Review Article

Mechanical properties, corrosion resistance and biocompatibilities of degradable Mg-RE alloys: A review

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ABSTRACT

Magnesium-rare earth (Mg-RE) alloys, as potential biodegradable materials, are attracting considerable attention owing to their good mechanical properties and biodegradation behavior. Indeed, some RE elements within certain amounts of addition have proved to exhibit biocompatibility. Two main strategies have been applied to develop biomedical Mg-RE alloys. One strategy depends on the industrial fabrication system for these alloys while the other is to redesign them from the viewpoint of biomaterials. In this work, the advances in new Mg-RE alloys design are reviewed. It is also summarized the mechanical properties, biocorrosion resistance and biocompatibilities of currently reported Mg-RE alloys. Then, several Mg-RE alloys that may be used in future medical applications are proposed. Finally, a strategy for ongoing development of biomedical Mg-RE alloys is suggested.

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1. Introduction

Magnesium based alloys and their use in medical implants have been the focus of significant recent research. Compared to conventional metallic implant materials, such as titanium alloys, stainless steels, and cobalt alloys, biomedical magnesium alloys have better degradability and absorbability [1]. Additionally, magnesium alloy implants have excellent biocompatibility and can enhance bone formation [2]. However, insufficient strength and a significant degradation rate are major obstacles to the use of magnesium in implant applications, as these factors can decrease the structural integrity of the implant, allowing the formation of gas cavities before the tissue is completely recovered [3]. Therefore, pure magnesium must be supplemented with other elements to improve the mechanical property [4] and corrosion resistance of these materials [5,6]. Rare earth (RE) elements are promising candidates as supplemental elements for magnesium alloys used in biodegradable devices for biomedical applications.

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Many studies have shown that rare earth-containing magnesium alloys can be used in biomedical applications due to their excellent biocompatibility, appropriate mechanical properties, and good corrosion resistance [9]. However, some rare earth elements, such as lanthanum, cerium and praseodymium, must be used cautiously in biomedical applications due to their potential toxicity [8,10].

2. Alloy strategy for biomedical magnesium alloys

An important step of current research is to optimize alloy design and processing to obtain magnesium-based biomaterials with excellent properties.

2.1. Mg-RE binary alloys

Several rare earth elements have been studied in binary magnesium alloys, including lanthanum (La), cerium (Ce), neodymium (Nd), gadolinium (Gd), dysprosium (Dy), yttrium (Y) and scandium (Sc). The addition of trace La and Ce elements effectively improved corrosion resistance and the plasticity of the resulting alloys, but in vitro tests indicated that materials prepared with La and Ce resulted in higher toxicity than ones made with other elements [8,10]. In vivo tests indicated that these elements localized in a small area around the implant [8,11]. According to Willbold et al. [8], no gas cavities appeared in the tissues of rabbits with Mg-La and Mg-Ce alloys implants, and the operation sites were recovered well after four weeks. As heavy RE elements, Gd and Dy have higher solid solubility, 23.49% and 25.3% respectively, than that of Nd, indicating these elements may be more suitable for use in alloys [10]. Hort et al. [12] found that the property profile of Mg-Gd alloys was much closer to the values of bone and the elongation of alloys was better than that of other metallic implant materials, like stainless steels, titanium alloys, and cobalt-chromium alloys. The high solubility of Gd in Mg allowed extremely wide ranges of the mechanical properties to meet different application requirements [12]. However, Myrissa et al. [13] studied the corrosion behavior of Mg-10Gd pins implanted in rats, and found that Gd concentration increased with the implantation time in some animal organs during a 36-week experiment, especially in the spleen, liver, lung and kidney. About Mg-Dy binary alloy, Yang et al. [14,15] found that as-cast Mg-10Dy alloy exhibited appropriate mechanical (ultimate tensile strength (UTS) up to 131 MPa, yield strength (YS) up to 83 MPa) and corrosion properties (0.8 mm/year in 0.9% NaCl) for use in biomedical implants. The in vitro result showed that Mg-10Dy alloys prepared by solutionizing heat treatment (T4) and artificial aging heat treatment (T6) exhibited excellent corrosion resistance (1.34 and 0.97 mm/year, respectively) in cell culture medium due to the formation of a relatively Dy-enriched film that was more resistant to corrosion. In binary magnesium alloys, Y addition has shown great hope for degradable implant applications [16]. Wang et al. [17] found that Y ion implantation of pure magnesium improved the resulting corrosion resistance. Peng et al. [18] investigated an effective zone solidification method to prepare high purity Mg-Y biomaterials, and the result showed that the corrosion resistance of Mg-8Y alloy was greatly improved compared to that of as-cast alloys lacking Y addition (2.17 mm/year vs 7.11 mm/year). As an alloy additive, Sc has been shown to exhibit a grain refining effect that is better than that of other rare earth elements like Y and Ce [19]. Brar et al. [20] studied as-cast Mg-3x alloys (x = Gd, Y, Sc). Compared with Y and Gd, there was better grain refinement by Sc (up to 119 µm) and the Mg-3Sc alloy showed the lowest corrosion rate (1.01 ml/cm²/day) in Hanks’ solution.

2.2. Classic Mg-RE alloys

Mg-Zn based, Mg-Ca based, Mg-Al based, Mg-Li based and WE systems have been considered for use in materials to be implanted in the human body. Screws, pins and stents made of commercial WE43 (W represents Y element, E represents RE elements, 4 wt.% Y, 3 wt.% RE) are currently being tested in clinical trials [21].

2.2.1. Mg-Zn-RE ternary alloys/Mg-Zn-X-RE quaternary alloys

Zn exists in all human tissues and is one of the most abundant nutritionally essential elements in the human body [21]. Zn is commonly used as an alloying element in magnesium alloys to improve the mechanical properties of the alloy, providing a maximum solubility of 6.2 wt.%. The addition of rare earth elements to Mg-Zn alloys is considered an effective way to weaken and modify the basal texture of magnesium alloys to obtain excellent properties [22,23]. Thus, a variety of Mg-Zn-RE alloys, such as Mg-Zn-Gd [22] and Mg-Zn-Y [23] alloys, were developed with high strength, ductility balance, and excellent corrosion resistance. Bian et al. [24] developed three magnesium alloys with both Gd and Zn added together at low levels. Of these, Mg-1.8Zn-0.2Gd alloy exhibited a relatively low level of corrosion rate (<0.28 mm/year) and no cytotoxicity in L929, MG63, and VSMC cells in vitro (cell viability of higher than 80% for all) and the implant maintained its structural integrity for two months, and only some residual parts were detected after 6 months in vivo, demonstrating the potential use of Mg-Zn-Gd alloys in implant materials. Miao et al. [25] also reported that Mg-2.4Zn-0.8Gd alloy was tolerant of solution treatment. Additionally, extrusion resulted in high mechanical properties (yield strength up to 284 MPa, ultimate tensile strength up to 338 MPa, and elongation up to 24%) and good corrosion resistance in Hanks’ solution (corrosion rate of 0.16 mm/year measured by hydrogen evolution or 0.21 mm/year measured by the mass loss) due to a homogeneous microstructure with uniformed grain size and dispersed secondary phases [25]. In studies of Mg-Zn-Y alloys, Kawamura et al. [26] found long period stacking ordered (LPSO) phase in ternary Mg-Zn-Y alloys, with high strength and usable ductility. Zhao et al. [27] further studied the WZ21 (2 wt.% Y, 1 wt.% Zn) alloy after it was micro alloyed with zirconium and warm extrusion. The result showed that LPSO exhibited high mechanical strength and low degradation rate, suitable characteristics for use as a candidate material for biodegradable orthopedic implants. Zhang et al. [28] found that increased Y content decreased the grain size of as-cast and as-extruded Mg-Zn-Y alloys (80–200 µm) but increased the tensile properties.
Immersion tests in Hanks’ solution indicated that alloys with single 1-phase (Mg2Zn5Y) as the second phase showed the lowest corrosion rate (<0.1 mg/cm²/h). Kraus et al. [29] compared two biodegradable magnesium alloys, ZKX50 and WZ21, implanted in the bones of rats. WZ21 persisted a longer time (more than 4 weeks) in the bone, and also generated enhanced bone neoformation around the implant, suggesting the good biocompatibility of WZ21. Hänzi et al. [30] studied the degradation performance and biological response of biodegradable WZ21 and ZW21 (2 wt.% Zn, 1 wt.% Y) alloys both in vitro and in simulated body fluid (SBF). Immersion testing showed that the Mg-Zn-Y alloys exhibited fairly homogeneous degradation behavior and corrosion rates were similar to that of WE43 (about 3.5 ml/cm²). An assay of cytocompatibility showed that an eluted pH value of ZW21 of 9.0, compared to 8.5 and 8.25 for WZ21 and WE43, respectively. After 27 days of in vivo testing, some hydrogen bubbles were observed, with significantly reduced gas after 91 days. These results suggested that WZ21 exhibits good biodegradable due to the addition of Y. Gao et al. [31] investigated a new Mg-5.62Zn-0.55Sr-0.9Y alloy by adding Y into ZK60 and found that the addition of the alloying element Y improved the corrosion resistance of Mg-Zn alloys (1.7% vs 3.1%, mass loss after 242h in SBF). ZEK100 (1 wt.% Zn, 0–0.5 wt.% Zr, 0–0.5 wt.% RE) was found to be a potential biodegradable implant material for osteosynthesis due to its good mechanical properties [32,33]. Waizy et al. [32] investigated the corrosion of ZEK100 in Hank’s Balanced Salt Solution (HBSS). The bending strength of the plates was lowest after 4 weeks impression (0.05 Nm), compared to 2 weeks (0.08 Nm) and 6 weeks (0.1 Nm). The highest amounts of O, P, and Ca were detected on the surface, indicating the precipitation of calcium phosphates on the surface of ZEK100 plates. Weibauer et al. [34] compared the corrosion behavior of ZEK100 and MgCa0.8 in HBSS. The corrosion rates of ZEK100 were significantly lower than that of MgCa0.8 after 4 days (0.63 mm/year vs 2.89 mm/year). The bending strength of ZEK100 (0.306 Nm) was stronger than that of MgCa0.8 (0.272 Nm) in the initial state. After 4 days, the bending strength of both alloys decreased by 7%. Huehnerschulte et al. [35], Dziuba et al. [33] and Reifenrath et al. [36] investigated the degradation behavior of ZEK100 in vivo. Huehnerschulte found that the degrading ZEK100 caused adverse host reactions by inducing the unfavorable osteoclastogenic resorption of bone and a rushed reactive formation of new bone periosteal after 6 months. Dziuba conducted a 9–12 month experiment, and found that ZEK100 had pathological effects on the host tissue following complete degradation. Reifenrath performed studies 4–6 weeks after implantation and observed a weight reduction of 7.5% and pull-out forces that were significantly decreased to 44.4% compared to the original value. These different in vivo tests suggest that ZEK100 is suitable for implant applications due to its very high initial stability and a positive biodegradation rate [33,36].

Nd element was also shown to improve mechanical properties and corrosion resistance with acceptable toxicity [37]. JDBM alloy (Mg-(2.0–4.0) Nd-(0.1–0.5) Zn-(0.3–0.6) Zr, wt.% has high mechanical property (UTS and YS of 300 MPa, elongation increased 15%) and excellent corrosion resistance (0.0125 mm/year in SBF) [37,38]. Niu et al. [39] found the JDBM alloy could be absorbed in vivo after 18 months (with an average corrosion rate of 0.122 mm/year).

Some references suggested that magnesium alloy containing 1 wt.% Zn and 1 wt.% Mn was easily absorbed in vivo as a bone implant [40]. Stulikova et al. [41] prepared and investigated Mg-4Y/4Ce-1Zn-1Mn alloys, in the T5 condition, and found that the equilibrium Mg52Ce and Mg24Y phase enhanced the mechanical properties of the alloys (UTS of about 180 MPa and YS of about 130 MPa). He et al. [42] studied the corrosion behavior of extruded Mg-Zn-Y alloy in Hank’s solution and found that a protective Y2O3 film formed on the surface of the alloy, improving the bio-corrosion properties (pH value 7–8).

Ca is the most important element of the human skeleton and is the preferred choice for alloying [43]. Zhang et al. [44] and Tong et al. [45] investigated the effect of La/Ge on the microstructure, mechanical properties, and corrosion performances of an as-cast/solid solution Mg-Zn-Ca alloy and an extruded Mg-Zn-Ca alloy. The results showed Ce/La effectively refined different states of Mg-Zn-Ca alloys and restrained grain growth (up to 2–5 μm). The addition of 0.5% Ce/La improved the mechanical property of the extruded Mg-Zn-Ca alloy (UTS of 311 MPa, YS of 270 MPa), while further addition reversed the effect. The corrosion resistance was improved with the increase of Ce/La from 0.5% to 1% (30 to 20 mm/year).

2.2.2. Mg-Ca-RE alloys/Mg-Ca-Zr-RE alloys
Ca is a major component in human bone and also beneficial to grain refinement of magnesium alloys. A recent study reported that the addition of Ca increased magnesium tensile property and corrosion resistance [46], suggesting better properties might be obtained by adding rare earth elements to the Mg-Ca alloy. Li et al. [46] developed a Mg-1Ca-1Y alloy as a potential biomaterial and reported increased elongation (up to 15.9%) and decreased corrosion resistance (up to 100 μg/mm²/day) for the Mg-Ca alloy with Y addition. You et al. [47] investigated the effect of Y addition on a Mg-Ca-Y-Zr alloy, and found that the strength was largely improved with increased addition of Y (UTS of 145–191 MPa, YS of 66–120 MPa, and elongation of 5.4%–8.3%).

2.2.3. Mg-Al-RE alloys
The addition of Al element can effectively promote grain refinement and improve the corrosion resistance of magnesium alloys through solution and precipitation strengthening [48,49]. Yokobayashi et al. [50] prepared a new ternary Mg-Al-Gd alloy by high frequency induction melting and observed two types of needle-like precipitation, including Mg2Gd and LPSO phases after heat treatment. Lu et al. [51] found that heat-treated (T4 and T6) alloy exhibited better corrosion resistance in 1 wt.% NaCl solution (331 μm/year vs 226 μm/year) due to the presence of these needle-like precipitations on the surface. However, Al can harm neurons and enhance the risk of Alzheimer’s disease [52]. El-Rahman et al. [52] concluded that accumulated aluminum in brain and altered amino acid neurotransmitters are important mechanisms of aluminum neurotoxicity. According to Rao et al. [53], the direct effect of aluminum depends on Al binding to different brain cells including astrocytes, neural cells and synaptosomes, but interactions with astrocytes inhibits activity of membrane-bound...
Na⁺, K⁺, and Ca²⁺ ATPase, leading to cellular alterations, and even death.

2.2.4. Mg-Li based alloys
In the past decade, Mg-Li based alloys have been studied for biomedical applications, especially LAE442 alloy (4 wt.% Li, 4 wt.% Al, 1.3 wt.% Ce, 0.37 wt.% Nd, 0.5 wt.% La) [54–58]. Witte et al. [54] investigated the corrosion resistance of gravity-cast LAE442 and AZ91D (Mg-9Al-1Zn, wt.%) in vivo and in vitro. AZ91D was more resistance to corrosion than LAE442 as determined by in vitro tests (-0.267 mm/year vs 5.535 mm/year) but LAE442 showed greater corrosion resistance than AZ91D in vivo (1.205 × 10⁻⁴ mm/year vs 3.516 × 10⁻⁴ mm/year). Witte et al. [55] also investigated the corrosion rates of extruded LAE442 with and without additional MgF₂ coating. The extruded LAE442 exhibited low corrosion rates (about 0.4 mm/year) in vivo and an acceptable host response, but the corrosion resistance was increased by the MgF₂ coating (up to about 0.2 mm/year). Krause et al. [57] compared the degradation behavior and mechanical properties of extruded LAE442 and WE43 after 6 months in vivo. The initial strength of WE43 implants (238.05 N) was lower than that of LAE442 implants (255.67 N), and after 6 months, the loss in strength continued at a constant rate. LAE442 implants degraded slower than WE43 as measured by the degradable volume (22.4% vs 33%), suggesting that LAE442 seems sufficient for an application in weight-bearing bones. Zhou et al. [59] compared the mechanical property, biocorrosion, and in vitro biocompatibility of Mg-Li-Al ternary and Mg-Li-Al-RE quaternary alloys. The addition of rare earth elements enhanced mechanical strength while intermetallic compounds distributed throughout the magnesium matrix decreased corrosion resistance. These Mg-Li-based alloys showed no significant reduction of ECV304 cell viabilities (>75%) except for the Mg-8.5Li-2Al-2RE alloy (<60%). Kramer et al. [60] investigated intramedullary nails made of extruded LAE442 by cyclic fatigue tests in both distilled water and HBSS until implant failure or a limit of 500,000 cycles. The result showed that five implants broke in HBSS within the first 70,000 bending cycles but the implants survived in distilled water after 500,000 cycles, which suggested that LAE442 might not have the required fatigue resistance for load-bearing applications in the human body environment. Recently, Minarik et al. [61] investigated the effect of equal channel angular pressing (ECAP) on in vitro degradation of LAE442 magnesium alloy. The corrosion rates of WE43 processed by twelve cycles of ECAP (12p) were 2.49 mg/cm²/day and 0.18 mg/cm²/day in 0.1 M NaCl and in SBF, respectively. In vitro cytotoxicity tests showed, that the ECAP-treated material allowed 80% viability of ECV304 and VSMC cells after 7 days. It was concluded that ECAP could be used to obtain excellent corrosion resistance of LAE442.

2.2.5. WE system alloys
Y added to magnesium alloys for biodegradable applications due to its beneficial effect on alloy corrosion and strength [62]. Due to the addition of Y, WE43 alloy containing 4 wt.% Y and 3 wt.% RE has excellent corrosion resistance. In the past decade, WE43 materials produced by various processing methods have been tested for biomedical application. Hänzi et al. [63], Chu et al. [64], Liu et al. [65] and Davenport et al. [66] investigated the corrosion performance of heat-treated WE43 in vitro. Hänzi found that the performance of annealed and polished WE43 exhibited parabolic behavior in SBF [63]. Degradation decreased over time due to the deposition of corrosion products on the surface while the sample in the thermally oxidized state exhibited more corrosion resistance at the beginning of immersion due to formation of a Y₂O₃ layer at the surface during annealing at 500°C. Chu reported that the corrosion rate decreased after heat treatment due to interactions between finely dispersed precipitates and due to corrosion reactions [64]. Liu concluded that WE43 materials subjected to extrusion and heat treatment transformed from severe diffusional corrosion to uniform corrosion and the corrosion rate decreased from 0.9 mm/a to less than 0.4 mm/a in PBS solution [65]. The YS, UTS, and elongation increased from 158 MPa to 190 MPa, from 224 MPa to 282 MPa, and from 10% to 37%, respectively. Davenport reported that Y-rich regions in the matrix of as-cast WE43 slowed the propagation of corrosion, indicating that the corrosion rate of heat-treated WE43 decreased due to the more homogenous distribution of Y [66]. Liu et al. [67] investigated the properties of WE43 alloy processed by hot extrusion and high-pressure torsion (HPT) and found that the initial grain size decreased to 12 μm and the UTS increased from 244 MPa to 256 MPa after 5 cycles of HPT. Gu et al. [68] investigated the corrosion fatigue behaviors of as-cast AZ91D and extruded WE43 in SBF. The corrosion fatigue limit of the extruded WE43 alloy was obviously higher than that of as-cast AZ91D alloy in SBF (40 MPa vs 20 MPa) and in air (110 MPa vs 50 MPa). Moreover, Jamesh et al. [69] investigated the corrosion fatigue of as-cast ZK60 (6% Zn and 0.5% Zr) and WE43 in Ringer’s solution and SBF. The corrosion current density (i corr) was 72 μA/cm² for WE43 and 82 μA/cm² for ZK60 in Ringer’s solution, but 409 μA/cm² and 419 μA/cm² respectively in SBF suggesting better corrosion resistance of WE43 compared to ZK60.

In addition, many surface modification technologies have been used to further improve the corrosion and biocompatibility of Mg-RE alloys [70]. Jamesh et al. [71] investigated the effect of Zr and N plasma immersion ion implantation on the corrosion behavior of WE43 alloy in SBF and Cell Culture Medium (DMEM). The i corr of treated WE43 was 12-fold lower than that of untreated WE43 in SBF (29.8 μA/cm² vs 368 μA/cm²) and was 71-fold lower than that of untreated WE43 in DMEM (0.51 μA/cm² vs 36.6 μA/cm²), suggesting that Zr and N plasma immersion ion implantation could improve corrosion resistance. Jin et al. [72] found significantly increased corrosion resistance and biocompatibility of WE43 magnesium alloy by neodymium self-ion implantation. A 70 nm thick Nd₂O₃ layer covered the surface after implantation, which could act as a protective barrier. Compared to untreated WE43 samples (555 μA/cm² in SBF and 2.55 μA/cm² in the cell culture medium), the treated WE43 samples showed significantly lower i corr values (11.9 μA/cm² in SBF and 0.5 μA/cm² in the cell culture medium). The viability of MC3T3-E1 preosteoblasts in the Nd-implanted WE43 extract was 102%, higher than 98% of untreated WE43 extract. Imwinkelried et al. [73] investigated the effect of a plasma electrolytic coating on WE43. In vitro testing showed high initial gas release rates of noncoated samples (more than 1 ml/cm²/day) that decreased to ~0.3 ml/cm²/day after 4–5 days, but the coated samples nearly
released no gas during the 4–8 day, and then increased to ~0.2 ml/cm²/day, lower than the non-coated samples. The average weight loss of coated plates in vitro was about 15 mg per week compared to 20 mg per week for the non-coated plates. In vivo testing showed large gas bubbles around the non-coated plates after one-week implantation that disappeared at the fourth week. No gas pockets were visible around the coated plates after one-week implantation, and tiny gas pockets appeared around the thread holes at the fourth week that remained throughout the lifetime of the animals. These results suggested improved corrosion resistance of coated WE43. Recently, the use of polypyrrole (PPy) coatings was studied as a way to decrease the degradation rate of WE43 alloy [74]. PPy is an electrically-conductive polymer with good biocompatibility and has been used in biomedical applications related to the development of artificial muscles, neural recording stimulation of nerve regeneration, biosensors, and controlled drug release [75]. Ascencio et al. [75] investigated the corrosion behavior of PPy-coated WE43 alloy in a modified simulated body fluid solution (m-SBF). The result showed that the PPy coating effectively decreased the corrosion rate of WE43 alloy due to the formation of a protective layer after 24 hours immersion, and the layer could also absorb CO₂ to impede charge transfer. Ye et al. [76] investigated a phosphate modified WE43 magnesium alloy and studied its corrosion and biocompatibility in vitro. Immersion test showed that the hydrogen evolution rate of non-coated WE43 (>4 ml/cm²/day) was far more than coated WE43 (about 1 ml/cm²/day) at the beginning of 50h, and the rate of two groups became more similar (about 1 ml/cm²/day) in the next 160h. 1·929 cell viability in coated WE43 extract was 96.21%, much higher than the 34.80% viability for the non-coated material. These tests demonstrated that phosphate treatment is an effective way to improve the corrosion resistance and biocompatibility of WE43 alloy for biomedical applications.

Other Mg-Y-Nd-Zr alloys have also been studied. Hakimi et al. [77] investigated a novel Mg alloy (Mg-6% Nd-2% Y-0.5% Zr (EW62)) by rapid solidification (RS) and studied the stress corrosion cracking resistance of the alloy in simulated electrolytes. Immersion tests were divided into short-term (1 day) and long-term (>10 days). In the short-term tests, the corrosion rate of the RS alloy was 0.5 mm/year, significantly lower than the 2.1 mm/year of conventionally cast (CC) alloy. In the long-term tests, the corrosion rates of the RS alloy and CC alloy were 0.078 mm/year and 0.152 mm/year, respectively. In the stress corrosion test, the UTS values of RS alloy (from 274 MPa in air to 223–262 MPa in corrosive environment) were higher than those of the CC alloy (from 181 MPa in air to 141–178 MPa in corrosive environment). Therefore, EW62 alloy prepared by rapidly solidification has the potential to be used as a biodegradable implant. Aghion et al. [78] compared corrosion performance of EW10X04 (1.16 wt.% Nd, 0.48 wt.% Y, 0.48 wt.% Zr, 0.43 wt.% Ca) and EW10 (1.15 wt.% Nd, 0.43 wt.% Y, 0.46 wt.% Zr) in 0.9%NaCl, and found a lower corrosion rate of EW10X04 (about 0.5 mm/year) compared to EW10 (more than 1 mm/year). However, the stress corrosion resistance of EW10X04 was lower than EW10 as determined by slow strain rate testing.

3. Summary of currently investigated Mg-RE alloys

3.1. Mechanical property

As shown in Figs. 1 and 2, Mg-RE alloys exhibited a large range of UTS (from 76 MPa to 354 MPa), YS (from 40 MPa to 316 MPa) and elongation (from 0.7% to 60%). With the increase of rare earth content in Mg-RE binary alloys, UTS and YS increased and elongation decreased. The strengthening effect of Gd was higher than that of Dy. The YS and UTS of most Mg-RE binary alloys were less than 100 MPa and 200 MPa respectively and the elongation was less than 10%. Overall, Mg-RE binary alloys have lower sufficient strength than that of WE43 alloy for use as implant materials. The elongation of extruded WE43 was more than 35%. Mg-Zn-Y alloys (Mg-1.73Zn-1.54Y, WZ21, ZW21 and ZEK100) exhibited similar yield strength and ultimate tensile strength to that of WE43 with elongation of only

![Fig. 1 - Ultimate tensile strength and yield strength of selected Mg-RE alloys.](image-url)
about 28%. However, the yield strength and ultimate tensile strength of JDBM and Mg-2.4Zn-0.8Gd alloys exceed those of WE43 reaching 280 MPa and 310 MPa respectively, with elongation of 15%-25%. The YS and UTS of Mg-4Y/CE-1Zn-1Mn alloys were about 120 MPa and 170 MPa, less than those for WE43. The elongation of Mg-4Ce-1Zn-1Mn alloy reached 60%, indicating that addition of Ce element promoted elongation better than the addition of Y. Moreover, hot extrusion [79] and solution treatment also generally improved the strength of Mg-RE alloys, though solution treatment decreased the strength of Mg-Dy binary alloys and Mg-2.4Zn-0.8Gd alloy. Overall, the results suggest that alterations in alloying or processing can be applied to obtain Mg-RE alloys with the appropriate range of mechanical properties for use in biomedical applications.

3.2. Degradation rate

Fig. 3 shows the corrosion rate and hydrogen evolution of Mg-RE alloys in 0.9%/1% NaCl, in vivo and in vitro. The extruded LAE442 and WE43 alloys exhibited the lowest in vivo corrosion rates. Simultaneously, its strength was reduced 40% when the decreased volume of LAE442 reached 15.2%, during the three months in vivo [57]. The loss in strength of WE43 in the three-point bending test was 22.04% after 3 months of implantation [21]. For orthopedic biomaterials, 3–4 months are typically required from fracture callus formation to new bone formation [21], which means that Mg-RE alloys should provide sufficient strength, and durability for bone restoration. Further efforts should focus on improved degradation and corrosion resistance, using methods such as surface treatment [80,81].
Table 1 – Cell viability of several cell lines cultured in Mg-RE alloys and its alloys extracts.

<table>
<thead>
<tr>
<th>Materials</th>
<th>Formation</th>
<th>Cell line</th>
<th>Culture time (day)</th>
<th>Cell viability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Mg</td>
<td>As-cast</td>
<td>L929</td>
<td>4</td>
<td>65.7</td>
</tr>
<tr>
<td></td>
<td>As-cast</td>
<td>MC3T3-E1</td>
<td>7</td>
<td>87.5</td>
</tr>
<tr>
<td></td>
<td>As-cast</td>
<td>ECV304</td>
<td>7</td>
<td>76.8</td>
</tr>
<tr>
<td></td>
<td>As-cast</td>
<td>VSMC</td>
<td>7</td>
<td>93.6</td>
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<td>78</td>
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<tr>
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<td>As-cast</td>
<td>MC3T3-E1</td>
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<td>51</td>
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<tr>
<td>Mg-2.13Nd</td>
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<td>MC3T3-E1</td>
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<td>78</td>
</tr>
<tr>
<td>Mg-1.8Zn-0.2Gd</td>
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<td>82</td>
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<td></td>
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<td>MG63</td>
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<td>100</td>
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<tr>
<td></td>
<td>As-rolled</td>
<td>VSMC</td>
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<td>90</td>
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<tr>
<td></td>
<td>As-rolled</td>
<td>ECV304</td>
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<td>75</td>
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<td>56</td>
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<td>110</td>
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<td>As-rolled</td>
<td>VSMC</td>
<td>5</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>As-rolled</td>
<td>ECV304</td>
<td>5</td>
<td>65</td>
</tr>
<tr>
<td>JDBM</td>
<td>As-extruded</td>
<td>L929</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>LAE442</td>
<td>ECAP</td>
<td>L929</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>WE43</td>
<td>Phosphating coated</td>
<td>L929</td>
<td>4</td>
<td>96</td>
</tr>
</tbody>
</table>

3.3. Biocompatibility

Table 1 shows the cell viability of several cell lines cultured in Mg-RE alloy extracts. According to ISO 10993-5:2009 [82], a reduction of cell viability of more than 30% is considered cytotoxic. Compared to pure Mg, the JDBM, Mg-1.8Zn-0.2Gd, WE43 and LAE442 alloys showed good biocompatibility (low cytotoxicity) with L929. The cell viability of Mg-0.69La, Mg-1.27Ce, and Mg-2.13Nd with MC3T3-E1 was lower than that of pure magnesium. Nevertheless, the cell viabilities of Mg-RE alloys with ECV304 and VSMC are roughly equal, and higher than that of Mg-1.8Zn-0.8Gd alloy. In vivo tests in rabbits showed no abnormal reaction after implantation of Mg-La and Mg-Ce alloys for 4 weeks [8]. The JDBM stent covered by brushite coating maintained its original shape after 4-month implantation, with a lower hemolysis rate and anti-vascular restenosis. As bone materials for rabbits, the Mg-1.8Zn-0.2Gd, WE43, and LAE442 implants were well integrated with the surrounding bone within two months, with mineralized areas larger than the magnesium alloy without rare earth elements (for example, AZ91) [55]. The magnesium ions stimulated the increased release of neurotransmitters such as calcitonin gene-related peptide (CGRP) at the peristium site to further promote osteogenic differentiation of stem cells in the periostem [83]. Eventually, a large amount of new bone formed at this site.

Although these magnesium implants showed great bio-compatibility at the treatment site in animal experiments, it is important to determine the RE content and evaluate RE effects on other organs. In the design of Mg-RE alloys, the toxicity of rare earth alloying elements must first be considered. The toxicity of several rare earth elements were measured in vivo as the amount giving a 50% lethal dose (LD₅₀) [10]. Ce showed the highest cytotoxicity (LD₅₀: 10 mg/kg), followed by La (LD₅₀: 150 mg/kg), and other rare earth elements (Gd, Nd, Dy, and Y) showed only a slight reduction of viability (LD₅₀: more than 550 mg/kg) [10]. In addition to cytotoxicity assays, RE pathology trials have been performed on animals. After GdCl₃ injection into the abdominal cavity of mice, the ulcer at the wound site developed into a muscular layer in 7 days [84]. In rabbits, GdCl₃ affected the contraction of the small intestine [84]. Du et al. [85] found that after treatment with 1000 μmol/L GdCl₃ in rat dorsal root ganglion neurons for 96 h, the cells did not show apoptosis. Additionally, Gd³⁺ at 100 μmol/L in the extracellular solution inhibited the transient outward potassium current (Iₒ). When DyCl₃ was injected into rat veins, there was increased activity of liver RNA polymerase II, with no effects on polymerase I. DyCl₃ also exhibited antibacterial effect on E. coli at 300 μmol/L concentration [86]. Clinically, lanthanum carbonate is used to treat hyperlipidemia in patients with end-stage renal failure. For patients treated for up to 6 years, the concentration of sputum in the blood did not increase during the initial treatment and after treatment, without any liver poisoning [87]. One day after the intravenous injection of CeCl₃, there was no Ce³⁺ in the blood of rats, but after three days, there was jaundice and elevated transglutaminases, with severe hepatotoxicity [88]. The proliferation of osteoclasts was greatly inhibited in the presence of Nd³⁺, especially at 1 × 10⁻⁷ mol/L [85]. In addition, Nd³⁺ promoted the differentiation and formation of mineralized matrix nodules of osteoclasts at concentrations of 1 × 10⁻⁸ mol/L and 1 × 10⁻⁵ mol/L, respectively.

Nevertheless these studies have not completely characterized the biocompatibility of all rare earth elements. Rare-earth elements can exist in magnesium alloys in solid solution, as precipitates, and as oxides, so the release forms, degradation, absorption, and metabolism of these elements in animals require more comprehensive characterization.

4. Mg-RE alloys most likely to be used in biomedical applications

Biocompatibility is a crucial determinant of whether Mg-RE alloys can be used for biomedical applications. Implanted Mg-RE alloy material should not cause great cytotoxicity or a strong host reaction. According to in vitro cytotoxicity tests
alloys was inhibited compared to that of pure Mg. The restoration of bone after the implantation of Mg-RE alloys was the most direct evaluation of biocompatibility. Newly formed bone was observed adjacent to the Mg-1.8Zn-0.2Gd implant, and no abnormal effect was observed for bones tissues surrounding the implant [24]. In addition, Witte et al. [54,55] investigated the corrosion behavior of WE43 and LAE442, compared to that of AZ91D. The result showed that the corrosion layer of these alloys contains a lot of Ca and P and was in direct contact with the surrounding bone tissue, which might slow the corrosion process. However, the AZ91D rod was almost destroyed by severe pitting after 18 weeks of implantation, while the LAE442 rod showed more uniform corrosion. Tornoni et al. [89] studied the corrosion behavior of WE43 in a cranial bone sheep model. As shown in Fig. 6, newly formed woven bone was observed due to blood clot chambers that formed between the periosteum (red arrows) and bone in regions surrounding the implants (depicted by white arrows in A and B), with virtually no formation of a hydrogen gas pocket. Niu et al. [39] conducted an 18-month implantation of JDBM screws and observed formation of some new bone around the screw, as shown in Fig. 7(a). As shown in Fig. 7(b), after four months, the screw maintained good integrity, with only 16% volume loss, but showed a volume reduction of nearly 90% at 18 months. In addition, Mao et al. [90] conducted a four-month implantation test of a JDBM stent, and as shown in Fig. 8, the stent still maintained its basic shape without fracture of the tube wall, indicating sufficient strength. Based on these studies, magnesium alloys containing RE elements are shown to be suitable as implant materials in bone surgery and vascular stent applications.

5. Concluding remarks

With the continued development of biodegradable magnesium alloys, many reports show that addition of RE results in increased corrosion resistance, grain refinement, and solubility of magnesium, enhancing the mechanical and degradable properties of alloys. The WE43 magnesium alloy is currently being clinically tested in the form of screws, pins, and stents and scientists are exploring the potential of other RE-based magnesium alloys. Specific implant materials may be designed for different functions in different parts of the human body. For example, a biodegradable vascular stent
should have the ability to undergo plastic deformation, with YS and UTS above 200 MPa and 250 MPa respectively, and with at least 20% elongation to fracture [93]. The material must be able to function for at least 6 months. A biodegradable screw requires a YS of at least 250 MPa, tensile strength of at least 275 MPa, elongation rate of at least 10%, and an offset elastic limit of $R_{p0.2}$ at least 250 MPa in addition [94]. Different RE elements and the amount added can affect the mechanical properties, degradable behavior, and cytotoxicity of alloy materials. As mentioned earlier, Dy, Gd, and Y have high solubility, while Sc has better corrosion resistance and grain refinement capability [19,20]. Some processing techniques can further improve material performance, such as heat-treatment, severe plastic deformation (SPD) [95], and surface modification. Cytotoxicity tests show that Dy, Y, Nd, and Gd are less toxic than La and Ce. However, the effect of RE
elements on the body is related to the degradation of metallic implants and the released form of RE elements, therefore systemic in vivo tests are required. Additionally, because in vivo assays are costly and time-consuming, there is a need to develop proper bio-reactors to mimic in vivo conditions for more rapid testing of materials.

**Conflicts of interest**

The authors declare no conflicts of interest.

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