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High performance resorbable composites for load-bearing bone fixation devices

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ABSTRACT

Bone fractures are some of the most common injuries annually, and many require a fixation device to help properly heal. The present study focuses on developing a bioresorbable composite that has high strength and stiffness for bone fixation applications. To achieve this, a design of experiments was performed, testing the effect of long fiber reinforcement type, matrix type, matrix amount, and particle reinforcement amount on the flexural properties of the composite. Based on these results, the ideal resorbable long fiber reinforcement, particle reinforcement, and matrix material are degummed silk fibroin, hydroxyapatite, and polylactic acid, respectively. Through further optimizations of the particle reinforcement phase a flexural modulus and strength of 13.7 GPa and 437 MPa, respectively, was achieved. Both values are among the highest found in literature, with the strength far exceeding the requirement for a fixation device and the highest for such a bioresorbable composite material, showing great promise for use as a bioresorbable fixation device.

1. Introduction

Investment in the biomaterials industry has been rapidly growing in recent years; the market for implantable biomaterials is projected to generate $11.9 billion in revenue by the year 2019 Elder (2014). In addition, the most common orthopedic-related trauma cases are bone fractures, which often require a fixation device to help heal the bone properly Ratner et al. (2014). Currently, metals are considered the clinical standard for bone fixation devices, however, there are many undesirable effects associated with using metal for fixation *in vivo,* including stress shielding and metal ion leaching. Stress shielding stems from the use fixation materials that are stiffer than natural bone (i.e. metals have an elastic modulus of 110–210 GPa (Oldani and Dominguez, 2012) while natural bone has a modulus ranging from about 8–25 GPa (Rho et al., 1997)), which results in load being imparted on the device rather than the bone and subsequently results in a localized decrease in bone mineral density. Meanwhile, metal ion leaching increases inflammation and irritation around the implant (Wu et al., 2016; Sun et al., 2012); Due to both effects, there is often a need for a second surgery to remove the fixation device, leading to higher medical costs and greatly increased patient discomfort. For these reasons, there has been great interest in making a fixation device that is mechanically sound enough to properly support the healing of bone, while being fully degradable to eliminate the need for a second surgery.

There have been many researched materials that are able to safely degrade *in vivo*, but their mechanical properties typically fall short of what is required for a load-bearing fracture Hasegawa et al. (2006). As such, composite materials have been investigated to provide better mechanical support than degradable polymers alone. An example of such a composite was made by Zhang et al. and consisted of polylactic acid (PLA) in addition to hydroxyapatite particle reinforcement Zhang et al. (2010). Using an in situ-precipitation method, Zhang et al. created a composite with a Young's modulus of 3.6 GPa and a strength of 155 MPa, which is neither strong nor stiff enough for load-bearing applications. The best results thus far using a polymer matrix reinforced with bioceramic particles came from Shikinami et al. Shikinami and Okuno (1999) Granules of PLLA with uniformly-distributed HA microparticles were hot compression molded to make HA-reinforced PLLA composites in this study. The resulting composite bars had a bending modulus and strength of 9.1 GPa and 270 MPa, respectively. Despite showing the best properties for such a composite, the composites still left much to be desired with regards to bending stiffness for use as a load-bearing implant To overcome the relatively poor mechanical properties of polymer-based degradable materials, degradable metals

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have been investigated as well, such as magnesium Castellani et al. (2011). Such materials have been shown to have mechanical properties similar to bone, however magnesium has been shown to release hydrogen gas when degrading *in vivo* and causes localized inflammation, indicating the need for further improvements to make viable degradable fixation devices. Most recently, Heimbach et al. produced a composite containing both biodegradable long-fiber reinforcement and particle reinforcement. With this formulation, the composite material achieved a bending modulus of 9.2 GPa and a bending strength of 187 MPa while showing remarkable toughness Heimbach et al. (2016).

Silk fibroin (SF) has been proven to be a degradable polymer with superb mechanical properties in tension Verari and Kaplan (2007). In the clinical setting and in literature, silk has been shown to be great for use as sutures and tissue engineering scaffolds due to mechanical properties that are superior to most other degradable polymers. However, SF has not been previously used to make a high performance dense composite in the field of biomaterials. With this in mind, the present study investigates the use of SF as the primary reinforcement material in composites made for load-bearing fixation applications. Using procedures similar to those outlined in previous work, methods for creating high performance composites were developed with the aid of a design of experiments (DOE), with further work focusing on the use of HA particle reinforcement in tandem with SF fiber reinforcement.

2. Materials and methods

2.1. Materials

The following materials were purchased from Fisher Scientific: calcium nitrate tetrahydrate ($Ca(NO_3)_2{\cdot}4H_2O$, ACS certified), ammonium phosphate dibasic ($(NH_4)_2HPO_4$, ACS certified), methyl ethyl ketone (MEK, ACS certified), and ammonium hydroxide (NH_4OH, certified ACS plus). Cetyltrimethylammonium bromide (CTAB, ≥ 99%) was purchased from Sigma Aldrich. Dichloromethane (DCM, stabilized with amylene, ≥ 99.8%, for analysis) was purchased from Arcos Organics. Both poly-L-lactic acid (PLLA) and silk fibroin (SF) fibers were generously supplied by Teleflex Medical Inc, and polycaprolactone (PCL, M_w = 80,000) was purchased from Instamorph.

2.2. HA Synthesis and surface treatment

Hydroxyapatite nanorods were synthesized via a wet precipitation method as previously described Heimbach et al. (2016). Briefly, 188.86 g of $Ca(NO_3)_2{\cdot}4H_2O$ was dissolved in 720 mL deionized water (DiW), where 24 mL of NH_4OH was added. Next, 696 mL DiW was added to dissolve the resulting precipitate, completing the formation of solution 1. To make solution 2, 63.36 g of $(NH_4)_2HPO_4$ was dissolved in 1200 mL of DiW. 600 mL of NH_4OH was added to solution, and subsequently 760 mL of DiW was added to dissolve the resulting precipitate, concluding solution 2. Next, solution 2 was added drop-wise to solution 1, and, upon completion, boiled for 3 h. Once cooled, the HA nanorods formed were surface treated to ensure even distribution and minimal aggregation in the dip-coating suspension, as previously described Heimbach et al. (2016). Briefly, the supernatant of the resulting suspension of HA particles from procedure previously outlined was poured off until a final HA concentration of ~3 g/dL was reached (final volume of ~2.5 L). Next, 4 g of CTAB was suspended in 60 mL of DCM and quickly added to the HA suspension under vigorous stirring. The suspension continued stirring for 2 h, and then was left to sit overnight at 60 °C to aid in the surface treatment. Following the surface treatment, the HA was washed with DiW 5 times to remove the NH_4OH and dried at 150 °C overnight. Based on these previous studies the final particles take the shape of nanorods with a final length, width, and aspect ratio of 70 nm, 12 nm, and 6, respectively Heimbach et al. (2016).

2.3. Design of experiments

Many materials were considered for the development of high performance bioabsorbable composites, with the final list of materials being SF fibers, PLLA fibers, PLA matrix, PCL matrix, and HA nanoparticles. These materials were selected because they have been shown in literature to safely degrade *in vivo* and are all already FDA approved materials (Bettinger et al., 2007; Alsaheb et al., 2015; Azimi et al., 2014; Bobo et al., 2016). Due to the many different materials used and possible formulations, a design of experiments (DOE) was utilized to assess the effect of key variables in the processing of the composite on the 3 mechanical properties (i.e. the dependent variables) of interest: flexural modulus, flexural strength, and relative flexural toughness. In total, five independent variables were chosen, including fiber type ratio (SF: PLLA vol% ratio), matrix type, matrix amount, and HA amount, as well as a blocking variable, which was the mold cavity.

For each of these variables, a “low” and a “high” value was chosen to use in the DOE. The SF: PLLA ratio was either 1:9 or 9:1, as these ratios allowed for the minimum of one full layer for each fiber type in the final composite bar (i.e. one layer of SF fibers for the 1:9 ratio and one layer of PLLA fibers for the 9:1 ratio). Matrix type, a categorical variable, was either PCL or PLA, test how matrix type affected the bending properties of the composite. Preliminary testing showed less than 2 wt/vol% matrix (PCL or PLA) in the dip coating suspension did not wet fibers sufficiently, and more than 10 wt/vol% matrix in the dip-coating suspension caused complications in processing the composite. So these values were chosen as the limits in the DOE. Similarly, preliminary tests showed that having greater than 15 wt/vol% HA in the dip-coating suspension caused complications in processing, as well as severe aggregation of HA in the final composite. As such, the HA amount for the DOE was either 0 wt/vol% or 15 wt/vol% in the dip-coating suspension. Lastly, the mold cavities were simply labeled A or B and were used to confirm that the mold cavity would not affect the properties of the composite samples (i.e. the samples should have the same properties regardless of which mold cavity they are pressed in).

To minimize the number of runs required to complete the DOE, an assumption was made that there would be negligible-to-zero three-way interactions of the factors on the three dependent variables of interest. As such, the number of runs was reduced from 2^n to 2^{n-1}, where n is the number of independent variables (5), for a total of 16 runs for the DOE. The run list and sample compositions are listed in Table 1, however the runs were completed in a randomized order to control for error. DOE analysis was performed using DOE analytics tools in the statistical analysis software Statistica. Factors were said to have a

Table 1
A list of the compositions that were made and tested for DOE in this study. Note, the order of the samples was randomized to further reduce outside factors.

Run Number	Mold Cavity	SF: PLLA Ratio	Matrix Material Used on SF	Matrix Amount in Suspension (wt/vol%)	HA Amount in Suspension (wt/vol%)
1	1	9:1	PCL	2	15
2	2	9:1	PCL	2	0
3	1	1:9	PCL	2	0
4	2	1:9	PCL	2	15
5	1	9:1	PLA	2	0
6	2	9:1	PLA	2	15
7	1	1:9	PLA	2	15
8	2	1:9	PLA	2	0
9	1	9:1	PCL	10	0
10	2	9:1	PCL	10	15
11	1	1:9	PCL	10	15
12	2	1:9	PCL	10	0
13	1	9:1	PLA	10	15
14	2	9:1	PLA	10	0
15	1	1:9	PLA	10	0
16	2	1:9	PLA	10	15