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Review

Porous magnesium-based scaffolds for tissue engineering

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ABSTRACT

Significant amount of research efforts have been dedicated to the development of scaffolds for tissue engineering. Although at present most of the studies are focused on non-load bearing scaffolds, many scaffolds have also been investigated for hard tissue repair. In particular, metallic scaffolds are being studied for hard tissue engineering due to their suitable mechanical properties. Several biocompatible metallic materials such as stainless steels, cobalt alloys, titanium alloys, tantalum, nitinol and magnesium alloys have been commonly employed as implants in orthopedic and dental treatments. They are often used to replace and regenerate the damaged bones or to provide structural support for healing bone defects. Among the common metallic biomaterials, magnesium (Mg) and a number of its alloys are effective because of their mechanical properties close to those of human bone, their natural ionic content that may have important functional roles in physiological systems, and their *in vivo* biodegradation characteristics in body fluids. Due to such collective properties, Mg based alloys can be employed as biocompatible, bioactive, and biodegradable scaffolds for load-bearing applications. Recently, porous Mg and Mg alloys have been specially suggested as metallic scaffolds for bone tissue engineering. With further optimization of the fabrication techniques, porous Mg is expected to make a promising hard substitute scaffold. The present review covers research conducted on the fabrication techniques, surface modifications, properties and biological characteristics of Mg alloys based scaffolds. Furthermore, the potential applications, challenges and future trends of such degradable metallic scaffolds are discussed in detail.

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1. Introduction

There is a wide variety of biocompatible materials used for different orthopedic applications. Among them, metallic biomaterials have been specifically utilized to produce an assortment of orthopedic implants such as the head of the femoral component of a total hip joint replacement (THJR), the tibial tray in a total knee joint replacement (TKJR), the stem of the total shoulder joint replacement, and the spinal fusion cage [1,2]. Biodegradable metals are a class of biodegradable materials that degrade slowly in the body with a suitable host reaction elicited by the released degradation products. The biodegradable metal should disappear entirely upon fulfilling the mission of supporting the tissue regeneration leaving no implant residues; hence, no further surgical operation is needed for the implant removal [3].

Appropriate biocompatibility, low *in vivo* corrosion rate and high strength are the main parameters for the selection of a metal for the mentioned applications [4]. The principal issue of metallic implants is their loosening due to bone resorption caused by stress shielding, weak interfacial bonding between the implant and the bone, and the lack of biological anchorage for the growing tissue [2]. To address these issues, there has been much effort on the development and characterization of metal implants with microstructures and properties close to those of trabecular bone. Accordingly, these materials are called open-cell porous metals, metallic foams, metallic scaffolds, or cellular metals with three-dimensional interconnected pores. The pore sizes are typically between 200 and 500 μm with total porosity of 50–75% [5].

The stability of an implant is mainly dependent on both its mechanical strength and its fixation ability to the host tissue. In the conventional approach, such stability was mostly achieved by means of pins, screws and bone cements [6]. However, in recent experiments, researchers are attempting to improve the fixation by tissue engineering techniques [7]. For this purpose, the metal is made porous to provide a scaffold for the bone tissue to grow into and through the pores thus making a suitable bond to the metallic implant [8]. Present tissue engineering approaches are focused on the development of porous scaffolds made of different biomaterials with the aim of replacing and restoring the pathologically altered tissues by transplantation of the cells [9,10]. Such scaffolds for engineering of hard tissues need suitable mechanical integrity [11]. A porous 3D material provides the required pathways for cells to grow, proliferate, and differentiate, while the architecture defines the final structure of the newly formed bone [12–15]. It is worth mentioning that the spontaneous renewal of the bone is restricted to only small defects. The treatment of large bone segments caused by tumors, trauma, implant failure, or osteitis is far more challenging to be addressed. An ideal bone tissue engineering scaffold must be biocompatible, osteoconductive, and biodegradable, with a high mechanical strength to fulfil the necessary load-bearing functions [8]. Also, it must have interconnected porous networks allowing cell migration, vascularization and nutrient delivery [16]. The challenge to achieve the above mentioned properties in existent scaffolds has made bone tissue engineering a very popular research field in the last decade in regards to the material selections and production techniques [13,17]. Although porosity is necessary for scaffolds, it considerably reduces the scaffold's strength which is vital, in particular, for the repair of large bone defects [18,19]. The trade-off between the mechanical strength and the porosity is one of the main challenges in designing tissue engineered bone scaffolds [6]. At present, various types of biomaterials have been employed for this aim, which are synthetic or naturally-derived.

2. Advantages and disadvantages of porous magnesium-based scaffold compared to other scaffolds

Early 1970s was the starting date for investigations on porous biomaterials such as ceramic [20], polymeric [21], and metallic materials [22], which identified several promising selections for porous implants that would allow bone in-growth. Although ceramics have shown outstanding corrosion properties, their inherent brittleness makes them difficult to be used for load bearing applications [16]. Porous polymeric scaffolds cannot resist the high mechanical stresses present in bone replacement operations [16]. This has led researchers to study porous metals, based on orthopedic metallic implants, due to their greater compressive strength, fracture toughness, and fatigue resistance, which are needed for load-bearing applications [6,16]. Due to the excellent physical and mechanical properties of magnesium compared to other permanent (non-degradable) metals, porous magnesium and Mg alloys became good candidates to develop biodegradable scaffolds for bone treatments [23,24].

Among the metal implants, Mg and a number of its alloys are effective because of 1) their mechanical properties, which are close to those of human bone, 2) their natural ionic content that has important functional roles in physiological systems, and 3) their *in vivo* biodegradation characteristics in body fluids. Some physical properties of Mg alloys, such as high specific strength and elastic modulus, are closer to those of natural human bone compared to other traditional metal implants [27,28]. For example, compared to titanium alloys with the elastic modulus of 110–117 GPa, Mg alloys have lower modulus (41–45 GPa) leading to a decreased stress-shielding effect [29,30]. Moreover, Mg alloys are 3–16 times stronger than biopolymers and, at the same time, they are more ductile compared to bioceramics, which can reduce the chance of the device fracturing throughout the implantation process. Moreover, compared to polymers, Mg alloys can encourage bone growth, which can help the implant to be properly fixed with the host bone to potentially allow full healing of bone defects after degradation [31,32]. Mg is an essential ion in metabolism and its deficiency in the body may cause some pathological conditions. Due to such collective properties, Mg based alloys can be employed as biocompatible, bioactive, and biodegradable scaffolds for load-bearing biomedical applications [25,26]. Such characteristics encourage employing biodegradable Mg and Mg alloys as lightweight metals for load bearing orthopedic implants, which would remain in the body and keep mechanical stability over a time scale of 3–4 months, while the natural bone tissue heals [33,34].

The main challenge for employing Mg and its alloys as an implant is its high corrosion rate resulting in the rapid release of degradation products in the body [35,36]. The low corrosion resistance in physiological environments can have an adverse effect on the mechanical stability of the implant prior to bone healing [37]. Mg's low corrosion resistance also leads to the rapid release of hydrogen gas and the formation of subcutaneous gas pockets close to the implant. These side products would collect around the implant and interrupt the tissue healing [38,39]. In addition, due to the hydrogen release, a local alkalization occurs around the implant, which affects the pH-dependent physiological processes in the surrounding area of the implant [17]. The need for a relatively low corrosion resistance, makes it necessary to take relevant measures to control Mg's high corrosion rate [40]. This review aims to bring together recent studies on Mg and Mg alloys based scaffolds with regards to production techniques, surface modifications, general properties, potential applications and future trends. If Mg based scaffolds with the proper