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Study on the biodegradability and biocompatibility of WE magnesium alloys

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ABSTRACT

Magnesium alloys have been widely applied in biomedical devices because of their high strength, toughness, processing performance and the trace release of Mg^{2+}. In this study, we investigated the biodegradability, cytocompatibility and hemocompatibility of four kinds of WE Mg alloys (where "W" indicates the metallic element Y and "E" represents mixed rare earth [RE] elements; Y: 2.5, 5.0, 6.5, and 7.5 wt.%; Nd: 1.0, 2.5, 2.6, and 4.2 wt.%; Zr: 0.8 wt.%) for their application in intravascular stent fabrication. The content of alloying elements affected not only mechanical properties of materials, but also their biocompatibility. We found that addition of RE elements could reduce the corrosion rates. Human umbilical vein endothelial cells (HUVECs) and vascular smooth muscle cells (VSMCs) were cultured in different extracts of WE Mg alloys. MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay was used to examine the cytotoxicity. The nitric oxide (NO) and lactate dehydrogenase (LDH) release were used to evaluate effects of Mg alloys on HUVECs. The addition of Y, Nd and Zr increased the cell viability and improved the hemocompatibility. Different alloy elements affected the morphology of samples, Mg^{2+} release, and pH values in the medium. The results of mechanical properties, biocompatibility and biodegradability showed that Mg–5.0Y–2.6Nd–0.8Zr might be used as alternative materials of stent. However, it still needs to be further modified for clinical use. These findings suggest that selecting suitable alloying elements is particularly important.

1. Introduction

The low corrosion potential of Mg and its alloys makes them susceptible to dissolution in aqueous solutions, particularly in electrolytes containing chloride ions [1,2]. The Mg alloys used in biomedical materials have received much attention in recent years because of their excellent degradability, which afford alternative biomedical materials for treating cardiovascular diseases [3–5]. Many researchers have reported animal experiments and clinical observations of cardiovascular stents made of Mg alloys [6]. Biotronik (Germany) produced the first biodegradable Mg alloy stent in 2003. Previous research has shown that experimental animals did not experience arterial narrowing or other related symptoms. Clinical trials have also shown that the stents could degrade after a few weeks and reduce restenosis [7–9]. The success of Mg alloy stents implanted in 63 case patients with coronary heart disease in 2007 confirmed the clinical feasibility of biodegradable Mg alloys [10].

As bioabsorbable materials, Mg alloys are expected to completely degrade in the body after a certain time. The biocorrosion products of biomaterials should cause no toxicity on surrounding tissues, so avoiding toxic elements from alloying elements is necessary. Although some Mg alloys need to improve their cytotoxicity and hemocompatibility, they were still expected as the novel biomaterials [11]. Careful selection of alloying elements is crucial in consideration their cytotoxicity and hemocompatibility. Adding two or more rare earth elements to magnesium alloys can reduce their mutual solid solubility in magnesium and increase the density of the casting due to the interaction among rare earth elements. The solubility of Zr in liquid magnesium is small, and it can promote grain refinement. Zr increases mechanical properties, improves corrosion resistance and heat resistance. Mg–Zr alloy castings have lower strength and need add other alloying elements to improve the mechanical properties. Y combination with other RE elements (containing Y, Nd, Zr, Er etc.) can improve tensile properties, high temperature creep properties and the corrosion behavior. Mg alloys with 5.2–9.9 wt.% RE and 3.7–5.5 wt.% Y have been claimed in a patent, and WE43 (4 wt.% Y and 3 wt.% RE) is one of the best commercially available Mg alloys [6,12].

Table 1
The extrusion process of alloy bars.

Extrusion alloys	Preheat temperature	Extrusion temperature	Extrusion rate	Extrusion ratio	Lubrication condition
All alloys	450 °C	420 °C	5–8 mm/s	6.25	Graphite + animal fat

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Table 2
Mg alloys compositions.

Identification code	Sample
Mg	Mg
2.5WE	Mg–2.5Y–1.0Nd–0.8Zr
5.0WE	Mg–5.0Y–2.6Nd–0.8Zr
6.5WE	Mg–6.5Y–2.5Nd–0.8Zr
7.5WE	Mg–7.5Y–4.2Nd–0.8Zr

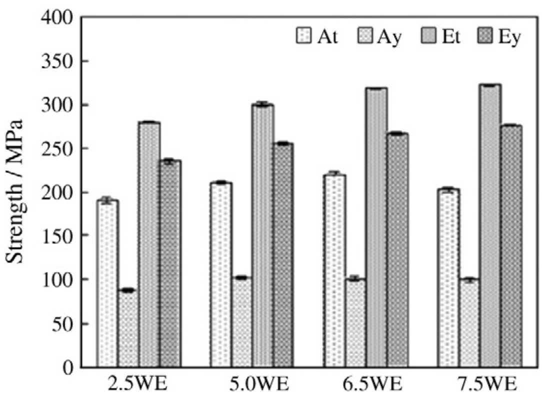

Fig. 1. Tensile strength and yield strength of as-cast alloys and extrusion alloys at room temperature. At: tensile strength of as-cast alloys, Ay: yield strength of as-cast alloys, Et: tensile strength of extrusion alloys, Ey: yield strength of extrusion alloys.

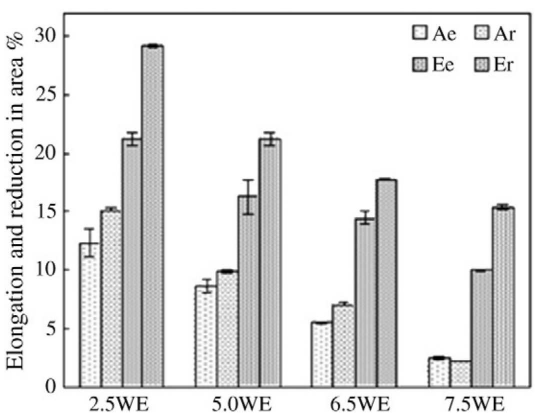

Fig. 2. Elongation and reduction in area of as-cast alloys and extrusion alloys at room temperature. Ae: elongation of as-cast alloys, Ar: reduction in area of as-cast alloys, Ee: elongation of extrusion alloys, Er: reduction in area of extrusion alloys.

Many studies have shown that Nd, Y and a small amount of Zr were non-cytotoxic [9,13]. However, the mechanical properties of Mg alloys are lower than carrying parts, and their corrosion resistance need to be further improved. So it is necessary to develop better performance of the new biodegradable magnesium alloy to meet clinical needs. Based on the above analysis, Zr, Nd and Y were used as alloying elements in this study, and pure Mg was used as control. The biocompatibility and biodegradability of these Mg alloys were evaluated to determine their feasibility as potential intravascular stent biomaterials.

2. Materials and methods

2.1. Preparation of materials

The extruded WE Mg alloys (generously donated by the National Engineering Research Center for Magnesium Alloys, China) were made by high-purity Mg (>99.99%) and Y, Nd, and Zr (>99.9%). The extrusion process of alloy bars is shown in Table 1. The total amount of impurities (Fe, Al, Cu, Si and Ni) did not exceed 0.05%. The compositions of Mg alloys were set during sample preparation. When Zr was added in 0.6%–0.8% of content, it could enhance the strength of alloys, inhibit grain growth in the deformation of magnesium alloys, and had strong grain refinement effect. Therefore, we chose 0.8% of Zr, Y and Nd as alloying elements. They could effectively refine the grain size, but their refinement was very limited. When Y content reached 5.0% and Nd content reached 2.6%, the grain refinement of alloys did not change essentially. However, the tensile strength and yield strength of alloys continued to increase with increasing the Y and Nd content. When the Y content reached 7.5% and the Nd content reached 4.2%, the strength of the alloys did not continue to increase. The content of Zr was fixed, whereas the contents of Y and Nd were increased. The components and identification codes of samples used in this study are summarized in Table 2. The mechanical properties of Mg alloys were measured by computer-controlled electronic universal testing machine (ASNS CMT5105) at room temperature. The test was repeated for three times. The tensile rate was 2 mm/min. The morphologies of tensile fracture and microstructures near the fractured surfaces of extrusion alloys were observed by scanning electron microscope (SEM, Hitachi S-4700).

The samples with a dimension of 8 mm in diameter and 7 mm in thickness were cut from extruded bars for the immersion test, the cytotoxicity and hemocompatibility test. Each sample was polished by 2000# grit sandpaper, ultrasonically cleaned in absolute ethanol for 10 min, and dried at room temperature. According to the methods in published paper [14], sample extracts were prepared using RPMI

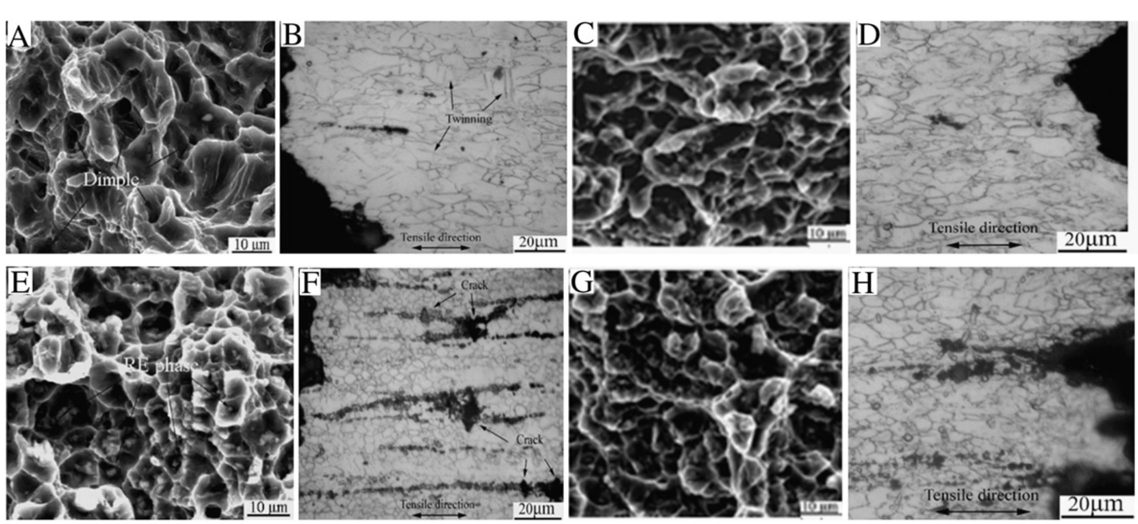

Fig. 3. Morphologies of tensile fracture and microstructures near the fractured surfaces of extrusion alloys, (A), (B) 2.5WE; (C), (D) 5.0WE; (E), (F) 6.5WE; (G), (H) 7.5WE.