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RESEARCH

The Potential of Magnesium Alloys as Bioabsorbable / Biodegradable Implants for Biomedical Applications

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A B S T R A C T

The potential of magnesium alloys as bioabsorbable / biodegradable implants for biomedical applications has been extensively studied as emerging direction. This paper gives a review of current topics in this field. Research activities related to biomedical magnesium alloys have been pursued in two main directions, orthopedic and cardiovascular implants, by investigating different aspects of alloying system design, novel structures, degradation rate control, and surface modification methods. Magnesium alloys are currently considered for applications as load-bearing implant devices such as plates, screws and pins for repairing bone fracture. Highly important direction of research is degradable coronary stents. Degradable vessel stents promote stable vessel regeneration, unlike permanent stents. Different combinations of alloying elements have been investigated in order to decrease corrosion rate.Tribological issues are also important for understanding of different phenomenon related to prolongation of Mg alloys corrosion degradation time/rate, such as tribocorrosion, corrosion fatigue, and fatigue crack growth behavior.

1. INTRODUCTION

The beginning of the resorbable implants concepts is related to using polymers with controlled dissolution rates: polylactides and polyglycolides, back in 1970s [1]. But the problem associated with use of polymers is their mechanical properties, where metals have better characteristics and represent the promising field for advancements. The history of biodegradable magnesium (Mg) implants started shortly after the discovery of elemental magnesium by Sir Humphrey Davy in 1808 [2]. It is supposed that the pure magnesium wires were used as ligatures to stop bleeding vessels of three human patients in 1878 [2]. They elaborated corrosion

induced degradation properties of pure magnesium and concluded that corrosion rate depended on the wire size. From those first attempts, many other solutions and ideas were tried, because magnesium has been recognised as the promising material for efficient degradable implants. Today, in vitro and in vivo study data exists, as well as some clinical trials data, but not so extensively present as for other biomedical metal materials, because degradable materials and Mg alloys are still having many unresolved issues if compared to the development of Ti biomedical alloys. Even today, several important drawbacks of the technology and material need to be resolved before its wide application in clinical practice.

Magnesium is the seventh most abundant element in earth's crust (2 % of the total mass) and also essential and major constituent element of human body, nontoxic and biocompatible accordingly [3]. It belongs to the group of alkaline earth metals and cannot be found in elemental form in nature, but only in chemical combinations, since being highly reactive. From aspects of the Mg alloys production, important mineral forms are: magnesite MgCO3 (27 % Mg), dolomite MgCO3•CaCO3 (13 % Mg), and carnallite KCl•MgCl2•6H2O (8 % Mg), as well as sea water, which contains 0.13 % Mg or 1.1 kg Mg per m3 (3rd most abundant among the dissolved minerals in sea water) [3]. However, Mg alloys are still lacking wide application due to several reasons, one of which is rather high price of base material and regarding degradable implants, too rapid corrosion rate when implanted, especially in solutions containing Cl^{-1}. In addition, there are certain limitations related to the processing temperatures and production protocols.

The usage of magnesium (Mg) has historically been limited by relatively high cost of production and associated energy costs. However, Mg market will steadily increase, mainly due to the low cost production in China. Magnesium is recovered by electrolysis of molten anhydrous MgCl2, by thermal reduction of dolomite, or by extraction of magnesium oxide from sea water. The global production of roughly 436,000 t (1997) is covered by melt electrolysis to 75 % and by thermal reduction to 25 %. Cast magnesium alloys dominate 85-90 % of all magnesium alloy products, with Mg-Al-Zn system being the most widely used. Rare earth alloying additions increase cost and are of uncertain supply. US and Canada dominated magnesium production during the 1990s, however, since the late 90s, China become the main producer. Today, China dominates the world production because of the relatively low operating costs. In general, electrolytic producers in the west have been replaced by Chinese pyrometallurgical production via the Pidgeon process (Pidgeon, 1944). For example, the capital cost for Australia Magnesium (AM) Process using an electrolytic route was estimated to be $10,000/tonne Mg, while the capital cost for the Pidgeon process was estimated to be $3,000/tonne Mg in 2008.

2. MAGNESIUM ALLOYS

Magnesium alloys are standardized by ASTM norm and they are marked with letters (A, B, C, etc.), indicating main alloying elements, followed by the rounded figures of each weight in percentage terms. The alloy AZ91D, for example, is an alloy with a rated content of 9 % aluminium (A) and 1 % zinc (Z) [3]. The corresponding DIN specification would be MgAl9Zn1. The most common alloying elements are given in Table 1.

Table 1. ASTM codes for magnesium's alloying elements [3].

Abbreviation letter	Alloying element	Abbreviation letter	Alloying element
A	aluminium	N	nickel
B	bismuth	P	lead
C	copper	Q	silver
D	cadmium	R	chromium
E	rare earths	S	silicon
F	iron	T	tin
H	thorium	W	yttrium
K	zirconium	Y	antimony
L	lithium	Z	zinc
M	manganese		

Different alloying elements influence the properties of the pure magnesium, depending on the wanted characteristics. The main mechanism for improving the mechanical properties is precipitation hardening and/or solid-solution hardening. One of the most important alloying elements is aluminium (Al) which increase tensile strength, by forming the intermetallic

phase Mg17Al12. The use of rare earth elements (e.g. Y, Nd, Ce) has become significant, especially for designing the medical grade Mg alloy for degradable implants, since they impart a significant increase in strength through precipitation hardening. But almost all elements used so far for alloying mostly increase susceptibility to corrosion. Review of commercially produced Mg alloys today is given in Table 2 [3].

Table 2. Chemical composition (in weight %; Mg is the balance; Cu, Ni in general <0.001 %) of the selected Mg alloys.

Alloy	Al	Zn	Si	Fe
Mg cp/cast	0.04	<0.01	0.05	<<
AZ91/cast	10.14	1.33	0.03	<<
AZ91 Fe0.03/cast	9.56	0.86	0.04	0.03
AZ91 Fe0.05/cast	10.12	1.05	0.06	0.05
AZ91/50	9.93	0.84	0.08	<<
AZ91/5	10.09	0.87	0.11	0.01
AZ91/2.5	4.75	0.02	<<	<<
AZ91E	8.22	0.65	0.01	<0.01
AZ31	3.00	0.83	0.01	0.003
MgZa5/cast	0.04	<<	<<	<<
Mg hp				
Mg0.6Ca				
Mg1.2Ca				
Mg1.6Ca				
Mg2.0Ca				

The important innovations are expected to emerge from the materials known as metal foams, where Mg foams are investigated from aspects of obtaining even lighter components. Although Mg belongs to the lightest elements used for biomedical purposes, its porous variant is also investigated, along with possibilities to keep oxidation rate under control. Very interesting results are achieved in production of Mg foams, such as AZ91 foam with open cellular structure having a density of 50 kg/m3, whereas a cubic meter of pure solid Mg weighs 1,740 kg [1].

Energy absorption during impact or loading is inherent property of the foams. Fig. 1 shows stress–strain behavior of the foams in compression, in general [1]. From Fig. 1, it can be seen that three zones exists: I. Elastic region: deformation of the pore walls; II. A plateau of nearly constant flow stress and large strain (10–50%) and III. Densification region with steep increase of flow stress where the plastic damage occurs. Relatively wide region of constant flow stress during compressive loading explains the fact that while foams are in this interval, any increasing strain hardly entails increasing stress. If tension is observed, the stress–strain behavior of foams is approximately similar to ductile metals (curve b in Fig. 1).

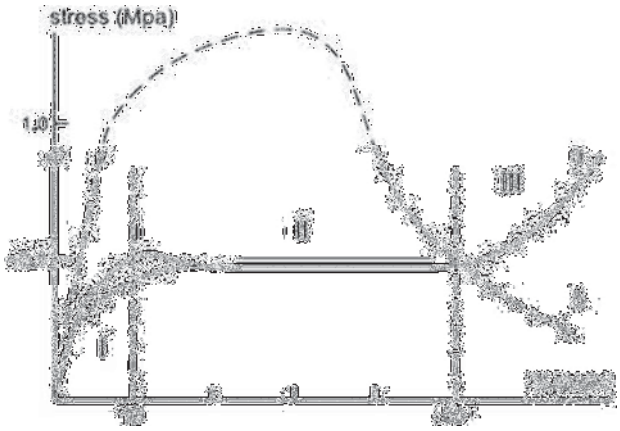

Fig. 1. Stress - strain behaviour of foams.

3. MAGNESIUM ALLOYS AS DEGRADABLE IMPLANTS

The application of Mg and its alloys for degradable implants started with ligatures for blood vessels (Huse, 1878, pure magnesium) and plates, arrows, wire, sheets, rods (Payr, 1905, pure magnesium) [2]. Mg alloys have been tried in different medical areas, such as: pure Mg for band, suture from woven Mg wires, fusiform pins (in 1940); Mg–Al2 %-wt. pure magnesium wires for clotting aneurysms (dog studies in 1951); Mg–Al2 %-wt. for intravascular wires (rat studies in 1980) [2]. The potential of magnesium alloys as bioabsorbable / biodegradable implants for biomedical applications has been extensively studied as emerging direction. Research activities related to biomedical magnesium alloys have been pursued in two main directions, orthopedic and cardiovascular implants, by investigating different aspects of alloying system design, novel structures, degradation rate control, and surface modification methods.

Magnesium alloys are currently considered for applications as load-bearing implant devices such as plates, screws and pins for repairing bone fracture. Other metals currently used for bone implants, such as stainless steels and titanium alloys, have elastic modulus that are much higher than natural bone, leading to unwanted stress shielding. The elastic modulus of magnesium and many magnesium alloys are much closer to bone. The advantage of Mg alloys is favorable elastic response during loading

(such as shown in Fig. 1). Also, the second surgery is avoided due to the degradation of the implant after its function in the body is finished. For example, compared with poly-96L/4D-lactide, the magnesium alloys AZ31 and AZ91 enhanced the osteogenesis response and increase newly formed bone [4]. Investigations showed that Mg–6Zn, Mg–Ca and Mg–Mn–Zn alloys gradually degrade within a bone and had good biocompatibility both in vitro and in vivo [4].

Highly important direction of research is degradable coronary stents. Degradable vessel stents promote stable vessel regeneration, unlike permanent stents [5-7]. However, as a vessel defect gets larger, stronger and degradable materials are paramount for stable vessel regeneration. Vessel scaffolding is necessary only for a certain, limited time, than the permanent stent has no known advantage. A stent is a miniature mesh tube, made of a biocompatible metal, biodegradable metal or polymer, placed inside of a blood vessel (cardiovascular, neurovascular and peripheral blood vessels) or a natural conduit (gastrointestinal, urinary and biliary tracts). The stent acts as a scaffold, pushing against the internal walls of the conduit/vessel to open a blocked area and thereby enables natural flow and prevents the vessel from collapsing, narrowing or closing. Stents differ greatly in their design, dimensions and material, depending on application. Coronary stents are now the most commonly implanted medical device for angioplasty, with more than 1 million implanted annually. Currently used metallic stents permanently remain in the artery and are associated with limitations such as continued mechanical stress, transfer to the tissue, and continued biological interaction with the surrounding tissue. Also, within 6 months, 30-35% patients suffer from restenosis. They are associated with late stent thrombosis and artifacts when non-invasive technologies such as MRI and MSCT are used. The stent presence is required for a period of 6 - 12 months during which arterial remodelling and healing is achieved. After this period the stent presence within the blood vessel cannot provide any beneficial effects. With the development of biodegradable implants, the concept of biomaterials has shifted from purely mechanical replacement devices towards true biological solutions. Bio-absorbable stents (Fig. 2) aim to mechanically prevent vessel recoil without the permanent presence of an artificial implant. The advantages of bioabsorbable stents are to leave no stent behind, fully compatible with MRI/MSCT imaging, and are not associated with late stent thrombosis.

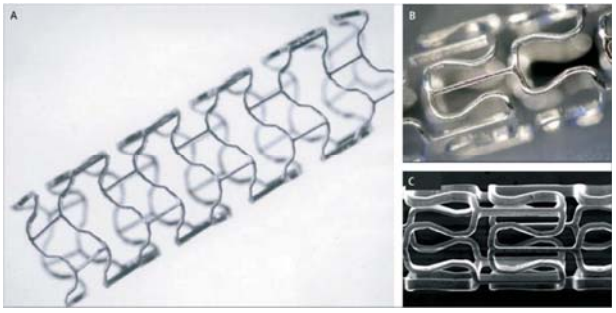

Fig. 2. Bioabsorbable magnesium stent (Biotronik, Berlin, Germany) [6].

Magnesium (Mg) alloys which has been developed in the last ten years showed great potential in cardiovascular applications where temporary stent is required. Biotronik Mg Alloy Balloon expanding stent with a delivery catheter has been clinically tested to some extent [7].

Different combinations of alloying elements have been investigated in order to decrease corrosion rate. The addition of aluminium (Al) and rare earth (RE) elements has been reported to increase its strength and improve corrosion resistance. But Al could cause nerve toxicity and restraining growth to human body. Alloy containing RE is very expensive. In some alloys, the low cost Ca has been used as alloying element and Mg–Ca alloy exhibited increased corrosion resistance. The addition of Zn into Mg–Ca alloys increases the tensile strength, ductility, hardness and the kinetics of age hardening. Commercial Mg alloys such as WE43 (Mg–Y–RE–Zr), AZ91 (Mg–Al–Zn), AZ31 (Mg–Al–Zn–Mn) are under investigation. There are number of studies related to corrosion mechanisms and degradation kinetics. Published results indicate that the mechanisms affecting the corrosion behaviour of Mg-based stents in service conditions can be: internal galvanic corrosion; localized corrosion (pitting and filiform); stress corrosion cracking (SCC) and fatigue corrosion. Simultaneous effect of different corrosion mechanisms influences a stent in service, which makes the identification of correlations between in vitro and in vivo experimental results very complex and many

issues has not yet been resolved. ASTM G31 (Standard Practice for Laboratory Immersion Corrosion Testing of Metals) offers general guidance for metal corrosion testing, but there are no standardized procedures for biocorrosion of biodegradable metal materials.

Low corrosion resistance of magnesium and its alloys, within the very aggressive environment in the physiological system, is the vital characteristic enabling degradability of the metal implant. On the other hand, too rapid loss of mechanical properties and/or toxic degradation products are major problems associated with Mg alloys. Also, the high corrosion rate produces rapid hydrogen gas evolution within the body. The pursued development direction is to control the speed of corrosion, along with optimization of the biological response to these implants to maximize recovery. Biologically compatible surface modifications through treatments or coating systems have been investigated as protective strategy in corrosive environments in order to optimize implant properties [8-10]. Corrosion resistant coatings are commonly used for metals in many applications, but in area of dergadable implamnts, these coatings need to degrade along with the magnesium, or yield to the environment, leaving no harmful traces. Some of the tried solutions are: anodization, pure magnesium coating on Mg alloy, PVD coating of aluminium, but all of them have some downsides. One of the most biocompatible coating options for orthopedics is calcium phosphate coatings. Zhang et al. [9] investigated ion plating of Ti-coating on pure Mg for biomedical applications, inspired by good properties of both Ti and Mg alloys. They reported good results in improvement of the corrosion resistance of Mg and promising further potentials, but comprehensive testing of this new coating is yet to come.

Another method for increasing the corrosion resistance of a magnesium alloy is the surface structure modifications. Magnesium alloys undergo microgalvanic corrosion when multiple phases exist in an alloy, one more cathodic than another and in order to slow the corrosion rate is to modify the surface to homogenize it [8]. Amorphous surface would eliminate the formation of galvanic cells between grains and boundaries. One such a way is to make the matrix a completely amorphous bulk metallic glass to completely remove corrosion difference due to crystal structure in the metal [8]. Amorphous MgZnCa alloys have been tested in vivo to show reduced hydrogen evolution [11]. Ion implantation is another method of surface modification to increase corrosion resistance, also creating a gradual transition between the modified surface and the bulk of the material. This makes strong, adherent surfaces that do not have the problems of adhesion, thermal stresses, and crackings that separate secondary coating phases tend to have [8]. Plasma immersion ion implantation of Al, Zr, and Ti has been used to create corrosion resistance on AZ91.

4. FRICTION AND WEAR ISSUES RELATED TO MG ALLOYS

Tribocorrosion is defined as an irreversible transformation of a material from concomitant physicochemical and mechanical surface interactions occurring at tribological contacts [12]. In general, metallic implants need to be tested to tribocorrosion and wear issues, regardless of their area of application. The realised contacts between implant material and either other implant material, or organic body constituent (e.g. bone) and elements of the aggressive physiological body environment, provoke certain responses (wear debris) that need to be investigated in more depth, especially for newly developed biomaterials. It is proven that even micro contacts within small regions sometimes influence significant responses, ranging from changes in contact environment up to increasing deterioration of implant surfaces due to wear related processes. Two- or three-body contacts are frequently associated with tribocorrosion [13]. Entrapped wear debris acts as an abrasive and is defined as the third body. The main concerns related to the simultaneous action of corrosion and wear in biomedical systems are the ability of the passive layer to withstand the mechanical stresses arising from wear, the ability of the metal surface to repassivate when the passive film is removed and the resistance of the new repassivated surface to both wear and corrosion [13]. Fretting has a big influence on the corrosion behavior of orthopedic devices.

The tribocorrosion and fretting corrosion mechanisms have been mainly related to in vitro laboratory investigations. However, the in vivo behavior of metallic implants under combined wear corrosion or fretting corrosion has been hardly studied [13]. Also, the corrosion fatigue of structural magnesium alloys has been studied by several authors in NaCl and borate-buffered solutions, but generally focused on applications in electronic, automotive and aerospace industries. The fatigue strength of magnesium alloys is significantly reduced in humid environments, and the fatigue limit drops drastically in NaCl solution [13]. Even though the corrosion behavior of biomedical magnesium-based alloys has been extensively studied, corrosion fatigue has received little attention and degradable material must maintain appropriate mechanical strength during the healing of the fractured bone, to provide safe orthopedic device. Also, fatigue crack propagation behavior needs to be studied for a wide variety of biodegradable Mg alloys [13]. Corrosion and wear resistances are frequently studied in synergy, because of the direct relationship between these properties and the biocompatibility of the biomedical device.

Regarding coronary stenting by using metallic implants, analysis of the fatigue crack growth behavior is of the utmost importance for its proper functioning. There are my mathematical models in the literature, but, in particular, the fatigue crack propagation approach simulating crevice corrosion conditions in physiological solutions has been hardly considered for biomedical magnesium alloys [13]. Very important aspect is tribology related phenomena during the production of magnesium biodegradable vascular stents minitubes, since magnesium alloys possess highly limited room-temperature formabilities [14]. Highly complex physical, chemical and mechanical characteristics of magnesium must be taken into consideration, in order to keep the magnesium alloy characteristics (microstructure, etc.) unchanged under the influence of e.g. severe abrasive friction and wear during cold drawing [14].

Highly important is the understanding of the Mg alloy stent behaviour at its positioning during the movement through the vasculature, at the initial interventional cardiovascular treatment. Lubricious coatings have been used for over 20 years [15] and the benefits are well established: (1) lower frictional force between the device and the vessel reduces tissue damage and prevents vasospasm; (2) improved maneuverability aids navigation of complex lesions and facilitates access to tortuous vascular sites leading to expansion of the patient population that can benefit from these treatments; and (3) reduces thrombogenicity. In addition, reduced friction between the therapy catheters and support catheters leads to improved outcomes, reduced procedure time, and, ultimately, reduced cost [15]. The stent is commonly placed at the one fixed position within a blood vessel, meaning that there are no further movement between the stent material and surrounding tissue, leading to the conclusion that wear plays no significant role. However, blood flow around the placed stent has micro influence and might provoke nano-wear debris, which is not investigated so far. Such tiny wear debris represents a form of particulate matter in the vasculature and it is well known that if large enough and in sufficient quantities, can cause occlusion of blood vessels and lead to tissue hypoxia and, ultimately, necrosis [15]. If alloying elements of Mg alloys, such as Al, Zn are considered as well, it is obvious that this area needs further studies. Since Mg alloys stents has not been widely tried in clinical practice, there are many tribology related questions to be addresses.

5. CONCLUSION

The magnesium alloys as bioabsorbable / biodegradable implants for biomedical applications are highly promising materials, but some issues need to be resolved and extensive research activities are pursued throughout the world. Different aspects of alloying system design, novel structures, degradation rate control, and surface modification methods have been tested, mainly in order to increase corrosion degradation time. Significant attention is still needed related to production processes, tribocorrosion, fatigue crack growth behaviour, wear and friction processes and other complex issues when observed within aggressive human body environment.

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