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PLGA-based drug delivery systems: Importance of the type of drug and device geometry

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Abstract

Different types of ibuprofen- and lidocaine-loaded, poly(lactic-co-glycolic acid) (PLGA)-based microparticles and thin, free films of various dimensions were prepared and physico-chemically characterized in vitro. The obtained experimental results were analyzed using mathematical theories based on Fick's second law of diffusion. Importantly, the initial drug loadings were low in all cases (4%, w/w), simplifying the mathematical treatment and minimizing potential effects of the acidic/basic nature of the two model drugs on polymer degradation. Interestingly, the type of drug and device geometry strongly affected the resulting release kinetics and relative importance of the involved mass transport mechanisms. For instance, the relative release rate was almost unaffected by the system size in the case of spherical microparticles, but strongly depended on the thickness of thin, free films, irrespective of the type of drug. Ibuprofen and lidocaine release was found to be primarily diffusion controlled from the investigated PLGA-based microparticles for all system sizes, whereas diffusion was only dominant in the case of the thinnest free films. Interestingly, the type of drug did not significantly affect the resulting polymer degradation kinetics. However, ibuprofen release was always much faster than lidocaine release for all system geometries and sizes. This can probably be attributed to attractive ionic interactions between protonated, positively charged lidocaine ions and negatively charged, deprotonated carboxylic end groups of PLGA, hindering drug diffusion. The determined apparent diffusion coefficients of the drugs clearly point out that the mobility of an active agent in PLGA-based delivery systems does not only depend on its own physico-chemical properties and the type of PLGA used, but also to a large extent on the size and shape of the device. This has to be carefully taken into account when developing/optimizing this type of advanced drug delivery systems.

Keywords: PLGA; Controlled release; Drug release mechanism; Diffusion; Microparticle; Film

1. Introduction

Parenteral controlled drug delivery systems are steadily gaining in practical importance. They are used to improve the therapeutic effects of drug treatments by providing optimized drug concentrations at the site of action over prolonged periods of time. In addition, undesired side effects can be reduced and patient compliance can be improved due to reduced administration frequency/simplified dosing schemes. One possibility to control the release rate of a drug out of a pharmaceutical dosage form is to embed the active agent within a polymeric matrix. The polymer must be biocompatible and – in the case of parenteral administration – preferably be biodegradable to avoid the need to remove empty remnants upon drug exhaust. Poly(lactic-co-glycolic acid) (PLGA) is currently the most frequently used, biodegradable (Anderson and Shive, 1997) and biocompatible (Middleton and Tipton, 2000; Fournier et al., 2003; Menei et al., 2004; Wu and Ding, 2004) matrix former for controlled parenteral drug delivery (O'Donnell and McGinity, 1997; Freiberg and Zhu, 2004). Several products are available on the market, for instance PLGA-based microparticles loaded with leuprolide (Lupron Depot) or triptorelin (Trelstar).

Although the practical importance of PLGA-based controlled drug delivery systems is steadily increasing, yet the underlying physical and chemical mass transport phenomena involved in the control of drug release are not fully understood (Siepmann and Goepferich, 2001). This can be attributed to the complexity

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of the mass transport mechanisms. Once in contact with aqueous media, water penetrates into the devices and starts to hydrolytically cleave the ester bonds. Importantly, shorter chain degradation products can alter the micro-pH within the dosage forms (Brunner et al., 1999; Fu et al., 2000; von Burkersroda et al., 2002; Li and Schwendeman, 2005), which can affect subsequent polymer chain cleavage (Siepmann et al., 2005). Diffusion of degradation products out into the bulk fluid and of bases from the surrounding environment into the delivery systems occurs simultaneously with drug diffusion and polymer degradation. Importantly, the environment for drug transport can significantly change during drug release, rendering a quantitative, mechanistic realistic description of the resulting release kinetics difficult.

Obviously, the physico-chemical properties of the incorporated drug(s) might significantly affect the resulting release patterns, especially at high initial drug loadings. For example, high contents of freely water-soluble drugs can facilitate water penetration and lead to the creation of highly porous polymer networks upon drug leaching. In contrast, lipophilic drugs can hinder water diffusion into the system, slowing down polymer degradation. In the case of significant amounts of acidic and basic active agents, additional effects on the PLGA degradation kinetics can be expected, because ester hydrolysis is catalyzed by acids and bases (Li et al., 1996; Frank et al., 2005). Furthermore, the geometry of PLGA-based controlled drug delivery systems can be expected to play a major role and strongly affect the relative importance of the involved physical and chemical processes controlling drug release: the rate at which the acidic polymer degradation products are neutralized can significantly depend on the device geometry. Thus, the importance of potential drops in micro-pH, resulting in accelerated polymer degradation can be strongly affected by the geometric design of the system.

The major aim of the present study was to better understand the importance of the type of drug and device geometry for the underlying mass transport mechanisms controlling drug release from PLGA-based delivery systems. Ibuprofen and lidocaine were chosen as model drugs, microparticles and thin films as pharmaceutical dosage forms. Differently sized devices were prepared and physico-chemically characterized in vitro. Mathematical theories based on Fick's second law of diffusion were used to quantitatively describe the experimental results.

2. Materials and methods

2.1. Materials

Poly(D,L-lactic-co-glycolic acid) (PLGA; Resomer RG 504H; PLGA 50:50; Boehringer Ingelheim, Ingelheim, Germany), lidocaine (free base; Sigma–Aldrich, Steinheim, Germany), ibuprofen (free acid; Salutas, Barleben, Germany), acetonitrile, dichloromethane, and chloroform (Carl Roth, Karlsruhe, Germany), and poly(vinylalcohol) (Mowiol 4–88; Kuraray, Frankfurt, Germany) were used as received.

2.2. Microparticle preparation

Drug-loaded, PLGA-based microparticles were prepared using an oil-in-water (O/W) solvent extraction/evaporation technique: 46 mg drug and 1 g PLGA were dissolved within 9 g dichloromethane. This organic solution was dispersed into 2.5 L of an outer aqueous poly(vinylalcohol) solution (0.25%, w/w) under stirring with a three-blade propeller for 30 min (2000 rpm). Upon solvent extraction/evaporation the microparticles formed. They were hardened by the subsequent addition of 2.5 L further outer aqueous phase and 4 h gentle stirring (700 rpm). The particles were then separated by filtration and subsequently freeze-dried to minimize the residual solvents' content. Differently sized fractions were obtained by sieving (average pore sizes of the sieves: 200, 125, 100, 63, and 40 μm; Retsch, Haan, Germany).

2.3. Film preparation

Drug-loaded (4%, w/w) films were prepared by casting drug-containing PLGA:chloroform (2.2:1, w/w) solutions onto Teflon plates using a casting knife (Multicator 411; Erichsen, Hemer, Germany). The thickness of the films (19–138 μm) was measured using a thickness gauge (Minitest 600; Erichsen). All films were clear (visual observation), indicating that the drug was molecularly dispersed within the system.

2.4. Particle size analysis

Particle size distributions and mean diameters of the complete batch and of each sieve fraction were determined using an optical microscope (Axioskop; Carl Zeiss, Jena, Germany) equipped with an optical imaging system (EasyMeasure; INTEQ, Berlin, Germany).

2.5. Determination of the initial drug loading

The initial, practical drug loading was determined by dissolving accurately weighed amounts of microparticles (approximately 15 mg) in 5 mL acetonitrile and subsequent UV drug detection ($\lambda_{lidocaine}$ = 263 nm, $\lambda_{ibuprofen}$ = 264 nm; UV-2101PC; Shimadzu, Kyoto, Japan).

2.6. In vitro drug release studies

Drug-loaded microparticles (approximately 400 mg) and drug-loaded films (1.5 cm × 1.5 cm) were placed into phosphate buffer pH 7.4 (USP 30) in 50 mL glass bottles. The containers were horizontally shaken at 37 °C (80 rpm; GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). To avoid film folding and floating during the experiment (resulting in potential variations of the surface area exposed to the release medium), the films were fixed within the plastic containers. At pre-determined time intervals, 1 mL samples were withdrawn (replaced with fresh medium) and analyzed UV-spectrophotometrically ($\lambda_{lidocaine}$ = 263 nm, $\lambda_{ibuprofen}$ = 264 nm; UV-2101PC). Each experiment was conducted in triplicate.

2.7. Monitoring of changes in the physico-chemical properties of the microparticles upon exposure to the release medium

To monitor changes in the physico-chemical properties of the delivery systems occurring during drug release, microparticles were treated as described in the Section 2.6. *In vitro drug release studies*. At pre-determined time intervals, the contents of the glass bottles was rinsed and filtered (0.45 μm), the obtained microparticles freeze-dried and stored at 4 °C for further analysis.

The average polymer molecular weight of PLGA was determined by size exclusion chromatography (SEC). Microparticles were dissolved in chloroform (2%, w/w). Fifty microlitre of this solution was injected into a SEC apparatus [SCL-10A; Shimadzu; column: PLgel 5 μm MIXED-D; 7.5 mm × 300 mm (Polymer Laboratories, Church Stretton, UK); mobile phase: chloroform containing 0.1% (w/w) triethanolamin; flow rate: 1 mL/min; column temperature 40 °C; detector: refractometer]. All indicated molecular weights are weight-average molecular weights (Mw), calculated using the Cirrus GPC software (Polymer Laboratories) and polystyrene standards (580–299400 Da) (Polymer Laboratories).

Scanning electron microscopy (SEM) was used to characterize the internal and external morphology of the microparticles (S-4000; Hitachi High-Technologies Europe, Krefeld, Germany). Samples were covered under an argon atmosphere with a fine gold layer (10 nm; SCD 040; Bal-tec, Witten, Germany). Cross-sections of the microparticles were obtained after inclusion into water-based glue and cutting with a razor blade.

The glass transition temperature (Tg) of the polymer was analyzed by differential scanning calorimetry (DSC; DSC821e; Mettler Toledo, Giessen, Germany). Approximately 10 mg samples were heated in sealed aluminum pans (investigated temperature range: −10 to +80 °C, heating rate: 5 °C/min, two heating cycles).

2.8. Mathematical modeling of drug release

Two mathematical models were used to quantitatively describe the drug release kinetics from the investigated microparticles and thin, free films. One theory considers spherical geometry, the other film geometry. Both models are based on Fick's second law of diffusion:

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

Here, c and D are the concentration and the diffusion coefficient of the drug, respectively; t represents time, and x, y, and z the three spatial coordinates. Considering the geometries of the respective devices and the following initial and boundary conditions:

(i) At $t = 0$ (before exposure to the release medium), the drug is homogeneously distributed throughout the devices.
(ii) The initial drug concentration is below the solubility of the drug (molecular dispersion, monolithic solution).
(iii) The diffusional resistance for drug release within the unstirred liquid boundary layers surrounding the devices is negligible compared to the diffusional resistance within the polymeric systems under the given experimental conditions.
(iv) Perfect sink conditions are provided throughout the experiments.
(v) In the case of thin films, edge effects are negligible due to the high "surface area:thickness" ratio.

the following analytical solutions of Fick's second law can be derived:

for spherical microparticles:

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

for thin films:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}\exp\left(-\frac{(2n+1)^2\pi^2}{4L^2}Dt\right) \quad (3)$$

where M_t and M_∞ are the absolute, cumulative amounts of drug released at time t and infinity, respectively; R denotes the radius of the microparticles, and L the half-thickness of the films. The diffusion coefficients of lidocaine and ibuprofen in the PLGA-based devices were determined by fitting Eqs. (2) or (3) to sets of experimentally measured drug release kinetics.

3. Results and discussion

3.1. In vitro drug release from microparticles and films

The model drugs ibuprofen and lidocaine (free base) were successfully incorporated within spherical PLGA-based microparticles and thin, free films. SEM pictures revealed that the surfaces of the microparticles were smooth and the inner structure dense/non-porous prior to exposure to the release medium, irrespective of the system size (Fig. 1). Only pictures of ibuprofen-loaded microparticles are shown, the inner and outer morphology of lidocaine-loaded systems was very similar (data not shown). Importantly, the initial drug content was low in all cases (practical loading = 4%, w/w). This is of major importance in the present study, because it assures that ibuprofen and lidocaine were molecularly dispersed within the systems (monolithic solutions). For instance, the films were clear and DSC measurements did not indicate any drug melting peaks. The low drug loading and molecular distribution of the drugs within the polymeric devices has three major consequences:

(i) The mathematical analysis is less complex compared to systems containing also non-dissolved drug crystals and/or amorphous aggregates (e.g., no drug dissolution step and no limited drug solubility effects).
(ii) The microparticles'/films' properties do not significantly change during drug release due to the creation of large

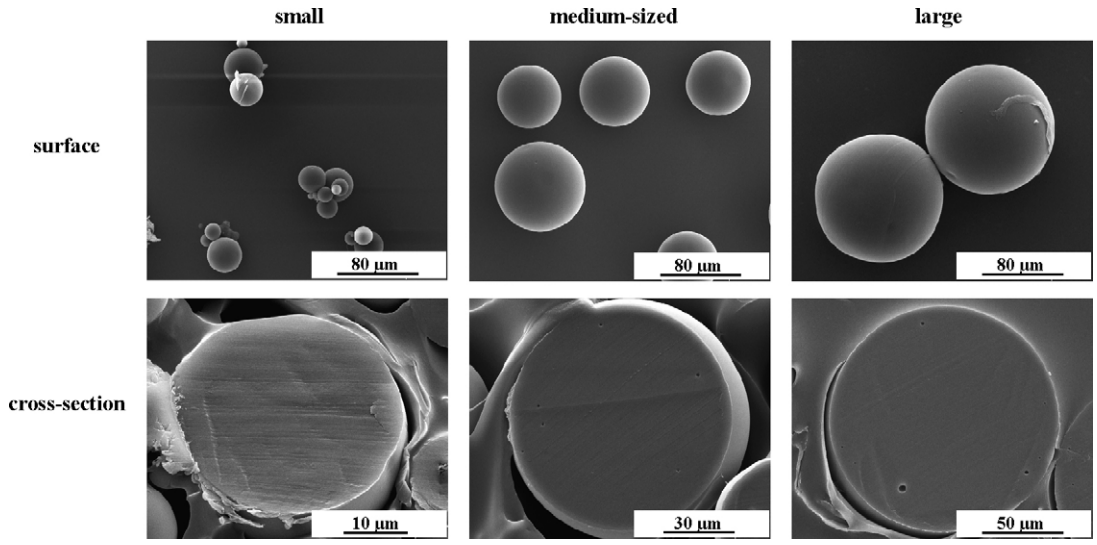

Fig. 1. Morphology of small, medium-sized and large ibuprofen-loaded, PLGA-based microparticles before exposure to phosphate buffer pH 7.4 ($t = 0$ day): SEM pictures of surfaces and cross-sections (note the different magnifications/scaling bars). Only pictures of ibuprofen-loaded microparticles are shown, the inner and outer morphology of lidocaine-loaded systems was very similar (data not shown).

pores upon drug leaching (resulting in time- and position-dependent porosities and, thus, drug diffusivities).

(iii) The acidic/basic nature of the model drugs is likely to be only of minor importance.

The experimentally measured drug release kinetics of ibuprofen and lidocaine from the PLGA-based microparticles and thin, free films of different size/thickness in phosphate buffer pH 7.4 are shown in Figs. 2 and 3 (symbols) (note the different scaling of the *x*-axes). The mean microparticle diameters and film thicknesses are indicated in the figures. The film thicknesses were chosen to be in the same order of magnitude as the microparticle diameters in order to assure similar maximal diffusion pathway lengths (ranging from 7 to 53 μm for the microparticles, and from 10 to 65 μm for the films; note that both sides of the films and the entire surface of the microparticles were exposed to the release medium).

Interestingly, the relative drug release rates from the investigated microparticles were almost independent of the system size, irrespective of the type of drug (Fig. 2). As diffusion is known to be of major importance in this type of controlled drug delivery systems, this is at a first glance surprising: increasing microparticle sizes lead to increasing diffusion pathway lengths and should, thus, result in decreasing relative release rates. The absence of this effect can be explained as follows: PLGA is a polyester that is hydrolytically degraded into smaller chain acids, which can catalyze further ester bond cleavage (Schwendeman, 2002; Siepmann et al., 2005). It is well known that water penetration into PLGA-based microparticles is much faster than the subsequent polymer hydrolysis (bulk erosion) (von Burkersroda et al., 2002). Consequently, ester bond cleavage occurs throughout the microparticles upon contact with aqueous media. Due to concentration gradients, the generated shorter chain acids diffuse out into the surrounding bulk fluid, where they are neutralized. In addition, bases from the phosphate buffer diffuse into the microparticles, neutralizing the generated acids. However, diffusional mass transport is relatively slow, and the rate at which the acids are generated can be higher than the rate at which they are neutralized, leading to potential significant drops in the micro-pH within the drug delivery system (Brunner et al., 1999; Li and Schwendeman, 2005). Consequently, polymer degradation can be accelerated (autocatalysis) and the mobility of the drug within the polymeric matrix can significantly increase, resulting in increased absolute and relative drug release rates. The importance of this "autocatalytic effect" can be expected to increase with increasing system size, because of the increasing length of the diffusion pathways (Fig. 4) (Dunne et al., 2000; Berkland et al., 2003; Siepmann et al., 2005; Klose et al., 2006). In the present case, the consequences of the decreasing drug concentration gradients with increasing microparticle size are about compensated by the increasing drug mobility due to accelerated polymer degradation, resulting in similar relative drug release rates for the investigated microparticles sizes (Fig. 2).

Importantly, ibuprofen release was much faster than that of lidocaine, irrespective of the system geometry (Fig. 2a versus 2b and Fig. 3a versus 3b; note the different scaling of the *x*-axes). This is despite of the very similar/identical preparation technique, amount and type of polymer, drug loading, microparticle sizes/film thicknesses as well as inner and outer morphology of the systems. For instance, drug release was complete after only 7 days in the case of ibuprofen-loaded microparticles, compared to 45 days in the case of lidocaine-loaded devices. As the molecular weights of the two drugs are similar (ibuprofen: 206 Da, lidocaine: 234 Da), differences in the hydrodynamic molecular dimensions are unlikely to be the reason for the tremendous differences in the relative drug release rates (Figs. 2 and 3).

3.2. Polymer degradation kinetics

As ibuprofen is an acid and lidocaine a base, and as PLGA hydrolysis is catalyzed by acids and bases, potential effects of the

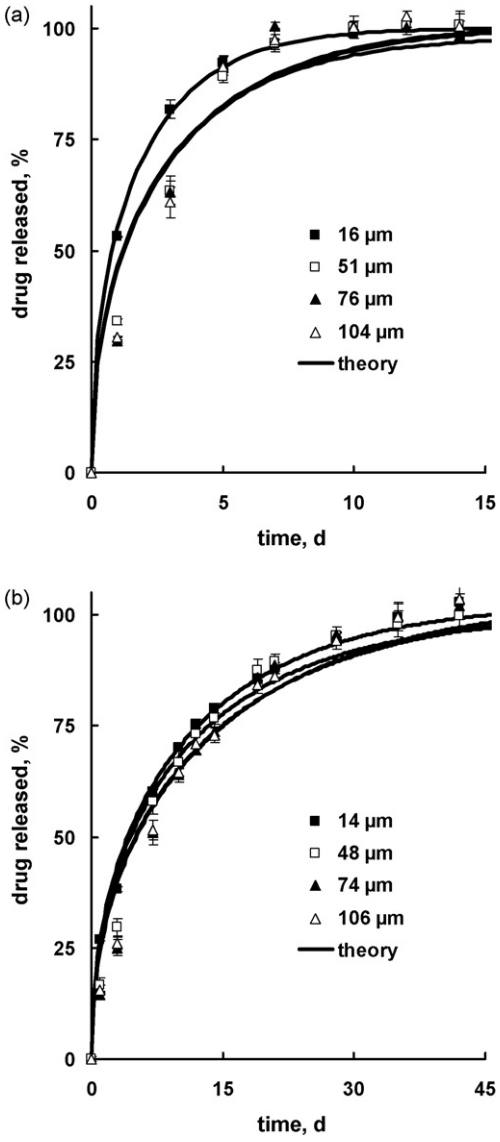

Fig. 2. Effects of the microparticle diameter (indicated in the figures) on drug release from PLGA-based microparticles in phosphate buffer pH 7.4: (a) ibuprofen-loaded systems and (b) lidocaine-loaded microparticles [symbols: experiments; curves: theory (Eq. (2))] (note the different scaling of the *x*-axes) [(b) is adapted from Siepmann et al., 2005; with permission].

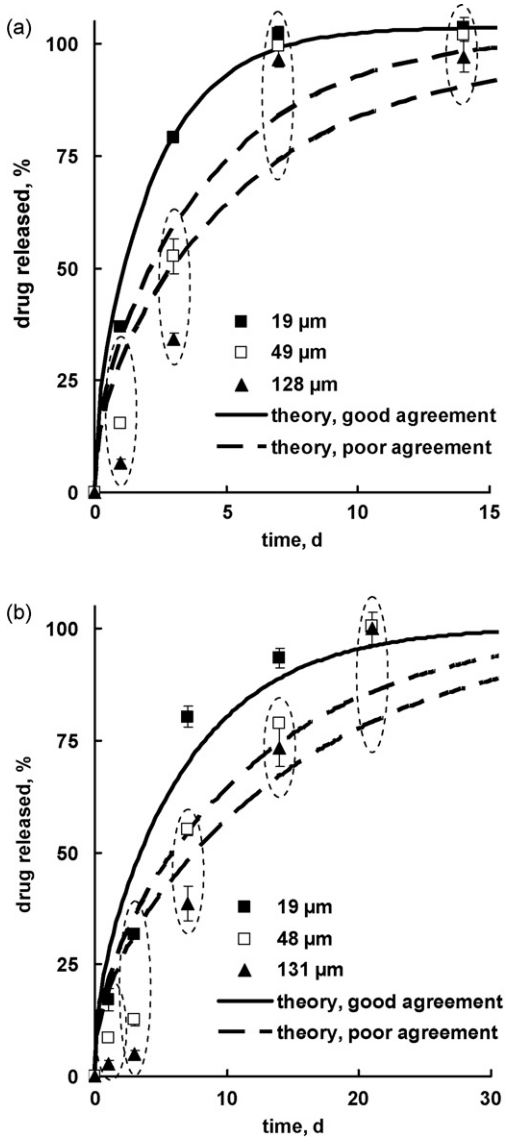

Fig. 3. Effects of the thickness of PLGA-based films (indicated in the figures) on drug release in phosphate buffer pH 7.4: (a) ibuprofen-loaded systems and (b) lidocaine-loaded films (note the different scaling of the *x*-axes) [symbols: experiments; curves: theory (Eq. (3))].

type of drug on the resulting polymer degradation kinetics were monitored. The symbols in Fig. 5a and b show the experimentally measured decrease in the average polymer molecular weight (Mw) of PLGA in the investigated ibuprofen- and lidocaine-loaded microparticles upon exposure to phosphate buffer pH 7.4, respectively. The mean microparticle sizes are indicated in the figures. Clearly, the polymer degradation rate significantly increased with increasing microparticle size, irrespective of the type of drug. This can be attributed to the above described increasing importance of decreasing micro-pH values and accelerated PLGA degradation with increasing microparticle size. To quantitatively describe the experimentally measured polymer degradation kinetics, the following (pseudo-)first order equation was fitted to the experimental results (Kenley et al., 1987;

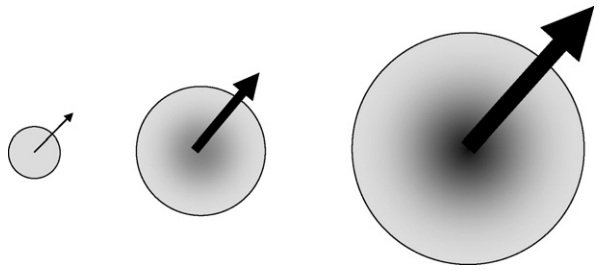

Fig. 4. Schematic illustration of the increasing importance of autocatalytic effects with increasing system size in PLGA-based microparticles. The arrows indicate drug mobility (small arrow—low mobility, big arrow—high mobility), the grey levels indicate the pH within the system (bright—neutral pH; dark—low pH).

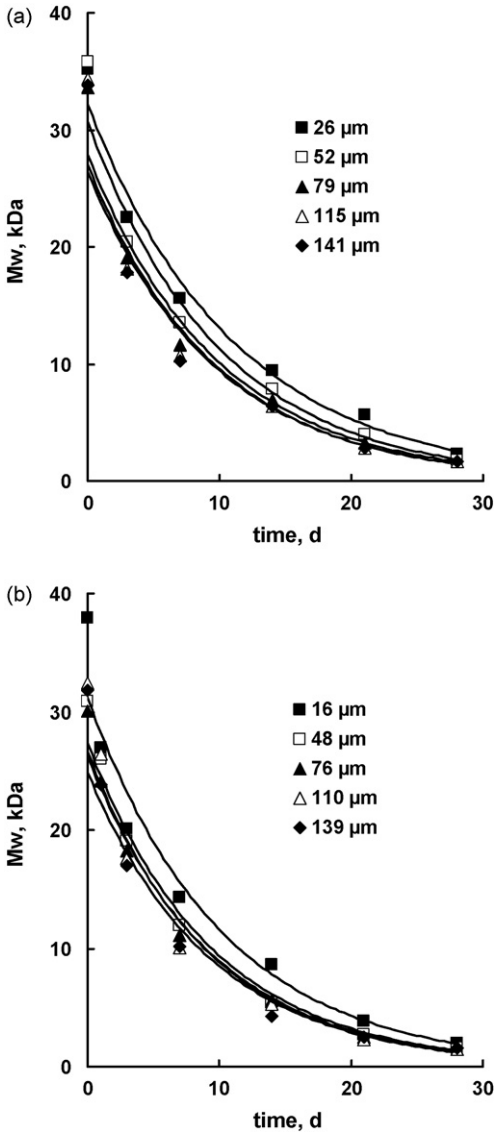

Fig. 5. Importance of the size of PLGA-based microparticles (indicated in the figures) on polymer degradation during drug release: decrease in polymer molecular weight (Mw) measured by SEC upon exposure to phosphate buffer pH 7.4: (a) ibuprofen-loaded systems and (b) lidocaine-loaded microparticles [symbols: experiments; curves: theory (Eq. (4))] [(b) is partially adapted from Siepmann et al., 2005; with permission].

Charlier et al., 2000):

$$\mathrm{Mw}(t) = \mathrm{Mw}_0 \exp(-k_{\mathrm{degr}} t) \quad (4)$$

where $\mathrm{Mw}(t)$ and Mw_0 are the average polymer molecular weight at time t and $t=0$ (before exposure to the release medium), respectively; k_{degr} denotes the apparent degradation rate constant of the polymer.

As it can be seen in Fig. 5, good agreement between theory (curves) and experiment (symbols) was obtained, irrespective of the microparticle size and type of drug (the coefficient of determination, R^2, was >0.98 in all cases). Based on these calculations, the apparent degradation rate constant (k_{degr}) of PLGA within the respective systems could be determined (Table 1). Clearly, the k_{degr} values increased with increasing microparticle size (from 0.63 to 0.73 week^{-1} for ibuprofen-loaded systems, and from 0.68 to 0.78 week^{-1} for lidocaine-containing microparticles), indicating accelerated polymer degradation. Importantly, this effect was independent of the type of incorporated drug and the determined PLGA degradation rate constants were rather similar for both types of drugs (the k_{degr} values were slightly higher in the case of lidocaine-loaded devices). Thus, potential changes in the micro-pH within the microparticles due to the acidic/basic nature of ibuprofen/lidocaine, resulting in altered polymer degradation kinetics cannot explain the major differences in the observed drug release kinetics (Fig. 2).

Table 1
Apparent degradation rate constant (in week^{-1}) of PLGA in the investigated microparticles (containing 4%, w/w ibuprofen or lidocaine, as indicated) upon exposure to phosphate buffer pH 7.4 as a function of the mean microparticle sizes [results for lidocaine are partially reprinted from Siepmann et al., 2005, with permission]

Mean size (µm)	26	52	79	115	141
Ibuprofen	0.63	0.70	0.71	0.73	0.72
Mean size (µm)	16	48	76	110	139
Lidocaine	0.68	0.75	0.76	0.78	0.75

As diffusion is known to play a major role in the control of drug release from PLGA-based microparticles (Siepmann and Goepferich, 2001), and as the investigated polymer is known to be in the amorphous state, it was important to monitor potential changes in the glass transition temperature (Tg) of PLGA in the different types of microparticles during drug release. Fig. 6a and b show the results obtained by DSC measurements for ibuprofen- and lidocaine-loaded systems, respectively. The mean diameter of the microparticles is indicated in the figures. Clearly, the glass transition temperature significantly decreases after a "lag-time" of about 1 week in both cases. This can be attributed to the decreasing average polymer molecular weight of PLGA: with decreasing chain length the mobility of the macromolecules increases. Importantly, there is no major difference in the decrease in Tg when comparing ibuprofen- and lidocaine-loaded microparticles (Fig. 6a versus 6b). Thus, the type of drug does not significantly affect the mobility of the polymer molecules within the drug delivery systems. As expected, the glass transition temperature decreased more rapidly in larger microparticles than in smaller ones, due to the above described autocatalytic effects. It has to be pointed out that the Tg's were all measured in the dry state and that water acts as a plasticizer for PLGA. It has previously been shown that the glass transition temperature is lowered by approximately 10–15 °C in PLGA-based microparticles due to water penetration (Faisant et al., 2002; Blasi et al., 2005). Thus, all the investigated systems can be expected to be in the rubbery state during drug release.

In addition to changes in the average polymer molecular weight and glass transition temperature of the matrix former also morphological changes occurring during drug release can be of major importance in PLGA-based controlled drug delivery systems. Fig. 7 shows exemplarily SEM pictures of surfaces and cross-sections of ibuprofen-loaded, PLGA-based microparticles after 7 days exposure to phosphate buffer pH 7.4. Small,

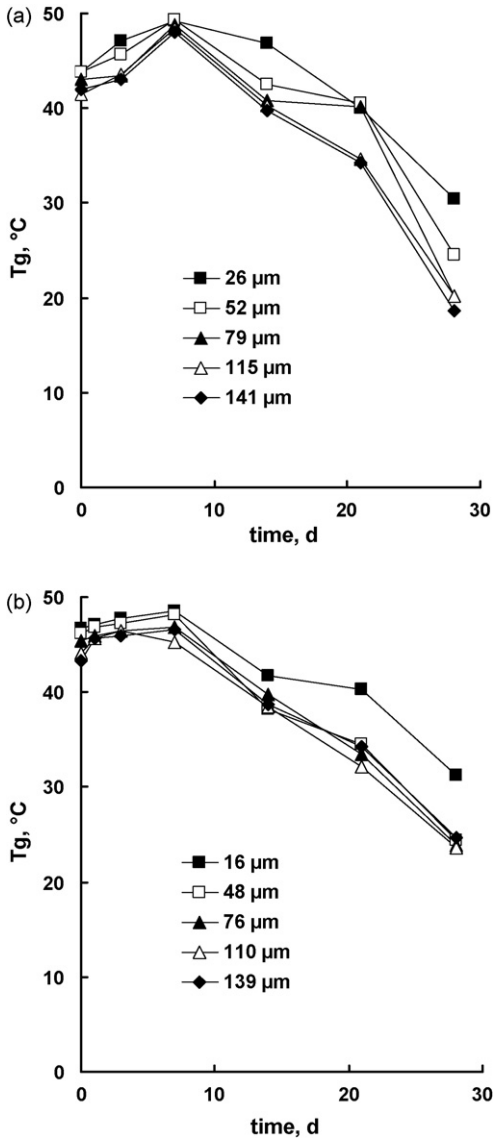

Fig. 6. Effects of the microparticle diameter (indicated in the figures) on changes in the glass transition temperature (Tg) of PLGA in microparticles loaded with: (a) ibuprofen and (b) lidocaine upon exposure to phosphate buffer pH 7.4 [(b) is partially adapted from Siepmann et al., 2005; with permission].

medium-sized and large particles were examined. Clearly, all types of microparticles became porous, due to the hydrolytic degradation of the polyester. Importantly, large microparticles became more rapidly porous than smaller ones (note the different scaling of the pictures). This can be explained by the above described increasing importance of autocatalytic effects with increasing particle size. The morphology of lidocaine-loaded microparticles was similar (data not shown). Thus, also changes in the inner and outer structure of the systems cannot explain the significant difference in drug release observed from ibuprofen- and lidocaine-loaded PLGA-based microparticles (Fig. 2). To better understand the underlying mass transport mechanisms controlling drug release in the investigated microparticles and thin, free films of different size/thickness, mathematical theories based on Fick's second law of diffusion were used to analyze the experimentally measured in vitro drug release kinetics.

3.3. Mathematical modeling of drug release

The curves in Figs. 2 and 3 show fittings of analytical solutions of Fick's law, taking into account the given initial and boundary conditions, in particular: (i) the homogeneous drug distribution at $t = 0$, (ii) the fact that the initial drug concentration was below drug solubility (monolithic solutions), (iii) perfect sink conditions maintained throughout the experiments, and (iv) the spherical geometry of the microparticles and the geometry of the thin, free films (neglecting edge effects). Under these conditions, Eqs. (2) and (3) can be derived. As it can be seen in Fig. 2, Eq. (2) (considering spherical geometry) could successfully be used to quantify drug release from all types of investigated microparticles, irrespective of the type of drug and system size. Thus, diffusion is the dominant mass transport mechanism in all cases. In contrast, when fitting Eq. (3) (considering the geometry of thin, free films) to the experimentally determined ibuprofen and lidocaine release kinetics from films of different thickness, good agreement was only observed in the case of the thinnest systems (Fig. 3). For films with a thickness of about 50 and 130 μm, significant deviations between theory (curves) and experiment (symbols) was observed, irrespective of the type of drug. Thus, also other phenomena are of importance in these types of systems (it was beyond the scope of this study to investigate this aspect in more detail).

Based on these calculations the apparent diffusion coefficients of ibuprofen and lidocaine could be determined in the differently sized microparticles and the thinnest types of films. As it can be seen in Fig. 8, the diffusivities of both drugs significantly increased with increasing microparticle size. This can be explained by the above described autocatalytic effects, resulting in increased macromolecular mobility with increasing system dimension. Importantly, the diffusion coefficients of ibuprofen and lidocaine were much higher in thin, free films than in spherical microparticles at comparable film thicknesses/microparticle diameters (assuring similar maximal diffusion pathway lengths). This can probably be attributed to the fact that the geometry of a sphere more easily allows acids to diffuse out into the bulk fluid and bases to diffuse into the systems compared to the geometry of thin, free films (shorter average diffusion pathways, higher surface area:volume ratio). Consequently, the pH within thin films can be expected to more easily decrease, resulting in more pronounced autocatalytic effects and, thus, higher drug mobility. Thus, the geometry of PLGA-based controlled drug delivery systems can significantly affect the underlying drug release mechanisms (good–poor agreement between theory and experiment in the case of medium-sized and large microparticles and free films and significant differences in the diffusion coefficients in the case of the thinnest films versus smallest microparticles). This needs to be carefully taken into account when developing/optimizing this type of advanced drug delivery devices.

When comparing the apparent diffusion coefficients of ibuprofen and lidocaine within the different types of PLGA-based microparticles and thin films (Fig. 8), it becomes obvious that the mobility of ibuprofen is always much higher than that of lidocaine. As the polymeric structures in the

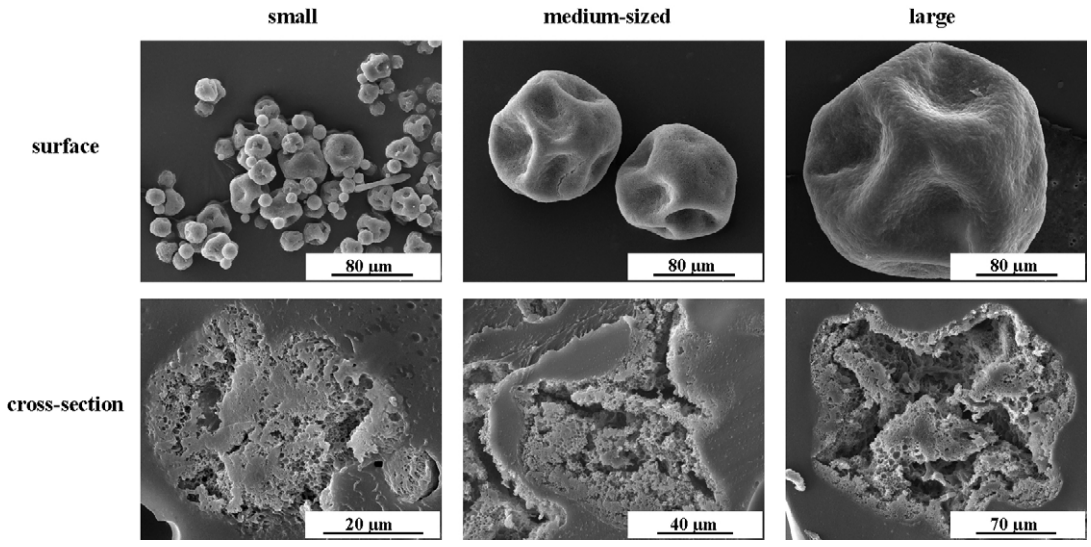

Fig. 7. Morphology of small, medium-sized and large ibuprofen-loaded, PLGA-based microparticles after 7 days exposure to phosphate buffer pH 7.4: SEM pictures of surfaces and cross-sections (note the different magnifications/scaling bars). Only pictures of ibuprofen-loaded microparticles are shown, the inner and outer morphology of lidocaine-loaded systems was similar (data not shown).

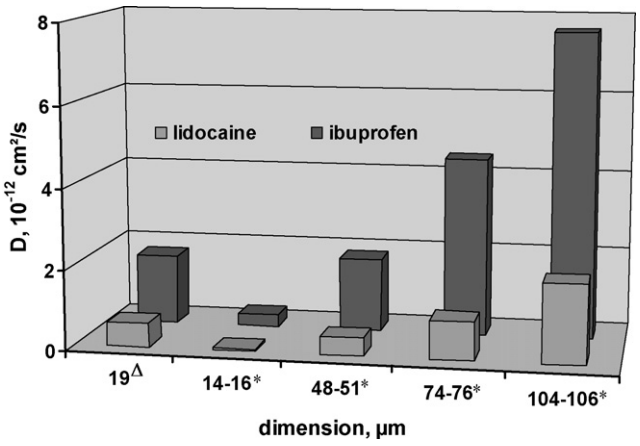

Fig. 8. Diffusion coefficients of lidocaine and ibuprofen (as indicated) as a function of the geometry and size of the delivery system: The open triangle indicates film geometry, the stars spherical geometry. The thickness of the films/diameters of the microparticles are given on the *x*-axis, in μm.

respective delivery systems can be expected to be very similar for both types of drugs (as discussed above), and as the molecular weights of ibuprofen and lidocaine are not very different (206 and 234 Da, respectively), it is likely that drug-polymer interactions are responsible for the observed significant differences in drug mobility. Ibuprofen is an acid with a pK_a of 4.4. Thus, it is deprotonated and negatively charged at pH 7.4, and neutral at acidic pH. In contrast, lidocaine is a base with a pK_a of 7.9. Thus, it is protonated at the pH values which can be expected within the PLGA-based microparticles during drug release. Importantly, the investigated PLGA as well as its degradation products exhibit free carboxylic end groups. Consequently, ionic attractive interactions are highly likely between these carboxylic end groups and the positively charged lidocaine ions. Such attractive forces can be expected to hinder drug diffusion within the polymeric network and, thus, explain the relatively low drug diffusion coefficients and drug release rates from lidocaine-loaded, PLGA-based microparticles and thin films. In contrast, no attractive ionic interactions can be expected between ibuprofen and PLGA as well as its degradation products, resulting higher drug release rates compared to lidocaine.

4. Conclusion

The mobility of a drug in PLGA-based delivery systems does not only depend on its own physico-chemical properties and the type of PLGA used, but also to a large extent on the size and shape of the device. In addition, attractive ionic drug-polymer interactions can lead to unexpected low release rates. This has to be carefully taken into account when developing/optimizing this type of advanced drug delivery systems.

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