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Drug release mechanisms of compressed lipid implants

F. Kreye[a,b], F. Siepmann[a,b], J. Siepmann[a,b,*]

[a] University Lille Nord de France, College of Pharmacy, 3 Rue du Prof. Laguesse, 59006 Lille, France
[b] INSERM U 1008, Controlled Drug Delivery Systems and Biomaterials, 3 Rue du Prof. Laguesse, 59006 Lille, France

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ABSTRACT

The aim of this study was to elucidate the mass transport mechanisms controlling drug release from compressed lipid implants. The latter steadily gain in importance as parenteral controlled release dosage forms, especially for acid-labile drugs. A variety of lipid powders were blended with theophylline and propranolol hydrochloride as sparingly and freely water-soluble model drugs. Cylindrical implants were prepared by direct compression and thoroughly characterized before and after exposure to phosphate buffer pH 7.4. Based on the experimental results, an appropriate mathematical theory was identified in order to quantitatively describe the resulting drug release patterns. Importantly, broad release spectra and release periods ranging from 1 d to several weeks could easily be achieved by varying the type of lipid, irrespective of the type of drug. Interestingly, diffusion with constant diffusivities was found to be the dominant mass transport mechanism, if the amount of water within the implant was sufficient to dissolve all of the drug. In these cases an analytical solution of Fick's second law could successfully describe the experimentally measured theophylline and propranolol hydrochloride release profiles, even if varying formulation and processing parameters, e.g. the type of lipid, initial drug loading, drug particles size as well as compression force and time. However, based on the available data it was not possible to distinguish between drug diffusion control and water diffusion control. The obtained new knowledge can nevertheless significantly help facilitating the optimization of this type of advanced drug delivery systems, in particular if long release periods are targeted, which require time consuming experimental trials.

1. Introduction

Many drugs, especially proteins and peptides, necessitate frequent injections or continuous infusion into the human body, due to their short half-lives. Oral administration is often not (yet) possible in these cases, since the drug is degraded within the gastro-intestinal tract. To overcome these restrictions, advanced controlled release implants can be used. The idea is to release the drug at/close to the site of action, providing high local drug concentrations and at the same time minimizing the drug concentrations in the rest of the human body and, thus, minimizing toxic side effects. Nowadays, poly(lactic-co-glycolic acid) (PLGA)-based devices are often the first choice for parenteral controlled drug delivery (Wischke and Schwendeman, 2008; Schoenhammer et al., 2009). But PLGA-based systems degrade into shorter chain acids during drug release, which can result in the creation of acidic microclimates in these systems (Brunner et al., 1999; Li and Schwendeman, 2005) and the subsequent inactivation of acid-labile drugs, e.g. proteins (Lucke and Goepferich, 2003; Na et al., 2003).

An interesting alternative to PLGA-based devices (especially for acid-labile drugs) are lipid implants, since the latter do not show inner acidification. Furthermore, they can be prepared without the use of organic solvents, which are often associated with potential toxicity issues (for the environment and the patient). In addition, no water/organic solvent interfaces are created during manufacturing (which might affect protein integrity) (Van de Weert et al., 2000). First in vivo trials show good biocompatibility of different types of lipid systems (Allababidi and Shah, 1998a; Guse et al., 2006b; Koennings et al., 2007b; Schwab et al., 2008) and long term release up to one month in vitro could be demonstrated for instance with glyceryl tristearate-based implants containing interferon α-2a (Mohl and Winter, 2004). Drug release from the same formulation in vivo (in rabbits) correlated well with the in vitro data during the fist 9 d (Schwab et al., 2008). Also, several studies proved the pharmacodynamic efficiency of lipid implants in vivo (Wang, 1989; Khan et al., 1991, 1993; Allababidi and Shah, 1998a). Of course, lipid implants can also be highly suitable for the controlled release of non-protein drugs (Allababidi and Shah, 1998b). For example, glyceryl monostearate-based implants were successfully used for

* Corresponding author at: University Lille Nord de France, College of Pharmacy, INSERM U 1008, 3, rue du Professeur Laguesse, 59006 Lille, France. Tel.: +33 3 20964708; fax: +33 3 20964942.
E-mail address: juergen.siepmann@univ-lille2.fr (J. Siepmann).

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the local release of vancomycin for the prophylaxis of prosthetic device-related infections (Chilukuri and Shah, 2005).

For these reasons research on lipid implants has gained increasing interest during the last years (Opdebeeck and Tucker, 1993; Wang, 1999; Mohl and Winter, 2004; Lee et al., 2005; Guse et al., 2006a; Koennings et al., 2006; Herrmann et al., 2007a, 2007b; Koennings et al., 2007c; Kreye et al., 2008; Myschik et al., 2008; Siepmann et al., 2008). However, the effects of various processing and formulation parameters on drug release are still not well understood and contradictory tendencies have been reported in the literature. For instance, increasing as well as decreasing drug release rates have been described when increasing the drug particle size (Siegel and Langer, 1984; Kaewvichit and Tucker, 1994; Guse et al., 2006a). Lipid implants can be prepared using different techniques, including direct compression (Mohl and Winter, 2004; Koennings et al., 2007b), melting techniques (Yamagata et al., 2000) and extrusion (Schulze and Winter, 2009). It can be expected that the type of preparation technique can significantly affect the resulting micro- and macro-structure of the implant. So far, the underlying mass transport mechanisms in the respective systems are not well understood and mathematical modeling of drug release has only been reported for a few cases (Siepmann and Siepmann, 2008).

The aim of this study was to elucidate the drug release mechanisms in implants prepared by direct compression of drug-lipid powder blends. Different matrix formers were studied, namely monoacid triglycerides [glyceryl trimyristate (Dynasan 114), glyceryl tripalmitate (Dynasan 116) and glyceryl tristearate (Dynasan 118)], blends of mono-, di- and triglycerides [glyceryl palmitostearate (Precirol ATO 5), or hydrogenated natural fats [hydrogenated cottonseed oil (Sterotex NF) and hydrogenated soybean oil (Dynasan 120)]. Two model drugs have been investigated: theophylline being sparingly water-soluble and propranolol hydrochloride being freely water-soluble. Based on a thorough physico-chemical characterization of the systems before and after exposure to the release medium, an appropriate mathematical theory was used to better understand the underlying mass transport mechanisms.

2. Materials and methods

2.1. Materials

Glyceryl trimyristate, glyceryl tripalmitate, glyceryl tristearate and hardened soybean oil (Dynasan 114, 116, 118, and 120; Sasol, Witten, Germany); hydrogenated cottonseed oil (Sterotex NF; Abitec, Ohio, USA); glyceryl palmitostearate (Precirol ATO 5; Gattefosse, Saint-Priest, France); propranolol hydrochloride (Salutas, Barleben, Germany); theophylline (anhydrous theophylline; BASF, Ludwigshafen, Germany); cyclohexane (Merck, Darmstadt, Germany); polysorbate20 (Montanox 20 DF; Seppic, Paris, France).

2.2. Particle size measurements

Particle sizes were determined by laser diffraction (Mastersizer S, 300F lens, measurement time 4 s, 1.5 bar; Malvern, Orsay, France). Indicated average particle sizes are *D* 0.5 values. All experiments were performed in triplicate.

2.3. Implant preparation

The lipid powders were sieved (selected sieve fraction: 50–100 μm; Retsch, Haan, Germany) and blended with the drugs [theophylline: used as received; propranolol hydrochloride was sieved (selected sieve fraction: 50–100 μm) or milled with a ball mill, as indicated] using a vortex mixer for 10 s (level 4, Vortex-2 Genie; Scientific Industries, Bohemia, NY, USA) in a glass vial. Potentially observed lumps were crushed with a spatula. The drug:lipid powder blends were compressed with a Frank press (Universalpruefmaschine 81816; Karl Frank, Weinheim-Birkenau, Germany) (matrix diameter: 2 mm, implant height: 2 mm). The compression force was 300 N and the compression time 10 s, if not otherwise stated. The drug loading was 10, 20 or 30% (w/w), as indicated.

2.4. In vitro release studies

Implants were placed in 2 mL Eppendorf tubes, filled with 1.5 mL phosphate buffer pH 7.4 (USP 32), optionally containing 0.1% polysorbate 20. The tubes were horizontally shaken at 37 °C (80 rpm; GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). In the case of hydrogenated cottonseed oil-based implants, device floating was avoided by a steel mesh, which was introduced into the Eppendorf tube (all other implants did not float during the observation period). At predetermined time points, the release medium was completely replaced with fresh phosphate buffer pH 7.4, and the drug content in the withdrawn bulk fluid 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 3 times extracted into 5 mL 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).

2.5. Water uptake and lipid matrix erosion studies

Implants were treated as described in Section 2.4. At predetermined time points the implants were withdrawn from the release medium, 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:

$$\text{water content}\,(\%)(t) = \frac{\text{wet mass}\,(t) - \text{dry mass}\,(t)}{\text{wet mass}\,(t)} \times 100 \qquad (1)$$

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

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.

2.6. 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 towards the implant). Load versus displacement curves were recorded until implant rupture and used to determine the energy required to break the systems as follows:

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

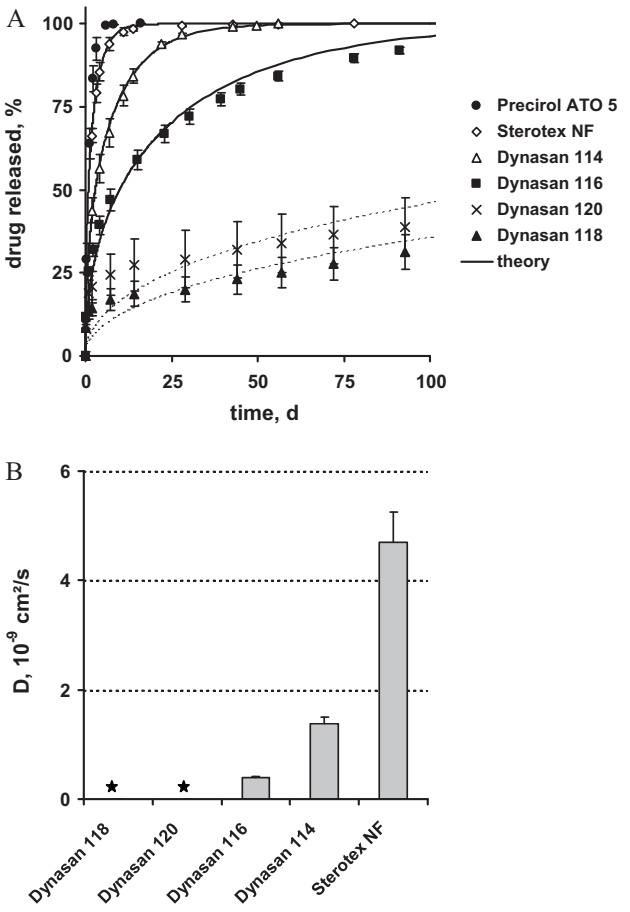

Fig. 1. Effects of the type of lipid on: (A) theophylline release from implants in phosphate buffer pH 7.4 [symbols: experimental results; curves: fitted theory (Eq. (4)); drug release from glyceryl palmitostearate-based implants was not modeled due to significant device swelling], (B) the apparent diffusion coefficient of theophylline or water within the implants (initial drug loading = 10%). The dotted curves and stars indicate that the agreement between theory and experiment was poor.

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

2.7. Implant morphology

Scanning electron microscopy (SEM) was used to characterize the internal and external morphology of the implants (S-2700; Hitachi High-Technologies Europe, Krefeld, Germany) at magnifications of 300× and 1000× after covering the samples under an argon atmosphere with a fine gold layer (20 nm; SCD 030; BAL-TEC, Witten, Germany). Macroscopic pictures were taken using a Nikon SMZ-U macroscope (Nikon, Tokyo, Japan), equipped with a Sony Hyper HAD camera (Sony, Tokyo, Japan).

3. Results and discussion

3.1. Theophylline release from lipid implants

The symbols in Fig. 1A show the experimentally determined theophylline release kinetics from implants based on different types of lipids into phosphate buffer pH 7.4. Clearly, broad spectra of drug release patterns can be provided by simply varying the type of matrix former. The initial drug loading of the systems was 10%, the mean particle size of the drug was 12 ± 0.8 μm. The release rate drastically decreased in the following ranking order: glyceryl palmitostearate (Precirol ATO 5) > hydrogenated cottonseed oil (Sterotex NF) > glyceryl trimyristate (Dynasan 114) > glyceryl tripalmitate (Dynasan 116) > hardened soybean oil (Dynasan 120) > glyceryl tristearate (Dynasan 118). Thus, selecting the appropriate type of lipid, desired drug release rates can easily be achieved. The ranking order of the triglycerides is in good agreement with the one observed by Koennings et al. (2007a) and Windbergs et al. (2009). Interestingly, even very long time periods with controlled drug release can be provided for this low molecular weight model drug. However, theophylline exhibits a relatively low water-solubility [12.0 ± 0.1 mg/mL at 37 °C in phosphate buffer pH 7.4 (Bodmeier and Chen, 1989)] and its release is likely to be more sustained than the release of a freely water-soluble drug, such as propranolol hydrochloride [solubility in phosphate buffer pH 7.4 at 37 °C: 219.9 ± 5.7 mg/mL (Bodmeier and Chen, 1989)].

3.2. Propranolol hydrochloride release from lipid implants

The symbols in Fig. 2A show the respective experimentally measured propranolol hydrochloride release profiles from implants based on the same types of lipids as shown in Fig. 1A, with the identical initial drug loading (10%, w/w). Clearly, drug release was much faster than in the case of theophylline, irrespective of the type of lipid (Fig. 2A vs. 1A, note the different scaling of the x-axes). This is likely to be at least partially attributable to the fact that the amount of water penetrating into the implants is limited and in the case of theophylline insufficient to dissolve all drug. Thus, parts of the latter remain un-dissolved and, hence, unavailable for diffusion. Note that the particle size of the two drugs is similar (average size = 12 μm in both cases). Consequently, the impact of this formulation parameter on drug release is likely to be negligible when comparing the two types of systems. It has to be pointed out that even in the case of the freely water-soluble propranolol hydrochloride controlled release during about 1 month can be achieved using glyceryl tristearate as matrix former. Interestingly, the ranking order, in which the release rate decreased, was almost identical to the ranking order observed with theophylline-loaded implants: glyceryl palmitostearate (Precirol ATO 5) > glyceryl trimyristate (Dynasan 114) > hydrogenated cottonseed oil (Sterotex NF) > glyceryl tripalmitate (Dynasan 116) > hardened soybean oil (Dynasan 120) > glyceryl tristearate (Dynasan 118). Importantly, as in the case of theophylline, the variation of the type of matrix former allowed to provide a large spectrum of possible drug release patterns (with release periods ranging in this case from 1 d to 1 month).

3.3. Drug release mechanisms

To better understand the underlying drug release mechanisms from this type of advanced delivery systems, the implants were physico-chemically characterized before and upon exposure to the release medium. Based on these experimental results, an appropriate mathematical theory was to be identified and used to determine system specific parameters. Fig. 3A shows a macroscopic picture of a propranolol hydrochloride-loaded implant based on hardened soybean oil before exposure to the release medium. As it can be seen, the implant's surface was smooth and did not show any evidence for inhomogeneous drug distribution. The same was true for all other types of implants (data not shown). Fig. 3B shows a SEM picture of the implant's surface. Clearly, very tiny pores are visible and likely to form a highly interconnected network. This hypothesis was confirmed by SEM pictures of cross-sections, an example being illustrated in Fig. 3C. In this cross-section, also a drug particle is visible (marked by a white circle) as well as an empty cavity, which probably hosted a drug particle prior to sample preparation (breaking of the implant). All other implants showed similar morphologies (data not shown). Thus, based on these pictures it can be hypothe-

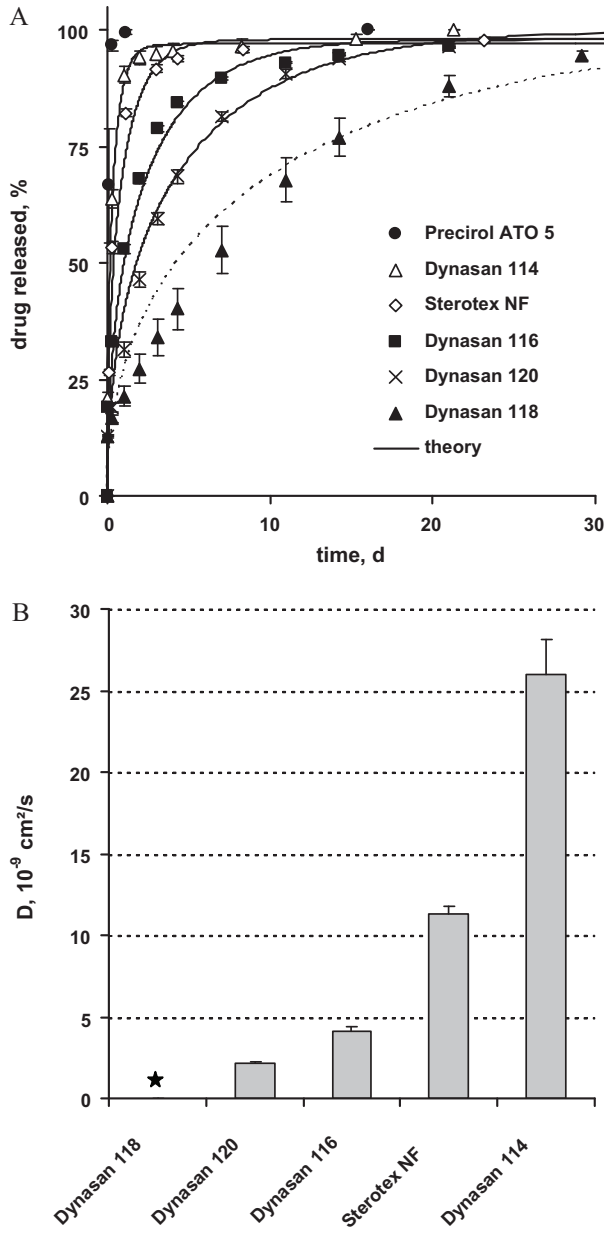

Fig. 2. Effects of the type of lipid on: (A) propranolol hydrochloride release from implants in phosphate buffer pH 7.4 (mean drug particle size: 12 μm) [symbols: experimental results; curves: fitted theory (Eq. (4)); drug release from glyceryl palmitostearate-based implants was not modeled due to significant device swelling], (B) the apparent diffusion coefficient of propranolol hydrochloride or water within the implants (initial drug loading = 10%). The dotted curve and the star indicate that the agreement between theory and experiment was poor.

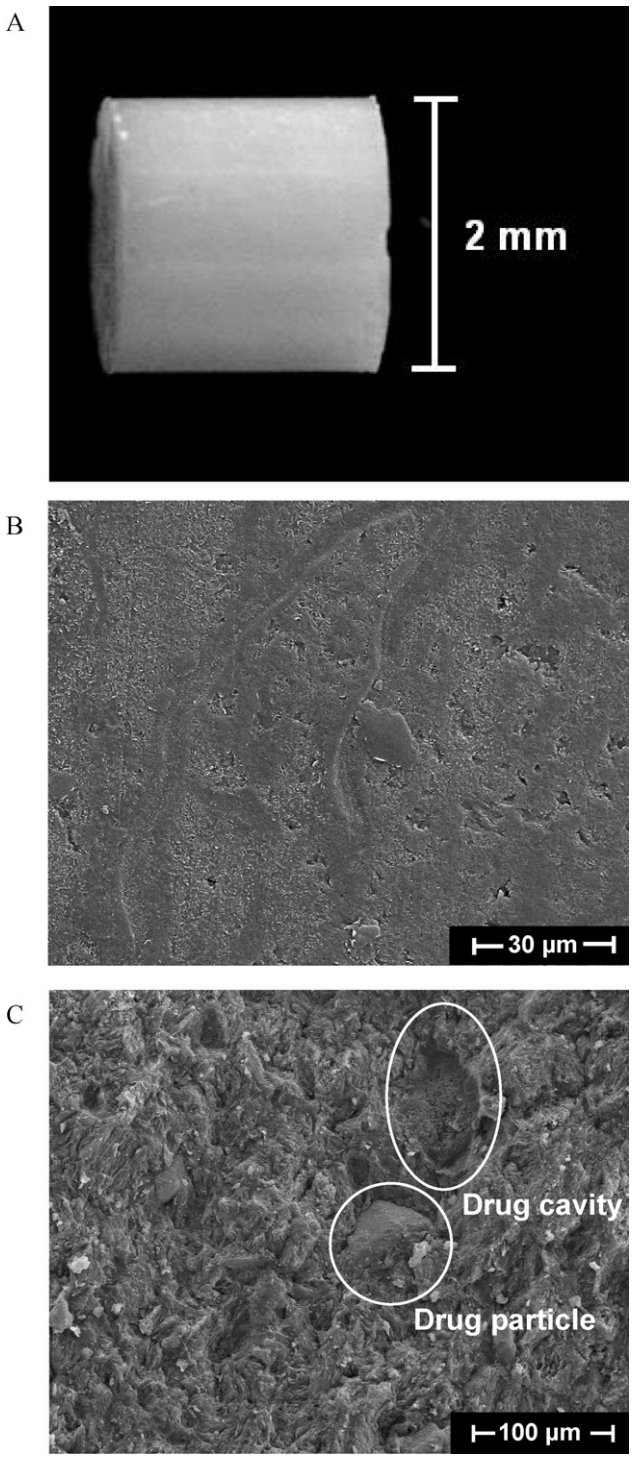

Fig. 3. Macro- and microscopic pictures of propranolol hydrochloride loaded implants based on hardened soybean oil before exposure to the release medium: (A) Macroscopic picture of the entire implant, (B) SEM picture of the implant's surface, and (C) SEM picture of a cross-section of the implant (a drug cavity and a drug particle are marked).

sized that highly interconnected networks of very tiny pores exist within the cylinders, which can be filled with water upon contact with aqueous body fluids. Due to concentration gradients dissolved drug can be expected to diffuse out through these channels into the surrounding bulk fluid. So, one of the major driving forces for drug release is likely to be diffusion.

Fig. 4 shows macroscopic pictures of: (A) glyceryl palmitostearate- based implants, and (B) hydrogenated cottonseed oil-based implants, loaded with theophylline after 1 d exposure to phosphate buffer pH 7.4 (the initial drug content was 10%). Clearly, glyceryl palmitostearate-based devices showed significant swelling and even crack formation, whereas hydrogenated cottonseed oil-based implants remained intact and did not significantly swell (the same was true for all other types of lipids, data not shown). Fig. 5 shows the water content of theophylline-loaded implants (mean particle size 12 μm) (white bars) and propranolol hydrochloride-loaded implants with a mean particle size of 12 μm (gray bars) or 68 μm (black bars) after 7 d exposure to phosphate buffer pH 7.4. As it can be seen, glyceryl palmitostearate-based implants took up much more water than

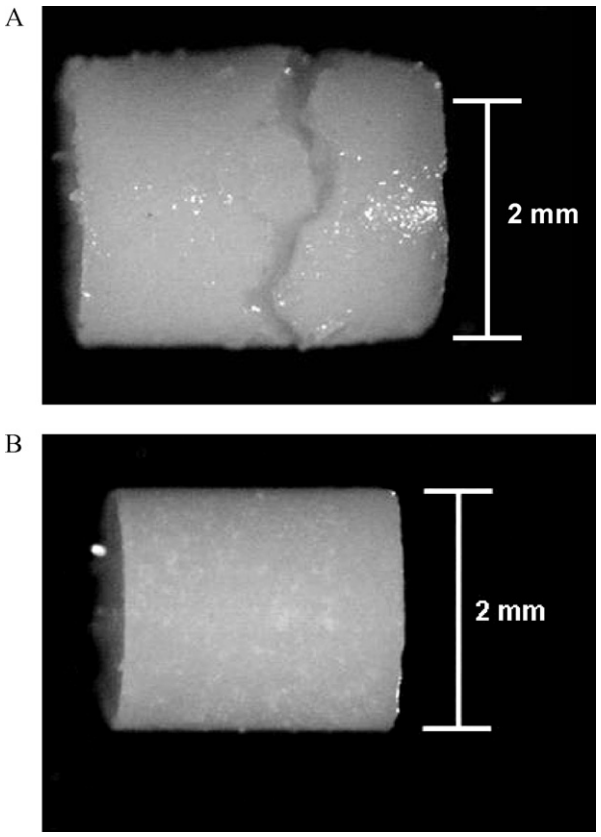

Fig. 4. Macroscopic pictures of theophylline loaded implants based on: (A) glyceryl palmitostearate, and (B) hydrogenated cottonseed oil after 1 d exposure to phosphate buffer pH 7.4 (initial drug loading = 10%).

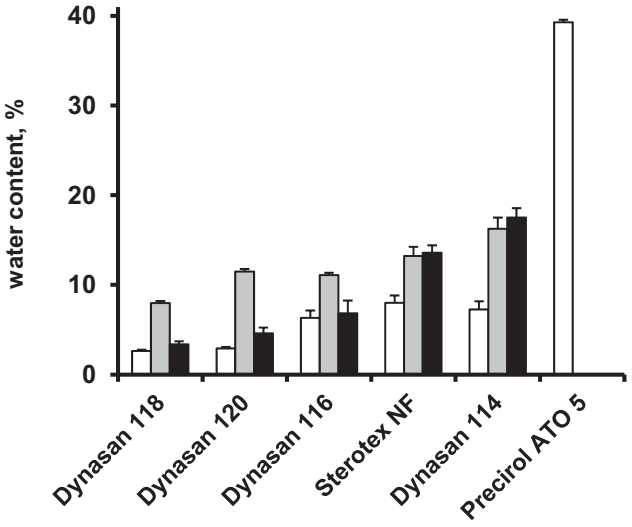

Fig. 5. Effects of the type of lipid on the water content of implants after 7 d exposure to phosphate buffer pH 7.4. White bars indicate implants loaded with theophylline and a mean particle size of 12 μm; gray bars indicate implants loaded with propranolol hydrochloride and a mean particle size of 12 μm; black bars indicate implants loaded with propranolol hydrochloride and a mean particle size of 68 μm (* = not detectable).

all other implants: Almost 40% of the system was pure water after only 7 d. This very high water content explains the significant swelling (Fig. 4A) and the very fast drug release, irrespective of the type of drug (Figs. 1 and 2). In contrast, the water uptake of all other implants was limited, not exceeding 8% in the case of theophylline, and 16% in the case of propranolol hydrochloride (mean particle size – 12 μm). This water uptake can at least partially be attributed to the replacement of released drug by water (Figs. 1 and 2A), but also to water penetration into already pre-existing pores (Fig. 3B and C). The first explanation is consistent with the observation that the ranking order of the water contents of the implants corresponds well to the ranking order of the observed drug release rates: glyceryl palmitostearate (Precirol ATO 5) > hydrogenated cottonseed oil (Sterotex NF) > glyceryl trimyristate (Dynasan 114) > glyceryl tripalmitate (Dynasan 116) > hardened soybean oil (Dynasan 120) > glyceryl tristearate (Dynasan 118) in the case of *theophylline*, and glyceryl palmitostearate (Precirol ATO 5) > glyceryl trimyristate (Dynasan 114) > hydrogenated cottonseed oil (Sterotex NF) > glyceryl tripalmitate (Dynasan 116) > hardened soybean oil (Dynasan 120) > glyceryl tristearate (Dynasan 118) in the case of *propranolol hydrochloride* (mean particle size 12 μm).

The mechanical stability of the investigated implants was determined using a texture analyzer. The energy required to break theophylline- and propranolol hydrochloride-loaded devices using a flat-face, cylindrical probe was measured before and after 7 d exposure to phosphate buffer pH 7.4 (Table 1). Importantly, all systems showed a sufficient mechanical stability allowing for convenient implant handling. Looking at Table 1 and Figs. 1 and 2A, it can be seen that there is no evident relationship between the mechanical stability of the implants and their release rates. For instance, glyceryl tripalmitate (Dynasan 116)-based devices required the *highest* energies to be broken, irrespective of the type of drug. However, *intermediate* theophylline and propranolol hydrochloride release rates were observed from these systems. Furthermore, it can be seen in Table 1 that the implants become more fragile upon drug exhaust, irrespective of the type of drug and type of lipid. This can at least partially be attributed to the increasing porosity of the systems upon theophylline and propranolol hydrochloride leaching. As the latter drug is released more rapidly, also the decrease in the mechanical stability is generally more pronounced (Table 1).

For the mathematical modeling of drug release from a matrix system, it is important to know whether the matrix former erodes during drug release, or not. Table 2 shows the % erosion of the investigated implants (containing either theophylline or propranolol hydrochloride) after 7 d exposure to phosphate buffer pH 7.4

Table 1
Energy at break (J/m^3) (± standard deviation, $n = 3$) of implants loaded with propranolol hydrochloride (mean particle size: 12 μm) or theophylline (mean particle size: 12 μm) before and after 7 d exposure to phosphate buffer pH 7.4 (* = not detectable).

Matrix former	Theophylline		Propranolol hydrochloride	
	Before exposure	After exposure	Before exposure	After exposure
Glyceryl palmitostearate	0.2 ± 0.0	0.0 ± 0.0	0.2 ± 0.0	*
Hydrogenated cottonseed oil	0.3 ± 0.0	0.1 ± 0.0	0.4 ± 0.0	0.2 ± 0.0
Dynasan 114	0.7 ± 0.1	0.3 ± 0.0	0.7 ± 0.2	0.2 ± 0.0
Dynasan 120	0.9 ± 0.1	0.7 ± 0.1	1.0 ± 0.1	0.4 ± 0.0
Dynasan 118	1.3 ± 0.1	0.8 ± 0.1	1.4 ± 0.1	0.4 ± 0.2
Dynasan 116	1.4 ± 0.1	0.6 ± 0.1	1.9 ± 0.2	0.4 ± 0.0

Table 2
Erosion (%) of the lipid matrices (± standard deviation, $n = 3$) of implants loaded with propranolol hydrochloride (mean particle size: 12 μm) or theophylline (mean particle size: 12 μm) after 7d exposure to phosphate buffer pH 7.4 (* = not detectable) [calculated according to Eq. (2)].

Matrix former	Erosion (± SD) (%) of implants loaded with	
	Propranolol HCl	Theophylline
Glyceryl palmitostearate	*	2.3 ± 0.4
Hydrogenated cottonseed oil	2.4 ± 2.5	0.8 ± 0.4
Dynasan 114	0.0 ± 0.2	1.4 ± 0.2
Dynasan 120	0.2 ± 0.2	0.2 ± 0.2
Dynasan 118	0.2 ± 0.2	0.2 ± 0.1
Dynasan 116	0.4 ± 0.2	0.4 ± 0.2

(calculated using Eq. (2)). Clearly, in all cases, the erosion was very limited.

3.4. Mathematical modeling

Based on these experimental results, the following mathematical theory was used to describe drug release from the investigated implants, which remained intact throughout the observation period [thus, all implants, except the systems based on glyceryl palmitostearate (Precirol ATO 5)]. The theory is based on the assumption that drug diffusion through the implant is the dominant mass transport step. The model considers:

- Radial as well as axial diffusion in cylinders
- Homogeneous initial drug and lipid distributions throughout the device at t = 0 (before exposure to the release medium)
- Perfect sink conditions throughout the experiments
- Constant implant dimensions during drug release
- Constant apparent drug diffusion coefficients
- Negligible mass transport resistance due to unstirred liquid boundary layers at the surface of the implant.

Under these conditions, the following analytical solution of Fick's second law can be derived using the method of Laplace transformation (Vergnaud, 1993):

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

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 [$J_0(q_n) = 0$], and R and H denote the radius and height of the cylinder. For the implementation of the mathematical model the programming language C++ was used.

The curves in Figs. 1 and 2A show the theoretically calculated theophylline and propranolol hydrochloride release kinetics from the investigated implants into phosphate buffer pH 7.4. The solid curves indicate the systems, for which good to rather good agreement between theory and experiments was observed, the dotted curves indicate significant and systematic deviations. Thus, in many implants diffusion with constant diffusivities seems to be the dominant mass transport mechanism. However, it should be pointed out that Eq. (4) also describes the penetration kinetics of a fluid into a cylindrical dosage form with constant diffusion coefficients and constant device dimensions. In this case, M_t and M_∞, represent the absolute cumulative amounts of the liquid (e.g., water) taken up by the system at time t, and infinite time, and D represents the apparent diffusion coefficient of water. Assuming that *water*, and not *drug* diffusion is release rate-limiting, the same good agreement between theory (Eq. (4)) and experiment could result (since the slowest process in a series of events is the determining one). This would mean that water penetration into the implants is slow, whereas subsequent drug dissolution and diffusion are fast. Consequently, the good agreement between theory and experiment observed in Figs. 1 and 2A (solid curves) might either be attributed to pure *drug* diffusion control, or to pure *water* diffusion control. Based on this data, it is not possible to distinguish between the two mechanisms.

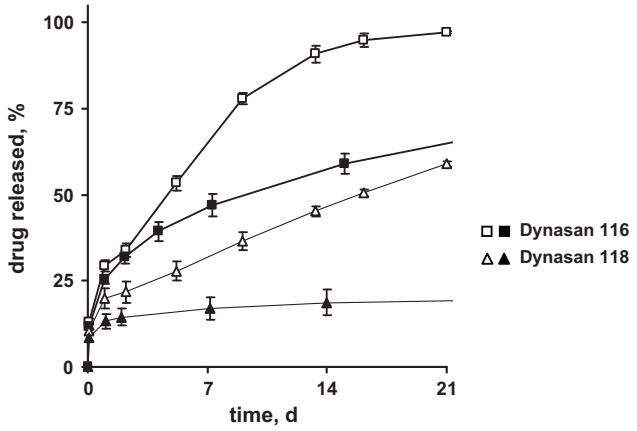

Fig. 6. Importance of the presence/absence of a surfactant (0.1% Polysorbate 20) in the release medium (phosphate buffer pH 7.4): Theophylline release from implants based on Dynasan 116 (squares) or Dynasan 118 (triangles) (filled symbols: without surfactant, open symbols: with surfactant; initial theophylline loading = 10%).

The fact that significant and systematic deviations were observed between Eq. (4) and the experimentally measured drug release patterns in the case of very slowly releasing implants (dotted curves in Figs. 1 and 2A) can serve as an indication for the fact that in these cases also limited drug solubility in the small amounts of available water inside the implants plays a major role (only dissolved drug is able to diffuse out). This hypothesis is consistent with the fact that hardened soybean oil (Dynasan 120)-based implants loaded with the sparingly water soluble drug theophylline show significant deviations between theory (Eq. (4)) and experiment (Fig. 1A), whereas Dynasan 120-based implants loaded with the freely water soluble drug propranolol hydrochloride do not (Fig. 2A) (the amount of water penetrating into these implants seems to be sufficient to dissolve all propranolol hydrochloride, but not all theophylline). Based on these calculations, the apparent diffusion coefficients of theophylline/propranolol hydrochloride or water within the various lipid implants could be determined (Figs. 1 and 2B). Clearly, the mobility of the drugs/water correlates very well with the water contents of the systems upon exposure to the release medium (Fig. 5).

3.5. Impact of a surfactant in the bulk fluid

In order to evaluate the impact of the presence of a surfactant in the surrounding bulk fluid on the resulting drug release kinetics, theophylline release from implants based on glyceryl tripalmitate (Dynasan 116) and glyceryl tristearate (Dynasan 118) into pure phosphate buffer pH 7.4 and into phosphate buffer pH 7.4 containing 0.1% Polysorbate 20 was studied (open versus closed symbols in Fig. 6). Clearly, in both cases, the release rates significantly increased in the presence of the surfactant. This might be attributable to a facilitated implant wetting upon exposure to the aqueous release medium, resulting in accelerated water uptake, and/or increased local theophylline solubility in the water filled pores of the implant. The results are in good agreement with those

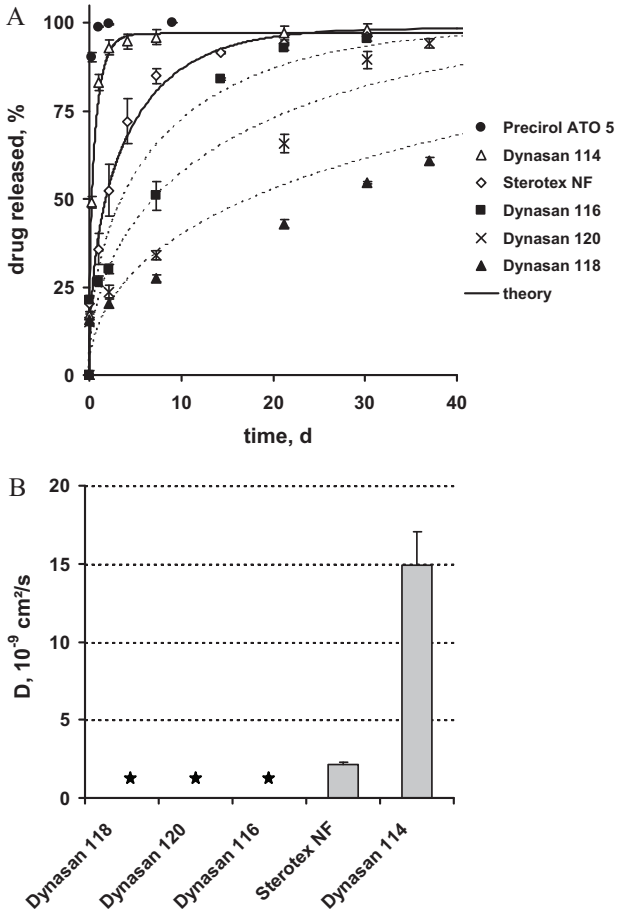

Fig. 7. Effects of the type of lipid on: (A) propranolol hydrochloride (mean particle size: 68 μm) release from implants in phosphate buffer pH 7.4 [symbols: experimental results; curves: fitted theory Eq. (4); drug release from glyceryl palmitostearate-based implants was not modeled due to significant device swelling], (B) the apparent diffusion coefficient of propranolol hydrochloride or water within the implants (initial drug loading = 10%). The dotted curves and the stars indicate that the agreement between theory and experiment was poor.

recently reported in the literature on lipid implants loaded with FITC-dextran (Koennings et al., 2007a).

3.6. Importance of the drug particle size, compression force and time and initial drug loading

In order to evaluate the impact of the size of the drug particles used for implant preparation, the different types of lipid implants were also prepared using propranolol hydrochloride with an average particle size of 68 μm (Fig. 7A). These release profiles are to be compared with those illustrated in Fig. 2A, showing drug release from implants prepared using propranolol hydrochloride with an average particle size of 12 μm (note the different scaling of the *x*-axes). The initial drug loading was identical in all cases (10%). Clearly, the same ranking order of the lipids with respect to the resulting release rate was observed: glyceryl palmitostearate (Precirol ATO 5) > glyceryl trimyristate (Dynasan 114) > hydrogenated cottonseed oil (Sterotex NF) > glyceryl tripalmitate (Dynasan 116) > hardened soybean oil (Dynasan 120) > glyceryl tristearate (Dynasan 118). Furthermore, drug release was faster from the implants containing smaller drug particles, irrespective of the type of lipid. This might be explained by the different pores structures, which are created upon drug leaching: In the case of smaller propranolol hydrochloride particles, more numerous and more interconnected pores are likely to be created, facilitating the diffusion of further water and drug. For this reason, the apparent diffusion coefficients of propranolol hydrochloride or water in the implants were smaller in the case of large drug particles than in the case of small drug particles (Fig. 7B versus 2B). Also, it can be seen that poor agreement between the fittings of Eq. (4) and the experimentally measured release rates was obtained in the case of glyceryl tripalmitate (Dynasan 116) and hardened soybean oil (Dynasan 120) implants prepared with larger drug particles (dotted curves in Fig. 7). This is consistent with the hypothesis that the amounts of water penetrating into the implants are not sufficient in these cases to dissolve all drug, as discussed above.

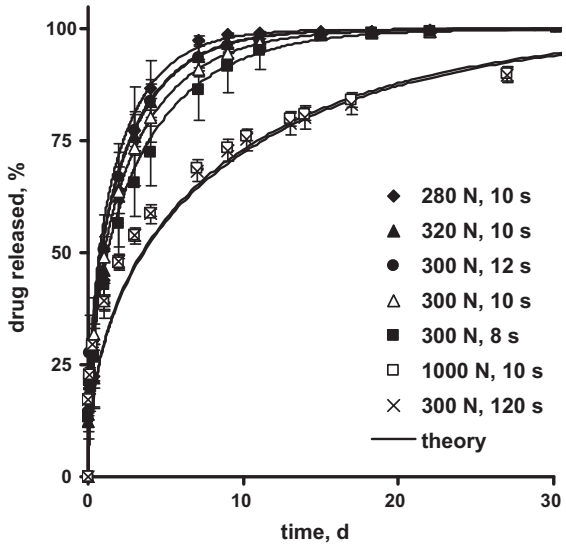

Fig. 8. Impact of the compression force and compression time (indicated in the diagram) on theophylline release from implants based on hydrogenated cottonseed oil in phosphate buffer pH 7.4 [symbols: experimental results; curves: fitted theory (Eq. (4))] (initial theophylline loading = 10%).

The importance of the compression pressure and time for the resulting drug release kinetics from the investigated lipid implants is exemplarily illustrated in Fig. 8. Theophylline-loaded implants based on hydrogenated cottonseed oil (Sterotex NF) were prepared applying 280, 300, 320 or 1000 N for 8 to 120 s. As it can be seen, relatively small variations in the compression force and compression time only have a limited impact on drug release. However, a significant increase in the compression force (1000 N instead of 300 N) led to a significant decrease in the theophylline release rate, probably due to a reduced initial porosity of the implant, resulting in narrower channels through which the water and drug must diffuse. The curves in Fig. 8 show the fitted theory (Eq. (4)). Clearly, good agreement was obtained in all cases. Thus, these processing parameters do not change the dominant underlying release mechanism in the investigated ranges. Based on these calculations, the following apparent theophylline or water diffusivities were determined: $D = 5.5 \times 10^{-9}/3.6 \times 10^{-9}/4.8 \times 10^{-9}/3.2 \times 10^{-9}/4.3 \times 10^{-9}/1.0 \times 10^{-9}/1.0 \times 10^{-9}$ cm/s for implants prepared applying 280 N for 10 s/300 N for 10 s/320 N for 10 s/300 N for 8 s/300 N for 12 s/300 N for 120 s/1000 N for 10 s. From a practical point of view, the importance of accidental variations in these processing parameters during production need to be studied, but are not likely to be a source of major difficulties.

Fig. 9 illustrates the impact of the initial drug loading of the lipid implants on the resulting drug release patterns. In this example, the initial theophylline content of hardened soybean oil (Dynasan 120)-based implants was varied from 10 to 30%. As it can be seen, the variation of this formulation parameter has a dramatic effect

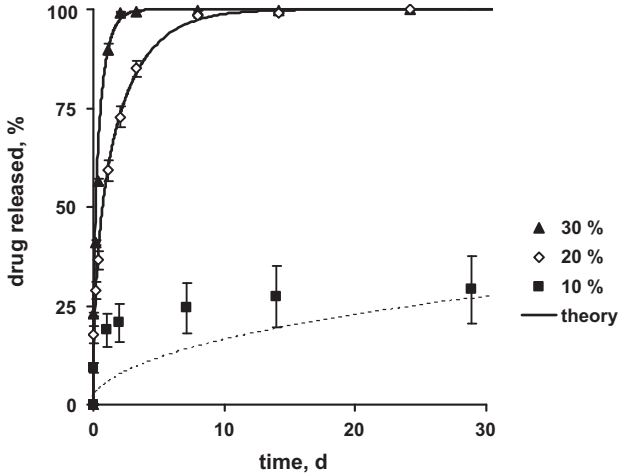

Fig. 9. Effects of the initial drug loading (indicated in the diagram) on theophylline release from implants based on Dynasan 120 in phosphate buffer pH 7.4 [symbols: experimental results; curves: fitted theory Eq. (4)].

on the drug release rate: With increasing drug content, the release rate drastically increased. This can be attributed to the increased porosity of the implants upon drug leaching into the bulk fluid. Interestingly, drug release became predominantly diffusion controlled at 20 and 30% initial drug content (solid curves versus dotted curve in Fig. 9). This is consistent with the hypothesis of limited drug solubility effects at lower initial drug contents, resulting in very limited water uptake upon exposure to the bulk fluid. In contrast, at higher drug loadings, water can much more easily access the drug particles and completely dissolve them. For example, the investigated implants contained 4 versus 29% water in the case of 10 versus 30% initial drug content after 31 d exposure to the release medium.

4. Conclusion

Based on the obtained new insight into the underlying drug release mechanisms in lipid implants the optimization of this type of advanced drug delivery systems can be facilitated. For instance, the impact of the device dimensions (radius and height) on the resulting drug release kinetics can be quantitatively predicted using Equation 4. But also the effects of changes in the formulation (e.g., drug loading or particle size) can be expected to be predictable, if a minimum of experimental results is provided (which allow the establishment of relationships between the diffusion coefficient and the respective formulation parameter). The predictability of drug release from these dosage forms in a mechanistic realistic and quantitative way is particularly helpful in the case of long release periods, which require time-intensive experimental trials.

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