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Fine Tuning and Sterilization of Biodegradable Polymer for Medical Use: Case PLGA

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Biodegradable polymers have gained significant interest in medical applications due to their ability to degrade into biocompatible by-products. Poly (lactic-co-glycolic acid) (PLGA) represents a biodegradable copolymer with widely adjustable degradation behaviour and mechanical properties, offering the possibility to adjust the polymer properties to specific applications. This thesis examines the properties and fine-tuning of PLGA for medical use, focusing on the factors influencing its degradation rate, and evaluates sterilization methods for PLGA-based implants.

Various factors influence the degradation behaviour of PLGA. In addition to copolymer composition, factors such as molecular weight, crystallinity, end-group functionalization, and monomer sequence affect the degradation rate of PLGA. Furthermore, biological factors, including enzymatic activity and inflammation, can alter the degradation rate and mechanism *in vivo*.

Sterilization of PLGA-based implants presents a challenge due to the polymer’s sensitivity to heat, moisture and irradiation. Commonly applied methods for PLGA include gamma irradiation, electron beam irradiation and ethylene oxide. The selection of a sterilization method must consider the efficacy with the preservation of material properties and biocompatibility.

Keywords: biodegradable polymer, PLGA, degradation rate, sterilization

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Biohajoavat polymeerit herättävät kiinnostusta lääketieteellisessä käytössä, sillä ne hajoavat bioyhteensopiviksi sivutuotteiksi. Poly(maito-ko-glykolihappo) (PLGA) on biohajoava kopolymeeri, jonka mekaanisia ominaisuuksia ja hajoamiskäyttäytymistä voidaan muokata laajasti. Tutkielmassa perehdytään PLGA:n ominaisuuksiin ja hienosäätöön, erityisesti sen hajoamisnopeuteen vaikuttaviin tekijöihin, sekä PLGA-pohjaisten implanttien sterilointimenetelmiin.

PLGA:n hajoamiskäyttäytymiseen vaikuttavia tekijöitä on useita. Kopolymeerin monomeerisuhteen lisäksi molekyylimassa, kiderakenne, pääteryhmät ja monomeerien järjestys vaikuttavat PLGA:n hajoamisnopeuteen. Lisäksi biologiset tekijät, kuten entsymaattinen aktiivisuus ja paikallinen tulehdusreaktio, vaikuttavat hajoamiskäyttäytymiseen in vivo -olosuhteissa.

Polymeerin herkkyys kuumuudelle, kosteudelle ja säteilylle vaikeuttaa PLGA-pohjaisten implanttien sterilointimenetelmän valintaa. Yleisimmin käytettyjä menetelmiä ovat gammasäteily, elektronisuihkusäteily ja etyleenioksidikaasu. Sopivan sterilointimenetelmän valinnassa tulee huomioida tehokkuus sekä polymeerin ominaisuuksien ja bioyhteensopivuuden säilyminen.

Avainsanat: biohajoava polymeeri, PLGA, hajoamisnopeus, sterilointi

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Abbreviations

EMA	European Medicines Agency
FBGC	Foreign body giant cells
SAL	Sterility Assurance Level
EO	Ethylene oxide
FDA	U.S. Food and Drug Administration
GA	Glycolic acid
LA	Lactic acid
PCL	Polycaprolactone
PDLA	Poly(D-lactic acid)
PDLGA	Poly(D-lactic-co-glycolic acid)
PDLLA	Poly(D,L-lactic acid)
PDO	Polydioxanone
PGA	Poly(glycolic acid)
PHB	Poly(b-hydroxybutyrate)
ROS	Reactive oxygen species
PLA	Poly(lactic acid)
PLGA	Poly(lactic-co-glycolic acid)
PLLA	Poly(L-lactic acid)
PLLGA	Poly(L-lactic-co-glycolic acid)
ROP	Ring-opening polymerization
VPH	Vaporised hydrogen peroxide
HPP	Hydrogen peroxide plasma

1 Introduction

Medical implants and devices placed inside or on the surface of the human body represent a rapidly advancing field of medicine. Medical implants are foreign materials used to replace, restore, maintain or enhance biological structures [1]. As a result of increased life expectancy and an aging population, more age-related biological issues require solutions, and the demand for implantable medical devices and applications is constantly increasing.

The successful use of medical implants depends on the use of appropriate biocompatible materials that can safely interact with the surrounding tissues. Biocompatibility has various definitions, but it has been stated that biocompatibility is *"the ability of a material to perform with an appropriate host response in a specific application"*, where host response defines as *"the response of a living system to the presence of a material, which may or may not be inert, nontoxic and which involves the various components of the immune system"* [1].

Depending on the intended application, materials may be required to either remain stable over time or to degrade in a controlled manner within the physiological environment, thereby requiring the material to be biodegradable. Biodegradable materials can be synthetic or natural, and they degrade enzymatically or non-enzymatically *in vivo*, producing non-toxic biocompatible products [2]. For biodegradable implants, the ability to regulate the degradation behaviour is essential to ensure safe and functional use. This concerns factors such as degradation kinetics and products.

Biodegradable polymers, especially polyesters, such as Poly(lactic-co-glycolic acid) (PLGA), are widely utilized in medical implants and crafts due to their biocompatibility, adjustable biodegradability and toxicological safety [3]. In addition, these polyesters are easy to process and can be degraded by hydrolysis, resulting in non-toxic degradation products [3]. The degradation rate and time can be influenced by modifying the polymer chemically, making it suitable for numerous variable applications, such as tissue engineering scaffolds, vascular tissue engineering and stents, and controlled drug delivery vehicles [2-4].

Implant materials must also withstand sterilization procedures before clinical use. Polyester materials must be sterilized after processing, but sterilization often has unwanted effects on the degradation and properties of the material [5]. This thesis investigates different techniques for fine-tuning the physicochemical properties of biodegradable polymers, focusing on PLGA. In addition, it evaluates sterilization methods, their efficiency and their potential impacts on material properties. The most suitable sterilization methods for biodegradable polymers and especially PLGA are discussed and identified.

This thesis aims to answer three research questions. The research questions are the following:

1. What makes PLGA a good material for biodegradable medical implants?
2. How can PLGAs degradation and properties be modified and fine-tuned for medical use?
3. How does sterilization affect PLGA, and how should PLGA be sterilized for medical use?

AI-assisted tool Grammarly has been used in the writing process of this thesis for revising spelling and grammar, to improve clarity and readability of the text.

2 Biodegradable polymer for medical use

2.1 Poly(lactic-co-glycolic acid)

2.1.1 Chemical structure and synthesis

Poly(lactic-co-glycolic acid) or PLGA is a linear aliphatic copolymer composed of lactic acid (LA) and glycolic acid (GA) monomer units. In addition to non-cyclic monomers, PLGA can also be synthesized from corresponding cyclic diesters (lactide and glycolide, Figure 1) [6]. PLGA can be obtained in different forms based on the ratio of lactic acid and glycolic acid monomers in the polymer. This composition of PLGA is expressed as the LA:GA ratio, which is a significant influencer of the copolymers' physicochemical properties [4]. Lactic acid is a chiral molecule and has two enantiomeric isomers (D-lactic acid and L-lactic acid). Consequently, PLGA can also exist as poly(D-lactide-co-glycolide), poly(L-lactide-co-glycolide) and poly(D,L-lactide-co-glycolide) [4].

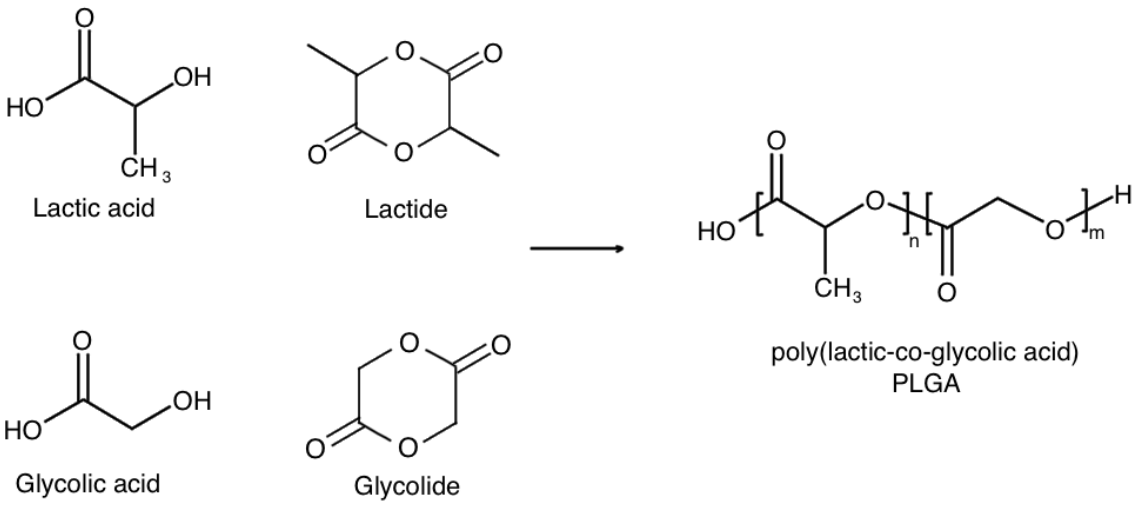

Figure 1. The chemical structure of lactic acid, glycolic acid, lactide, glycolide and poly(lactic-co-glycolic acid)

PLGA can be synthesized with ring-opening polymerization (ROP) or the polycondensation method, and the choice of synthesis method strongly influences the copolymer's properties, such as the molecular weight [7]. PLGA is more commonly synthesised from previously mentioned cyclic diesters using ring-opening polymerization [6]. Enzymatic polymerization is presented as an additional mechanism that produces

low-molecular-weight PLGA under mild conditions, but it requires greater amounts of time for the process [4].

Ring-opening polymerization polymerizes lactide with glycolide utilizing metal catalysts like tin(II)2-ethylhexanoate, tin(II) alkoxides, etc., at high temperatures [4]. Ring-opening polymerization requires initially polycondensation to form lactic acid and glycolic acid monomers into oligomers [7]. The oligomers are depolymerized into the ring-structured lactide and glycolide, which, as a result of ring-opening polymerization, form the PLGA polymer [7]. With ring-opening polymerization, high-molecular-weight PLGA can be obtained [4].

Different polycondensation synthesis mechanisms include direct polycondensation, solution polycondensation and melt/solid polycondensation [4]. In direct polycondensation, lactic acid and glycolic acid monomers are polymerized with a catalyst [7]. The reaction generates the cyclic dimers, lactide and glycolide, as well as water as byproducts, and therefore requires high temperature and vacuum to remove the water [7]. With direct polycondensation, only low-molecular-weight PLGA can be synthesized [7]. Polycondensation in solution also requires water-removal conditions and it enables the synthesis of low-molecular-weight PLGA with a molecular weight of under 10 kDa [4].

2.1.2 Hydrolytic degradation

PLGA is a biodegradable polymer and degrades into biocompatible, safe byproducts that can be eliminated by normal metabolic routes [2]. Degradation of polymers can be classified into surface eroding, also known as heterogeneous degradation, and bulk eroding, known as homogeneous degradation [8]. For surface-eroding polymers, hydrolysis happens on the outer surface, and the interior remains unchanged, whereas for bulk eroding polymers, the degradation happens homogenously at a steady rate throughout the polymer matrix, and water diffuses throughout the polymer matrix faster than degradation occurs [8].

PLGA degrades homogenously through bulk degradation [9]. PLGA degrades through hydrolysis of its ester linkages, resulting in lactic and glycolic acid monomers, which can

safely be metabolised [6]. PLGA's covalent ester bonds are hydrolytically unstable and degrade randomly in an aqueous environment, resulting in the formation of new hydroxyl and carboxyl groups, increasing hydrophilicity and autocatalyzing the hydrolytic degradation [6]. PLGA hydrolysis proceeds typically through random chain scission at different parts of the polymer backbone, but also through chain-end scission at chain ends [6]. Chain-end scission progresses depending on the conditions, occurring via a backbiting mechanism in an alkaline environment and an unzipping mechanism in an acidic environment [6].

The hydrolysis of PLGA begins with hydration, causing disruption of van der Waals and hydrogen bonds, resulting in a decrease of the glass transition temperature [4]. Hydration causes the polymer to absorb more water and swell [9]. Second, the initial degradation causes a decrease in the molecular weight through cleavage of covalent ester bonds and generates carboxyl groups that further autocatalyze the process [4,9]. Cleavage of covalent bonds leads to a loss of mass and integrity [4]. Finally, solubilization occurs, resulting in left fragments to be cleaved into molecules that hydrolyse into free monomers [4,9].

Following hydrolysis, the degradation products can be metabolized by the body's own process, the tricarboxylic acid cycle, known as the Krebs cycle, into water and carbon dioxide [10]. The monomers are decomposed by phagocytes into negatively charged monomeric anions, lactate and glycolate [11]. L-lactate is converted into carbon dioxide and pyruvate, D-lactate is removed with excreta and glycolate is removed in urine or converted into glycerine, serine and pyruvate by oxidation [11]. Pyruvate enters the Krebs cycle and turns into carbon dioxide and water [12]. The degradation products can also be turned into glycogen in the liver and eventually converted to carbon dioxide and water, which are removed from the body primarily through the lungs or kidneys [6].

2.1.3 Properties

As a copolymer, PLGA exhibits properties from the initial polymers of lactic acid and glycolic acid, poly(lactic acid) (PLA) and poly(glycolic acid) (PGA), that are copolymerized to combine the benefits and optimize properties [6]. Mechanical properties of PLGA are affected by the LA:GA ratio, but also other factors such as crystallinity and molecular

weight [6]. For (50DL/50G) poly(D,L-lactide-co-glycolic acid), tensile strength is 40-50 MPa, Young's modulus is 2-4 GPa and elongation at break is 1-4% [12]. For (85L/15G) poly(lactic-co-glycolic acid) tensile strength is 40-70 MPa, Young's modulus is 2-4 GPa and elongation at break is 2-6% [12]. The typical molecular weight of PLGA is around 10-150 kDa [4,6].

Because lactic acid contains a hydrophobic methyl side group, it is less hydrophilic than glycolic acid [9]. PLGA polymers with higher lactic acid content are more hydrophobic and therefore absorb less water, resulting in slower degradation [6]. However, PLGA polymers with a 50:50 ratio show the fastest degradation rate [10]. For poly(D,L-lactide-co-glycolic acid) with a ratio of 50DL/50G, the degradation time is 1-2 months, whereas for (85L/15G) poly(lactic-co-glycolic acid) it is 12-18 months [12].

Crystallinity is a factor that affects multiple properties such as mechanical, thermal and degradation [6]. Poly(L-lactic acid) (PLLA) is a semicrystalline polymer, poly(D,L-lactic acid) (PDLLA) and poly(D-lactic acid) (PDLA) are amorphous, and poly(glycolic acid) (PGA) is a crystalline polymer [9,13]. PLGA with L-lactic acid (PLLGA) forms a semicrystalline copolymer, whereas PLGA with D-lactic acid (PDLGA) is typically amorphous, and poly(D,L-lactic-co-glycolic) acid can be either [6]. Higher glycolic acid content increases crystallinity of PLGA and usually results in better mechanical properties [6].

The glass transition temperature of PLA is around 60°C and of PGA around 35-40°C, with the higher glass transition temperature of PLA resulting from the bulkier lactic acid units [14]. The glass transition temperature of PLGA is typically between the glass transition temperatures of PLA and PGA, and can be adjusted by changing the LA:GA ratio [6]. The glass transition temperature of PLGA is typically higher than the usual body temperature of 37°C, and increases with higher molecular weight and higher PLA content [4]. Below the glass transition temperature, PLGA is glossy and has a rigid structure [4]. Melting temperature of PLGA depends on the crystallinity, LA:GA ratio and molecular weight [6]. The melting temperature of semicrystalline PLGA is usually between PLA's melting temperature of 150-180°C and PGA's melting temperature of 220-230°C, whereas amorphous PLGA does not have a sharp melting point [6].

2.2 PLGA as an implant material

PLGA is one of the most widely used and investigated synthetic biodegradable polymers in clinical applications such as implantable medical devices and drug delivery systems [7]. PLGA is a bioinert material and considered a resorbable polymer, meaning that it can be broken down and metabolized by the host body [6], making it a suitable material for degradable implants. A key advantage of PLGA is that it has been approved for multiple clinical applications by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [15]. PLGA-based clinical devices and products have been developed and commercialized from the 1990s, and over 20 grades of PLGA have been FDA-approved for implant and drug delivery device manufacture since [6].

Considering medical use, one of the most significant advantages of PLGA is its tunability. The physical and chemical properties of the polymer can be adjusted by modifying several parameters, including the copolymer ratio of lactic acid to glycolic acid, molecular weight, crystallinity, and end-group chemistry [6]. These parameters influence important characteristics such as degradation kinetics, mechanical strength, hydrophilicity, and thermal properties [6]. Therefore, PLGA materials can be tailored to meet the requirements of specific biomedical applications. For example, PLGA with a lower molecular weight typically shows faster degradation and reduced mechanical strength, making it suitable for short-term applications such as drug delivery systems [6]. In contrast, high molecular weight PLGA shows improved mechanical stability and a longer degradation time, which is more suitable for structural implants that must maintain their integrity for longer [6].

Another important advantage of PLGA is its processability. The polymer can be fabricated into a wide range of structures and geometries using various manufacturing techniques, including solvent casting, extrusion, electrospinning, and additive manufacturing [6]. This versatility allows PLGA to be produced in forms such as films, fibres, microspheres, porous scaffolds, and three-dimensional implants [6]. As a result, PLGA can be adapted for diverse biomedical applications ranging from tissue engineering scaffolds to controlled drug delivery implants.

2.3 Other biodegradable polymers for medical use

In addition to PLGA, several other resorbable polymers are used in implants, including polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), polydioxanone (PDO) and poly(b-hydroxybutyrate) (PHB) [6]. As previously discussed, the chirality of lactic acid causes PLA to exist in the different forms PLLA, PDLA, and PDLLA. Among these, PLLA and PDLLA have shown the most promise to biomedical applications [16]. PLLA exhibits relatively high tensile properties among the most used biodegradable polymers [14], with a reported mechanical strength of 4,8 GPa [16]. PLLA has a slow degradation rate and high molecular weight PLLA can require more than five years to fully degrade *in vivo* [16]. Consequently, PLLA is primarily used in long-term biomedical applications [16].

In contrast, PGA degrades rapidly, with significant strength loss occurring in 1-2 months [17], making it most suitable for short-term applications [16]. PGA exhibits a high tensile strength of 12,5 GPa [16]. PGA's degradation product, glycolic acid, can be metabolized through the Krebs cycle, but high amounts of glycolic acid have been associated with an inflammatory response [16]. PDO exhibits intermediate degradation behaviour, typically degrading completely in 6-12 months [16]. It has a low modulus of 1,5 GPa and high flexibility, which has resulted in it being widely used in suture materials [16].

PCL has a very slow degradation rate with degradation occurring over 24-36 months, making PCL suitable for long-term applications [14]. However, the slow degradation rate causes difficulty in predicting the degradation behaviour [6]. PCL has a relatively low tensile strength of 23 MPa, but has exceptionally high elongation at break, reported to reach over 4000% [14]. PCL is highly elastic and tough, but it is also brittle and has limited thermal stability [3].

Similarly, PHB degrades slowly and is used for long-term tissue engineering applications [16]. However, PHB is relatively brittle and has a higher melting temperature compared to other resorbable polymers, and is therefore more difficult to process [6]. The hydrolytic degradation of PHB produces D-3-hydroxybutyric acid, which is a component of blood and is therefore nontoxic [16].

Additionally, more options and properties can be achieved by copolymerization and polymer blending. PLGA stands as an example of copolymerization of PLA and PGA to tailor degradation rates and mechanical properties. Similarly, PCL or PHB can be copolymerized with polymers such as PLLA or PLGA to modify the degradation or mechanical performance [16].

3 Fine-tuning the degradation and properties of PLGA

As discussed, the properties of PLGA can be tailored widely. In addition to the ratio of lactic and glycolic acid, the rate and mechanism of PLGA degradation are influenced by several factors, including molecular weight, crystallinity, monomer sequencing and end group chemistry [6,8]. The degradation of PLGA is primarily hydrolytic, although enzymatic degradation may contribute under certain conditions [6]. Therefore, the effects of enzymatic and inflammatory processes should also be considered for medical applications. Key factors influencing PLGA degradation are presented in Figure 2.

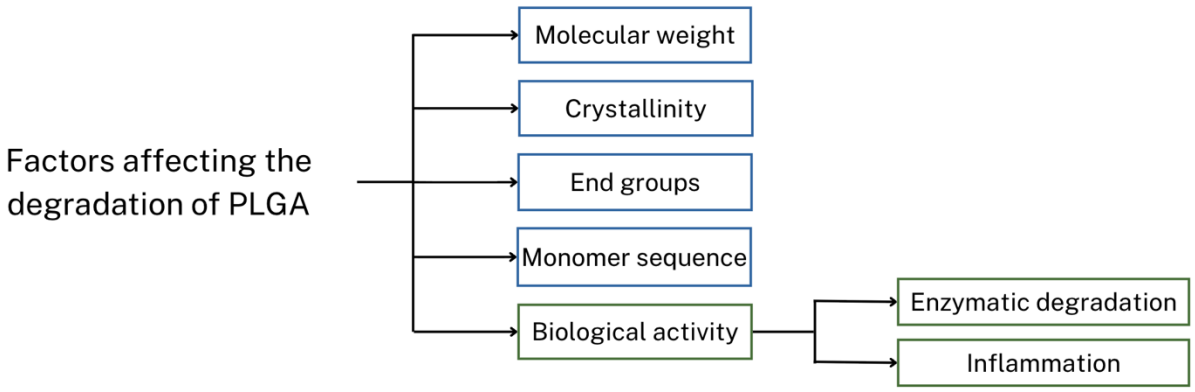

Figure 2. Factors affecting the degradation of PLGA

Understanding the factors that influence the degradation profile of PLGA allows for matching the degradation to the healing of the surrounding tissue [6]. Furthermore, the mechanical properties of PLGA depend not only on the ratio of lactic and glycolic acid but also on interrelated factors such as molecular weight and crystallinity [6]. The mechanical properties change as degradation progresses [6], emphasising the importance of understanding the degradation behaviour in implant design.

3.1 Molecular weight

The average molecular weight (molecular weight, Mw) affects both physical and thermal properties of PLGA polymers. The molecular weight of the polymer is strongly influenced by the polymerization method [7]. Molecular weight affects the mechanical strength of PLGA and is also related to the polymer's crystallinity, glass transition temperature and melting point [2]. For example, the glass transition temperature generally decreases with

decreasing molecular weight [2]. Furthermore, higher molecular weight polymers usually exhibit increased crystallinity [7].

Molecular weight is directly related to the viscosity of PLGA [2]. Higher molecular weight generally leads to higher viscosity, which presents as better strength and durability of the polymer [6]. This increase in viscosity for high-molecular-weight polymer is a result of stronger intermolecular interactions and a higher degree of chain entanglement in the polymer matrix [6]. It has been reported that the tensile strength, yield strength and Young's modulus of PLGA decrease with decreasing molecular weight [18]. A higher degree of chain entanglement distributes the applied stress, limits the movement of individual chains and allows for more plastic deformation and absorption of energy before failure [13].

In a study regarding the properties of PLGA films with a ratio of 53:47 under *in vitro* conditions, it was reported that the PLGA film with a molecular weight of 110 kDa exhibited a Young's modulus of 3,7 MPa and tensile strength of 5,60 MPa [18]. In comparison, PLGA film with a molecular weight of 20 kDa had a Young's modulus of 0,6 MPa and tensile strength of 0,32 MPa [18]. Although these are low values compared to general values for 50:50 PLGA (tensile strength 40-50 MPa and Young's modulus 2-4 GPa [12]), they present the trend of PLGA's mechanical strength decreasing with its molecular weight.

The degradation time of PLGA is affected by interrelated factors such as LA:GA ratio, crystallinity, glass transition temperature and the polymer's molecular weight [2]. The molecular weight is directly related to the chain size of the polymer [2]. The longer chains of a high-molecular-weight polymer matrix require more chain scission for degradation, resulting in a slower degradation rate [6]. The stronger intermolecular bonding of high-molecular-weight polymer chains also allows less water penetration, resulting in slower hydrolysis [6]. Moreover, the molecular weight reflects the relative amount of chain ends and end groups available to promote hydrolytic degradation [19]. The molecular weight decreases as hydrolysis proceeds, further increasing the degradation [6].

In addition to molecular weight, crystallinity also influences PLGA's degradation behaviour. Crystallinity is affected by the stereochemistry of the lactic acid used in PLGA,

in addition to the LA:GA ratio [6]. Crystalline regions degrade more slowly than amorphous regions due to their stronger intermolecular bonds and dense structure, which limit water penetration and hydrolysis [6]. Consequently, degradation occurs first in the amorphous regions of PLGA [13]. This results in an increase in the relative crystallinity during hydrolysis, with the addition of increased mobility of forming shorter chains, possibly contributing to the formation of new crystalline structures [13]. During hydrolysis, as crystallinity increases and molecular weight decreases, the glass transition temperature decreases [13].

3.2 End group functionalization

The chemistry of the ends of polymer chains also affects the degradation of PLGA [6]. End groups are the functional groups located at the ends of polymer chains. While molecular weight strongly affects the mechanical properties and the glass transition temperature, end group functionalization has a greater effect on water absorption, mass loss and degradation kinetics [18]. The end groups are formed during polymerization and depend on the initiator and catalyst used, but can also be modified after polymer synthesis [11].

PLGA is most commonly terminated with carboxylic acid (-COOH) or ester (-COOR) groups [6]. The effect of end groups is largely based on their influence on hydrophilicity. Ester-terminated (end-capped) PLGA is more hydrophobic, which reduces water uptake and slows degradation, making it more suitable for long-term applications [6]. In contrast, acid-terminated PLGA is more hydrophilic due to the presence of carboxylic acid groups, which accelerate water uptake and degradation [18]. A certain study presented that acid-terminated PLGA films went through water absorption and mass loss in roughly half the time of ester-terminated films [18].

It has been reported that the ester or acid-termination affects water adsorption and degradation significantly, but does not remarkably change mechanical properties or glass transition temperature [18]. In addition, PLGA can also be functionalized with hydroxyl (-OH) (uncapped PLGA) and amine (-NH_2) end groups, and for example alkyl chains such as n-hexyl, dodecyl or hexadecyl [15,20]. Studies indicate that hydroxyl-terminated (-OH) PLGA exhibits slower degradation than acid-terminated and amine-terminated PLGA [20]. In addition, amine-terminated (-NH_2) PLGA has higher

hydrophilicity and accelerated degradation compared to acid-terminated and hydroxyl-terminated PLGA [20]. The order of degradation times of these end groups from fastest to slowest degradation would be amine (-NH_2), carboxylic acid (-COOH), hydroxyl (-OH) and ester (-COOR), respectively [18,20].

End groups are closely related to the autocatalysis of PLGA degradation. As PLGA degrades through the hydrolysis of its ester bonds, each ester bond cleavage causes formation of two new hydrophilic end groups, hydroxyl (-OH) and carboxylic acid (-COOH) [19]. The formation of these groups as degradation progresses enhances water uptake and accelerates hydrolysis. This is supported by observations that esterification of carboxylic ends slows degradation [11].

3.3 Monomer sequence

The degradation behaviour of PLGA is influenced by the sequencing of lactic acid and glycolic acid along the polymer chain [6]. In random PLGA, lactic acid and glycolic acid units are distributed irregularly in varying-sized blocks of the same monomers, whereas in sequenced PLGA, the LA and GA units are in segments that continue the same size along the chain [21]. Sequenced PLGA can also be alternating, with singular LA and GA units alternating along the chain [21]. Random PLGA degrades fast initially, as GA units degrade first, and the degradation continues more slowly as LA units remain to degrade [6]. Sequenced PLGA offers a more steady and controlled degradation rate [6]. Despite affecting the degradation rate, sequence information is not typically widely provided by manufacturers [22].

The hydrolysis of linkages between monomers occurs at different rates, which significantly affects the degradation rates between sequenced and random polymers [21]. LA-LA linkages exhibit the slowest hydrolysis and GA-GA linkages the fastest, while LA-GA and GA-LA linkages both exhibit intermediate rate [21]. In addition, the stereochemistry matters as PLGA with only L-lactic acid degrades more slowly than a racemic with both L- and D-lactic acid [21]. It was demonstrated in a study that after four weeks, randomly sequenced racemic PLGA with a 50:50 ratio had largely degraded, while sequenced 50:50 PLGA with glycolic acid units alternating with L-lactic acid units showed barely any degradation [21].

3.4 Enzymatic degradation

As previously stated, PLGA degrades primarily through hydrolysis, in which water cleaves its ester bonds, leading to polymer degradation. However, enzymatic activity may also influence the degradation behaviour of PLGA [6]. PLGA has been observed to degrade faster *in vivo* than *in vitro*, which could be explained by the fact that *in vitro* models do not fully account for factors such as enzymatic activity, immune responses and fluid flow, that are present *in vivo* [6]. Varying information about the significance of enzymatic degradation is available in the literature. Enzymatic degradation is commonly regarded as secondary to hydrolysis [23]. The degradation pathways of hydrolysis and enzymatic degradation of PLGA are presented in Figure 2.

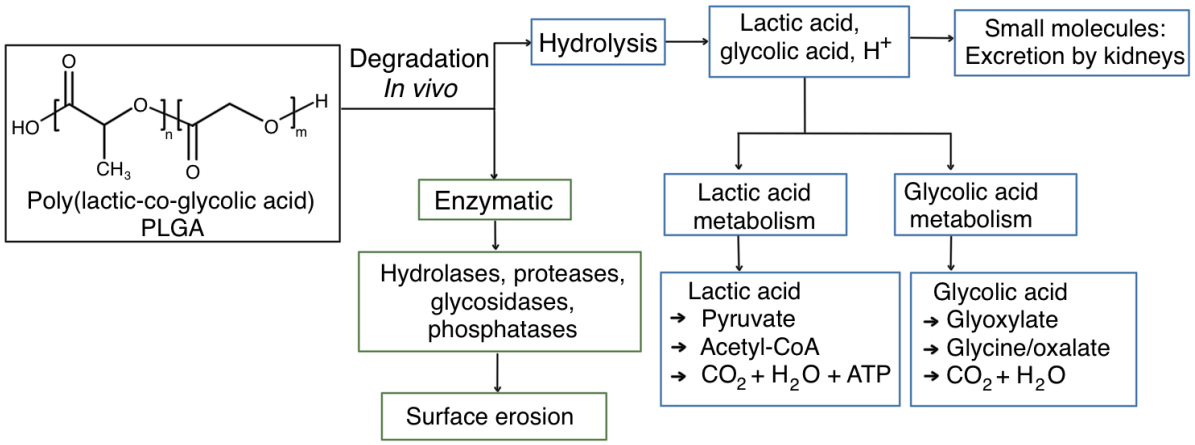

Figure 3. The pathways of hydrolytic and enzymatic degradation of PLGA in vivo. Modified from Das et al. [6].

Due to the hydrophilic nature of enzymes, they exhibit limited penetration into the hydrophobic polymer matrix [23]. Consequently, enzymes and proteins remain mostly on the polymer's surface while water penetrates the polymer matrix, leading to pronounced surface erosion compared to *in vitro* conditions [6]. Since enzymatic degradation mainly occurs at the polymer surface, the polymer surface area is considered a critical factor influencing its contribution to overall degradation behaviour [23].

The literature presents varying information about the mechanisms of enzymatic degradation of PLGA. It has been presented that certain enzymes, such as trypsin, may affect the degradation of PLGA by enhancing the dissolution and removal of degradation

products from the polymer matrix, rather than by accelerating ester bond cleavage [23]. Other studies suggest that the presence of hydrolase enzymes, such as lipases and some esterases, can catalyse ester bond cleavage [24]. It has also been demonstrated that lipase degradation is temperature-dependent, with the highest degradation occurring at 28°C and decreasing with higher temperatures of 37°C and 50°C [24].

3.5 Inflammation

Implantation of PLGA into the human body causes a mild inflammatory response, distinguished by the presence of white blood cells, such as lymphocytes, plasma cells, monocytes and macrophages [11]. This local inflammation arises as a response to the implant being a foreign body [9]. In addition, inflammation can be promoted by the acidic degradation products of PLGA [6]. Elevated levels of these degradation products, lactic acid and glycolic acid, have been associated with causing an inflammatory reaction [16,25]. The accumulation of acidic degradation products can lower the local pH, which can accelerate the hydrolysis and promote the autocatalytic degradation of PLGA [9]. The physiological environment, which can change due to inflammation, can cause variation to the degradation rate [26].

The foreign body response is mainly regulated by macrophages, which have been suggested to accelerate polymer degradation [26]. Macrophages attach to the surface of PLGA [27] and, along with other phagocytes, synthesize reactive oxygen species (ROS) and enzymes such as lipases [28]. Macrophages can also form foreign body giant cells (FBGC), which release ROS, enzymes and acids that cleave the polymer chains to promote degradation [28]. The activity of macrophages and FBGCs has been demonstrated to cause surface erosion of PLGA [27]. However, other studies have indicated that inflammation does not significantly affect the degradation rate of PLGA [26]. It is also worth noting that macrophages introduced by the inflammatory reaction produce cytokines, which participate in tissue regeneration and wound healing, which is beneficial for healing of the implant site [27].

4 Sterilization of implantable biodegradable polymers

Sterilization is the destruction or removal of all living cells, viable spores, viruses and viroids from an object [29]. Sterilization of implantable medical devices is necessary to prevent infection and ensure the safety of the implantable device and the patient. Sterilization is a factor to be considered in the development, and needs to consider both the bulk material of the device and the packaging [30]. The sterilization of medical devices can be categorised into terminal sterilization and aseptic processing [29]. Terminal sterilization refers to a method in which sterilization is performed on the final product inside its packaging container as the final step of the manufacturing process, while aseptic processing means of fabrication from sterile materials in a sterile environment [30]. Due to aseptic processing being expensive, terminal sterilization is the preferred method [29]. The sterilization efficiency is evaluated with the Sterility Assurance Level (SAL), which is 10^{-6} for implantable devices, meaning that no more than one viable microorganism is present in one million sterilized items [29].

4.1 Sterilization methods

Polymers have their limitations as implantable medical device materials when it comes to sterilization, as not all sterilization methods are suitable [21]. Terminal sterilization can be further divided into chemical and physical methods [30]. Physical methods include dry and steam-based heat treatments and ionizing radiation, while chemical methods sterilize through chemical agents like ethylene oxide, hydrogen peroxide and ozone [30]. Established sterilization methods used for polymer-based implantable medical devices include dry heat, steam, ethylene oxide, radiation, hydrogen peroxide, and ozone sterilization (Figure 4) [29].

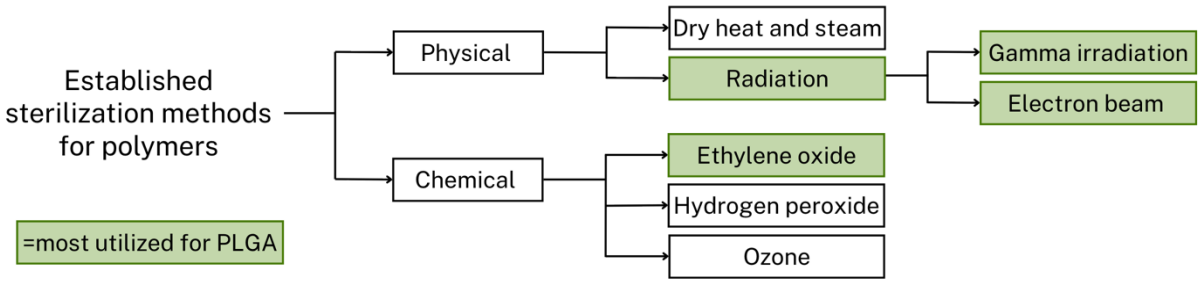

Figure 4. Established sterilization methods for polymers and the most utilized methods for PLGA

4.1.1 Physical sterilization methods

Dry heat sterilization is based on the coagulation of proteins as a result of the product being placed in an oven at a high temperature of around 160°C for a few hours [29]. As a heat-based method, the applicability is limited for biomaterials [30]. Dry heat sterilization is a functioning method for heat-resistant polymers, but not for heat-sensitive PLA, PGA or PLGA [29]. Similarly, steam sterilization also utilizes high temperature, combining heat (around 120°C) with moisture and pressure using an autoclave, causing coagulation and denaturation of enzymes and proteins [29]. Heat- and moisture-resistant polymers can be treated with steam sterilization, but it may cause thermal degradation and hydrolysis in sensitive polymers such as PLGA [29]. Since the glass transition temperature of PLGA is between 30 and 60°C, heat-based sterilization methods may cause thermal transitions and major structural damage in PLGA [6,31].

Ionizing radiation sterilization refers to gamma sterilization or electron beam sterilization, both of which utilize high-energy radiation [29]. Gamma sterilization utilizes ionizing gamma rays, typically from Cobalt 60 [31]. Electron beam sterilization uses a constant stream of fast-accelerating electrons [29]. Both gamma irradiation and electron beam irradiation are relatively quick methods and use an average dose of 25 kGy of radiation at room temperature [31]. Radiation sterilization functions by directly damaging the DNA or the formation of free radicals, which damage the DNA and prevent the survival of microorganisms [31].

Irradiation may break molecular bonds and cause chain scission, depending on the bond strength of the polymer [29]. In addition, the free radicals generated from irradiation can promote cross-linking of the polymer [29]. Irradiation-induced changes in the polymer structure may alter the mechanical and thermal behaviour and the degradation of polymers [31]. It has been reported that gamma irradiation can affect mechanical properties such as Young's modulus of lactide-based polymers [32]. However, studies have shown that gamma irradiation does not significantly change the mechanical strength of PLGA, but the resulting decrease in molecular weight can accelerate the degradation rate and therefore decrease the time it holds its required strength [32]. Studies have suggested that a low temperature and an oxygen-free environment could

reduce the harmful impacts of gamma irradiation on polymers, but temperature was found to be insignificant in the case of PLGA [32]. However, the oxygen-free environment has shown promise in reducing the damage to PLGA [33].

Gamma irradiation has a very high penetration power into most materials, but the dose and the distribution are difficult to control, which often leads to a wider range of received doses [30]. The electron beam offers better control over the radiation dose and the possibility to control the beam through the electric current used to accelerate the electrons [30]. However, electron beam typically exhibits reduced penetration compared to gamma irradiation [31]. Electron beam sterilization can be classified into high-energy electron irradiation (HEEI) and low-energy electron irradiation (LEEI) based on the acceleration voltage of the electrons, with the limit being 300-500 keV [30]. In a study where LEEI was compared to gamma irradiation, it was found that LEEI and gamma irradiation produce similar changes to material properties, but LEEI offers better control of the irradiation dose, allowing for prediction and planning of the changes [30].

4.1.2 Chemical sterilization methods

Ethylene oxide (EO) is a chemical lower-temperature sterilization method suitable for heat-sensitive materials [29]. Ethylene oxide's boiling point is 10.4°C, allowing EO gas sterilization to be executed at temperatures around 30-60°C, within a humid chamber [29]. Ethylene oxide's sterilizing effect is based on alkylating the DNA's nitrogenous backbone [31]. EO gas reacts with functional groups on proteins and DNA, such as carboxyl (-COOH), hydroxyl (-OH) and amino ($-NH_2$) groups, disrupting and damaging the structure [29]. Ethylene oxide sterilization has more gentle processing conditions compared to dry heat, steam and radiation-based methods and has relatively minor effects on polymer degradation [29].

However, the applicability depends on the chemistry of the polymer, as EO can react with functional groups and cause changes in the chemical structure and mechanical properties [31]. In addition, the possible residue left from the sterilization process is toxic and carcinogenic, as it can react with the DNA of the host [31]. The sterilization temperature of ethylene oxide is close to the glass transition temperatures of PLGAs constituents PLA and PGA. Thereby, the temperature of EO sterilization can result in

structural changes in PLGA, and the presence of humidity can promote hydrolytic degradation [32].

Hydrogen peroxide (H_2O_2) is a chemical sterilant used as either vaporised hydrogen peroxide (VHP) or hydrogen peroxide plasma (HPP) for sterilization [29]. The sterilizing effect of hydrogen peroxide is due to the generation of reactive oxygen species (ROS), which damage DNA, proteins and other essential cellular components [31]. VHP sterilization takes approximately 1,5 hours at 25-50°C, while HPP sterilization lasts 1-3 hours at 40-65°C [29]. For comparison, vaporised hydrogen peroxide has lower penetration than ethylene oxide and affects polymers more than hydrogen peroxide plasma [29].

Hydrogen peroxide is less widely applicable for polymers than ethylene oxide due to its strong oxidising nature [29], as oxidation may also affect the degradation of polymers [34]. Hydrogen peroxide sterilization has been reported to affect the mechanical and degradational behaviour in degradable polymers [31]. Hydrogen peroxide is a faster process and leaves no toxic residue compared to ethylene oxide [29]. However, hydrogen peroxide offers limited penetration and is commonly utilized as a surface sterilization method [29].

Ozone (O_3) sterilization is a chemical process that destroys pathogens with oxidation [29]. Sterilization with ozone is performed at 30-35°C in cycles for approximately 4.5 hours [31]. Ozone sterilization can be applied to polymers that are resistant to oxidation [29]. Ozone sterilization can be applied to polymers such as polyesters, although it may affect their degradation behaviour and biomechanical properties [31]. Ozone sterilization offers a lower penetration power compared to ethylene oxide, and is more suitable for surface sterilization [29].

Moreover, novel sterilization techniques include vaporized peracetic acid, ultraviolet light, high-intensity or pulse light, microwave radiation, and sound-wave sterilization [29]. However, these methods are not established and therefore do not have sufficient validation, increasing the regulatory burden of the manufacturer [31].

4.2 Sterilization of PLGA-based implantable devices

The sterilization of PLGA-based implantable devices presents a challenge, as PLGA is susceptible to structural changes and changes in degradation behaviour when exposed to heat, moisture and irradiation [5]. Moreover, the sterilization method must be sufficiently effective to ensure the required sterilization level (SAL) [31]. Therefore, the selection of a sterilization method for PLGA requires considering sterilization efficacy and stability of the polymer. Due to the relatively low glass transition temperature of PLGA and its tendency to hydrolytic degradation, heat- and steam-based methods are generally unsuitable [29].

Gamma sterilization is one of the most utilized methods for biodegradable polymers [30]. Gamma sterilization's advantages are its high penetration power and relatively low temperature [31]. However, the high energy of gamma irradiation can cause chain scission, leading to a lowering of molecular weight and accelerating the degradation of PLGA-based devices [32]. The decrease of molecular weight is dependent on the irradiation dose [30]. The standard dose for gamma irradiation is 25 kGy, which is considered to ensure sufficient sterilization [35]. Lowering the dose could limit the degradation resulting from irradiation, since the reduction of molecular weight increases with the irradiation dose [35]. However, for lower dosages such as 15 kGy, it must be validated that the required sterilization level (SAL) is achieved [35].

Similar to gamma irradiation, electron beam sterilization occurs at room temperature and is, in that regard, suitable for PLGA sterilization [29]. Electron beam has similar effects on the degradation of PLGA as gamma irradiation [31]. The dose can be more precisely controlled, but the penetration power is limited compared to gamma irradiation [30]. Ethylene oxide is also widely utilized in the sterilization of biodegradable polymers, as it is a gentle method compared to irradiation [29]. However, ethylene oxide sterilization is performed in temperatures similar to PLGA's glass transition temperature and in relatively high humidity, requiring careful control of the process conditions to ensure its suitability for PLGA [32]. Furthermore, the possible residue absorbed or left from the chemical sterilant raises a risk for biocompatibility [31].

5 Conclusions

Biodegradable polymers represent an advancement in the development of medical implants. Materials such as poly(lactic-co-glycolic acid) (PLGA) offer the ability to degrade *in vivo* into harmless by-products, primarily carbon dioxide and water, which are naturally eliminated from the body. As a result, PLGA-based devices are completely bioresorbable, eliminating the need for surgical removal and enabling them to be utilized in support of the body's natural healing processes.

The properties of PLGA are strongly influenced by the composition of its constituent monomers, lactic acid and glycolic acid. PLGA degrades primarily through hydrolysis of its ester linkages, after which the resulting monomers are metabolized by the tricarboxylic acid cycle. However, the degradation rate and mechanism of PLGA depend on a combination of interrelated factors. Understanding the factors behind the degradation and mechanical properties is essential for designing implants with appropriate mechanical behaviour and controlled degradation profiles.

Among these factors, chain length determines molecular weight, the entanglement of the bonds and the viscosity of the polymer. Molecular weight also describes the amount of chain scission required for degradation. Higher molecular weight PLGA exhibits longer degradation times and increased mechanical strength. In addition, crystallinity affects the water diffusion to the polymer matrix, with more crystalline regions degrading more slowly than amorphous regions. End-group functionalization affects the hydrophilicity of the polymer. Commonly, ester end groups decrease hydrophilicity and degradation rate, whereas acid termination accelerates degradation. Moreover, the sequence distribution of lactic and glycolic acid units affects the degradation rate, since the linkages between glycolic acid units degrade fastest and the linkages between lactic acid units the slowest.

Many studies of the degradation of PLGA are done *in vitro*. However, in a biological environment, enzymatic activity and inflammation may affect the degradation rate and method of PLGA. Variable information on the enzymatic degradation of PLGA is available, but it has been suggested that enzymatic activity may contribute to surface erosion and removal of degradation products. Inflammatory responses can lower the local pH and introduce macrophages and other white blood cells, which may cause surface erosion.

The influence of enzymatic and inflammatory processes on the degradation of PLGA has limited evidence and remains an area for further investigation.

The sterilization of PLGA-based devices requires evaluating the effectiveness and the harmful impact of the sterilization methods. PLGA's glass transition temperature and hydrolytic degradation behaviour make it not suitable for heat- and steam-based sterilization methods. Gamma irradiation is a commonly utilized method for the sterilization of PLGA-based devices. It offers efficacy and a high penetration power. However, gamma irradiation affects the mechanical properties and degradation behaviour in a dose-dependent way. While reducing the dose from the standard dose of 25 kGy to a lower dose, such as 15 kGy, would reduce the chain scission, achieving the required sterility assurance level must be ensured.

Electron beam irradiation offers improved dose control and faster process, but its limited penetration depth restricts its use. Similarly to gamma irradiation, it causes chain scission. Ethylene oxide presents a chemical alternative for sterilization at a relatively low temperature. However, for PLGA, its temperature and humidity conditions are not ideal. The possible chemical residue left on or within the polymer from ethylene oxide treatment presents a challenge in toxicological safety and biocompatibility.

Overall, it seems that gamma irradiation shows the most promise as a method for large-scale sterilization of implantable PLGA-based devices. The possibility of lowering the irradiation dose shows promise for minimizing the polymer damage but requires further assessment. In addition, an oxygen-free environment in gamma irradiation may decrease the harmful effects. With fine-tuning of the polymer properties, understanding of the biological influences, and optimization of the sterilization method, PLGA offers a widely applicable material for implantable devices.

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