WATER DEGRADATION STUDY OF ALIPHATIC POLYESTERS

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ABSTRACT

The most popular and important biodegradable polymers are aliphatic polyesters, such as polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), polyhydoxyalkanoates (PHA's) and polyethylene oxide (PEO). However, each of these has some shortcomings which restrict its applications. Blending techniques are an extremely promising approach which can improve or tune the original properties of the polymers [1]. A composite solution of several materials with different degradation rates also enables tuning the rate of degradation of a particular cord device. Mixture rule can be used for this property. Aliphatic polyesters are a central class of biodegradable polymers, because hydrolytic and/or enzymatic chain cleavage of these materials leads to α-hydroxyacids, which in most cases are ultimately metabolized in human body. This is particularly useful for controlled release devices and for other biomedical applications like suture fibers and ligaments. For aliphatic polyesters, hydrolysis rates are affected by the temperature, molecular structure, and ester group density as well as by the species of enzyme used. The degree of crystallinity may be a crucial factor, since enzymes attack mainly the amorphous domains of a polymer.

1. INTRODUCTION

Biodegradable polymers have been used in implantable medical devices, such as suture fibers and ligaments. There are many considerations that should be taken into account when engineering such cords. Early in the repair process, the construct material should sustain the forces, but allow graded exposure to loading at later time points, avoiding the need to remove it. This is mainly important in the particular case of ligaments, allowing the tissue to develop more naturally and function more efficiently. In order to avoid stress shielding, the cord would ideally degrade at the same rate that new tissue is created. In order to ensure final clinical use, neither the cord nor its degradation products should be harmful to the surrounding tissue and they should not result in unresolved inflammation or other deleterious biological responses. Different combinations of fibers can be used to tune the degradation rate of cords. Apart from biological compatibility, these devices shall also be functional compatible and perform adequate mechanical support during the healing process.

Braiding is a technique that has been used to create products designed to bear axial loads and provide extension. Their design makes them shear resistant and conformable. The simplest braids are composed of sets of yarns that follow circular paths in opposite directions with a sequence of crossovers that cause the yarns to interlace forming a fabric. The twisting of fibers is used frequently in the textile industry to form yarns that

can withstand the weaving or knitting process. Both the twisting direction and degree of twisting affect yarn strength, abrasion resistance, and flexibility [2]. Low twist produces weaker yarns that pull apart more easily [2]. As the amount of twist is increased the strength and level of abrasion resistance of the yarns are increased. If the yarns are wound too tightly (and the fibers become more perpendicular to the long axis of the yarn) the strength and abrasion resistance decrease [2]. The composite architecture should be designed to accurately mimic the biomechanical profile and mechanical properties of the tissue. For ligament tissues, braid–twist cords resulted in a significant increase in the ultimate tensile strength, an increase in ultimate strain, and an increase in the length of the toe region when compared to braided and twisted fiber scaffolds alone [3].

Cords can vary in terms of architecture (pore diameter, porosity, surface area), and mechanical properties (tensile modulus, maximum tensile load) under tensile testing, according to fabrication parameters such as fibers diameter, braiding angle and yarn density [4]. The architecture of a cord is an important design consideration, for ligament applications, that can modulate biological response and long-term clinical success of the scaffold. It has been reported that calcified tissue ingrowth can occur at a minimum pore size of 100 μm [5]. In addition, a minimum pore diameter of 150μm is suggested for bone and 200-250μm for soft tissue ingrowth [6][7][8]. As the braiding angle increased both the porosity and mode pore diameter significantly decreased, whereas the pore surface area significantly increased. Overall scaffold porosity can this way modulate the functionality and gross cellular response to the implant.

To control the degradation rate, in order to match the dimensioning requests, during all the healing process, the project designer can use different yarns of fibers, composed of materials with different degradation rates. A wide range of degradation times and mechanical properties are possible using different fibers and varying diameter, architecture, and many commercial available materials. Using fast degrading fibers as outer fibers, and slow degrading fibers as inner fibers, one can thus produce a yarn with high degradation rate at the beginning of the healing process, and less degradable at the end.

2. MATERIALS REVIEW

The FDA has approved the use of the poly-α-hydroxyesters [polylactic acid (PLA), polyglycolic acid (PGA) and copolymers, polylactide-co-glycolide (PLAGA)] for a variety of clinical applications since the 1970s. PLLA is a rather brittle and rigid polymer, and compounding of the material with other polymers is frequently employed to improve physical properties or to control biodegradability.

Polyhydoxyalkanoates (PHA's) comprise the largest class of aliphatic polyesters, which includes poly 3-hydroxybutyrate (PHB), copolymers of 3-hydroxybutyrate and 3-hydroxyvalerate (PHBV), poly 4-hydroxybutyrate (P4HB), copolymers of 3-hydroxybutyrate and 3-hydroxyhexanoate (PHBHHx) and poly 3-hydroxyoctanoate (PHO) and its blends. The changing PHA compositions also allow favorable mechanical properties, biocompatibility, and degradation times within desirable time frames under specific physiological conditions [9].

Polycaprolactone is also an important member of the aliphatic polyester family [10], produced with very high molecular weight by ring opening polymerization of ε-caprolactone (ε-CL). PCL is miscible only with a limited number of polymers like poly(4-vinyl phenol) [11], poly(vinyl chloride) [12], poly(vinyl alcohol) [13], poly(vinyl methyl ether) [14] and bisphenol-A-type epoxy resin [15], while most of its blends with other aliphatic polyesters are immiscible [16][17][18]. As a biodegradable

material, is used extensively for the preparation of injection moulding products, films, etc. Additionally, PCL due to its biocompatibility has gained increasing interest for uses such as tissue engineering and appropriate drug release carrier [19].

Poly(ethylene glycol) (PEG), which is a hydrophilic, water soluble and fully biodegradable polymer, was extensively used in such block copolymer preparation [20]. PEG's lack of toxicity allows its usage in many biomedical and pharmaceutical applications [21][22].

Poly(propylene succinate) (PPSu) is a relatively new polyester with very high thermal stability similar with other familiar polyesters like poly (butylenes succinate) (PBSu) or poly(ethylene succinate) (PESu) [23][24][25]. Additionally, its biodegradation rate is very high compared with other aliphatic polyesters with similar structure, like poly(ethylene succinate) and poly(butylene succinate) [26]. Introduction of a flexible PPSu domain, with melting temperature close to the body temperature, into the rigid PCL matrix, could generate a class of innovative materials. Additionally, PPSu has a very slow crystallization rate, which could favour its miscibility with other aliphatic polyesters [27].

The chemical structures of aliphatic polyesters are presented in table 1. They represent a wide range of mechanical properties and degradation times, as can be seen in table 2 and figure 1.

Table 1 – Chemical structure of aliphatic polyesters

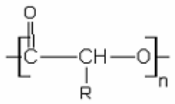
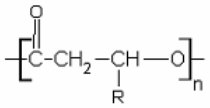
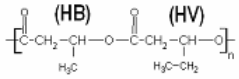
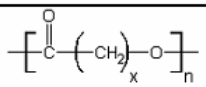
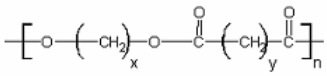
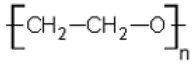
CHEMICAL STRUCTURE	EXAMPLES
 Poly(α-hydroxy acid)	☑ **R=H** → Poly(glycolic acid): **PGA** ☑ **R=CH_3** → Poly(L-lactic acid): **PLLA**
 Poly(β-hydroxyalkanoate)	☑ **R=CH_3** → Poly(β-hydroxybutyrate): **PHB** ☑ **R= CH_3, C_2H_5** → Poly(β-hydroxybutyrate-co-valerate): **PHBV**  (**PHBV** co-polymer containing 3HB and 3HV units)
 Poly(ω-hydroxyalkanoate)	☑ **x=5** → Poly(ε-caprolactone): **PCL**
 Poly(alkylene dicarboxylate)	☑ **x=2 e y=2** → Poly(ethylene succianate): **PESu** ☑ **x=4 e y=2** → Poly(butylene succianate): **PBSu** ☑ **x=4 e y=2,4** → Poly(butylene succianate-co- butylene adipate): **PBSuA**
	☑ Poly(ethyleneglycol): **PEG** ☑ Poly(ethylene oxide): **PEO**

Table 2 – Material properties of biodegradable thermoplastics; Tm, melting temperature; Tg, glass transition temperature; %Xc, crystallization percentage; Mw, number average molecular weight.

MATERIAL	Tg (ºC)	Tm (ºC)	% Xc	Mw (g/mol)	Elastic Modulus (MPa)	Tensile Strength (MPa)	Tensile Elongation (%)
PLA	62,21	138,88					
					$3.4x10^3$	60	
	58,61		2.41±1.6	$3.34x10^5$			
	45 - 60	150 - 162			350 - 3500	21 - 60	2.5 - 6
					3300 ± 0.08	57.8 ± 0.86	
PLLA				$4.5x10^5$			
	53	170-180					
	57	174		$1.37x10^5$	19.8 ± 3.0	31.5 ± 4.5	11,9
		169			107.7±16.3	3.2 ± 0.4	
	65	175	70	$1.10x10^5$	3200 - 3700	55 - 60	
	55 - 65	170 - 200			2700 - 4140	15.5 - 150	3 - 10
	60	178		$2.0x10^5$			
PGA						37,33	
	35 - 45	220 - 233			6000 - 7000	60 - 99.7	1.5 - 20
PDO			32	$1.5x10^5$		139,21	62
PDLLA				$3.25x10^5$			
	51,6				2.8 ± 0.4	25.9 ± 3.3	11.4 ± 1.0
	50 - 60				1000 - 3450	27.6 - 50	2 - 10
PDLGA				$1.18x10^5$			
PCL	-60			$2.66x10^5$			
		53,1		$2.7x10^4$			
	-60 - -65	58 - 65			210 - 440	20.7 - 42	300 - 1000
	-60	60		$1.20x10^5$			
PLLA/PCL (50:50)					8.1 ± 2.8	16.3 ± 1.3	18.3 ± 3.7
PDLLA/PGA (50:50)	40 - 50				1000 - 4340	41.4 - 55.2	2 - 10
PGA/PCL			34	$1.5x10^5$		192,1	55
PEO PEG				$3.0x10^5$			
				10^5- $8x10^6$	390		
	-64						
PHB	5 - 15	168 - 182			3500 - 4000	40	5 - 8
PELA					14	26-31	
PESu	-11,5	104	40				
PPSu	-35	44	32				
PBSu	-44	113	48				

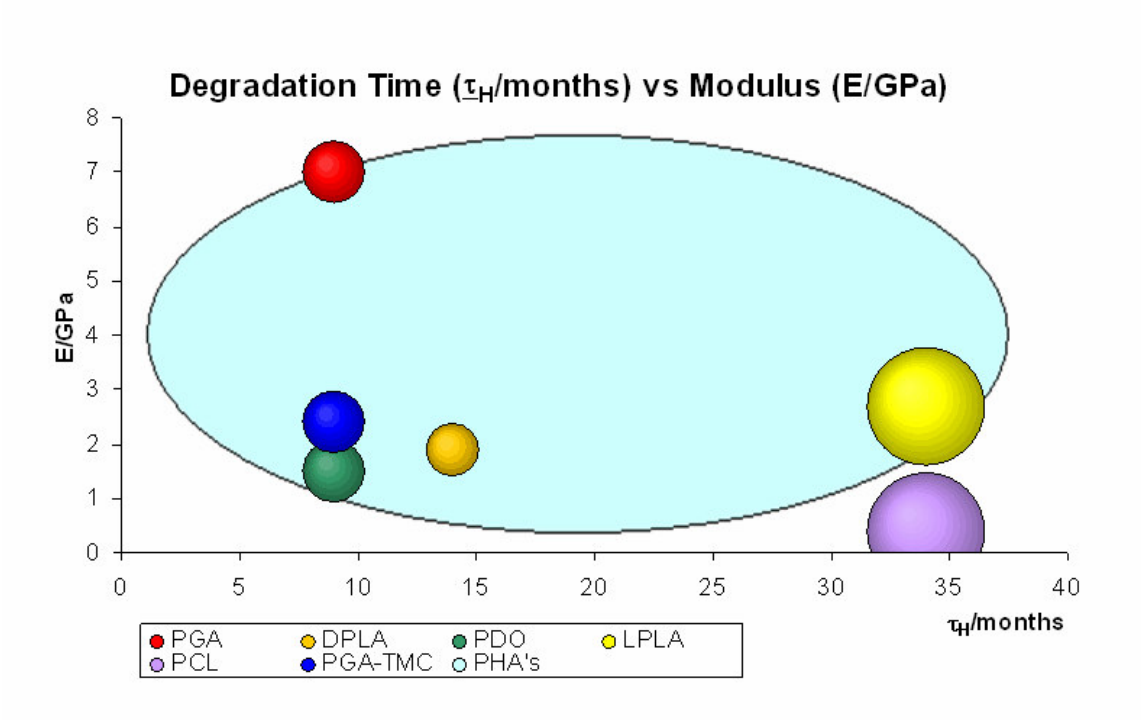


Figure 1 - Range of mechanical properties and degradation times

3. HYDROLYTIC DEGRADATION

After immersion of an aliphatic polyesters device in an aqueous medium or implantation in vivo, the very first event which occurs is water uptake. The penetrating water rapidly creates a negative gradient of water concentrations from the surface to the centre as expected from a pure diffusion viewpoint. However, this gradient vanishes in a couple of days, diffusion of small molecules like water being rather fast as compared with degradation rates. Therefore, one can consider that hydrolysis of ester bonds starts homogeneously from the beginning in agreement with the monomodal size exclusion chromatograms observed at the onset of molecular weight decreases [28].

The macromolecular skeleton of aliphatic polyesters comprises ester groups. These groups can go through hydrolysis leading to chain scissions. Hydrolysis has traditionally been modeled according to a first order kinetics. In the ideal case of hydrolytic degradation the following first-order equation describes the hydrolytic process to occur relative to the ester concentration (E) and water concentration (W):

$$\frac{dE}{dt} = -kEW = -V_m W \qquad (1)$$

V_m is the hydrolysis rate, and W is constant and water is spread out uniformly in the sample volume (no diffusion control). In this ideal case, the hydrolysis rate constant, k, depends only on temperature and does not vary with the conversion (no autocatalysis).

By assuming that the concentration of ester groups is equivalent to the inverse of number-average molecular weight ($E = 1/M_{n_t}$), it can thus be shown that:

$$M_{n_t} = M_{n_0} e^{-kWt} \qquad (2)$$

where M_{n_t} and M_{n_0}, are the number-average molecular weight, at a given time *t* and initially at *t=0*, respectively.

For aliphatic polyesters, its hydrolysis rates is affected by the temperature, molecular structure, ester group density as well as by the species of enzyme used. According to Marten et al. [29], the biodegradation rate of the copolyesters is mainly controlled by the chain mobility of the polymers, being correlated with the difference between the melting point of the polyester and the degradation temperature.

In the design phase of a biomedical cord device, it is important to predict the evolution of mechanical properties like tensile strength and stiffness, instead of molecular weight. It has been shown [30] that the fracture strength of a polymer can, in many cases, be related to M_n through the relationship:

$$\sigma = \sigma_\infty - \frac{B}{M_{n_t}} = \sigma_\infty - \frac{B}{M_{n_0} e^{-kWt}} \qquad (3)$$

where σ is the fracture strength, σ_∞ is the fracture strength at infinite molecular weight, and *B* is an empirical constant of the material. One can thus determine the limit strength for the material that can weaken during time, $\sigma_d = f(t)$.

4. EXPERIMENTAL PROCEDURE

Four different thermoplastic aliphatic polyesters (PGA, LPLA, PCL, PDO), representing a wide range of degradation times and mechanical properties, were provided by Chirmax. Suture fibers with two different diameters were selected for measuring degradation properties. Initial weights and number-average molecular weights will be determined using micro scale weight and GPC analysis. Initial mechanical properties (strength and stiffness) will also be measured form tensile tests to single fibers. Fibers specimens will then be submitted to six different degradation stages under water, NaCl solution and PSB, at constant temperature (37ºC). These stages will be different depending on materials, according to the previewed degradation times. Wet and dry weight will be measured at each stage, to determine water absorption and material erosion. Number-average molecular weights and mechanical properties will also be repeatedly evaluated at each stage. Using this methodology, the evolution curve of these physical properties during degradation will be determined, similarly to figure 3.

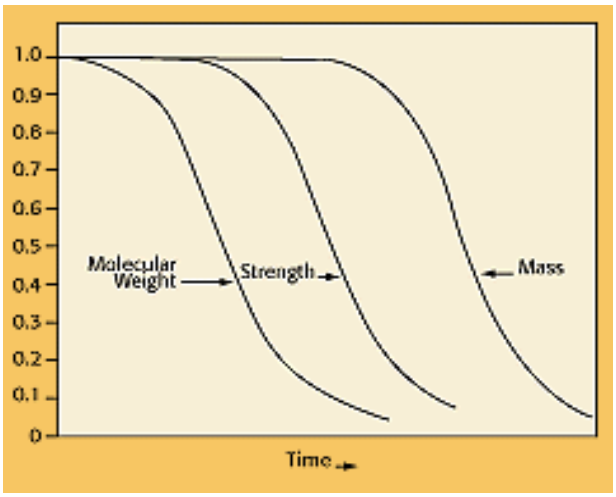


Figure 3 – Molecular weight, strength and mass evolution during degradation

5. CONCLUSIONS

Mechanical properties evolution during degradation can be tailored to match the tissue rehabilitation/remodeling and its strength recovering during the healing process, making use of the first-order kinetics to describe this evolution. This is possible since hydrolytic reaction is the limiting step of overall degradation process. Compatibility of biodegradable devices, in terms of strength, stiffness, strain at break and degradation time can so be accomplished by material selection and dimensioning to respond to functional requests. As the degradation products are naturally metabolized in human body, these materials are also biocompatible. Though, acidic groups may cause prolonged inflammatory response.
Biocompatibility can furthermore be enhanced, in terms of cell attachment and proliferation, by surface modification. However, the employed technologies must be accomplished at low temperature, to avoid damaging the thermoplastic substrate. Another limitation of aliphatic polyesters is its sterilization, since autoclave temperature is incompatible with most of them, and UV radiation pre degrades the material. Aliphatic polyester devices can be sterilized by ethylene oxide.

6. REFERENCES

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