REVIEW PAPER

A review on synthesis and biomedical applications of polyglycolic acid

Kamil Budak[1] · Oguz Sogut[1] · Umran Aydemir Sezer[1,2,3]

Abstract

Poly(glycolic acid) (PGA) is an essential biopolymer due to its thermal and mechanical properties and biodegradability which provide utility for medical applications and renewable industry. For biomedical applications, production of PGA with high molecular weight is an essential factor to possess adequate mechanical stability. Primary pathways for PGA synthesis are ring-opening polymerization of glycolide (ROP), direct polycondensation of glycolic acid, and solid-state polycondensation of halogen acetates. For PGA synthesis, different systems have been developed with using varying parameters including catalysis, initiators, solvents, and reaction temperature. This review summarizes the different synthesis pathways and physicochemical properties of PGA. Biomedical applications of PGA are also discussed.

Keywords Polyglycolic acid · Synthesis · Glycolic acid · Glycolide · Biomedical applications

Introduction

Biopolymers have been used in a wide range of applications such as surgical operations and regenerative medicine [1]. Synthetic biopolymers may have better mechanical properties and thermal stability compared to some natural polymers [2]. Poly(α-hydroxy acids) group of synthetic biopolymers has been studied extensively and the most widely used polymers in this category are poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA) which are degradable under in vivo conditions and serve as proper matrix for regenerative medicine. Among them, PGA is precious biopolymer because of the its high cost regarding no technology found for cost-efficient high-scale production.

PGA is a highly crystalline polymer (45–55%) with a high melting point (220–225 °C) and a glass-transition temperature

(T_g) about 35–40 °C [3, 4]. PGA has a faster degradation rate and higher mechanical properties compared to PLA and PLGA with different PGA/PLA ratio. PGA is insoluble in many solvents due to its high crystallinity but just soluble in highly fluorinated solvents such as hexafluoroisopropanol (HFIP) until a molar mass of 45,000 g/mol [5]. Synthesis of PGA and its industrial production is challenging especially in the case of obtaining high molecular weight due to unstable and easily degradable nature of PGA [6]. Glycolic acid and glycolide are used as monomers for PGA synthesis (Fig. 1). A method for synthesizing high-molecular-weight PGA via ring-opening polymerization of glycolide is valid however it allows small quantity of PGA at high cost [7]. Yamane and coworkers reported that PGA can be also produced via condensation of glycolic acid using a dehydrating reaction which is a comparatively cost-efficient method. However, obtaining of high-molecular weight PGA with this method has an obstacle due to the equilibrium between glycolide and chain extension for the hydroxyl termination of PGA [8]. Additionally, the ring-opening polymerization of glycolide was appeared for synthesizing high-molecular-weight PGA. However, there are still obstacles in the industrial scale of high-molecular-weight PGA such as deposition of glycolide on the inside wall of the distillation lines [8].

According to the reported market research by Global Market Insights Inc., the PGA is estimated to grow with a value of more than $6 billion to over $9 billion by 2024. The global PGA market is becoming increasingly important

✉ Umran Aydemir Sezer
  umransezer@sdu.edu.tr

1 Faculty of Medicine, Department of Pharmacology, Medicine, Medical Device and Dermocosmetic Research and Application Laboratory-IDAL, Suleyman Demirel University, 32260 Isparta, Turkey

2 Department of Regenerative Medicine, Suleyman Demirel University, Institute of Health Sciences, 32200 Isparta, Turkey

3 YETEM, Innovative Technologies Research and Application Center, Suleyman Demirel University, 32260 Isparta, Turkey

Fig. 1 Chemical structure of
PGA and monomers used for
PGA synthesis

Glycolic acid Δ, vacum / Δ, H_2O Glycolide

catalyst   catalyst, initiator

Poly(glycolic acid)
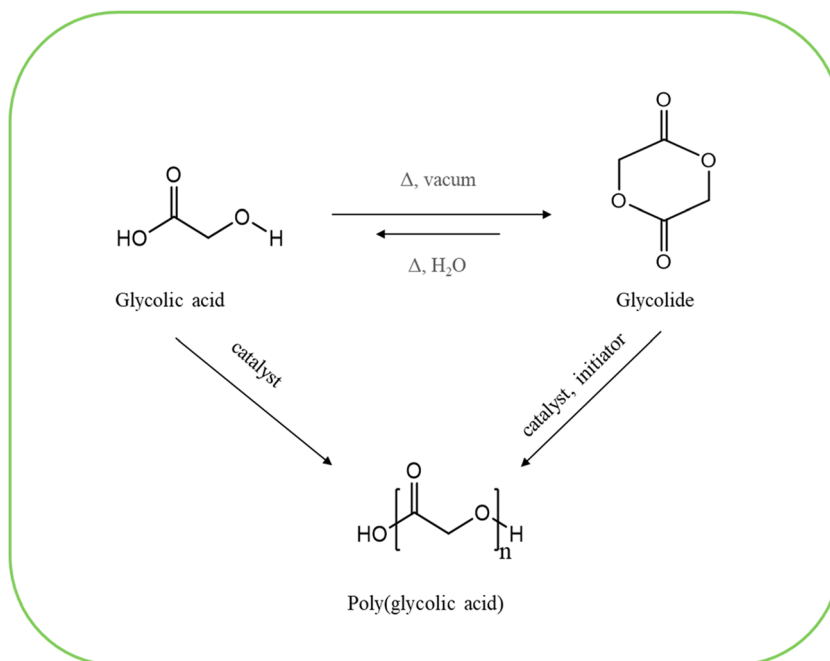
especially in the medical industry. The main applications of
the PGA in the medical area are absorbable sutures and other
advanced materials such as biodegradable bone grafts, dental
materials, scaffolds in tissue engineering and drug delivery
vehicles. It is estimated that PGA market will increase in near
future with the advances of PGA in different applications such
as packaging industry and shale gas extraction [9].

The first application of PGA as a biomaterial has been
declared in 1954 [10], and synthetic and biodegradable su-
tures made of PGA called Dexon® was developed in 1962
by American Cyanamide company [11, 12]. Dexon® suture
loses its mechanical stability in up to several weeks and
quickly absorbed by body [13]. Dexon® as an biomedical
application of PGA has been approved by the US Food and
Drug Administration (FDA) in 1969 and interest in PGA
has rapidly increased over time in terms of its use in other
biomedical applications [14–17]. PGA and its copolymers
have been used in medical fields such as in drug delivery
systems, dental and orthopedic applications due to their
good biocompatibility and biodegradability in addition to
the sufficient mechanical characteristics [1]. PGA is used in
the production of medical materials like screws, stents, and
grafts for regenerative medicine applications. Higher mo-
lecular weight reduces the degradation rate of the biopoly-
mer and this feature is crucial for tissues having longer
regeneration period such as bone and cartilage [18]. In ad-
dition, the polymer gains mechanical stability with increase
in molecular weight and crystallinity [19]. Applications of
PGA was restricted to the medical field because of the high
price of PGA. By decreasing the cost, new applications area
can appear related to the certain characteristics of PGA

including high gas-barrier properties and mechanical
strength.

Achieving and producing high molecular weight PGA
($M_n > 45,000$ g/mol and $M_w > 93,000$ g/mol) is important
for further processes [20]. In addition, sufficient mechani-
cal stability of PGA is generally obtained at molecular
weights >30,000 g/mol [20, 21]. It is very hard to achieve
to the desired molecular weight with direct condensation
method. For this purpose, the glycolide chain opening po-
lymerization is used. However, there are some difficulties
in this method such as necessity of high temperature and
expensive raw material [22]. Additionally, catalysis used
during ring-opening polymerization of glycolide could in-
dicate toxic effect. For example, tin (II) octanoate/benzyl
alcohol catalyst system give high molecular weight PGA
but tin compound is known to be toxic and should rather
be removed from the produced PGA [23].

Despite its importance and use in clinical applications,
when we look at the literature there are fewer reports on
PGA because PGA and glycolic acid are more expensive that
compared to lactic acid and PLA and PGA have highly crys-
talline properties that it is almost insoluble in widely used
organic solvents such as tetrahydrofuran, chloroform, tolu-
ene, or dimethyl sulfoxide thus it is hard to characterize and
process [22, 24]. However, PGA remains the most remark-
able material among biopolymers due to its high mechanical
strength and biocompatibility and obtaining high molecular
weight has been a focus of researchers. Different approaches
have been developed for PGA synthesis. Those synthesis
approaches can be divided into three main parts: Ring-
opening polymerization of glycolide, direct polycondensation

of glycolic acid and solid-state polycondensation of halogenoacetates [7] (Fig. 2).

PGA with different physicochemical properties can be obtained according to the selected reagents, reaction initiators and synthesis procedures which affect the characteristics of the PGA including hydrophilicity, crystallinity, melting and glass transition temperatures, molecular weight, distribution of molecular weight, terminal end groups, and the residual monomers and additives [19]. Different approaches have been investigated for the production of high molecular weight PGA [7, 22, 23]. As mentioned above, high molecular weight PGA has unique properties, which opens the door to new applications of PGA. In this study, synthesis procedures and biomedical applications of PGA will be reviewed. The copolymers of PGA such as PLGA is not concern of this review.

Different pathways for the synthesis of PGA

There are various polymerization approaches in PGA synthesis depending on factors such as initiator catalysis, solvent, pressure, and temperature. Because the mechanical properties of PGA were directly related to the molecular weight, researchers have mainly focused on obtaining high molecular weight PGA. Synthesis approaches of PGA are shown in Fig. 3.

Synthesis of PGA by direct polycondensation

This commonly used method for obtaining PGA is simple, but it is not an effective approach for high molecular weight PGA production. This method is based on the procedure of obtaining PGA by heating the glycolic acid to 175-200 °C under atmospheric pressure and then maintaining the pressure at 150 mm-Hg for up to 2 h. PGA obtained with this procedure has low molecular weight less than 10,000 g/mol due to the water appeared during the synthesis which is hard to remove from the polycondensation process [25, 26]. Zhaoyang and his colleagues have stated that the synthesis of low-molecular weight PGA by conducting the reaction at 165 °C and 70 Pa during 10 h in the presence of tin(II) chloride as catalyst [27]. The obtained PGA with low molecular weight could be suitable for use in drug delivery systems.

Synthesis of PGA by azeotropic polycondensation

High molecular weight-PGA ($M_w > 930,000$ g/mol) can be obtained by polycondensation in azeotropic solution called azeotropic condensation polymerization [22, 28–30]. In this method, the problem of removing the water formed during the reaction is overcome with the selected organic solvent. In addition, azeotropic distillation has some advantages for industrial production such as low cost and high efficiency [22, 31]. In the patent study US5444143A stated that,
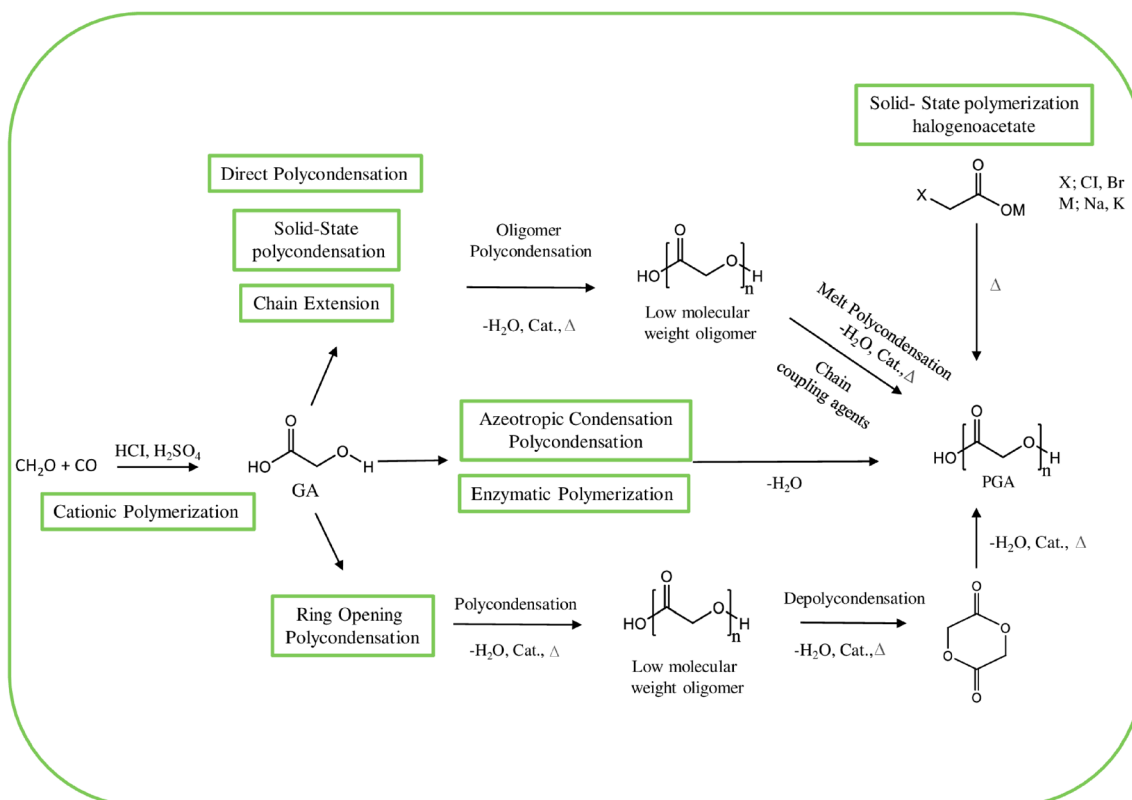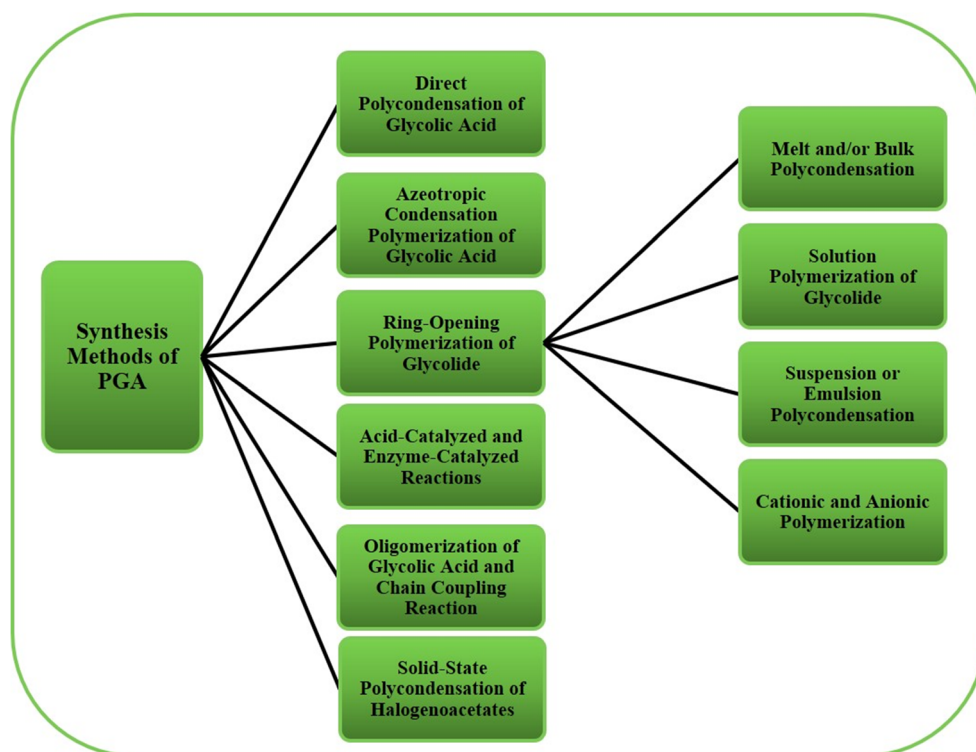

Fig. 2 Different pathways for PGA synthesis

Fig. 3 Synthesis approaches of
PGA

polyhydroxcarboxylic acid having a high molecular weight
($M_w = 20{,}000\text{--}460{,}000$ g/mol) can be obtained by dehydra-
tion condensation of hydroxycarboxylic acid with azeotropic
distillation method [32]. In another patent study high molec-
ular weight ($M_w = 50{,}000\text{--}200{,}000$ g/mol) polyhydroxy acids
were also obtained by using dean stark apparatus via
azeotropic distillation method [33]. However, glycolic acid
and lactic acid blend was used as hydroxycarboxylic acid in
these studies and therefore, these studies give us an idea for
obtaining high molecular weight PGA. In a recent study, high
molecular weight-PGA ($M_n = 32{,}100$ g/mol) with high crys-
tallinity (77%) and high solubility (147.3 mg/mL) was obtain-
ed from glycolic acid by azeotropic distillation with Dean
stark apparatus. In this study, solvent-catalyst binary interac-
tions are found to be more effective than temperature of
azeotropic distillation reaction [22].

Synthesis of PGA by acid and enzyme-catalyzed

Acid-catalyzed and enzyme-catalyzed reactions have been de-
veloped for the production of PGA. Masuda et al. conducted
acid-catalyzed reaction with trioxane and paraformaldehyde
used as reagent compounds and formaldehyde and carbon
monoxide used as sources respectively, in the presence of
chlorosulfonic acid as catalyst. The reaction is conducted at
about 180 °C for 2 h which finally give a mixture of low and
high molecular weight-PGA [34, 35]. Enzyme-catalyzed re-
actions are eco-friendly approach due to the non-synthetic
pathway which carries out PGA synthesis via isolated

enzymes. Kataoka et al. used ethylene glycol with *Pichia
naganishii* which is a bacterium from isolated soil and obtain-
ed high molecular weight PGA [36].

Synthesis of PGA by oligomerization of glycolic acid and chain coupling reactions

A different approach to increase the molecular weight of PGA
is oligomerization and chain coupling. In this method, a vari-
ety of chain linking and esterifying agents which react with
hydroxyl or carboxyl functional groups on the molecular
structure can be used [37]. However, the main drawback of
this method is being a multi-step procedure including flam-
mable solvents [38].

Synthesis of PGA by solid-state polycondensation of halogenoacetates

Another pathway for PGA synthesis is thermally induced
solid-state polycondensation of halogenoacetates which is
a solvent-free process. The homopolymerization of PGA is
accompanied by the creation of sodium chloride. In this
method, the obtained polymers usually have a lower degree
of polymerization than from solution- or melt polymeriza-
tion methods [39]. PGA can be obtained from 11 different
halogenoacetate precursors with the general formula of
$MOOCCH_2X$ which the composition of metal varies
(M = Li, Na, K, Rb, Ag, Cs) and halogen (X = Cl, Br, I)
[40]. In the study of Subramanyam, high molecular weight

PGA (M_n = 100,000 g/mol) was obtained from halogenoacetates [41].

Synthesis of PGA by ring-opening polymerization

As to the ring-opening polymerization of glycolide method, which was first used by Carothers in 1932 to obtain poly(α-hydroxy acids), the product was low molecular weight PLA [42]. So far, different approaches have carried out on ring-opening polimerization for high molecular weight polymer synthesis and first attempt was high- molecular-weight-PLA obtained in 1950 using ring opening polymerization (ROP) technique with efficient monomer purification [31]. In a recent study, Schmidt and coworkers performed high-molecular-weight-PGA synthesis in supercritical carbon dioxide using ROP method. In this study, supercritical carbon dioxide (scCO$_2$) was used as a reaction medium because of scCO$_2$ allowed for a reduction in reaction temperature compared to conventional processes. Finally, they obtained PGA with number average molecular weight of 31,200 g/mol [43]. ROP process can be divided into four reaction subtypes according to the catalyst, initiator or reaction conditions and these are melt and/or bulk polymerization of glycolide, suspension or emulsion polymerization of glycolide, solution polymerization of glycolide, cationic and anionic polymerization.

Melt or bulk polymerization of glycolide

Regarding melt or bulk polymerization of glycolide reaction mechanism, in first step, the water is removed from polymer and oligomer is obtained low molecular weight polymer. Oligomer is heated under high vacuum and to prepare raw monomer is uses proper catalysts which known as chain coupling agents. Finally, high molecular weight polymer is obtained after several purification steps. The most important issue in this process that water must be removed which composed in the reaction process otherwise water molecules attack ester bond on the polymer, which occur decreases molecular weight of polymer. Takahashi and colleagues used the melt/solid state polycondensation method of glycolic acid to obtain high molecular weight PGA [20]. In this method, firstly, low molecular weight oligomer was obtained from glycolic acid at 190 °C and then suitable catalysts were selected and continued reaction at the same temperature finally obtained PGA which possess high molecular weight. After scanning catalysis, they found that zinc acetate dihydrate is the most suitable catalyst and as a result, they have been synthesized PGA with an average molecular weight of 91,000 g/mol. Shen et al. were achieved using two different catalysis, zinc acetate dihydrate and tin dichloride dehydrate, the PGA with a molecular weight of 45,000 g/mol in their work [44].

Solution polymerization

Although the melt/bulk polymerization method has a simple procedure and high molecular weight polymer is obtained according to the selected reaction conditions, the high temperature formed during synthesis cannot be removed due to poor heat conduction. In a study by Leenslag and Pennings, it is stated that the heat produced during the reaction reduces the molecular weight [45]. There are two types of polymerization methods where this problem is relatively uncommon. These are suspension and solution polymerization methods. In one study [46], solution and suspension polymerization methods of lactide and glycolide were studied, advantages or disadvantages of these studies were compared with melt and/or bulk polymerization methods.

In the solution polymerization process, the reaction is initiated with a relatively low concentration of monomer than compared melt/bulk polymerization and as the lower viscosity allows mixing during the reaction, heat transfer takes place and thus the heat generated in exothermic reactions can be avoided. However, this method has some disadvantages as in other polymerization methods. For example, the solvent used should be removed after the polymers has been synthesis. Another disadvantage is that racemization occurs during solution polymerization. In this study by Nieuwenhuis, they stated that obtained 90,100 g/mol molecular weight polymer by using solution polymerization method with a yield between 96 and 100% [46].

Suspension or emulsion polymerization

The basis of the suspension or emulsion polycondensation methods is the vigorous mixing of water-insoluble or slightly soluble monomers to prevent the particles from interacting with each other during the polymerization process. Larger particles (20 μm and above diameters) are obtained compared to emulsion polymerization, which can be easily isolated by filtration or sedimentation [47]. British patent GB825335A is describes a suspension polymerization method for the polymerization of lactide and glycolide. In this study, inert liquid hydrocarbons with boiling point between 80 °C and 250 °C were used. However, the explosive effects of these liquids make it difficult to study. Silicone-oil was selected for stabilizer and one, two, four, five, six and seventh groups of metal halides were used as catalyst and low molecular weight polymer was synthesized at the end of the reaction [48]. Nieuwenhuis carried out various suspension polymerization studies based on the system mentioned in the patent study. In one experiment, he used gasoil-L lactide stannous octoate system, maintained the reaction temperature between 80 and 160 °C and continued the reaction time which a period of 1–2 h to 20–30 h, after that was obtained polymer which have 175,000 g/mol molecular weight [46].

Cationic and anionic polymerization

In polymerization there is a direct link between the selected catalysis and the quality of the final product. Cationic and anionic compounds can be used in the polymerization of glycolic acid or glycolide as the monomer and are separated as cationic-anionic polymerization methods. Protonic acids such as sulfuric acid and phosphoric acid are used in cationic polymerization, also Lewis acids such as zinc chloride, ferric chloride, aluminum chloride, titanium tetrachloride, boron triflouride etherate, and antimony trifluoride can be used, which provide high mass polymers [49].

There are a few studies in the literature for the polymerization of glycolide with cationic and anionic compounds used as catalysts, but there are many methods with lactone. Studies with lactones may provide ideas for preparing PGA [50]. In another study carried out recently, high molecular weight PGA (M_n = 600,000 g/mol) was synthesized in two steps by carbon monoxide (CO) and formaldehyde cationic copolymerization method [7]. In this study, biomethanol or biogas was used as a sustainable raw material source for carbon monoxide (CO), while trioxane was used as a source of formaldehyde. In first step, oligomer (M_n ~ 1800 g/mol) obtained from cationic polymerization esterification and then $Zn(OAc)_2 \cdot 2H_2O$ was used as catalysis in the second step of this study. Surprisingly, polymer having a molecular weight of approximately M_n ~ 600,000 g/mol was synthesized with this method. However, they explained that this number must be juxtaposed with the solubility limits of PGA in HFIP [7]. In other study based on the previous study, under the same reaction conditions, additionally epoxides derived from long-chain fatty acids were used this study and approximately, obtained PGA with number average molecular weight 49,000–132,000 g/mol in this study and it has also been stated that massively advanced the solubility and reduced the melting temperature of the PGA [23]. Reyhanoglu and Gokturk, similar to their previous studies, they have been used polyethylene glycol (PEG) as an epoxy derivative in the system compared previous studies and finally, were produced up to weight average molecular weight 194,000 g/mol PGA [51].

As regards anionic polymerization, catalysts which are effective for lactones include alkali metals, alkali metal oxides, alkali metal naphthalene complexes and crown ethers can be given sample. The reaction is initiated by a nucleophilic attack of a negatively charged initiator to the carbon of the carbonyl group or alkyl-oxygen, resulting in linear polyester formation [52]. Anionic polymerization of lactic and glycolide have been less studied than the coordination-insertion approach. In a study conducted with alkali metal solutions, in polymerization of ß-lactone, it is stated that a polymer having with number average molecular weight 110,000 g/mol and with over 90% yield is obtained [53]. In addition to the abovementioned methods, PGA was synthesized by different polycondensation methods using clay, ionic liquids, diphenyl bismuth bromide as catalysis [6, 54, 55]. Different approaches have been developed for PGA synthesis and low or high molecular weight PGA synthesis has been made with these methods (Table 1).

Although the ring-opening polymerization method of glycolide has drawbacks such as expensive raw material and the toxic effects of the catalysis, this method has been used still industrially. However, the relatively expensive monomer limits production of PGA and synthesis methods of PGA which have low cost, high yield and high mass has always been of interest to researchers and leads to new alternative approaches. Azeotropic condensation polymerization method with Dean-Stark apparatus is remarkable and stands out as an alternative approach for industrial applications. This method can replace ring-opening polymerization method in the future.

Evaluation of physicochemical properties of PGA

PGA and its degradation products has been shown to be non-toxic and biocompatible. The importance of PGA comes from its physical and chemical properties provided that opportunity to use of this material in different regions where are from range pharmaceutical and biomedical applications to packaging targets [57]. The properties of PGA are associated with its high molecular weight, highly crystalline structure, melting temperature, glass-transition temperature, modulus, tensile strength, elongation-at-break, and actually it is the most hydrophilic molecule according to other polyesters (Table 2).

Effect of chemical structure on the degradation rate of PGA

The degradation rate of biopolymers depends on some significant factors such as the implanted area, molecular weight and distribution, mechanical properties, chemical structure, crystallinity, morphology, surface roughness, porosity, surface charge, surface free energy, pH, presence of additives etc. As such, biopolymers displays dissimilar degradation rates from each other, give rise to different degradation duration range from days to months [19]. The degradation characteristics of PGA depend on many factors such as accessibility to amorphous phase and degree of crystallinity. X-ray diffraction, Raman and Infrared spectroscopy can give us information about crystalline structure of PGA. Two glycolic units depends on each other through orthorhombic cell. Glycolic acid macromolecules form a planar zigzag conformation passing the orthorhombic unit cell with the dimensions of a = 5.22 Å, b = 6.19 Å, and c = 7.02 Å being the fiber axis. High density of PGA (1.69 g/cm^3) demonstrate that it has crystallite

Table 1   A framework on the molecular weights of PGA obtained by different methods

No	Methods	Catalyst	Solvent(s)	Reaction temperature (°C)	Reaction time	Molecular weight (Da)	Reference(s)
1	Direct Polycondensation of Glycolic acid	–	Aromatic ethers	175–185	Up to 2 h	$M_w < 10,000$	[25, 26]
2	Azeotropic Condensation Polymerization	Group I, II, III, IV, and V metals, or salts, hydroxides and oxides of these metals.	Aromatic hydrocarbons and aromatic ethers	100–200	17–50 h	$M_w = 20,000$–460000^a $M_n = 32100^b$	[22, 32]
3	Acid-Catalyzed Reaction	Chlorosulfonic acid	Common solvents such as toluene, xylene	180	2 h	$M_w = 10,000$–$30,000$	[34, 35]
4	Enzyme-Catalyzed Reactions	Microorganism such as *Pichia naganishii*	Potassium phosphate buffer	28	1 or 2 days	$M_w < 35,000$	[36]
5	Oligomerization of Glycolic Acid and Chain Coupling	Acylation catalyst such as pyridine or pyridine derivatives	Dichloromethane, trichloromethane or ethers	100–120	3–6 h	$M_n = 25,000$–$45,000$	[37, 38]
6	Solid-statep Polymerization of Halogenoacetates	–	–	115–200	11 h	$M_n = 100,000$	[41, 56]
7	Ring Opening Polycondensation	Tin(II) ethyl hexanoate ($SnEH_2$)	Butanol	120–150	1–15 h	$M_n = 3900$–$31,200$	[43]
8	Melt or Bulk/Solid State Polycondensation	Zinc acetate dihydrate	–	190	1 and 20 h	$M_w = 91,000$	[20]
9	Solution Polymerization	Metal-alkoxides and carboxylates	Common solvents such as aromatic hydrocarbons	140–230	5–25 h	$M_w = 90,100$	[46]
10	Suspension Polymerization	Halide of metal of the first, second, fourth, fifth, sixth or seventh group	Inert liquid hydrocarbon	80–160	1 to 30 h	$M_w = 175,000$	[46]
11	Cationic Polmerization	Brønsted acids	Dichloromethane	25	3–6 h	$M_n = 20,000$	[49]
12	Anionic Polymerization	Alkali metals, alkali metal oxides, crown ethers	Tetrahydrofuran	25	10	$M_n = 110000^c$	[53]

Number-average (M_n) and weight-average molecular weights (M_w) of a commercial PGA sample were 45,000 Da and 93,000 Da, respectively [20]

[a] Polyhydroxcarboxylic acids obtained by dehydration condensation of hydroxycarboxylic acid mixture

[b] Synthesis high molecular weight PGA using Dean-Stark apparatus in azeotropic distillation

[c] Estimated from viscosimetric measurements

Table 2 Characteristics of PGA

| Property	Amount	Reference
Glass-Transition Temp (T_g)	35–40 °C	[3]
Melting Point (T_m)	225–230 °C	[3]
Crystallization Temp (T_c)	180~200 °C	[58]
Crystallinity Degree (X_c)	45–55%	[3]
Melting Enthalpy (ΔH_m)	103.5 J/g	[58]
Degradation Duration	6 weeks	[59]
Density (ρ)	1.50–1.71 g/cm^3	[60]
Tensile strength (σ)	60–99.7 MPa	[60]
Tensile modulus (E)	6.0–7.0 GPa	[60]
Elongation-at-break (ε)	1.5–20%	[60]
Specific tensile strength (σ^*)	40.0–45.1 Nm/g	[60]
Specific tensile modulus (E^*)	4.00–4.51 kNm/g	[60]

structure which consist of the strict molecular packing and the close access of the ester groups can stabilize the crystal cage and lead to the high melting point of this polymer. Additionally, the configuration lead to the insolubility of PGA in common organic solvents [61, 62].

Glycolic acid which is degradation product of PGA is a natural metabolite. This feature, with PLA, give rise to make its attractiveness among biopolymers in medical applications (Fig. 4). PGA degrades in mainly two processes: Firstly, water penetrates in the amorphous regions of the PGA matrix and hydrolytic chain scission occurs in main chains. In the second stage, when the amorphous regions are corroded, its biodegradation process maintain with degradation of the crystalline regions. The first stage of biodegradation of Dexon® sutures continued along 21 days, while the second stage continued 28 days under in vitro conditions. Weight of polymer decreased almost 42% at the end of the biodegradation stage and PGA losses all of mechanical properties [63] due to the bulk degradation of PGA leading to rapidly reduce of mechanical properties. In addition, PGA can degrade enzymatically in the presence of enzymes which display esterase activity [64]. Degradation product (glycolic acid) is removed via urinary system from the body. Despite of natural characteristics of glycolic acid, it has an acidic nature and decrease pH of the area at which the degradation process occurs and may led to necrosis.

Thermal and mechanical properties of PGA

Different synthetic pathways and catalysts supply options to modify the molecular properties of PGA such as molecular weight, molar mass dispersion, end groups, form of GA units, and chain structure. Those factors decide substantially the physico-chemical features of PGA such as, elongation-at-break, tensile strength, modulus, thermal properties and density [65]. Thermal properties including melting, crystallization and glass transition temperature are essential for processing conditions of polymers, although they are not directly relevant
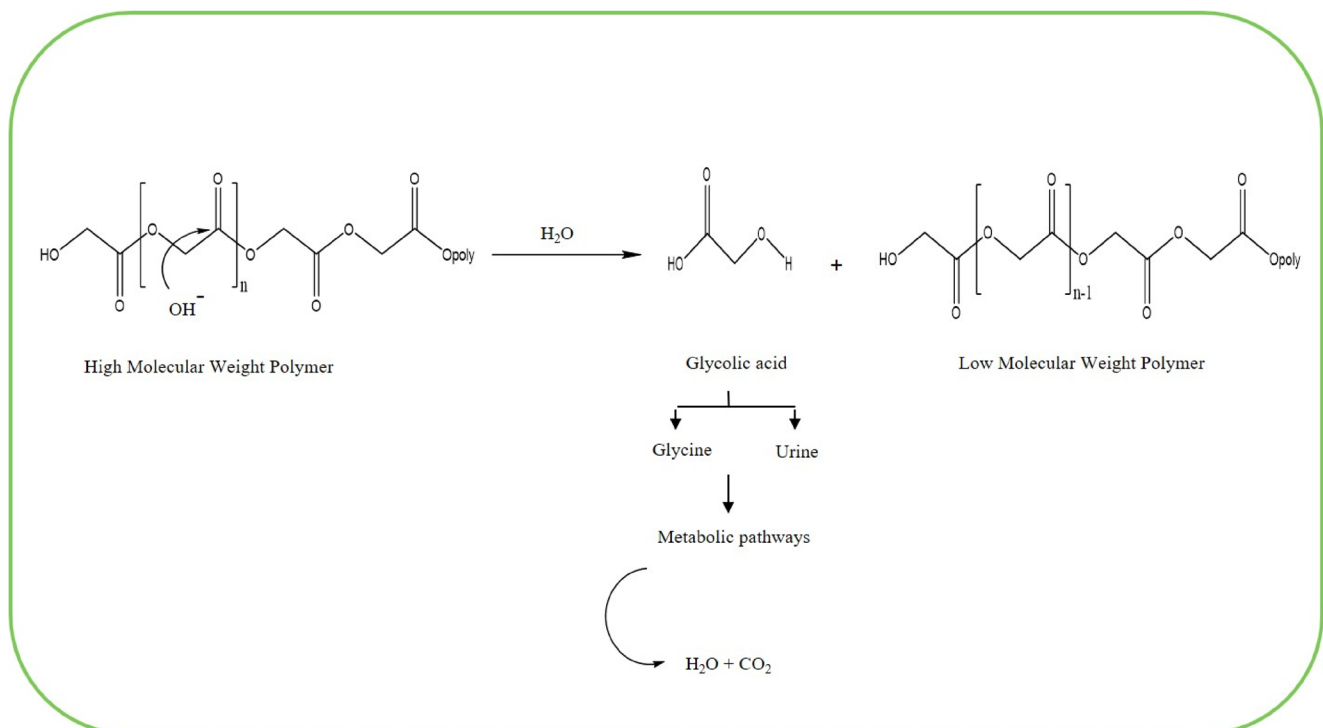
Fig. 4 Biodegradation of PGA

to biocompatibility. Differential scanning calorimetry (DSC) is used to determine the thermal properties of polymers which are important for polymers applications and give information about mechanical behavior and degradability. Glass transition temperature (T_g) value is relevant to biodegradability of biopolymers. If the T_g of a biopolymer is close to the body temperature, biopolymers can be more elastic in implanted area [66]. Melting temperature (T_m) is also another significant parameter of thermal characteristics. Upon T_m, whole polymer chain mobility happens and mechanical features of a biopolymer are nearly decreased to zero [67]. With regard to crystallization temperature (T_c), the rate of crystallization a polymer is affected by T_c [68]. High crystallinity of polymer indicate that it has high T_c at the same time [58].

Mechanical properties (Young's modulus, tensile strength, and elongation-at-break) are another important properties for biopolymers applications [69]. The mechanical properties and crystallization behavior of PGA are very dependent on the M_w and its molecular chain structure [21]. Characteristics of PGA including thermal, mechanical and degradation properties are given in Table 2. T_g of PGA is in the range of the body temperature (37 °C) which gives elasticity at the implanted area. Both T_m and T_c of PGA are high due to the its high crystallization structure.

Biomedical applications of PGA

The developments in regenerative medicine and drugs as well as requirements for biocompatible and safer materials have accelerated the tendency towards use of biodegradable materials for medical applications (Fig. 5). The general purposes of biodegradable materials use in medical applications include drug release (anti-infection, anti-tumor), operative assist (hemostasis, blood flow arrest), damage healing (organ regeneration, tissue growth), isolation (anti-adhesion), synthesis (suture, surgical bonding), reinforcement (regeneration of ligament), scaffold (cartilage, vessels), and incorporation (slow release) [70]. PGA is one of the typical biodegradable synthetic material used in medical applications through its biocompatible nature and toxicological safety due to being metabolic molecules found in humans [70, 71]. However, there are significant concerns about PGA due to its rapid degradation causing loss of mechanical strength [71]. Besides, high levels of glycolic acid leads to an inflammatory response after being resorbed by cells via the citric acid cycle [72]. PGA is also unsuitable for preventing intra-pericardial adhesions [73] and facilitating colonic anastomosis formation [74]. The studies related to the medical applications of PGA are explained in detail below.

Barrier membranes

Polymer barrier membranes are necessary for methods of guided tissue regeneration (GTR) and guided bone regeneration (GBR) [75]. A barrier membrane has important role which prevents epithelial or undesirable tissues migration in healing process of GTR and GBR applications [76]. Many barrier membranes have been improved, which are generally used in clinical applications [77]. A barrier membrane should possess specific properties such as biocompatibility, space-making, cell-occlusiveness, tissue integration and clinical manageability [78]. Also, the barrier membrane must match

Fig. 5 Reported medical applications of PGA
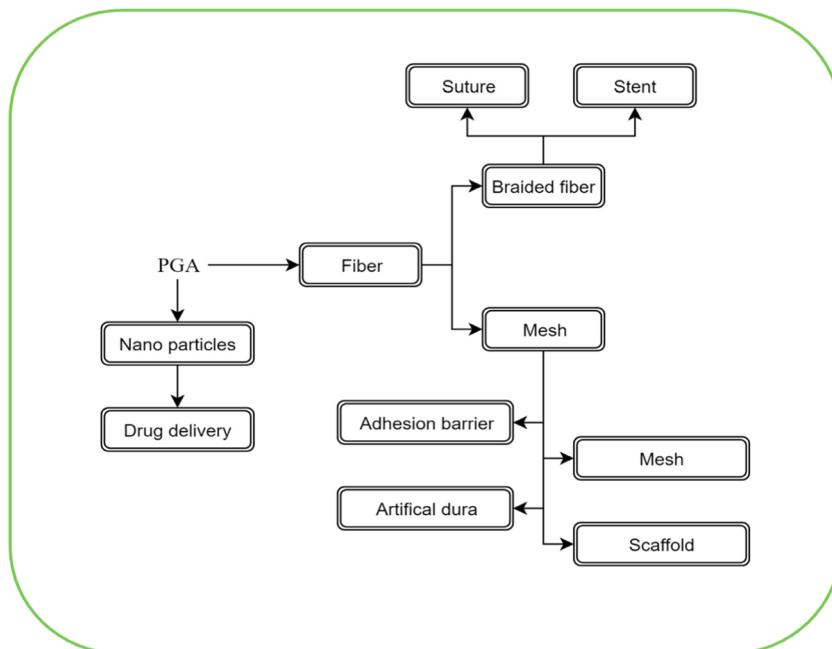
mechanical properties of the target tissue. Generally, these membranes are divided according to their degradation as resorbable and non-resorbable membranes [75, 77]. Non-resorbable membranes include expanded polytetrafluoroethylene material and titanium mesh which have restriction due to the requirement of a second surgical procedure to remove the biomaterial [79, 80]. Collagen and polyhydroxy acids such as polyglycolic acid (PGA) or polylactic acid (PLA) are the most used polymers in degradable membranes [81]. Their main advantage is non-requirement for a second surgical procedure to remove the biomaterial in addition to the elimination of potential effects of stress shielding of the regenerated tissue [82].

A barrier membrane such as artificial skin should maintain the humidity inside and should resistant to infection without inducing inflammation [70]. For this purpose, bio-based polymers like collagen and chitosan are preferred due to their high cell affinity and antimicrobial properties. However, biodegradable synthetic polymers like PGA is also used as artificial skin [83] successfully formed a joint like tissue including bone and cartilage by seeding chondrocytes and tenocytes into PGA scaffold. Besides, McVicar et al. proposed a self-reinforced PGA membrane for orbital floor repair [84]. The authors indicated that nobody faced clinical consequences because of hydrolysis of self-reinforced PGA membranes. In these applications, the tensile strength of self-reinforced PGA reduces within 4 weeks because the membrane is replaced by reorganizing tissue [85].

Drug delivery applications

A range of different materials have been employed for controlled release of drugs with a desirable physical property. The general requirement for a material to be used in drug delivery system includes being inert, free of impurities, having appropriate physical structure, and processability. In recent years, biodegradable polymers have been chosen as drug carriers for various formulations and medical use due to their deradable nature within the body [86]. These materials have been accepted due to the fact that the properties can be enhanced or changed by incorporating varius molecules such as ester, orthoester, anhydride, carbonate, amide, urea, and urethane in their basic structure [87]. Langer has studied various polymers for drug delivery and characterized the release of macromolecules from polymers [88]. Generally, PLA, PGA and their copolymers PLGA have been designed for drug delivery applications [89]. It is also possible to modify the mechanical, thermal, and biological properties of these polymers by altering its stereochemistry.

PGA has been widely used as absorbable sutures as a step for controlled drug delivery systems [90–92]. The advantage of PGA use as a drug delivery material is that PGA is broken down into metabolized molecules by body and removed from body through normal metabolic pathways. On the other hand, the insolubility in many common solvents, high melting point, cannot forming films/rods/capsules, unsuitable for solvent or melting based methods, and rapid degradation of PGA has resulted in limited studies on drug delivery systems [71, 93].

The release behavior of PGA, and thus degradation, depends on its' initial molecular weight, crystallinity, and porosity [94]. The drug delivery rates of PGA can be altered by controlling the molecular weight distribution via changes in the routes of PGA synthesis or via addition of crystals to change particle size distribution [40]. Moll and Ries explained that the release from a low molecular weight structure occurred over within a few hours rather than days, suggesting that the polymer was solubilized immediately [95]. Hurrel and Cameron showed that the release of a model drug, theophylline, from polyglycolide also depended on buffer concentration, pH and particular buffer ions on the hydrolysis reaction [96]. PGA has a great potential on and widely use as wound closure materials, surgical sutures, and tissue engineering scaffolds. However, its limited potential on drug release systems was also studied by researchers by using different parameters [97–99].

Dental applications

Biodegredable polymers are generally used for two different dental applications: as a void filler and as a guided tissue regeneration membrane. Tooth extraction is followed by packing into the cavity as a healing agent with the help of porous polymer particles [100]. On the other hand, biodegredable polymers are applied as in the film form for GTR membrane applications. The polymer film is positioned by periodontal surgery to exclude epithelial migration with the aim of supporting, slower growing tissue (also connective and ligament cells) to proliferate [101]. The crystalline structure and high molecular weight of PGA limits the clinical use of PGA for some dental applications such as osteosynthesis due to being susceptible to degradation [102, 103]. A typical complete bone healing requires more than 7 weeks, however within 4–7 weeks PGA generally loses its mechanical strength [104, 105]. On the other hand, it has been reported some negative effects arising from the difficulties in clearing the accumulated acid-degradation products [102, 105]. Okuyama and colleagues studied PGA sheets using fibrin glue to cover open wounds after resection of oral mucosal lesions of selected patients between 2010 and 2016 [106]. The authors observed a significant risk for granuloma like neoplasm (GLN) development when PGA was used on the raw surface of the tongue while no immediate abnormal postoperative bleeding (APB) was observed. It was stated that among these minor complications, GLN did not involve the recurrence of a

tumor. However, APB occurred due to PGA sheets with fluctuating adhesive forces and fibrin glue might sometimes induce life threatening situations.

The physico-chemical properties of PGA made it suitable for sustaining drug release under in vivo conditions. However, its faster degradation rates and solubility problem have limited the use of PGA-based drug delivery systems [107]. During the degradation of PGA, glycolic acid released to medium and inflammatory response might occur. Thus, medical structures including anti-inflammatory drugs, surface modifiers, or agents for enhancement of periodontal regeneration would be beneficial [108]. The mechanical integrity of PGA can be lost easily due to the rapid degradation, allowing to the release of glycolic acid, which might cause inflammatory response [107]. PGA in different forms such as fiber meshes has been accepted as attractive candidate to transplant cells however the resistance of PGA to compressional forces have been found as low [109]. Thus, PGA has been stabilized by different techniques such as copolymerization. The tensile strength and modulus of PGA are around 89 MPa and 7 GPa, respectively [110] and shows strong and flexible structure with a potential use in periodontal and oral mucosa grafts [111]. For instance, Mizutani et al. studied the suitability of polymers such as PGA as screw post materials in primary teeth and reported that PGA had appropriate strength and hydrolysis ability [112].

Orthopedic applications

Human bone exposes to different mechanical forces such as daily activities, exercises, weight bearing in a dynamic environment [113]. Bone tissue engineering and orthopedics have some successful application in addressing issues associated with three-dimensional scaffold materials and architecture [114]. PGA and their copolymers have been widely used for orthopedic applications such as bone, tendon, ligament, articular-cartilage scaffolds [113]. PGA degrades by simple hydrolysis or non-specific enzymes and produced some molecules, which can be excreted in urine or enter the tricarboxylic acid cycle [115].

A tissue-engineering alternative to cancellous bone have been developed towards mimicking structure and properties by some researchers with bioresorbable polymers such as polymer microspheres [116, 117] and porous polymer scaffolds [118, 119]. The biodegradable polymers used for tendons and ligaments replacements should maintain their tensile strength for at least 12 months for fibrous tissue to regenerate [113]. Cooper and Lu reported PGA implant showed the highest time zero mechanical strength but showed the lowest cell attachment in tendon and ligament applications [120, 121]. PGA was evaluated for tendon and ligament repair due to the limit of strength of widely used collagen [113]. On the other hand, nonwoven structures such as PGA has been also studied for cartilage repair [122]. Mikos et al. have studied a

coated PGA nonwoven mesh to overcome the loss of mechanical strength arising from proliferation and reported greater mechanical properties [123]. Besides, Moran et al. showed the effect of coating on strength and degradation and reported a less chondrocyte attachment on coated scaffold compared with PGA controls [124].

PGA is one of the suitable material for bone internal fixation devices however the hydrolytic degradation of PGA leads to the loss of mass within 12 months and loss of strength within 2 months [16]. Some researchers reported a lack of sufficient mechanical integrity in vivo with significant decrease in performance within 4 weeks when a more soluble form of PGA was used [125, 126]. On the other hand, Liu et al. indicated that PGA produced granulomatous inflammation after brain resection [127]. In the study of Hosseini et al., PGA microfibrillar scaffold was coated with poly(4-hydroxybutirate) (PHB) acid and then aligned before heating above the glass transition temperature [128]. The heat application is followed by stretching the coated scaffold to obtain an aligned and three dimensional (3D) porous fibrillar scaffolds. The authors aimed to obtain a partial welding of randomly oriented microfibers at their intersection points by coating polymer to a non-woven mesh (Fig. 6). The results showed that fibroblasts cell alignment along the direction of the PGA fibers was increased under in vitro conditions.

Kodama et al. studied islets tissue engineering from cultured cells for pancreatic islet transplantation for treatment of type 1 diabetes [129]. For this purpose, the authors enzymatically dissociated rat pancreatic islets into a single-cell suspension followed by seeding onto a PGA scaffold. To collect the tissue engineered islets, PGA and cells were isolated from medium including epidermal growth factor, nerve growth factor, and insulin-like growth factor to suspend in a thermosreversible gelatin polymer (TGP) with insulin, transferring and selenous acid. Collected cells were transplanted beneath the kidney capsule of Streptozotocin-induced diabetic nude mice. Authors concluded that the use of PGA and TGP has high potential implications for the treatment type 1 diabetes.

The enhancement and changes in molecular weight and crystallinity degree of PGA cause differences in mechanical strength. Generally, it was reported that PGA lost its mechanical strength within 6 weeks and resorbed in a few months depending on the molecular weight, purity, crystallinity and the size and shape of the implant [130]. In clinical applications, PGA structures should retain adequate tensile strength over the critical period requiring suitable conditions. Thus, it is necessary to determine the mechanical properties of PGA structures such as tensile strength, stiffness, toughness, etc., before, after or during implantation. For instance, the increase in crystallinity of PGA will increase the brittleness of implant, thus altering the resistance during healing [131]. In orthopedics applications, PGA has been also used to form a controlled release medium for drugs and other bioactive agents. Controlled release of active agents is achieved during the
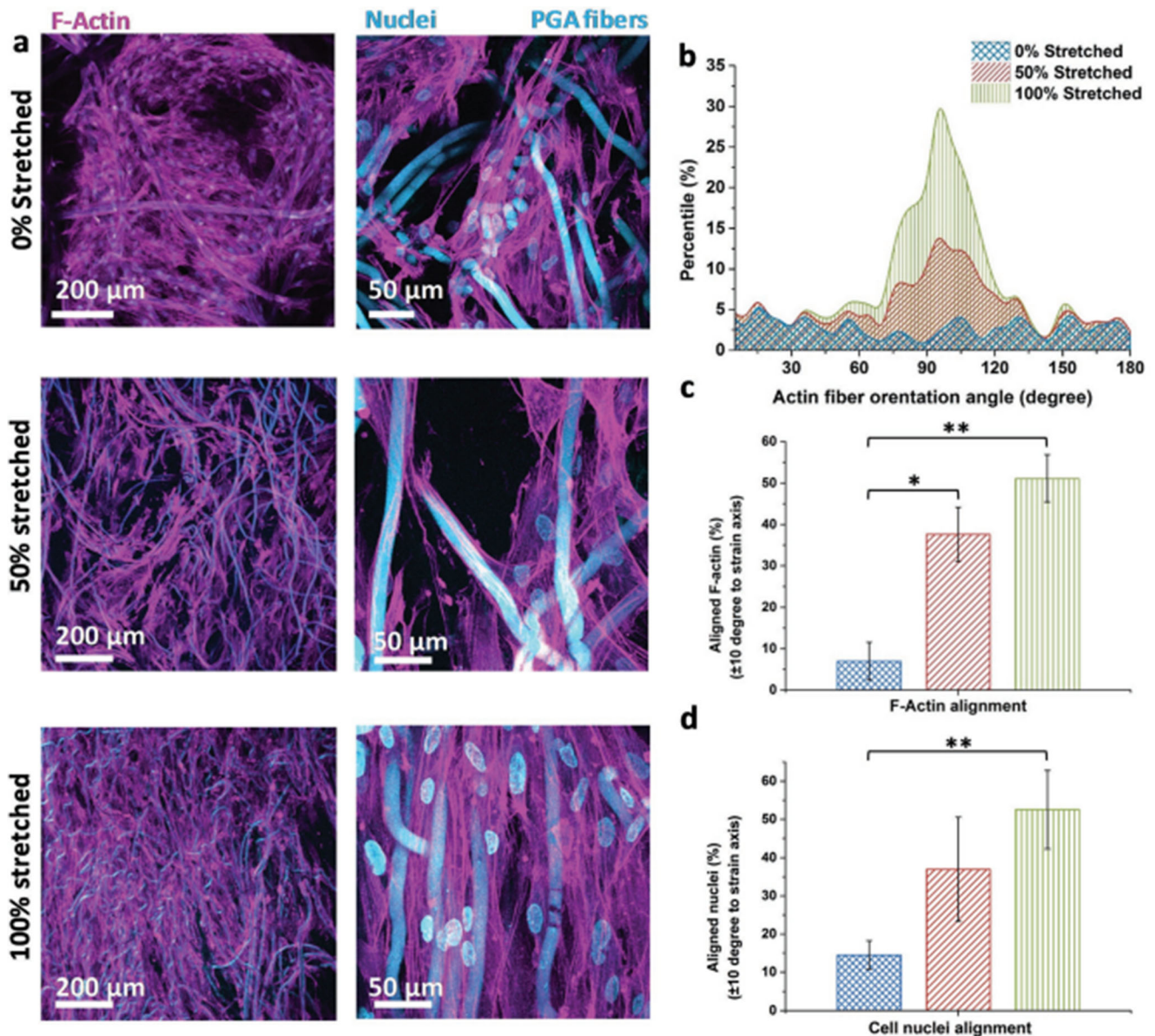
Fig. 6 F-actin (magenta) and cell nuclei (cyan) alignment analysis of cells on pre-stretched PGA scaffolds after 1 week in cell culture: **a** Maximum z-projection intensity of multi-plane confocal images of cells, **b** Respective actin fiber alignment quantifications, **c** %actin fibers and d) %cell nuclei within ±10° of the strain axis [128]. PGA fiber autofluorescence are indicated as cyan. Copyright 2017. Reproduced with permission from Wiley Online Library

degradation of PGA over time. In scaffold applications, a porous structure releasing growth factor for repair could be obtained with a simultaneous loss in mechanical properties [132]. Braunecker et al. studied PGA scaffolds with drug release ability and reported that decreasing the molecular weight in addition to the increasing the pore size and volume led to accelerated drug release [94].

Stents

Stents made of biodegradable polymers have been used as a support of the arterial wall only during vessel healing. These materials gradually transfer the mechanical load to the tissue while the stent mass and strength decrease over time without a necessity for a second surgery to remove the device. They also provide longer-term delivery of drug and/or gene therapy to the vessel wall from an internal reservoir [133]. PGA is one of the most frequently used materials for biodegradable stents [134, 135]. PGA has less strength, but faster degradation rates among the other biodegradable polymers. PGA has been successfully combined with other materials as copolymers/blends to improve its flexibility [136, 137]. These materials can degrade by simple hydrolysis of the ester bond in the polymer backbone [133]. In typical formulations, PGA degrades over a period of 6–12 months. Van der Giessen et al. have studied the effects of five

different biodegradable polymers, including PGA and reported extensive inflammatory responses within the coronary arterial wall, which might be due to the parent polymer compound, additives of polymer, biodegradation products, the implant geometry or bacterial or nonbacterial contamination [137].

Sutures

The first absorbable polymeric surgical sutures were made of PGA and have been introduced in 1970's. All polyesters are degradable however, aliphatic polyesters such as PGA, can degrade over time required for suture materials [16]. PGA has been widely used as suture materials due to its low melting temperature (>200 °C) and impressive tensile strength (≈12.5 GPa) [138, 139]. However, the degradation can occur faster than expected, as in the case of infected urogenital tract. The reason for this behavior was explained as that the bacterial enzymes digests urea and decreases the pH, leading an acceleration on the degradation rate of PGA suture [140].

In pulmonary surgery, non-woven fabric made of PGA is preferred instead of non-degradable materials since foreign body granuloma often occurs due to non-degradable polymers. To overcome these problems, PGA has been developed as a reinforcing agent for suturing native tissues [141]. However, Munteanu et al. diagnosed foreign body granuloma at PGA suture site after 10 months from resection of a cerebral glioblastoma [142]. Chu studied the effect of buffer on the degradation of PGA in terms of mechanical properties [63]. The results of this study indicated that the tensile strength of buffered PGA reduced, probably due to Na_2HPO_4, which increases hydrolysis and loss of strength. Besides, the buffers with lower pH presented higher degradation rates, as in the case of tied-chain segments of macromolecules theory. Chu and Campell analyzed the morphological changes of PGA sutures when exposed to different dosages of γ irradiation (0, 2.5, 5, 10, 20, and 40 Mrad) at different immersion days (0, 7, 14, 28, 48, 60, and 90 days) by using scanning electron microscopy (Fig. 7) [143]. The authors reported that the increase in γ irradiation caused an increase in surface cracks on

the filaments with the suture hydrolytic degradation whereas there were no cracks on the irradiated suture surface when any hydrolytic degradation was not applied. Additionally, Chu studied the effect of γ irradiation (0–20 mrad) on the enzymatic (esterase, α-chymotrypsin, and trypsin) and in vivo degradation of PGA sutures [144]. These sutures were and implanted in inbred black-and-white hooded hister rats (Liverpool strain). Different from in vitro study results, implanted PGA sutures maintained slightly higher tensile strength after in vivo degradation.

Jang et al. prepared PGA mesh to prevent T postoperative pancreatic fistula (POPF) after distal pancreatectomy and tested its effect on 97 patients (aged 20–85 years) with curable benign, premalignant, or malignant disease of the pancreatic body or tail between, on November 2011 and April 2014 [145]. The authors applied PGA with fibrin glue followed by wrapping the PGA mesh around the remnant pancreatic stump. It was reported that the rate of clinically relevant POPF was significantly lower in the PGA group than in the control group with the help of wrapping of the cut surface of the pancreas with PGA mesh. It was also stated that there was no significant difference between the PGA and control groups by means of male to female ratio, malignancy, pancreatic duct diameter, soft pancreatic texture, and thickness of the transection margin parameters.

Tissue engineering

In recent years, PGA has been utilized as fillers combined with other degradable polymers and has been used in short-term tissue engineering scaffolds such as scaffold for bone [146–149], tendon [150, 151], tooth [152], cartilage [153, 154], vaginal [155], intestinal [74], lymphatic [156], and spinal regeneration [157]. The archetypal tissue engineering technology using a biodegradable synthetic polymer scaffold involves seeding cultured cells onto a preformed porous scaffold, which is chemically designed to degrade over time in the physiological environment [158]. In vascular applications, PGA is one of the most commonly used degradable polymer
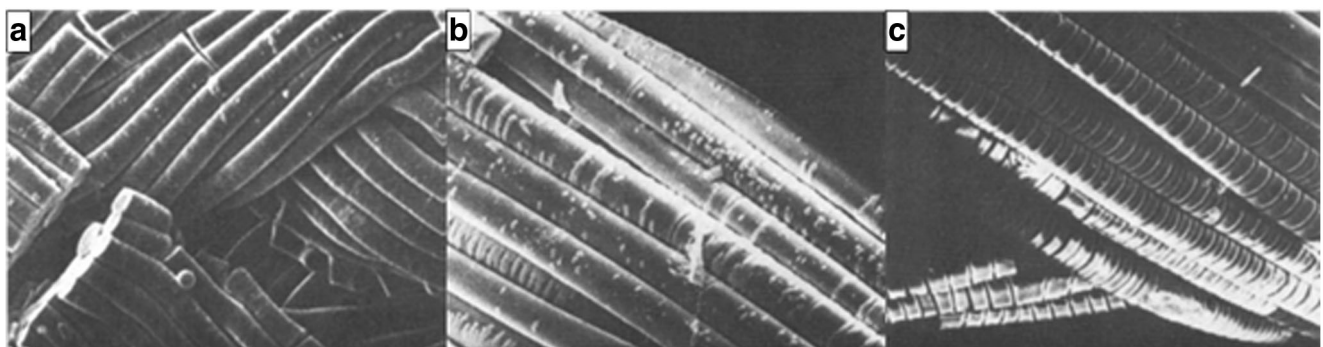
Fig. 7 SEM images of Dexon sutures subjected to 90, 14 and 40 days-degradation under in vitro conditions (PBS at pH = 7.4, 37 °C), respectively: **a** unirradiated 2–0 Dexon sutures, **b** 10 Mrad irradiated 2–0 Dexon sutures, **c** 20 Mrad irradiated 2–0 Dexon sutures. Adapted from [143]

scaffolds. PGA–polyglactin copolymers seeded in stages with autologous fibroblasts, smooth muscle cells and endothelial cells have been the first attempt in an ovine model [159]. In this study, the scaffold had been completely degraded in 11 weeks under in vivo conditions, but the resulting tissues were not deemed suitable for implantation in the higher pressure systemic circulation [159]. In another study, PGA has been used with polyhydroxyalkanoate to augment the longer term mechanical properties of the construct [160]. On the other hand, Niklason et al. showed that bovine and porcine cell seeded PGA scaffolds implanted into a porcine model had very promising results. In this study has used a bioreactor system, which showed that these engineered vessels could remain patent for up to 4 weeks, and that application of pulsatile strain in vitro improved patency rates as well as graft morphology and function [161]. Other studies include the modification of PGA scaffold to guide cell function and better control the biological response [162–164]. On the other hand, the degradation products of these systems may have some negative effects such as changing the environment by decreasing the pH leading damage to nearby cells [165] or activating the inflammatory and immune responses [165]. Wang et al.

reported that PGA degraded in vitro and changed the tissue reconstruction inducing fibrosis [166]. Aghdam et al. improved a polymer composite made of poly(ε-caprolactone) (PCL) and PGA for soft tissue engineering applications [167]. The authors found that PGA inclusion into PCL caused an increase in the average diameter of the nanofibers (Fig. 8). Thus, PGA increased the hydrophilicity and water uptake of the nanofibrous scaffolds while improving the mechanical properties of prepared scaffold with a potential for soft-tissue engineering applications.

Bailey et al. studied about a treatment for the temporomandibular joint (TMJ) disorders [168]. The authors used a spinner flask to seed PGA scaffolds with either TMJ condylar chondrocytes or mesenchymal-like stem cells derived from human umbilical cord matrix (HUCM). It was reported that HUCM constructs revealed higher amounts of collagen I and little amount of collagen II while TMJ constructs revealed little collagen I and no collagen II. This means that HUCM stem cells may therefore be an attractive alternative to condylar cartilage cells for TMJ tissue engineering applications. Weiser et al. utilized a model system based on 3 T3-L1 cells and tested this model for long term in vivo development of

Fig. 8 SEM images of electrospun: **a** PCL, **b** PCL/PGA (80/20), **c** PCL/PGA (65/35), **d** PCL/PGA (50/50), and **e** PGA nanofibers [167]. Copyright 2012. Reproduced with permission from Wiley Online Library
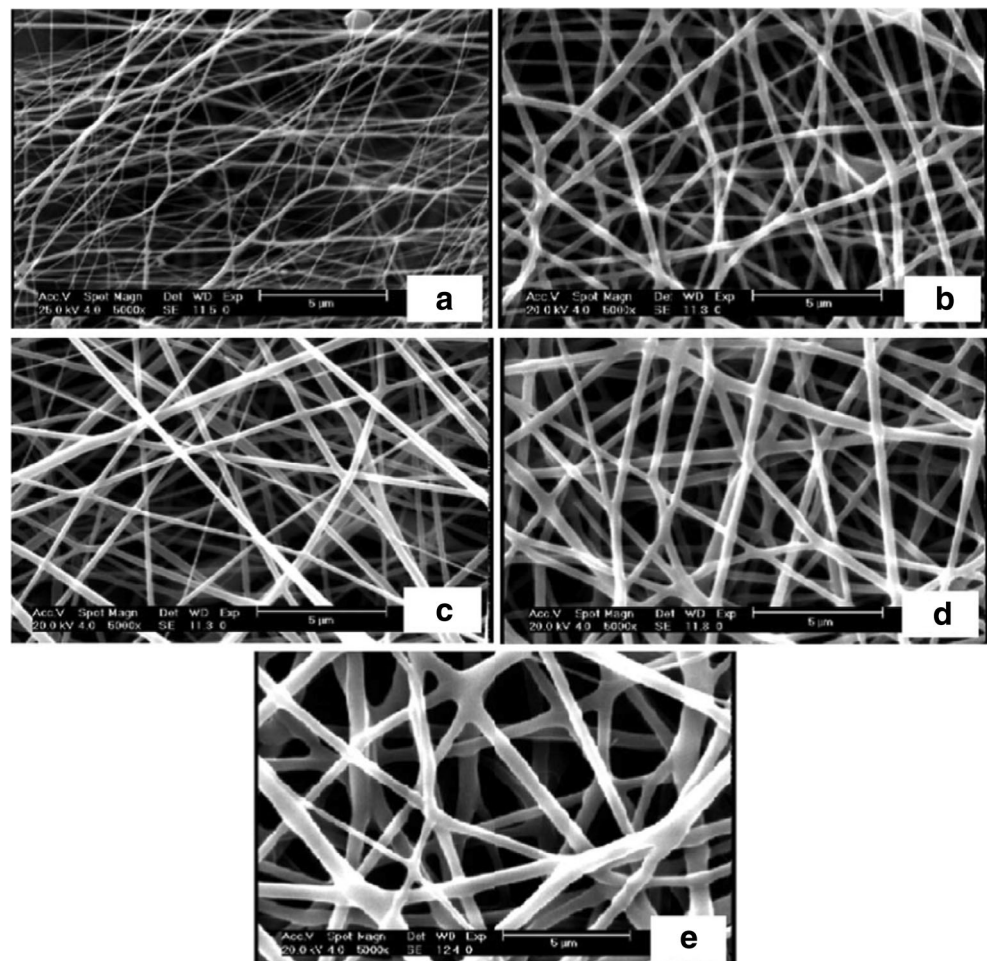
cellular constructs with varying stages of adipogenic development [169]. The authors used blank PGA fiber meshes, scaffolds seeded with uninduced 3 T3-L1 preadipocytes, and cell–polymer constructs precultivated under adipogenic conditions to implant subcutaneously into nude mice. It was reported that no fat formation occurred in constructs without adipogenic precultivation and implantation of mature fat pads resulted in adiponecrosis within the constructs. Besides, these engineered adipose tissues showed long-term survival over the period of 24 weeks.

Conclusions and future perspective

PGA is one of the most important biopolymer which has biocompatible, mechanically strong and biodegradable characteristics. The demand to PGA has an increasing trend with encouragement of environment-friendly polymer for packaging, increasing use of medical devices and extraction of shale gas. On the other hand, still, there is a few industrial producer of PGA due to extinction of cost-effective industrial scale production method. Thus, to make intense research activities, the main challenge is cost-effective production of high molecular weight PGA. Future studies will obviously focus on obtaining high molecular weight ($M_n \geq 45,000$ g/mol) PGA with cost-efficient approaches. Different application areas and novel composites or processes will also be focus of the research in PGA in future.

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