4. Results and discussion

4.1. Solid lipid extrudates – solid-state characterization of lipids after processing and storage in correlation to dissolution characteristics

4.1.1. Introduction

Even though solid lipid extrusion has already been performed in different working groups (Breitkreutz et al, 2003; Pinto and Silverio, 2001; Reitz et al, 2007), complete understanding of the lipid solid-state behaviour during extrusion has not been achieved. In this section, a comprehensive overview of the underlying principles of solid-state behaviour of different lipids during processing and storage is given that could be correlated to the dissolution behaviour. In addition, the influence of the matrix composition of solid lipid extrudates on solid-state behaviour and drug release could be elucidated.

Corresponding articles: 1 and 2.

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

Three pure monoacid triglycerides differing in their fatty acid chain lengths (trilaurin, tripalmitin and tristearin) were extruded below their melting points. The aim of extrusion in general was to obtain reproducible cylindrical extrudates with a smooth surface and high mechanical stability. Therefore, the equipment variables were kept constant whereas the process variables, screw speed and feed rate, were adjusted to obtain a continuous product flow. As the lipids melt at different temperatures depending on the chain length, the extrusion temperature was individually chosen for each lipid. The best extrusion results were obtained a few degrees (6-11 °C) below the melting point of the stable polymorphic form of the individual lipid. The physical characterization of powders and extrudates with a combination of DSC, XRPD and vibrational spectroscopy techniques gave further insight into the solid-state behaviour of the lipids during processing and storage. Depending on the extrusion temperature, the extrudate contained different polymorphic forms of the lipid after extrusion (figure

1). All lipid powders were in the stable β-form before manufacturing. Tristearin extrudates exhibited α- and β-form of the lipid after extrusion at 55 °C having their melting endotherms with the onsets at 50.2 °C (α-form) and 70.7 °C (β-form) respectively whereas extrusion at 65 °C resulted in pure tristearin β-form (figure 1) (Hagemann, 1988).

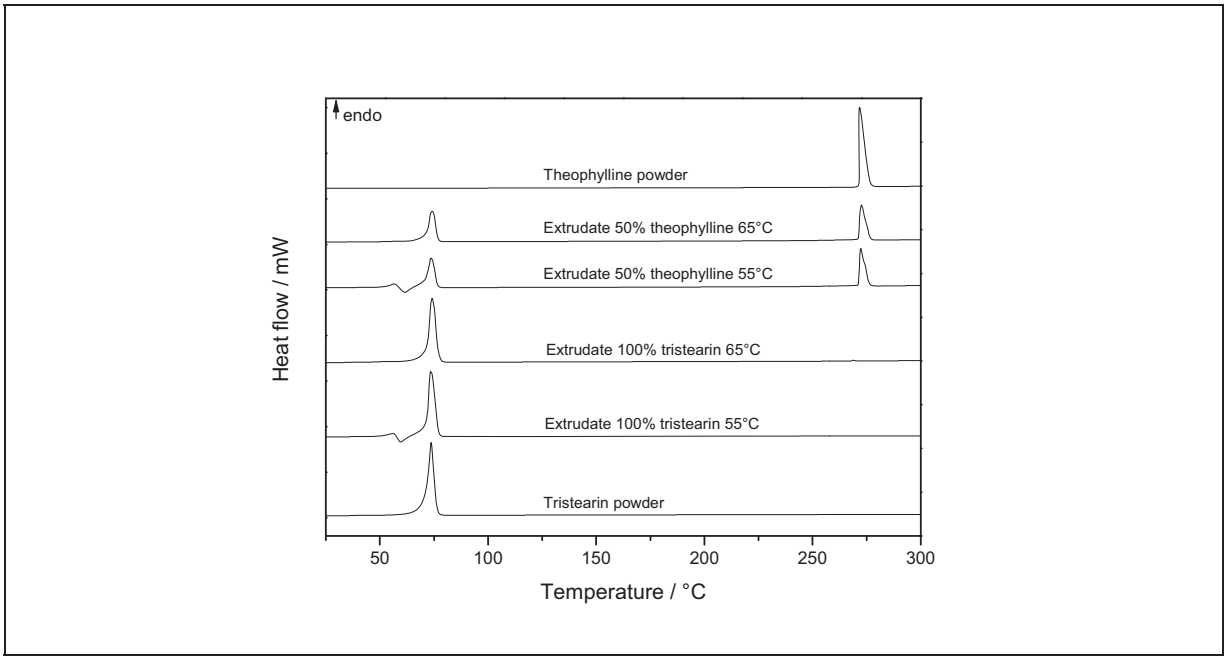

Figure 1: DSC thermograms of tristearin and theophylline powders and extrudates.

The combination of extrusion temperature and friction was found to be a key factor for the polymorphic behaviour of the lipid after extrusion. Friction causes temperature to rise which leads to melting at the edges of the lipid mass inside the extruder barrel. After leaving the die plate the molten parts of the lipid directly resolidify. The temperature at which the extrudate leaves the extruder determines the crystallization behaviour from the molten component of the extruded lipid (MacNaughtan et al, 2006).

This hypothesis was backed up with XRPD measurements during which the sample was heated up in the range of 25-75 °C in 5 °C steps. There was no incidence of solid-state changes until melting and as the polymorphs exhibit a monotropic relationship the α-form must be created via the melt (Sato, 2001; Sato et al, 1999). Variable temperature XRPD was also performed on the resolidified melts of the lipid powders as figure 2 depicts for tristearin. Depending on the temperature the α-form peak (21.4°)

or the β-form peaks (19.4°, 23.1° and 24.05°) were detected (Kellens et al, 1991; Van Langevelde et al, 2001). The results were in good agreement with the results obtained for the extrudates and could be corroborated with ATR-IR measurements (Kobayashi, 1988; Yano et Sato, 1999). The influence of pressure applied to the lipid mass inside the extruder barrel could be excluded as it was too low to have an effect on polymorphic transformations. The pressure during extrusion never exceeded 0.7 MPa and the previously reported pressure values which affect lipid polymorphic transitions are above this range (Wagner and Schneider, 1996). In conclusion, to obtain extrudates which only contain the stable β-form of the lipid the extrusion temperature has to be adjusted above the melting point of any unstable polymorphic form.

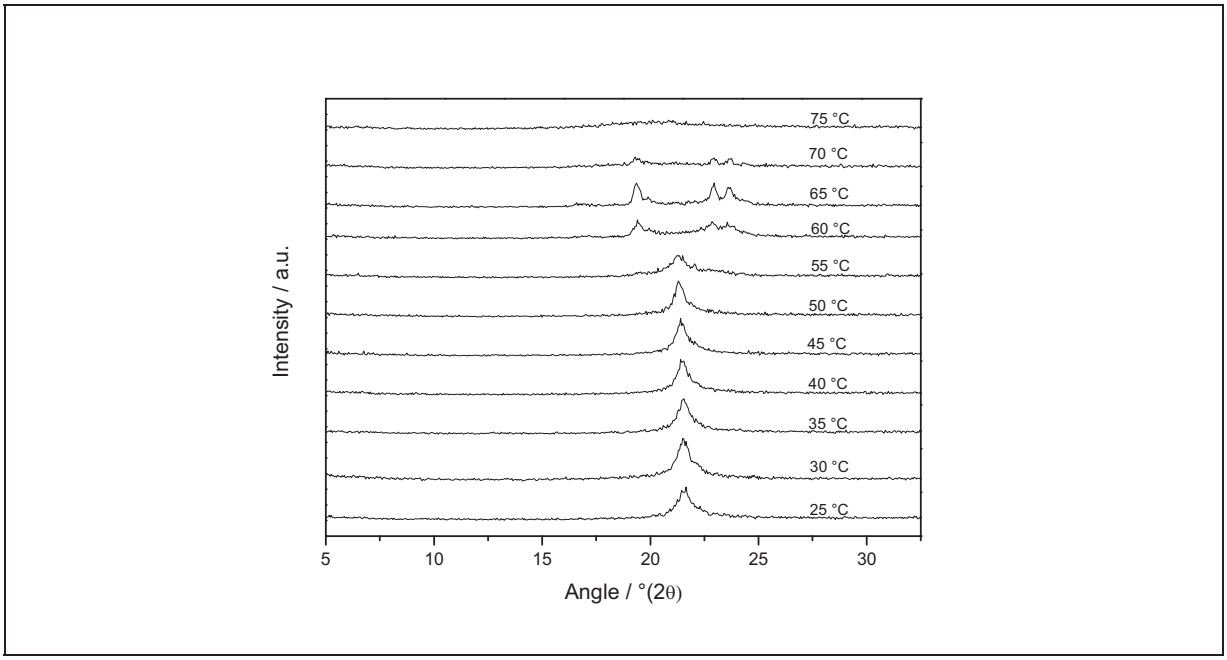

Figure 2: Variable temperature XRPD patterns of resolidified tristearin melts.

Release of the incorporated model drug theophylline anhydrate was found to be chain-length dependant (figure 3a) as lipids with a shorter chain length like trilaurin (12 C-atoms) led to faster release profiles than tripalmitin (16 C–atoms) or tristearin (18 C-atoms). Polymorphic transitions after manufacturing 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. In case of tristearin the extrudate produced at 55 °C exhibiting partly α-form which transforms to β-form over time was found to exhibit a slower dissolution rate than the pure β-form tristearin extrudate produced at 65 °C (figure 3b). On the first glance these results are unintuitive as the release is purely

diffusion controlled and the α-form is the less dense packing mode which should therefore lead to an equal or higher dissolution rate. But SEM images of the surface revealed sharp fractal structures covering the surface (‘blooming effect’), increasing the contact angle and hence being expected to decrease the wetting and the dissolution rate (Khan and Craig, 2004; Fang et al, 2007).

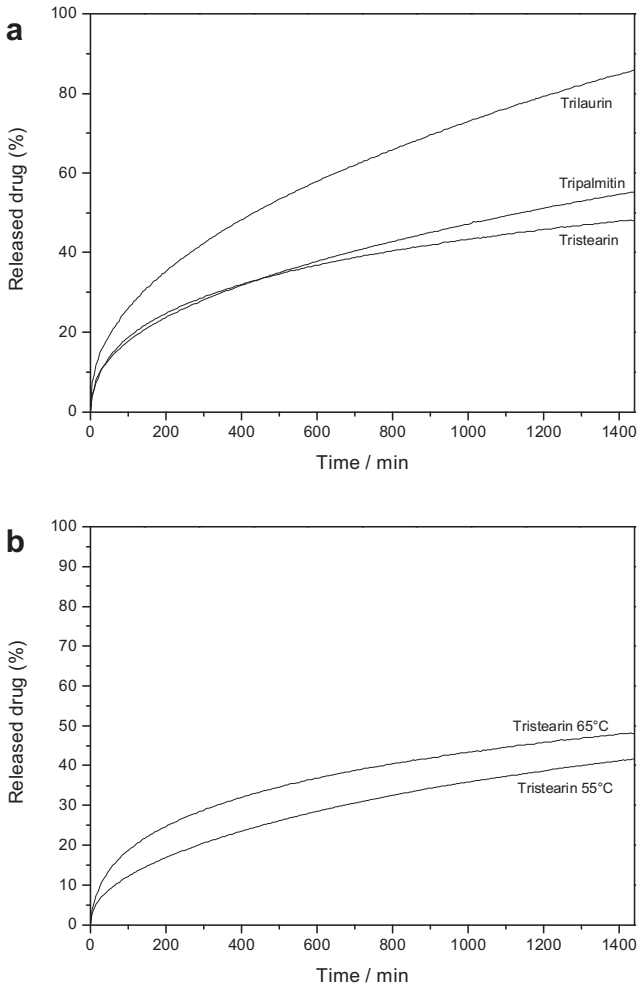

Figure 3: Dissolution curves of triglyceride extrudates. (a) comparison of different triglycerides and (b) comparison of tristearin extrudates produced at different temperatures (n = 3, mean, cv < 3%, not shown).

Triglyceride solid lipid extrudates remained stable during open storage in accelerated conditions (40 °C; 75 %RH) for 10 months. There was no evidence of solid-state changes of lipid and drug and no interactions could be detected. Despite there being

some evidence that theophylline monohydrate is the thermodynamically stable form in these conditions the drug remained as the anhydrate (Ticehurst et al, 2002). This is probably due to the hydrophobic barrier provided by the lipid matrix and a slow transformation rate.

In conclusion, these results led to a deeper understanding of the solid-state behaviour of lipids during extrusion and storage and help to avoid process conditions which lead to undesirable dosage form properties. The solid-state behaviour of triglycerides is influenced by different factors during processing and has to be well understood and monitored to obtain reproducible dosage forms of high quality. Understanding the polymorphic behaviour of triglycerides in solid lipid extrudates and its effect on dissolution will help in the development of solid lipid extrudates with desired dissolution behaviour.

4.1.3. Influence of the composition of glycerides on the solid-state behaviour and the dissolution profiles of solid lipid extrudates

Based on the results of the study performed on the extrusion of triglycerides, the composition of the lipid matrix was modified under controlled conditions to broaden the range of dissolution profiles from these dosage forms. A partial glyceride was extruded alone and in different ratios with a triglyceride to evaluate the effect of the lipid matrix composition and possible interactions between either the lipids or lipid and model drug. Solid-state analysis was conducted on the powders and on the extrudates and correlated to the results of dissolution testing. In addition, the storage stability under accelerated conditions was tested.

The partial glyceride, glyceryl monostearate, was successfully extruded alone and with 50% theophylline anhydrate as a model drug. The extrudates contained pure β-form of the lipid (Hagemann, 1988). DSC measurements revealed a limited interaction between lipid and drug during the measurement as the drug is able to partially dissolve into the lipid when the melting temperature of the lipid is exceeded (Chen et al, 1997). Non-destructive analysis of the extrudates using XRPD (Yajima et al, 2002) and ATR-IR spectroscopy (Nolasco et al, 2006; Kobayashi, 1988) revealed that no polymorphic transitions occurred in the lipid or drug.

Mixtures of the monoglyceride, glyceryl monostearate, and the triglyceride tristearin in two ratios (9+1 tristearin/glyceryl monostearate and 5+5 tristearin/glyceryl monostearate (w/w)) could successfully be extruded containing 50% drug. Solid-state analysis of the extrudates revealed interactions between the two lipids as the unstable tristearin α-form could be detected even though the temperature was sufficiently high enough to prevent this formation compared to a pure tristearin extrudate. Modified DSC measurements led to deeper insight into these solid-state phenomena. The extrudates were measured once and stored at room temperature for 24 hours in ambient conditions. These resolidified melts were measured a second time by DSC. Comparison of the thermograms of these samples led to the conclusion that the partial glyceride is able to hinder the formation of the β-form in the triglyceride. The structure of the partial glyceride exhibits some compatibility with the triglyceride structure and therefore stabilizes the less packed α-form of the triglyceride during recrystallization after melting (Garti et al, 1988; Garti, 1988). This effect is known in the literature and used in the chocolate industry to stabilize the favoured polymorph of cocoa butter (Schlichter-Aronhime and Garti, 1988). As a small quantity of the lipid mass in the extruder barrel melts due to the combination of temperature and friction the same phenomena can be observed for the extrudates. The degree of α-form formation can be correlated to the amount of partial glyceride in the matrix.

During storage, recrystallization of the tristearin α-form to the more stable β-form was detected. In this context, surface analysis using SEM and contact angle measurements was performed as the surface is very important with regard to dissolution behaviour. The release of the drug is purely diffusion controlled and the matrix stays intact, therefore transformations at the surface can have a pronounced effect on the release profile. Figure 4 depicts the SEM images of the extrudate surfaces with their corresponding contact angles. The glyceryl monstearate extrudate exhibits a smooth surface (figure 4 a) and the lowest contact angle due to its surfactant properties. The 5+5 (w/w) mixture of tristearin and glyceryl monostearate (figure 4b) also provides a relatively smooth surface. The increased contact angle of 116° is due to the presence of tristearin. Differences between the pure triglyceride (figure 4c) and the 9+1 (w/w) mixture of tristearin and glyceryl monostearate both produced at 65 °C were revealed using solid-state analysis. The mixed extrudate should be expected to exhibit a significantly lower contact angle than the pure triglyceride sample. Instead, the mixed extrudate surface was partly covered with needle-like structures increasing the contact

angle. This effect was accentuated at a processing temperature of 55 °C. Figure 4e depicts the surface of the tristearin extrudates whereas figure 4f depicts the surface of the tristearin / glyceryl monostearate (9+1 w/w) mixed extrudate. The surface of both extrudates was completely covered with sharp needles and the contact angle was 125° in both cases. As the contact angle defines wettability it is evident that the needles at the extrudate surface strongly affect the dissolution behaviour (Fang et al, 2007; Khan and Craig, 2004).

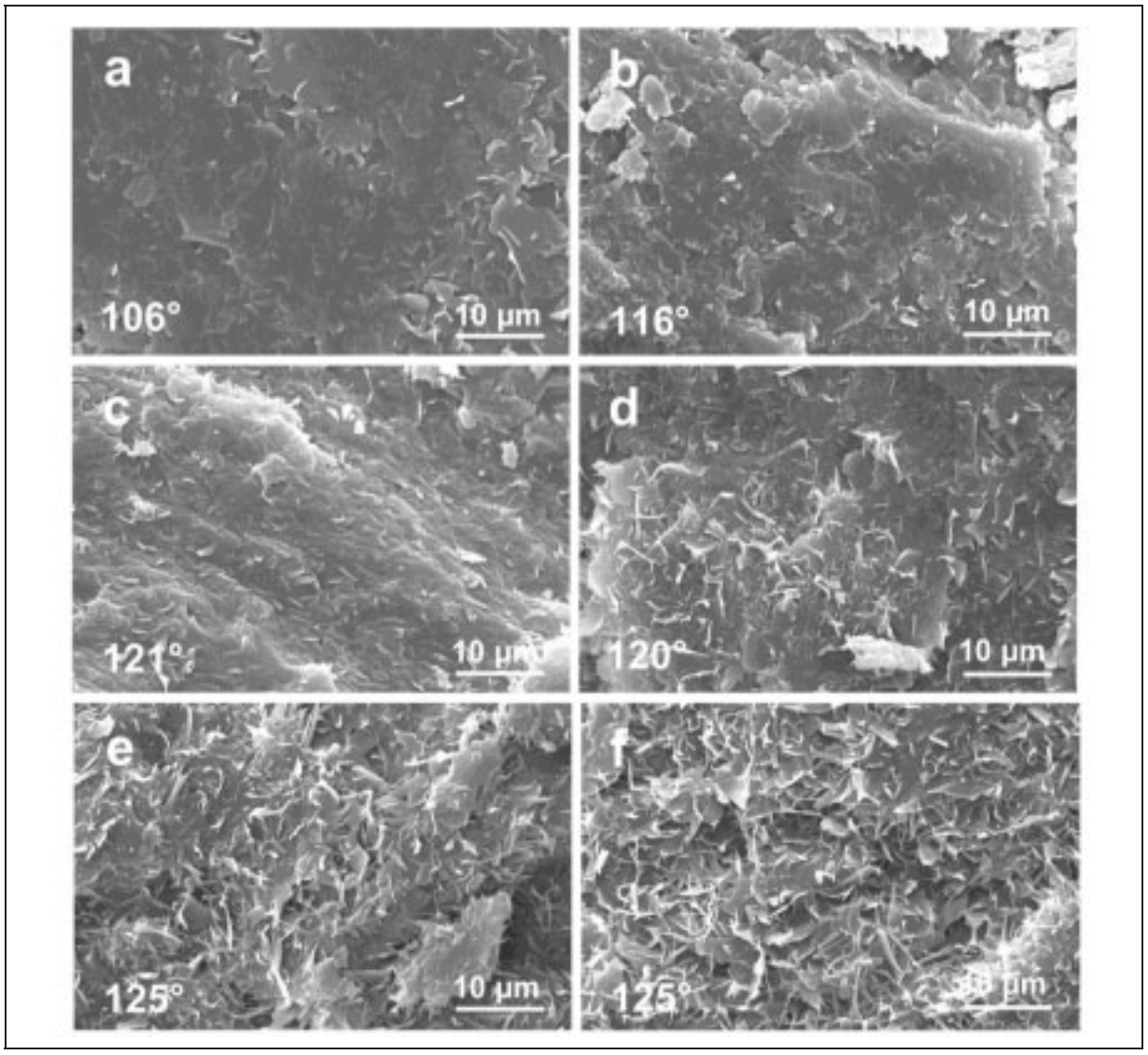

Figure 4: SEM images of extrudate surfaces containing 50% theophylline anhydrate produced at different temperatures (a) glyceryl monostearate 65 °C (b) tristearin/ glyceryl monostearate (5+5 w/w) 65 °C (c) tristearin 65 °C (d) tristearin/ glyceryl monostearate (9+1 w/w) 65 °C (e) tristearin 55 °C and (f) tristearin/ glyceryl monostearate (9+1 w/w) 55 °C.