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REVIEW ARTICLE

Controlling Degradation Rate of Poly(lactic acid) for Its Biomedical Applications

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Abstract
Poly(lactic acid) (PLA) is widely used in many different biomedical applications due to its biocompatibility, complete biodegradability, and non-toxic degradation products. However, PLA may be limited in particularly long degradation, which is not always desirable in many biomedical applications. In this short review, we summarized some of the most recent studies on controlling the degradation rate of PLA, employing copolymerization, blending, additives and irradiation. This review discussed the pros and cons of those methods considering their applications to bioabsorbable fixation or drug delivery devices. We also suggested the design parameters for PLA treatment for its wide applicability to biomedical fields.

Keywords Poly(lactic acid), Biodegradation, Copolymerization, Polymer blends, E-beam radiation, Polymer additives

INTRODUCTION

Poly(lactic acid) (PLA) has been recognized as biodegradable polymer material used in a number of biomedical applications, including scaffolds, drug delivery and internal fixation devices [1-4]. PLA has attracted a great deal of interest due to its good mechanical properties paired with biocompatibility and biologically decomposed products that can be naturally metabolized *in vivo*, yielding carbon dioxide and water. Yet, the polymer isn't without its shortcomings, particularly, a slow degradation rate and long reabsorption time, complexity of variables affecting the degradation rate, and unpredictable elements in its degradation profile.

PLA undergoes hydrolysis and heterogeneous bulk degradation by the invasion of water into the material. PLA also exhibits a characteristically autocatalytic degradation. PLA degrades by cleavage of ester bonds, producing a hydroxyl end group and a carboxyl end group. The carboxyl group acts as a catalyst for hydrolysis during the degradation of the PLA. As the generated carboxyl groups cannot escape into the surroundings and thus, are trapped mostly inside the bulk of PLA, the autocatalytic nature often results in faster degradation of the inside of a PLA component. For this reason, PLA characteristically degrades from the inside-out, giving hollow and porous structures before complete bioabsorption [2].

As PLA would fully degrade under the lifespan of the host with a loss of tensile strength on the time scale of weeks and complete degradation in years [5], controlling this degradation rate is now considered as one of the important parameters to determine its applicability in certain biomedical areas. In most cases for PLA applications, the timescale of a full mass degradation is considered too long, which often takes years until complete bioabsorption [6]. Therefore, on-going research is trying to find ways to increase the degradation rate (i.e., faster degradation) while not decreasing the polymer's biocompatibility. The rate of degradation is influenced by many characteristics of the polymer, including morphology and chain orientation, initial crystallinity, molecular weight, presence of residual monomers and oligomers, size and shape, and purity [2]. As PLA and other aliphatic polyesters find more and more applications in the biomedical field, new studies are appearing trying to control this degradation rate, hoping to make the selection and processing of PLA less complex for medical device design [7].

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This review will cover some of the recent studies pursuing to improve the degradation profile of PLA, first reviewing the methods found to increase the degradation rate of PLA in a predictable way. We will cover the modifiable properties of PLA as a pure material, including the ways to adjust the degradation rate and to induce a homogenous degradation profile [8]. Next, we will briefly describe certain additives, copolymers, and blends which create the proper environment for catalyzing PLA degradation [2, 9-12]. and to use E-beam radiation creating surface erosion behavior [13]. These enhancements show promise for the future of aliphatic polymers, encouraging more widespread use for various biomedical applications.

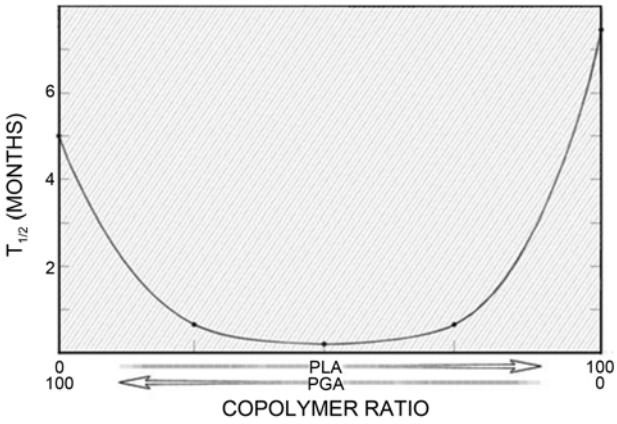

Fig. 1. The relationship between the degradation half-life of PLGA and the lactide-glycolide ratio (reprinted with permission from [4]).

METHODS FOR CONTROLLING DEGRADATION RATE

Early in the study of PLA, many researchers successfully increased the degradation rate by changing the polymer itself, i.e., by changing the PLA structure to suppress crystallization and increase the concentration of terminal groups in order to increase the hydrolysis rate. Also, the amorphous quality of copolymerizing with poly(D,L-lactic acid) (PDLLA) to provide poly(L-lactic-D,L-lactide) (PLDL) was shown to intrinsically increase hydrolysis due to the preferential degradation of amorphous regions in the first phase of degradation of poly(lactic acid)-based devices. Regardless, the poly(L-lactic acid) (PLLA) and PLDLA polymers exhibited comparably slow degradation rates, still taking a number of years for complete erosion [14]. The size and shape of the device itself can also change the degradation profile of the polymer. Whereas PLA is known for heterogeneous bulk degradation, the devices of small size or large surface area-to-volume ratio can yield homogeneous degradation through the whole device. For example, thin fibers, microspheres, and thin films have all been reported to show homogenous bulk degradation [8].

Copolymerization

Researchers took on a copolymerization approach to control the degradation rate of PLA. Namely, copolymers of lactic and glycolic acids (PLGA) have shown promise as the ratio of lactic acids and glycolic acids can determine the degradation rate of polymer. The degradation mechanism of poly(glycolic acids) (PGA) is the same as PLA, but PGA is known for a much higher degradation rate than PLA. Copolymerization showed a decrease in degradation time over both PLA and sometimes PGA, depending on the ratio of the two polymers: the fastest degradation with a 50:50 lactide-glycolide ratio, showing a degradation half-life of as short as a few weeks. This increased degradation rate is most likely due to a less-hydrophobic nature of PGA and the autocatalytic properties of copolymers. However, as shown in Fig. 1, this relationship between the degradation rate and composition ratio is not simple, giving a wide range of degradation half-life periods from weeks to years, and varied mechanical properties. Furthermore, this rate not only depends on the composition ratio but also on crystallinity, polymer morphology, and molecular weight of the copolymer [2, 4].

Another strategy to increase the degradation rate of PLG includes incorporation of hydrophilicity into the polymer chains, employing the polymers, such as poly(ethylene glycol) (PEG) and poly(oxypropylene) (PPG). Copolymerizing with PEG or PPG adds more “soft” regions to the plastic (i.e., PLA) and thus, provides more amorphous regions, which are preferentially degraded during the first phase of semicrystalline aliphatic polyester degradation [15, 16]. The approaches, however, have the drawbacks in that such copolymerization often causes a significant change in mechanical property, that both PEG and PPG are not bioreabsorbable, and that PPG has poor biocompatibility.

Blending

Often PLA is blended with a number of polymers, including some of the polymers used for copolymerization. Polymer blends also affect the degradation rate often by influencing the first phase of degradation by affecting the crystallinity of the initial polymer matrix. Often these materials have a wide range of mechanical properties that have to be individually understood before used as a biomaterial [14]. Yet, there is a recent case which reported blends of PLA and poly(aspartic acid-co-L-lactide) (PAL) decrease the degradation time without significant influence on the mechanical properties. PAL can be produced without toxic catalyst and solvent, and it is degraded by hydrolysis, giving a degradation product, aspartic acid [17]. The results revealed that blending with PAL accelerated the degradation due to hydrophilicity of

aspartic acid units and the additional terminal carboxylic acid groups in the lactide component of PAL, thereby an increase in degradation rate with an increase in the incorporated amount of PAL. PAL was also reported to not show a hygroscopic nature, hence no need of special packaging and handling, often required for PLA or PLGA polymers [17-19].

Additives

A number of additives have been introduced in order to increase the degradation rate. In general, the addition of acidic elements to the polymer acts as a catalyst for degradation while addition of some basic components can either increase or decrease the degradation rate [2, 10]. Other additives act as plasticizers, changing both the mechanical properties and degradation properties. Some plasticizers are water soluble, such as citrate esters, which diffuse out of the polymer bulk to provide a porous structure for rapid water infiltration, thereby increasing the degradation rate [9]. Though additives may be beneficial for certain applications, the decrease in mechanical strength is still a major hindrance and many additives often have unpredictable effects on the degradation rate.

In a recent study, lauric acid is added to increase the degradation rate of PLA, while showing the same degradation mechanism as pure PLA. Lauric acid is commonly used in soaps and as a food additive and can be found in strawberries. PLA containing 4.5% lauric acid (near the solubility limit of lauric acid in PLA) was shown to degrade at a much faster time scale, showing loss of tensile strength in 12 days. The addition of lauric acid plasticizes the PLA, causing a faster degradation rate, but the lauric acid appears not to leech out of the bulk for a period of over 100 days. Notably, there was a direct relationship between the concentration of lauric acid and the degradation rate of PLA, which could allow for easy medical device design based on PLA. Controlling the degradation times of PLA with lauric acid appeared to aid the healing process of weight-bearing applications: allowing the adequate mechanical support for a number of days until the loss of strength, and then the transfer of stresses to the wounded area without extended stress shielding. However, the challenge still remains as lauric acid is not yet approved for clinical use [11, 12].

Irradiation

The γ irradiation, commonly used to sterilize medical devices, increases the degradation rate of PLA by means of forming free radicals which react to each other, leading to chain transfer, subsequent splitting, and ultimately chain scission

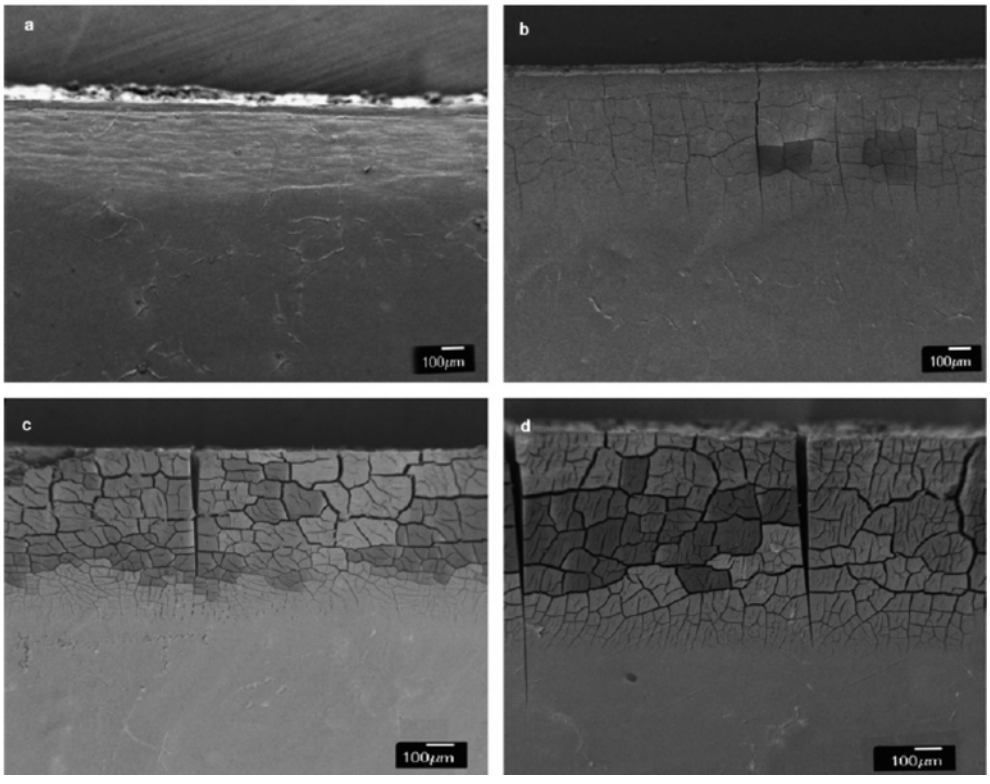

Fig. 2. SEM micrographs showing in vitro degradation after 17 days near the surfaces of (a) PLGA control (b) PLG treated with 150 kGy of irradiation and (c) PLG treated with 500 kGy of irradiation, and (d) PLG treated with 500 kGy of unshielded irradiation (reprinted with permission from [13]).

[2, 20]. Therefore, recent studies have utilized electron beam (e-beam) radiation to degrade the polymer and decrease the molecular weight, where the grade of this degradation is fairly controllable by the dose of radiation [21]. A mass loss study of stacks of PLA and PLGA sheets revealed that this degradation was more pronounced near the irradiated top of the stack [22]. Then, using this principle, pseudo-surface erosion was also enabled using the e-beam radiation technique [13]. This degradation profile was obtained by the penetration of e-beam radiation from one side of a 10-mm thick sample of PLGA or PLA. The molecular weight of the sample could be varied by distance, exhibiting the increased degradation rate near the irradiated regions of the sample, i.e., the surface (Fig. 2). These studies revealed the usefulness of utilizing radiation to change the morphology, molecular weight, and mechanical strength of the polymer, hence controlling its degradation profile.

DISCUSSION

PLA and PLA copolymers gained their popularity as a biomaterial because of desirable characteristics in mechanical strength, biocompatibility, and biodegradability. However, the low degradation rate of PLA polymers often impedes their applications especially requiring a relatively fast reabsorption, such as drug delivery devices and implantable fixation devices. One proposed device is an absorbable bone screw. If the screw degrades for a long time, the lifespan of the screw would outlive the healing period of the wound site, hindering wound repair. Particularly, copolymerization with PAL and use of an additive lauric acid have proven to be useful to increase the degradation rate, causing loss of strength of the polymer in less than 2 weeks, as opposed to months of intact PLA.This would provide a proper transfer of stress from the device to the healing site in a proper amount of time [11]. This stress was reported to trigger some of the anisotropic growth of human tissues.

Although the methods to control PLA degradation have been widely investigated, the issues still remain: the factors controlling degradation, such as copolymerization and additives, are rather complex and often not predictable. For example, one may be able to expedite the degradation at the early stage, but the autocatalytic degradation cannot be concurrently controlled. In this sense, although the increase in amount of added lauric acid or ratio of PAL in PLA facilitates the polymer degradation, more sophisticated control over the dimension of a PLA bulk in perspectives of a medical device may not be very easy. In addition, an undesirable hygroscopic nature often incorporated with a hydrophilic additive material possibly results in a significant reduction in shelf-life of the polymer product. Radiation produces a geometric variation of molecular weights through a PLA bulk (i.e., lower molecular weights at the irradiated surface than the center). With proper control, this variation can induces a surface erosion behavior, which may be advantageous for the medical devices needing a gradual volume change or drug release starting from the surface. Although the radiation technique is known to not affect inherent biocompatibility of PLA, the method may not be applicable to the devices loaded with the bioactive ingredients susceptible to degradation by irradiation.

In conclusion, “rule of thumb” enhancements of PLA degradation are often employed to broaden the usability and applicability of PLA-based medical devices. The techniques for enhancing degradation should not interfere with the desirable properties of PLA itself, particularly its initial mechanical properties and biocompatibility. Therefore, future research is suggested to focus on finding the methods or materials to be incorporated that can change the degradation profile in a more sophisticated pattern possibly without affecting the bioactive components carried by PLA-based devices. In this way, PLA can easily become a go-to polymer with wide applicability to biomedical fields.

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