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In-situ forming PLGA implants: How additives affect swelling and drug release

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ABSTRACT

The aim of this study was to investigate the impact of the addition of very different types of additives on the key features of *in-situ* forming implants based on poly(D,L-lactic-co-glycolic acid) (PLGA, Resomer RG 502H) loaded with dexamethasone. All ingredients were dissolved in N-methyl-pyrrolidone (NMP), the implants formed upon solvent exchange. Crosslinked poly(acrylic acid) (Carbopol), poly(ethylene glycol) (PEG 400), hydroxypropyl methylcellulose (HPMC K100, HPMC E15), stearic acid and acetyltributyl citrate (ATBC) were studied as additives, in concentrations up to 5% (except for ATBC: up to 20%). Dynamic changes in the implants' wet mass, pH of the release medium, NMP leaching as well as dexamethasone release were monitored upon exposure to phosphate buffer pH 7.4. Also the implants' inner and outer morphology was studied, using optical and scanning electron microscopy. Interestingly, the addition of the very different types of additives partially substantially altered the morphology and swelling kinetics of the investigated *in-situ* forming PLGA implants, whereas the impact on dexamethasone release was rather limited in all cases. Generally, the release rate slightly increased in the presence of the additives, only in the case of ATBC it slightly decreased. The overall limited effect on drug release might at least partially be attributed to the fact that: (i) *water-soluble* additives might rapidly leach out into the aqueous release medium during implant formation and/or promote implant swelling, and (ii) *lipophilic* additives might induce phase separation.

1. Introduction

In-situ forming, poly(D,L-lactic-co-glycolic acid) (PLGA)-based implants offer an interesting potential as parenteral controlled drug delivery systems [1–8], since: (i) PLGA is biocompatible and biodegradable [9–11]. (ii) The degradation products are lactic and glycolic acid, both being non-toxic [12]. (iii) The liquid formulations can generally more easily be administered than larger, pre-formed implants [13,14]. (iv) They offer the possibility to control drug release during periods ranging from a few days up to several months [15–17]. (v) They can potentially directly be administered at the site of action and can, thus, allow overcoming crucial physiological barriers [18].

This makes *in-situ* forming PLGA implants attractive as advanced drug delivery systems for the treatment of posterior eye diseases and disorders. Unfortunately, drug administration is highly challenging in these cases: For example, only a very small portion of the administered drug dose (approximately 0.001–0.0004%) reaches the inside of the vitreous when using eye drops [19]. This is because of the limited residence time of the eye drops at the site of administration (rapid clearance), limited permeability through the cornea and subsequent tissues/barriers to be overcome before reaching the site of action [20–22]. To pass these hurdles, drug solutions might be directly administered into the vitreous, but this is painful and bears the risk of infections [22–24]. Also, the half-life of many drugs is limited in the vitreous, requiring frequent administration. For example, dexamethasone has a half-life of only a few hours in the vitreous [25]. To provide therapeutic dexamethasone concentrations over prolonged periods of time after one single injection, controlled drug delivery systems might be used. However, in the case of pre-formed, slow releasing implants, generally relatively large needle sizes are required (due to the implants' dimensions), causing painful administration.

In-situ forming implants might allow overcoming all these hurdles: Using thin needles, the liquid formulation is directly injected into the vitreous and solidifies *in-situ*. Different mechanisms can be used to induce implant formation, such as the change in temperature (room temperature to body temperature) or solvent exchange. In the latter case, the matrix former (e.g. PLGA) is dissolved in an appropriate organic solvent, which is miscible with water. The drug is dissolved and/

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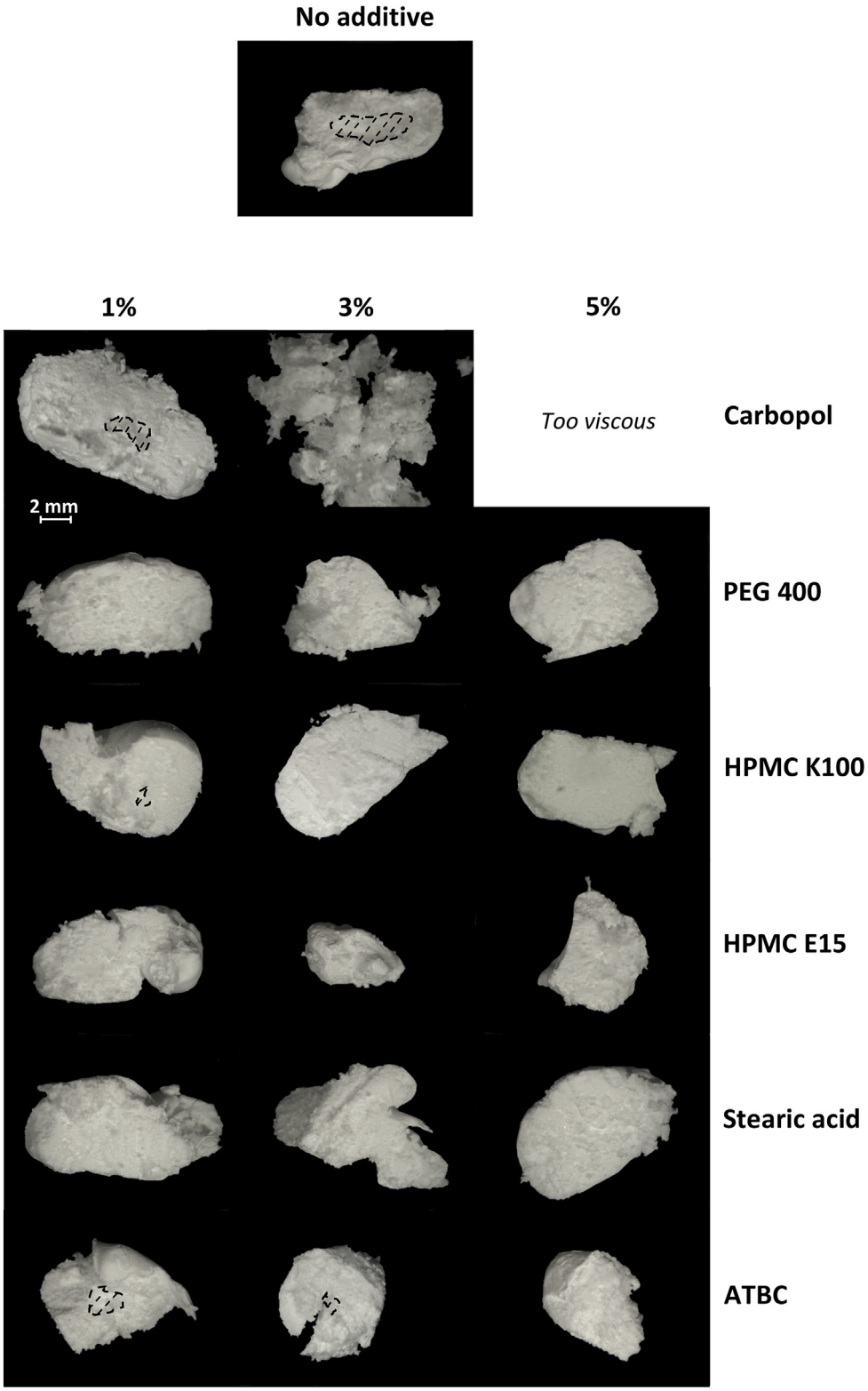

Fig. 1. Macroscopic pictures of cross-sections of *in-situ* formed implants after 3 d exposure to phosphate buffer pH 7.4 (and subsequent freeze-drying). Optionally different concentrations of additives were added (as indicated). The dashed curves indicate the presence of hollow cavities. Note that formulations containing 5% Carbopol were too viscous to be injected.

or dispersed within this polymer solution. Upon contact with aqueous body fluid, the solvent diffuses into the surrounding environment, and water diffuses into the formulation [26,27]. Since PLGA is not soluble in water, it precipitates and the implant forms. The drug is trapped in the polymeric system and is subsequently slowly released at a pre-programmed rate [28]. Recently, *in-situ* forming, dexamethasone loaded, PLGA-based implants have been proposed [29]. The effects of the volume of the release medium used for in vitro studies, of the drug

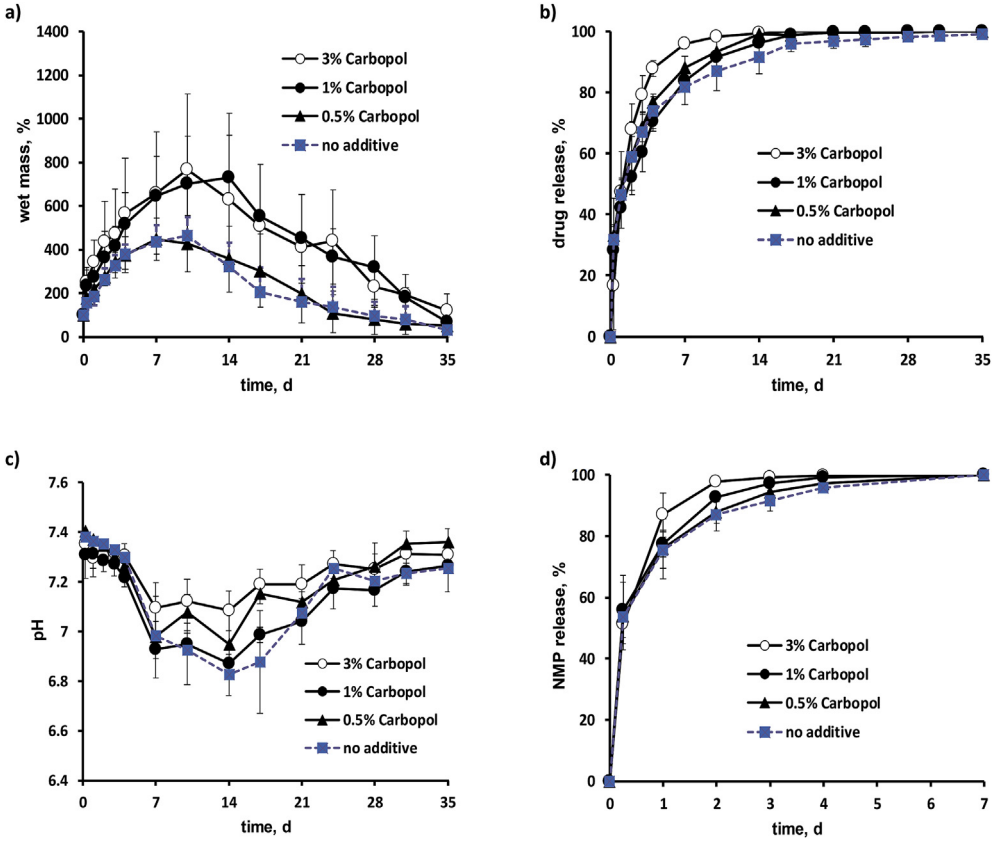

Fig. 2. Impact of the addition of different amounts of Carbopol on the: a) wet mass, b) drug release, c) pH of the release medium, and d) NMP release of/from *in-situ* forming implants upon exposure to phosphate buffer pH 7.4 at 37 °C. Mean values ± standard deviation are indicated (n = 3).

loading and of the type & concentration of the polymer were studied. However, no additives were incorporated and the potential effects of such compounds on the implants' key features (in particular drug release and system swelling) are yet unknown.

Several research groups have studied the impact of additives for *in-situ* forming controlled release implant formulations [30]. Interestingly, partially opposite trends were observed. For example, Do et al. added up to 30% hydroxypropyl methylcellulose (HPMC) to *in-situ* forming PLGA implants loaded with doxycycline or metronidazole for local periodontitis treatment [31,32]. Depending on the chain length of the PLGA (Resomer RG 502H vs. Resomer RG 504H) the resulting drug release rate either decreased or increased. A variety of potential additives has been suggested for *in-situ* forming implants, for example hydroxypropyl methylcellulose (HPMC) and ethylbenzoate [31–34]. They can have multiple effects, e.g. impact the resulting organic solvent – water exchange rates and porosity of the implants. Also, the implant swelling might be altered by the presence of additives. For instance, Brodbeck et al. [35] have shown that a lower water uptake can reduce the burst release of a drug. But additives might not only be used to optimize the resulting drug release kinetics, they can also help improving other key properties of the *in-situ* formed implants, such as their bioadhesion in periodontal pockets [31,32,34,36].

The aim of this study was to investigate the effects of adding small amounts of a variety of additives [crosslinked poly(acrylic acid), poly (ethylene glycol), hydroxypropyl methylcellulose, stearic acid and acetyltributyl citrate] on the key features of *in-situ* forming PLGA implants loaded with dexamethasone. N-methyl-pyrrolidone (NMP) was used as water-miscible solvent. The implants formed upon exposure to phosphate buffer pH 7.4. Dynamic changes in the implants' wet mass were measured gravimetrically, the pH of the release medium was monitored as well as NMP leaching and drug release. In addition, the implants' inner and outer morphologies were studied, using optical and scanning electron microscopy.

2. Materials and methods

2.1. Materials

Poly(D,L-lactic-co-glycolic acid) (50:50, -COOH end groups; PLGA, Resomer RG 502 H; Evonik, Darmstadt, Germany); dexamethasone (Discovery Fine Chemicals, Dorset, UK); crosslinked poly(acrylic acid) (Carbopol 980 Polymer, Carbopol; Lubrizol, Wickliffe, Ohio, USA); poly (ethylene glycol) (PEG 400; Acros organics, Geel, Belgium); acetyltributyl citrate (ATBC) (Morflex, Greensboro, NC, USA); hydroxypropyl methylcellulose (HPMC, Methocel E15 and K100; Colorcon, Dartford, UK); stearic acid, N-methyl-pyrrolidone (NMP), acetonitrile and tetrahydrofuran (Fisher Scientific, Illkirch, France); formic acid (Riedel-de Haën, Seelze, Germany); ethanol (96%; VWR, Fontenay-sous-Bois, France).

2.2. Preparation of the liquid formulations

PLGA (40%), dexamethasone (1%) and varying amounts of different additives (Carbopol, PEG 400, HPMC K100, HPMC E15, stearic acid or ATBC were dissolved in NMP (in all cases clear solutions were obtained) in glass vials under stirring at 500 rpm (Multipoint Stirrer, Thermo Scientific, Loughborough, UK) at room temperature for 60 min. All percentages refer to the total liquid formulation mass (100% = polymer + drug + additive + NMP). The NMP content was adjusted accordingly (as a function of the additive content). Afterwards, the vials were kept for 1 h at room temperature without stirring to remove air bubbles. The formulations were stored at 2-8 °C, and allowed to reach room temperature prior to use.

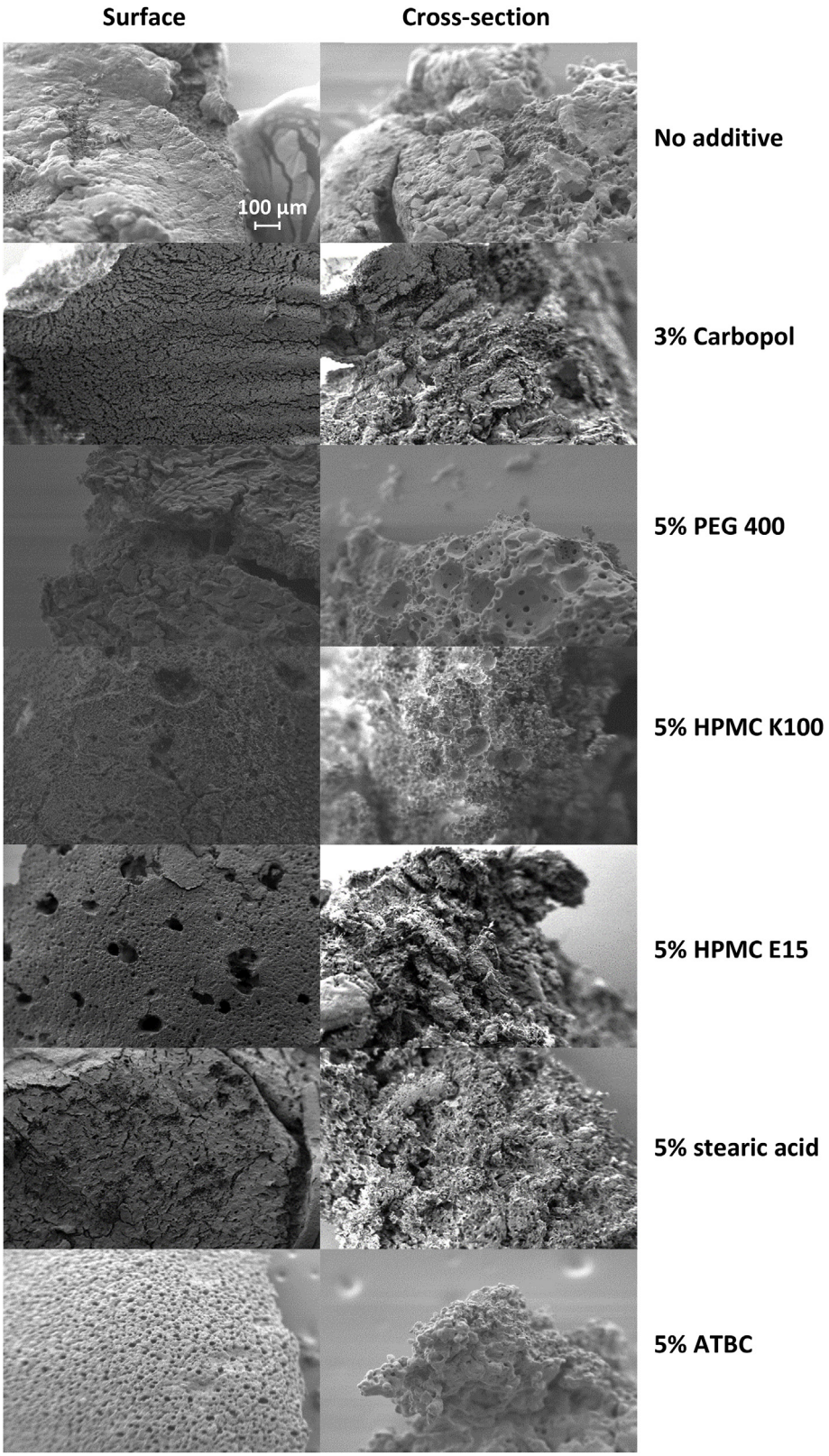

Fig. 3. SEM pictures of surfaces and cross-sections of *in-situ* formed implants after 3 d exposure to phosphate buffer pH 7.4 (upon freeze-drying). Optionally different concentrations of additives were added (as indicated).

2.3. In-situ implant formation

Eppendorf vials were filled with 4 mL phosphate buffer pH 7.4 (USP 40) (37 °C). One hundred µL of the liquid PLGA/dexamethasone/additive/NMP formulations (prepared as described in section 2.2) were injected using a syringe pump (2 mL/min; PHD 2000; Harvard Apparatus, Holliston, USA). Solvent exchange initiated polymer precipitation and *in-situ* implant formation. The Eppendorf vials were placed into a

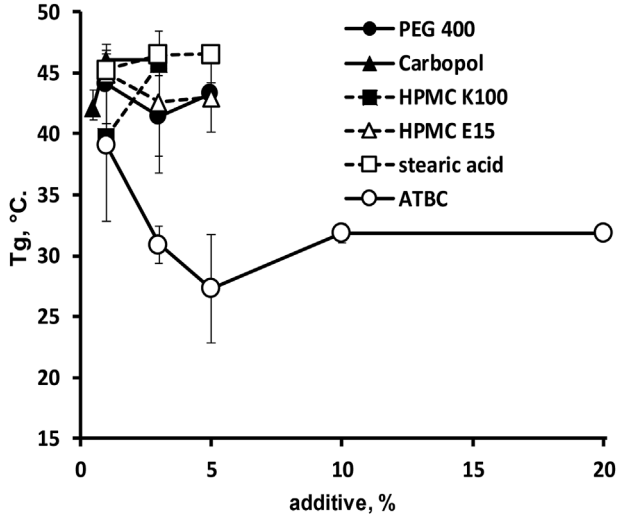

Fig. 4. Impact of the addition of different amounts of additives (indicated in the diagram) on the glass transition temperature (Tg) of *in-situ* formed implants formed after 3 d exposure to phosphate buffer pH 7.4 and subsequent freeze-drying. Mean values ± standard deviation are indicated (n = 3).

horizontal shaker (80 rpm, 37 °C; GFL 3033, Gesellschaft fuer Labortechnik, Burgwedel, Germany).

2.4. Characterization of in-situ formed implants

In vitro drug release: At determined time points, the phosphate buffer pH 7.4 in the vials in which the implants formed was completely renewed. The amount of dexamethasone in the withdrawn bulk fluid was determined by HPLC-UV analysis, using a Thermo Fisher Scientific Ultimate 3000 Series HPLC, equipped with a LPG 3400 SD/RS pump, an auto sampler (WPS-3000 SL) and a UV–Vis detector (VWD-3400RS) (Thermo Fisher Scientific, Waltham, USA). Samples were centrifuged for 2.5 min at 10,000 rpm (Centrifuge Universal 320; Hettich, Tuttlingen, Germany), and filtered with a 0.45 µm PVDF syringe filter (Millex-HV, Merck Millipore, Tullagreen, Ireland). One hundred µL samples were injected into an A C18 RP column (Gemini 3 µm C18 110 Å, 100 mm × 4.6 mm; Phenomenex, Le Pecq, France). The mobile phase consisted of acetonitrile and water (33:67 v/v), the flow rate was 1.5 mL/min. Dexamethasone had a retention time of approximately 3.8 min, the detection wavelength was λ = 254 nm. The calibration curve was linear (R > 0.999) within the range of 0.06 to 0.00003 mg/mL. To determine the amount of dexamethasone potentially remaining in the implants at the end of the observation period, the remnants were dissolved in a mixture of acetonitrile and ethanol (2:1 v/v). The solutions were filtered using 0.45 µm PVDF filter syringes, and analyzed for their drug contents by HPLC-UV (as described above). In all cases, no noteworthy drug amounts were detected in implant remnants. All experiments were conducted in triplicate. In addition, the pH of the release medium was measured at pre-determined time points using a pH meter (InoLab pH Level 1; WTW, Weilheim, Germany) (n = 3). Mean values ± standard deviations are reported.

Implant swelling: At pre-determined time points, implant samples were withdrawn, excess water carefully removed using Kimtech precision wipes (Kimberly-Clark, Rouen, France) and weighed [*wet mass (t)*]. The *wet mass (%) (t)* was calculated as follows:

$$wet\ mass\ (\%)(t) = \frac{wet\ mass\ (t)}{formulation\ mass} \times 100\ \% \quad (1)$$

where *formulation mass* is the initial total mass of the liquid formulation (PLGA + dexamethasone + additive + NMP). All experiments were

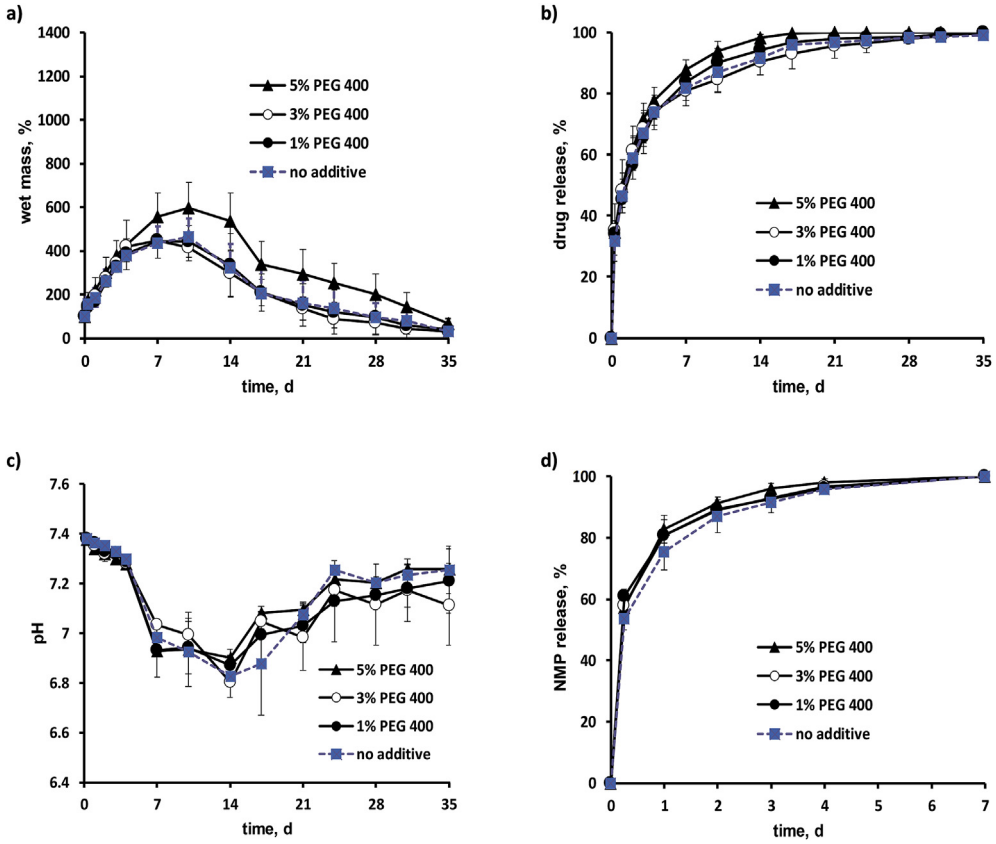

Fig. 5. Effects of the addition of different amounts of PEG 400 on the: a) wet mass, b) drug release, c) pH of the release medium, and d) NMP release of/from *in-situ* forming implants upon exposure to phosphate buffer pH 7.4 at 37 °C. Mean values ± standard deviation are indicated (n = 3).

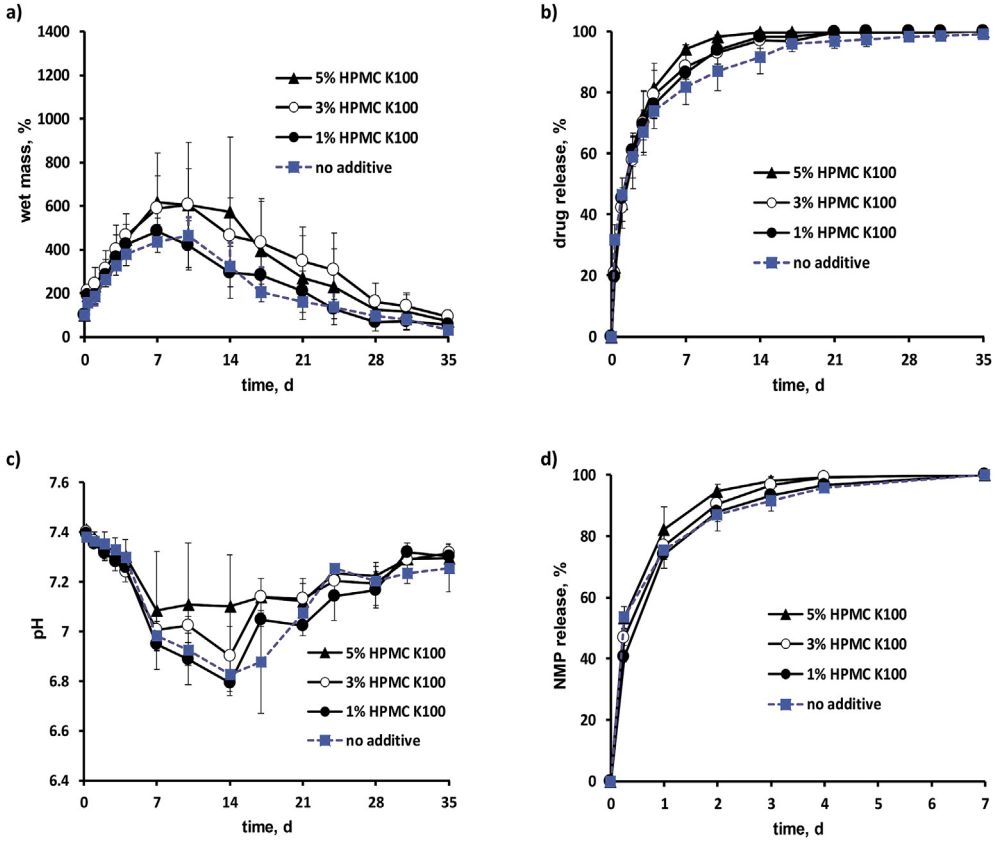

Fig. 6. Impact of the addition of different amounts of HPMC K100 on the: a) wet mass, b) drug release, c) pH of the release medium, and d) NMP release of/from *in-situ* forming implants upon exposure to phosphate buffer pH 7.4 at 37 °C. Mean values ± standard deviation are indicated (n = 3).

conducted in triplicate. Mean values ± standard deviations are reported.

NMP release: At pre-determined time points, the phosphate buffer pH 7.4 in the vials in which the implants formed was completely renewed. The amount of NMP in the withdrawn bulk fluid was determined by HPLC-UV analysis, using a Thermo Fisher Scientific Ultimate 3000 Series HPLC, equipped with a LPG 3400 SD/RS pump, an auto sampler (WPS-3000 SL) and a UV–Vis detector (VWD-3400RS). Samples were centrifuged for 2.5 min at 10,000 rpm (Centrifuge Universal 320), and filtered with a 0.45 µm PVDF syringe filter (Millex-HV). Ten µL samples were injected into a polar column (Luna 3 µm HILIC 200 Å, 150 mm × 4.6 mm; Phenomenex). The mobile phase consisted of acetonitrile and water (50:50 v/v) containing 0.1% formic acid, the flow rate was 1.5 mL/min. NMP had a retention time of approximately 4.8 min, the detection wavelength was λ = 210 nm. The calibration curve was linear (R > 0.999) within the range of 0.55 to 0.025 mg/mL. After more than 7 d exposure time to the release medium, NMP was no more detected in the bulk fluid (= 100% NMP release). All experiments were conducted in triplicate. Mean values ± standard deviations are reported.

Implant morphology: At pre-determined time points, implants were withdrawn and freeze-dried for 3 d (Christ Epsilon 2–4 LSC; Martin Christ, Osterode, Germany). Cross-sections were obtained by manual breaking. *Macroscopic* pictures of freeze-dried implants were obtained with an optical image analysis system (Nikon SMZ-U; Nikon, Tokyo, Japan), equipped with a Zeiss camera (AxioCam ICc1; Zeiss, Jena, Germany). *SEM* pictures of freeze-dried implants were made with a JEOL Field Emission Scanning Electron Microscope JSM-7800F (Tokyo, Japan). Samples were fixed with a ribbon carbon double-sided adhesive on the sample holder and covered with a fine chrome layer using the Gatan Model 682 Precision Etching and Coating System (Pleasanton, CA, USA).

Glass transition temperature: The glass transition temperature (Tg) of freeze-dried implants was determined by differential scanning calorimetry (DSC 1 Star System; Mettler Toledo, Greifensee, Switzerland). After 3 d exposure to the release medium, samples were removed and freeze-dried for 3 d (Christ Epsilon 2–4 LSC). Approximately 3 mg samples were accurately weighed in sealed aluminum pans. The pans were heated to 120 °C, cooled to −70 °C, and reheated to 120 °C (at a rate of 10 °C/min in nitrogen atmosphere). The Tg was determined during the second heating cycle. All experiments were conducted in triplicate. Mean values ± standard deviations are reported.

3. Results and discussion

3.1. Carbopol

In the case of Carbopol, only 0.5, 1 and 3% additive were investigated, since formulations containing 5% Carbopol were too viscous to be injected. The percentages refer to the total formulation mass (polymer + drug + additive + NMP). As it can be seen in Fig. 1 (top row), the addition of these small amounts of Carbopol (PLGA content = 40%) fundamentally altered the morphology of the *in-situ* formed implants. Optical macroscopy pictures of cross-sections of systems formed after 3 d exposure to the release medium and subsequent freeze-drying are shown (the cross-sections were obtained by manual breaking). In the case of 1% Carbopol content, highly porous (and fragile) systems were observed. At 3% Carbopol content, the implants already started disintegrating into smaller fragments at this time point. Importantly, this disintegration was already observed prior to the freeze-drying. In contrast, much denser (and mechanically stronger) implants were formed in the absence of Carbopol (picture at the very top in Fig. 1). Note that some caution needs to be paid, since freeze-drying can create artefacts. The impact of the addition of Carbopol can

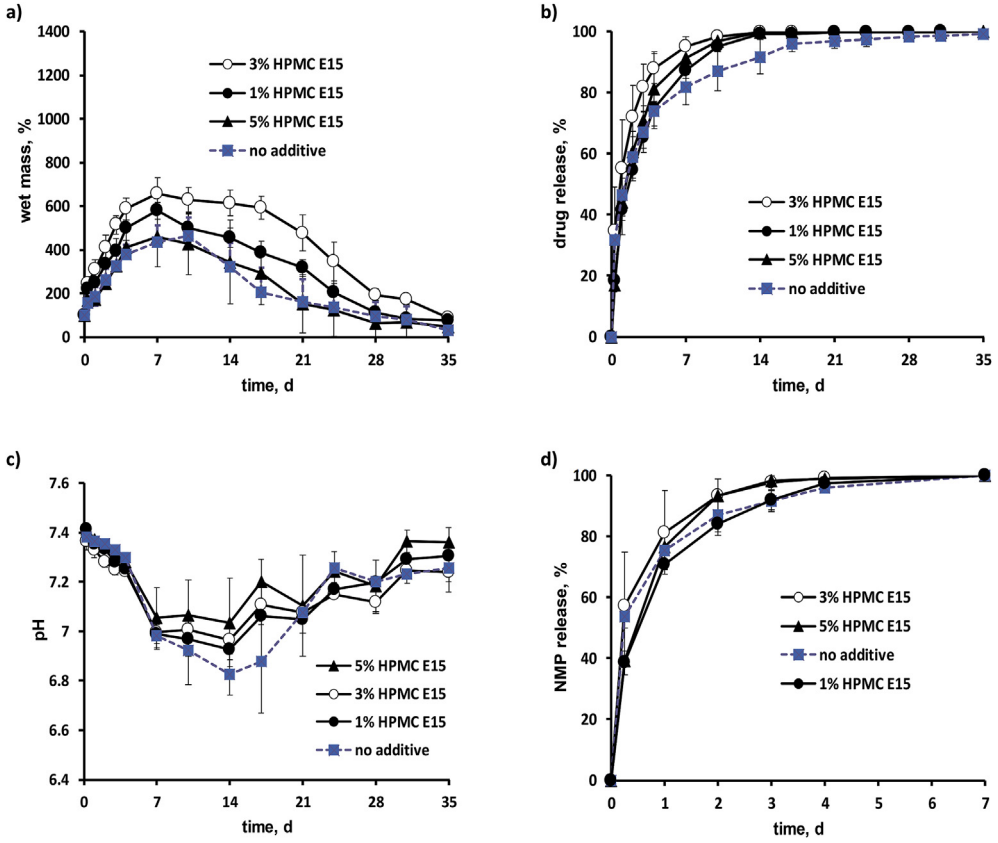

Fig. 7. Effects of the addition of different amounts of HPMC E15 on the: a) wet mass, b) drug release, c) pH of the release medium, and d) NMP release of/from *in-situ* forming implants upon exposure to phosphate buffer pH 7.4 at 37 °C. Mean values ± standard deviation are indicated (n = 3).

be explained by the hydrophilicity of this crosslinked poly(acrylic acid) and its considerable swelling capacity in water at neutral pH: The polymer attracts important amounts of water into the system (Fig. 2a), accelerating implant disintegration (Fig. 1). Consequently, drug release is facilitated (Fig. 2b): the drug is more mobile and the diffusion pathways to be overcome are shorter (since the systems disintegrate into smaller fragments). Also the neutralization of the short chain acids generated upon PLGA degradation can be expected to be faster in these highly porous and rapidly disintegrating implants. Hence, the importance of autocatalytic effects is likely reduced, resulting in less pronounced drops in the pH of the release medium (Fig. 2c). Furthermore, the addition of 3% Carbopol slightly accelerated the leaching of NMP into the surrounding bulk fluid (Fig. 2d). The impact of the addition of 3% Carbopol on the inner and outer morphology of implants formed after 3 d contact with the release medium and subsequent freeze-drying, observed by scanning electron microscopy, is illustrated in Fig. 3. Again, care should be taken, because the freeze-drying of the highly swollen systems created artefacts. Furthermore, the addition of up to 3% Carbopol had only a very limited effect on the glass transition temperature (Tg) of the implants formed *in-situ* after 3 d exposure to the release medium (Fig. 4, the Tg of the respective Carbopol free implants was 46.5 ± 0.2 °C).

In brief, the addition of small amounts of Carbopol substantially increased the implant porosity and accelerated implant disintegration, but the resulting increase in the drug release rate was only slight/moderate. Please also note that the investigated cross-linked Carbopol is not soluble in water. Thus, is not an ideal candidate for an additive to a PLGA-based implant (which itself is biodegradable).

3.2. PEG 400

Fig. 1 (second row from the top) shows optical macroscopy pictures of cross-sections of *in-situ* formed implants after 3 d exposure to the release medium and subsequent freeze-drying, initially containing 1, 3 or 5% PEG 400. Importantly, PEG 400 is a water-miscible liquid, and known to act as a plasticizer for PLGA [37]. Since the glass transition temperature (Tg) of the implants formed in this study after 3 d exposure to the release medium (and subsequent freeze-drying) (Fig. 4) were rather similar to the Tg of PEG free implants obtained under the same conditions (46.5 ± 0.2 °C), it can be hypothesized that major parts of the PEG rapidly leached out into the surrounding bulk fluid during implant formation. This is consistent with the numerous pores that are visible in cross-sections of freeze-dried implants (Fig. 3). However, again, note that artefact creation during freeze-drying is likely to occur and conclusions should be viewed with caution. As it can be seen in Fig. 5, the impact of the addition of up to 5% PEG had only a slight effect (if at all) on the resulting dexamethasone release kinetics, NMP leaching and dynamic changes in the pH of the bulk fluid. There was a slight to moderate increase in the implants' swelling after 7 d, but drug release was almost complete at this stage.

Thus, the addition of small amounts of PEG 400 to the investigated *in-situ* forming implant formulations was only limited, probably due to rapid PEG leaching into the release medium during implant formation.

3.3. HPMC

The impact of the addition of 1, 3 and 5% HPMC K100 or HPMC E15 (differing in their chain length and substitution patterns) on the morphology, swelling and drug release kinetics of/from the investigated *in-situ* forming implants is shown in Figs. 1, 3, 6 and 7. The macroscopic pictures of cross-sections of freeze-dried implants (Fig. 1) indicate relatively dense and intact implants, compared to the Carbopol containing formulations described above. Interestingly, various small holes were visible on the systems' surfaces observed by SEM (Fig. 3). If these

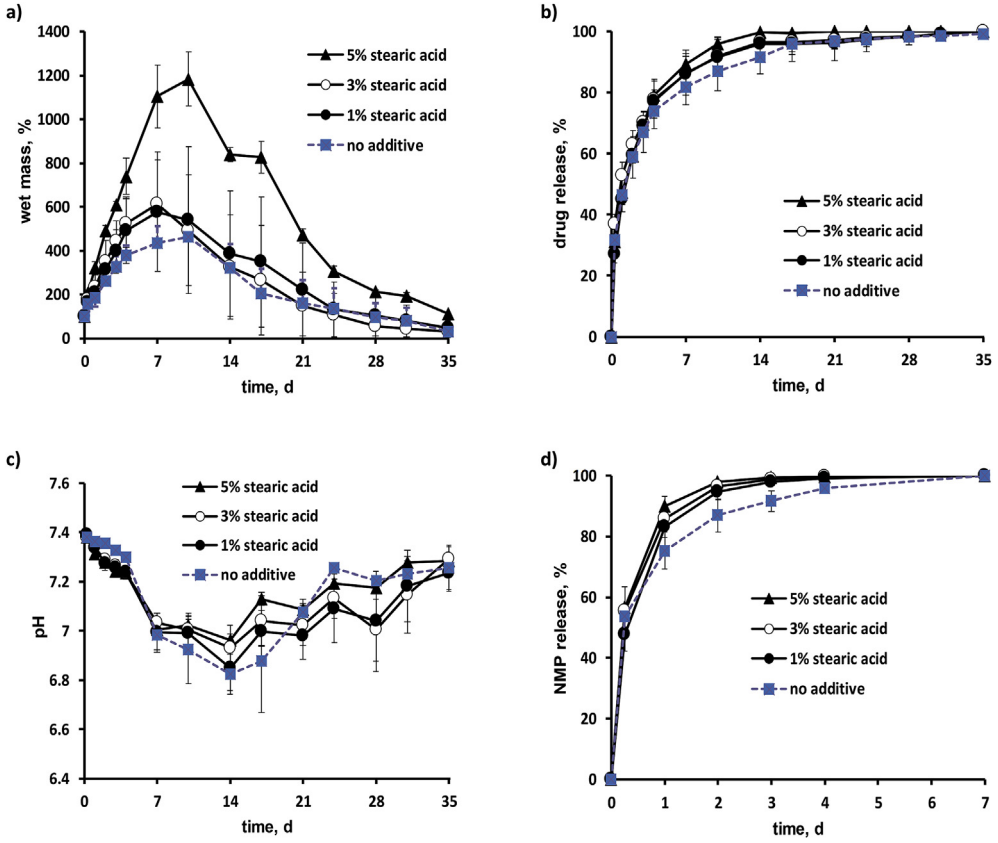

Fig. 8. Impact of the addition of different amounts of stearic acid on the: a) wet mass, b) drug release, c) pH of the release medium, and d) NMP release of/from *in-situ* forming implants upon exposure to phosphate buffer pH 7.4 at 37 °C. Mean values ± standard deviation are indicated (n = 3).

holes are not artefacts, they might indicate that HPMC eventually (at least partially) phase separated during implant formation, and subsequently leached out. But this is just a hypothesis. Being hydrophilic, the presence of the HPMC can be expected to attract more water into the PLGA-based implants (Figs. 6a and 7a), facilitating acid neutralization (generated upon polyester cleavage) and decreasing the importance of the pH drop in the bulk fluid (Figs. 6c and 7c). The impact on NMP release was only very minor, irrespective of the investigated HPMC chain length (Figs. 6d and 7d). Importantly, there was only a slight increase in the dexamethasone release rate in all cases (Figs. 6b and 7b). This effect can at least partially be attributed to the increased water content of the systems (Figs. 6a and 7a). Note that Do et al. [31,32] recently reported on slightly *de*creasing drug release rates from *in-situ* forming PLGA Resomer RG 502 H-based implants containing doxycycline or metronidazole upon HPMC addition. This might at least in part be attributable to the substantially higher HPMC contents in the Do reports. Furthermore, the fact that the glass transition temperature (Tg) of the freeze-dried implants obtained after 3 d exposure to the release medium did not show any substantial difference to HPMC free systems (values in Fig. 4 versus 46.5 ± 0.2 °C in additive-free implants), indicates that the HPMC either already leached out into the bulk fluid and/or phase separated from the PLGA.

Hence, also the addition of small amounts of HPMC did not fundamentally alter the dexamethasone release kinetics and only moderately affected system swelling.

3.4. Stearic acid

Stearic acid is a saturated fatty acid which is not soluble in water. The addition of 1, 3 or 5% of this lipophilic compound to the *in-situ* forming implant formulations had a relatively limited impact on the macroscopic morphology of cross-sections of implants formed after 3 d exposure to phosphate buffer pH 7.4 and subsequent freeze-drying (Fig. 1). The SEM pictures of surfaces (Fig. 3) might indicate that phase separation took place at the *formulation – release medium* interface, but again, great caution should be paid, due to the risk of artefact creation upon sample drying. Interestingly, the wet mass of the implants substantially increased at the highest investigated stearic acid content (5%), and to a much lesser extent at lower stearic acid contents (Fig. 8a). The exact reasons for this behavior are not clear, potential plasticizing effects are unlikely (Fig. 4). Importantly, the impact on drug release was limited in all cases (Fig. 8b), probably because the increasing length of the diffusion pathways was compensated by the increasing amounts of water in the system (water being mandatory for drug dissolution and leading to increased drug mobility). Furthermore, there was a slight increase in the NMP leaching rate (Fig. 8d) and a slight impact on the dynamic changes in the pH of the release medium upon stearic acid addition (Fig. 8c).

Thus, also the presence of up to 5% lipophilic stearic acid had only a limited effect on dexamethasone release from the investigated *in-situ* forming implants.

3.5. ATBC

ATBC is a liquid with very limited solubility in water. Importantly, it acts as a plasticizer for PLGA: As it can be seen in Fig. 4, the glass transition temperature (Tg) of the implants formed after 3 d exposure to the release medium and subsequent freeze-drying, decreased upon ATBC addition. But this was only the case up to about 5% ATBC. Afterwards, a plateau was reached. Hence, a few percent of ATBC can be expected to be more or less homogenously distributed throughout the PLGA phase. This renders the implants more hydrophobic and reduces their swelling (Fig. 9a). However, higher ATBC contents do not further decrease the Tg of the polymeric phase. Thus, they might phase

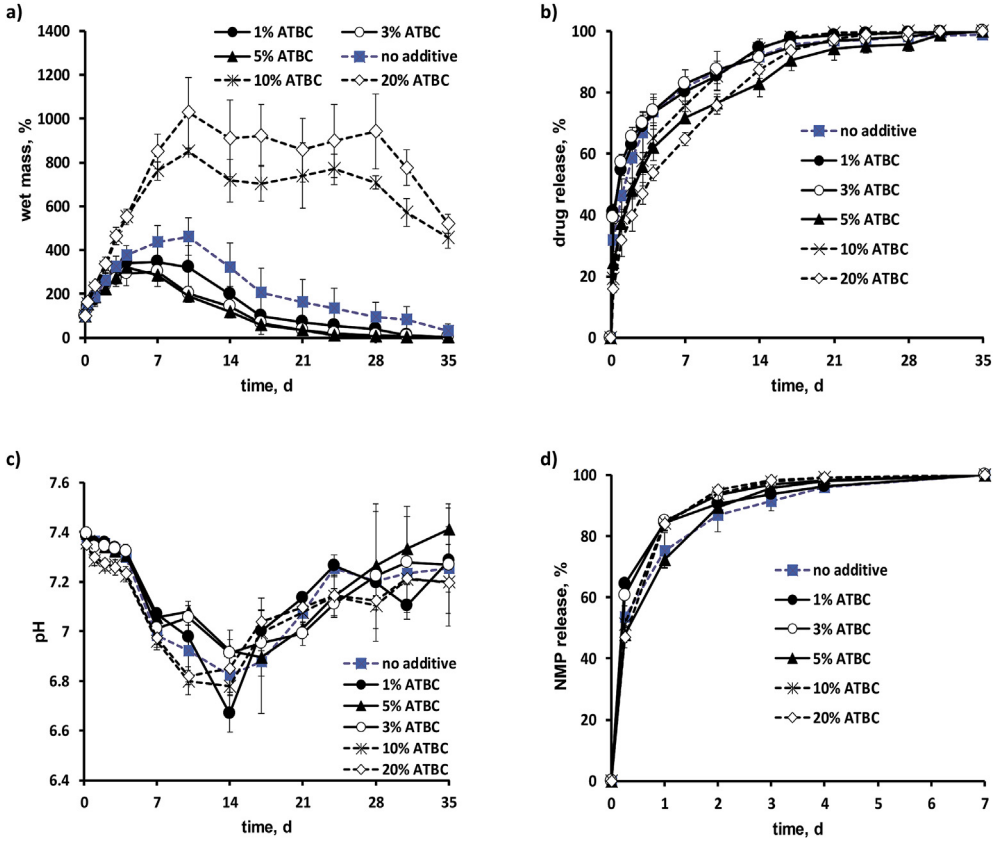

Fig. 9. Effects of the addition of different amounts of ATBC on the: a) wet mass, b) drug release, c) pH of the release medium, and d) NMP release of/from *in-situ* forming implants upon exposure to phosphate buffer pH 7.4 at 37 °C. Mean values ± standard deviation are indicated (n = 3).

separate. Interestingly, at 10 and 20% initial ATBC contents, implant swelling substantially increased (Fig. 9a). The exact reasons for this behavior are unclear. Importantly, at all ATBC loadings the resulting dexamethasone release rates were slightly/moderately slower compared to implants free of ATBC (Fig. 9b). This is at least partially likely due to increased implant hydrophobicity, increased diffusion pathway lengths and plasticizing effects, the relative importance of these phenomena depending on the ATBC content. NMP leaching was not strongly affected (Fig. 9d). Also, the impact of ATBC addition on the dynamic changes in the pH of the release medium was limited (Fig. 9c). The same was true for the macroscopic morphology of cross-sections of freeze-dried implants: Fig. 1 shows examples for 1-3% ATBC content, Fig. S1 for 10 and 20% ATBC content. The SEM pictures of surfaces of implants formed upon 3 d exposure to the release medium (and subsequent freeze-drying) showed numerous tiny pores, which might be artefacts or indicate phase separation (e.g., Fig. 3).

So, ATBC was the only additive in this study, which slightly *decreased* the resulting dexamethasone release rate from the investigated PLGA implants forming *in-situ*. It was also the only additive, which decreased the swelling of the implants, at low ATBC contents.

4. Conclusion

Interestingly, the addition of very different types of additives (Carbopol, PEG 400, HPMC, stearic acid and ATBC) partially had pronounced effects on the morphology and swelling kinetics of the investigated *in-situ* forming PLGA implants. For instance, Carbopol containing systems rapidly disintegrated. However, the impact on dexamethasone release was relatively limited in all cases. Generally, the release rate increased when additives were present, only in the case of ATBC the release rate slightly decreased. The observed rather limited impact of the various additives on drug release might at least partially be attributed to the fact that: (i) *water-soluble* additives might rapidly leach out into the aqueous release medium during implant formation and/or promote implant swelling, and (ii) *lipophilic* additives might induce phase separation.

Conflicts of interest

The Editor-in-Chief of the journal is one of the co-authors of this article. The manuscript has been subject to all of the journal's usual procedures, including peer review, which has been handled independently of the Editor-in-Chief.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2019.101180.

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