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제조조건에 따른 생분해성 PDO 필라멘트의 물리적 특성

최상선 · 이준혁* · 이순홍†

안양대학교 환경공학과, *한양대학교 화학공학과

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Physical Nature of Biodegradable Polydioxanone Filaments upon Synthetic Conditions

Sang Sun Choi, Joon Hyuk Lee*, and Soon Hong Lee†

Department of Environmental Engineering, Anyang University, Anyang 14028, Korea
**Department of Chemical Engineering, Hanyang University, Seoul 04763, Korea*

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초록: 의학분야에서 polydioxanone(PDO)는 생체 안전성, 생분해도 및 기계적 강성의 이점으로 인해 기초적 및 실용적 연구 분야에서 큰 관심을 받고 있다. 선행연구 결과에서 PDO의 생화학적 구조는 증명되었으나, 단계별 제조조건 중 촉매와 세척 간 상관관계가 PDO의 물리적 특성에 미치는 영향에 대한 연구는 미미한 실정이다. 따라서 본 연구에서는 PDO의 촉매와 세척의 변화에 따른 물리적 강성 및 생분해도의 변화를 추적하였다. 샘플 중 가장 많은 ppm의 촉매(30 ppm)와 진공세척시간(3시간)을 도입한 PDO-3-30 샘플은 물리적 특성에서 가장 우수한 결과를 도출하였으나, 열역학 및 생분해도에서는 타 샘플대비 상대적으로 낮은 결과를 드러냈다. 모든 샘플의 특성을 비교하였을 때, 촉매의 양은 중합에서 가장 중요한 역할을 한다. 여기에서, 세척등급 또한 보다 세밀한 PDO 필라멘트의 물리적 특성을 제어할 수 있는 보조조건이 될 수 있다.

Abstract: In the medical field, polydioxanone (PDO) has increasingly attracted scientific interests in both fundamental research and applications for synthesizing sutures due to its safety, biodegradability, and mechanical strength. Chemical pathways of the aforementioned architecture have already been proven via a plethora of multidisciplinary researches, however, the physical nature of PDO filaments by each stage of the synthetic condition has yet been solely observed in detail. The scope of the present study tracks a couple of pre- and post-fiberation to tailor the success in tunable physical strength with the variance of purification time and the dosage of a catalyst. We first fabricated PDO filaments using lauryl alcohol ($C_{12}H_{26}O$) and stannous octoate ($C_{16}H_{30}O_4Sn$) as an initiator and a catalyst, respectively. PDO-3-30 with 3 h of vacuum purification and 30 ppm dosage of a catalyst led to unfavorable thermal properties and degradability but an increase in physical properties including tensile, flexural, and Izod impact strengths. From thermal and physical profiles, it was confirmed that the amount of a catalyst is a major driving factor of polymerization while the degree of purification could be an additive aid for more sensitive control of the physical nature of PDO filaments.

Keywords: polydioxanone, suture wire, catalyst, purification, physical strength.

Introduction

Sutures and surgery have been tied together throughout the history of modern medical therapeutics, since the first use of metal wires to set a broken humerus in 1775.[1] One way to classify sutures is with respect to their synthetic materials, i.e., non-degradable and biodegradable. Non-degradable sutures have been taking center stage over recent decades using titanium and its alloys, nitinol, and stainless steels for various medical applications including orthopedic surgery and sternal closure in cardiac surgery.[2,3] In all cases, non-degradable sutures require a secondary surgical event for removal regardless of the duration time in the human body. In this regard, biodegradable sutures may present an appealing alternative to traditionally used non-degradable sutures. In addition to not necessitate a secondary operation for removal, the biodeg-

†To whom correspondence should be addressed.
leesh@anyang.ac.kr, ORCID 0000-0002-9585-3836

radation offers a slow transfer load to the healing bone and also has a potential use for drug delivery in conjunction with medical devices.[4,5] With the advent of synthetic polymers such as polylactic acid, polycaprolactone, and polydioxanone (PDO), the research and development for medical applications has boosted in recent years.[6] Herein, PDO filaments have received wide attention for wound-closure sutures as early reported in clinical studies.[7,8] The ideal suture should possess nontoxicity, biodegradability, and mechanical strength. As a suture, PDO filaments have revealed an attractive safety profile and complete degradation from previous *in vivo* studies.[9,10] Moreover, a driving motivation for PDO filaments is their usefulness in high-stressed applications with high crystallinity and mechanical strength.[11]

It is evident that many sutures were developed by envisaging the trinity of requirements. Notably, the use of sutures coupled with robotic technology has enabled teleoperated surgery under harsh conditions for provisional exploration missions.[12] With this content, one may assume that exhibiting the excellent mechanical strength before the degradation could influence the range of its potential clinical applications. However, high-tensile strength sutures could cut through tendon tissue in regard to the rotator cuff and other tendon repairs.[13] Thus, utilizing the physics in conjunction with contextual chemistry could aid for a professional and structural design of sutures which may meet all the complexity of mechanical properties. Based on the material-by-synthesis approach, we observe the physical nature of PDO filaments by each stage of synthetic condition. PDO is a semi-crystalline polymer with a glass transition temperature of -10 ºC and a melting temperature of 110 ºC. For successive polymerization, the removal of impurities from the catalyst is one crucial factor since the impurity may influence the polymer growth and mechanical strength of the final product. There have been a plethora of attempts to bridge the gap between mechanical properties and suitable chemical aids, however, the influence of purification is hampered by the lack of experimental studies.[14,15] To the best of our knowledge, this is the sole report that fully observes the influence of purification over the physical nature of PDO filaments. In the present study, we synthesized PDO filaments by varying the purification and chemical dosage. Thereafter, mechanical and degradation properties of prepared PDO filaments were analyzed using the *in vitro* degradation with an emphasis on the effects of purification and polymerization characteristics. Throughout our experiments, we hypothesized that the overall characteristics of PDO filament depends on the purification as well as the dosage of a catalyst. We also postulated that this finding could contribute to expanding the range of medical-grade sutures for further surgical functionality.

Experimental

Materials and the Synthesis of PDO Filaments. Polymerization solutions were prepared by dissolving p-dioxanone as a monomer with lauryl alcohol ($C_{12}H_{26}O$) and stannous octoate ($C_{16}H_{30}O_4Sn$) as an initiator and a catalyst, respectively. All chemicals were purchased from Sigma-Aldrich and used without further purification unless otherwise specified. About 200 mL of reagent grade of toluene were added in a three-necked polymerization flask and heated by means of temperature up to 150 ºC. One cleaned boiling chip was added to control bubbling for preparing toluene with its boiling temperature of 111 ºC. After the reflux for 3 h, stannous octoate was added by syringe for the purification with respect to the time variance of 1, 2, and 3 h.[16] As depicted in Figure 1, purification enables the removal of cumulative groups such as H-C-X and/or H-C-O. Herein, X represents the single group of electronegative atoms including F, Cl, and Br. Lastly, toluene was evaporated off under the nitrogen steam and the residue was dried under vacuum at room temperature. Herein, samples were namely labeled by the purification time and the concentration (ppm) of a catalyst; PDO-1-20, PDO-1-30, PDO-2-20, PDO-2-30, PDO-3-20, and PDO-3-30. In sum then, bulk polymerization was successfully modulated via oil bath.

The typical procedure used to prepare the PDO filaments was as follows. Polymerization for PDO was performed in bulk at 65 ºC for 2 h under the nitrogen steam. With a fixed amount of an initiator (1800 ppm), 30 ppm of the purified catalyst was used for polymerization. The precipitated product was dried in a vacuum oven for overnight at 45 ºC to achieve a white form of crystallized polymer out of solution. Subsequently, thus-prepared polymer was tailored using the electrospinning process with 5 and 20 rpm of an extruder and gear pump speed, respectively. The tip-to-collector distance was 20 cm and filaments were spun under an electric field of 10 kV. Typically, low nozzle and spinning temperature could influence the crystallinity of electrospun filaments.[17] On the contrary, more than 110 ºC could melt the polymer chains. During fabrication, an average temperature of eight holes in the nozzle with 15 bar pressure was 68 ºC (Figure 2). After annealing, drawn PDO filaments were manually stretched until resistance was felt and kept at room temperature in a vacuum

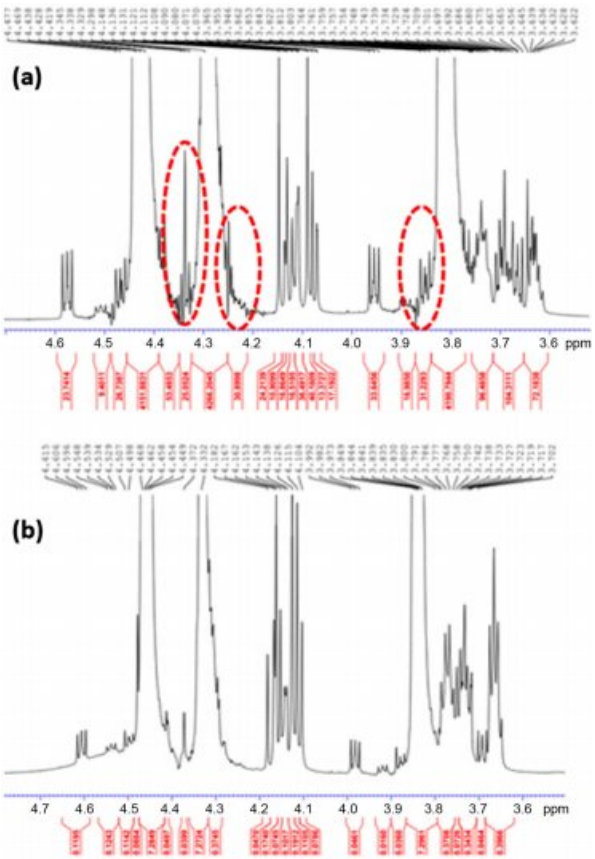


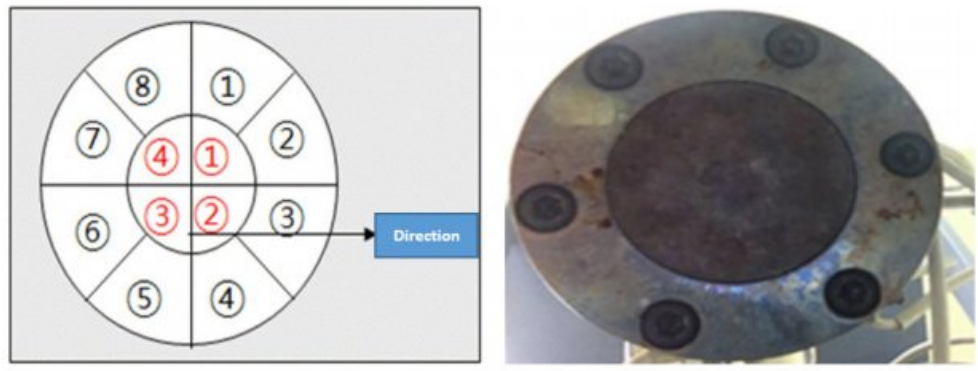
Figure 1. Chemical shifts in the ^{1}H NMR spectra of PDO with regard to (a) before; (b) after the purification. Note that major shifts occurred within the range of 3.8–3.9, 4.2–4.3, and 4.3–4.4 ppm, respectively.

oven until further use.

Methodology. Thermal properties of PDO were measured with differential scanning calorimeter (DSC 2910, TA instruments). A flow of nitrogen gas was maintained to eliminate any air oxidation of samples. From each annealing and degradation condition, 5 mg of each sample was mounted in aluminum pans, along with an empty pan as the reference. The analysis was performed at a temperature range of 0~200 °C with a heating rate of 10 °C min^{-1}. After the electrospinning, randomly selected PDO filaments from multiple lots of a given suture type were tested for physical and degradable properties. The strength properties of each sample were measured with the universal tensile testing machine (Instron 3343, Instron) and the impact tester (Impact tester, KATECH) according to the relevant ASTM standards; ASTM D246, ASTM D638, ASTM D790, and ASTM D792. The measurements of the force at break (N) and clamp-to-clamp breaking strain were recorded, and samples were tested per sample type for each condition and experimental repeat. The *in vitro* degradation characteristics were examined to compare the degradability of samples by different synthesis conditions. Prior to the *in vitro* degradation, 3 cm of each sample was washed with deionized H_2O and placed in a vacuum for 3 h.[18] Thereafter, the samples were immersed in a shaking incubator at 37 °C with a phosphate-buffered saline solution after adjusting pH to 7.4. Knot tensile strength and breaking strength retention were tested under time points of 168, 336, 504, and 672 h, respectively. The experimental uncertainties were averaged during 5 trials (n=5).

Results and Discussion

The T_m test could hint shreds of evidence for the successive polymerization. In general, T_m increases as the concentration of a catalyst (ring-opener) increases and may decrease in vice



Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	Zone 7	Zone 8
66 °C	68 °C	70 °C	67 °C	68 °C	66 °C	70 °C	69 °C

Figure 2. An average temperature range of holes during fabrication.

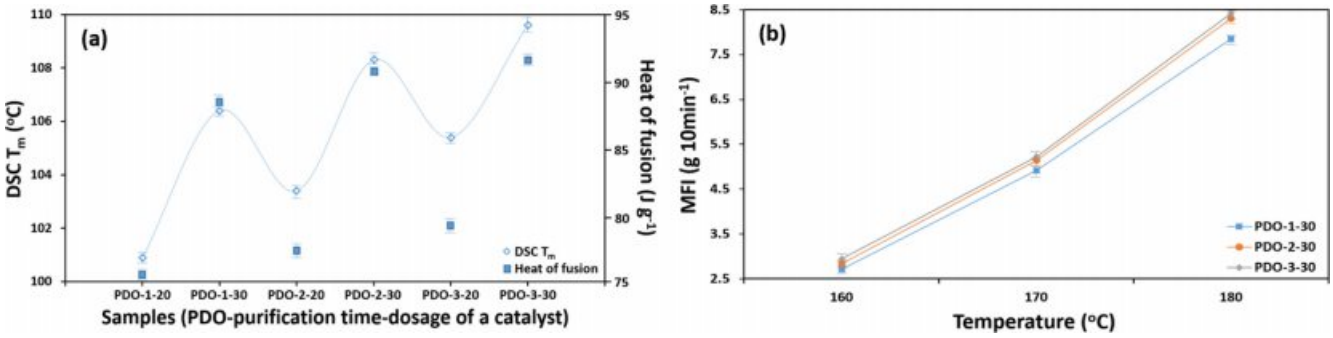


Figure 3. Thermal properties of samples by various purification time and the concentration of a catalyst: (a) DSC T_m and heat of fusion; (b) Melt flow index by various temperature range.

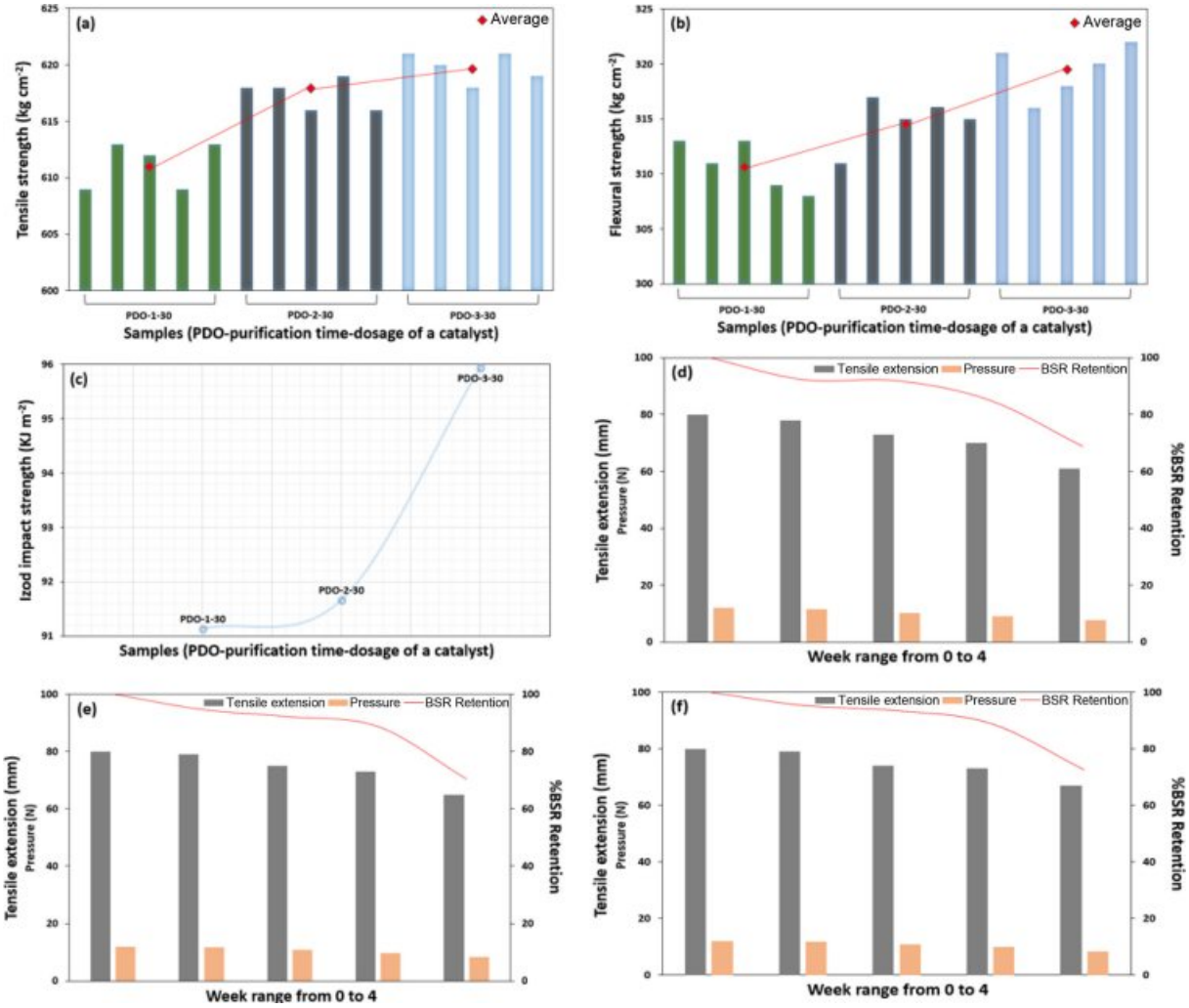


Figure 4. Physical properties of samples by various purification time; (a) tensile strength; (b) flexural strength; (c) Izod impact strength. Degradability of samples by various purification time with a given week range from 0 to 4; (d) PDO-1-30; (e) PDO-2-30; (f) PDO-3-30.

versa. The results in Figure 3(a) revealed that the values of each sample were in a linear relation with the purification time and the concentration of a catalyst. Narrowing the topic down to a catalyst, all samples had the tendency to undergo increased T_m as the dosage increases; PDO-1-*n* (5.17%), PDO-2-*n* (12.68%), and PDO-3-*n* (6.95%). T_m values by the purification

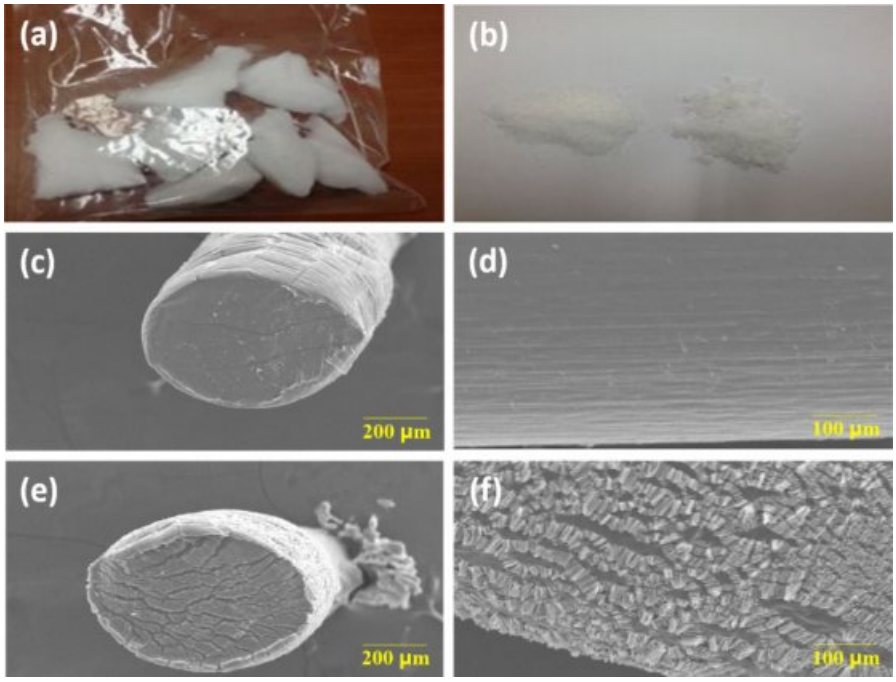


Figure 5. Visualized characteristics of PDO before and after fabrication. (a) After the 1st crush of samples; (b) After the 2nd crush of samples. Herein, PDO-3-30 (right side) reveal better aggregate grade than PDO-1-30 (left side). Degradation profiles of PDO-3-30 by the 1st and the 4th week are represented in (c)-(d) and (e)-(f), respectively.

time were also in accordance with the concentration of a catalyst, since impurities (i.e., monomer and/or oligomer) could not affect the overall quality of polymerization as the purification time increases. Specifying samples labeled as PDO-*n*-30, it seems that the amount of dosage is one driving force for the polymerization compare to the purification time; PDO-1-30 to PDO-2-30 (1.75% increased) and PDO-2-30 to PDO-3-30 (1.66% increased). A similar behavior was also observed in the heat of fusion and melt flow index (Figures 3(a)-(b)). We further tracked PDO-*n*-30 in a form of filament whether the purification affects their physical properties, probably as a result of the removal of impurities.

The tensile strength of the samples is plotted in Figure 4(a). An increase in tensile strength with increasing purification time is generally observed in all samples. Based on the results, the value from PDO-1-30 to PDO-2-30 had better tensile strength increment (1.00%) compare to the value from PDO-2-30 to PDO-3-30 (0.39%). On the contrary, 3 h of purification time-shifted the values more dramatically in flexural strength and Izod impact strength than 2 h as depicted in Figures 4(b) and 4(c). Yet, the overall purification time showed a rising linear plot implying that the purification has successfully limited some of the imperfect bonding. Samples from PDO-1-30 to PDO-3-30 experienced 2.69 and 5.01% increased flexural and Izod impact strength, respectively. Herein, PDO-3-30 recorded the highest increment, or "plateau" value, in Izod impact strength within the overall physical properties. The aforementioned presumes that PDO-3-30 with the most catalyst dosage and the longest purification time may have the highest molecular weight due to the most successive polymerization (Table 1 and Figures 5(a)-(b)). On the basis of the preceding results, it can be pointed out that while the dosage of a catalyst leads to the major shift in polymerization, the degree of polymerization is also non-negligible. We therefore suggest that a decent purification control could aid in the occurrence of bonding around the polymer interfaces and the formation of voids, which are known to increase the physical properties.

Table 1. Chip-type Yield Rates by Each Stage of Polymerization of PDO before Fabrication

Classification	Initial PDO dosage (g)	1st crush (g)	2nd crush (g)	Final yield rate (%)
PDO-1-30	5000	4901	4855	74.42
PDO-2-30	5000	4966	4891	79.32
PDO-3-30	5000	4983	4913	82.54

Table 2. Degradation Profiles of Samples by Various Purification Time

Classification	Week	Tensile extension (mm)	Pressure (N)	BSR retention (%)
PDO-1-30	0	80	12.0	100
	1	78	11.5	92.3
	2	73	10.2	91.94
	3	70	9.1	85.08
	4	61	7.8	68.8
PDO-2-30	0	80	12.0	100
	1	79	11.7	94.65
	2	75	10.8	92.08
	3	73	9.6	88.65
	4	65	8.3	70.35
PDO-3-30	0	80	12.0	100
	1	79	11.8	95.32
	2	74	10.9	93.46
	3	73	9.9	88.95
	4	67	8.5	72.49

In vitro degradation profiles of samples are exhibited in Figures 4(d)-(f) and Table 2. The degradation of samples results from the hydrolytic cleavage of ester bonds, thus the pH environment is closely related to the degradation profile of PDO.[19] However, *in vitro* does not correspond to an actual degradation profile *in vivo* due to the pH variance environment instead of physiological homeostasis.[20] This method is yet a facile method to observe the effects of additives and synthetic conditions on the degradation of polymers.[21,22] All samples revealed typical biodegradable properties within 4 weeks of time-period. Tensile extension, pressure, and BSR retention were in the order of PDO-3-30 (highest) > PDO-2-30 > PDO-1-30 (lowest), respectively. PDO-1-30 has recorded the highest BSR retention of 68.60% at the 4th week, redeeming the shortcoming in tensile, flexural, and Izod impact strengths. Meanwhile, PDO-3-30 showed 3.69% more BSR retention at 4th week compare to PDO-1-30, indicating the less degradation behavior. These results are in agreement with the discussion above, based on the grade of polymerization and the variation of synthetic conditions. In line with the results from *in vitro* degradation, PDO-1-30 and/or PDO-2-30 could be treated in certain medical cases, where decent physical strength and fast degradation is needed. On the other hand, PDO-3-30 was found to be more efficient in case a high level of physical strength with less degradation profile is required (Figures 5(c)-(f)).

Conclusions

An increased dosage of a catalyst was found to be a major factor for the successive polymerization as early suggested. For the first time, we demonstrated the synthetic condition by varying the time of purification. It led to more sensitive quality control of as-synthesized PDO filament. Therefore, such an approach could arise the importance and further research under the topic of sufficient purification. From a mechanical point of view, there is a consensus that our work could root for further filament-quality research. Especially, it is crucial to pay attention to purification to achieve a high-quality polymerization in relevant industries and to promote the low material consumption from an economic point of view. Our work will further focus on the degree of polymerization by varying the purification time.

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