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Design of a pseudo-physiological test bench specific to the development of biodegradable metallic biomaterials

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Abstract

Endovascular stents have proven effective in treating coronary and peripheral arterial occlusions. Since the first attempts, metals used to make these devices have been generally selected, and designed to be highly resistant to corrosion. Therefore, as almost the totality of metallic biomaterials, they are implanted on a long-term basis. However, complications associated with permanent stents, such as in-stent restenosis and thrombosis, have often been reported. In order to reduce those complications, it would be clinically useful to develop a new family of degradable stents. An interesting material for fabrication of degradable stents is based on magnesium, an essential element involved in human metabolism. Success in using magnesium alloys for the fabrication of endovascular devices is closely related to the properties of the selected alloy. In this context, a test bench was specifically designed to reproduce the physiological conditions to which stents are submitted when implanted in the coronary arteries. Then the test bench was validated using a magnesium-based alloy. Results showed that the corrosion rate and the corrosion mechanisms vary with the applied shear stress and that corrosion products strongly depend on the composition of the corrosive solution. This test bench will thus be useful in further investigations for the development of metallic alloys as degradable biomaterials.

Keywords: Biodegradable stents; Magnesium alloys; Corrosion process; Degradable metals; Pseudo-physiological tests

1. Introduction

Clinical introduction of coronary stenting dates back to 1987, when Sigwart et al. implanted a stent in humans and described its use for blood vessel scaffolding after balloon angioplasty [1]. Stenting has now become the preferred standard in treating coronary artery diseases [2]. There were more than half a million hospital discharges in the USA during 2002–2003 with at least one coronary stent insertion procedure performed among adults [3].

Once implanted, the stent is expected to remain inside the treated blood vessel for the rest of the patient's life. From a clinical point of view, this permanent implantation is unnecessary since the occluded artery undergoes a 6- to 12-month-long healing (remodelling) process [4]. The continued presence of stents may inhibit the ongoing arterial remodelling and provoke in-stent restenosis [5]. Moreover, even though considered as corrosion resistant, stent materials such as austenitic stainless steel and Ni–Ti alloy, are evidently prone to release their metallic ions in vivo [6,7]. Specific metallic ions, such as those potentially released from nickel, chrome and molybdenum, have been categorized as potentially carcinogenic by International Agency for Research on Cancer (IARC) [8]. Considering those short-term clinical needs and the potential long-term complications with permanently implanted stents, a biodegradable stent would represent the ideal solution [9]. This stent is expected to scaffold the arterial wall until the healing

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process is completed, then it is supposed to degrade and be expelled from the body. However, although challenging and limited to this specific application (and perhaps few other), this concept breaks the paradigm requiring biomaterials to be corrosion resistant. From a historical point of view, after the development of stainless steel, metals susceptible to degradation have raised only minor interest at both the industrial and academic levels. Therefore, the development of specific tests devoted to degradable metallic biomaterials is mandatory.

Polymers were the first material selected for the development of biodegradable stents. Poly-L-lactic acid (PLLA) is the most studied polymer due to its high biocompatibility among others [10]. However, the development of biodegradable polymeric stents has been hampered by difficulties in replicating the properties of stainless steel stents [11]. Degradable metals, which present better mechanical properties compared with the current biodegradable polymers were then become the next choice. Magnesium is present in large amounts in the body and is involved in many metabolic reactions and biological mechanisms [12]. Although pure magnesium displays limited mechanical properties and poor corrosion resistance, alloying and subsequent metallurgical process can improve those limitations [13]. Several pioneering works have been carried out in the last years, and it appears evident today that magnesium alloys are promising candidates for the development of degradable endovascular stents. Several studies highlighting the potential of different magnesium-based alloys, such as AZ31, AZ91, LAE442 [14], AM60B [15] and WE43 [14,16–18], have been reported recently. The implantation of stents prototypes made of AE21 in pigs confirmed the potential of magnesium alloys as biodegradable stent material [19]. Recently, stent prototypes made of WE43 were pre-clinically implanted in lower limb ischemia in adult patients [16] and used to treat congenital heart diseases in newborn babies [17,18]. However, magnesium alloys still showed rapid corrosion rate both in vitro and in vivo [20]. This could lead to premature failure of a stent before the arterial remodelling process is completed.

From a material science and engineering point of view, finding the optimal alloy composition for degradable stents is not a trivial task. Among the number of requirements for the selection of the alloy and its specific composition, the following need to be considered:

1. Mechanical properties, including elasticity, ductility, elastic yield and resistance to rupture (in particular after the deployment required by the implantation of the stent). Ideally, these mechanical properties should be as close as possible to those of stainless steel, which today represents the referred standard for clinicians and industrials.
2. The mechanical properties as a function of the degradation time. Ideally, the corrosion process will not affect the mechanical properties until the physiological arterial remodelling (after stenting) will be completed.
3. The corrosion process that the alloys will undergo in vivo should not clinically induce negative side effects on the physiology or the health of the stented patient. For example, the corrosion products must not: (i) generate toxic, carcinogenic, or mutagenic effects; or (ii) block vessels somewhere in the vascular bed. Ideally, the corrosion products should be eliminated by the conventional physiological mechanisms, and the corrosion process leading to the degradation of the alloy should be homogeneous and not generate particles with geometries larger than a few microns (i.e. preferentially lower than the dimensions of capillaries).

To date, works on degradable implants have focused on assessing the potential of corrodible metals, toward both cardiovascular [15–19] and orthopaedic [21] applications. In general, in these works, specific magnesium-based alloys were selected and tested in vitro or implanted in vivo. In the context of developing a specific alloy fulfilling the requirements described above, this approach requires a number of trials, including in vitro experiments and in vivo studies. In this context, from a material science and engineering point of view, it is possible to approximate in vitro the corrosion process that these alloys will undergo in vivo. Although conventional corrosion tests (potentiometric, for example) are valuable tools for assessing the potential of the alloys to corrode [20], they do not provide information specific to the ability of the materials to be considered as degradable biomaterials. The use of a specific test bench will be helpful for the investigation of the interactions between the degradation rate of experimental alloys (not specifically magnesium-based alloys, but even other potential degradable metallic biomaterials) and major physiological parameters such as pH, temperature and shear stress. Therefore, the aim of this work was first to design a test bench that simulates the physiological conditions (therefore called pseudo-physiological) in narrowed arteries with an internal diameter between 1 and 6 mm. Then static and dynamic tests were carried out on magnesium alloy AM60B-F, mainly to validate the test bench.

2. Materials and methods

2.1. Test bench

A test bench was developed to approximate physiological conditions encountered in coronary arteries. Table 1 summarizes the conditions that were taken into consideration during design, development and utilization of the test bench. The choice of the final dimensions was made in determining the compromise that best fulfilled all the criteria described in Table 1. This consisted of a "test channel" placed in a closed-loop system in which a special saline solution is flowing (schematic view shown in Fig. 1). This test channel was used to apply a predetermined shear stress onto the surface of a sample.