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Towards a better understanding of the different release phases from PLGA microparticles: Dexamethasone-loaded systems

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ABSTRACT

Dexamethasone-loaded, poly(lactic-*co*-glycolic acid) (PLGA) microparticles were prepared using an oil-in-water solvent extraction/evaporation method. The drug loading was varied from 2.4 to 61.9%, keeping the mean particle size in the range of 52–61 μm. In vitro drug release was characterized by up to 3 phases: (1) an (optional) initial burst release, (2) a phase with an about constant drug release rate, and (3) a final, again rapid, drug release phase. The importance and durations of these phases strongly depended on the initial drug loading. To better understand the underlying mass transport mechanisms, the microparticles were thoroughly characterized before and after exposure to the release medium. The initial burst release seems to be mainly due to the dissolution of drug particles with direct access to the microparticles' surface. The extent of the burst was negligible at low drug loadings, whereas it exceeded 60% at high drug loadings. The second release phase seems to be controlled by limited drug solubility effects and drug diffusion through the polymeric systems. The third drug release phase is likely to be a consequence of substantial microparticle swelling, leading to a considerable increase in the systems' water content and, thus, fundamentally increased drug mobility.

1. Introduction

Poly(lactic-*co*-glycolic acid) (PLGA)-based microparticles offer an interesting potential as advanced drug delivery systems, since they: (i) are biodegradable (avoiding the removal of empty remnants), (ii) are generally biocompatible (Fournier et al., 2003), (iii) allow for a precise control of the resulting drug release kinetics during time periods ranging from a few hours up to several weeks or months, (iv) can rather easily be injected using standard syringes, and (v) can be used for a variety of drugs and medical treatments. Since many years a number of drug products based on PLGA microparticles are commercially available.

However, despite the considerable practical success of PLGA microparticles as advanced drug delivery systems, the underlying mass transport mechanisms controlling drug release are often not fully understood (Faisant et al., 2002; Siepmann et al., 2002; Siepmann and Siepmann, 2008). This can at least partially be explained by the potential complexity of the involved physical and chemical phenomena (Siepmann and Goepferich, 2001; Fredenberg et al., 2011). For instance, the following processes might play a role in the control of drug release from PLGA-based microparticles: Water penetration into the systems upon contact with aqueous body fluids, drug dissolution (Siepmann and Siepmann, 2013), drug diffusion through the intact PLGA matrix and/or drug diffusion through water-filled pores, drug partitioning between an aqueous phase located in pores and a continuous PLGA matrix, limited drug solubility effects, pore closing effects (Kang and Schwendeman, 2007; Huang et al., 2015), plasticization of PLGA by water (Blasi et al., 2005) or drugs (Albertini et al., 2015; Gasmi et al., 2015a,b), polymer chain cleavage and the diffusion of water-soluble degradation products through the eroding microparticles into the surrounding environment, osmotically driven water-influx into the system, diffusion of bases form the surrounding bulk fluid into the microparticles, as well as microparticle swelling (note that this list is not exhaustive). In addition, autocatalytic effects might play a major role (Fu et al., 2000; von Burkersroda et al., 2002; Dunne et al., 2000; Siepmann et al., 2005; Li and Schwendeman, 2005; Gu et al., 2016) as explained in the following: The rate at which water penetrates into the system is much higher than the

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rate of ester bond cleavage. Consequently, the polymer chains are cleaved throughout the system and short chain acids are generated everywhere in the microparticles. Often, the rate at which these acids are generated is higher than the rate at which they are neutralized (since the diffusion of acids and bases in the systems is often slower compared to the generation of the acids). Thus, the micro-pH within the PLGA particles might locally substantially drop (Brunner et al., 1999; Li and Schwendeman, 2005). This is particularly true for the center of the microparticles (since the length of the diffusion pathways is the longest). Since protons catalyze the ester bond cleavage in PLGA, this results in autocatalytic effects (this means that one of the products of the chemical reaction catalyzes the reaction itself).

Interestingly, often mono-, bi-, or tri-phasic drug release is reported from PLGA microparticles (Siepmann et al., 2005; Klose et al., 2006; Fredenberg et al., 2011). Generally, an initial burst release is followed by a second phase with an about constant release rate, and a final (again rapid) drug release phase. This can serve as an indication that the conditions for drug release are likely to substantially change with time. The fact that drug release from PLGA microparticles is not always tri-phasic, might be explained as follows: In certain systems the drug is already completely released once the conditions for the second or third drug release phase are provided (Siepmann et al., 2005; Klose et al., 2006). Note that the relative importance of the different, potentially involved mass transport phenomena might substantially vary between different types of PLGA-based microparticles. For instance, the type of drug might substantially affect its release: Certain drugs act as plasticizers for PLGA (Albertini et al., 2015; Gasmi et al., 2015a, b). Also, the drug can be more or less soluble in the polymer matrix, and the physical state of the drug in the system might affect the release mechanism (Siepmann and Siepmann, 2008, 2012, 2013). Furthermore, if the drug is an acid or a base, its presence might affect PLGA degradation (ester bond cleavage being catalyzed by protons and hydroxide ions). In addition, the drug loading and preparation method of the microparticles might impact the systems' inner and outer morphology and, thus, the relative importance of the involved mass transport phenomena (Wang et al., 2015; Klose et al., 2006). Furthermore, the PLGA microparticle size and porosity might impact the importance of potentially involved autocatalytic effects, determining the pathway lengths to be overcome and altering the mobility of acids leaving and of bases entering the systems (Siepmann et al., 2005; Klose et al., 2006). Moreover, the surrounding environment might substantially impact the observed drug release kinetics, for example via limited drug solubility effects and/or alterations in the pH values (potentially accelerating PLGA degradation) (Klose et al., 2009, 2011; Zolnik and Burgess, 2008).

In order to better understand which physical and chemical processes are of importance for the control of drug release from a particular type of PLGA particles, the latter should ideally be thoroughly characterized before and after exposure to the release medium. This includes for instance thermal analyses (e.g., DSC), X-ray diffraction measurements, SEM, optical microscopy, GPC and the monitoring of *single* microparticle swelling (Gasmi et al., 2015a, b). It has recently been shown with an acidic and a basic drug (ketoprofen and prilocaine free base, both acting as efficient plasticizers for PLGA) that the third drug release phase seems to be initiated by substantial microparticle swelling (Gasmi et al., 2015a, b). However, as yet it is unknown whether this phenomenon also plays a role for neutral drugs, and/or drugs which do not plasticize PLGA.

The aim of this study was to prepare different types of dexamethasone-loaded PLGA microparticles using an oil-in-water solvent extraction/evaporation method. The initial drug loading was varied from 2.4 to 61.9%, while the mean microparticle size was intentionally kept in the range of 52–61 μm, in order to avoid particle size effects (Siepmann et al., 2004). One of the reasons for selecting dexamethasone-loaded PLGA microparticles was their interesting therapeutic potential, for instance for the reduction of foreign body reactions to glucose sensors (prolonging the latter's lifetime) (Gu et al., 2015; Gu and Burgess, 2015). The different types of systems were thoroughly characterized before and after exposure to phosphate buffer pH 7.4. The idea was to better understand the underlying mass transport mechanisms controlling the different release phases from PLGA-based microparticles based on the obtained results.

2. Materials and methods

2.1. Materials

Poly(D,L lactic-*co*-glycolic acid) (PLGA; Resomer RG 504H; 50:50 lactic acid:glycolic acid; Evonik; Darmstadt; Germany), dexamethasone (99.0% purity; Discovery Fine Chemicals, Dorset, United Kingdom), dichloromethane (VWR, Fontenoy-sous-Bois, France); dimethylsulfoxide (DMSO) and tetrahydrofurane (HPLC Grade; Fisher Scientific, Illkirch, France); poly(vinyl alcohol) (Mowiol 4-88; Sigma-Aldrich, Steinheim, Germany).

2.2. Microparticle preparation

Dexamethasone-loaded, PLGA-based microparticles were prepared using an oil-in-water (O/W) emulsion solvent extraction/evaporation technique. Depending on the theoretical drug loading (which was varied between 3.9% to 63.2% w/w), 41.3–722.1 mg drug and 420.1–1016.1 mg PLGA were dissolved in a mixture of dimethylsulfoxide (DMSO) and dichloromethane (CH_2Cl_2) (Table 1). The composition and volume of the organic phase was adjusted to provide similar viscosities and, most importantly, a similar mean microparticle diameter (in the range of about 50–60 μm). This organic phase was emulsified within 400 mL of an outer aqueous poly(vinyl alcohol) solution (0.25% w/w; previously cooled to +4 °C) using a three-blade propeller (Eurostar power-b; Ika-Werke, Staufen, Germany; 2000 rpm), inducing microparticle formation. Stirring was continued for 30 min. The particles were hardened by adding 1 L of the same outer aqueous poly(vinyl alcohol) solution (cooled to +4 °C) and further stirring at 700 rpm during 4 h. The particles were then separated by filtration (Nylon, 0.45 μm, 13 mm; GE Healthcare Life Sciences Whatman, Kent, UK, vacuum pump) and subsequently freeze-dried (Christ Epsilon 2-4 LSC; Martin Christ, Osterode, Germany; freezing at −45 °C for 2 h, primary drying at −9 °C/0.014 mbar for 10 h, secondary drying at +20 °C/0.0014 mbar for 10 h).

2.3. Microparticle characterization

Particles sizes were determined by optical microscopy (diameters of surface equivalent circles). Pictures were taken using an Axiovision Zeiss Scope-A1 microscope, AxioCam ICc1 camera and Axiovision Zeiss Software (Carl Zeiss, Jena, Germany). Each measurement included 200 microparticles.

Table 1
Composition of the inner organic phase used for microparticle preparation.

Theoretical drug loading (%)	3.9	9.8	14.9	22.4	33.7	63.2
DMSO (mL)	2.0	2.0	2.0	2.0	2.0	2.5
CH_2Cl_2 (mL)	5.0	5.0	4.6	4.3	4.3	3.8
PLGA (mg)	1016.1	1014.6	910.2	835.2	623.3	420.1
Drug (mg)	41.3	110.6	159.6	240.6	317.2	722.1