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INFLUENCE OF THERMAL AND THERMO-MECHANICAL TREATMENT
Comparison of two lipids with respect to their suitability for solid lipid extrusion

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Two lipids with similar melting ranges but of different composition were analyzed using differential scanning calorimetry and X-ray diffraction. The lipids were processed via extrusion or were tempered at different temperatures; they were analyzed directly after extrusion and after storage at 40°C. Precirol ATO 5® showed high sensitivity to storage time and varied temperature exposure. Extrusion showed only marginal influences on the solid state. Melting peaks were narrower and shifted to higher temperatures in comparison to the untreated powder. Dynasan 114® was more robust, changes in the solid state could only be shown for samples treated above the melting range. Thus, Dynasan 114® is more appropriate for solid lipid extrusion of pharmaceutical products.

Keywords: *acylglycerides, aging lipids, Dynasan 114®, Precirol ATO 5®, solid lipid extrusion*

Introduction

Solid lipids become more and more interesting as natural pharmaceutical excipients for solid dosage forms. Their outstanding properties, the high hydrophobicity and low density, can be utilized to create sustained released matrices, to mask bitter tasting drugs, to solubilize lipophilic drugs or to form floating dosage forms [1–4]. Nevertheless there is still the need of developing manageable and effective preparation methods as well as of analyzing the solid state characteristics of lipids. Changes in the solid state, by effects of temperature, pressure or aging, should be understood and well controllable as they may influence drug release characteristics of lipid dosage forms. Few studies have been carried out on thermal characterization of commonly used pharmaceutical lipids and the influence of preparation conditions [5–9]. Solid lipid extrusion is a preparation method combining mechanical and thermal treatment. Lipids are processed below their melting ranges, with the effect of conserving solid lipid structures within the matrix.

Two different lipids, Precirol ATO 5®, a heterogeneous lipid mixture with glyceryl palmitostearate as principal content and Dynasan 114®, a homogeneous lipid, containing more than 90% glyceryl trimyristate, were central focus of the present study. Lipids were treated thermally and thermo-mechanically by extrusion and were afterwards analyzed using differential scanning calorimetry (DSC) and X-ray diffraction. Powdered lipids were tempered at different temperatures and they were extruded at different temperatures below their melting ranges. The untreated powders and extrudates were stored at an elevated temperature of 40°C.

The aim of the study is to compare the two lipids with respect to their suitability for solid lipid extrusion in terms of physical stability.

Experimental

Materials

Following materials were used as received: glyceryl palmitostearate powder (Precirol ATO 5®) and glyceryl dibehenate powder (Compritol 888 ATO®) from Gattefossé GmbH, Weil am Rhein, Germany, glyceryl trimyristate powder (Dynasan 114®), a powdered hardfat based on hardened soya oil (Dynasan 120®) and a powdered hardfat based on hardened palm oil (Dynasan P60®) from Sasol GmbH, Witten, Germany.

Methods

Extrusion

Powdered lipids of different chemical compositions were fed from a gravimetric dosing device into the

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barrel of a twin-screw extruder (Mikro 27GL-28D, Leistritz, Nürnberg, Germany) with a feed rate of 40 g min^{-1}. They were extruded at a constant screw speed of 30 rpm through a die plate with 23 dies of 1 mm diameter and 2.5 mm length. Different samples were obtained after extrusion at five different temperatures below the melting range of the lipids. Extrusion temperature was adjusted by tempering the different cylinder segments at the same temperature.

Tempering of the lipids

For DSC measurements tempering of the powdered lipids took place in a DSC apparatus according to a graduated scheme. Samples were heated at the required temperature for 2 min; they were cooled down and stored at 20°C for 30 min. For X-ray measurements the powdered samples were heated for 30 min in a hot air cabinet type UT6060 (Heraeus, Hanau, Germany) and were then stored at 20°C for 30 min. For both methods it was assured that equilibrium was achieved within the tempering period.

Differential scanning calorimetry (DSC) studies

The thermal characteristics were studied with a Mettler DSC 821^e (Mettler Toledo, Giessen, Germany). Powdered lipids were analyzed as received, after different storage conditions and after different tempering conditions. DSC scans were recorded at a heating rate of 5°C min^{-1}. The samples with an initial mass of approximately 5 mg were heated from 20 to 100°C.

X-ray diffraction measurements

X-ray diffraction measurements were carried out with a powder diffractometer Miniflex (Rigaku, Tokio, Japan) with Bragg-Brentano-geometry using CuK_α radiation. Samples were analyzed at an angular speed of 2° min^{-1} in an angle range between 40–3° 2Θ. Powdered lipids were analyzed as received, after different storage conditions and after different tempering conditions.

Results and discussion

In the course of establishment of solid lipid extrusion as gentle preparation method for lipids, the solid state characterization became of central interest in these investigations. Initially different lipids were stored at 40°C and were analyzed using DSC measurements. All lipids showed an increase of melting enthalpy with storage time (Fig. 1), mostly going along with a shift of melting peaks to higher temperatures. In further experiments the main focus laid on the solid state analysis of two very distinct lipids (Table 1), Dynasan 114®, which showed only slight changes in melting enthalpy after storage and on Precirol ATO 5®, which showed rather high changes in melting enthalpy, especially during the first 100 days of storage.

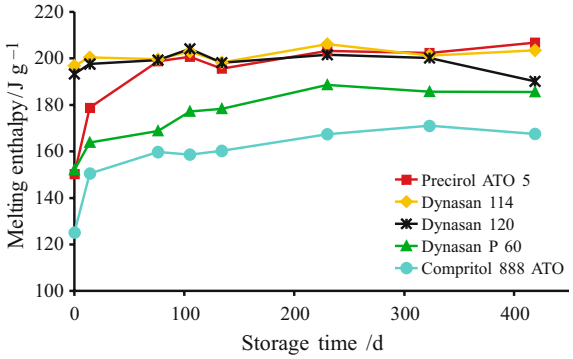

Fig. 1 Melting enthalpy (DSC) of five different lipids after storage at 40°C

Table 1 Properties of different lipids

	Precirol ATO 5®	Dynasan 114®
Fatty acids	stearic acid palmitic acid	myristic acid
Composition	25–35% triester 40–60% diester 8–22% monoester	>90% triester
Melting range	53–57°C	55–58°C

In a tempering study the effect of exposure to different temperatures was analyzed in order to obtain information about the sensitivity of the solid state to the temperature degree and especially the kind of solidification after partly melting of the lipid substance. The central question is whether there is an influence of the conserved solid structures on the recrystallization of the melt.

Melting of the untreated Dynasan 114® powder occurred in a narrow temperature range between 50 and 60°C with a peak maximum at 58.5°C. Accordingly thermal treatment of up to 56°C did not lead to significant changes in the solid state of the lipid (Figs 2 and 3). Exceeding a temperature of 58°C, tempering led to melting of the lipid with further solidification and significant changes in the solid state. In DSC curves the α-polymorphic form could be detected with a melting point at 32.5°C. The subsequent two exothermal peaks indicated the transformation from the α- to the β′-polymorphic form and from the β′- to the β-polymorphic form, which lastly melted at 58°C [10]. X-ray measurements showed the same trend, exceeding 58°C the formation of a so-called layered structure at 21.8° [11] could be detected (Fig. 3).

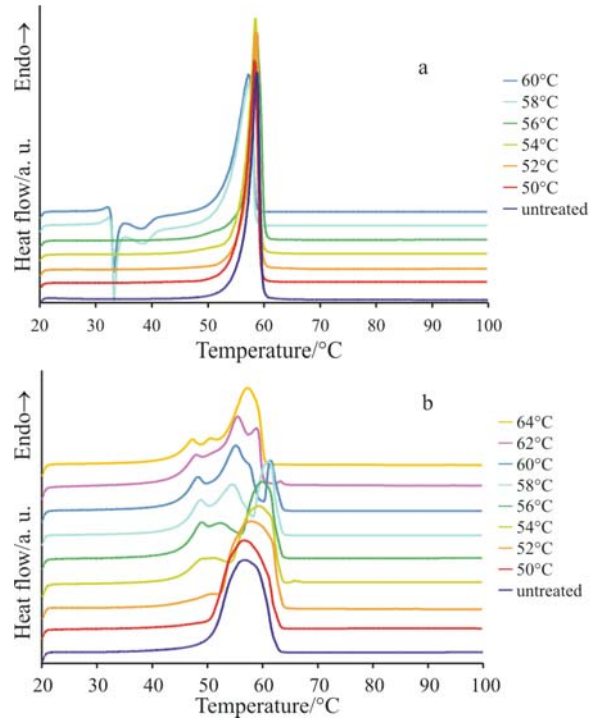

Fig. 2 DSC measurements of a – Dynasan 114® and b – Precirol ATO 5® after different tempering conditions

Due to its diverse composition untreated powdered Precirol ATO 5® showed instead a broad melting range between 40 and 64°C. The detected DSC curves showed a strong dependency on the exposed temperature (Fig. 2). Multidomain structures could be observed in DSC curves due to the high diversity of the lipid composition. Obviously a partly melting of the lipid compounds took place after single tempering procedures wherever no tendency was observed according to the melting behaviour of the new solidified structures. Even at tempering temperatures below a complete melting the formation of new peaks occurs. The melting behaviour of Precirol ATO 5® is strongly dependent on tempering conditions. In X-ray measurements temperature dependent changes could be detected up to a tempering temperature of 58°C; at 60°C a complete loss in structure could be observed (Fig. 3). Changes in the solid state of Precirol ATO 5® after thermal treatment led to low melting structures that melt at temperatures down to 47.5°C. This phenomenon could influence the characteristics of the final solid dosage forms. The storage stability can be affected and in consequence the dissolution profile.

In contrast, the variation of extrusion conditions led to different results; the interaction of multiple effects, like temperature exposure, shear forces and pressures of up to 2.5 MPa, make the process more complex than the simple heating of a lipid sample.

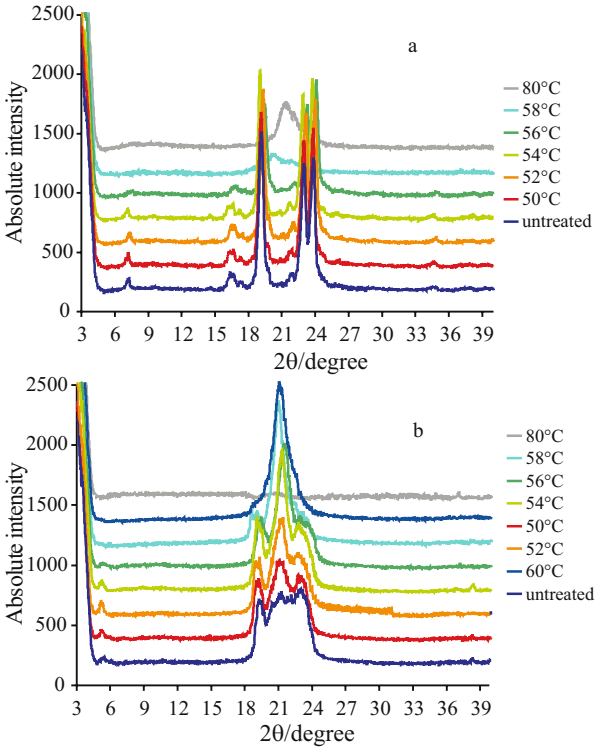

Fig. 3 X-ray measurements of a – Dynasan 114® and b – Precirol ATO 5® after different tempering conditions

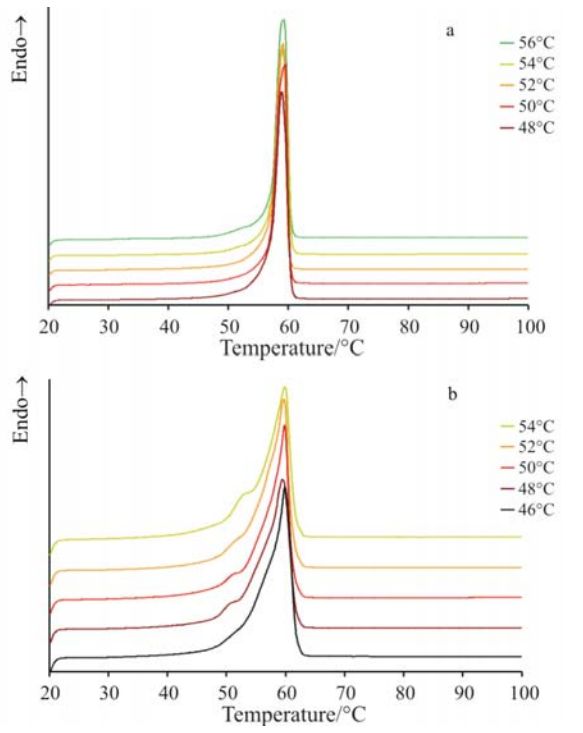

Fig. 4 DSC measurements of a – Dynasan 114® and b – Precirol ATO 5® after different extrusion conditions

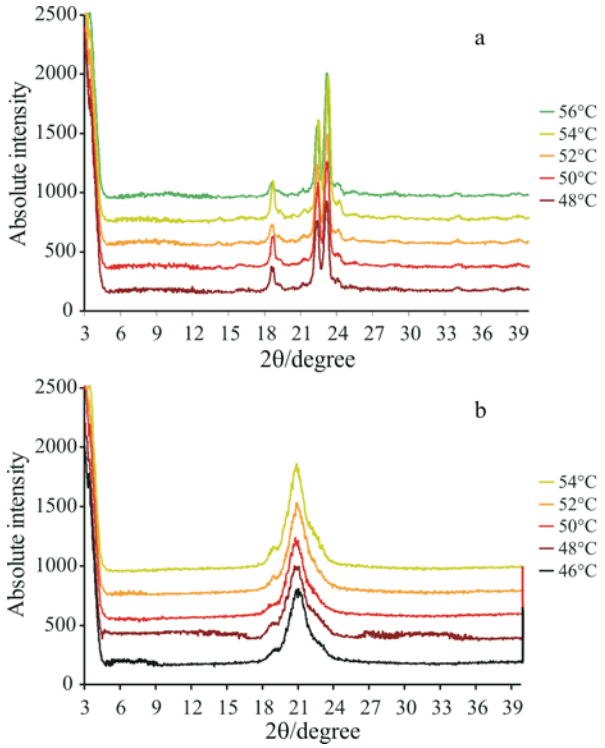

Fig. 5 X-ray measurements of a – Dynasan 114® and b – Precirol ATO 5® after different extrusion conditions

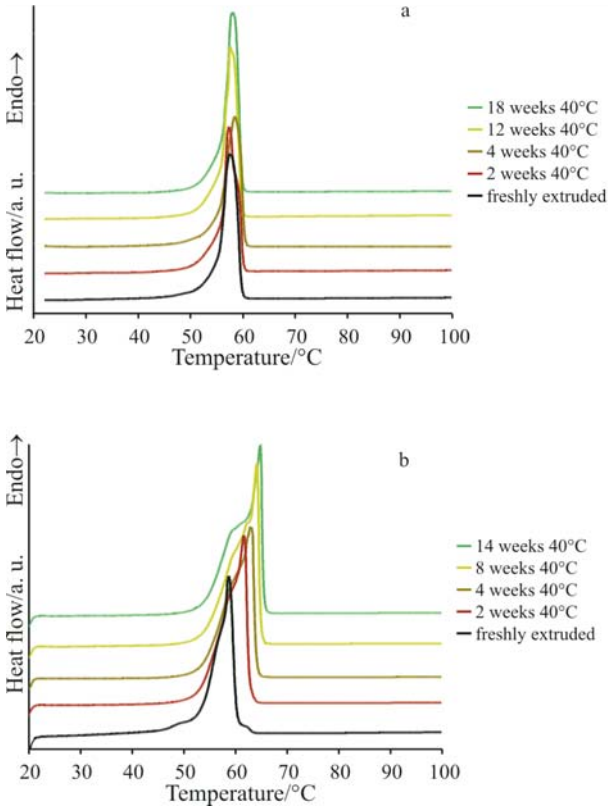

Fig. 6 DSC measurements of extrudates of a – Dynasan 114® and b – Precirol ATO 5® after different storage periods at 40°C

For Dynasan 114® it can be concluded that extrusion led to a narrower melting peak with a shift to higher temperatures (Fig. 4), so that the new melting peak maximum was located at approximately 59°C. At an extrusion temperature of 56°C the formation of an endothermic peak became apparent at 52.5°C. X-ray diffraction diagrams showed differences to the untreated powder, as the diffraction peaks at 7.2 and 16.5° disappeared completely and the main peaks were shifted (Fig. 5). The diffractograms of the extrudates were very similar, independent from the temperature during extrusion.

DSC measurements of Precirol ATO 5® showed conspicuous results in comparison to the tempered material. Five different extrusion temperatures, which were provided below the melting peak of the lipid, had comparable effects on the melting behaviour of the freshly extruded material (Fig. 4). The resulting extrudates showed relatively narrow melting peaks with a maximum at 59.5°C. With increasing extrusion temperature a small melting shoulder at 50–53°C became more distinctive. The formation of this lower melting fraction seemed to be the consequence of partly melting of the lipid mass. Loss in structural order, changes in the polymorphic form or eutectic effects may be the reason for the new melting behaviour. In the same way also the X-ray measurements gave results which were independent from the extrusion temperature, although indicating an entire change in the solid state during extrusion compared to the thermally treated lipid (Fig. 5).

A stability study was conducted to find out whether storage at 40°C had an influence on the solid state of the extruded lipids, measured by DSC. Extrudates made from Dynasan 114® remained almost stable under chosen conditions while extrudates of Precirol ATO 5® tended to important changes in their melting behaviour (Fig. 6). There was an obvious shift of the melting peak to higher temperatures, which was not completed in within a storage period of up to 14 weeks at 40°C.

Conclusions

Extrusion of solid lipids below their melting ranges led to changes in the solid state of the lipids. Large differences were found between the two tested lipids. The solid state of Dynasan 114®, a triglyceride with a narrow distribution of fatty acids, remained stable after different pre-treatments below its melting range and after storage. The solid state characteristics of Precirol ATO® showed a high sensitivity towards changes in pre-treatments below its melting range and during storage. This can be attributed to the more heterogeneous composition of the lipid. Due to its better

physical stability Dynasan 114® is more appropriate for solid lipid extrusion of pharmaceutical products.

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