Recent advances on the development of magnesium alloys for biodegradable implants

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A B S T R A C T
In recent years, much progress has been made on the development of biodegradable magnesium alloys as “smart” implants in cardiovascular and orthopedic applications. Mg-based alloys as biodegradable implants have outstanding advantages over Fe-based and Zn-based ones. However, the extensive applications of Mg-based alloys are still inhibited mainly by their high degradation rates and consequent loss in mechanical integrity. Consequently, extensive studies have been conducted to develop Mg-based alloys with superior mechanical and corrosion performance. This review focuses on the following topics: (i) the design criteria of biodegradable materials; (ii) alloy development strategy; (iii) in vitro performances of currently developed Mg-based alloys; and (iv) in vivo performances of currently developed Mg-based implants, especially Mg-based alloys under clinical trials.

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1. Introduction: smart implants of magnesium-based alloys

Biodegradable implants, acting as “smart” implants, have attracted increasing interest in the last few years. The main driving force to develop biodegradable implants is their degradation properties in the physiological environment (the terms “degradation” and “corrosion” convey similar meanings but are used in the context of in vivo and in vitro, respectively, in this paper). The opportunity afforded by this class of material is that the clinical function of permanent implants can be achieved and, once complete, the devices may disappear completely when they are no longer useful. One of the main advantages of biodegradable implants is the elimination of follow-up surgery to remove the implant after the tissue has healed sufficiently [1,2]. Consequently, there is a reduction in or exclusion of lifelong problems caused by permanent implants, including long-term endothelial dysfunction, permanent physical disability and chronic inflammatory local reactions [3]. Although polymers are dominant in the current medical market, Mg-based [4–6], Fe-based [7–9] and Zn-based alloys [10,11] have been proposed as better biodegradable materials for load-bearing applications due to their superior combination of strength and ductility over polymers.

Mg-based alloys as biodegradable implants have remarkable advantages over Fe-based and Zn-based ones. Therefore, the study of Fe-based and Zn-based alloys as biodegradable implants is limited to only a few groups worldwide [7–11]. Although iron, magnesium and zinc are all essential nutritional elements for a healthy body, the recommended daily intake for adults of magnesium (240–420 mg day$^{-1}$) is up to 52.5 times more than that of iron (8–18 mg day$^{-1}$) and zinc (8–11 mg day$^{-1}$) [12]. Pure zinc implants may be a concern for patients because a daily intake of 100–300 mg can induce health problems and a higher dosage can be even more harmful [13]. The elastic modulus of magnesium (41–45 GPa) is closer to that of natural bone (3–20 GPa) than that of iron (~211.4 GPa) or zinc (~90 GPa) [1,11,14]. The mismatch of elastic moduli can lead to the implant carrying a greater portion of the load and cause stress shielding of the bone [15]. This biomedical incompatibility can result in critical clinical issues, such as early implant loosening, damage to the healing process, skeletal thickening and chronic inflammation [16]. Both pure iron and pure magnesium have been reported to possess excellent biocompatibility in the human body and show no signs of local or systemic toxicity [1,17]. However, researchers have recently concluded that iron is a poor choice for biodegradable stents because the corrosion products from the iron accumulate over 9 months and are retained in the arterial wall of the living rat model as voluminous flakes [18,19]. Moreover, magnesium implants have been proven to stimulate the formation of new bone when they are implanted as bone fixtures [20].

The investigation of magnesium alloys as cardiovascular and orthopedic implants is not a new concept [21]. The first clinical application was reported in 1878 by the physician Edward C. Huse,
who successfully used magnesium wire ligatures to stop bleeding vessels [22]. However, early clinical investigators [23,24] soon found that magnesium was too brittle, had limited mechanical properties and degraded too quickly. As a result, the application of magnesium and its alloys as medical implants had nearly ceased. With the technological advances in developing high-purity magnesium with high mechanical and corrosion performance, renewed interest in bioapplications of Mg-based alloys began with studies in 2000–2003 by Heublein et al. [25,26], who took advantage of the degradation characteristic of magnesium alloys to develop cardiovascular stents. Since then, BIOTRONIK has fabricated three generations of absorbable metal stents (AMSs) [27] from WE43 and modified Mg-based alloys, an example of which shown in Fig. 1a. Clinical trials have shown no symptoms of allergic or toxic reactions to magnesium stents. Magnesium stents can achieve an immediate angiographic result similar to the other permanent metallic stents, and can degrade completely and safely after 4 months [28–31]. Recently, the first commercially available Mg-based orthopedic product has emerged. The MAGNEZIX® screw (Fig. 1b) obtained the CE mark for medical devices used in medical applications within Europe [32]. Animal models have already been conducted on other potential magnesium products (Fig. 1c–e), including microclips for laryngeal microsurgery [33], plates and nails [34], and wound-closing devices [35].

Despite the remarkable progress that has been made on the development of Mg-based alloys as biodegradable implants over the last 15 years, a number of fundamental challenges are still unsolved. The extensive range of applications of Mg-based alloys is still inhibited mainly by their high degradation rates and consequent loss in mechanical integrity at pH levels between 7.4 and 7.6 and in the high chloride environments of physiological systems [37]. Moreover, the rapid formation of hydrogen gas bubbles, usually within the first week after surgery, could be a negative effect of Mg-based implants [38]. This paper aims to review the recent advances of Mg-based alloys for biodegradable implants, with emphasis on the alloy development strategy and the in vitro and in vivo performances of currently developed Mg-based alloys, as well as to provide a picture of current challenges and future trends. The major difference between this and previously published reviews [38–43] is that this review not only summarizes the latest advances on the development of Mg-based alloys and their performances in vitro and in vivo, but also reviews the alloy development strategies to address the fundamental issues in Mg-based alloys.

2. The design criteria of the biodegradable materials

Biodegradable materials are designed to provide temporary support during the healing process of a diseased or damaged tissue and to progressively degrade thereafter [44]. This concept requires the materials to provide appropriate mechanical properties for the intended use and suitable corrosion resistance for progressive degradation. It also requires the materials to possess acceptable biocompatibility and bioactivity within the human body, as new-generation biomaterials [45,46]. Obviously, the specific design and selection criteria of biodegradable materials depend on the intended applications. Screws, pins, needles and other load-bearing orthopedic applications are implanted in the bone to maintain mechanical integrity over 12–18 weeks while the bone tissue heals [1]. Thus dedicated Mg-based alloys should combine both high strength and a low modulus close to that of bone to avoid “stress shielding”. Erinc et al. [47] proposed specific mechanical and corrosion requirements for biomaterials purposed for bone fixtures: the corrosion rate needs to be less than 0.5 mm year$^{-1}$ in simulated body fluid at 37 °C, the strength higher than 200 MPa and the elongation greater than 10%. Coronary stents, which are another exciting medical application for Mg-based alloys, are implanted to open blood vessels and must function in dynamic blood flow. The ideal biodegradable stent should possess sufficient mechanical properties, appropriate degradation rate, excellent hemocompatibility and biocompatibility, and drug delivery capacity. The stents are

Fig. 1. Real/possible applications of biodegradable magnesium implants: (a) cardiovascular stents (BIOTRONIK, Berlin, Germany, under clinical trial) [31], (b) MAGNEZIX screw (received CE mark in Europe) [36], (c) microclip for laryngeal microsurgery (pure magnesium) [33], (d) biodegradable orthopedic implants [34], (e) wound-closing devices (WZ21) [35].
expected to degrade at a very slow rate for the first 6–12 months to maintain optimal mechanical integrity during arterial vessel remodeling. Afterwards, the degradation should progress at a sufficient rate without causing an intolerable accumulation of degradation products around the implantation site. Ultimately, stents should completely degrade within 12–24 months after implantation [48].

A summary of the mechanical properties of metals designed for stents undergoing clinical trials or approved by the US Food and Drug Administration (FDA) is listed in Table 1. The metal most commonly used for stents is SS316L, which has been approved by the FDA [43]. Its mechanical properties are often used as benchmark criteria to evaluate other alloys for stent applications. It is clear that the yield strength (YS) of Mg-based alloy WE43 is comparable to SS316L and is better than the pure iron or tantalum. Furthermore, the WE43 alloy has the lowest elastic modulus of all the metals in Table 1, which gives it a significant benefit over the others, as explained earlier. The main concern regarding the used of Mg-based alloys for stents is their limited ductility.

### 3. Alloy development strategy

#### 3.1. Design strategy

Pure magnesium in the as-cast condition has a very low strength, at just under 30 MPa, and a very fast corrosion rate of 2.89 mm year⁻¹ in 0.9% NaCl solution [51]. Generally, alloying elements can directly strengthen the mechanical properties by solid-solution strengthening, precipitation hardening and grain-refinement strengthening [52]. Alloying elements introduced to strengthen the matrix must have high and temperature-dependent solubility in magnesium. The solubility mainly depends on the atomic size of the element with regard to magnesium and its valency (the relative-valency effect) [53,54]. The hexagonal close-packed structure of magnesium (c/a = 1.624) and its atomic diameter (0.320 nm) ensure that it forms solid solutions with a diverse range of elements [54]. In Fig. 2, the elements within the dashed lines have a size factor that is favorable for the formation of a solid solution with magnesium because the atomic size is within ±15% of the atomic size of magnesium [54]. Mostly investigated biodegradable Mg-based alloys, such as Mg–Al-based, Mg–Zn-based and most Mg–rare earth (RE)-based alloys, have obvious precipitation hardening due to high solubility of the secondary element in magnesium (Table 2). By contrast, other Mg-based alloys, such as Mg–Ca-based and Mg–Si-based alloys, may be unable to strengthen by heat treatment (Table 2). The normal solution heat-treating temperature lies within 340–565 °C and the temperature for aging may be in the range of 150–260 °C [55]. Heat treatment can obviously improve not only the strength but also the corrosion resistance of the alloys [51]. The size, shape, type, volume fraction and coherency of second-phase precipitates can influence the precipitation hardening [56] and corrosion performance.

Grain refinement is another effective approach to increase the mechanical properties and corrosion resistance of Mg-based alloys. Grain size strengthening is described by the well-known Hall–Petch relation

\[ \sigma = \sigma_0 + k d^{-1/2} \]

where \( \sigma \) is the YS, \( \sigma_0 \) is the material constant, \( d \) is the average grain diameter and \( k \) is the strengthening coefficient. A very attractive attribute of Mg-based alloys is that the strengthening coefficient (280–320 MPa μm⁻¹/²) is several times higher than those of face-centered cubic and body-centered cubic metals. For example, the strengthening coefficient is over four times higher than that of Al-based alloys (68 MPa μm⁻¹/²), indicating that the strengthening of Mg-based alloys by grain refinement is much more effective [60].

The methods of grain refinement during solidification have recently been reviewed by StJohn et al. [61,62]. It is now widely accepted that both the undercooling required for nucleation and the growth restriction factor (GRF) calculated by binary phase diagrams are critical in determining the final grain size. The GRF is equal to \( \sum m_i C_{ai}(k_i - 1) \), where \( m_i \) is the slope of the liquidus line (assumed to be a straight line), \( k_i \) is the distribution coefficient and \( C_{ai} \) is the initial concentration of element \( i \). Table 3 lists the GRF parameters of several alloying elements [61,62]. Extensive studies have proven that Zr, Ca, Si, etc. have excellent grain refinement efficiency in magnesium.

In addition to alloying-element-induced grain refinement, plastic deformation and/or severe plastic deformation (SPD) are the most efficient ways to refine the grain size and introduce a high density of dislocations and stacking faults in the microstructure. Therefore, grain size strengthening and defect strengthening can be obtained simultaneously. Normal deformation temperatures of most wrought Mg-based alloys range from 250 to 450 °C [63]. Jan et al. [64] introduced nanospaced stacking faults into the Mg–8.5Gd–2.3Y–1.8Ag–0.4Zr (wt.%) alloy by conventional hot rolling and produced ultrastrong Mg-based alloy, with a YS of ~575 MPa, an ultimate strength of ~800 MPa and a uniform elongation of ~5.2%. It was found that a high density of nanospaced stacking faults induced the superior mechanical properties by impeding dislocation slips and promoting dislocation accumulation.

#### 3.2. Element selection

There are several considerations for element selection in developing bio-Mg alloys, as shown schematically in Fig. 3. The first consideration is elemental toxicity. The degradation products of the designed alloys should be non-toxic and absorbable by the surrounding tissues or dissolvable for excretion via the kidneys [38]. Elements can be classified into the following groups [58,65,66]: (i) well-known toxic elements: Be, Ba, Pb, Cd, Th; (ii) elements that are likely to cause severe hepatotoxicity or other allergic problems in human: Al, V, Cr, Co, Ni, Cu, La, Ce, Pr; (iv) nutrient elements found in the human body: Ca, Mn, Zn, Sn, Si; and (iv) nutrient elements found in plants and animals: Al, Bi, Li, Ag, Sr, Zr.

### Table 1

Mechanical properties of biomedical metals for stents [43,48–50].

<table>
<thead>
<tr>
<th>Metals</th>
<th>Young's modulus (GPa)</th>
<th>Density (g cm⁻³)</th>
<th>YS (MPa)</th>
<th>UTS (MPa)</th>
<th>Elongation (%)</th>
<th>FDA approval</th>
<th>Biodegradability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stainless steel (SS316L, annealed plate, ASTM F138)</td>
<td>193</td>
<td>8</td>
<td>190</td>
<td>490</td>
<td>40</td>
<td>Yes</td>
<td>Biostable</td>
</tr>
<tr>
<td>Co–Cr alloys (ASTM F90)</td>
<td>210</td>
<td>9.2</td>
<td>210</td>
<td>860</td>
<td>20</td>
<td>Yes</td>
<td>Biostable</td>
</tr>
<tr>
<td>Tantalum (annealed)</td>
<td>185</td>
<td>16.6</td>
<td>138</td>
<td>207</td>
<td>–</td>
<td>No</td>
<td>Biodegradable</td>
</tr>
<tr>
<td>Pure iron (99.8 wt.%)⁴</td>
<td>200</td>
<td>7.87</td>
<td>150</td>
<td>210</td>
<td>40</td>
<td>No</td>
<td>Biodegradable</td>
</tr>
<tr>
<td>Mg-based alloy (WE43, ASTM B107/B107M)</td>
<td>44</td>
<td>1.84</td>
<td>170</td>
<td>220</td>
<td>2</td>
<td>No</td>
<td>Biodegradable</td>
</tr>
</tbody>
</table>

* Fe stents are only under the animal model and are cited for comparison purposes.
The second consideration is the strengthening ability of the elements. Four groups can be categorized [53,54,67]: (i) impurities: Fe, Ni, Cu, Co; (ii) elements that can improve the strength and ductility simultaneously: ranging in increasing strength, they are Al, Zn, Ca, Ag, Ce, Ni, Cu, Th; ranging in increasing ductility, they are Th, Zn, Ag, Ce, Ca, Al, Ni, Cu; (iii) elements that can only improve ductility with little effect on the strength of magnesium: ranging in increasing ductility, they are Cd, Tl, Li; and (iv) elements that decrease the ductility but increase the strength of magnesium: ranging in increasing strength, they are Sn, Pb, Bi, Sb.

The third consideration is the influence on the corrosion behavior. Alloying elements that have a close electrochemical potential to, or that form intermetallic phases with a similar potential to, magnesium (−2.37 V) can improve the corrosion resistance by reducing the internal galvanic corrosion. Such elements include: Y, −2.37 V; Nd, −2.43 V; and Ce, −2.48 V.

### 3.3. Alloy families

The earliest Mg-based alloys investigated as a new class of implant material are the commercial alloy systems because they have well-known strength and ductility in engineering applications. So far, pure magnesium [68], AZ31 [69], AZ61 [68], AZ91 [37,68,70,71], AM60 [71], ZK30 [72], ZK60 [72–74] and WE43 [70,75] have been extensively investigated. Calcium, as a major component in human bone and a great grain refiner in magnesium alloys (Table 3), has been added to commercial Mg-based alloys such as AZ61 and AZ91 in order to improve their corrosion resistance and mechanical integrity [37]. However, in designing alloys for engineering applications, the toxicity and biocompatibility in biological environments are not considered. For example, aluminum is a well-known neurotoxic element. Researchers have to develop new Mg-based alloys with low/no toxicity levels for biological applications. With this consideration in mind, Mg–Ca [6], Mg–Zn [47,66], Mg–Si [77], Mg–Gd [78], Mg–Zr [79,80], Mg–Sr [81,82] and Mg–Y [83] binary alloys have been developed and investigated (Table 4). However, most binary alloys have a YS of less than 150 MPa and a corrosion rate higher than 2 mm year\(^{-1}\), as summarized in Table 4. These binary alloys have been mainly
investigated to achieve the optimal composition for the development of multi-elemental Mg-based alloys with better performance, instead of being used directly as implants.

Representative multi-element Mg-based alloys developed for biomaterials are Mg–Zn-based [76,87–90], Mg–Si-based [77,91], Mg–Zr-based [79,80,92] and Mg–RE-based alloys [5,69,93,94], and these are detailed below. The typical YS and elongation at failure of currently developed Mg-based alloys are summarized in Fig. 4. Each alloying family in Fig. 4 includes both as-cast and as-deformed alloys in an effort to convey an authentic examination of the performance of each alloying system. Among these Mg-based alloys, Mg–RE-based alloys normally exhibit the highest strength and the best elongation. Mg–Zn-based alloys are very promising because not only are they the second strongest ductile alloy system, but their corrosion rates can also be greatly reduced by utilizing certain strategies, as described below. More importantly, Mg–Zn-based alloys may be RE free. Mg–Zr-based alloys exhibit the lowest strength and ductility in this summary.

The corrosion rates of typical Mg-based alloys in different test solutions and with different test methods are summarized in Fig. 5. Several obvious conclusions can be drawn from the figure. First, the corrosion resistance can be greatly improved by processing, as seen in as-cast [68] and as-extruded [99] AZ31 alloy. Second, alloys normally show better corrosion resistance in vivo than in vitro. Witte et al. [20] found that degradation in an in vivo animal model was about four orders of magnitude lower than the in vitro corrosion of AZ91D and LAE442 alloys. The major difference in corrosion rates is clearly caused by the dynamic nature of the in vivo environment and the static nature of the in vitro environment. Specifically, a covering of proteins on implants, the remodeling of bones and possibly a protective corrosion layer being formed by the accelerated corrosion rate shortly after surgery in response to the initial pH drop in the in vivo environment may be responsible for the reduced corrosion rate [20]. Third, Mg–RE-based alloys normally exhibit the best corrosion performance of all the investigated alloys, especially in the as-deformed condition, such as Mg–Nd–Zn–Zr [99], WE43 [99] and Mg–Gd–Zn–Zr alloys [100]. Fourth, Mg–Zn-based alloys [85], which are non-RE Mg-based alloys, show very promising corrosion resistance. Finally, the corrosion rates tested in different groups may be significantly different. Typical examples can be seen in Fig. 5, in which the corrosion rate of as-extruded ZK61 (related to Mg–6Zn) is totally different from that of as-extruded Mg–6Zn, so is as-cast Mg–1Si from as-cast Mg–0.6Si.

3.4. Impurity control

The common impurities found in magnesium (Be, Fe, Ni and Cu), which are known to deteriorate corrosion resistance, should be strictly controlled. These elements are very harmful because of their low solubility in magnesium and because they serve as active cathodic sites for the formation of corrosion cells in Mg-based alloys [41]. Moreover, the existence of the impurities reduces the effective content of alloying elements and threatens the mechanical integrity of the alloys by reacting with the alloying elements to form phases containing both impurities and alloying elements.
4.1.1. Mg–Al-based alloys

Aluminum has a very high maximum solubility in Mg (12.7 wt.%). Al dissolved in the Mg matrix forms $\gamma$-Mg$_{17}$Al$_{12}$ and $\alpha$-Mg phases, resulting in obvious solid-solution strengthening. Mg–Al-based alloys exhibit excellent castability, moderate mechanical properties and good corrosion resistance [52]. Increasing the amount of Al can greatly improve the corrosion resistance of Mg–Al-based alloys [68]. Zn or Mn is often used in combination with Al to improve the room-temperature strength and ductility. AZ31 [68,70,71,104,105], AZ61 [68], AZ91 [37,68,70,71] and AM60 [71] alloys are the Mg–Al-based alloys that have been most heavily investigated as biodegradable materials. Ce, Ca, Y, Nd and Sr have all been reported to improve the mechanical properties of Mg–Al alloys by sharply refining the microstructure [37,106,107]. The typical YS, ultimate tensile strength (UTS) and elongation of as-cast AZ91 are 145 MPa, 275 MPa and 6%, respectively [20,95], which can be improved remarkably by two-step equal-channel angular pressing (ECAP) to 290 MPa, 417 MPa and 8.45%, respectively [108]. The UTS and elongation of as-cast AM60 are just 160 MPa and 3%, respectively. After large-strain rolling with 80% reduction, the UTS and elongation were increased sharply to 378 MPa and 12%, respectively [109]. The high strength of Mg–Al-based alloys induced by deformation is due to the grain refinement and the precipitation of Mg$_{17}$Al$_{12}$ phase during processing. Despite Mg–Al-based alloys having excellent mechanical properties after deformation, Al is known to be harmful to neurons and osteoblasts [4], especially at the higher concentrations in such alloys as AZ91 and AM60.

4.1.2. Mg–Zn-based alloys

Unlike Al, which is toxic, Zn is an essential trace element in human body. Zn has a solubility limit of 6.2 wt.% in magnesium, and Mg–Zn alloys mainly consist of an $\alpha$-Mg matrix and a $\gamma$-MgZn phase [76]. The addition of Zn to Mg does result in a continuous increase in YS as Zn increases from 1 to 6 wt.%. However, the Zn content should be limited to 4 wt.% to achieve the maximum UTS (216.8 MPa) and elongation (15.8%) [76]. Ca, Zr, Sr, Y, Mn and Si are the most intensively investigated elements to add to Mg–Zn-based alloys to improve the mechanical properties by refining microstructure or forming special structures [72,87,90,103,110,111]. As already mentioned, Ca is an effective grain refiner in Mg-based alloys. The only drawback of Ca is that its maximum solubility in magnesium is only 1.34 wt.%. The strength and ductility of Mg-based alloys decrease with increasing Ca content when it is more than 1 wt.% [6]. The UTS and ductility of Mg–4Zn-based alloys decrease as Ca addition increases beyond 0.5 wt.% [76]. Zr is the best grain refiner in Mg-based alloys without Al, such as Mg–Zn and Mg–RE, because it reacts with Al [106]. The addition of only 0.4–0.6 wt.% of Zr to Mg–3Zn and Mg–6Zn alloys produces the very fine grained ZK30 and ZK60 alloys, respectively. Both ZK30 (YS = 215 MPa, UTS = 300 MPa and elongation = 9%) and ZK60 (YS = 235 MPa, UTS = 315 MPa and elongation = 8%) have much better mechanical properties than the RE-enriched WE43 (YS = 160 MPa, UTS = 260 MPa and elongation = 6%) [72]. The strongest Mg-based alloy so far is Mg$_{50}$Zn$_{20}$Y$_{20}$ (at.%.) alloy (YS = 610 MPa and elongation = 5%), produced by rapidly solidified powder metallurgy. The strength of Mg$_{50}$Zn$_{20}$Y$_{20}$ is higher than that of conventional titanium (Ti–6Al–4V) and Al (5075-T6) alloys [112]. The extruded Mg$_{50}$Zn$_{20}$Y$_{20}$ alloy exhibits a high YS of 390 MPa and an elongation of 5% [113]. The high strength of Mg–Zn–Y alloys originates from the fine grain size, the wide dispersion of a hard lamellar phase and the long-period stacking ordered (LPSO) structure [113].

4.1.3. Mg–Si-based alloys

The maximum solid solubility of silicon in magnesium is only 0.003 wt.%. Silicon reacts with magnesium to form the intermetallic compound Mg$_x$Si, which exhibits a high melting temperature, a low density, a high hardness and a low thermal expansion. Therefore, Mg–Si-based alloys have been originally developed as in situ magnesium matrix composites [114]. Silicon is also an essential mineral in the human body and plays an important role in aiding the healing process and helping to build the immune system [77]. However, the coarse Chinese script Mg$_x$Si phase results in a low ductility in Mg–Si alloys. The ductility is normally less than 10% in the Si addition ranges of 0.3–2.3 wt.%. The highest YS, UTS and elongation, obtained at 0.8 wt.% Si addition, are 52 MPa, 152 MPa and 9.5%, respectively [91]. Zhang et al. [77] reported that the Ca element can slightly refine the grain size and the morphology of Mg$_x$Si in the Mg–Si-based alloy but it cannot improve the strength or ductility. A low Zn content (1.5 wt.%) addition to Mg–Si-based alloy has been suggested in an attempt to improve both strength and elongation.
4.1.4. Mg–Zr-based alloys

Zirconium is normally added to magnesium as a powerful grain refiner to improve the mechanical properties and corrosion behavior (Table 3). The maximum solubility limit of Zr in magnesium is 3.8 wt.%. Zr has low ionic cytotoxicity in vitro, excellent biocompatibility in vivo, good corrosion resistance and an osteo-compatibility equal to or exceeding that of Ti [80]. Strontium can promote osteoblast maturation and osteocyte differentiation and stimulate bone formation. Li et al. [80] studied the influence of Zr and Sr on the mechanical and biological properties of Mg–Zr–ySr alloys (x and y ≤ 5 wt.%). The results show that Mg–(1–5)Zr–(2–5) Sr alloys are composed of α-Mg matrix, Mg17Sr2 intermetallic phase and unalloyed Zr. The obtained Mg–Zr–Sr alloys exhibit moderate strength (compressive YSs of 65–125 MPa and ultimate compressive strengths of 200–290 MPa) and good ductility (ultimate strains of 14–38%). Excessive Mg17Sr2 phase dispersed along the grain boundary and the unalloyed Zr phase in the alloy have been revealed to reduce the corrosion resistance. The Mg–1Zr–2Sr alloy has been shown to exhibit the best combination of corrosion rate, suitable mechanical properties, and in vivo and in vitro compatibility. Mg–Zr–Ca alloys fabricated by Zhou et al. [115] indicate that only a single phase (α-Mg) is detectable in the Mg–0.5Zr–1Ca alloy. Mg–0.5Zr–2Ca and Mg–1Zr–(1, 2)Ca alloys consist of both α-Mg and Mg56Ca phases. All of the Mg–(0.5, 1)Zr–1Ca alloys exhibit low strength (≤135 MPa) and poor ductility (≤8%). It is considered that the formation of the Mg56Ca phase along the grain boundaries decreases the strength. Adding Sr and Sn simultaneously to Mg–Zr–Ca alloy can improve the corrosion resistance [116].

4.1.5. Mg–RE-based alloys

Rare earth elements (REEs) were originally used in Mg-based alloys to significantly improve the creep and corrosion resistance and to increase the mechanical properties at both room and elevated temperatures [117–119]. The REE group comprises 17 elements, which can be subdivided into two groups according to their solid solubility in magnesium (Table 2), indicating their strengthening ability: (i) high solid solubilities (Y, Gd, Tb, Dy, Ho, Er, Tm) and has very low cell cytotoxicity. It is clear that REEs are the most important elements in the patented alloys.

Bjoern Klocke et al. [129] claimed WE43 and WE alloy series consisting of 5.2–9.8 wt.% RE for stents in a patent. Nagura [130] claimed an Mg–Gd–Nd (1–5 wt.%)–Zn–Sr alloy produced for intravascular implants. This alloy is free of yttrium and has very low cell cytotoxicity. It is clear that REEs are the most important elements in the patented alloys.

Apart from strength and ductility, elastic modulus is one of the important parameters for biometals and is one of the benefits of using Mg-based alloys as biodegradable implants. However, from the data of the Mg-based alloys developed in our group and the limited data in the literature, the elastic moduli of Mg-based alloys vary across a small range, which is relatively insensitive to composition, heat treatment and processing. This may be the reason why most papers do not report the elastic moduli for their newly developed biodegradable Mg-based alloys.

4.2. Corrosion

Although the electrochemical potential series provides the potential for pure metals and the Pourbaix diagrams show the corrosion mechanism of magnesium, the corrosion behavior of multi-elemental Mg-based alloys are still difficult to predict. This stems from microgalvanic corrosion in multi-elemental alloys, which mainly depends on the potential difference between intermetallic phases and the matrix [131]. The potentials and types of phases are normally not available, especially in newly developed alloys. The corrosion reaction of magnesium in aqueous environments is

\[
\text{Mg}_{(s)} + 2\text{H}_2\text{O}_{(aq)} \rightarrow \text{Mg(OH)}_{2(s)} + \text{H}_2(g)
\]
which produces magnesium hydroxide and hydrogen gas [132]. Magnesium hydroxide can act as a corrosion protective layer in water but it starts to lose this useful function and convert into highly soluble magnesium chloride when the chloride concentration is above 30 mmol l⁻¹ [132]. Hydrogen gas is a major concern for using Mg-based alloys for orthopedic applications because bone vascularizes and transports the excessive hydrogen gas poorly, thus resulting in the formation of potentially harmful gas pockets [41]. Although recent research has shown that the hydrogen gas can be exchanged rapidly through the skin and/or accumulate in fatty tissue and therefore hydrogen gas adjacent to an implant may not be of major concern, it is better to eliminate it by improving the material itself. One successful strategy to overcome this problem is to fabricate metal glasses with a high Zn content, particularly above the Zn-alloying threshold [133]. Another effective strategy is to improve the corrosion resistance of Mg-based alloys, which can significantly reduce the amount of hydrogen gas. Although pure magnesium corrodes very fast, the corrosion rate of the newly developed Mg-based alloy can be significantly reduced by alloying adjustment, heat treatment, processing and surface modification.

Processing can significantly improve the corrosion resistance, as shown in Fig. 5. Wang et al. [134] studied the corrosion rate of as-cast, as-rolled and ECAPed AZ31 samples in Hanks’ solution. It was revealed that in all three conditions the corrosion rate reduced continuously with time. The corrosion rate was shown to be significantly reduced in as-rolled AZ31 compared to the as-cast AZ31. However, ECAPed AZ31, which had much finer grain size than the as-rolled AZ31, did not result in a further reduction in the corrosion rate compared to the as-rolled AZ31. The reason behind this phenomenon is still unclear. Previous investigations have shown that alloys with reduced grain size after extrusion also exhibits a much slower corrosion rate than the same alloys in the as-cast condition: examples include Mg–Nd–Zn–Zr [5], Mg–Ca [6] and ZK60 [74] alloys. The improved corrosion resistance is believed to be related to the high grain boundary density and dislocation density and the redistribution of the second phase, but the fundamental principle is not clearly understood. Ralston et al. [135] reported that a relationship exists between grain size and corrosion rate, and is similar to the classic Hall–Petch relationship. However, this proposed relationship, which considers just grain size and corrosion rate, cannot explain the fact that the static corrosion rates (open air) of the extruded samples, which are in the order WE43 < AZ61 < AZ31 < ZM21 < ZK60, are in a different order to the hydrodynamic (air bubbling) corrosion rates (WE43 < AZ31 < AZ61 < ZM21 < AZ60 < ZK60) tested in SBF [2]. It is interesting to note that the order of the corrosion rate of Mg-based alloys may vary with the processing history and corrosive time. For example, in the as-cast condition, the corrosion rate is in order of AZ91D < AZ61 < AZ31 < pure Mg after 1 day of immersion in modified SBF. This order is changed to AZ91D < pure Mg < AZ61 < AZ31 after 24 days immersion [68]. These results agree with the order of the extruded AZ31, AZ61, AZ80 (related to AZ91) alloys in Ref. [2] but contrast to the order of the rolled Mg-based alloys (ZK60 < AM60 < AZ31 < AZ91) tested in 1 mol l⁻¹ sodium chloride solution [136].

The alloying elements have a direct influence on the corrosion resistance of Mg-based alloys. Al [68], Zn [77,87], Mn [41], Ca [77], Zr [80], Sr and Sn [116], and most of the REEs, including Nd [124] and Gd [86], have been proven to improve the corrosion resistance. It should be noted that most elements have a critical limit with regard to their improvement of corrosion resistance that falls within their solubility in magnesium: beyond the critical limit, further addition leads to the deterioration of the corrosion resistance [68,86,87]. Heat treatment, including solution [51] and aging treatments [78,124], can significantly improve the corrosion resistance by creating a single-phase microstructure and a microstructure containing fine, well-distributed precipitations, respectively. Surface modification can be an effective strategy to improve the corrosion resistance, as reviewed by Wu et al. [137], Nayeb-Hashemi and Clark [59], and Shadanbaz and Dias [138]. However, once the coating has broken down, the problem of excessive corrosion remains [134].

Corrosion fatigue, which is the failure of a material under the simultaneous action of cyclic loads (tension, compression or bending) and corrosive attack, is mainly responsible for the mechanical failures of metallic implants [139]. In general, the corrosion fatigue limits of Mg-based alloys in vivo are smaller than the fatigue limits in air [140–142]. Fatigue crack initiation is frequently reported to occur at stress concentration sites, manufacturing defects, casting defects, grain boundaries and inclusions of the metallic implants [139,141]. Gu et al. [140] studied the normal fatigue and corrosion fatigue in SBF of as-cast AZ91D and as-extruded WE43 alloys. The results showed that the as-cast AZ91D alloy had a corrosion fatigue limit of 20 MPa at 10⁶ cycles in SBF at 37 °C compared to a fatigue limit of 50 MPa at 10⁶ cycles in air. Furthermore, the as-extruded WE43 alloy had a corrosion fatigue limit of 40 MPa at 10⁶ cycles in SBF at 37 °C compared to 110 MPa at 10⁶ cycles in air. The fatigue cracks for the corrosion fatigue initiated from corrosion pits, whereas in air they were generated from micropores. Although, the results from these two commercial alloys, AZ91D and WE43, have paved the way for a basic understanding of corrosion fatigue behavior, there is still a need for more in-depth studies of this behavior on biomedical Mg-based alloys.

4.3. Cytotoxicity

Cytotoxicity testing serves as a key indicator for quickly screening the biocompatibility of alloys. In theory, no metals have an unlimited intake in the human body. Many alloying elements may cause toxic reactions beyond the tolerance limit [1,143]. The biocompatibility of developed alloys is influenced by the amount of the released elements, which is related to the corrosion rate of the alloy in the application environment. Magnesium is well known to be biocompatible in the human body, though a magnesium level in serum exceeding 1.05 mmol l⁻¹ can lead to muscular paralysis, hypotension and respiratory distress. Also, cardiac arrest is known to occur for a severely high serum level of 6–7 mmol l⁻¹ [1]. Recently, cerium, praseodymium and yttrium have been found to cause severe hepatotoxicity [40], and more elements may be revealed to be toxic as testing techniques develop. However, in our opinion, alloys containing Ce, Pr or Y may also be safe if their release from the alloy is within the tolerance limits. The toxicity limits of elements relevant to Mg-based alloys are listed in Table 5 [143]. It is clear that Ca has the highest maximum daily allowable dosage, followed by magnesium, while Be has the lowest maximum dosage in the table. A coronary Mg-based stent weighs about 10 mg and the RE concentration may be 5–10%. Therefore, the daily amount of the released metal ions is calculated to be 5.6–11.1 μg, assuming a linear degradation over 3 months [144], which is far below the toxicity limits of RE in Table 5. It should be noted that the maximum daily allowable dosage of elements in Table 5 is the daily intake allowance, which is related to, but may be different from, the toxicity limits present in biodegradable implants. The determination of allowable limits of released species would likely depend upon the location of the implant and available localized pathways or mechanisms for dealing with corrosion products. For example, it is reasonable to expect that there would be different considerations given to the release of corrosion product from stents exposed directly to blood as compared with orthopedic implants.

Feyerabend et al. [120] evaluated the in vitro cytotoxicity of Y, Nd, Dy, Pr, Gd, La, Ce, Eu, Li and Zr and revealed that the cytotoxicity of these elements could be significantly different to the cell lines used in the study and appear to be related to their
Table 5
Summary of toxicity limits for elements relevant to Mg-based alloys [143].

<table>
<thead>
<tr>
<th>Element</th>
<th>Maximum daily allowable dosage (mg)</th>
<th>Element</th>
<th>Maximum daily allowable dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al</td>
<td>14</td>
<td>Nd</td>
<td>4.2</td>
</tr>
<tr>
<td>Be</td>
<td>0.01</td>
<td>Ni</td>
<td>0.6</td>
</tr>
<tr>
<td>Ca</td>
<td>1400</td>
<td>Pr</td>
<td>4.2</td>
</tr>
<tr>
<td>Ce</td>
<td>4.2</td>
<td>RE</td>
<td>4.2</td>
</tr>
<tr>
<td>Cu</td>
<td>6</td>
<td>Sn</td>
<td>3.5</td>
</tr>
<tr>
<td>Fe</td>
<td>40</td>
<td>Sr</td>
<td>5</td>
</tr>
<tr>
<td>La</td>
<td>4.2</td>
<td>Ti</td>
<td>0.8</td>
</tr>
<tr>
<td>Zn</td>
<td>15</td>
<td>Y</td>
<td>0.016</td>
</tr>
<tr>
<td>Mg</td>
<td>400</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The total amount of these RE elements (Ce, La, Nd, Pr, Y) combined should not exceed a value of 4.2 mg day\(^{-1}\).

ionic radii. La and Ce showed the highest cytotoxicity of the elements analyzed. Jablonska et al. [145] evaluated five commonly alloyed elements in magnesium, namely Zn, Mn, Y, Gd and Nd. A 30% decrease in viability was considered to be cytotoxic according to the ISO 10993-5:2009 standard. They found that only Zn (at a concentration of 200 \(\mu\)mol l\(^{-1}\)) and Mn (at concentrations of 80 and 200 \(\mu\)mol l\(^{-1}\)) were observed to show cytotoxic effects after immersion in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 5% fetal bovine serum for 24 h. Only magnesium was observed to have a non-cytotoxic response in HEPES buffer after 1 h. Y was considered to be the most toxic of the three RE elements tested (Y, Gd and Nd). Drynda et al. [144] assessed the cytocompatibility of Ce, Nd, Y and Yb in the form of trivalent chlorides with regard to metabolic activity of human vascular smooth muscle cells. The results showed that these four elements did not cause any significant changes in metabolic activity over a wide concentration range (below 10 \(\mu\)g ml\(^{-1}\)), but a decrease was observed at higher concentrations [144]. However, a summary of the cell viability of several cell lines cultured in extracts of Mg-based alloys (pure Mg, Mg-(1, 3)Ca, Mg-(1, 6)Zn, Mg-(1Zn–Mn, Mg-(1, 2, 3)Zn–1Ca, Mg-1Si, Mg-(1, 2, 3, 4)Sr) has shown that pure Mg and Mg–3Ca, and Mg-(3, 4)Sr alloys have a cytotoxic effect on L929 and MG63 cells, respectively, according to ISO 10993-5 [40,58]. Magnesium and calcium are well-known biocompatible elements and have the highest daily allowable dosages (Table 5). Apart from the different tolerance abilities of cell lines, the reason behind these results could be related to the corrosion rate. Corrosion of Mg-based alloys leads to changes in the pH value and ion concentration, which have a negative effect on cell viability. Some of the present authors have studied the influence of pure magnesium with different corrosion rates obtained by different extrusion ratios and extrusion temperatures. The results confirm that the corrosion rate has a significant influence on the cell viability, as well as on cell attachment and spreading [146].

5. In vivo performance of currently developed Mg-based implants

5.1. Stents

Stent implantation has been proven to be an effective therapy for pulmonary artery branch stenosis, as well as for coarctation and obstruction within the venous system, saving millions of patients [28]. Heublein et al. [25,26] were the first to investigate the possibility of making biodegradable stents with Mg-based alloys in 2000–2003. Twenty stents (with a length of 10 mm, an unequal strut thickness of 150–200 \(\mu\)m and a mass of 4 mg) fabricated from AE21 Mg-based alloy were implanted into the coronary artery of 11 domestic pigs. No initial breakage or thromboembolic events were observed. However, the stents corroded too quickly and lost mechanical integrity between 35 and 56 days. In addition, significant neointimal proliferation and inflammatory response were also observed. The Lekton Magic coronary stent (3 mm in diameter, 10 and 15 mm in length), fabricated by BIOTRONIK, was made from the Mg-based alloy WE43 and successfully implanted into 33 mini-pigs [29]. Mg-based stents (AE21 and WE43) are radiolucent and cannot be visualized by X-rays, but are MRI compatible [147]. Successful animal tests paved the way for clinical trials. In 2005, Peeters et al. [30] reported that AMSs (BIOTRONIK, Germany) were implanted into 20 patients for the treatment of below-knee lesions. No patients showed any symptoms of allergic or toxic reaction to the stent material and no major or minor amputation was necessary in all patients. The stents were almost completely degraded 6 weeks after implantation [30]. The first successful implantation of an Mg-based stent into the pulmonary artery of a preterm baby was reported by Zartner et al. in 2005 [28]. In this successful clinical trial, a Lekton Magic AMS was implanted into the left pulmonary artery of a preterm baby. The results showed that the maximum level of serum magnesium was 1.7 mmol l\(^{-1}\), which is slightly higher than normal (0.38–1.2 mmol l\(^{-1}\)), but on the second day after implantation this decreased to the normal level. The reperfusion of the left lung was established and persisted throughout the 4 month follow-up period. At month 5, the degradation process had been completed. In 2007, the PROGRESS-AMS clinical trial [31], sponsored by BIOTRONIK GMBH & Co. (Berlin, Germany), was conducted to assess the efficacy and safety of AMSs in eight centers. A total of 71 stents, 10–15 mm in length and 3–3.5 mm in diameter, were successfully implanted after pre-dilation into 63 patients. No myocardial infarction, subacute or late thrombosis or death occurred. The latest generation of AMSs (DREAMS) is a drug-eluting AMS and is designed to reduce neointimal hyperplasia by incorporating a biodegradable polymer matrix for the controlled release of an antiproliferative drug [148]. In 2013, Haude et al. [149] reported the first-in-man trial (BIO-SOLVE-I), which was conducted with 46 patients at five European centers. The 12 month results showed no cardiac death or scaffold thrombosis. As shown in Fig. 6, the representative optical coherence tomographs (OCTs) after implantation confirmed that DREAMS stents had been optimized to provide much better degradation resistance than their predecessors (the degradation process is complete after 9–12 months). Immediately after implantation, the apposition of the struts to the vessel wall was very good. At 6 months, the metallic stent-like appearance changed to remnants due to the degradation. Neither the in-scaffold diameter nor the minimum lumen diameter differed significantly between 6 and 12 months.

5.2. Orthopedic applications

Millions of people suffer from broken bones or bone fractures each year in the United States alone. Thus fractured bone fixtures, such as plates, screws, pins, nails, wires and needles, made of Mg-based alloys have a huge potential market. So far, ZEK 100 [150], LAE442 [151], MgCa0.8 [152] and MgYREZr [36] Mg-based alloys have been fabricated into screws for animal models and even for clinical trials. A comparison animal model followed for 12 months confirmed the osteogenetic effect of Mg-based alloys. No gas generation was detected next to the implants of both MgCa0.8 and LAE442 alloys. After 12 months, the bone–implant contact was clearly stronger in the MgCa0.8 group than in the LAE442, indicating that the MgCa0.8 alloy had better biocompatibility [84]. MgCa0.8 screws also showed good tolerability and biomechanical properties comparable with S316L screws in the first 2–3 weeks after implantation in adult rabbits [152]. The MgYREZr alloy (MAGNEZIX\textsuperscript{®} screw) was shown to be clinically equivalent to a standard titanium screw for the treatment of mild hallux valgus deformities [36]. During the 6 month follow-up period, no foreign
body reactions, osteolysis or systemic inflammatory reactions were detected in this clinical trial.

6. Conclusion and future trends

The present review shows that significant progress has been made over the last 15 years in both the development of Mg-based alloys and the characterization of in vitro and in vivo performances of possible “smart implants”. The design criteria for the next-generation implants require the materials to provide appropriate mechanical properties, suitable corrosion and excellent biocompatibility, and to be bioactive in the human body \cite{45,46}. To achieve these benchmarks, the key is to develop the next generation of Mg-based alloys with superior performance. Mechanical and corrosive performances strongly depend on the microstructure of the alloys, which result from alloy design, element selection, processing history, heat treatment and amount of impurities. Mg–RE-based alloys exhibit the highest strength and ductility, the best corrosion resistance and great biosafety in the form of Mg–RE-based alloys exhibit the highest strength and ductility, the best corrosion resistance and great biosafety in the form of

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Appendix A. Figures with essential color discrimination

Certain figures in this article, particularly Figs. 1, 2, 4–6 are difficult to interpret in black and white. The full color images can be found in the on-line version, at http://dx.doi.org/10.1016/j.actbio.2014.07.005.

References


