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Research paper

Drug release mechanisms of cast lipid implants

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ABSTRACT

The aim of this work was to better understand which physicochemical processes are involved in the control of drug release from lipid implants prepared by melting and casting. Lipid implants gain steadily in importance as controlled parenteral drug delivery systems: In contrast to PLGA-based devices, no acidic microclimates are created, which can inactivate incorporated drugs. The melting and casting method offers various advantages over the commonly used direct compression technique. For example, powder de-mixing during manufacturing and highly challenging scale-up due to poor powder flowability are avoided. Importantly, broad spectra of drug release patterns can be easily provided by varying the type of lipid. The resulting drug release rates are generally lower than those of implants prepared by direct compression. This is probably due to the differences in the microstructure of the pore network of the systems. Drug or water diffusion plays a dominant role for the control of drug release, potentially combined with limited drug solubility effects, caused by the low amounts of water available within the implants. In the case of pure diffusion control, a mechanistic realistic mathematical theory is proposed, which allows for quantitative predictions of the effects of formulation parameters on the resulting drug release kinetics. Importantly, these theoretical predictions could be successfully confirmed by independent experiments. Thus, the obtained new insight into the underlying drug release mechanisms can significantly facilitate the optimization of this type of advanced drug delivery systems. This is particularly helpful if long release periods are targeted, requiring time-consuming experimental studies.

1. Introduction

Lipid implants are steadily gaining interest as advanced drug delivery systems [1–9]. The pharmacodynamic efficiency of this type of dosage forms has been demonstrated in vivo [10–13] as well as their generally good biocompatibility [10,14,15]. Importantly, no acidic microclimates are created within the systems, in contrast to the widely used poly(lactic-co-glycolic acid) (PLGA)-based devices [16]. Such acidic microenvironments can cause the inactivation of incorporated drugs, especially of acid-labile proteins [17]. In addition, no organic solvents are required during the manufacturing of lipid implants. Thus, there is no risk of drug denaturation at water/solvent interfaces and no risk of solvent toxicity (neither for the patient nor for the environment). Hence, lipid implants present an interesting alternative to PLGA-devices for controlled parenteral drug delivery.

So far, research on lipid implants has mainly been focused on systems prepared by direct compression of drug:lipid powder blends [1,5,9,18,19]. This technique is well known in the pharmaceutical industry, since tablets are the most important dosage form from a practical point of view. It has been shown that broad spectra of drug release patterns can be provided with compressed lipid implants, the release periods ranging from a few days to several weeks [9]. However, drug:lipid powder blends generally show poor flowability. Thus, scaling-up of the production process can be a major challenge. For example, de-mixing can lead to inhomogeneous drug contents. These restrictions can be overcome when using a different implant preparation technique: melting and casting [20,21]. The idea is to heat the lipid (which generally exhibits a relatively low melting temperature), homogeneously distribute the drug(s) in the melt, and to cast the solutions/suspensions into molds of arbitrary geometry and size. Ideally, the device dimensions should allow for easy administration, e.g., tiny cylinders which can be injected using conventional needles. Obviously, the incorporated drug must be stable at the applied production temperatures. It has to be pointed out that even many proteins are stable at elevated temperatures, if water is absent [22,23]. For instance, Yamagata et al. showed that the activity of interferon-α 2a upon heating to 60 °C (together with polyglycerol esters of fatty acids) decreased by only 5% during the first 6 min and then remained constant for up to 5 h [12].

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But great care has to be taken when preparing lipid implants by melting and casting, because various lipids are known to show polymorphism [24–26]. Once molten, the lipid might solidify in an instable/metastable polymorphic form during device preparation [25]. Both thermodynamic and kinetic factors are determining which polymorph is formed upon cooling. Often, lipids first crystallize in the least stable form and then transform successively to more stable ones [26]. Importantly, these alterations in the physical state of the lipid can affect the resulting drug release patterns [27,28]. Thus, it is important to thoroughly characterize the lipid implants.

Despite the increasing interest in lipid implants as advanced drug delivery systems, yet only little is known on the mass transport mechanisms controlling drug release from these systems. Furthermore, there is a significant lack of mechanistic realistic mathematical models that able to describe drug release in a quantitative way [2,5,29,30]. It has recently been shown that water or drug diffusion plays a major role in lipid implants prepared by direct compression [9,31]. But due to the fundamental differences in the preparation procedure (compression versus melting and casting), differences in the implants' microstructure can be expected. So far, it is unclear how this affects the underlying drug release mechanisms and which theories can be used to quantitatively predict the impact of formulation and processing parameters on the resulting drug release kinetics from implants prepared by melting and casting.

The major aim of this work was to better understand how drug release is controlled from lipid implants prepared by melting and casting. Various types of lipids were studied, and the obtained systems were thoroughly characterized before and after exposure to the release medium. Based on the experimental results, a mechanistic realistic mathematical model was to be identified allowing for the in silico simulation of the effects of the device dimensions on drug release. The validity of this theory was to be evaluated by independent experiments.

2. Materials and methods

2.1. Materials

Glyceryl tripalmitate, glyceryl tristearate, and hardened soybean oil (Dynasan 116, Dynasan 118 and Dynasan 120) (Sasol, Witten, Germany); hydrogenated cottonseed oil (Sterotex NF, Abitec, Ohio, USA); glyceryl palmitostearate and glyceryl behenate (Precirol ATO 5 and Compritol 888 ATO) (Gattefosse, Saint Priest, France); propranolol hydrochloride (Salutas, Barleben, Germany); anhydrous theophylline powder 200 (BASF, Ludwigshafen, Germany).

2.2. Implant preparation

Lipid powder was heated in a glass vial on a water bath until a clear melt was obtained. The sieved drug (50–100 μm) was homogeneously dispersed within the latter upon stirring (250/min; RET basic, IKA-Werke, Staufen, Germany). Stirring was continued to avoid sedimentation until casting the dispersion into cylindrical plastic molds (diameter: 2, 3 or 4 mm, height: 2 mm), using a heated glass pipette. The systems were subsequently cooled down to room temperature. To assure complete filling of the molds, an excess of formulation was cast into each cylindrical hole, the excess being removed with a heated blade upon solidification. The implants were tempered for 2 weeks at 50 °C in an oven.

2.3. In vitro release studies

Implants were placed into 2-mL Eppendorf tubes, which were filled with 1.5 mL phosphate buffer pH 7.4 (USP 33) and horizontally shaken at 37 °C (80 rpm; GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany) (1 implant per tube). At predetermined time points, the release medium was completely replaced with fresh phosphate buffer, and the drug content in the withdrawn bulk fluid was measured by UV-spectrophotometry at λ = 289.4 nm (propranolol hydrochloride) or λ = 271.8 nm (theophylline) (UV-1650PC; Shimadzu, Kyoto, Japan). Perfect sink conditions were maintained throughout all experiments. In case of incomplete drug release during the observation period, the amount of drug remaining within the implant was determined experimentally as follows. The system was dissolved in 1 mL cyclohexane at 37 °C (80 rpm; GFL 3033). The drug was three times extracted into phosphate buffer pH 7.4 at 37 °C in a horizontal shaker (80 rpm; GFL 3033). The amount of drug in the aqueous phase was detected UV-spectrophotometrically at λ = 289.4 nm (propranolol hydrochloride) or λ = 271.8 nm (theophylline) (UV-1650PC).

2.4. Water uptake and erosion studies

Implants were treated as described in Section 2.3. At predetermined time points, implants were withdrawn, access surface water carefully removed, the systems accurately weighed [wet mass (t)] and dried to constant weight in an oven at 37 °C [dry mass (t)]. The water content (%) (t) and lipid matrix erosion (%) (t) were calculated as follows:

$$\text{water content } (\%)(t) = \frac{\text{wet mass } (t) - \text{drymass } (t)}{\text{wet mass } (t)} \times 100\% \quad (1)$$

$$\text{Lipid matrix erosion } (\%)(t) = \frac{\text{dry mass } (0) - \text{drug released } (t) - \text{dry mass } (t)}{\text{dry mass } (0)} \times 100\% \quad (2)$$

where "dry mass (0)" denotes the dry implant mass at t = 0 and "drug released (t)" the cumulative amount of drug released at time t.

2.5. Mechanical properties of the implants

The mechanical properties of the implants were determined using a texture analyzer (TAXT.Plus; Winopal Forschungsbedarf, Ahnsbeck, Germany). The implants were placed in the upright position on a metal plate. A flat-faced cylindrical probe (6 mm diameter) was fixed on the load cell (50 kg) and driven downwards with a speed of 0.01 mm/s (flat surface toward the implant). Load versus displacement curves were recorded until implant rupture and used to determine the energy required to break the systems as follows:

$$\text{Energy at break per unit volume} = \frac{\text{AUC}}{V} \quad (3)$$

where AUC is the area under the load versus displacement curve and V the volume of the implant.

2.6. Differential scanning calorimetry (DSC)

The thermal properties of lipid powders and implants were determined by differential scanning calorimetry (DSC Q1000; TA Instruments, Guyancourt, France). Temperature and enthalpy readings were calibrated with pure indium. Approximately 2–3 mg samples were heated in sealed aluminum pans [temperature range: 20–90 °C; heating rate: 5 °C/min; bulk lipids: two heating cycles (after the first heating cycle the samples were hold for

5 min at 90 °C and then cooled down at 10 °C/min); implants: one heating cycle].

3. Results and discussion

3.1. Effects of the type of lipid

The symbols in Fig. 1 show the experimentally measured release kinetics of propranolol hydrochloride from lipid implants prepared by melting and casting as well as the effects of the type of matrix former (indicated in the diagram). All systems were cylindrical in shape with a radius of 3 mm, and the initial drug content was 10%. Clearly, a broad range of drug release patterns could be obtained by varying the type of lipid. Importantly, not only the slope of the curves but also their shape was significantly affected, indicating potential differences in the underlying drug release mechanisms. Interestingly, the observed release rates were much lower compared with those observed with the implants of identical composition, but prepared by direct compression of drug–lipid powder blends, irrespective of the type of lipid [9]. For example, 50% propranolol hydrochloride was released from Dynasan 120/Dynasan 118-based implants after 14/30 d versus 56/72 d from implants prepared by direct compression versus melting and casting (implant diameter = 2 mm, average drug particle size = 68 μm). This might be attributable to differences in the inner system structure. In the case of melting and casting, less porous cylinders are likely to be obtained. It has recently been shown that water or drug diffusion in compressed lipid implants (through a highly interconnected, tiny channel network) is of major importance for the control of drug release [9]. Thus, a reduced total porosity and reduced pore size can be expected to slow down water and drug diffusion and hence drug release. Interestingly, the ranking order of the lipids, in which the drug release rate decreased, was the same for both types of preparation techniques: glyceryl palmitostearate (Precirol ATO 5) > hydrogenated cottonseed oil (Sterotex NF) > glyceryl tripalmitate (Dynasan 116) > hardened soybean oil (Dynasan 120) > glyceryl tristearate (Dynasan 118). This is also in good agreement with data reported in the literature for implants prepared by extrusion [32].

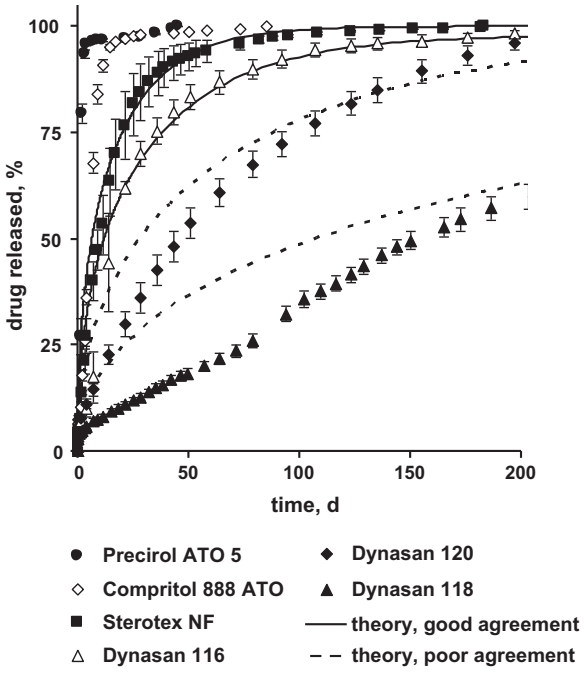

Fig. 1. Experiment and theory: Propranolol hydrochloride release from implants based on different types of lipids (indicated in the diagram) [diameter: 3 mm; 10% initial drug loading; symbols: experimental results; curves: fitted theory (Eq. (4)) (solid curves: good agreement; dashed curves: poor agreement)].

From a practical point of view, the melting and casting method, thus, seems to be more appropriate if *longer* release periods are targeted (provided that the drug is thermostable). Importantly, desired release rates can easily be adjusted by varying the type of lipid, irrespective of the preparation method.

3.2. Physicochemical characterization of the implants

In order to better understand the underlying mass transport mechanisms controlling drug release from these implants, the latter were thoroughly characterized before and after exposure to the release medium. Based on these experimental results, an appropriate mathematical theory was to be identified in order to quantitatively describe the experimentally measured drug release patterns and to determine system-specific parameters.

Fig. 2A shows the experimentally determined water content of the different types of implants initially containing 10% propranolol hydrochloride after 3 weeks exposure to phosphate buffer pH 7.4. The observed ranking order: Dynasan 118 (glyceryl tristearate) < Dynasan 120 (hardened soybean oil) < Dynasan 116 (glyceryl tripalmitate) < Sterotex NF (hydrogenated cottonseed oil) < Compritol 888 ATO (glyceryl behenate) < Precirol ATO 5 (glyceryl palmitostearate) agrees very well with the ranking order for drug release. Thus, major parts of the water uptake can be explained by the replacement of released drug. Fig. 2B shows the experimentally measured% lipid erosion of the different implants after 3-week exposure to phosphate buffer pH 7.4 (calculated according to Eq. (2)). Importantly, the loss of matrix former is very limited (below 2%), except for Compritol 888 ATO (glyceryl behenate)-based and Precirol ATO 5 (glyceryl palmitostearate)-based devices (above 5%). This corresponds well with the high drug release rates observed with these two types of implants (Fig. 1). Interestingly, systems based on Precirol ATO 5 of identical composition, but prepared by direct compression, showed significant swelling and crack formation upon contact with the release medium [9]. This was not the case, when the implants were prepared by melting and casting during the observation period (visual observation). This phenomenon can probably be attributed to differences in the microstructure of the implants: In the case of direct compression, the lipid particles are likely to be less intensively bound to each other. As the mathematical modeling of matrix former erosion was beyond the scope of this study, no effort was taken to quantitatively describe drug release from Compritol 888 ATO (glyceryl behenate)- and Precirol ATO 5 (glyceryl palmitostearate)-based implants.

The energy required to break the different types of implants (determined using a texture analyzer) is shown in Fig. 2C. Importantly, the observed ranking order of the lipids does not correspond to the lipid ranking order for drug release (Fig. 1). This is in good agreement with implants of the same composition, but prepared by direct compression [9] and indicates that the mechanical strength of the systems in the dry state (before exposure to the release medium) is not of crucial importance for the control of drug release. From a practical point of view, all implants were sufficiently stable to allow for convenient handling. Interestingly, all implants required less energy to be broken than systems of identical composition prepared by direct compression [9].

3.3. Thermal properties

When using lipid matrix formers, great attention must be paid to their physical state in the dosage form and potential changes

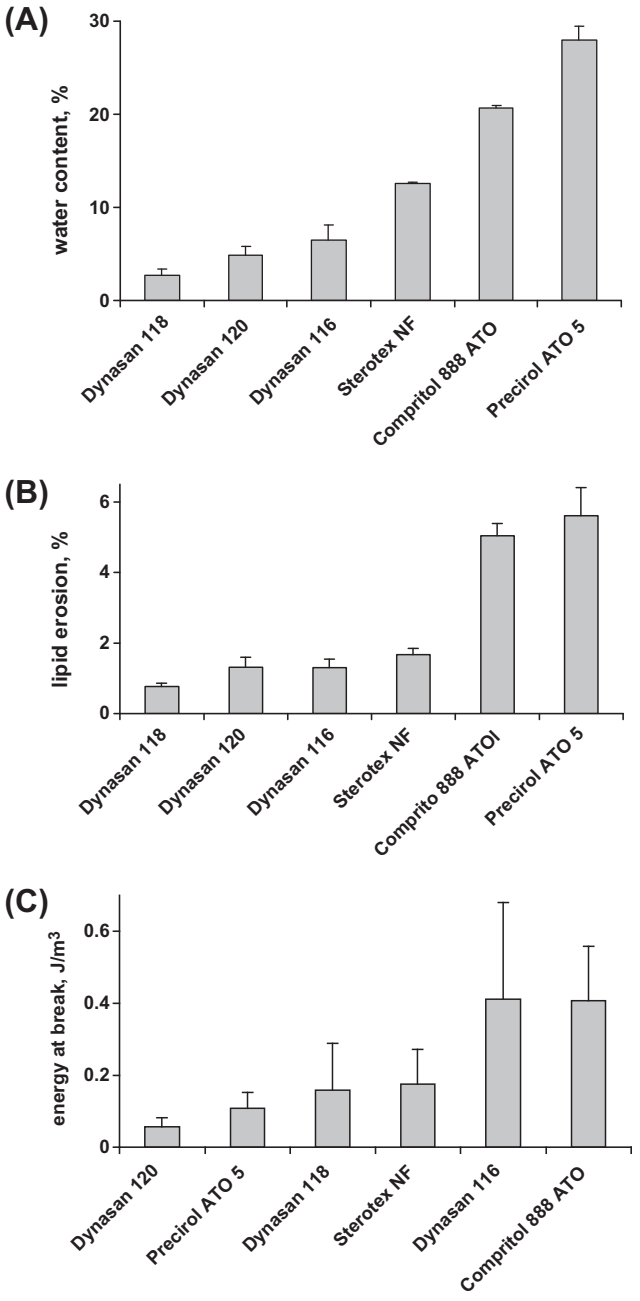

Fig. 2. Effects of the type of matrix former on the: (A) water content of propranolol hydrochloride-loaded implants after 3 weeks exposure to phosphate buffer pH 7.4, (B) % lipid erosion of propranolol hydrochloride-loaded implants after 3 weeks exposure to phosphate buffer pH 7.4, and (C) energy at break of propranolol hydrochloride-loaded implants before exposure to the release medium (10% initial drug loading).

thereof during long-term storage. Many lipids are well known to be able to crystallize in different polymorphs [24,25,33]. As the implants in this study were prepared by melting and casting, it was important to determine the physical state of the lipids in the systems. To allow for potential transformations from instable/metastable polymorphs into the most stable crystalline form, all implants were tempered for 2 weeks at 50 °C in an oven after preparation. Fig. 3 shows the DSC thermograms of the different types of implants (thin black curves) (one heating cycle, heating rate = 5 °C/min). For reasons of comparison, also the DSC thermograms of the lipid powders (sieved raw materials) used for implant preparation are shown. In these cases, 2 heating cycles were run. The thin black curves show the first heating cycle (heating rate = 5 °C/min), at the end of which the samples were hold for 5 min at 90 °C before cooling at 10 °C/min (gray curves) and reheating at 5 °C/min (thick black curves). As it can be seen, all lipid raw materials showed one unique melting peak at relatively high temperatures, indicating that the lipid is likely to be present in a stable crystalline modification. In contrast, upon cooling at 10 °C/min, several instable/metastable modifications were crystallized, which melted at lower temperatures than the raw materials. The only exception was Compritol 888 ATO (glyceryl behenate), which crystallized during the DSC measurements in a stable modification. Most importantly, all implants (tempered for 2 weeks at 50 °C) showed only one unique melting peak of the respective lipids, which corresponded to the melting peak of the most stable crystalline state. This is very important from a practical point of view: changes of the lipids' structure due to polymorph transformations during long-term storage are highly unlikely.

3.4. Drug release mechanisms

Based on these experimental results, an appropriate mathematical theory was to be identified allowing to quantitatively describe drug release from the investigated lipid implants prepared by melting and casting. The model considers that:

- The implants are cylindrical in shape.
- The systems do not significantly swell and do not erode during the observation period [Compritol 888 ATO (glyceryl behenate)- and Precirol ATO 5 (glyceryl palmitostearate)-based systems were not modeled].
- Perfect sink conditions are maintained in the surrounding bulk fluid during the entire release periods.
- Drug dissolution and drug diffusion though the liquid unstirred boundary layers surrounding the implants are much more rapid than water and drug diffusion through the implant.

It has recently been reported that water diffusion into lipid implants or the diffusion of dissolved drug out of the systems plays a major role for the control of drug release, if the dosage forms were prepared by direct compression of drug–lipid powder blends [9]. For this reason, in the present study, the analogous assumption was made for implants prepared by melting and casting. However, it must be pointed out that significant differences are likely to exist with respect to the microstructure of the systems, as discussed earlier. And the microstructure of these implants is of crucial importance for diffusional mass transport of water and dissolved drug molecules.

Based on these hypotheses, the following analytical solution of Fick's second law (considering time-independent diffusivities) can be derived using the method of Laplace transformation [34]:

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot \exp\left(-\frac{q_n^2}{R^2} \cdot D \cdot t\right) \cdot \sum_{p=0}^{\infty} \frac{1}{(2 \cdot p + 1)^2} \cdot \exp\left(-\frac{(2 \cdot p + 1)^2 \cdot \pi^2}{H^2} \cdot D \cdot t\right) \quad (4)$$

where M_t and M_∞ represent the absolute cumulative amounts of drug released at time t and infinite time, respectively; q_n are the roots of the Bessel function of the first kind of zero-order [$J_0(q_n) = 0$], R and H denote the radius and height of the cylinder, and D represents either the diffusion coefficient of the drug or of water. For the implementation of the mathematical model, the programming language C++ was used.

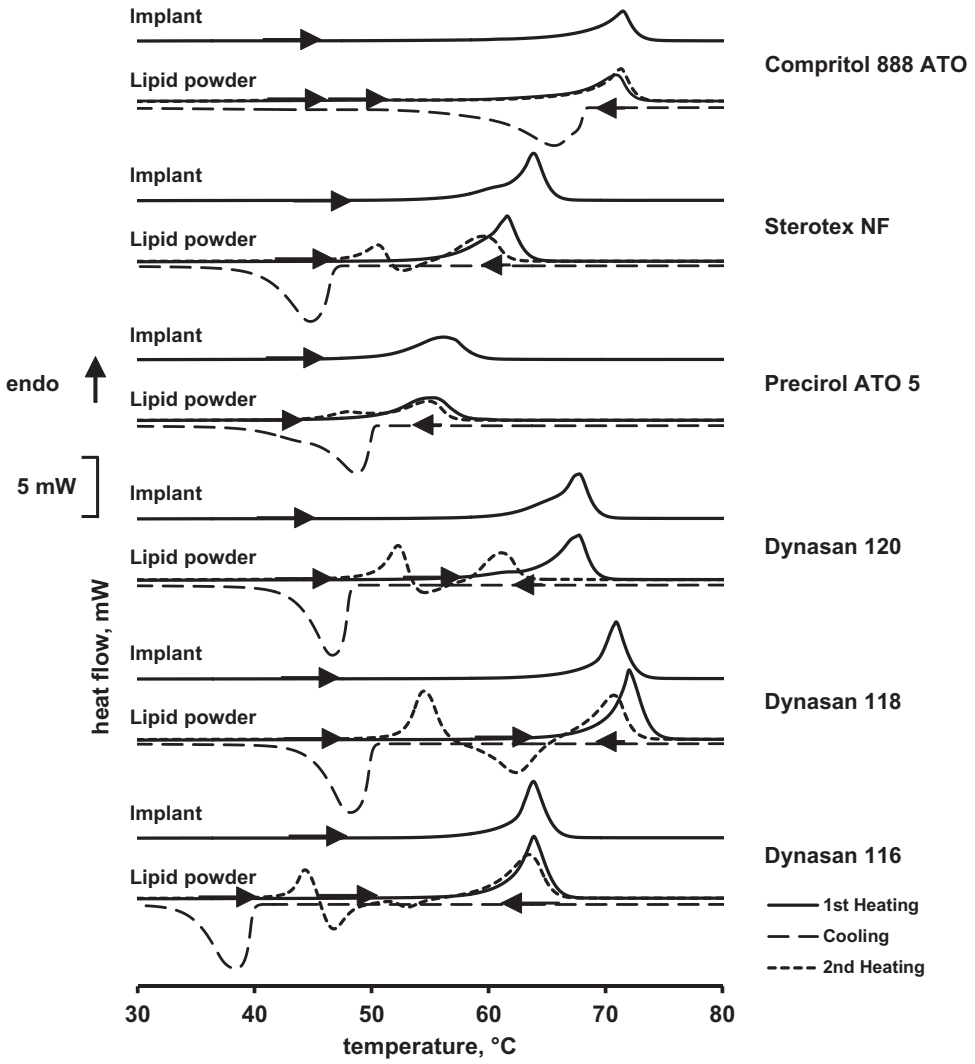

Fig. 3. DSC thermograms of implants based on different types of matrix formers (indicated in the diagram) containing 10% propranolol hydrochloride after 2 weeks tempering at 50 °C (thin black curves). For reasons of comparison, also DSC thermograms of the respective lipid powders are shown.

When fitting Eq. (4) to the experimentally determined drug release kinetics from Sterotex NF (hydrogenated cottonseed oil)-based, Dynasan 116 (glyceryl tripalmitate)-based, Dynasan 120 (hardened soybean oil)-based and Dynasan 118 (glyceryl tristearate)-based implants into phosphate buffer pH 7.4, good agreement was obtained in the first two cases, but significant and systematic deviations were observed in the latter two cases (Fig. 1: curves = theory, symbols = experiments). This indicates that either the diffusion of water into the Sterotex NF (hydrogenated cottonseed oil)-and Dynasan 116(glyceryl tripalmitate)-based implants or the diffusion of propranolol hydrochloride out of these systems is release rate controlling. Based on these calculations, the apparent diffusion coefficients of water or propranolol hydrochloride in the investigated implants could be determined: $D = 1.1 \times 10^{-9}\,cm^2/s$ and $0.7 \times 10^{-9}\,cm^2/s$ for Sterotex NF (hydrogenated cottonseed oil)- and Dynasan 116 (glyceryl tripalmitate)-based systems. It has to be pointed out that the available experimental data do not allow distinguishing between a drug release control by *water* diffusion or by *drug* diffusion. In contrast, the poor agreement between theory and experiment in the case of Dynasan 120 (hardened soybean oil)- and Dynasan 118 (glyceryl tristearate)-based implants clearly indicates that not only diffusional mass transport is of importance. One possible explanation is the fact that only very limited amounts of water penetrate into these systems (Fig. 2A), not being able to dissolve all drug. Thus, parts of the propranolol hydrochloride are likely to be not dissolved and hence not available for diffusion. This is consistent with the observation that the poor agreement was observed in the case of the most slowly releasing implants (Fig. 1).

3.5. Impact of the initial drug loading, implant dimensions and type of drug

Fig. 4A shows the effects of increasing the initial propranolol hydrochloride loading of Dynasan 120 (hardened soybean oil)-based implants on the resulting drug release kinetics in phosphate buffer pH 7.4. The drug content was varied from 10% to 40%, as indicated. Clearly, there was a significant increase in the release rate, which is consistent with reports in the literature [2,9] and can be attributed to the higher implant porosity upon drug depletion: many more and much larger pores are created in the lipid matrix, facilitating the release of the remaining drug. Importantly, the underlying drug release mechanism changed when increasing the initial drug content from 10 to 20 (and more)%: The curves in Fig. 4A show the fittings of Eq. (4) to the experimentally measured drug release kinetics. Only at the lowest initial drug loading, the

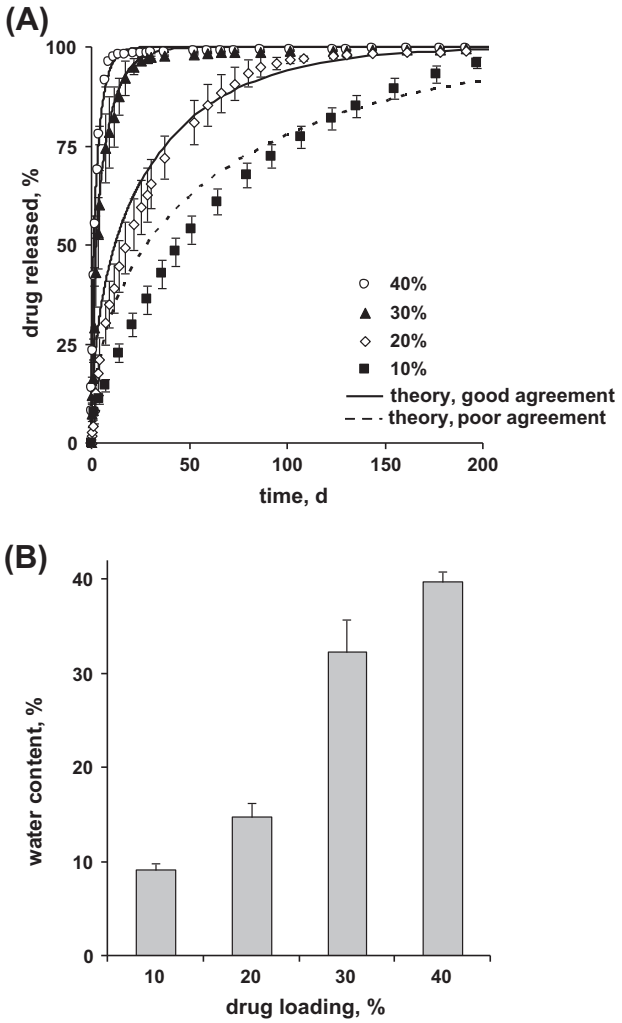

Fig. 4. Effects of the drug loading (indicated in the diagrams) on: (A) propranolol hydrochloride release from Dynasan 120-based implants into phosphate buffer pH 7.4 [diameter: 3 mm; symbols: experimental results; curves: fitted theory (Eq. (4)) (solid curves: good agreement; dashed curve: poor agreement)] and (B) the water contents of Dynasan 120-based implants after 270 d exposure to the release medium.

agreement between theory and experiment was poor (dashed curve). This is consistent with the hypothesis that the observed deviation can at least partially be attributed to limited drug solubility effects, as discussed earlier. At higher initial drug contents, more water penetrates into the system (replacing released propranolol hydrochloride) (Fig. 4B), allowing for complete dissolution of the remaining drug.

According to the hypothesized drug release mechanism (diffusion of water or drug playing a decisive role in all systems), it should be expected that changes in the device dimensions should affect the resulting drug release kinetics. Fig. 5 shows the release of propranolol hydrochloride from Precirol ATO 5 (glyceryl palmitostearate)-, Sterotex NF (hydrogenated cottonseed oil)-, Dynasan 120 (hardened soybean oil)- and Dynasan 118 (glyceryl tristearate)-based implants into phosphate buffer pH 7.4 with a diameter of only 2 mm. These release profiles can be compared with those illustrated in Fig. 1 from implants of identical composition, but with a diameter of 3 mm (the height was constant in all cases = 2 mm) (note the different scaling of the *x*-axis). As it can be seen, decreasing the implants diameter resulted in an increase in the release rate, irrespective of the type of lipid. This is in good agreement with the hypothesized drug release mechanism:

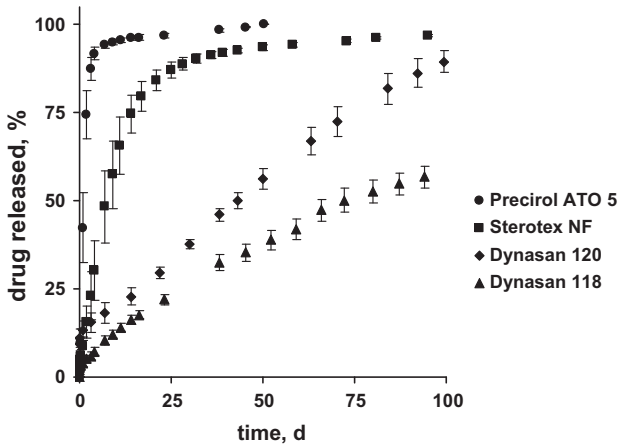

Fig. 5. Propranolol hydrochloride release into phosphate buffer pH 7.4 from implants based on different types of lipids (indicated in the diagram) with a diameter of 2 mm (10% initial drug loading).

a decrease in the cylinder's diameter results in decreased lengths of the diffusion pathways for water and the drug and thus increased concentration gradients, the driving forces for diffusion.

In the case of predominantly diffusion controlled drug delivery systems [Sterotex NF (hydrogenated cottonseed oil) and Dynasan 116 (glyceryl tripalmitate)-based implants], the presented mathematical theory allows to quantitatively *predict* the effects of the implant dimensions on the resulting drug release kinetics. Once the apparent diffusion coefficient of water or the drug in the respective implants is known, Eq. (4) can be used to calculate the release profiles for arbitrary implants heights and diameters. To evaluate the validity of the proposed theory, the effects of varying the system's diameter from 3 to 2 or 4 mm were theoretically predicted (dotted curves in Fig. 6). As it can be seen, a moderate impact of this formulation parameter on drug release was calculated. The symbols in Fig. 6 represent the independently measured drug release kinetics from these implants. Clearly, good agreement was obtained in all cases. Thus, the hypothesized release mechanism has been confirmed and the practical benefit of Eq. (4) has been demonstrated.

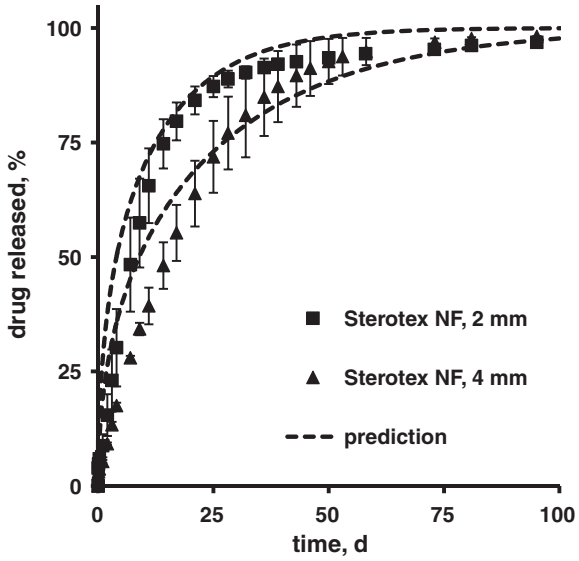

Fig. 6. Theoretical predictions [dotted curves (Eq. (4))] and independent experiments (symbols): Propranolol hydrochloride release into phosphate buffer pH 7.4 from lipid implants with a diameter of 2 or 4 mm, based on Sterotex NF (10% initial drug loading).

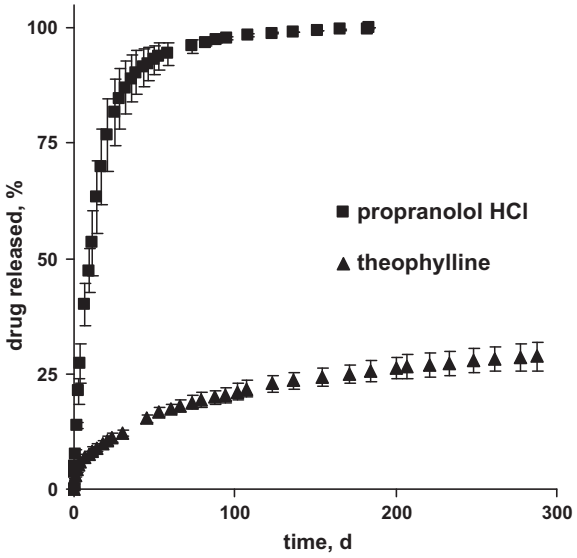

Fig. 7. Effects of the type of drug (indicated in the diagram) on the release kinetics from Sterotex NF-based implants into phosphate buffer pH 7.4 (10% initial drug loading).

Within a few seconds, the effects of changing device dimensions can be simulated in silico, avoiding highly time-consuming experiments.

In order to evaluate the suitability of the presented lipid implants prepared by melting and casting to other types of drugs, also implants containing the sparingly water-soluble drug theophylline were prepared. Fig. 7 shows the drug release from these systems into phosphate buffer pH 7.4. For reasons of comparison, also drug release from propranolol hydrochloride-loaded implants prepared in the same way with the same lipid [in this example Sterotex NF (hydrogenated cottonseed oil)] and with the identical drug:lipid ratio is illustrated. Clearly, theophylline release was much slower than propranolol hydrochloride release, which can probably at least partially be attributed to the lower solubility of this drug. Importantly, the example shows that this type of implants is likely to be appropriate for many drugs.

4. Conclusion

The obtained new insight into the mass transport mechanisms controlling drug release from lipid implants prepared by melting and casting can help facilitating the optimization of this type of advanced drug delivery systems: the effects of formulation parameters on the resulting drug release patterns can be simulated in silico. This is particularly important if long release periods are targeted, requiring time-intensive experimental studies. Drug or water diffusion plays a major role for the control of drug release, potentially combined with limited drug solubility effects, due to the low amounts of water available within the implants. The resulting drug release rates from cast lipid implants are generally lower than those of implants prepared by direct compression, due to the differences in the microstructure of the systems.

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