Official Journal of TESMA
Regenerative Research
www.regres.tesma.org.my
E-ISSN 2232-0822
Tissue Engineering and Regenerative Medicine Society of Malaysia

Regenerative Research 1(1) 2012 58-61

MATHEMATICAL MODELING ON DEGRADATION OF 3D TISSUE ENGINEERING SCAFFOLD MATERIALS

Hoque ME*, Yong LC, Ian P

Department of Mechanical, Materials and Manufacturing Engineering
University of Nottingham Malaysia Campus

ARTICLE INFO

Submitted: 29-02-2012
Accepted: 24-05-2012
*Corresponding Author: Md Enamul Hoque

Email:
Enamul.Hoque@nottingham.edu.my

KEYWORDS

Computational Model,
Tissue Engineering,
Scaffold,
Degradation,
Biopolymer

ABSTRACT

Computer simulation could be a novel approach to inspect biomaterials for tissue engineering applications. This study performs a mathematical simulation on 3D scaffold to investigate their degradation behaviors.

Scaffold models consisted of various biopolymers were investigated. Polycaprolactone (PCL), poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and polyethylene glycol (PEG) were taken into consideration to build the scaffold models. The in vitro degradation rate and change in molecular weight with respect to time were investigated for different scaffold models. The simulation was performed using MATLAB R2010b (MathWorks).

Upon degradation, the molecular weights of the scaffolds were changed significantly. The results indicate that the scaffolds' material nature influence the degradation rate and lifetime. This simulation results help to predict the scaffold life span, and ultimately to select an optimal design of a scaffold for particular tissue engineering application.

The type of biopolymer and their degradation rate play significant role in determining optimal scaffold for tissue engineering applications. Mathematical modelling has the potential to generate a statistically perfect instant molecular weight decay curve. Scaffolds may also be optimized to suit site-specific loading requirements indicating the need for greater control over scaffold manufacturing techniques.

1.0 Introduction

There is a persistent challenge associated with the modeling, design and fabrication of tissue engineering scaffolds to meet various biological and biophysical conditions in regenerative tissues. For example, designing load bearing scaffolds for bone and cartilage tissue applications is a complicated process [1-5]. Bone and cartilage tissue scaffolds usually have complex architecture, porosity, pore size, shape, and interconnectivity in order to provide the needed structural integrity, strength, transport, and an ideal micro-environment for the growth of cells and tissues in growth [6-7]. So far, there is no systematic study that has been conducted alone to assess how the exact match of mechanical properties is indeed crucial for optimal tissue regeneration [8]. For instance, since mechanical properties are intimately related to the porosity of porous structures, a stiffer and less porous scaffold will provide a better integration with the surrounding natural tissues, or a more flexible and porous one will allow cells to attach and proliferate in a more efficient way [9-10].

So far in this research, most of the interactions between biomaterials and scaffolds are simulated through the

definition of structure properties, such as scaffold stiffness or pore size [11-12]. In tissue engineering (TE) scaffolds design, the possibilities of scaffolds design are huge. Computer models can only be as good as the input data, which need to be sufficient. More experimental tests and biological information are needed to validate scaffold design more precisely. Therefore, it becomes necessary to include such properties in a computer model to model effectively the integration between biomaterials and surrounding tissues.

Based on literature review done so far, we have found that limited studies have performed degradation of TE scaffold. So far, only simulations of a perfusion bioreactor and basic mechanical studies have been investigated [13-14]. By understanding the degradation characteristics which are optimal for each of these scaffolds, we will be able to design better scaffolds by customizing specific design of the scaffold for each material type. This paper mainly presents the degradation rate and lifetime prediction of biopolymers by mathematical model.

2.0 Materials and Methods

The pre-assumptions of the simulation process are that the entire samples are dried, dissolved, and the molecular weights of chains in the samples are calculated. The bulk polymer in surface-eroding polymers remains unaffected during degradation; only the surface-attacked polymer is degraded. Here, we assumed that the entire polymer is experiencing a reduction in molecular weight; this is the characteristic feature of bulk erosion.

In degradation analysis, the rate of degradation can be expressed as functions of mass and time, i.e.

$$M = M_0 e^{-kt} \quad (1)$$

Where, M and Mo are the initial and final masses of the polymer, k is degradation rate constant and t is time, respectively.

The useful lifetime of biopolymer can be expressed as functions of change toward the critical molecular weight (MW) i.e.

$$MW = MW_0 e^{-kt} \quad (2)$$

MW is molecular weight of the biopolymer and MW_o is the critical molecular weight and t is the useful lifetime of the polymer.

Based on the rate equations for scaffold degradation described, mathematical simulation for biomaterials degradation properties was conducted. Hence, the value of MW change and useful lifetime of the biopolymer can be calculated by mathematical software, MATLAB R2010b (MathWorks) for any particular biopolymer. In simulation procedures, all MW and degradation rate constants were taken into consideration [15-16] to calculate the effective rate constant for degradation of each polymer.

3.0 Results and Discussion

The degradation kinetic is biphasic; the first phase of degradation occurs by diffusion of water to the amorphous regions and subsequent hydrolysis. The second phase begins as water penetrates and hydrolyzes the more crystalline regions. The degree of crystallinity of the polymer is potentially important because it is generally recognized that hydrolysis is restricted to the amorphous phase of the polymer. However, the similar crystallinities of the materials used in this study would appear to rule out a morphological explanation for the rate differences.

Table 1 Chemical structure and microstructure of biodegradable polymers

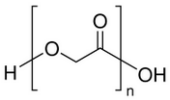
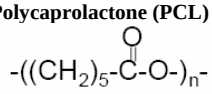
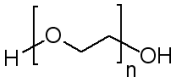
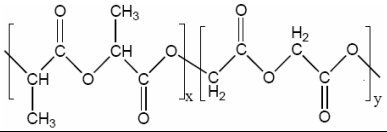
Biodegradable polymer	Microstructure
Poly(lactic acid) (PLA) 	Semicrystalline
Polycaprolactone (PCL) 	Semicrystalline
Polyethylene glycol (PEG) 	Semicrystalline
Poly(lactide-co-glycolide) (PLGA) 	Amorphous

Table 1 shows the chemical structures and microstructures of biodegradable polymers. The kinetic of MW change is used to determine when the materials have degraded to completely soluble products —this is by far the longest possible time the samples could serve as a scaffold. The biodegradation properties of polylactide (PLA), polycaprolactone (PCL), polyethylene glycol (PEG) and poly(lactide-co-glycolide) (PLGA) are summarised in Table 2. Simulation results reveal

that these materials rank in terms of their rate of degradation as follows: PLA < PCL < PEG < PLGA.

Table 2 Comparison of biomaterials' degradation properties

Polymers	Degradation rate constant / hr-1	Critical Mw to be eliminated /kDa	Initial Mw wt /kDa	Maximum useful lifetime (years)
PCL	9.65×10^{-5}	5	61.8	3
PLGA	1.9×10^{-3}	1.2	24.6	66 days
PLA	7.4×10^{-5}	5	10.8	3.2
PEG	6×10^{-4}	4	10	63 days

This ranking can be rationalized via the chemical and physicochemical factors that control degradation rates. All of the materials are comprised of degradable ester linkages; biopolymers cannot be differentiated based on purely bond differences. The two slowest-degrading materials have a number of factors lowering their degradation rate. They are both semicrystalline –PCL and PLA, which are much more quickly degraded than the other materials due to the greatly enhanced entry of water into the hydrophilic domains.

PCL is aliphatic polyester which has been shown to degrade by random hydrolytic separate from its ester groups, and under certain circumstances, by enzymatic degradation. There is a linear relationship between weight loss and lactic acid release suggesting surface erosion. It is similar to PLA in that, it degrades into a critical MW of 5000 as shown in Figure 1. However, PCL degrades a bit slower than PLA. The degradation rate constant for PCL and PLA are 9.65×10^{-5} hr^{-1} and 7.4×10^{-5} hr^{-1}, respectively. For PCL and PLA, too little degradation occurs over the time. Therefore, these materials can serve more than 3 years.

PEG is a highly hydrophilic, linear, unsaturated polymer composed of alternating PEG. PEG block gives its hydrophilicity. In addition, the properties of PEG are controlled by the molecular weight of the PEG.

Increase of MW of PEG results in less crosslinking. The MW of PEG here is 10000, and the degradation rate constant is 6 x 10-4 hr -1.

The final type of biopolymer discussed, PLGA is the copolymer of PGA and PLA. PGA is highly crystalline, hydrophilic, linear aliphatic polyester. As such, it has a high melting point and a relatively low solubility in most common organic solvents. The degradation rate constant of PLGA is 1.9×10^{-3} hr^{-1}. PLGA degrades because the mixture of lactide and glycolide repeat units in the chain prevents crystallization, which is more readily attacked by water. Due to the dependence of the degradation rate of PLGA copolymers on pH, a phenomenon known as autocatalysis occurs where the carboxylic group further induces degradation. For large-scale polymers, autocatalysis causes heterogeneous degradation where the pH decreases in the center of the polymer, and a difference in the degradation rate are created.

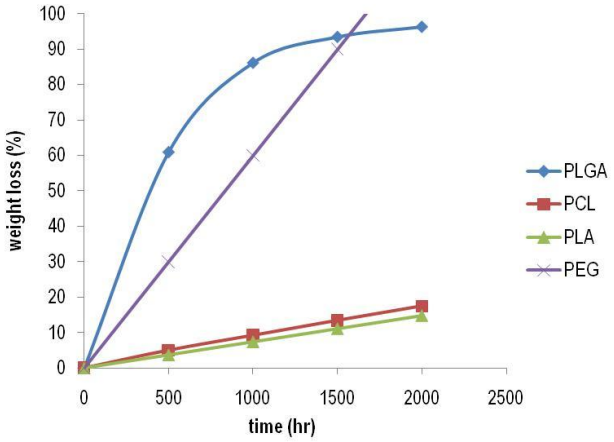


Fig. 1 Percentage weight loss vs time for degradation of PLGA, PCL, PLA and PEG

This estimated time is clearly far-outside limit of useful lifetime. Any real device will lose mechanical integrity significantly before the MW have degraded to this extreme limit, and thus the actual lifetime in many applications may be significantly shorter. These results provide a platform to predict and optimize scaffolds' biodegradation kinetics, thus reducing the number of experimental studies necessary to validate design performance. Experimentally validating this

model would involve implanting a scaffold into a bone defect in an animal model and making histological measurements of tissue phenotype at several time points.

4.0 Conclusion

The results presented in this paper show that the type of biopolymer and their degradation rate play significant role in determining optimal scaffold for TE applications. Mathematical modelling has the potential to generate a statistically perfect instant molecular weight decay curve. Scaffolds may also be optimized to suit site-specific loading requirements indicating the need for greater control over scaffold manufacturing techniques. The future of computational models applied to TE is very promising with the establishment of more powerful and realistic models that can simulate more accurately the biological processes. In the future, degradation studies of the TE scaffolds are needed to simulate the dynamic loading conditions of the in vitro system. The degradation properties are important for predicting the lifetime of biomaterials and components. Accelerated tests are available to help understand the aging processes in materials under a variety of conditions. With special attention to scaffold design and rapid prototyping technique, scaffold could be fabricated successfully for further cell culture and animal tests.

References

1) Melchels FPW, Bertoldi K, Gabbrielli R, Velders AH, Feijen J, Grijpma DW. Mathematically defined tissue engineering scaffold architectures prepared by stereolithography. Biomaterials. 2010; 31: 6909-16.

2) Liao J, Guo X, Grande-Allen KJ, Kasper FK, Mikos AG. Bioactive polymer/extracellular matrix scaffolds fabricated with a flow perfusion bioreactor for cartilage tissue engineering. Biomaterials. 2010; 31: 8911-20.

3) Jeong CG, Hollister SJ. A comparison of the influence of material on in vitro cartilage tissue engineering with PCL, PGS, and POC 3D scaffold architecture seeded with chrondrocytes. Biomaterials. 2010;31:4304-12.

4) Dai W, Kawazoe N, Lin X, Dong J, Chen G. The influence of structural design of PLGA/collagen hybrid scaffolds in cartilage tissue engineering. Biomaterials. 2010; 31: 2141-52.

5) Drury JL, Mooney DJ. Hydrogels for tissue engineering: scaffold design variables and applications. Biomaterials. 2003; 24: 4337-51.

6) Hutmacher DW. Scaffolds in tissue engineering bone and cartilage. Biomaterials. 2000; 21: 2529-43.

7) Hoque, M. E., Chuan, Y. L. & Pashby, I. Extrusion based rapid prototyping technique - An advanced platform for tissue engineering scaffold fabrication. Biopolymers. 2012; 97: 83.

8) Moroni L, Schotel R, Sohier J, de Wijn JR, van Blitterswijk CA. Polymer hollow fiber three-dimensional matrices with controllable cavity and shell thickness. Biomaterials. 2006; 27: 5918-26.

9) Cioffi M, Galbusera F, Raimondi MT. An in silico bioreactor for simulating laboratory experiments in tissue engineering. Biomed Microdevices. 2008; 10: 547-54.

10) Hoque, M. E., Chuan, Y. L., Pashby, I., Hwei, A. N. M. & Idrus, R. Process Optimization to Improve the Processing of Poly(DL-Lactide-co-Glycolide) into 3D Tissue Engineering Scaffolds. International Federation for Medical and Biological Engineering. 2011; 35: 836.

11) Kerl, J., Parittotokkaporn, T., Frasson, L., Oldfield, M., Rodriguez Y Baena, F. & Beyrau, F. Tissue deformation analysis using a laser based digital image correlation technique. Journal of the Mechanical Behavior of Biomedical Materials. 2012; 6: 159-165.

12) Erdemir, A., Guess, T. M., Halloran, J., Tadepalli, S. C. & Morrison, T. M. Considerations for reporting finite element analysis studies in biomechanics. Journal of Biomechanics. (In press)

13) Sandino C, Planell JA, Lacroix D. A finite element study of mechanical stimuli in scaffolds for bone tissue engineering. J Biomech. 2008; 41: 1005-14.

14) Pitt CG, Zhong-wei G. Modification of the rates of chain cleavage of poly([epsilon]-caprolactone) and related polyesters in the solid state. J Control Release. 1987; 4: 283-92.

15) Shiaw-Guang Hu D, Liu H-J. Effect of soft segment on degradation kinetics in polyethylene glycol/poly(l-lactide) block copolymers. Polymer Bulletin. 1993; 30: 669-76.

16) Suggs LJ, Moore SA, Mikos AG. In: Mark JE, editor. Physical Properties of Polymers Handbook. Cincinnati: Springer Science. 2007.