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In vitro and in vivo studies on biodegradable CaMgZnSrYb high-entropy bulk metallic glass ☆

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ABSTRACT

In order to enhance the corrosion resistance of the $Ca_{65}Mg_{15}Zn_{20}$ bulk metallic glass, which has too fast a degradation rate for biomedical applications, we fabricated the $Ca_{20}Mg_{20}Zn_{20}Sr_{20}Yb_{20}$ high-entropy bulk metallic glass because of the unique properties of high-entropy alloys. Our results showed that the mechanical properties and corrosion behavior were enhanced. The in vitro tests showed that the $Ca_{20}Mg_{20}Zn_{20}Sr_{20}Yb_{20}$ high-entropy bulk metallic glass could stimulate the proliferation and differentiation of cultured osteoblasts. The in vivo animal tests showed that the $Ca_{20}Mg_{20}Zn_{20}Sr_{20}Yb_{20}$ high-entropy bulk metallic glass did not show any obvious degradation after 4 weeks of implantation, and they can promote osteogenesis and new bone formation after 2 weeks of implantation. The improved mechanical properties and corrosion behavior can be attributed to the different chemical composition as well as the formation of a unique high-entropy atomic structure with a maximum degree of disorder.

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1. Introduction

Bulk metallic glasses (BMGs) are a neoteric class of alloys with a fully amorphous microstructure, unlike conventional crystalline alloys. Due to their unique atomic structure, BMGs have superior strength, low Young's modulus, high elastic strain limit, enhanced wear resistance, excellent corrosion resistance, relatively flexible composition, and broader solubility for alloy elements [1]. Bulk metallic glasses have attracted much attention in recent years as candidates for biomaterials. Ti-based [2,3], Zr-based [4–6] and Fe-based BMGs [7,8] have all been investigated as new kinds of non-degradable materials, whilst Ca-based [9,10], Mg-based [11,12], Zn-based [13,14] and Sr-based BMGs [15] have been developed as the new generation of biodegradable metals.

In our previous study [9], $Ca_{65}Mg_{15}Zn_{20}$ BMG was evaluated by both in vitro tests on corrosion behavior, ion release and biocompatibility and in vivo implantation, aiming at exploring its feasibility for potential skeletal applications. Our results imply that $Ca_{65}Mg_{15}Zn_{20}$ BMG is nontoxic and could actually stimulate bone tissue healing. However, $Ca_{65}Mg_{15}Zn_{20}$ BMG degraded completely after 4 h in vitro and within 4 weeks in vivo, which is too rapid to allow sufficient time for healing, as it is desirable to have the implanted fixture present for at least 12 weeks. The rapid degradation rate of $Ca_{65}Mg_{15}Zn_{20}$ BMG is one of the greatest limitations for its use in orthopedic applications. In an effort to improve the corrosion resistance of metal materials, two different strategies are usually applied: surface treatment and alloying. Although surface coatings could enhance the corrosion resistance of CaMgZn ternary BMG according to our previous study [16], there is great concern about the loosening, flaking or peeling-off of coatings, especially when immersed in an aggressive physiological medium for a long period.

In recent years, high-entropy alloys (HEAs), an advanced alloy system that contains multiple principal elements in equimolar ratios instead of a single major element, have been developed. According to the regular solution approach, with an increasing number of principal elements in the system, the configurational entropy of mixing increases, reaching a maximum when the concentrations of all the elements are equal. This feature forms the core concept of HEAs. HEAs are been defined as alloys composed of five or more principal elements in equimolar ratios. HEAs have a stable simple solid-solution structure, and can easily form nanoprecipitates and an amorphous phase due to the high mixing entropy [17]. HEAs have many unique mechanical and electrochemical

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properties that conventional alloys lack. For instance, HEAs have high strength, high hardness, good oxidation resistance, excellent corrosion resistance and excellent abrasion resistance. Consequently, HEAs have great potential for practical applications [18].

Considering that BMGs and HEAs both have unique properties that conventional metals and alloys are unlikely to match and the fact that an amorphous phase can be easily formed in HEAs, we believe that the research and development of new types of alloys that combine BMG and HEA concepts together would be of great importance for future novel material studies. In the present study, the system and composition of $Ca_{20}Mg_{20}Zn_{20}Sr_{20}Yb_{20}$ alloy was determined from the prototype ternary $Ca_{65}Mg_{15}Zn_{20}$ BMG in accordance with the following strategic alloy designs: (i) HEAs defined by an equiatomic alloy with five or more elements; (ii) the exchangeability of the constituent elements with a similar chemical nature in the periodic table, significant atomic size ratios above 12% and negative heats of mixing to satisfy the empirical rules of BMG formation which were first put forward by Inoue [19]; and (iii) to guarantee the biosafety of biodegradable materials, the constitutional elements should be non-toxic, since all the elements will enter into the human body. Therefore, strontium and ytterbium were selected as elements for addition to CaMgZn alloy in consideration of both their atomic radii matching and physiological roles.

Strontium, calcium and magnesium are in the same group of periodic table. The distribution of Sr is similar to Ca, with 99% of the element being stored in bone [20]. Under normal conditions, the bone strontium/calcium ratio varies between 1:1000 and 1:2000, and the highest concentration is present in newly formed bone [21]. Strontium can inhibit bone resorption and stimulate bone formation in both rodents [22] and osteoporotic patients [23]. Sr-based drug treatments for osteoporosis, such as Protelos, can reduce the risk of fracture in patients after 1 year of treatment. In vitro studies have shown that Protelos inhibits osteoclast activity [24] and stimulates osteoblast proliferation [25].

The rare earth element ytterbium is chosen mainly in consideration of its BMG forming ability due to its atomic radius and mixing entropy. Ytterbium has unlimited solubility in calcium and has been found to be effective in improving corrosion resistance, glass-forming ability and the mechanical properties of metallic glass [13]. Fluorides of ytterbium have low toxicity and accumulation, inducing no local irritation of skin and eyes and not causing intoxication if administered via the stomach [26]. Rare-earth-doped β-$NaYF_4$:Yb, Er up-conversion nanoparticles can be used in the in vivo imaging, detection and diagnosis of cancers [27]. ^{175}Yb-labeled hydroxyapatite (HA) particle can be used as an agent for radiation synovectomy of small-sized joints [28].

The aim of this study is to introduce the concept of high entropy into the field of BMGs in the hope of obtaining high-entropy BMGs (HE-BMGs) with excellent properties. The feasibility of the newly developed HE-BMGs as biomaterials for orthopedic applications will be investigated by both in vitro and in vivo evaluations.

2. Materials and methods

2.1. Preparation of materials

CaMgZnSrYb HE-BMGs (CMZSY HE-BMGs), with nominal compositions (at.%) of $Ca_{20}Mg_{20}Zn_{20}Sr_{20}Yb_{20}$, were prepared by the induction-melting method. The base elements Ca (99%), Mg (99.9%), Zn (99.9%), Sr (99%) and Yb (99.5%) (Beijing Cuibolin Non-Ferrous Technology Developing Co., Ltd.) were melted in a quartz tube under a high vacuum (better than 3.0×10^{-3} Pa) at 900 °C. The melt was then cast into a liquid-nitrogen-cooled copper mould with a cavity of $50 \times 5 \times 2$ mm. The CMZSY HE-BMG samples were further cut into $5 \times 5 \times 2$ mm plates by a low-speed precision diamond saw (SYJ-150, MTI) for corrosion and biocompatibility tests, with the surface being polished up to 2000# grit. All the samples were then ultrasonically cleaned in acetone, absolute ethanol and deionized water for 15 min respectively. For the biocompatibility tests, the samples were sterilized by ultraviolet radiation for at least 2 h on one side before being turned over for another 2 h of sterilization.

2.2. Microstructural characterization and composition analysis

An X-ray diffraction (XRD) with a Rigaku DMAX 2400 diffractometer using Cu K_α radiation at a scan rate of 4° min^{-1}, operated at 40 kV and 100 mA at room temperature, was employed for the identification of the amorphous structure of samples. Differential scanning calorimetry (DSC; Mettler Toledo DSC822e) was performed under a purified argon atmosphere with a constant heating rate of 20 K min^{-1} to identify the thermodynamic parameters of the CMZSY HE-BMG alloys.

2.3. Mechanical tests and density measurement

Uniaxial compression testing was conducted with an Instron 8562 testing machine at a constant nominal strain rate of 1×10^{-4} s^{-1} at room temperature. Test samples, 2 mm in diameter and 4 mm in length, were prepared according to ASTM E9-89a (2000) standards [29], which suggested a length-to-diameter ratio of 2 for cylindrical specimens.

The density ρ was measured by Archimedes' principle in absolute alcohol ($\geqslant$99.9%). The travel time of the ultrasonic waves propagating through the sample was measured using a MATEC 6600 ultrasonic system with a measuring sensitive of 0.5 ns and a carrying frequency of 10 MHz. The elastic constants (including the Young's modulus E, the shear modulus G and the bulk modulus K) were derived from the acoustic data and density.

2.4. Immersion test

The immersion test was carried out in Hanks's solution [30] (NaCl 8.0 g, $CaCl_2$ 0.14 g, KCl 0.4 g, $NaHCO_3$ 0.35 g, glucose 1.0 g, $MgCl_2 \cdot 6H_2O$ 0.1 g, $Na_2HPO_4 \cdot 2H_2O$ 0.06 g, KH_2PO_4 0.06 g, $MgSO_4 \cdot 7H_2O$ 0.06 g, dissolved in 1 l of deionized water) according to ASTM-G31-72 [31]. After different immersion times, the samples were removed from the Hanks's solution, gently rinsed with distilled water and dried at room temperature. The weight was measured on an electronic balance (Mettler Toledo AL204) with a measuring sensitivity of 0.1 mg. The pH value of the solution was also recorded during the immersion tests, using a Lei-ci PHS-3C pH meter. The surface and cross-sectional morphologies after immersion were observed by scanning electron microscopy (SEM; Hitachi S-4800), followed by energy-disperse spectrometer (EDS) analysis. XRD using a diffractometer with Cu K_α radiation at a scan rate of 2° min^{-1}, operated at 40 kV and 100 mA at room temperature, was used to identify the phase composition of the corrosion product. The amount of hydrogen generated by the CMZSY HE-BMG was measured in accordance to Ref. [32]; for this, the sample is placed in a beaker containing the immersion solution and a measuring cylinder filled with the liquid is placed over it to collect the hydrogen formed during corrosion of the sample. Inductively coupled plasma atomic emission spectrometry (Leeman, Profile ICP-AES) was employed to measure the concentrations of the alloying element ions which had dissolved from the alloy plates. The prototype ternary $Ca_{65}Mg_{15}Zn_{20}$ BMG was used as a

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