PLGA implants: How Poloxamer/PEO addition slows down or accelerates polymer degradation and drug release

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ABSTRACT

The aim of this study was to evaluate the impact of the addition of small amounts of hydrophilic polymers (Poloxamer 188 and PEO 200 kDa) to PLGA-based implants loaded with prilocaine. Special emphasis was placed on the importance of the type of preparation technique: direct compression of milled drug-polymer powder blends versus compression of drug loaded microparticles (prepared by spray-drying). The implants were thoroughly characterized before and upon exposure to phosphate buffer pH 7.4, e.g. using optical and scanning electron microscopy, X-ray diffraction, DSC and GPC. Interestingly, the addition of Poloxamer/PEO to the PLGA implants had opposite effects on the resulting drug release kinetics, depending on the type of preparation method: in the case of implants prepared by compression of milled drug-polymer powder blends, drug release was accelerated, whereas it was slowed down when the implants were prepared by compression of drug loaded PLGA microparticles. These phenomena could be explained by the swelling/disintegration behavior of the implants upon exposure to the release medium. Systems consisting of compressed microparticles remained intact and autocatalytic effects were of major importance. The presence of a hydrophilic polymer facilitated water penetration into these devices, slowing down PLGA degradation and drug release. In contrast, implants consisting of compressed drug-polymer powder blends rapidly (at least partially) disintegrated and autocatalysis was much less important. In these cases, the addition of a hydrophilic polymer facilitated ester bond cleavage, leading to accelerated PLGA degradation and drug release.

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1. Introduction

Poly(lactic-co-glycolic acid) PLGA-based implants offer an interesting potential as advanced drug delivery systems, allowing for time-controlled release over prolonged periods of time [1–3]. Being a polyester, PLGA is degraded into short chain acids upon contact with aqueous body fluids. The final degradation products are water-soluble, hence there is no need to remove empty implant remnants upon drug exhaust. Also, PLGA is biocompatible and used in a variety of controlled release drug products available on the market. A broad range of drugs can be incorporated into PLGA-based implants and their release can be controlled over variable time periods [4–6]. Importantly, different techniques can be used to prepare PLGA-based implants, including for example hot melt extrusion, injection molding, solvent extrusion, compression or in-situ formation [7–10]. A major advantage of implant preparation by compression is the fact that organic solvents can be avoided and no heat treatments are required. This is particularly interesting for labile drugs, such as proteins and peptides.

Despite of these multiple advantages and significant practical importance of PLGA-based implants as advanced drug delivery systems, the underlying mass transport phenomena controlling drug release are often not fully understood. This can be attributed to the complexity of the involved physico-chemical processes [11–14]: upon contact with aqueous media, water penetrates into the implants and hydrolytic polymer chain cleavage starts. This is a random process, which is known to be slower than water penetration into the systems [15,16]. Consequently, PLGA implants undergo "bulk erosion": upon contact with water, the entire implants are relatively rapidly wetted and ester bond cleavage occurs throughout the systems. In addition, once the drug comes into contact with water, it dissolves (if it is not already molecularly dispersed) and diffuses out, due to concentration gradients. Importantly, the PLGA ester bond cleavage results in the creation of shorter chain acids (and alcohols). The generated water-soluble acids [17] and protons diffuse out of the implants (due to concentration gradients), and are neutralized in the surrounding bulk fluid. In addition, bases from the environment diffuse into the PLGA implants and neutralize the generated

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acids. But often, these diffusional mass transport processes are relatively slow, and the rate at which acids are generated within PLGA implants is higher than the rate at which they are neutralized. Consequently, the micro-pH within the devices can significantly drop [18]. This phenomenon is often particularly pronounced at the center of the implants, since the diffusion pathways to be overcome for the acids and bases are the longest at this position. Importantly, hydrolytic ester bond cleavage is catalyzed by protons. Thus, local drops in micro-pH can lead to accelerated PLGA degradation (autocatalysis) [19,20]. Consequently, the systems are more rapidly degraded and drug release is often accelerated. The importance of such autocatalytic effects can strongly depend on the formulation and preparation technique of the system. For example, more porous implants allow for faster diffusion of acids and bases (through water-filled pores) and, hence, generally exhibit less pronounced autocatalytic effects. Unfortunately, in addition to the impact on drug release, local drops in micro-pH might also inactivate acid-labile drugs (e.g. proteins). But not only water penetration, drug dissolution, polymer degradation, the diffusion of acids, bases and drugs as well as autocatalytic effects might be involved in the control of drug release from PLGA-based dosage forms, also substantial system swelling might play a crucial role [21–23]. For instance, it has recently been shown that in the case of PLGA microparticles exhibiting tri-phasic drug release, the third (final and rapid) drug release phase might be attributable to pronounced system swelling: once a critical PLGA polymer molecular weight is reached, substantial amounts of water penetrate into the system, resulting in significantly increased drug mobility and, hence, accelerated drug release (leading to complete drug exhaust). Monitoring the swelling of *single* PLGA microparticles allowed revealing this release mechanism. Also, the group of Schwendeman reported very interesting studies on the importance of PLGA swelling, especially at the early phases of drug release from microparticles: tiny pores, responsible for the initial burst release, can be closed due to PLGA swelling [24,25].

To alter polymer degradation and drug release from PLGA-based dosage forms, a variety of additives has been proposed [8,26–29], including for example magnesium carbonate, magnesium hydroxide, sucrose, cyclodextrins, polyoxyethylene–polyoxypropylene block copolymer, poly(ethylene glycol), hydroxypropyl methylcellulose, acetyltributyl citrate and dibutyl sebacate [30–34]. The observed effects were for instance attributed to altered micro-pH environments, leaching of water-soluble additives into the surrounding environment (resulting in pore formation) and/or plasticizing effects. However, there is still a lack of knowledge on how the distribution of such additives within PLGA implants might impact polymer degradation and drug release. For example, different preparation techniques can lead to different drug, PLGA and additive distributions within the system, which might substantially alter crucial key properties of the devices, e.g. implant integrity and water penetration kinetics.

The aim of this study was to evaluate how the addition of 10% of a hydrophilic polymer (namely Poloxamer 188 and PEO 200 kDa) can affect PLGA degradation and drug release in/from PLGA implants. Importantly, two different preparation techniques were studied. Implants were prepared by: (i) compression of milled drug-polymer powder blends, or (ii) by compression of drug loaded PLGA-Poloxamer/PEO microparticles (obtained by spray-drying organic solutions). The resulting changes in the release patterns of prilocaine (free base) were explained based on the swelling/disintegration behavior of the systems upon exposure to the release medium, the polymer degradation kinetics as well as optical and scanning electron microscopy, DSC and X-ray diffraction and particle size measurements.

2. Materials and methods

2.1. Materials

Poly(D,L lactic-co-glycolic acid) (PLGA, Resomer RG 504H; 50:50 lactic acid: glycolic acid) was purchased from Evonik (Darmstadt;

Germany). Prilocaine (free base) and polyoxyethylene–polyoxypropylene block copolymer (Poloxamer 188, Lutrol F68) were kindly provided by BASF (Ludwigshafen; Germany), and poly(ethylene oxide) (PEO, molecular weight = 200 kDa, Polyox N80) by Colorcon (Dartfort, UK). Acetonitrile and dichloromethane were purchased from VWR (Fontenay-sous-Bois, France), tetrahydrofuran (HPLC grade) from Fischer Scientific (Illkirch-Graffenstaden, France), and nitrogen from Oliver (Lille, France).

2.2. Microparticle preparation

Prilocaine-loaded PLGA microparticles were prepared by spray-drying. Four grams of a mixture of prilocaine, PLGA and optionally Poloxamer or PEO were dissolved in 100 mL dichloromethane. The theoretical drug content was kept constant at 1% (w/w). The (optional) Poloxamer or PEO content was 9.9% (w/w). The organic solutions were spray-dried using a Buechi B-290 (Buechi, Basel, Switzerland), equipped with a 0.7 mm nozzle (feed rate: 5 mL/min; air flow rate: 601 L/h; inlet temperature: 45 °C; outlet temperature: 32 ± 2 °C; concurrent feed flow/inlet drying gas-nitrogen).

2.3. Implant preparation

Flat-faced, cylindrical implants were prepared by compressing: (i) drug loaded microparticles (obtained by spray-drying as described above), or (ii) milled drug-polymer powder blends, using a Frank press (Universalpruefmaschine 81,816; Karl Frank, Weinheim-Birkenau, Germany). The matrix diameter was 2 mm, the compression force 300 N and the compression time 10 s. Milled drug-polymer powder blends were obtained using a ball mill (planetary micro mill, Pulverisette 7; Fritsch, Markt Einersheim, Germany) (1.2 g batches; zirconium oxide jars containing 7 zirconium oxide beads; 400 rpm; 3 milling cycles of 15 min, separated by 5 min breaks). To minimize heating, the mill was placed in a cold room at -10 °C.

2.4. Particle size measurements

The sizes and size distributions of microparticles and particles of milled drug-polymer powder blends were determined by laser diffraction (Mastersizer S; Malvern, Orsay, France). Each experiment was conducted in triplicate.

2.5. Determination of the practical drug loadings

The practical prilocaine loadings of the investigated microparticles and implants were determined as follows: accurately weighed amounts of samples were dissolved in acetonitrile. The drug contents of these organic solutions were determined by HPLC analysis. An Alliance e2695 system (pump, auto sampler, 2489 UV–Vis detector, Empower software; Waters, Milford, USA), equipped with a reversed phase column C18 (Gemini 5 μm; 110 Å; 150 mm × 4.6 mm; Phenomenex, Le Pecq, France) was used. Fifty microliter samples were injected (PTFE syringe filters - 0.45 μm), the mobile phase was an acetonitrile: phosphate buffer pH 8 (Eur. Pharm. 7) (50:50, v/v) blend. The detection wavelength was 254 nm, the flow rate 0.8 mL/min. The standard curve was prepared with a series of prilocaine solutions in acetonitrile of known concentration, ranging from 0.25 to 100 μg/mL. Each experiment was conducted in triplicate. In all cases, the practical drug loading was within $\pm 10\%$ of the theoretical loading.

2.6. Drug release measurements

Ten milligram microparticles or 1 implant were/was placed in an Eppendorf tube, filled with 2 mL phosphate buffer pH 7.4 (USP 35). The tubes were horizontally shaken at 37 °C (80 rpm, GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). At predetermined time points,

Table 1

Average sizes (in μm, mean ± SD) of the particles in milled drug-polymer powder blends and of drug loaded microparticles, prepared by spray-drying. In all cases, the drug content was 1%. The (optional) Poloxamer/PEO content was 9.9%.

	Pure PLGA	PLGA + Poloxamer	PLGA + PEO
Milled powder blends	132.7 ± 8.1	108.5 ± 2.8	122.6 ± 1.8
Microparticles	4.2 ± 1.8	6.3 ± 2.9	5.7 ± 2.2

the release medium was completely replaced with fresh phosphate buffer, and the drug content in the withdrawn bulk fluid was analyzed by HPLC as described above [using a standard curve prepared with a series of prilocaine solutions in phosphate buffer pH 7.4 (USP 35) of known concentration (ranging from 0.1 to 50 μg/mL)]. Perfect sink conditions were maintained throughout the observation periods. Each experiment was conducted in triplicate.

2.7. X-ray powder diffraction

X-ray diffraction patterns of raw materials (as received: prilocaine, PLGA, Poloxamer and PEO), physical mixtures thereof, microparticles and milled drug-polymer powder blends were recorded with a Panalytical X'pert Pro diffractometer (Cu anode tube of wavelength $K\alpha1 = 1.541$ Å and $K\alpha2 = 1.544$ Å) (Panalytical, Almelo, Netherlands). Rotatory Lyndemann capillaries (diameter: 0.7 mm) were used.

2.8. Differential scanning calorimetry (DSC)

DSC thermograms of raw materials (as received: prilocaine, PLGA, Poloxamer and PEO), physical mixtures thereof, microparticles and milled drug-polymer powder blends were recorded using a DSC 1 Star (Mettler Toledo, Greifensee, Switzerland). Approximately 2–3 mg samples were heated in sealed aluminum pans from 20 to 120 °C, cooled to −70 °C and reheated to 120 °C, at a rate of 10 °C/min. Each experiment was conducted in triplicate.

2.9. Implant morphology and dimensions/swelling

Macroscopic pictures of implants were taken using a Nikon SMZ-U macroscope (Nikon, Tokyo, Japan), equipped with a Sony Hyper HAD camera (Sony, Tokyo, Japan). Implants were studied before and after exposure to the release medium (under the same conditions as used for the drug release measurements). The imaging software AxioVision (Carl Zeiss, Jena, Germany) allowed for the measurements of the implants' dimensions (height and diameter, which were used to calculate the implants' volumes; n = 3).

The external and internal morphologies of the implants were also observed using a Hitachi S-4000 scanning electron microscope (Hitachi High-Technologies Europe, Krefeld, Germany). Samples were fixed with a ribbon carbon double-sided adhesive and covered with a fine carbon layer. Cross-sections were obtained by manual breaking.

2.10. Gel permeation chromatography

The decrease in polymer molecular weight (Mw) of PLGA during drug release was measured by gel permeation chromatography (GPC). Implants were treated as described for the drug release measurements. At predetermined time points, implants were withdrawn and freeze-dried. Three milligrams of the obtained lyophilisates were dissolved in 1 mL tetrahydrofuran. Fifty microliter samples were injected into an Alliance system (separation modules e2695 and e2695 D, 2419 RI detector) (column: PLgel 5 μm Mixed-D, 7.5 × 300 mm; Polymer Laboratories, Varian, Les Ulis, France). Tetrahydrofuran was used as mobile phase at a flow rate of 1 mL/min. Molecular weights were calculated using the Empower GPC software (Waters) and polystyrene standards (Polymer Laboratories).

3. Results and discussion

3.1. Particle sizes and morphologies

Table 1 shows the average sizes (± standard deviation) of the particles in milled prilocaine–polymer powder blends, and of the microparticles prepared by spray-drying. The prilocaine content was kept constant at 1% (w/w), whereas the optional Poloxamer/PEO content was 9.9%. Clearly, in all cases the microparticles were much smaller than the respective milled powder particles: very roughly 20 times smaller. Fig. 1 shows optical and scanning electron microscopy pictures of the different milled drug-polymer powder blends. As it can be seen, the particles were irregular in shape and exhibited rough surfaces. In
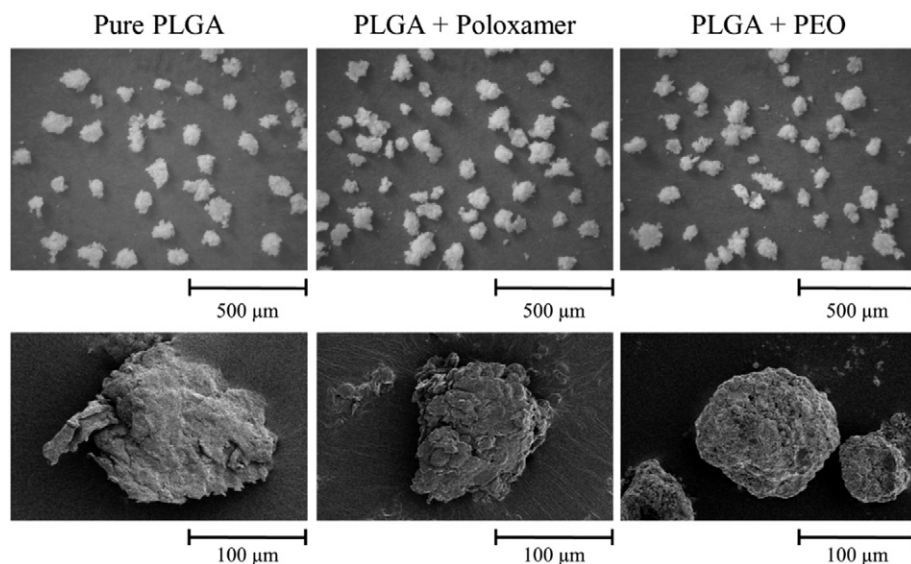

Fig. 1. Optical microscopy pictures (top row) and SEM pictures (bottom row) of milled drug-polymer powder blends. In all cases, the drug content was 1%. The (optional) Poloxamer/PEO content was 9.9%.

Pure PLGA   PLGA + Poloxamer   PLGA + PEO

10 μm

Fig. 2. SEM pictures of spray-dried prilocaine loaded microparticles before exposure to phosphate buffer pH 7.4. All formulations contained 1% drug. The (optional) Poloxamer/PEO content was 9.9%.

contrast, the respective spray-dried microparticles had a much smoother surface and were more or less spherical (Fig. 2). Importantly, the presence of Poloxamer or PEO in the milled powder blends or spray-dried microparticles had no fundamental impact on the resulting particle sizes or morphologies (Table 1, Figs. 1 and 2).

3.2. Drug release

Fig. 3 shows the release kinetics of prilocaine from the investigated: (i) microparticles, (ii) implants prepared by compressing milled drug-polymer powder blends, and (iii) implants prepared by compressing drug loaded microparticles. The red symbols represent systems based on drug and PLGA only. The green and blue symbols illustrate drug release from microparticles/implants containing 9.9% PEO or Poloxamer, respectively. In all cases, the drug loading was 1%. Clearly, the addition of the hydrophilic polymers had pronounced effects on the resulting drug release kinetics from the PLGA-based implants. Interestingly, the release rate substantially increased upon Poloxamer/PEO addition in the case of systems prepared by compression of milled drug-polymer powder blends, whereas it decreased in the case of implants prepared by compression of drug loaded microparticles. The impact on drug release from PLGA based microparticles was less pronounced. To better understand these phenomena, the systems were characterized with respect to their key properties, including changes in system size and shape upon exposure to the release medium, thermal properties, X-ray diffraction patterns and PLGA degradation kinetics.

3.3. Physical states of the drug and polymers

The X-ray diffraction patterns and DSC thermograms (1st and 2nd heating cycles) of the raw materials, physical mixtures thereof, milled drug-polymer powder blends and of the investigated microparticles are shown in Figs. 4–6. The drug content was kept at 1%, the optional

Poloxamer/PEO content at 9.9%. As it can be seen, the drug, Poloxamer and PEO raw materials exhibited sharp X-ray diffraction and clear melting peaks (1st heating cycles), indicating their crystalline or semi-crystalline nature. In contrast, PLGA was X-ray amorphous and showed a glass transition temperature (Tg) at about 47 °C.

Interestingly, crystalline prilocaine was clearly visible in the physical drug-PLGA mixtures (X-ray diffraction peaks in Fig. 4 and drug melting peak in Fig. 5), despite of the low drug content (1%). In contrast, milled prilocaine-PLGA powder blends and prilocaine-PLGA microparticles were X-ray amorphous and showed no drug melting peaks. This can serve as an indication for the fact that the drug was at least partially dissolved in the polymer and/or dispersed in an amorphous state. In the case of spray-dried microparticles, the change in the physical state of the drug can be explained by the fact that prilocaine was dissolved in dichloromethane during the manufacturing procedure. In the case of milled drug-polymer powder blends, the mechanical forces acting on the drug molecules during milling were sufficient to cause this physical state transformation [35,36]. Also in the case of physical mixtures of prilocaine-PLGA-Poloxamer and prilocaine-PLGA-PEO the crystallinity of the drug was visible in the DSC thermograms (Fig. 5) and X-ray diffraction patterns (Fig. 4), although less clearly. Again, in the respective milled drug-polymer powder blends and microparticles, no drug melting peaks or X-ray diffraction peaks of drug crystals were visible, indicating that the drug was transformed into an amorphous state and/or dissolved in a polymeric matrix.

Importantly, X-ray diffraction peaks of Poloxamer were clearly visible in the investigated physical mixtures and milled powder blends of prilocaine-PLGA-Poloxamer, but not in the spray-dried microparticles. This indicates that Poloxamer was probably completely amorphized during microparticle preparation, but not during milling. The fact that the Tg of the PLGA in the microparticles was not shifted during the first heating cycles (Fig. 5), but was lowered during the second heating cycle (Fig. 6), indicates that Poloxamer acts as a plasticizer for PLGA and that the two polymers
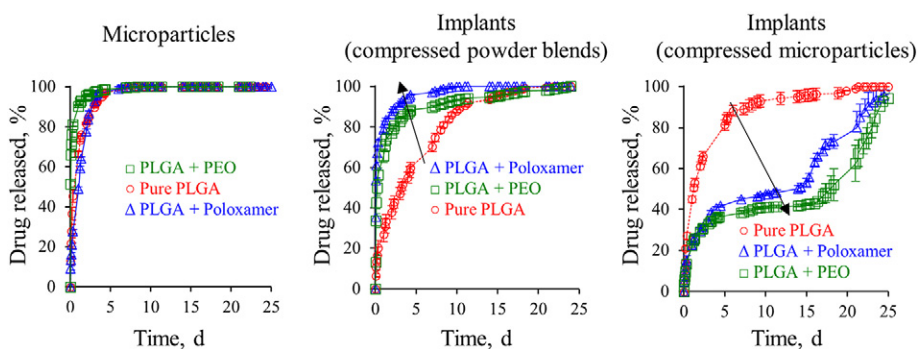

Fig. 3. Impact of the addition of Poloxamer or PEO on prilocaine release from PLGA microparticles, implants prepared by compression of milled drug-polymer powder blends and implants prepared by compression of microparticles. All formulations contained 1% drug. The (optional) Poloxamer/PEO content was 9.9%.

are not mixed at the molecular level in the microparticles (forming a co-amorphous, phase-separated system). In the case of prilocaine-PLGA-PEO, the PEO X-ray diffraction peaks were visible in physical mixtures and milled powder blends, and much less in the microparticles (Fig. 4). This is consistent with the dissolution peaks observed in the DSC thermograms in the case of physical mixtures and milled powder blends (1st heating cycles, Fig. 5): The crystalline parts of the PEO dissolved in the rubbery PLGA. Note that no separate PEO melting peak was observed in prilocaine-PLGA-PEO microparticles, probably because the much larger glass transition peak of the PLGA masked the small dissolution peak of the minor amounts of crystalline PEO (small X-ray diffraction peaks were visible in this case, Fig. 4) in the glassy polymer. Thus, the PEO was mainly (but not completely) amorphized during microparticle preparation. Analogous to the case of prilocaine-PLGA-Poloxamer, the absence of a Tg shift of the PLGA during the first heating cycle, and the presence of such a Tg shift to lower temperatures in the second heating cycle upon PEO addition, indicates: (i) the plasticizing effect of PEO for

PLGA, and (ii) the fact that the PEO and PLGA are not molecularly blended in the microparticles, but form a phase-separated, co-amorphous system. Note that in the case of physical blends, the Tg of the PLGA in the second heating cycle was not altered by the addition of Poloxamer/PEO (in contrast to the lowering observed in the case of milled drug-polymer powder blends and microparticles). This can be attributed to the fact that the PLGA and Poloxamer/PEO must be intimately mixed at the scale of very small particles to allow for an efficient polymer-polymer blending at the molecular level upon heating in the DSC pans.

The facts that: (i) X-ray diffraction peaks of Poloxamer and PEO were clearly visible in the respective drug-polymer powder blends, and not or hardly visible in the microparticles (Fig. 4), and (ii) a dissolution peak of crystalline PEO in rubbery PLGA was visible in milled powder blends, but not in microparticles (1st heating cycles, Fig. 5), indicate a difference in the crystallinity of these polymers in milled powder blends versus microparticles. This difference might affect various key properties of implants prepared with these materials,
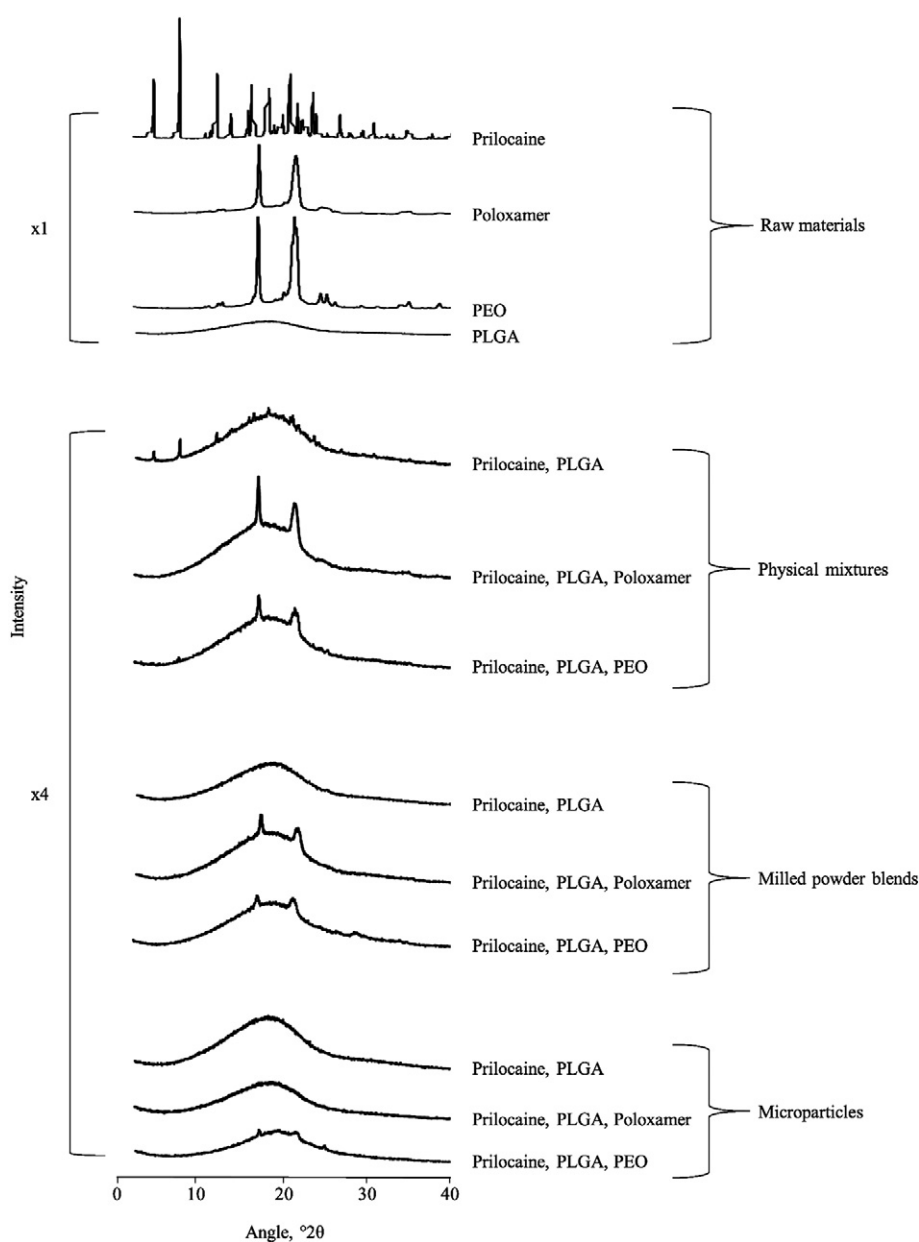

Fig. 4. X-ray diffraction patterns of the raw materials (as received), physical mixtures thereof, milled drug-polymer powder blends and of microparticles. In the case of physical mixtures, milled powder blends and microparticles, the drug content was 1% and the (optional) Poloxamer/PEO content 9.9%.
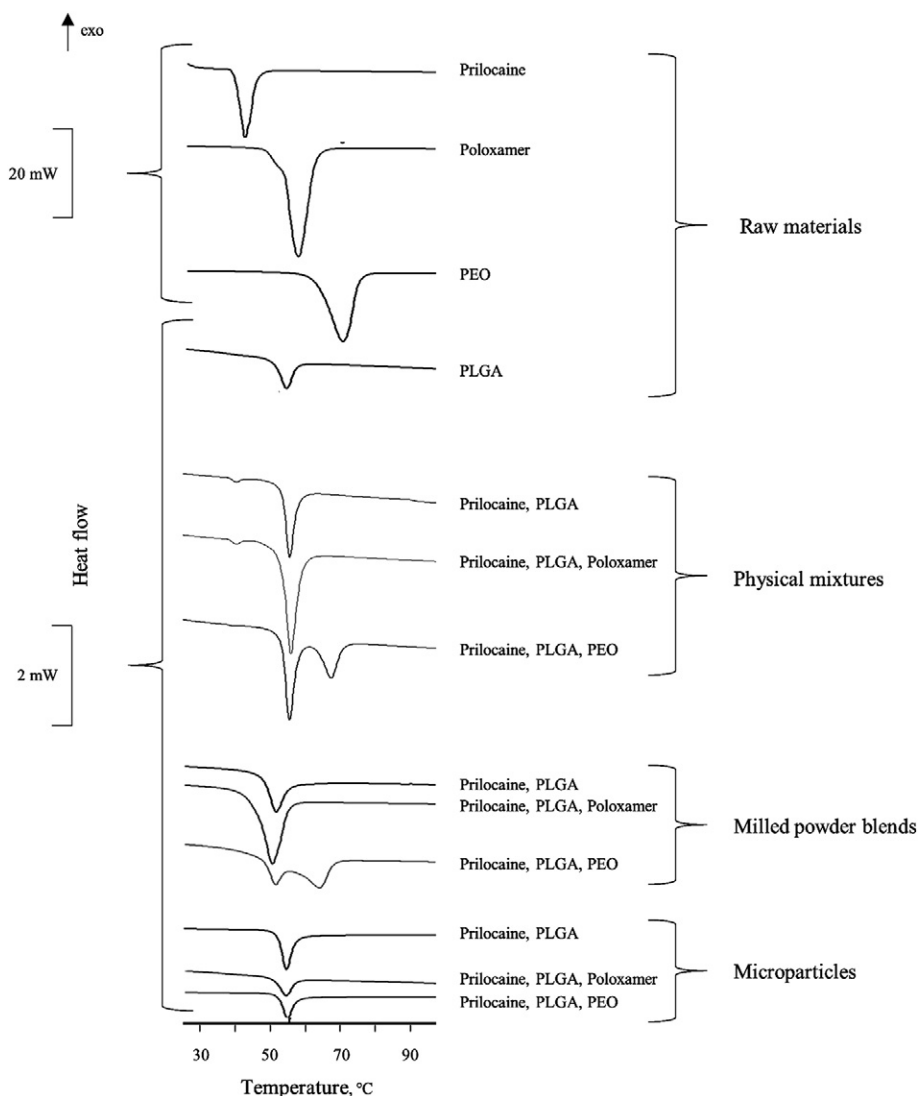
Fig. 5. DSC thermograms (1st heating cycles) of the raw materials (as received), physical mixtures thereof, milled drug-polymer powder blends and of microparticles. In the case of physical mixtures, milled powder blends and microparticles, the drug content was 1% and the (optional) Poloxamer/PEO content 9.9%.

for instance the systems' swelling and disintegration kinetics upon exposure to the release medium.

3.4. Implant morphology

Fig. 7 shows macroscopic pictures of implants prepared by compression of prilocaine–polymer powder blends (top rows), and of implants prepared by compressing drug loaded microparticles (bottom rows). The systems were observed before (t = 0) and after 1 h exposure to the release medium. As it can be seen, implants prepared by compressing drug-polymer powder blends rapidly lost their initial cylindrical shape and partially disintegrated. In contrast, implants prepared by compressing drug loaded microparticles remained intact and kept their cylindrical shape. Importantly, this was true for all the investigated implants, including those free of Poloxamer or PEO. Thus, differences in the degree of Poloxamer/PEO crystallinity cannot explain this phenomenon. In contrast, the difference in particle size might at least partially be the root cause: as discussed above and shown in Table 1, the spray-dried microparticles were much smaller than the milled drug-polymer powder particles. Hence, the packing of the particles during compression can be expected to be different, much more air being

included in the case of the larger drug-polymer powder blends, hindering the formation of stable matrices.

Note that different samples were observed at different time points.

Fig. 8 shows SEM pictures of surfaces and cross-sections (obtained by manual breaking) of implants prepared by compression of the drug loaded microparticles shown in Fig. 2, before exposure to the release medium. Interestingly, in all cases the microparticles were still visible, in particular in the cross-sections. For reasons of comparison, Fig. 9 shows SEM pictures of surfaces and cross-sections of the respective systems prepared by compression of milled drug-polymer powder blends.

Importantly, the observed differences in the implant disintegration behavior (systems prepared by compression of milled drug-polymer powder blends vs. drug loaded microparticles) can be expected to substantially affect the degree of water exposure of the PLGA and, thus, polymer degradation.

3.5. PLGA degradation

Fig. 10 shows the decrease in PLGA polymer molecular weight in implants prepared by compression of milled drug-polymer powder
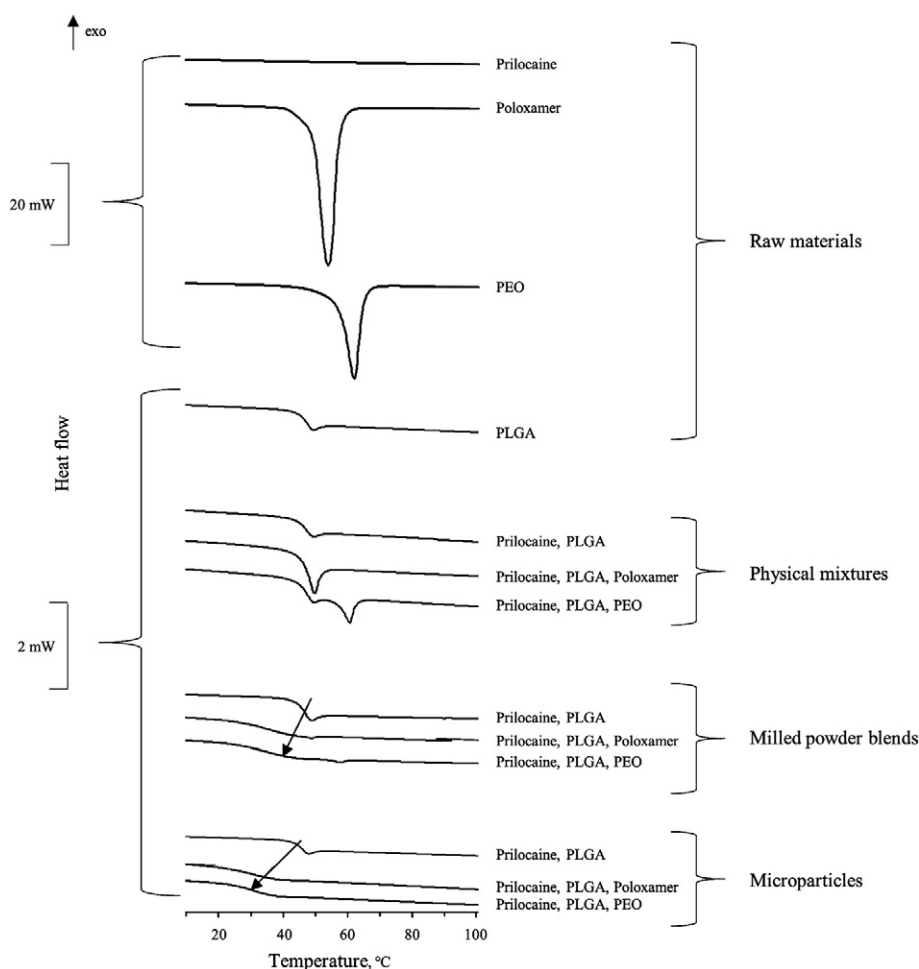
Fig. 6. DSC thermograms (2nd heating cycles) of the raw materials (as received), physical mixtures thereof, milled drug-polymer powder blends and of microparticles. In the case of physical mixtures, milled powder blends and microparticles, the drug content was 1% and the (optional) Poloxamer/PEO content 9.9%.

blends (left hand side), and in implants prepared by compression of drug loaded microparticles (right hand side). The systems optionally contained 9.9% Poloxamer or PEO, as indicated. Interestingly, the presence of the hydrophilic polymers substantially *accelerated* PLGA degradation in the case of implants prepared by compression of drug-polymer powder blends, whereas it *slowed down* polymer degradation in the case of implants prepared by compression of drug loaded microparticles. This can be explained as follows:

- In the case of implants prepared by compression of prilocaine loaded microparticles, the implants stayed intact upon exposure to the release medium (Fig. 7). Thus, the occurrence of autocatalytic effects is highly likely: upon exposure to the release medium, water penetration into the system is faster than subsequent PLGA degradation. Consequently, shorter chain acids are generated throughout the implants. Due to concentration gradients they diffuse out into the surrounding bulk fluid, where they are neutralized. In addition, bases from the surrounding environment diffuse into the system, neutralizing the generated acids. However, diffusional mass transport is relatively slow and the rate at which acids are generated in the investigated implants is likely to be higher than the rate at which they are neutralized [15, 37]. Consequently, the local micro-pH within the implants can substantially decrease. Since ester bond cleavage is catalyzed by protons, this leads to accelerated PLGA degradation (autocatalysis). Importantly, the addition of the hydrophilic polymers Poloxamer or PEO to the implants can be expected to facilitate water penetration into the

systems. Hence, the mobility of the generated acids (and of bases coming from the environmental bulk fluid) is increased within these implants. Consequently, the acids are more rapidly neutralized and the drops in the micro-pH are less pronounced. Thus, autocatalytic effects are less important and PLGA degradation is slower in Poloxamer/PEO-containing implants compared to pure PLGA-prilocaine implants (Fig. 10, right hand side). This phenomenon has major consequences for the resulting drug release kinetics (Fig. 3): the length of the PLGA chains is decisive for the mobility of the incorporated prilocaine: the shorter the polymer chains, the more mobile is the incorporated drug. This can result from different phenomena. *Firstly*, shorter PLGA chains are more hydrophilic than longer PLGA chains (since they contain more —COOH groups in the same mass of material). Thus, water can more easily penetrate into the system, leading to more pronounced implant swelling: Fig. 11 shows the dynamic changes in the volumes of implants prepared by compression of drug loaded microparticles upon exposure to the release medium. The pictures at the bottom show samples observed after 2 and 12 d. Clearly, pure PLGA-prilocaine implants swelled substantially more than prilocaine-PLGA-Poloxamer or prilocaine-PLGA-PEO implants. The much higher water content (resulting from the lower polymer molecular weight, right hand side of Fig. 10) can be expected to lead to substantially increased drug mobility. *Secondly*, implant erosion (mass loss due to the leaching of degradation products into the surrounding bulk fluid) is accelerated, since it is driven by the leaching of water-soluble monomers and oligomers (which are more rapidly generated from shorter PLGA chains). This results in accelerated pore formation and drug
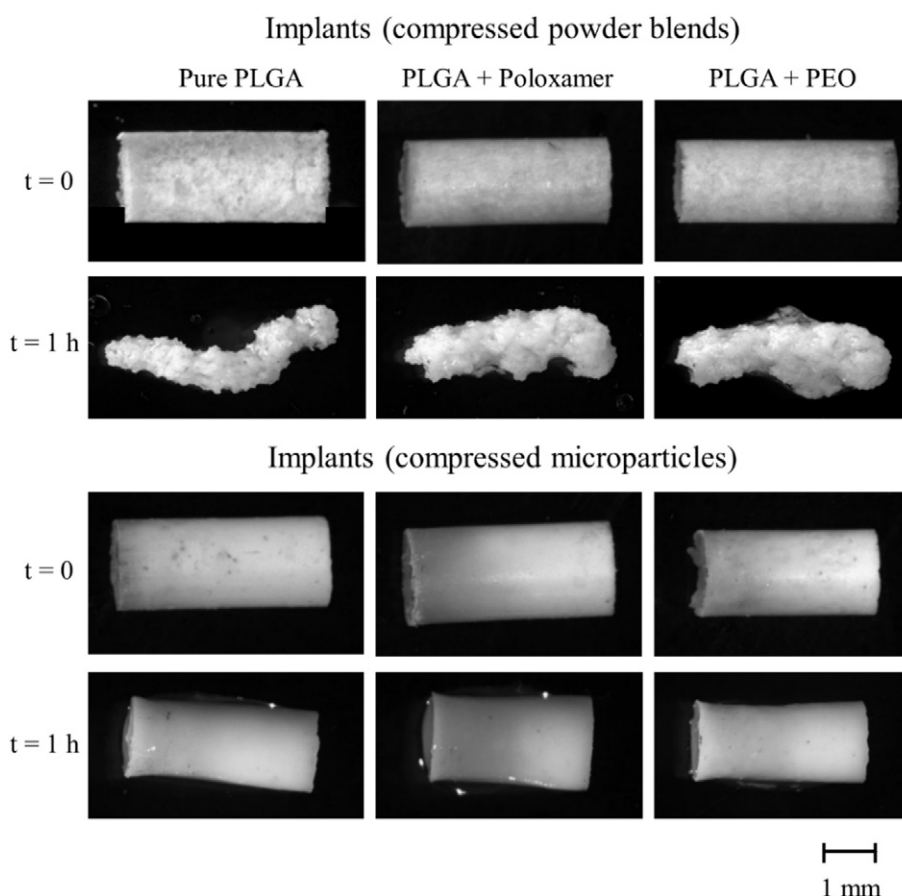
Fig. 7. Macroscopic pictures of implants prepared by compression of milled prilocaine-polymer powder blends, and of implants prepared by compression of prilocaine loaded microparticles before and after 1 h exposure to the release medium. All formulations contained 1% drug. The (optional) Poloxamer/PEO content was 9.9%.

release through water-filled pores. *Thirdly*, shorter polymer chains are less entangled and, hence, more mobile. Drug molecules diffusing though the intact polymer network are, thus, also more mobile. In summary, the addition of Poloxamer or PEO to PLGA implants prepared by compression of drug loaded microparticles leads to slower polymer degradation, system erosion and implant swelling, explaining the observed slower drug release (Fig. 3).

- In contrast, in the case of implants prepared by compression of milled drug-polymer powder blends, the implants rapidly lost their initial cylindrical shape and partially disintegrated (Fig. 7). Consequently, the lengths of the diffusion pathways for acids and bases are much shorter and autocatalytic effects can be expected to be less important compared to implants prepared by compression of microparticles (which stayed intact). Again, the presence of hydrophilic Poloxamer or PEO likely facilitates water penetration into the systems, but in this case (where autocatalysis is much less important), the presence of more water leads to accelerated PLGA degradation: more hydrolytically cleavable ester bonds are in direct contact with water. Hence, the addition of Poloxamer/PEO to implants prepared by compression of milled drug-polymer powder blends leads to accelerated PLGA degradation (Fig. 10, left hand side). The resulting increased drug mobility (due to the different reasons discussed above) explains the observed accelerated drug release (Fig. 3).

When comparing PLGA degradation in *implants based on PLGA and drug only* (red curves in Fig. 10), it can be seen that polymer chain cleavage is faster in systems prepared by compression of microparticles vs. milled powder blends. This can again be explained by the fact that implants prepared by compression of microparticles remain intact upon exposure to the release medium, in contrast to implants prepared by compression of milled powder blends (which partially disintegrate) (Fig. 7). Consequently, the autocatalytic effects in implants consisting of compressed microparticles are more important, resulting in accelerated PLGA degradation (Fig. 10). For the reasons described above, the resulting prilocaine release rate is, thus, higher from implants prepared by compression of microparticles vs. milled powder blends (Fig. 3, red curves in the right vs. middle diagram).

4. Conclusions

The addition of small amounts of hydrophilic polymers (such as Poloxamer or PEO) to PLGA-based implants offers an interesting potential to adjust crucial key properties of this type of advanced drug delivery systems. Water penetration into the implants can be facilitated, altering PLGA degradation and drug mobility. Importantly, the type of preparation technique of the implants is of utmost importance: Poloxamer/PEO addition to PLGA implants prepared by compressing milled drug-polymer powder blends accelerates drug release, whereas the opposite effect is observed with implants prepared by compressing drug loaded PLGA microparticles. These phenomena could be explained based on the disintegration/swelling behavior of the implants upon exposure to the release medium, determining the polymer degradation kinetics. For acid-labile drugs the addition of hydrophilic polymers to PLGA implants might also be very helpful to reduce the importance of local drops in the micro-pH.
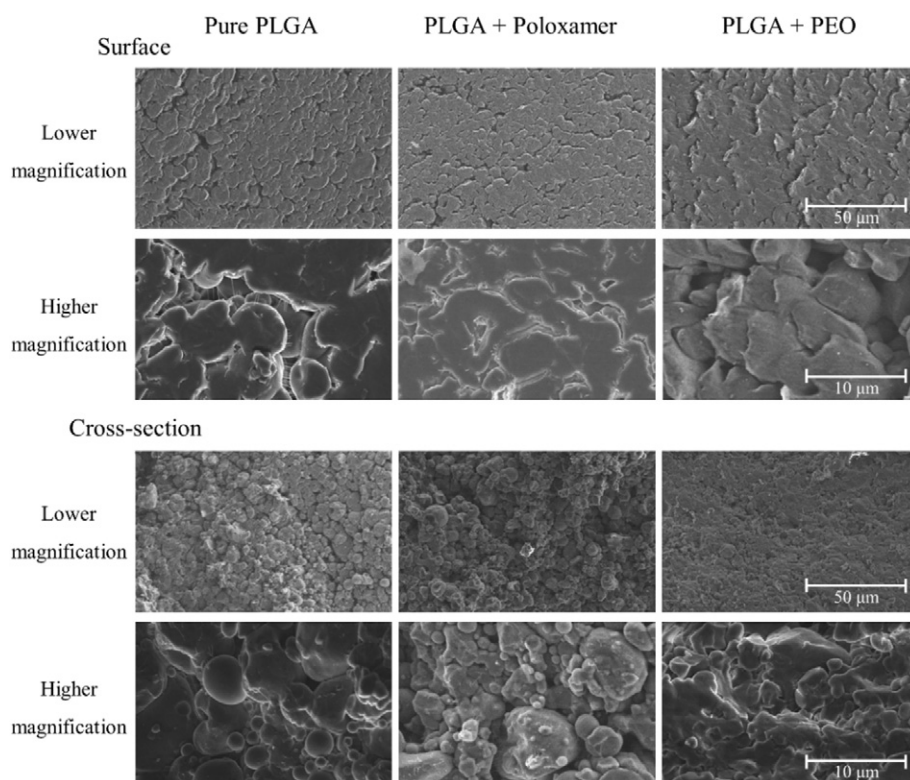
Fig. 8. SEM pictures of surfaces and cross-sections of implants prepared by compression of prilocaine loaded microparticles, before exposure to the release medium. All formulations contained 1% drug. The (optional) Poloxamer/PEO content was 9.9%.
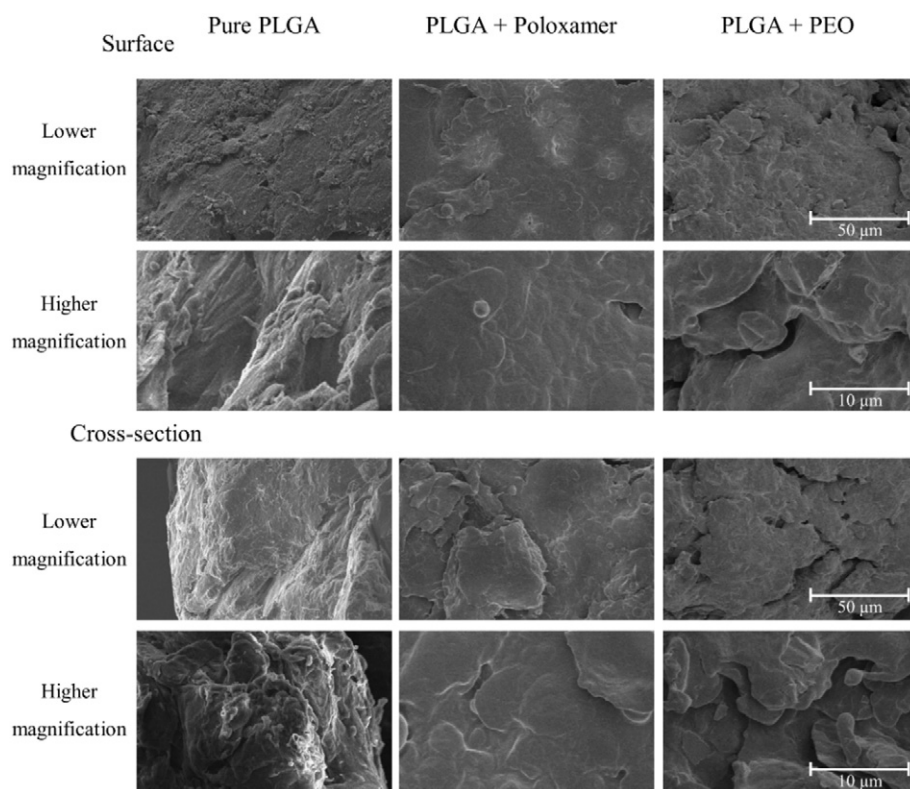

Fig. 9. SEM pictures of surfaces and cross-sections of implants prepared by compression of milled prilocaine-polymer powder blends, before exposure to the release medium. All formulations contained 1% drug. The (optional) Poloxamer/PEO content was 9.9%.
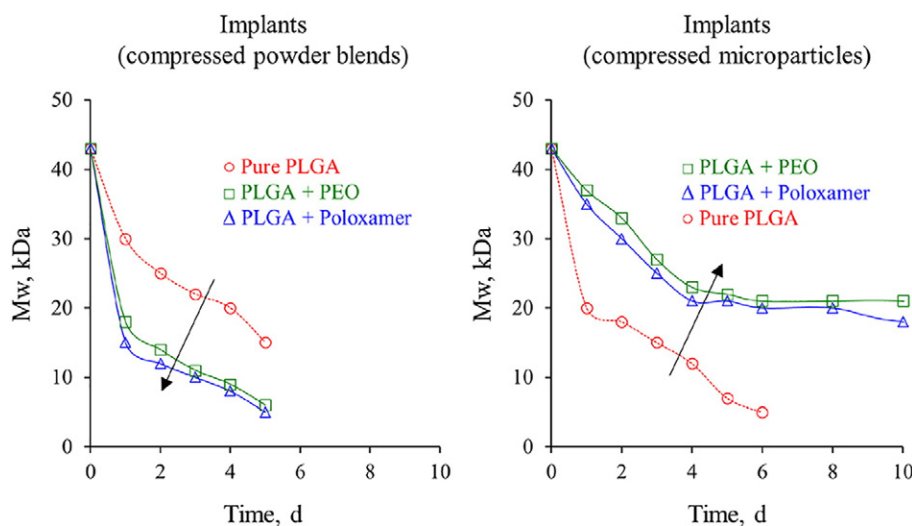
Fig. 10. PLGA degradation in implants prepared by compression of milled drug-polymer powder blends or by compression of drug loaded microparticles upon exposure to phosphate buffer 7.4. All formulations contained 1% drug. The (optional) Poloxamer/PEO content was 9.9%.
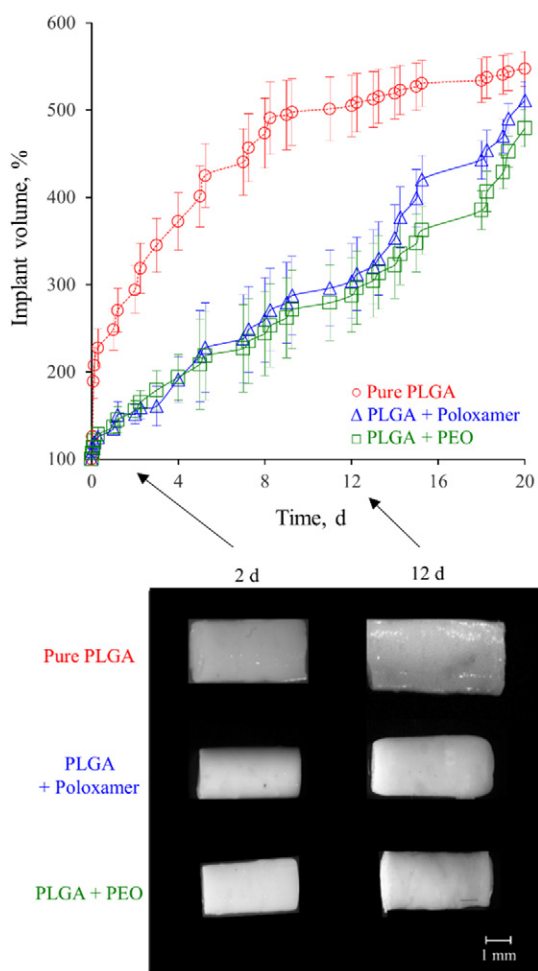

Fig. 11. Swelling of prilocaine-loaded implants prepared by compression of drug loaded microparticles upon exposure to phosphate buffer 7.4. The photos show optical microscopy pictures of implants after 2 and 12 d exposure to the release medium. All formulations contained 1% drug. The (optional) Poloxamer/PEO content was 9.9%.

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