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Compositional and Structural Determinants of Polymeric Scaffold Degradation

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Abstract: Fully-erodible scaffolds are increasingly considered for endovascular interventions due to the inherent potential for complete vessel healing. As with all erodible implants, the interactions between material by-products and local biological tissues must be understood to ensure safe and efficacious scaffold deployment. Our study is focused on the autocatalytic degradation of poly-L-lactide (PLLA), a material which constitutes the primary basis for a variety of erodible implants across multiple clinical applications. To predict the compositional and structural determinants of PLLA scaffold performance, we performed a series of simulations that examine how controlled variations in initial PLLA molecular weight distribution, lactide doping, and crystalline structure impact polymer degradation kinetics and transient by-product concentrations throughout the erosion process. Computational results suggest multiple strategies for scaffold optimization that could ultimately be used to minimize the adverse biological responses to erodible endovascular implants.

Keywords: Poly-L-lactide, Molecular weight distribution, Random scission, Autocatalysis, Hydrolytic degradation

1. Introduction

Erodible polymeric scaffolds can mitigate long-term risks associated with permanent implants currently used to treat ischemic artery disease.[1] Poly-L-lactide (PLLA) is one of most widely used degradable polymers for endovascular scaffold applications. A ubiquitous concern with all erodible implants is the effects of material by-products on local tissues.[2] Several bench-top investigations have been performed to characterize a wide-range of tissue-material interactions throughout erosion processes,[2-3] yet many of the physical and chemical factors that dictate by-product fate are difficult to isolate with traditional experimental techniques.

Computational modeling provides a complementary tool to predict the behavior of degradable scaffolds when subjected to the dynamic endovascular environment. PLLA degradation is a random scission process that is dictated by an autocatalytic hydrolysis mechanism.[4-6] Initial polymer characteristics, including molecular weight, polydispersity, and degree of crystallinity, cumulatively control the degradation process and release of material by-products.[7] Computational modeling enables independent analyses of multiple compositional determinants of scaffold performance, and thus is an efficient tool for scaffold characterization and optimization.

We developed a computational model to investigate how initial molecular weight distribution (MWD), lactide doping, and crystalline structure modulate the degradation kinetics and by-product release from PLLA scaffolds. Our model enables detailed assessment of scaffold degradation and a basis for strategic design of erodible scaffolds.

2. Methods

A one-dimensional computational model was constructed to study the autocatalytic degradation by random scission of the ester bonds of a fully-erodible poly-L-lactide (PLLA) scaffold. All ester bonds were assumed to have equal probability to break and generate daughter polymers of lower molecular weight (Figure 1).[8] Moreover, only amorphous regions of the scaffold were subjected to degradation processes, where water penetration and content are much higher compared to crystalline regions. All the initial and generated polymer chains were assumed to have carboxylic acid end groups that catalyze subsequent degradation. Oligomers below the solubility limit (8° of polymerization)

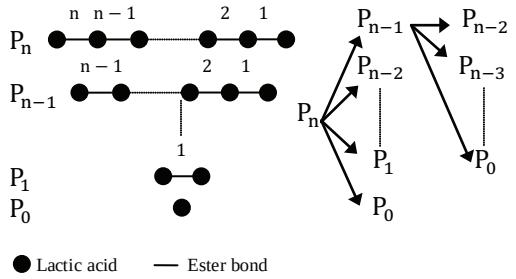

Figure 1. Random scission of PLLA scaffold. All constituent ester bonds have an equal probability of cleavage.

were assumed to undergo transient release from the scaffold into the surrounding medium.[9]

The degradation rate of the polymer with the longest chain, P_n, was described as follows:

$$\frac{dC_n}{dt} = -nkC_nA$$

where n, C_n, k, and A are respectively the number of ester bonds, P_n concentration, hydrolytic degradation rate, and autocatalysis factor, whereas, A is the summation of all polymer species concentrations in the scaffold as follows:

$$A = \sum_{m=0}^{n} C_m$$

Similarly, degradation rates for all the insoluble oligomers with number of ester bond lower than n were modeled as follows:

$$\frac{dC_i}{dt} = -ikC_iA + 2\sum_{m=i+1}^{n} kC_mA \;\; ; \;\; n > i > 6$$

where C_i is polymer concentration with i number of ester bonds.

The degradation rates of oligomers below the solubility limit were modeled as follows:

$$\frac{dC_j}{dt} = \frac{d}{dx}\left(D_j\frac{dC_j}{dx}\right) - jkC_jA + 2\sum_{m=j+1}^{n} kC_mA \;\; ; \;\; 7 > j > 0$$

where C_j and D_j are respectively concentration and diffusion coefficient of polymer with j number of ester bonds.

Monomer (P_0) degradation rate was described as follows:

$$\frac{dC_0}{dt} = \frac{d}{dx}\left(D_0\frac{dC_0}{dx}\right) + 2\sum_{m=1}^{n} kC_mA$$

where C_0 and D_0 are respectively P_0 concentration and diffusion coefficient. Polymer degradation increases the scaffold porosity and eventually increases diffusion coefficients. Hence, soluble species diffusion coefficient any time (t), D^t, was calculated as follows:[10]

$$D^t = D^o[1 + \alpha p]$$

where D^o, α, and p are respectively species initial diffusion coefficient, a material-specific proportionality constant, and scaffold porosity.

The ratio of crystalline to amorphous PLLA varies over time due differential degradation kinetics within these regions, as described by an adaptation of the Avrami equation as follows:[11]

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

where X_c, X_{c0}, k_c, and n_A are respectively degree of crystallinity at t, initial degree of crystallinity, degree of crystallinity change rate, and an Avrami constant.

Mesh-independent solutions of all above mentioned equations were achieved using COMSOL Multiphysics™. Symmetry boundary condition was considered along the device axis-of-symmetry, whereas zero concentration boundary condition was used where the device was in contact with the surrounding medium.

4. Results and Discussions

The employed random scission degradation model is validated (R = 0.99) by comparison of predicted PLLA weight average molecular weight (WAMW) to previously published results that track material degradation of PLLA disc over four weeks (Figure 2).[12] Initial WAMW of 7600 Da with polydispersity index (PDI) of 1.34 were used in the simulation for consistence with experimental conditions.

Increasing initial PLLA dispersity at fixed number averaged molecular weight (NAMW) protracted scaffold degradation kinetics in the expected manner (Figure 3), further validating the random scission model and suggesting the range of scaffold retention times achievable through simple compositional manipulation. The degree of polymer dispersion is reflected by the standard deviation of MWD, σ. After 120 days, a monodisperse scaffold ($\sigma = 0$) has a 40% greater WAMW compared to a polydisperse scaffold with $\sigma = 6000$, which is a direct consequence of the autocatalytic effect. However, despite the accelerated degradation, only a 10% higher peak scaffold lactic acid (LA) concentration is predicted (data not shown).

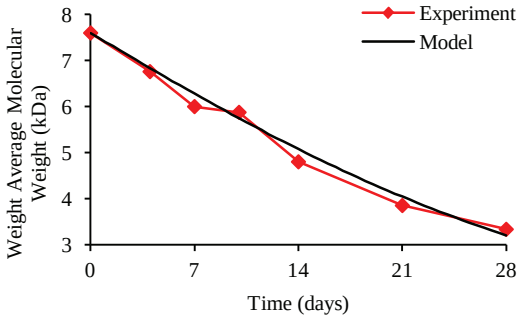

Figure 2. Molecular weight (MW) profile comparison between predicted results and experimentally published values.[12] Initial weight average MW of 7600 Da, initial polydispersity index of 1.34, Hydrolytic degradation rate of $1.17 \times 10^{-11}\ m^3 mol^{-1} s^{-1}$, initial monomer diffusion coefficient of $1 \times 10^{-13}\ m^2 s^{-1}$, constant value of $\alpha = 4.5$, degree of crystallization change rate of $4.63 \times 10^{-8}\ s^{-1}$, and Avrami constant = 1 were used in the depicted simulation results.[10-12]

Inclusion of trace lactide within the scaffold enhances the degradation process and results in more LA generation (Figure 4). The consequence of lactide addition is more prominent at the early stage of degradation, when the soluble species generation rates are greater than the corresponding release rates into the surrounding medium. Scaffold peak LA concentration is almost doubled when 5 wt% lactide is added to the initial polymer profile. Scaffold LA concentration is a critical performance metric as excessive release into the surrounding tissue could induce toxicity and necrosis. While lactide doping can potentially be used to tune scaffold erosion kinetics, the concomitant increase in tissue LA concentration should also be considered.

Higher initial polymer degree of crystallinity (X_{c0}) dramatically slows down the degradation process (Figure 5A) and reduces scaffold LA concentration (Figure 5B). In all semi-crystalline materials undergoing hydrolytic degradation, the degree of crystallinity (X_c) increases as degradation proceeds since hydrolytic breakage of polymer ester bonds are favored in the amorphous regions. Our model predicts that increase in X_{c0} provides an additional avenue for tuning degradation kinetics and scaffold LA concentration.

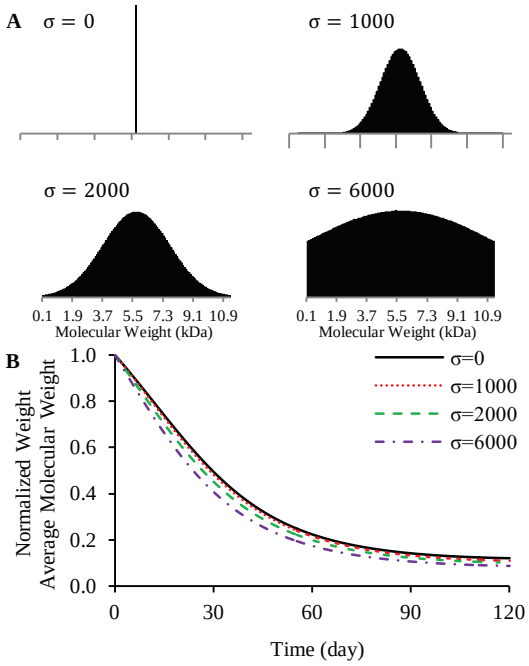

Figure 3. Initial molecular weight distribution (MWD) (A) effect on scaffold degradation (B). Weight average molecular weight (WAMW) is normalized with respect to initial scaffold WAMW. σ represents standard deviation of initial scaffold MWD.

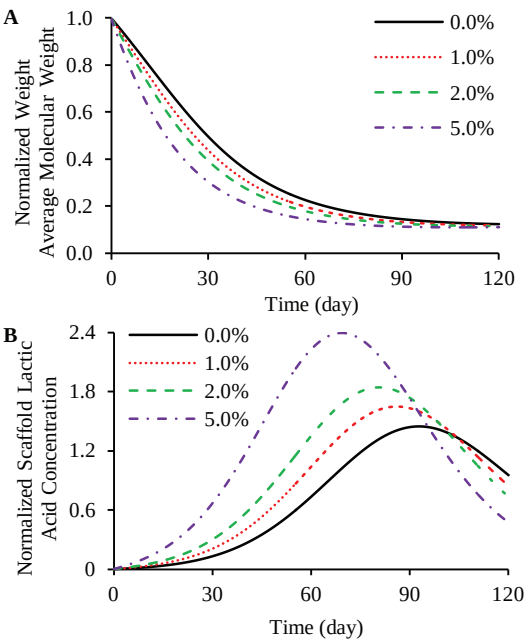

Figure 4. Initial lactide doping results in relatively rapid scaffold degradation (A) and higher LA generation in the scaffold (B). Lactide doping levels are represented in terms of initial polymer weight percentage. Scaffold LA concentration is normalized with respect to the initial polymer concentration.

5. Future Work

The developed computational framework will be extended to higher spatial dimensions. In addition, the model will be improved to capture realistic physiologic conditions through characterizing by-product transport/interaction within the arterial wall and lumen. Finally, material design strategies will be developed to enable greater control of by-product fate in the dynamic endovascular environment.

6. Conclusions

Adjustment of initial polymer scaffold MWD, lactide content, and structure can be used to control the degradation kinetics of PLLA scaffolds. Rational tuning of PLLA composition and structure within scaffold manufacturing processes can be aided by computational modeling and has the potential to improve by-product clearance from local tissues in endovascular applications.

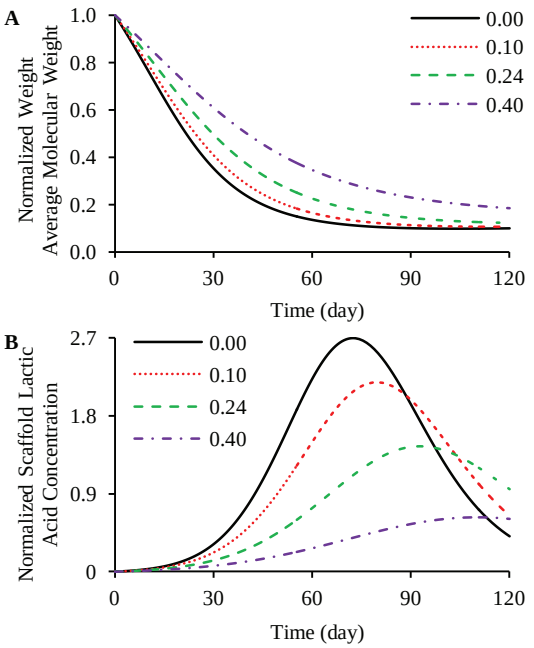

Figure 5. Increase in initial polymer degree of crystallinity enhances scaffold degradation (A), but results less LA concentration in the scaffold (B). Initial polymer degree of crystallinity is presented as the ratio of crystalline to amorphous regions in the polymer.

7. References

1. Colombo, A., and E. Karvouni, Biodegradable stents : "fulfilling the mission and stepping away", Circulation, **102**, 371-373, (2000)
2. Leenslag, J. W., A. J. Pennings, R. R. M. Bos, F. R. Rozema, and G. Boering, Resorbable materials of poly(l-lactide): VII. *In vivo* and *in vitro* degradation, Biomaterials, **8**, 311-314, (1987)
3. Pamula, E., and E. Menaszek, *In vitro* and *in vivo* degradation of poly(L:-lactide-co-glycolide) films and scaffolds, Journal of Materials Science: Materials in Medicine, **19(5)**, 2063-2070, (2008)
4. Göpferich, A., Mechanisms of polymer degradation and erosion, Biomaterials, **17(2)**, 103-114, (1996)
5. Siepmann, J., K. Elkharraz, F. Siepmann, and D. Klose, How autocatalysis accelerates drug release from PLGA-based microparticles: a quantitative treatment, Biomacromolecules, **6(4)**, 2312-2319, (2005)
6. von Burkersroda, F., L. Schedl, and A. Göpferich, Why degradable polymers undergo surface erosion or bulk erosion, Biomaterials, **23(21)**, 4221-4231, (2002)
7. Alexis, F., Factors affecting the degradation and drug-release mechanism of poly(lactic acid) and poly[(lactic acid)-*co*-(glycolic acid)], Polymer International, **54**, 36-46, (2005)
8. Antheunis, H., J.-C. van der Meer, M. de Geus, W. Kingma, and C. E. Koning, Improved mathematical model for the hydrolytic degradation of aliphatic polyesters, Macromolecules, **42**, 2462-2471, (2009)
9. Cameron, R. E. and A. Kamvari-Moghaddam, A Synthetic bioresorbable polymers, Degradation rate of bioresorbable materials prediction and evaluation, Boca Raton, FL, CRC Press, p.3-43-66, (2008)
10. Wang, Y., J. Pan , X. Han, C. Sinka, and L. Ding, A phenomenological model for the degradation of biodegradable polymers, Biomaterials, **29(23)**, 3393-340, (2008)
11. Avrami, M., Kinetics of phase change I: general theory, Journal of Chemical Physics, **7**, 1103-1112, (1939)
12. von Recum, H. A., R. L. Cleek, S. G. Eskin, and A. G. Mikos, Degradation of polydispersed poly(L-lactic acid) to modulate lactic acid release, Biomaterials, **16**, 441-447, (1995)