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Biocompatible Ni-free Zr-based bulk metallic glasses with high-Zr-content: Compositional optimization for potential biomedical applications

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ABSTRACT

The present study designs and prepares Ni-free $Zr_{60+x}Ti_{2.5}Al_{10}Fe_{12.5-x}Cu_{10}Ag_5$ (at.%, $x = 0, 2.5, 5$) bulk metallic glasses (BMGs) by copper mold casting for potential biomedical application. The effects of Zr content on the *in vitro* biocompatibility of the Zr-based BMGs are evaluated by investigating mechanical properties, bio-corrosion behavior, and cellular responses. It is found that increasing the content of Zr is favorable for the mechanical compatibility with a combination of low Young's modulus, large plasticity, and high notch toughness. Electrochemical measurements demonstrate that the Zr-based BMGs are corrosion resistant in a phosphate buffered saline solution. The bio-corrosion resistance of BMGs is improved with the increase in Zr content, which is attributed to the enrichment in Zr and decrease in Al concentration in the surface passive film of alloys. Regular cell responses of mouse MC3T3-E1 cells, including cell adhesion and proliferation, are observed on the Zr–Ti–Al–Fe–Cu–Ag BMGs, which reveals their general biosafety. The high-Zr-based BMGs exhibit a higher cell proliferation activity in comparison with that of pure Zr and Ti-6Al-4V alloy. The effects of Zr content on the *in vitro* biocompatibility can be used to guide the future design of biocompatible Zr-based BMGs.

1. Introduction

Unlike traditional crystalline alloys, bulk metallic glasses (BMGs) exhibit unique properties due to the absence of grain boundaries, dislocation, and slip planes. During the past two decades, increasing attention has been drawn to the biomedical application of BMGs [1–3]. Their high strength and elasticity, exceeding those of currently used biomaterials, together with good wear and corrosion resistance are desirable properties as biomaterials [4–6]. In addition, their thermoplasticity permits precision net-shaping of complex geometries, which is of great benefit for the processing of biomaterials [7,8].

Among the various metallic glass-forming systems, Zr-based BMGs are the most developed and investigated one. They yield a unique combination of superior strength (~2 GPa), high elastic strain limit (~2%), relatively low Young's modulus (~80 GPa), high wear resistance, and excellent bio-corrosion resistance, all of which motivate their potential applications as biomaterials, including as orthopedic implants [9–15]. Pioneer researches have been carried out to evaluate the bio-corrosion resistance of Zr–Al–Ni–Cu and Zr–Ti–Ni–Cu–Be BMGs, which are well known for their high glass forming ability (GFA) [12,16]. The Zr-based BMGs show as high bio-corrosion resistance as that of crystalline pure Ti and Ti-based alloys, which ensures good biosafety of BMGs in physiological environment. However, those Zr-based BMGs contain "toxic" elements of Ni and Be, important alloy elements to achieve high GFA. To overcome this drawback, Jin et al. have developed a series of Ni-free Zr–Al–Fe–Cu BMGs with excellent glass forming ability and satisfactory biocompatibility [13,17]. In the last decade, series of BMGs with less hazardous elements have been developed to ensure good biocompatibility. Ni-free glass forming systems such as Zr–Al–Fe, Zr–Al–Cu–Fe–Ag, Zr–Cu–Pd–Al–Nb, Zr–Al–Cu–Fe-(Ti/Nb), and Zr–Al–Co–Ag alloys have been fabricated to eliminate the possible allergic response caused by toxic elements [15,18–22]. The biocompatibility of those Ni-free Zr-based BMGs was evaluated by the *in vitro* and *in vivo* assays [13–22]. Zr-based BMGs support similar or better cell adhesion and proliferation compared with commercial biomedical alloys. Moreover, a lower level of macrophage activation has been found on Zr-based BMGs as compared with Ti-6Al-4V alloy, demonstrating a lower inflammatory response of BMGs [14]. A common foreign body response characterized by fibrous encapsulation has been observed in animal tests of

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Zr-based BMGs. The thickness of fibrous encapsulation varies with different glass-forming compositions, which provides opportunity to tune the foreign body response by alloy design [2].

Mechanical compatibility and biocompatibility are the two selection criteria for biomedical implant materials. From the perspective of mechanical compatibility, low Young's modulus is required for reducing the concern of bone resorption. This is because the mismatch of Young's modulus between implants and bone causes the removal of sufficient loading to the newly formed bone [3]. It has been found that Zr-based BMGs with high content of Zr usually exhibit low Young's modulus. For instance, the $Zr_{75}Al_{7.5}Fe_{17.5}$, $Zr_{70}Al_8Ni_{16}Cu_6$, and $Zr_{72}Ni_{7.5}Cu_{13}Al_{7.5}$ glassy alloys possess low Young's modulus of about 70 GPa, which is closer to the modulus of human bone (~30 GPa) than the 80–90 GPa of the conventional Zr-based BMGs with 40–60 at.% Zr [18,23–25]. Moreover, the compressive plasticity and fracture toughness of Zr-based BMGs increase with the increase in Zr content. By tailoring compositions in the Zr–Al–Ni–Cu and Zr–Al–Fe alloy systems, $Zr_{70}Al_7(Ni_{1/3}Cu_{2/3})_{23}$ and $Zr_{75}Al_{7.5}Fe_{17.5}$ BMGs exhibit excellent room temperature compressive plasticity and high notch toughness, which increases the reliability by preventing catastrophic failure in load-bearing conditions [18,25]. From the viewpoint of biocompatibility, high bio-corrosion resistance can prevent metallic ions from releasing into the human body, which ensures their general biosafety [2,3]. For instance, $Zr_{70}Al_8Ni_{16}Cu_6$ BMG shows more homogeneous and stable Zr-enriched passive film than that of $Zr_{50}Cu_{40}Al_{10}$ BMG, which results in a higher corrosion resistance [26]. In addition, the Zr/Cu content ratio in the alloy composition affects the biocompatibility of the Zr-based BMGs, by increasing their corrosion resistance and surface wettability with the increase of the Zr/Cu ratio in Zr–Cu–Al–Nb–Pd BMGs [20]. To sum up, high-Zr-based BMGs possess better mechanical compatibility and biocompatibility than those of conventional Zr-based BMGs. Therefore, high-Zr-based BMGs are considered to be more promising biomaterials. However, most of the high-Zr-based BMGs developed to date contain "toxic" element of Ni, which restricts their bio-application. To overcome this problem, we developed a new Ni-free high-Zr-content BMG of $Zr_{65}Ti_{2.5}Al_{10}Fe_{7.5}Cu_{10}Ag_5$ [27], which consisted of higher content of Zr and lower content of Cu compared to those of the classical Ni-free $Zr_{58}Cu_{22}Fe_8Al_{12}$ BMG [17]. Minor additions of Ag and Ti were introduced to enhance the GFA, plasticity, and corrosion resistance of BMGs according to the previous reports [19,21,22,27–29]. However, the mechanism of the excellent mechanical compatibility and biocompatibility resulting from high-Zr-bearing is still unknown.

Before any material can be used *in vivo*, the *in vitro* biocompatibility is a subject requiring a great number of investigations. Thus, in this study, we design and fabricate a series of Ni-free $Zr_{60+x}Ti_{2.5}Al_{10}Fe_{12.5-x}Cu_{10}Ag_5$ (at.%, $x = 0, 2.5, 5$) BMGs. The critical issues of this work are (1) to investigate the effect of Zr content on the mechanical properties of Zr–Ti–Al–Fe–Cu–Ag BMGs and discuss the possible mechanism of the excellent mechanical compatibility of high-Zr-based BMGs; (2) to study the effect of Zr content on the corrosion behavior of BMGs in a physiologically relevant environment and propose mechanistic understanding of their bio-corrosion behavior; and (3) to study the cellular response of present Zr-based BMGs and compare with that of commercial biomaterials. All of the results provide the foundational information of this family of High-Zr-based BMGs and can be used to guide the future design of biocompatible Zr-based BMGs.

2. Experimental

2.1. Materials preparation and characterization

Master alloys with nominal compositions of $Zr_{60+x}Ti_{2.5}Al_{10}Fe_{12.5-x}Cu_{10}Ag_5$ (at.%, $x = 0, 2.5, 5$) were prepared by arc melting the mixtures of pure Zr, Ti, Al, Fe, Cu, and Ag metals under Ti-gettered high-purity argon atmosphere. From the master ingots, alloy rods (ϕ 2 mm × 50 mm), rectangular bars (2 mm × 2 mm × 50 mm), and plates (1 mm × 10 mm × 50 mm) were cast in copper molds. The glassy structure of the as-cast alloy specimens was verified by X-ray diffraction (XRD, Bruker AXS D8) with Cu Kα radiation. Thermal properties of the as-cast BMGs including glass transition, crystallization, and melting were investigated by differential scanning calorimetry (DSC, NETZSCH DSC 404 C) at a heating rate of 0.33 K s^{-1} in a flowing argon atmosphere.

2.2. Mechanical tests

Compression and notch toughness tests were carried out using mechanical testing systems (Instron, 5565) with a strain rate of 2.1×10^{-4} s^{-1} at room temperature. The specimen gauge for compressive tests was 2 mm in diameter and 4 mm in length. Rectangular bars were prepared for notch toughness measurements into the geometry of 2 mm × 2 mm × 30 mm. The notch toughness of BMG was examined by three-point bending (3-PB) test with a 20 mm span. The notch with a depth of about 1 mm and root radius of about 200 μm was cut by a slow diamond saw. At least four samples were measured to ensure statistical reliability of the data. The morphology of samples after deformation was examined with a scanning electron microscope (SEM, CS 3400). The elastic constants of the BMGs, including Young's modulus (E), bulk modulus (B), shear modulus (μ), Poisson's ratio (ν) were measured using resonant ultrasound spectroscopy (RUS, NDT 5703PR). The mass density (ρ) of the BMG samples was measured using the Archimedes method. Microhardness tests were carried out using a load of 300 g applied during 10 s. The reported values were the average of five measurements. The mechanical properties of commercial implant alloys and bone are also listed for comparison [12]. $Ti_{90}Al_6V_4$ (wt.%) [$Ti_{86.2}Al_{10.2}$ $V_{3.6}$ (at.%), ASTM F136] was denoted as Ti-6Al-4V; $Co_{63}Cr_{28}Mo_6$ (wt.%) [$Co_{61.4}Cr_{30.9}Mo_{3.6}$ (at.%), ASTM F799] was denoted as Co-Cr; and 316 L stainless steel [$Fe_{62.5}Cr_{19.3}Ni_{13.3}$ (at %), ASTM F138] was denoted as 316 L SS.

2.3. Bio-corrosion measurements

The bio-corrosion behavior of the BMGs was examined by electrochemical polarization measurements. The electrochemical parameters of pure Zr and Ti-6Al-4V alloy were also shown for comparison. Electrochemical measurements were conducted using a three-electrode cell composed of a working electrode, a platinum counter electrode, and a saturated calomel reference electrode (SCE). Potentiodynamic polarization curves were measured at a potential sweep rate of 50 mV min^{-1} after open-circuit immersion for about 20 min when the open-circuit potential became almost steady. In order to characterize the composition and chemical states of elements on the passive films of BMGs, the specimens were immersed in phosphate buffer saline (PBS) solution for 24 h after mechanical polishing, rinsed with deionization water, dried in air, and then taken out for X-ray photoelectron spectroscopy (XPS, ESCALab250) analysis using a photoelectron spectrometer with Al Kα radiation.

2.4. Cell culture and responses

The cellular responses on the surface of alloy samples were evaluated by characterizing the initial attachment, viability, and proliferation of mouse MC3T3-E1 pre-osteoblasts (ATCC). All samples (5 mm × 5 mm × 1 mm) for cell behavior tests were well polished to #2000. Cells (passages 12–16) were maintained in T25 cell culture flasks (Corning) in growth medium, comprising alpha minimum essential medium (Invitrogen) supplemented with 10% fetal bovine serum (FBS) (Invitrogen), and 1% penicillin–streptomycin (Invitrogen). Cells were incubated in a 5% CO_2 balanced air incubator at 37 °C. The medium was changed every 2–3 days.