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Dissolution from solid lipid extrudates containing release modifiers

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ABSTRACT

The influence of different types of release modifiers on the dissolution from solid lipid extrudates was investigated. Diprophylline was extruded together with 45% tristearin and 5% (w/w) of a release modifier to suitable extrudates. Three groups of release modifiers were defined: Hydrocolloids, disintegrants and pore formers. All of the release modifier-containing extrudates showed a faster release compared to the reference extrudate, which contained 50% (w/w) of each, API and lipid. Increasing the amount of diprophylline in the binary mixture up to 55% (w/w) also increased its release rate. Compared to this new reference, not all of the release modifier-containing extrudates exhibited an increased dissolution rate. Within the group of pore formers, there was a great discrepancy concerning the dissolution rates. Extrudates containing polyethylene glycol (PEG) exhibited a much higher release rate compared with extrudates containing sodium chloride or mannitol. This behaviour was assumed to be based on the extrusion temperature of 65 °C at which PEG exists in the molten state. The hypothesis was tested using different PEGs and another solid lipid.

1. Introduction

Solid lipid extrusion is a suitable technique to manufacture solid dosage forms with defined and stable physical properties (Windbergs et al., 2009a, Breitkreutz et al., 2003, Pinto and Silverio, 2001; Michalk et al., 2008; Reitz and Kleinebudde, 2007). Extrusion temperatures below the melting point of the used lipid ensure a gentle processing, which is especially important for thermolabile APIs. The composition of the blend to be extruded determines the release properties of the substance. Due to their hydrophobic nature lipids have a poor water solubility and wettability, which leads to prolonged dissolution of an incorporated drug (Hamdani et al., 2002). By adding a hydrophilic substance the release kinetics can be modified in different ways. In general this results in an accelerated release rate. Former studies discussed these findings especially for PEG as a readily water soluble substance having pore forming properties (Cleek et al., 1997; Hermann et al., 2007). This kind of preparation offers a wide scope to tailor dissolution profiles. In fact this is valuable to optimize therapy with solid dosage forms. The fraction of the added excipient is one important parameter, which can be used to control the release rate (Windbergs et al., 2009a). But also the chemical and physical properties of a substance contribute to the release rate and its mechanism. Release profiles can also be modified by the use of substances, which have swelling characteristics and expand in contact with water.

Hydrocolloids play an important role in the production of pharmaceutical dosage forms. Not only in semisolids as gel formers or stabilizers, but also in solid dosage forms they have high relevance. Their application varies from forming tablet cores to forming coatings on the surface of tablets. Based on their physical properties, hydrocolloids can be used as prolonging, delaying or just taste masking substances. Placed in a solid dosage form, they can expand their volume in contact with water. This makes them suitable for release enhancement (Ahmed et al., 2010). Using different types of polymers the release rate can be modulated (Baveja et al., 1987). Depending on their molecular weight or viscosity level, respectively, their volume increase can result in a stable gel matrix or in an erodible system. An increase of the viscosity leads to a decrease of the release rate (Huber and Christenson, 1968; Lapidus and Lordi, 1968; Harwood and Schwartz, 1982; Nakano et al., 1983; Daly et al., 1984).

Another group of pharmaceutical excipients are superdisintegrants. These are used to accelerate the disintegration of a solid dosage form before or readily after intake. A rapid rupture of the matrix into smaller particles leads to an increase of the surface, which usually results in an accelerated dissolution of the incorporated drug (Balasubramaniam and Bee, 2009). The general property of a superdisintegrant is a combination of high water affinity and swelling efficiency. Contact with water leads to an intake into the

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dosage form (Quadir and Kolter, 2006). At the same time the disintegrant starts to swell, reaching a volume of maximum swelling. Often disintegrants are water insoluble polymeric compounds with crosslinked structures in the molecule. The degree of crosslinking is the main characteristic, which determines the swelling properties. A small portion of a disintegrant is enough to accelerate the disintegration process substantially. This makes them suitable substances for immediate release dosage forms but they can also be used to modify the dissolution (Yen et al., 1997; Law and Chiang, 1990).

Three groups of excipients, each having hydrophilic properties but with different physical behaviour in contact with water were integrated separately into a solid lipid matrix in a portion of 5%. The aim of this study is to get an insight into the release modifying effects of these excipients and to evaluate their potency. SEM surface images shall give information about changes in the surface morphology during dissolution. By DSC analysis possible changes in the solid state shall be detected. A further aim is to evaluate the influence of different mean molecular weight PEGs/PEOs in order to see a correlation between the molecular weight and the release enhancing effect.

2. Materials and methods

2.1. Materials

The pure powdered monoacid triglycerides tristearin (glycerol tristearate, Dynasan 118®) and trimyristin (glycerol trimyristate, Dynasan 114®), provided by Sasol (Witten, Germany), were used as the solid fat components for the extrusion experiments. Release modification was achieved by different types of substances. On the one hand readily water soluble substances were integrated into the solid lipid matrix. Sodium chloride (AnalaR NORMAPUR sodium chloride, VWR International GmbH, Darmstadt, Germany), mannitol (Pearlitol® 160 C, Lestrem; France) and polyethylene glycols (PEG) (Polyglykol® 1500, 4000, 6000, 10000, 20000 (Clariant, Sulzbach, Germany))/polyethylene oxides (PEO) (Sentry (TM) Polyox (TM) WSR N10-LEO NF Grade, Sentry (TM) Polyox (TM) WSR 303-LEO NF Grade (Dow Chemical Company, Midland MI, USA)) of different mean molecular weights were used as readily water soluble excipients which are expected to leave pores in the matrix. On the other hand cellulose derivates such as hydroxyethylcelluloses (HEC) (Tylose® H 20 P2, Tylose® H 30000 P2, SETylose GmbH, Wiesbaden, Gemany) and hydroxypropylmethylcelluloses (HPMC) (Metolose® 65 SH 50, Metolose® 65 SH 4000, Chemical Co., Ltd., Tokyo, Japan) were used as hydrocolloidal release enhancers. Cross-linked polyvinylpyrolidones of two different mean particle sizes (Kollidon® CL, Kollidon® CL SF, BASF, Ludwigshafen, Germany), croscarmellose sodium (Ac-Di-Sol® SD7 M, FMC Biopolymer, Philadelphia, USA) and sodium starch glycolate (Primojel®, Avebe, The Netherlands) were used as disintegrative release modifiers. Diprophylline base (diprophylline fine powder, BASF, Ludwigshafen, Germany) having a water solubility of 330 g/L was used as a model drug.

2.2. Methods

2.2.1. Blending

Blends of 800 g were prepared in a laboratory mixer (LM 20 Bohle; Ennigerloh, Germany) at 25 rpm for 15 min. The reference extrudates consisted either of a 50%/50% (w/w) ratio of diprophylline and solid fat or a 55%/45% (w/w) (model drug/solid fat) ratio only in case of tristearin. All other blends always consisted of 50% diprophylline, 45% tristearin or trimyristin and 5% of a release modifier.

2.2.2. Extrusion

Extrusion experiments were performed with a co-rotating twin-screw extruder (Mikro 27GL-28D, Leistritz, Nürnberg, Germany). The blend was transferred into a dosing device (KT20K-Tron Soder, Lenzhard, Switzerland) that fed the powder into the barrel of the twin-screw extruder gravimetrically. Setting a powder feeding rate of 40 g min^{-1} and a screw speed of 60 rpm the powder was forced through a die plate containing 23 holes of 1 mm diameter and 2.5 mm length. The temperature of the extrusion process complied with the type of fat used for the extrusion. In the case of tristearin a temperature of 62 °C was kept constant. Using trimyristin 50 °C were appropriate to form suitable extrudates.

2.2.3. Differential scanning calorimetry (DSC)

A DSC 821e calorimeter (Mettler-Toledo, Gießen, Germany) was used to take thermograms of extrudates and pure powders. Approximately 5 mg of the sample was weighed into 40 μL aluminium pans that were completely sealed. Using a heating rate of 10 °C min^{-1} the temperature in the pans was increased from 20 °C up to 250 °C. Each experiment was conducted including two heating cycles.

2.2.4. Dissolution

Dissolution testing was performed in a basket apparatus (Sotax AT7 smart, Sotax, Lörrach, Germany) according to USP 29 method 1. Extrudates of 10 mm length were used for the release measurements. Each vessel contained approximately 50 mg sample. 900 mL of purified water was used as dissolution medium. The experiments were conducted with a stirring speed of 50 rpm and a medium temperature of 37 ± 0.5 °C. For the detection of diprophylline a UV-Vis spectrometer (Lambda 40, Perkin-Elmer, Rodgau-Juegesheim, Germany) at a wavelength of 273 nm was used. The samples were measured in a continuous flow-through cuvette at 5 min intervals. The experiments were performed in triplicate and the mean of the concentration at each time point was calculated for the construction of the dissolution curves. The standard deviations (not shown in the dissolution curves) were below 6% in each case.

2.2.5. Calculation of the similarity factor (f_2)

The calculation of the f_2 values was accomplished according to the FDA's suggestion (Shah et al., 1998) (Eq. (1)).

$$f_2 = 50\log_{10}\left(\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right) \quad (1)$$

In this equation R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the reference and the test product. At least 12 time points were used in form of their mean dissolution values to estimate the similarity factor. Due to its sensitivity to the number of dissolution time points, only one measurement point was considered after 85% release. f_2 values of 50 or higher (50–100) indicate equivalence of the two analysed curves. Thus, a value of lower than 50 ensures a significant difference between these curves.

2.2.6. Dissolution analysis according to Korsmeyer-Peppas model

The mechanism of drug release from extrudates was determined using Eq. (2), the so-called power law (Peppas, 1985):

$$\frac{M(t)}{M_\infty} = k \times t^n \quad (2)$$

where $M(t)$ represents the amount of drug released in time t and M_∞ the total amount of drug released, k a constant, and n the release exponent. $M(t)/M_\infty \leq 0.6$ were used to calculate the release exponent n.

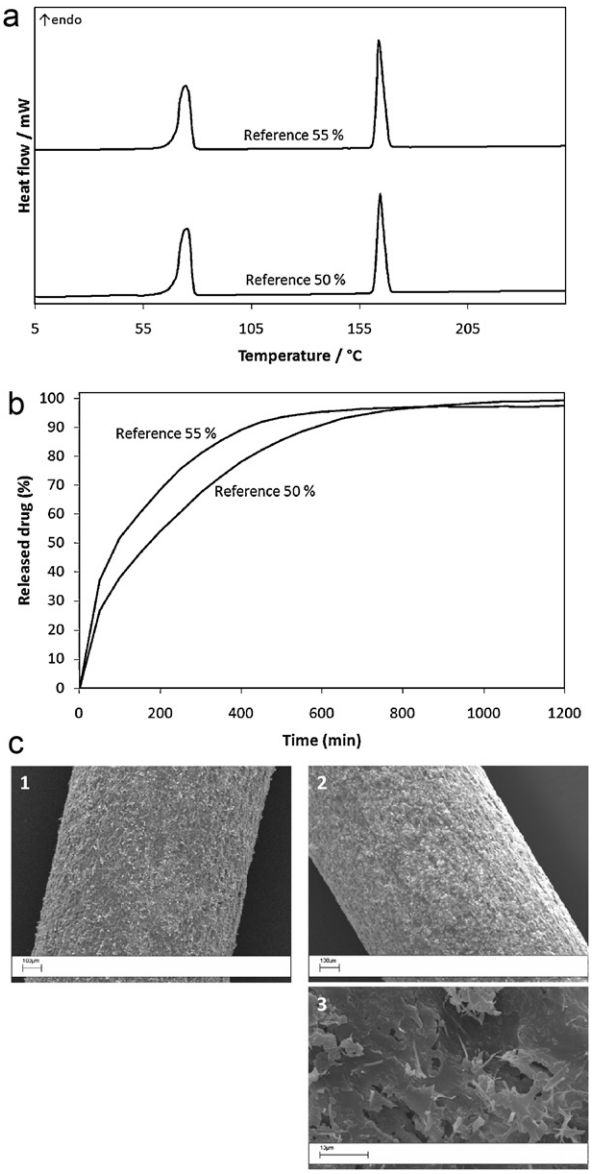

Fig. 1. Physicochemical characterization of the reference extrudates, (a) DSC thermograms, (b) dissolution profiles ($n = 3$, SD < 5% not shown), (c) SEM surface images before (1) and after (2, 3) dissolution.

2.2.7. Scanning electron microscopy (SEM)

A scanning electron microscope (Leo 1430VP, Leo Elektron Microscopy, Cambridge; UK) with a voltage of 18 kV was used to take SEM images. By using a double-sided carbon tape the extrudates were fixed on aluminium discs. Before imaging, the extrudates were sputtered on their surface. This was accomplished by a sputter coater (Agar Manual Sputter Coater B7340, Agar Scientific, Stansted, UK). To prevent any structural damage on the surface of the extrudates due to heat, the sputtering was conducted three times, each for 60 s.

3. Results and discussion

3.1. Solid state characterization and release behaviour of the reference extrudates

Fig. 1a depicts the thermograms of the reference extrudates, one consisting of a 50%/50% (w/w) ratio of diprophylline and tristearin (Reference 50%) and the other consisting of a 55%/45% (w/w) ratio of the same components (Reference 55%). The melting temperatures can be clearly distinguished since the difference is around 100 °C. Tristearin exhibits a melting endotherm at 73.5 °C which is caused by the β-modification of tristearin (onset 70.08 °C). This value is in good accordance to values in the literature (Hagemann, 1988; Van Langevelde et al., 2001). The existence of just a single peak at 73.5 °C verifies the absence of any other detectable polymorphic form of the triglyceride. A thermal processing of triglycerides can lead to a presence of more than one modification at the same time. This is an important aspect concerning the release behaviour of the solid dosage form insofar as different lipid modifications can cause different dissolution profiles. Former studies showed that especially for tristearin an extrusion temperature above the melting temperature of the α-modification (55 °C) is necessary to avoid the forming of the α-modification (Windbergs et al., 2009b). Due to this fact an extrusion temperature of 62 °C was set. The melting endotherm of diprophylline at 164.5 °C (onset 161.8 °C) also correlates to values that can be found in the literature 434 K (160.85 °C) (Wesolowski and Szynkaruk, 2001).

A difference of 5% diprophylline in the solid lipid matrix is clearly evident concerning the release rate (Fig. 1b). Whereas 80% release is reached after 300 min in the case of the reference 55%, the reference 50% needs 430 min for the same release value ($f_2 = 45.1$). The model drug itself acts like a pore former. Similar extrudates were manufactured in former studies with theophylline as a model drug instead of diprophylline (Windbergs et al., 2009b). The release rate of theophylline is not as high as that of diprophylline since its solubility is much lower. In case of theophylline just 45% release were reached after 24 h. The same value is reached by tristearin extrudates containing diprophylline within 2.5 h.

The SEM images (Fig. 1c) let assume that the dissolution happens through pores that are generated by the drug itself. This is visible in the higher magnified Fig. 1c (3). Small pores can be seen which seem to extend into the matrix.

3.2. The effect of 5% of a hydrocolloid in the solid lipid matrix

A substitution of 5% tristearin by 5% of a hydrocolloid does not lead to any shift in the melting temperatures of the drug or fat. The melting endotherms of both are still existent and show the same appearance as in the reference extrudates (Fig. 2a). Glass transition temperatures of the polymers could not be detected by DSC analysis.

On the other hand the release rate is clearly influenced by the presence of a hydrocolloid. In all cases the release rate is increased (Fig. 2b). At most after 120 min nearly 80% drug is released in each case. By contact with water the hydrocolloids accelerate the water intake into the matrix which results in an increased release rate. This effect is a consequence of their property to swell in contact with water. A volume expansion takes place which leads to an opening of the solid lipid matrix. Finally this results in a better wetting of the matrix core beside an increase of the wetted surface. However, there are some differences in the release enhancing effects of the hydrocolloids. There somehow seems to be a correlation of the release rate and the viscosity grade of the cellulose derivative. In both cases, Tylose and Metolose, the derivatives with higher viscosity grades lead to faster release rates (Tylose® H 30000 and Metolose® 65 SH 4000). Former studies about the relation between the viscosity grade and the release rate of cellulose derivative-containing dosage forms showed that an increase of the viscosity grade results in a decrease of the release rate (Baveja et al., 1987; Bhosale et al., 2010). But this is only valid for stable and coherent gel systems that decrease the diffusion of the drug through it. In the present study the hydrocolloids behave conversely. This is due to their low fraction in the matrix. They are not able to form a stable gel matrix. Instead, they swell and finally open the lipid

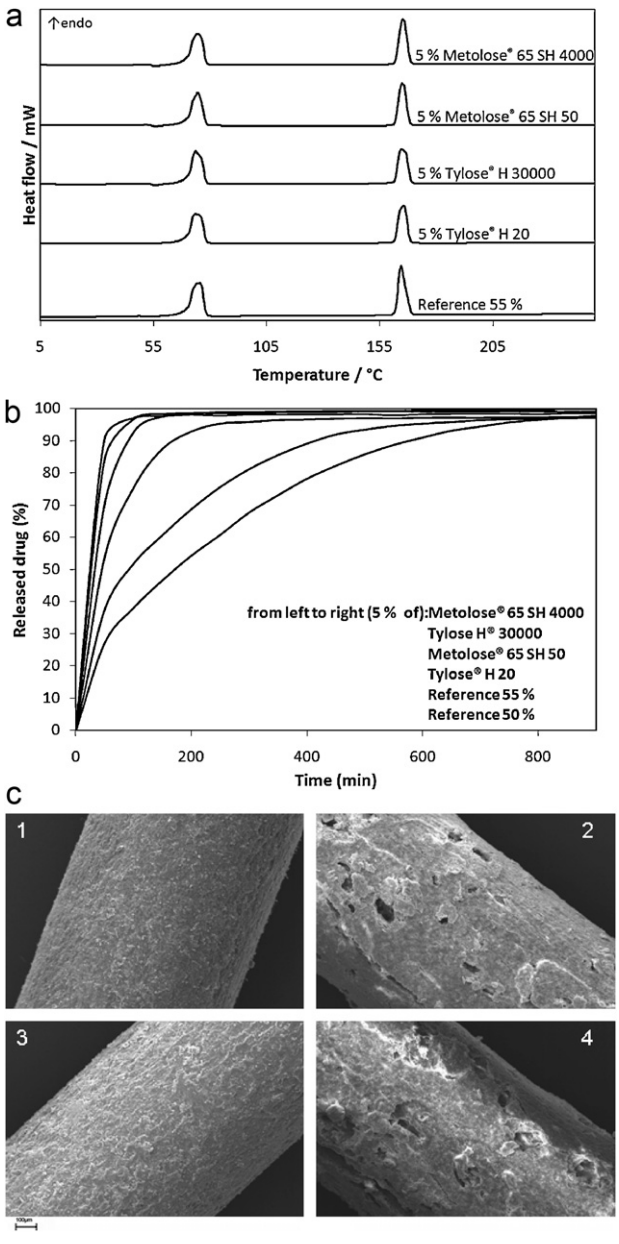

Fig. 2. Physicochemical characterization of extrudates containing 5% (w/w) of a cellulose derivative, (a) DSC thermograms, (b) dissolution profiles ($n = 3$, SD < 4% not shown), (c) SEM surface images of extrudates containing either 5% (w/w) Tylose® H 20 or Metolose® 65 SH 50 before (1, 3) and after (2, 4) dissolution.

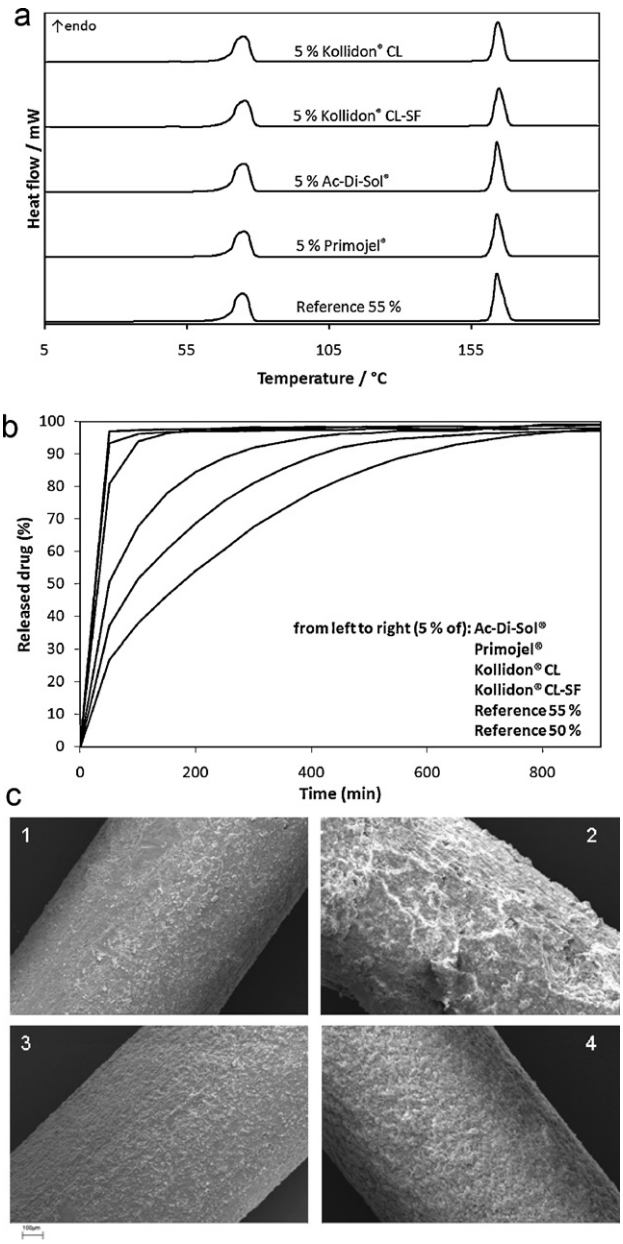

Fig. 3. Physicochemical characterization of extrrudates containing 5% (w/w) of a disintegrant, (a) DSC thermograms, (b) dissolution profiles ($n = 3$, SD < 4% not shown), (c) SEM surface images of extrudates containing either 5% (w/w) Kollidon® CL or Kollidon® CL-SF before (1, 3) and after (2, 4) dissolution.

matrix as a result of their swelling efficiency. This property is much more distinct for hydrocolloids of high viscosity grades. Low viscosity grades do also swell, but their swelling is not strong enough to break down the matrix (Tylose® H 20 and Metolose® 65 SH 50). In these cases only an erosion of the extrudate surface can be seen in Fig. 2c (2+4). The drug seems to be released through bigger larger pores and ruptures that are generated by the low viscosity cellulose derivatives.

3.3. The effect of 5% of a disintegrant in the solid lipid matrix

The extrusion conditions do not lead to any change in the solid state of the extrudates (Fig. 3a). Again the melting endotherms of tristearin and diprophylline appear at the same temperatures as in the reference extrudates. The glass transition of the disintegrants cannot be detected by DSC analysis.

The influence of disintegrants on the release rate of solid lipid extrudates is also pronounced. Especially Ac-Di-Sol®, Primojel® and Kollidon® CL show a very strong effect on the release rate (Fig. 3b). Ac-Di-Sol® and Primojel® lead to full disintegration of the matrix during dissolution within 20 min explaining the high release rates. The high water absorbing property of Ac-Di-Sol® is also characterized in the literature (Bhardwaj et al., 2010; Modasia et al., 2009; Singh et al., 2009). Further Zhao and Augsburger (2005) showed that Ac-Di-Sol® leads to uniform and fine disintegrated particles. The effect of Primojel® was found to be comparable to that of Ac-Di-Sol®. A closer look to the swelling pressures of superdisintegrants underlines the present findings (Quadir and Kolter, 2006). Ac-Di-Sol® and Kollidon® CL have the highest swelling pressures (271 and 171 kPa) followed by Primojel® with a value of 158 kPa. Kollidon® CL-SF on the other hand has a swelling pressure of 22 kPa, which is also an explanation for the absence of a

disintegration, compared to the other disintegrants. These facts state to some extent the release data of the present study. Fig. 3c shows the surfaces of Kollidon® CL and Kollidon® CL-SF-containing extrudates before and after dissolution. In the case of Kollidon® CL the matrix in fact is still intact after dissolution, but the surface is eroded more or less evenly (Fig. 3c (2)). Kollidon® CL-SF has not the same influence. Here the matrix is also still intact after dissolution testing but the surface is smooth (Fig. 3c (4)). Another difference can be seen by the comparison of the extrudate diameters in the SEM images. The extrudate containing Kollidon® CL has a bigger diameter after dissolution whereas the Kollidon® CL-SF-containing extrudate does not show any visible changes. This could be explained by its much smaller mean particle size (17 μm) than that of Kollidon® CL (118 μm) that again correlates with the smaller swelling pressure of Kollidon® CL-SF.

3.4. The effect of 5% of a pore former in the solid lipid matrix

The DSC analysis of pore former-containing extrudates shows no indication of any relevant change in the solid state. Fig. 4a shows the thermoanalytical results. The diagram exhibits two distinctive features compared to the other ones. The DSC curve of the PEG-containing extrudate exhibits a small peak at 62 °C (peak onset 60 °C) below the melting endotherm of tristearin (74 °C). This melting endotherm is due to the melting of polyethylene glycol. The value is in good accordance with literature values (Craig and Newton, 1991). Extrudates containing mannitol as a release modifier show a broader peak at the point of the melting endotherm of diprophylline. This is probably caused by an overlapping of two melting processes, one of the mannitol and the other of diprophylline with an onset at 153 °C. Another explanation could be a generation of a eutectic. Values for the melting temperature of mannitol given in the literature (165 °C) correlate with the findings of the DSC analysis (Telang et al., 2003).

The dissolution data (Fig. 4b) show clear differences in the release modifying behaviour of the pore formers in solid lipid extrudates. In comparison to the reference 55% mannitol increases only slightly the release rate and NaCl not at all. The extrudate containing PEG 10000 behaves completely different resulting in an acceleration of dissolution. 80% release is reached within 100 min compared to the reference 55% which needs around 300 min for the same release. f_2-values were calculated to estimate the significant difference of the release profiles. Values between 50 and 100 ($50 < f_2 < 100$) indicate a similarity between two dissolution profiles, whereas values of 50 and below ($0 < f_2 < 50$) represent significantly different release profiles (Shah et al., 1998). A calculated f_2-value of 23.0 underlines the significance in the difference of the release profile of PEG-containing extrudates to the reference 55%. In contrary, the release profiles of mannitol- or NaCl-containing extrudates do not differ significantly from the dissolution profile of the reference 55% ($f_2 = 83.4$ and 91.7). Probably the polymeric structure of PEG 10000 is the reason for its special behaviour. It forms a coherent structure in the lipid matrix which again increases the water intake. Another explanation might be suitable by analysing the extrusion process itself. The extrusion temperature for tristearin extrudates is 62 °C, which is exactly in the melting range of the PEG. In conclusion one might assume that PEG 10000 exists in molten state during the extrusion process. This results in an increased mobility with the effect, that PEG 10000 is more homogeneously distributed in the extrudate. Finally water can penetrate faster into the extrudate resulting in higher release rates. Surface analysis of the extrudates before and after dissolution does not show any difference of the PEG-containing extrudate compared to mannitol-containing extrudates e.g. (Fig. 4c) so that an explanation for this behaviour has to be found in deeper layers.

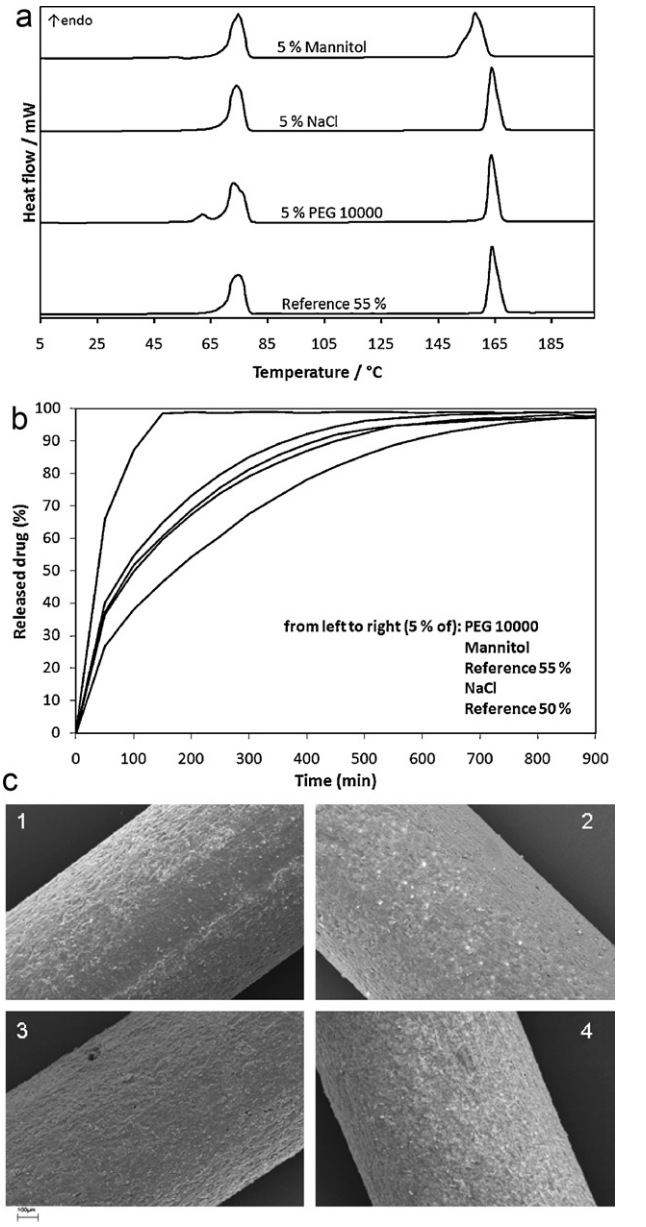

Fig. 4. Physicochemical characterization of extrudates containing 5% (w/w) of a pore former, (a) DSC thermograms, (b) dissolution profiles ($n = 3$, SD < 5% not shown), (c) SEM surface images of extrudates containing either 5% (w/w) PEG or mannitol before (1, 3) and after (2, 4) dissolution.

3.5. Korsmeyer-Peppas equation analysis for release kinetic determination

An evaluation according to the power law (Eq. (2)) derived by Korsmeyer-Peppas was performed in order to determine the type of release. Since the extrudates used in this study were of cylindrical shape, 0.45 and 0.89 for the release exponent n were taken as values indicating release according to the square root of time (0.45) and zero order (0.89), respectively. Values between these two indicate a so-called anomalous transport (Ritger and Peppas, 1987a,b). Table 1 gives an overview of the calculated values for the coefficient of determination (r^2) and the release exponent. The coefficient of determination is close to 1 in each case, indicating a good fit of the release values. A closer look to the release exponents n and the extrudate compositions shows a good accordance between these. If the matrix is stable and does not break or erode during dissolution

Table 1
Dissolution analysis according to the power model.

Composition	R^2	n
Diprophylline/tristearin 50/50%	0.999	0.51
Diprophylline/tristearin 55/45%	0.999	0.45
Diprophylline/tristearin 50/45 + 5% of:		
Tylose® H 20	0.998	0.56
Tylose® H 30000	0.999	0.82
Metolose® 65 SH 50	0.999	0.62
Metolose® 65 SH 4000	0.999	0.8
Ac-Di-Sol®	1	0.81
Primojel®	0.999	0.81
Kollidon® CL	0.998	0.72
Kollidon® CL-SF	0.998	0.47
Mannitol	0.997	0.45
NaCl	0.999	0.46
PEG 10000	0.999	0.49

testing, the release exponent has values close to 0.45. This is the case in the pore forming group of extrudates. The reference extrudates behave similar. In these cases the drug dissolution is controlled by diffusion through pores, which are formed by an excipient or the drug itself. A disintegration of the matrix during release experiments, as it can be found in the group of disintegrant containing extrudates (except from Kollidon® CL-SF), leads to higher values of n because the drug release rate is controlled by the dissolution of the drug particles themselves. Same conditions can be found for Tylose® H 30000 and Metolose® 65 SH 4000 in the hydrocolloid containing extrudate group. However, for matrices which erode partly, as in the cases of Tylose® H 20 and Metolose® 65 SH 50 (see SEM images), the release exponent shows values between 0.45 and 0.89. Here a coexistence of pore diffusion and particle dissolution is the case.

3.6. Influence of the particle size of the release modifiers on the release rate

In an additional trial the raw release modifiers, having a different mean particle size (Table 2), were sifted to a particle size range of 50–80 μm and extrudates of identical compositions were manufactured again to ensure a better comparability. DSC analysis did not show any abnormality (data not shown). Dissolution studies resulted in different behaviour compared to extrudates with unsieved release modifier (data not shown). Within the group of the pore formers no significant effect could be detected. In all cases the release rate was enhanced insignificantly ($f_{2\ \text{mannitol}} = 80.7$, $f_{2\ \text{PEG}} = 56.7$, $f_{2\ \text{NaCl}} = 56.4$).

Hydrocolloid-containing extrudates react in a various but systematic way to the shift in the particle size. Extrudates containing the sifted high viscosity grade cellulose derivatives Tylose® H 30000 and Metolose® 65 SH 4000 did not differ in the release profiles compared to the extrudates containing the unsifted powders ($f_2 = 68.9$ and 59.8). The low viscosity grades Tylose® H 20 and Metolose® 65 SH 50 of the same particle size range lead to a significantly lower release rate ($f_2 = 49.2$ and 35.4).

Sifting the superdisintegrants to a particle size range of 50–80 μm did not lead to significant changes in the release rates. In all cases (Ac-Di-Sol®, Primojel®, Kollidon® CL and Kollidon® CL-SF) the extrudates containing release modifier particle sizes of 50–80 μm did not show a significantly different release rate ($f_2 = 55.4$, 52.8, 51.51 and 59.5).

Table 2
Particle size of the release modifiers measured by laser diffraction ($n = 3$).

Excipient	Mean particle size ± SD unsieved in μm
Tylose® H 20	107.6 ± 1.5
Tylose® H 30000	104.8 ± 2.0
Metolose® 65 SH 50	85.3 ± 2.0
Metolose® 65 SH 4000	70.3 ± 2.0
Ac-Di-Sol®	48.6 ± 0.7
Primojel®	40.6 ± 0.3
Kollidon® CL	117.8 ± 0.8
Kollidon® CL-SF	17.2 ± 0.8
Pearlitol®	160.5 ± 0.8
Polyglykol® 10000	259.5 ± 1.2
Sodium chloride	579.9 ± 1.5

3.7. Different PEGs/PEOs and their release modifying effects in a tristearin matrix

To get a deeper insight into the behaviour of PEG in lipid matrices different PEGs/PEOs were integrated into tristearin matrix extrudates. Polyethylene glycols of different molecular weights were used to investigate whether their melting temperatures have any relevance concerning the release rates of the extrudates. This hypothesis based on the fact that the higher the molecular weight of the PEG is, the higher its melting temperature is. Finally mean molecular weights up to 7 million were chosen and used for the investigations. Fig. 5a gives an overview of the melting temperatures of the used PEGs/PEOs identified by DSC analysis. The dotted line indicates the extrusion temperature of 62 °C for extrudates consisting of a tristearin matrix. From this illustration it can be assumed that except from PEG 7,000,000 each PEG melts partly (PEO 100,000) or even completely (PEG 20000, 10000, 6000, 4000 and 1500). If the hypothesis, that molten PEG influences the release rate more effectively, is correct, the release rate should be higher in the cases of PEG 1500, 4000, 6000, 10000, 20000 and partly in the case of PEO 100.000. The release rate of extrudates containing PEO 7,000,000 should be lower.

In Fig. 5b the thermograms of extrudates consisting of 5% PEG/PEO are depicted. The melting endotherms of diprophylline and tristearin at around 160 °C and 70 °C (peak onsets) are visible in each case and are in good accordance to the previous results. Due to their small portion in the matrix of just 5% the melting endotherms of the PEGs/PEOs are not visible as good as the others. But they appear at the same temperatures as the pure substances (arrows in Fig. 5a). The singular melting endotherms of the three components and the absence of any other additional peak in each curve shows that the extrusion process did not change the solid state properties of the extrudates.

The results of the dissolution testing (Fig. 5c) correlate with the DSC results in Fig. 5a. Extrudates comprising PEG/PEO that melts during the extrusion process behave differently compared to PEG that persist in a solid form. The release rates of extrudates containing PEG 1500–100,000 exhibit nearly the same release rates. The differences are not significant ($f_{2\ (\text{PEG 4000–100,000})} = 55.0$). It seems as if the melting of PEG/PEO has a leveling effect on the release rates of the extrudates. No matter which PEG/PEO is used, the resulting release rate is the same if the PEG/PEO melts during the extrusion. The release profile of PEO 7,000,000 on the other hand differs significantly from this curve accumulation ($f_{2\ (\text{PEG 100,000–PEO 7,000,000})} = 43.1$). Apart from the difference of the molecular weights, the melting of PEG/PEO seems to have a significant influence on the release rate. These findings suggest that melting of the PEG is an important process determining the release behaviour of the extrudates to some extent.

3.8. Different PEGs/PEOs and their release modifying effects in a trimyristin matrix

To underline these findings the same investigations have been conducted by replacing tristearin by trimyristin, a solid fat that

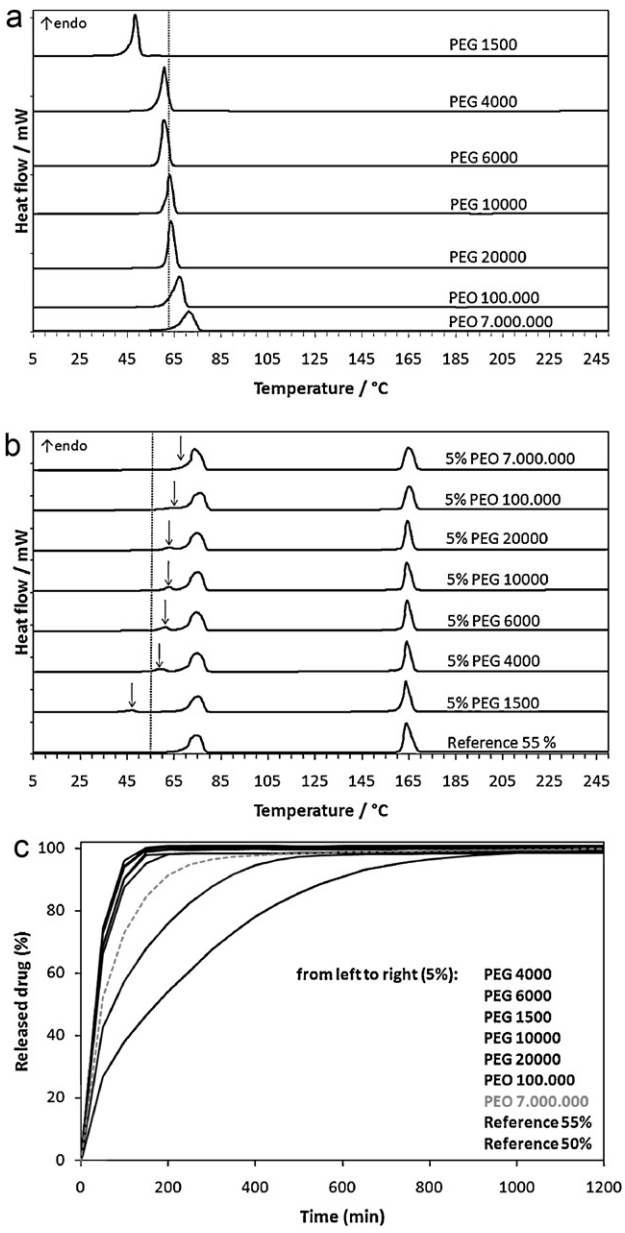

Fig. 5. Physicochemical characterization of powders and extrudates, (a) DSC thermograms of different PEG/PEO powders (dotted line indicates the extrusion temperature of 62 °C), (b) DSC thermograms of extrudates containing 5% (w/w) of different PEGs/PEOs (dotted line indicates the extrusion temperature of 50 °C), (c) dissolution profiles of tristearin extrudates each containing 5% (w/w) of a different mean molecular weight PEG/PEO ($n = 3$, SD < 5% not shown).

melts at 58 °C. Thus, the extrusion temperature has to be decreased to 50 °C. Under these conditions only PEG 1500 melts and the others exist in a solid state (dotted line in Fig. 5b). This results in the assumption that in the case of PEG 1500-containing extrudates the release rate should be clearly higher than in the others.

The release data of the correspondent trimyristin based extrudates confirm the findings of the tristearin test run (Fig. 6). Except from PEG 1500-containing extrudates, the release rate is nearly the same for the extrudates with different PEGs/PEOs, thus the molecular weight seems not to influence the release rate. On the other hand the state of the polymer in the barrel of the extruder during the extrusion has a significant influence on the release behaviour of the produced extrudates. PEG 1500 melts during extrusion. This can be assumed with respect to the DSC data (Fig. 5a and b). Accordingly PEG 1500 is assumed to be dispersed extensively in the lipid

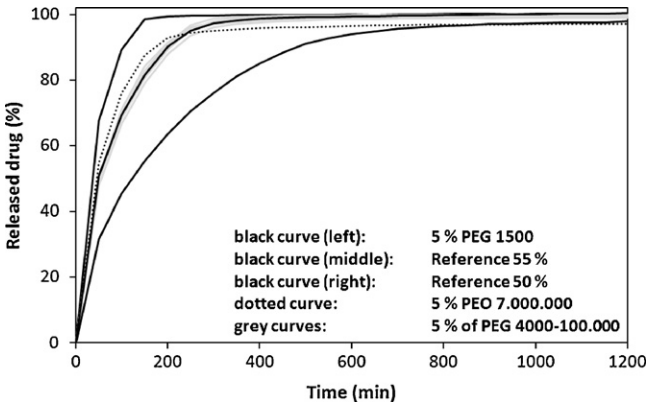

Fig. 6. Dissolution profiles of trimyristin extrudates each containing 5% (w/w) of a different mean molecular weight PEG/PEO ($n = 3$, SD < 4% not shown).

matrix and therefore the release rate is significantly higher than that of the others (e.g. $f_{2\,(\text{PEG 1500–7,000,000})} = 34.7$).

4. Conclusions

The influence of several hydrophilic excipients on the release rate of diprophylline from solid lipid extrudates was studied. By using components that have different physico-chemical properties the process of pore forming, swelling and disintegration was analysed. Disintegrants showed the most powerful influence on the release rate due to their surface increasing effects. The analysis of different hydrocolloids showed that the extent of release modification depends on the viscosity grade of the hydrocolloid. Low viscosity grades do not influence the release rate as much as the high viscosity grades. Pore formers exhibited a diverse behaviour. PEG increases the release rate stronger than mannitol or sodium chloride. The melting of PEG was assumed to be the reason for this fact. A melting of PEG during the extrusion process seems to lead to better distribution, which correlates with a faster water intake into the matrix. Complementary trials with another lipid underline this hypothesis.

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