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Impact of polymer structure and composition on fully resorbable endovascular scaffold performance

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Abstract

Fully erodible endovascular scaffolds are being increasingly considered for the treatment of obstructive arterial disease owing to their potential to mitigate long-term risks associated with permanent alternatives. While complete scaffold erosion facilitates vessel healing, generation and release of material degradation by-products from candidate materials such as poly-L-lactide (PLLA) may elicit local inflammatory responses that limit implant efficacy. We developed a computational framework to quantify how the compositional and structural parameters of PLLA-based fully erodible endovascular scaffolds affect degradation kinetics, erosion kinetics and the transient accumulation of material by-products within the arterial wall. Parametric studies reveal that, while some material properties have similar effects on these critical processes, others induce qualitatively opposing responses. For example, scaffold degradation is only mildly responsive to changes in either PLLA polydispersity or the initial degree of crystallinity, while the erosion kinetics is comparatively sensitive to crystallinity. Moreover, lactide doping can effectively tune both scaffold degradation and erosion, but a concomitant increase in local byproduct accumulation raises concerns about implant safety. Optimized erodible endovascular scaffolds must precisely balance therapeutic function and biological response over the implant lifetime, where compositional and structural parameters will have differential effects on implant performance.

Keywords

Degradation; Erosion; Poly-L-lactide; Lactic acid; Endovascular

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Appendix A. Figures with essential colour discrimination

Certain figures in this article, particularly Fig. 1, are difficult to interpret in black and white. The full colour images can be found in the on-line version, at <http://dx.doi.org/10.1016/j.actbio.2012.12.011>.

1. Introduction

Poly-L-lactide (PLLA) is a bioresorbable polymer considered for multiple clinical applications due to generally acceptable biocompatibility and tunable physicochemical properties [1,2]. It is currently used in the fabrication of resorbable sutures, wound healing scaffolds, orthopedic fixation devices and controlled drug/gene delivery systems [3–5]. Resorbable endovascular scaffolds composed primarily of PLLA have been recently proposed as an alternative to permanent metallic devices [6]. Like traditional stents, resorbable scaffolds can provide sufficient structural support to prevent acute vessel renarrowing and serve as a platform for the controlled release of anti-proliferative or anti-inflammatory drugs. Additionally, resorbable scaffolds have the inherent potential to reduce the occurrence of untoward events, such as vessel renarrowing or thrombosis, by virtue of undergoing complete resorption over a period of 2–3 years following implantation [6,7].

Following deployment, endovascular implants are gradually embedded within tissue due to fiber capsule formation and vessel remodeling over the course of approximately 4 weeks [7]. In the case of fully erodible PLLA scaffolds that degrade in vivo over much longer periods, a significant portion of the erosion process will occur while the implant is in a tissue-embedded state. Embedding will promote local accumulation of implant-derived soluble byproducts, thereby increasing the risk of inflammatory or immune responses. Risks associated with by-product accumulation can detract from the benefits of complete resorption for vascular repair, and motivate comprehensive assessment of how material design parameters impact polymer degradation and erosion in the arterial environment.

PLLA degrades via an autocatalytic hydrolysis reaction, where an irreversible ester bond scission process creates oligomers and ultimately lactic acid (LA) [8,9]. Though LA and the readily deprotonated anion L-lactate are common by-products of the Krebs cycle, excessive concentrations in arterial tissue could alter the local pH and induce toxicity. Bulk erosion of PLLA scaffolds occurs via diffusion of soluble degradation by-products out of the material network and into the surrounding medium, resulting in a near-homogeneous mass loss [10,11]. A complex combination of factors governing scaffold degradation, generated by-product transport and metabolism will determine the transient LA concentrations in arterial tissue. Previous studies suggest that scaffold-derived by-product clearance from local arterial tissue is dominated by transport as opposed to metabolic processes, and that environmental factors such as the properties of arterial wall and the extent of tissue-embedding significantly impact the peak LA concentration over the implant lifetime [12]. While environmental properties and tissue-embedding kinetics vary among individuals, several intrinsic PLLA properties can be altered in the scaffold manufacturing process and tuned to control degradation and erosion.

Although several studies characterize the generation, release and transport of PLLA degradation by-products in various environments [13–15], the physical and chemical factors that influence transient LA concentrations in arterial tissue are difficult to independently assess with conventional experimental techniques. Degradation and erosion processes are affected not only by initial scaffold characteristics, including molecular weight, polydispersity, crystallinity, presence of plasticizers, additives and size, but also by the

operating temperature, pH, blood flow rate and enzymatic activity [16]. As compared to bench-top or in vivo studies, computational models can readily provide insight as to how these factors independently or collectively impact scaffold performance in situ and insomuch provide design guidelines for scaffold development. To the best of our knowledge, no computational model has been reported which relates scaffold degradation and erosion kinetics under arterial flow conditions to material parameters that can be controlled in the manufacturing process [9,17–24]. While our earlier work simulated the evolution and transport of soluble species within both the scaffold and the arterial wall [12], we did not explore how material parameters impacted by-product fate. These aspects are thus the focus of the current study.

A two-dimensional computational model of a tissue-embedded PLLA scaffold was developed to characterize the effects of compositional and structural parameters on LA accumulation within the arterial wall. Degradation and erosion kinetics were quantified for 120 days from initial deployment using metrics such as reduction in scaffold weight-average molecular weight (M_w) and weight (W_t), respectively. Within the same period, transient LA tissue levels were quantified via a surface integral of the concentration field in the local arterial wall. Model predictions suggest that some material parameters have a similar effect on degradation and erosion processes, while others induce qualitatively opposing responses. Moreover, peak LA levels in surrounding tissue and the times at which these levels occur exhibit high sensitivity to scaffold molecular structure and the amount of lactide doping. PLLA composition and structure can be tuned to control both degradation and erosion processes, and ultimately mitigate the risk associated with by-product accumulation in endovascular scaffold applications.

2. Methods

A two-dimensional computational model of a tissue-embedded PLLA scaffold was developed with geometrical regions representing a single scaffold strut (S) fully embedded within the arterial wall (W), a segment of the arterial wall adjacent to the strut termed the critical zone (CZ) and the arterial lumen (L) (Fig. 1A). The diameter and length of the lumen were 3×10^{-3} m and 1×10^{-2} m, respectively, the thickness of the arterial wall was 1×10^{-3} m, the side-length of the square strut was 1×10^{-4} m, and the width and thickness of the critical zone were 8×10^{-4} m and 4×10^{-4} m, respectively. Blood was considered as an incompressible and Newtonian fluid. Blood flow through the lumen was assumed to be steady, laminar and fully developed, and was modeled using momentum and continuity equations as follows:

$$\rho_L (\mathbf{u}_L \cdot \nabla \mathbf{u}_L) = -\nabla P_L + \mu_L \nabla^2 \mathbf{u}_L \quad (1)$$

$$\nabla \cdot \mathbf{u}_L = 0 \quad (2)$$

where $\mathbf{u}_L$, $\rho_L = 1060 \text{ kgm}^{-3}$, $\mu_L = 3.5 \times 10^{-3} \text{ Pa} \cdot \text{s}$, [12] and P_L are respectively luminal blood velocity, density, viscosity and pressure.

Steady blood plasma flow through the porous arterial wall was modeled using momentum and continuity equations as follows:

$$\rho_w(u_w \cdot \nabla u_w) = -\nabla P_w + \left(\frac{1}{\varepsilon_w}\right) \mu_w \nabla^2 u_w - \left(\frac{\mu_w}{K_w}\right) u_w \quad (3)$$

$$\nabla \cdot u_w = 0 \quad (4)$$

where u_w , $\rho_w = 1025 \text{ kg m}^{-3}$, $\mu_w = 7.2 \times 10^{-4} \text{ Pa} \cdot \text{s}$, [12,25] and P_w are respectively transmural blood plasma velocity, density, viscosity and pressure, and $K_w = 1.43 \times 10^{-18} \text{ m}^2$ and $\varepsilon_w = 0.43$ [26,27] are respectively Darcy's permeability and porosity of the arterial wall.

In the present study, degradation refers to a chain scission process where polymer chains are cleaved into oligomers and monomers, while erosion reflects material loss from the bulk polymer due to release of water soluble oligomers and monomers. Though PLLA can undergo both autocatalytic and uncatalytic reactions [19], only autocatalytic reaction was considered in this study as the scaffold was fully embedded in the arterial wall and water-soluble by-products were unlikely to be washed away immediately from the scaffold but instead acted as catalysts that enhance further degradation. Further, the thickness of the scaffold was 0.1 mm, which was well below the critical thickness for surface erosion (0.2–0.3 mm) [28], suggesting that the scaffold underwent primarily bulk erosion.

Each ester bond within constituent PLLA chains was assumed to undergo random scission with equal probability and generate two daughter oligomers of lower molecular weight [18,22]. Hence, production of any specific constituents from a longer chain can randomly occur in two ways. Amorphous regions of the scaffold were subjected to degradation due to a favorable water penetration condition, while the crystalline polymer regions were considered stable [13,29]. Initial and generated polymer chains with carboxylic acid end groups were assumed to catalyze subsequent degradation [22]. Moreover, polymeric constituents below the solubility limit (8° of polymerization) were assumed to undergo transient release from the scaffold into the surrounding medium [10]. Degradation of the longest constituent chain in the scaffold, P_n , is described by the following rate equation:

$$\frac{dC_n^s}{dt} = -nkC_n^sA \quad (5)$$

where n , C_n^s , k and A are respectively the number of ester bonds, concentration of P_n in the scaffold, hydrolytic degradation rate and autocatalysis factor, which accounts for all constituents containing carboxylic acid end groups. The hydrolytic degradation rate was assumed to be equal irrespective of chain length.

Similarly, the transient concentration of other insoluble constituents in the scaffold with a number of ester bonds lower than n were modeled by the following rate equation:

$$\frac{dC_i^s}{dt} = -ikC_i^sA + 2 \sum_{m=i+1}^n kC_m^sA; 8 \leq i < n \quad (6)$$

where C_i^s is the insoluble constituent concentration, i is number of ester bonds and C_m^s is any insoluble constituent's concentration with number of ester bonds between n and $i + 1$ in the scaffold. The concentration and transport of scaffold constituents below the solubility limit were modeled by diffusion–reaction equations as follows:

$$\frac{\partial C_j^s}{\partial t} = \nabla \cdot (D_j^s \nabla C_j^s) - j k C_j^s A + 2 \sum_{m=j+1}^n k C_m^s A; 0 < j < 8 \quad (7)$$

where C_j^s and D_j^s are the soluble constituent concentration and the diffusion coefficient, respectively, j is the number of ester bonds and C_m^s is any constituent's concentration with the number of ester bonds between n and $j + 1$ in the scaffold.

The concentration of the monomer LA (P_0) within the scaffold was described as follows:

$$\frac{\partial C_0^s}{\partial t} = \nabla \cdot (D_0^s \nabla C_0^s) + 2 \sum_{m=1}^n k C_m^s A \quad (8)$$

where C_0^s and D_0^s are the LA concentration and diffusion coefficient, respectively, and C_m^s is any constituent's concentration with the number of ester bonds between n and 1 in the scaffold. Polymer degradation increases the scaffold porosity and the diffusion coefficients of all mobile chains. Hence, the diffusion coefficients of soluble constituents at any time, D^t , were calculated as follows [19]:

$$D^t = D^0 [1 + \alpha p] \quad (9)$$

where D^0 , α and p are respectively the initial diffusion coefficient, a material-specific proportionality constant and scaffold porosity. In typical two-dimensional computational models, porosity is the fraction of void area in comparison to total area. Because quantifying the void area is not within the scope of this model, transient porosity was calculated by comparing the current scaffold species concentration with respect to their initial concentration [19].

The degree of polymer crystallinity X_{c0} represents the volume fraction of crystalline regions throughout the scaffold, and can change in two ways: (i) crystallization of small degradation byproducts because of their greater mobility and (ii) accelerated degradation and erosion of amorphous regions as compared to crystalline regions [29]. The temporal variation in the x_{c0} of PLLA was described by an adaptation of the Avrami equation that ignores degradation within crystalline domains [19,30]:

$$X_c - X_{c0} = 1 - \exp[-(k_c t)^{n_A}] \quad (10)$$

where X_{c0} , k_c and n_A are respectively the initial degree of crystallinity, the temperature dependent degree of crystallinity change rate related to nucleation and growth parameters at isothermal conditions, and an Avrami constant that depends on the nucleation mechanism and crystal growth geometry/mechanism.

The transport of scaffold-derived soluble constituents in the arterial wall were modeled by transient diffusion–convection–reaction processes as follows:

$$\frac{\partial C_j^w}{\partial t} + u_w \cdot \nabla C_j^w = \nabla \cdot (D_j^w \nabla C_j^w) - jkC_j^w A_1 + 2 \sum_{m=j+1}^7 KC_m^w A_1; 0 < j < 8 \quad (11)$$

$$\frac{\partial C_0^w}{\partial t} + u_w \cdot \nabla C_0^w = \nabla \cdot (D_0^w \nabla C_0^w) + 2 \sum_{m=1}^7 kC_m^w A_1 - k_m C_0^w \quad (12)$$

where C_j^w and D_j^w are respectively the soluble constituent's concentration and the diffusion coefficient in the arterial wall; j is the number of ester bonds; C_m^w is the concentration of any soluble constituents with the number of ester bonds between 7 and $j + 1$; C_0^w and D_0^w are respectively LA concentration and diffusion coefficient in the arterial wall; A_1 is the total concentration of constituents with carboxylic acid end groups; and k_m is the irreversible first-order reaction rate constant that characterizes metabolism of LA in the arterial wall.

Lastly, transport of soluble constituents in the lumen were modeled as transient diffusion–convection–reaction processes as follows:

$$\frac{\partial C_j^1}{\partial t} + u_1 \cdot \nabla C_j^1 = \nabla \cdot (D_j^1 \nabla C_j^1) - jkC_j^1 A_1 + 2 \sum_{m=j+1}^7 kC_m^1 A_1; 0 < j < 8 \quad (13)$$

$$\frac{\partial C_0^1}{\partial t} + u_1 \cdot \nabla C_0^1 = \nabla \cdot (D_0^1 \nabla C_0^1) + 2 \sum_{m=1}^7 kC_m^1 A_1 \quad (14)$$

where C_j^1 and D_j^1 are respectively the soluble constituent's concentration and the diffusion coefficient in the lumen; j is the number of ester bonds; and C_0^1 and D_0^1 are respectively the LA concentration and the diffusion coefficient in the lumen.

A steady Poiseuille parabolic velocity profile with peak velocity of 0.53 m s^{-1} was imposed at the luminal inlet and a zero pressure boundary condition was applied at the luminal outlet to simulate coronary arterial flow [12]. The Kedem–Katchalsky equation was used at the mural interface to define the transport of blood plasma from the lumen to the arterial wall and a constant pressure boundary condition was assumed at the perivascular wall [31,32]. For simulating mass transfer, the initial scaffold molecular weight distribution (MWD) was prescribed to achieve specific M_w and poly-dispersity index (PDI). A zero concentration boundary condition was assumed at the luminal inlet and a convective flux boundary condition was imposed at the luminal outlet and on the perivascular wall. The continuity of soluble constituents was assumed at the scaffold–arterial wall and mural wall interfaces. The Delaunay triangular scheme was used to perform the mesh generation with maximum intensity of elements focused around the scaffold and critical zone. A finite-element model (COMSOL Multiphysics™) was used to perform numerical simulations and the iterations were continued until the relative error tolerance magnitude reached 10^{-5} . The computational

solution was considered to be mesh independent when the relative changes in scaffold M_w and LA concentration were less than 0.1% at any simulated time step between successive mesh iterations. The average computational runtime for each simulation was around 5 h using an Intel Xeon CPU (2.80 GHz) processor with 20 GB of RAM.

The accumulation of scaffold-derived LA may lower the local pH below a critical value and induce toxicity in the arterial wall [33]. The critical zone maximum LA concentration ($C_{LA,max}^{cr}$) and the time at which $C_{LA,max}^{cr}$ occurs (t_{max}) are therefore considered as performance metrics for scaffold safety assessment. Degradation and erosion kinetics are typically monitored by tracking the changes in the M_w and W_t of the scaffold over time.

Hence, the degradation and erosion half-lives ($t_{deg}^{1/2}$ and $t_{ero}^{1/2}$), defined as the times at which the initial M_w and W_t are reduced by 50%, respectively, are reported as reduced metrics of the degradation and erosion processes.

3. Results

The developed random scission degradation model was validated by comparison to published data describing the transient reduction in M_w of a PLLA disc maintained in static phosphate buffer solution [14]. An initial PLLA M_w of 7.6 kDa and PDI of 1.34 were imposed in the model to recreate experimental conditions. A theoretical degradation curve that exhibited excellent correlation ($R = 0.99$) with experimental results was generated by tuning the model parameters, yielding a hydrolytic degradation rate of $1.17 \times 10^{-11} \text{ m}^3 \text{ mo}^{-1} \text{ s}^{-1}$ and an initial monomer diffusion coefficient of $1 \times 10^{-13} \text{ m}^2 \text{ s}^{-1}$ (Fig. 2A). Several experimentally verified models quantified a PLLA hydrolytic degradation rate with the same order of magnitude [22,23] and a monomer diffusion coefficient between $1 \times 10^{-12} - 1 \times 10^{-14} \text{ m}^2 \text{ s}^{-1}$ [20,34], indicating that both fitted parameters are within a plausible range. The degree of crystallinity change rate and Avrami constant were calculated by fitting the Avrami equation against experimental results with an initial degree of crystallization of 0.24 [14].

Isotropic diffusion of all mobile constituents within the scaffold results in a maximal LA concentration at the strut center and a monotonic decrease towards all boundaries (Fig. 1B). Within the defined critical zone, by-product clearance is augmented by luminal and transmural flow, resulting in reduced LA concentrations in tissue adjacent to the mural interface as compared to other regions. Upon reaching the mural interface, LA is rapidly transported downstream by the luminal blood flow (Fig. 1D). Conversely, transmural flow convects LA towards the perivascular wall, resulting in higher concentrations beneath the scaffold strut (Fig. 1C and E). All larger mobile constituents are transported in the same qualitative manner as LA but at relatively slower rates.

For the case of monodisperse PLLA, scaffold degradation is initiated upon deployment, as indicated by the immediate decrease in M_w (Fig. 2B). The scaffold M_w change rate is nearly constant for the first 40 days and then is gradually reduced, resulting in a more than 50% decrease in M_w within the first 40 days, followed by less than 25% additional reduction over the next 80 days. Scaffold erosion exhibits qualitatively reversed kinetics, with a slow rate

of mass loss at early times ($t < 30$ days) followed by comparatively rapid mass loss for the remaining time (Fig. 2C). Transient concentrations of scaffold-derived LA within different model regions exhibit order-of-magnitude differences over 120 days (Fig. 2D). The LA concentration is always highest within the scaffold, followed by the critical zone, arterial wall and lumen. The maximum LA concentration in the critical zone is 7.6% greater than in the surrounding arterial wall, motivating the subsequent focus on this region of tissue for risk assessment associated with by-product accumulation.

While maintaining a constant number-average molecular weight (M_N), the initial scaffold MWD was systematically varied by increasing the standard deviation (r) of the initial chain length distribution. Both $C_{LA,max}^{cr}$ and t_{max} are minimally affected by the initial scaffold MWD profiles (Fig. 3A and B). In comparison to the monodisperse scaffold ($\sigma = 0$), maximal polydispersity within our investigated range ($\sigma = 6000$) results in the same $C_{LA,max}^{cr}$ at essentially the same time post-implantation (1.5 days later). Conversely, faster PLLA degradation, as indicated by a reduction in $t_{deg}^{1/2}$, is predicted for scaffolds with greater polymeric dispersion (Fig. 3C). An approximately 30% decrease in $t_{deg}^{1/2}$ is observed for polydisperse scaffold with $\sigma = 6000$ in comparison to the monodisperse scaffold. Polydispersity has an insignificant effect on erosion kinetics, as indicated by almost equal $t_{ero}^{1/2}$ among all PLLA variants (Fig. 3D). Transient scaffold profiles reveal that after 30 days the MWD is largely independent of the initial PLLA composition (Fig. 4). These results suggest that the transformation of large constituents into shorter insoluble oligomers is a rapid process in comparison to soluble by-product generation and mass loss. As a consequence, the amount of soluble constituents in the scaffold is insignificant compared to insoluble constituents at all times, irrespective of the initial MWD. Over the range of considered PLLA formulations, degradation and erosion processes essentially homogenize all scaffold PDIs by 120 days post-implantation (data not shown).

A higher initial scaffold degree of crystallinity (X_{c0}) results in a linear decrease in $C_{LA,max}^{cr}$ and a linear increase in t_{max} within the investigated range (Fig. 5A and B). While both degradation and erosion kinetics are depressed with increasing X_{c0} , the comparative responses of $t_{deg}^{1/2}$ and $t_{ero}^{1/2}$ suggest that erosion is the more sensitive process (Fig. 5C and D).

While $t_{deg}^{1/2}$ is increased by 53%, $t_{ero}^{1/2}$ is increased by 130% within the investigated range. The degree of crystallinity change rate (k_c) dictates how fast crystalline regions become amorphous. Similar to the effect of increasing X_{c0} a higher k_c causes a decrease in $C_{LA,max}^{cr}$ (Fig. 6A) with a negligible change in t_{max} (Fig. 6B). Increasing the k_c slows down both the degradation and erosion processes, with a more pronounced effect on the latter, as observed by the 109% increase within the investigated range (Fig. 6C and D).

Lactide doping is expected to have a profound effect on all scaffold performance metrics via the stimulation of autocatalytic processes. Simulation results predict that inclusion of lactide within the scaffold significantly increases $C_{LA,max}^{cr}$ and reduces t_{max} (Fig. 7A and B), and accelerates both degradation and erosion (Fig. 7C and D). The effect of lactide inclusion on

degradation and erosion is similar, as both $t_{\text{deg}}^{1/2}$ and $t_{\text{ero}}^{1/2}$ are reduced by 50% when 5 wt.% lactide is added to the initial scaffold.

4. Discussion

The performance of PLLA-based fully resorbable endovascular scaffolds critically depends on scaffold degradation and erosion kinetics. Modulations in the molecular weight profile, average molecular weight and microstructure (crystallinity and porosity), as well as incorporation of additives such as LA, are some of the design aspects that can be adjusted during the manufacturing stages to control the fate of in vivo by-product distribution. A deeper understanding of these tunable parameters is required to enhance overall scaffold performance and thereby improve the biocompatibility and clinical efficacy of erodible devices. We have used computational modeling to gain insight into the critical determinants of PLLA scaffold degradation and erosion by accounting for the effects of autocatalysis, polydispersity, degree of crystallinity, species-specific transport of scaffold-derived constituents and porosity change due to degradation, blood flow and LA metabolism.

Transient concentrations of scaffold-derived degradation byproducts are concurrently modulated by the rates of diffusion, convection, generation and metabolism. A parametric sensitivity analysis was performed to quantify the relative influence of structural and compositional factors on scaffold performance (Table 1). A relative change index (RCI) was calculated to quantify the percent change in defined performance indicators when material parameters are varied in isolation from the lowest to the highest considered values. The safety assessment of PLLA modifications is based on the RCIs of $C_{\text{LA,max}}^{\text{cr}}$ and t_{max} , whereas degradation and erosion assessments are based on $t_{\text{deg}}^{1/2}$ and $t_{\text{ero}}^{1/2}$, respectively.

The fine tuning of polydispersity was expected to enable a reduction in the inflammatory potential of PLLA scaffolds through the protraction of LA generation [14]. A mixture theory based on a previously proposed model suggested that bulk polymer erosion was significantly affected by initial polydispersity due to the overall enhanced diffusivities of early-stage soluble constituents [21]. However, our results show that, though initial polydispersity affects scaffold LA production, it has a negligible effect on LA accumulation adjacent to the scaffold and only mildly affects degradation (RCI = +29%). This finding reinforces the notion that it is difficult to predict how a single material parameter will impact critical zone LA pharmacokinetics that are modulated by the relative rates of LA generation, diffusion within the scaffold, release into local tissue, transport within the arterial wall and metabolism.

Increasing the degree of crystallinity due to the degradation of the amorphous regions gradually slows the overall degradation and erosion rates, as crystalline regions are relatively resistant to hydrolytic breakdown [16]. Because the degradation rate at early times is maximal, t_{deg} exhibits a moderate sensitivity to X_{c0} (RCI = +53%) and a mild response to k_{c} (RCI = +15%). On the other hand, erosion rates are initially slow and are thus highly sensitive to both X_{c0} and k_{c} , as reflected in the corresponding t_{ero} RCIs. Previous studies have reported that PLLA degradation is accelerated with increasing X_{c0} due to two factors:

(i) a decreased density of effective tie chains between adjacent crystalline blocks; and (ii) increased void spaces in the amorphous regions, which ultimately prompt hydrolysis by enhancing water diffusion [13]. However, the degradation response to X_{c0} was reported to vary substantially with polymer processing methodologies, most notably the employed film annealing temperature, which may account for the contradiction with our current findings [16]. Scaffold X_{c0} can be controlled by modifying the annealing and/or quenching protocols, whereas k_c at a specific temperature can be controlled by adding nucleating agents during the manufacturing process [35]. Hence, both X_{c0} and k_c provide potential avenues for selective tuning of scaffold degradation and erosion kinetics.

While lactide doping can potentially be used to tune scaffold degradation and erosion kinetics, the concomitant increase in tissue LA concentration should also be considered. Our study suggests that lactide doping should be employed with high precision in scaffold manufacturing due to the promotion of byproduct accumulation. Although the inclusion of lactide has been considered previously and remains a promising scaffold design strategy, the risk associated with an elevated tissue response is significant and should be assessed with in vivo studies [36].

4.1. Study limitations

Although the proposed degradation model has been verified using previously reported values from a static experimental study [14], the predicted degradation kinetics under physiological conditions have not been validated with or compared to published data. While only in vivo studies can validate the predictions of this computational model, the requisite number of studies that would be needed, considering the complexity of synthesizing scaffolds with precise variations of structural properties, precludes inclusion of this validation from the current body of work. Our computational study is nevertheless a valuable contribution to the field as it suggests critical parameters that one may focus on when performing future animal studies. The model could also be extended to three dimensions to better account for flow-mediated processes. However, due to the symmetry of the vessel (and most scaffolds as well) and the computational cost, the study was conducted in two dimensions. In comparison to our earlier study, in which all the degradable species were divided into only five groups to identify the dominating factors that modulate the fate of scaffold-derived by-products clearance [12], here we tracked all individual species generated during scaffold degradation to better understand the consequences of structural variations – which resulted in a substantially more complex model. With our current resources, coupling three-dimensional geometry effects with our detailed degradation model would have dramatically increased the computational time of the simulations (most likely an exponential increase). Computational costs also limit the examination of very high initial M_w scaffolds that are typically used in endovascular applications. Modeling the performance of high M_w scaffolds in three-dimensional environments will be interesting to investigate in future.

Although degradation processes are theoretically initiated at the time of implantation, PLLA-based bioresorbable scaffolds have been shown to provide structural support to vessel walls for prolonged times with minimum risk of restenosis [37]. Specifically, the PLLA-

based bioabsorbable Everolimus eluting stent results in an acceptable angiographic in-stent late loss, low stent area obstruction, no late thrombosis and minimal neointimal hyperplasia after 6 months post-implantation [38]. While these factors are certainly related to the mechanical strength of the scaffold, which may impact long-term performance, predicting the degradation-induced change in scaffold mechanical properties is not within the scope of this study. Moreover, a fully embedded scaffold was considered in this simulation from the initial stage, though it has been reported that fully bioresorbable vascular scaffolds are completely covered by the fibromuscular neointima by 4 weeks after implantation [7]. Finally, the pulsatility of the blood flow was ignored due to the fully embedded scaffold position and the minimal effect on constituent transport within the arterial wall. These are important aspects that need to be considered in developing a model to fully appreciate the efficacy of endovascular therapy using biodegradable scaffolds. Our current study lays a foundation to address these issues which we plan to explore in our future studies.

5. Conclusion

Advanced design of erodible endovascular scaffolds requires careful assessment of material properties that impact implant performance and safety in the arterial environment. Our study reveals that potential variations in polymer composition and structure differentially impact the metrics of performance. Specifically, we found that degradation is minimally affected by changes in either the PLLA polydispersity or the initial degree of crystallinity, while erosion is sensitive to crystallinity. Additionally, scaffold degradation, erosion and by-product accumulation were all responsive to lactide doping. Computational modeling serves as an efficient means to evaluate possible tuning strategies and enable improved design of erodible scaffolds.

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Fig. 1.

(A) Schematic of the two-dimensional computational framework consisting of a scaffold strut (S) fully embedded within the arterial wall (W), a critical zone (Cr) in the arterial wall surrounding the scaffold, and the arterial lumen (L) (not to scale). Surface plots of LA concentration in the scaffold (B), critical zone (C), lumen (D) and arterial wall (E) at 30 days post-implantation. Color bars represent LA concentration for each inset.

Fig. 2.

(A) Transient molecular weight (M_w) profile comparison between predicted results and experimentally published values [14]. Best-fit model parameters included an initial weight-average M_w of 7.6 kDa, an initial PDI of 1.34, a hydrolytic degradation rate of $1.17 \times 10^{-11} \text{ m}^3 \text{ mol}^{-1} \text{ s}^{-1}$, an initial monomer diffusion coefficient of $1 \times 10^{-13} \text{ m}^2 \text{ s}^{-1}$, a constant value of $\alpha = 4.5$, an initial degree of crystallinity of 0.24 and a degree of crystallization change rate of $4.63 \times 10^{-8} \text{ s}^{-1}$. (B, C) Scaffold weight-average molecular weight (M_w) and weight (W_t) decrease nonlinearly with time, with relatively fast degradation and slow erosion at early times. (D) Transient lactic acid (LA) concentration profiles in different regions show that the accumulation of scaffold-derived by-product is orders-of-magnitude higher in the critical zone compared to other regions within the computational domain.

Fig. 3.

(A, B) Maximum critical zone LA concentration ($C^{\text{cr}}_{\text{LA,max}}$) and the time at which $C^{\text{cr}}_{\text{LA,max}}$ occurs (t_{max}) are independent of the standard deviation (σ) of the scaffold's molecular weight distribution (MWD). (C, D) A higher σ results in faster degradation, as indicated by the time required for 50% reduction of the initial weight-average molecular weight $t^{1/2}_{\text{deg}}$, but does not alter the erosion kinetics, as indicated by the analogous measure of weight loss ($t^{1/2}_{\text{ero}}$).

Fig. 4.

Comparative evolution of PLLA molecular profiles with varying initial standard deviations (σ) of the molecular weight distribution. The number of molecules are normalized with respect to the total number of molecules present in the scaffold at $t = 0$ and are presented in the vertical axis.

Fig. 5.

(A, B) A higher scaffold initial degree of crystallinity (X_{c0}) decreases the critical zone maximum LA concentration ($C_{cr,LA,max}^{cr}$) and delays the time at which $C_{cr,LA,max}^{cr}$ occurs (t_{max}). (C, D) Degradation and erosion kinetics are protracted by increasing (X_{c0}), as represented by increases in the times at which the initial scaffold weight-average molecular weight ($t_{deg}^{1/2}$) and weight ($t_{ero}^{1/2}$) diminish by 50%.

Fig. 6.

(A, B) An increased crystallinity change rate (k_c) reduces the critical zone maximum LA concentration ($C_{LA,max}^{cr}$) and delays the time at which $C_{LA,max}^{cr}$ occurs (t_{max}). (C, D) Trends in $t_{deg}^{1/2}$ and $t_{ero}^{1/2}$ suggest that degradation kinetics are independent of k_c , whereas erosion kinetics are protracted with increasing k_c .

Fig. 7.

(A, B) Incorporation of free lactide increases the critical zone maximum LA concentration ($C^{\text{Cr}}_{\text{LA,max}}$) and decreases the time at which $C^{\text{Cr}}_{\text{LA,max}}$ occurs (t_{max}). (C, D) Excess lactide and its degradation products enhance autocatalytic hydrolysis and accelerate both the degradation and erosion, as indicated by reductions in $t^{1/2}_{\text{deg}}$ and $t^{1/2}_{\text{ero}}$.

Table 1

Sensitivity analyses on PLLA structural and compositional parameters.

Parameter	Range	Relative change index (RCI)			
		Safety assessment (Concentration) (%)	Safety assessment (Time) (%)	Degradation assessment (%)	Erosion assessment (%)
Initial Scaffold MWD Standard Deviation	0–6000	+2	–2	29	–2
Initial scaffold degree of crystallinity	0–0.3	–47	+36	+53	130
Degree of crystallinity change rate, s ^{–1}	0– 5.8 × 10 ^{–8}	–40	–4	+15	109
Initial lactide doping, wt.%	0–5	157	–48	–51	–49

The relative change index (RCI) is based on the percent increase (+) or decrease (–) of defined performance metrics due to isolated changes in material parameters. Safety assessment is based on the maximum critical zone lactic acid concentration and the time at which it occurs. Degradation and erosion assessments are based on the corresponding half-lives ($t_{deg}^{1/2}$ and $t_{ero}^{1/2}$), when initial scaffold weight-average molecular weight and weight are reduced by 50% respectively.