Magnesium as a Biodegradable and Bioabsorbable Material for Medical Implants

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Abstract

For many years, stainless steel, cobalt-chromium, and titanium alloys have been the primary biomaterials used for load-bearing applications. However, as the need for structural materials in temporary implant applications has grown, materials that provide short-term structural support and can be reabsorbed into the body after healing are being sought. Since traditional metallic biomaterials are biocompatible but not biodegradable, the potential for magnesium-based alloys, which are biodegradable and bioabsorbable, in biomedical applications has gained more interest. Biodegradable and bioabsorbable magnesium-based alloys provide a number of benefits over traditional permanent implants. This paper summarizes the history and current status of magnesium as a bioabsorbable implant material. Also discussed is the development of a magnesium-zinc-calcium alloy that demonstrates promising degradation behavior relative to a commercially available Mg and magnesium-aluminum-zinc alloy.

Introduction

Biomaterial implants can either be used to replace a diseased part or to assist in the healing process. While the former application requires implants to stay in the body permanently, the latter application only requires that the implant remain in the body temporarily. Thus, in situations where a permanent implant is used for a temporary application, additional surgeries are required to remove these devices once the healing process is complete. This removal process increases the cost and patient morbidity[1]. In contrast, biodegradable materials dissolve after the healing process is complete and thus, no additional surgeries are required for removal of these implants. This also eliminates the complications associated with the long-term presence of implants in the body. Lastly, once these materials degrade within the body, it is important that the degradation products are able to be metabolized by the body, and thus bioabsorbable[2,3].

Polymers were the first materials to be used as commercial biodegradable and bioabsorbable implant materials. The earliest and most commonly used absorbable materials include Poly-Glycolic Acid (PGA), Poly-Lactic Acid (PLA), Poly-Dioxanone (PDS)[4,5]. However, these materials are limited by their low strength and radio-opacity[6]. Low mechanical strength severely restricts the applications of polymeric materials in load bearing and tissue supporting applications, as a greater amount of material is required to meet the mechanical needs of the body. Metals have more desirable mechanical properties due to their relatively high strength and fracture toughness, however, the majority of metals are biologically non-absorbable or toxic. Studies have shown that conventional surgical alloys, like stainless steel, cobalt, chromium and nickel-based alloys produce corrosion products, which are harmful for human body[7-10]. On the other hand Mg and its corrosion products have excellent biocompatibility and are considered to be a promising technology for temporary medical implants[8,11]. As a result, the use of magnesium (Mg) as a biodegradable and bioabsorbable medical material has gained significant attention in the area of biomaterials.

Magnesium as a Biomaterial

Magnesium shows great promise as a potential biocompatible and biodegradable material. The most attractive physical characteristics of Mg are its high specific strength and an elastic modulus that closely resembles human bone (as shown in Table I). The properties are of great importance as high mechanical

strength reduces the amount of implant material needed for a given applied load and reducing the elastic modulus mismatch alleviates stress-shielding effects between bone and the implant material.

Magnesium is an essential mineral for human metabolism and its deficiency has been linked to various pathological conditions[7]. The human body contains about 1 mole (24g) of Mg. It is the second most common intracellular ion and serves as a cofactor for more than 300 enzymatic reactions ranging from muscle contraction to neuronal control[12]. Most of the Mg in the body (53%) is stored in bone, in an apatite inorganic matrix subject to regulated release[13]. Magnesium-based materials were first introduced for orthopedic applications in the beginning of twentieth century. Lambotte[14,15] first reported the use of a pure Mg plate along with gold plated steel nails to secure lower leg bone fracture. However, the *in vivo* corrosion of the implant was too rapid as it degraded in just 8 days. Since then, several attempts have been made to increase the corrosion resistance of Mg implants and a variety of new alloys have been tested *in vitro* and *in vivo*[16-18]. These studies highlighted Mg's additional beneficial attributes, namely its ability to stimulate bone growth and healing. Latter experiments have confirmed that the presence of Mg enhances the bone cell adhesion on alumina[19] and has no inhibitory effect on cell growth[20]. Furthermore, corrosion and degradation of Mg leads to the formation of harmless corrosion products, which are excreted through urine[21].

However, the major limitation of Mg is its low corrosion resistance. Low corrosion resistance results in the rapid release of degradation products. A high rate of degradation under physiological conditions can cause a reduction in the mechanical integrity of the implant before the bone or tissue is sufficiently healed[15]. Magnesium's low corrosion resistance also leads to the rapid production of hydrogen gas that leads to the formation of gas bubbles. These bubbles can accumulate around the implant and delay the healing of the tissue[15]. The localized formation of hydrogen gas can also result in a pH increase around the implant[22]. This can cause local alkalization and severely affect the pH dependent physiological processes in the vicinity of the implant[23].

To successfully employ bioabsorbable metal implants, the time frame of degradation must be sufficient such that the cells can synthesize and deposit an extracellular matrix for their own support and function before the structural integrity of the implant is compromised. Surfaces have been treated or coated with a variety of chemistries and polymers to encourage cell attachment[24-26]. Once adhered, cells create a substrate on the implant comprised of the proteins necessary for their function and survival. For example, osteoblasts are bone forming cells that lay down the tough protein collagen, and then mineralize it to make new bone. Growing these cells on collagen increases their bone mineralization activity[27]. Alternatively, an elastic protein, aptly named "elastin," is abundant in arteries to expand and recoil when the large volume of blood comes from heart contraction[28]. After the cells are supported, absorption of the implant would leave behind a naturally synthesized protein structure appropriate for those cells at that specific site. For these reasons, a significant, uncontrolled, local change in Mg concentration due to implant degradation can have a deleterious effect on human physiology and must be managed through proper engineering design. Hence for extensive use of Mg and its alloys in biomedical implant applications, a better understanding and control over the degradation rate is required.

Controlled Degradation and Alloy Design

Although the general biocompatibility of Mg is high, increased degradation rates under physiological pH conditions can locally reduce the biocompatibility near the implant surface. Under typical atmospheric conditions, Mg reacts with water to produce mildly protective film of magnesium hydroxide ($Mg(OH)_2$)[29]. Although this film slows corrosion under aqueous conditions, it reacts with chlorine ions present in physiological conditions to produce $MgCl_2$ and hydrogen gas[15].

Efforts to control the corrosion rate of Mg have utilized various processing methods such as purification, alloying, anodizing, and surface coating. Studies have shown that purification of Mg reduces the corrosion rate considerably, however, due to low yield strength of pure Mg[30], its application in orthopedics and other load bearing applications is limited[23]. Alloying elements can be added to increase the strength of pure Mg[31]but alloying elements should be selected carefully to maintain the Mg's biocompatibility. Elements like iron (Fe), nickel (Ni), copper (Cu), and cobalt (Co) have extremely deleterious effects on the corrosion

properties of Mg, rapidly increasing the degradation rate. Cadmium (Cd), manganese (Mn), tin (Sn), zinc (Zn), and calcium (Ca) have mild effect on the corrosion rate of Mg with their efficacy being dependent on solute concentration[29]. Aluminum (Al) is a major alloying element in Mg-based alloys and is considered to enhance the strength and corrosion resistance. However, it has poor biocompatibility, which causes phosphate depletion in tissues and lowers phosphate absorption from digestive tract. The depletion of phosphates can lead to progressive senile dementia[32]. Zirconium, which is added as a grain refiner in Mg-based alloys has been linked to breast and lung cancer, and rare earth elements, such as cerium (Ce), lutetium (Lu), and praseodymium (Pr), are generally considered toxic for the human body[23]. Hence, the selection of appropriate alloying elements is critically in the design of a biocompatible implant material. Using materials essential to human body as alloying elements, we can greatly reduce the chance of toxicity and develop a completely biodegradable and biocompatible alloy.

Calcium and Zn are two essential elements in human body that also provide mechanical strengthening in Mg-based alloys. Calcium has been reported to improve the corrosion resistance of Mg-based alloys in simulated body fluid[33]. Meanwhile, Zn additions increase the strength of Mg-based alloys primarily through to precipitation strengthening. Thus a new Mg-Zn-Ca alloy has been designed for potential use as a biodegradable and bioabsorbable implant material. The following is a presentation of our study on the degradation behavior of this alloy.

Degradation Study of Pure Magnesium and Mg-Zn-Ca alloy

In vitro testing was performed on Mg-15wt%Zn-2wt%Ca (ZX152) and commercially pure Mg (99.95%) samples. Disc shaped samples were cut from cylindrical rods. The samples were then mounted in epoxy and polished up to 0.3 microns. The mounted samples were immersed in Hank's solution at 37.2^{o}C for different times ranging from 30 minutes to 4 days. Samples were removed from the solution and washed with ethanol. Inductively coupled plasma (ICP) spectroscopy was then used to calculate the amount of Mg, Ca, and Zn present in the Hank's solution. Some of the samples were cross-sectioned to observe the interface between corrosion layer and the metal using scanning electron microscopy (SEM).

The degradation rates of pure Mg, Mg-Zn-Ca and Mg-9wt%Al–1 wt% Zn (AZ91) are shown in Figure 1. The dissolution rates for AZ91 were obtained from Xin *et al*.[34] who performed corrosion testing of the alloy in simulated body fluid (SBF). The ion concentrations for Hank's solution and SBF are shown in Table II. The relative ion concentrations for both solutions are similar except that Hank's solution does not contain Mg, Ca, or sulfate ions prior to sample immersion. Although this allows for increased resolution in the ICP measurements, the large concentration gradients between the sample surface and the solution may increase the degradation rate relative the same sample tested in SBF. Additionally, the increase chlorine ion concentration in the Hank's solution is expected to further increase the degradation rate relative to sample immersion in SBF.

Both pure Mg and AZ91 show a rapid degradation rate during the first 10 hours of immersion. Initial degradation rates for AZ91 and pure Mg are approximately 0.15 and 0.11 mg/hr-cm^2, respectively. This is contrasted with the lower degradation rate of 0.06 mg/hr-cm^2 in the ZX152 alloy.

The SEM micrographs of the cross-section of the Mg and ZX152 samples immersed after 219 hours are shown in Figure 2. It can be seen that the morphologies of the interfaces between the corrosion layer and the substrate are different in pure Mg and ZX152. Pure Mg displays uniform surface degradation whereas site-specific pitting can be seen in ZX152 alloy. This is mainly due to the microstructural differences as the ZX152 alloy contains a eutectic phase whereas pure Mg is single phase. In the ZX152 alloy, the eutectic phase seems to be more corrosion resistant as compared to the matrix, thereby resulting in the preferential corrosion of matrix, thereby resulting in the preferential corrosion of the Mg-rich matrix over the eutectic. Xin et al.[34] made a similar observation in AZ91 where β-$Mg_{17}Al_{12}$ phase shows a more passive behavior than the matrix. It has been suggested that β-$Mg_{17}Al_{12}$ affects corrosion in two ways[35]. Apart from acting as a corrosion barrier, it acts as a cathode for Mg-rich matrix, thereby creating a galvanic couple with the matrix and increasing the corrosion rate. Making a similar conclusion about the cathodic nature of eutectic phase in ZX152 is beyond the scope of this paper. However, plots depicting degradation rates suggest that ZX152 alloy has a lower degradation rate than AZ91 and pure

magnesium. It is also seen that the eutectic phase in ZX152 is corrosion resistant and acting as a corrosion barrier.

Conclusion

The degradation behaviors of pure Mg and a Mg-15wt%Zn-2wt%Ca (ZX152) alloy were studied using *in vitro* testing in Hank's solution and SEM analysis. These tests were then compared against the performance of a commercially available Mg-based alloy, AZ91. Additionally, morphological analysis was performed on samples that had undergone 219 hours of immersion in Hank's solution to study the effect of microstructural features on the degradation behavior of these alloys. It was observed that the initial degradation rate of the pure Mg and AZ91 alloy were approximately double that of ZX152. It is believed that addition of Ca and the formation of a eutectic phase increases the corrosion resistance of the alloy, and thus reduces the degradation rate. Microstructural analysis reveals that after several hours of immersion, the Mg-rich solid solution phase has preferentially dissolved away leaving a surface primarily composed of the eutectic phase.

In past few years, significant advances have been made in the field of bioabsorbable materials and Mg has shown a great potential as a material for bioabsorbable implants. Although a substantial amount of research has been performed on the use of Mg and its commercially available alloys for biomedical applications, further research is needed to fully evaluate the potential of research grade Mg-based alloys for use in biological implants. An integrated approach involving chemists, experimental and computational material scientists, and medical professionals is needed to understand the fundamental mechanisms involved with the application of Mg alloys in physiological conditions. Understanding the fundamental questions like the effect of secondary phases on the degradation rate, interaction of corrosion surface with tissue, influence of degradation products on surroundings, and toxicity of alloying elements is necessary to achieve the goal of a fully biocompatible and biodegradable Mg alloy implant.

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Table I: Summary of Mechanical Properties of Natural and Implant Materials

	Material	Tensile Strength (MPa)	Elastic Modulus (GPa)	Bio-degradable
Natural Materials	Collagen	60 [b]	1 [b]	Yes
	Cortical bone	100-200 [b]	10-20 [b]	Yes
Inorganic Materials	Magnesium	185-232[c]	73-117[d]	Yes
	Stainless Steels	480-834 [b]	193 [b]	No
	Cobalt Alloys	655-1400 [b]	195-210 [b]	No
	Titanium Alloys	550-985 [b]	100-105 [b]	No
	Platinum Alloys	152-485 [b]	147 [b]	No
	Synthetic Hydroxyapatite	600 [d,*]	41-45[d]	No
Organic Materials	L-PLA	28-50 [a]	1.2-3 [a]	Yes
	D,L-PLA	29-35 [a]	1.9-2.4 [a]	Yes
	UHMWPE	39-40 [b]	0.94-1.05 [b]	Yes

*Indicates compressive strength (MPa)
(a) Reference [36]; (b) Reference [37]; (c) Reference [30] ; (d) Reference [15]

Table II. Ion Concentrations of Simulated Body Fluid (SBF)[34] and Hank's Solution

Ion Concentration (mmol/L)	Na^+	K^+	Ca^{2+}	Mg^{2+}	HCO_3^-	Cl^-	HPO_4^{2-}	SO_4^{2-}
SBF	**142.0**	**5.0**	**2.5**	**1.5**	**4.2**	**148.5**	**1.0**	**0.5**
Hank's Solution	**141.4**	**5.8**	**-**	**-**	**4.2**	**142.2**	**0.8**	**-**

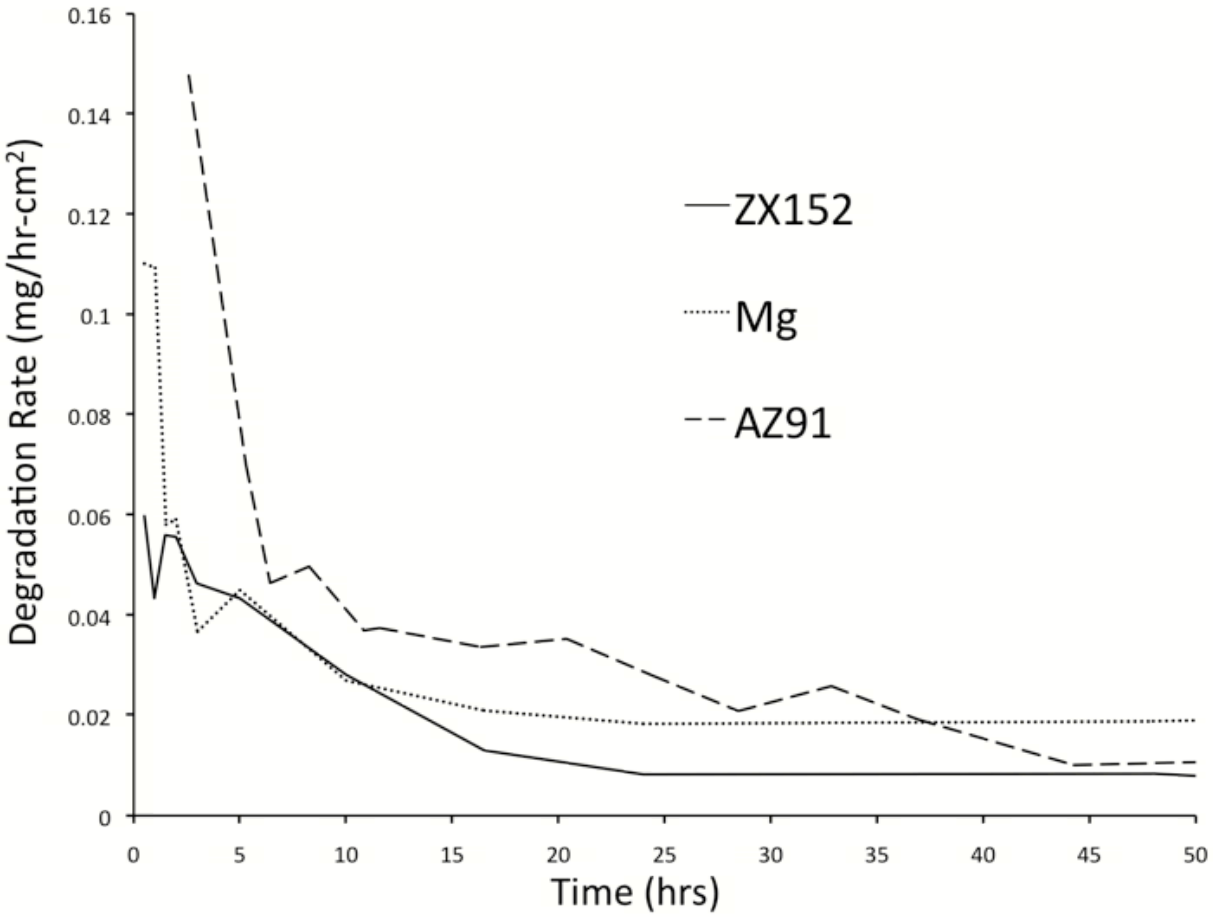

Figure 1. Plot of degradation rate versus time for three materials: Mg-15wt%Zn-2wt%Ca (ZX152), pure Mg, and Mg-9wt%Al-1wt%Zn (AZ91).

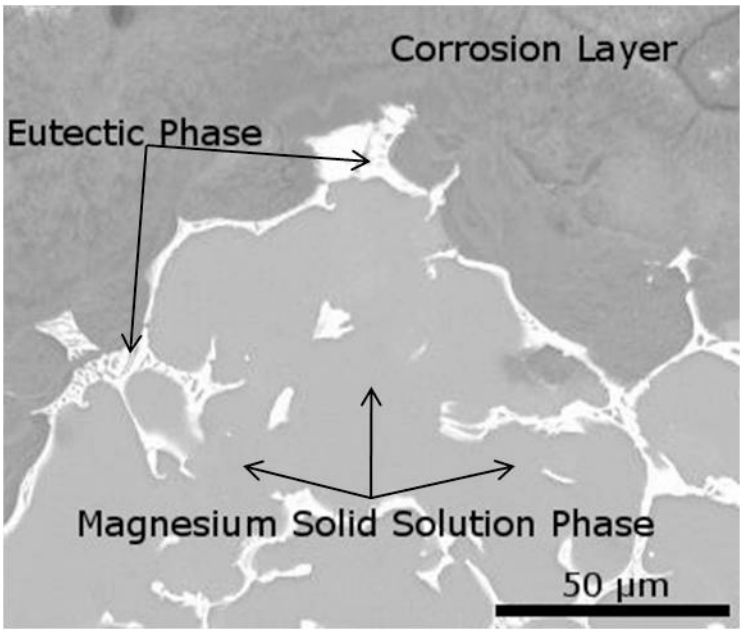

Figure 2. SEM micrograph highlighting the morphology of the corrosion layer forming on a ZX152 sample after 219 hours of exposure to Hank's solution. The eutectic (light colored phase) phase can be seen acting as a corrosion barrier.

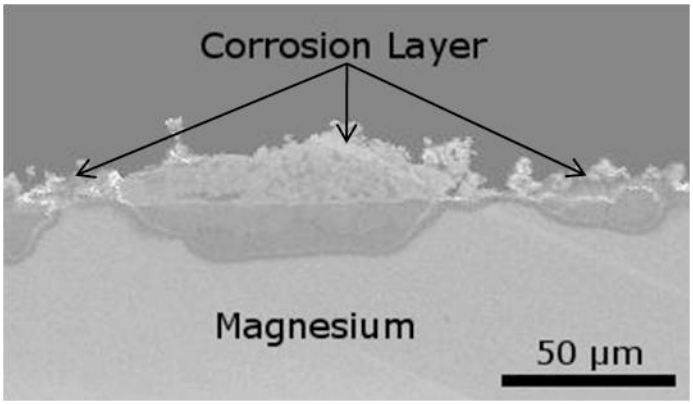

Figure 3. SEM micrograph highlighting the morphology of the corrosion layer forming on a pure Mg sample after 219 hours of exposure to Hank's solution.