investigate the impact of possible interactions between the two lipids on their solid-state behavior. The mixing ratios were 90% tristearin/10% glyceryl monostearate and 50% tristearin/50% glyceryl monostearate (*w*/*w*).

After mixing for 15 min, the powder mixtures were melted as described in MATERIALS AND METHODS and resolidified. The DSC thermograms are depicted in Fig. 6. The 90:10% mixture of tristearin and glyceryl monostearate (Fig. 6a, b) exhibits only one melting endotherm with an onset of 53°C for the freshly resolidified sample, which corresponds to the tristearin α-form

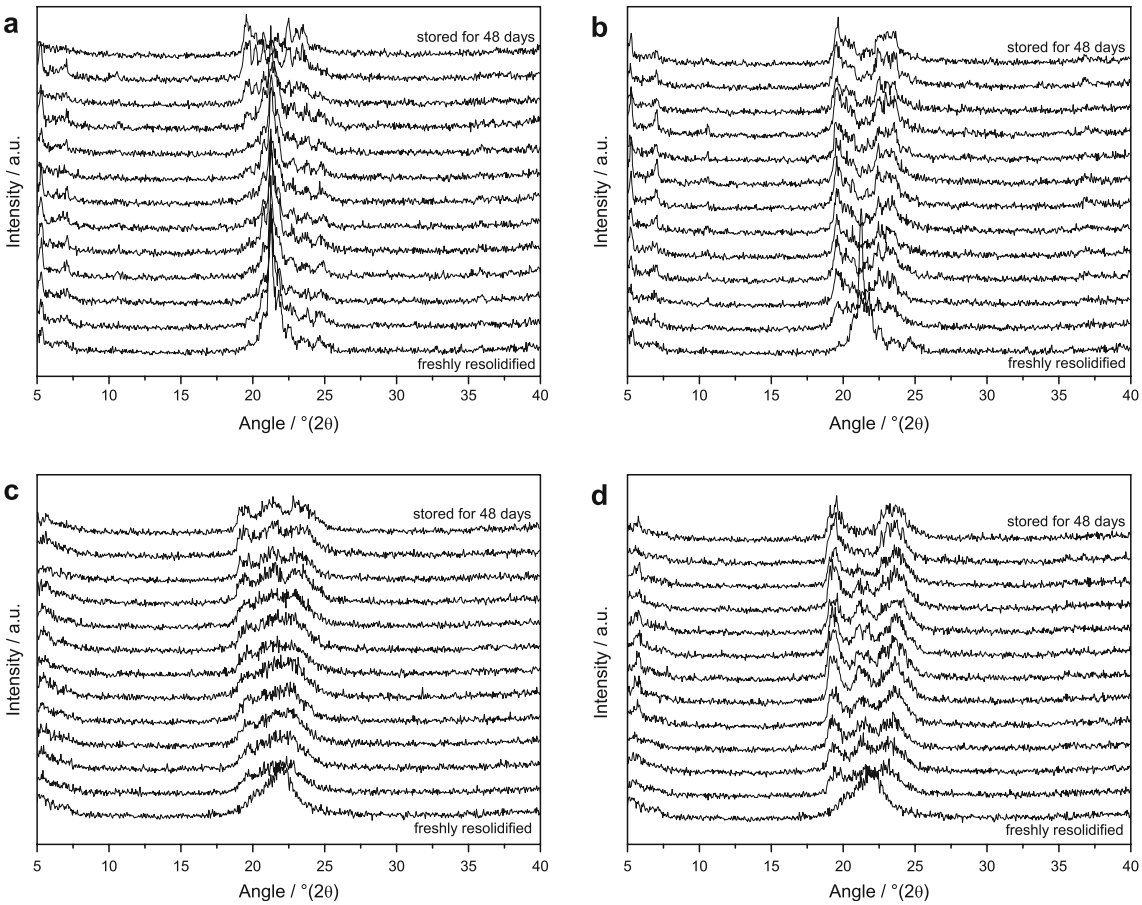

Fig. 5. XRPD diffractograms of resolidified partial glycerides during storage. Glyceryl monostearate **a** at room conditions, **b** at 40°C, glyceryl stearate **c** at room conditions and **d** at 40°C

(28). As there are no further melting peaks, it can be assumed that glyceryl monostearate is in a crystal form which melts within the temperature range of the tristearin α-form. For the samples stored at room temperature, this melting endotherm remains essentially the same for 60 days of storage. In addition, after 24 h of storage, a tiny melting endotherm (onset 65°C) appears, which becomes more intense over time. This peak is due to the recrystallization of the tristearin β-form from the molten sample during DSC measurement (28). The XRPD patterns (Fig. 7a) only depict the tristearin α-form peak (21.4°) during the whole storage time (29).

The samples stored at 40°C exhibit substantially different thermal behavior (Fig. 6b). After storage for 24 h, a large endotherm (onset 66°C) can be detected corresponding to the stable β-form of tristearin (28). In addition, up to a storage duration of 16 days, a small melting endotherm with an onset at 53°C is present and corresponds to the α-form of tristearin (28).

Since glyceryl monostearate is only present in a very low concentration and the melting ranges of tristearin and glyceryl monostearate overlap, it is very difficult to make a statement about the polymorphic forms of the partial glyceride. The XRPD patterns (Fig. 7b) correspond to the results obtained by DSC measurements. The freshly resolidified sample contains tristearin in its α-form (peak 21.4°) which transforms to a mixture of α- and β-forms (peaks at 19.4°, 23.1°, and 24.05°) (29) over time. After 24 days of storage, only the tristearin β-form is evident.

It is interesting to compare the recrystallization behavior of pure tristearin melts with melts consisting of 90% tristearin and 10% glyceryl monostearate. The XRPD patterns (Figs. 2e, f and 7a, b) do not show any significant differences. In this case, DSC measurements are the method of choice to investigate solid-state differences (Figs. 1e, f and 6a, b). For samples stored in room temperature (Figs. 1e and 6a), an increased incidence of the unstable tristearin α-form can be detected for the sample containing the mixture in comparison to the pure tristearin melt. During the DSC measurement, the tristearin α-form melts, and hence, recrystallization of more stable polymorphs can occur. In the mixture, it appears that the glyceryl monostearate is able to prevent or delay the transformation from the tristearin α-form (peak onset 63°C) to the stable β-form as the β-form peak (onset 69°C) exhibits a much reduced intensity compared to the pure tristearin sample (28). The α-form is probably stabilized by combined structures of tristearin and glyceryl monostearate on the intermolecular level. The ability of a partial glyceride to hinder another lipid transforming into its stable polymorph has been previously reported (31,32). In the chocolate industry, this specific effect is used to maintain an unstable polymorph of cocoa butter which appears more glossy than the recrystallised stable polymorph (33).

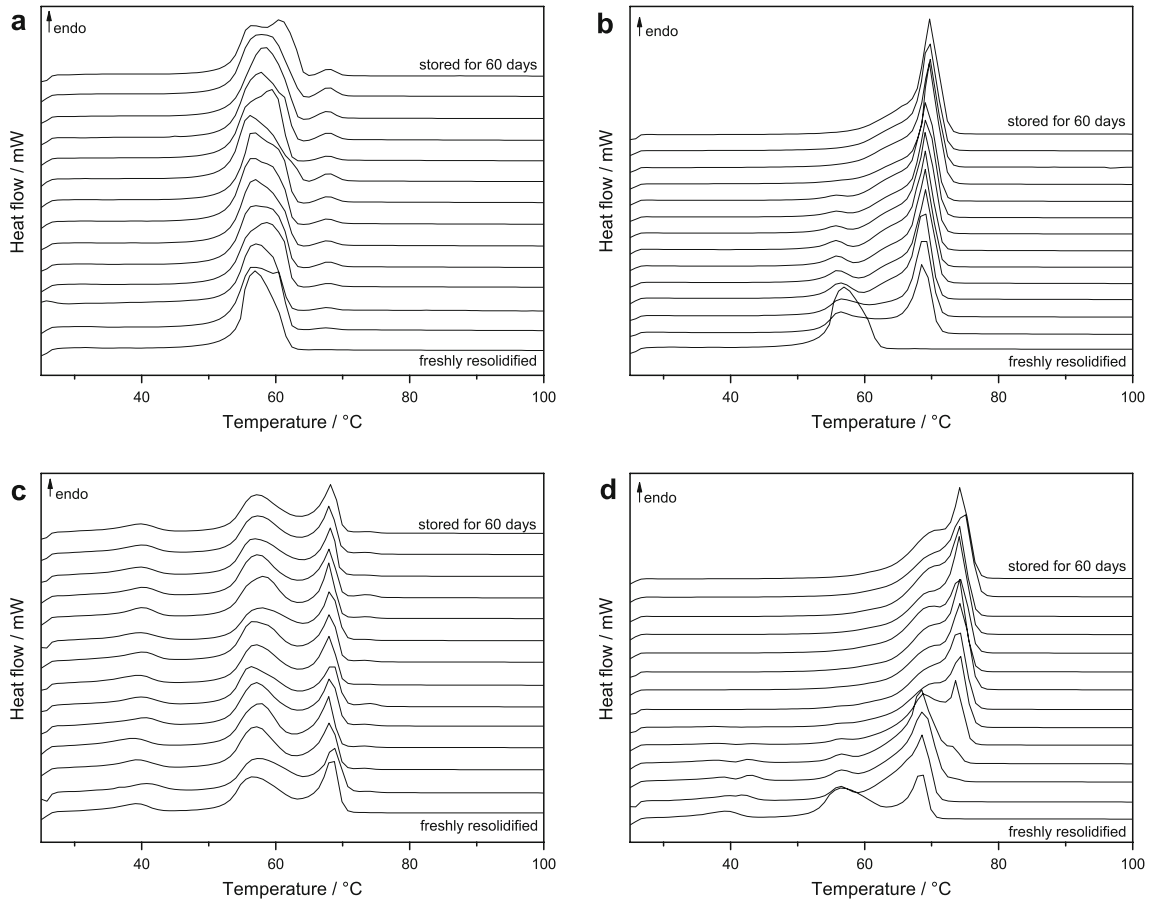

Fig. 6. DSC thermograms of resolidified lipid mixtures during storage. 90% tristearin/10% glyceryl monostearate (*w*/*w*) **a** at room conditions, **b** at 40°C, 50% tristearin/50% glyceryl monostearate (*w*/*w*) **c** at room conditions and **d** at 40°C

It is also interesting to compare the DSC pattern of the tristearin and the mixed samples stored at 40°C (Figs. 2f and 7b). Even though the presence of the partial glyceride, glyceryl monostearate, hinders the formation of the β-form during DSC measurement, complete transformation to the tristearin β-form is faster and more pronounced than in the case of pure tristearin during storage. For the pure tristearin sample (Fig. 1f), the melting peak of the α-form can be observed for up to 48 days of storage, whereas in the thermogram of the mixed sample, the melting endotherm of the α-form is absent after only 24 days of storage (28). This phenomenon is probably associated with a less organized and energetically favorable packing and higher molecular mobility in the resolidified melt of the combined lipids due to the different structures of the two lipids which are mixing. This might affect the mixed melt in terms of recrystallization rate at higher temperatures.

The extent of interactions between the partial glyceride and the triglyceride was investigated further in the lipid mixture containing 50% tristearin and 50% glyceryl monostearate (*w*/*w*). The DSC thermograms are depicted in Fig. 6c, d. The freshly resolidified sample exhibits three melting endotherms. Their onsets can be detected at 37°C, 53°C, and 66°C, respectively (28). The first peak is due to the unstable sub-α-form of glyceryl monostearate. The melting endotherm having its onset at 53°C corresponds to the α-form of tristearin, whereas the last endotherm (onset 66°C) is a mixture of melting events of both lipids which is difficult to assign to the exact polymorphic forms of the lipids (28). During storage at room temperature, the sub-α-form of glyceryl monostearate as well as the α-form of tristearin remain in the resolidified sample for the whole storage time. The melting endotherm with an onset at 66°C also persists. After 6 days of storage, a tiny melting endotherm (onset 72°C) occurs corresponding to the tristearin β-form. In contrast, in the sample stored at 40°C, the sub α-form is only detected up to 6 days of storage with the peak onset shifting from 37°C up to 41°C (Fig. 4d). The tristearin α-form (onset 54°C) is detectable up to 8 days of storage. The melting endotherm with an onset at 65°C corresponding to both glycerides in the resolidified melt can be detected for 4 days. After 6 days of storage, this peak becomes bimodal, and then the peak completely shifts to higher temperatures (onset 71°C) with a shoulder remaining at lower temperatures. The maximum of this endotherm is likely to be due to a mixture of the stable β-forms of tristearin and glyceryl monostearate (28). The XRPD patterns (Fig. 7c, d) did not offer any additional information.

In conclusion, resolidified melts consisting of mixtures of triglyceride and partial glyceride show diverse solid-state behavior. Small quantities of partial glyceride (10%) increased the amount of unstable α-form of the triglyceride compared to that of a pure tristearin melt. This behavior was also observed for the mixture containing 50% partial

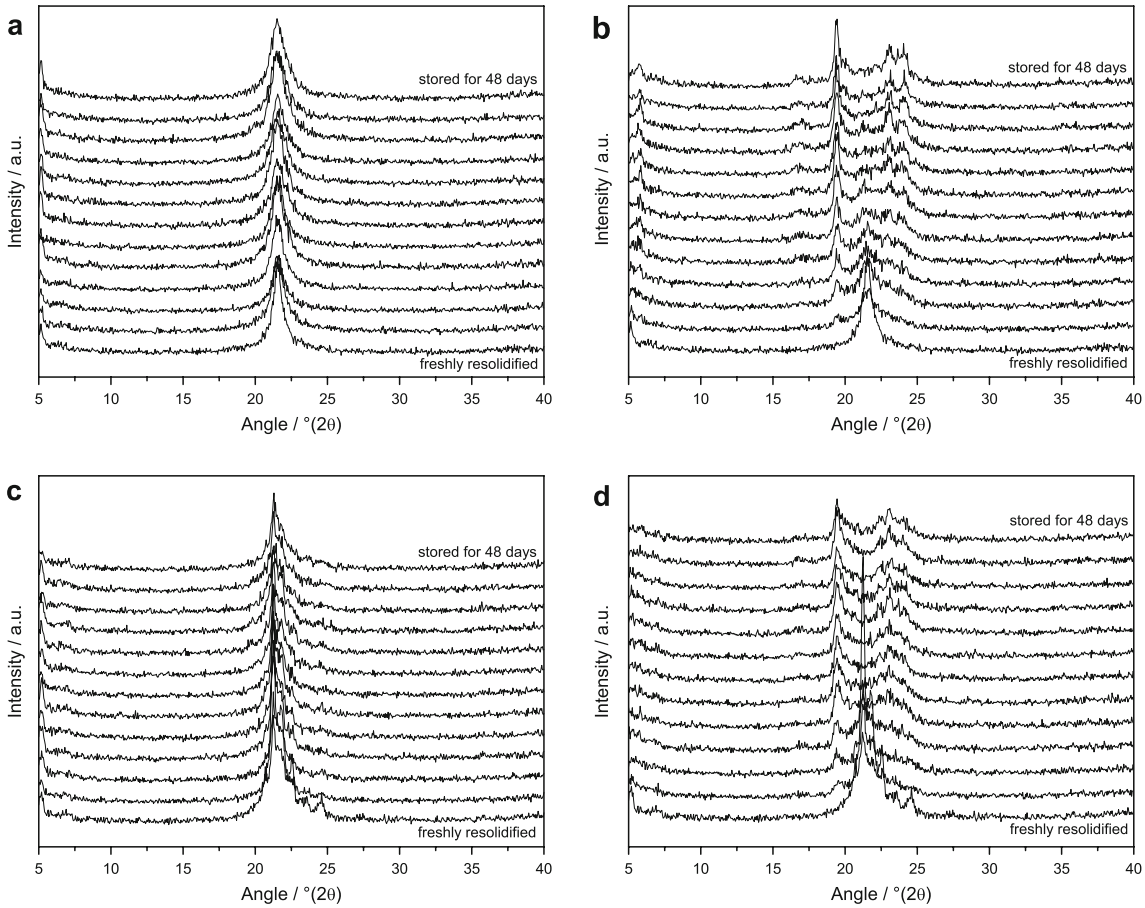

Fig. 7. XRPD diffractograms of resolidified lipid mixtures during storage. 90% tristearin/10% glyceryl monostearate (*w*/*w*) **a** at room conditions, **b** at 40°C, 50% tristearin/50% glyceryl monostearate (*w*/*w*) **c** at room conditions and **d** at 40°C

glyceride. Nevertheless, the mixtures allow faster recrystallization of the stable β-form than pure tristearin melts during storage. This becomes obvious upon comparison of the pure tristearin sample (Fig. 1f) and the mixtures (Fig. 6b, d) after storage in 40°C. Again, increasing the temperature accelerated the transformation rate to more stable polymorphic forms. Comparing the different mixing ratios suggests that the ability of the solid state form of the triglyceride to incorporate different amounts of the partial glyceride molecules affects the transformation rate to a large extent. The mixture containing 10% glyceryl monostearate exhibits the tristearin α-form for 16 days (Fig. 6b), whereas the mixture containing 50% glyceryl monostearate features the tristearin α-form just for 10 days (Fig. 6d).

CONCLUSION

Solid-state analysis of thin glyceride layers of pure triglycerides or mixtures of a triglyceride and a partial glyceride as model systems for lipid-based dosage forms led to a deeper insight into the principles of recrystallization from melts and during storage. The combination of DSC and XRPD measurements was found to give a comprehensive overview of the recrystallization from the melts. It could be shown that the results of only one method can be misleading for the interpretation.

Triglycerides exhibited chain-length-dependent recrystallization behavior. With increasing chain length, the recrystallization to the stable polymorph was decelerated at each storage temperature. Partial glycerides exhibited a more complex recrystallization behavior due to the fact that the melting ranges of their different polymorphs overlap. The combination of a triglyceride and a partial glyceride led to interactions influencing the recrystallization. Generally, temperature was shown to have a pronounced impact on the rate of recrystallization with the higher temperature accelerating the recrystallization. But storage at elevated temperatures does not necessarily lead to a fast transformation to the stable form of the lipid. Based on these results, changes in solid dosage forms based on glycerides during processing and storage can be better understood. A deeper knowledge of the underlying principles of solid-state changes in lipids used in the pharmaceutical setting is mandatory to avoid unpredictable and undesirable changes in glyceride-based dosage forms during processing and storage.

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