Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 67 (2007) 440–448
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Solid lipid extrusion of sustained release dosage forms

Claudia Reitz, Peter Kleinebudde *

Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany

Received 18 August 2006; accepted in revised form 8 March 2007
Available online 16 March 2007

Abstract

The applicability of the solid lipid extrusion process as preparations method for sustained release dosage forms was investigated in this study. Two lipids with similar melting ranges but of different composition, glyceryl palmitostearate (Precirol ATO 5®) and glyceryl trimyristate (Dynasan 114®), and mixtures of each lipid with 50% or 75% theophylline were extruded at temperatures below their melting ranges. Extrudates were analyzed using differential scanning calorimetry, scanning electron microscopy, porosity measurements and in vitro drug dissolution studies. The possibility of processing lipids by softening instead of complete melting and without subsequent formation of low-melting, metastable polymorphs could be demonstrated. Extrudates based on formulations of glyceryl palmitostearate/theophylline (50:50) and glyceryl trimyristate/theophylline (50:50) showed sustained release properties.

An influence of extrusion conditions on the matrix structure was shown for extrudates based on a mixture of glyceryl trimyristate and theophylline (50:50). Glyceryl trimyristate tended to solidify in porous structures after melting. Exceeding a material temperature of 50.5 °C led to porous extrudate matrices with a faster drug release. The production of novel, non porous sustained release matrices was possible at a material temperature of 49.5 °C. Extrudates based on glyceryl trimyristate/theophylline (50:50) only slight changes in melting enthalpy and stable drug release profiles.
© 2007 Elsevier B.V. All rights reserved.

Keywords: Solid lipid extrusion; Lipid matrix; Sustained release; Acylglycerides; DSC

1. Introduction

Solid lipids are advantageous pharmaceutical excipients being low cost, natural and biodegradable products with physiological, non-toxic properties. They are commonly used as lipid matrices with a variety of different functions, that lead to: (1) sustained release of highly soluble drugs, (2) enhancement of bioavailability of poorly soluble drugs, especially with solid dispersions [1], (3) taste masking of bitter tasting drugs [2], (4) floating of dosage forms [3,4] and (5) a decrease of the effect of drugs having gastric irritant properties [5]. Many studies have reported the use of lipids for sustained release matrices [6–12].

The major disadvantage when using lipids in pharmaceutical formulations is the instability of their physical properties during storage. Lipid aging may lead for example to an increase of melting ranges, an increase of melting enthalpy, formation of pores in the surface [3], changes in rheological properties and a decrease in tensile strength [13].

Aging of lipids going along with changes of physical properties is of great significance for sustained release dosage forms, as they contain large doses. A number of studies have demonstrated that lipid matrices may exhibit a change in drug release properties after storage [3,11,13–16]. Moricout et al. [17] reported changes in the melting properties of Gelucires and correlated them to changes in dissolution of incorporated drugs. San Vicente et al. [18] stored different lipid matrices with salbutamol sulphate at room temperature for one year and noticed a decrease in drug release for Gelucire 35/10 and 48/09.

* Corresponding author. Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Universitaetsstr.1, 40225 Duesseldorf, Germany. Tel.: +49 211 81 14220; fax: +49 211 81 14251.
E-mail address: Kleinebudde@uni-duesseldorf.de (P. Kleinebudde).

0939-6411/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2007.03.008

Sutananta et al. [19] observed an increase in theophylline release for Gelucire 55/18 and 50/13 matrices during storage. Capsules filled with Gelucire 50/02 and 62/05 were stored at different temperatures up to 50 °C. An increase in dissolution of the highly soluble drug was observed after 3 months [20]. In vitro 50% Ketoprofen release from mixtures of Gelucire 50/13 and 50/02 decreased after 28 days storage at 30 °C [21].

The most common preparation methods for lipids are: (1) liquid filling of hard gelatine capsules, (2) hot melt extrusion [12,22], (3) spray-congealing using ultrasound [23], (4) production of tablets by melting or compression and (5) melt granulation.

In most cases the preparation process involves melting of the lipids followed by some method of solidification. On the other hand, it was demonstrated that lipids could be extruded at temperatures below their melting ranges [24,25]. It is common knowledge that the generation of different lipid polymorphic forms is strongly dependent on the presence of nucleating agents [26]. It is also suggested that mechanical treatment, e.g. grinding, accelerates the crystallization of tricaprin, as could be demonstrated by X-ray diffraction [27].

Therefore, the purpose of this work was to obtain physically stable sustained release matrices, prepared by solid lipid extrusion. It represents a production process at preferably low temperatures, in which lipids were treated clearly below their melting ranges. A thermomechanical treatment by moderate pressure and temperature exposure results in plastic mouldability of the lipid mass under conditions of conserving nucleating agents.

In order to prove the applicability of the solid lipid extrusion process at low temperatures, two commercially available powdered lipids were extruded below their melting ranges. The aim of the study was to compare two lipids with different composition, but similar melting range: glyceryl palmitostearate and glyceryl trimyristate were chosen for this purpose. The two lipids possess different constituents and structures which allow the generation of broad information about the dependency between the observed results and the lipid composition. The effect of solid lipid extrusion on the solid state of the lipids was analyzed. The pure lipids and their mixtures with theophylline were used to determine the effect of extrusion conditions on the physical properties of the lipid matrices. Drug release and melting enthalpy of the obtained extrudates were measured in order to analyze their stability during storage influenced by time, structure and storage conditions.

2. Materials and methods

2.1. Materials

The following materials were used as received, theophylline anhydrous powder from BASF AG, Ludwigshafen, Germany, glyceryl palmitostearate powder (Precirol ATO 5®) from Gattefossé GmbH, Weil am Rhein, Germany, and glyceryl trimyristate powder (Dynasan 114®) from Sasol GmbH, Witten, Germany. Physical properties of the used materials are given in Table 1.

2.2. Differential scanning calorimetry (DSC)

Thermal characteristics of the powdered lipids and extrudates were studied with a Mettler DSC 821e (Mettler Toledo, Giessen, Germany) at defined storage times. DSC scans were recorded at a heating rate of 5 °C/min. Samples with an initial weight of approximately 5 mg were heated from 20 to 100 °C or from 20 to 300 °C.

2.3. Evaluation of extrudates

The extrudates were visually analyzed for any apparent defects: shark-skinning, cracks, hairlines, curling or deformation by melting. The absence of defects gave information about the process conditions of good extrudability.

2.4. Extrusion

Powdered lipids of different chemical compositions or mixtures of these lipids with different amounts of theophylline were fed from a gravimetric dosing device into the barrel of a twin-screw extruder (Mikro 27GL-28D, Leistritz, Nürnberg, Germany) with a constant feed rate of 40 g/min. The mass was extruded through a die plate with 23 dies of 1 mm diameter and 2.5 mm length. They were extruded at a constant screw speed of 30 rpm. Material temperature was measured next to the die plate just before the extrusion step. In experiments carried out for Section 3.1 powdered lipids and lipid/drug mixtures were extruded successively at different cylinder temperatures. At each temperature level the different cylinder segments were tempered at the same cylinder temperature. Process parameters were measured and are elucidated in Fig. 1. In experiments carried out for Section 3.3 extrusion parameters were adjusted as listed in Table 2.

Glyceryl trimyristate was processed above its melting range in one experiment (Section 3.3). For this purpose the extruder was loaded with the lipid/drug mass, the screw

Table 1
Physical properties of the extruded materials (manufacturer's specifications)

	Dynasan 114®	Precirol ATO 5®	Theophylline anhydrous
Melting point	55–58 °C	53–57 °C	272 °C
Particle size	95% <125 μm 2% >250 μm	30–40 μm	~110 μm
HLB	2	2	

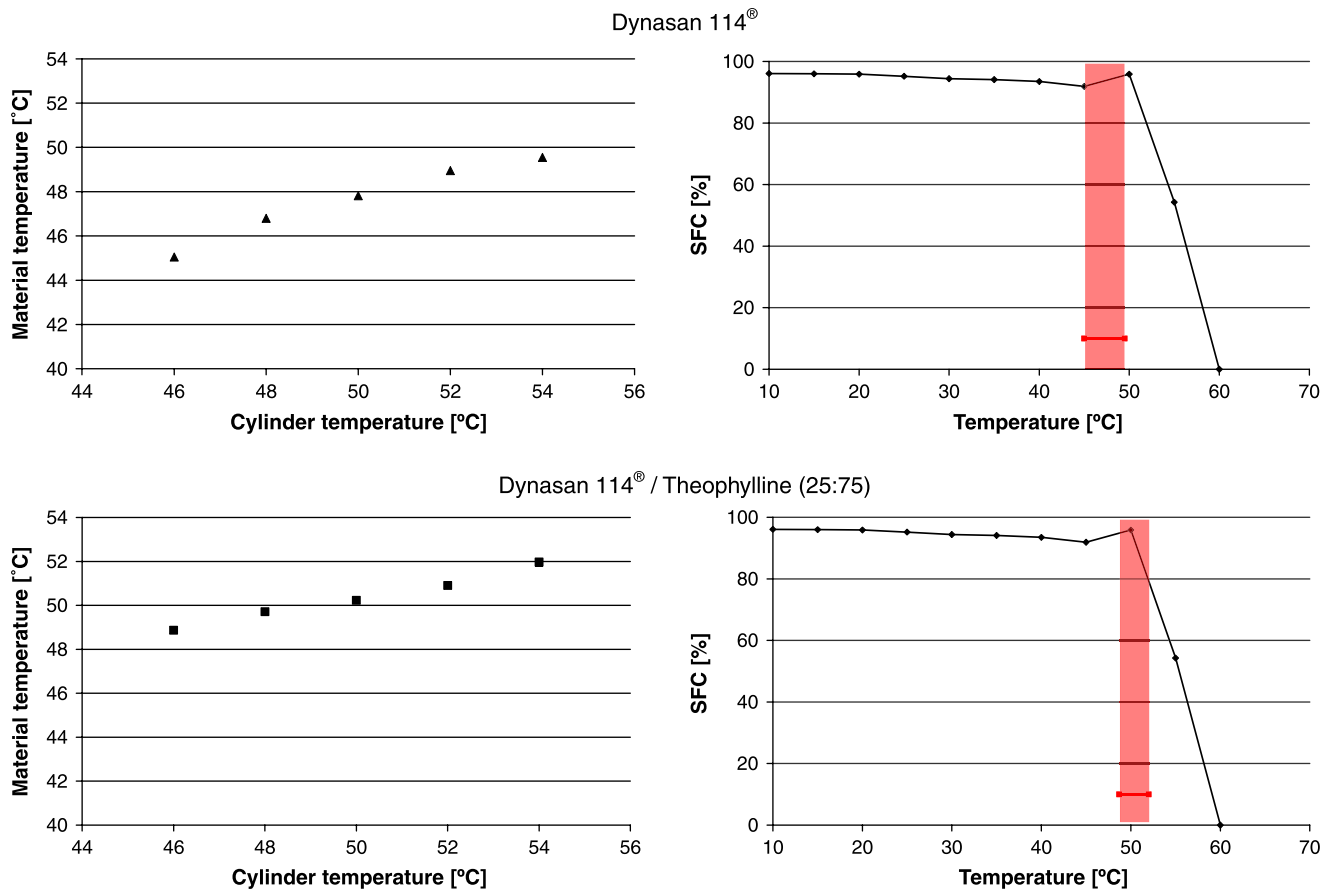
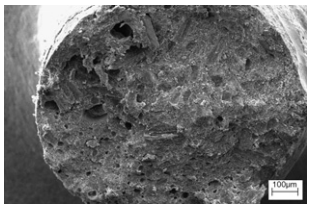
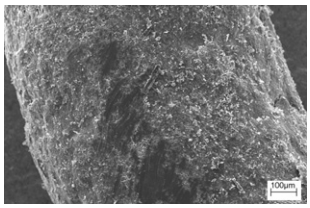
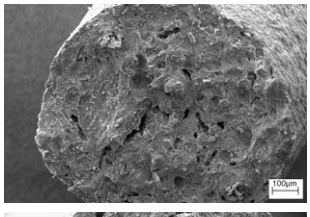
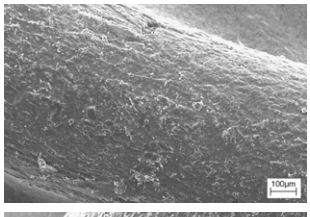
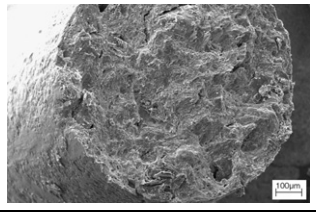
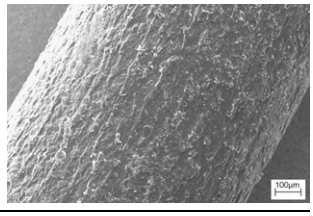


Fig. 1. Correlation between material- and cylinder temperature during extrusion of different Dynasan 114® mixtures (left-hand side) and the correlation between solid fat content and the material temperature range of good extrudability (▮) (right-hand side).

Table 2
Influence of different extrusion parameters on the porosity and structure of Dynasan 114®/theophylline (50:50) extrudates

No.	Material temp. (°C)	Extrusion pressure (MPa)	Porosity ε (%)	SEM picture cross section	SEM picture surface
3.3.1	>55	<0.1	12.6 ± 0.5		
3.3.2	50.5	0.2	6.8 ± 0.7		
3.3.3	49.5	0.5	1.5 ± 1.1		

transport was stopped and the cylinder segments were heated to 100 °C. After a 20 min tempering period the cylinder segments were cooled down to 50 °C and the lipid mass was extruded through the die plate.

2.5. Pycnometric density

Pycnometric density measurements of the extrudates were performed using a Helium-pycnometer AccuPyc™ 1330 (Micromeritics, USA-Norcross) at 25 °C. The extrudates were transferred into a sample chamber of a volume of 10 cm^3 and were flushed tenfold with helium. The particle density was determined as average value of five single measurements.

2.6. In vitro drug dissolution studies

Extrudates were cut to a length of approximately 1cm and analyzed according to USP 29 method 2, in a rotating paddle-apparatus (Sotax AT 7 smart, Sotax, Lörrach, Germany) at 37 ± 0.5 °C and 50 rpm using 900 ml water containing 0.001% polysorbate 20 as dissolution medium. Each sample (80–120 mg) contained about 50 mg of theophylline anhydrous. The amount of drug dissolved was analyzed spectrophotometrically at 242 nm using a continuous flow-through system attached to a UV spectrometer (Lamda 40, Perkin Elmer, Rodgau-Juegesheim, Germany). The dissolution tests were performed in triplicate.

2.7. Mercury porosimeter density

Mercury porosimeter density of the extrudates was determined using a PASCAL 140 mercury porosimeter (Thermo Finnigan Italia S.p.A., Rodano, Italy). A dilatometer (type CD3P) containing a sample of approximately 2 g was evacuated for 15 min. Mercury was filled into the dilatometer. Each batch was analyzed 2–3 times.

2.8. Porosity

Porosity ε of the extrudates was calculated using the following equation:

$$\varepsilon = 1 - (\text{mercury porosimeter density}/\text{pycnometric density})$$

2.9. Scanning electron microscopy (SEM)

Cross sections of the extrudates were optically inspected using a scanning electron microscope LEO VP 1430 (Carl Zeiss NTS GmbH, Oberkochen, Germany). Samples were fixed with conductive silver on brazen specimen holders. Gold sputtering was conducted with an Agar Sputter Coater B7340 (Agar Scientific Ltd, Essex, UK) in overall 12 U intervals consisting out of a 15 s sputtering phase and a 30 s cooling down break. In the microscope samples were tempered at 5 °C; SEM pictures were taken at an operating voltage of 15 ± 2 kV.

2.10. Solid fat content (SFC)

SFC measurements of the lipids were performed using a Bruker Minispec 120 (Bruker, Rheinstetten, Germany). The molten lipids were filled into a test tube and were cooled down to 0 °C. Samples were tempered for a 20 min period at different rising temperatures and were measured with pulsed nuclear magnetic resonance spectroscopy to determine the solid fat content of the lipid at the adjusted temperature.

2.11. Storage stability studies

Samples were hermetically packed and stored at room temperature and at stressed conditions with an elevated temperature of 40 °C. Dissolution studies and DSC analyses were performed after different periods of storage.

3. Results and discussion

3.1. Extrusion of Dynasan 114® and Precirol ATO 5®and their mixtures with 75% theophylline at temperatures below their melting ranges

Cylinder temperatures were modified in order to analyze the extrusion conditions influenced by lipid structure and drug load. Utilizable lipid extrudates should be obtained. Therefore material temperatures had to be high enough to allow the lipid mass to be extruded uniformly through every die of the die plate which was not possible at too low temperatures. Otherwise the lipid mass had to be rigid enough to give compact extrudates; after extrusion through the die plate curling and deliquescence of the extrudate must not occur which were the effects of too high material temperatures.

Powders of pure Dynasan 114® or Precirol ATO 5® and mixtures of each lipid with 75% theophylline could be processed in a twin screw extruder at different cylinder temperatures below their melting ranges (46–54 °C). An equilibration of the material temperature at the die plate was reached after several minutes of extrusion. The correlation between the adjusted cylinder temperature of the extruder and the material temperature at the die plate is illustrated in Figs. 1 and 2.

In experiments with pure powdered lipids the material temperature was always similar to or even clearly smaller than the adjusted cylinder temperature. The shift between both temperatures was the effect of a short residence time of the lipid material in the extruder. Even an extrusion speed of 30 rpm, which results in a residence time of about 2 min, did not allow the material to be thoroughly tempered at the adjusted cylinder temperature. The dependency between both temperatures was shown to be nearly linear. The difference augmented with increasing cylinder temperatures and therefore also with an increase of temperature difference between the raw powder and the cylinder of the extruder. Accordingly more time was needed to

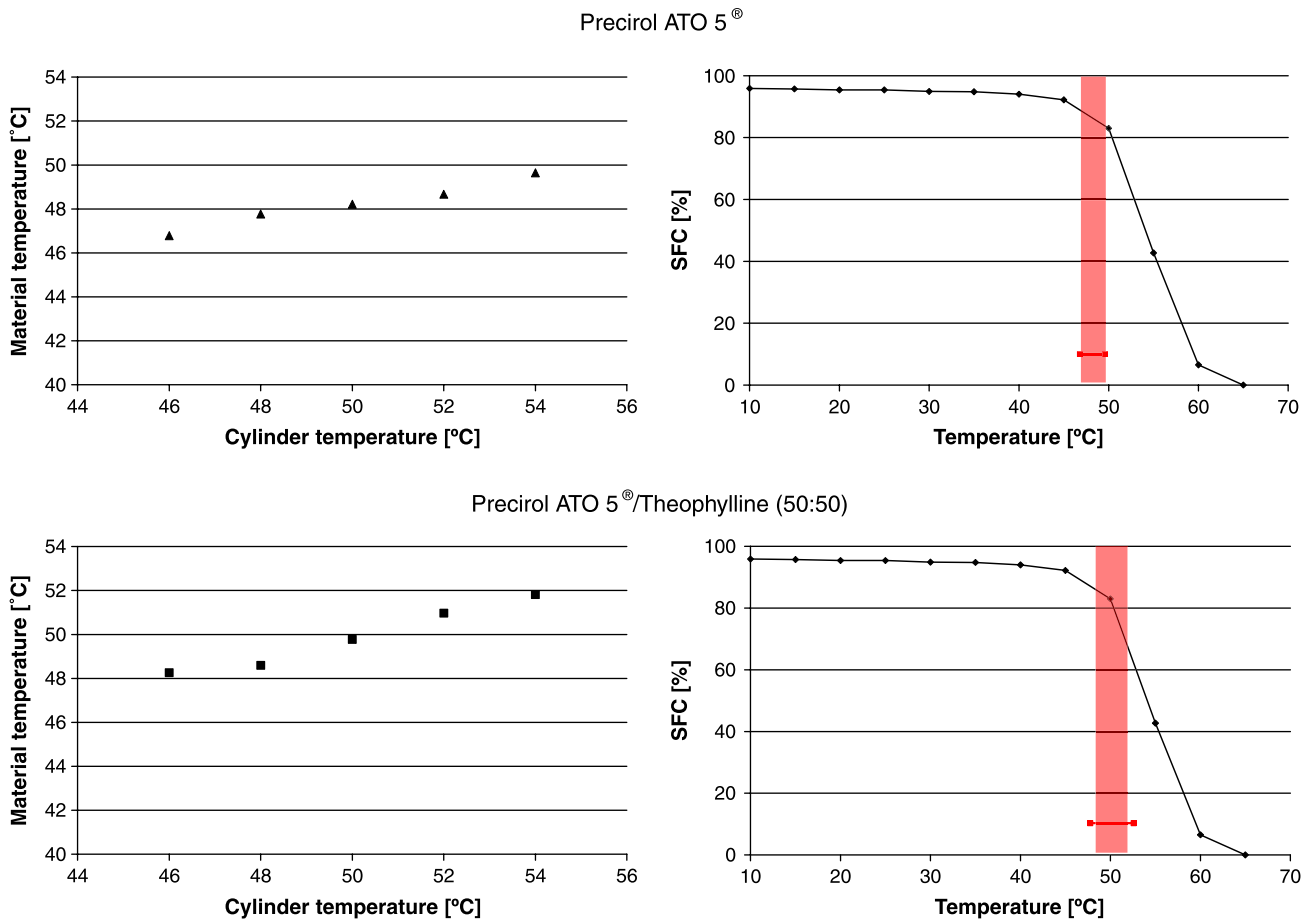


Fig. 2. Correlation between material- and cylinder temperature during extrusion of different Precirol ATO 5® mixtures (left-hand side) and the correlation between solid fat content and the material temperature range of good extrudability (▮) (right-hand side).

temper the material. Comparing both lipids Dynasan 114® and Precirol ATO 5® it can be concluded that Precirol ATO 5® was tempered to higher temperatures during the extrusion step. This could be due to the heterogeneous composition and possibly a better heat transmission of the low melting liquid amount in the material. Extrusion took place at solid fat contents of over 80%. Under the same experimental settings Dynasan 114® was extruded at higher solid fat contents of over 90%.

The effect of a high drug load on the extrudability was analyzed in a further experiment. For this purpose the powdered lipids were mixed with 75% of theophylline powder as model drug. Again, the material temperature was measured in dependence of the adjusted cylinder temperature. Drug amounts of 75% theophylline could be processed without any restrictions. At lower temperatures of 46 and 48 °C, material temperatures at the die plate clearly exceeded the cylinder temperature. This increase in temperature was supposed to be the result of friction forces between the particles, as theophylline is insoluble in the lipid base and remained solid during extrusion. At higher cylinder temperatures above 50 °C the material temperature remained below the adjusted temperature again. Friction effects only seemed to be relevant at low temperatures in mixtures with small amounts of softened lipid. During extrusion the solid fat content of Precirol ATO 5® was between 68% and 86% and was lower than in experiments with the pure lipid. In comparison, the solid fat content of Dynasan 114® was higher with 80–95%.

Dynasan 114® was sensitive to extrusion conditions. At low die plate temperatures the mass could not be extruded homogeneously through the dies and the dies were blocked. To circumvent this problem the die plate had to be preheated to a temperature close to the cylinder temperature before extrusion to accelerate the achievement of the equilibrium temperature. A constant and homogeneous extrudate was obtained by this measure.

Optical evaluation of the extrudates led to the conclusion of having the best extrusion conditions at material temperatures between 48 and 50 °C for the pure lipids and between 50 and 52 °C for the 75% drug loaded mixtures.

3.2. The effect of solid lipid extrusion on the solid state of the extruded lipids

During the extrusion process the extruded lipids underwent mechanical and thermal stress. Stress was mainly

determined by applied heat energy, shear- and friction forces. In most cases stress factors can be controlled and also determined to some extent. They are specific and product dependent. This could be a certain disadvantage in the case of processing thermo- or pressure-sensitive products. Nevertheless, there are many possibilities for investigating and understanding process conditions. On the one hand pressure and temperature of the mass can be determined at the die plate, on the other hand information about the effects of stress exposure can be obtained by analyzing the freshly extruded material. In the present study two different lipids, Dynasan 114® and Precirol ATO 5®, were extruded at different temperatures and were analyzed using differential scanning calorimetry in order to detect changes in the solid state of the lipids. DSC measurements allowed an objective quantification of melting point ranges and also provided data regarding the energy associated with the various transitions [28]. For the investigated lipids a strong dependency between extrusion temperature and resulting melting properties of the lipids after extrusion was observed (Fig. 3).

In the case of Dynasan 114®, a homogeneous glyceryl trimyristate, complete melting led to the formation of the low melting hexagonal α-polymorph at 32.8 °C [29] which could not be observed with lipids being extruded at temperatures up to 54 °C. The observed metastable α-phase underwent transition to the metastable β′-phase and then to the stable β-phase above its melting temperature, as shown in DSC measurement.

With the lipid Precirol ATO 5® a shift of melting peaks to higher temperatures took place at a broad temperature range below the melting range of the lipids. The melting peak got narrower due to the formation of crystal structures with a closer distribution of melting peaks. When the extrusion temperature exceeded a certain value, the formation of a second melting peak at lower temperatures could be observed. This was caused by partly melting of the lipid mass and recrystallization of lower melting crystal structures. When melting both lipids at temperatures clearly above their melting ranges the formation of a melting peak at low temperatures could also be observed. This in fact tended to undergo transitions to higher melting crystal structures during storage.

In addition, the effect of drug loads of 75% on the solid state of the lipids and on the solid state of theophylline was

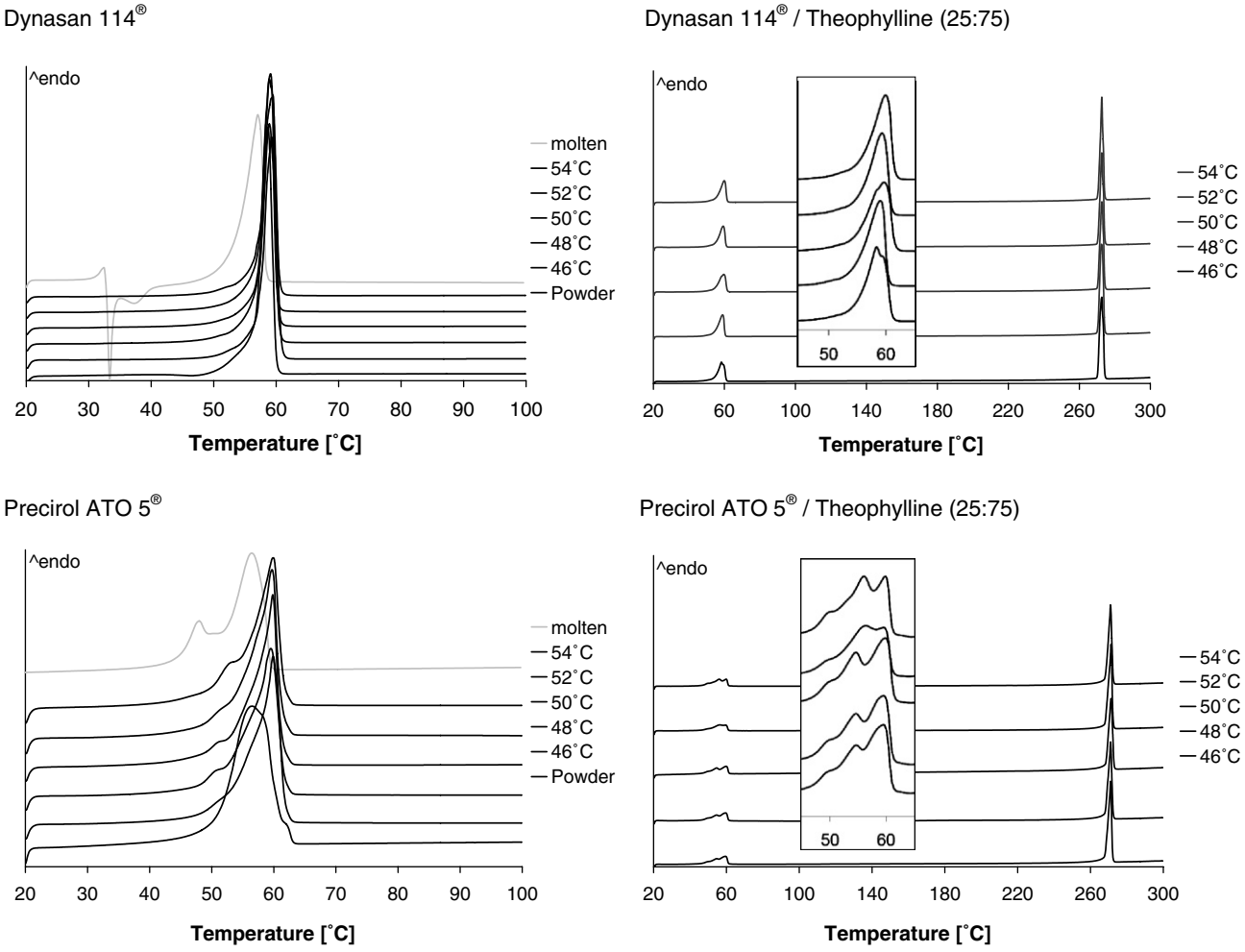


Fig. 3. DSC measurements of untreated lipid powders, of melted lipids and of lipid extrudates after extrusion at different temperatures.

analyzed (Fig. 3). The melting properties of Dynasan 114® were not influenced by changes of temperature or changes of the drug load. The theophylline peak was not affected by different extrusion temperatures either.

Thermal characteristics of Precirol ATO 5® instead were influenced by changes of the cylinder temperature. At lower temperatures the melting peak was similar to the peak of the pure lipid extrudate, but the high drug load led to higher material temperatures during extrusion with the effect of higher amounts of the molten lipid (Figs. 1 and 2). This could be seen in an increase of the lower melting peak after extrusion at 52 and 54 °C cylinder temperatures.

3.3. The effect of different extrusion temperatures on matrix porosity and drug release of Dynasan 114®/theophylline (50:50) extrudates

Dynasan 114® contains more than 90% glyceryl trimyristate. The melt of glyceryl trimyristate solidifies in a way becoming white and clouded [29]. This change of color is the effect of recrystallization going along with an increase in volume and porosity. This increase in porosity after melting was used as indicator for the amount of molten lipid during extrusion at different temperatures. For this purpose a mixture of Dynasan 114® and theophylline (50:50) was mixed and extruded at three different temperatures. The effect of temperature exposure on the solid state of the lipid/theophylline mixture during extrusion was analyzed using drug release studies, scanning electron microscopy and porosity measurements of the lipid matrices (Table 2 and Fig. 4). In the first case, extrusion of the lipid/drug mixture was carried out at temperatures above the melting range of Dynasan 114®. The obtained extrudates tended to curl after passing through the die plate; they were white colored and showed a porous surface structure. In porosimetry measurements a porosity of 12.6% could be determined. In drug release studies these extrudates showed the fastest drug release of all analyzed extrudates, 80% of the drug was released after less than 8 h. Extruding lipid/drug mixtures at material temperatures of approximately 50.5 °C, about 7.5 °C below the melting point of the lipid, resulted in extrudates of higher transparency. Porosities of 6.8% could be determined and drug release studies showed slower drug release profiles. Drug release of 80% of the drug took more than 15 h. Extrusion at even lower temperatures, at a material temperature of 49.5 °C, produced extrudates with porosities below 2%. Accordingly, drug release studies showed profiles of the slowest drug release in this study, 80% of the drug was released in more than 30 h. In SEM pictures an increase of pores could be seen for the extrudates prepared at higher temperatures. Pores seemed to be of diverse size and structure and are irregularly distributed in the matrix (Table 2). It could be shown for this experiment that particular melting of the extruded lipid took place at a material temperature above 49.5 °C. By increasing the material temperature slightly from 49.5 to 50.5 °C the porosity increased from 1.5% to 6.8%. These results could be correlated with SFC measurements, in which the solid fat content decreased abruptly at temperatures exceeding 50 °C, due to particular melting of the solid lipid. It could be demonstrated that solid lipid extrusion is a suitable preparation method for glyceryl trimyristate. It was possible to obtain sustained release matrices of low porosity which cannot be produced by techniques in which lipids have to be melted.

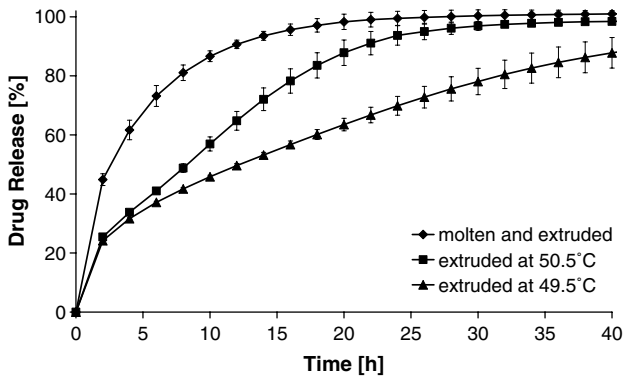


Fig. 4. Drug release of Dynasan 114®/theophylline (50:50) extrudates, processed at different extrusion temperatures, $n = 3$.

The observed interaction between extrusion temperature and matrix porosity based on special properties of glyceryl trimyristate cannot be correlated to earlier studies conducted in order to determine the influence of lipid preparation conditions on drug release properties [7] and [30].

3.4. Storage stability studies of Dynasan 114®/theophylline (50:50) and Precirol ATO 5®/theophylline (50:50) extrudates

Mixtures of Precirol ATO 5® or Dynasan 114® with theophylline were extruded below the melting range of the lipids. The obtained extrudates were stored at an elevated temperature of 40 °C, which is about 15 °C below the melting range of the lipids. Studies were performed in order to determine long term changes, influenced by higher temperatures. Drug release and melting enthalpy were determined at different storage times in order to analyze their stability during the storage influenced by time and structure.

Precirol ATO 5®/theophylline (50:50) extrudates showed changes in drug release after long storage periods (Fig. 5). In the first eight days drug release slowed down. After 9 months of storage a remarkable increase of the drug release rate could be measured. This conflictive drug release behaviour is supposed to be an effect of different aging processes within the lipid matrix. Aging of the lipid matrix seemed to be a heterogeneous process. The observed changes in drug release were accompanied by a remarkable increase in melting enthalpy of the extruded matrix (Fig. 6). DSC studies demonstrated that melting enthalpy increased by more than 40% during the storage at 40 °C for about

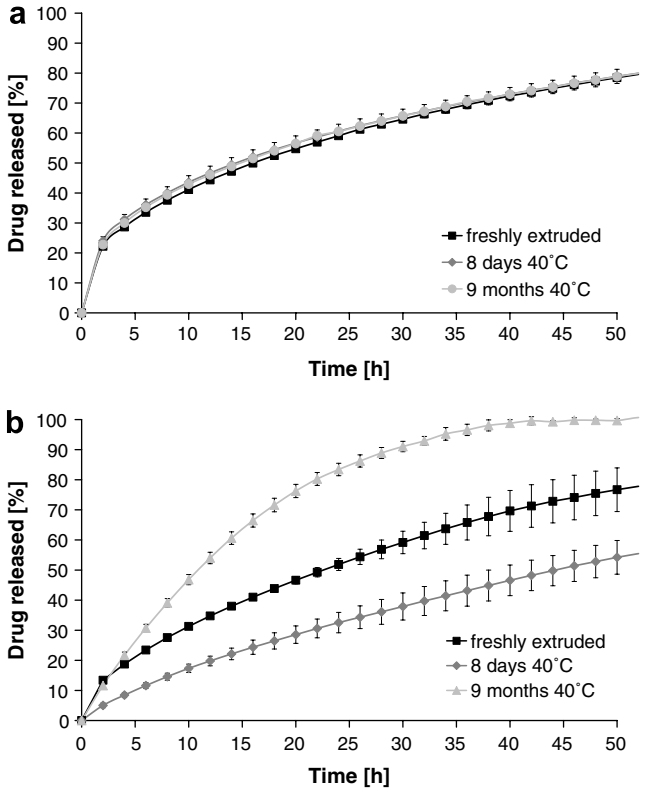


Fig. 5. Drug release studies after storage: (a) Dynasan 114®/theophylline (50:50) extrudates; (b) Precirol ATO 5®/theophylline (50:50) extrudates, $n = 3$.

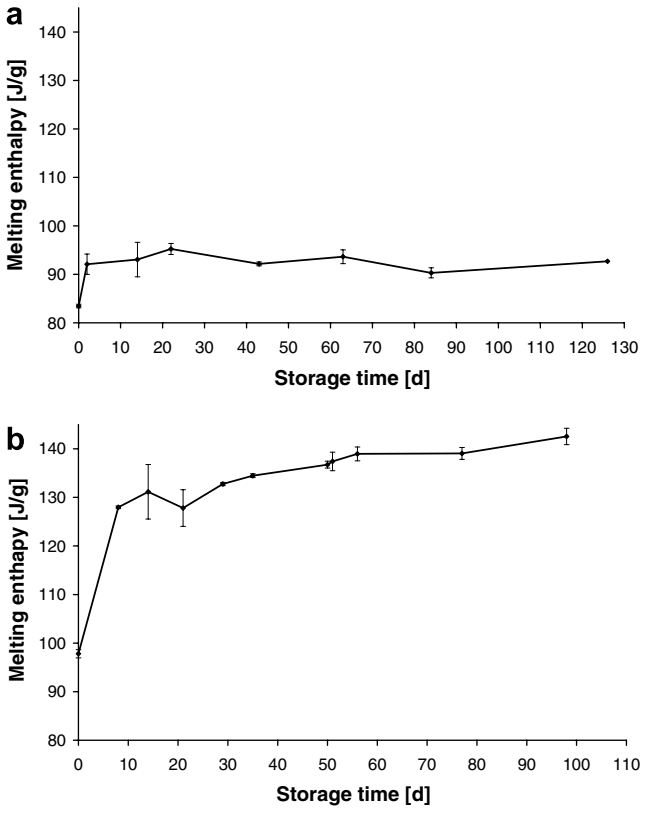


Fig. 6. DSC measurements after storage at 40 °C: (a) Dynasan 114®/theophylline (50:50) extrudates; (b) Precirol ATO 5®/theophylline (50:50) extrudates.

100 d. The major increase of melting enthalpy happened during the first days of storage.

Extrudates of glyceryl trimyristate (Dynasan 114®) and theophylline (50:50) were stored at 40 °C. Drug release was analyzed 8 d and 9 months after extrusion and was compared with the release profile obtained one day after extrusion (Fig. 5). For both storage periods the drug release properties remained stable and significant changes in drug release kinetics could not be observed. The stability of drug release properties went along with small changes in the melting enthalpy during storage. In DSC measurements there was no relevant change in melting enthalpy after more than three months of storage at 40 °C (Fig. 6).

4. Conclusions

Solid lipid extrusion represents a manufacturing technique for sustained release dosage forms at preferably low temperatures. Lipids of different composition can be extruded at temperatures below their melting ranges at solid fat contents of approximately 80–90%. The effect of solid lipid extrusion on the melting properties of the lipids is smaller in comparison with the effect of thorough melting of the lipids. Lipid extrudates with drug loads of 75% can be obtained at broad temperature ranges. Extrusion conditions can have an effect on the lipid matrix structure and on drug release properties. This could be demonstrated for glyceryl trimyristate/theophylline extrudates, in which matrix porosity and drug release rate decreased with decreasing extrusion temperatures. In stability studies lipids of heterogeneous composition showed long crystallization periods even under promoted conditions at 40 °C. More homogeneous lipids instead tended to crystallize faster after extrusion and showed constant drug release properties.

Acknowledgements

The authors thank Gattefossé (Weil am Rhein, Germany) for supplying Precirol ATO 5®, Sasol (Witten, Germany) for supplying Dynasan 114® and BASF (Ludwigshafen, Germany) for supplying theophylline anhydrous powder. The authors also thank Walter Rau AG (Neuss, Germany) for the technical and practical support for solid fat content measurements. Karin Matthée is gratefully acknowledged for her assistance during DSC measurements.

References

[1] B. Chauhan, S. Shimpi, A. Paradkar, Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique, AAPS PharmSciTech 6 (2005).
[2] H. Suzuki, H. Onishi, S. Hisamatsu, K. Masuda, Y. Takahashi, M. Iwata, Y. Machida, Acetaminophen-containing chewable tablets with suppressed bitterness and improved oral feeling, International Journal of Pharmaceutics 278 (2004) 51–61.
[3] B. Chauhan, S. Shimpi, K.R. Mahadik, A. Paradkar, Preparation and evaluation of floating risedronate sodium-Gelucire (R) 43/01 formulations, Drug Development and Industrial Pharmacy 31 (2005) 851–860.

[4] S. Li, S. Lin, Y.W. Chien, B.P. Daggy, H.L. Mirchandani, Statistical optimization of gastric floating system for oral controlled delivery of calcium, AAPS PharmSciTech 2 (1) (2001) E1.
[5] C.W. Pouton, Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification, International Journal of Pharmaceutics 27 (1985) 335–348.
[6] D.Q.M. Craig, Lipid matrices for sustained release: an academic overview, B T Gattefossé 97 (2004) 9–19.
[7] D. Saraiya, S. Bolton, The use of precirol to prepare sustained-release tablets of theophylline and quinidine gluconate, Drug Development and Industrial Pharmacy 16 (1990) 1963–1969.
[8] K. Kumar, M.H. Shah, A.R. Kethar, S.S. Kadam, A. Paradkar, Effect of drug solubility and different excipients on floating behaviour and release from glyceryl mono-oleate matrices, International Journal of Pharmaceutics 272 (2004) 151–160.
[9] S.A. Barker, S.P. Yap, K.H. Yuen, C.P. Mccoy, J.R. Murphy, D.Q.M. Craig, An investigation into the structure and bioavailability of alpha-tocopherol dispersions in Gelucire 44/14, Journal of Controlled Release 91 (2003) 477–488.
[10] M.T. Sheu, A.H.O. Hsia, Polyglycolized saturated glycerides as carrier and enhancer for drug penetration, Chinese Pharmaceutical Journal 53 (2001) 107–111.
[11] J. Hamdani, A.J. Moes, K. Amighi, Development and evaluation of prolonged release pellets obtained by the melt pelletization process, International Journal of Pharmaceutics 245 (2002) 167–177.
[12] W. Prapaitrakul, O.L. Sprockel, P. Shivanand, Release of chlorpheniramine maleate from fatty-acid ester matrix disks prepared by melt-extrusion, Journal of Pharmacy and Pharmacology 43 (1991) 377–381.
[13] W. Sutananta, D.Q.M. Craig, J.M. Newton, The effects of aging on the thermal-behavior and mechanical-properties of pharmaceutical glycerides, International Journal of Pharmaceutics 111 (1994) 51–62.
[14] S. Galal, M.A. El Massik, O.Y. Abdallah, N.A. Daabis, Study of in-vitro release characteristics of carbamazepine extended release semi-solid matrix filled capsules based on gelucires, Drug Development and Industrial Pharmacy 30 (2004) 817–829.
[15] S. Shimpi, B. Chauhan, K.R. Mahadik, A. Paradkar, Preparation and evaluation of diltiazem hydrochloride-gelucire 43/01 floating granules prepared by melt granulation, AAPS PharmSciTech 5 (2004).
[16] W. Sutananta, D.Q.M. Craig, J.M. Newton, Characterization of Gelucire® using differential scanning calorimetry, Workbook Symposium on Pharmacy and Thermal Analysis, Freiburg (1993) 24–25.
[17] A.M. Moricout, D. Gerbaud, C. Brossard, D. Lefort des Ylouses, Gélules á matrice semi-solide de Gélucire Lyodisponibilité et étude structural, S T P Pharma 6 (1990) 368–375.
[18] A. San Vicente, R.M. Hernandez, A.R. Gascon, M.B. Calvo, J.L. Pedraz, Effect of aging on the release of salbutamol sulfate from lipid matrices, International Journal of Pharmaceutics 208 (2000) 13–21.
[19] W. Sutananta, D.Q.M. Craig, J.M. Newton, An investigation into the effects of preparation conditions and storage on the rate of drug-release from pharmaceutical glyceride bases, Journal of Pharmacy and Pharmacology 47 (1995) 355–359.
[20] B. Huet de Barochez, S. Hirvath, A. Cuiné, Formes á libération prolongée présentées en gélules. Comparison microgranules matrice lipophile, B T Gattefossé 82 (1989) 51–59.
[21] A.B. Dennis, S.J. Farr, I.W. Kellaway, G. Taylor, R. Davidson, Evaluation of rapid release and sustained release Gelucire capsule formulations, International Journal of Pharmaceutics 65 (1990) 85–100.
[22] J.P. Liu, F. Zhang, J.W. McGinity, Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion, European Journal of Pharmaceutics and Biopharmaceutics 52 (2001) 181–190.
[23] K. Koga, S. Kawashima, M. Murakami, In vitro and in situ evidence for the contribution of Labrasol (R) and Gelucire 44/14 on transport of cephalexin and cefoperazone by rat intestine, European Journal of Pharmaceutics and Biopharmaceutics 54 (2002) 311–318.
[24] J.F. Pinto, N.P. Silverio, Assessment of the extrudability of three different mixtures of saturated polyglycolysed glycerides by determination of the "specific work of extrusion" and by capillary rheometry, Pharmaceutical Development and Technology 6 (2001) 117–128.
[25] J. Breitkreutz, F. El Saleh, C. Kiera, P. Kleinebudde, W. Wiedey, Pediatric drug formulations of sodium benzoate: II. Coated granules with a lipophilic binder, European Journal of Pharmaceutics and Biopharmaceutics 56 (2003) 255–260.
[26] K. Sato, N. Garti, Crystallization and Polymorphic Transformation: An Introduction, Crystallization and Polymorphism of Fats and Fatty Acids, Marcel Dekker, New York, 1988.
[27] E. Laine, P. Auramo, P. Kahela, On the structural behavior of triglycerides with time, International Journal of Pharmaceutics 43 (1988) 241–247.
[28] W. Sutananta, D.Q.M. Craig, J.M. Newton, An investigation into the effect of preparation conditions on the structure and mechanical-properties of pharmaceutical glyceride bases, International Journal of Pharmaceutics 110 (1994) 75–91.
[29] J.H. Whittam, H.L. Rosano, Physical aging of even saturated monoacid triglycerides, Journal of the American Oil Chemists Society 52 (1975) 128–133.
[30] S. Malamataris, A. Panagopoulou, P. Hatzipantou, Controlled release from glycerol palmito-stearate matrices prepared by dry-heat granulation and compression at elevated-temperature, Drug Development and Industrial Pharmacy 17 (1991) 1765–1777.