# Modulating drug release from poly(lactic-co-glycolic acid) thin 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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# Cover Letter

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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

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

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

## 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.

## 1. Introduction

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

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

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

## 2. Materials & Methods

### 2.1 Materials

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

### 2.2 Methods

***Film Preparation***

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

***Surface Hydrophobicity***

Films were cut into rectangular strips (3 cm × 1 cm) and their surface properties analyzed by contact angle and wetting tension using a static sessile drop technique on a contact angle goniometer. The static measurements were carried out at room temperature at five locations, with distilled $H_2O$ being pumped out at a rate of 5 μL/s. A still image was captured for analysis after allowing the droplet to relax for 10 s and analyzed with FTA32 software, version 2.0 build 276.2.

***In-vitro Paclitaxel/FDAc Release Study (as previously described and cite)***

The *in-vitro* release of paclitaxel (PCTX) was conducted in 2 mL of PBS spiked with 2% Tween 80 in release buffer (pH 7.4) at 37 $^{o}$C, using 1 cm × 1 cm cut-outs, in triplicate. At predetermined

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

The *in-vitro* release of FDAc was monitored by Fluorescence Microplate Reader (Tecan, Seestrasse, Männedorf, Switzerland). Sodium hydroxide (100 mM, 180μl) was first added into the wells of the 96-well Greiner black plate. Subsequently 20μL of aliquot was pipetted into the wells of the microarray plate. The fluorescence units were recorded and its concentration calculated from standard curves set up at various gain settings.

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

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

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

***Mechanical Properties***

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

***Thermal Analysis***

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

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

***Data Analysis***

Linear regressions and Pearson's correlations were calculated with Origin 8.5 SR1. Linear regression was determined with No Weighting. Pearson's correlations (r) were determined with a 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

## 3. Results

### 3.1 Surface Hydrophobicity

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

### 3.2 Thermal & Mechanical Properties

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

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

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

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

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

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

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

### 3.5 Surface & Cross-sectional Morphology

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

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

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

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

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

## 4. Discussion

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

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

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

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

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

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

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

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

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

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

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

## 5. Conclusion

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

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List of Figures

Fig. 1. Contact angle and wetting tension measurements of neat PLGA and PCTX-PLGA films. The surface hydrophobicity of the films remained the same despite variation in MW and terminating end-groups on PLGA.

Fig. 2. Glass transition temperature ($T_g$) of the PLGA films with degradation time. The decreasing $T_g$ indicates increasing chain mobility in the PLGA films.

Fig. 3. Representative stress-strain curves of the PLGA films. A significant reduction in tensile properties in lower MW PLGA films was recorded under *in-vitro* conditions as compared to P103E.

Fig. 4. Plot of water absorption with degradation time. The acid-terminated PLGA films generally showed higher water uptake than ester-terminated films.

Fig. 5. Plot of mass loss with degradation time. The acid-terminated PLGA films generally showed higher mass loss than ester-terminated films.

Fig. 6. Log plot of MW decay with degradation time. The acid-terminated PLGA experienced a higher degradation rate as compared to the ester-terminated PLGA films. The solid symbols represent acid-terminated PLGA films up to day 20, while the open symbols represent ester-terminated PLGA films up to day 25. Significance, *, was $p > 0.95$. Numbers in parentheses are std. dev.

Fig. 7. SEM micrographs showing the surface and respective cross-sectional morphology of the low MW PLGA films, namely in sequence P04E, P04A, P02E and P02A.

Fig. 8. A) Plot of cumulative release of FDAc with time for initial screening of the various PLGA films. FDAc/P02A, the lowest acid-terminated MW film showed the fastest release of FDAc as compared to the other PLGA films. B) Cumulative plot of paclitaxel release against time for neat and PLGA blend consisting of P02A:P103E in the ratio 7:3. The onset of rapid release of paclitaxel in acid-terminated PLGA films occurred earlier, depending on the initial amount of carboxylic terminal end-groups.

Fig. 9. Relationships of how acid terminal polymer end-groups control paclitaxel release and how intrinsic viscosity/MW can influence the mechanical properties. A) Cumulative release of FDAc and PCTX at 30 day plotted against normalized concentration of terminal acid-groups, [COOH]. Data taken from: Fig. 08A- P04E, P04A, and P02A for 0, 0.33, and 1.0 initial [COOH], respectively; Fig. 08B- P04E, P04A, 7:3 P02A:P103E and P02A for 0, 0.33, 0.7, and 1.0 initial [COOH] Normalized initial [COOH] value was set using P02A films. Numbers in parentheses are std. dev. B) Tensile modulus, yield and tensile strength vs. intrinsic viscosity (dL/g). Intrinsic viscosity data provided by manufacturer (Purac Asia Pacific Pte Ltd, Singapore). (r) = Pearson's correlation, n=5 (P02A, P02E, P04A, P04E, and P103E). Numbers in parentheses are std. dev.

**Table**

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 (µm) | Half-life ($g/mol.day^{-1}$) |
|---|---|---|---|---|---|
| PCTX-PLGA Ester | P103E | 110 | 1.03 | 49 ± 2 | 16.12 ± 0.002 |
| PCTX-PLGA Ester | P04E | 50 | 0.4 | 48 ± 2 | 18.24 ± 0.003 |
| PCTX-PLGA Acid | P04A | 40 | 0.4 | 54 ± 2 | 8.06 ± 0.003 |
| PCTX-PLGA Ester | P02E | 20 | 0.2 | 38 ± 2 | 57.76 ± 0.002 |
| PCTX-PLGA Acid | P02A | 15 | 0.2 | 45 ± 2 | 9.90 ± 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 ± 1.56 | 2.30 ± 0.07 | 5.60 ± 0.23 | 496 ± 9 |
| P04E | 2.90 ± 0.98 | 0.56 ± 0.06 | 0.60 ± 0.05 | 562 ± 116 |
| P04A | 1.10 ± 0.15 | 0.47 ± 0.03 | 0.60 ± 0.04 | 635 ± 73 |
| P02E | 0.61 ± 0.21 | 0.32 ± 0.06 | *0.32 ± 0.01 | ** |
| P02A | 0.58 ± 0.08 | 0.38 ± 0.01 | *0.41 ± 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† 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 | **0.919** | 0.851 |
| | Significance | -- | 0.132 | **0.027** | 0.067 |
| PCTX Release @ 30 days | Pearson Corr. (r) | 0.765 | 1 | **0.902** | 0.459 |
| | Significance | 0.132 | -- | **0.037** | 0.436 |
| Mass Loss @ 30 days | Pearson Corr. (r) | **0.919** | **0.902** | 1 | 0.790 |
| | Significance | **0.027** | **0.037** | -- | 0.112 |
| Water absorption @ 30 days | Pearson Corr. (r) | 0.851 | 0.459 | 0.790 | 1 |
| | Significance | 0.067 | 0.436 | 0.112 | -- |

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

Fig. 1.

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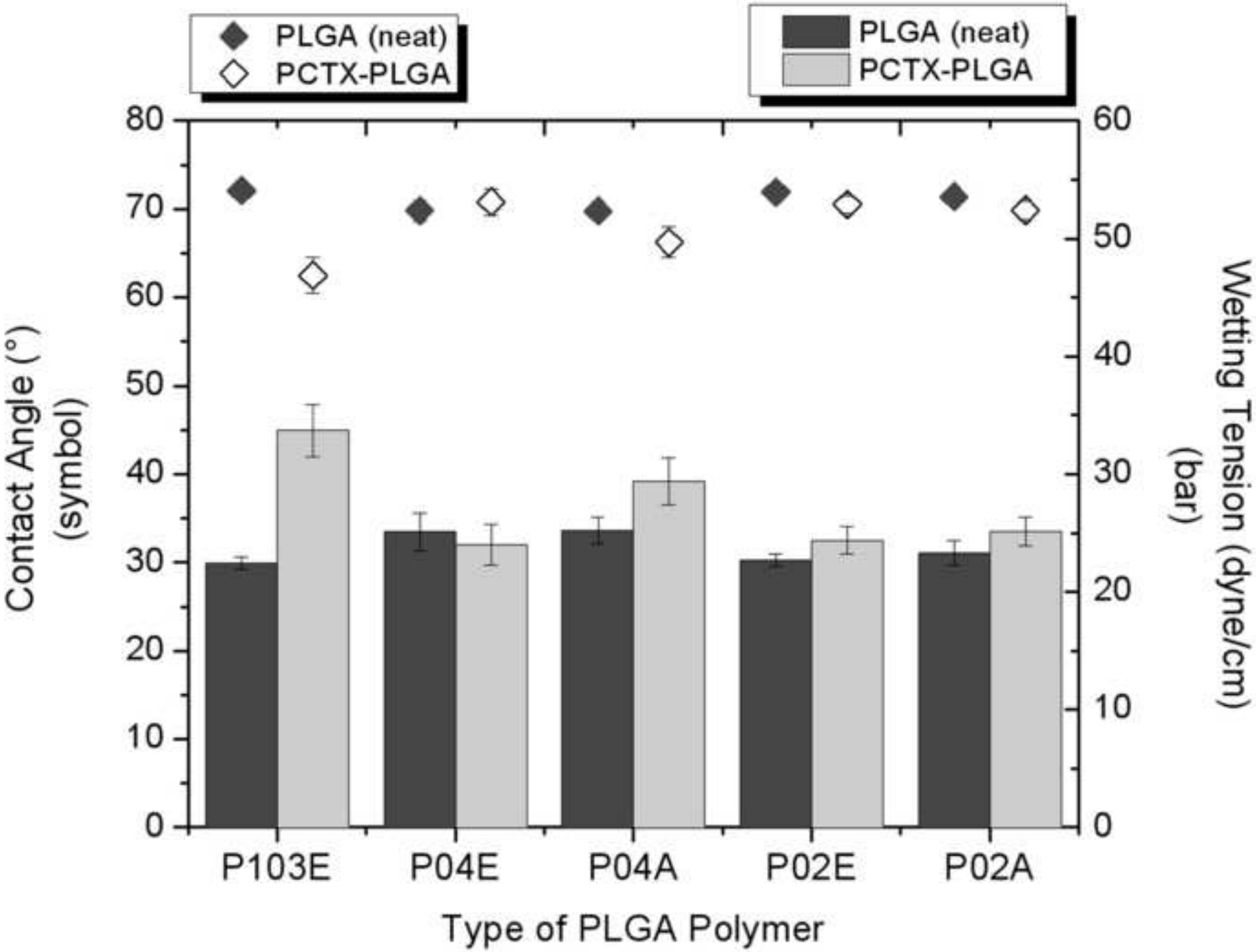

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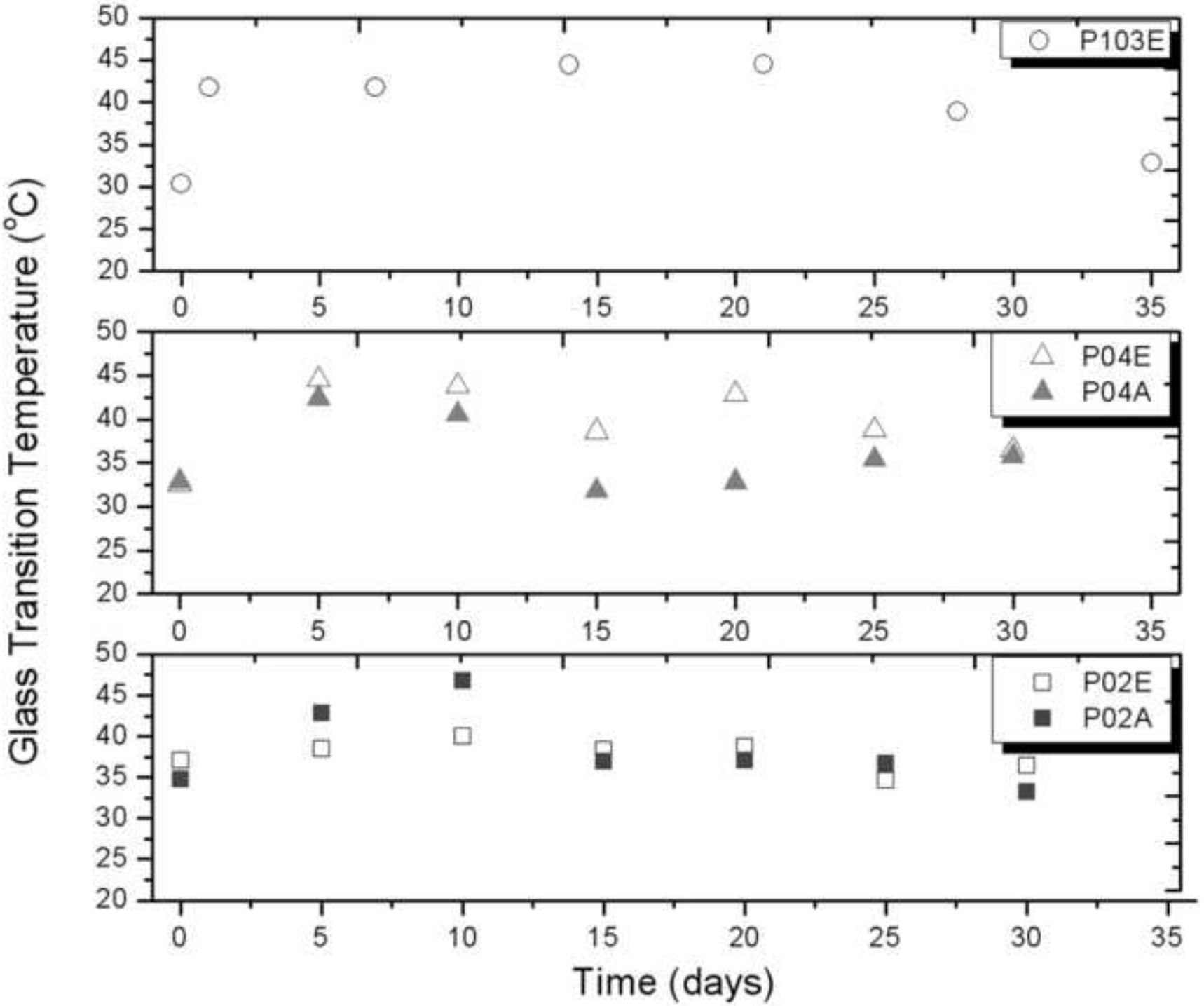

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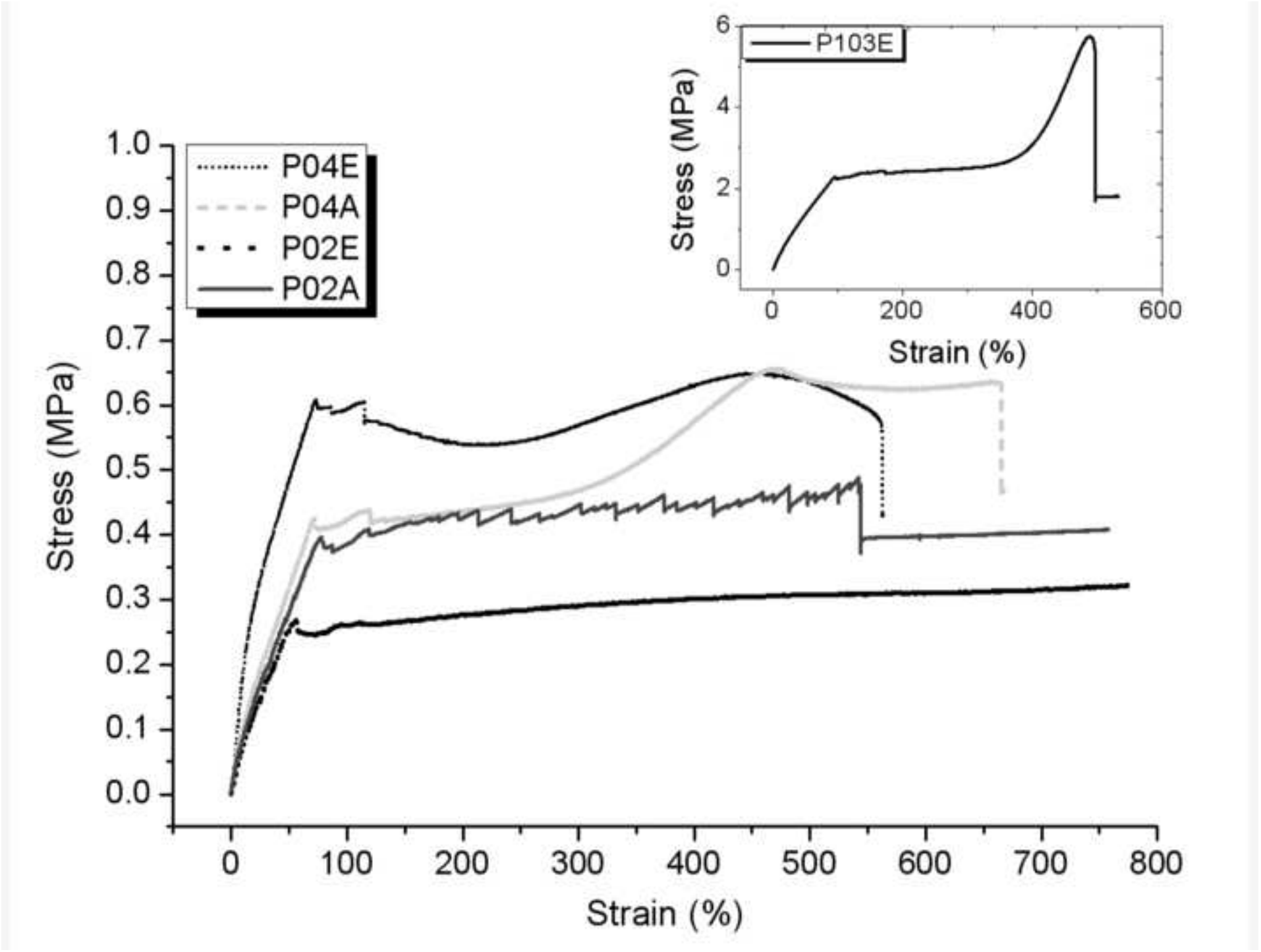

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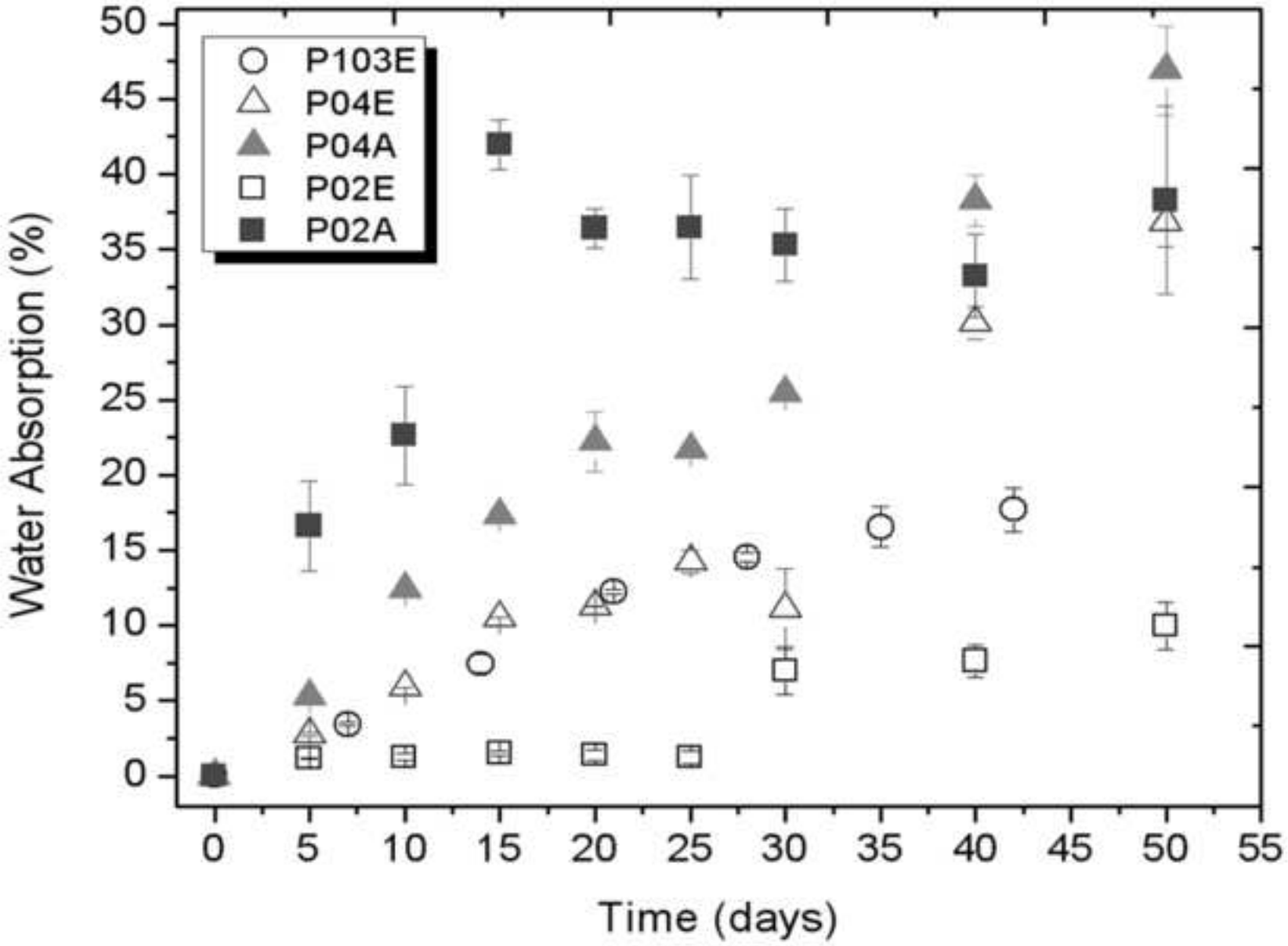

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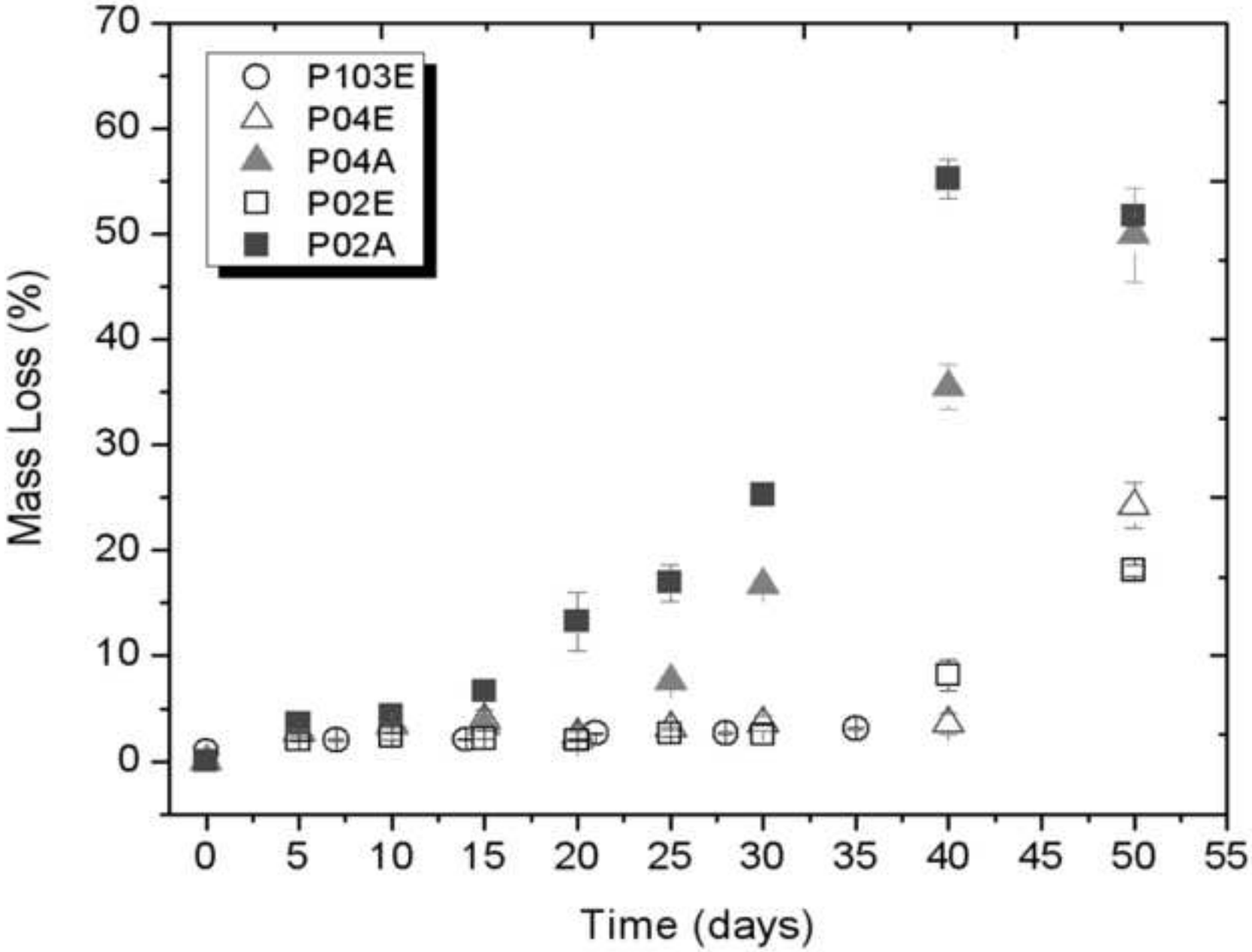

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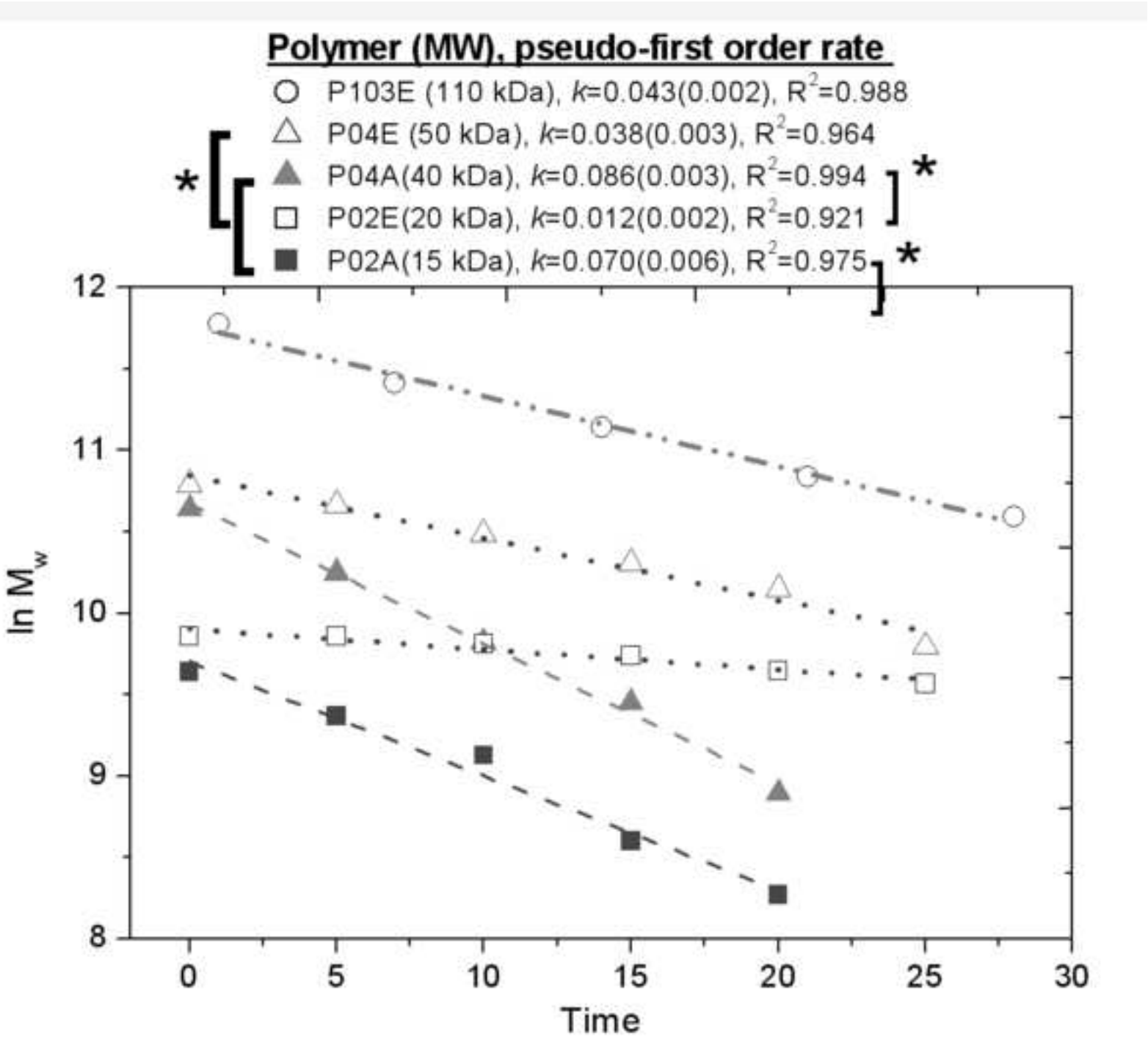

**Fig. 7.**

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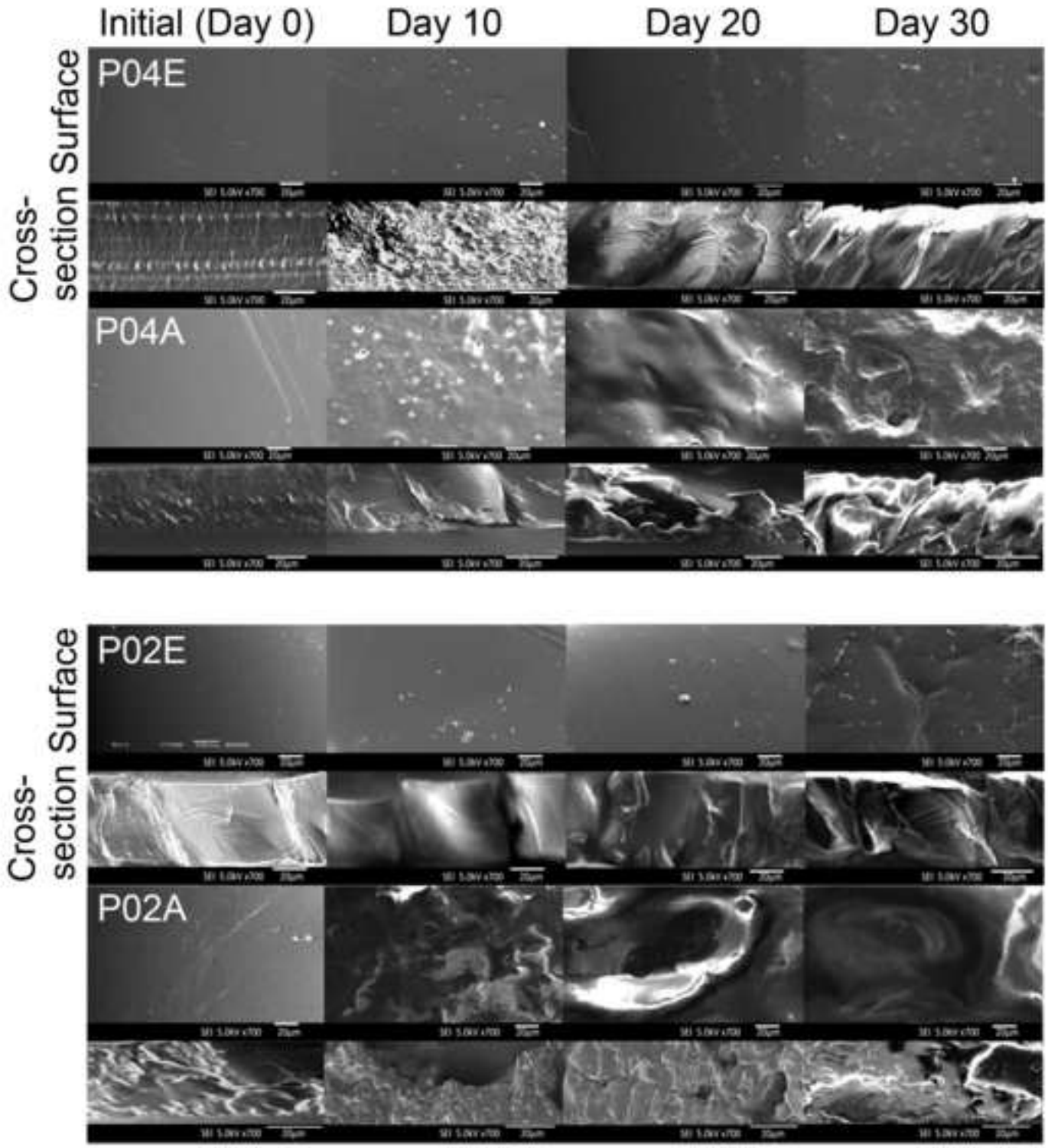

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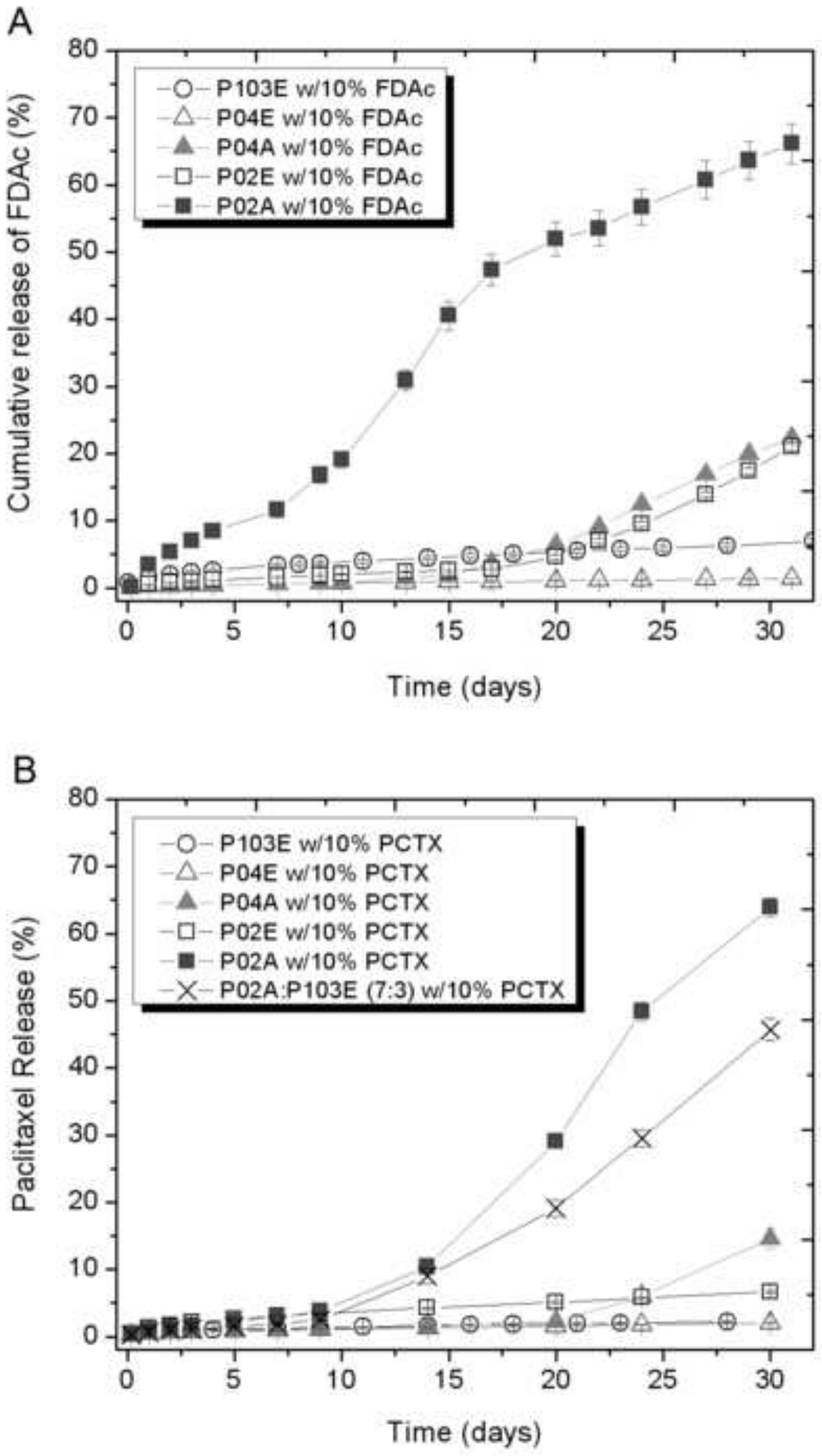

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