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Research paper

Drug release from extruded solid lipid matrices: Theoretical predictions and independent experiments

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ABSTRACT

The aim of this study was to use a mechanistically realistic mathematical model based on Fick's second law to quantitatively predict the release profiles from solid lipid extrudates consisting of a ternary matrix. Diprophylline was studied as a freely water-soluble model drug, glycerol tristearate as a matrix former and polyethylene glycol or crospovidone as a pore former (blend ratio: 50:45:5% w/w/w). The choice of these ratios is based on former studies. Strains with a diameter of 0.6, 1, 1.5, 2.7 and 3.5 mm were prepared using a twin-screw extruder at 65 °C and cut into cylinders of varying lengths. Drug release in demineralised water was measured using the USP 32 basket apparatus. Based on SEM pictures of extrudates before and after exposure to the release medium as well as on DSC measurements and visual observations, an analytical solution of Fick's second law of diffusion was identified in order to quantify the resulting diprophylline release kinetics from the systems. Fitting the model to one set of experimentally determined diprophylline release kinetics from PEG containing extrudates allowed determining the apparent diffusion coefficient of this drug (or water) in this lipid matrix. Knowing this value, the impact of the dimensions of the cylinders on drug release could be quantitatively predicted. Importantly, these theoretical predictions could be confirmed by independent experimental results. Thus, diffusion is the dominant mass transport mechanism controlling drug release in this type of advanced drug delivery systems. In contrast, theoretical predictions of the impact of the device dimensions in the case of crospovidone containing extrudates significantly underestimated the real diprophylline release rates. This could be attributed to the disintegration of this type of dosage forms when exceeding a specific minimal device diameter. Thus, mathematical modelling can potentially significantly speed up the development of solid lipid extrudates, but care has to be taken that none of the assumptions the mathematical theory is based on is violated.

1. Introduction

The release mechanism of a dosage form is an important topic in pharmaceutical research and development. Information about the mass transport in the drug device can be crucial since it delivers basic data for an optimisation of the dosage form. Dissolution studies play an essential role in this regard and contribute to a standardised tool in quality control and product safety [1–4]. Once administered to a human, generally no direct influence can be exerted on the fate of the dosage form. Therefore, it is important to study the release behaviour in order to minimise the risk of undesired events in the human body, e.g. dose dumping or premature termination of release. Nowadays, this is done by conventional dissolution apparatuses according to current pharmacopoeias [2]. But there are also more modern approaches to cope with the requirements of novel dosage forms [1]. Dissolution studies are often easy to perform and usually have a low cost of materials. However, depending on the dosage form, they are time-consuming. Furthermore, the information that is gained by release experiments is generally not sufficient to fully describe the mass transport since only the amount of released drug is measured. One option to quantify the similarity of two dissolution curves is to calculate the so-called "f_2 value" (values above 50 are considered to indicate similar curves) [5].

The identification or development of a mechanistic realistic mathematical theory describing drug release from a specific type of dosage forms should always be based on comprehensive

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experimental data sets [6–8]. This includes of course drug release measurements, but ideally also morphology studies (e.g. via scanning electron microscopy, SEM), visual observations (identifying for example potential device disintegration) and other investigations, such as thermal analysis using differential scanning calorimetry (DSC). Based on these experimental results, an appropriate set of mass transport equations can be defined and solved [9,10]. Fitting such a model to sets of experimental results then allows determining system specific parameters, for example the diffusion coefficient of a drug within the dosage form. Once all characteristic parameters are known, the mathematical theory can be used to quantitatively predict the effects of formulation/processing parameters and/or device dimensions on the resulting drug release kinetics [11]. It has to be pointed out that the validity of a mathematical model for a specific type of drug delivery system should be evaluated by comparing such theoretical predictions with independent experimental results.

Powdered lipids are already known as excipients, which are able to form a stable matrix incorporating a drug substance [12]. Due to their hydrophobic nature, the release rate of the incorporated drug can be limited [13]. By addition of a pore former, drug release can generally be accelerated and well adjusted [14]. Importantly, in most cases, exposure to the release medium does not significantly change the geometry of this type of dosage forms during drug release [15]. The outer matrix dimensions generally remain unaltered, whereas the inner porosity of the system steadily increases due to drug and (potentially) excipient leaching into the surrounding bulk fluid. The influence of different hydrophilic additives like pore formers or disintegrants on the dissolution from solid lipid extrudates has been described previously [16].

It has previously been shown that diffusional mass transport plays a major role in the control of drug release from lipid implants releasing a drug during periods of several days up to various months. They can be prepared either by direct compression of lipid – drug powder blends [17–20], or by melting & casting [21–23]. However, it is yet unclear whether water diffusion into the system or drug diffusion out of the devices is the release rate limiting step [24].

The aim of this study was (i) to prepare different types of lipid cylinders by solid lipid extrusion, releasing the drug in much shorter time periods than the above described implants (only a few hours) and (ii) to identify a mechanistic realistic mathematical theory allowing for the quantitative prediction of the effects of the device dimensions on the resulting drug release kinetics. These theoretical predictions were to be compared with independent experimental results. Two types of "pore formers" were added: polyethylene glycol (PEG) as well as crospovidone. It has to be considered that dissolution experiments were performed in demineralised water, so that physiological conditions were not assured. In vivo additional effects, such as the presence of enzymes and bile salts, might also have an impact.

2. Materials and methods

2.1. Materials

Pure powdered monoacid glycerol tristearate (Dynasan 118®, Sasol, Witten, Germany) was used as solid fat compound for the extrusion experiments. To modify the release rate, polyethylene glycol (PEG) of a mean molecular weight of 20000 (Polyglykol® 20000, Clariant, Sulzbach, Germany) or crospovidone (Kollidon® CL SF, BASF, Ludwigshafen, Germany) was incorporated into the lipid matrix. Diprophylline base (fine powder, BASF, Ludwigshafen, Germany) (water solubility at 25 °C = 330 g/L [25]) was used as a model drug.

2.2. Methods

2.2.1. Blending

Physical mixtures of 50% diprophylline, 45% glycerol tristearate and 5% (w/w/w) polyethylene glycol (Polyglykol® 20000) or Kollidon® CL SF were prepared in a laboratory mixer (LM 20 Bohle; Ennigerloh, Germany) at 25 rpm for 15 min.

2.2.2. Extrusion

A co-rotating twin-screw extruder (Mikro 27GL-28D, Leistritz, Nuernberg, Germany) containing a gravimetric dosing device (KT20 K-Tron Soder, Lenzhard, Switzerland) was used to perform the extrusion experiments. Setting a powder feeding rate of 40 g min^{-1}, the blends were transferred into the barrels of the twin-screw extruder. At a screw speed of 60 rpm, the powder was forced through different die plates, specified in the following:

1. 63 holes of 0.6 mm diameter and 3.00 mm length,
2. 23 holes of 1.0 mm diameter and 2.50 mm length,
3. 11 holes of 1.5 mm diameter and 3.75 mm length,
4. 3 holes of 2.7 mm diameter and 7.50 mm length,
5. 2 holes of 3.5 mm diameter and 7.00 mm length,
6. 2 holes of 4.0 mm diameter and 7.5 mm length.

The temperatures of the barrel segments were set at 65 °C. The die plate reached a temperature of 62 °C. The obtained strains were cut into cylinders of various lengths (as indicated).

2.2.3. Differential scanning calorimetry (DSC)

Thermograms of the extrudates were recorded using a DSC 821e calorimeter (Mettler-Toledo, Giessen, Germany). Approximately 5 mg of the sample was weighed into completely sealed 40 µl aluminium pans. A heating rate of 10 °C min^{-1} was set to increase the temperature in the pans from 20 °C up to 250 °C. Each experiment was conducted twice.

2.2.4. Dissolution

Dissolution experiments were performed according to USP 32 method 1 in a basket apparatus (Sotax AT7 smart, Sotax, Loerrach, Germany). Since the dimensions of the cylindrical extrudates were altered, varying numbers of devices were placed in the baskets in order to assure similar masses of diprophylline (25–30 mg) in each case. The following list gives an overview on the extrudate dimensions (diameter × length) and the number of cylinders per basket:

5% PEG – containing extrudates:

- 0.6 mm × 14.0 mm (10 cylinders),
- 1.0 mm × 10.0 mm (5 cylinders),
- 1.5 mm × 29.0 mm (1 cylinder),
- 2.7 mm × 8.0 mm (1 cylinder),
- 3.5 mm × 5.0 mm (1 cylinder).

5% Kollidon® CL SF – containing extrudates:

- 1.0 mm × 10.0 mm (5 cylinders),
- 2.7 mm × 10.0 mm (1 cylinder),
- 4.0 mm × 10.0 mm (1 cylinder).

The dissolution medium was demineralised water, kept constant at 37 ± 0.5 °C. The stirring speed was 50 rpm, and the drug was detected by UV–Vis spectroscopy (Lambda 40, Perkin-Elmer, Rodgau-Juegesheim, Germany) at a wavelength of 273 nm. The samples were measured in a continuous flow-through cuvette at 5 min intervals. The mean concentrations and standard deviations (not shown in the figures curves: below 5% in all cases) were calculated at each time point from three samples.

2.2.5. Scanning electron microscopy (SEM)

A scanning electron microscope (Leo 1430VP, Leo Elektron Microscopy, Cambridge, UK) with a voltage of 18–21 kV was used to image the surfaces of the extrudates. The extrudates, dried at room temperature in an exsiccator (no vacuum) for several days, were fixed on aluminium discs with a double-sided carbon tape. A sputtering process, accomplished by a sputter coater (Agar Manual Sputter Coater B7340, Agar Scientific, Stansted, UK), was preceded to the imaging. Sputtering was conducted three times, each for a period of 60 s, in order to avoid melting or structural changing of the sample surface.

2.2.6. Calculation of the similarity factor (f_2)

f_2 Values were calculated using the following equation (Eq. (1)), a formula suggested by the FDA [5]:

$$F_2 = 50log_{10}\left(\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} * 100\right) \quad (1)$$

R_t and T_t are the cumulative percentages dissolved at each of the selected n time points t of the reference and the test sample. Dissolution values of at least 12 time points were used to determine the similarity factor. Only one measurement point was considered above 85% release since the f_2 value is sensitive to number of time points; f_2 values of 50 or higher ensure equivalence of the two considered curves. A value of lower than 50 indicates significant difference between two curves.

3. Results and discussion

3.1. Physico-chemical characterisation of PEG containing extrudates

Fig. 1 depicts the thermograms of extrudates consisting of diprophylline, glycerol tristearate and polyethylene glycol in a 50:45:5% (w/w/w) ratio. In each thermogram, three peaks are visible caused by the three different components: the first at temperatures around 63 °C (peak onset 59 °C) referring to PEG, the second at 73 °C (peak onset 70 °C) indicating the β-modification of glycerol tristearate and the third at temperatures around 163 °C (peak onsets around 162 °C) caused by the melting of the drug. Single peaks, especially in the case of glycerol tristearate, can serve as an indication for the absence of other polymorphic forms (of the drug and the excipients). Each value is in good agreement with the literature [26–29]. These calorimetric results indicate a gentle processing of the physical mixtures during extrusion since no transformations of the solid phase are detectable. The pressure measured in front of the die plate was held constant in order to avoid varying densities of the different dimensioned extrudates.

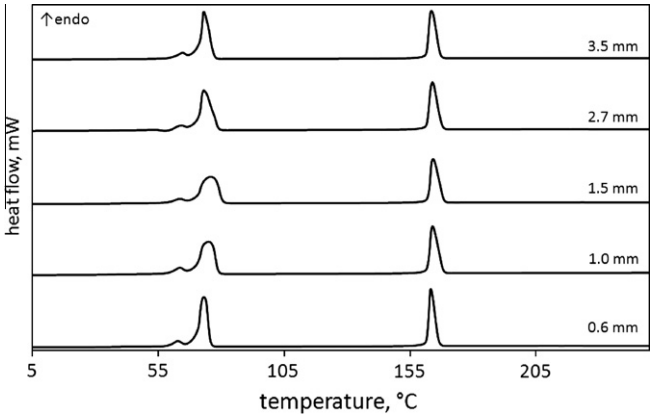

Fig. 1. Thermograms of solid lipid extrudates consisting of diprophylline, glycerol tristearate and PEG 20000 (50:45:5% w/w/w) with different diameter (indicated in the diagram).

In Fig. 2, SEM pictures of the surfaces of the extrudates prior to exposure to the release medium are shown. As it can be seen, the surfaces of the extrudates exhibiting a diameter of 2.7 and 3.5 mm were smoother than the others. This is because the die plate holes used for manufacturing were longer (7.5 and 7.0 mm) than in the other cases (3.0, 2.75 and 3.75 mm). Longer holes result in longer residence times within the die plate, leading to a more pronounced smoothening of the extrudate surfaces. Fig. 3 illustrates SEM pictures of the surfaces of the same type of extrudates as shown in Fig. 2, but after 20 h exposure to the release medium. Importantly, the diameters of the systems remained unchanged (no significant swelling), but the porosity increased in all cases. The increase in porosity can be attributed to the leaching of the drug and PEG into the bulk fluid.

The symbols in Fig. 4 illustrate the experimentally measured release of diprophylline from glycerol tristearate based extrudates containing 5% PEG (initial drug content = 50%) in demineralised water. As it can be seen, the release rate monotonically decreased with time (decreasing slope of the curve). This might serve as an indication for the fact that diffusional mass transport plays a major role in the control of drug release from this type of dosage forms.

3.2. Elucidation of the underlying drug release mechanism in PEG containing extrudates

In order to better understand the mass transport mechanisms controlling drug release from the investigated solid lipid extrudates, an analytical solution of Fick's second law of diffusion was used to quantify the experimentally measured diprophylline release kinetics. The model is based on the following assumptions:

- Perfect sink conditions are maintained throughout the experiments (this was the case due to the high aqueous solubility of diprophylline of 330 g/L and the chosen device/bulk fluid volume ratios).
- The matrices stay intact during the drug release measurements and their dimensions do not significantly change.
- Diffusional mass transport (in radial and axial direction) is the release rate controlling mass transport step: either of water into the solid lipid extrudates or of diprophylline out of the systems [24].
- The drug, lipid and the pore former are homogenously distributed in extrudates before exposure to the release medium.
- Erosion of the lipid matrix is negligible during the observation period.
- Limited drug solubility effects within the cylinders are negligible.

In order to quantify diffusional mass transport in axial and radial direction within the solid lipid extrudates, Fick's second law of diffusion for cylindrical geometry was used:

$$\frac{\partial c}{\partial t} = \frac{1}{r}\left\{\frac{\partial}{\partial r}\left(rD\frac{\partial c}{\partial r}\right) + \frac{\partial}{\partial \theta}\left(\frac{D}{r}\frac{\partial c}{\partial \theta}\right) + \frac{\partial}{\partial z}\left(rD\frac{\partial c}{\partial z}\right)\right\} \quad (2)$$

where c is the concentration of the diffusing species (drug or water); t represents time; r denotes the radial and z the axial coordinate of the cylinder and θ the angle perpendicular to the r–z-plane; and D is the apparent diffusion coefficient of water or drug.

This partial differential equation can be solved under the given initial and boundary conditions (homogeneous initial compound distribution within the extrudates and perfect sink conditions/

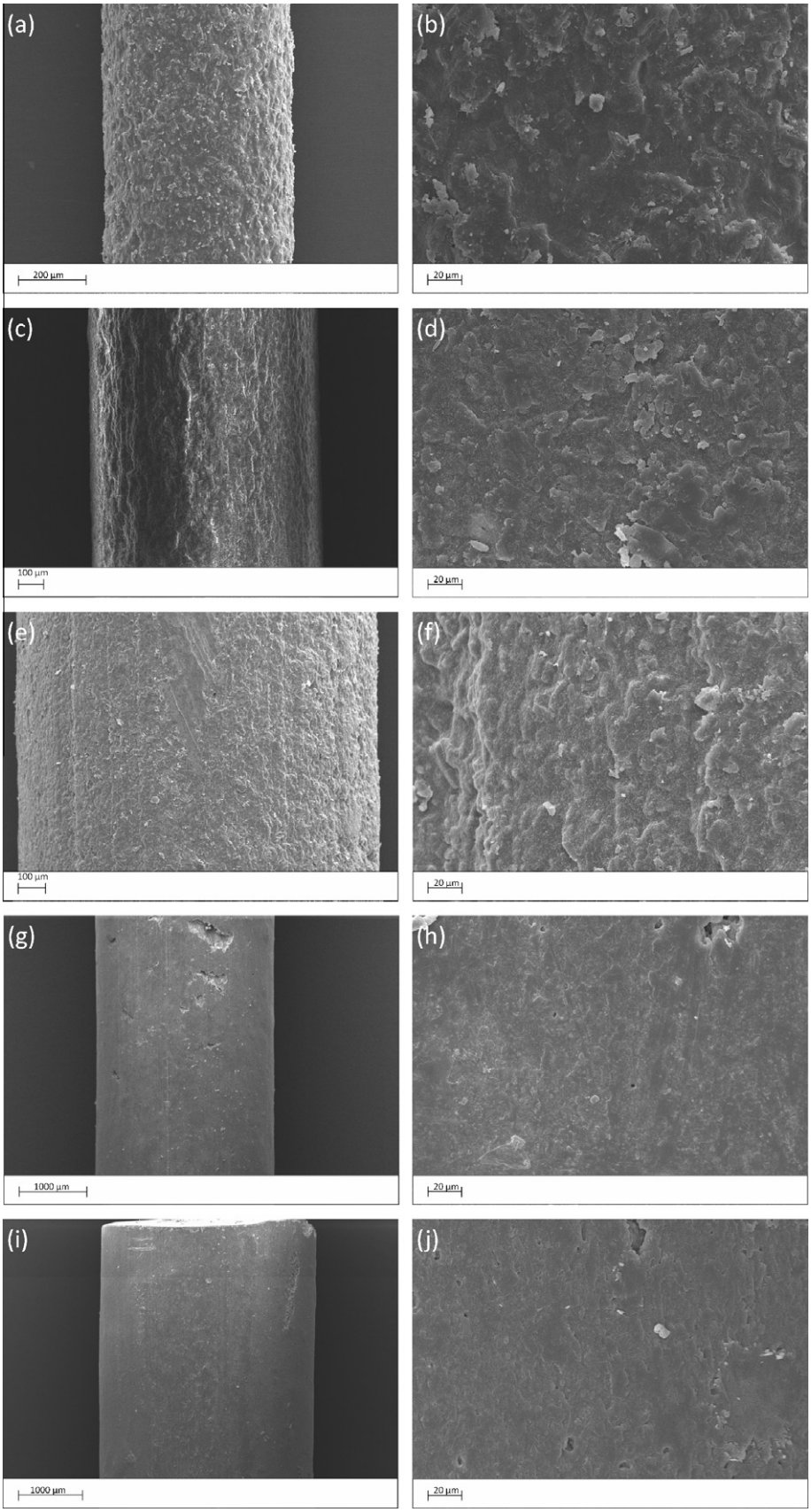

Fig. 2. SEM pictures of surfaces of differently sized solid lipid extrudates consisting of diprophylline, glycerol tristearate and PEG 20000 (50:45:5% w/w/w) before exposure to the release medium (diameter * length): 0.6 * 14.0 mm (a, b), 1.0 * 10.0 mm (c, d), 1.5 * 29.0 mm (e, f), 2.7 * 8.0 mm (g, h) and 3.5 * 5.0 mm (i, j).

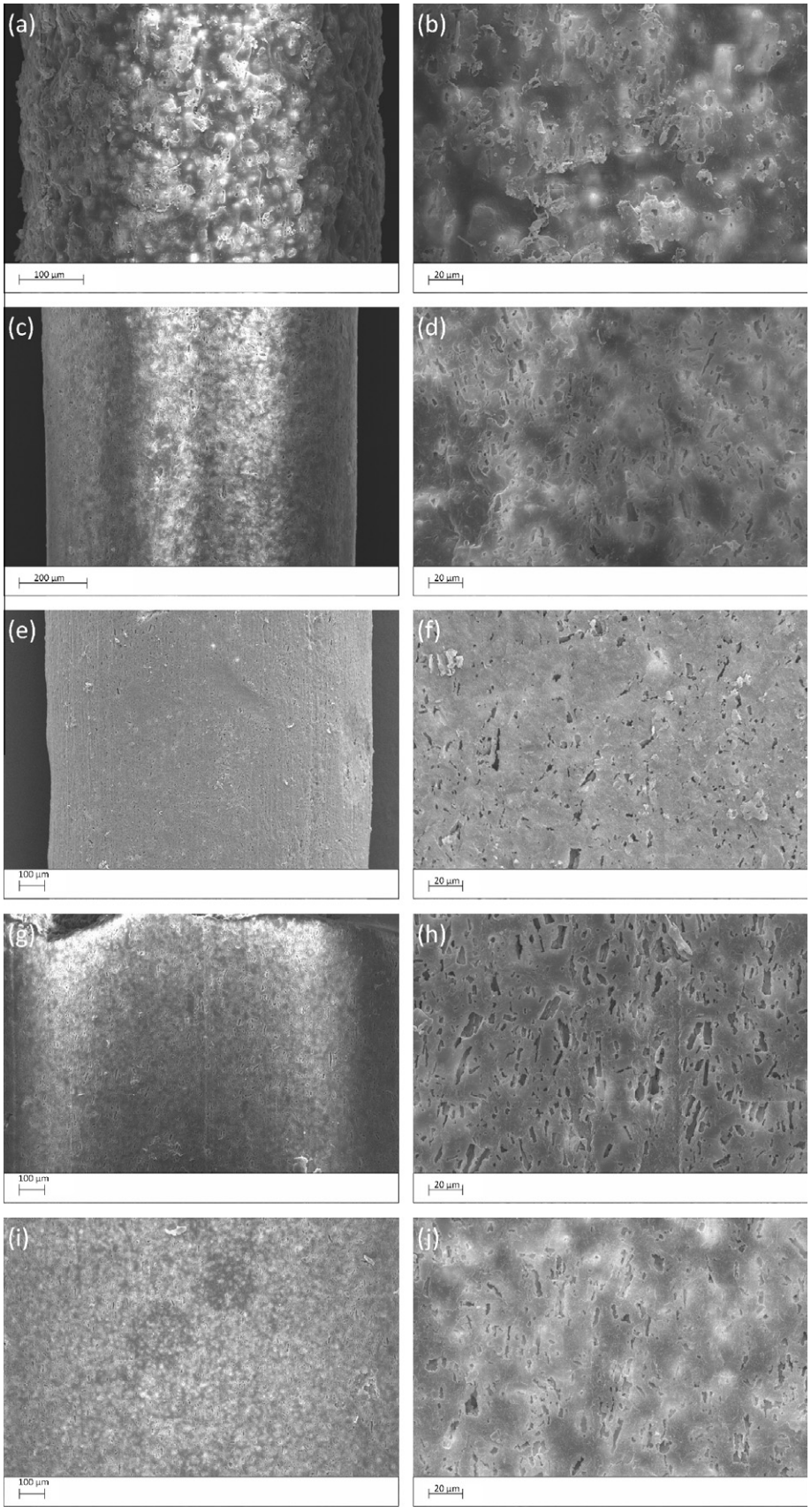

Fig. 3. SEM pictures of surfaces of differently sized solid lipid extrudates consisting of diprophylline, glycerol tristearate and PEG 20000 (50:45:5% w/w/w) after 20 h exposure to the release medium (diameter * length): 0.6 * 14.0 mm (a, b), 1.0 * 10.0 mm (c, d), 1.5 * 29.0 mm (e, f), 2.7 * 8.0 mm (g, h) and 3.5 * 5.0 mm (i, j).

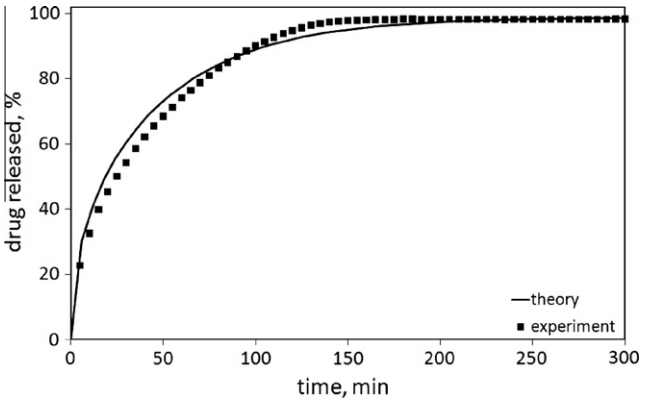

Fig. 4. Experiment (symbols) and theory (solid curve): diprophylline release from extrudates consisting of diprophylline, glycerol tristearate and PEG 20000 (50:45:5% w/w/w): diameter: 1.0 mm, height: 10.0 mm. The theoretical curve was obtained by fitting Eq. (3) to the experimental results.

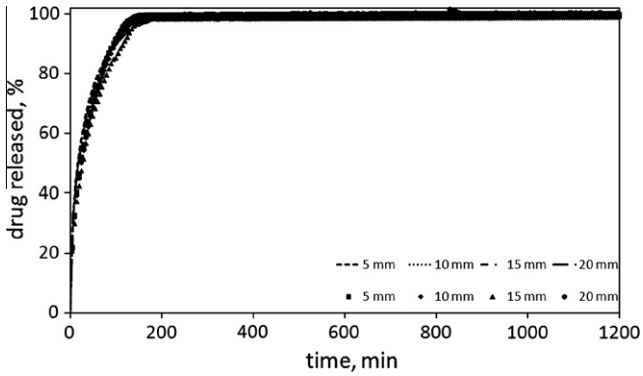

Fig. 5. Theoretically predicted (dotted curves, Eq. (2)) impact of the length of solid lipid extrudates (indicated in the diagram) on diprophylline release in demineralised water ($n = 3$, SD < 5%, not shown). The cylinders consisted of 50% diprophylline, 45% glycerol tristearate and 5% PEG 20000, and their diameter was 1 mm in all cases. The symbols represent the independently measured drug release kinetics from the systems.

constant water concentration at the extrudates' surface) using the method of Laplace transformation [30], leading to

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot \exp\left(-\frac{q_n^2}{R^2} \cdot D \cdot t\right) \cdot \sum_{p=0}^{\infty} \frac{1}{(2 \cdot p + 1)^2} \cdot \exp\left(-\frac{(2 \cdot p + 1)^2 \cdot \pi^2}{H^2} \cdot D \cdot t\right) \quad (3)$$

Here, M_t and M_∞ represent the absolute cumulative amounts of drug released or water taken up at time t and infinite time, respectively; q_n are the roots of the Bessel function of the first kind of zero order; R and H denote the radius and the height of the cylinder.

Fitting Eq. (3) to the experimentally determined release of diprophylline from glycerol tristearate based extrudates containing 5% PEG (50% initial drug content) led to good agreement between theory (curve) and experiment (symbols), as it can be seen in Fig. 4. Thus, diffusion is likely to be the dominant mass transport mechanism in these solid lipid extrudates. Note that it is not possible – based on the available data – to distinguish between "drug diffusion control" and "water diffusion control": Both processes take place and both can be quantified by Eq. (3).

3.3. Theoretical predictions for PEG containing extrudates

Importantly, the apparent diffusion coefficient of diprophylline or of water in these solid lipid extrudates could be determined based on the fitting shown in Fig. 4: $D = 1.35 * 10^{-7}$ cm^2/s. Knowing this value, it is possible to use Eq. (3) to theoretically predict the impact of the cylinders' dimensions on the resulting drug release kinetics. Examples for such predictions are shown in Fig. 5 (dotted curves). The release of diprophylline from solid lipid extrudates containing 50% drug and 5% PEG was predicted from cylinders with a constant diameter of 1 mm and varying lengths: ranging from 5 to 20 mm. Clearly, the relative drug release rate was predicted to be almost unaffected by the length of the extrudate. This can be explained by the difference in the lengths of the diffusion pathways to be overcome in radial versus axial direction: In all cases, the maximal distance to be overcome in radial direction is 0.5 mm. This is much shorter than the maximal distance to be overcome in axial direction: 2.5–10 mm. Consequently, radial drug or water diffusion can be expected to be much more important than axial diffusion.

To evaluate the validity of these theoretical predictions, the respective solid lipid extrudates were prepared in reality and diprophylline release was experimentally measured in demineralised water. Importantly, the obtained experimental results were in good agreement with the theoretical predictions (symbols and dotted curves in Fig. 5). Thus, the diffusion of diprophylline or water out of or into the devices is likely to be the dominant mass transport process during drug release.

Eq. (3) was also used to theoretically predict the impact of the diameter of the solid lipid extrudates on the resulting diprophylline release kinetics. The solid curves in Fig. 6 show the calculated release kinetics from cylinders containing 50% drug, 45% glycerol tristearate and 5% PEG. The radius was increased from 0.6 to 3.5 mm (note that the variation of the system's length is likely to be of only minor importance, as discussed above). Clearly, significantly decreasing relative drug release rates were predicted when increasing the diameter of the extrudate. This can be attributed to the increased length of the diffusion pathways. Again, the respective devices were prepared in reality, and in a second step, diprophylline was measured experimentally. As it can be seen in Fig. 6 and from the f_2 values in Table 1, good agreement was obtained between the theoretical predictions (dotted curves) and the independent experiments (symbols). This is a further confirmation for the hypothesis that diffusional mass transport is the dominant control mechanism in this type of advanced drug delivery systems.

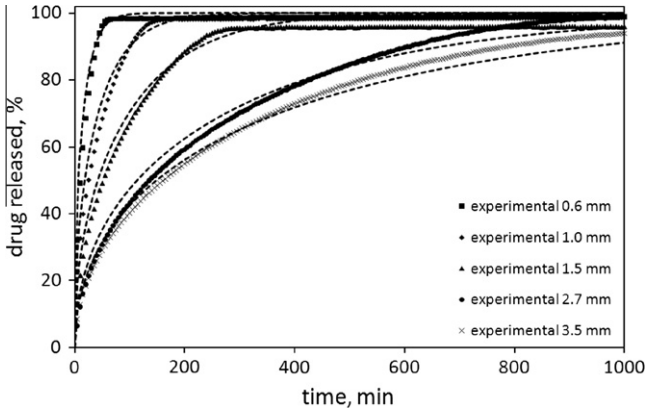

Fig. 6. Theoretically predicted (dotted curves, Eq. (3)) impact of the diameter and length of solid lipid extrudates (indicated in the diagram) on diprophylline release in demineralised water ($n = 3$, SD < 2%, not shown). The cylinders consisted of 50% diprophylline, 45% glycerol tristearate and 5% PEG 20000. The symbols represent the independently measured drug release kinetics from the systems.

Table 1
Calculation of similarity factors for theoretically and experimentally obtained dissolution curves.

Extrudate dimensions $D \times L$ (mm × mm)	$f_{2(\text{theory/experiment})}$
0.6 × 14	51.7
1.0 × 10	50.7
1.5 × 29	56.0
2.7 × 8	57.2
3.5 × 5	67.6

3.4. Crospovidone containing extrudates

To further evaluate the applicability of the proposed mathematical model, the pore former PEG was replaced by the disintegrant crospovidone. The other compounds of the system were not changed. Extrudates of 2.7 and 4.0 mm in diameter were produced and physico-chemically characterised. The thermograms in Fig. 7 show that the extrusion process does not lead to changes in the solid state of the matrix formers. The melting endotherm of the stable β-modification of glycerol tristearate can be found at a temperature of 73 °C. The diprophylline melting peak appears at 163 °C. Both values are again in good agreement with the literature [27–29]. A physico-chemical alteration of Kollidon® CL SF in the extrudate during processing is not likely since the glass transition temperature of crospovidone is around 180 °C [31].

The symbols in Fig. 8a show the experimentally determined release kinetics of diprophylline from extrudate consisting of 50% drug, 45% glycerol tristearate and 5% crospovidone, with a diameter of 1.0 mm and a height of 10.0 mm. As is the case of PEG containing devices, the relative drug release rate decreased with time. Fitting Eq. (3) to this set of experimental data also resulted in good agreement between theory (curve) and experiment (symbols), indicating that diffusional mass transport is likely to be the dominant mass transport mechanisms in these solid lipid extrudates as well. Note that the cylinders remained intact during the observation period. Based on these calculations, the apparent diffusion coefficient of diprophylline in these systems was determined to be equal to $4.5 * 10^{-7}$ cm²/s. Knowing this value parameter, again the effects of the device dimensions on drug release could be quantitatively predicted using Eq. (3). The dotted curves in Fig. 8b illustrate the theoretically expected release of diprophylline from solid lipid extrudates consisting of 50% drug, 45% glycerol tristearate and 5% crospovidone, with a length of 10 mm and a diameter of 2.7 and 4.0 mm (as indicated). With increasing diameter, the relative drug release rate was predicted to decrease, due to the increasing length of the diffusion pathways. In order to verify the validity of these predictions, the respective extrudates were prepared in reality and drug release was experimentally measured. As it can be seen in Fig. 8b, there were significant and systemic deviations between theory and experiment (curves and symbols): The mathematical model underestimated the real drug release kinetics in both cases. This disagreement can be explained by the fact that these solid lipid extrudates partially disintegrated upon exposure to the release medium, due to the presence of the swellable crospovidone. This disintegration results in a significantly increasing surface area available for diffusion and decreased diffusion pathway length. The applied model does not take this phenomenon into account and is, thus, not able to accurately predict the resulting diprophylline release kinetics.

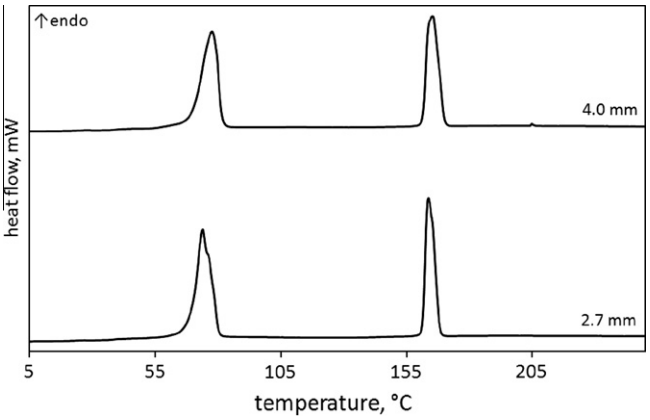

Fig. 7. Thermograms of solid lipid extrudates consisting of diprophylline, glycerol tristearate and Kollidon® CL SF (50:45:5% w/w/w) with different diameter (indicated in the diagram) and 10 mm length.

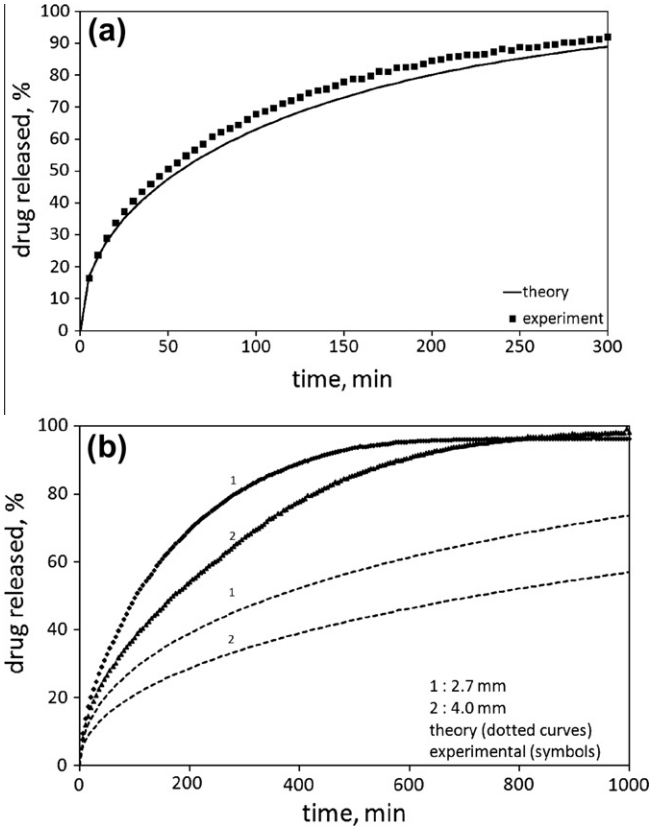

Fig. 8. (a) Experiment (symbols) and theory (solid curve): diprophylline release from extrudates consisting of diprophylline, glycerol tristearate and Kollidon® CL SF (50:45:5% w/w/w): diameter: 1.0 mm, height: 10.0 mm. The theoretical curve was obtained by fitting Eq. (3) to the experimental results. (b) Theoretically predicted (dotted curves, Eq. (3)) impact of the diameter (and length) of solid lipid extrudates (indicated in the diagram) on diprophylline release in demineralised water ($n = 3$, SD < 5%, not shown). The cylinders consisted of 50% diprophylline, 45% glycerol tristearate and 5% Kollidon® CL SF. The symbols represent the independently measured drug release kinetics from the systems.

4. Conclusions

The proposed mathematical model is able to theoretically predict the impact of the device dimensions of solid lipid extrudates containing the pore former PEG. It can, hence, allow for a facilitated and accelerated optimisation of this type of advanced drug delivery systems. However, if swellable compounds are added, resulting in partial disintegration of the dosage forms during drug release, the model underestimates the resulting drug release kinetics. Thus, the

proposed theory can be highly useful, but care has to be taken, not to violate any of the assumptions it is based on.

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