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Research article

Hot melt extruded PLGA implants loaded with ibuprofen:

How heat exposure alters the physical drug state

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Abstract

Hot melt extrusion offers an interesting potential for the manufacturing of poly(lactic-co-glycolic acid) (PLGA)-based implants. However, the heat treatment might substantially alter the polymer, drug and degree of drug-polymer mixing. The aim of this study was to better understand the impact of varying the exposure time to 105 °C in the case of ibuprofen-loaded PLGA implants. In vitro drug release was measured in phosphate buffer pH 7.4. Optical and scanning electron microscopy, DSC, GPC, X-ray diffraction as well as gravimetric analysis were used to monitor dynamic changes of the implants' morphology, dry & wet mass and average polymer molecular weight. Interestingly, increasing the exposure time from 3 to 15 min led to a decrease in the amount of *crystalline* drug present in the system, resulting in a slight decrease in the initial burst release. The average PLGA molecular weight also slightly decreased during the heat treatment. In contrast, the relatively rapid penetration of water into the implant and subsequent polymer degradation throughout the device did not seem to be affected to a noteworthy extent. Also the onset of substantial implant swelling after about 1 week and the subsequent beginning of the final rapid drug release phase (accounting for about 80 % of the total drug dose) were not significantly altered. Thus, in this study, the changes in the physical state of the drug in the implant induced by prolonged heat exposure had only a limited impact on system performance. However, for different drugs and polymers, changes in their physical state as a function of the heat exposure time might have more importance consequences. Careful monitoring of these kinetic aspects is recommended to assure desired product quality.

Keywords: PLGA; implant; drug release mechanism; swelling; monolithic solution; solid dispersion

1. Introduction

Poly(lactic-co-glycolic acid) (PLGA) is frequently used a matrix former for controlled drug delivery systems [1–5], because it is: (i) completely biodegradable (avoiding the removal of empty remnants upon drug exhaust), (ii) biocompatible [6], (iii) and offers the possibility to provide a considerable range of release periods, ranging from a few hours to several months [2,7,8]. Different types of dosage forms can be produced, such as cylindrical implants [9–11], spherical microparticles [12–14] and thin films [2,5]. A variety of manufacturing procedures can be applied to produce these systems, for instance solvent evaporation methods [10,15], direct compression [16,17], 3D printing [18,19], and hot melt extrusion [4,11,20,21]. PLGA-based implants can for instance be prepared by direct compression, hot melt extrusion, 3D printing, solvent extrusion and solvent casting [4, 9-11, 18-21]. Direct compression often leads to more porous systems, while hot melt extrusion and 3D printing might degrade thermolabile drugs. If organic solvents are used, the systems must be thoroughly dried.

The release mechanisms from PLGA-based drug delivery systems can be rather complex, because a variety of physic-chemical phenomena can be involved [12,22–25]. This includes for example water penetration into the system, PLGA degradation via hydrolytic ester bond cleavage, physical water-polymer interactions (e.g., plasticizing effects) [26], drug particle dissolution, the diffusion of dissolved drug and water-soluble PLGA degradation products, the creation of local, acidic microenvironments leading to accelerated polymer degradation and drug release (“autocatalytic effects”) [27–31], polymer swelling [32–35], pore formation & closure [36–39], limited solubility effects, drug-polymer interactions [40], as well as osmotic effects [41]. The relative importance of these phenomena can strongly depend on the type of drug, type of polymer (e.g. average polymer molecular weight and type of end groups), composition of the system [8,42,43], and type of manufacturing procedure. The latter might fundamentally affect the resulting inner and outer system structure, in particular its porosity

[44,45] and the physical state of the drug in the polymeric matrix [46,47]. The drug might be dissolved in the PLGA (*molecularly* distributed throughout the polymer network), or dispersed in the form of crystalline or amorphous particles. The degree of possible drug-PLGA interactions obviously strongly depends on their physical states and degree of mixing. Thus, it is very interesting to characterize them and monitor potential changes during drug release.

Due to the frequently encountered complexity of the underlying mass transport mechanisms in PLGA-based dosage forms, it is often not fully understood how a specific device controls drug release. Consequently, unexpected tendencies might be observed when varying the systems' composition or process parameters used during manufacturing. This can render system optimization and troubleshooting during production highly challenging. As an example: It can generally be expected that the increase in dosage form dimensions leads to a decrease in the resulting relative drug release rate, if diffusional mass transport plays a major role (because the lengths of the diffusion pathways to be overcome increase) [48]. However, it has been shown that in the case of initially non-porous, lidocaine-loaded PLGA-based microparticles a 7-fold increase in the systems' diameter did virtually not affect the relative drug release rate [49]. This could be attributed to a compensating mechanism: an increase in the importance of autocatalytic effects in the system: the pH becomes more acidic *inside* larger microparticles, leading to accelerated polymer degradation and higher drug mobility. In contrast, in *initially highly porous* lidocaine-loaded PLGA microparticles, the generated water-soluble acids were more rapidly neutralized, resulting in decreasing drug release rates with increasing system size [50].

The aim of this study was to prepare ibuprofen-loaded PLGA implants by hot melt extrusion, varying the exposure time to 105 °C from 3 to 15 min, and to thoroughly characterize the systems before and during drug release in phosphate buffer pH 7.4. Ibuprofen can be used as an anti-inflammatory drug in certain applications, but it can also be considered as low

molecular weight, acidic model drug. Optical & scanning electron microscopy were used to evaluate the inner and outer system structure. DSC and X-ray diffraction were applied to better understand the physical state of the drug. Gravimetric analysis was used to measure changes in the dry and wet mass of the systems, and GPC analysis to monitor the average PLGA molecular weight.

2. Materials and methods

2.1. Materials

Poly (D,L lactic-co-glycolic acid) (PLGA, 50:50 lactic acid: glycolic acid; Resomer RG 503H; Evonik, Darmstadt, Germany); ibuprofen (BASF, Ludwigshafen, Germany); tetrahydrofuran (HPLC grade) (Fisher Scientific, Illkirch, France); potassium dihydrogen orthophosphate and sodium hydroxide (Acros Organics, Geel, Belgium); acetonitrile (VWR, Fontenay-sous-Bois, France); sodium hydrogen phosphate (Na_2HPO_4 ; Panreac Quimica, Barcelona, Spain).

2.2. Implant preparation

PLGA was milled for 4 x 30 s in a grinder (Valentin, Seb, Ecully, France). Ibuprofen was used as received. Appropriate amounts of polymer and drug powders were blended for 5 min at 20 rpm in a Turbula T2C Shaker-Mixer (Willy A Bachofen, Basel, Switzerland). Three hundred mg mixture were filled into a 1 mL syringe (Henke Sass Wolf, Tuttlingen, Germany), followed by heating for 3, 6, 9, 12 or 15 min in an oven (105°C; FP115, Binder, Tuttlingen, Germany) (Figure 1A). The molten blend was manually extruded using the syringe. The extrudate was cut with a hot scalpel into cylindrical implants of approximately 5 mm length.

2.3. Practical drug loading

Implants were dissolved in 5 mL acetonitrile, followed by filtration (PVDF syringe filters, 0.45 μm ; Agilent Technologies, Santa Clara, USA) and drug content determination by HPLC-UV analysis using a Thermo Fisher Scientific Ultimate 3000 Series HPLC, equipped with a LPG 3400 SD/RS pump, an autosampler (WPS-3000 SL) and UV-Vis detector (VWD-3400RS) (Thermo Fisher Scientific, Waltham, USA). A reversed-phase column C18 (Gemini 5 μm ;

110 Å; 150 x 4.6 mm; Phenomenex, Le Pecq, France) was used. The mobile phase was a mixture of 30 mM Na₂HPO₄ pH 7.0: acetonitrile (60:40, v:v). The detection wavelength was 265 nm, and the flow rate 0.5 mL/min. Ten microliter samples were injected. All experiments were conducted in triplicate. Mean values +/- standard deviations are reported.

2.4. *In vitro* drug release

Implants were placed in 5 mL Eppendorf tubes (1 implant per tube), filled with 5 mL phosphate buffer pH 7.4 (USP 42). A metal mesh assured that the implants did not sink to the bottom of the tube (Figure 1B), potentially limiting the systems' surface area in direct contact with the release medium. The mesh size was 250 µm, allowing for convective flow and rapid exchange of medium inside and outside the metal "basket". The tubes were placed in a horizontal shaker (80 rpm, 37°C; GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). At predetermined time points, the entire bulk fluid was replaced by fresh release medium. The withdrawn samples were filtered (PVDF syringe filter, 0.45 µm; Agilent) and analyzed for their ibuprofen contents by HPLC-UV as described in *section 2.3*. In all cases, sink conditions were provided throughout the experiments. The latter were conducted in triplicate. Mean values +/- standard deviations are reported.

2.5. *Implant swelling*

Implants were treated as for the *in vitro* drug release studies (described in *section 2.4*). At pre-determined time points, implant samples were withdrawn, and:

- (i) Pictures of the implants were taken with a SZN-6 trinocular stereo zoom microscope (Optika, Ponteranica, Italy), equipped with an optical camera (Optika Vision Lite 2.1 software). Unless otherwise indicated, the light came from the top. The lengths and diameters of the implants were determined using the ImageJ software (US National

Institutes of Health). Dynamic changes in the systems' volume were calculated considering cylindrical geometry.

- (ii) Excess water was carefully removed using Kimtech precision wipes (Kimberly-Clark, Rouen, France) and weighed [*wet mass* (*t*)]. The *change in wet mass (%)* (*t*) was calculated as follows:

$$\text{change in wet mass } (\%)(t) = \frac{\text{wet mass } (t) - \text{mass } (t=0)}{\text{mass } (t=0)} \times 100 \% \quad (1)$$

where *mass* (*t* = 0) denotes the implant mass before exposure to the release medium.

All experiments were conducted in triplicate. Mean values +/- standard deviations are reported.

2.6. Implant erosion and PLGA degradation

Implants were treated as for the in vitro drug release studies (described in *section 2.4*). At pre-determined time points, implant samples were withdrawn and freeze-dried (freezing at -45°C for 2 h 35 min, primary drying at -20 °C/0.940 mbar for 35 h 10 min, secondary drying at +20 °C/0.0050 mbar for 35 h; Christ Alpha 2-4 LSC+; Martin Christ, Osterode, Germany).

The *dry mass (%)* (*t*) was calculated as follows:

$$\text{dry mass } (\%)(t) = \frac{\text{dry mass } (t)}{\text{mass } (t=0)} \times 100 \% \quad (2)$$

where *mass* (*t* = 0) denotes the implant mass before exposure to the release medium. All experiments were conducted in triplicate. Mean values +/- standard deviations are reported.

The average polymer molecular weight (Mw) of the PLGA was determined by gel permeation chromatography (GPC) as follows: Freeze-dried implant samples were dissolved in tetrahydrofuran (3 mg/mL). One hundred μL samples were injected into an Alliance GPC (refractometer detector: 2414 RI, separation module e2695, Empower GPC software; Waters,

Milford, USA), equipped with a PLgel 5 μm MIXED-D column (kept at 35°C, 7.8 \times 300 mm; Agilent). Tetrahydrofuran was the mobile phase (flow rate: 1 mL/min). Polystyrene standards with molecular weights between 1,480 and 70,950 Da (Polymer Laboratories, Varian, Les Ulis, France) were used to prepare the calibration curve. All experiments were conducted in triplicate. Mean values \pm standard deviations are reported.

2.7. *Differential scanning calorimetry (DSC)*

DSC thermograms were recorded using a DCS1 Star System (Mettler Toledo, Greifensee, Switzerland). Samples (approximately 5 mg in the case of raw materials & their physical blends, about 10 mg in the case of implants) were heated in aluminum pans as follows: from -70 to 120 °C, cooling to -70 °C, re-heating to 120 °C (heating and cooling rates = 10 °C/min). In the case of implants, the pans were open and the glass temperatures (T_gs) were determined from the 1st heating cycles (the thermal history being of interest). In the case of physical blends, the pans were closed and the reported T_gs were determined from the 2nd heating cycles (the thermal history not being of interest). In the case of the raw materials, the pans were open. The melting peak of the crystalline drug was observed during the 1st heating cycle (upon cooling, amorphous ibuprofen solidified). In the case of PLGA, the T_g was determined from the 2nd heating cycle (the thermal history not being of interest). All experiments were conducted in triplicate. Mean values \pm standard deviations are reported.

2.8. *X ray powder diffraction*

X-ray powder diffraction patterns were recorded using a PANalytical X'Pert pro MPD powder diffractometer (PANalytical, Almelo, Netherlands), equipped with a Cu X-ray tube ($\lambda\text{CuK}\alpha = 1.54 \text{ \AA}$) and the X'celerator detector. Samples were placed in a spinning flat sample

holder. The measurements were performed in Bragg–Brentano θ - θ geometry. The diffractograms were recorded from 3 to 60° (2 θ) (0.0167 ° steps, 100 s/step).

2.9. Scanning electronic microscopy (SEM)

The internal and external morphology of the implants before and after exposure to the release medium was studied using a JEOL Field Emission Scanning Electron Microscope (JSM-7800F, Japan), equipped with the Aztec 3.3 software (Oxford Instruments, Oxford, England). Samples were fixed with a ribbon carbon double-sided adhesive and covered with a fine chrome layer. If indicated, the investigated implants had been exposed to the release medium before, as described for the in vitro release studies (please see *section 2.4*). At predetermined time points, implant samples were withdrawn and freeze-dried (as described in *section 2.6*). Cross sections were obtained by manual cutting with a scalpel, prior to freeze drying.

3. Results and discussion

Different types of ibuprofen-loaded, PLGA-based implants were prepared by hot melt extrusion using a syringe, as illustrated in Figure 1A. The drug and PLGA powders were blended and filled into a glass syringe, which was heated to 105 °C for 3, 6, 9, 12 or 15 min. The blends were manually extruded, and the extrudates were cut with a hot scalpel into cylindrical implants of approximately 5 mm length. The mean diameter was in the range of 2.5-2.8 mm in all cases (Table 1). The practical drug loading varied between about 13 and 10 % (w/w). The average polymer molecular weight decreased from about 21 to 18 kDa when prolonging the exposure time to 105 °C from 3 to 15 min. The Mw of the PLGA raw material was 23.1±1.1 kDa. This indicates that the polymer chains were partially cut upon heat exposure, which is consistent with reports in the literature [19,51].

3.1. Implants before exposure to the release medium

Figure 2 shows SEM pictures of surfaces and cross sections of the investigated ibuprofen-loaded PLGA implants before exposure to the release medium. The heating times applied during manufacturing are indicated on the left-hand side. As it can be seen, the internal and external structure was predominantly non-porous. Interestingly, evidence for the presence of crystalline drug particles could be seen in some of the cross sections, especially of implants prepared with shorter heating times (highlighted by the dotted red circles in Figure 2).

To better understand the physical state of the drug in the hot melt extruded implants, DSC thermograms of the systems were recorded (Figure 3A), as well as of the raw materials (drug and polymer) for reasons of comparison (Figure 3B). Importantly, the ibuprofen powder as received showed a sharp melting peak at 79.7 ± 0.5 °C. This peak was also visible in the hot melt extruded implants, but its intensity substantially decreased with prolonged heat exposure during production. This suggests that the drug is initially present in the form of tiny crystals, which partially: (i) *dissolve* in the PLGA during processing (the temperature is raised to 105 °C, forming a “monolithic solution”), (ii) melt and re-solidify in the form of *amorphous* drug particles upon cooling (forming a “solid-in-solid dispersion”: amorphous-in-amorphous), and/or (iii) melt and re-solidify in the form of *crystalline* drug particles upon cooling (forming a “solid-in-solid dispersion”: crystalline-in-amorphous). To estimate the capacity of ibuprofen to *dissolve* in the investigated PLGA, the DSC thermograms of different drug-polymer blends were recorded, varying the ibuprofen content from 0 to 20 % (w/w). As it can be seen in Figure 4, the glass transition temperature (T_g) of the blends decreased with increasing ibuprofen content up to about 10-15 % drug and then seems to level off. This indicates that ibuprofen acts as a plasticizer for PLGA and, under the conditions provided during the DSC measurements, at least about 10 % (w/w) drug can *dissolve* in the polymer. Interestingly, the T_g values of the

implants prepared by hot melt extrusion was about constant in the investigated heating time range (varying between about 33-34 °C, Table 1; please also see the DSC thermograms in Figure 3). This suggests that already after 3 min heating, major parts of the ibuprofen are dissolved in the PLGA. This hypothesis is consistent with the amounts of crystalline ibuprofen determined in the PLGA implants when integrating the surfaces of the melting peaks observed during the DSC measurements (Figure 3): The amounts of crystalline drug are relatively small in all cases. Thus, most of the ibuprofen is likely molecularly dispersed in the polymer matrix.

To further confirm the hypothesis of the presence of (some) crystalline ibuprofen in the PLGA implants, also X-ray diffraction patterns of the systems were recorded before exposure to the release medium. As it can be seen in Figure 5A, all implants exhibited sharp diffraction peaks as well as an underlying amorphous halo. The X-ray diffraction patterns of the raw materials are shown in Figure 5B for comparison. Clearly, the ibuprofen powder (as received) was crystalline, and the PLGA amorphous (confirming the DSC data discussed above). Importantly, the positions of the diffraction peaks observed with the drug-loaded implants corresponded well to the positions observed with the crystalline ibuprofen raw material. The dashed orange ovals in Figure 5A highlight some of these peaks.

In conclusion, based on the obtained SEM pictures of surfaces and cross sections, DSC thermograms and X-ray diffraction patterns of the implants, it can be hypothesized that major parts of the ibuprofen are *dissolved* in the PLGA matrix in the implants (are present in the form of *individual* drug molecules). And that a minor proportion is also present in the form of tiny drug crystals.

3.2. Implants after exposure to the release medium

The diagrams at the top of Figure 6 show the resulting ibuprofen release kinetics from the investigated implants upon exposure to phosphate buffer pH 7.4 in well agitated Eppendorf

vials at 37 °C. The diagram on the right-hand side is a zoom on the first 10 d of drug release. The heating time applied during implant manufacturing is indicated in the legends. As it can be seen, tri-phasic drug release was observed in all cases: A (limited) initial rapid drug release phase (“burst release”) during the first few hours was followed by a zero-order release phase (with an about constant drug release rate), and a final, again more rapid drug release phase, leading to complete drug exhaust. The impact of the heating time (3 to 15 min) during implant preparation was only minor.

The zoom on the right-hand side at the top shows that during the burst release phase the following ranking order was observed with respect to the release rate: 3 min > 6 min > 9 min > 12 min > 15 min. This can probably be explained by the fact that more drug crystals are present in the implants when prepared with shorter heating times (as discussed above). The initial burst release is likely due to drug with direct surface access once the system gets into contact with water. This includes tiny drug crystals located directly at the implants’ surface, or very close to it and with access to surface pores. If such a drug crystal gets into contact with the release medium, it rapidly dissolves. In contrast, if the drug is *dissolved* in the polymer matrix, the probability that a drug molecule has direct surface access is lower (most of the molecules are separated from it, even if only by minor amounts of polymer).

The onset of the final rapid drug release phase of the investigated implants is observed after about 1 week exposure to the release medium (Figure 6). This coincides with the onset of the penetration of substantial amounts of water into the systems, as illustrated in the diagrams in the middle and at the bottom of Figure 6: showing the dynamic changes in the volume and wet mass of the implants upon contact with the release medium. This was true for all the investigated heating times. The optical macroscopy pictures shown in Figure 7 illustrate these considerable changes in implant size and morphology: During the first couple of days the system dimensions remained about constant. But after 1 week the implants started to substantially swell,

irrespective of the heating time applied during manufacturing. The pictures on the right-hand side of Figure 7 were obtained with light coming from the bottom (for the other pictures the light came from the top). As it can be seen, after 10 d exposure to the release medium, some darker regions (= probably less swollen) are visible close to the center of the implants. Figure 8 shows SEM pictures of surfaces and cross sections of the implants prepared with 3 to 15 min heating time, after 2, 6 and 8 d exposure to the release medium. Please note that the implants were freeze-dried prior to SEM analysis. Thus, the observed structures are in great part artefacts: The optical macroscopy pictures in Figure 7 indicate that upon contact with the aqueous bulk fluid the implant *surface* starts to swell (well before substantial swelling of the *entire* system sets on after about 1 week). This is consistent with the highly wizened and porous surface structure observed by SEM with all implants (Figure 8): Upon drying during sample preparation, the highly swollen, thin surface layer of “PLGA gel” shrinks.

The SEM pictures on the right-hand side of Figure 8 show cross sections of the different implants after exposure to the release medium. The dotted red rectangles highlight zones in which swollen and “non-swollen” PLGA can be distinguished. With time the swollen zone becomes more and more important. However, it has to be pointed out that PLGA undergoes “*bulk erosion*”: The *entire* system is rather rapidly wetted upon exposure to an aqueous medium and polymer chain degradation takes place *throughout* the system (not only in highly swollen, surface-near zones). The average polymer molecular weight exponentially decreases right from the beginning, as shown in Figure 9A. This renders the polymeric system more and more hydrophilic: Upon hydrolytic cleavage of an ester bond, two new *hydrophilic* end groups are created: an -OH and a -COOH end group. In addition, the degree of polymer chain entanglement decreases (since the chains become shorter). Furthermore, generated water-soluble degradation products (short chain acids) accumulate, because they are poorly mobile in the wetted, but “non-swollen” polymer matrix. This generates a continuously increasing osmotic pressure in the

system. At a certain time point, the PLGA matrix becomes sufficiently hydrophilic and mechanically instable to allow for the penetration of substantial amounts of water into the system. Importantly, the conditions for the release of drug and water-soluble short chain acids fundamentally change at this time point: They become much more mobile in the highly swollen PLGA gel and can rather rapidly diffuse out: This leads to the onset of the final, again more rapid drug release phase (Figure 6). The limited mobility in the wetted, but “non-swollen” PLGA matrix during the first week also explains why implant erosion does not set on before: As it can be seen in Figure 9B, the dry mass of the systems remains about constant (irrespective of the applied heating time).

Since the increase in heating time from 3 to 15 min during implant preparation does not impact the rate at which the limited amounts of water penetrate into the implants right upon contact with an aqueous medium, the subsequent polymer degradation is also not affected to a noteworthy extent (Figure 9A). Consequently, neither the onset of substantial polymer swelling (Figures 6- 8), nor the onset of the final, rapid drug release phase (Figure 6) are altered.

4. Conclusions

Hot melt extrusion offers an interesting potential for the preparation of PLGA-based implants. However, the exposure to heat can decrease the average polymer molecular weight and alter the physical state of the drug in the polymeric matrix (and of course, thermally degrade heat sensitive drugs). The drug might be present in the form of individual molecules/ions distributed throughout the PLGA network (“dissolved”), or dispersed in the form of crystalline or amorphous tiny particles. It is worth to monitor the state of the drug and potential transformations during implant manufacturing. For instance, increasing exposure times to heat might increase the relative amount of drug, which is dissolved in the PLGA, altering the importance of the initial “burst release”. In the present study, this phenomenon could be

monitored, but its importance on drug release was limited. However, the impact for other drugs and other polymers might be more pronounced and certain systems might be less robust and “forgiving”.

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Conflict of interests

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.

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Table 1:

Physical key properties of the investigated ibuprofen-loaded PLGA implants (T_g: glass transition temperature, M_w: average polymer molecular weight). The heating time applied during implant manufacturing is indicated in the top row. Mean values ± standard deviations are indicated (n = 3).

<i>Heating time</i>	<i>3 min</i>	<i>6 min</i>	<i>9 min</i>	<i>12 min</i>	<i>15 min</i>
Practical drug loading (%)	12.8 ± 0.6	11.2 ± 0.3	9.7 ± 1.0	10.9 ± 1.0	11.4 ± 1.0
Diameter (mm)	2.8 ± 0.1	2.5 ± 0.1	2.7 ± 0.1	2.6 ± 0.1	2.5 ± 0.1
T_g (°C)	33.9 ± 0.6	34.0 ± 0.3	34.3 ± 0.1	34.5 ± 0.4	33.3 ± 0.2
M_w (kDa)	21.2 ± 1.2	19.7 ± 0.8	18.9 ± 0.2	19.4 ± 0.8	18.4 ± 1.2

Figure captions

- Fig 1 Schematic presentations of the experimental set-ups used to: (A) prepare ibuprofen-loaded PLGA implants by hot melt extrusion, and (B) monitor drug release from the implants upon exposure to phosphate buffer pH 7.4 in well agitated Eppendorf tubes. Details are described in the text.
- Fig 2 Optical macroscopy pictures and SEM pictures of surfaces and cross sections of ibuprofen-loaded implants before exposure to release medium. The PLGA-ibuprofen blends were heated for 3 to 15 min during implant preparation (as indicated). Drug crystals are highlighted by dotted red circles.
- Fig 3 DSC thermograms of the: (A) investigated ibuprofen-loaded PLGA implants (before exposure to the release medium), and (B) raw materials (PLGA & ibuprofen). During implant preparation, ibuprofen-PLGA blends were heated for 3 to 15 min (as indicated). The dashed orange oval highlights ibuprofen melting events in the implants. Please note the different scaling of the y-axes in (A) and (B).
- Fig 4 Dependence of the glass transition temperature (T_g) of ibuprofen:PLGA powder blends measured by DSC (second heating cycles) on the drug contents of the mixtures.
- Fig 5 X-ray diffraction patterns of the: (A) investigated ibuprofen-loaded PLGA implants, and (B) raw materials (PLGA & ibuprofen, for reasons of comparison). During implant preparation, ibuprofen-PLGA blends were heated for 3 to 15 min (as indicated). The orange ovals highlight specific peaks. Please note the different scaling of the y-axes in (A) and (B).
- Fig 6 Ibuprofen release and swelling behavior of the investigated PLGA-based implants upon exposure to phosphate buffer pH 7.4. The diagram on the right-hand side at the top is a zoom on the first 10 h. The heating times of the ibuprofen-PLGA blends during implant preparation are indicated in the diagrams.

Fig 7 Optical macroscopy pictures of the investigated ibuprofen-loaded PLGA implants upon exposure to phosphate buffer pH 7.4. At the top, the time periods of implant exposure to the release medium are shown. On the left-hand side, the heating times of the ibuprofen-PLGA blends during implant preparation are indicated. The pictures on the right-hand side were obtained with light coming from the bottom.

Fig 8 SEM pictures (surfaces and cross sections) of the investigated ibuprofen-loaded PLGA implants after 2, 6 and 8 days exposure to phosphate buffer pH 7.4. The heating times (in min) of the ibuprofen-PLGA blends during implant preparation are indicated on the left-hand side. The dotted red circles highlight drug crystals, the dotted red rectangles surface-near regions including a highly swollen surface layer and the “not yet swollen” inner implant region. Caution must be paid since the drying of the samples prior to SEM analysis created artefacts (details are discussed in the text).

Fig 9 Dynamic changes in the: (A) average polymer molecular weight (M_w) of the PLGA, and (B) dry mass of the investigated ibuprofen-loaded implants upon exposure of the systems to phosphate buffer pH 7.4. The heating times of the ibuprofen-PLGA blends during implant preparation are indicated in the diagrams.

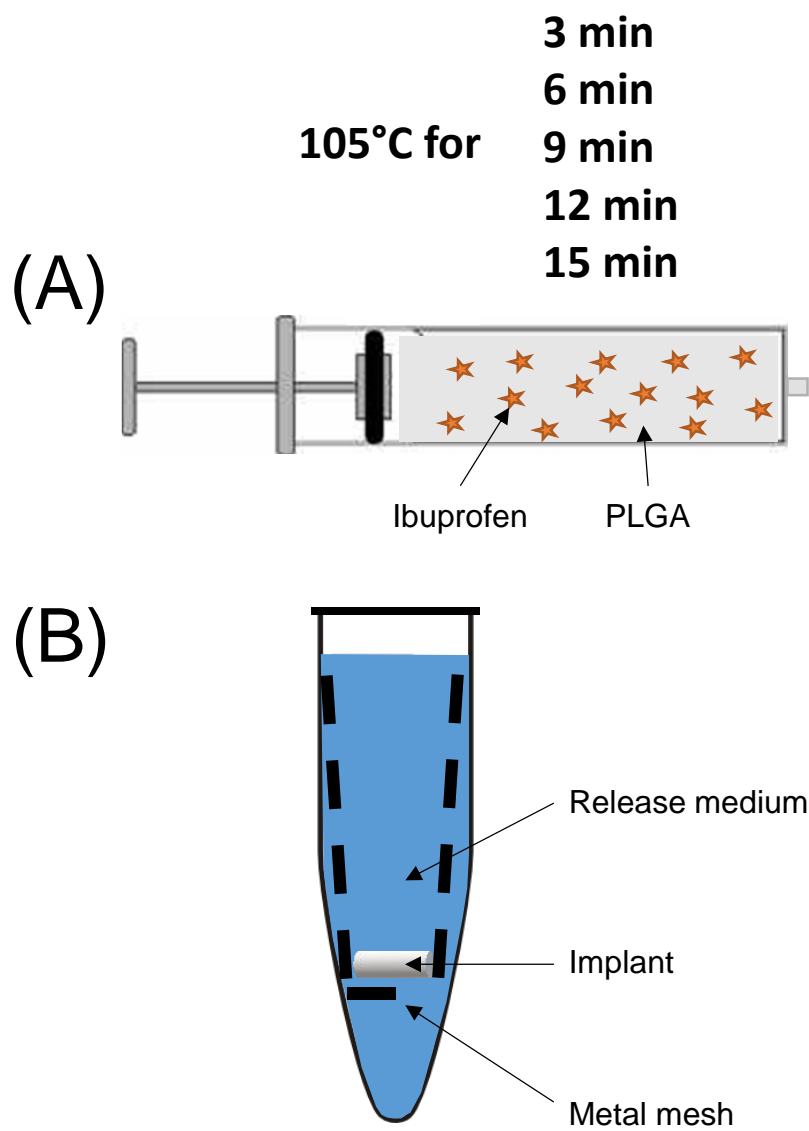


Figure 1

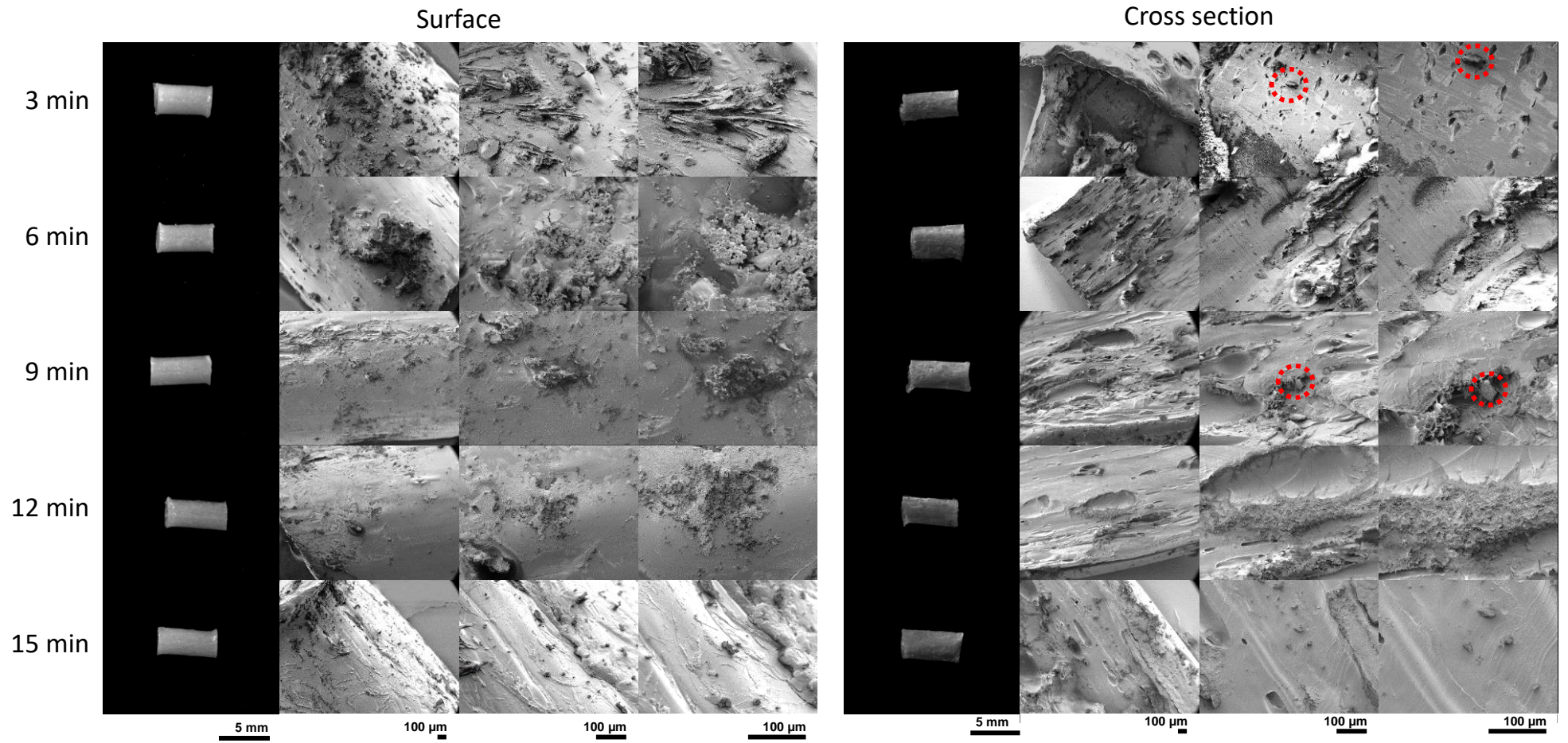


Figure 2

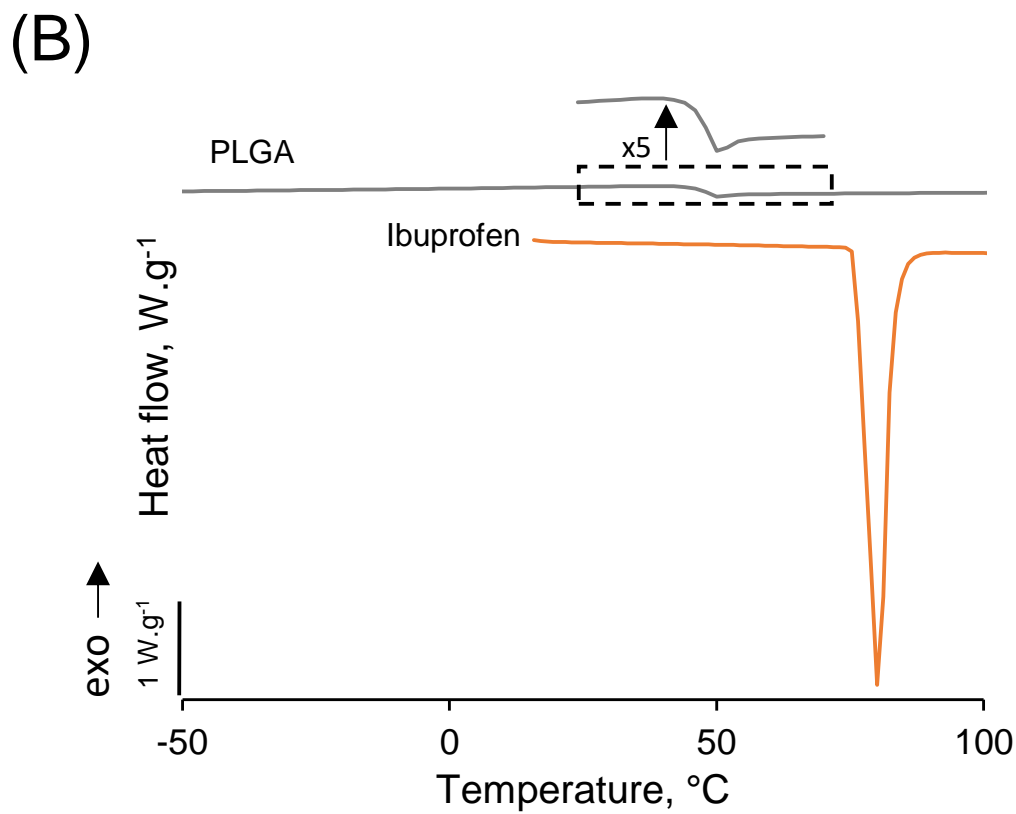
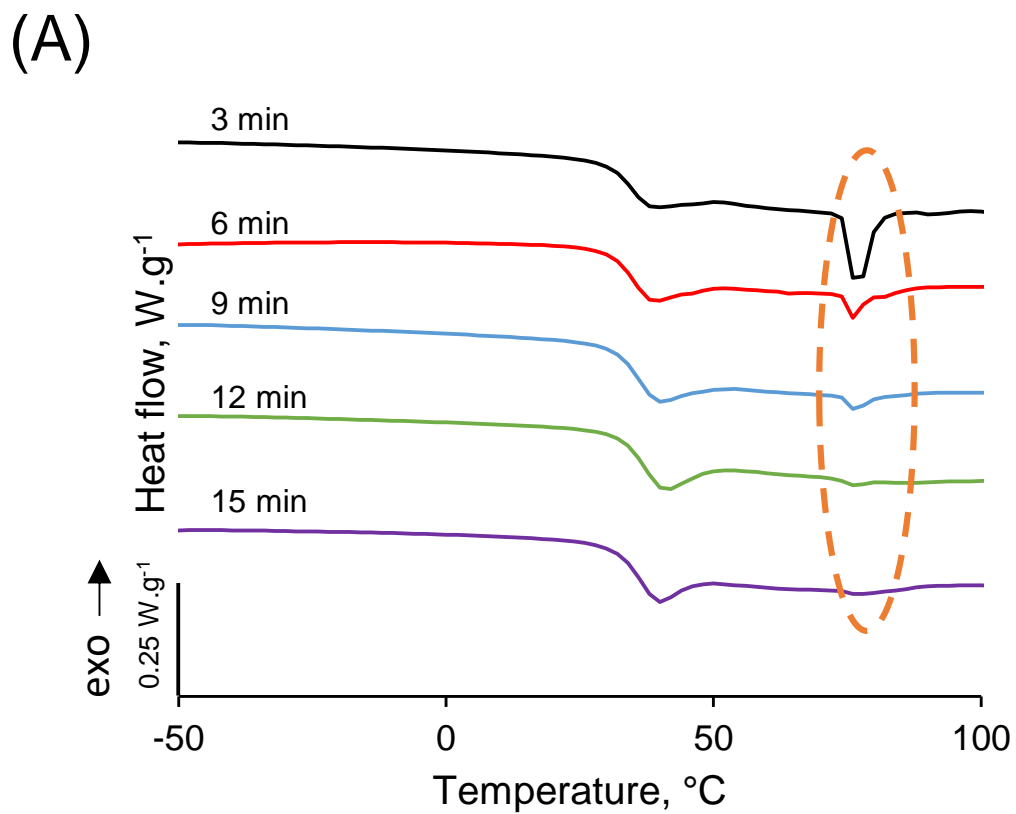


Figure 3

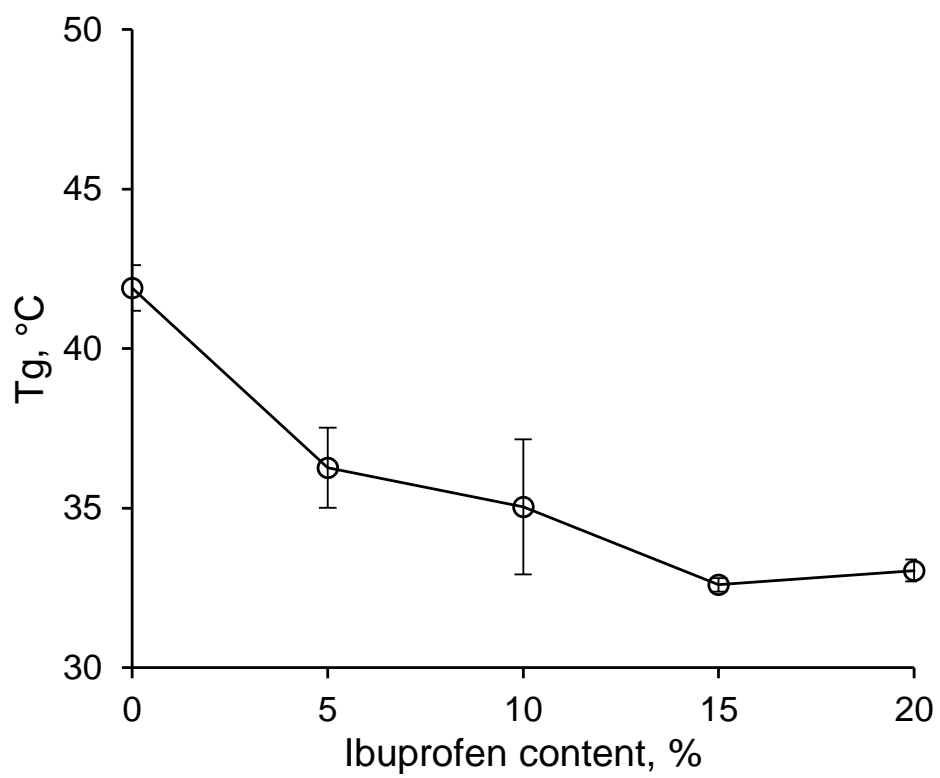


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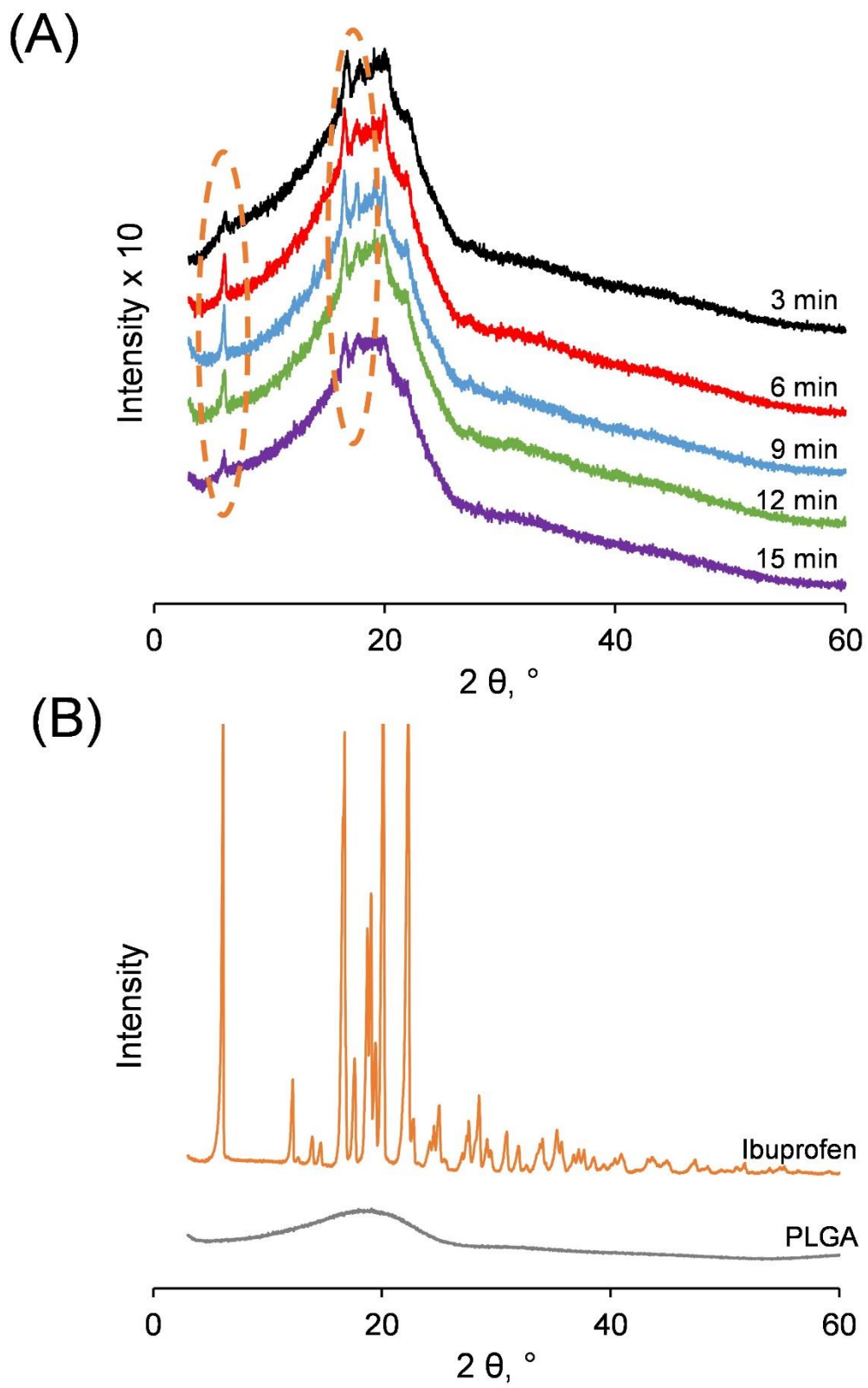


Figure 5

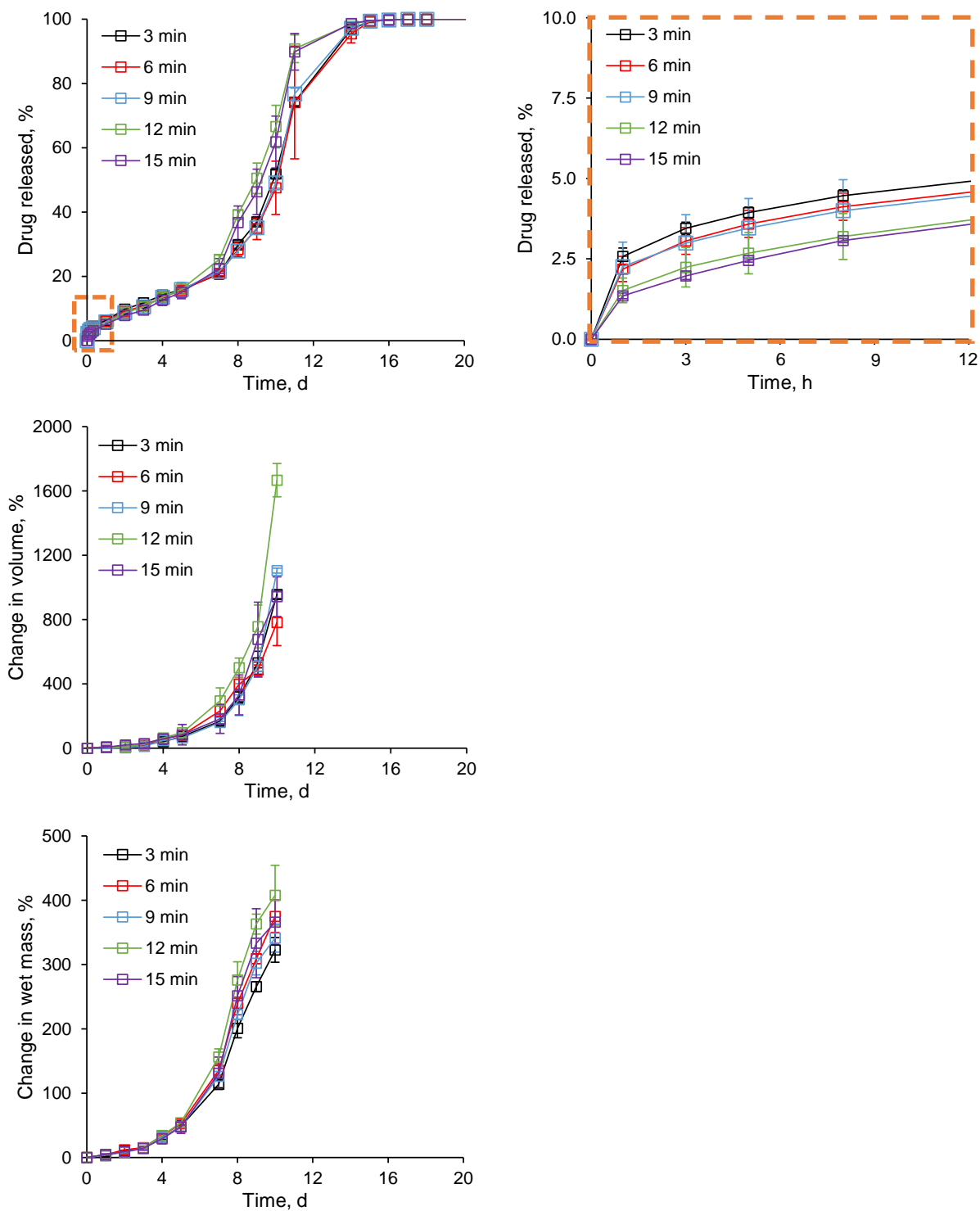


Figure 6

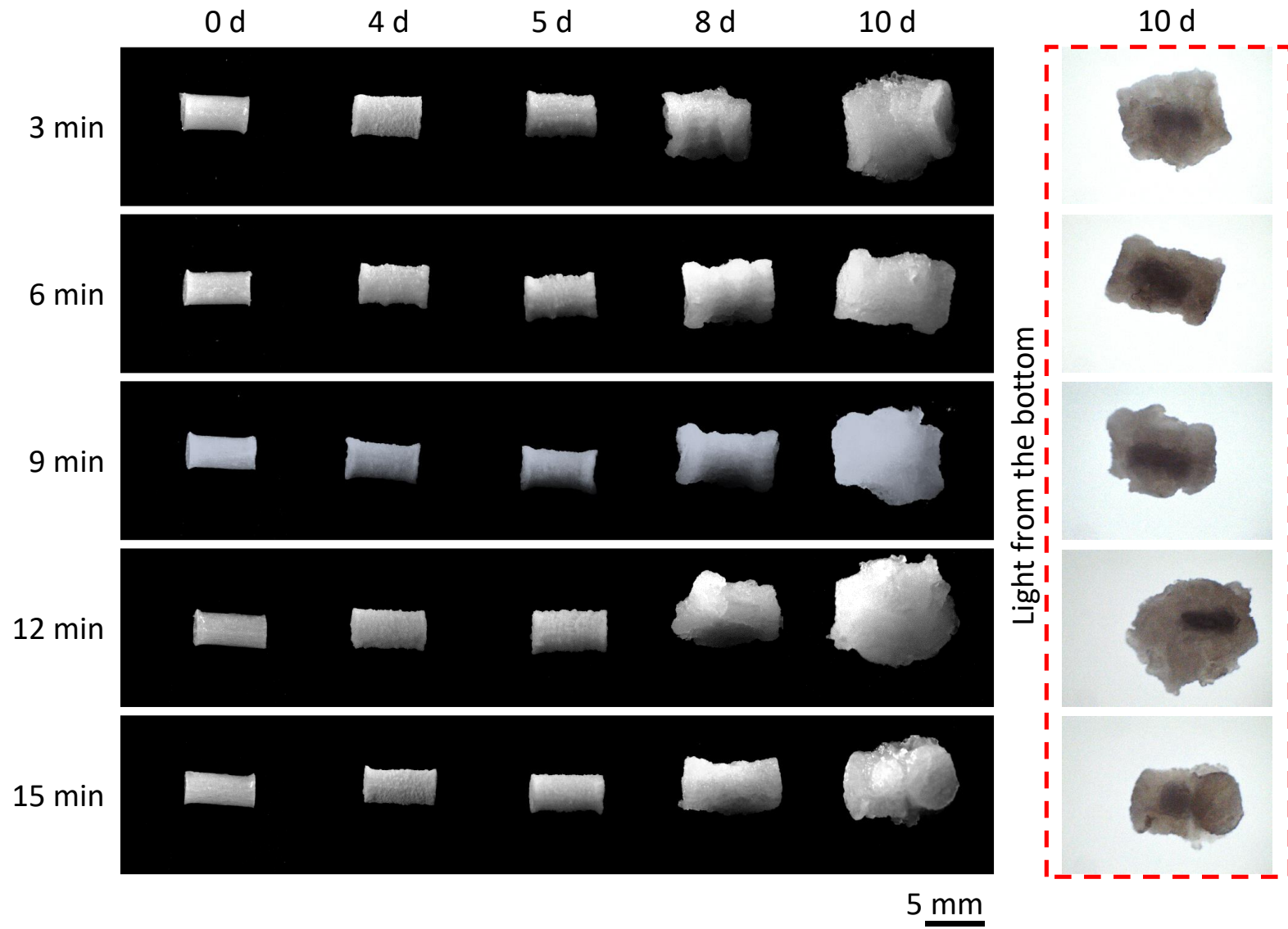


Figure 7

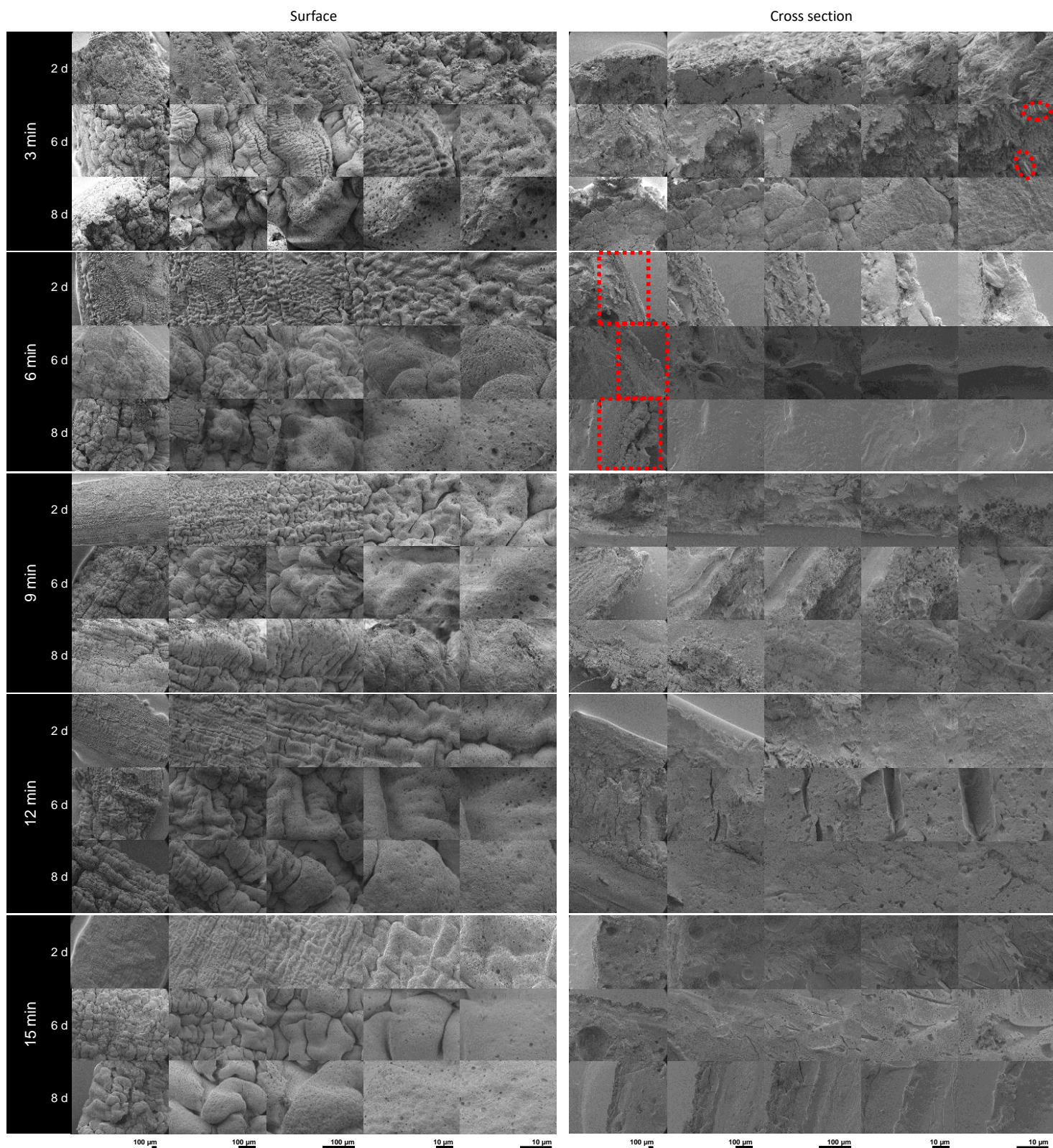


Figure 8

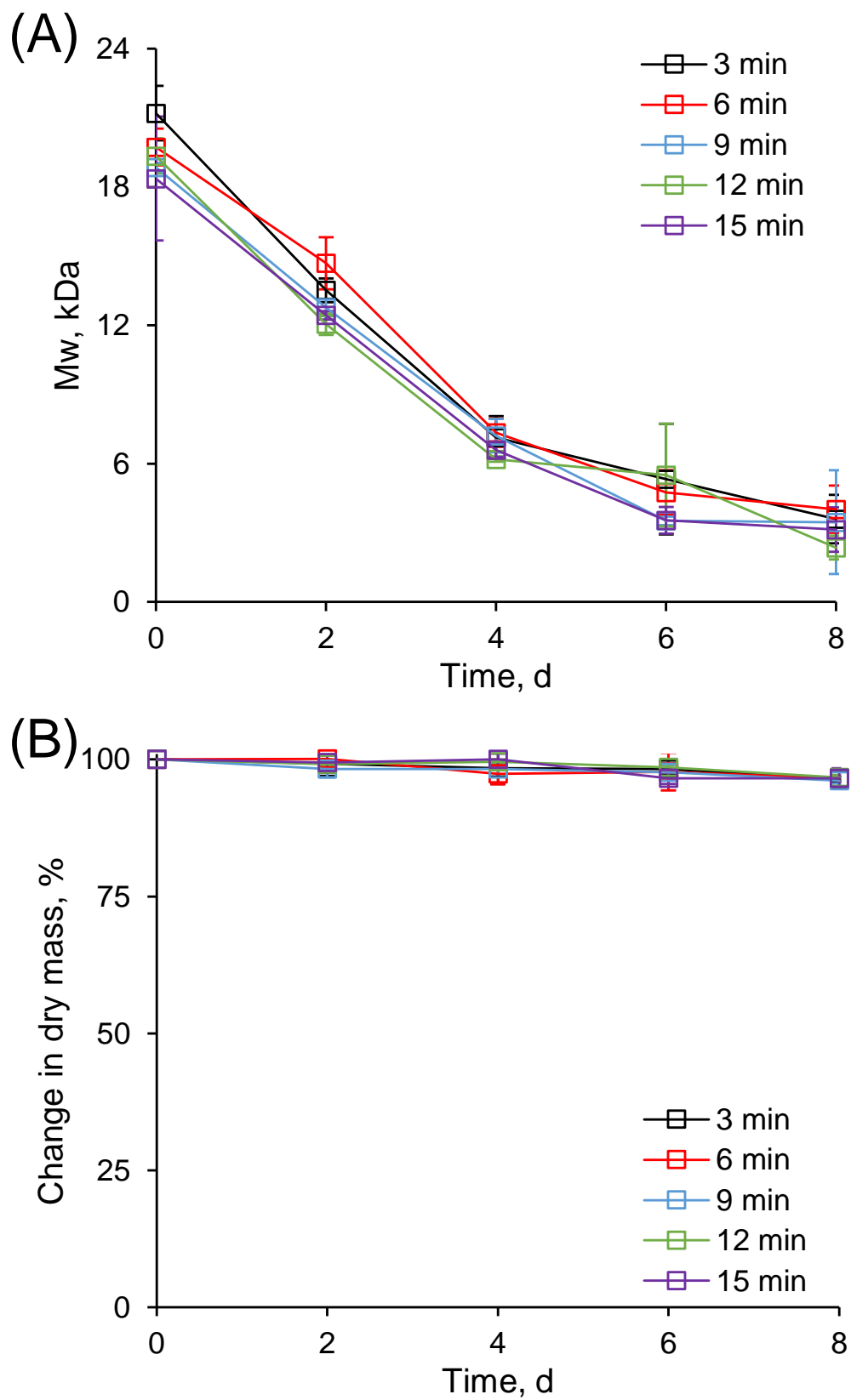


Figure 9