Polymer Journal (2019) 51:637–647
https://doi.org/10.1038/s41428-019-0182-7

ORIGINAL ARTICLE

A versatile method for the synthesis of poly(glycolic acid): high solubility and tunable molecular weights

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Received: 3 August 2018 / Revised: 14 February 2019 / Accepted: 15 February 2019 / Published online: 8 March 2019

Abstract

Poly(glycolic acid) (PGA) is an important biopolymer, especially in medical applications because of its suitable mechanical, biocompatible, and biodegradable properties. PGA can degrade within weeks, depending on its molecular weight. Production of high molecular weight PGA is important to achieve sufficient mechanical stability for biomedical applications. High molecular weight PGA is difficult to obtain by direct condensation of the related carboxylic acids; therefore, polyglycolide is typically made by ring opening polymerization of the cyclic diester glycolide. However, this procedure is restrictive because of the high cost of the raw material (glycolide) and the associated high energy consumption. Here, we describe the synthesis of PGA via an azeotropic distillation method that enables tunable molecular weights. The synthesized PGA is highly soluble in organic solvents and degrades faster than reference PGA.

Introduction

Poly(glycolic acid) is the simplest aliphatic polyester that is obtained by the polymerization of glycolic acid in which alpha-hydroxy acid groups are located in the backbone [1–3]. Poly(glycolic acid) has good biocompatible and biodegradable properties, non-toxic degradation products [4], and mechanical stability [5]. The US Food and Drug Administration (FDA) has approved and promoted applications of PGA in the medical field [6, 7], such as in sutures, drug delivery systems, tissue scaffolding structures, and disposable medical devices [8, 9]. The first application was developed by the DuPont chemical company, and PGA has been commercially available as synthetic and absorbable sutures (Dexon®) since 1970 [1, 2, 10–12]. Thermogravimetric analysis indicates a glass transition temperature in the range of 35−40 °C and a melting point between 220 °C and 225 °C [1].

Degradation of PGA occurs in the body by hydrolysis, and glycolic acid appears as a degradation by-product [6, 13]. Complete degradation of PGA occurs within several weeks and is mostly dependent on its molecular weight and degree of crystallinity [14]. Moreover, adequate mechanical stability of PGA is usually obtained at molecular weights >30,000 g/mol [15]. Aside from the advantages of PGA in medical materials, PGA has poor solubility due to its high crystallinity which restricts its processing. Glycolic acid and glycolide, which have linear and bicyclic structures, respectively, are utilized as monomers for the synthesis of PGA. PGA is obtained from glycolide by ring opening polymerization, and from glycolic acid by direct condensation polymerization. Takahashi and colleagues obtained a high molecular weight PGA by melt/solid polymerization of glycolic acid in a 2-step reaction at a temperature of 230 °C [16]. Another study by Dali et al. used ionic liquids, such as butanesulfonic acid trifluoromethanesulfonate and propanesulfonic acid-4-toluenesulfonate, and produced oligomeric

Supplementary information The online version of this article (https://doi.org/10.1038/s41428-019-0182-7) contains supplementary material, which is available to authorized users.

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macromolecules. PGA was then synthesized at a low M_n using a post polycondensation reaction in the presence of tin (II) ethylhexanoate [17]. Murugan et al. studied polycondensation to produce PGA via antimontrioxide (Sb_2O_3) and clay as catalyst. The molecular weight was related to the viscosity, and higher clay content resulted in higher viscosity [18]. During the polymerization via direct condensation of glycolic acid, the formation of water in the reaction medium affected the reaction due to hydrolysis of pre-polymers and oligomers. Therefore, the most widely used method for obtaining high molecular weight PGA is by ring opening polymerization of glycolide [19, 20]. Shorter reaction times and higher yields render this method more advantageous. However, the main drawbacks of ring opening polymerization are the high temperature requirements and the expensive starting material (glycolide) compared to glycolic acid. On the other hand, polymerization by azeotropic distillation is a fairly simple process [21]. In this method, the water and excess monomer that are produced during condensation are removed from the reaction medium using selected organic solvents. High yield, low cost, simple reaction conditions, and suitability for industrial production are the main advantages of polymerization by azeotropic distillation [22]. Moreover, catalyst and solvent can be recycled and reused. Various organic solvents, such as toluene, xylene, mesitylene, anisole and so on, that produce azeotropic mixtures with water can be used [20, 23].

In this study, for the first time, PGA synthesis was achieved by an azeotropic distillation method using a Dean-Stark apparatus. This method offers an alternative to ring opening polymerization for the production of high molecular weight PGA which requires high temperature and relatively expensive starting materials, thereby increasing the cost of production of PGA. The reaction conditions and parameters were optimized for increasing the molecular weight of PGA by using different catalysts, organic solvents, and reaction times. Gel permeation chromatography (GPC) analysis indicated that the molecular weight mostly depends on the solvent and catalyst combination. PGA was synthesized with tunable molecular weights and had fine powder structures that enabled ease of handling and higher solubility compared to commercially available PGA, thereby providing opportunities for a variety of applications.

Materials and methods

Materials

Glycolic acid, toluene, anisole, tin chloride dihydrate ($SnCl_2$), triflic acid, hexafluoroisopropanol (HFIP), chloroform-d ($CDCl_3$) and trifluoroacetic acid-d (TFA-d) were purchased from Merck (Germany). Mesitylene, tin (II) 2-ethylhexanoate, and phenetole were obtained from Sigma (USA). *p*-Toluenesulfonic acid (*p*-TSA), poly(glycolic acid) (The M_w and M_n were 62,000 and 41,000 g/mol, respectively.) and sodium trifluoroacetate were purchased from Aldrich (USA). All chemicals were used directly without further purification.

Instrumentation

Fourier transform infrared spectroscopy (FTIR, Perkin Elmer, USA) was used for chemical characterization at ambient temperature. The spectra were obtained at a 4 cm^{-1} resolution for 1 s, and a minimum of 10 scans were averaged. An X-ray diffractometer (XRD) (Rigaku, Japan) was used to obtain X-ray scans at a fixed voltage of 30 kV and a current of 15 mA. The divergence slit was fixed at 1.25° and the receiving slit was fixed at 0.3 mm. The instrument used Cu-Kα radiation ($\lambda = 0.154$ nm), and Cu Kβ radiation was eliminated using a monochromator. Samples were analyzed at a scanning speed of 1°/min within a Bragg angle 2θ range of 3–90° at ambient temperature. ^{1}HNMR analysis of the synthesized polymers was performed using a Bruker 500 MHz instrument. The samples were prepared by dissolving the synthesized PGA samples in a TFA-d/chloroform-d mixture (25:75, v/v). Thermal properties of the polymers were determined under a nitrogen atmosphere by differential scanning calorimetry (DSC) (Perkin Elmer Jade, USA) between 0 and 250 °C at 10 °C min^{-1}, and by thermogravimetric analysis (TGA) (Perkin Elmer Pyris, USA) between 15 and 510 °C at 10 °C min^{-1}. Relative molecular weight distributions were determined by GPC (Thermo SCM 1000 HPLC, USA and Viscotec VE 3580 RI, United Kingdom) using two Shodex HFIP 804 and 806 columns in combination and HFIP containing 1 mM sodium trifluoroacetate as the eluent at a flow rate of 1 mL/min. Poly (methylmethacrylate) standards were used for calibration. The particle size of sample 25 was measured by dynamic light scattering (DLS) using a Zetasizer Nano ZSP instrument from Malvern Instrument (Westborough, MA, USA). The sample was dispersed in water by sonication prior to measurement (concentration: 0.0145%, w/v). For inherent viscosity measurements, 2 g/dL solutions of both the reference polymer and the synthesized samples were prepared in HFIP and viscosity measurements were conducted at 25 °C using an Ubbelohde type capillary viscometer. Five measurements were made on each sample and the average results were determined by the mean values of these measurements. No filtration was performed due to the clarity of the solutions. Sample morphology was determined using a TESCAN Vega 3 SBH (Czech Republic) scanning electron microscope (SEM). Samples were coated with gold-palladium alloy for 120 s prior to analysis.

Synthesis

5.00 g of glycolic acid and different amounts of catalysts (1, 5, and 10 mole%, catalyst/monomer) were weighed into flasks and were maintained under an argon atmosphere. A Dean-Stark trap was used to remove water that formed during the condensation reaction. Toluene, anisole, mesitylene, and phenetole were used as solvents for azeotropic condensation polymerization and the polymerization temperatures were 110, 154, 164, and 170 °C for each solvent, respectively. Solvent amounts were utilized at 1:15, 2:15, and 1:30 ratios (glycolic acid/solvent, g/mL). The mixture was heated to the boiling point of the solvent used and magnetically stirred during the reaction. At the end of the reaction (5, 20, or 30 h), the resulting solid was precipitated and filtered. The obtained polymer was further refluxed with ethyl acetate, then filtered and dried under vacuum. Each reaction was conducted twice. Table 1 summarizes the reaction conditions.

Solubility

The solubility of reference PGA (Aldrich, USA) and PGA synthesized in anisole (Table 1, sample 25), which has the highest molecular weight obtained with the azeotropic distillation method, were measured. PGA samples (450 mg) were added to 3 mL of HFIP and stirred at 50 °C for 24 h. The solutions were filtered under vacuum and the precipitates (non-dissolved PGA particles) were weighed. The solubility values were calculated according to the equation:

$$Solubility\% = \frac{PGA(initial\,weight) - PGA(weight\,of\,precipitate)}{PGA(initial\,weight)} \times 100$$

In vitro degradation

A pellet press apparatus was used for the preparation of samples of the commercial polymer that was used as the control, and the polymer having the highest molecular weight obtained after the reactions (Table 1, sample 25). The samples were produced by compression with high pressure as pellets containing ~0.5 g of polymer. Commercial PGA was crushed prior to pellet preparation to minimize the particle size. The samples were then placed in vials containing 2 mL of PBS and incubated at 37 °C and at 50 rpm. In vitro degradation was determined by weight loss and was monitored for 4 weeks. The pH of the media was measured every day during the degradation study and 0.5 mL of fresh PBS was used to replace the medium at 2-day intervals. Every 7 days the pellets were removed from the PBS solution, washed with distilled water, and then dried by lyophilization. Dried samples were weighed and the results were recorded. The experiment was conducted in triplicate for each sample.

Results and discussion

PGA is a biodegradable polymer that is widely used in biomedical applications. However, little research has been conducted on the synthesis and methods of production of PGA. The initial purpose of this study was to develop a facile synthesis method to produce high molecular weight PGA ($M_n = 30000–45000$ g/mol) since a high molecular weight is crucial for producing adequate mechanical properties. In addition, obtaining a white, solid PGA in powder form was another essential goal of this study, as it improves the processability for further applications compared to the amorphous waxy materials that have been reported in the literature [24]. Interestingly, in contrast to literature reports where only catalyst activity and temperature are important for yielding high molecular weight PGA by a melt-solid condensation method, solvent-catalyst binary interactions are more important than temperature in azeotropic distillation of PGA [16]. We investigated different solvents, reaction times, catalysts, and their varying amounts to evaluate the effects of these parameters on PGA properties. The polymerization temperature also changed and was dependent on the boiling point of the organic solvent that was used. Tin (II) 2-ethylhexanoate, $SnCl_2•2H_2O$, *p*-TSA, $SnCl_2•2H_2O$/*p*-TSA and triflic acid were tested with toluene and anisole, and then triflic acid was further used as a catalyst in the presence of phenetole and mesitylene by evaluating the conditions that produced the highest molecular weight of PGA with toluene and anisole. Table 1 lists the molecular weight of PGA, polydispersity index (*Đ*), melting temperature, crystallinity (%), inherent viscosity, and yield (%).

To achieve higher molecular weights, basically, two conditions should be optimized: (1) the solvent, and (2) the catalyst type. Following these two conditions, the reaction time, catalyst amount, and solvent ratio could also cause changes in the molecular weight of the PGA obtained. In a typical reaction, 5 g of glycolic acid was mixed with *p*-TSA, $SnCl_2•2H_2O$, triflic acid, tin (II) 2-ethylhexanoate or $SnCl_2•2H_2O$/*p*TSA with a catalyst amount of either 1 or 5 (mole%) in toluene (solvent ratio: 1:15, g/mL) with stirring for 5 h at 110 °C (Table 1, samples 2–11). The temperature was not raised above 110 °C to avoid boiling the solvent. A reaction was also performed without catalyst for comparison (Table 1, sample 1). After polymerization, GPC analysis (in HFIP) indicated a high molecular weight of $M_n =$ 13600 g/mol when the mole% was 5, and 9000 g/mol when the mole% was 1 for triflic acid and $SnCl_2•2H_2O$/*p*TSA, respectively (Table 1, samples 1–11).

Table 1 Reaction conditions and characteristics of PGA samples

Sample code	Catalyst	Catalyst amount (mole%)	Solvent	Solvent ratio (g/mL)	Reaction time (h)	M_w (g/mol)	M_n (g/mol)	$Đ$	T_m (°C)	Crystallinity%[a]	Inherent viscosity	Yield%
1	–	–	Toluene	1:15	5	8400	7800	1.07	ND	ND	0.102	30
2	$SnCl_2•2H_2O$	1	Toluene	1:15	5	5400	5000	1.08	ND	ND	0.064	78
3	*p*-TSA	1	Toluene	1:15	5	6100	5700	1.07	133	67	0.074	78
4	$SnCI_2$-*p*TSA	1	Toluene	1:15	5	11000	9000	1.20	174–209	81	0.210	76
5	Triflic acid	1	Toluene	1:15	5	6500	6100	1.06	175–185	ND	0.108	79
6	Tin (II) EH	1	Toluene	1:15	5	7400	7100	1.04	218	19	0.162	75
7	$SnCl_2•2H_2O$	5	Toluene	1:15	5	10600	8800	1.20	157–205	28–21	0.196	90
8	*p*-TSA	5	Toluene	1:15	5	8100	8000	1.01	175–209	16–73	0.118	83
9	$SnCI_2$-pTSA	5	Toluene	1:15	5	8900	8700	1.02	164–219	53–46	0.138	88
10	Triflic acid	5	Toluene	1:15	5	14600	13600	1.07	183	36.1	0.186	89
11	Tin (II) EH	5	Toluene	1:15	5	9400	8600	1.09	162–212	40–20	0.069	76
12	$SnCI_2$-*p*TSA	1	Toluene	1:15	20	15600	14400	1.08	168–212	16–34	0.118	76
13	Triflic acid	1	Toluene	1:15	20	7300	6900	1.06	ND	ND	0.055	76
14	$SnCI_2$-*p*TSA	1	Toluene	1:15	30	17900	16300	1.10	174–218	16	0.177	72
15	Triflic acid	1	Toluene	1:15	30	16500	15000	1.10	219	72	0.152	73
16	–	–	Anisole	1:15	5	15200	14000	1.09	135	35	0.147	ND
17	$SnCl_2•2H_2O$	1	Anisole	1:15	5	8900	7900	1.13	ND	ND	0.123	39
18	*p*-TSA	1	Anisole	1:15	5	8100	7700	1.05	195	23	0.142	52
19	$SnCI_2$-*p*TSA	1	Anisole	1:15	5	27100	23400	1.16	206–218	47–17	0.403	57
20	Triflic acid	1	Anisole	1:15	5	27900	23000	1.20	207	55	0.408	56
21	Tin (II) EH	1	Anisole	1:15	5	6300	6000	1.05	217–132	28–27	0.123	27
22	$SnCI_2$-*p*TSA	1	Anisole	1:15	20	30800	25600	1.20	191–212	73	0.435	63
23	Triflic acid	1	Anisole	1:15	20	26400	20400	1.29	213	63	0.394	55
24	$SnCI_2$-*p*TSA	1	Anisole	1:15	30	28000	22400	1.25	214	77	0.403	62
25	Triflic acid	1	Anisole	1:15	30	40300	32100	1.25	218	77	0.430	51
26	Triflic acid	1	Mesitylene	1:15	30	22400	16900	1.32	219	75	0.330	55
27	Triflic acid	1	Phenetole	1:15	30	25700	17400	1.47	202–214	70	0.384	53
28	Triflic acid	1	Anisole	2:15	30	33000	23000	1.43	212	70	0.415	65
29	Triflic acid	1	Anisole	1:30	30	32000	27000	1.18	174–210	16–43	0.405	33
30[b]	–	–	–	–	–	62000	41000	1.51	222	49	0.667	-

Tin (II) EH: Tin (II) 2-ethylhexanoate

$SnCI_2$-pTSA: $SnCl_2•2H_2O$/pTSA (1:1 mol/mol)

[a]Crystallinity% values are calculated from DSC.

[b]Sample 30 is the commercially available PGA that was used as the reference.

In the second step, to increase the molecular weight of the PGA, the reaction time was increased while using these two catalysts. Thus, reactions in toluene (solvent ratio: 1:15, g/mL) and with either triflic acid or $SnCl_2•2H_2O$/*p*TSA, were conducted for either 20 or 30 h (Table 1, samples 12–15). Reaction time of 30 h produced the highest molecular weight with the presence of both catalysts with values of $M_n = 16300$ g/mol and 15000 g/mol for $SnCl_2•2H_2O$/*p*TSA and triflic acid, respectively (Table 1, samples 14 and 15). The same catalyst series were applied in anisole for 5 h, using a 1:15 solvent ratio (g/mL) and a catalyst amount of 1 (mole%; Table 1, samples 17–21). Again, a reaction was also performed without catalyst to determine the effect of anisole alone and for comparison (Table 1, sample 16). As observed with toluene, higher molecular weights were obtained in the presence of $SnCl_2•2H_2O$/*p*TSA and triflic acid (Table 1, samples 19 and 20).

For the fourth set of optimization conditions, to increase the molecular weight of the PGA obtained, the reaction time was increased to 20 and 30 h in the presence of triflic acid and $SnCl_2•2H_2O$/*p*TSA in anisole (Table 1, samples 22–25). The molecular weight was significantly increased when the reaction time was 30 h in the presence of triflic acid (Table 1, sample 25). The M_n values were found to be

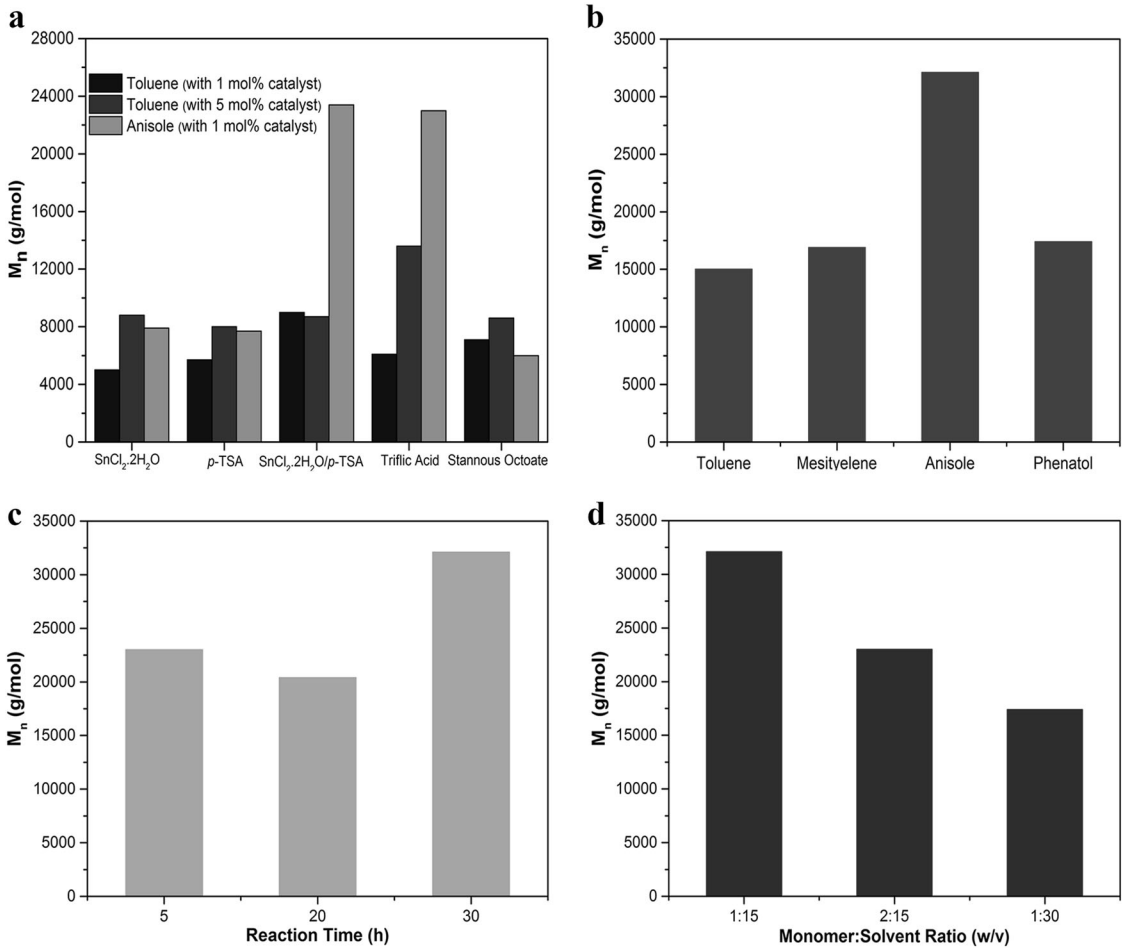

Fig. 1 **a** Molecular weight distributions as a function of catalyst, solvent, and solvent amount, **b–d** reactions catalyzed with triflic acid, **b** denotes solvent used for the reaction duration of 30 h, **c** denotes reaction duration in anisole and **d** represents anisole amount for the duration of 30 h

22400 g/mol and 32100 g/mol using $SnCl_2$•$2H_2O$/*p*TSA or triflic acid, respectively. An opposing result was obtained for those two catalysts with longer reaction times (40 h, the results are not shown here). Figure 1a summarizes the dependence of molecular weight on catalyst, solvent, and solvent amount.

Mesitylene and phenetole (Table 1, samples 26 and 27), which have higher boiling points (164 °C and 170 °C for mesitylene and phenetole, respectively) compared to anisole, were also used as solvents to determined optimized conditions (Table 1, sample 25). Both solvents resulted in much lower molecular weight products. Other catalysts were not evaluated, due to waxy products which are difficult to handle. The final attempt evaluated the solvent to monomer ratio (Table 1, samples 28 and 29). Both higher and lower ratios did not increase the molecular weight; however, this condition was shown to affect the molecular weight of PGA under other conditions. As a result, the solvent type had more an effect on the molecular weight than the reaction temperature. Fig. 1b shows a comparison of reaction parameters (reaction duration, solvent type, and solvent amount) on the molecular weight. White, solid, and easily handled products were obtained for PGA synthesized in anisole. In addition, triflic acid appears to be the most effective catalyst with a best yield in anisole in terms of molecular weight. PGA synthesized in anisole for 5 h with triflic acid yielded a molecular weight of 23000 g/mol (Table 1, sample 20). The molecular weight slightly decreased for a higher reaction time of 20 h (Table 1, sample 23). However, when the reaction time was increased to 30 h, the highest molecular weight was obtained in the study. However, increasing the reaction time to 40 h resulted in a slightly lower molecular weight (the result is not shown). A similar trend was observed for the reaction conducted in toluene. This situation may be explained by the presence of homogeneity in the catalytically active sites for only a given time interval [25]. The optimum solvent ratio was found to be 1:15 (g/mL) which yielded the highest molecular weight (Table 1, samples 25, 28, and 29). Solvent ratios below or above 1:15 resulted in lower molecular weights.

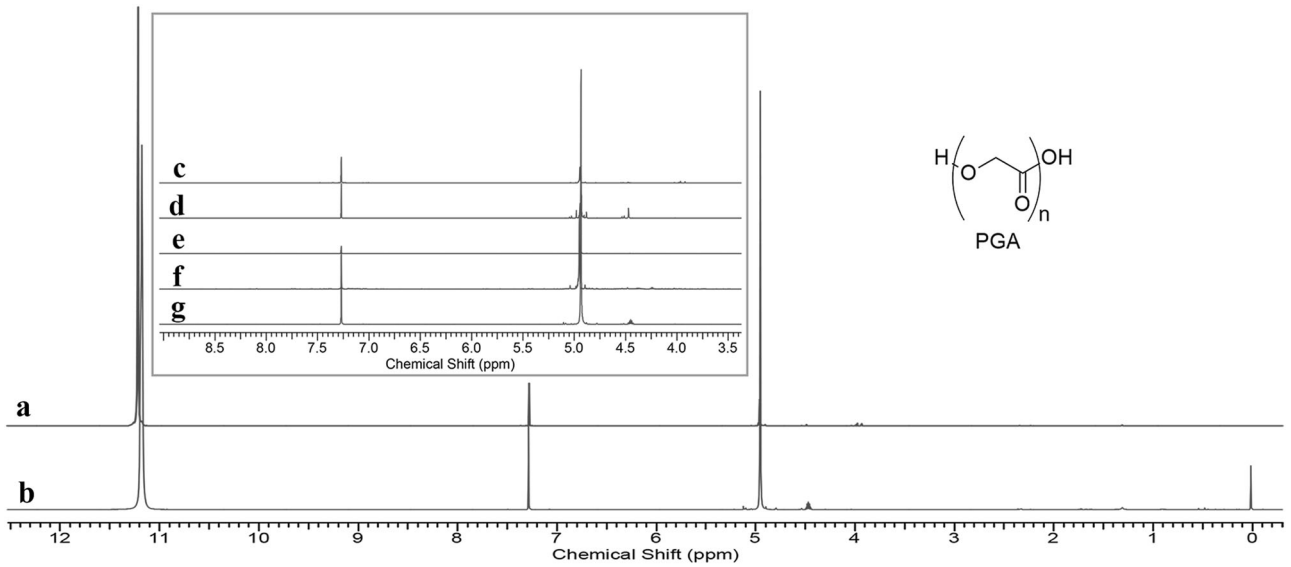

Fig. 2 **a** Full ^{1}H NMR spectra for sample 25, **b** reference PGA (sample 30); partial ^{1}H NMR spectra for PGA synthesized in **c** anisole (sample 25), **d** phenetole (sample 27), **e** mesitylene (sample 26), **f** toluene (sample 15) catalyzed with triflic acid for 30 h, and **g** reference PGA

The effects of catalyst type were primarily determined by the combination with the solvent used. Considering solvent-catalyst binary systems, the anisole-triflic acid system was found to be the most effective for producing high molecular weight PGA (32100 g/mol, Table 1, sample 25). Thus, PGA samples produced under the same reaction conditions (duration, catalyst, catalyst amount, and solvent ratio) as sample 25, but in different solvents (anisole, toluene, phenetole, and mesitylene) were selected to compare the characteristics of synthesized PGA samples (Table 1, sample 15, 26, and 27).

Figure 2 shows the ^{1}H NMR spectra for PGA synthesized in the presence of anisole, phenetole, mesitylene, and toluene, and triflic acid as catalyst for 30 h. Reference PGA (Sigma Aldrich, USA) was used for comparison. Figure 2 compares the ^{1}H NMR spectra of reference PGA with that obtained via azeotropic distillation of glycolic acid. The peaks at 7.3 and 11.2 ppm are due to residual non-deuterated peaks of chloroform-d and TFA-d, respectively. The matching of resonances at 4.95 ppm that are due to polymeric methylene groups suggests a presence for the structure of PGA from glycolic acid via azeotropic distillation. When the NMR spectra are examined, methylene peaks resulting from oligomer formation in the vicinity of the polymeric methylene peak are seen in samples 15 and 27, whose molecular weights are less than 20000 g/mol. In sample 25, since the molecular weight is above 20000 g/mol, by-product peaks do not appear in the main spectrum. Furthermore, although the spectra of polymers having molecular weights lower than 20000 g/mol were obtained in mesitylene, the by-product peaks are also not observed in the main spectrum.

Figure 3a shows the FTIR spectra of the reference PGA overlaying that of PGA synthesized via azeotropic distillation. There is a clear match in the spectra of the carbonyl stretching band at 1741 cm^{-1} of reference PGA with a band at 1742 cm^{-1} of the synthesized PGA, suggesting evidence of structure for the PGA synthesized from glycolic acid (Fig. 3a). Other bands in the spectrum of reference PGA and synthesized PGA also completely overlay. The stretching related to the C–O–C bond appeared at 1156 cm^{-1}, while the peaks at ~1420, 1220, 1096, 974, and 902 cm^{-1} are characteristic of crystal regions in PGA [18, 26].

Figure 3b shows the XRD pattern of reference PGA and PGA samples that were synthesized in different solvents. As seen from the patterns, two crystallites, which are observed at 22° and 28°, are dominantly present in PGA [27]. With regard to peak intensities, the reference PGA has the lowest amount of these two crystallites compared to the synthesized PGA. Samples 25, 26, and 15 have similar intensities, while sample 27, which was synthesized in phenetole, displays lower intensities, meaning a lower amount of crystallites. However, the intensities of the peaks vary depending on the crystallinity. Thus, phenetole produced less crystallite formation compared to other solvents. Regarding the full-width at half-maximum (FWHM) values of the peaks, the reference PGA has the lowest values, which means it has the largest crystallites compared to other PGA samples. Sample 25 follows the reference PGA, while samples 15 and 27 have similar crystallite sizes with the lowest values (for the calculated results, see the supporting information).

The degree of crystallinity could not be determined from the XRD patterns since the amorphous regions were not

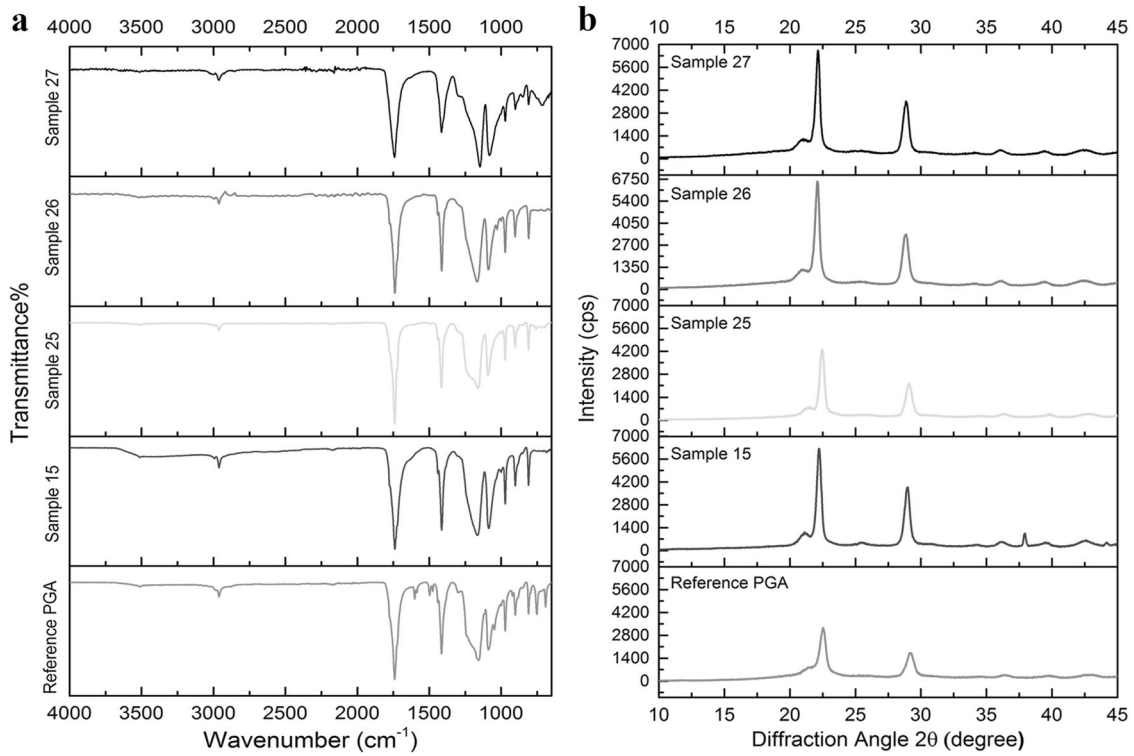

Fig. 3 **a** FTIR Spectra and **b** XRD patterns of PGA synthesized in phenetole, mesitylene, anisole, and toluene catalyzed with triflic acid for 30 h and reference PGA

clear. Using the values obtained from the X-ray diffraction spectrum, the crystal dimensions of the samples were calculated using the Scherrer equation. The crystal dimensions were calculated separately for each sample as D1 and D2 for the 22° and 28° peaks that were obtained from the XRD spectra of PGA, respectively. The Scherrer equation used for this calculation is as follows:

$$D = \frac{K\lambda}{\beta \cos\theta}$$

The results of the crystal sizes obtained are given in Table 2. λ and K were taken as 1.5406 Å and 0.9, respectively.

In addition, crystallinity values were obtained from the DSC thermographs (Fig. 4a). The melting temperatures (T_m) of PGA synthesized in toluene, anisole, mesitylene, and phenetole are between 214 and 219 °C, which are less than that for the commercial material (222 °C; Table 1). These small differences in thermal parameters could be a result of the lower molecular weight compared to the commercial sample of PGA. There exists a rough correlation between the polymer molecular weight and the T_m [28]. Generally, those polymers with a M_n >15000 g/mol exhibit higher T_m values of 130–220 °C. T_m values for a small number of PGAs were not detectable (Table 1, samples 1, 2, 13, and 17). The crystallinity could not be measured due to a lack of ΔH. As the melting points of amorphous polymers are not detectable, the reason could also be attributed to the very low crystallinity of those samples. Considering lower molecular weights (under $M_n = 10000$ g/mol), $SnCl_2$-*p*TSA and *p*-TSA produced higher crystallinity compared to other catalysts (Table 1, samples 3, 4, 8, 9, and 18). Alternatively, catalyst-solvent binary combinations appear to have a more dominant effect on the crystallinity degree with increasing molecular weight.

TGA analysis was conducted under nitrogen and the thermographs obtained are shown in Fig. 4b. In comparison, the thermal stability of the commercial product is close to that of sample 25, which has the highest molecular weight that was obtained in all of the experiments. In addition, from the DSC diagram for sample 27, it can be seen that the melting point is not homogeneous and is followed by decomposition at 210 °C in the TGA diagram. The ^{1}H NMR spectrum of the polymer from sample 27 that was obtained from the reaction in phenetole did not yield a single peak when compared to the other results, and the small peaks that appear in the ^{1}H NMR spectrum at 4.7 and 4.8 ppm indicate non-homogeneous chains. Therefore, this result is reflected in the DSC and TGA spectra, and the resulting graphs show heterogeneous results. Although the molecular weight of sample 15 is lower than that of the other samples, the high crystallinity remains high due to the thermal stability.

The molecular weights obtained by GPC analysis were determined in HFIP (Fig. 5). The polymers synthesized in the absence of catalyst exhibited lower molecular weights (Table 1, samples 1 and 16), with M_n values in the range of 7800 to 14000 g/mol. Apparently, the PGA formed in these reactions is of low molecular weight, and the incorporation of catalysts in the reaction medium is not associated with a substantial increase in the molecular weight in 5 h (Table 1, samples 2–6), with M_n falling to the range of 5000–9000 g/mol. According to the GPC chromatograms for these products (see the supplementary information, Fig. S33–S37), multiple peak structures led to confusion in determining the actual molecular weights. When the molecular weights are considered, an acid catalyst appears to be necessary for activation of the carbonyl group [24]. Gokturk et al. reported the synthesis of PGA starting with trioxane and carbon monoxide for monomer synthesis (glycolic acid); with the use of boron trifluoride diethyl etherate, *p*-toluene sulfonic acid, and triflic acid initiators/catalysts by cationic polymerization, and they achieved the best results with the triflic acid initiated/catalyzed reaction [24]. We also obtained the highest molecular weight using triflic acid. To process properly, the molecular weight of PGA should be optimized at ~45000 g/mol.

Table 2 Calculated crystal dimensions of the PGA samples

Sample	*D*1 (Å)	*D*2 (Å)
Sample 27	260.63	224.36
Sample 26	212.13	155.27
Sample 25	204.74	149.09
Sample 15	263.25	227.67
Reference PGA	187.87	162.17

Moreover, an improvement of solubility is also very important when considering the processability of high molecular weight PGA due to poor solubility. PGA is insoluble in organic solvents except for HFIP, and its poor solubility restricts its use in many processes that require dissolution. In this study, we only compared the solubility of sample 25, due to its higher molecular weight, which makes it comparable with commercially available PGA. In addition, low molecular weight PGA is not recommended for use in medical materials because of its poor mechanical properties. Despite the higher crystallinity of sample 25, the PGA produced in anisole by azeotropic distillation indicated a high solubility of 147.3 mg/mL, while the solubility of reference PGA was found to be 40 mg/mL in HFIP. This situation most probably resulted from the smaller and porous PGA particles produced from the reaction of sample 25 compared to reference PGA (Fig. 6a–d). Figure 6a, b indicate the morphological characteristics of reference PGA

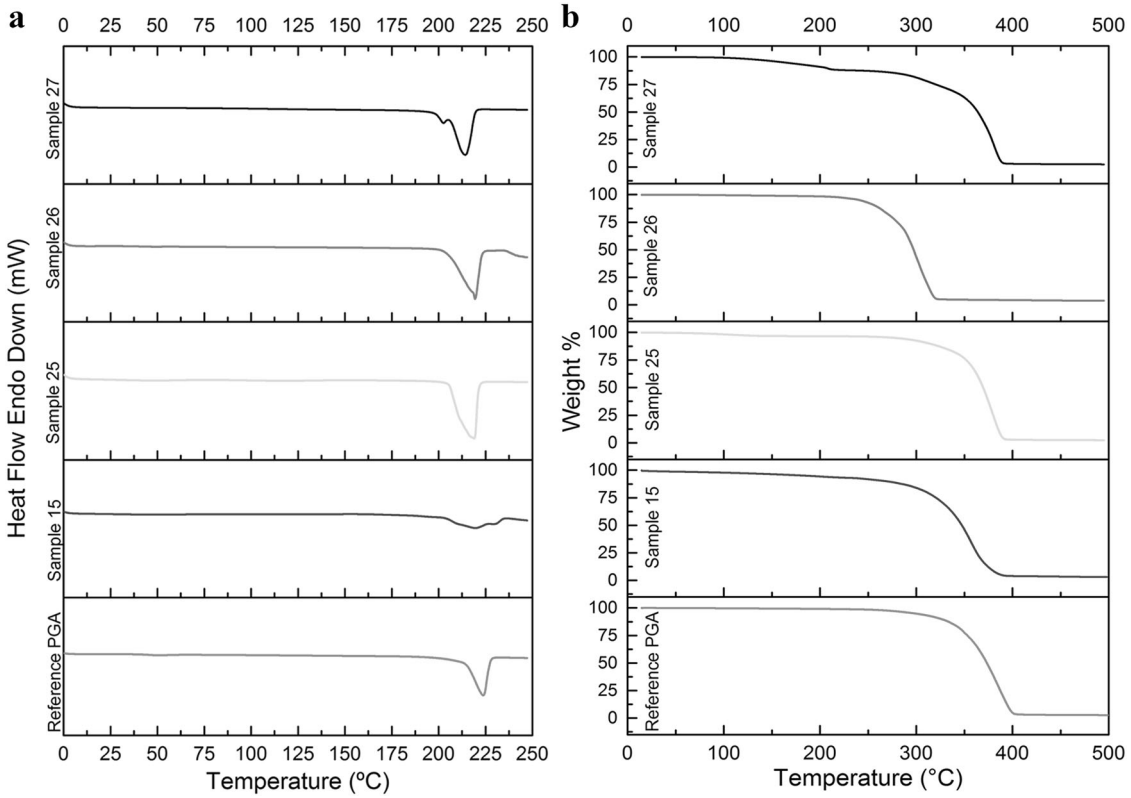

Fig. 4 **a** DSC analysis and **b** TGA patterns of PGA synthesized in toluene, anisole, mesitylene, and phenetole catalyzed with triflic acid for 30 h

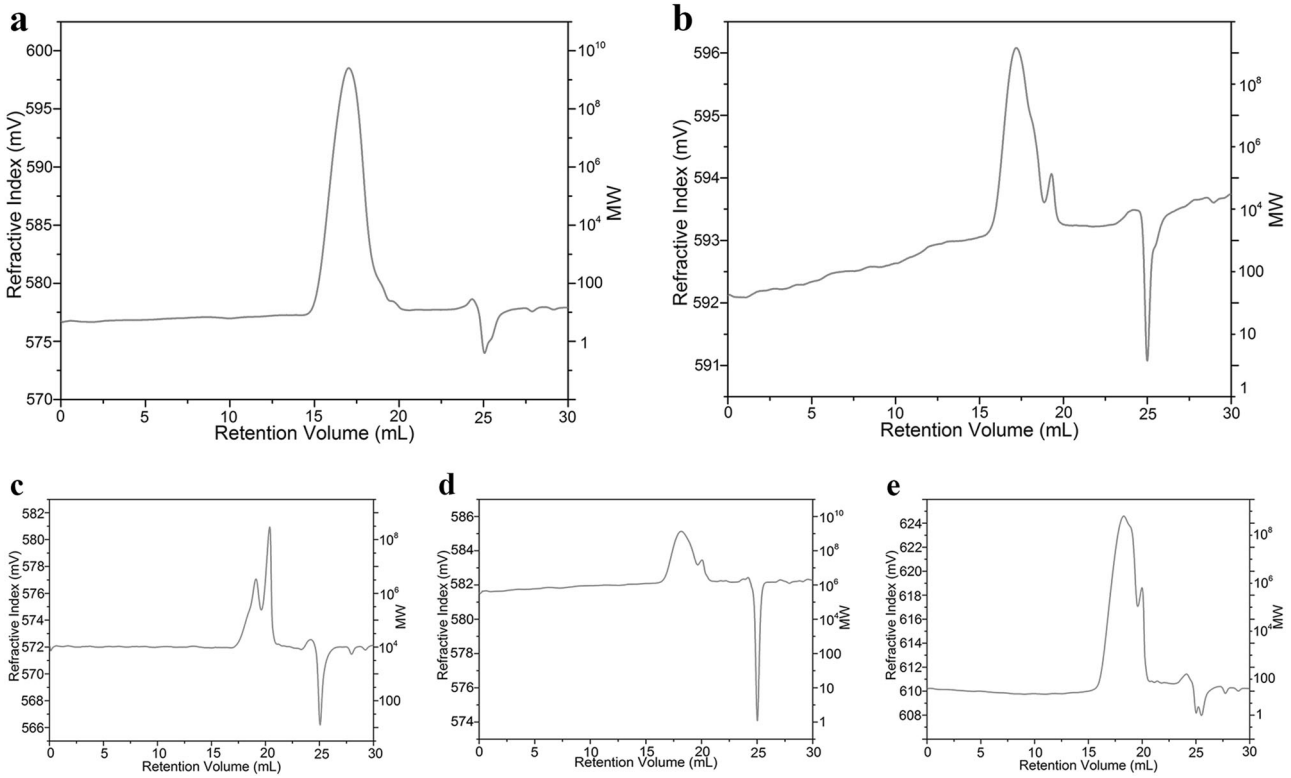

Fig. 5 GPC results of PGA synthesized in **a** standard, **b** anisole, **c** toluene, **d** mesitylene, and **e** phenetole catalyzed with triflic acid for 30 h

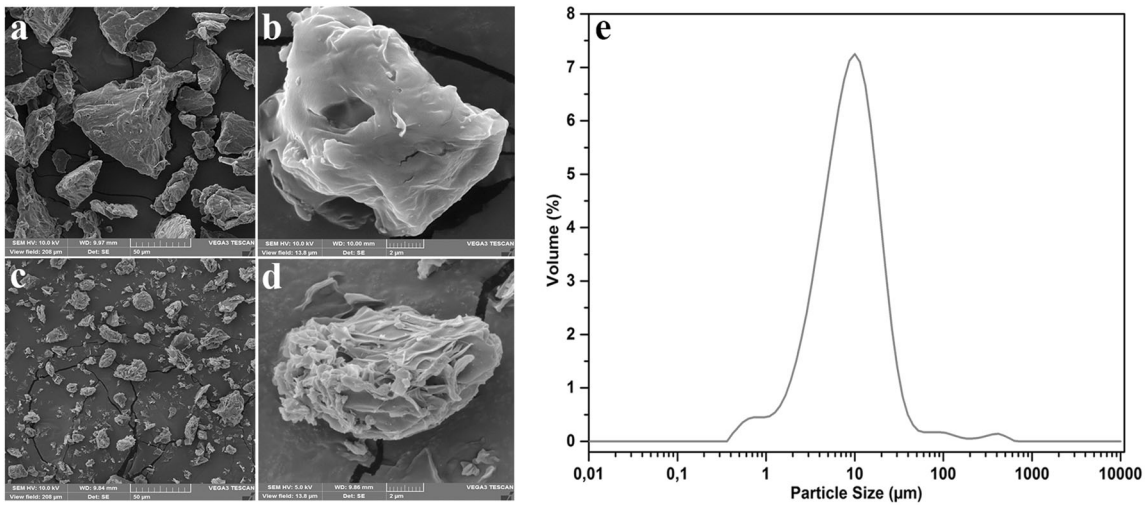

Fig. 6 SEM images of **a**, **b** reference PGA (sample 30 in Table 1), and **c**, **d** sample 25, **e** particle size distribution of sample 25

after grinding since, in this study, ground particles were used in all experiments, while Fig. 6c, d indicate results for the original PGA particles that were obtained from sample 25. A rough distribution analysis obtained from DLS indicates a highly uniform particle with a value of 1.07 and an average particle size of 9.3 μm (Fig. 6e).

The degradation of PGA over 2–4 months varied depending on the crystallinity and the molecular weight. Shawe et al. studied degradation of PGA samples with different thicknesses in PBS for 24 days. They reported a significant mass loss after 9 days [29]. Similarly, we observed a significant mass loss after 7 days during the degradation of reference PGA (Fig. 7a). However, sample 25 degraded gradually from the beginning of the experiment until the 4th week. Until week 4, sample 25 degraded slightly more rapidly compared to reference PGA: 25.83 ± 0.99% and

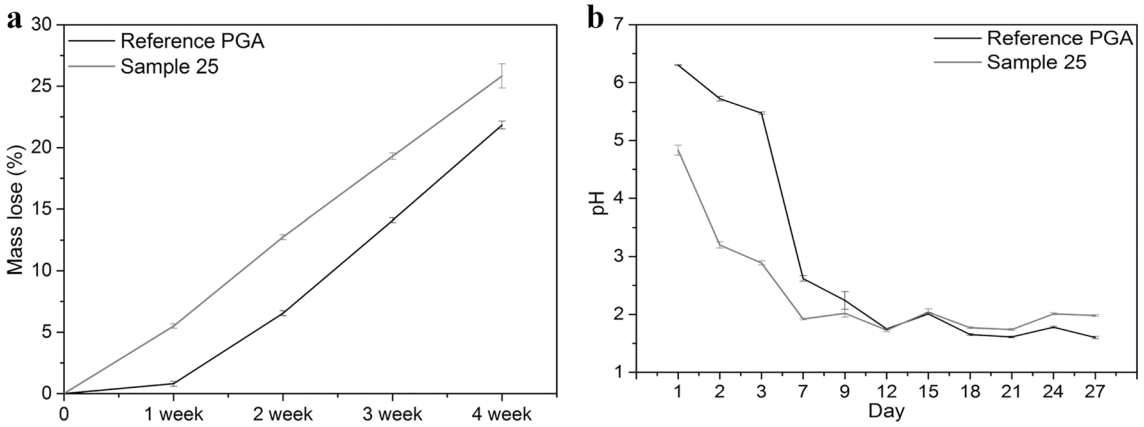

Fig. 7 **a** Degradation profiles for samples 25 and 30, and **b** pH change during degradation

21.83 ± 0.32%, respectively (Fig. 7a). After 4 weeks, the pellets were broken up and mass loss was not detected due to dispersion of the powders in the PBS. We also investigated pH changes of the PBS medium with degradation. As seen in Fig. 7b, sample 25 produced a lower pH until the 12th day and then similar profiles were obtained after the 12th day. Dramatic differences were obtained in the first 3 days. After 1 day, the pH of the medium containing reference PGA was 6.31 ± 0.01, while the pH was 4.83 ± 0.09 for sample 25 (Fig. 7b). Similar to the solubility experiment, sample 25, which has a smaller size and is a highly porous particle with a higher surface area to volume ratio, resulted in a more rapid degradation and hence a lower pH in the medium due to acidic degradation by-products (glycolic acid).

In conclusion, a simple and efficient method was developed for the synthesis of PGA, which is one of the most useful medical polymers in the clinics. The high cost and solubility of PGA are the main restrictions for the use of PGA in addition to its synthesis with a high molecular weight. This method presents a synthetic strategy that can be further extended to obtain higher molecular weights for use in clinical applications (M_w ~20000–140000 g/mol) [30], and produces uniform and easily handled PGA with high solubility, which is a challenge for the processability of PGA.

Conclusion

A versatile, cost-efficient method for synthesizing high molecular weight PGA was developed. This alternative method produces a white powdered PGA rather than a waxy brown product that is obtained by conventional melt-solid condensation methods. In this method, the solvent could be recycled and reused. In addition, improved solubility renders this method useful for producing soluble high molecular weight PGA for further applications. Highly crystalline PGA with a high melting point and a high molecular weight (M_n = 32100 g/mol) was obtained with a homogenous polydispersity index of 1.2–1.4 over 5–30 h at 154 °C with triflic acid and anisole serving as the catalyst and reaction medium, respectively. To conclude, molecular weights can be increased substantially by azeotropic distillation with anisole catalyzed by triflic acid. This method constitutes a simple, economical, and efficient path for the synthesis of PGA directly from glycolic acid without a requirement for high pressure and temperature.

Acknowledgements We gratefully acknowledge financial support by the Scientific and Technological Research Council of Turkey (BIYOTEG-5130028 Project) and Suleyman Demirel University BAP (TSG-2018–6749 Project). We also thank Zeynep Kocer for graphical designs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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