The potential of oxalic - and glycolic acid based polyesters (review). Towards CO2 as a feedstock (Carbon Capture and Utilization - CCU)

Valderrama, M.A. Murcia; van Putten, R.-J.; Gruter, G.-J.M.

Published in:
European Polymer Journal

DOI:
10.1016/j.eurpolymj.2019.07.036

Link to publication

License
CC BY

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
The potential of oxalic – and glycolic acid based polyesters (review). Towards CO₂ as a feedstock (Carbon Capture and Utilization – CCU)

Maria A. Murcia Valderrama, Robert-Jan van Putten, Gert-Jan M. Gruter

Van’t Hoff Institute of Molecular Sciences, University of Amsterdam, P.O. box 94720, 1090GS Amsterdam, the Netherlands
Avantium Chemicals BV, Zekeringstraat 29, 1014BV Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Polyester
Copolymer
Glycolic acid
Lactic acid
Oxalic acid
CO₂ utilization
CCU
Biodegradable

Abstract
Plastic materials are indispensable in everyday life because of their versatility, high durability, lightness and cost-effectiveness. As a consequence, worldwide plastic consumption will continue to grow from around 350 million metric tons per annum today to an estimated 1 billion metric tons per annum in 2050. For applications where polymers are applied in the environment or for applications where polymers have a bigger chance of ending up in the environment, (bio)degradable polymers need to be developed to stop endless accumulation of non-degradable polymers irreversibly littering our planet.

As monomers and polymers represent more than 80% of the chemical industry’s total production volume, a transition from fossil feedstock today (99% of the current feedstock for polymers is fossil-based) to a significantly larger percentage of renewable feedstock in the future (carbon that is already “above the ground”) will be required to meet the greenhouse gas reduction targets of the Paris Agreement (> 80% CO₂ reduction target for the European Chemical Industry sector in 2050). The combination of the predicted polymer market growth and the emergence of new feedstocks creates a fantastic opportunity for novel sustainable polymers. To replace fossil based feedstock, there are only three sustainable alternative sources: biomass, CO₂ and existing plastics (via recycling). The ultimate circular feedstock would be CO₂; it can be electrochemically reduced to formic acid derivatives that can subsequently be converted into useful monomers such as glycolic acid and oxalic acid. In order to assess the future potential for these polyester building blocks, we will review the current field of polyesters based on these two monomers. Representative synthesis methods, general properties, general degradation mechanisms, and recent applications will be discussed in this review. The application potential of these polyesters for a wide range of purposes, as a function of production cost, will also be assessed. It is important to note that polymers derived from CO₂ do not necessarily always lead to lower net overall CO₂ emissions (during production of after use, e.g. degradation in landfills). This needs to be evaluated using robust LCA’s and this information is currently not available for the materials discussed in this review.

1. Introduction

In December 2015, a global climate agreement was adopted at the Paris climate conference. The long-term goal (by 2050) is to ensure that the increase in global average temperature does not exceed 2 °C above pre-industrial levels [1]. This initiative arose from the growing concern over worldwide CO₂ emissions, which have been proven to contribute significantly not only to global warming but also to ocean acidification [2].

While for energy many alternatives are available, for plastic materials the only alternative carbon sources for (virgin) materials are biomass and in the long-term CO₂. As can be seen in Fig. 1, worldwide plastic consumption is increasing significantly. In 2016 production reached 355 million tons per year with China and Europe leading the market [3]. Future plastic production is projected to double by 2035 [4] and almost quadruple by 2050 [5].

By 2016, packaging represented 26% of the total volume of plastics used. However, in the same year, 95% of the plastic packaging material value was lost to the economy after short single-use application [6]. At the same time, these single-use products show low recycling rates, which is typically caused by lower value applications, complex logistics for collection and low quality recycling inputs. Traditional plastic recycling can be energy intensive and not economically viable. Feedstock (chemical) recycling for example, offers the advantage of recovering the
petrochemical constituents of the polymer. However, today the price of the petrochemical feedstock is very low compared to the cost of producing monomers from plastic waste [7]. Another example is closed-loop mechanical recycling (2% of all plastic) which keeps the quality of the materials at a similar level by cycling materials into the same application (e.g. from PET bottle to PET bottle) [6]. The approach of open-loop mechanical recycling has been more broadly adopted for large-scale treatment of plastic waste, but there are still limitations with the technology. Each type of plastic responds differently to the process according to its chemical makeup (inherent immiscibility), mechanical behavior, and thermal properties, which makes the production of recycled resins more challenging [8,9]. Furthermore, it is not possible to mechanically process certain plastics, such as temperature-sensitive plastics, composites and plastics that do not flow at elevated temperatures (as in the case of thermosets) [8]. Also, the technologies used currently cannot be applied to many polymeric materials (poly(ethylene terephthalate) (PET) and polyethylene are the focus).

Implementing strategies to decouple plastics from fossil feedstocks, to reduce leakage into ecosystems and ultimately to make plastics re-enter the economy by reuse, repurposing or recycling remain a major challenge. In Europe, a complete ban on single-use plastics has been proposed and implementation is expected in phases in the next 5–10 years [10]. This ban is suggested, because 70% of the plastic in our oceans is single-use plastic. Although Asia is a major source for ocean plastic, the EU initiative will influence consumer mind-set by encouraging more responsible material use initially in Europe. This will hopefully also have an effect around the globe.

With this in mind, strategies first and foremost for recycling of existing and novel plastic materials, either by mechanical means or via chemical pathways, need to be further developed. When recycling is not feasible, sustainable waste disposal options need to be developed and materials used in these products need to be selected with “end-of-life” as an important design parameter. In addition, reuse and repurposing should be very high on the agenda. This may require better materials to allow cheap and efficient cleaning. For applications where materials inevitably end up in nature (e.g. seed- and fertilizer coatings), (bio) degradability of polymers becomes ever more important.

Biodegradable polymers have received increasing attention since the 1970’s. Whether a polymer can be considered biodegradable or not, is defined in guidelines and definitions established by national and international standardization organizations [11]. According to the ASTM (American Society for Testing and Materials) definition, a polymer is considered biodegradable if it can be decomposed or degraded into simple molecules from the action of naturally occurring micro-organisms such as bacteria, fungi and algae [12]. Degradation is a process of polymer chain breakage by the cleavage of bonds in the polymer backbone. This is characterized by a reduction in molecular weight and mechanical properties [13]. Depending on the environment (e.g. soil, aquatic sediments, sealed vessels), different standardized tests can be applied to evaluate the biodegradability of a polymer (e.g. ISO and OECD norms).

Biodegradability is a valuable property regarding environmental and economic sustainability for agricultural applications where plastic material leads to high leakage in the environment. Currently, the agricultural sector is increasingly oriented towards the replacement of traditional plastics for biodegradable materials [14] with the formulation of novel films [15–18], compost bags, plant pots, etc. Therefore, disposal also represents a challenge for agricultural applications when there is interest in crop production growth. Collection and recycling of the agricultural plastic films becomes more demanding considering the world’s increasing population; films for greenhouses, silage and mulching are among those in higher demand, with Asia as the fastest growing market. The latter accounted for over 40% of the total plastic films used in agriculture in 2012 [19]. Some of the advantages offered by mulch films include insect and weed control, increase in air and soil temperature, minimization of soil erosion and reduced evaporation [20]. These plastics, however, are contaminated with soil after use and therefore not collected by many recycling facilities [21]. Consequently, higher costs for landfilling are involved in the production process. With this in mind, the need for replacement with biodegradable plastics becomes more apparent.

Another agrochemical application with promising prospects for biodegradable polymers is the controlled release fertilizer (CRF) technology. The factors determining the rate, pattern, and duration of release are well known and can be tuned during the preparation of the product [22]. By encapsulating the fertilizer in polymeric membranes, nutrients are continuously provided to a crop in a controlled manner [23]. In fact, about half of the applied fertilizers, depending on the application and soil conditions, are lost to the environment, resulting in water contamination [24]. Hence, the release of nutrients from CRF should ideally be linked to the nutrient uptake of the crop [17], thereby minimizing environmental pollution. The use of polymers for seed coatings also benefits agricultural systems: by covering the seeds, improvements in size, weight, and shape of crops can be achieved. This is important for an improved precision of planting. Furthermore, this technology helps to protect the seeds from pests and diseases, thus contributing to germination enhancement and a decrease of the need for fungicides [25].

Before continuing, it is good to emphasize the distinction between “biopolymers” and “bio-based polymers”. Biopolymers are polymers that occur in nature and are produced in biological systems: cellulose, chitin, starch, DNA, proteins, polyesters made by bacteria (poly-hydroxyalkanoates or PHA’s), etc. Biopolymers (under this definition) are therefore always biodegradable. Bio-based polymers are polymers (partly) derived from biomass feedstock. The bio-based content is defined by the fraction of bio-based carbon and ranges from approximately 20% (Coca-Cola’s ‘plant-bottle’ PET) to 100% (Natureworks PLA) [26]. The fact that a material is bio-based is unrelated to its biodegradability. Biodegradability is linked to the chemical structure and not to the origin of the feedstock. Poly(lactic acid) (PLA), for instance, is both bio-based and compostable, while some fossil-based polymers can also be completely biodegradable, exemplified by polycaprolactone [27]. Bio-based polyethylene (PE) or partly bio-based “plant-bottle” PET are not biodegradable nor compostable; they are identical to fossil-based PE and PET. For a material to be considered compostable it has to fulfill a set of harmonized guidelines established under the main standards ASTM, ISO or EN. According to the European standard norm UNI EN 13432 (2002) for instance, a product can be defined as compostable if under defined conditions (58 °C for 12 weeks) it is for at least 90% converted under influence of microorganisms into water, carbon dioxide and biomass [28].

The combination of the predicted polymer market growth and the emergence of new feedstocks is creating a great opportunity to develop and commercialize novel (sustainable) polymers. Polymers derived from the renewable monomers glycolic acid and oxalic acid have been previously studied for applications where biodegradability is a relevant characteristic. However, their use has been limited to high-end industries (the biomedical field and the oil and gas sector). This is related
CO₂, the electrochemical route has received significant attention, formaldehyde and methanol. Amongst the strategies to reduce the conversion of CO₂ to formate and the product tree therefrom (Fig. 2).

Based polymer building blocks. Their focus is on the 2 electron reduction (versus 1991) by 2050) reduction of CO₂ emission is required in all sectors, therefore also in the chemical industry. This is also reflected in the European reduction targets as published by the European Committee (Fig. 3).

Although CO₂ possesses a low free energy (it is thermodynamically stable), there are reactions where no external energy input is needed because the co-reactant can supply enough energy to achieve sufficient conversion. Some examples of co-reactants are hydroxides, amines and olefins [34]. In other cases, a moderate energy supply is required and the reaction occurs by attaching the entire CO₂ moiety to the other reactant to make polycarbonates from epoxides and CO₂ [35–38].

Carboxylates, ureas, lactones, isocyanates and polycarbonates can be produced in this way. Muthuraj et al. [39] recently reviewed the progress on polymer blends of CO₂-based polymers and copolymers, with a focus on materials containing aliphatic polycarbonates. Finally, some reactions require high external energy supply in the form of heat, electrons or irradiation to produce reduced forms of CO₂ such as formate, formaldehyde and methanol. Amongst the strategies to reduce CO₂, the electrochemical route has received significant attention recently.

Ganesh et al. [40] reviewed the developments in the electrochemical conversion of carbon dioxide into renewable fuel and chemicals. In this publication, the authors highlight some of the companies that are currently using this strategy to develop technologies to produce value-added chemicals or fuels. Liquid Light Inc., which was acquired by Avantium in 2016, is an example of a company that develops CO₂-based polymer building blocks. Their focus is on the 2 electron reduction of CO₂ to formate and the product tree therefrom (Fig. 2).

Avantium is looking into existing and new polyester materials that can be produced from these CO₂-based building blocks. In fact, the production of CO₂-derived polymers as a Carbon Capture and Utilization (CCU) option is still in its infancy [41].

Monomers and polymers represent more than 80% of the chemical industry’s total product volume and 99% of the current feedstock for polymeric materials is fossil-based. A transition to renewable feedstocks is required to achieve a significant effect in reducing CO₂ accumulation. One can of course debate if the chemical use of CO₂ as a polymer building block will actually have an impact on the climate or not, even if these polymers would be deployed in bulk applications. It is, however, our firm belief that in order to reach the extremely ambitious CO₂ reduction targets defined in the Paris agreement (90% CO₂ emission reduction (versus 1991) by 2050) reduction of CO₂ emission is required in all sectors, therefore also in the chemical industry. This is also reflected in the European reduction targets as published by the European Committee (Fig. 3).

Taking all of this into account, this review intends to assess the state of the art and potential future potential of oxalic acid - and glycolic acid based polyesters and their copolymers. Synthesis methods, general properties, general degradation mechanisms, and recent and potential applications will be discussed. The application volume potential of these polyesters will also be assessed as a function of production cost for a wide range of applications.

It is important to note that polymers derived from CO₂ do not necessarily always lead to lower net overall CO₂ emissions (during production of after use, e.g. degradation in landfills). This needs to be evaluated using robust LCA’s and this information is currently not available for the materials discussed in this review.

2. Polyesters as a promising CO₂ outlet

Polyesters are polymers built from repeating units linked together by ester groups. They have been proven suitable for numerous applications, in particular packaging, by providing ease of fabrication into structural materials such as films with excellent clarity, dielectric strength, tear resistance, dimensional stability, chemical inertness and good barrier properties. Polymers can be synthesized with step-growth and chain-growth polymerization. In the first process, condensation products are formed by the reaction between bifunctional molecules, with each new bond created in an individual step. During initiation, monomers react to generate first dimers, trimers and longer oligomers. This trend continues until most monomer units are used. For polyesters, a straightforward approach for step-growth polymerization involves esterification reactions between dicarboxylic acids and diols. High molecular weight polymers tend to appear only towards the end of the reaction, which implies that long reaction times and/or high degrees of polymerization are necessary when this characteristic is required.

Chain-growth polymerization involves chains with active end groups that react with unreacted monomer. Unlike the step-growth polymerization, chain-growth polymers increase only from the chain-
ends. Thus the chains expand linearly throughout the process. Radicals, carbanions and organometallic complexes are among the reactive end-groups for this type of polymerization. Common monomers for chain-growth include cyclic compounds such as lactones [43]. For certain polymers, such as poly(lactic acid) (PLA) or poly(glycolic acid) (PGA), ring opening polymerization (ROP), via a chain-growth mechanism, is preferred over step-growth polymerization. With that approach polymers with high molecular weight, better processability and more accurate property control are obtained [44].

3. Glycolic acid and its polyesters

3.1. Glycolic acid

DuPont has been one of the pioneers in developing and optimizing technologies to produce Glycolic acid (GA). In 1939 they proposed a continuous process to form glycolic acid by a reaction of formaldehyde with water and excess carbon monoxide using sulfuric acid as catalyst [45]. The reaction was carried out at a pressure above 5 atm and at a temperature between 140 and 225 °C. As part of the continuous process, a solvent mixture containing GA, water and sulfuric acid was used to absorb formaldehyde and water, was passed through a conversion chamber filled with glass beads, where it wascontacted with carbon monoxide. The formaldehyde was then converted to give a product containing GA, water and sulfuric acid. Subsequently, a part of the GA was removed by distillation or crystallization and the residue, still containing a high amount of GA, was returned to the scrubber to absorb more formaldehyde and water. In 2004, DuPont patented a technology using enzymatic synthesis to produce highly pure GA [46]. A flow of formaldehyde and hydrogen cyanide is reacted at 90–150 °C to produce highly pure glycolonitrile. The glycolonitrile is subsequently contacted with a biocatalyst with nitrilase activity, derived from the gender Acidovorax facilis, resulting in an aqueous solution containing ammonium glycolate. The GA, with a claimed purity of 99.9%, is recovered from the aqueous ammonium glycolate solution using ion exchange. The energy requirements are lowered by implementing this enzymatic biochemical process, which is reflected in economic advantages for the overall production.

Glycolic acid is currently produced by ethylene glycol oxidizing microorganisms [47], or by hydrolisis of glycolonitrile [48]. Chemo-lithotrophic iron- and sulfur-oxidizing bacteria have also been used for producing glycolate [49]. The two leaders covering the Glycolic acid market are DuPont and the Chinese company Zhonglan Industry Co. Between 1965 and 1966 the production capacity of Dupont was already estimated at 60,000 tons per year [50]. Furthermore, glycolic acid can be produced from formate, obtained from the electrocatalytical reduction of CO₂ in an electrochemical cell, as described in Fig. 2 and paragraph 4.1.

3.2. Poly(glycolic acid)

The fact that glycolic acid is a monomer that can be obtained from CO₂ makes poly(glycolic acid) (PGA) a very appealing polymer from a sustainability standpoint. PGA is the simplest aliphatic polyester, since it possesses a linear molecular structure without any side chains (Fig. 4a).

The first synthesis attempts by Carothers in 1932 [51] did not succeed in the production of high molecular weight polymer. An improved strategy achieving this goal was reported in 1954, with a process to prepare PGA directly from glycolide (GL), the cyclic diester of glycolic acid (Fig. 4b). GL was polymerized to PGA using ring opening polymerization (ROP) [52]. One of the interesting properties of PGA is its relatively facile degradability (2–4 weeks in vivo) [53]. This property has resulted in medical applications such as sutures.

PGA is hydrophilic and has a melting temperature (T_m) of about 225 °C, a glass transition temperature (T_g) between 35 °C and 40 °C, and a crystallization temperature (T_c) between 190 and 200 °C [54]. It is thermally stable until approximately 280 °C. A weight loss of 3% has been reported to occur at about 300 °C, according to the TGA thermogram (no heating rate or duration was stated) [55]. The Melt Flow Index (MFI) reported for the commercial PGA resin is 22 – 6 g 10 min⁻¹ (at 2.16 kg of load and 250 °C)[56]. It has been observed that the use of additives during processing, such as nucleating agents, plasticizers, antioxidants and catalyst deactivators, can deteriorate the melt stability of PGA [57]. PGA has a density of 1.5 g cm⁻³ and very high mechanical strength and toughness with an elastic modulus of around 6.5 GPa and tensile strength of 225 MPa (commercial resin) [56]. Bio-absorbable sutures was the first application that made use of these favorable mechanical properties [58].

Good barrier properties have been reported for PGA in several patents by the Kureha company. These properties have been compared to other important high barrier polymers for food packaging applications. Interestingly, polyvinylidene chloride (PVDC), polyethylene vinyl alcohol (EVOH) and the polyamide containing meta-xylene groups (PA MXD6) show higher oxygen permeability (OP) under high relative humidity (RH) conditions compared to PGA [64] (Table 1). Furthermore, PGA has comparable water vapor permeability (WVP) (0.165 g mL⁻¹ m⁻² day⁻¹ at 40 °C and 90% RH) to Nylon 12, the least water absorbable polyamide available on the market [64].

PGA is highly crystalline (46–60%) compared to other biodegradable polymers such as polycaprolactone (PCL) and poly-(Lactic acid) (PLLA). It exhibits a very unique molecular and crystalline structure. Montes de Oca et al. [65] have investigated the structure of PGA fibers using solid-state NMR spectroscopy; they proposed that the dipolar intermolecular interactions exist between adjacent chains packed in the crystal unit cell. This can explain the unusually high density of PGA and the slower degradation rate of PGA crystals compared to its amorphous counterpart [66]. In a different study, Yu et al. [66] investigated the crystallization and structural evolution of PGA via temperature-variable WAXD and FTIR analysis. The authors found that the intermolecular dipolar interactions and C–H···OC H-bonds were formed in the crystalline phase of PGA; this might explain the unusual physical performances of PGA compared to the other aliphatic polyesters. Furthermore, it was observed through polarized optical microscopy that PGA does not form normal spherulites but unique hedrites during crystallization. This differs from the typical morphology of other aliphatic polyesters with similar chemical structure (e.g. PLLA).

The high degree of crystallinity limits the solubility of PGA in most organic solvents with the exception of highly fluorinated organic solvents such as hexafluorisopropanol (HFIP) [67]. Although typical processing techniques, such as extrusion, injection molding and compression molding can be utilized to manufacture PGA products in the melt, rigorous control of operational conditions is required, given the polymer’s high sensitivity to hydrolytic degradation [68].

The Japanese corporation Kureha started commercial production of PGA in 2011 at the DuPont Belle plant in the USA with an annual production capacity of 4000 tons [64]. This established them as the world’s first industrial scale manufacturing facility for high molecular
weight PGA with the trademark Kuredux® [56,64]. Kureha obtains its primary feedstock, glycolic acid, from the DuPont Belle site located in the same area [50].

3.2.1. Polymerization techniques

Currently, the two most studied routes to polymerize PGA are polycondensation of Glycolic acid (GA) and Ring Opening Polymerization (ROP) of glycolide (GL). In the direct polycondensation, water is formed as a condensation product. Complete removal of water is difficult, which is avoided when polymerizing GL.

3.2.1.1. Direct polycondensation of glycolic acid. One of the first reported PGA syntheses [69] was a polycondensation of GA (step growth polymerization) at 215–245°C using antimony trioxide as catalyst, starting at atmospheric pressure and subsequently reducing this to 7 mbar. This (Scheme 1) did not become the preferred method for PGA production since the formation of water triggers the reverse reaction of the equilibrium, resulting in low molecular weight products.

Two equilibrium reactions are involved in the polymer polycondensation: (1) the dehydraion equilibrium for esterification and (2) the ring-chain equilibrium involving depolymerization to glycolide (Scheme 2).

As explained by Takahashi et al. [70], the polycondensation reaction tends to generate an oligomer with low molecular weight. This oligomer decomposes into glycolide under high temperature and high vacuum conditions required for water removal, hindering chain growth to high molecular weight polyester. This polymer degradation by formation of glycolide is in equilibrium with PGA formation.

In 2013, the VTT Technical Research Centre of Finland patented a simplified production method for producing high molecular weight PGA directly from GA [71]. The process is based on subjecting GA to condensation polymerization in the presence of a hydroxy-terminated monomer (e.g. hexanediol, butanediol) and stannous octoate (SnOct2) as catalyst. The reaction is first carried out in the molten state under a nitrogen atmosphere; subsequently, the pressure is reduced in the course of four hours from 500 to 30 mbar and the temperature is gradually increased to 190°C. Both the pressure and the temperature are maintained for 24 h; the water formed during the condensation polymerization is continuously removed. The products formed have a number average molecular weight (Mn) of about 10,800 g mol⁻¹. This is too low for applications that require the other characteristics of this material, like crystallinity and good barrier properties. For this reason, the obtained products are considered “prepolymers” and are subsequently introduced in melt mixing equipment with a chain extender (e.g. diepoxides and diisocyanates) to provide a linear polymer having a Mn between 45,500 g mol⁻¹ and 52,300 g mol⁻¹. With the described procedure, the VTT technology provides telechelic polymers of glycolic acid. The term “telechelic” indicates that the polymers/prepolymers are capable of being subjected to polymerization through their reactive end-groups. In other words, the obtained prepolymer can be copolymerized with for instance a disocyanate through reactive extrusion in a twin screw extruder. In this way, molded objects can be directly prepared once the high molecular weight has been produced.

3.2.1.2. Ring opening polymerization of glycolide. ROP of Glycolide (GL) can proceed through anionic, cationic, or coordination mechanisms using antimony, zinc, lead or tin catalysts [52] (Scheme 3). GL is usually formed in a depolymerization process of PGA [72]. Initially, low molecular weight PGA oligomers are generated from the glycolic acid by esterification (step-growth polymerization). Subsequently, these oligomers are thermally degraded through intramolecular transesterification to cyclic dimers in a backbiting mechanism. The GL formed is isolated using overhead removal by operating under reduced pressure.

3.2.1.2.1. Glycolide formation. Bathia et al. [73] obtained GL with a continuous method by heating glycolic acid at 180–200°C and gradually decreasing the pressure from 1000 to 200 mbar. The reaction occurred in the presence of an antimony catalyst (0.5–0.8 wt %). However, the process generated polymers with strong viscosity, which complicated the material’s flow. Because of this, further treatment was required to lower the molecular weight before it could be used for the glycolide preparation step. In 1993 DuPont patented an improved process [74] to obtain GL from glycolic acid oligomers using yttrium, rare earth metals, tin or antimony compounds as catalysts at relatively high amounts (2–6 wt%). The process was carried out at 180–280°C starting at atmospheric pressure and reducing this gradually to 10 mbar with continuous distillation of the cyclic dimer. By increasing the catalyst concentration, the glycolide synthesis reactions can be accelerated relative to the dehydration reactions. In this way, the molecular weight and viscosity can be maintained at low, manageable level.

An improved methodology for synthesizing high purity glycolide for subsequent ROP polymerization was patented by the Kureha Corporation in 2014 [75]. According to Yamane et al. [64], upscaaling of the conventional method used until then to prepare GL had significant issues. One of them is the high viscosity and instability of GA oligomer, which makes effective heat transfer difficult. This can promote undesired side reactions like tar formation. Another issue occurs with the

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Temperature [°C]</th>
<th>RH [%]</th>
<th>OP [mL mm m⁻² day⁻¹ bar⁻¹]</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA</td>
<td>20</td>
<td>80</td>
<td>0.0135</td>
<td>[59,60]</td>
</tr>
<tr>
<td>PLA Biophan 121</td>
<td>23</td>
<td>50</td>
<td>0.0205</td>
<td>[61]</td>
</tr>
<tr>
<td>PET</td>
<td>23</td>
<td>50</td>
<td>0.5</td>
<td>[62]</td>
</tr>
<tr>
<td>Polyethylene (PE)</td>
<td>23</td>
<td>50</td>
<td>2.00</td>
<td>[62]</td>
</tr>
<tr>
<td>EVOH 70% crystalline</td>
<td>20</td>
<td>100</td>
<td>0.15</td>
<td>[63]</td>
</tr>
<tr>
<td>PA MXD6</td>
<td>30</td>
<td>80</td>
<td>0.2</td>
<td>[64]</td>
</tr>
</tbody>
</table>

### Table 1

**Oxygen permeability of polyesters of interest.**
evaporated GL, since it tends to deposit and polymerize, resulting in obstructed distillation lines.

The process proposed by the Kureha involves initial solubilization of the oligomer using tetraethylene glycol dimethyl ether (TEGDME); a high boiling (280–420 °C) polar organic solvent. The mixture is heated to 240–290 °C at reduced pressure under inert atmosphere. Under these conditions, depolymerization reactions occur. The resulting glycolide and solvent are co-distilled out of the system and the GL is subsequently recovered. Because the obtained product is co-distilled with the organic solvent, the accumulation on the walls of the reaction vessel and distillation lines can be avoided. The mother liquor from which glycolide was isolated is then recycled to the process. In order to carry out the continuous depolymerization reaction in the same vessel, fresh amounts of the GA oligomer and organic solvent must be constantly supplied. By using this method, the production efficiency was improved and adverse reactions were suppressed.

Another issue in this process is the formation of organic acids, such as diglycolic acid (the ether formed from two glycolic acid molecules) and methoxyacetic acid, in the process, contaminating the GA oligomer. The acids were observed when using an industrial grade aqueous solution of glycolic acid for the GL production. The presence of dicarboxylic acids has a negative impact on the GL production process since dicarboxylic acids “seal” the hydroxyl termini of the GA oligomer and can suppress the depolymerization reaction. The above was solved by adding a diol (e.g. ethylene glycol, propylene glycol, and butylene glycol), which increases the solubility of the glycolic acid oligomer in TGDME and helps the depolymerization reaction system over an extended period of time. When the process is continuous, impurities can accumulate in the reaction system. These impurities can negatively affect the formation of glycolide, since a condensation reaction might compete with the depolymerization reaction. The authors found that when an alcohol is added in the depolymerization reaction system, the formation rate of glycolide is stabilized. They suggested that stoichiometric amounts of the alcohol react or otherwise combine chemically with the organic acid impurities. No explanation is provided for the high selectivity of the added alcohol for the acid impurities.

a) Cationic polymerization

In the late 1960’s Chudo et al. [76] reported a ROP of glycolide catalyzed by Brønsted acids such as sulfuric acid and phosphoric acid. This strategy led to brittle and considerably colored polymers. PGA homopolymers and copolymers have been synthesized via ROP with other cationic catalysts such as iron compounds. Dobrzenski et al. [77] for instance produced copolymers with Fe(acac)3 and Fe(OEt)3 as initiators. According to the authors, the produced polymers exhibit similar mechanical properties to analogous copolymers obtained with Sn(Oc)2 as the catalyst. Similarly, Sanina et al. [78] studied the cationic GL polymerization in the melt, catalyzed by antimony trifluoride (SbF3). The research reported a narrow polymerization temperature window (160–175 °C). At temperatures below 160 °C at low conversion, the polymer was observed to solidify; above 175 °C, a decay of the active species was observed. Similar thermal behavior was found for the bulk cationic polymerization of PGA catalyzed by a montmorillonite clay catalyst [79]. The cationic ROP mechanism (Scheme 4) was studied in the presence of Maghnite-H+ at 100 °C for 30 min.

The authors propose that the GL monomer inserts into the growing chain via the acyl-oxygen bond scission rather than via the breaking of the alkyl-oxygen bond. Furthermore, the effect of temperature on the polymer yield after 3 h at different weight ratios of Maghnite-H+ was studied. The polymerization of GL reached a maximum yield of about 95% using 15% of Maghnite-H+ content at 140 °C. Above this temperature, after 3 h, the polymer yield is lower. Although the reported information for cationic ROP of GL is scarce, the studies for other lactones, such as lactide, may be utilized to predict the course of PGA synthesis through this pathway.

b) Anionic polymerization

As is the case for lactide, possible initiators for this ROP include alkali metals, alkali metal oxides and alkali metal naphthalenide complexes with crown ethers, among others [80]. The general mechanism (Scheme 5) consists of initiation by nucleophilic attack of the negatively charged initiator on the carbonyl carbon [81]. Chudo et al. [76] reported that anionic polymerization catalysts, like KOH and pyridine, produce brittle and highly colored PGA with low
yields. In a more recent study Baez et al. [82] synthesized nine different PGA oligomers through ROP of glycolide, catalyzed by ammonium decamolybdate (NH₄)ₓ[Mo₁₀O₄ₓ] using aliphatic primary alcohols (ROH) as initiators/chain transfer agents at 190 °C for 15 min. Different molar ratios of GL/ROH in the feed led to the generation of polymers with controlled Mₙ between 1350 and 1830 g mol⁻¹. Even with such a low number average molecular weight, the polymers where observed to be insoluble in common solvents like CHCl₃, THF, DMF or DMSO. The Mₙ was determined via NMR analysis in HFIP. The low solubility of PGA polymer in most common solvents complicates characterization. Published information related to anionic ROP of GL is currently limited. However, previous studies on lactones such as PLA may serve as information base to understand possible mechanisms translated to PGA synthesis.

(c) Coordination-insertion mechanism

Certain catalysts can act as coordination polymerization initiators and are capable of producing stereoregular polymers with narrow molecular weight distribution and controlled molecular mass with well-defined end groups [51]. Some of these commonly used initiators include aluminum and tin alkoxides or carboxylates. The carboxylates are weaker nucleophiles and act more like a catalyst than an initiator when compared to alkoxides [77]. GL metal carboxylates are normally applied together with an active hydrogen compound as co-initiator in a manner analogous to that for PLA [84]. One of the most common catalysts for ring-opening polymerization, especially for lactide, is stannous octoate (Sn(Oct)₂). Adapted from [87].

According to Kricheldorf et al. [88], the alcohol functionality and the dimer are both coordinated to the Sn(Oct)₂ complex during propagation and this coordination step can occur with retention of the octanoate ligands (equation (1)) or with the liberation of octanoic acid (equation (2)).

\[
\text{Sn(Oct)₂} + \text{ROH} = \text{ROH}\text{Sn(Oct)₂} \quad (1)
\]

\[
\text{Sn(Oct)₂} + \text{ROH} = \text{RO}\text{Sn(Oct)} + \text{OctH} \quad (2)
\]

It has also been accepted that impurities (e.g. water, lactic acid, and alcohols) in the monomer can act as co-initiators, especially when Sn (Oct)₂ is used without protic additives [86]. Possible side reactions, like chain transfer, intramolecular chain scission and termination, are still obstacles that can become important when transferring to industrial scale. Intermolecular and intramolecular transesterification reactions can be influenced by temperature, reaction time, type and concentration of catalyst or initiator, and the nature of the lactone [89]. In the case of organometallic initiators, long reaction times and high temperatures favor these reactions.

When using stannous octoate as the catalyst, the general process for ROP of glycolide requires an initial temperature of approximately 175 °C, which can be gradually increased to 220 °C for a total reaction time of 2 to 6 h [90,91]. Accurate thermal control is necessary, since the polymer starts degrading above 245 °C. In addition a highly pure acid-free GL is required to obtain high molecular weight polymer. The polymer’s low solubility in most practical solvents, combined with the increase in melting point with growth, can easily lead to early polymer precipitation in the molten GL reaction medium at low reaction temperatures. This can limit the reaction yield and the molecular weight, which becomes an even bigger issue when scaling up the manufacturing process.

The complications of the traditional ROP method for PGA at mass production were overcome with a new technology proposed by the Kureha Corporation [92]. Once the pure GL monomer has been obtained, ROP is induced in the molten state and when the GL has completely reacted, the polymer is recovered as a solid to subsequently undergo solid state polymerization. Temperatures used in the process start with the melting point of glycolide (~90 °C) and increase as the polymerization progresses to that of the melting point of high molecular weight PGA (~220 °C). Overall, Kureha’s technology allows easy recovery of the obtained polymer, resulting in superior production efficiency with reasonable operational costs.

In a different study, Fisher et al. [93] introduced branching points into the PGA structure. Branching is a specific example of transesterification reaction used for control of molecular architecture. The research combined ROP with condensation of a trifunctional AB₂ monomer, catalyzed by Sn(Oct)₂. An example of this is the copolymerization of GL with 2,2-bis(hydroxymethyl) butyric acid (BHB). The authors achieved a structure with linear PGA segments of short average chain length between every branching point. As also observed by Wolf et al. [94] the branching led to a reduction in the degree of crystallinity. In research by Mhiri et al. [95] two biodegradable PGA networks with different architectures, catalyzed by the same organometallic compound, were studied. The first (Fig. 5) uses a one-step strategy by condensation of a PGA hydroxyl-telechelic oligomer, a bi-functional Diels-Alder adduct (from furfuryl alcohol and N-hydroxymaleimide), polyols (glycerol or pentaerythritol) and a diisocyanate to generate thermoreversible structures; the Diels Alder reaction allows formation of reversible covalent bonds while preserving the possibility of re-processing [96].

The second architecture (Fig. 6) was synthesized using furan-functionalized prepolymers of GL and a multimaleimide cross-linker in stoichiometric amounts. Low molar mass networks were generated to facilitate the processing and dynamic rheological analyses were conducted to confirm the polymer’s thermoreversibility. Furthermore, the viscoelastic behavior of the material was studied with a creep test. The observed long-term elastic behavior suggests the successful formation
Temperature sweep tests were performed between 150 and 50 °C in order to determine cross-linking and decrosslinking temperatures of the systems and to confirm the reversibility of the polymer networks. At 135 °C, before the crosslinking starts, the system is liquid-like. With time and decreasing temperature, the network is gradually developed until densely connected networks are formed at 50 °C. Hence, the authors proposed that the lowest temperature within the studied range is the most suitable temperature to perform the crosslinking step, which occurs through the rebuilding of connections. Since the polymer undergoes gelation (with crosslinker connecting polymer chains) in response to heating/cooling cycles, re-processing is possible within this temperature range.

Furthermore, the influence of temperature on viscoelasticity was investigated with a frequency test. At 50 °C dominant elastic behavior was observed with a storage modulus ($G'$) higher than the loss modulus ($G''$) for all samples. The modulus values remained constant until 80 °C, but above this temperature they decreased until reaching a common value at 135 °C. The performance of these networks shows the potential of tailoring the thermal, mechanical and degradation properties of the polymer.

More recently, Aijun et al. [97] proposed a method for improving the thermal stability of PGA during processing; three dihydrazide metal chelators (Fig. 7) were synthesized and melt mixed with PGA in a twin screw extruder using stannous chloride (SnCl$_2$) as the catalyst. The chelator N,N-bis(salicyloyl) dodecanedioic acid dihydrazide (Fig. 7a) showed the highest efficiency in improving the polymer’s thermal stability by contributing to catalyst deactivation. Polymer degradation studies were carried out at different temperatures (260–320 °C) in the presence and absence of this chelator, where the remaining PGA polymer weight percentage was followed in time. The TGA results (heating rate 10 °C min$^{-1}$) revealed that at 240 °C the amount of remaining PGA is much higher in the presence of the metal chelator (88.5%) than for pure PGA (23.3%). Above 280 °C the thermal stabilization caused by the metal chelator is less significant. This research contributes to the development of more efficient PGA processing conditions, which could benefit commercial scale production.

Nevertheless, the requirements for some of the previous protocols include high temperatures, multistep processes, high vacuum conditions and long reaction times, which are all unfavorable for the implementation at commercial scale. Until now, the majority of studies dealing with the property assessment of PGA (mechanical and barrier properties) have been performed by the Japanese corporation Kureha.

### 3.3. Copolymers with glycolic acid

Copolymerization of GL/GA with other monomers allows, among other advantages, the tailoring of properties by variation in the macromolecular architecture. At small scale, copolymers of PGA with different structures have been prepared mainly via ROP. Studies have reported the decrease of melting/processing temperatures, improvements in mechanical properties and resistance to hydrolysis of PGA copolymers in comparison to the homopolymer. The effect of monomer sequence on the degradation rate has also been assessed.

#### 3.3.1. Poly(lactic-co-glycolic acid)

Copolymerization of GL/GA with lactide has gained significant
attention through the years since a wide range of products with modulated properties can be achieved through this approach. Poly(lactic-co-glycolic acid) (PLGA) is an aliphatic polyester of increasing interest for the biomedical field due to its biocompatibility and degradability in vivo. The mechanical and physicochemical properties of this copolymer are strongly determined by the ratio of the monomers.

Lactic acid (LA; 2-hydroxypropionic acid), the constituent unit of poly(lactic acid) (PLA) and one of the monomers for PLGA synthesis, is produced via fermentation or chemical synthesis and it has two enantiomeric forms: L- and D-lactic acid [98]. Therefore, PLA can be synthesized in three general forms: poly(L-lactic acid) (PLLA), poly(D-lactic acid) (PDLLA), and poly(D,L-lactic acid) (PDLLA) [99]. Most of the lactic acid produced for commercial purposes is made by the bacterial fermentation of carbohydrates (corn, beet and sugar cane) using homolactic organisms. Homolactic fermentation yields two molecules of lactic acid, respectively. Lactide is obtained form of the lactic acid), catalyst and temperature [102]. Castro-Aguirre

percentages of lactide isomers depend on the starting polymer (isomeric PLGA degrades by hydrolysis of its ester linkages [104]. Because PLA properties and degradation reactions by incorporating GL. In water, has methyl side groups, it is more hydrophobic than PGA. PLGA co-

et al. [103] reviewed the status of PLA production, processing techniques and found amorphous structures for both of the copolymers with Tg determined at ~35 and ~41°C, respectively and the copolymers were found to thermally degrade above ~269°C (PLGA 70/30) and ~276°C (PLGA 50/50).

Sousa et al. [111] studied PLGA membranes for tissue regeneration. The samples were divided into three separate groups to investigate the following variables: heat, humidity and/or the effect of saline water as plasticizer. Plasticization can augment plastic elongation and reduce brittleness. It can also contribute to reduced processing temperatures, reduced sticking to molds and enhanced wetting. The membranes from the first group were only dried at room temperature. The ones from the second group were plasticized in a saline solution at 55°C for 10 s and then cooled down at room temperature, while the membranes from the third group were additionally cooled down in the saline solution until 10°C. Tensile strength tests performed on the samples revealed a higher performance for the first group (16.7 MPa) when compared to groups II and III (14.6 MPa and 13.9 MPa, respectively). Although dried membranes showed the highest tensile strength compared to membranes that had been plasticized or cooled after plasticizing, the differences are not significant enough to confirm that this is the most suitable option in terms of mechanical behavior. Some of the general properties reported for copolymers with different LA/GA ratios are presented in Table 2.

3.3.1.1. Polymerization techniques. Similar to PGA, two synthetic strategies can be applied to synthesize PLGA. The first is a direct polycondensation reaction of lactic acid with glycolic acid, which tends to result in a low molecular weight polymer [112]. The second is ROP of lactic and glycolic acid, which allows the synthesis of high molecular weight copolymers with competitive mechanical properties [72,110]. The process parameters for both polymerization routes depend on the co-monomer composition. Copolymers with high GL/GA content require temperatures closer to those used for polymerization of PGA. With higher lactide content in the feed, required polymerization temperatures are lower, comparable to those used for PLA synthesis.

Table 2

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Tg (°C)</th>
<th>Tm (°C)</th>
<th>Td (°C)</th>
<th>σ (Mpa)</th>
<th>Elongation (%)</th>
<th>Degradation (in water)</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(D,L-lactide-co-glycolide) 85/15</td>
<td>50–55</td>
<td>*</td>
<td>n.r</td>
<td>64</td>
<td>3–10</td>
<td>5–6</td>
<td>37 [107,108]</td>
</tr>
<tr>
<td>Poly(D,L-lactide-co-glycolide) 10/90</td>
<td>40</td>
<td>205</td>
<td>n.r</td>
<td>111</td>
<td>n.r</td>
<td>6</td>
<td>25 [96]</td>
</tr>
<tr>
<td>Poly(glycolic acid)</td>
<td>35</td>
<td>225</td>
<td>280</td>
<td>117</td>
<td>13</td>
<td>2</td>
<td>99 [56]</td>
</tr>
<tr>
<td>D,L-lactide acid</td>
<td>55–60</td>
<td>*</td>
<td>250</td>
<td>60</td>
<td>10</td>
<td>9</td>
<td>37 [44,114]</td>
</tr>
</tbody>
</table>

* Amorphous; Td = onset of decomposition; σ = Tensile strength; n.r = not reported.
3.3.1.1.1. Direct polycondensation. High molecular weight PLGA produced via melt polycondensation (Scheme 7) in the absence of solvent has hardly been reported so far [113]. Removal of water from the system and purity of the co-monomers are the most challenging aspects of the process. However, some studies in which azotropic distillation was combined with the condensation process showed the generation of high molecular weight copolymers.

Ajioka et al. [113] prepared high molecular weight PLGA through a condensation reaction. L-lactic acid and glycolic acid can be converted into glycolic acid (G) and L-lactic acid (L) in the presence of a tin powder catalyst. Water was removed using a tube packed with molecular sieves mounted on top of the reactor. After the reaction, the mixture was first concentrated by removing 50% of the volume, followed by chloroform addition. Catalyst was subsequently removed using an HCl solution. The final product, with a Mw of 160,000 g mol$^{-1}$ and a melting point of 135 °C, was obtained after precipitation in methanol, followed by recovery through decantation. These last purification steps are necessary to eliminate solvent traces, unreacted monomers and catalyst in order to generate a polymer with optimal properties for specific applications. Although high molecular weight polymers can be obtained with this method, the complexity and cost of the process are high compared to other strategies. Given the amount of solvent and anti-solvent this would require, such a process is essentially impossible to commercialise. Furthermore higher Mw fractions are more susceptible to precipitation, skewing the numbers to higher Mw’s.

Gao et al. [115] synthesized PLGA (LA/GA 90/10 and 70/30) with high Mw (70,000 and 45,000 g mol$^{-1}$, respectively) inspired by a similar procedure of melt polycondensation using azotropic removal of water. Initial dehydration of LA and GA into oligomers was followed by gradual heating to 180 °C at 0.013 MPa using equal amounts (0.5 wt%) of SnCl$_2$ and p-toluene sulfonic acid monohydrate (PTSA). Polycondensation was maintained under these conditions for twenty hours. Interestingly, the study discusses the effect of GA addition on the racemization of PLGA blocks. For this purpose, samples of poly(D,L-lactic acid) PDLLA and poly(L-lactic acid) PLLA were synthesized with the same process and used as the references of racemization for the microstructural analysis. At high temperature and high vacuum, ROP can induce the racemization of L-LA units and transesterification, which increases with initiator basicity and reaction time. This was found by Kricheldorf et al. [116] who studied the influence of various catalysts (metal oxides, carbonates or carboxylates) on the optical purity of poly(L-lactide). According to this research, the extent of racemization increases with increasing basicity of the catalyst. The authors suggested that deprotonation of the monomer is the main source of racemization, which is accelerated with increasing temperature. Gao et al. [115] stated that similarly to the ROP, racemization of L-LA units can also be induced in polycondensation of PLGA under high temperature and high vacuum. This racemization was found to increase with increasing fraction of Glycolic Acid. In the melt polymerization of PLLA with Sn(II) catalysts (e.g. SnO, SnCl$_2$) and TSA, the terminal groups of PLLA are coordinated with the catalyst center of Sn(II). TSA is used as a ligand to fill the open coordination sites of the catalyst, so side reactions that can lead to racemization of PLLA are prevented [117]. The authors suggested that in L-LA/GA copolymerization, the terminal groups of GA with high reactivity could be preferentially coordinated to the catalyst. Thus, the coordination of L-LA and TSA to prevent side reactions could be hindered. Consequently, racemization of PLGA increases with GA fractions.

The authors observed that PLGA’s solubility in common organic solvents gradually decreased when the polymerization was carried out for up to six hours. With longer reaction time, the solubility of PLGA was improved. Such behavior suggests higher reactivity of GA, which may lead to PLGA copolymer chains containing GA rich blocks, formed initially and L-LA rich blocks formed later rather than randomly incorporated sequences obtained when both monomers would have the same reactivity such as for example using L- and D-lactide [113]. This higher reactivity of GA compared to LA and other monomer combinations has been reported before [72] and can be explained by the fact that GA has a primary alcohol. In addition, GA is less stable and more prone to nucleophilic attack than LA [118]. The authors proposed that randomization via transesterification may reduce both GA and LA block lengths in a gradual manner, which can promote PLGA solubility and lower PLGA crystallinity. PLPGA 90/10 showed a degree of crystallinity of 25% with smaller crystallites than those of PLLA with 58% degree of crystallinity. Gao et al. [115] explained that the crystal lattice of L-LA blocks tends to exclude GA units, and that the incorporation of GA units in the L-LA blocks causes lattice defects. 3.3.1.1.2. Ring opening polymerization of glycolide and lactide. Although the ROP route involves more steps than direct polycondensation, this is the preferred synthesis method when high molecular weight PLGA is desired (Scheme 8). Crystallinity and polymer properties can be modulated via the ratio of the monomers and the monomer distribution. Molecular weight control during
polymerization is crucial when a specific application is targeted. In order to achieve this, some strategies are available: adjusting polymerization temperature, polymerization time, catalyst type and concentration, the vacuum profile and the addition of molecular weight controllers [119,120].

In some cases, under appropriate polymerization conditions, the termination and transfer reactions can be limited to such an extent that the ROP can be treated as living. In a living polymerization, the propagating centers on the growing chains do not terminate and do not undergo chain transfer. When this occurs, a linear dependence between the mean degree of polymerization (DP) and the monomer to initiator molar ratio is observed [86]. As a consequence, controlled molecular weights and narrow distributions are obtained.

However, under typical conditions for the copolymerization of glycolide and lactide the incorporation of glycolide induces primary alcohol chain ends, for which transesterification side reactions are likely to take place [86]. This was observed by Gilding et al. [72] when using stannous octoate (0.3 wt%) as the catalyst at a reaction temperature of \( \sim 220 \) °C. Under these conditions, approximatively 80% of the monomers was converted to polymer within the first 30 min of the polymerization. An additional 3½ hours of reaction yielded a further 16% conversion, thus 96% was determined as the limit of the polymerization. The residual 4% consisted of glycolide and lactide in equal amounts. At reaction times over 4 h, molecular weight distribution broadening was found as a consequence of additional transfer reactions. According to the authors, besides its role as polymerization catalyst, stannous octoate may also be associated with the growing chain in reversible chain transfer reactions. Additionally, temperature control is one of the essential actions in the polymerization process. If the temperature is too high, the reaction is thermodynamically unfavorable and the polymers can undergo depolymerization [86].

Vacuum control as an alternative parameter to control molecular weight was found to be effective in the PLGA synthesis when keeping the other parameters constant [119]. However, it is not an easy factor to keep constant, especially at high vacuum (below 1 mbar). Other process variables, such as temperature, polymerization time and catalyst concentration, have not proven to affect molecular weight control, mainly when low molecular weight polymers are desired. The use of molecular weight controllers, such as lauryl alcohol (C\(_{12}\)H\(_{26}\)O), is a favorable option to control polymer growth. They react with the carboxylic endgroup of the growing polymer chain, which blocks the reactive group for propagation. Wu et al. [121] studied the effect of lauryl alcohol addition as a molecular weight controller on PLGA synthesis. A linear relationship between the amount of lauryl alcohol incorporated in the PLGA and the molecular weight was observed. These results showed a more accurate control of the polymerization process, which allows for improved reproducibility of the polymer's molecular weight.

Avgoustakis et al. [96] studied the effect of catalyst concentration on the molecular weight at different temperatures for ROP of lactide and glycolide using Sn(Oct)\(_2\). At low catalyst concentrations an increase in the molecular weight was observed with increasing catalyst concentration for 130 and 190 °C. Interestingly, this behavior continued until reaching a maximum molecular weight after which a decrease in molecular weight was observed for the highest levels of Sn(Oct)\(_2\) catalyst. Above 190 °C, the authors observed polymer decomposition and brown coloration. These results are in line with previous research by Gilding et al. [72], according to whom Sn\(^{2+}\) can accelerate both the polymerization and depolymerization rate.

Gorrasi et al. [122] recently reported an anionic mechanism for ROP of glycolide and L-lactide, using sodium hydride as the initiator. The synthesis was performed for three hours at 140 °C under inert atmosphere. Here, the sodium hydride did not only act as the initiator but also as reducing agent for the carbonyl groups. Based on the presence of alcohol-functionalized end groups in the \(^1\)H NMR spectra, the authors concluded that a hydride reaction involves cleavage of the acyl-oxygen bond of the cyclic diesters (Scheme 9). According to Albertsson et al. [80], anionic polymerization can also occur through alkyl-oxygen cleavage, resulting in both carboxylate and alkoxide end groups; this was confirmed in the study conducted by Gorrasi, who also observed the appearance of carboxyl end groups in the MALDI mass spectra. The obtained polymer with random structure evidences the possibility of exploring less harmful, non-toxic catalysts (e.g. metals based on aluminum, zinc, yttrium, calcium, etc.) as alternatives to those generally used for polyester synthesis in general and PLGA synthesis specifically.

### 3.3.1.2. Polymers derived from PLGA

Currently, the majority of studies regarding PLGA copolymers have focused on biomedical applications. Copolymers of PLGA with polyethylene glycol (PEG), forming diblock (AB) or triblock (ABA or BAB) molecules, for instance, have been proposed for drug delivery applications, typically in the form of nanoparticles, hydrogels and micelles. PEG can be used as hydrophilic segment in copolymers with hydrophobic and biodegradable polyesters [123]. The absence of functional groups in PEG’s structure prevents interactions with biological components [124]. Currently, polyethylene glycol (PEG) is often covalently bound to a drug or therapeutic protein (“Pegylation”) to “mask” the agent from the host’s immune system and increase its hydrodynamic size, which prolongs its circulatory time (effectiveness).

Wang et al. [125] reported the synthesis of PEG-PLGA nanoparticles (NPs) as carriers for arsenic trioxide, an effective therapeutic agent for acute promyelocytic leukemia used in medical treatment. The PEG-PLGA copolymer was prepared by ROP using D,L-lactide, glycolide (molar ratio 1:1) and methoxy poly(ethylene glycol) (MePEG) in the presence of Sn(Oct)\(_2\) as the catalyst. The reaction was carried out at 180 °C for five hours under vacuum, forming a copolymer with a M\(_{\text{wp}}\) of 16,500 g mol\(^{-1}\). Subsequently, the product was used to prepare PEG-PLGA NPs via the emulsification solvent diffusion method. In vitro, the NPs exhibited a release time of more than 26 days. The same synthesis method has been proposed by Liu et al. [123] to produce PLGA-PEG micelles (amphiphilic block copolymers in aqueous solution) using a cosolvent evaporation method with different ratios of PEG, L-lactide and glycolide. The copolymer was dissolved in chloroform and the solution was then mixed with water to induce microphase separation of PEG and PLGA blocks. Finally the solvent was evaporated under stirring and the micellar solution was filtered. Micelles of spherical shape with a diameter of about 50 nm were obtained. Interestingly, besides good compatibility in vitro, it was observed that the composition and molecular weight of the copolymers do not affect this biocompatibility. In previous work by Tobio et al. [126] it was demonstrated that in a diblock conformation of PLGA-PEG, PEG chains orient themselves towards the external aqueous phase in micelles, surrounding the encapsulated species. The PEG layer acts as a barrier, reducing interactions with foreign molecules by steric and hydrated repulsion, improving the stability and therefore the shelf-life.

This coexistence of hydrophilic and hydrophobic properties within a polymer has been studied extensively for biomedical applications. In fact, an appropriate balance between these two types of blocks can lead
to the development of valuable degradable materials as well as the formation of aqueous solutions that are able to generate a gel when exposed to heat (thermogelation) [127]. Jeong et al. [128] prepared ABA type biodegradable thermal gels for drug release systems. The ROP of D,L-lactide and glycolide initiated by monomethoxy(poly(ethylene glycol) led to the generation of a low molecular weight copolymer hydrogel: poly(ethylene glycol-b-(D,L-lactic acid-co-glycolic acid)) (PEG-PLGA). The diblock polymer was then coupled by hexamethylene diisocyanate to form ABA triblock copolymers. The obtained structures were water soluble, biodegradable, and thermally reversible. Furthermore, they could be injected as liquids and form a highly viscous gel in response to body temperature. For thermally responsive polymers, the PLGA hydrophobic units form associative crosslinks and the hydrophilic units of PEG guarantee that the copolymer molecules stay in solution. At low temperatures, the aqueous solution is dominated by hydrogen bonding between PEG segments and water molecules. With increasing temperature, the hydrogen bonding becomes weaker, while hydrophobic forces involving the hydrophobic PEG segments are strengthened, leading to the formation of a gel [104]. Ewoniq (Essen, Germany), commercializes a PEGylated PLGA with a PEG content between 3 and 7 wt%. This product has a Mw = 33,500 g mol⁻¹ and inherent viscosity of 0.93 dl g⁻¹ [129].

In a different study, Ho Choi et al. [130] prepared degradable elastic matrices for scaffolds in tissue engineering using copolymers with a triblock ABA structure. PLGAs with different LA/PGA ratios were used as the A block and PCL as the middle block. Because PCL has a very low Tg, it was observed that an increase of the Mn of P(LGA-CL-g-PLGA) diblock copolymers produced at GL content of 50% and lower. Furthermore, it was found that the nature of the sequence distribution also has an effect on the degradation rate in tissue engineering. The di-block copolymers showed an elastic and rubber-like behavior in comparison to PLGA. Although the values observed for mechanical strength of these two samples were water soluble, biodegradable, and thermally reversible. Furthermore, they could be injected as liquids and form a highly viscous gel in response to body temperature. For thermally responsive polymers, the PLGA hydrophobic units form associative crosslinks and the hydrophilic units of PEG guarantee that the copolymer molecules stay in solution. At low temperatures, the aqueous solution is dominated by hydrogen bonding between PEG segments and water molecules. With increasing temperature, the hydrogen bonding becomes weaker, while hydrophobic forces involving the hydrophobic PEG segments are strengthened, leading to the formation of a gel [104]. Ewoniq (Essen, Germany), commercializes a PEGylated PLGA with a PEG content between 3 and 7 wt%. This product has a Mw = 33,500 g mol⁻¹ and inherent viscosity of 0.93 dl g⁻¹ [129].

In a different study, Ho Choi et al. [130] prepared degradable elastic matrices for scaffolds in tissue engineering using copolymers with a triblock ABA structure. PLGAs with different LA/PGA ratios were used as the A block and PCL as the middle block. Because PCL has a very low Tg, it was observed that an increase of the Mn of P(LGA-CL-g-PLGA) diblock copolymers produced at GL content of 50% and lower. Furthermore, it was found that the nature of the sequence distribution also has an effect on the degradation rate in tissue engineering. The di-block copolymers showed an elastic and rubber-like behavior in comparison to PLGA. Although the values observed for mechanical strength of these two samples were water soluble, biodegradable, and thermally reversible. Furthermore, they could be injected as liquids and form a highly viscous gel in response to body temperature. For thermally responsive polymers, the PLGA hydrophobic units form associative crosslinks and the hydrophilic units of PEG guarantee that the copolymer molecules stay in solution. At low temperatures, the aqueous solution is dominated by hydrogen bonding between PEG segments and water molecules. With increasing temperature, the hydrogen bonding becomes weaker, while hydrophobic forces involving the hydrophobic PEG segments are strengthened, leading to the formation of a gel [104]. Ewoniq (Essen, Germany), commercializes a PEGylated PLGA with a PEG content between 3 and 7 wt%. This product has a Mw = 33,500 g mol⁻¹ and inherent viscosity of 0.93 dl g⁻¹ [129].

In a different study, Ho Choi et al. [130] prepared degradable elastic matrices for scaffolds in tissue engineering using copolymers with a triblock ABA structure. PLGAs with different LA/PGA ratios were used as the A block and PCL as the middle block. Because PCL has a very low Tg, it was observed that an increase of the Mn of P(LGA-CL-g-PLGA) diblock copolymers produced at GL content of 50% and lower. Furthermore, it was found that the nature of the sequence distribution also has an effect on the degradation rate in tissue engineering. The di-block copolymers showed an elastic and rubber-like behavior in comparison to PLGA. Although the values observed for mechanical strength of these two samples were water soluble, biodegradable, and thermally reversible. Furthermore, they could be injected as liquids and form a highly viscous gel in response to body temperature. For thermally responsive polymers, the PLGA hydrophobic units form associative crosslinks and the hydrophilic units of PEG guarantee that the copolymer molecules stay in solution. At low temperatures, the aqueous solution is dominated by hydrogen bonding between PEG segments and water molecules. With increasing temperature, the hydrogen bonding becomes weaker, while hydrophobic forces involving the hydrophobic PEG segments are strengthened, leading to the formation of a gel [104]. Ewoniq (Essen, Germany), commercializes a PEGylated PLGA with a PEG content between 3 and 7 wt%. This product has a Mw = 33,500 g mol⁻¹ and inherent viscosity of 0.93 dl g⁻¹ [129].

In a different study, Ho Choi et al. [130] prepared degradable elastic matrices for scaffolds in tissue engineering using copolymers with a triblock ABA structure. PLGAs with different LA/PGA ratios were used as the A block and PCL as the middle block. Because PCL has a very low Tg, it was observed that an increase of the Mn of P(LGA-CL-g-PLGA) diblock copolymers produced at GL content of 50% and lower. Furthermore, it was found that the nature of the sequence distribution also has an effect on the degradation rate in tissue engineering. The di-block copolymers showed an elastic and rubber-like behavior in comparison to PLGA. Although the values observed for mechanical strength of these two samples were water soluble, biodegradable, and thermally reversible. Furthermore, they could be injected as liquids and form a highly viscous gel in response to body temperature. For thermally responsive polymers, the PLGA hydrophobic units form associative crosslinks and the hydrophilic units of PEG guarantee that the copolymer molecules stay in solution. At low temperatures, the aqueous solution is dominated by hydrogen bonding between PEG segments and water molecules. With increasing temperature, the hydrogen bonding becomes weaker, while hydrophobic forces involving the hydrophobic PEG segments are strengthened, leading to the formation of a gel [104]. Ewoniq (Essen, Germany), commercializes a PEGylated PLGA with a PEG content between 3 and 7 wt%. This product has a Mw = 33,500 g mol⁻¹ and inherent viscosity of 0.93 dl g⁻¹ [129].
chain microstructure and crystallinity rather than only on the copolymer composition. The crystallinity of each compositional component in the copolymer is associated with the block length. Because in general copolymers with a high degree of randomness showed a short average block length and an amorphous structure, their degradation rate was faster than the degradation rate observed for copolymers with a more blocky chain microstructure.

The authors state that glycolidyl sequences (GG) can undergo bond cleavage as a result of transesterification reactions, which lead to the formation of sequences with odd numbers of glycolyl (G) units, such as -GGC- and -GGGGC-. Usually, copolymers with a high degree of randomness exhibit fast degradation. However, in this study it was found that unexpectedly these sequences showed more resistance to hydrolysis than C-C sequences and in consequence the degradation residues at the latest stages of degradation were composed in their majority of sequences linked by -GGC- and -GGGGC- units.

Copolymers with improved mechanical properties can be obtained by combining the stiffness of highly crystalline polyglycolide with the elastomeric characteristics of poly(trimethylene carbonate) (PTMC). A copolymer constituted of both elements (65% GL and 35% TMC) is elastomeric characteristics of poly(trimethylene carbonate) (PTMC). A by combining the stiffness of highly crystalline polyglycolide with the elastomeric characteristics of poly(trimethylene carbonate) (PTMC). A copolymer constituted of both elements (65% GL and 35% TMC) is currently commercialized under the tradename Maxon™ as a bioabsorbable monofilament suture. Celorio et al. [135, 136] have synthesized copolymers with variable TMC architectures and compositions (close to 32.5% TMC as in the case of Maxon™) through ROP and reported the influence of the microstructure on the final properties. The synthesis proceeds in two steps: first, a middle soft segment with a theoretically random distribution of the two monomer units is prepared by copolymerization of GL and TMC. This is followed by incorporation of two hard segments (60 wt% of the total content) at each end of the middle segment by polymerization of glycolide. Although significant transesterification was observed at the first step of the process, the addition of the hard blocks did not influence the transesterification percentage. Good miscibility of the two monomers was observed and a strong influence of the length of the polyglycolide hard segments on the thermal properties was demonstrated. According to the thermogravimetric analyses, all the synthesized copolymers degrade in a similar fashion upon heating, despite the differences in microstructure, ranging from a random to a blocky monomer distribution. It was reported that microstructure did not have a strong influence on thermal degradation temperature, since a maximum weight loss was observed close to 344 °C for all samples in the TGA thermogram (10 °C/min). This suggested transesterification reactions during the heating run, which can lead to a random microstructure independently of the initial monomer distribution or also, a possible stabilizing effect caused by the presence of polyglycolide units. According to the authors the degradation mechanism proceeded via a non-radical backbiting ester interchange.

4. Oxalic acid and its polyesters

4.1. Oxalic acid

Numerous methods for oxalic acid synthesis are known in the art, but only some of them are utilized at commercial scale while the others are still at the research stage. Asia is estimated to be the largest consumer of oxalic acid in the world by volume with China as a major consumer, producer and exporter [137]. In 2016, the total production of oxalic acid in China exceeded 200 kilotons [138]. Some other major players in the oxalic acid market include Ube Industries in Japan, Ox-aquim S.A in Spain and Indian Oxalate.

Oxalic acid can be commercially produced via the oxidation of carbohydrates, such as glucose, sucrose, starch, dextrin and cellulose, with nitric acid in the presence of sulfuric acid and a catalyst, such as vanadium pentoxide or other vanadium compounds, molybdenum or manganese [139–141]. The process is highly exothermic with large amounts of heat generated, especially during the first stages of the reaction. Since the reaction is very sensitive to temperature, a controlled range between 65 and 70 °C is required to avoid side reactions and thus optimize oxalic acid yield [141]. Other commercial processes, such as the ethylene glycol process, propylene process dialkyl oxalate process and sodium formate process have been reviewed by Sawada et al. [142].

Some setbacks of the initial nitric acid based synthesis methods were mainly related to the high cost of recovery of oxides of nitrogen formed in the reaction. This situation was addressed later by other researchers. Fuchs et al. [140] for example, proposed a process where the nitrogen oxides that escape the reaction medium are led to an absorption system to be oxidized in nitrogen dioxide, which can be recirculated to the reactor with the mother liquor. Another reported strategy is the oxidation of propylene with nitric acid or with a mixture of sulphuric and nitric acids [143]. The intermediate oxidation products α-nitrolactic acid and lactic acid subsequently reacted in the presence of oxygen to produce oxalic acid. Suitable catalysts include sulfite, nitrate, chloride or phosphate salts of iron, aluminum, chromium, tin or bismuth, ferrous oxide and ferric oxide. Continuous research and improvement of the production techniques have been crucial to large-scale oxalic acid production. In 1971 the Japanese company Mitsubishi patented a method for oxalic acid production that is still used today. The process starts from oxidizing ethylene glycol or glycolic acid in an atmosphere of molecular oxygen with nitric acid and/or sulphuric acid, using a vanadium compound as the catalyst [144]. In conventional processes, gases such as nitrogen monoxide or molecular nitrogen which are not converted to nitric acid, are formed during oxidation. In the proposed process, the formation of those byproducts is prevented. Furthermore, when nitrogen oxides are oxidized with oxygen containing gas and absorbed in water for producing nitric acid, the gases and the water require cooling for a sufficient oxidation rate and absorption efficiency to make it an efficient process. If the water contains sulfuric acid, the efficiency of absorption is significantly decreased, and a large absorber is required. Since such absorber can become more expensive than the main reactor, this represents an important economical drawback. With the above, the new process eliminates the need for large absorbers for the generated nitrogen oxides and results in a yield of 90–94%.

Another successful process, using carbon monoxide (CO) to prepare a diester of oxalic acid (starting material for oxalic acid production), was reported by the Japanese company UBE Industries [145–147]. The synthesis utilizes a co-catalyst in order to increase selectivity and catalyst lifetime compared to the conventional processes using CO reported before [148]. Traditionally, the mechanism consists of reacting CO with an ester of nitrous acid in the gas phase at a temperature between 80 and 150 °C at 1–5 bar pressure (Eq. (3)).

\[
2CO4+2RONO \rightarrow COOR + 2NO = \text{alkyloxyl or cycloalkyloxyl} \]

This improved process is carried out in the presence of a heterogeneous catalyst. The oxidative carbylation generates nitric oxide as a byproduct, which is recirculated through reaction with an alcohol. This, together with the oxygen fed in the reaction medium, leads to the formation of nitric esters.

More recently, new technologies to produce oxalic acid from carbon dioxide (CO2) by electrochemical reduction have emerged. The goal of mitigating harmful CO2 emissions by converting them into economically valuable materials such as fuels and industrial chemicals, is currently gaining relevance for many industries. This so-called Carbon Capture and Utilization (CCU) is a superior long term solution than the costly Carbon Capture and Storage (CCS). The former company Liquid Light, now part of Avantium in Amsterdam, developed a process to convert CO2 to formate and formate to oxalate at the start of the decade. The process involved the electrocatalytic reduction of CO2 in an electrochemical cell. The formate is subsequently passed through a thermal reactor in the presence of a base catalyst to produce oxalate. Oxalate is then converted into oxalic acid by a membrane-based
electrochemical acidification process. In a collaboration with Liquid Light, Lakkaraju optimized the formate to oxalate coupling reaction and elaborated on the reaction mechanism [149].

An alternative strategy consists of reacting CO₂ with a metal hydroxide, which generates a stream of metal bicarbonate (MHCO₃), which can be reduced to formate. The Shell Oil Company utilizes a bromide (CH₂Br₂). The solution was refluxed for about 6 h and then cooled to room temperature. Subsequently, the precipitate formed was recovered by centrifugation and washed with methanol. The product was nonflammable, resistant to high temperatures (above 430 °C) and insoluble in common organic solvents. According to the authors, this material would be suitable for applications that require light weight and exposure to elevated temperatures (e.g. structural material in air craft and space vehicles).

One of the first established methods for the synthesis of polyoxalates was proposed by Carothers et al. in 1930[152] and later reported again by the same authors, in a simplified manner. The methodology consisted of the preparation of linear condensation polymers with high molecular weight, capable of being drawn into fibers. Subsequent studies adopted this method for polyoxalate synthesis[153,154]: the general protocol involves a two step melt polycondensation of an oxalic acid diester and a diol (Scheme 11), with an initial pre-polymerization reaction taking place in a reactor under inert atmosphere.

The reaction mixture is gradually heated above 100 °C and the reaction pressure is first maintained at atmospheric pressure while allowing the resulting alcohol to distill off as the prepolymer is obtained. As for the PGA-based polymers discussed previously, rigorous control of the water content, especially at the start of the reaction, is important to obtain a high molecular weight polymer. Preferred catalysts for the first polymerization stage include titanium alkoxides like titanium tetraalkoxide, antimony compounds like antimony trioxide, and tin compounds such as butylindilaurate[154]. Once the alcohol has ceased to distill at the first stage of the reaction, the second stage, where the principal polymerization occurs is executed. At this point, the pressure in the reactor is reduced, combined with suitable continuous heating under a nitrogen atmosphere. The reaction proceeds with the removal of the remaining excess alcohol. The final product is cooled gradually to room temperature[154]. This approach has also been used for the synthesis of poly(alkylene oxalates) with diols such as ethylene glycol, 1,3-propanediol, 1,4-butanediol or 1,6-hexanediol in combination with diethyl oxalate or dimethyl oxalate[153,155-157].

Different methods have been proposed for producing high molecular weight polyoxalates (POX). Synthesis via ROP of a cyclic oxalate monomer has been reported exclusively for the preparation of poly(ethylene oxalate). The cyclic monomer can be obtained by heating oligo(ethylene oxalate) with subsequent depolymerization under nitrogen atmosphere[158-160]. The depolymerization is performed at 190–220 °C and a pressure of 0.003-1.35 kPa. This is followed by purification of the cyclic monomer by recrystallization[160]. The ROP is conducted by heating the cyclic monomer to a temperature lower than 200 °C in the presence of a catalyst at ambient pressure under an inert atmosphere. An alternative process for the preparation of the cyclic ethylene oxalate consists of preparing a mixture of ethylene oxalate oligomer dissolved in a high boiling solvent (285–420 °C), which is subsequently heated to a temperature (235–245 °C) at which depolymerization of the oligomer occurs. This additional heating of the solution leads to the formation of the cyclic monomer, which is then distilled out together with the polar organic solvent[158]. A POX with a density of about 1.48 g cm⁻³ measured in amorphous state and a melt viscosity of 30 Pa s (determined at 190 °C and a shear rate of 1000 sec⁻¹) was claimed to result from this synthesis method.

Some of the mentioned polyester resins have been produced using oxalic acid as starting material[44,152,161,162]. Alknsnis et al. [161] reported a two-step polycondensation reaction for the production of high molecular weight PEOX from ethylene glycol and oxalic acid in the presence of benzene and thiorium carbonate as the catalyst. The process was initiated with oligomer synthesis at low temperature (below 80 °C) followed by a second stage where the oligo(ethylene oxalate) was subjected to transesterification in the melt at 170–180 °C for six hours under argon flow. The thermal conditions were selected in view of the melting temperature (170 °C) and the decomposition temperature (230 °C) of PEOX. Temperature regulation is crucial for this synthesis, since it has been reported that oxalic acid can decarboxylate to CO₂ and formic acid when heated above 140 °C. In fact, this decarboxylation may occur at lower temperatures, influenced by the reaction medium (e.g. solvent, water content, oxalic acid concentration etc). This also influences the degradation pathway, as there are several ways oxalic acid can decompose[162]. Furthermore, the presence of formic acid leads to blocking of the polyester's hydroxyl groups[13]. Decomposition to formate seems to incease steadily until no more free oxalic acid/ oxalic acid ester end groups are present. This shows that even if oxalic acid reacts once with an alcohol to form the ester, there is still the possibility for decomposition at temperatures above 140 °C[163].

4.1.1. Polymerization techniques

In 1996 Pinkus et al. [151] patented a process to produce a poly(methylene oxalate) (PMO). The polymer was prepared by dissolving bis(tetramethylene ammonium) oxalate in chlorobenzene and methylene bromide (CH₂Br₂). The solution was refluxed for about 6 h and then cooled to room temperature. Subsequently, the precipitate formed was recovered by centrifugation and washed with methanol. The product was nonflammable, resistant to high temperatures (above 430 °C) and insoluble in common organic solvents. According to the authors, this material would be suitable for applications that require light weight and exposure to elevated temperatures (e.g. structural material in air craft and space vehicles).

One of the first established methods for the synthesis of polyoxalates was proposed by Carothers et al. in 1930[152] and later reported again by the same authors, in a simplified manner. The methodology consisted of the preparation of linear condensation polymers with high molecular weight, capable of being drawn into fibers. Subsequent studies adopted this method for polyoxalate synthesis[153,154]: the general protocol involves a two step melt polycondensation of an oxalic acid diester and a diol (Scheme 11), with an initial pre-polymerization reaction taking place in a reactor under inert atmosphere.

The reaction mixture is gradually heated above 100 °C and the reaction pressure is first maintained at atmospheric pressure while allowing the resulting alcohol to distill off as the prepolymer is obtained. As for the PGA-based polymers discussed previously, rigorous control of the water content, especially at the start of the reaction, is important to obtain a high molecular weight polymer. Preferred catalysts for the first polymerization stage include titanium alkoxides like titanium tetraalkoxide, antimony compounds like antimony trioxide, and tin compounds such as butylindilaurate[154]. Once the alcohol has ceased to distill at the first stage of the reaction, the second stage, where the principal polymerization occurs is executed. At this point, the pressure in the reactor is reduced, combined with suitable continuous heating under a nitrogen atmosphere. The reaction proceeds with the removal of the remaining excess alcohol. The final product is cooled gradually to room temperature[154]. This approach has also been used for the synthesis of poly(alkylene oxalates) with diols such as ethylene glycol, 1,3-propanediol, 1,4-butanediol or 1,6-hexanediol in combination with diethyl oxalate or dimethyl oxalate[153,155-157].

Different methods have been proposed for producing high molecular weight polyoxalates (POX). Synthesis via ROP of a cyclic oxalate monomer has been reported exclusively for the preparation of poly(ethylene oxalate). The cyclic monomer can be obtained by heating oligo(ethylene oxalate) with subsequent depolymerization under nitrogen atmosphere[158-160]. The depolymerization is performed at 190–220 °C and a pressure of 0.003-1.35 kPa. This is followed by purification of the cyclic monomer by recrystallization[160]. The ROP is conducted by heating the cyclic monomer to a temperature lower than 200 °C in the presence of a catalyst at ambient pressure under an inert atmosphere. An alternative process for the preparation of the cyclic ethylene oxalate consists of preparing a mixture of ethylene oxalate oligomer dissolved in a high boiling solvent (285–420 °C), which is subsequently heated to a temperature (235–245 °C) at which depolymerization of the oligomer occurs. This additional heating of the solution leads to the formation of the cyclic monomer, which is then distilled out together with the polar organic solvent[158]. A POX with a density of about 1.48 g cm⁻³ measured in amorphous state and a melt viscosity of 30 Pa s (determined at 190 °C and a shear rate of 1000 sec⁻¹) was claimed to result from this synthesis method.

Some of the mentioned polyester resins have been produced using oxalic acid as starting material[44,152,161,162]. Alknsnis et al. [161] reported a two-step polycondensation reaction for the production of high molecular weight PEOX from ethylene glycol and oxalic acid in the presence of benzene and thiorium carbonate as the catalyst. The process was initiated with oligomer synthesis at low temperature (below 80 °C) followed by a second stage where the oligo(ethylene oxalate) was subjected to transesterification in the melt at 170–180 °C for six hours under argon flow. The thermal conditions were selected in view of the melting temperature (170 °C) and the decomposition temperature (230 °C) of PEOX. Temperature regulation is crucial for this synthesis, since it has been reported that oxalic acid can decarboxylate to CO₂ and formic acid when heated above 140 °C. In fact, this decarboxylation may occur at lower temperatures, influenced by the reaction medium (e.g. solvent, water content, oxalic acid concentration etc). This also influences the degradation pathway, as there are several ways oxalic acid can decompose[162]. Furthermore, the presence of formic acid leads to blocking of the polyester’s hydroxyl groups[13]. Decomposition to formate seems to increase steadily until no more free oxalic acid/ oxalic acid ester end groups are present. This shows that even if oxalic acid reacts once with an alcohol to form the ester, there is still the possibility for decomposition at temperatures above 140 °C[163].
with an even n. The same study established that rigidity, \( T_g \) and \( T_m \) of the structure can be increased by including rigid co-monomers, such as aromatic diols, into the polymer backbone.

Resorcinol bis(hydroxyethyl) ether (RBHE) or hydroquinone bis(hydroxyethyl) ether (HBHE) and the aliphatic diol 1,10-decanediol (Fig. 10) were investigated. The polymer’s \( T_m \) decreased with increasing aromatic comonomer content up to 40%. Above 50% aromatic comonomer content, the \( T_m \) increased steadily with increasing aromatic co-monomer content. The behavior encountered initially is presumably due to the aromatic units functioning as chain defects in the poly(decylenoic ester) [168]. Although poly(alkylene oxalates) offer sufficient mechanical behavior, in general a significant limitation for certain applications is related to the unsatisfactory thermal properties.

Aldknsis et al. [161] synthesized and reported a poly(ethylene oxalate) (PEOX) with fiber forming properties and a \( T_g \) and \( T_m \) of about 32 °C and 178 °C, respectively. Later, Shiiki et al. [158] claimed the production of a PEOX with the same molecular weight, crystalline properties, excellent behavior for melt processability and good degradability in soil. The authors tested the mechanical properties of some biaxially oriented PEOX films. A tensile strength of 240 MPa, a modulus in tension of 5200 MPa and a 75% elongation at break were found when the films were stretched at 40–45 °C. More satisfying mechanical behavior was observed for filaments stretched at 50–55 °C, with a modulus in tension of 100,000 MPa, a tensile strength of 500 MPa and a 30% elongation at break. Zhao et al. [169] investigated materials derived from diethylene oxalate (DEOX), poly(ethylene sebacate) (PES) and PET. The resulting poly(ethylene terephthalate-co-oxalate-co-sebacate) (PETOXS) (Fig. 11) showed an augmentation on the Young’s modulus and a maximum tensile stress with increasing content of PEOX in aliphatic units: 60/24/16 PET/PEOX/PES had a tensile strength of 7.6 MPa and a modulus in tension of 39 MPa, while 60/32/8 PET/PEOX/PES showed a tensile strength of 23.6 MPa and a Young’s modulus of 584 MPa. A contrary result was found for the elongation at break, which decreased from 478% to 170% for the above-mentioned copolymers.

A thermal stability up to \( \sim 390 \) °C was reported for this polymer. Higher melting and crystallization temperatures were observed for the sample with a higher PEOX content. According to the authors, the effect of PETOXS composition in the crystallization mechanism is not straight forward, as it can act in two ways. On the one hand, the aromatic repeating unit of PET and the aliphatic unit of PEOX are more rigid than the aliphatic unit of PES, which may favor easier formation of regular crystalline entities. On the other hand, when the flexible units of PES are added to the main chain, segments of copolymers tend to have improved mobility, which can lead to rearrangements, therefore increasing the crystallinity.

In another study, interesting barrier properties have been found for films made of PEOX blended with PLA [154]: an oxygen permeation of 4.8 mL mm day\(^{-1}\) bar\(^{-1}\) was observed at 23 °C and 65% RH and a water vapor permeation of 1.6 g m\(^{-2}\) day\(^{-1}\) was measured at 40 °C and 90% RH. This is comparable to PVC, which shows an oxygen permeation of 2–8 mL mm day\(^{-1}\) bar\(^{-1}\) and a water vapor permeation of 1–2 g m\(^{-2}\) day\(^{-1}\) at 23 °C and 85% RH.

The crystallization mechanism and microstructure of another POX derivative, poly(butylene oxalate) (PBO), was studied by Kuo et al. [155]. The DSC analysis for different PBO crystals revealed \( T_m \) ranging from 99.8 °C to 102.2 °C at crystallization temperatures between 70 °C and 85 °C. Furthermore, a morphological study showed the formation of thicker crystalline layers at the highest crystallization temperatures. Independently, the thermal behavior of PBO copolymerized with azelaic acid (nonanedioic acid) was studied [170]; The copolymers were found to be partially crystalline and thermally stable up to \( \sim 290 °C \). At room temperature, all the synthesized samples appeared as semi-crystalline, with the same crystal structure as the PBO polymer. According to the authors, the main effect of the copolymerization was a decrease in \( T_g \) and \( T_x \) with respect to PBO. Furthermore, \( T_g \) values decreased with increasing butylene azelate unit content, notably due to the increased presence of methylene groups, which contribute more flexibility to the polymeric chain. The reported thermal properties for some of the previously discussed polymers are presented in Table 3.

5. Polymer degradation pathways

Polymer degradation can be defined as “a deleterious change in the chemical structure, physical properties, or appearance of a polymer, which may result from chemical cleavage of the macromolecules forming a polymeric item, regardless of the mechanism of chain cleavage” [171]. From the physical angle, cleavage of the backbone can occur in a heterogeneous or homogeneous fashion [172]. In homogeneous (or bulk) degradation, via hydrolysis for example, water penetrates the interior of the matrix and hydrolysis of the ester bonds of the interior chains lead to uniform backbone cleavage. There is minimal loss of mass until the molecular weight reaches a threshold value, below which the sample is rapidly decomposed. The rate of backbone cleavage for heterogeneous (or surface) degradation, on the other hand, is much faster than the rate of penetration of water into the matrix. Therefore, hydrolysis is concentrated on the polymer surface and a gradual decrease in mass and size of the sample occurs with time [173].

The main process involved in the degradation of glycolic acid and oxalic acid based polyesters is hydrolysis. A decrease in molecular weight and the release of soluble oligomers and monomers result from cleavage of the ester groups. In general, the mechanism leads to an increase in the number of carboxylic acid chain ends, known to auto-catalyze ester hydrolysis with the subsequent release of soluble oligomers from the matrix, as shown for PLA in Scheme 12. Some of these oligomers (closer to the surface) can be leached out while those in the core of the matrix remain entrapped.

For PLA for example, degradation of the amorphous portions into
to be catalyzed by certain enzymes, especially those with esterase ac-

cleavage, preferentially in the amorphous regions, which leads to an

crystallinity during this stage [177]. A similar mechanism has been observed for all the polyesters reviewed in this
document.

PGA degradation and the in vitro toxicity of the degradation pro-
ducts have been previously studied [178]. Hydrolysis of PGA was found
to be catalyzed by certain enzymes, especially those with esterase ac-
tivity [179]. Similar to the PLA case, bulk degradation of PGA via hy-
drolysis is detrimental to the mechanical properties, due to decreasing
molecular weight and the eventual generation of the monomer, glycolic
acid. Despite the fact that glycolic acid is resorbable at high concen-
trations, it has been reported that for some biomedical applications the acid catalyzed hydrolytic degradation can lead to tissue damage
[178]. Kuredux®, the PGA resin from the Kurah Corporation, is
claimed to degrade into CO₂ and water under composting conditions
within one month [64]. However, no support for this statement has
been published and the lack of results from compostability tests makes
the confirmation of PGA’s bio-compostable character under standard
backyard conditions difficult.

With a similar mechanism, hydrolytic PLGA degradation involves
complete solubilization of oligomer fragments. As in the case of the
previously discussed polymers (PLA and PGA), the formation of an
acidic microclimate within the matrix [180] has been reported to cause
issues for some biomedical applications, notably for protein stability
during preparation and storage for controlled release systems [181].

In general, the rate of the hydrolytic degradation is primarily tem-
perature and humidity dependent [26], although degradation of gly-
colic acid and oxalic acid based polyesters has been found to also de-
pend on additional factors such as molecular weight, crystallinity,
purity, pH, the presence of terminal carboxyl or hydroxyl groups and
water permeability. Additives acting catalytically, like bacteria
(through the use of enzymes), inorganic fillers and metal residues also
contribute to this mechanism [90,182]. Furthermore, the polymer’s
degradation can be induced by several natural factors besides hydro-
dysis, such as oxidation, light and heat [183].

Miller et al. [184] tested resorbable implants in vivo and observed a
half-life of 6.6 months for the ones made of PLA, compared to 5 months
for those prepared with PGA. Later, Song et al. [185] reviewed the
composting of different biodegradable packaging materials under
backyard composting conditions. PLA can be classified as a slow bio-
degradation rate plastic with an observed mass loss of only 5% after
90 days and no visual evidence of microbial breakdown after 180 days.
Under industrial composting conditions (60 °C and 63% RH) Kale et al.
[114] demonstrated in a different study that PLA degrades completely
within 30–45 days.

In the same way as PLA and PGA, PLGA can undergo in vivo de-
gradation by non-enzymatic hydrolysis and through enzymes. The de-
gradation time can vary from several months to several years, de-
pending on the molecular weight, copolymer ratio, chain composition,
hydrophobic/hydrophilic balance and crystallinity [176]. From the
commercial copolymers of PLGA (D,L-lactide/glycolide) (50/50, 65/35,
75/25, 80/20 and 10/90), Vicryl rapideᵀᴹ (PLGA 10/90) has the fastest
hydrolysis rate with a degradation time of 42 days at room temperature.
The most widely used composition for biomedical applications (50/50)
has a degradation time of about 50–60 days in vivo. Other compositi-
sions, such as 65/35, 75/25 and 80/20, have progressively longer in
vivo lifetimes [181]. Houchin et al. [180] studied the effect of moisture
on certain properties of PLGA films subjected to storage at 70 °C and up
to 95% RH. Following a similar mechanism as PLA and PGA, increasing
moisture levels led to a decrease in the molecular weight and thereafter,
reduction of the T<sub>c</sub>.

In a different study, Li et al. [186] demonstrated that the monomer
distribution influences the hydrolysis degradation kinetics of PLGA:
random polymer degrades quicker than analog-sequence PLGA. In
this same research, materials with highly controlled sequences and stereo-
chemistry were obtained using 1,3-diisopropyl carbodiimide (DIC) and
4-(dimethylaminopyridinium) p-toluenesulphonate (DPTS) as catalysts.
The different tacticities allowed tuning of the hydrolysis rate. Although
in principle, these results were considered by the authors as potentially
useful for drug delivery systems, it can be inferred that agricultural and
packaging applications could also benefit from this tailored degrada-
tion. With the previous information in mind, it becomes clear that the
PLA/PGA copolymers offer an undeniable advantage of hydrolysis rate
tailoring. This is important for any type of application as it ultimately
allows controlling the lifetime of the polymeric material.

Oxalate based polymers degrade in a similar fashion through hy-
drolytic cleavage of oxalate ester linkages in their backbone (ester hy-
drolysis). Their degradation in vivo typically generates nontoxic low
molecular weight substances that can be easily excreted such as diols
and oxalic acid, both considered biocompatible [164,187]. Ad-
ditionally, polymers with aromatic rings adjacent to oxalate ester
linkages are rapidly hydrolyzed by water [51]. This suggests that poly
(alkylene) oxalates derived from 1,4-cyclohexanediimethanol, which
have poor electron-withdrawing properties, exhibit increased stability
for microparticle and nanoparticle formation and drug encapsulation in
the aqueous environment compared to other oxalate containing poly-
mers. According to Kim et al. [187] oxalate nanoparticles synthe-
sized using 1,4-cyclohexanediimethanol can be degraded by hydrogen
peroxide and water faster than PLGA nanoparticles. Their half-life in

Table 3
Thermal properties of some polyoxalates of interest.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>T&lt;sub&gt;c&lt;/sub&gt; (°C)</th>
<th>T&lt;sub&gt;m&lt;/sub&gt; (°C)</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEOX</td>
<td>32</td>
<td>178</td>
<td>[158,161]</td>
</tr>
<tr>
<td>Poly(butylene oxalate) (PBO)</td>
<td>−32</td>
<td>96–102</td>
<td>[155,170]</td>
</tr>
<tr>
<td>PBO-Butylene azelate 70/30</td>
<td>−47</td>
<td>62</td>
<td>[170]</td>
</tr>
</tbody>
</table>

Fig. 11. Structure of poly(ethylene ter-
ephthalate-co-oxalate-co-sebacate) (PETOXS)
[169].
water at 37°C and pH 7.4 was 6.5 days. In a different study, microparticles prepared with the same composition also showed a half-life of 6.5 days at similar conditions (pH 7.4 and 5) [187].

In addition to the above, all the polyesters discussed previously are prone to thermal degradation during processing. Jamshidi et al. [188] conducted research on this topic with a focus on polylactides. According to the authors, transesterification reactions are involved in this process (Scheme 13).

The first two are intramolecular transesterifications that result in the formation of cyclic oligomers, catalyzed by the residual polymerization catalyst. Both of these reactions can lead to the generation of low molecular weight compounds that may evaporate at high temperatures resulting in a gradual reduction of the polymer’s weight. The third transesterification reaction involves random chain scission with a possible sharp drop in molecular weight. This indicates that polymerization catalysts will have a strong effect in lowering the molecular weight of lactides at high temperature.

Because the onset of thermal degradation of PGA begins 30°C above the T_m (230°C), it is more vulnerable to thermal conditions than PLA and therefore a more rigorous control of processing temperatures is required. Erbetta et al. [110] determined the temperature at which thermal degradation starts for PLGA copolymers with two LA/GL built-in ratios, 50/50 and 70/30. According to the authors, a single stage weight loss of close to 100% is shown at temperatures between 261 and 283°C.

Essentially, in summary, all the polyesters discussed in this review show hydrolytic degradation through cleavage of ester linkages in their backbone. From the group reviewed, PLA has the highest T_g and the slowest hydrolytic degradation rate when compared under similar temperature and pressure conditions. As a consequence PGA exhibits a faster hydrolytic degradation than PLA and this behavior is accentuated in ratios, 50/50 and 70/30. According to the authors, a single stage weight loss of close to 100% is shown at temperatures between 261 and 283°C.

6. Applications

6.1. Packaging applications

The strong barrier properties of PGA, accompanied by its biodegradability, make it a good candidate for the packaging industry. Polymer grade PGA is commercialized for packaging applications under the registered trademark Kuredux® by Kureha Corporation, which runs the world’s first industrial-scale PGA manufacturing facility. Their bi-axially oriented film exhibits a tensile strength of about 380 MPa and tensile modulus of 7000 MPa, both higher than those of some engineering polymers, including PET (σ_UTS = 230 MPa, E = 3900 MPa) and PA6 (σ_UTS = 206 MPa, E = 1500 MPa) [56]. In addition to the abuse resistance, the material provides excellent barrier integrity, making it suitable for flexible packaging and various industrial films.

Despite the evident potential, PGA is a costly material facing severe difficulty in its large-scale commercialization, which creates challenges for its implementation in a broad range of application areas. Although glycolide is also produced in pilot scale quantities by companies other than Kureha, the current commercial production cost is €5-10 per kilo, which is still high compared to other monomers used in the production of renewable polymers (e.g. lactide production cost €2-3 per kilo [190]). In 2014, the Kureha company held a market share of nearly 84% and was the only commercial producer of PLGA for non-biomedical applications. Although other players, such as Teleflex, DuPont and Huizhou Foryou Medical Devices are also active in the field as providers for medical and biomedical applications, Kureha is still expected to maintain the monopolistic landscape for 2018–2023 [191]. In 2015, the corporation stated that the current focus of PGA commercialization is on downstream businesses with a high margin such as shale gas extraction [192]. In fact, downhole tools with nontoxic and biodegradable character using PGA resin have been patented in the past years [193,194]. Extraction-molded bars form the basic structures for “frac plugs” used in shale oil and gas extraction. Interestingly, shale gas extraction accounted for over 35% of the global demand for poly(glycolic acid) in 2014 [191].

Despite the aforementioned downsides related to the packaging applications, utilization of PGA has been reported for packaging components. Multilayer polymeric systems for containers and films for food contact, using at least one layer of PGA have been made [195]. Improved performance regarding gas permeability and adhesion between layers was reported. However, it was difficult to obtain satisfactory mechanical strength under molding conditions. A similar multilayer container, claimed to be potentially useful for, among others, carbonated fruit juices, dairy products, beers, wines and soups, showed improved heat resistance, capable of withstanding hot filling at 93°C for 20 s. The container was composed of a PGA intermediate layer (Kuredux resin) and another thermoplastic polyester resin (PET or Polyethylene naphthalene, PEN), forming an inner and outer layer. The element was manufactured by a co-injection stress blow molding production process. Good moldability, transparency and durability, accompanied by enhanced barrier properties were achieved [196]. Other similar multilayer systems using PGA have been reported for packaging applications [197–199]. Although multilayer systems with PET or PEN improve valuable properties for the packaging industry, they are not expected to biodegrade or to be compostable and therefore waste disposal remains an issue.

The possibility of tailoring PLGA’s mechanical, thermal and optical properties place it among the biodegradable polyesters with a promising performance in the packaging industry.

Oxidation can be a spontaneous process or can be induced by environmental and catalytic systems, such as light, temperature, enzymes, metals, metalloproteins and micro-organisms. To deal with this, the addition of antioxidants is common practice in polymer applications. The release of antioxidants from PLGA films (50/50) into milk powder products was studied by Van Aardt et al. [200]. For this purpose 2% α-tocopherol and 1% butylated hydroxytoluene (BHT), combined with 1% butylated hydroxyanisole (BHA), were used as antioxidants in the PLGA. Biodegradation tests were performed in the presence of water and oil. Lipid oxidation in fat-containing foods that are high in phospholipids is a major cause of deterioration during processing and
storage. NMR analysis conducted for the study showed a decrease in the antioxidant content of PLGA films over 4 weeks of storage and a subsequent increase in the antioxidant content in the whole milk powder. Migration of antioxidants from antioxidant loaded films into dry milk products, with a water content lower than 4.60%, was found to be driven by volatilization and surface contact rather than by hydrolytic degradation of PLGA (50/50) when the dairy products were exposed to light. Apparently, as a response to this contact, the milk fat in the products was partially stabilized. Interestingly, BHT was found to be the only antioxidant that was released through diffusion and hydrolytic degradation of the polymer when stored in water at room temperature for 8 weeks. Volatile compounds (hexanal, pentanal, and heptanal) may serve as an indicator of lipid oxidation. The authors were not able to confirm complete control of the formation of these compounds under the conditions applied for the study. Yet, the potential for these degradable films on the protection of milk quality was acknowledged.

Ube Industries patented PEOX films copolymerized with lactacid acid [154] that exhibit good performance for food packaging, medicines, cosmetics, precision machines, and home electric appliances. The inventors claimed that the resin composition can also be employed for multi-layered films in agriculture for compost bags, seed tapes, and germination sheets. High molecular weight PEOX with enhanced processability has also been claimed in a different invention as a suitable material for food packaging, and wrapping for electronic items in the form of films and heat sealing sheets [158]. A different polyester derived from PEOX and Glycolic Acid oligomers was patented by Alksnis et al. [201]. The claimed polymer with below 5 mol% of glycolic acid units had a Tm of about 170 °C and a Tg close to 210 °C (heating rate was not specified). According to the authors, this material can be shaped into films and fibers and could be used for packaging applications in the food and medical industry.

The published information currently available suggests that a process for large-scale production of PLGA and the discussed polyoxalates is still not well developed. Available information on related studies for packaging applications is scarce. Overall, it seems that further optimization of the synthesis process and complete techno-economical assessments need to be conducted before conclusions can be drawn with respect to the feasibility of these materials for applications where well-established commodity polymers are currently utilized.

6.2. Agricultural applications

Plastic films are widely used in agriculture. The world’s growing population leads to an increasing demand for food with an accompanying increase in the use of agricultural plastics. Films for greenhouses, silage and mulching are among those in high demand, with Asia as the fastest growing market. The latter accounted for over 40% of the total plastic films used in agriculture in 2012 [19]. Some of the advantages offered by mulch films include insect and weed control, increase in air and soil temperature, minimization of soil erosion and reduced water evaporation [202]. These plastics are contaminated with soil after use and therefore not collected by most recycling facilities [21], leading to higher costs for landfilling. Since this is a growing market and recycling does not appear to be a viable option, the need for replacement with biodegradable plastics becomes apparent. Considering that hydrolysis is the major degradation mechanism, it is important to assess the fate of the monomers and their impact on soil productivity and other environments where depolymerization may occur. For PLA, the degradation pathway and degradation products have been studied. However, for other systems, for example multilayered systems containing PET, which degrades very slowly via hydrolysis [203,204], the effect of the monomer terephthalic acid has not been assessed yet.

The use of PLA as homopolymer in agriculture has been limited due to its mechanical and thermal properties not always being suitable for all applications. For the production of commercial mulch films it is usually blended with other biodegradable polyesters and plasticizers. BASF offers ecovio® F Mulch, consisting of the copolyester ecoflex® (polybutylene adipate terephthalate) blended with PL [205]. The improved strength of this material allows its use in other applications, such as silage and cover film. In 2012 Showa Denko launched a completely biodegradable resin under the trademark Bionolle Starcela. This material, which consists of different PLA grades blended with poly(ethylene/butylene succinate), demonstrated suitability for mulching films [206]. Furthermore, the previously mentioned Ingeo™ PLA is widely used for this same application and also to manufacture pots, yard waste bags, tomato clips and pegs, among others [207]. Other Ingeo™ based derivatives include BI-OLP, a biodegradable film by Oerlemans Plastics, mainly used in greenhouses and DS Technical Nonwovens with HortaFlex®, a mulch matting and weed control product [208].

The need for more efficient fertilizer technology in the agrochemical sector to control the dosage and avoid excessive local concentration levels of nutrients is evident. Strategies to deal with this situation have involved the use of biodegradable PLA. Jintakanon et al. [209] studied the suitability of poly(lactic acid-co-ethylene terephthalate) as a coating material for controlled release of urea, a common source of nitrogen nutrition for plants. The urea granules were first coated with commercial PLA and PLAD(poly(lactic acid-co-ethylene terephthalate) synthesized by the authors. The release properties were assessed by monitoring the urea concentration through measurement of the refractive index in a rotating bottle of water, containing the coated urea granules. The release was found to be a function of the applied coating percentage, which was shown to depend directly on the molecular weight and nature of the polymer coating and concentration of the polymer solution. Additionally, it was concluded that the morphology of the coating’s surface influenced the release. Later, Calabria et al. [210] reported a slow release fertilizer system with blends of soy protein isolate (SPI) and PLA plasticized with triacetin (TA) to be used as a matrix for nitrogen, phosphorus and potassium (NPK) fertilizer. Sustained release of nutrients was achieved with the composite material, forming a highly ordered porous matrix of SPI with homogeneous dispersion of the NPK salts. Additional systems for successful control of fertilizer release rate have been reported [209,211], using a double layer granular urea fertilizer coated with PLA and other lactic acid oligomers. A second exterior coating (sealant) can be applied to decrease the water permeability. To the best of our knowledge, commercialization of polyoxalates or PGA derived polymers for the agrochemical industry has not been reported yet. Based on both PGA and PLGA polymer’s general properties and the possibility of tailoring them, it could be very beneficial to the agrochemical industry.

Currently, some players in the agricultural market, such as Bayer CropScience AG (Germany), BASF SE (Germany) and Germins Seed Technology (UK), commercialize polymer seed coatings. New regulations for coating materials are forcing manufacturers to look for more sustainable (degradable) polymer solutions. Often, these sustainable options (e.g. PGA copolymers) are more expensive; increasing cost of raw material causes higher production cost and therefore higher prices in the market. With this in mind, the potential of the polyesters mentioned in this review for seed coatings do not depend exclusively on the technical requirements. The use of coated seeds needs to increase, for the most common human consumption products (e.g. grains, vegetables, fruits). This would lead to a marked growth in the demand for new polymer coatings, which should affect scale and thus increase the efficiency of monomer production, benefiting price and availability.

6.3. Biomedical applications

The biomedical field is the most extensively studied application area for the polymers reviewed in this document. Numerous investigations have been published using PLA, PGA, PLGA or polyoxalates for purposes related to this field. However, this review aims to focus on other
applications and therefore it will only be treated briefly.

An extensive increase has been reported regarding the use of PLA for biomedical applications where specific chemical, mechanical, physical, biological and degradation properties are required. Some uses include: stents [212], surgical sutures [213], plates and screws for cranio-maxillofacial bone fixation, interference screws in ankle, knee, and hand; tacks and pins for ligament attachment, anchors, spinal cages, soft-tissue implants, tissue engineering scaffolds, tissue cultures, drug delivery devices [214–216]. Craniofacial augmentations in plastic surgery are also part of the potential applications [213]. A limitation related to the use of PLA involves the viscoplastic flow that can lead to premature failure at stress magnitudes that are significantly lower than the yield strength and the ultimate tensile strength of the material. This behavior can lead to creep rupture or fatigue failure; this is an issue since it means that for some applications, device failure can occur long before the material is estimated to fail due to degradation in vivo [217].

3D printing is already used for some of the aforementioned devices. However, the generation of complex tissues such as bone, cartilage, muscles, vessels and organs with intricate 3D microarchitecture (liver, lymphoid organs), presents several technical limitations related to the balance between physical/mechanical properties and biodegradation kinetics [218].

For biomedical applications, PGA appears attractive since the polymer’s biodegradation generates glycolic acid, a natural metabolite [90]. One of the first industrial applications of PGA was proposed in 1962 by the former American Cyanamid Company now part of Pfizer. The company developed the first absorbable surgical sutures with the trademark Dexon®, which benefited from the good mechanical strength and biodegradable character of PGA [219]. Surgical sewing threads formed from braided multifilaments of this PGA exhibit a 50% breaking strength loss within 21 days [220].

Absorbable sutures are widely commercialized these days by different corporations under registered marks such as Triso® [221] and Saff® [222]. Efforts for enhancing its mechanical performance have resulted in some proposed core and shell filament structures composed of the fast absorb ing polymer PGA and for example a slow absorbing polymer like poly(caprolactone). These models allow prolonged mechanical strength by delaying bioabsorption. Resorb’a successfully commercializes this type of surgical suture as Glycolon™ [223].

Scaffolds constituted of fibers are a pioneering application of PGA in tissue engineering [67]. Although melt spinning and extrusion represent the most widely reported processes for PGA fiber manufacturing, different fabrication techniques using PGA fibers and fillers have been reported to obtain highly porous scaffolds with an increased surface area to incentivize cell attachment. Fiber bonding [68], gas foaming and phase separation emulsification [224] are among them. Additionally, prosthetic structures with PGA, such as reinforcing pins [55], plates and screws [225], have also been formulated. You et al. [226] prepared porous ultrafine PGA fibers by electrospinning (PGA/PLA) (30/70) fibers and then removing the PLA via a selective dissolution technique with chloroform. Three-dimensionally interconnected pores with narrow size distribution and circular shape with average diameters ranging from 200 to 500 nm were obtained. The product was recognized to be potentially useful for nanofiltration and functional nanotubes.

Combined applications in the packaging and medical fields are also of potential interest for PGA. A multilayer film for the production of pouching systems in ophthalmic applications with about 4 to 80 wt% of PGA, in combination with a noise dampening polymer resin, was reported by Bekele et al. [227]. Pouches are typically made of poly(vinylidene chloride) PVDC or copolymers of vinylidene chloride; both hazardous to the environment when disposed of by open-air incineration (still a common practice in many countries) or in combustion systems where some fractions escape unburned and other portions are converted into new organic compounds (e.g. dioxins). Pouches require good odor and moisture barrier properties, softness, heat or radio frequency sealability, skin compatibility, comfort and oxygen and moisture vapor impermeability. In addition, such pouches should not emit noise during use. The obtained packaging device with the highest composition of PGA proved to fulfill the aforementioned criteria with an oxygen transmission rate (OTR) of less than 60 cm³ m⁻² day⁻¹ bar⁻¹ at 23 °C at 100% of relative humidity. Nylon6 coated with PVDC at the same temperature and 90% RH exhibits an OTR of 10 cm³ m⁻² day⁻¹ bar⁻¹ [228]. Another very competitive gas and aroma barrier material, PVDC-coated BOPP (biaxially oriented polypropylene), has an OTR of 13 cm³ m⁻² day⁻¹ bar⁻¹ at 23 °C at 0% RH [229].

The potential of PLGA for biomedical applications, including sutures, fibers, micro- and nanostructures for controlled release and scaffolds for tissue engineering has extensively been studied. During the late 1960s and early 1970s, successful research in terms of tissue compatibility on absorbable suture materials opened the door to the use of biodegradable polymer implants for other clinical applications [230–232]. Ethicon became the first company developing and commercializing a multifilament suture of PLGA today known as Vicryl™ (polyglycolin 910), made from 90% glycolide and 10% L-lactide. The copolymer, synthesized by ROP of lactide and glycolide is initially made in the form of pellets. The pellets are melted and the material is extruded as filaments that are subsequently strengthened by stretching to allow molecular alignment. The filaments are braided and once again submitted to a stretching process to increase their tensile strength. Complete absorption by hydrolysis of the resulting suture occurs in approximately 80 days [232]. Currently, surgical sutures are combined with bioactive materials. Vycril Plus (10:90 LA/GA) coated with triclosan is an available commercial example that offers the ability to inhibit bacterial growth on the suture [233]. Vicryl rapide, a suture with the same LA/GA composition, provides a faster breakdown by hydrolysis (42 days).

Other applications for PLGA include scaffolds for tissue engineering [234–236], bone tissue engineering [237], and drug delivery systems [181,238]. Limitations for other biomedical applications are related to the common inflammatory response triggered by the acid catalyzed in vivo degradation [124,239].

Composites of PLGA with fillers such as calcium phosphates [240], magnesium [241,242] and iron oxide particles [243], TiO₂ nanotube [244] and hydroxyapatite [245,246] have been reported for biomedical applications that include tissue engineering and preparation of scaffolds. According to these studies, the addition of one of these elements in the dispersed phase, enhances the physical and biological properties of the matrix. Although in most cases this incorporation improved the mechanical properties of the composite, allowing better performance, this showed high dependency on the filler content and fabrication processes (e.g. electrospinning, encapsulation, supercritical gas foaming and phase separation).

Another component reported in the last years for the synthesis of PLGA composites is chitosan. Boukari et al. [247] prepared a scaffold composite system made of porous PLGA and protein loaded PLGA-chitosan microspheres. Different studies for the same application have also incorporated alginate in the PLGA matrix [248,249]. The addition of chitosan and alginate in the dispersive phase, has been reported to retain cytocompatibility and increase the encapsulation efficiency. Furthermore, it preserves the release function of the antibody in the microspheres since it helps preventing initial burst release of the protein, a challenging aspect according to the encapsulated substance. Although certain advantages related to biocompatibility, encapsulation efficiency and mechanical performance have been reported by the preparation of PLGA composites, issues remain to be addressed for a wider utilization of these materials at least in clinical applications. Inflammation in vivo, degradation profile tuning, optimization of filler amount and scaling up are the most relevant aspects that still need further research.

Despite its versatile potential, biomedicine is the field where POX
has received the most attention, while utilization for packaging or agricultural applications has been scarcely reported. Biodegradable nanoparticles and microparticles have been synthesized for targeted drug delivery of therapeutic agents [164,187,250,251]. For poly(alkylene oxalate) oxalates one of the first reported applications still in use exploits their good tensile strength for in vivo degradable surgical sutures [252] and coatings for multifilmчатure sutures [142]. Scaffolds and other surgical devices have also been studied as applications. Reports on composites containing POX are very scarce and only studied for the biomedical field. Phromviyo et al. [239] studied a biodegradable polyoxalate blended with poly(vinyl alcohol) to create composite nanofibers for controlled release of drugs. The release was found to occur with a diffusion stage followed by degradation. The drug release rate for the composite nanofibers was found to depend on the POX content, being the slowest for high POX amounts. This is reasonable since the hydrophilicity of the system is affected by the hydrophobic contribution of the POX. Overall, some contributions to the drug delivery field can be subtracted from this research. Yet, in vivo studies to confirm the biocompatibility and cytotoxicity of this system still have to be performed in order to draw more realistic conclusions.

7. Concluding remarks

The increasing government norms and regulations for the reduction of plastic waste have boosted the demand for new materials. Europe leads the shift to renewable polymers in major industries such as the pharmaceutical, textile, cosmetics and packaging industries. The Asia Pacific region is becoming more relevant in the sustainable polymer market with some of the major producers of glycolide and oxalic acid in China, India and Japan. Opportunities for polymers to contribute to a circular economy are definitely promising.

CO₂ is a valuable feedstock since it is naturally abundant, nontoxic, inexpensive, a non-oxidant and renewable. Currently, transformation of CO₂ into building blocks for materials is a promising option with environmental benefit for production of the polyesters discussed in this review. A relevant example of this technology has been developed by Liquid Light Inc., now part of Avantium. The process is based on an electrochemical reduction of CO₂ to formic acid derivatives that can subsequently be converted into useful monomers such as oxalic acid and glycolic acid. The development of this kind of technology targets future monomer production costs that can at scale compete with fossil counterparts (€1.2/kg). This will allow the development of a promising landscape for new polyesters, especially taking into account the reduction in all unit operations and reduced sensitivities to energy demand in all unit operations and reduced sensitivities to counter parts ([36]). In order to start using glycolic acid derived polymers in large-scale applications (e.g. for degradable drinking straws, degradable barrier films, degradable seed/fertilizer coatings, etc.) it is necessary to develop both extremely efficient monomer and polymer production routes as well as developing the market by matching of the novel polymer properties to current unmet market needs in various applications.

Acknowledgement

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 767798.

References

Coated VICRYL®


