Research article

PLGA implants for controlled dexamethasone delivery: Impact of the polymer chemistry

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Abstract

The aim of this study was to better understand the impact of the chemistry of poly(lactic-co-glycolic acid) (PLGA) polymers on the resulting drug release kinetics from implants prepared by melting and molding. Dexamethasone was incorporated as the drug. The polymer molecular weight of the PLGA, lactic acid:glycolic acid ratio and type of end groups (ester versus free acid) were varied. The implants were characterized using optical macroscopy, SEM, X-ray powder diffraction, DSC, gravimetric monitoring of dynamic changes in the systems' dry and wet mass upon exposure to the release medium as well as drug release and pH measurements. Interestingly, the *shape* of the drug release profiles was similar in all cases: No noteworthy burst effect was observed. Dexamethasone release set on after a lag time, the length of which strongly depended on the PLGA chemistry: The lag time decreased with decreasing polymer molecular weight, increasing glycolic acid content and was shorter for -COOH end groups compared to ester end groups. In all cases, drug release set on as soon as a critical hydrophilicity and polymer molecular weight were reached and substantial system swelling started: The penetration of large amounts of water into the implants allowed for complete dexamethasone dissolution and relatively rapid diffusion of the dissolved drug molecules through a highly swollen PLGA gel up to 100 % drug release.

Keywords: PLGA; implants; controlled release; dexamethasone; swelling.

1. Introduction

Implants are often used to provide controlled release of drugs during periods ranging from days to years, in order to reduce the administration frequency, increase patient comfort, minimize undesired side effects, enhance the efficacy of the treatment and limit the overall drug dose [1-4]. *Biodegradable* polymers offer the advantage of avoiding the removal of empty remnants upon drug exhaust. Frequently, synthetic aliphatic polyesters, such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) are used for this purpose [5-11].

PLGA offers several key advantages as polymeric matrix former in biodegradable, controlled release implants, including:(i) complete biodegradability into nontoxic degradation products, which can be safely eliminated and do not cause foreign body reactions [12,13], (ii) good biocompatibility with tissues and cells [13,14] and (iii) the possibility to adjust desired drug release rates during time periods ranging from a few days up to several months [15-22]. Several drug products have been approved by the FDA for parenteral controlled drug delivery [23-25]. A variety of PLGA grades are used, differing in their polymer molecular weight, lactic acid:glycolic acid ratio, and type of end groups: free acid versus ester groups [26-31]. The specific chemistry of each PLGA determines its key characteristics, such as hydrophilicity, degradation rate and permeability for the drug. Consequently, the PLGA chemistry can strongly affect the resulting drug release kinetics [32-34]. Differences in PLGA chemistry are also important for other fields of application, e.g. for the stabilization of emulsions [35].

A variety of manufacturing procedures can be used to prepare PLGA-based controlled release implants, for example: hot melt extrusion [36-38], melting and molding [39], compression [40,41], or 3D printing [42]. In addition, liquid formulations can be injected into the patient, which form solid implants in-situ in the patient's body [43].

Despite the great practical importance of PLGA-based implants, the underlying mass transport mechanisms are often not fully understood. This can be attributed to their complexity [41, 44-46]. Upon exposure to aqueous media, water penetrates into the system and initiates polymer degradation. The rate of water penetration is much higher than the rate of ester bond cleavage. Thus, the entire device is degrading and undergoing "bulk erosion". If the drug is present in the form of solid particles, it can dissolve upon contact with water and diffuse out of the implant. The diffusion pathways can be either water-filled pores, the polymeric matrix, or a combination of both. Furthermore, autocatalytic effects might play a role: The rate at which acidic degradation products are generated within the implant can be higher than the rate at which they are neutralized or diffuse out of the system [44]. Consequently, the micro pH within the dosage form can locally drop and accelerate PLGA degradation and drug release [47]. Recently, polymer swelling has been reported to play an "orchestrating" role for drug release from PLGA-based implants prepared by hot melt extrusion [48]. After a certain lag-time, the polymeric matrix becomes sufficiently hydrophilic, the polymeric network weak enough, and the osmotic pressure within the implant sufficiently high to allow large amounts of water to penetrate into the system (amounts, which are much higher than those initially penetrating into the much more hydrophobic and denser polymeric device upon first contact with aqueous media). These high amounts of water lead to substantially increased drug mobility and accelerated drug release. However, the relative importance of all these phenomena can very much depend on the polymer chemistry. So far, relatively little is known on how the PLGA chemistry affects the underlying drug release mechanisms in controlled release implants.

The aim of this study was to prepare PLGA implants loaded with dexamethasone by melting and molding and to characterize the systems thoroughly before and after exposure to phosphate buffer pH 7.4 at 37°C. The impact of the chemistry of the PLGA on implants properties was studied, in particular of the: (i) lactic acid:glycolic acid blend ratio, (ii) type of

end groups: ester versus acid, and (iii) polymer molecular weight. Dexamethasone was chosen as drug for several reasons: (i) It does not act as a plasticizer for PLGA. (ii) It is neither acidic nor basic (and does, thus, not accelerate polyester hydrolysis). (iii) It has a limited aqueous solubility. Thus, even a saturated drug solution does not exhibit a high osmotic pressure. (iv) It is a widely used glucocorticoid and used for example in the marketed drug product Ozurdex®: a PLGA implant which is injected into the eye to treat adults with impaired vision caused by macular oedema.

Optical macroscopy, SEM, X- ray powder diffraction, DSC, gravimetric monitoring of dynamic changes in the systems' dry and wet mass upon exposure to the release medium and pH measurements of the bulk fluid were performed to better understand the underlying drug release mechanisms.

2. Materials and Methods

1. Materials

Poly(D,L-lactic-co-glycolic acid) (PLGA) 50/50 A [50:50 lactic acid:glycolic acid, –COOH end groups, Mw = 92 kDa], PLGA 50/50 E [50:50 lactic acid:glycolic acid, – ester end groups, Mw = 50 kDa] and PLGA 75/25 A [75:25 lactic acid:glycolic acid, –COOH end groups, Mw = 70 kDa] (Ashland, Dublin, Ireland); PLGA 504H [50:50 lactic acid:glycolic acid, –COOH end groups, Mw = 38 kDa] (Evonik, Darmstadt, Germany); dexamethasone (Discovery Fine Chemicals, Dorset, UK); acetonitrile and tetrahydrofuran (Carlo Erba, Val-de-Reuil, France).

2. Implant preparation

Cylindrical, flat-faced implants were prepared by melting and molding drug-polymer powder blends (10:90, w:w, %). The latter were obtained using a cryo-mill (1 g batches; Retsch, Germany), equipped with 50 mL zirconium oxide jars, containing 20 mm diameter zirconium oxide beads (1 bead per jar). The blends were cooled to -196 °C for 20 min, followed by cryo-milling for 5 min at 30 Hz. Ten mg cryo-milled drug-polymer powder blend was filled into a cylindrical mold (2 mm diameter) and heated to 95°C for 15 min, followed by cooling to room temperature.

3. *Optical macroscopy*

Pictures of implants before exposure to the release medium were taken using a Nikon SMZ-U macroscope (Nikon, Tokyo, Japan), equipped with an AxioCam ICc1 camera.

The lengths and diameters of the implants were determined using the ImageJ software (US National Institutes of Health, Bethesda, Maryland, USA).

4. *Practical drug loading*

Implants were dissolved in 5 mL acetonitrile followed by filtration (0.45 µm PVDF Syringe Filter, Millex-HV, Merck Millipore, Tullagreen, Ireland) 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 auto sampler (WPS-3000 SL) and a UV-Vis detector (VWD-3400RS) (Thermo Fisher Scientific, Waltham, USA). Ten µL samples were injected into an A C18 RP column (Gemini 3 µm C18 110 Å, 100 mm x 4.6 mm; Phenomenex, Le Pecq, France). The mobile phase consisted of a 33:67 (v/v) acetonitrile:water mixture, the flow rate was 1.5 mL/min. The detection wavelength was λ = 254 nm. All experiments were conducted in triplicate. Mean values +/- standard deviations are reported.

5. X- ray powder diffraction

X-ray diffraction patterns of raw materials and drug loaded implants were recorded with a Panalytical X'pert Pro diffractometer (Cu anode tube of wavelength Kα1 = 1.541 Å and Kα2 = 1.544 Å) (Panalytical, Almelo, Netherlands). Rotatory Lyndemann capillaries (diameter: 0.7 mm) were used.

6. Differential scanning calorimetry (DSC)

DSC thermograms of raw materials and drug loaded implants were recorded using a DSC 1 Star (Mettler Toledo, Greifensee, Switzerland). Approximately 3-5 mg samples were accurately weighed in sealed aluminum pans. The pans were heated from 20 to 300°C, cooled to −70°C and reheated to 300°C, at a rate of 10°C/min (in nitrogen atmosphere). Each experiment was conducted in triplicate. Mean values +/- standard deviations are reported.

7. In vitro drug release

Implants were placed in 2 mL Eppendorf tubes (1 implant per tube), filled with 2 mL phosphate buffer pH 7.4 (USP 42), and horizontally shaken (80 rpm, 37°C, GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). At pre-determined time points, the entire release medium was completely withdrawn and replaced with 2 mL pre-heated, fresh phosphate buffer pH 7.4. The amount of dexamethasone in the withdrawn, filtered (0.45 µm PVDF Syringe Filter, Millex-HV, Merck Millipore, Tullagreen, Ireland) bulk fluid was determined by HPLC-UV analysis, as described above in section 2.4. In this case, the injected volume was 100 µL. All experiments were conducted in triplicate. Mean values +/− standard deviations are reported.

8. Implant swelling

Implants were treated as for the *in vitro* drug release measurements described in section 2.7. At pre-determined time points:

(a) Pictures of implants were taken with a Nikon SMZ-U macroscope. Dynamic changes in the systems' volume were estimated considering cylindrical geometry using the following equation:

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

(b) Implant samples were withdrawn, excess water was carefully removed and weighed [wet mass (t)]. The wet mass (%) (t) was calculated as follows:

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

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

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

9. Implant erosion and PLGA degradation

(a) Implants were treated as for the *in vitro* drug release measurements described in section 2.7. At pre-determined time points, implant samples were withdrawn, freeze-dried (freezing at -45°C for 1h 45 min, primary drying at -40°C and 0.07 mbar for 35h and secondary drying at +20°C and 0.0014 mbar for 35h) (Christ Epsilon 2-4 LSC+; Martin Christ, Osterode, Germany), and accurately weighed [dry mass (t)].

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

$$\text{dry mass } (t)\% = \frac{\text{dry mass (t)}}{\text{mass (t=0)}} \times 100\% \quad (3)$$

where *mass (t = 0) is* the implant's mass before exposure to the release medium.

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

(b) The decrease in polymer molecular weight of different PLGA during drug release was determined by gel permeation chromatography (GPC). Implants were treated as described for the *in vitro* drug release measurements in section 2.7. At predetermined time points, implants were withdrawn and freeze-dried. Three mg of the obtained lyophilisates were dissolved in 1 mL tetrahydrofuran. One hundred µL samples were injected into an Alliance system (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 × 300 mm; Agilent). Tetrahydrofuran was used as mobile phase at a flowrate of 1 mL/min. Molecular weights were calculated using the Empower GPC software (Waters) and polystyrene standards

with molecular weights between 1,480 and 70,950 Da (Polymer Laboratories, Varian, Les Ulis, France).

10. *Scanning electronic microscopy (SEM)*

The internal and external microstructures of the implants before and after two weeks exposure to the release medium were studied using a JEOL Field Emission Scanning Electron Microscope (JSM-7800F, Japan), equipped with the Aztec 3.3 software (Oxford Instruments, Oxfordshire, England). Samples were fixed with a ribbon carbon double-sided adhesive and covered with a fine carbon layer. Implants, which had been exposed to the release medium, were treated as described in section 2.7 for the *in vitro* drug release measurements. After two weeks, implant samples were withdrawn, freeze-dried (as described in section 2.9) and cut using a scalpel to observe cross sections.

3. Results and discussion

The aim of this study was to better understand the impact of the polymer chemistry of PLGA-based implants on the resulting drug release kinetics, in particular of the (i) lactic acid:glycolic acid blend ration, (ii) type of end groups: ester versus acid, and (iii) polymer molecular weight. Dexamethasone loaded implants were prepared by melting and molding. The implants were thoroughly characterized before and after exposure to phosphate buffer pH 7.4: with respect to the physical states of the drug and PLGA, dynamic changes in dry and wet mass of the systems, inner and outer morphology, polymer swelling and degradation, changes in the pH of the release medium and drug release.

1. Physico-chemical key properties of the implants

The optical microscopy pictures on the left hand side of Figure 1 show implants based on

PLGA 50/50 A (38 kDa), PLGA 50/50 A (92 kDa), PLGA 75/25 A (70 kDa) and PLGA 50/50 E (50 kDa). The ratio "50/50" or "75/25" indicates the lactic acid:glycolic acid ratio, "A" and "E" indicate the nature of the end groups (acid or ester), and the polymer molecular weight is indicated in the brackets. The theoretical dexamethasone loading was 10% in all cases, the practical loading 9.1 +/- 0.3% (and homogeneous in different parts of the implants). As it can be seen, the obtained implants were white, had a smooth surface and appeared to be homogeneous, irrespective of the PLGA grade. The SEM pictures on the left hand side of Figure 2 show surfaces and cross-sections of dexamethasone loaded implants before exposure to the release medium. In all cases, the systems looked dense (with a certain micro-porosity) and homogeneous.

Figure 3 shows the X-ray diffraction patterns of the raw materials (drug and polymers) as well as of the dexamethasone loaded implants before exposure to the release medium. Clearly, the drug powder as received was crystalline. Its melting point was 264°C, as evidenced by a sharp endothermic peak in its DSC thermogram (Figure S1). In contrast, all PLGA raw materials and dexamethasone loaded implants were X-ray amorphous (Figure 3). DSC thermograms of the PLGA raw materials and of drug loaded implants are illustrated in Figure 4. In the case of the raw materials, 2^{nd} heating cycles are shown (the thermal history of the samples not being of interest), whereas in the case of the implants 1^{st} heating cycles are illustrated (the thermal history being of interest). As it can be seen, glass transitions were clearly visible in all cases. Table 1 lists the corresponding temperatures. Interestingly, the Tgs did not substantially differ between the polymer raw materials and the drug loaded implants, indicating that the manufacturing procedure did not seem to significantly degrade the PLGA and that the presence of the drug did not alter the Tg. This might indicate that the dexamethasone is present in the form of amorphous *particles* distributed throughout the PLGA matrices (and is not *dissolved*). The limited PLGA degradation during implant manufacturing was also evidenced

by only minor decreases in the average polymer molecular weights: PLGA 50/50 A (38 kDa) decreased from 37.5±1.2 to 36.1 ±2.0, PLGA 50/50 A (92 kDa) from 92.3±2.3 to 90.7± 1.7, PLGA 50/50 E (50 kDa) from 52.4±1.0 to 51.1 ±1.9, and PLGA 75/25 A (70 kDa) from 72.1±2.2 to 71.5 ±1.4 kDa.

2. Dexamethasone release kinetics and mass transport mechanisms

Figure 5A shows the experimentally measured dexamethasone release kinetics from the investigated PLGA implants into phosphate buffer pH 7.4. As it can be seen, drug release set on after an initial lag time. The latter depended on the PLGA grade, increasing in the following rank order: PLGA 50/50 A (38 kDa) < PLGA 50/50 A (92 kDa) < PLGA 75/25 A (70 kDa) < PLGA 50/50 E (50 kDa). Figure 5B illustrates the respective changes in the wet mass of the implants as a function of the exposure time to the release medium. In all cases, substantial system swelling was observed, setting on after a certain lag time. Again, the latter increased in the following rank order: PLGA 50/50 A (38 kDa) < PLGA 50/50 A (92 kDa) < PLGA 75/25 A (70 kDa) < PLGA 50/50 E (50 kDa). The decrease in polymer molecular weight of the investigated PLGAs during drug release is shown in Figure 5C: Interestingly, the reaching of about 8 kDa coincided rather well with the onset of substantial implant swelling and the onset of drug release (illustrated by the dotted lines in Figure 5).

It has previously been reported that drug release from PLGA and PLA based implants might be "orchestrated" by substantial polymer swelling (Figure 6) [48]: Initially, the polymeric matrices are rather hydrophobic and only limited amounts of water rapidly wet the entire implants. Once water gets into contact with the ester bonds, polymer degradation sets on throughout the systems (bulk degradation). Upon each ester bond cleavage, 2 new hydrophilic end groups are created: a -COOH and a -OH end group, rendering the matrices more and more "water loving". In addition, the degree of polymer chain entanglement decreases, leading to a

decreasing mechanical resistance against substantial swelling. Furthermore, a steadily increasing osmotic pressure is created within the implants due to the generation of water-soluble degradation products. At a certain time point (at the end of the above discussed lag phase), the matrices are sufficiently hydrophilic, mechanically fragile and osmotically active that they attract considerable amounts of water: The solid implants are transformed into highly swollen PLGA gels. This fundamentally alters the conditions for drug release: The drug particles can dissolve in the high amounts of water and can rather easily diffuse out into the release medium. Depending on the chemistry of the PLGA, this time point is more or less rapidly reached: For example, comparing the behavior of implants based on PLGA 50/50 A (38 kDa) and PLGA 50/50 A (92 kDa) (blue versus orange curves in Figure 5), it can be seen that the lag time increased when increasing the polymer molecular weight (while keeping the monomer ratio and type of end groups the same). This is consistent with the above described release mechanism: If the initial polymer molecular weight is higher, it takes more time to reach the "critical" molecular weight to allow for substantial system swelling. Also, when changing the lactic acid:glycolic acid ratio from 50/50 to 75/25, the lag time increased (orange versus red curves in Figure 5, despite a higher initial molecular weight). This can likely be explained by the higher hydrophilicity of PLGA 50/50 compared to PLGA 75/25: It contains less lactic acid, which is more hydrophobic than glycolic acid, due to an additional methyl group. If the system allows more water to come in initially, polymer degradation is faster. Furthermore, comparing the black and orange curves in Figure 5, it becomes obvious that the lag time is higher in the case of PLGA with ester end groups compared to free acid end groups (even if the molecular weight is lower). The PLGA terminal end groups influence the degradation rate. For instance, carboxyl terminal groups can catalyze the hydrolysis of ester bonds, thus producing more acidic groups and potentially leading to autocatalytic effects, accelerating polymer degradation [49]. In addition, free acid end groups render the implants less hydrophobic from the beginning,

allowing more water to penetrate into the system. Both, this lower initial hydrophobicity as well as the potential acid catalysis lead to faster polymer degradation. Thus, it takes less time to reach the critical molecular weight (as it can be seen in Figure 5C).

Figure 7 shows further experimental evidence for the hypothesized drug release mechanisms and impact of the PLGA chemistry: The dynamic changes in the implants' volume, dry mass and in the pH of the release medium are shown. The dotted lines show the same lag times as in Figure 5. As it can be seen, the implants' volume substantially increased after the lag times, due to the penetration of considerable amounts of water into the systems (Figure 7A). This coincides with the onset of important dry mass loss (Figure 7B). The latter can in part be explained by drug release but is in major part caused by the leaching of water-soluble degradation products into the release medium: Analogous to dissolved dexamethasone molecules, water-soluble short chain acids are rather mobile in the highly swollen PLGA gels and diffuse out, due to concentration gradients. This leads to significant drops in the pH of the bulk fluid (Figure 7C). The optical microscopy pictures in Figure 1 further illustrate the fundamental changes in the conditions for drug release: Depending on the PLGA grade, after a certain lag time, the implants substantially swell. SEM pictures of surfaces and cross-sections of the different types of implants are shown in Figure 2: On the right hand side, implants based on PLGA 50/50 A (38 kDa), PLGA 50/50 A (92 kDa), PLGA 75/25 A (70 kDa) and PLGA 50/50 E (50 kDa) are illustrated after 2 weeks exposure to phosphate buffer pH 7.4. Please note that the samples had been dried prior to analysis, thus, artefact creation is highly likely. Furthermore, please also note that at t = 2 weeks, only the implants based on PLGA 50/50 A (38 kDa) were entering the "substantial system swelling phase". Comparing these pictures to those on the *left hand* side of Figure 2 (taken before exposure to the release medium), signs for polymer degradation throughout the matrices are visible (indicating bulk degradation).

4. Conclusion

In this study, the chemistry of PLGA did not fundamentally change the underlying drug release mechanisms from dexamethasone loaded implants, neither the *shape* of the observed release patterns. But the polymer chemistry determined the length of the lag time, after which drug release set on. This could be explained by the fact that the polymer molecular weight, "lactic acid:glycolic acid ratio" and type of end groups (free acids versus esters) affect the time point, at which a sufficient system hydrophilicity and macromolecular chain length are reached to allow the beginning of substantial implant swelling. The latter fundamentally changes the conditions for drug release. This improved understanding of the importance of the polymer chemistry on the control of drug release can be expected to facilitate the development of innovative biodegradable implants.

Declaration 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:

Glass transition temperatures (Tgs, °C) of the raw materials (as received, second heating cycles) and of the investigated dexamethasone loaded PLGA implants (first heating cycles) before exposure to the release medium. The lactic acid/glycolic acid ratio, type of end groups (A: acid, E: ester) and initial polymer molecular weight are indicated in the left column. Mean values +/- standard deviations are reported.

PLGA grade	Raw materials	Drug loaded implants
50/50 A (38kDa)	43.3 ± 0.2	43.6 ± 0.2
50/50 A (92kDa)	47.0 ± 0.1	46.8 ± 0.2
75/25 A (70kDa)	46.9 ± 0.2	47.1 ± 0.2
50/50 E (50kDa)	45.9 ± 0.1	46.0 ± 0.1

Figure captions

Fig. 1 Optical macroscopy pictures of dexamethasone loaded PLGA implants upon different exposure times to phosphate buffer pH 7.4 (indicated at the top). The lactic acid/glycolic acid ratio, type of end groups (A: acid, E: ester) and initial polymer molecular weight are given on the left-hand side. As indicated, some of the samples became too fragile to be withdrawn from the release medium without damage.

Fig. 2 SEM pictures of surfaces and cross-sections of dexamethasone loaded PLGA implants before and after 2 weeks exposure to phosphate buffer pH 7.4. The lactic acid/glycolic acid ratio, type of end groups (A: acid, E: ester) and initial polymer molecular weight are indicated on the left-hand side. Please note that the implants, which had been exposed to the release medium, were freeze-dried prior to analysis, creating artefacts.

Fig. 3 X-ray diffraction patterns of the raw materials and dexamethasone loaded PLGA implants before exposure to the release medium. The lactic acid/glycolic acid ratio, type of end groups (A: acid, E: ester) and initial polymer molecular weight are indicated in the diagram.

Fig. 4 DSC thermograms of the raw materials (second heating cycles) and of the investigated dexamethasone loaded PLGA implants (first heating cycles) before exposure to the release medium. The lactic acid/glycolic acid ratio, type of end groups (A: acid, E: ester) and initial polymer molecular weight are indicated in the diagram.

Fig. 5 Impact of the PLGA chemistry on: (A) dexamethasone release, (B) dynamic changes in the implants' wet mass, and (C) dynamic changes in the polymer molecular weight (Mw), upon exposure to phosphate buffer pH 7.4. The lactic acid/glycolic acid ratio, type of end groups (A: acid, E: ester) and initial polymer molecular weight are indicated in the diagrams.

Fig. 6 Schematic presentation of the mass transport phenomena involved in the control of drug release from the investigated implants. Polymer swelling "orchestrates" drug release: after a certain lag time, it fundamentally changes the conditions for drug dissolution and diffusion, and drug release sets on. Reprinted from [48], with permission.

Fig. 7 Dynamic changes in the: (A) volume of the implants, (B) dry mass of the implants and (C) pH of the release medium, upon exposure to phosphate buffer pH 7.4. The lactic acid/glycolic acid ratio, type of end groups (A: acid, E: ester) and initial polymer molecular weight are indicated in the diagrams.

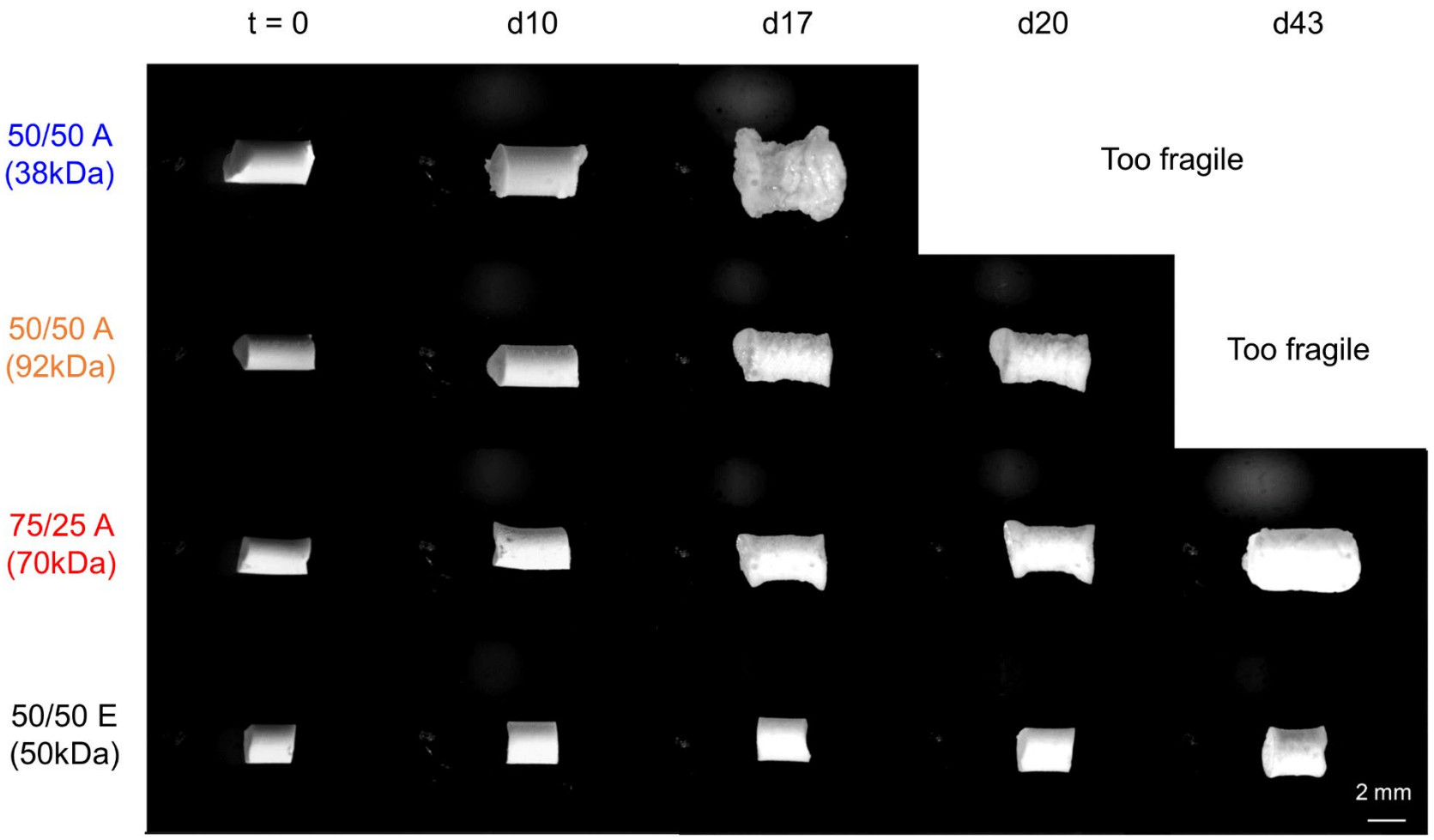
t = 0
d10
d17
d20
d43
50/50 A
(38kDa)
50/50 A
(92kDa)
75/25 A
(70kDa)
50/50 E
(50kDa)
Too fragile
Too fragile
2 mm

Figure 1

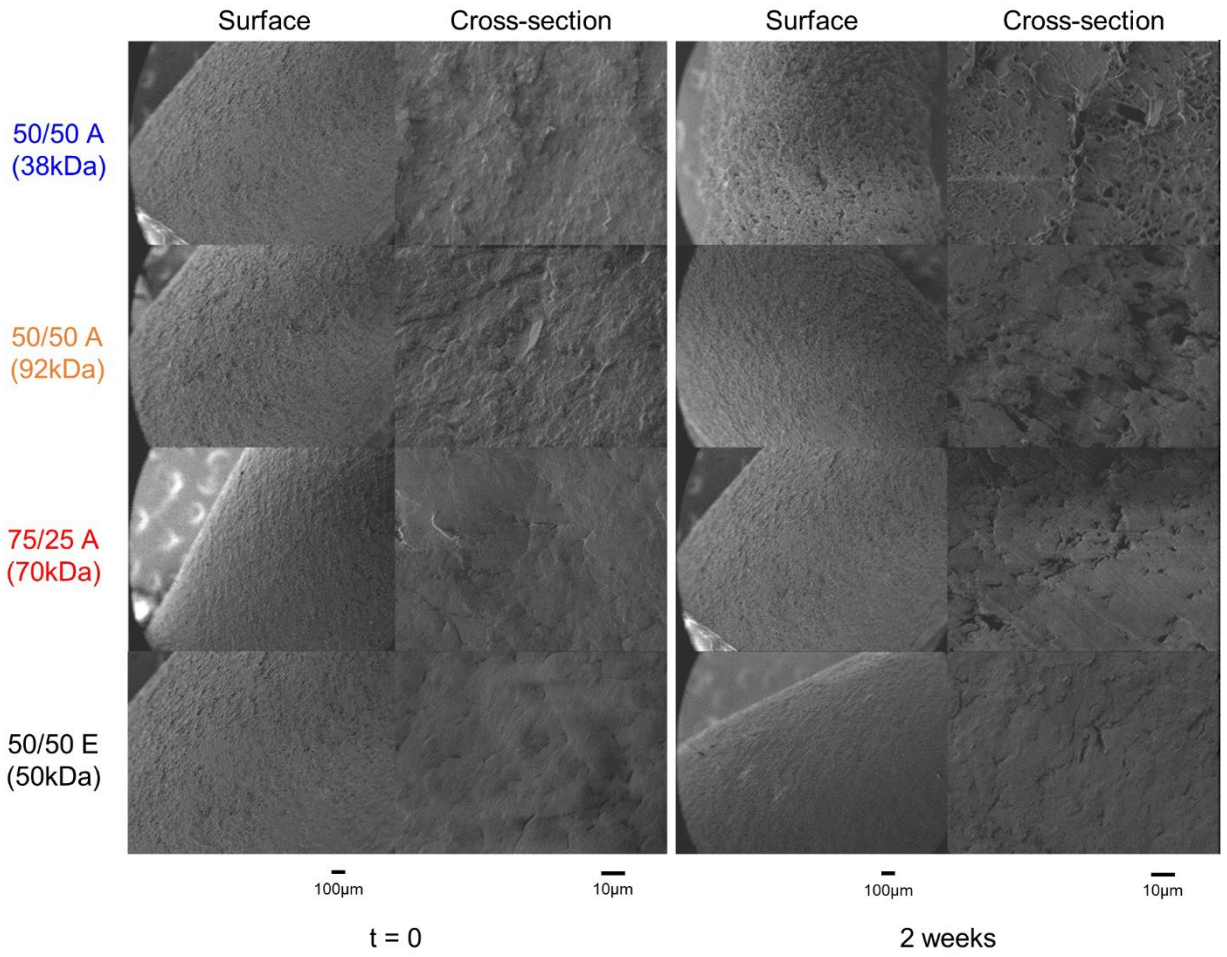
Surface
Cross-section
Surface
Cross-section
50/50 A
(38kDa)
50/50 A
(92kDa)
75/25 A
(70kDa)
50/50 E
(50kDa)
100µm
10µm
100µm
10µm
t = 0
2 weeks

Figure 2

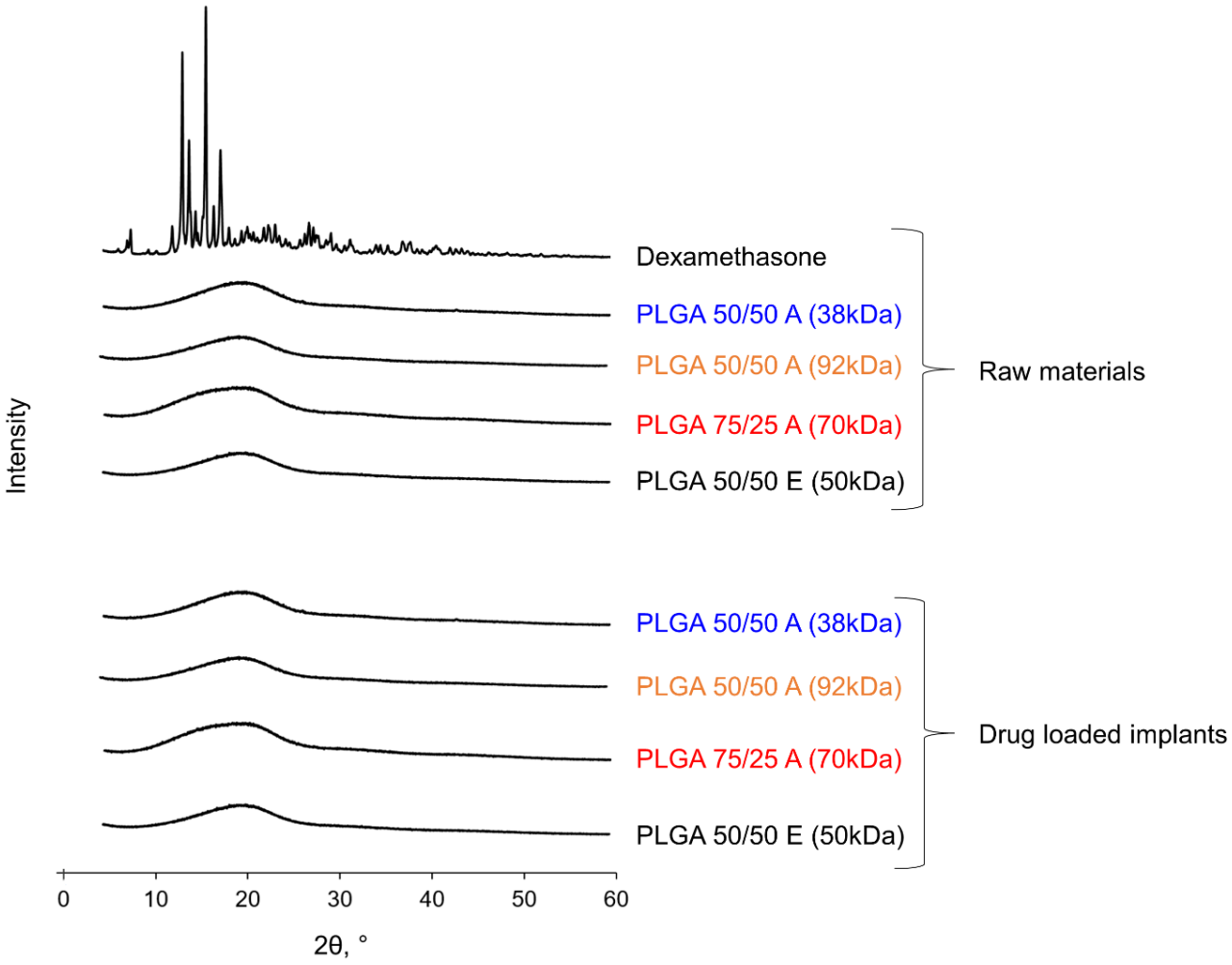
Intensity
Dexamethasone
PLGA 50/50 A (38kDa)
PLGA 50/50 A (92kDa)
PLGA 75/25 A (70kDa)
PLGA 50/50 E (50kDa)
Raw materials
PLGA 50/50 A (38kDa)
PLGA 50/50 A (92kDa)
PLGA 75/25 A (70kDa)
PLGA 50/50 E (50kDa)
Drug loaded implants
0
10
20
30
40
50
60
2θ, °

Figure 3

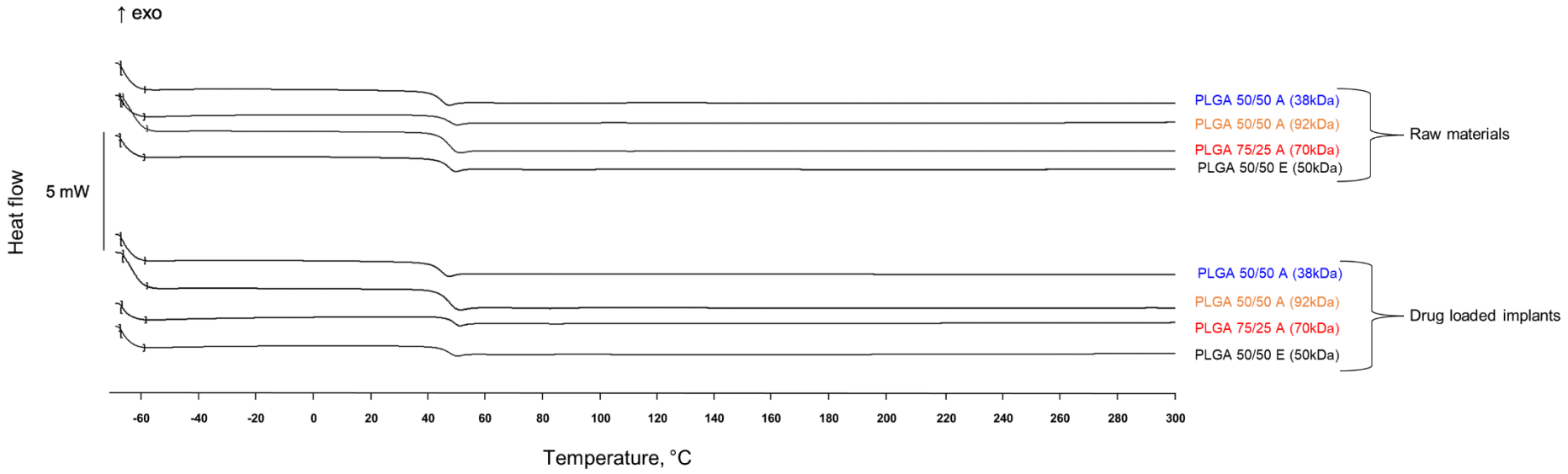
↑ exo
Heat flow
5 mW
PLGA 50/50 A (38kDa)
PLGA 50/50 A (92kDa)
PLGA 75/25 A (70kDa)
PLGA 50/50 E (50kDa)
Raw materials
PLGA 50/50 A (38kDa)
PLGA 50/50 A (92kDa)
PLGA 75/25 A (70kDa)
PLGA 50/50 E (50kDa)
Drug loaded implants
-60 -40 -20 0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300
Temperature, °C

Figure 4

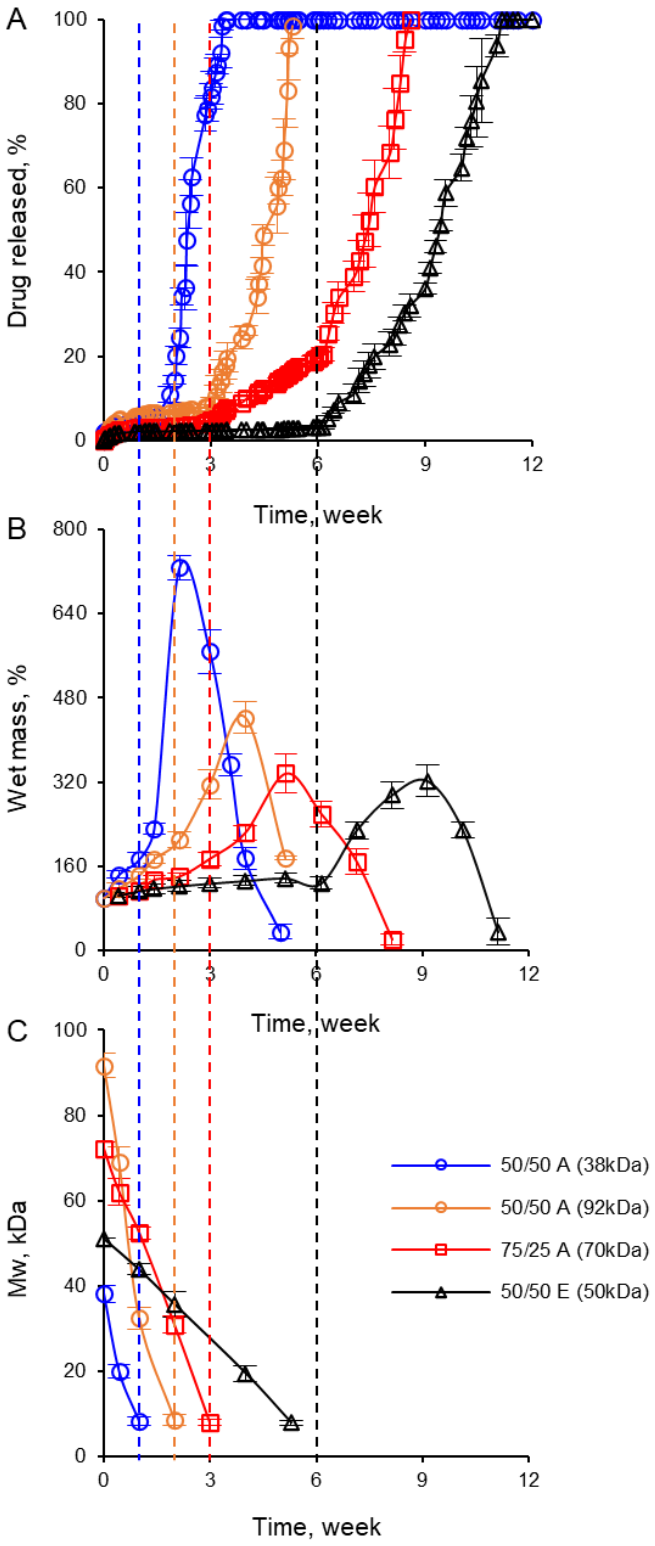
A
Drug released, %
100
80
60
40
20
0
0
3
6
9
12
Time, week
B
Wet mass, %
800
640
480
320
160
0
Time, week
C
Mw, kDa
50/50 A (38kDa)
50/50 A (92kDa)
75/25 A (70kDa)
50/50 E (50kDa)
Time, week

Figure 5

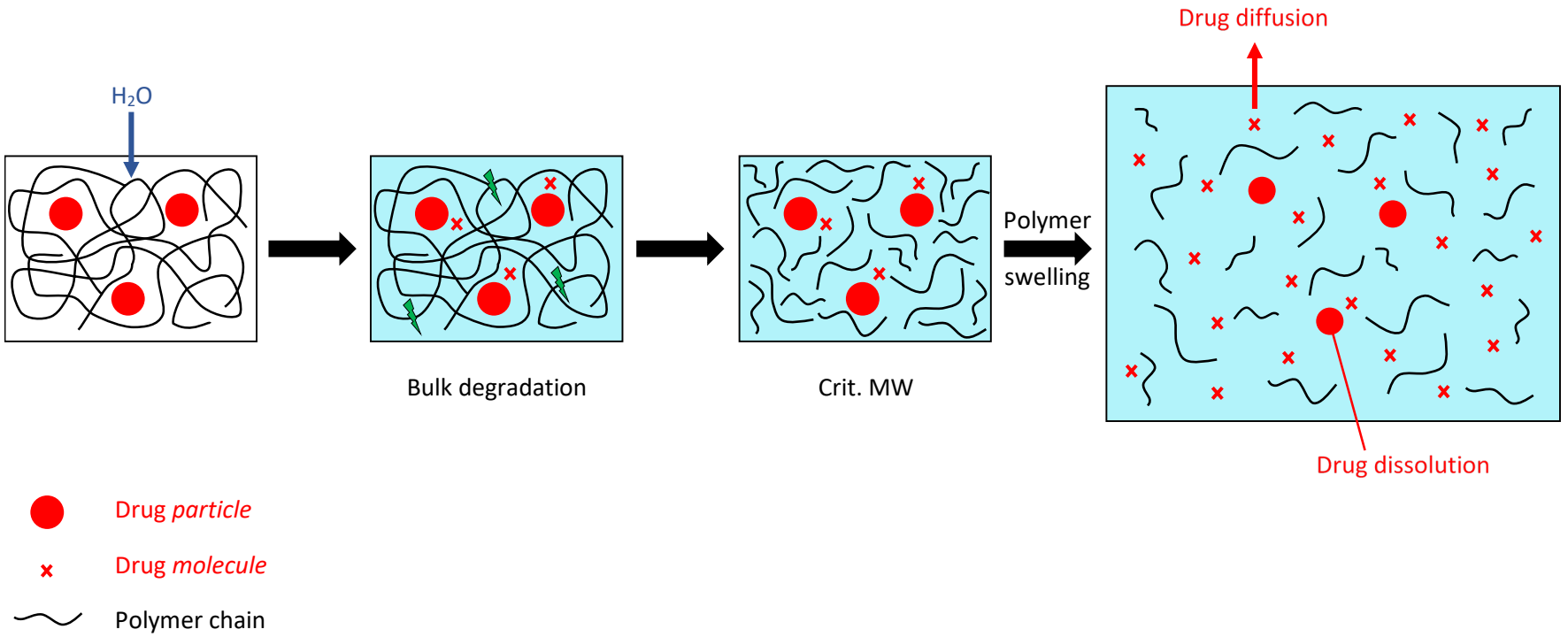
H_2O
Bulk degradation
Crit. MW
Polymer
swelling
Drug diffusion
Drug dissolution
Drug *particle*
Drug *molecule*
Polymer chain

Figure 6

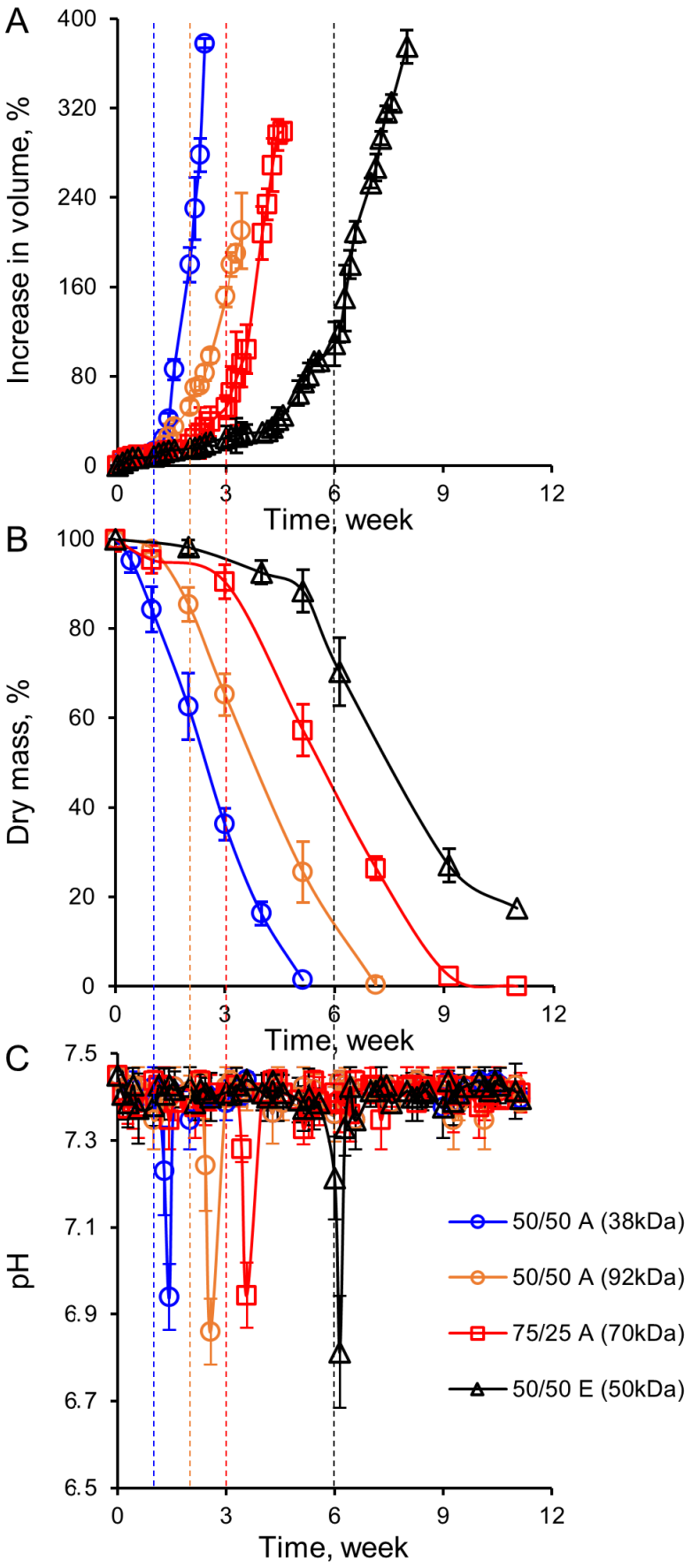
A
Increase in volume, %
400
320
240
160
80
0
0
3
6
9
12
Time, week
B
Dry mass, %
100
80
60
40
20
0
0
3
6
9
12
Time, week
C
pH
7.5
7.3
7.1
6.9
6.7
6.5
0
3
6
9
12
Time, week
50/50 A (38kDa)
50/50 A (92kDa)
75/25 A (70kDa)
50/50 E (50kDa)

Figure 7