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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.

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 generatedwater-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, cyclodextrines, 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 ± 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,