A review on the thermomechanical properties and biodegradation behaviour of polyesters

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Abstract

The increasing societal concerns about the environmental impact of plastic waste, together with the depletion of petroleum resources, makes it imperative to develop environmentally friendly products that would potentially replace conventional petroleum based materials. Due to their inherent thermomechanical behaviour and biodegradability, biodegradable polyesters have shown explosive growth and underpin the global shift towards sustainability. In fact, the potential of ester groups to undergo hydrolytic chain scissions has brought biodegradable polyesters to the forefront of polymer science, both in fundamental research and industry level. Although the field of biodegradable polymers has been traditionally limited to aliphatic polyesters, recently, the introduction of aromatic rings into the polymer structure has allowed obtaining aliphatic/aromatic polyesters with much broader thermal, mechanical and biodegradation properties.

The discovery of new synthetic approaches has boosted the development of novel biodegradable polyesters, with reported properties equivalent or even superior to conventional polymers. As polymer chemistry is a property driven science, the thermomechanical properties are often the most relevant aspects that determine product performance specifications and play a pivotal role towards the definition of the specific end-use applications of polymeric materials. Coupled with an understanding of polymer biodegradability, including hydrolytic and enzymatic degradation behaviour, the stage is set for a broadening impact of these systems on global sustainable polymer challenges. Accordingly, this review establishes an up-to-date state-of-the-art in the field of biodegradable polyesters, thoroughly analyzing and comparing their thermal, mechanical and biodegradation properties.

Keywords: aliphatic/aromatic polyesters; glass transition temperature; melting temperature; mechanical properties; biodegradation; hydrolysis.

Contents

1. Introduction

Massive amounts of non-degradable petroleum-based polymers are being produced worldwide, which after their use are mainly discarded into the ecosystems as industrial waste products. Such materials end up in landfill burial sites or are directly disposed into oceans and remain in such environments for long time as a form of microplastics as they are resistant to microbial attack [1]. There is no doubt that the accumulation of this polymeric waste, known as "white-pollution", represents a serious threat to the balance of our ecosystem. Moreover, this extensive use of synthetic plastics is also generating serious concerns about their environmental footprint related to the intensive use of non-renewable resources and energy. The unpredictable petroleum price fluctuations and its inevitable depletion is stimulating novel alternatives to these non-renewable materials [2]. Similarly, the waste management issues associated with these synthetic non-degradable materials produces enormous environmental and economic concerns and represents a serious threat to the planet. In this framework, most of the countries are trying to establish novel green alternatives to face the environmental burdens associated with the use of fossil resources and their related pollution.

Thanks to inherent biodegradability, biocompatibility, thermomechanical behaviour and renewability, biodegradable polymers have emerged as a sustainable alternative to lessen our dependence of petroleum-based plastics and play a pivotal role towards the development of a greener economy. These developments have come out of extensive research, both in industry and academia, highlighted by the increasing number of works published in the last two decades. These sustainable biodegradable materials could be broken down under physiological environments through macromolecular cleavage reactions into shorter chains, which ultimately form non-toxic simpler by-products. Consequently, biodegradable polymers could successfully replace traditional commodity petroleum-based polymers such as polypropylene (PP) or polyethylene (PE) in applications as varied as packaging, agriculture, tissue engineering and fibre-technology [3–5]. More than perhaps any biodegradable polymer class, biodegradable polyesters have shown explosive growth and underpin the global shift towards sustainability. According to recently compiled market data by European Bioplastics Association, the global production of biodegradable polymers is estimated to grow up to 1.086.000 tonnes by 2022, which is a 24 % increase in comparison with what was produced in 2017 (880.000 tonnes) [6]. In this burgeoning trend, the potential of ester groups to undergo hydrolytic chain scissions has brought biodegradable polyesters to the forefront of polymer science, both in fundamental research and industry level. Biodegradable polyesters truly appear as a solution to the increasing environmental concerns aroused from the use of non-biodegradable polymers for short-life applications.

Polyesters are a group of polymers where the repeating units are bonded via ester linkages. Although the use of biomass-based polyesters such as polyhydroxyalkanoates (PHAs) and polylactides (PLAs) offers advantages on low cost and ease of access, a wide variety of synthetic polyesters are been developed in the recent years. These synthetic polyesters are commonly obtained either by polycondensation reaction of anhydride, hydroxyacid or diacid and a secondary alcohol or by ring opening polymerization (ROP) reactions. Synthetic polyesters offer the additional advantage of providing materials with tailored physico-mechanical properties and improved processability in comparison with naturally occurring polyesters. They also present a much better batch-to-batch uniformity as their synthesis conditions are more reproducible. Therefore, synthetic polyesters are currently considered as economically competitive materials that can be fabricated to match a wide range of characteristics. Apart from being biodegradable, most of these polyesters are also biocompatible, allowing their use in tissue engineering and drug delivery applications. Last, but not least, the majority of the monomers used for the synthesis of such biodegradable polyesters can be obtained from renewable resources (either natural feedstock or from bacterial fermentation), reducing greenhouse emissions and limiting our dependence on fossil resources [7,8].

Traditionally, the field of biodegradable polymers has been limited to aliphatic polyesters, where the most used biodegradable polyesters are the linear polyglycolide (PGA), PLAs, polycaprolactone

(PCL) or PHAs. Although generally speaking aliphatic polyesters show good degradation properties, their physico-mechanical performance (i.e., mechanical strength, gas permeability, UV-transparency, mechanical strength, thermal resistance) remains somewhat low in comparison with petro-based polymers. On the contrary, aromatic polyesters such as poly(ethylene terephthalate) (PET), poly(propylene terephthalate) (PPT) and poly(butylene terephthalate) (PBT) display excellent properties, although they cannot be biodegraded. In this framework, an increasing field of interest is the introduction of aromatic rings into the polymer structure (pendant to the backbone or into the main chain) to obtain biodegradable aliphatic/aromatic polyesters with much broader thermal, mechanical and (bio)degradation properties. In this line, since the development of poly(butylene adipate-co-terephthalate) (PBAT), extensive research is being done for the custom design of novel biodegradable aliphatic/aromatic polyester systems with improved physico-mechanical performance [9]. The discovery of such synthetic approach has boosted the development of novel biodegradable polyesters with reported properties equivalent or even superior to conventional polymers. Accordingly, many polyester types could be designed so as to develop green products according to eco-design philosophies.

As polymer chemistry is a property driven science, the physical (especially thermomechanical) properties are often the most relevant aspects that determine product performance specifications and play a pivotal role towards the definition of the specific end-use applications of polymeric materials. In spite of the enormous relevance of biodegradable polyesters at both scientific and industrial levels and the many reviews published on the synthesis of such materials, to the best of our knowledge, a comprehensive review aimed to catalogue their thermal, mechanical and degradation behaviour is still lacking. The polymeric materials shown in this review have been classified according to their chain structure into aliphatic (a linear main chain) and aliphatic/aromatic (containing rings in the main chain) polyesters. Biodegradable aliphatic polyesters such as those obtained after the incorporation of carbohydrates or vegetal oils into the polyester backbone, poly(phosphate ester)s, poly(anhydride ester)s and polyester-urethanes / polyester-urethane-ureas are not covered in this review. Overall, the objective of this review is to establish an up-to-date state-of-the-art in the field of biodegradable polyesters, thoroughly analyzing and comparing the thermal, mechanical and biodegradation properties reported during the last decade and highlighting the most widely studied and promising biodegradable polyesters.

2. Polyesters and their thermomechanical properties

Several structural and chemical factors determine the thermomechanical behavior of polymers. Among the structural factors, the molecular weight (and its distribution), crosslinking and branching, degree of crystallinity (and crystal morphology) and molecular orientation play a major role in some important thermal (e.g., glass transition (T_g) and melting temperature (T_m)) and mechanical (e.g., elastic modulus, tensile strength and elongation at break) properties of polymers. Additionally, blending or copolymerizing with other polymers/comonomers or adding fillers to the polymeric matrix are common strategies to tune the thermomechanical properties of these systems. Thus, special care has to be taken when comparing the thermomechanical properties of polymers since, even with the same chemical structure, a given polymer may display different behaviour depending on the aforementioned structural factors. Since we are dealing here with biodegradable polymers, it has to be also considered that some of these factors (e.g., molecular weight and its distribution, degree of crystallinity) vary along their lifespan, having a direct impact on the thermomechanical behaviour of the material.

Considering the profound changes the mechanical properties suffer around the T_g (i.e., the elastic modulus may decrease by a factor of 1.000 when the temperature is increased above the T_g) some of the factors that affect this transition will be briefly summarized. In general terms, polymers are hard, rigid and display a glassy behaviour below their T_g, whereas they are soft and flexible above this temperature. Increasing chain flexibility, which can be achieved by increasing the number of the main-chain aliphatic groups, ether linkages or aliphatic side chains, generally lowers the T_g. In

contrast, increasing the chain stiffness via the incorporation of large or rigid groups (e.g., aromatic structures) raises the T_g. Enhancing the intermolecular forces between polymer chains also shifts the T_g to higher values. Therefore, increasing the polarity of the polymer chain or promoting the formation of strong hydrogen bonds between polymer chains results in polymers with increased T_g values. Apart from these chemical factors, there are also structural factors that have a strong impact on the glass transition of polymers, including the molecular weight, crosslinking degree, presence of plasticizers, etc. [10]. With all this in mind, the following section presents the main thermal and mechanical properties of most relevant biodegradable polyesters.

2.1. Aliphatic polyesters

2.1.1. Short-chain (x=1) polyesters: Polyglycolide (PGA) and Polylactide (PLA)

Figure 1 shows the typical structure of polyesters. Polyglycolide or poly(glycolic acid) (PGA) represents the simplest polymer within this category and was firstly reported in 1949 by Sporzynki et al. [11]. It is one of the most popular biodegradable polyester and can be obtained after the polycondensation of glycolic acid (GA). However, ROP of glycolide is the preferred method to obtain high molecular weight PGA [12]. Thanks to its simple chemical structure and stereo-regularity, it develops a high degree of crystallinity (X_c) upon processing [13]. PGA shows a glass T_g that ranges from 35 to 40 ºC and a T_m at 220-225 ºC [14]. Regarding its mechanical properties, PGA is a brittle and stiff material displaying low elongation at break, high elastic modulus (6.5 GPa) and high tensile strength (~60 MPa) [15,16].

Poly(lactic acid) (PLA) is among the most studied and applied biodegradable aliphatic polyesters. The first pioneering works with the biodegradable and biocompatible PLA were developed by Carothers back in the 1930s [17]. Polylactides are considered as one of the most promising biodegradable polymers and they represent a sustainable alternative to petro-based polymers because the lactides from which PLAs are synthesized can be produced under an economically viable fashion by microbial fermentation of agricultural by-products [18]. The synthetic approaches for the synthesis of PLA include condensation polymerization of lactic acid (LA) or the heavy metal-catalyzed ROP of lactide, the cyclic dimer of lactic acid. ROP is the preferred approach for PLA fabrication as polycondensation reactions only yield low molecular weight polylactide, while ROP enables obtaining high molecular weight PLA with better control of the chain structure [19,20]. As a result of a chiral carbon atom in its structure, three different stereochemical forms of polylactides could be found: i) stereoregular semicrystalline poly(L-lactic acid) (PLLA) and ii) poly(D-lactic acid) (PDLA), and iii) the atactic (having a random distribution of L- and D-lactide units) amorphous poly (DL-lactic acid) (PDLLA). An optically pure lactic acid is necessary to obtain high crystalline PLA with high mechanical strength that is suitable for commercial use [21]. It should be considered that biologically produced polylactide exclusively leads to PLLA (L-lactide is a naturally occurring isomer), while chemical synthesis enables to properly tune the ratio of L- and D-lactic acid [18]. Under certain conditions, the physical blend of PLLA and PDLA gives rise to a highly regular stereocomplex, which shows rather different thermal (T_g = 65 to 72 ºC and T_m = 220 to 230 ºC) and mechanical properties when compared with PLLA and PDLA homopolymers. Thanks to its processability through common thermoplastic processing technologies, and its biodegradability, polylactide is being mainly used as a commodity polymer for general packaging applications (e.g., compostable tableware, plastic bags, food packaging, etc.). However, the inherent brittleness, poor thermal resistance, restricted barrier performance (for both gases and light) and marked physical aging limit the use of PLAs in industrial sectors [22,23]. A special niche market for PLA is also found in textile and biomedical fields, where it could be used as disposable garments, nappies, stents, sutures or as bone-fixation materials. Optically pure PLLA shows a T_g of 55-65 ºC and a T_m at 170-200 ºC [24]. Reducing the optical purity by approaching to the racemic mixture of L- and D-enantiomers, reduces both the crystallinity and the melting point of the resulting polymer [25]. In this sense, a polylactide with an optical purity of 47% showed a melting enthalpy of 18 J/g and a T_m at 105 ºC. Similar to PGA, PLAs show stiff yet brittle

behaviour with high elastic modulus (~3.5 GPa) and tensile strength (~60 MPa) [16]. As for thermal transitions, the mechanical properties of PLAs are largely affected by molecular weight, optical purity and crystallinity degree [26].
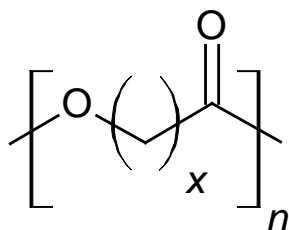

Figure 1. General structure of polyesters.

Copolymerization of lactide and glycolide has been used to overcome the shortcomings of both PLA and PGA homopolymers at the same time that their advantages are combined in a new copolymer. A series of poly(lactic acid-co-glycolic acid) (PLGA) copolyesters with different lactide-to-glycolide composition has been proven an efficient method to tune the physico-mechanical properties of this polyester [27]. However, the copolymers of lactide and glycolide remain stiff and brittle, limiting their use in those applications requiring highly flexible biodegradable materials. Its degradability could be easily tailored during the synthesis, which has opened new opportunities in the field of drug delivery systems [28].

2.1.2. Long-chain (x>1) polyesters: toward soft elastomeric aliphatic polyesters

x=2. Increasing the chain length within the repetitive unit represents a valid strategy to tune the thermo-mechanical properties of aliphatic polyesters towards softer and elastomeric alternatives. For instance, poly(β-propiolactone) (PPL) is a biocompatible aliphatic polyester that displays the same structure than poly(3-hydroxypropionate) (P3HP, a microbial polyhydroxyalkanoate). To overcome the limitations of both condensation polymerization from 3-hydroxypropionic acid or ROP of β-propiolactone, alternative synthetic procedures have been considered for the synthesis of high molecular weight PPL, including the ROP of 3-hydroxypropionate macrocyclic ester [29] or enzymatic polymerization of methyl 3-hydroxypropionate using an immobilized lipase such as Novozym® 435 [30], among others. PPL is a highly crystalline polymer that displays a T_g at -20 to -15ºC [31,32], and a T_m at around 80 ºC [33]. Thus, at room temperature, it shows improved ductility with respect to short-chain aliphatic polyesters (i.e., PGA and PLA) with elongation at break values from 29 to 160%, elastic modulus of 0.34-1.85 GPa and tensile strengths of 20-107 MPa [34]. Poly(malic acid) (PMLA) is a type of water-soluble poly(β-hydroxy acid) that can be synthetically obtained from aspartic acid or malic acid and also can be extracted from natural resources such as *Physarum polycephalum* [35]. Similarly to polylactide, PMLA has a chirality centre along its backbone, yielding PMLA with different structures. Accordingly, poly(α-malic acid) has been obtained by ROP of malide dibenzyl ester followed by acid deprotection [36], while poly(β-malic acid) has been synthesized upon polymerization of benzyl malolactonate followed by the removal of benzyl protecting groups by catalytic hydrogenolysis [37]. Poly(α,β-malic acid) is synthesized by direct polycondensation using tin(II) chloride as a catalyst [38]. Besides, the carboxylic groups within the main chain are prone to be substituted, offering the possibility to functionalize the polymer with bioactive molecules and/or to modulate the overall hydrophobicity [39]. However, the synthesis of high molecular weight PMLA is difficult to achieve at high yields [40]. Therefore, the use of these polymers has been limited to their copolymerization with other comonomers, mainly lactide [41,42] and caprolactone [43], yielding aliphatic copolyesters with functional pendant groups and amphiphilic block copolymers that can self-assemble into micelles or polymer vesicles.

x=4. ROP of δ-valerolactone, δ-hexalactone, ε-caprolactone, ε-decalactone and other macrolactones (e.g., ethylene brassylate, ω-pentadecalactone) is the preferred method to synthesize

high molecular weight aliphatic polyesters showing elastomeric behavior [44]. Poly(δ-valerolactone) (PVL) is a semicrystalline aliphatic polymer with a T_g and a T_m at -66 and 62 ℃, respectively [45]. Regarding its mechanical properties, it shows high elongation at break (150-200%), tensile strength of ~11 MPa and an elastic modulus of 0.57 GPa [46]. δ-valerolactone has been successfully copolymerized via ROP with other cyclic esters (e.g., lactide, caprolactone) to produce thermoplastic elastomers with reduced crystallinity and faster degradation rates [47,48]. δ-hexalactone shows identical structure to δ-valerolactone but possessing a methyl pendant group, which is sufficient to disrupt crystallinity of the resulting polymer, resulting in amorphous (T_g = -51 ℃) viscous liquids at room temperature with limited applicability [49]. However, its copolymerization with other comonomers (e.g., ε-caprolactone [50], ω-pentadecalactone [51], ethylene brassylate [52]) has been proven a satisfactory strategy to tune the crystallinity, degradability and mechanical properties of the resulting copolymers.

x=5. A representative example of a poly(ω-hydroxy acid)s is poly(ε-caprolactone) (PCL), a petroleum-based semicrystalline linear aliphatic polyester composed of hexanoate repeating units. It is synthesized from the ROP of ε-caprolactone in presence of metal alkoxides (tin octoate, aluminium isopropoxide) and is being mainly used for packaging and drug release applications [53]. PCL is a semycrystalline aliphatic polyester showing a T_g of -60 ℃ and a T_m at ~60 ℃ [54]. Regarding its mechanical properties, it shows very large elongation at break (300-1000%), tensile strength of ~20 MPa and elastic modulus of ~0.34 GPa [15,16,55]. It can be blended or copolymerized with a very wide variety of polymers [56,57], which has markedly increased its use. Poly(ε-decalactone) (PεDL) has been synthesized in order to obtain biodegradable polyesters using monomers which are not derived from petrochemical sources. ε-decalactone (ε-DL) shows identical structure to ε-caprolactone but possesses a butyl pendant group at the ring-closing position. It has emerged as a good alternative to ε-caprolactone as it is obtained from castor oil and its polymerization can be achieved via ROP utilising benzyl alcohol as the initiator and Triazabicyclo[4.4.0]dec-5-ene as a catalyst [58]. The resulting product is an amorphous viscous liquid with a T_g at approximately -53 ℃ [59]. ε-decalactone has been successfully copolymerized with other comonomers, including lactide [59], and ω-pentadecalactone [60], yielding exceptionally tough materials with tunable elastomeric behaviour.

x>5 (macrolactones). Longer chain aliphatic polyesters are promising sustainable alternatives to commonly employed polymers such as PE. Although ROP of several macrolactones has been considered in bibliography, including nonadecalactone and tricosalactone [61], ω-pentadecalactone is by far the most studied monomer within this category. Poly(ω-pentadecalactone) (PPDL) is a semicrytalline aliphatic polyester with a T_g at ~ - 30 ℃, and a T_m close to 100 ℃ [61,62]. It shows high elongation at break (>800%) with an elastic modulus of 0.3 GPa and a tensile strength of ~ 29 MPa [60].

Table 1. Thermo-mechanical properties of some representative aliphatic polyesters.

x	Name	Structure	T_g (ºC)	T_m (ºC)	E(GPa)	σ(MPa)	ε(%)
1	PGA		35-40	220-225	6.5	60	<10
	PLA		55-65	170-200	3.5	60	<10
2	PPL		-20 to -15	80	0.34-1.85	20-107	29-160
3	*ROP γ-butyrolactone and γ-valerolactone is difficult to achieve so the bacterially derived poly(4-hydroxybutyrate) (P4HB) is usually employed* [63].						
4	PVL		-66	62	0.57	11	150-200
	PHL		-51	amorphous	-	-	-
5	PCL		-60	60	0.34	20	300-1000
	PεDL		-53	amorphous	-	-	-
>5	PPDL		-30	100	0.3	29	>800

2.1.3. Microbial polyesters

Microbial polyhydroxyalkanoates (PHAs) are a family of naturally occurring biodegradable and biocompatible polyesters known as bacterial polyesters and constitute the family which comprises most of the poly(β-hydroxy acid)s [64,65]. They are intracellularly produced by the *PHA synthase* (PhaC) enzymes via the polymerization of hydroxyacyl-CoA monomers as a means to store carbon and energy storage compounds for the cells [65]. Approximately 30% of soil inhabiting bacteria can synthesize some kind of PHAs [66], and several prokaryotic organism could accumulate up to 80% of their cellular dry weight in the form of PHA [67]. More than 300 different microorganisms have been found to produce PHAs, although few of them (*Cupriavidus necator, Alcaligenes latus, Azotobacter vinelandii, Pseudomonas oleovorans, Paracoccus denitrificans, Protomonas extorquens, E. coli*) can produce in a sufficient quantity for large-scale production [68]. During the last years PHAs have attracted a great deal of attention due to their renewable nature (they can be also chemically synthesized) and to their ability to undergo biodegradation under both aerobic and anaerobic conditions without forming toxic products. The general molecular structure of PHAs is

depicted in Table 2. It should be taken into account that x refers to the chain length and could range from 1 to 3. When x=1, a poly(β-hydroxy acid) is obtained, but for larger values, a poly(ω-hydroxy acid) may be obtained. Nonetheless, as typically x=1, microbial PHAs have been classified as poly(β-hydroxy acid)s. The monomeric composition of PHAs could be controlled by modifying fermentation conditions (i.e., carbon substrate, temperature, microorganisms metabolism) to yield any of the more than 150 types of PHAs that are reported so far [69]. Pure PHAs could be also synthetically produced by ROP of several lactones similarly to the ROP of β-butyrolactone, which yields synthetic poly(3-hydroxybutyrate (P3HB) identical from the bacterial one [63]. In some cases, such as γ-butyrolactone and γ-valerolactone, the synthetic ROP is restricted due to the small ring strain with low geometric distortion in the ester group, being the fermentation route the preferred one to yield the aliphatic polyester (e.g., poly(4-hydroxybutyrate) (P4HB)) [63,70].

PHAs could be classified according to the length of their side chain; i.e., depending on the number of carbon atoms in their structure. Accordingly, PHAs having 3 to 5 carbon atoms (C_3 - C_5) are termed as short-chain-length PHAs (*scl*-PHAs) and are produced by *Ralstonia eutropha* and other bacteria. P3HB, P4HB and poly(3-hydroxyvalerate) (P3HV) are typical examples of *scl*-PHAs. P3HB is a highly crystalline thermoplastic polymer showing a T_g at 4 °C and a T_m at 180 °C. It shows a stiff yet brittle behaviour with an elastic modulus of 3.5 GPa, a tensile strength of 40 MPa and an elongation at break of 5% [71]. P3HV has a T_g at ~ -10 °C and a T_m at 100-120 °C. Regarding the mechanical properties, P3HV is not as stiff as P3HB and shows a tensile strength of 31.2 MPa and an elongation a break of 14.0% [72–74]. P4HB, being a *scl*-PHA, shows completely different properties with respect to P3HB and P3HV presented so far. With low T_g (-48 °C) and T_m (53 °C), high elongation at break (1000%), high tensile strength (104 MPa) and an elastic modulus of 0.149 GPa [75,76], P4HB has been considered as an alternative absorbable material for implantable medical applications [70]. Mechanical properties of these homopolyesters can be finely tuned by copolymerization. Some of the properties of *scl*-PHA (co)polymers are summarized in Table 2.

Longer PHAs with 6 to 14 carbon atoms (C_6 - C_{14}) are referred as medium-chain-length PHAs (*mcl*-PHAs) and can be produced using *Pseudomonas oleovorans* and other *pseudomonas sensu strictu* [77]. Examples include poly(3-hydroxyhexanoate) (P3HHx), poly(3-hydroxyoctanoate) (P3HO) and poly(3-hydroxydodecanoate) (P3HDD), among others. However, the resulting *mcl*-PHAs are usually an uncontrollable random mixture of repeating units with differing side chain lengths. Thermal and mechanical properties of these random copolymers will be affected by several parameters, such as composition, crystallinity and molecular weight. In general, random *mcl*-PHAs display glass transition temperatures below room temperature (from -65 to -25 °C) and low melting points ranging from 42 to 75 °C. In terms of mechanical properties, they show elastomeric behaviour with relatively high elongation at break and low elastic modulus. For the sake of example, Table 2 includes the thermal and mechanical properties of few random *mcl*-PHAs [78–80]. Genetically modified organisms, including *Pseudomonas putida, Pseudomonas entomophila* or *Escherichia coli*, have enabled the production of *mcl*-homopolymers and the elucidation of some of their thermal properties (Table 2) [81–88]. Thanks to their inherent biodegradability, biocompatibility and elastomeric behaviour, some of these *mcl*-PHAs and their composites are being considered for biomedical applications requiring soft polymers [64,89].

Copolymers composed of both *scl* and *mcl* monomers can combine respectively the strength and elasticity associated with *scl*-PHAs and *mcl*-PHAs, leading to (co)polymers that can resemble the mechanical properties of PE or PP [79,90]. Advances in metabolic and genetic engineering have enabled the production of *scl*-co-*mcl*-PHAs with controlled repeating unit composition and predictable physical properties, which is of vital importance for the use of these materials in growing number of applications, including medical uses. In case of P3HB-co-3HHx copolymers, increasing the amount of HHx results in a decreased T_m and X_c. In terms of mechanical properties, incorporation of HHx results in softer and more flexible samples (Table 2) [91–93]. Copolymerization of 3HB with 3HO has been also reported as a valid strategy to tune the thermal and mechanical properties of the resulting copolyesters. As for P3HB-co-3HHx copolymers,

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increasing the amount of *mcl* monomer reduces the T_m of the copolymer. At the same time, the sample turns elastomeric with increased elongation at break and reduced elastic modulus (Table 2) [94]. Interestingly, those copolymers with concentrations of 3HO above 15% show two distinct glass transition temperatures, which may indicate a blocky character of the P3HB-co-3HO copolymer. Other copolymers of 3HB and longer chain 3-hydroxyalkanoates, including 3HD and 3HDD, were recently produced by engineered *Pseudomonas entomophila* [95]. The precise control over the amount of 3HDD in the copolymer yield materials that can meet specific requirements in terms of mechanical and thermal properties (Table 2).

Table 2. Thermo-mechanical properties of some representative *scl-* and *mcl*-PHAs.

General structure		x	R	Name	T_g (°C)	T_m (°C)	E(GPa)	σ(MPa)	ε(%)
scl-homopolymers		1	CH_3	P3HB	4	180	3.5	43.0	5
		1	C_2H_5	P3HV	-10	100 to 120	<3.5	31.2	14
		2	H	P4HB	-48	53	0.15	104.0	1000
scl-copolymers	**P(3HB-co-3HV)**								
	80%-3HB	20%-HV			-1	145	1.2	32.0	50
	16%-3HB	84%-3HV			~ -8	-	-	20.4	35
	P(3HB-co-4HB)								
	36%-3HB	64%-4HB			-35	50	0.030	17.0	591
	22%-3HB	78%-4HB			-37	49	0.024	42.0	1120
	18%-3HB	82%-4HB			-39	52	0.045	58.0	1320
	10%-3HB	90%-4HB			-42	50	0.10	65.0	1080
mcl-homopolymers		1	C_3H_7	P3HHx	-28	amorphous	-	-	-
		1	C_4H_9	P3HHp	-32	amorphous	-	-	-
		1[a]	C_5H_{11}	P3HO	-43 to -38	61 to 66	0.005-0.008	6.4	425
		1[b]	C_9H_{19}	P3HDD	-49	72 to 82	0.061	5.5	60
mcl-copolymers	P(3HO-co-12%3HHx-co-2%3HD)				-	-	0.0076	9.3	380
	P(3HO-co-15%3HHx-co-30%HD-co-15%3HDD)				-44	53	0.0036	5.0	189
	P(3HD-co-84.26%HDD)				-33	78	0.10	3.9	88
	P(15%3HDD-co-x%3HHx-co-y%3HO-co-z%3HD)				-44	53	0.0036	5.0	189
	P(39%3HDD-co-x%3HHx-co-y%3HO-co-z%3HD)				-43	65	0.012	8.9	125
scl-mcl-copolymers	**P(3HB-co-3HHx)**								
	95%-3HB	5%-3HHx			0 - -5	151	-	12.8	164
	90%-3HB	10%-3HHx			-1 - -6	127	-	14.9-21.0	400
	85%-3HB	15%-3HHx			0	115	-	23.0	760
	82%-3HB	18%-3HHx			-2 - -8	120	-	12.7-20.0	850
	P(3HB-co-3HO)								
	93.6%-3HB	6.4%-3HO			-1	158	0.17	10.5	53
	85.3%-3HB	14.7%-3HO			-2	159	0.032	3.2	110
	68.7%-3HB	31.3%-3HO			-26/-6	amorphous	0.012	1.7	230
	P(3HB-co-3HD)								
	95%-3HB	5%-3HD			-2	154	0.083	5.5	28
	69%-3HB	31%-3HD			-42	151	0.014	2.3	87
	50%-3HB	50%-3HD			-43	amorphous	0.001	1.2	1155
	27%-3HB	73%-3HD			-44	54	0.007	12.0	1416
	8%-3HB	92%-3HD			-44	57	0.007	12.3	1367
	2%-3HB	98%-3HD			-45	57	0.007	12.4	1315

[a] the mechanical properties are referred to a copolymer with high 3HO content (>90%). [b] the mechanical properties are referred to a copolymer with high 3HDD content (97.9%).
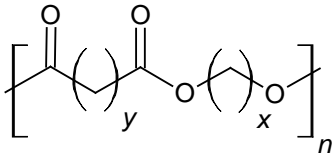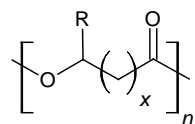
2.1.4. Poly(alkylene dicarboxylate)s

Poly(alkylene dicarboxylate)s (PADC)s are a family of biodegradable aliphatic polyesters derived from dicarboxylic acids and dihydroxy compounds. Poly(alkylene alkanoate)s (PAA)s are PADCs derived solely from aliphatic dicarboxylic acids containing 4-10 carbon atoms and a diol of 2-6 carbon atoms. A series of biodegradable PAAs could be prepared using diols having different length and aliphatic diacids with increasing number of methylene units. In this sense, poly(ethylene alkanedicarboxylate)s, poly(propylene alkanedicarboxylate)s and poly(butylene alkanedicarboxylate)s are the most studied PAAs due to their easily tunable physico-mechanical properties. Despite the wide variety of possible combinations between diols and dicarboxylic acids, only few PADCs have been thoroughly characterized in terms of thermo-mechanical properties (Table 3 and 4). This can be associated to the low molecular weight and poor mechanical properties of some of the synthesized PADCs or commercial unavailability of the reagents needed for the synthesis. Apart from the poly(ethylene alkanedicarboxylate)s, poly(propylene alkanedicarboxylate)s and poly(butylene alkanedicarboxylate)s presented herein, PADCs derived from diols and dicarboxylic acids having higher number of carbon atoms (e.g., 1,5-pentanediol, dodecanedioic acid, etc.) are being intensively investigated, providing the possibility to synthesize high molecular weight aliphatic polyesters from biobased monomers and renewable biomass [96].

The chemical structure of poly(ethylene alkanedicarboxylate)s is shown in Table 3, together with their most relevant thermal properties [97–105]. For instance, poly(ethylene succinate) (PESu) could be synthesized by polycondensation of succinic acid and ethylene glycol or by either ROP of succinic anhydride with ethylene oxide [106]. It is highly permeable to oxygen and it shows an excellent biodegradability. In terms of mechanical properties, PESu shows an elastic modulus of 0.28 GPa, a tensile strength of 25 MPa and a high elongation at break (~500%). Thus, it has been blended with brittle polymers (e.g., PLLA, P(3HB-co-3HV)) [107,108], to increase their elongation at break and toughness. Polyethylene adipate (PEAd) is an aliphatic polyester formed from polyethylene glycol and adipic acid. As it presents a very low T_g (-50 to -46 ℃), it is commonly blended with other polyester as a soft segment [109].

Table 3. Thermal properties of some representative PADCs.

General structure	x	y	Name	T_g (℃)	T_m (℃)
		2	PESu	-17 to -9	96 to 105
		3	PEG	-	-
		4	PEAd	-50 to -46	48
	2	5	PEPi	-	36
		6	PESub	-	71
		7	PEAz	-60	62
		8	PESe	-40	77
		2	PPSu	-35 to -29	44 to 49
		3	PPG	-53	46
		4	PPAd	-59 to -54	29 to 43
	3	5	PPPi	-63	45
		6	PPSub	-65 to -58	47
		7	PPAz	-63 to -57	49 to 57
		8	PPSe	-	55
		2	PBSu	-32	114
		3	PBG	-	-
		4	PBAd	-61 to -54	41 to 61
	4	5	PBPi	-	-
		6	PBSub	-61	55
		7	PBAz	-63	41
		8	PBSe	-62	65

As shown in Table 3, poly(propylene alkanedicarboxylate)s have an even number of methylene groups in their repeating units (or an odd number of methylene groups in the diol segment), which provides rather special physico-mechanical [110–119] and degradation properties in comparison with poly(ethylene alkanedicarboxylate)s and poly(butylene alkanedicarboxylate)s [120]. For example, polypropylene succinate (PPSu) shows rather low melting point (T_m=44-49 ºC) in comparison to PESu and polybutylene succinate (PBSu) counterparts (T_m=96-105 ºC and T_m=114 ºC, respectively). In terms of mechanical properties, PPSu displays low elastic modulus (0.21 GPa) and low tensile strength (5 MPa) and has been successfully copolymerized with aromatic monomers (e.g., furandicarboxylic acid) yielding fully bio-based and degradable aliphatic/aromatic copolyesters with tunable mechanical properties [121]. Poly(propylene adipate) (PPAd), obtained after esterification and polycondensation reaction, has also gained some interest as its T_m is close to physiological temperature [97,111]. The tensile strength of PPAd is slightly lower than the one of PEAd and polybutylene adipate (PBAd) (12 MPa *vs.* 17 and 16 MPa for PEAd and PBAd, respectively) and it shows high elongation at break (>400%) [97].

Poly(butylene alkanedicarboxylate)s, displayed in Table 3, are the most widely used and studied poly(alkylene dicarboxylate)s [109,122–130]. Poly(butylene succinate) (PBSu) is the most utilized polyester belonging to this group as it presents improved physico-mechanical properties in comparison to the majority of aliphatic polyesters, it is relatively cheap and can be easily processed [131]. PBSu is commercially available since 1993 under the tradenames of Bionolle[TM] and GS Pla[TM] by Showa-Denko and Mitsubishi Chemical Corporation respectively. PBSu directly competes with other biodegradable plastics due to its improved performance, good processability and chemical resistance. It is obtained after a direct esterification of succinic acid with 1,4-butanediol, which are monomers that are extracted from renewable resources and are readily available on the market [113]. In terms of mechanical properties, PBSu shows an elastic modulus of 0.30-0.50 GPa, a tensile strength of 34 MPa and high elongation at break (>500%). A huge variety of PBSu-based copolymers and blends [126,127] have been prepared to modify its properties, which have been recently reviewed Gigli et al.[132]. Poly(butylene adipate) (PBAd) is another biodegradable polyester with potential uses for biomedicine that can be synthetized via polycondensation of adipic acid or its lower alkyl ester with 1,4-butanediol in the presence of a catalyst. Due to its low melting temperature (41-61 ºC) and brittleness, it is usually copolymerized to obtain segmented polyesters with improved physico-mechanical properties while keeping the inherent biodegradability of PBAd [133]. One example is the poly(butylene succinate-co-adipate) (PBSA) copolyester, which could be obtained by a combination of adipic acid, succinic acid and 1,4-butanediol. It is traditionally obtained from petro-derived resources, although its constituent monomers can also be obtained from bio-based feedstock. The addition of adipic acid decreases the crystallinity at the same time that increases the degradation rate [109].

Table 4. Mechanical properties of some representative PADCs.

Name	E(GPa)	σ(MPa)	ε(%)
PESu	0.28-29	25	500
PEAd	-	17	520
PPSu	0.21	5	-
PPAd	-	12	410
PBSu	0.30-0.50	34	560
PBAd	0.17	11-16	380-560

2.1.5. *Other biodegradable aliphatic polyesters*

In this section several relevant and recently reported biodegradable polyesters that do not fit among the above mentioned categories are presented. The first example is polydioxanone (PDO or PDS) (Figure 2), which is a colourless and highly crystalline synthetic polymer that presents multiple repeating ether-ester units. It is therefore considered as a poly(ester-ether) and can be

obtained by ROP of *p*-dioxanone [134]. Thanks to the incorporation of an ether bond in its backbone it shows an accelerated hydrolytic scission of ester bond [135]. PDO is a Food and Drug Administration-approved (FDA) polymer and has been intensively employed as surgical suture. This semicrystalline polymer shows a T_g and a T_m at -10 and ~100 °C [136], respectively, and the reported elastic modulus, tensile strength and elongation at break for PDO fibers are 0.37 GPa, 583 MPa and 161 % [137].
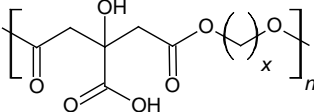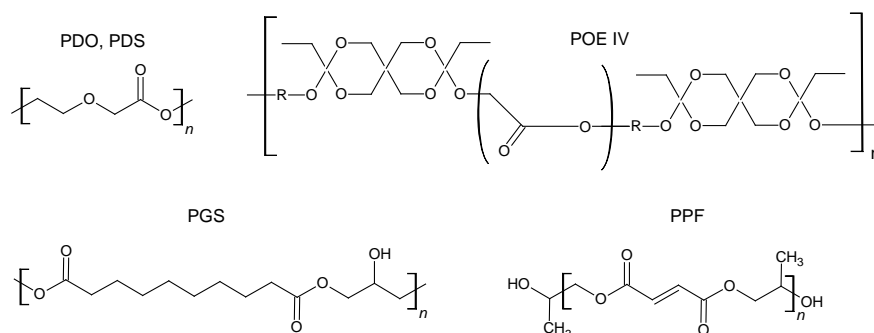

Figure 2. Chemical structure of polydioxanone (PDO or PDS, 4th generation poly(ortho esters) (POE IV), poly(glycerol sebacate) (PGS) and poly(propylene fumarate) (PPF)).

Poly(ortho esters) (POEs) are a group of biodegradable polyesters that were firstly synthesized in the 1970s by the ALZA Corporation in order to develop materials that may potentially undergo surface erosion degradation process, which is not commonly found in biodegradable polyesters [138,139]. The high hydrophobicity provided by the orthoesther linkages ensures that the degradation proceeds faster than the H_2O diffusion into the material. POEs are synthesized by using diols having different chain flexibility. Till the date, four types of these surface eroding materials have been reported [140,141]. 1st generation POEs (or POE I) are obtained upon transesterification of a diol together with diethoxytetrahydrofuran. POE II (2nd generation) were developed to avoid the release of acidic by-products during its degradation (as occurring in POE I). Such materials are obtained by reacting diols with diketene acetal 3,9-bis(ethylidene 2,4,8,10-tetraoxaspiro[5,5]undecane). POE III (3rd generation) could be obtained upon direct polymerization of a triol together with an orthoester, yielding a highly mechanically flexible gel-like material. Finally, 4th generation POEs (POE IV, Figure 2) were developed to solve the up-scaling difficulties of POE III and, similarly to POE II, they can be obtained by incorporating soft segments based on LA and GA into the chain backbone. Although generally speaking POE IV show weak mechanical properties, their good biodegradability has boosted their use in tissue engineering and drug delivery applications [142]. This last group of POE presents a scalable synthetic procedure and has the highest versatility as their properties could be tuned by properly selecting the nature of diols and the amount of LA or GA in the main chain [141,143,144]. Thus, depending on the flexibility of the diol chain, a wide variety of thermo-mechanical properties can be achieved; from hard, glassy materials showing a high glass transition temperature to semi-solid polymers showing low glass transition temperature.

As polyesters usually display rather brittle mechanical behaviour which is not adequate for some biomedical applications, novel elastomeric biodegradable polyesters such as poly(diol citrates) and poly(glycerol sebacate) (PGS) have been synthesized for soft tissue engineering applications (Figure 2) [145,146]. Poly(diol citrates) can be synthesized via polycondensation reactions using non-toxic and inexpensive monomers, such as citric acid. Besides, considering the availability of various diols with different chain flexibility, biodegradable elastomers with tuneable mechanical properties can be obtained through relatively simple synthesis procedures. In this sense, a series of poly(diol citrates) were synthesized by reacting citric acid with various diols: poly(1,6-hexanediol-co-citrate) (PHC), poly(1,8-octanediol-co-citrate) (POC), poly(1,10-decanediol-co-citrate) (PDC) and poly(1,12-dodecanediol-co-citrate) (PDDC) [147]. All the synthesized polymers were totally amorphous and displayed low T_g ranging from -5 to 10 °C. Regarding the mechanical properties, which are summarized in Table 5, all the poly(diol citrates) displayed an elastomeric behaviour with

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no permanent deformation. Moreover, these mechanical properties were finely adjusted, not only by the selected diol, but also through cross-link density, by adjusting the post-polymerization temperature and time [148]. Similar to the poly(alkylene dicarboxylate)s based on dicarboxylic acids and dihydroxy compounds analysed in the previous section, polymers based on glycerol can also be synthesized, being PGS the most studied one within this category. The first polymerization of PGS was reported in 2002 through polycondensation reaction of equimolar ratios of glycerol and sebacic acid reacted at 120 ºC in the absence of a catalyst under inert conditions [145]. Owing to its physico-mechanical properties and easy of synthesis, these non-toxic polyesters show a huge potential for developing inexpensive and biodegradable elastomeric materials for tissue engineering applications [146]. The thermo-mechanical properties of PGS, which have been recently reviewed by Rai et al. [149], can be adjusted by varying the glycerol to sebacic acid ratio, curing temperature and time. In general, this thermoset polymer shows a T_g at around -37 ºC. Regarding its mechanical properties, it shows elastomeric behaviour with elastic modulus ranging from 0.025 to 1.2 MPa, ultimate tensile strength >0.5 MPa and elongation at break >330%.

Table 5. Mechanical properties of some representative poly(diol citrates). Post-polymerization temperature and time were respectively, 80 ºC and 4 days (except otherwise stated).

General structure	x	Name	E(MPa)	σ(MPa)	ε(%)
	6	PHC	12.1	6.0	389
	8	POC	1.9	2.9	367
		(120ºC, 1 day)	2.8	3.6	235
		(120ºC, 3 days)	4.7	5.3	160
		(120ºC, 6 days)	6.4	5.8	117
	10	PDC	1.9	3.5	338
	12	PDDX	1.6	6.2	502

Poly(propylene fumarate) (PPF), depicted in Figure 2, is another type of linear polyester. It has an unsaturated linear structure and could be obtained via a transesterification reaction of fumaric diester [150]. Thanks to the presence of fumarate double groups in its main backbone, PPF shows a unique property to form crosslinked structures [151], resulting in higher mechanical strength material that can be employed as an injectable material as bone cement [152]. Overall, the physico-mechanical properties of PPF are mainly dependant on the molecular weight and crosslinking. For example, the compressive strengths and modulus of PPF samples crosslinked with biocompatible poly(ethylene glycol)-dimethacrylate (PEG-DMA) increased from 5.9 to 11.2 MPa and from 30.2 to 58.4 MPa, respectively, when the double-bond ratio of PEG-DMA/PPF increased from 0.38 to 1.88 [153]. In a different study [154], where PPF-diacrylate was employed as a crosslinking agent, compressive modulus up to 1.7 GPa were reported.

Polyesteramides (PEAs) are other remarkable family of aliphatic polyesters combining both ester and amide groups in the main chains [155,156]. These biodegradable polymers show intermediate properties between polyesters and polyamides; indeed they display good thermal and mechanical properties as a result of the combination of the susceptibility of ester groups for undergo degradation reactions together with the hydrogen bonding capacity of amide groups [133]. A wide variety of PEAs incorporating monomers such as α-amino acids, α-hydroxyacids, cyclic depsipeptides, fatty diacids, diols, α,ω-aminoalcohols or carbohydrates have been synthesized so far [19,156,157]. Among all the possibilities, PEAs based on α-amino acids and/or α-hydroxy acids constitute an attractive group of polymers with a bright future for the biomedical field because they combine the advantages of α-amino acids together with the good properties of PEAs. These biodegradable polyesters could be synthesized either by the ROP of depsipeptides or by the polycondensation reactions (interfacial, solution or melt) of α-amino acids with α-hydroxy acids or dicarboxylic acids and diols. A very interesting review focused on such PEAs has been published in 2014 by Fonseca et al. [157]. Overall, this combination of amide and ester groups offers novel alternatives for the fine tuning of biodegradable polymer with tuneable physico-mechanical

properties. Since a very wide variety of PEAs could be synthesized, here only 3 representative PEA are shown (Figure 3). These include a PEA based on α-amino acids, fatty dicarboxylic acids and diols synthesized by melt-polycondensation of a diol with a diamide–diester (a); PEA based on α-amino acids by solution or interfacial polycondensation reactions where the carboxylic acid is activated to yield activated esters which subsequently react with the amino groups (b) and polydepsipeptides obtained through solution polycondensation of α-hydroxy acids with α-amino acids (c).
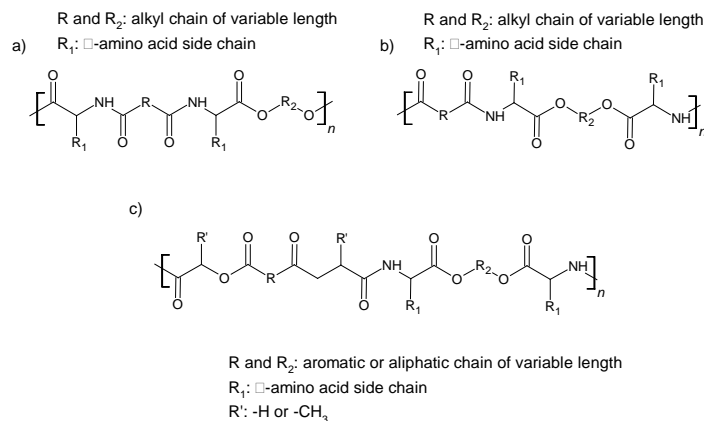

Figure 3. Chemical structures of 3 representative of polyesteramides.

2.2. Aliphatic/aromatic polyesters

Aliphatic/aromatic polyesters display remarkable thermal and mechanical properties conferred by the aromatic structures while aliphatic ester moieties ensure a proper biodegradability of the polymer [158]. They are generally synthesized by condensing aliphatic diols, aliphatic dicarboxylic acids/esters and aromatic dicarboxylic acids/esters. The presence of aliphatic moieties along the chain backbone allows its biodegradability, while aromatic moieties bestow good thermal (high T_g and T_m) and mechanical (elastic modulus) properties. Biodegradable aliphatic/aromatic polyesters typically contain a large fraction of aliphatic ester groups since such groups are much more electrophilic than their analogous aromatic derivatives. Therefore, above a threshold, the presence of aromatic groups within the chain markedly decreases or even suppresses the biodegradability of the resulting material.
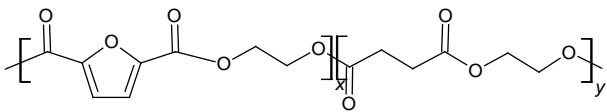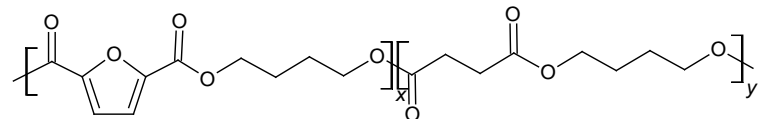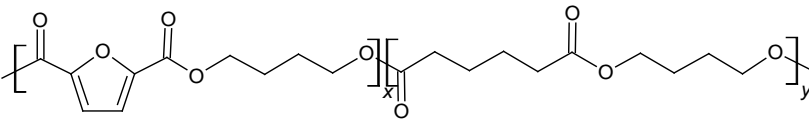
Several furanic-aliphatic polyesters based on the renewable 2,5-furandicarboxylic acid (FDCA) have been recently synthesized. Although furanic based copolyesters are known since the pioneering work done by Moore and Kelly back in the 1970s [159], these polymers are showing a renewed scientific interest, especially during the last 10 years, thanks to their inherent thermal and mechanical properties. Overall, these polymers show a FDCA related monomer and an aliphatic monomer (typically a linear carbon chain from C_2 to C_{18}) at their backbone [160]. Due to the biobased nature of FDCA, these polyesters can be fully obtained from renewable resources if the selected monomers are also based on renewable resources. The most well known polyester of this family is poly(ethylene 2,5-furandicarboxylate) (PEF), whith physico-mechanical properties comparable to those of the poly(ethylene terephthalate) (PET). Furthermore, a series of high-performance poly(2,5-furan dicarboxylate) homopolymers such as poly(1,4-butylene 2,5-furandicarboxylate) (PBF), poly(1,6-hexylene 2,5-furandicarboxylate) (PHF) and poly(1,8-octylene 2,5-furandicarboxylate) (POF) have been synthesized [161]. Since all these polyesters are non-biodegradable, aliphatic poly(2,5-furan dicarboxylate)s incorporating lactic, succinic and adipic acids (SA and AA respectively) have been recently developed to tackle the biodegradability lack of such furan polyesters.

In this framework, a 100% renewable-based poly(ethylene 2,5-furandicarboxylate)-co-poly-(lactic acid) (PEF-co-PLA) copolyesters with varying ratios were obtained upon a

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polytransesterification reaction of bis(2-hydroxyethyl)terephthalate and PLA using Sb_2O_3 or $SnCl_2·2H_2O$ as a catalyst [162]. Copolymers with lactide content up to 39 mol.% displayed a completely amorphous character with increased T_g (from 54 °C for pure PLLA to 76 °C for PEF-co-PLA copolymer having 8 mol.% of lactide). Following a similar approach, PBF-co-PLA copolymers with lactide content up to 38 mol.% were synthesized and fully characterized in terms of thermo-mechanical properties [163]. All the synthesized aliphatic/aromatic copolyesters, with lactide content ranging from 10 to 38 mol.%, showed elastic modulus, tensile strength and elongation at break higher than 1 GPa, 38 MPa and 230%, respectively. ε-caprolactone has been also employed as a comonomer for the synthesis of both PEF-co-PCL and PBF-co-PCL copolymers. Through a combination of esterification, ring-opening and polycondensation reactions, PEF-co-PCL copolymers with caprolactone contents up to 65 mol.% were satisfactorily synthesized [164]. The incorporation of caprolactone units shifted the T_g of PEF from 86 °C to -12 °C for the PEF-co-PCL having 65 mol.% of caprolactone. Regarding the mechanical properties, the copolymer having 35 mol.% of caprolactone showed excellent mechanical properties with elastic modulus, tensile strength and elongation at break of 1.2 GPa, 51 MPa and 981%. Following a similar synthetic approach PBF-co-PCL copolymers have been also synthesized [165]. However, an optimization of the synthesis procedure is needed to yield polymers with enhanced mechanical performance, which could be accomplished via enzymatic ROP of cyclic comonomers (i.e., oligo(butylene 2,5-furandicarboxylate) and ε-caprolactone) [166].

Poly(ethylene 2,5-furandicarboxylate-co-ethylene succinate) (PEF-co-PESu) copolymers have been also considered as degradable aliphatic/aromatic copolyesters. A series of PEF-co-PESu copolymers were synthesised via the two-stage melt polycondensation reaction using an excess of ethylene glycol (EG) and Ti(OBu)₄ as a catalyst [167]. In a similar study, the thermal properties of PEF-co-PESu copolymers with a wide range of compositions were thoroughly characterized [168] (Table 6). Accordingly, a series of semicrystalline and completely amorphous copolymers were obtained, showing T_g values that monotonically varied between the values for the neat homopolymers (i.e., 87°C for PEF and -8°C for PESu). These polyesters show promising properties to replace terephthalic based counterparts (PET-co-PESu) at the same time that display promising shape memory behaviour. The mechanical and thermal properties of poly(butylene 2,5-furandicarboxylate-co-butylene succinate) (PBF-co-PBSu) copolymers synthesized via an esterification and polycondensation process using tetrabutyl titanate (TBT) or TBT/La(acac)₃ as catalyst have been reported by Wu et al. [169]. As expected from the random distribution of sequences, the synthesized copolymers showed a single T_g that increased continuously with the butylene furandicarboxylate content from -40 °C to 45 °C for the pure PBSu and PBF, respectively (Table 6). Due to the crystallizability decrease, the elastic modulus and tensile strength of the resulting copolymers was below the values for the pure homopolymers. Semicrystalline copolymers having butylene furandicarboxylate contents below 20 mol.% displayed good elastic modulus (0.4-0.6 GPa) and strength (~20 MPa) and elongation at breaks ranging from 160-320%. Amorphous copolymers with butylene furandicarboxylate contents ranging from 40 to 50 mol.% showed much lower elastic modulus (~0.1 GPa) and tensile strength (10-15 MPa) but improved elongation at break (580-660%). Poly(butylene 2,5-furandicarboxylate-co-butylene adipate) (PBF-co-PBAd) copolyesters were also obtained from 2,5-furandicarboxylic acid, adipic acid and 1,4-butanediol through polycondensation reactions [170–172]. Similar to the PBF-co-PBSu discussed above, the PBF-co-PBAd copolyesters displayed a single T_g that increased monotonously from -62 °C to 36 °C for the pure PBAd and PBF, respectively (Table 6). Regarding the mechanical properties, for butylene furandicarboxylate contents below 50 mol.%, the PBF-co-PBAd copolyesters kept the elastomeric behaviour of PBAd, with low elastic modulus and tensile strength, but high elongation at break. As the content of butylene furandicarboxylate increases, the elastic modulus and strength of the resulting copolymers increased while the elongation at break shifted to lower values. Apart from the representative copolyesters presented so far, other alternatives based on 2,5-furandicarboxylic acid have been explored, including poly(propylene furandicarboxylate-co-propylene succinate) (PPF-co-PPSu) [121].

Table 6. Thermo-mechanical properties of some representative aliphatic-aromatic copolyesters.

Name	Structure	Composition	T_g (°C)	T_m (°C)	E(GPa)	σ(MPa)	ε(%)
PEF-co-PESu		0%-EF	-8	110	-	-	-
		2%-EF	-7	100	-	-	-
		11%-EF	-3	98	-	-	-
		17%-EF	0	95	-	-	-
		35%-EF	15	amorphous	-	-	-
		37%-EF	20	amorphous	-	-	-
		49%-EF	30	110	-	-	-
		61%-EF	38	130	-	-	-
		81%-EF	60	180	-	-	-
		87%-EF	72	200	-	-	-
		92%-EF	78	212	-	-	-
		100%-EF	87	220	-	-	-
PBF-co-PBSu		0%-BF	-40	114	0.7	30	125
		10%-BF	-25	104	0.6	22	175
		19%-BF	-24	93	0.4	19	325
		31%-BF	-17	amorphous	0.2	-	-
		40%-BF	-10	amorphous	0.1	10	675
		50%-BF	-4	amorphous	0.1	14	600
		60%-BF	7	amorphous	0.1	32	600
		71%-BF	15	132	0.3	26	400
		80%-BF	22	146	0.1	18	550
		90%-BF	31	159	0.5	36	500
		100%-BF	45	170	1.8	30	3
PBF-co-PBAd		0%-BF	-62	56	0.2	14	680
		13%-BF	-53	47	0.1	17	750
		21%-BF	-48	29	-	-	-
		33%-BF	-38	amorphous	-	-	-
		43%-BF	-30	amorphous	0.02	9	615
		52%-BF	-20	amorphous	0.04	15	365
		62%-BF	-11	117	0.06	30	420
		70%-BF	0	131	0.04	35	470
		80%-BF	11	146	0.05	42	410
		90%-BF	23	155	0.1	36	310
		100%-BF	36	167	1.8	56	255

Aliphatic/aromatic polyesters containing the petrochemical terephthalic acid (PTA) have been traditionally the most investigated polymers belonging to this group. Poly(butylene adipate-co-terephthalate) (PBAT), shown in Figure 4, is produced by BASF (Germany) under the brand name Ecoflex® and represents one of the most remarkable examples of biodegradable aliphatic/aromatic polyesters [173]. The thermo-mechanical properties of these copolyesters can be adjusted by the content of terephtalic acid. In this regard, the T_g, T_m, tensile strength and elongation at break shifted from -61 ℃, 79 ℃, 8 MPa and 650 % for a copolymer containing 31 mol.% of terephtalic acid to -23 ℃, 137 ℃, 12 MPa and 180 % for a copolymer containing 48 mol.% of terephtalic acid [174]. A plethora of opportunities exist for the development of novel aliphatic/aromatic polyesters upon the introduction of different esters within the chain structure. Some of such relevant examples include poly(butylene succinate-co-terephthalate) (PBST) (synthesized by direct esterification and polycondensation route using titanium tetraisopropoxide as a catalyst) [175], or poly (butylene adipate-co-succinate-co-glutarate-co-terephthalate) (PBASGT) (prepared by a two-step melt polycondensation by mixing butylene terephthalate ester, adipate esters, succinate esters and glutarate esters) [176]. As for the PBAT copolymers previously mentioned, the thermo-mechanical properties of PBST can be tuned by the copolymer composition. In general terms, PBST copolymers with increasing content of butylene terephthalate showed increased T_m (e.g., from 113 ℃ for pure PBS to 179 ℃ for a PBST copolymer containing 70 mol.% of butylene terephthalate) and elastic modulus but lower elongation at break (e.g., from 850% to 450% for a PBST copolymer containing 50 mol.% and 70 mol.%, respectively) [177]. PBASGT is an aliphatic/aromatic copolyester containing three different aliphatic comonomers (i.e., butylene adipate, butylene succinate and butylene glutarate) where the thermo-mechanical properties can be finely tuned by adjusting the specific composition of the copolymer. A series of PBASGT copolymers with increasing content of butylene terephthalate have been recently reported [176]. The synthesized copolymers displayed a wide variety of thermo-mechanical properties clearly influenced by the amount of butylene terephthalate showing T_g, T_m, elastic modulus, yield strength and elongation at breaks ranging from -42 to 32 ℃, 46 to 211 ℃, 0.07 to 1.7 GPa, 0.5 to 43 MPa and 1775 to 30%, respectively.
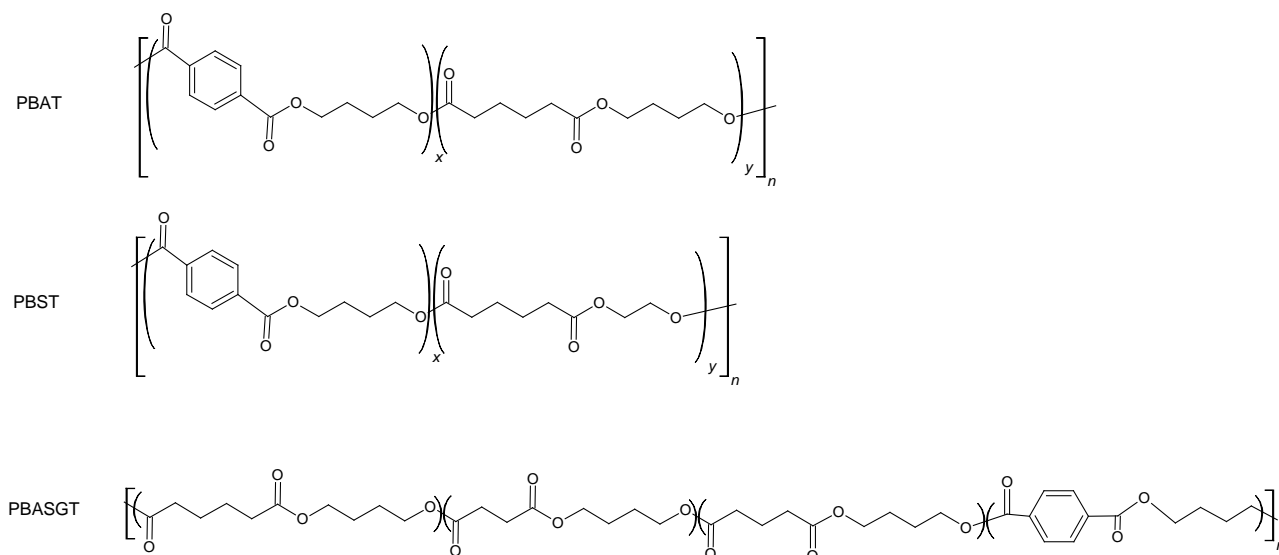

Figure 4. Chemical structures of 3 representative aliphatic-aromatic biodegradable polyesters based on PTA.

Recent advances in monomer design have expanded the range of accessible biodegradable aliphatic/aromatic polyesters. In this framework, ROP has been proven as a plausible strategy to introduce aromaticity into the polymer backbone. A good example of that is poly(2-(2-hydroxyethoxy)benzoate) (P2HEB) (Figure 5), which could be obtained upon ROP of 2,3-dihydro-5H-1,4-benzodioxepin-5-one catalysed by an aluminium salen catalyst [178]. The P2HEB polymer

showed a T_g and a T_m at 26.5 and 68.8 °C, respectively, that slightly shifted to higher values with the increased molecular weight. The mechanical properties of this polymer indicated that P2HEB had an elastic modulus of ~1 GPa below its T_g which dramatically decreased at the glass transition. Besides, the reported low *tan δ* value of 0.17 at the glass transition indicates an elastic character of the synthesized P2HEB rather than a viscoelastic one. Its thermal, optical and mechanical properties can be upgraded upon copolymerization with PLLA [179]. In an attempt to obtain sustainable PET mimics, Mialon et al. obtained poly(dihydroferulic acid) (PHFA) from acetic acid and lignin-derived vanillin upon condensation polymerization with loss of acetic acid (Figure 5) [180]. With a T_g and a T_m at 73 and 234 °C respectively, authors reported that the PHFA was the first wholly biorenewable polymer that successfully mimics the thermal properties of PET. Similarly, the biodegradable aliphatic/aromatic poly(ethylene vanilate) (PEV) has been obtained from vanillin through a fully sustainable synthetic pathway (Figure 5). The synthesized polymer showed a T_g and a T_m at 74 and 264 °C, respectively, which resembles those thermal transition temperatures of PET. According to such properties and its structure, authors considered PEV a bio-based PET mimic [181]. However, probably due to its low molecular weight, the synthesized PEV displayed a brittle behaviour, so the authors prepared PEV-co-PCL random copolymers with improved properties. PEV-co-PCL copolymers containing 20, 50 and 80 mol.% of ε-caprolactone displayed intermediate glass transition and melting temperatures (T_g: 59, 35 and -18 °C and T_m: 241, 181, 104 °C for PEV-co-PCL copolymers containing 20, 50 and 80 mol.% of ε-caprolactone, respectively).
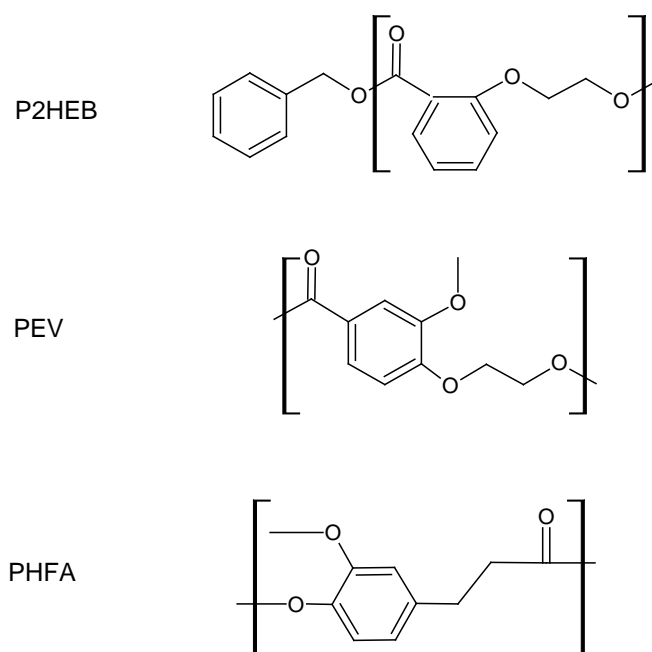

Figure 5. Chemical structures of recently reported aliphatic-aromatic biodegradable polyesters.

3. Biodegradation of polyesters

With the environmental concerns raised from the 1990s on, biodegradable polyesters (either pure aliphatic or aliphatic/aromatic ones) arise as one of the most suitable and yet promising solutions to face the pollution challenge of 21st century [182,183]. The inherent ability of ester linkages to undergo through hydrolysis processes has made polyesters a perfect choice for the ever-increasing demand of sustainable alternatives to traditional petroleum-based non-biodegradable polymeric materials.

Polymer degradation is defined as the *"chemical changes in a polymeric material that usually result in undesirable changes in the in-use properties of the material"* [184]. In spite of such definition and within the framework here discussed, the term degradation is considered an enormous asset instead of an undesirable property as many polymers should be degradable to avoid their accumulation in the environment. Polymer degradation is an irreversible phenomenon that

20

takes place through scission of the main chain or side chain of the macromolecules. Under natural conditions, polymer degradation may be induced by processes such as photolysis, oxidation, radiolysis, thermal activation, hydrolysis or biological activity [185].

It should be taken into account that *degradable* does not necessarily mean *biodegradable*. A wide number of polymers which undergo fragmentation into smaller pieces and even degrade into invisible residues to the naked eye are available. Although these materials are eroded (or degraded) into microscopic pieces and several synthetic approaches are available to accelerate this process, such microgranules may accumulate in the oceans or landfills as they are not completely degraded within a reasonable period of time [186]. Henceforth, this fragmentation does not mean biodegradation *per se*. Accordingly, the American Society of Testing and Materials (ASTM), in its standard D6813 defines the term biodegradability as *"capable of undergoing decomposition into carbon dioxide, methane, water, inorganic compounds, or biomass in which the predominant mechanism is the enzymatic action of microorganisms, that can be measured by standardized tests in a specified period of time, reflecting available disposal conditions"*. Similarly, the International Union of Pure and Applied Chemistry (IUPAC) defined a biodegradable polymer as a *"polymer susceptible to degradation by biological activity, with the degradation accompanied by a lowering of its molar mass"* [184]. Essentially, during biodegradation, long macromolecular chains are broken down *in vitro* or *in vivo* by enzymes (and other biologically active entities) into shorter chains, which are further metabolized by microorganisms.

Among all the available degradation processes, hydrolytic and enzymatic degradation are of special interest as they allow closed-loop recycling processes which are seen as the preferred choice to face current plastic waste issues [187]. Indeed, hydrolytic and enzymatic degradation are the most important degradation mechanisms in polyesters thanks to the high susceptibility of the ester linkages to chemical hydrolysis and microbial/enzymatic chain cleavage reactions. Polyester hydrolytic degradation is defined as the scission of ester bond linkages in the backbone via H_2O uptake to yield first oligomers, and then monomers [188]. Enzymatic degradation occurs when the action of living organisms such as enzymes cut down the macromolecules into lower molar mass chains, which are then bio-assimilated and mineralized by such living organism to yield H_2O and CO_2 or CH_4 depending if the process is aerobic or anaerobic respectively [188–190]. In some cases, the degradation could also undergo through combined mechanisms of microbial, enzymatic and chemical hydrolysis.

It is interesting to note that for biomedical applications, the *in vivo* degradation of polyesters should ideally proceed in such a way that the following aspects are fulfilled [70,191]:

- the material shelf-life should be adequate, or in other words, the degradation time of the polymer should match the healing process of the tissue.

- the changes on the mechanical properties upon degradation should be compatible with the healing process.

- the degradation products should not evoke any toxic response, which is often manifested as inflammation of the surrounding tissues. Therefore, the degradation products should be able to get metabolized and expelled from the body.

During degradation reactions, environmental factors such as humidity, temperature, pH, supply of nutrients, etc. influence the degradation kinetic of polymers and have crucial influence on the microbial population and their activity. Similarly, the chemical and physical characteristics of the material to be studied, (i.e., its molecular weight, morphology, porosity, etc.) also influence dramatically the resulting degradation profile. Therefore, all these conditions must be carefully considered when the biodegradation of polymers is studied.

As generally speaking hydrolytic and enzymatic degradation yield environmentally acceptable substances, many researchers have been focused on the search of further enzymes able to degrade plastics. Since enzyme-catalyzed degradation reactions also involve polymer degradation through

hydrolysis, in this review we will firstly focus on hydrolytic degradation of polyesters, and then we will continue with their enzymatic degradation.

3.1. Hydrolytic degradation

3.1.1. Hydrolytic degradation: mechanism

Hydrolytic degradation can be defined as the cleavage of susceptible bonds of a polymer through H_2O uptake to form two or more products with lower molecular weight than the initial material (typically oligomers and ultimately monomers) [192]. In the case of polyesters, hydrolytic degradation reactions occur after water uptake and subsequent ester linkage scission. The susceptibility of this chemical bond that undergoes through scission reactions mainly depends on the charge value of the reacting carbon atoms, where functional groups having charge values higher than 0.3 display large susceptibility to hydrolysis [193]. Steric effects and conjugate structures also influence the overall hydrolytic degradation behaviour of polymeric materials. Indeed, stable conjugate structures increase the resistance to hydrolytic degradation as a result of the delocalization of the positive charge in the carbonyl group. Similarly, the bond inaccessibility provided by steric effects delay the hydrolytic degradation as water cannot interact with the hydrolysable bonds.

Generally speaking, hydrolytic degradation in polymers takes place via random scission, i.e., chemically identical bonds show the same reactivity irrespectively of their chain position [194]. Upon random scission, polyester chains comprising carboxylic and alcohol end groups are cut into two parts, increasing the relative number of carboxylic end groups and decreasing the medium pH. Therefore, acid-catalyzed hydrolysis is commonly found [195].

As during hydrolytic degradation of polymers water needs to diffuse through the material to react with hydrolysable bonds, such process could be seen as a combination between water diffusion across the material followed by a random scission of macromolecules at the susceptible bonds [196]. Thereby, as schematically depicted in Figure 6, two main modes of hydrolytic degradation exist; surface degradation and bulk degradation [197]. Depending on the conditions, these processes could occur independently or combined. As stated before, hydrolytic degradation is the result of the hydrolysis time of macromolecules into shorter chains (t_c) and the water diffusion in this time frame (D_T) through the material. D_T depends on several properties of the polymer such as density, hydrophobicity and crystallinity degree as well as on the medium characteristics (i.e., temperature, pH, flow) [198].

When the diffusion of water molecules is faster than the hydrolytic attack ($D_T > t_c$), bulk degradation occurs. At the beginning of this process the molecular weight decreases and, because of the higher mobility of shorter segments, crystallinity degree may increase. Once the chains are short enough to be solubilised and expelled out into the surrounding medium, a second stage characterized by weight loss is achieved [199]. Bulk degradation is typical for many polyesters such as PCL, PGA and PLA, and results in a non-linear mass-loss over the time as a result of chain scission and further release into the surrounding medium. As the decrease of the weight average molecular weight (M_w), mechanical properties and weight loss occurs simultaneously across the whole specimen, this degradation process is also known as homogeneous degradation. Degrading chains cannot be expelled out, which results in a risk of a sudden loss in the structural integrity of the polyester structure during the last stages of degradation. Polyesters can shift its hydrolysis mechanism from surface to bulk erosion given their thickness drops below a critical value known as the critical sample thickness (L_{crit})[20]. On the contrary, when $D_T \leq t_c$, surface erosion occurs, and the material linearly losses its mass as chain-scission proceeds [200]. The hydrolysis occurs near the surface of the sample being degraded, while the bulk remains barely unchanged. Upon surface erosion (and solubilisation) the hydrolysis front continuously moves through the core of the material. This avoids the chance of burst release occurring when polyesters suffer from bulk degradation as the shorted water-soluble chains are continuously being leached out into the

surrounding medium. Therefore, these polymers are good candidates to develop products intended for delivery purposes, including drugs, aroma or fertilizers.

It should be taken into account that upon chain cleavage, macromolecular mobility increases, leading to a continuous and notable increase in the overall degree of crystallinity and apparent crystal size [201]. In this sense, supported by existing experimental data, Gleadall et al. developed a simplified theory for the crystallization of polyesters during biodegradation [202], where it was found that polyester crystal growth proceeds much faster than its hydrolysis process. At late stages of degradation, these formed crystallites remain highly resistant to hydrolysis, delaying the weight loss process and yielding undesired foreign body reactions".
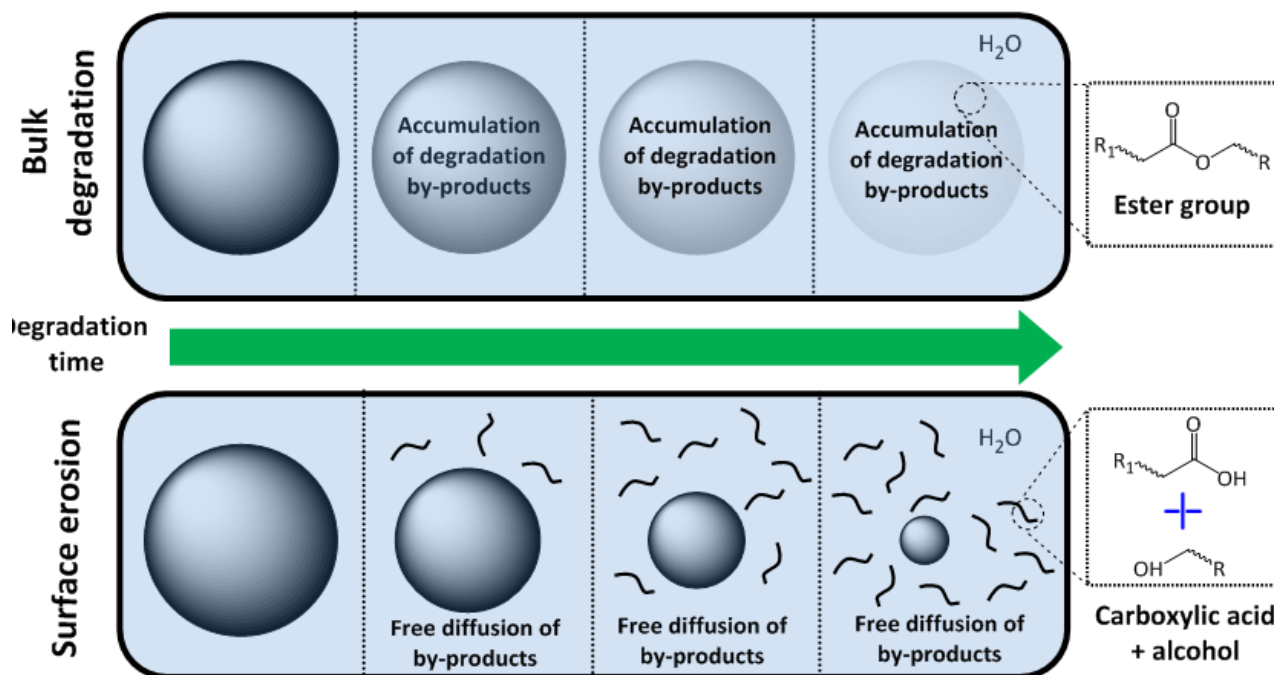

Figure 6. Simplified scheme showing the two main degradation mechanisms in polyesters; bulk degradation and surface erosion. The degradation products consist on carboxylic acids and alcohols, which could accumulate within the material (bulk degradation) or can be leached out into the surrounding aqueous medium (surface erosion).

One of the most characteristic difference between bulk and surface degradation processes lies on the differences on the diffusion of degradation products. During bulk degradation of polyesters, these carboxylic acid and hydroxyl degradation by-products are accumulated within the material as they cannot diffuse into the outside medium, leading to autocatalytic degradation effects which in turn accelerate the overall degradation kinetic [203]. The accumulation of these leachable acidic by-products in biodegradable medical devices produces non-desired side-effects such as the inflammation of surrounding tissues and should be carefully considered when polyesters are used for such applications [204].

3.1.2. Factors affecting the hydrolytic degradation of polyesters

A myriad of factors control the kinetics of the hydrolytic degradation of polyesters, many of which can be controlled by synthetic approaches. Figure 7 classifies such factors into two groups, which are divided according to the characteristics of the polymer itself (mainly determined by its inherent chemistry and processing parameters) and the physicochemical properties of the degradation medium, namely temperature and pH.

The monomeric composition is one of the most determining factors on the resulting hydrolytic degradation as some monomeric units show higher susceptibility to undergo through chain scission

reactions than other. For instance, the degradation profile of PLGA could be delayed upon the introduction of more resistant lactide units [205]. Similarly, the hydrolytic degradation of a given polyester could be delayed upon the introduction of aromatic groups into its chain structure [206]. When different enantiomers are found, the optical purity also affects the final hydrolytic degradation. A substantially faster hydrolysis was found for a polylactide containing 4.5 % of D units (and 95.5 % of L) than for an optically pure polylactide having 100 % of L units (both polylactides had similar molar mass but were produced using monomers of different optical purity) [207]. Several works have reported that the hydrolytic degradation proceeds slower as the molecular weight of the degrading polymer increases due to the reduced molecular mobility imposed by long chains [208]. Contrarily, the presence of residual monomers speed up the reduction of molecular weight and accelerate mass loss [209]. Polymer-water interaction could be tuned by phase-structure and surface wettability. The phase-structure is determined by the crystallinity degree of the sample, which accounts for the regions having well-ordered chains (crystalline regions) and loosely packed chains. Therefore, a lower crystallinity degree implies the presence of a less organized and packed amorphous domains, which are more easily attacked by water molecules and thus suffer from faster hydrolytic degradation reactions [210]. Similarly, the higher the hydrophilicity the higher the hydrolysis rate due to a greater water adsorption [211]. Accordingly, faster hydrolysis rates have been observed for aliphatic polyester structures having lower C/O ratios (i.e., more hydrophilic) [212].
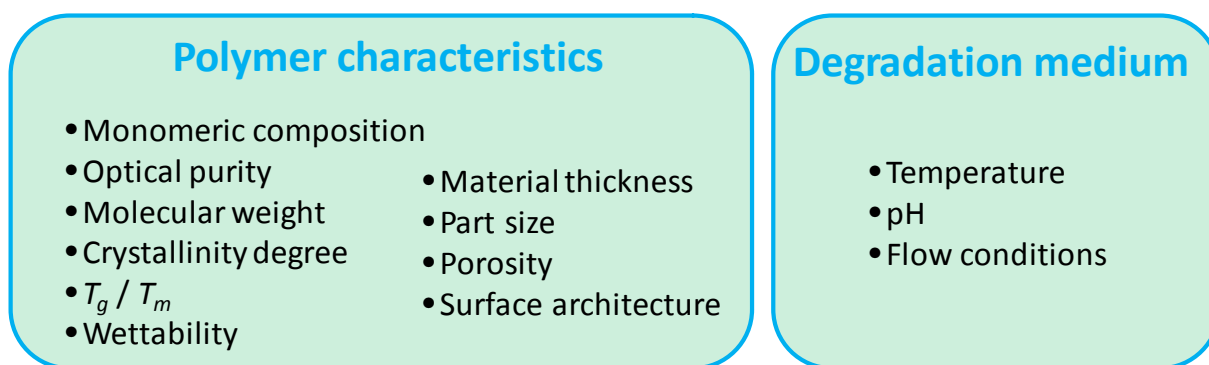
Polymer characteristics

- Monomeric composition
- Optical purity
- Molecular weight
- Crystallinity degree
- T_g / T_m
- Wettability
- Material thickness
- Part size
- Porosity
- Surface architecture

Degradation medium

- Temperature
- pH
- Flow conditions

Figure 7. Factors affecting the hydrolytic degradation of polyesters.

Part geometry (i.e., surface characteristics, porosity, material thickness and size), which is defined during polymer processing, markedly affects the degradation of polyesters. As the contact surface area of a given sample influences the interaction of water with the polymer and its prospective diffusion through its bulk, material thickness and part size are parameters that need to be carefully controlled. In fact, when surface erosion occurs, a higher surface-to-volume ratio (as in the case of microparticles) increases the degradation kinetic as further polymer chains are available to undergo through chain scission reactions [213]. On the contrary, when bulk degradation occurs, the thicker the sample the faster the degradation would proceed as the degradation by-products auto-catalyze the hydrolysis as they may cause a decrease in local pH (as in the case of PLA, where these products are carboxylic acids) [214]. It has been proven that sample porosity affects the resulting hydrolytic degradation of polyesters. When the acidic by-products released by polymers such as PLA and PGA could not be expelled out to the surrounding medium, which occurs for non-porous samples, they are accumulated within the interior of the material [203]. Indeed, when macromolecules are short enough to become water-soluble oligomers, the entrapment of resulting acidic by-product into the bulk material causes an autocatalytic effect on degradation, which in the case of non-porous samples could yield to undesired hollow structures as the acidic trapped by-products accelerate the local degradation rate [215]. On the contrary, when sample morphology allows the release of such acidic by-products to the outside medium through its pores, the hydrolytic degradation proceeds slower. As a result of such mechanism, and although it may be counterintuitive, highly porous materials are more resistant to the hydrolytic degradation than solid

bulk materials [203,216]. Surface architecture (micro- and nanostructuring) could as well affect the water-polymer interaction by modifying its wettablity [213,217]. Generally speaking, the majority of the polyesters present an autocatalytic hydrolysis process, where a chain end scission process generates oligomers which in turn yield to mass loss when they become soluble, while random scission dominates molecular weight reduction [218]. Interestingly, the interplay between chain scission, oligomer production (occurring at the molecular scale) and the resulting oligomer diffusion/mass loss (occurring at macroscale) can be computed using existing models [219].

Medium temperature affects the hydrolytic degradation of polyesters. Polymer chain mobility increases with medium temperature, increasing the susceptibility of ester bonds to undergo chain cleavage reactions. For instance, PLA undergoes much faster degradation in aqueous medium at 58 °C than at physiological temperature [220]. Similarly, PLA can be rapidly hydrolyzed down into L-lactic acid at 180 ºC for 30 minutes, allowing a simple and yet effective way for its molecular recycling [221]. This allows studying the hydrolytic degradation of polyesters within a relatively short-time period (to then be extrapolated into actual situations) as fully degraded samples could be obtained by increasing the temperature [222]. In any case, it should be noted that some researchers have suggested that in order to predict the long-term hydrolytic degradation of polyesters, tests should be carried out at temperatures below T_g as rather different activation energies are obtained below and above T_g [223].
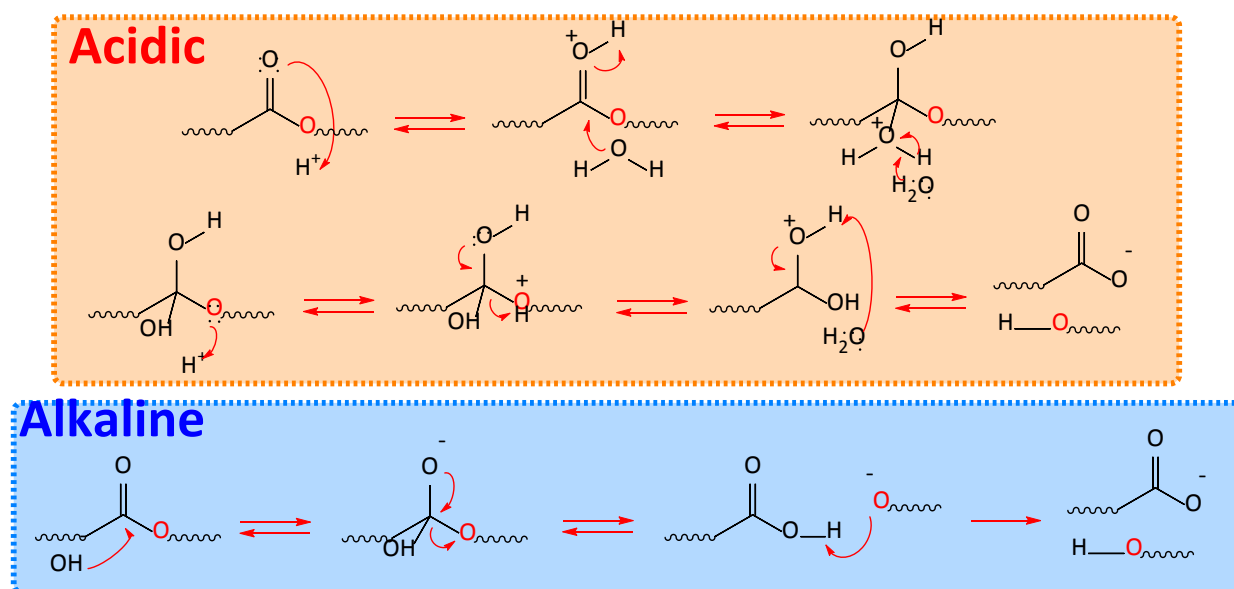

Figure 8. Hydrolytic degradation mechanisms of PLA under acidic and alkaline conditions.

Medium pH also influences the hydrolytic degradation mechanism of polyesters, which in turn affects the degradation kinetics. As shown in Figure 8, under alkaline environments, PLA depolymerises by a continuous release of dimmers, where the end-chain degradation occurs via intramolecular transesterification [224]. Such intramolecular degradation occurs by a random alkaline attack on the carbon of the ester group, followed by the hydrolysis of the ester link to release dilactide and decrease the molecular weight of PLA. On the contrary, under acidic conditions an intramolecular hydrogen bond is formed as a result of the protonation of the hydroxyl end-group, conducing to the hydrolysis of ester linkages to give lactic acid [224]. Overall, polyesters undergo faster hydrolytic degradation under basic conditions [225].

3.1.3. Hydrolytic degradation of polyesters

This section aims to provide an updated summary of the hydrolytic degradation of aliphatic and aliphatic/aromatic polyesters. With the aim of cataloguing the degradation characteristics of biodegradable polyesters, the degradation time of each polymer is listed for a given medium

characteristics (temperature, pH). A relevant aspect worthy of note is the nature of the formed by-products during degradation as such by-products may result toxic for their surroundings, either human body or environment. The most glaring example is PLA, which releases acidic LA that could drop the surrounding pH to levels that could even cause cell necrosis [226]. Therefore, the logarithmic acid dissociation constant (pK_a) of degradation by-products is shown as it accounts for their acidity, which in turn gives an idea about the prospective inflammation of surrounding tissue.

PLA, PGA and PLGA constitute the earlier and most extensively studied hydrolytically degradable polymers. Upon hydrolysis, PLA suffers a bulk degradation mechanism with a random scission of the ester backbone [227], displays a reduced hydrolytic degradation when compared with other polyesters as the methyl group hinders the attack by water [192]. Although the material losses its mechanical strength in about 6 months, no significant mass loss is observed for a long period of time (a total resorption of PLLA *in vivo* takes up to 5.6 years [228]). Due to its random distribution of L- and D-lactic units, PDLLA shows an amorphous nature and therefore presents faster hydrolytic degradation profiles than the PLLA and PDLA homopolymers, losing its mechanical strength and mass after 1-2 and 12-16 months respectively [196]. It has been shown that PLLA/PDLA stereocomplex presents even a lower susceptibility to hydrolytic degradation than PLLA or PDLA, which have been ascribed to the highly crystalline structure of the stereocomplex (the mechanical properties remain barely unchanged up to 16 months) [229]. PGA degrades by the non-specific scission of the ester backbone in a bulk degradation mechanism with a ~90 % mass loss in 50 days due to high hydrophilicity arising from the lack of additional asymmetrical methyl groups [230]. Besides, the degradation kinetics of PGA are accelerated under basic conditions (pH >10) [231]. Copolymerization of glycolide and lactide to yield PLGA has been extensively studied in order to obtain tailored hydrolytic degradation profiles between those obtained for the individual homopolymers. Completely amorphous PLGA copolymers with controllable susceptibility to hydrolytic degradation (bulk degradation mechanism) can be obtained by controlling the glycolide ratio. A PLGA copolymer having 50:50 mol% composition of LA:GA displays the shorted hydrolytic degradation times (of about 1-2 months), while a 85:15 mol% compositions degrades after 5-6 months [232]. As PLA, PGA and PLGA are obtained from monomers that are natural human body metabolites, their degradation results in non-toxic by-products [196]. The degradation by-products of PLA are LA ($pK_a = 3.08$), CO_2 and H_2O, which are non-toxic to the human body and are eliminated by the Cori cycle as glucose and in the urine, which allows the use of polylactides as biomedical materials [233,234]. Similarly, when in the human body, the GA ($pK_a = 3.83$) resulting from PGA or PLGA hydrolytic degradation is broken down into glycine which is further converted into CO_2 and H_2O via the citric acid cycle or expelled in the urine [235]. Thanks to their inherent degradability and non-toxicity, these polyesters have entered pre-clinical / clinical evaluation. One year follow-up clinical trials carried out with up to 30 patients have shown that bioresorbable vascular scaffold (BVS) composed of PLLA / PDLLA (known as ABSORB Cohort A) PLLA / PDLA (ABSORB BVS 1.1) present success rates for devices exceeding 90% [236,237]. These Abbott BVS were the first biodegradable stent to be FDA approved [238].

Mathisen et al. studied the hydrolytic degradation of poly(β-propiolactone) (PPL) fibres in PBS at 37 °C [33,239]. A random chain scission with bulk degradation with a rapid initial reduction of M_w (50% in M_w reduction after 49 days) and a slow mass loss of 14.6 % after 260 days was observed. A pH drop from 7.2 to 5.3 of the buffered solution was achieved at late stages of degradation, which was ascribed to the release of 3-hydroxypropionic acid ($pK_a = 4.51$). A strong effect of the crystalline structure on the degradability of PPL was reported [240]. Polymalic acid (PMA) is a water-soluble biodegradable polyester and its hydrolytic degradation takes place via random scission of main chain ester bonds to produce the natural molecule malic acid, which can be metabolized in the mammalian tricarboxylic acid (TCA) cycle [36,241]. The degradation occurs faster at lower pH and higher temperatures. Hydrolytic degradation tests of poly(α,β-malic acid) in phosphate buffer having a pH from 5.5 to 8.0 showed a very fast degrading behaviour with more than 90 % weight loss after 7 days, making this polymer especially interesting for drug-delivery systems requiring fast biodegradabilities [242].

Very few works have studied the hydrolytic degradation of PVL homopolymer. However, Fernández et al. analyzed the hydrolytic degradation of different poly(lactide/δ-valerolactone) copolymers and concluded that δ-VL units have a higher resistance to hydrolysis compared to LA units thanks to the combination of their more hydrophobic character and less proportion of ester groups [243]. Results suggested a bulk erosion mechanism for the synthesized copolymers. Faÿ and co-workers detected very low amounts of hydroxypentanoic acid and hydroxycaproic acid after >100 days of hydrolytic degradation of poly(ε-caprolactone-co-δ-valerolactone) copolymers, suggesting a very slow degradation provided by δ-valerolactone units [244]. When submerged in aqueous environments, PCL presents a random hydrolytic scission with a bulk erosion process, displaying long degradation times of about 2-3 years as a result of its high hydrophobicity, which could prospectively limit its use in the biomedical field [245]. It yields caproic acid as a by-product (pK_a= 4.88) [246], which after further degradation it could be eliminated in the human body through the citric acid cycle as 6-hydroxyl caproic acid/acetyl coenzyme A [53]. Very few works have addressed the hydrolytic degradation of poly(δ-decalactone) (PDL) homopolymers till the date as most of the works have focused on the development of copolymers having δ-decalactone [247]. Arias et al. recently suggested that PDL suffers a bulk degradation process with a rather slow degradation, with a mass loss of ~ 25% after 570 days in water (pH:7.4) at 37 °C [212]. Overall, PDL is more resistant to hydrolytic attack than PLA but more susceptible than PCL probably because of its amorphous character. Interestingly, upon degradation of PCL and PDL a slight pH drop of the medium up to nearly 4.5 is observed, which contrast with the more marked pH drop induced by the degradation by-products of PLA [212].

Polyhydroxyalkanoates (PHAs) are water-insoluble polyesters which undergo a surface erosion process by the hydrolytic cleavage of ester bonds [248]. Most of the commonly used PHAs are those found within the "short-chain-length PHAs". The hydrolytic degradation of P3HB, P(3HB-co-3HV), and P(3HB-co-4HB) in PBS (pH 7.4) at 37 °C were studied by Doi et al. in 1989 [249]. Initially a random chain scission of the esters occurs, which is then followed by a weight loss process when the M_n is below 13.000 g·mol^{-1}. The molecular weight of pure P3HB is reduced by 50% after 1 year in a buffer solution (pH 7.4) at 37 °C (faster degradation upon increasing medium pH and temperature) [250]. This somewhat slow degradation in comparison with other polyesters is ascribed to the inherent high crystallinity of PHAs [251]. P4HB degrades faster than P3HB but slower than PGA. The presence of 3HV and 4HB units accelerated the hydrolysis process as an increase on the valerate composition decreases the crystallinity of the materials to yield molecular weight loss rates of P(3HB-co-4HB) > P(3HB-co-3HV) > P3HB [196]. Interestingly, the degradation by-products 3-hydroxybutyric acid (3HB) (pK_a = 4.7), 3-hydroxyvaleric acid (3HV) (pK_a = 4.72), and 4-hydroxybutyrate (4HB) (pK_a = 4.72) are common metabolites in the human blood and can be metabolized quickly through the Krebs cycle by the human body to be ultimately converted into CO_2 and H_2O [252]. Moreover, their less acidic character in comparison with the by-products from PLA, PGA and PLGA make them interesting candidates for tissue engineering applications. Poly(3-hydroxyoctanoate) (P3HO) is a notable example of a medium-chain-length PHA presenting a slow degradation process. Due to a combination of its high crystallinity and the hydrophobic nature of long alkyl pendant chains, the hydrolytic degradation of P3HO is a process exceeding one year [253]. It is worthy to note that the hydrolytic degradation of few from the many microbial polyhydroxyalkanoates currently available has been investigated till the date, making the comprehensive determination of the hydrolytic degradation of PHAs a research field open to novel contributions.

Generally, in poly(alkylene dicarboxylates), the smaller the ester bond density, the weaker becomes the hydrophilicity, resulting in slower hydrolytic degradation rates [254]. It results hard to obtain comparable results concerning the hydrolytic degradation of poly(alkylene dicarboxylates) as many of the works dealing with the hydrolytic degradation carried out so far have been accomplished under different conditions of pH and temperature. Bikiaris et al. studied the hydrolytic degradation of several poly(propylene alkanedicarboxylate)s with increasing number of methylene and reported mass loss of 2% for PPGlu and PPAd, while PPSu and PPPi showed a mass

loss of 1% [111]. The slower degrading polyesters were PPSe, PPAz and PPSub, with degradation rates similar to those for PCL. Overall, poly(propylene alkane dicarboxylate)s with lower T_m and X_c suffer a faster degradation. The hydrolytic degradation of PBSu under physiological conditions (37 °C, pH:7.4) shows a weight loss of 25 % after the initial 63 days, while ~65% of mass is loss after 105 days [255]. PBSu yields succinic acid (pK_a = 4.21 and 5.64 for 1st and 2nd hydroxyl) and 1,4-butanediol (pK_a = 14.5) as a degradation by-product [256], which is found as an intermediate in the Krebs cycle. Therefore, within the human body it is degraded in CO_2 and H_2O yielding non-toxic products [257]. After 105 degradation days, the medium pH drops from 7.4 up to 5.5 because of the random chain scission by ester hydrolysis that generates carboxylic acid end groups. Similarly to PLA or PGA, PBSu shows an autocatalytic effect impaired by the formed carboxylic end-groups [258]. To speed up the degradation of PBSu, copolymerization with hydrophilic sequences has been pursued, including segments based on urethanes [259], or polyethylene glycol (PEG) [260]. Similarly, synthesis of succinic acid and adipic acid with 1,4-butanediol yields poly(butylene adipate) (PBAd) and poly(butylene succinate-co-butylene adipate) (PBSA). Adipate incorporation yields a faster degrading aliphatic polyester (with succinic acid, adipic acid (pK_a= 4.41, 5.41)) and 1,4-butanediol as by-products) as a result of its lower crystallinity and the presence of adipate moieties which are able to degrade faster than succinate segments [261]. The hydrolytic degradation of PBSu and PBSA proceeds much slower than the corresponding enzymatic degradation [261].

Polydioxanone (PDO, PDS) undergoes hydrolytic degradation through a combination of both surface and bulk erosion mechanisms. When degraded in aqueous buffer solution (pH:7.4) at 37 °C, PDO films show a mass loss of ~50% after 270 days [212], which can be accelerated to yield a mass loss of ~50% after 50 days by increasing the surface area of the material [262]. A pH drop from 7.40 to 5.64 after 10 weeks was observed, suggesting the release of acidic by-products to the degrading medium (the resulting glyoxylic acid (pK_a = 3.3) can be excreted in the urine or converted into glycine and then into CO_2 and H_2O by the human body) [262]. Poly(ortho ester)s are hydrophobic polyesters having hydrolytically labile linkages that undergo through surface erosion degradation. POEs display a degradation profile that could be easily tuned by controlling the pH of the degrading medium by using acidic or basic excipients [141]. The hydrolytic degradation of POE I yields the initial diol and γ-butyrolactone as a by-product, which is further hydrolyzed to 4-hydroxybutanoic acid. To avoid the autocatalytic behaviour during the degradation of POE I, POE II was developed, which yields neutral products as a by-product (which include pentaerythritol dipropionate and the diol) [5]. The degradation rate of this polymer can be modulated by adding acid excipient such as itaconic and adipic acids. POE III yields 5-flurouracil, acetic acid and 1,2,6-hexanetriol. POE IV yields LA or GA which further autocatalyze the degradation, which can be tuned by the proportion of glycolic or lactic acid in the sequence to last from days to months [198]. Overall, as a segment having a carboxylic acid end-group initially catalyzed the ortho ester hydrolysis to generate a diol (or a mixture of them), the hydrolytic degradation profile of POEs can be tuned upon controlling the ratio of the diol to the latent acid in the backbone [141]. Segmented poly(ester amide)s (PEAs) consisting on amide blocks linked to amorphous polyester matrix display tuneable mechanical, thermal and degradation properties depending on their hard-to-soft ratio [133]. The scission of ester bonds result in the formation of water-soluble and non-toxic bisamide-diol monomers/oligomers which can be excreted by the kidneys [263]. In this line, Lips et al. thoroughly studied the *in vitro* and *in vivo* degradation of aliphatic poly(ester amide)s comprising 1,4-butanediol / dimethyl adipate and dimethyl adipate / ε-caprolactone / 1,4-diaminobutane or 1,2-diaminoethane [133]. Degradation tests carried out in PBS at 37 °C (0.03wt.% sodium azide as antibacterial agent) showed a weight loss of ~3 % (depending on the composition) after 7 months. Results suggested that the degradation takes place via ester bond cleavage with a bulk degradation process. The degradation of polyesters containing below 50% amide content showed no cytotoxic response, while the sample having 50% of amide content resulted in mild undesired body reactions. Other PEAs based on L-alanine showed a weight loss of 7.5% after 150 days at 37 °C in PBS medium, suggesting that the α-amino acid contributes to speed-up the degradation rate of PEAs [264]. Due to these inherent characteristics, PEAs emerge as perfect candidates for long-term

biomedical implants as they offer tuneable degradation rate (the degradation is favoured with the ester content) with lower pH drop in comparison with more widely used polyesters [265]. As poly(propylene fumarate) (PPF) is usually crosslinked to obtain polymer networks, it is difficult to find the time required for the hydrolytic degradation of neat PPF. A slow degradation rate with a mass loss of 22% after 70 days in PBS solution at 37 ºC was found (bulk degradation process) [266], yielding fumaric acid ($pK_a = 4.4$) and propylene glycol ($pK_a = 14.9$) as a by-product [267]. As a combination of these two by-products, medium pH remains unchanged (±0.1) upon degradation [268], which is in contrast with the pH decrease suffered by the medium degrading other polyesters.

Poly(glycerol sebacate) (PGS) is other interesting biodegradable polyester which shows a surface erosion mechanism [269]. Agitation for 60 days in PBS solution at 37°C yields a weight loss of 17%, while the *in vivo* degradation is much faster in comparison with *in vitro* conditions [145]. The degradation rate of PGS could be varied by modifying processing parameters; i.e., when PGS is synthesized at 110 ºC it shows a fast degradation, while a negligible degradation was observed when synthesized at 130 ºC [146]. Degradation products are non-toxic as sebacic acid is the natural metabolic intermediate in ω-oxidation of medium- to long-chain fatty acids and glycerol has been approved by the FDA to be used as humectant in foods [149]. Poly(diol citrate)s are an interesting family of biodegradable and elastomeric polyesters with potential for tissue engineering applications. Poly(1,8-octanediol-co-citrate) (POC) is the most prominent type of poly(diol citrate). POC is degraded by hydrolysis of its ester linkages [148], with a weight loss of 8 % after being immersed for 3 weeks in PBS at 37 °C [270]. Such degradation time is expected to fall within the appropriate time-scales required for most tissue engineering applications [148]. Jeon et al. suggested a concomitant effect of bulk (with autocatalysis) and surface degradation for POC scaffolds degraded in PBS (pH:7.4) and 0.1 M NaOH solutions at 37 ºC (scaffolds showed a pore collapse after 3 week degradation in PBS and after 24 h in 0.1 NaOH) [270]. Yang et al. synthesized a series of poly(diol citrate)s including poly(1,6-hexanediol-co-citrate) (PHC), poly(1,8-octanediol-co-citrate) (POC), poly(1,10-decanediol-co-citrate) (PDC), poly(1,12-dodecanediol-co-citrate) (PDDC) and observed that the degradation rate could be increased with decreasing number of methylene units in the diol monomer [147]. When tested *in vivo*, a mild acute inflammatory response was observed at 1 week after implantation, suggesting that non-toxic degradation products were expelled. Indeed, produced citric acid during degradation may be metabolized in the body via Krebs or citric acid cycles. A fast degrading poly(diol citrate) was obtained by Lei et al. [271], who showed that when degraded in PBS at 37 ºC, poly((1,2-propanediol-sebacate)-citrate) (PPSC) suffers a weight loss of nearly 90% after 14 days (PGS and POC need 2 and 6 months respectively for a complete degradation). Fast degradation was ascribed to a higher density of ester bonds and an increased number of methyl side groups which decrease the regularity of the chain and increase diffusion coefficients.

Till the date, most of the works dealing with biodegradable polyesters have been focused on pure aliphatic polyesters as ester linkages in the main chain could be relatively easily cleaved. In comparison, traditional aromatic polymers show a much larger resistance to hydrolytic degradation (they even tend to be non-biodegradable). However, recent advances in polymer chemistry have expanded the range of biodegradable polymers, including those known as aliphatic/aromatic polyesters through the introduction of aromaticity into either the backbone or pendant to the main chain. Furanic-based polyesters based on the renewable 2,5-furandicarboxylic acid (FDCA) represent an interesting group of novel aliphatic aromatic polyesters, from which poly(ethylene 2,5-furandicarboxylate) (PEF) is the best known one. Despite to its relatively slow hydrolytic degradation rate, where only 2 % of weight loss is achieved after 84 days in PBS at 37 ºC (for comparison PLLA displays a weight loss of 7 % under the same conditions), PEF shows an improved degradability in comparison with fossil-based PET and it degrades to yield non-toxic 2,5-furandicarboxylic acid (FDCA) and ethylene glycol as by-products [162,272]. As the furan ring makes the attack of water molecules more difficult because it results in a rigid macromolecule due to the rig-flipping hindering by the nonlinear axis of furan ring rotation coupled with the ring polarity [168], Matos et al. copolymerized FDCA with other easily degradable aliphatic precursor to

obtain potentially biodegradable aliphatic/aromatic polyesters [162]. Degradation studies performed in PBS (pH 6.9) at 37 ºC reveal that the incorporation of lactyl units accelerated the degradation rate of the resulting PEF-co-PLA up to a 60 % of weight loss after 84 days (in comparison with 2 % for neat PEF). Interestingly, the degradation could be finely tuned upon the variation of the relative amount of 2,5-furandicarboxylate, allowing FDCA-based polyesters to hydrolyze on a reasonable timescale. Similarly, Terzopoulou et al. synthesized further FDCA-based polyesters upon the incorporation of succinic acid to obtain biodegradability [168]. The hydrolytic degradation in PBS (pH:7) at 25 ºC of poly(butylene 2,5-furandicarboxylate-co-butylene adipate) (PBF-co-PBAd) and poly(butylene 2,5-furandicarboxylate-co-butylene succinate) (PBF-co-PBSu) was studied by the group of Prof. Dubois [273]. A reduced weight loss of 1-2 % was found to occur after 150 days, although marked changes on the molecular weight were observed. Indeed, it was concluded that the hydrolysis proceeds through a random chain scission mechanism, where the hydrolytic degradation rate of both PBF-co-PBAd and PBF-co-PBSu decreased with increasing butylene furandicarboxylate content. They also found that, although PBF-co-PBSu has more hydrophilic chains than PBF-co-PBAd, for a given composition PBF-co-PBAd degraded slightly faster than PBF-co-PBSu, which suggests that crystallinity plays a significant role in influencing the hydrolytic degradability of these copolyesters. Although till the date several works have highlighted the potential of furan-based aliphatic/aromatic polyesters to develop novel materials such as poly(propylene 2,5-furan dicarboxylate) (PPF) [274], poly(butylene 2,5-furan dicarboxylate) (PBF) [275], poly(trimethylene furandicarboxylate) (PTF) [276], their hydrolytic degradation behaviour remains barely investigated. This fact emphasizes the need of comprehensive works aimed at determining the end-of-life of furanic aliphatic/aromatic polyesters.

Although aromatic polyesters having terephthalates moieties such as poly(butylene terephthalate) (PBT) present attractive thermal and mechanical properties, they lack biodegradability. In an attempt to boost its hydrolytic degradation, different aliphatic polyester soft segments can be introduced in the main chain. Poly(butylene adipate-co-terephthalate) (PBAT) can be seen as the most prominent hydrolytically degradable aliphatic/aromatic polyester based on terephthalate. PBAT shows a characteristic bulk degradation process with a weight loss of about 8% during the first 100 days immersed in PBS at 37 ºC, which is followed by a more marked weight loss up to ~50% after 300 days [277]. Molecular weight analyses during degradation suggest that initially a random scission plays a major role (marked M_w decrease), while at later stages a chain end scission process controls the degradation. The degradation products are water-soluble oligomers which are further fragmented by secondary hydrolysis into adipic, terephthalic acid and 1,4-butanediol, where the aromatic compound may result cytotoxic depending on its concentration [278]. Overall, PBAT shows a better resistance to hydrolysis than aliphatic polyesters such as PLA due to its steric hindrance to large repeating units [279]. As the soft aliphatic domain (BA) consisting of 1,4-butanediol and adipic acid monomers is more susceptible to hydrolysis than the hard aromatic domain (BT), PBAT displays a good biodegradability when the aromatic moiety concentration is kept below 55 mol %. Through the introduction of different groups within the structure, other hydrolytically degradable examples could be found, including poly(butylene succinate-co-terephthalate) (PBST), poly(butylene adipate-co-terephthalate) (PBAT), poly(butylene sebacate-co-terephthalate) (PBSeT) or poly (butylene adipate-co-succinate-co-glutarate-co-terephthalate) (PBASGT). Heidarzadeh et al. found that after 60 days immersed in PBS under accelerated conditions (70 ºC) a weight loss of 30, 40 and 45% was found for PBSeT, PBST and PBAT respectively [280]. The molecular weight rapidly decreased at the beginning, reaching a practically constant value after 19 days of exposure, suggesting a bulk degradation process. The differences on the degradation rate were explained by the fact that copolyesters with long aliphatic dicarboxylic acids display a more marked degradation rate than those with shorter ones [281]. Papageorgiou et al. synthesized hydrolytically degradable poly(propylene terephthalate-co-adipate) (PPTAd) random copolymers, although their degradation rate was very slow [282].

Further examples of potentially biodegradable bio-based PET mimic could be found in the literature, although their hydrolytic degradation has not been fully studied. Some examples include

poly(dihydroferulic acid) (PHFA), whose hydrolytic degradation yields the antioxidant dihydroferulic acid as a product, which can be found in tea, coffee and whole grains. However, no insights on the time required to undergo through chain scission has been provided in its invention, which is protected by a US Patent [283]. Similarly, the synthetic approach for the development of the bio-based semiaromatic poly(ethylene vanillate) (PEV) together with its thermal and mechanical properties was provided by Gioia et al., although no reference was done to its degradability [181]. Although the hydrolytic degradation of poly(2-(2-hydroxyethoxy)benzoate) (P2HEB) was not studied, its degradation was investigated in the presence of aluminium salen 1 by Lizundia et al [178]. It was reported that after 1h in toluene at 70 ºC, the molecular weight was reduced by 80%. Very interestingly, the depolymerisation was found to be selective as the cyclic monomer of P2HEB was the only product formed during degradation. Such rapid recycling to the monomer emerges as a novel and promising way to rethink the polymer life-cycle as the cyclic monomer obtained upon degradation could be prospectively used for repolymerisation without additional processing.

In the light of reported results, eco-toxicity studies on the degradation products of polyesters need to be carried out to get a bigger picture on the environmental impact of such polymers and ensure that no harmful products are released [284]. Despite to the generally observed pH drop and high oxygen demand (due to an increased microbial activity) during degradation that could present some minor negative impacts [285], overall no relevant harmful effects of the degradation products arising from polyesters such as PBAT or PBSu are detected [286,287]. However, polyesters releasing low pK_a species may yield to cytotoxic/genotoxic effects. In this sense, PLA degradation products have been found to have an aneugenic action onto common onion, resulting in slightly cytotoxic/genotoxic effects [288]. Other aspect that has traditionally limited the applicability of biodegradable polyesters is their tendency to undergo through bulk degradation reactions, resulting in non-linear release of by-products with burst-release characteristics and sudden changes in mechanical properties. On the contrary, poly(ortho esters) and poly(anhydrides) are able to undergo surface erosion [143,289]. Since the primary driving force for bulk erosion of polyesters is their hydrophilicity ($D_T > t_c$), a plausible approach to develop surface eroding polyesters and expand their applicability would be the modification of the water penetration kinetics. Accordingly, Xu et al. synthesized a library of over 50 surface eroding polyesters derived from poly(α-hydroxy acids) with a M_w ranging from 20.000 to 130.000 g·mol^{-1} by increasing the hydrophobicity of the polymer backbone [290]. Using a two step synthetic approach by macromer formation and a coupling step, building blocks with differing hydrophilic-lipophilic balance (HLB) were synthesized. The newly obtained polyesters showed steady and linear mass loss profiles upon hydrolytic degradation (37 ºC; pH:10), while morphological observations revealed porous surface and dense bulk structures indicative of surface erosion mechanisms (i.e. hydrolytic reactions are limited to the surface).

Table 7. Summary of the hydrolytic degradation of polyesters presenting the medium characteristics, the time required for a given weight loss and the resulting by-products together with its logarithmic acid dissociation constant (pK_a). PBS: phosphate buffer solution; n.r.: non reported; [a]When no data dealing with hydrolytic degradation at 37 ºC, comparative data are provided.

Group	Name	Medium properties	Weight loss	By-products and pK_a	Degrad. mechanism	Ref.
Short linear	PGA	PBS (pH 7) at 37 ºC	~90% in 50d	GA (pK_a = 3.88), CO_2, H_2O	Bulk	[230]
	PLA	H_2O/PBS (pH 7.4) at 37ºC	~15/25% in 180d	LA (pK_a = 3.08), CO_2, H_2O	Bulk	[207]
	PLGA(50/50)	H_2O/PBS (pH 7.4) at 37ºC	~82/80% in 35d	GA, LA, CO_2, H_2O	Bulk	[291]
Other linear	PPL	PBS (pH 7.2) at 37 ºC	14.6% in 260d	3- hydroxypropionic acid (pK_a = 4.51)	Bulk	[33]
	PVL	PBS (pH 7.4) at 37 ºC	Slower than PLLA	5-hydroxyvaleric acid (pK_a = 4.59)	Bulk	[243,244]
	PCL	PBS (pH 7.4) at 37 ºC	~ 3% in 770d	6-hydroxyhexanoic acid (pK_a= 4.71)	Bulk	[292]
	PDL	H_2O (pH 7.4) at 37 ºC	~ 25% in 570d	6-hydroxydecanoic acid (pK_a = 4.67)	Bulk	[212]

	PMA	PBS (pH 7.4) at 37ºC	> 90% in 7d	Malic acid (pK_{a1}= 3.51; pK_{a2}= 5.03)	n.r	[241,242]
	PDO	PBS (pH 7.4) at 37ºC	~50% in 50 or 270 d	Glyoxylic acid (pK_a= 3.3)	Bulk+surface	[212,293]
Polyalkylene dicarboxylate	PPSu	PBS (pH 7.2) at 37 ºC	~1% in 1d (as PCL)	n.r	Bulk	[111]
	PPGlu	PBS (pH 7.2) at 37 ºC	~2% in 1d	n.r	Bulk	[111]
	PPAd	PBS (pH 7.2) at 37 ºC	~2% in 1d	n.r	Bulk	[111]
	PPPim	PBS (pH 7.2) at 37 ºC	~1% in 1d	n.r	Bulk	[111]
	PPSub	PBS (pH 7.2) at 37 ºC	~0% in 1d	n.r	Bulk	[111]
	PPAz	PBS (pH 7.2) at 37 ºC	~0% in 1d (as PCL)	n.r	Bulk	[111]
	PPSeb	PBS (pH 7.2) at 37 ºC	~0% in 1d (as PCL)	n.r	Bulk	[111]
	PBS	PBS (pH 7.4) at 37 ºC	~65% in 105d	Succinic acid (pK_a= 4.21, 5.64 for 1st and 2nd hydroxyl) and 1,4-butanediol (pK_a= 14.5)	Bulk	[255]
	PBSA	Compost (58 ºC, 53.1% moisture)[a]	~62% in 140d (~28% for PBS)	Succinic acid, 1,4-butanediol and adipic acid (pK_a= 4.41, 5.41)	Bulk	[261]
Others	PEAs	PBS (pH 7.4) at 37 ºC	~3% in 200d	Bisamide-diol monomers/oligomers	Bulk	[133]
	PPF	PBS (pH 7.4) at 37 ºC	~22% in 70d	Fumaric acid (pK_a= 4.4) and propylene glycol (pK_a= 14.9)	Bulk	[266]
	POEs	PBS (pH 7.4) at 37 ºC	From days to few months depending on the diol/acid segments	Diols, γ-butyrolactone, LA, GA	Surface	[140,141,143,294]
	PDCs	PBS (pH 7.4) at 37 ºC	~90% in 14d for PPSC ~8% in 21d for POC Boosted increasing ester bond density	Citric acid (pK_{a1}=3.13, pK_{a2}=4.76, pK_{a3}=6.40) for POC	Bulk + surface	[270,271]
	PGS	PBS (pH 7.4) at 37 ºC	~17% in 60d Strong X_c effect	Sebacic acid (pK_a= 4.72), glycerol (pK_a= 14.4)	Surface	[145]
Microbial polyesters	P3HB	PBS (pH 7.4) at 37 ºC	~0% in 180d	3-hydroxybutyric acid (pK_a=4.7)	Bulk (slow), sometimes considered as surface eroding (dominant mode during enzymatic hydrolysis)	[295]
	P(3HB-4HV)	PBS (pH 7.4) at 37 ºC	~1.5% in 95d	3-hydroxybutyric acid + 3-hydroxyvaleric acid (pK_a=4.72)		[295]
	P4HB	In vivo degradation	100% in 6-18 months	4-hydroxybutyrate (pK_a= 4.72)		[296]
	P3HO	Acetate buffer (pH 6.8) at 37 ºC	3.3% in 31d	3-hydroxy octanoate (pK_a= 4.84)		[297,298]
	PEF	PBS (pH 6.9) at 37 ºC	2% in 84d	2,5- furandicarboxylic acid (pK_a= 2.76), ethylene glycol (pK_a= 14.22)	Bulk	[162]
	PEG-co-PLA	PBS (pH 6.9) at 37 ºC	60% in 84d	2,5- furandicarboxylic acid, ethylene glycol, LA	Bulk	[162]
	PBAF	PBS (pH 7) at 25 ºC	1-2% in 150d	n.r	Bulk	[273]
	PBSF	PBS (pH 7) at 25 ºC	1-2% in 150d (slightly slower than PBAF)	n.r	Bulk	[273]
	PBAT	PBS (pH 7.4) at 25 ºC	50% in 300d	Adipic acid (pK_a= 4.41, 5.41), terephthalic acid (pK_a= 3.54, 4.46) and 1,4-butanediol (pK_a= 14.5)	Bulk	[277]
	PBST	PBS (pH 7.4) at 70 ºC	40% in 60d	n.r	Bulk	[280]
	PBSeT	PBS (pH 7.4) at 70 ºC	30% in 60d	n.r	Bulk	[280]
	PBAdT	PBS (pH 7.4) at 70 ºC	45% in 60d	n.r	Bulk	[280]
	PHFA	n.r.	n.r.	Dihydroferulic acid (pK_a= 3.95)	n.r	[283]
	P2HEB	Toluene at 70 °C + aluminium salen 1	80% of M_w in 1h	Its cyclic monomer (2,3-DHB)	n.r	[178]

3.2. Enzymatic degradation

3.2.1. Enzymatic degradation: mechanism

Some naturally occurring polymers such as PHAs are biodegradable as they are susceptible to enzymatic degradation. Tokiwa and Suzuki showed back in 1977 that apart from such natural polymers, other synthetic polymers also have the ability of being degraded by some isolated enzymes [299]. Afterwards, lipases extracted from hog pancreas and *Rhizopus arrihzus* were used by Tokiwa et al. to investigate the degradation behavior of several aliphatic polyesters [300,301]. Since this pioneering work carried out using lipases, a plethora of works have studied the degradation of both aliphatic and aliphatic/aromatic polyesters using different enzymes [302–304], which opened the door to the synthetic design of polymers capable to undergo depolymerisation reactions under microbial attack.
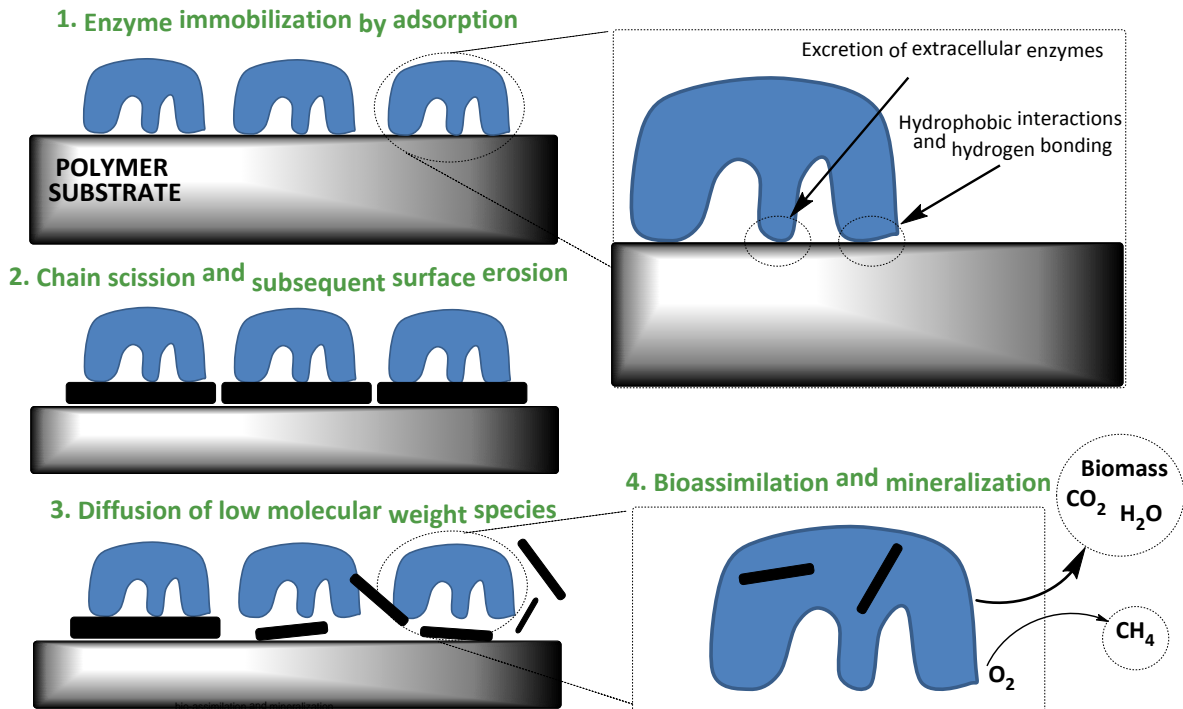

Figure 9. Schematic representation showing different stages of the enzymatic hydrolysis process of polyesters.

Enzymatic degradation is mediated by water, enzymes and microorganisms and takes place when an enzyme catalyzes chain scission reactions to form two or more compounds. In order to trigger such degradation process, enzymes need to proceed through a conformational change induced by adsorptive binding at the substrate surface [305]. Due to their size, these enzymes exclusively act at the polymer surface, resulting in a surface erosion process. According to Figure 9, enzymatic degradation process occurs in several steps. First of all, microorganisms must adhere onto the surface of the polymer to excrete extracellular enzymes which are responsible of depolymerising the macromolecular chains outside the microorganisms. The polymer fragmentation down into lower molecular weight species occurs at the surface of the polymeric material as a result of the enzymatic attack (endo- or exo-type hydrolysis if the hydrolysis takes place at the interior bonds of the polymer or at the terminal ones, respectively) and could proceed via either biotic (degradation by microorganisms) or abiotic (hydrolysis) reactions. During this enzymatic cleavage the surface of the material is continuously eroded and the newly generated shorter chains consisting of oligomers, dimmers and monomes become water-soluble if their molecular weight is low enough. Upon solubilisation, these low-molecular weight species diffuse away from the polymeric substrate to feed different metabolic pathways within the microorganism [306]. This bio-assimilation and mineralization (mainly a conversion to CO_2 and H_2O) of the shorter chains by microorganisms could occur either in the presence or absence of oxygen (aerobic and anaerobic conditions respectively) and the resulting end-products are CO_2, H_2O, N_2 and new biomass (and CH_4 if

degradation occurs under anaerobic conditions). Overall, upon enzymatic degradation, microorganisms use the polymeric surfaces as a carbon source to extract energy in the following fashion:

$$\text{C-substrate} + 6 \cdot O_2 \rightarrow 6 \cdot CO_2 + 6 \cdot H_2O, \Delta G_0 = -686 \text{ kcal/mol } (CH_2O)_x; x = 6 \qquad (1)$$

Therefore, the determination of the evolved CO_2 as a function of total carbon input is typically used to monitor the biodegradation process of polyesters (C-substrate) [307].

3.2.2. Factors affecting the enzymatic degradation of polyesters

Similarly to the hydrolytic degradation, a wide variety of characteristics markedly influence the enzymatic degradation of polyesters. Enzymatic degradation is a complex process resulting from the combination of polymer characteristics and many abiotic and biotic factors. The inherent physico-chemical properties of the polymer in question (i.e., monomeric composition, molecular weight, crystallinity, chemical reactivity, melting temperature), the surface morphology (i.e., surface area, shape, size, hydrophilicity, water permeability, and hydrophobic characteristics) and abiotic parameters such as pH, temperature, moisture, oxygen presence, salinity and nutrient supply should be also taken into account when considering the biodegradation of polymers. Such abiotic parameters not only directly affect the polymer biodegradation, but they also determine several biotic factors such as microbial population and diversity.

Enzymatic degradation is affected by the chemical nature of the chain. Herzog et al. studied the dependence of enzymatic degradation rate constants (k) on both the ester bond density (ρ_{EB}) and chain length of the diacid by using a lipase from *Candida cylindracea* (CcL) [304]. Four polyesters were synthesized from aliphatic acids with 1,3-propanediol, 1,4-butanediol, 1,5-pentanediol and 1,6- hexanediol and were enzymatically degraded at 40 ºC. It was found that the rate of degradation was higher at lower ρ_{EB} and larger diacid chains, indicating that increased chain flexibility results in faster degradation rates. Contrarily, polyesters having side chains [308] and higher molecular weights present an increased resistance to enzymatic degradation [309]. The presence of aromatic moieties within the chain backbone has been proven to determine the resulting degradability of polyesters. Generally, lipases can only depolymerise aliphatic polyesters, while aromatic polyesters remain barely inert. In between, aliphatic/aromatic polyesters display a degradability that mainly depends on the content of aromatic constituents.

It is generally accepted that not only the chemical nature surrounding the ester bonds affects the degradability of the material, but also its ratio in comparison with the whole chain. As the presence of aromatic moieties limits the accessibility of the enzymes to catalyze ester-bond cleavage reactions of the bonds nearby the aromatic groups, the larger the presence of aromatic compounds the slower the enzymatic degradation may result. Marten et al. showed that, for aliphatic/aromatic polyesters synthesized from adipic acid, terephthalic acid and 1,4-butanediol, a terephthalic content of nearly 30 mol% is enough to drop the enzymatic degradation rate by one order of magnitude in comparison with the pure aliphatic poly(butylene adipate) material (Figure 10a) [303]. At terephthalic acid concentrations above 60 mol% the degradation becomes so sluggish that the resulting polyesters are considered non-biodegradable similarly to the pure aromatic polybutylene terephthalate (PBT). Despite to such observation, Marten el at. proved that lipases are able to hydrolyze some low molecular weight model esters containing aromatic moieties in their structure which resemble the structure of non-degradable aromatic polyesters [302].

The stereochemical isomerism within the chain also affects its potential for biodegradation. For instance, at 37 ºC and a pH of 8.6 proteinase K is able to degrade PLA stereoisomers in the following order: L-L > L-D > D-L > D-D [310]. In the same trend, PLA_{50}-meso undergoes a faster degradation than PLA_{50}-racemic (obtained from the ROP of meso-lactide and DL-lactide, respectively) as a result of the increased water uptake that prompts the enzymatic degradation [310].

Overall, polyesters having an optically active carbon such as PLA and P3HB are resistant to lipases, an important group of esterases useful for the enzymatic degradation of polyesters [3].

As in semicrystalline polymers amorphous regions are loosely packed in comparison with crystalline phases where the chains are tightly arranged, amorphous phases become more susceptible to enzymatic attack [311]. As depicted in Figure 10b, scanning electron microscopy images of a PES film undergoing enzymatic degradation show that the initial smooth surface becomes continuously rougher with degradation time [312]. This substantial surface erosion occurs as a result of the removal of the amorphous regions which expose the more resistant spherulites (crystalline aggregates) that were buried within the bulk of the material. Similarly, spherulite size has been also proven to affect enzymatic degradation of polyesters as large spherulites reduce the susceptibility of the polymer to undergo through enzymatic degradation reactions [313]. To confront the effect of the crystallinity against the effect of the chemical structure on the resulting enzymatic degradation behaviour, Bikiaris et al. synthetized three poly(alkylene succinates) from succinic acid and aliphatic diols with 2 to 4 methylene groups (poly(ethylene succinate) (PESu), poly(propylene succinate) (PPSu) and poly(butylene succinate) (PBSu)) [113]. Enzymatic degradation studies performed using *Rhizopus delemar* lipase at pH 7.2 and 30 °C showed that the biodegradation rates were PPSu > PESu ≥ PBSu. Since the hydrolysis would have been faster in PBSu according to the chain structure, it was concluded that the enzymatic degradation was governed by the crystalline/amorphous character of the polyesters.
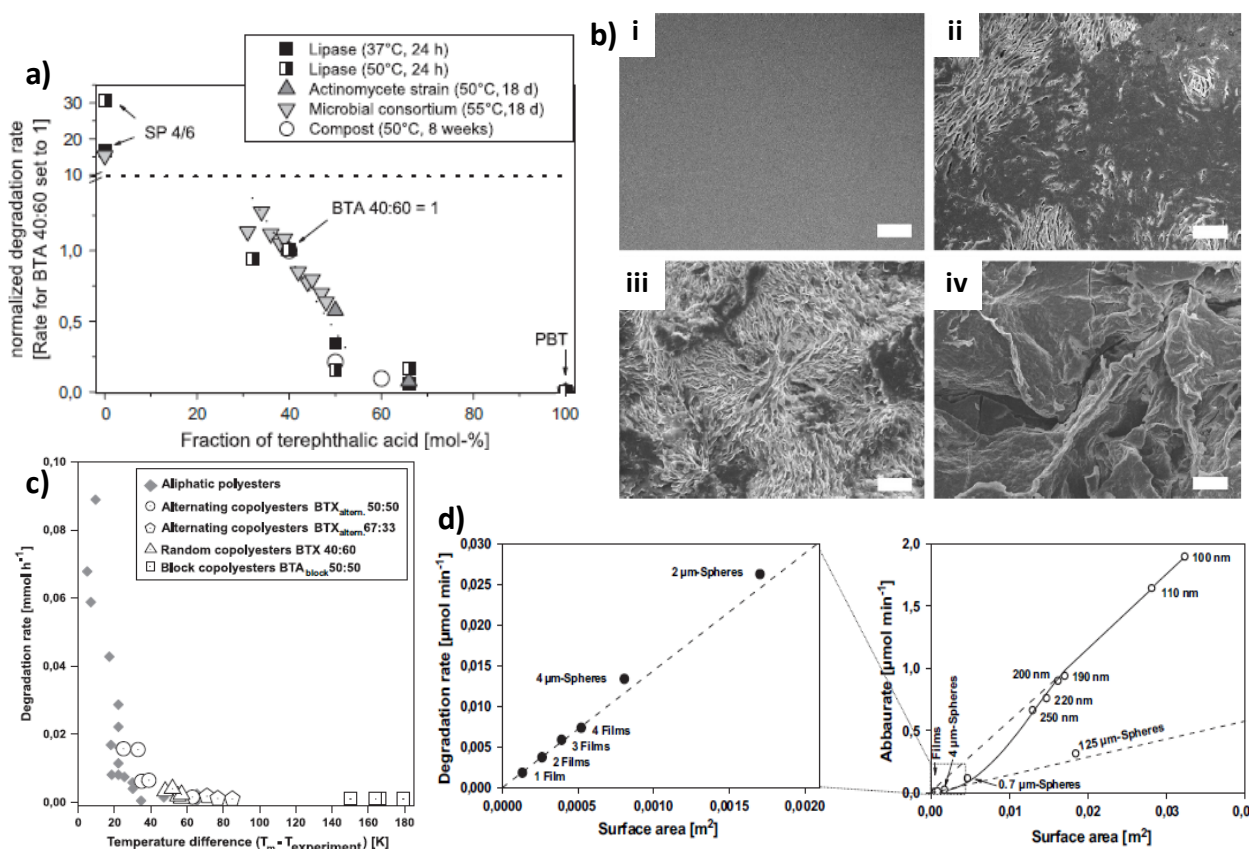

Figure 10. (a) Enzymatic degradation rate dependence aliphatic/aromatic polyesters synthetized from adipic acid, terephthalic acid and 1,4-butanediol on the fraction of terephthalic acid (mol.%) for different degradation environments. For the sake of clarity, degradation rates have been normalized to the rate of the random polyester containing 40 mol% of aromatic units [303]; (b) Scanning electron microscopy images showing the surface morphology of a PESu film before (i) and during the degradation by strain NKCM1003 for 5 days (ii), 10 days (iii) and 20 days (iv). Scale bars represents 20 μm [312]; (c) Influence of surface area on the resulting enzymatic degradation rate (*Candida cylindracea* lipase) of a polyester made of 1,4-butanediol and adipic acid (M_w: 54.500 g·mol^{-1}) [304]. Samples having different surface areas were obtained by shaping the same polymer into films, spheres and nanoparticles; (d) Enzymatic degradation rate (*Pseudomonas sp.* lipase) influence on the temperature difference between the melting point (T_m) and degradation temperature ($T_{experiment}$) for different aliphatic and aliphatic/aromatic polyesters [303].

As extracellular enzymes result too large to be able to penetrate into the bulk of the polymers, they can only act on the surface of the material, making enzymatic degradation of polyesters a surface-driven process. Therefore, the surface area of the material has a marked impact on the resulting degradation kinetics. Herzog et al. comprehensively studied the effect of surface area on the kinetics of enzymatic degradation (*Candida cylindracea*, 40 °C) for a polyester made of 1,4-butanediol and adipic acid (M_w: 54.500 g·mol^{-1}) [304]. As highlighted in Figure 10c, a 1000-fold increase on the degradation rate could be accomplished by synthesizing nanoparticles of 100 nm in diameter in comparison with 110 μm thick films (the degradation of films lasted for several days, while nanoparticles where degraded just in few minutes) [304].

Similarly, the hydrophilic-to-hydrophobic balance of polyesters is a key factor for enzyme binding (and thus the enzymatic degradation) as hydrophobic surfaces do not allow intimate contact between the polymer and the active sites of the enzymes. On the contrary, water-soluble intermediates do not undergo through further chain scission reaction by some enzymes, indicating that a proper hydrophilic-to-hydrophobic balance is needed for a proper enzymatic degradation [302]. In this sense, the enzymatic degradation proceeds faster for a balanced hydrophobicity–hydrophilicity ratio, as the interaction of enzymes with the polymer surface is controlled by this parameter [314].

The temperature of the degrading medium influences the resulting enzymatic degradation process as the enzymatic degradation of polyesters depends on the difference at which the degradation takes place and the melting temperature of the polymer itself ($\Delta T = T_m - T_{experiment}$). As the melting temperature of a polymeric material is related with the ratio between the change in enthalpy (ΔH_f) and entropy (ΔS_f) associated with the transition from the crystalline phase to the melt ($T_m = \Delta H_f / \Delta S_f$), ΔT is considered as an indicator for the capacity of chains to leave the ordered crystalline domains and to form a loose loop that would prospectively undergo degradation reactions by the microorganism [303]. This fact applies irrespectively of the microstructures of the polyesters as shown in Figure 10d, where aliphatic and different aliphatic/aromatic polyesters show high susceptibility to enzymatic attack when the difference between the melting temperature of the polyester that is being degraded and the experiment temperature is below 30 °C [303]. A general trend has been found that polyesters having higher T_m suffer slower enzymatic degradation processes against *Rhizopus arrhizus* lipase [315]. Similarly, the time required for obtaining a degree of mineralization of 60 % has been found to increase from 40 to 100 days by reducing the biodegradation temperature from 52 to 37 °C [316].

Medium pH modifies enzyme conformation, changing together the active sites of the enzymes and altering the overall biodegradation rate [317]. The protonation of ionisable chains at low pH values result in charge-charge repulsion forces which in turn yield to protein unfolding, suppressing the structure and function of the enzyme [318]. In this sense, the activity of *Pseudomonas cepacia* lipase towards PLA and PCL displays their maximum efficiency at pH values of 7.2 and 7.7 respectively [317].

The type of microorganisms determines the prospective enzymatic degradation of polyesters. Contrarily to the majority of the lipases, thermophilic actinomycetes such as *Thermobifida fusca (TfH)* hydrolases can hydrolyze not only hydrophobic but also hydrophilic esters. This is exemplified by the fact that although hydrolases such as AoL lipase from *Aspergillus oryzae*, PsL lipase from *Pseudomonas sp.* can degrade poly(butylene adipate) up to a certain level, only *TfH* is able to produce an ester cleavage above 95 % in 400 minutes [319]. This is due to the fact that AoL and PsL could not induce chain cleavage reactions in all aliphatic polyesters as they need an hydrophobic surface to get active (they cannot hydrolyze ester bonds of water-soluble intermediates). On the contrary, *TfH* displays combined characteristics of lipases as they cleave ester bonds at a hydrophobic surface, and esterases, which can also hydrolyze dissolved esters [319]. Some polyesters such as P(3HB-co-3HV) degrade faster in anaerobic conditions than under aerobic ones [320]. Overall, elevated temperature, high moisture content and abundance of microorganisms are proven to be effective ways of accelerating the biodegradation of polyesters

[321,322]. Bacterial copolyesters such as PHBV undergo enzymatic degradation reactions faster than the homopolymers (P3HB, P3HV). Similarly, synthetic polyesters display a higher resistance to enzymatic attack than bacterial homopolymers [315].

Overall, commercially available enzymes such as lipases, esterases and chitinases are the preferred choice for the degradation of polyesters as they preferentially catalyze the cleavage of ester bonds in both pure aliphatic and aliphatic/aromatic polyesters [323,324]. However, especial care should be taken when selecting the appropriate enzyme as each polyester presents its own peculiarities. For instance, lipases hydrolyze the ester bonds of polyesters having a relatively large number of methylene groups such as PCL, PESu, PBSu and PBSA, but cannot catalyze degradation reactions in polyesters having optically active carbons [325]. Such optically active polyesters with high melting temperature; i.e. PLLA, P3HB and P3HV, require the use of proteinase-like enzymes or PHB-depolymerases [316,326].

3.2.3. Enzymatic degradation of polyesters

Since the discovery of the conversion of starch into sugars by diastase in 1833, the role of enzymes as biocatalysts has been deeply investigated [327]. Given the vast range of opportunities to isolate and design new enzymes with enhanced activity, biological catalysis procedures for polymer chain scission is becoming a growing area of interest at both academic and industrial levels. Despite to the fact that pioneering biodegradability studies were limited to aliphatic polyesters [299], further research efforts have shown that different aliphatic/aromatic polyesters could also be enzymatically degraded under proper circumstances [178]. These recent results opened the path towards the design and synthesis of novel biodegradable polyesters with improved physico-mechanical performance. Moreover, pure aromatic polyesters such as PBT or PET have been traditionally considered as inert against biological attack due to steric hindrance of aromatic groups inside the enzyme catalytic site [303,315,328]. However, in 2016 Yoshida et al. showed that PET can be enzimatically converted down into its two monomers, terephthalic acid and ethylene glycol [329], paving the way towards new viable recycling strategies for polymer waste.

In contrast with traditional degradation chemical approaches which often involve harsh conditions (i.e., high temperatures, use of toxic compounds), enzymatic degradation proceeds under non-toxic mild-conditions. Enzymes are proteins formed by many different amino acids with a peculiar three-dimensional structure and become essential to support life as they are responsible of catalyzing *in vivo* metabolic reactions in living cells [330–332]. The specific region where the catalytic reactions takes place within enzymes is known as the active site, whose activity is determined by the spatial arrangement and the electrostatic properties of the amino acids that surround this site [333,334]. Enzymes could be classified into 6 main classes according to Enzyme Commission (EC) number: oxidoreductases (EC.1), transferases (EC.2), hydrolases (EC.3), lyases (EC.4), isomerases (EC.5) and ligases (EC.6) [335]. These 6 classes can be divided into further sub-classes and sub-sub-classes depending on the reaction centre, transferred chemical group, etc. As hydrolases can cleave substrate bonds in the presence of H_2O, different hydrolases including proteases, glycosidades, lipases, cutinases, esterases and P3HB depolymerases have been reported to show specific activity for the degradation of polyesters [336]. For instance, lipases can hydrolyze the ester bonds of aliphatic polyesters provided they are hydrophobic, showing good activity in the pH range of 4-9 and temperature range of 20-80 °C [337]. In the presence of a lipid-water interface, lipases open their structure so the active site can get access to the substrate molecules, that is, the polyester that undergoes degradation reactions [338]. Cutinases are multifunctional enzymes with good stability in the 20–50 °C temperature range and pH 8–11 which are able to hydrolyze ester bonds of cutin [339].

PGA can be enzymatically degraded provided the adequate enzymes are selected. *Carboxypeptidase A*, *alpha-chymotrypsin*, *clostridiopeptidase A*, *ficin* and *esterase* can significantly degrade this aliphatic polyester [231,340], while other enzymes such as *α-chymortrypsin* and *trypsin* cannot yield to chain-cleavage reactions [340]. PLA can be biodegraded by microorganisms

until mineralization to obtain CO_2 (aerobic) or CH_4 (anaerobic) and H_2O. In 1981 Williams reported for the first time the enzymatic degradability of PLA by *proteinase K* [341]. The susceptibility of polylactides to enzymatic degradation results quite low in comparison with other aliphatic polyesters, requiring also longer times than other polyesters [342]. The enzymatic degradation of PLA proceeds faster than its hydrolytic degradation. Accordingly, an *Amycolatopsis sp.* isolate is able to degrade 60% of a PLA film in 14 days when incubated at 30 °C [342]. Moreover, the availability of PLA degrading enzymes is rather poor when comparing with other aliphatic polyesters such as PCL, P3HB or PBSu [313,343]. Most of the PLA degrading strains belong to *Pseudonocardiaceae* family and related genera, including *Amycolatopsis, Lentzea, Kibdelosporangium, Streptoalloteichus* and *Saccharothrix* [344], while PCL, P3HB or PBSu—degrading enzymes could be found distributed among many families [345].Microorganisms cannot digest the PLA to produce CO_2 and H_2O until the M_w reaches 10.000 $g \cdot mol^{-1}$ [346]. Excluding specific cases such as the esterase *Bacillus smithii* which is able to degrade PLLA [347], these optically-active polyesters show higher resistance to degradation and require the use of proteinase-like enzymes [341]. More precisely, while *proteinase K* and other serine proteases (*trypsin, elastase* and *subtilisin*) degrade PLLA and PDLLA, they cannot degrade PDLA [348]. Similarly, although lipases cannot in general hydrolyze PLA, *Candida cylindracea* and *Rhizopus arrhizus* lipases can cleave the amorphous PDLLA, suggesting that lipases are efficient when degrading amorphous polyesters having low T_m, but are not able to degrade polyesters with optically active carbons [325]. Under thermophilic conditions the anaerobic biodegradation of PLLA takes place much faster than the corresponding aerobic biodegradation [316]. Due to its similarity on the structural units, PPL shows similar enzymatic degradation characteristics to PCL [349]. A wide range of bacteria able to degrade PPL have been isolated from pond water [349]. PCL is degraded under both aerobic and anaerobic conditions [320]; i.e. it undergoes lipase-type enzymatic degradation in the presence of *Rhizopus delemar* lipase [350], *Rhizopus arrhizus* lipase, and *Pseudomonas* lipase [351]. Among these enzymes, *Pseudomonas* lipase significantly accelerates the process to totally degrade the highly crystalline PCL within four days [352], in contrast to hydrolytic degradation, which lasts several years. Several esterases have also been proven efficient for degrading PCL [353].

Naturally occurring polymers tend to be highly susceptible to enzymatic degradation processes. In this sense, PHAs show a high susceptibility to be degraded by many microorganisms under both aerobic and anaerobic conditions [320]. Since 1963 when Chodhury reported the first example of a PHA degrading microorganism [354], many PHA-degrading microorganisms have been isolated. A remarkable study done in 1991 demonstrated that commercial PHA bottles can be *in situ* degraded within a period of 254 days in a freshwater lake ecosystem under harsh conditions of no sunlight exposure, temperatures below 6 °C, water depths of 85 meters and oxygen variation [355]. In any case, it should be considered that despite to large variety of natural microorganisms able to degrade PHAs (estimated in the 0.5-9.9 % range of the total colonies depending on the environment), most of them solely are able to degrade P3HB (the most ubiquitous and most extensively studied PHA) under ambient of mesophilic temperatures, which typically range between 20 and 45 °C [356]. Tokiwa and Jarerat showed that enzymes that hydrolyze P3HB are found among the families of *Pseudonocardiaceae, Micromonosporaceae, Thermonosporaceae, Streptosporangiaceae* and *Streptomycetaceae* [345] (lipases are not capable of hydrolyzing P3HB and P3HV [357]). Overall, microbial polyesters such as P3HB and P(3HB-co-3HV) show faster degradation when comparing with other aliphatic polyesters such as PLA and PCL [320]. The degradation rate of P(3HB-co-3HV) polyesters notably increases with 3HV-unit content to reach a maximum rate at nearly 40 mol%, and then decreased steeply with the presence of 3HV [358]. P3HB is degraded anaerobically more rapidly than P(3HB-co-3HV), while in the presence of oxygen the opposite effect occurs [320]. In this line, Kanesawa studied the enzymatic degradation of PHAs having 3-hydroxyalkanoate units with different chain lengths (C_4–C_{10}) and concluded that an increase on the side-chain length continuously lowers the hydrolysis rate of the resulting PHAs [359]. Although depolymerases do not efficiently hydrolyze PHAs having monomers with more than five carbon atoms, several depolymerases have been proven to attack PHAs having monomeric units other than

3-hydroxybutyric acid [360]. Neat P3HP and poly(3HB-co-3HP) copolymer films having different 3HP-content are degraded with *Pseudomonas stutzeri* depolymerase, where faster degradation was obtained for intermediate 3HP-contents as a result of their lower crystallinity [361].

So far few enzymes have been reported to enzymatically degrade poly(alkylene succinate)s. For example, PBSu proceeds through slow enzymatic degradation with a 4 and 5 % weight loss in 30 days upon exposure to *Pseudomonas cepacia* lipase and protease XIV from *Streptomyces griseus* at 37 °C [362]. Such slow degradation can be boosted upon the selection of the proper enzyme; for example, upon incubation in the presence of *Fusarium sp.* FS1301, a 80 % mass loss is achieved after 24 days [363], while a 60% mass of PBSu powder can be assimilated by the HT-6 actinomycete after 8 days of cultivation [364]. PBSu can be degraded by other enzymes including *Candida antartica* and porcine pancreas lipases [365], *Rizopus delemar* lipase [366], *Aspergillus oryzae* lipase [367], or thermophilic actinomycetes such as *Microbispora rosea, Excellospora japonica* and *E. viridilutea* [368]. Umare et al. showed that upon incubation at 37 °C with *Rhizopus delemar* lipase for 3 days, PPSu, PPAd and PPSe ($M_w \approx 7000\text{-}8000$ g·mol^{-1}) present weigh losses of 2.7 mg·cm^{-2}, 2.3 mg·cm^{-2} and 0.6 mg·cm^{-2} respectively [369]. Thanks to its lower degree of crystallinity and T_m, PPSu also degrades faster than PESu and PBSu, making it an interesting polyester for many biomedical applications [113]. Apart from degrading PBSu, P3HB depolymerase extracted from the thermophilic *Streptomyces sp.* can also degrade other aliphatic polyesters such as PESu and PEAd (pH of 8.5 and 60 °C) [370]. Other remarkable enzymes with the ability of hydrolyzing polyesters based on succinic acid are microorganisms of the genera *Bacillus* and *Paenibacillus* [371] and a P(3HB) depolymerase [312] for PESu, *Burkholderia cepacia* and *Pseudomonas aeruginosa* for PBSA (78% of degradation after 40 days at 37 °C) [372].

Nagata studied the enzymatic degradation of PEA powders based on 1,6-hexanediol, sabacoyl chloride and alanine upon incubation with proteolytic enzymes (*proteinase-K, papain* and *α-chymotrypsin*) and lipase enzymes (*R. delemar, P. cepacia* and *C. rugosa*) at pH of 7.2 and 37 °C [373]. Results showed that the degradation proceeds through the hydrolysis of ester linkages instead of the hydrolysis of the semi-peptide linkage. Among all the studied enzymes, *proteinase-K* showed the higher degradation ability with a weight loss of 78% after 8 h of incubation. Further studies carried out on the enzymatic degradation of PEAs based on 1,12-dodecanodiol, sebacid acid and L-alanine showed that while *pronase, trypsin* and *chymotrypsin* barely hydrolyze such polyester, *papain* is able to completely hydrolyze the material in 13 days via a surface eroding process [374]. PEA films based on α-amino acids L-phenylalanine and L-methionine show a faster degradation (a drop of 50% on the M_w during the first 24h) with a rapid initial bulk degradation followed by a surface erosion when incubated with α-chymotrypsin at 37 °C [375]. Overall, a remarkable advantage of PEAs is that the resulting bisamide-diol monomer by-products are easily solubilized in water, preventing the formation of crystalline amide aggregates.

Although aromatic polyesters have been traditionally recognized as biologically inert materials, several works have shown that enzymes could efficiently hydrolyze aliphatic/aromatic polyesters. For instance, *Rhizopus delemar* lipase randomly splits the ester bonds of aromatic/aliphatic polyesters containing PET-PCL and PBT-PEIP (poly(ethylene isophythalate)), reaching degradation extents up to 40% in 100 minutes at 37 °C for the PCL-PET 90/10 molar ratio system [300]. The enzymatic degradation slowed down as the aromatic polyester content increased. Other enzymes such as *TfH* also successfully biodegrades several aliphatic/aromatic polyesters based on adipic and terephtalic acids [376,377]. Grivalský et al. recently studied the biodegradation of PBAT [378]. Morphological observations reveal that PBAT surface remains covered by bacteria, indicating PBAT provides enough nutrients for microorganisms. *Brevibacterium luteolum, Bacillus thuringiensis, Aeromonas media, Geobacillus kaustophilus* and *Serratia sp* where able to enzymatically degrade PBAT, being *Geobacillus kaustophilus* the strain with greatest activity. Moreover, PBST or poly(butylene succinate/terephthalate/isophthalate)-co-(lactate) (PBSTIL) are susceptible to hydrolysis by *Leptothrix sp.* [379] and *Roseateles depolymerans* depolymerases [380], where enzymes attack succinic acid segments first instead of adipic acid and

terephthalic/isophthalic acid segments. In this sense, Papageorgiou et al. synthesized a new series of high molecular weight aliphatic/aromatic polyesters, poly(propylene terephthalate-co-succinate) (PPTSu) and showed that upon incubation with *Rhizopus delemar* and *Pseudomonas Cepacia* lipases (pH 7.2; 37 °C) these polyesters are degradable up to a terephthalate content up to 60 mol % (4% weight loss after 5 days for the polyester containing 50 mol %) [9]. The maximum aromatic content of around 50-60 mol% recognized as the limit for biodegradability is ascribed to the fact that the hydrolysable ester bonds close to aromatic groups moieties show a hindered accessibility for the enzymes to catalyze chain-scission reactions [381]. Other novel enzymatically degradable aliphatic/aromatic polyesters have also been recently reported. For example, Lizundia et al. showed in 2017 that P2HEB could be hydrolyzed by enzymes (*proteinase K*), showing a 39% decrease in molecular weight over 60 h when incubated at 37 °C [178]. Such degradability is ascribed to the fact that the ester linkage orientates 90º to the phenyl ring, providing an easy access for enzymatic attack P2HEB.

Although polyesters containing aromatic groups present an enhanced resistance to enzymatic attack, the isolation of new enzymes is providing novel avenues towards the development of biodegradable aromatic polyesters outcomes. For example, Eberl et al. proved that a cutinase (*TfH*) and a lipase (*Thermomyces lanuginosus*) could hydrolyze the aromatic poly(trimethylene terephthalate) (PTT) [382]. In any case, such enzymes show a limited hydrolysis activity as *TfH* could degrade PTT fibers and films, while *Thermomyces lanuginosus* could only degrade films. More interestingly, Müller et al. reported in 2005 that nearly amorphous ($X_c \approx 10\%$) PET can be degraded to a certain extent with erosion rates up to 17 µm/week upon incubation with a hydrolase from the actinomycete *TfH* at 55 °C [383]. 4 years later, Ronkvist et. al showed that cutinases can partially hydrolyze the surface ester bonds on low-crystallinity PET fibers with a loss in film thickness up to 30 µm/day [384]. In 2016, Yoshida et al. showed that the *Ideonella sakaiensis* 201-F6 bacterium can degrade and assimilate PET, with a weight loss of nearly 60% in 40 days of cultivation (pH of 7.0, 30 °C) [329]. Those examples clearly evidence the progresses made on the enzymatic degradation of aromatic polyesters which have been traditionally recognized as non-biodegradable.

Currently many different polyesters are being explored as potential candidates for green packaging as they can easily break down under controlled composting conditions. Composting is known as the process in which a given material is rapidly degraded into a humus-like substance under a controlled mixed microbial population in an environment with high moisture contents and elevated temperatures [385]. Kale et al. compared the composting degradation of PLA bottles under simulated composting conditions according to ASTM and ISO standards with biodegradation experiments under real composting conditions [386]. For studies carried out at 65 ± 5 °C, the molecular weight dropped from the initial 210.000 g·mol^{-1} to 4.100 g·mol^{-1} after 30 days under real composting conditions; while the mineralization was around 81% after 58 days (ASTM requires a 60% or higher mineralization value for a material containing a single polymer to certify that the material is biodegradable). Ghorpade et al. showed that relatively low amounts of PLA are preferred (below 30/70 ratio PLA to yard waste) for efficient composting as large amounts of PLA dropped the compost pH from 6.0 to 4.0 after 4 weeks as a result of the lactic acid formation, which in turn suppresses the microbial activity [387]. If the amount of PLA is kept within the optimum concentration, no pH decay is observed as water soluble products arising from PLA fragmentation are assimilated by microorganisms [388]. These results highlight that compost results the most suitable environment for the rapid biodegradation of PLA. The composting degradation of other polyesters has also been evaluated. In this line, pure polyhydroxybutyrate disintegrates after 10 days under composting (faster than PLA), while PBAT is able to retain its shape after 45 days [389]. CO_2 evolution during the metabolic conversion is the preferred indicator to study the composting rate of polymers as it provides quantitative means for the determination of the degradation extent [390]. In this line, after 28 days P3HB, PLA and PBAT showed a CO_2 evolution of ~80, ~70 and ~35 %, indicating that the composting degradation was P3HB > PLA > PBAT. Finally, the tensile modulus of both PLA and PHB drops by nearly 75% after 5 days under composting conditions, while PBAT

is able to keep more than 40 % of its initial modulus after 30 days [389]. The degradation of other polyesters containing aromatic constituents under composting conditions was deeply studied by Witt and Müeller. Aliphatic/aromatic polyesters based on terephthalic acid, adipic acid, sebacic acid and 1,3-propanediol [376], and aliphatic/aromatic polyesters based on 1,4-butanediol, terephthalic acid and adipic acid [281], were submitted to compost degradation conditions. It was shown that for all the systems the degradation slows down in the presence of larger terephthalic acid contents (above nearly 50 mol% terephthalic acid content results in non-compostable materials). While oligomers containing up to two terephthalate units were degraded and metabolized rapidly, longer aromatic sequences showed a higher resistance to degradation [391,392]. Interestingly, no acute ecotoxic effect resulting from the degradation intermediates was observed and the final degradation by-products can be metabolized by the microbial compost population.

Besides of reusing and traditional recycling, composting emerges as an attractive practice in order to fulfil a cradle-to-cradle approach as it offers the advantage for a relatively quick process (in comparison with pure hydrolytic processes) with low-cost disposal of post-consumer aliphatic and aliphatic/aromatic packaging waste. However, still limited knowledge exists on the detailed mechanisms governing composting degradation of many polyesters. As the synthetic methods for the development of novel aliphatic, and especially aliphatic/aromatic polyesters progresses, further works are required to elucidate the time window, the mechanisms and the associated possible toxicity issues during the composting degradation of polyesters.

4. Perspectives and concluding remarks

During the last decade, polymer science has witnessed a notable increase in the development and commercialization of novel biodegradable polyesters. This review serves to the increasing demand of such materials with well defined physico-mechanical performance, which in turn defines their application field. Currently, biodegradable polyesters are at the forefront of polymer science and technology because they could be degraded through enzymatic and hydrolytic reactions and demonstrate proper physico-mechanical properties for a wide range of applications. Some of such materials have exhibited features comparable to non-biodegradable commodity plastics such as PP or PE, but with a significantly lower environmental impact when discarded. Other biodegradable polyesters, mainly aliphatic ones, suffer from serious limitations regarding their functional properties, although they present proper biodegradation profiles.

Accordingly, the development of novel aliphatic and aliphatic/aromatic biodegradable polyesters with upgraded properties is a hot topic in current polymer science thanks to their potential application as sustainable alternatives to traditional petroleum-based polymers. Due to the decreased biodegradability introduced by aromatic groups, the design of novel aliphatic/aromatic polyester with upgraded degradability should be a priority in order to facilitate their post-use treatment in industrial composting facilities. In this regard, huge efforts are also being made in order to use new genetically engineered enzymes as biocatalysts for hydrolyze aromatic polyesters that were considered as biologically inert until not long ago. For example, a recently isolated bacterium has been proven to successfully hydrolyze PET into its two environmentally benign monomers [329], paving the path towards the development of novel environmental remediation strategies for the recycling/biodegradation of polyesters.

Apart from the enormous variety of physico-mechanical and degradation properties of polyesters, such materials also present a great potential for upgrading their properties upon the development of novel synthetic approaches, copolymerization, blending, or composite/nanocomposite fabrication. Owing to environmental concerns and the limited availability of petrochemical feedstock, a completely green process for biodegradable polyester production would be the preferred method. In this framework, we expect an increase in the commercialization of PHAs and PLAs as these polyesters could be synthesized from renewable resources. We

anticipate that novel developments in the field of polymer science may broad the impact of biodegradable polymers on global sustainable polymer challenges.

Last but not least, the increasing impact of biodegradable polyesters in the biomedical field needs to be highlighted. Biodegradable polyesters are being widely employed as bone fixation devices, coronary stents, drug-delivery devices and scaffolds for tissue engineering applications to overcome the limitations of non-degradable alternatives. The design of devices with predictable thermomechanical properties and degradation rates is of vital importance for the use of these materials in the biomedical field. However, considering that several aspects (e.g., polymer chain scission, crystallization during degradation, oligomer diffusion, autocatalytic hydrolysis reaction, initial molecular weight, etc.) govern the complex degradation process, it results nearly impossible to predict how the properties will vary during the application of such devices within the human body. In this scenario, the trial-and-error approach is time consuming and may be problematic. Thus, several mathematical models have been developed in the last decade that help to understand the insights of the degradation process [209,218], and provide a valuable tool for material selection and devices design. Back in 2008 [393], Wang et al. developed a phenomenological model using a set of simplified reaction-diffusion equations that were applied to both simple (i.e., plates and pins) and complex geometries. This model was further improved to include the crystallization phenomena during degradation via the coupling of modified equations in the Avrami´s theory and diffusion-reaction equations [394]. Models of higher complexity have been developed in recent years facing the degradation process from a multi-scale perspective (from the molecular to the macroscopic scale) through the combination of several approaches (e.g., kinetic Monte Carlo method, Fick´s laws, etc.) [219,395]. These recent models accurately describe many aspects occurring during the degradation of polymers and allow considering polymer characteristics (i.e., initial molecular weight, degree of crystallinity, copolymer ratio) as the input data. Apart from predicting the degradation profile of many (co)polymers and blends, advances in computer modelling can help to anticipate how several important properties (e.g., elastic modulus, tensile strength) evolve as degradation reactions occur within the polymer chains [396–398].

Notes

The authors declare no competing financial interest.

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