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Title: Modulating drug release from poly(lactic-co-glycolic acid) films through terminal end-groups and molecular weight

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Abstract: Biodegradable PLGA is commonly employed for controlled drug release on the order of weeks to months. Hydrophobic drugs distribute homogeneously in PLGA, but their strong hydrophobic interaction typically results in narrow release profiles. In this study, three molecular weights (MW) and two different terminal end-groups of biodegradable PLGA were applied to broaden the range of drug release and vary the mechanical properties without the use of additives. Films knife-casted from PLGA polymers with terminal carboxylic acid end-groups were found to 1) absorb more water, 2) have higher rates of polymer mass loss, 3) increased hydrophobic drug release as compared to films knife casted from similar MW PLGA polymers with terminal ester end-groups. The highest drug release rates were obtained from low MW PLGA that had the densest surface concentration of terminal acid groups. An intermediate drug release profile was obtained with a blend of high and low MW PLGA. The various PLGA polymers (differing in MW, terminal groups, and combinations thereof) described herein could give rise to PLGA\PLGA blends that would allow independent tuning of drug release and mechanical properties without the inclusion of non-degradable additives with respect to hydrophobic, small molecule drugs.

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**Re: Submission of Research Article for Review**

Dear Dr. Billingham,

My co-authors and I are submitting an original full-length paper entitled "*Modulating drug release from poly(lactic-co-glycolic acid) films through terminal end-groups and molecular weight*" to the Journal of Polymer Degradation and Stability for peer review. In this manuscript, we report the use of commercially available poly(lactic-co-glycolic acid) (PLGA) polymers to widen the range of hydrophobic drug therapy. This study would provide the better understanding of how the release profile of hydrophobic drugs can be modulated without the use of hydrophilic or non-degradable additives such as polyethylene glycol. Our studies showed dependence of drug release on the concentration of terminal end-groups and molecular weight of PLGA. An intermediate drug release profile can be obtained with blending PLGA polymers, thereby giving a wider array of independent modulation of drug release and mechanical properties without the inclusion of additives.

We hereby state that this submission has not been published previously, that it is not under consideration for publication elsewhere, and that if accepted it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the publisher.

Any correspondences with regards to this submitted manuscript can be referred directly to me through email at joachimloo@ntu.edu.sg. Alternatively, I can also be contacted through telephone (+65 6790 4603) or fax (+65 6790 9081). My co-authors and I would greatly appreciate if you could kindly review this article for publication in the Journal of Polymer Degradation and Stability.

Thank you.

Best Regards,  
Joachim Loo

1 **Modulating drug release from poly(lactic-co-glycolic acid) thin films through**  
2 **terminal end-groups and molecular weight**

3

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18

19 **KEYWORDS:** Poly(lactic-co-glycolic acid) (PLGA), terminal end-group, paclitaxel, controlled  
20 drug delivery, mechanical properties

21 **Abstract**

22 Biodegradable PLGA is commonly employed for controlled drug release on the order of weeks  
23 to months. Hydrophobic drugs distribute homogeneously in PLGA, but their strong hydrophobic  
24 interaction typically results in narrow release profiles. In this study, three molecular weights  
25 (MW) and two different terminal end-groups of biodegradable PLGA were applied to broaden  
26 the range of drug release and vary the mechanical properties without the use of additives. Films  
27 knife-casted from PLGA polymers with terminal carboxylic acid end-groups were found to 1)  
28 absorb more water, 2) have higher rates of polymer mass loss, 3) increased hydrophobic drug  
29 release as compared to films knife casted from similar MW PLGA polymers with terminal ester  
30 end-groups. The highest drug release rates were obtained from low MW PLGA that had the  
31 densest surface concentration of terminal acid groups. An intermediate drug release profile was  
32 obtained with a blend of high and low MW PLGA. The various PLGA polymers (differing in  
33 MW, terminal groups, and combinations thereof) described herein could give rise to  
34 PLGA\PLGA blends that would allow independent tuning of drug release and mechanical  
35 properties without the inclusion of non-degradable additives with respect to hydrophobic, small  
36 molecule drugs.

37 **1. Introduction**

38 Resorbable polymers have been commonly chosen as materials for drug delivery and medical  
39 device implants [1, 2]. Polyesters such as poly(lactic-*co*-glycolic acid) (PLGA), are a class of  
40 biodegradable polymers commonly employed in drug delivery systems. They have been widely  
41 used in the development of biodegradable nanoparticles, microparticles, scaffolds, films and bulk  
42 implants, giving a wide range of drug delivering capabilities [3-7].

43  
44 Anti-proliferative drugs such as paclitaxel are often loaded into PLGA carrier systems for  
45 sustained drug therapies [1, 8-13]. Due to the strong interaction between paclitaxel and PLGA,  
46 such a drug delivery system is often limited to a narrow range of drug therapy. The hydrophobic  
47 nature and poor aqueous solubility of paclitaxel (~0.5 µg/mL) also influence the drug release  
48 characteristics [14, 15]. Additives such as leachants or porogens are commonly used to enhance  
49 drug release by increasing water infiltration [5, 7, 14, 16-20]. However, the effects are usually  
50 short lived and may negatively affect the mechanical properties. Therefore, one of the aims of  
51 this study is to exploit the different molecular weights (MW) and terminal end-groups of  
52 commercially available PLGA to widen the range of drug release profiles without the use of  
53 hydrophilic or non-degradable additives such as salt particles, polyethylene glycol, etc.

54  
55 In this study, PLGA films were synthesized of three MW PLGAs with terminal ester, terminal  
56 acid end-groups, or combination thereof, to modulate the release of hydrophobic paclitaxel. An  
57 initial high-throughput screening method using fluorescein diacetate (FDAC) provided a quick  
58 indication of the release characteristics from these PLGA polymer films [21]. The release of  
59 paclitaxel was then monitored in tandem with the degradation of these PLGA films. A blend that  
60 gave the lowest and highest release was subsequently assessed for their combined release  
61 characteristics. Our subsequent investigations (manuscript in preparation) will focus on high-  
62 throughput gradient films that display tuning of drug delivery by exploiting the five PLGA  
63 variants characterized herein.

## 64 **2. Materials & Methods**

65

### 66 **2.1 Materials**

67 Poly(DL-lactide-co-glycolide) (PLGA 53/47) with inherent viscosity (i.v.) 1.03, 0.4, 0.4A, 0.2,  
68 0.2A dL/g (abbreviated P103E, P04E, P04A, P02E, P02A) were purchased from Purac, (The  
69 Netherlands). Dichloromethane (DCM) was purchased from Tedia (USA). Paclitaxel (PCTX)  
70 was purchased from Yunnan Hande Bio-Tech, China (>99%). Fluorescein diacetate (FDAC) was  
71 purchased from Tokyo Kasei Kogyo Co., Ltd Japan. All other polar solvents used were of high  
72 performance liquid chromatography (HPLC) grade and purchased from Sigma-Aldrich,  
73 Singapore. All chemicals and materials were used as received.

74

### 75 **2.2 Methods**

#### 76 *Film Preparation*

77 The respective polymer solutions of P103E, P04E, P04A, P02E, P02A (15% w/v) were prepared  
78 with 10% w/w PCTX or FDAC in DCM. A typical film formulation consisted of 150 mg of  
79 PCTX or FDAC and 1500 mg of PLGA in 10 mL of DCM. Film applicator height was fixed at  
80 500  $\mu\text{m}$  and the polymer solution was casted onto polyethylene terephthalate (PET) sheets at 50  
81 mm/s, under room temperature and pressure in a fume hood. The use of PET layer serves to  
82 provide mechanical support to the fast-degrading films. The casted films were left to dry in a  
83 solvent saturated atmosphere before transferring to vacuum oven for further drying at RT for 5 d.

84

#### 85 *Surface Hydrophobicity*

86 Films were cut into rectangular strips (3 cm  $\times$  1 cm) and their surface properties analyzed by  
87 contact angle and wetting tension using a static sessile drop technique on a contact angle  
88 goniometer. The static measurements were carried out at room temperature at five locations, with  
89 distilled H<sub>2</sub>O being pumped out at a rate of 5  $\mu\text{L/s}$ . A still image was captured for analysis after  
90 allowing the droplet to relax for 10 s and analyzed with FTA32 software, version 2.0 build 276.2.

91

#### 92 *In-vitro Paclitaxel/FDAC Release Study (as previously described and cite)*

93 The *in-vitro* release of paclitaxel (PCTX) was conducted in 2 mL of PBS spiked with 2% Tween  
94 80 in release buffer (pH 7.4) at 37 °C, using 1 cm  $\times$  1 cm cut-outs, in triplicate. At predetermined

95 time points, 1 mL of buffer was withdrawn and filtered through a 0.2  $\mu\text{m}$  cellulose syringe filter  
96 directly into HPLC vials and immediately capped. The remaining 1 mL is discarded and replaced  
97 with 2 mL of fresh buffer. PCTX was quantified with an Agilent Series 1100 HPLC (Santa  
98 Clara, CA, USA) equipped with UV/Vis detector. Acetonitrile/water 70/30 (% v/v) served as the  
99 mobile phase, eluting the PCTX peak approximately at 2 minutes with a flow rate 1.0 mL/min  
100 through Poroshell 120 EC-C18 column of pore size 2.8  $\mu\text{m}$  (Agilent Technologies) with UV/Vis  
101 detector of HPLC recorded at 227 nm. A total dissolution quantification of the 1 cm  $\times$  1 cm  
102 samples was conducted by dissolving the films in acetone, in triplicate.

103 The *in-vitro* release of FDAc was monitored by Fluorescence Microplate Reader (Tecan,  
104 Seestrasse, Männedorf, Switzerland). Sodium hydroxide (100 mM, 180 $\mu\text{l}$ ) was first added into  
105 the wells of the 96-well Greiner black plate. Subsequently 20 $\mu\text{L}$  of aliquot was pipetted into the  
106 wells of the microarray plate. The fluorescence units were recorded and its concentration  
107 calculated from standard curves set up at various gain settings.

108

#### 109 ***In-vitro Degradation and Mass Loss Study***

110 1 cm  $\times$  1 cm film samples were initially weighed ( $W_o$ ) prior to incubation in PBS maintained at  
111 37  $^{\circ}\text{C}$ , in triplicate. At predetermined time points, the films were rinsed with deionized water and  
112 the excess blotted off before measuring the wet weight ( $W_{\text{wet}}$ ). The samples were then dried  
113 thoroughly in a vacuum oven for at least a week before measuring the dry weight ( $W_{\text{dry}}$ )  
114 gravimetrically. These samples were then dissolved in 1 mL of chloroform for at least an hour,  
115 vortexed and filtered through 0.2  $\mu\text{m}$  cellulose filters into HPLC vials and immediately capped.  
116 GPC (Agilent series 1100 Santa Clara, USA) was used to monitor the MW change in the films as  
117 degradation proceeds. At each time point, each dried sample was dissolved in 1 ml chloroform,  
118 filtered and injected into GPC that was fixed with PLgel 5  $\mu\text{m}$  column maintained at 35 $^{\circ}\text{C}$  and  
119 coupled to a refractive index detector. The flow rate was set at 1 mL/min and the mobile phase  
120 was chloroform. The calibration was done prior to sample analysis using a series of standard  
121 polystyrene of known molecular weight.

122 Water absorption and mass loss were calculated using the equations as follows:

$$\frac{\text{---}}{\text{---}}$$

123

### 124 ***Mechanical Properties***

125 To assess the mechanical properties of these films, they had to be separately casted onto a  
126 Teflon-coated base instead of PET. These films were dried similarly as described earlier. Each 8  
127 cm × 1 cm rectangular film was clamped to the water grip setup designed to mount onto the  
128 Instron Tensile Tester, Model 5567. The samples were subjected to tensile stress at rate of 5  
129 mm/min in PBS medium maintained at 37 °C via a circulator to mimic physiological conditions.  
130 The data was plotted and analyzed with Bluehill software version 3.00. The Young's modulus  
131 (E), yield strength ( $\sigma_{ys}$ ), tensile stress at break ( $\sigma_b$ ) and elongation-to-break ( $\epsilon_b$ ), in MPa, were  
132 recorded and calculated, in triplicate. No isotropic effects on the mechanical properties were  
133 investigated.

134

### 135 ***Thermal Analysis***

136 The thermal properties of pure polymers and films were characterized by differential scanning  
137 calorimetry (Q500 DSC, TA Instruments). Film samples were sealed in crimped aluminum pans  
138 with lids before purging with purified nitrogen gas in the chamber to avoid oxidative  
139 degradation. Empty crimped aluminum pan was used as a reference. Both reference and sample  
140 pans were heated and cooled at a rate of 10 °C/min. The change in glass transition temperature  
141 ( $T_g$ ) from the second DSC thermogram was plotted as a function of degradation time.

142

143 ***Film Surface and Film Cross-section Topography*** Film surfaces and cross-sections were coated  
144 with platinum for 50 s under a chamber pressure of less than 5 Pa at 20 mA (JEOL JFC-1600  
145 Auto Fine Coater, Japan). Secondary electron images of the film surface were acquired at 5.0  
146 kV, 12  $\mu$ A, at a working distance of 8 mm (SEM) (JEOL JSM-6360, Japan). Film cross-sections  
147 were prepared by flash freezing the films in Tissue-Tek OCT compound at -80 °C and were  
148 subsequently sliced at 10  $\mu$ m.

149

### 150 ***Data Analysis***

151 Linear regressions and Pearson's correlations were calculated with Origin 8.5 SR1. Linear  
152 regression was determined with No Weighting. Pearson's correlations (r) were determined with a  
153 minimum of n = 5 data point comparisons and a 2-tailed test of significance. Significance was

154 determined if  $p < 0.05$ . Analysis of covariance was used to determine significance in linear  
155 regression comparisons, with  $p > 0.95$  marked by a \*.

156

### 157 3. Results

#### 158 3.1 Surface Hydrophobicity

159 The surface properties of PLGA consisting of different terminating end-groups remained  
160 consistent across the three MW as shown in **Fig. 1**. With the exception of P103E, the addition of  
161 PCTX affected neither the contact angles nor wetting tension for the lower MW PLGA films.  
162 Similarly, no substantial differences were seen between terminal ester and terminal acid groups,  
163 or across the three MWs. This suggests that the paclitaxel was homogenously distributed.  
164 Moreover, the terminal functional groups did not affect the surface energies of the films upon  
165 initial water contact.

166

#### 167 3.2 Thermal & Mechanical Properties

168 Upon submersion, all PLGA films increased in  $T_g$  ranging between 40 – 48 °C up to day 10.  $T_g$   
169 of PLGA was known to increase with MW and decrease with absorbed humidity[22, 23],  
170 however the trend observed was an increase in  $T_g$  for the first 10 days, which could be due to a  
171 rise in crystallinity, extraction of any organic solvent, or combination thereof. This  $T_g$  trend has  
172 also been seen for other PLGA microparticles during the first weeks of aqueous incubation [24].  
173 Mass loss and humidity are unlikely to be factors, since little to no polymer mass loss was  
174 observed for the first 10 days (see below) and our film preparation for DSC measurements  
175 removed any absorbed water (see Materials and Methods). After 10 days,  $T_g$  of the various  
176 PLGA films was reduced over time as shown in **Fig. 2**. A subsequent decrease in  $T_g$  was  
177 observed across the PLGA films as the MW decreased. The acid-terminated PLGA films  
178 generally displayed a lower  $T_g$  as compared to the ester-terminated films over time, due to the  
179 faster ester cleavage kinetics of the acid-terminated PLGA films (see below).

180

181 The mechanical properties of these films were assessed and recorded under *in-vitro* conditions;  
182 submersion in PBS buffer at 37°C, as summarized in **Table 2**. The Young's modulus, yield  
183 strength, and tensile strength was decreased significantly with decreasing MW of PLGA in the  
184 order from P103E, P04E, P04A, P02E to P02A as shown in the representative stress versus strain  
185 plot in **Fig. 3**. Conversely, the percentage of elongation-to-break increased with decreasing MW.  
186 The lowest MW PLGA of both ester- and acid-terminated films exhibited the highest percentage  
187 of elongation-to-break (>750%). However, no actual value could be recorded as the elongation

188 exceeded the testing limits of the instrumentation. Generally, changes in MW, rather than  
189 differences in terminal groups of PLGA, seemed to have the greater influence on the mechanical  
190 properties.

191

### 192 **3.4 Water Absorption, mass loss, and MW rate decay kinetics, k**

193 The water absorption and mass loss was monitored in regards to incubation time in in-vitro  
194 conditions. The acid-terminated PLGA films, P04A and P02A, absorbed 22% and 35% water  
195 respectively after 20 days, with higher rates of water uptake from 0 – 20 days. The ester-  
196 terminated PLGA films (P103E, P04E and P02E) lie in the range of 1 – 12% after 20 days, as  
197 shown in **Fig. 4**. Rates of water absorption quickly increased after this however.

198 Rates of polymer mass loss substantially increased around the time points where water  
199 absorption had showed plateau (15 – 20 days, depending on film formulation). This exponential  
200 increase in mass loss for the acid-terminated films began ~20 days before that of the ester-  
201 terminated films. Comparing the two different MW acid-terminated films, which differed by 35  
202 kDa, it was noticed that the larger MW P04A lagged behind P02A by 5 – 10 days, as seen in Fig.  
203 5.

204 The initial MW of these films was indicated by the first time-point at day 0, listed in Fig. 6 table  
205 inset. The MW decay of these films was determined by GPC, after incubation in aqueous  
206 conditions. These films were then retrieved and dried at the predetermined time points prior to  
207 GPC analysis. The pseudo-first order degradation rate constant was calculated based on the  
208 slope of semi-log plot of MW versus time. From the rate constants, the MW half-lives ( $t_{1/2}$ )  
209 could be calculated (see **Table 1**). The acid terminated films had MW half-lives half that of the  
210 ester-terminated films, which were about 9 and 18 days, respectively for the first 20 days. The  
211 P02E kinetics displayed the slowest degradation kinetics for the first 25 days. However, this was  
212 not unusual, as higher MW PLGA has been known to have accelerated decay due to  
213 autocatalysis effects [22].

214

### 215 **3.5 Surface & Cross-sectional Morphology**

216 The surface and cross-sectional morphology of the PLGA films were characterized at x700  
217 magnification by SEM imaging at selected time intervals (see **Fig. 7**). Surface topography of  
218 dried knife-casted films before aqueous incubation reveals smooth exteriors with no pores,

219 ripples, gross phase separations. Cross-sections of the day 0 monolithic films reveal a  
220 homogenous bulk within the ~50 micron thick films. Upon incubation, the acid-terminated films  
221 revealed obvious changes in the surface and bulk properties after only 10 days; the formation of  
222 pores and channels was attributed to the fast absorption of water with subsequent mass loss  
223 (polymer and drug, see below) after this time point. After 20 days, the same features could be  
224 seen in the cross-sections of the ester-terminated films, and after 30 days, on the surface of the  
225 ester films as well.

226

### 227 **3.3 Unique drug release profiles through changes in terminal functional groups and MW.**

228 Our previously published high throughput screening method was used to give a quick initial  
229 indication of the release profiles across the five PLGA films as shown in **Fig. 8** [21]. Overall, all  
230 the fluorescein diacetate (FDAC) films remained colorless after knife casting, drying, and during  
231 in vitro release, a qualitative indication of ester-drug stability. Had the esters in fluorescein  
232 diacetate been in a labile environment, fluorescein would form, turning the PLGA films green.  
233 Cumulative release rates of FDAC increased with decreasing MW. However, when comparing  
234 acid- vs. ester-terminated PLGA films at similar MW, one can realize the considerable impact of  
235 the terminal groups. The release ‘lag time’ lies in-between the burst release (drug diffusion from  
236 the film surface) and polymer mass loss associated drug release[25]. For the P02A film, the lag  
237 time was substantially diminished for the FDAC, but was still seen in the less soluble, paclitaxel  
238 containing films (see Fig. 8). Otherwise, FDAC and PCTX had similar release curves across the  
239 other four films.

240 A blend of the highest and lowest PCTX-releasing PLGA was studied to further explore the  
241 capabilities of these polyesters. P02A and P103E were blended in the ratio 7:3 and its PCTX  
242 release profile was recorded in **Fig. 8B**. The combined release characteristics of P103E and  
243 P02A were clearly observed as its release profile lies in between that of the respective PLGA  
244 films.

245

## 246 **4. Discussion**

### 247 **4.1 Governing factors in thin film controlled drug release**

248 The degradation profiles of PLGA (and other similar polyesters), typically has the most influence  
249 concerning rates of drug release. The degradation of PLGA is dependent on several factors such  
250 as lactide:glycolide ratio, MW, terminating end-group, pH of surrounding medium, geometry,  
251 and porosity among many other factors. These parameters in turn govern the drug release, where  
252 drug parameters such as log P, solubility, MW, etc. can influence the release profiles as well  
253 [21]. Herein we investigated the influence of varying MWs and terminating end-groups on the  
254 PLGA degradation kinetics, mass loss, water absorption, and hydrophobic drug release  
255 characteristics.

256  
257 Hydrophobic drugs had been previously reported to be homogeneously distributed throughout  
258 PLGA matrices by Raman spectroscopy [20, 26, 27]. As shown in this manuscript and our  
259 previous articles, a sluggish paclitaxel release profile was seen in the terminal ester-containing  
260 films, with typical rates of 1-3  $\mu\text{g cm}^{-2}\text{ day}^{-1}$  over 30 days. To enhance the paclitaxel rate to  $> 3$   
261  $\mu\text{g cm}^{-2}\text{ day}^{-1}$ , several approaches can be employed (and have been) through non-degradable  
262 additives (i.e. polyethylene glycol [28], pluronics [29]), PLGA co-polymer grafting [30],  
263 polymer crystallinity [31], and even irradiation [32]. However, these methods lack the ability to  
264 easily tune drug release for various drugs at varying rates.

### 265 266 **4.2 Two methods of controlling drug delivery: increasing acid-terminating groups [COOH] 267 vs. varying PLGA MWs**

268 A method that has yet to be exploited for tuned drug delivery involves subtly controlling the  
269 chemistry of the PLGA polymer-end groups. As shown in results, acid versus ester-terminating  
270 groups on PLGA polymers substantially changes several film properties (water absorption, mass  
271 loss, polymer degradation), but have little to no effect on other properties (mechanical,  $T_g$ , and  
272 wetting tension). The latter properties will likely change after in vitro incubation however. It is  
273 generally known that drug release can be controlled through different PLGA MWs,  
274 lactide/glycolide ratios, or drug-loading/polymer ratios. These options do not allow a wide range  
275 of controlled release rates (order of magnitude or more), especially concerning time frames

276 between 1- 6 weeks. We believe that by controlling the matrix conc. of acid-terminating groups  
277 on PLGA polymers, a wide range of control can be established, perhaps in a predictable manner.  
278 Fig. 9 attempts to compare how drug release and the mechanical properties may be controlled  
279 independently; 1) normalized increases in acid-terminating groups [COOH] within PLGA films  
280 and 2) varying MWs of PLGA. It is readily apparent that increasing the acid-terminating groups  
281 per sq. cm yielded a linear and predictable cumulative release after 30 day with all  $R^2$  values  $>$   
282 0.95. Similar analyses based on changes in MW (for controlled drug delivery) yielded only a  
283 trend that as MW increases, controlled drug delivery decreases, with no predictive-statistics  
284 possible ( $R^2$  values  $\ll 0.95$ , data not shown). However, PLGA MW did display a strong  
285 correlation with the mechanical properties, which may allow properties such as yield strength  
286 and tensile strength to be independently adjusted (see below).

287

#### 288 **4.3 Correlations of Cumulative Release of Paclitaxel vs. water absorption, mass loss, and** 289 **pseudo-first order rate constant, $k$ .**

290 **Table 3** displays the results of a Pearson's correlation analysis between paclitaxel release, water  
291 absorption, mass loss, and rate constant  $k$ . Significant correlations were seen between drug  
292 release/mass loss and mass loss/rate constant  $k$ . The least correlated was drug release/water  
293 absorption. These correlations suggest the mechanism of paclitaxel release was not by pore  
294 diffusion or transport through the polymer, but subsequent release into the medium as the eroded  
295 PLGA oligomers become ever more soluble as their MW decayed [33]. Thus, any approach that  
296 wanted to tune the release of hydrophobic drugs, such as PCTX, would need to take such  
297 mechanisms of release into consideration [34].

298

#### 299 **4.4 PLGA\PLGA Blending could allow independent selection of mechanical properties and** 300 **controlled drug release profiles.**

301 In the combination of the fastest (P02A) and slowest degrading PLGA (P103E), a linear release  
302 based on the substituent blends was achieved, suggesting that a combination of PLGA blends  
303 could tune the release of PCTX to specific rates a formulation scientist would desire. Our data  
304 analysis suggested such blends would not significantly change the wetting tension, or  $T_g$ . The  
305 mechanical properties may be modified independently by adjusting MW. Ideally, PLGA MW  
306 ratios (weight-averaged molecular weight and polydispersity) could be exploited to

307 independently select physical properties, while ester/acid terminal end-group ratios could be used  
308 to alter the hydrophobic drug release. Our follow up investigation (manuscript in preparation)  
309 will describe our results towards this end, employing our recently developed gradient film-  
310 casting techniques [35].

311 **5. Conclusion**

312 The exploitation of commercially available PLGAs with varying MWs and terminal end groups  
313 may allow array of parameters that could be used to adjust drug release profiles and mechanical  
314 properties, without the use of additives. Typically, the degradation of PLGA of a certain MW is  
315 determined by its lactide/glycolide ratio, device geometry, and inclusion of additives. In this  
316 study, lactide/glycolide ratio and device geometry were kept constant, with no addition of  
317 additive except that of hydrophobic drug. Only the MW and terminating end-groups of PLGA  
318 polymer were changed to explore their differences in  $T_g$ , mechanical properties, water  
319 absorption, mass loss, kinetic rate constant  $k$ , and drug release profiles. PLGA MW tended to  
320 influence the  $T_g$  and mechanical properties the most, while an acid versus ester terminal end-  
321 groups in the PLGA polymer films tended to have more influence on water absorption, mass  
322 loss, kinetic rate constant  $k$ , and drug release profiles. A blend of the slowest and fastest  
323 degrading PLGAs gave rise to an intermediate PCTX release profile. This suggests that by  
324 varying terminal polymer end-groups, the possibility exists to modulate the release of  
325 hydrophobic paclitaxel through PLGA/PLGA blends alone, without the use of additives. Our  
326 follow up investigation (manuscript in preparation) will describe our results towards this end.

327

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335

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457 Fig. 9. Relationships of how acid terminal polymer end-groups control paclitaxel release and how  
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464 (Purac Asia Pacific Pte Ltd, Singapore). ( $r$ ) = Pearson's correlation,  $n=5$  (P02A, P02E, P04A, P04E, and  
465 P103E). Numbers in parentheses are std. dev.

466

Table 1. Summary of the abbreviations used for PCTX-PLGA films and their respective physiochemical characteristics.

Sample/ (Initial MW)	Abbreviation	MW (kDa)	Inherent Viscosity (dL/g)	Thickness ( $\mu\text{m}$ )	Half-life ( $\text{g/mol}\cdot\text{day}^{-1}$ )
PCTX-PLGA Ester	P103E	110	1.03	$49 \pm 2$	$16.12 \pm 0.002$
PCTX-PLGA Ester	P04E	50	0.4	$48 \pm 2$	$18.24 \pm 0.003$
PCTX-PLGA Acid	P04A	40	0.4	$54 \pm 2$	$8.06 \pm 0.003$
PCTX-PLGA Ester	P02E	20	0.2	$38 \pm 2$	$57.76 \pm 0.002$
PCTX-PLGA Acid	P02A	15	0.2	$45 \pm 2$	$9.90 \pm 0.006$

Table 2. Summary of the mechanical properties for each film formulation.

Film Sample	Tensile Modulus (MPa)	Yield Strength (MPa)	Tensile Strength (MPa)	Elongation at Break (%)
P103E	$3.74 \pm 1.56$	$2.30 \pm 0.07$	$5.60 \pm 0.23$	$496 \pm 9$
P04E	$2.90 \pm 0.98$	$0.56 \pm 0.06$	$0.60 \pm 0.05$	$562 \pm 116$
P04A	$1.10 \pm 0.15$	$0.47 \pm 0.03$	$0.60 \pm 0.04$	$635 \pm 73$
P02E	$0.61 \pm 0.21$	$0.32 \pm 0.06$	* $0.32 \pm 0.01$	**
P02A	$0.58 \pm 0.08$	$0.38 \pm 0.01$	* $0.41 \pm 0.01$	**

\* Tensile strength measured at end-point at 750% strain.

\*\* Elongation of films > 750%, exceeding the limits of the Instron tensile tester.

Table 3. Pearson's correlations among the physical and chemical properties calculated.

	Pearson's <sup>†</sup> Correlations	Rate constant (k)	PCTX Release @ 30 days	Mass Loss @ 30 days	Water absorption @ 30 days
Rate constant (k)	Pearson Corr. (r)	1	0.765	<b>0.919</b>	0.851
	Significance	--	0.132	<b>0.027</b>	0.067
PCTX Release @ 30 days	Pearson Corr. (r)	0.765	1	<b>0.902</b>	0.459
	Significance	0.132	--	<b>0.037</b>	0.436
Mass Loss @ 30 days	Pearson Corr. (r)	<b>0.919</b>	<b>0.902</b>	1	0.790
	Significance	<b>0.027</b>	<b>0.037</b>	--	0.112
Water absorption @ 30 days	Pearson Corr. (r)	0.851	0.459	0.790	1
	Significance	0.067	0.436	0.112	--

<sup>†</sup>2-tailed test of significance is used (n =5). Significance (bold type) was determined if p < 0.05.

Fig. 1.

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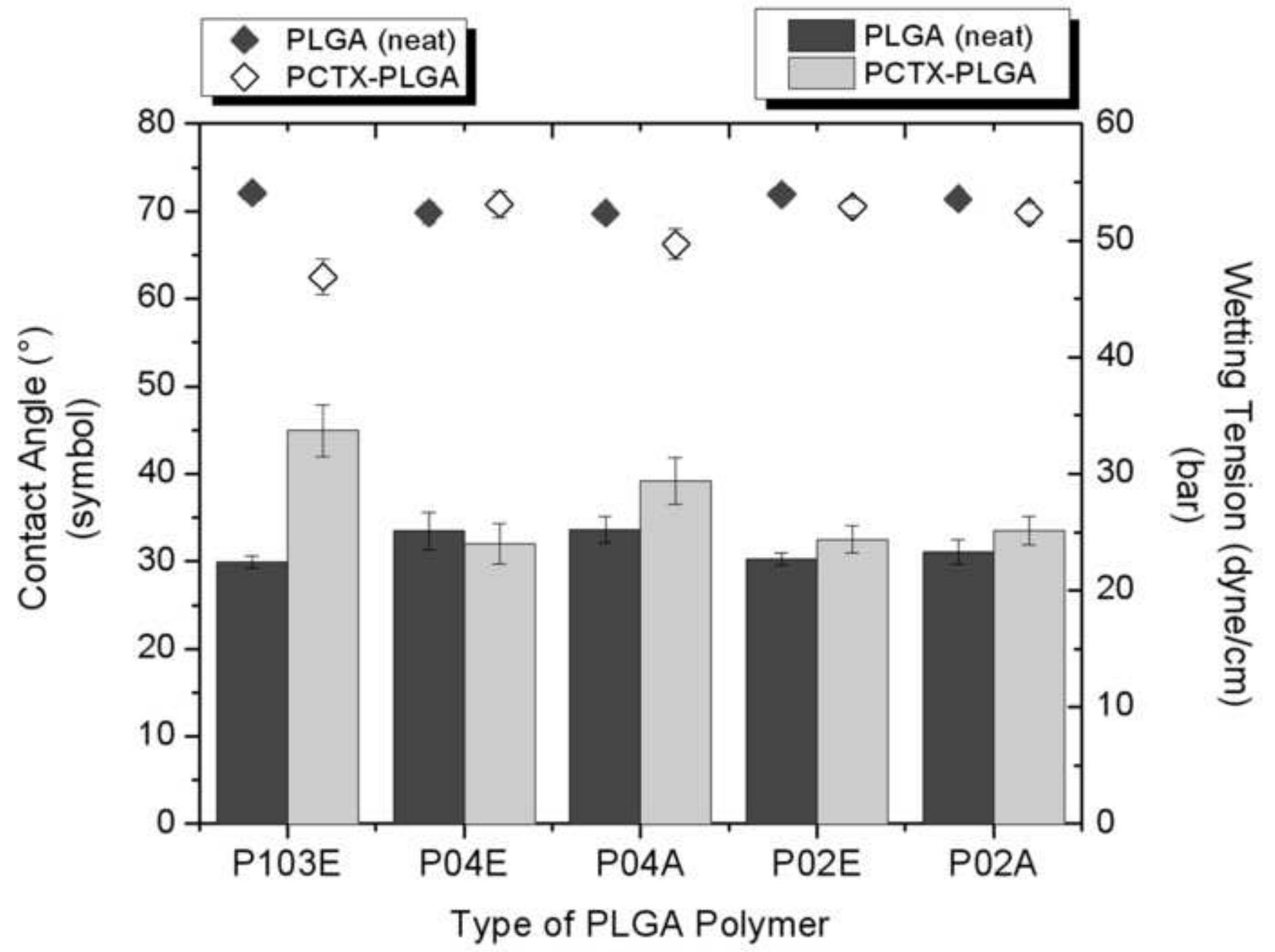


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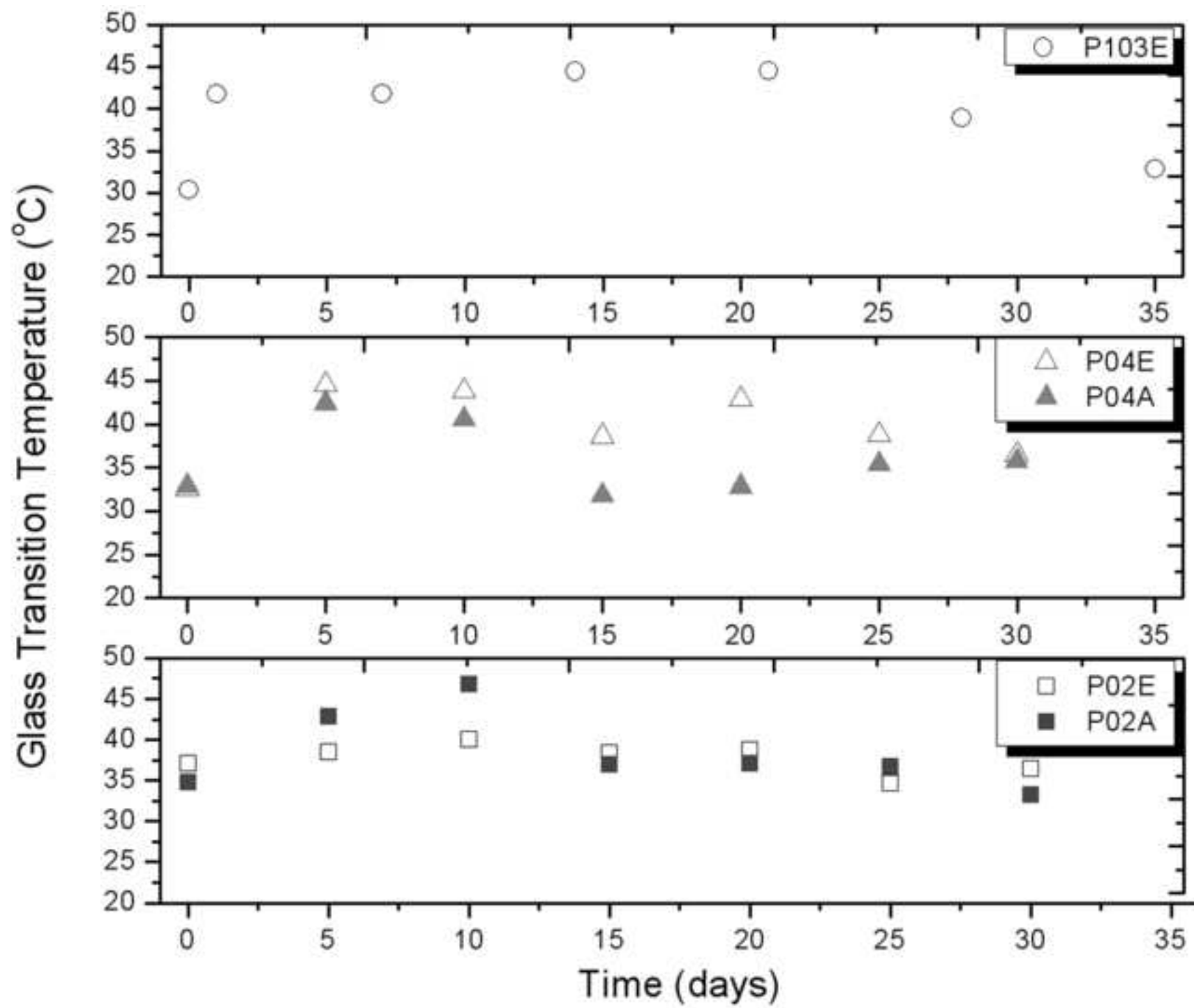


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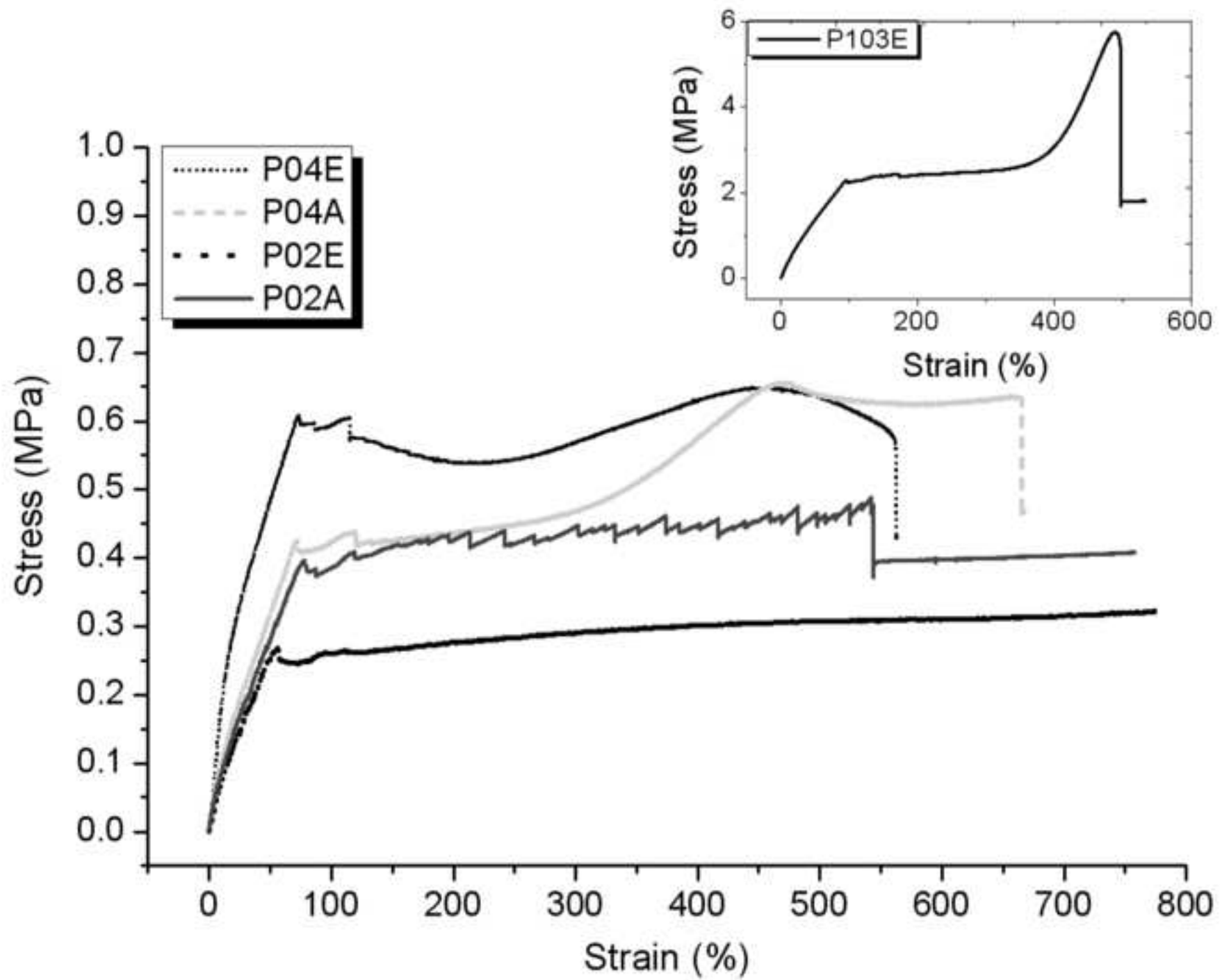


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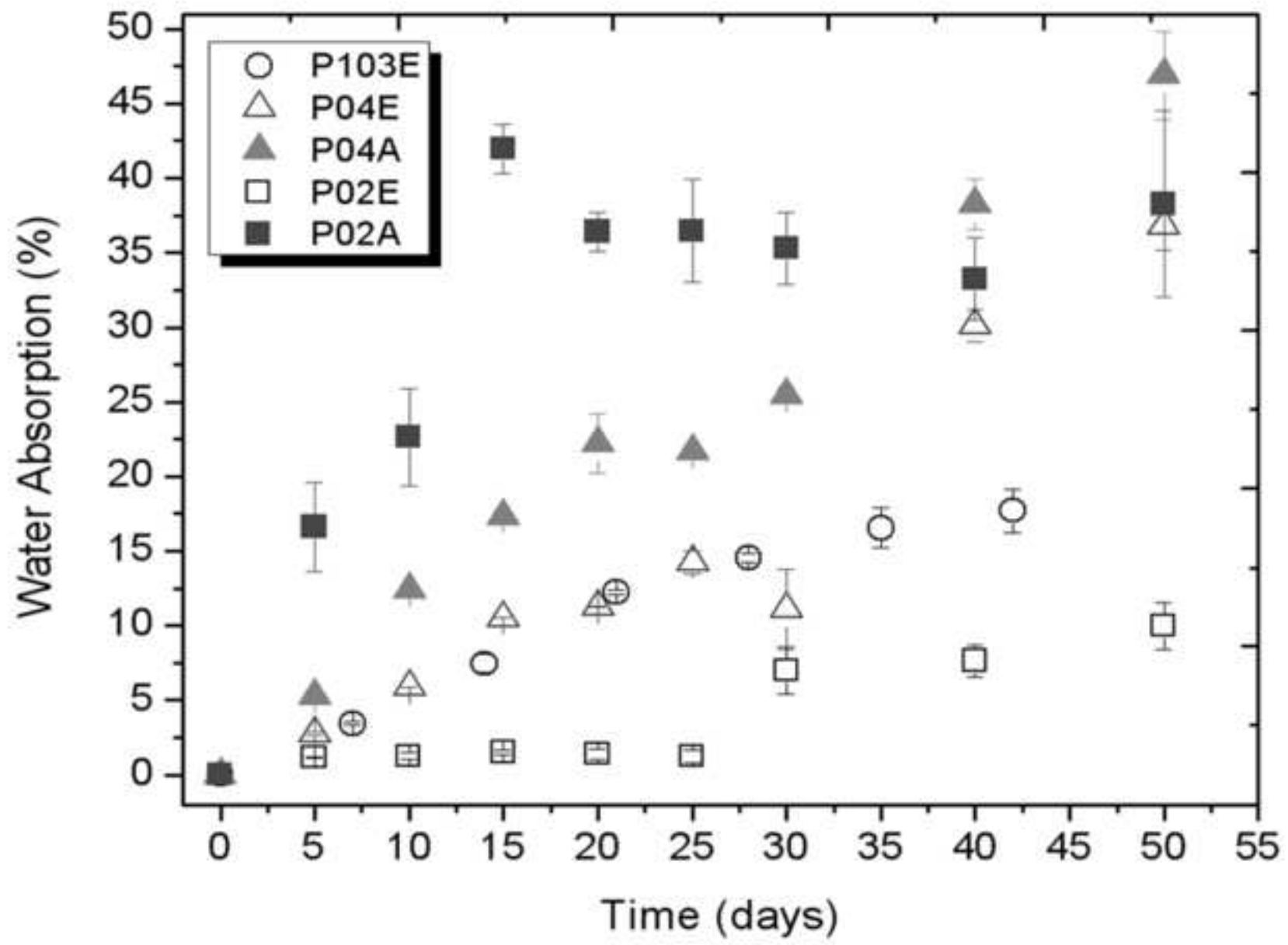


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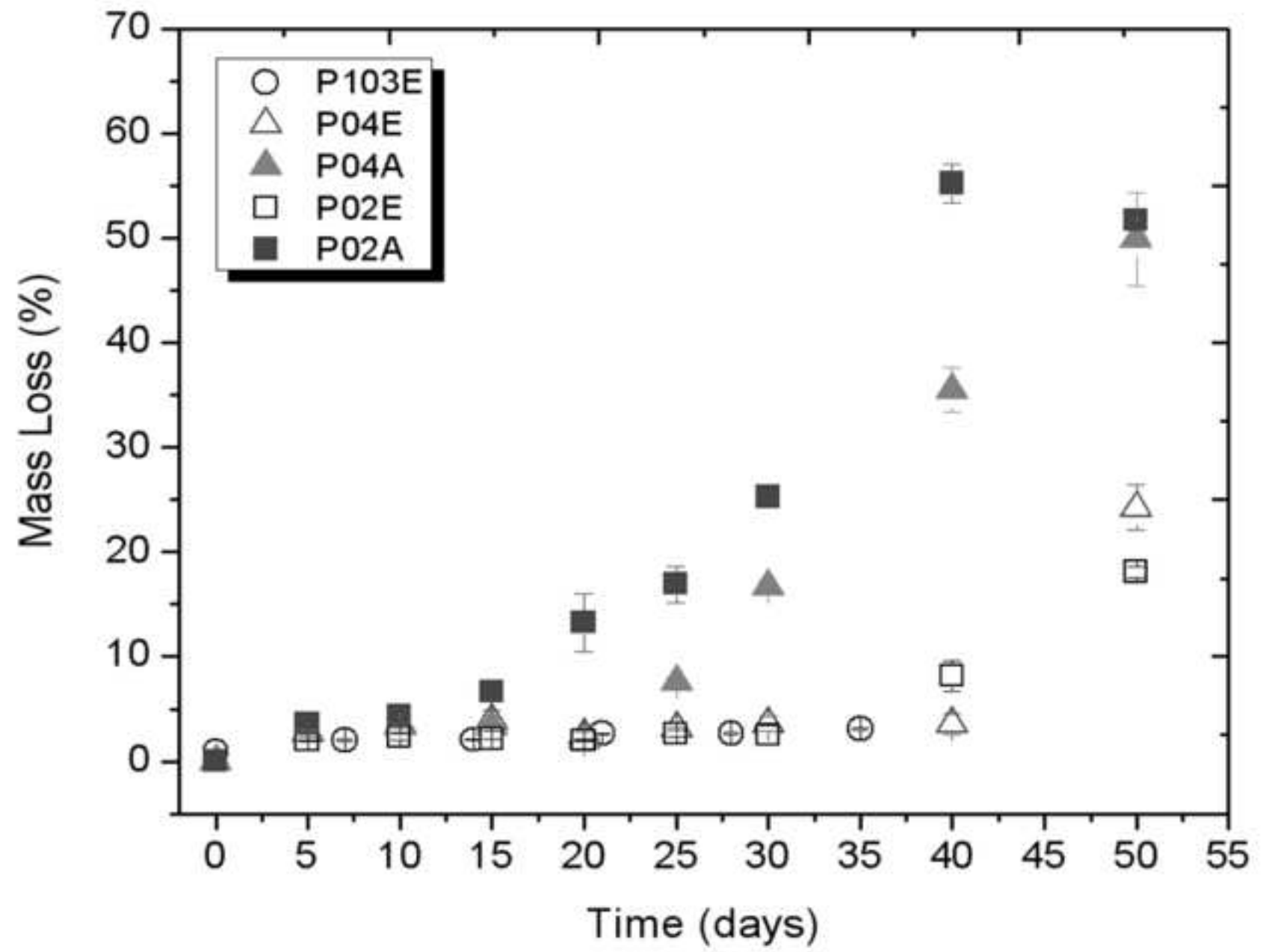


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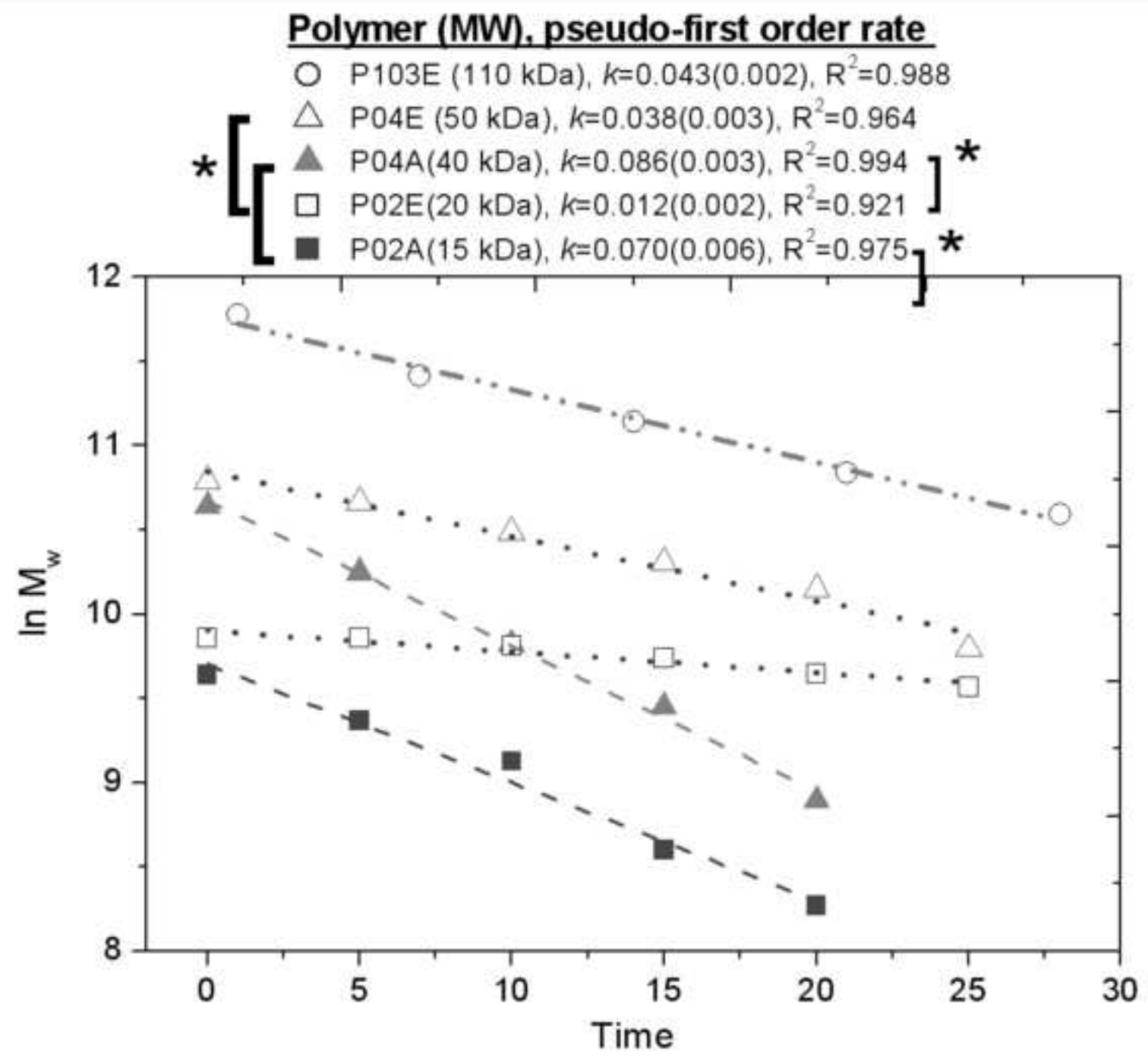


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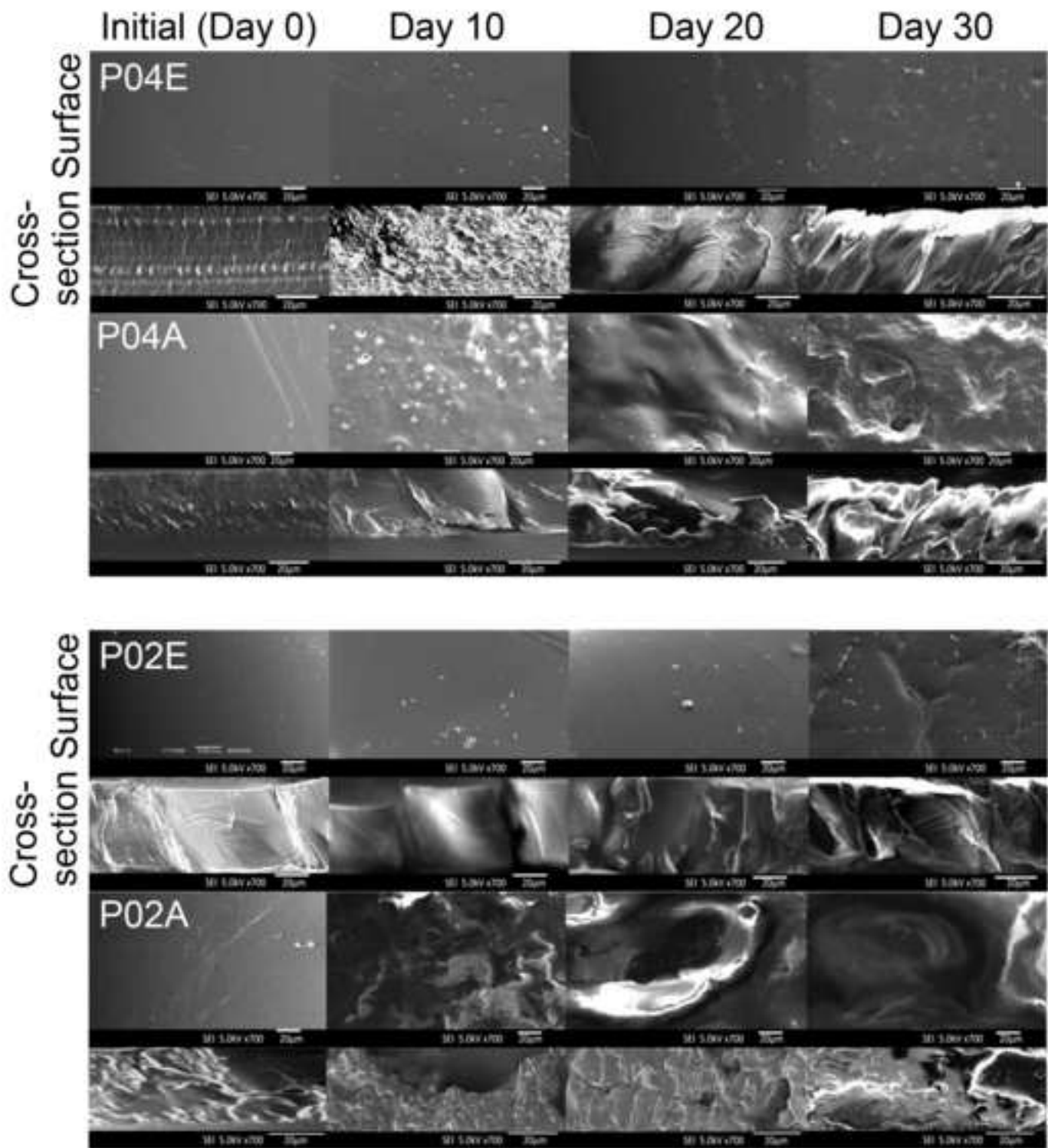


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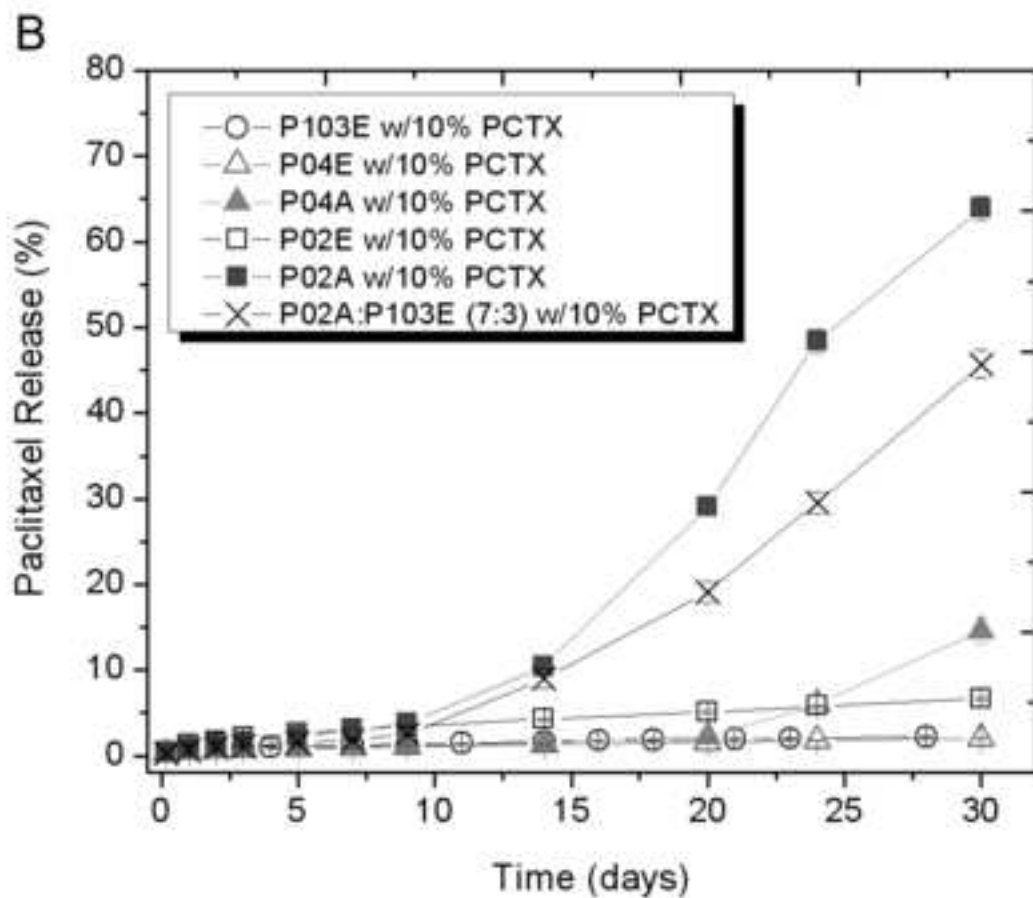
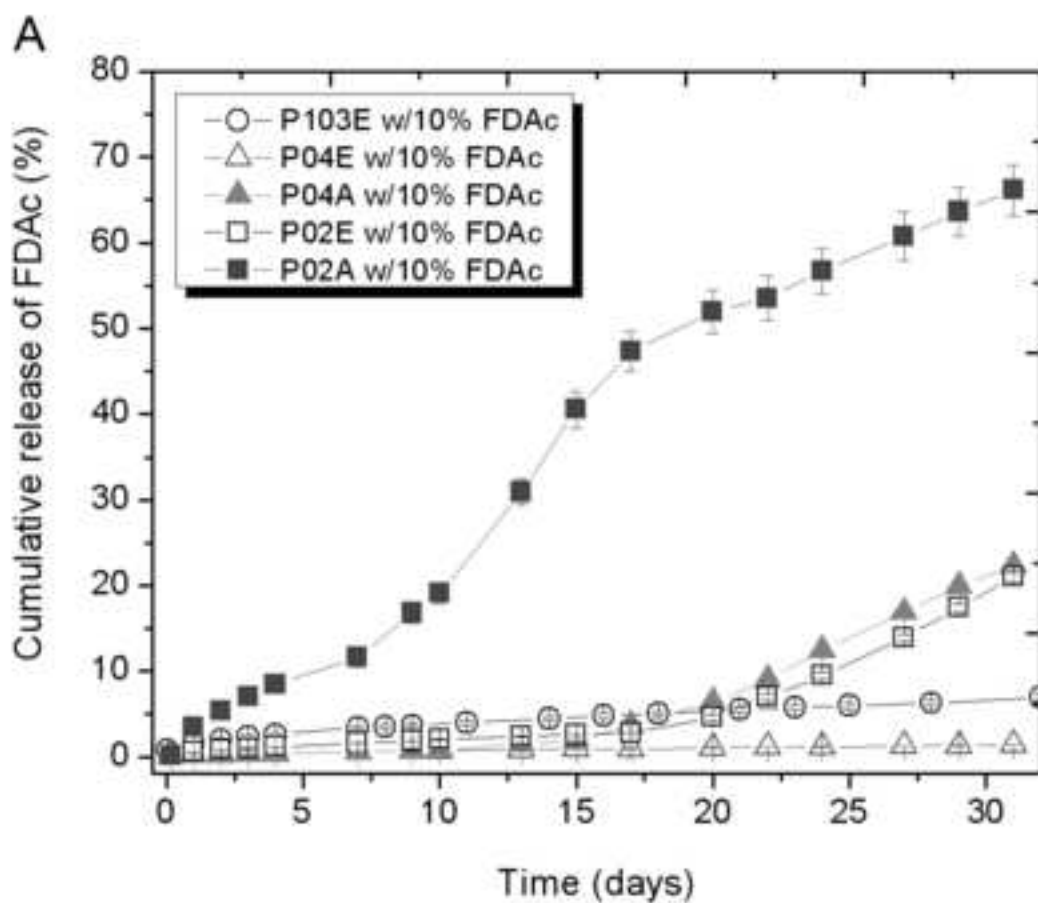


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