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Controlled drug release from Gelucire-based matrix pellets: Experiment and theory

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Abstract

The aim of this work was to elucidate the underlying drug release mechanisms from lipidic matrix pellets, using theophylline and Gelucire 50/02 as model drug and carrier material, respectively. Pellets were prepared by two different techniques: melt-solidification and extrusion-spheronization. The effects of different formulations and processing parameters on the resulting drug release kinetics in 0.1N HCl and phosphate buffer pH 7.4 were studied and the obtained results analyzed using adequate mathematical models in order to get further insight into the underlying mass transport mechanisms. The type of preparation technique was found to strongly affect the underlying drug release mechanisms. Drug release from pellets prepared by the melt-solidification method was primarily controlled by pure diffusion, whereas drug release from pellets prepared by the extrusion-spheronization method was purely diffusion-controlled only at early time points. After approximately 2 h, the pellets started to disintegrate, resulting in decreased diffusion pathway lengths and, thus, increased drug release rates. Furthermore, the curing conditions significantly affected the theophylline release kinetics, whereas varying the initial drug loading from 20 to 50% (w/w) resulted only in a slight increase in the relative drug release rate. Interestingly, the effects of the size of pellets prepared by the melt-solidification method on the resulting drug release kinetics could be quantitatively predicted using an analytical solution of Fick's second law of diffusion. These predictions could be verified by independent experiments.

Keywords: Pellets; Controlled release; Extrusion-spheronization; Release mechanism; Diffusion; Gelucire

1. Introduction

Major advantages of *multiparticulate* controlled drug delivery systems compared to single unit dosage forms include the low intra- and inter-subject variability in gastric emptying times and their more homogeneous distribution within the contents of the gastro-intestinal tract. Moreover, the risk of dose dumping can significantly be reduced with multiparticulates (e.g., pellets) compared to single unit dosage forms (Ghebre-Sellassie, 1989; Gandhi et al., 1999).

Multiparticulate controlled release dosage forms can be classified into reservoir and matrix systems. In the first case, a drug-containing core is surrounded by a (generally polymeric) membrane, which controls the release rate of the drug out of the device. Although coated pellets are widely used in the pharmaceutical industry, their preparation is often complex, time-consuming and cost-intensive. In contrast, the production of controlled release matrix systems is generally much easier. In these devices, the drug is embedded within a solid carrier material, which controls the release rate of the drug out of the system. The physicochemical nature of the matrix determines the underlying drug release mechanisms and resulting release patterns. Various processes, such as drug dissolution and diffusion, swelling and erosion of the matrix former, or a combination of two or more of these processes can be involved in the overall control of drug release (Gandhi et al., 1999). Different polymers have been proven to be suitable matrix formers, allowing to provide desired drug release kinetics, including ethylcellulose (Goskonda et al., 1994; Kojima and Nakagami, 2002), poly(vinylacetate) (Novoa et al., 2005), water-insoluble derivates of poly(acrylic acid) (Goskonda et al., 1994; Krogars et al., 2000; Young et al., 2002), as well as hydroxypropyl methylcellulose and derivatives thereof (Kojima and Nakagami, 2002).

But not only polymers, also *lipids* offer a great potential as matrix formers in controlled drug delivery systems. For example, Zhou et al. (1996) prepared drug-loaded matrix pellets

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based on combinations of waxes, starches and maltodextrins. These blends could successfully control the resulting release rates even at high initial drug loadings. Varying the type of blend and blend ratio, different types of release patterns could be provided. In contrast, the addition of glycerol monostearate to microcrystalline cellulose-based pellets prepared by extrusion-spheronization did not result in a retardation of drug release (in the case of paracetamol, diclofenac sodium, ibuprofen, indomethacin) (Chatchawalsaisin et al., 2005). The latter was only controlled by the solubility of the drug. Thomsen et al. (1994) investigated the ability of 12 meltable substances blended with calcium hydrogen phosphate to prolong paracetamol release from pellets prepared by melt-pelletization. Interestingly, a combination of glycerol monostearate and microcrystalline wax could effectively prolong drug release. Broad ranges of release patterns could be achieved by varying the composition of the lipidic matrix former. Gelucires [being blends of mono-, di- and tri-glycerides and mono- and di-fatty acid esters of poly(ethylene glycol)] were successfully used by Montousse et al. (1999) to prepare controlled release matrices pellets.

Several techniques can be applied for the preparation of lipidic dosage forms, including extrusion-spheronization (Dupont et al., 2002; Flament et al., 2004), melt-pelletization (Thomsen et al., 1994; Vergote et al., 2002) and melt-solidification (Maheshwari et al., 2003). However, little is yet known on the underlying drug release mechanisms in these systems and the importance of the type of preparation technique and device composition for the occurring mass transport phenomena. Kopcha et al. (1991) studied blends containing Gelucire 50/13 and 50/02 (the first number indicates the melting point, the second number the HLB value of the substance) as matrix formers. Increasing the Gelucire 50/02 content led to a decrease in the drug release rate. Also Sutananta et al. (1995) investigated delivery systems consisting of different Gelucire types. The nature of the lipid was found to strongly affect the underlying drug release mechanisms: drug release was primarily controlled by diffusion in the case of Gelucire 43/01 and 54/02, whereas erosion predominated in the case of Gelucire 55/18 and 50/13. Interesting mathematical theories quantifying drug release from lipidic dosage forms have been proposed by Vergnaud and co-workers (Bidah and Vergnaud, 1990; Bidah et al., 1992). Analytical models for different delivery systems have been presented. However, yet the importance of the type of preparation technique of the lipidic matrices for the resulting drug release kinetics and the underlying mass transport mechanisms are not fully understood and there is still a significant lack of physicochemically realistic mathematical theories allowing to quantitatively predict the effects of the design of the dosage forms on the resulting drug release kinetics.

The major objectives of the present study were: (i) to prepare theophylline-loaded, lipidic matrix pellets, (ii) to investigate the effects of several formulation and processing parameters on the resulting drug release patterns, (iii) to better understand the underlying mass transport mechanisms, and (iv) to be able to predict the effects of processing variables on the resulting drug release kinetics in a quantitative way.

2. Materials

Theophylline (anhydrous; BASF AG, Ludwigshafen, Germany) and sodium dodecyl sulfate (SDS; Cognis, Saint Fargeau, Ponthierry, France) were used as received. Blocks of Gelucire 50/02 [being a blend of mono-, di- and tri-glycerides and mono- and di-fatty acid esters of poly(ethylene glycol) with a melting point of 50 °C and a hydrophilic lipophilic balance (HLB) value of 2; Gattefossé, Saint Priest, France] were cooled to +7 °C and ground in a rotative rasp into small pieces, which were subsequently deep-frozen at −15 °C for 12 h and passed through an oscillating granulator (Frewitt, type MG, Fribourg, Switzerland), equipped with a 1 mm grid.

3. Experimental methods

3.1. Preparation of matrix pellets

Theophylline-loaded, Gelucire-based matrix pellets [20–50%, w/w, drug loading] were prepared by the following two techniques.

3.1.1. Extrusion-spheronization method

Theophylline, Gelucire and an aqueous SDS solution (0.5%, w/w) were manually mixed in a mortar. The obtained wet masses (compositions indicated in Table 1) were extruded using a piston extruder (1 mm orifice, 5000N; Alexanderwerk GA 65, Alexanderwerk AG, Remscheid, Germany). The extrudates were immediately spheronized (Caleva model 15; Caleva, Dorset, UK) for 40–70 s (depending on the formulation) at a rotational speed of 765 rpm. The obtained beads were sieved and dried overnight at room temperature. Optionally, the pellets were cured at 40 or 45 °C for 24 h (as indicated).

3.1.2. Melt-solidification method

Theophylline (1 g) was dispersed into a Gelucire melt (4 g). Using a pipette this dispersion was dropped into water of ambient temperature (under stirring at 750 rpm), resulting in pellet solidification upon cooling. The beads were separated by sieving, washed with demineralized water, divided into different size fractions (by sieving) and dried at 40 °C for 24 h.

3.2. Characterization of matrix pellets

The morphology of the lipid-based pellets was studied using an optical imaging system (Nikon SMZ-U; Nikon, Tokyo,

Table 1
Composition of the wet masses used for the preparation of theophylline-loaded, Gelucire-based pellets by the extrusion-spheronization method

Drug loading (%)	Theophylline (g)	Gelucire (g)	Aqueous SDS solution (g)
20	10	40	19
30	15	35	19
40	20	30	19
50	25	25	19

Japan), equipped with a Sony camera (Hyper HAD model SSC-DC38DP; Elvetec, Templemars, France) and the Optimas 6.0 software (Media Cybernetics, Silver Spring, USA).

The moisture content of the pellets was measured gravimetrically using a halogen moisture analyzer (Mettler LJ 16 Moisture Analyzer; Elvetec, Templemars, France) at 60 °C.

In vitro drug release from the pellets was studied in 0.1N HCl and phosphate buffer pH 7.4 (USP XXVII) using the paddle apparatus (USP XXVII; Sotax, Basel, Switzerland) (900 mL; 37 °C, 50 rpm, $n = 3$). At pre-determined time intervals, 3 mL samples were withdrawn and analyzed UV-spectrophotometrically ($\lambda = 271$ nm; Anthelie Advanced; Secomam, Domont, France).

3.3. Mathematical analysis

The following two mathematical theories were used to analyze the experimentally measured in vitro drug release kinetics and to determine the apparent diffusion coefficient of theophylline within the lipidic pellets.

3.3.1. Monolithic solution model

This theory considers that drug release is primarily controlled by pure diffusion. It is based on Fick's second law of diffusion (Crank, 1975):

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right) + \frac{\partial}{\partial y}\left(D\frac{\partial c}{\partial y}\right) + \frac{\partial}{\partial z}\left(D\frac{\partial c}{\partial z}\right) \quad (1)$$

where c and D are the concentration and diffusion coefficient of theophylline, t the time, and x, y and z are the three spatial coordinates.

Taking into account the following initial and boundary conditions:

(i) Perfect sink conditions are maintained throughout the experiment.
(ii) The pellets are spherical in shape.
(iii) The diffusion coefficient of theophylline is constant.
(iv) The drug is initially uniformly distributed throughout the pellets.
(v) The initial drug concentration is below its solubility (monolithic solution).

The following analytical solution of Eq. (1) can be derived (Crank, 1975):

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{Dn^2\pi^2 t}{R^2}\right) \quad (2)$$

where M_t and M_∞ represent the absolute cumulative amounts of theophylline released at time t and infinite time, respectively; D is the diffusion coefficient of the drug and R denotes the radius of the pellets.

3.3.2. Monolithic dispersion model

This theory considers that theophylline release is controlled by diffusion through the spherical pellets as well as by the limited solubility of the drug within lipidic beads. Based on a pseudo-steady state approach, Higuchi (1963) presented an implicit mathematical equation quantifying drug release from spherical dosage forms with an initial drug concentration that significantly exceeds its solubility. The drug particles are initially homogeneously distributed within the device (monolithic dispersion) and perfect sink conditions are maintained throughout the experiment. A very similar approach was used by Koizumi and Panomsuk (1995). The advantage of their solution is that the obtained (approximate) equation is in an explicit form and, thus, easier to handle than the respective Higuchi equation:

$$\frac{M_t}{M_\infty} = 4\pi R^2\sqrt{(2c_0 - c_s)c_s Dt} + \frac{4c_s Dt}{9R}\left(\frac{c_s}{2c_0 - c_s} - 3\right) \quad (3)$$

where M_t and M_∞ represent the absolute cumulative amounts of theophylline released at time t and infinite time, respectively; D is the diffusion coefficient of the drug and R denotes the radius of the spherical device; c_0 and c_s are the initial drug concentration and the solubility of the drug within the system, respectively. This model is only valid as long as the drug concentration in the pellets largely exceeds its solubility.

By fitting Eqs. (2) and (3) to sets of experimentally determined drug release data, the apparent diffusion coefficient of theophylline within the lipidic pellets could be determined.

4. Results and discussion

4.1. Pellets prepared by the melt-solidification method

The mean particle diameters, practical drug loading and encapsulation efficiency of the obtained theophylline-loaded, Gelucire-based pellets prepared by the melt-solidification method are given in Table 2. Clearly, the practical drug loading decreased with decreasing bead size, resulting in decreasing encapsulation efficiencies (from 90.2 to 70.1% for 3.4–1.2 mm sized pellets). This can be explained by the increase in the relative surface area of the lipidic beads, leading to increased drug loss into the water phase during pellet preparation.

Fig. 1 shows the experimentally measured in vitro drug release kinetics from medium-sized pellets into: (a) 0.1N HCl and (b) phosphate buffer pH 7.4 (symbols). Irrespective of the type of medium, theophylline release was relatively rapid: within approximately 2 h all drug was released. Interestingly, the release rate was particularly high at early time points and then monotonically declined with time. This is a typical behavior of diffusion-controlled drug delivery systems: at early time

Table 2
Characteristics of theophylline-loaded, Gelucire-based pellets prepared by the melt-solidification method (theoretical drug loading = 20%, w/w)

Mean particle diameter (mm)	Practical drug loading (%)	Encapsulation efficiency (%)
3.4	18.0	90.2
1.9	17.7	88.4
1.2	14.0	70.1

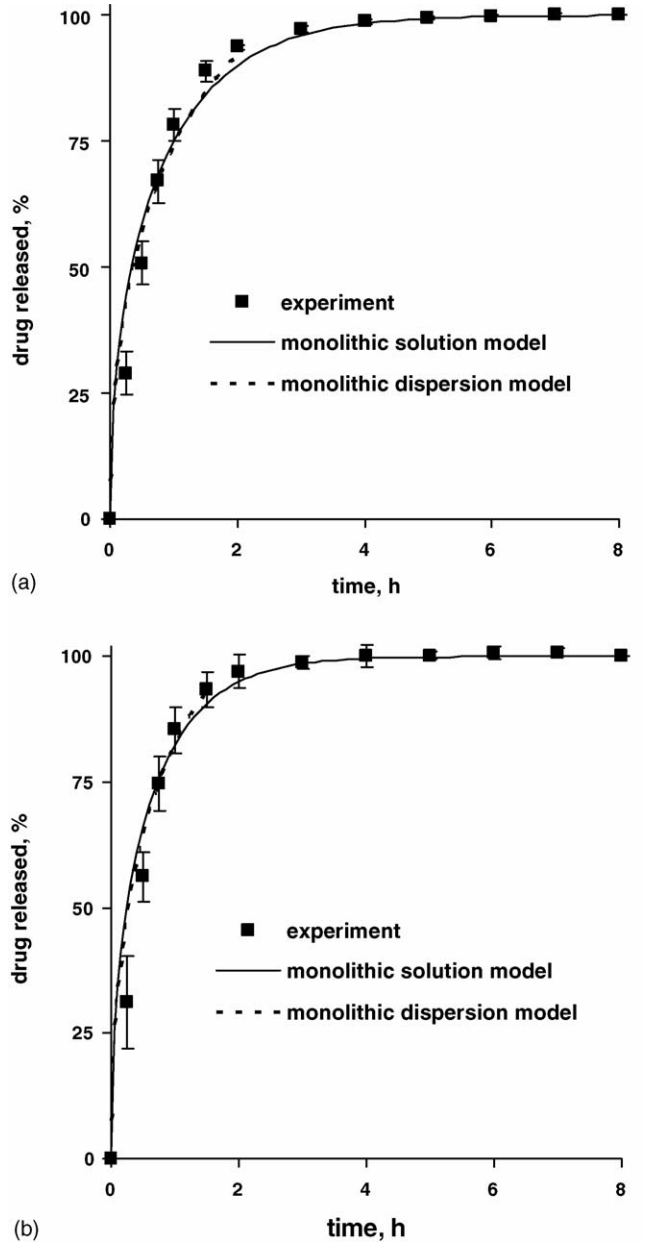

Fig. 1. Experiment and theory: theophylline release from Gelucire-based pellets prepared by the melt-solidification method in: (a) 0.1N HCl and (b) phosphate buffer pH 7.4. The symbols represent the experimentally measured release kinetics, the curves the fitted "monolithic solution model" and "monolithic dispersion model", respectively (as indicated in the figures) (mean diameter = 1.9 mm).

points, the diffusion pathways are short, resulting in steep concentration gradients (being the driving forces for diffusion) and, thus, high drug release rates. With increasing time, the length of the diffusion pathways increases, resulting in decreased drug concentration gradients and, thus, decreased drug release rates.

To better understand the underlying drug release mechanisms, an analytical solution of Fick's second law of diffusion (Eq. (2)) was fitted to the experimentally determined theophylline release kinetics (Fig. 1, solid curves). This theory ("monolithic solution model") is based on the assumption that drug release is purely diffusion-controlled. It considers the spherical geometry of the pellets and the fact that perfect sink conditions are maintained throughout the experiments. As it can be seen, good agreement between theory and experiment was obtained, irrespective of the type of release medium, indicating that diffusion plays a major role in this type of controlled drug delivery system. Based on these fittings, the apparent diffusion coefficients of theophylline in this type of Gelucire-based pellets could be determined, being equal to 2.4×10^{-7} cm^2/s upon exposure to 0.1N HCl, and 3.3×10^{-7} cm^2/s upon exposure to phosphate buffer pH 7.4. The relatively small difference corresponds to the observed similar drug release patterns in these two media (Fig. 1). Importantly, knowing these values the resulting drug release kinetics from arbitrary-sized pellets can be predicted in a quantitative way.

However, it has to be pointed out that the "monolithic solution model" assumes that the entire drug dose is immediately dissolved upon water penetration and available for diffusion. As the practical theophylline loading in the pellets is relatively high (17.7%), and as the solubility of the drug in the release media is limited [at 37 °C: 0.1N HCl: 15.4 mg/mL, phosphate buffer pH 7.4: 12.0 mg/mL; Bodmeier and Chen, 1989], it cannot be excluded that dissolved and non-dissolved drug co-exist within the lipidic matrices upon exposure to the release media. Importantly, only dissolved drug is available for diffusion. Thus, if the initial drug loading exceeds the solubility of the drug, not only diffusion, but also limited solubility effects contribute to the overall control of drug release. In this case, diffusion coefficients would be underestimated when determined with the "monolithic solution model". Unfortunately, the measurement of the solubility of theophylline in the investigated pellets upon exposure to the different release media is not straight forward. It can be expected that the presence of Gelucire [being a blend of mono-, di- and tri-glycerides and mono- and di-fatty acid esters of poly(ethylene glycol)] leads to an increase in drug solubility compared to pure phosphate buffer, but it is not certain that the entire drug dose is instantaneously dissolved upon penetration of the release medium into the beads. That is why also a second mathematical theory ("monolithic dispersion model") was fitted to the experimentally determined drug release kinetics (Fig. 1, dotted curves). This model takes into account that only a part of the drug dose is dissolved and available for diffusion upon exposure to the release media, that perfect sink conditions are maintained throughout the experiments and that drug diffusion through the lipidic beads is of fundamental importance. As it can be seen, again good agreement between theory (Eq. (3)) and experiment was obtained (Fig. 1). Without knowing the exact solubility of the drug within the wetted delivery system, it is not possible to determine the relative importance of drug diffusion and its limited solubility for the overall control of theophylline release. However, the diffusion coefficients of the drug in the investigated pellets can be roughly estimated: considering a minimal solubility of 15.4 mg/mL for drug release in 0.1N HCl and of 12.0 mg/mL for drug release in phosphate buffer pH 7.4, apparent theophylline diffusion coefficients of 1.7×10^{-6} and 2.9×10^{-6} cm^2/s were determined. Thus, the real diffusivity of theophylline in the lipidic pellets should be in the range of 2.4×10^{-7} to 1.7×10^{-6} cm^2/s upon exposure to 0.1N HCl, and in the range of 3.3×10^{-7} to 2.9×10^{-6} cm^2/s upon exposure to

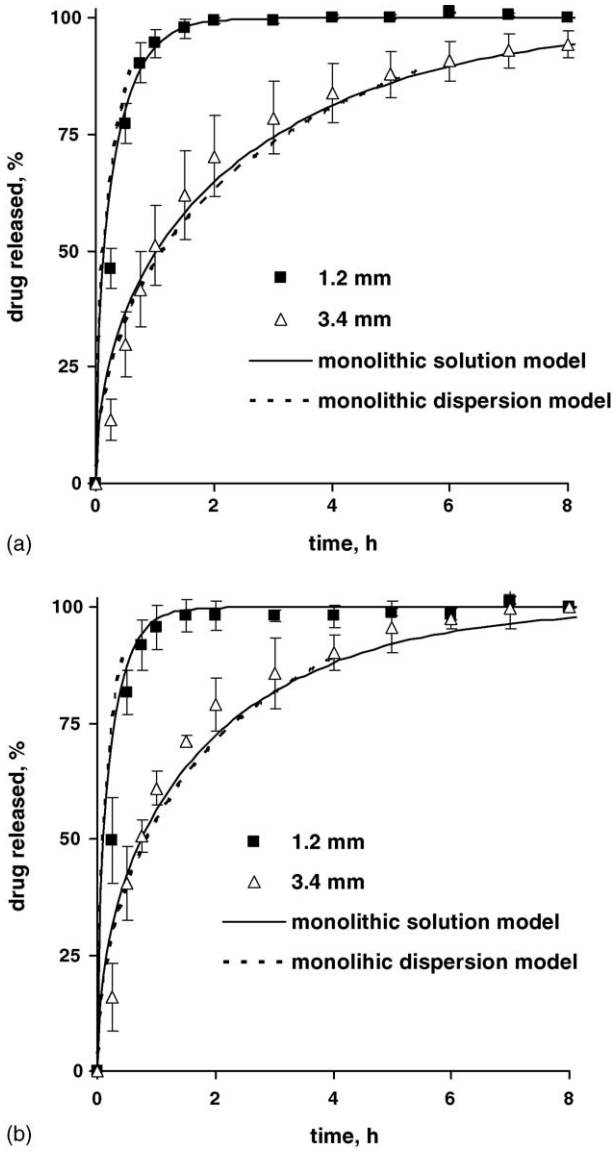

Fig. 2. Theoretical prediction and experimental verification: effects of the pellet size (indicated in the figures) on the resulting theophylline release kinetics from Gelucire-based pellets in: (a) 0.1N HCl and (b) phosphate buffer pH 7.4. The curves show the theoretical predictions (the respective models are indicated). The symbols represent the experimentally measured release kinetics (pellets prepared by the melt-solidification method).

phosphate buffer pH 7.4, respectively. [*Remark*: in the dry state, the investigated pellets are monolithic dispersions, because the drug is not (completely) dissolved in the lipidic matrix. However, upon exposure to the release media, water penetrates into the devices. For the underlying drug release mechanisms, the state of the drug in the wetted systems is decisive.]

Based on these calculations, the resulting theophylline release kinetics from arbitrary-sized Gelucire-based pellets can be predicted in a quantitative way. Fig. 2 shows examples for such predictions. Both theories (the "monolithic solution model" and the "monolithic dispersion model") were used to predict theophylline release from beads with mean diameters of 1.2 and 3.4 mm (solid and dotted curves), respectively. Clearly, the release profiles predicted by the two models are very similar. This is due to the fact that the limited solubility effects considered in the "monolithic dispersion model" are compensated by the higher drug diffusion coefficients used in this model. As the diffusion pathway lengths increase/decrease with increasing/decreasing pellet size, the resulting relative drug release rates decrease/increase with increasing/decreasing system dimension. Interestingly, controlled drug release over 8 h is theoretically predicted for the 3.4 mm sized beads. Importantly, these theoretical predictions could be confirmed by independent experiments (symbols in Fig. 2), irrespective of the type of release medium and pellet dimension. Thus, diffusion (and the limited solubility of theophylline) is (are) the dominating drug release rate controlling mechanism(s) in the investigated lipidic pellets. Furthermore, the presented mathematical models have an interesting practical application: they can be used to quantitatively predict the effects of the system size on the resulting drug release rates.

4.2. Pellets prepared by the extrusion-spheronization method

The in vitro drug release kinetics of theophylline in 0.1N HCl and phosphate buffer pH 7.4 from pellets prepared by the extrusion-spheronization method are illustrated in Fig. 3. In contrast to the beads prepared by the melt-solidification method, the observed drug release rates were about constant during significant time periods, irrespective of the type of medium. Consequently, fitting the "monolithic solution model" and "monolithic dispersion model" to these data did not result in good agreement between theory and experiment. Only up to approximately 60% drug release relatively good agreement could be obtained (Fig. 3, solid and dotted curves versus symbols). Afterwards, the two theories significantly underestimated drug release.

To better understand these phenomena the morphology of the beads and potential changes thereof upon exposure to the release media were monitored macroscopically. Fig. 4 shows photographs of theophylline-loaded, Gelucire-based pellets before and after 30 min and 2 h exposure to 0.1N HCl (only pellets exposed to 0.1N HCl are shown, their behavior upon exposure to phosphate buffer pH 7.4 being very similar). Clearly, the beads were initially spherical in shape, and remained unaltered for up to approximately 2 h. However, then they started to disintegrate (Fig. 4c). This agrees very well with the observed in vitro drug release kinetics: at early time points, drug release is primarily controlled by diffusion (and the limited solubility of the drug), leading to good agreement between the presented theories and the experimentally determined results. However, after about 2 h the pellets start to disintegrate, resulting in decreasing diffusion pathway lengths and, thus, increasing drug release rates. As the two mathematical models do not take this phenomenon into account, drug release at late time points is underestimated. As the disintegration behavior of the pellets is complex and difficult to be described in a quantitative way, no effort was made in the present study to mathematically model this process in a physically realistic way.

Comparing Fig. 3a and b, it can be seen that the type of release medium (0.1N HCl versus phosphate buffer pH 7.4) did not significantly affect the resulting theophylline release kinet-

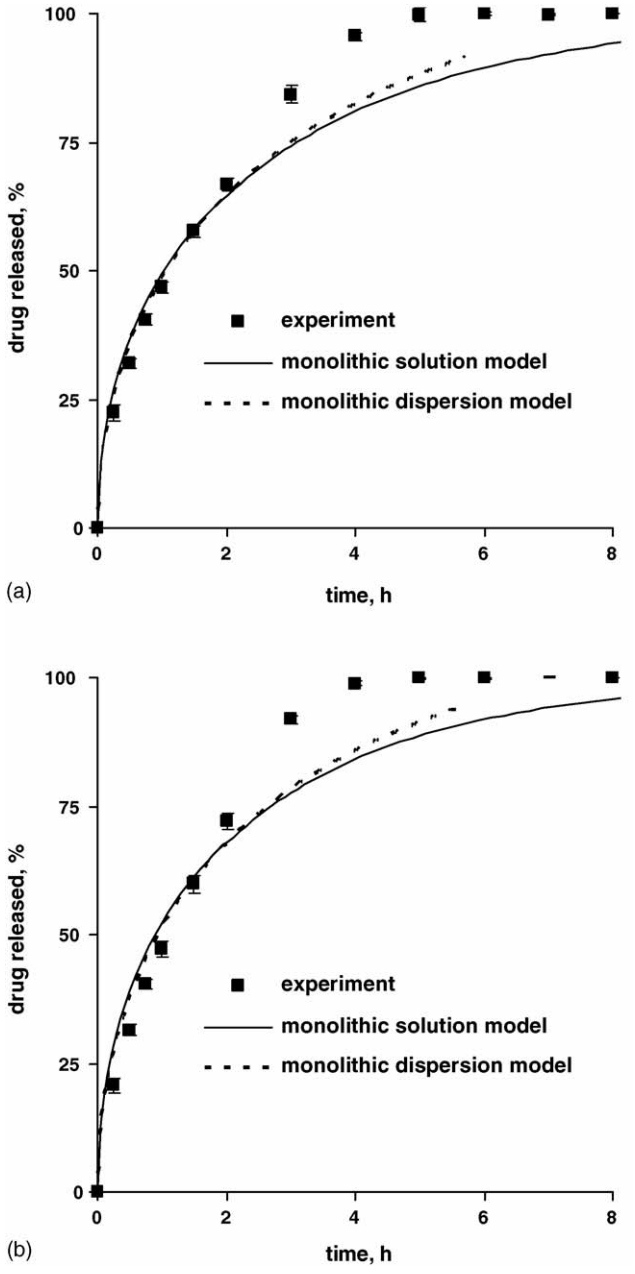

Fig. 3. Experiment and theory: theophylline release from Gelucire-based pellets prepared by the extrusion-spheronization method in: (a) 0.1N HCl and (b) phosphate buffer pH 7.4. The symbols represent the experimentally measured release kinetics, the curves the fitted theories (indicated in the figures) (20%, w/w, drug loading).

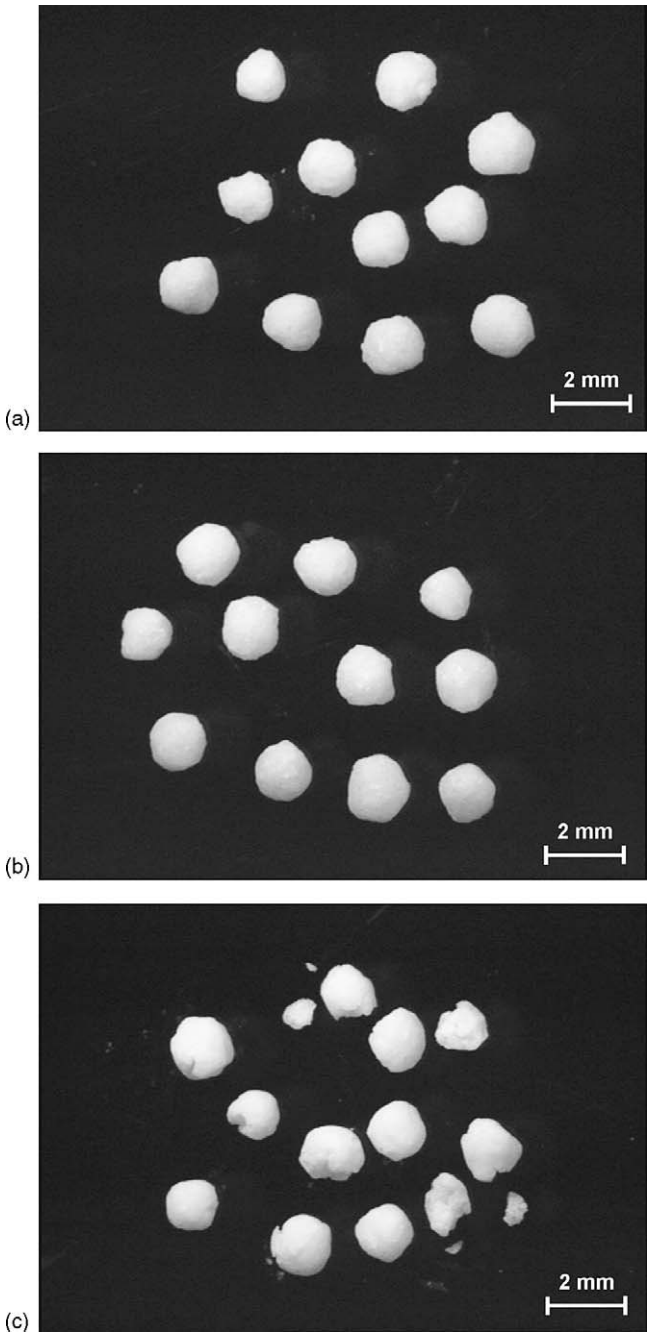

Fig. 4. Macroscopic pictures of theophylline-loaded, Gelucire-based pellets prepared by the extrusion-spheronization method: (a) before exposure; (b) 30 min after exposure; (c) 2 h after exposure to 0.1N HCl (20%, w/w, drug loading).

ics (as in the case of pellets prepared by the melt-solidification method).

4.3. Effects of formulation and processing parameters on the resulting drug release patterns

The effects of pellet curing at different temperatures on theophylline release in phosphate buffer pH 7.4 are illustrated in Fig. 5 for beads prepared by the extrusion-spheronization method (20%, w/w, drug loading). Interestingly, curing for 24 h at 40 °C led to an increase in the release rate, whereas curing for 24 h at 45 °C led to a decrease. The acceleration of drug release upon curing at 40 °C can be attributed to a decrease in the residual moisture content of the pellets, which dropped from 3.0 to 0.8% (w/w). This results in a decrease of the cohesive forces within the system and, thus, facilitated water and drug diffusion and accelerated pellet disintegration (as confirmed visually). In contrast, curing at 45 °C improves the mechanical stability of the lipidic matrices. This can be explained by the close vicinity of the melting point of the investigated Gelucire (50 °C). At only 5 °C below their melting temperature, the lipidic particles are

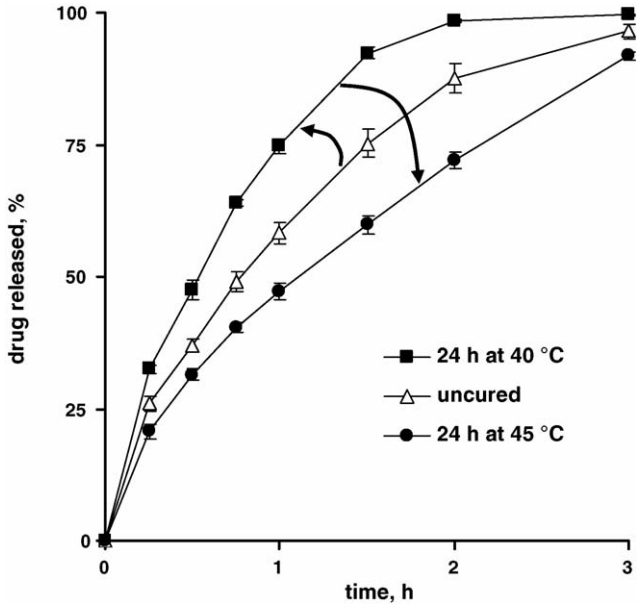

Fig. 5. Effects of pellet curing at different temperatures for 24 h on theophylline release in phosphate buffer pH 7.4 from Gelucire-based beads prepared by the extrusion-spheronization method (20%, w/w, drug loading).

softened and partially coalesce with each other. This results in a denser structure, being less permeable for water and theophylline and a delayed onset of pellet disintegration (as confirmed visually). Importantly, these effects overcompensate the effects of the decrease in moisture content of the pellets, resulting in an overall decrease in the drug release rate.

The importance of the initial drug loading of lipidic pellets prepared by the extrusion-spheronization method (and cured for 24 h at 45 °C) for the resulting drug release kinetics in 0.1N HCl and phosphate buffer pH 7.4 is illustrated in Fig. 6. Interestingly, increasing the theophylline loading from 20 to 50% (w/w) resulted only in a slight increase in the relative drug release rate, irrespective of the type of medium (Fig. 6a and c). In contrast, the respective absolute theophylline release rates significantly increased with increasing drug loading in 0.1N HCl as well as in phosphate buffer pH 7.4 (Fig. 6b and d). These phenomena can be explained as follows: with increasing initial drug loading the porosity of the lipidic pellets increases upon drug exhaust. Thus, the permeability for the drug increases, resulting in increased absolute drug release rates (Fig. 6b and d). On the other hand, if not all of the drug is immediately dissolved, not the entire drug amount is available for diffusion. Thus, increasing the initial drug loading does not increase the resulting concen-

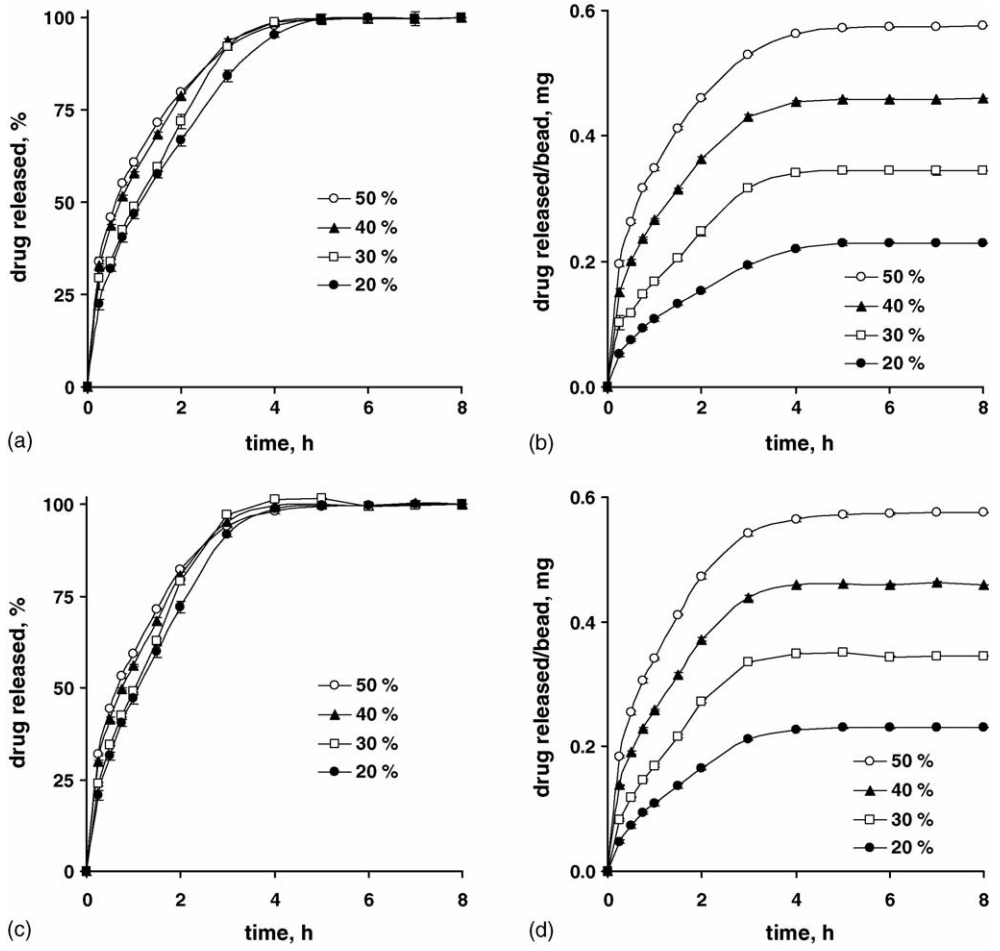

Fig. 6. Effects of the initial theophylline loading (indicated in the figures) of Gelucire-based pellets on the: (a) relative release rate in 0.1N HCl; (b) absolute release rate in 0.1N HCl; (c) relative release rate in phosphate buffer pH 7.4; (d) absolute release rate in phosphate buffer pH 7.4 (beads prepared by the extrusion-spheronization method, cured for 24 h at 45 °C).

tration gradients (being the driving forces for diffusion) and absolute drug release rates, but increases the 100% reference value for the relative drug release rates. Consequently, the latter decrease. In the present case, both phenomena superimpose. As it can be seen, the increasing porosity effect slightly overcompensates the increasing 100% reference value effect for the relative drug release rates (Fig. 6a and c). Importantly, the disintegration behavior of the pellets was not affected by the drug loading in the investigated range and the drug release mechanisms remained unaltered.

5. Conclusion

Lipid-based matrix pellets containing theophylline as model drug were prepared and physicochemically characterized. The effects of different formulation and processing parameters on the resulting drug release kinetics were studied and the obtained results analyzed using adequate mathematical theories to gain further insight into the underlying drug release mechanisms. It was shown that the type of preparation technique strongly affects the underlying mass transport mechanisms. Drug release from pellets prepared by the melt-solidification method was purely diffusion-controlled, whereas this was true only during the first 2 h upon exposure to 0.1N HCl and phosphate buffer pH 7.4 in the case of pellets prepared by the extrusion-spheronization method. The latter then started to disintegrate, resulting in an altered device geometry and dimensions. The curing conditions for this type of controlled drug delivery system should carefully be selected, as both, increasing as well as decreasing drug release rates were observed upon curing at different temperatures. In contrast, the initial drug loading only slightly affected the resulting relative drug release rates.

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