Assessment of magnesium wire coatings for absorbable medical devices

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Abstract

Absorbable magnesium (Mg) wires have the potential to replace many permanent medical devices. Permanent devices endure as an unnatural material in the body whereas eventual staples, stents, and sternal wires made from absorbable magnesium can enable complete tissue healing by elimination of most long-term foreign material. Due to magnesium's relatively rapid degradation rate, thin devices may not provide adequate mechanical support during the entire healing phase without surface modifications or coatings to delay the onset of corrosion. This study aimed to assess the feasibility and effectiveness of absorbable coatings which could be suitable for a range of Mg based biomedical devices, spanning cardiovascular, orthopedic, and wound closure implants. Mg alloy LZ21 wire was drawn to 0.3 mm and annealed to impart high ductility. A portion of the wire was then anodized in an experimental electrolyte. Anodized wire was then coated with an absorbable polymer jacket of polycaprolactone (PCL). Bare, anodized, and PCL-coated wire was then subjected to both in-vitro and in-vivo degradation testing to assess coating impact.

Introduction

Many medical devices such as stents, staples, sutures, and ligation clips are comprised of wires with diameters less than one millimeter. Often, these devices only serve a temporary purpose and their continued presence is unnecessary, and in some cases even harmful. Magnesium alloys, with an inherent ability to degrade and absorb into the body harmlessly, are an attractive material for new iterations of these medical devices. However, the relatively rapid degradation rate of magnesium may not allow for sufficient mechanical strength for a sufficient length of time, especially in these fine diameters [1].

Many studies have explored extending the lifetime of magnesium alloys with surface modification in the form of conversion coatings (e.g. anodization, plasma electrolytic oxidation (PEO), MgF_2) and polymeric coatings (e.g. PLA, PLLA, PLGA, PCL) with some success [2] [3] [4], though data on coated Mg wire is sparse. Ali et al showed promising results with a continuous PEO coating on Mg wire [5] [6], but relatively hard and thick oxide layers may not be suitable in applications requiring flexural deformation of the wire. There is also some evidence that dual layer comprising a conversion coat and a polymer perform better than either coating alone [7]. An ideal coating would be pliable enough to withstand large wire bends, tough enough to withstand mild abrasion, and protective enough to delay corrosion past some critical time point, which will be application-specific.

A promising Mg alloy candidate, LZ21 [8] [9], possesses excellent ductility and moderate strength, properties which could lend it well to the aforementioned medical devices
However, like most magnesium alloys, the degradation rate may not be sufficient without a coating.

The aim of the present study is to 1) determine the influence of anodization and polymer coating on degradation of LZ21 wire, 2) determine for the first time an in vivo degradation rate of LZ21, and 3) establish an in vitro in vivo correlation (IVIVC) factor.

Materials and Methods

Magnesium alloy LZ21 wire preparation has been described previously [8]. In this study, wire was cold drawn to a final diameter of 0.3 mm and annealed. The wire was then divided into one of three surface conditions. Bare wire was left in the as-drawn, bright state. Anodized wire was prepared through a proprietary process which induced a thin surface layer containing Mg, F, O, and P. PCL wire was produced by melt extruding a thin layer (approximately 20 μm) of M_n 80,000 PCL (MilliporeSigma, Burlington, MA) onto the Anodized wire.

Baseline mechanical properties of the three conditions were assessed via tensile testing (127 mm gauge length, 25.4 mm/min crosshead speed, N=3).

In vitro corrosion properties of the wire were tested by using custom PVC and Nylon "kitewinder" test fixtures, in which multiple lengths of wire were wrapped across 250 mm spans. The wire sections experiencing bending stresses around the ends of the fixture were masked with paraffin wax, to prevent premature fracture at these locations during corrosion. Loaded kitewinders were fully submerged in 2 L of a modified Hanks's balanced salt solution, held in an incubator at 37ºC and 5% CO_2 to buffer the pH to 7.4 +/- 0.2. Samples were then allowed to corrode for 3, 7, 14, and 28 days with 4 samples for each time point. Of the four samples, three were tensile tested as described above to determine residual mechanical strength while one sample was designated for cross-sectional analysis.

In vivo corrosion properties of bare and PCL wires were assessed via subcutaneous implantation of 10 mm lengths in mice for 7 and 33 days. Briefly, a subcutaneous pouch was created via blunt dissection after a midline abdominal incision. Materials were inserted into the pouch, and the would closed with surgical staples. After euthanasia at the designated time points, the wires were carefully removed from the pouches and placed into 200 proof ethanol and desiccated overnight in a ventilated fume hood. The animal study was approved by the Michigan Technological University Institutional Animal Care and Use Committee (IACUC) and in accordance with guidelines set by the Panel on Euthanasia of the American Veterinary Medical Association. After each time point, the wires were explanted, and corrosion was assessed via cross-sectional analysis.

Cross-sectional analysis was conducted by mounting wire sections in a cold-curing epoxy and then progressively grinding and polishing to 4000 grit sandpaper with isopropyl alcohol lubricant. For each in vitro condition and time point, 11 sections were imaged. For each in vivo condition and time point, 16-26 sections were imaged. Residual area and pitting factor were measured for each cross section using ImageJ. Residual areas of both in vitro and in vivo samples were compared to establish a preliminary IVIVC.

Results

Representative tensile properties of the three wire conditions prior to corrosion are shown in Figure 1. The triplicate testing revealed high consistency between samples. The bare wire exhibited an ultimate tensile strength of 245 MPa, a yield strength of 189 MPa, and an elongation of 15%. Neither coating process impacted the strength properties but the elongation to fracture did decrease slightly.
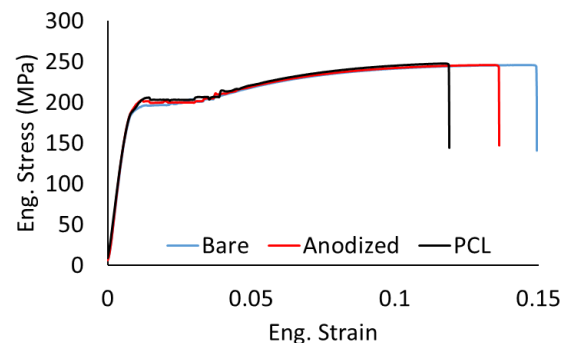

Figure 1. Representative tensile curves of the three conditions prior to corrosion.

In vitro corrosion testing showed marked differences between coating types. As shown in Figure 2, Bare wire fell to 18% of its original strength within 7 days while Anodized wire

retained 60% of its original strength over the same time period. The PCL wire still had over 90% of its original strength out to 14 days. These strength values largely corresponded with cross-sectional area loss ($R^2 = 0.945$), illustrated in Figures 3-5 with representative images at each of the time points for which intact wire specimens remained. In the case of Bare wire, no wires were intact at the 14 and 28 day timepoints. No Anodized wire specimens were intact at the 28 day timepoint.
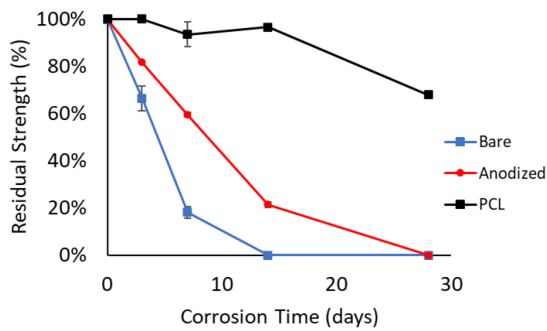

Figure 2. Residual strength of wire over time after degrading in vitro. Data shown is mean values with standard deviation error bars.
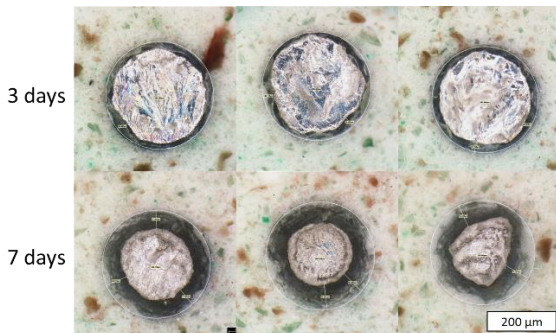

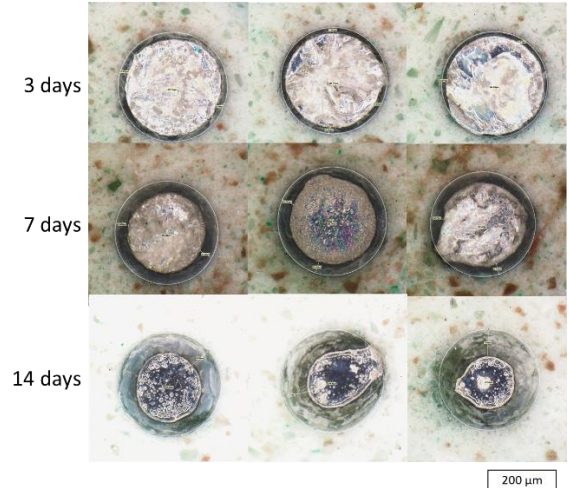**Figure 3.** Representative transverse cross-sections of bare wire degraded 3 and 7 days in vitro.

Figure 4. Representative transverse cross sections of Anodized wire degraded 3, 7, and 14 days in vitro.
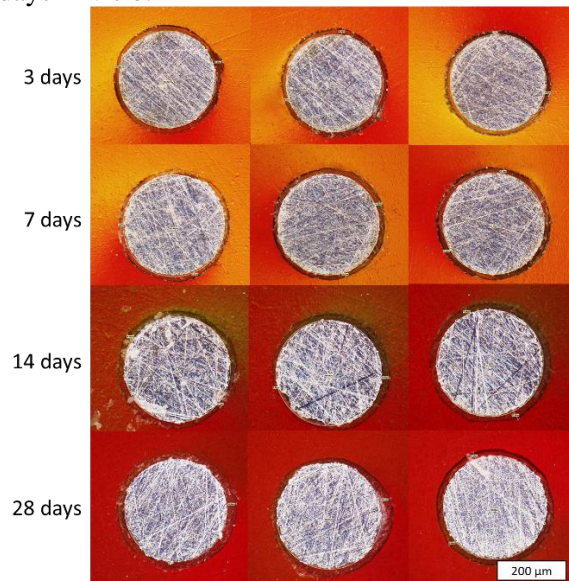

Figure 5. Representative transverse cross sections of the PCL wire degraded 3, 7, 14, and 28 days in vitro.

In vivo degradation testing of Bare wires indicated a much slower degradation rate than the in vitro test (Fig. 6), with 84% of the metal cross section remaining after 7 days in the mouse as opposed to only 37% in the Hank's solution. After 33 days in vivo, 60% of the cross section remained on average. The PCL wire showed almost no sign of corrosion at both 7 and 33 day time points (Figure 7). Residual area over time for all 5 condition sets is shown in Figure 8.

Taking the residual area measurements and assuming a uniform loss, average corrosion rates for the bare wire were 2.1 and 3.0 mm/yr at 3 and 7 days in Hank's solution, respectively, and 0.63 and 0.37 mm/yr at 7 and 33 days in mice, respectively. Taking the 7 day time point, we calculate an IVIVC factor of 8.1.
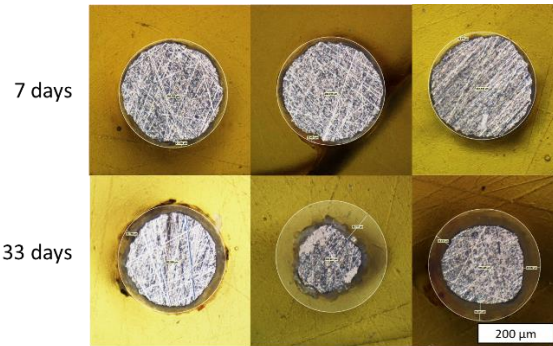

Figure 6. Representative transverse cross sections of the bare wire degraded 7 and 33 days in vivo.
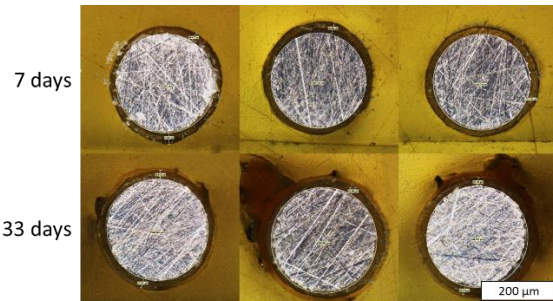

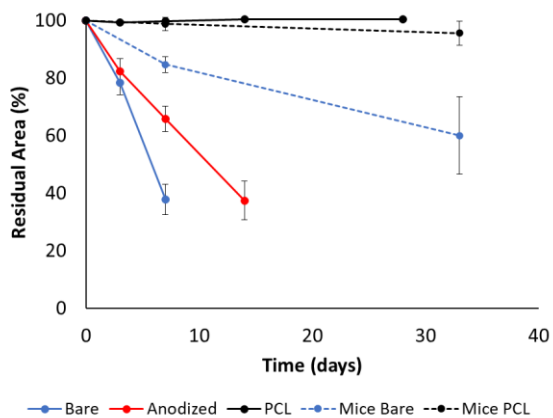**Figure 7.** Representative transverse cross sections of the PCL wire degraded at 7 and 33 days in vivo.

Figure 8. Residual cross-sectional area (mean ± standard deviation) of the various wires in vitro (solid) and in vivo (dashed).

Discussion

The aim of this study was to 1) determine the influence of anodization and polymer coating on degradation of LZ21 wire, 2) determine for the first time an in vivo degradation rate of LZ21, and 3) establish an in vitro in vivo correlation factor. The data presented here substantially addresses each of these aims.

The in vitro testing clearly indicates that anodization surface treatment of Mg wire can offer some corrosion protection and extend functional lifetime. Incorporating a PCL jacket on top of this anodization layer can provide even further corrosion delay. The present results indicate that the PCL jacket used in this study might be too protective for some applications, as little to no degradation of the wire was seen in vitro or in vivo. It is possible that corrosion delay could be tuned by using a thinner layer of PCL or a different PCL grade [10]. Other polymer coatings might offer optimized degradation rates as well.

The in vivo degradation data indicate a relatively low and uniform corrosion rate for the LZ21 alloy, with no visible adverse histological effects. Lithium is primarily added to the alloy to enhance bending ductility, but it may be the case that this relatively small amount of Li is able to increase the passivity of the corrosion layer through formation of a Li_2CO_3 film [11], inhibition of MgO to $Mg(OH)_2$ conversion [12], or some other mechanism. Additional work to elucidate the elemental composition and evolution of corrosion products on LZ21 wire is warranted.

The establishment of an IVIVC is an important step for the development of medical devices containing the LZ21 alloy. The factor of 8.1 determined here using 7 day time points is substantially higher than that reported by Bowen [1]. That study calculated an IVIVC factor of 1.2-1.9 for pure Mg, but the in vitro testing was conducted in DMEM rather than Hank's solution. This indicates that in vitro testing in Hank's can allow for effective accelerated corrosion testing. The high correlation between measured area and measured tensile strength of these wires aligns with other studies by Bowen [13] [14], and

suggests that residual mechanical strength of a partially corroded device can be inferred by the remaining metallic cross sectional area, provided corrosion is sufficiently uniform.

There are several areas of inquiry which are ripe for investigation. Future work should seek to understand the influence of thermomechanical processing on LZ21 degradation behavior. As many medical devices will undergo plastic deformation during implantation, testing corrosion properties of the coated materials after experiencing a relevant amount of plastic deformation may provide additional insights into the limitations of these coating strategies. And finally, a more in-depth investigation of the corrosion layer could explain the relatively low corrosion rate seen in this mouse model.

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