A Review of Magnesium Alloys for Use in Biodegradable Cardiovascular Stents

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Abstract: Metallic stents can be permanent or biodegradable. Permanent stents made from inert metals have several disadvantages for long-term applications and need to be removed after the vessels heal. Therefore, biodegradable stents, including stents made from biodegradable metals, have been used for the treatment of cardiovascular diseases. Ideally, implanted stents can maintain their mechanical integrity during the healing of the vessel wall and then dissolve after healing. The mechanical strength and properties of magnesium are suitable for biodegradable implants, especially for stent application. Magnesium is biocompatible because it is essential for several biological reactions and as a co-factor for enzymes. However, magnesium also has a disadvantage; its degradation is accelerated in chloride-abundant environments such as human body fluid. Therefore, magnesium must be modified to improve its corrosion resistance. This paper addresses the potential of a magnesium alloy as a cardiovascular stent material by discussing its corrosion resistance behavior.

Key words: Magnesium alloy • Corrosion resistance • Biodegradable • Stent

INTRODUCTION

Cardiovascular disease refers to any disease affecting the cardiovascular system, including the heart and blood vessels [1]. The disease is caused by fat deposition on vessel walls, which can narrow and weaken the vessels. This deposition can lead to the deposition of blood clots on the vessel walls. Stents can be inserted to prevent vessel rupture and to open up the vessel. Stents are perforated tubular-shaped materials used as arterial scaffolding for the treatment of cardiovascular disease. Stents are implanted by surgeons to open up weakened and narrowed vessels [2]. A stent must have good mechanical strength to hold it shape and to prevent the vessel from closing up and it also has to be ductile because it will be expanded using a balloon catheter [3].

Stents are typically manufactured using a polymeric, metallic or combination scaffolding. Metallic stents have good mechanical integrity and have been used to treat cardiovascular disease for decades. Initially, stents used permanent or corrosion-resistant metals, e.g., 316L stainless steel (ASTM F138 and F139; annealed), tantalum (annealed), Cp-titanium (F67; 30% cold worked), nitinol and cobalt-chromium (ASTM F90) alloy. During arterial healing, permanent stents must provide excellent mechanical integrity and arterial wall support [4-6].

An implanted stent is required to last for 6-12 months to enable vessel healing [5]. After that time, the presence of a stent in the blood vessel does not provide any benefit. Another surgery is required to remove permanent metallic stents after healing, resulting in additional risk to the patient and incurring additional cost. The implanted stent could cause long term vessel wall dysfunction, blood clotting and an inability to adapt to vessel growth, necessitating further surgery [2].

These considerations led to interest in the development of biodegradable metal stents. Biodegradable stents can maintain the integrity of the
artery wall during the healing process and then dissolve in the body fluid without any surgery after the artery wall heals [7]. These stents provide temporary vessel opening until the vessel remodeling is complete and then the stent will dissolve and disappear. Biodegradable stents have mechanical strengths similar to those of permanent implants, making them able to maintain the integrity of the artery wall during the healing process. After the artery wall is healed, the stent will dissolve in the body fluid without any surgery [7-9].

During the implantation procedure, the stent is mounted on a balloon catheter in the collapsed state. When the balloon is inflated, the stent expands or opens up and pushes itself against the inner wall of the artery. This holds the artery open when the balloon is deflated and removed. Thus, the metals used in stents should have (1) the ability to be compacted at the normal state so that the stent can be crimped in the balloon catheter; (2) the ability to expand to push and widen the artery; (3) the ability to support the artery wall and remain still after the balloon catheter is removed; (4) sufficient flexibility, as the stent will be delivered through the artery to a certain location in the artery; (5) sufficient magnetic resonance imaging compatibility, which is needed to help clinicians locate the stent; and (6) thromboresistivity so that the stent material does not induce blood clot and deposition, as well as compatibility with body fluids [10-13].

**Materials Perspective on Magnesium as a Biodegradable Stent:** Magnesium (Mg)-Alloy has potential as a candidate base alloy because it has the required properties for stent design, a low Young’s modulus, good biocompatibility and most importantly biodegradability. In chloride-abundant environments such as body fluid, its degradation is faster than expected, in the range of 3-6 months [14]. Longer applications could be enabled by increasing the resistance to bio-corrosion. Thus, Mg alloy must be modified to improve its degradation resistance in the human body [15].

Table 1 summarizes the mechanical properties of different magnesium based alloys, with the properties of stainless steel (316L SS) included as a reference. The gold standard for the mechanical strength of a stent is 316L SS. However, stainless steel is pure metal and non-degradable. Thus, a good goal for biodegradable stent design is to achieve a mechanical strength comparable to that of 316L SS.

Pure Mg has a lower mechanical strength than 316L SS. The yield strength, tensile strength and elongation are all weaker than those of stainless steel. Pure Mg exhibited faster degradation than its alloys. Mg alloying is important to increase the material strength and to decrease the degradation rate.

**Mechanical Properties of Magnesium as a Biomaterial:** The biocompatibility of a material is the main issue in the development of biodegradable implants. The body should be able to resorb implanted material and the materials and their degradation products should be nontoxic. Practically, we should choose materials that are abundant in the body. Mg is the eleventh most abundant element by mass in the human body. Mg ions are involved in many reactions in the body and are essential to all living cells, especially for enzymatic function [17].

Stents are expanded using a balloon catheter during implantation. Therefore, biomaterials used in stents need to be sufficiently elastic to allow for this expansion. This elastic deformation could be provided by changes in atomic spacing and bonds stretching [18].

**Alloying:** Alloys are solid solutions in which alloying element atoms are present between base metal atoms. The alloying element atoms serve as substitution point defects, creating lattice strains and increasing the energy. This energy is needed for dislocation motion and to strengthen the material. Alloys are almost always stronger than pure metals. Alloying could also make Mg more highly packed and alloying elements reduce direct water contact and decrease the Young’s modulus [8].

![Table 1: Mechanical Properties, Degradation Rate and Average Grain Size of Stent Material [16].](image)

<table>
<thead>
<tr>
<th>Material</th>
<th>Yield Strength (Mpa)</th>
<th>Tensile Strength (Mpa)</th>
<th>Elongation (%)</th>
<th>In vitro degradation rate (mm y⁻¹)</th>
<th>Average grain size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>316L SS: Annealed (ASTM F138)</td>
<td>190</td>
<td>490</td>
<td>40</td>
<td>-</td>
<td>12-30</td>
</tr>
<tr>
<td>2.1.1. Pure Mg: as cast</td>
<td>20</td>
<td>86</td>
<td>13</td>
<td>407</td>
<td>-</td>
</tr>
<tr>
<td>WE43 alloy: extruded</td>
<td>195</td>
<td>280</td>
<td>2</td>
<td>1.35</td>
<td>10</td>
</tr>
<tr>
<td>AM60B-F: die cast</td>
<td>-220</td>
<td>6-8</td>
<td>8.97</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>ZW21: extruded</td>
<td>200</td>
<td>270</td>
<td>17</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>WZ21: extruded</td>
<td>140</td>
<td>250</td>
<td>20</td>
<td>-</td>
<td>7</td>
</tr>
</tbody>
</table>
However, no elements have been found to be effective in improving the corrosive behavior of Mg rather than just improving its mechanical properties because the alloying elements are somehow nobler than Mg [18].

**Grain Size Refinement:** Metals are commonly polycrystalline, consisting of non-oriented grains. Plastic deformation requires cross-dislocation between grains and a uniform grain orientation. This could be achieved using small grains. Using the finest grain in AZ91 could lead to a compact layer of P-containing compounds and magnesium hydroxide, increasing the protection against chloride ions [19].

**Degradation of Mg:** As human body fluids contain 90% water, Mg will be oxidized, producing magnesium hydroxide as indicated in reactions 1 to 4. Magnesium hydroxide will form a surface layer, protecting magnesium from further corrosion [14]. However, if the environment has a chloride ion concentration greater than 30 mmol/l[17], Mg will be converted into the highly soluble salt magnesium chloride as in reaction (5). Human body fluids contain a chloride ion concentration of approximately 150 mmol/l [20].

**Partial Reaction of Magnesium Oxide Formation:**

\[
\text{Mg}^{2+} + 2\text{OH}^- \leftrightarrow \text{Mg(OH)}_2(s) \quad (3)
\]

**Overall Reaction:**

\[
\text{Mg} + 2\text{H}_2\text{O} \leftrightarrow \text{Mg(OH)}_2(s) + \text{H}_2(g) \quad (4)
\]

**Reaction Between Chloride Ion and Magnesium Hydroxide:**

\[
\text{Mg(OH)}_2(s) + \text{Cl}^- \leftrightarrow \text{MgCl}_2(s) + 2\text{OH}^-(aq) \quad (5)
\]

Biomaterials could be processed to alter their bulk properties, surface properties and other properties with the goal of altering their biocompatibility. Although Mg based alloys have been proven to be biocompatible, the degradation rate was found to be too fast [16]. One of the main challenges for biodegradable metallic stents is to control the degradation rate.

**Mg Alloy:** One method to improve the mechanical strength and corrosion resistance of Mg is alloying. The metals commonly used for alloying with Mg are Al, Mn, Zn, Ca, Li, Zr, Y and RE elements [11, 20-35]. Metals used in the human body must be safe and biocompatible. Table 2 summarizes the biocompatibility of several elements used in implant applications.

Fe and Mg have the highest normal blood serum levels among these elements and both are used as base metals for stent applications. Pure Fe has been used as a stent material in rabbit aortas and while these stents held for 18 months, damage has been reported to the vessel media and the internal elastic membrane [36]. However, the corrosion was assumed to be too slow to enable use as a biodegradable implant. Mg exhibits good biocompatibility, but it needs to be alloyed with other elements to improve its corrosion resistance. Based on the galvanic series, the metals nobler than magnesium are Zn, Be, Cd, Cu and Ni. These metals could protect Mg from corrosion, but based on the table above, we also need to consider its biocompatibility.

Alloying will alter the mechanical properties of a material, improving its corrosion resistance, mechanical strength and grain refinement. Table 3 summarizes the effects of the addition of alloying elements and impurities on the mechanical properties of Mg alloys.

Alloying elements led to both improvements and declines in grain refinement and corrosion resistance. Rare earth metals, Al, Ca, Sr and Y improved grain refinement, whereas Cu harmed this property. Ca, Cu, Fe, Li, Ni and Si also decreased the corrosion resistance of Mg alloy. Manganese (Mn) improved both properties.

**Corrosion resistance of Mg alloy:** The corrosion resistance of Mg alloys can be expressed in the unit mm year\(^{-1}\). The corrosion resistance of Mg and its alloys is summarized in Table 4. The corrosion rate of pure Mg in MgCl\(_2\) and as-cast pure Mg are 300 and 407 mm year\(^{-1}\), respectively. Alloying decreased the rate of corrosion to the range of 10\(^{-3}\) mm year\(^{-1}\) depending on the alloying element.

Mg alloys with Al, Mn, Zn, Gd, Cu, Fe, Si (AZ91DgDA, AZ91DgDB, AZ91NDnB and AZ91NDnA) exhibit the lowest corrosion rates. These alloying elements effectively suppressed the rapid corrosion of Mg. Based on Table 3 and Table 4, Mn, Zn and Al can effectively decrease the corrosion rate of Mg alloy.
Table 2: Alloying Elements, Impurities and their Toxicology and Pathophysiology [18]

<table>
<thead>
<tr>
<th>Element</th>
<th>Normal blood serum level</th>
<th>Effect and Function</th>
</tr>
</thead>
</table>
| Magnesium     | (17.74-25.76)x10^6 ng/l  | _ Co-regulator for energy metabolism, cell proliferation, protein synthesis, onset of DNA synthesis  
_ Regulator of more than 350 proteins  
_ Stabilizer of DNA and RNA  
_ At high concentrations causes asphyxia, a drop in blood pressure, confusion, abnormal cardiac rhythm and a deterioration of kidney function |
| Calcium       | 2.1-4.8 x10^3 ng/l       | _ Most abundant mineral in the human body (1-1.1 kg)  
_ Mainly stored in bone, teeth  
_ Tightly regulated by skeletal, renal and intestinal mechanisms of homeostasis |
| Aluminum      | (2.1-4.8) x10^3 ng/l     | _ Established alloying element in titanium implants  
_ Risk factor for Alzheimer’s disease  
_ Can cause muscle fiber damage  
_ Decreases osteoclast viability  
_ In magnesium alloy; mild foreign body reactions were observed in vivo |
| Zinc          | (0.8-1.14) x 10^3 ng/l   | _ Trace element  
_ Essential for the immune system  
_ Co-factor for specific enzymes in bone and cartilage  
_ Neurotoxic at higher concentrations |
| Manganese     | <0.8x10^3 ng/l           | _ Essential trace element  
_ Important role in the metabolic cycles of lipids, amino acids and carbohydrates  
_ Influences the function of the immune system, bone growth, blood clotting, cellular energy regulation and neurotransmitter synthesis  
_ Scavenger of free radicals in manganese superoxide dismutase  
_ Neurotoxic at higher concentrations |
| Lithium       | 2-4 ng/l                 | _ Present in drugs for the treatment of psychiatric disorders  
_ Overdosage causes nephrological or lung dysfunction  
_ Possible teratogenic effects |
| Nickel        | (0.5-2.3) x10^2 ng/l     | _ Many rare-earth elements exhibit anti-tumorigenic properties  
_ Strong allergic agent that can induce metal sensitivity  
_ Carcinogenic and genotoxic |
| Beryllium     | <2 ng/l                  | _ Induce metal sensitivity, highly carcinogenic  
_ Essential for life and metabolically regulated and stored  
_ Contributes to the development of age-related diseases by generating reactive oxygen species |
| Iron          | (0.5-1.76) x10^3 ng/l    | _ Essential for life and metabolically regulated and stored  
_ Contributes to the development of age-related diseases by generating reactive oxygen species |
| Copper        | (4.70-8.33) x10^3 ng/l   | _ Essential for life and metabolically regulated and stored  
_ Contributes to the development of age-related diseases by generating reactive oxygen species |

Table 3: Influence of Alloying Elements on the Properties and Processing of Mg Alloys at Ambient Temperatures [45].

<table>
<thead>
<tr>
<th>Alloying Element</th>
<th>Grain Refinement</th>
<th>Corrosion Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>RE</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Manganese</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Nickel</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Silicon</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Strontium</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Yttrium</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

+improvement in properties  
-decline in properties
Table 4: Corrosion Resistance of Mg Alloy.

<table>
<thead>
<tr>
<th>No</th>
<th>Alloy#</th>
<th>Alloying elements, wt%</th>
<th>Corrosion Rate (mm year$^{-1}$)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pure Mg in MgCl$_2$</td>
<td></td>
<td>300</td>
<td>[17]</td>
</tr>
<tr>
<td>2</td>
<td>Pure Mg: as cast</td>
<td></td>
<td>407</td>
<td>[16]</td>
</tr>
<tr>
<td>3</td>
<td>AZ91C</td>
<td>0.18 Mn, 0.087 Fe</td>
<td>18</td>
<td>[17]</td>
</tr>
<tr>
<td>4</td>
<td>AZ91E</td>
<td>0.23 Mn, 0.008 Fe</td>
<td>0.64</td>
<td>[17]</td>
</tr>
<tr>
<td>5</td>
<td>AZ91E</td>
<td>0.33 Mn, 0.004 Fe</td>
<td>0.35</td>
<td>[17]</td>
</tr>
<tr>
<td>6</td>
<td>Mg-xCa</td>
<td>0.5Ca</td>
<td>1.52</td>
<td>[37]</td>
</tr>
<tr>
<td>7</td>
<td>Mg-xCa</td>
<td>1.0Ca</td>
<td>1.97</td>
<td>[37]</td>
</tr>
<tr>
<td>8</td>
<td>Mg-xCa</td>
<td>1.5Ca</td>
<td>2.12</td>
<td>[37]</td>
</tr>
<tr>
<td>9</td>
<td>Mg-xCa</td>
<td>2.0Ca</td>
<td>3.94</td>
<td>[37]</td>
</tr>
<tr>
<td>10</td>
<td>Mg-xCa</td>
<td>2.5Ca</td>
<td>7.24</td>
<td>[37]</td>
</tr>
<tr>
<td>11</td>
<td>AM50</td>
<td>4.9Al, 0.26 Mn, 0.2 Zn, 0.006 Cu, 0.004 Fe, 0.06 Si</td>
<td>4.5x10$^{-3}$</td>
<td>[38]</td>
</tr>
<tr>
<td>12</td>
<td>AM50GdB</td>
<td>4 Al, 0.3 Mn, 0.2 Zn, 0.7 Gd, 0.006 Cu, 0.004 Fe, 0.06 Si</td>
<td>3.6x10$^{-3}$</td>
<td>[38]</td>
</tr>
<tr>
<td>13</td>
<td>AM50GdA</td>
<td>4.4 Al, 0.24 Mn, 0.2 Zn, 1 Gd, 0.006 Cu, 0.004 Fe, 0.06 Si</td>
<td>4.0x10$^{-3}$</td>
<td>[38]</td>
</tr>
<tr>
<td>14</td>
<td>AM50NdB</td>
<td>4.4 Al, 0.21 Mn, 0.2 Zn, 0.8 Gd, 0.006 Cu, 0.004 Fe, 0.06 Si</td>
<td>3.0x10$^{-3}$</td>
<td>[38]</td>
</tr>
<tr>
<td>15</td>
<td>AM50NdA</td>
<td>4 Al, 0.24 Mn, 0.2 Zn, 1.5 Nd, 0.006 Cu, 0.004 Fe, 0.06 Si</td>
<td>3.6x10$^{-3}$</td>
<td>[38]</td>
</tr>
<tr>
<td>16</td>
<td>AM60B-F: die cast</td>
<td>6.5 Al, 0.01 Cu, 0.005 Fe, 0.6 Mn, 0.002 Ni, 0.1 Si, 0.22 Zn</td>
<td>8.97</td>
<td>[16]</td>
</tr>
<tr>
<td>17</td>
<td>AZ91D</td>
<td>8.9 Al, 0.19 Mn, 0.52 Zn, 0.001 Cu, 0.004 Fe, 0.01 Si</td>
<td>2.1x10$^{-3}$</td>
<td>[38]</td>
</tr>
<tr>
<td>18</td>
<td>AZ91DGB</td>
<td>8.9 Al, 0.15 Mn, 0.52 Zn, 0.2 Gd, 0.001 Cu, 0.004 Fe, 0.01 Si</td>
<td>1.8x10$^{-3}$</td>
<td>[38]</td>
</tr>
<tr>
<td>19</td>
<td>AZ91DGA</td>
<td>8.0 Al, 0.14 Mn, 0.52 Zn, 0.7 Gd, 0.001 Cu, 0.004 Fe, 0.01 Si</td>
<td>1.7x10$^{-3}$</td>
<td>[38]</td>
</tr>
<tr>
<td>20</td>
<td>AZ91DNB</td>
<td>8.1 Al, 0.13 Mn, 0.52 Zn, 0.7 Nd, 0.001 Cu, 0.004 Fe, 0.01 Si</td>
<td>2.5x10$^{-3}$</td>
<td>[38]</td>
</tr>
<tr>
<td>21</td>
<td>AZ91DNA</td>
<td>8.1 Al, 0.16 Mn, 0.52 Zn, 1.4 Nd, 0.001 Cu, 0.004 Fe, 0.01 Si</td>
<td>3.0x10$^{-3}$</td>
<td>[38]</td>
</tr>
<tr>
<td>22</td>
<td>WE43</td>
<td>3.94 Y, 2.29 Nd, 0.88 Gd, 0.32 Zr, 0.003 Fe, 0.001 Ni, 0.0001 Cu, 0.002 Si, 0.001 Mn</td>
<td>0.25</td>
<td>[38, 39]</td>
</tr>
<tr>
<td>23</td>
<td>WE43: extruded</td>
<td>3.94 Y, 2.29 Nd, 0.88 Gd, 0.32 Zr, 0.003 Fe, 0.001 Ni, 0.0001 Cu, 0.002 Si, 0.001 Mn</td>
<td>1.35</td>
<td>[16]</td>
</tr>
<tr>
<td>24</td>
<td>AZ31</td>
<td>2.89 Al, 0.92 Zn, 0.25 Mn, 0.004 Fe, 0.002 Ni, 0.002 Cu, 0.003 Si</td>
<td>0.21</td>
<td>[39]</td>
</tr>
<tr>
<td>25</td>
<td>JDBM</td>
<td>3.09 Nd, 0.22 Zn, 0.44 Zr, 0.003 Fe, 0.001 Ni, 0.001 Cu, 0.003 Si, 0.001 Mn</td>
<td>0.125</td>
<td>[39]</td>
</tr>
</tbody>
</table>

#ASTM specification B275 presents a code format for alloy naming using one or two prefix letters, two or three numerals and a suffix letter. For example, AZ91 indicate an alloy containing aluminum and zinc at 9 and 1 percent, respectively. Abbreviations for alloying elements: A (aluminum), H (thorium), O (silver), B (bismuth), K (zirconium), R (chromium), C (copper), L (beryllium), S (silicon), D (cadmium), M (manganese), T (tin), E (rare earth), N (nickel), Z (zinc), F (iron), W (yttrium) and P (icad).

Concluding Remarks: Magnesium has great potential for use as a base material in biodegradable cardiovascular stents due to its biocompatibility. However, its high degradation rate is not desirable for treatments that require longer healing times. Therefore, modification of this material is necessary to reduce its rapid corrosion. Alloying has the potential to increase the corrosion resistance and to improve the mechanical properties of magnesium. A limited selection of alloying elements is appropriate for inclusion in Mg alloys for use in blood vessels. The elements must be safe for implantation in the human body and this factor must be considered in the development of Mg alloys with lower degradation rates.

REFERENCES


