REVIEW

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Mg–Zn alloys, most suitable for biomedical applications

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Abstract

In this review are highlighted the corrosion and biocompatibility of biodegradable Mg alloys for their use in orthopedic applications. It was revealed that mixing with alloying elements, such as Mn and Zn, provides improved corrosion resistance to Mg alloys; this pursuit is built on the fact that Mg and its alloys are degradable through their time in the human body. Furthermore, Mg alloys afford a characteristic profile that is very close or even almost identical to that of human bone. Minimizing the rate of corrosion of Mg is the most adequate method, because a low corrosion rate of an Mg implant involves a decrease in the extent of hydrogen evolution and alkalization, which allow the human body to gradually absorb or consume the corrosion products.

Keywords: Mg–Zn alloys, biocompatible, biodegradable, biomedical applications, orthopedics.

Introduction

A significant progress has been made in the evolution of materials for orthopedic applications, in the last years. The most complex type of tissue is bone, with a relatively high stiffness and hardness. To create an ideal bone implant, certain condition must be met such as bioactivity, biocompatibility and fully degradability, if it is to be replaced by the newly formed bone without formation of toxic degradation products. Moreover, it should exhibit mechanical integrity with the bone tissue, *i.e.*, mechanical strength, fracture toughness and Young's modulus should be close to those of the bone. In terms of the properties of materials used in bone regeneration, they depend on the place of implantation [1].

Biodegradable Mg alloys are suitable for bone applications, because of their high mechanical strength. Furthermore, considering of their elastic properties similar to those of bone, they are considered excellent for hard tissue implants implicated in fracture stabilization as long as bone regeneration is increased and stress shielding is avoided [2, 3]. Because of their good biocompatibility, biodegradability or bioabsorbability, high strength compared to polymers and high ductility compared to bioceramics, Mg alloys proved to have much potential for bone implants. Moreover, could significantly reduce the "stress shielding" existed in the metallic bone implants due to the closer mechanical properties of Mg alloys to natural bone than those of other metallic materials [1]. The elastic modulus of Mg alloys is about 40–45 GPa, which is very close to that of human bone (10–40 GPa) [4]. The specific density of Mg and its alloys are approximately 1.7 g/cm^3, which is very similar to that of human calvarium bone (1.75 g/cm^3) [5]. The biodegradability ensures the possibility to resolve the bone/implant interface problem, such as interface loose and inflammation. In the case of Mg implants, due to their biodegradability or bioabsorbability, the second surgery for removal of the metal bone plates and screws is not needed. This is an advantage because morbidity associated to repeated surgery is reduced and additional health costs are avoided [6, 7].

In the human body, Mg is an essential element. Deficiency of Mg cause shrinkage of small arteries, changes in the bone structure, reduction of the activity of osteoblasts and osteoclasts, osteopenia, and may even lead to death. Mg is used especially for cardiovascular stent applications and musculoskeletal devices like screws, plates, pins and rods. Mg and its alloys are characterized by their susceptibility to corrosion in a body environment and there is no toxic risk related with the alloys elements dissolving in the body fluids through biodegradation. Mg is not visible on plain X-ray, computed tomography (CT) or magnetic resonance imaging (MRI), so it does not cause any artifacts [1].

The high corrosion rate of Mg and its alloys, which results in the subcutaneous gas bubbles, limits their clinical application. The main research activities are focused on how to increase the strength and protect from fast corrosion of Mg alloys [8, 9]. The mechanical properties and the corrosion resistance of Mg have been significantly improved due to the evolution of the processing technology applied to Mg, such as surface modification and element alloying [4, 10].

Mg-based materials were first introduced as orthopedic biomaterials in the first half of 20th century, in 1907, reported by Lambotte, who use the first Mg in trauma surgery to secure a fracture involving the bones of the lower leg. Recently, Witte *et al.* conducted a cartilage repair on Mg scaffolds (AZ91) used as a subchondral bone replacement [8].

Biomedical properties for implant application

All the properties of the material and the implant design must be select in association to its application in the musculoskeletal or cardiovascular system of the human body. The first step is to select a suitable application, it is essential to analyze the biological environment, as a second step. In the human body, Mg alloys can be absorbed. It is fundamental that the released elements are non-toxic, particularly in the case of biodegradable materials [11–13]. The effect of the release of alloying components is recommended that be operated on human cells or cell lines *in vitro* tests along with the accepted standard tests [11, 13, 14]. The standard tests like 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay are not completely suitable [15]. The standard tests should be investigated to see if they can be safely for Mg alloys. Because no real correlation between *in vitro* and *in vivo* outcome can be establish, the *in vivo* studies also needs to be accomplished [8, 11]. The implant material must acquire certain degradation behavior, compression, strength under tension, torsion and bending, to assure suitable mechanical behavior, and also to avoid stress shielding as far as possible when is used in orthopedic implant. All these properties depend on the microstructure [16].

To produces materials with a feature profile that is similar to that of the bone in the area of application, it is recommended that the alloying elements be selected in correlation with a processing route. If the target conditions are not met, the alloy and development needs to be repeated, and also test the profile and the *in vitro* and *in vivo* posture, until the target requirements are met [16].

The highest concentrations of Mn are found in the bones, liver and pancreas; it is an essential element, has no toxic effect and plays a primary role in the activation of multiple enzyme systems, *i.e.*, hydrolases, kinases, transferases and mitochondrial respiration [17, 18]. The recommended daily amount of Mn for ages 11–51+ is 2–5 mg [17]. Another essential component is Zn, which is found in over 200 enzymes in the body, including ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) polymerases [19–21]. Zn hence participate, *via* enzymes, a catalytic role, a regulatory role, *e.g.*, in controlling and coordinating cell growth, and a structural role, *e.g.*, as Zn finger proteins in body hormones [17, 20, 22]. Mn does not have much effect on tensile strength, but it does increase the saltwater resistance of Mg alloys by eliminating iron and other heavy metal elements into relatively harmless intermetallic compounds [23]. As an alloying element in Mg implants, Zn is used to improve room temperature strength and also helps against the harmful corrosive effect of Fe and Ni impurities [24].

The role of alloy coatings

The most crucial constraints in using Mg and its alloys as implant materials are the rapid corrosion, accumulation of hydrogen bubbles in gas pockets adjacent to the implant, and an increase in the local pH of body fluid. Reducing the rate of Mg corrosion is the most suitable method because a low corrosion rate of an Mg implant contributes to a decrease in the extent of hydrogen evolution and alkalization, which allow the human body to eliminate or consume the corrosion products. Therefore, to reduce corrosion rate and to improve the biocompatibility of Mg and its alloys, surface treatment/coatings and alloying process were investigated. The evolution of Mg alloys with preferable corrosion resistance, mechanical integrity, and biocompatibility is a challenging work [25].

Coatings for biomaterials have the same necessity as the base materials themselves of being biocompatible and fully degradable. In the situation of Mg, coatings themselves cannot be ideal barriers to corrosion, but to allow the biodegrade process of Mg implant, the coating must not have a barrier effect. Ideally, the coating would itself degrade cautiously, helping to management the overall corrosion process while leaving no damaging evidence. A large number of possible coating technologies for Mg biomaterials exist, including anodization, metal–metal coatings, plasma spray, chemical vapor deposition (CVD), pulsed laser deposition (PLD), ion beam-assisted deposition (IBAD), solution coatings, calcium phosphate (CaP) deposition achieved by various means, and the well-known methods of electrodeposition and conversion coating [26].

Effects of alloying element on mechanical and corrosion properties

The Mg-based biodegradable materials can be distributed into four major groups: (*i*) pure Mg, (*ii*) Al-containing alloys (AZ91, AZ31, LAE422, AM60, etc.), (*iii*) rare earth elements (AE21, WE43, etc.), and (*iv*) Al-free alloys (WE43, MgCa 0.8, MgZn6, etc.). These alloying elements enhance the mechanical and physical properties of Mg alloys for orthopedic applications by: (*i*) optimizing grain size, (*ii*) improve corrosion resistance, (*iii*) supply mechanical strength by the formation of inter-metallic states, and (*iv*) facilitate the manufacture process of Mg alloys [27].

Manganese

To improve their corrosion resistance Mn is mainly included to Mg alloys. This is acquired by decrease the harmful result of impurities [28]. It has been demonstrated that when Mn is added to Mg, the corrosion aspect, which derives from the Fe impurities, is restored inactive because Mn atoms enclose the Fe atoms and play as local cathodes [29]. Mn assists in numerous functions within cellular systems, especially as various cofactors for many metalloenzymes, such as: DNA and RNA polymerases, oxidases and dehydrogenases, decarboxylases, sugar transferases and kinases [30, 31]. In humans, excessive quantity of Mn has been proven to induce “manganism”, which is a neurological disorder most the same to Parkinson’s disease [32].

Zinc

Zn is often used as an alloying element for Mg alloys, and the efficiency strength of Mg alloys enhance with its Zn content [33]. Mg alloys are mainly important for orthopedic applications due to Young’s modulus with a value of 3–20 GPa, which is highly similar to the Young’s modulus for bone (20 GPa) [34].

To overcome the problem of hydrogen gas evolution from Mg alloys, one of the method is to alloy the material with Zn. Hydrogen evolution and electrochemical impedance spectroscopy (EIS) tests demonstrate that in alloys with lower quantity of Zn, outcome in strong H_2 gas evolution through degradation in simulated body fluids (SBFs), because Zn-rich alloys hardly form any hydrogen gas [35].

Zn is also a vital sign mineral to animals, plants, humans, and microorganisms [36–38]. If in an alloying material for biomedical implant, is used Zn as an alloying element, its dissolution from the bulk material, as a result of the corrosion when placed *in vivo*, would be less damaging than other elements like Al and Mn, because Zn is easily absorbable by biological activity within the cell [39–42].

Hydrogen gas evolution

The critical complication is that pure Mg corrodes too quickly in the physiological pH (7.4–7.6) and high chloride environment of the physiological system, develop hydrogen gas in the corrosion process, at a rate that is too fast to handle with the tissue [43]. The *in vivo* corrosion study by Witte *et al.* [44] shows all Mg implants exhibited clinically and radiographically visible subcutaneous gas bubbles, which appeared within one week after surgery and disappeared after 2–3 weeks. Song managed corrosion tests of a variety of Mg alloys in SBF and the results show that the rate of hydrogen evolution of commercial pure Mg, ZE41, Mg1.0Zn, AZ91, Mg2Zn0.2Mn and HP-Mg is 26, 1.502, 0.28, 0.068, 0.012 and 0.008 mL/cm^2/day, respectively. He postulated hydrogen gas evolution rate 0.01 mL/cm^2/day as a tolerated level in the human body. Therefore, the hydrogen gas is not a serious problem, if an adequate Mg alloy with a suitable coating is used as an implant material [45].

In vitro tests of Mg alloy for bone implant application

Xu *et al.* have studied, in 2007, the corrosion behavior in a phosphate-buffered SBF of Mg–Mn and Mg–Mn–Zn alloy, examined by electrochemical testing and weight loss investigation for bone implant application [24]. As well known, the corrosion of metal materials is mainly dependent on their composition. High purity Mg alloy, such as 99.9999% Mg (or 6 N Mg), has shown good corrosion resistance [46]. They prepared samples of high purity Mg–Mn (Mg-1.2Mn, in wt%), Mg–Mn–Zn (Mg-1.2Mn-1Zn, in wt%) and WE43 (Mg-4.0Y-3.0Nd-0.5Zr, in wt%), cut from Mg alloys cast ingots. The samples were molded within epoxy resin just with one side of 1 cm^2 exposed in a SBF as corrosion medium, for the purpose of electrochemical and immersion tests. Before testing, in order to keep the pH value in a range of 7.3–7.5 during experiments, they used phosphates (KH_2PO_4 and Na_2HPO_4) as buffer and they adjusted the pH of the SBF solution to 7.3 by addition of NaOH [24]. They carried out the electrochemical test with the following parameters: temperature of solution at 37±1°C, used an automatic laboratory corrosion measurement system. As a function of time, they monitored the open circuit potential (E_{ocp}) and the working electrode was immersed in the solution for 20 minutes and then the polarization curve was determined at a scanning rate of 0.3 mV/s [24]. Following the testing, they compiled the results for E_{ocp} curves and polarization curves of three alloys, demonstrating that the highest E_{ocp} was found for Mg–Mn–Zn alloy and the lowest E_{ocp} for Mg–Mn alloy, and a noble breakdown potential and long passivation stage was observed at the anodic polarization stage for all alloys in the polarization curves. Although the corrosion current densities (i_{corr}) of all alloys were of the same order of magnitude, WE43 alloy showed the lowest i_{corr}, five times lower than Mg–Mn and Mg–Mn–Zn alloys, indicating that WE43 has the most acceptable corrosion resistance [24].

For the weight gain/loss test, samples were immersed in a 500 mL solution (total surface area to solution volume 1 cm^2/500 mL) at 37±1°C for 24, 48, 96 and 216 hours, respectively. Then, the samples were supersonically washed and measured the weights before and after the immersion to calculate the weight gain [(weight after immersion – weight before immersion)/surface area]. They cleaned the immersed samples in a boiling solution of 180 g/L chromic acid, to remove the surface corrosion product, and calculated the weight loss [(weight before immersion – weight after clean)/surface area] [24].

They analyzed the microstructure using scanning electron microscopy (SEM) and determined the chemical composition of the surface layer or products using energy-dispersive spectroscopy (EDS). The X-ray photoelectron spectroscopy (XPS) measurements for the surface structure were performed using an X-ray source of Mg Kα (1253.6 eV). To detect the phase constitutes of the surface reaction product on the Mg samples immersed for 216 hours, they examined the surface with small-angle X-ray scattering (SAXS) and measured with a continuous scanning process at a rate of 4°/min [24].

After 24 hours immersion, they observed approximately 4 mg/cm^2 weight gain and that the weight gain increases with the increase of the immersion time. After 216 hours immersion, approximately 15 mg/cm^2 weight is gained. Microstructure observation shows that, after 24 hours immersion, the Mg surface is completely covered by a reaction layer with many cracks. The EDS result indicate that the layer is particularly composed of O, P, Mg, Na and Ca, small amount of K and insignificant amount of Mn. By increasing the immersion time (*e.g.*, after 96 hours immersion), there is slight difference in the surface morphology and some small particles are formed in the reaction layer. No significant difference was found in the element analysis results by EDS [24].

A SAXS was attended on the Mg surface immersed for 216 hours, with the purpose to detect the phase constitute of this reaction layer, detecting a large amount of amorphous phase, as well as Mg matrix. An XPS spectrum (P_{2p}, Ca_{2p}, O_{1s}, Mg_{1s} and Mn_{2p}) of the surface of Mg–Mn, immersed for 216 hours, was analyzed. The $P_{2p3/2}$ spectrum is detected as single peak at 132.9 eV and Ca_{2p} spectrum is detected as double peaks of $Ca_{2p\ 3/2}$, at 347.6 eV and $Ca_{2p\ 1/2}$, at 350.7 eV. Analyzing the bonding energies of $P_{2p\ 3/2}$ and Ca_{2p}, it was concluded that P element exists in the layer in a form of a phosphate group. O_{1s} and Mg_{1s} spectra are detected as single peak at 531.2 eV and

1304.1 eV, respectively. Small amount of Mn is also detected by XPS and Mn2p spectra are detected as double peaks of Mn2p 3/2, at 641.9 eV and Mn2p 1/2, at 654.2 eV, demonstrating that Mn exists in a form of MnO. Correlated with SAXS, it was concluded that the surface reaction layer is mainly an amorphous Mg-containing phosphate layer with small amount of MnO for Mg–Mn–Zn alloy [24].

Also, for the surface of Mg–Mn–Zn, immersed for 216 hours, was effectuated an XPS spectra (P2p, Ca2p, O1s, Mg1s, Mn2p and Zn2p). Small amount of Zn is detected by XPS as double peaks of Zn2p 3/2, at 1022.8 eV and Zn2p 1/2, at 1045.7 eV. From the XPS and SAXS results, they confirmed that the surface reaction layer is also mainly an amorphous Mg-containing phosphate layer with small amount of MnO [24].

They concluded that, the weight gain rates for Mg–Mn, Mg–Mn–Zn and WE43 alloys decrease abruptly with the increase of the immersion time within the first 48 hours, and then it decreases very slowly or does not change within further immersion. The highest weight gain rate throughout the whole immersion time was established for Mg–Mn alloy. The lowest rate is observed for Mg–Mn–Zn alloy. Some notable information was resumed after the results in the case of weight loss of three Mg alloys in SBF. The weight loss gradually increases with the increase of the immersion time for all alloys. After 216 hours immersion, the highest weight loss is observed for Mg–Mn alloy and the lowest for Mg–Mn–Zn alloy. The weight loss rate of Mg–Mn alloy increases rapidly with immersion time within 24–48 hours and decreases rapidly within 48–96 hours, with no change when increasing the immersion time further. For Mg–Mn–Zn alloy, the weight loss rate, increases rapidly within 24–48 hours and decreases when increasing the immersion time [24].

In vivo studies of Mn alloy for implant application

Kraus *et al.* have studied, in 2012, the bone and tissue response to degrading Mg pin implants in the growing rat skeleton by continuous *in vivo* microfocus computed tomography (μCT) monitoring over the entire pin degradation period [5].

In this study, they used machined cylindrical pins made of two different Mg–Zn alloys. The biodegradable Mg alloys ZX50 and WZ21 were recently developed for the purpose of degradable implant applications [47, 48].

The study was conducted on 32 Sprague–Dawley male rats, with a body weight of 140–160 g and five weeks of age, divided in two groups: 16 rats belonged to the "continuous μCT" group and 16 to the "histological" group. Each rat in each group got two identical pins (either WZ21 or ZX50) implanted into its femoral bones. Accordingly, eight rats with ZX50 and eight rats with WZ21 were assigned to the "continuous μCT" group while eight rats per alloy belonged to the "histological" group. Starting with the seventh day after operation, the rodents in the "continuous μCT" group underwent μCT evaluation every four weeks up to the 24th week and histological examinations were performed after four, 12, 24, and 36 weeks. Explanted bones were dissected from soft tissues and fixed in 4% neutral buffered formalin solution [5].

Regarding the degradation performance, the volume and surface have modified and the quantity of hydrogen gas formation of the ZX50 and WZ21 pins were attended by *in vivo* μCT analysis all over the entire study period of 24 weeks. As they expected, the change in volume in the alloys ZX50 and WZ21 display very different degradation rates. The ZX50 pins started to corrode right away after implantation and displayed surface holes already within the first week. As a result, the surface area of the ZX50 pins and implant volume decreased after four weeks. The total volume reduction of ZX50 pins was ~1.2% per day and 50% average degradation was achieved after ~6.5 weeks. Another interesting thing is that simultaneously to pin degradation, considerable release of hydrogen gas occurred within a short time period [5].

In contrast, the volume of the WZ21 pins decreased only moderately during the initial months after implantation, with a merely 2.3% pin volume degraded within the first two months. After four weeks, a slight increase in pin volume was observed, due to the formation of corrosion products on the Mg pin. After eight weeks, the degradation continued in a rather linear manner with an average volume loss of ~0.5% per day. After ~21.5 weeks, 50% pin degradation was reached. Since the degradation occurred slower in WZ21 pins, a large surface area was measured over the whole period of 24 weeks, with a maximum at 12 weeks. For WZ21 implants, the type of the surrounding tissue significantly affects the degradation characteristics. Soft tissue pin parts degraded the fastest, corroding after four weeks, followed by a degradation in the intramedullary cavity, after 16 weeks. They also observed that the hydrogen gas volume was moderate and nearly constant for the whole period of observation of the WZ21 corrosion, averaging ~7 mm^3. As ~50% of the pin volume degraded from week 8 to week 21 in a more-or-less linear manner, a corresponding hydrogen gas evolution was ~130 mm^3 H_2 per day. Since the observed gas volume around the implant did not change significantly and was always ~7 mm^3, the important conclusion can be drawn that the surrounding tissue is able to carry away a daily dosage of 130 mm^3 H_2 [5].

This research reveals that important actions are involved in the process, in this sense they highlighted the most relevant one. As part of the biological response testing, both implant materials were well tolerated by the rats. Clinically, no wound infections were observed and all animals tolerated full weight-bearing post operation. Regarding bone reaction to the inserted ZX50 implants, the fast Mg ion release during degradation led to an enhanced neo-formation of bone tissue around the implant. Consequently, substantial gas formation appeared in the intramedullary cavity and extraosseous around the ZX50 pins. The gas pressure induced some mechanical disturbance of bone regeneration, resulting in distinct callus formation, especially at the medial pin outlet. Both new bone formation and bone resorption were noticed to great extent at the same time. In week 12, the major pin volume was degraded and no further hydrogen formation appeared, the gas bubbles were resorbed, and the bone remodeled fast. In week 16, cortical bone defects were almost entirely healed. After 24 weeks, the medullary cavity was regenerated. The WZ21 alloy resulted in enhanced bone

formation around the pins from weeks 4 to 8. Histological analysis did not reveal obvious adverse tissue reactions around this alloy. Gas formation amount did not affect bone regeneration and was almost entirely resorbed by surrounding tissue. New bone formation around the pin was observed in the medullary cavity and more in the medial corticalis. Some important information was described like, as degradation started in the medullary cavity, both bone resorption and formation occurred simultaneously. Almost no signs of corrosion were seen within the 36-week study period and the junction between cortical bone and WZ21 implant surface remained tight [5].

Conclusions

This review of the literature pointed out that a wide range of coatings on Mg and Mg alloys can increase the corrosion resistance of these materials. Mg and Mg-based alloys are very biocompatible, have similar mechanical properties to natural bone and develop a pleasant material. The competence to select alloying elements and surface modifications ensure the occasion to create a specific Mg alloy implant that can be convenient to the specific orthopedic application. If the selected materials have already been examined *in vivo* and do not own any negative effects on biological environment and revealed an advantageous corrosion rate, this make a proper solution. It is also fundamental to use high purity Mg as even very small amount of impurities may have a harmful effect on the Mg corrosion rate.

Conflict of interests

The authors declare that they have no conflict of interests.

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