Corrosion and biocompatibility improvement of magnesium-based alloys as bone implant materials: a review

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Abstract
Magnesium (Mg) or its alloys are widely tested as potential orthopedic implants, particularly as biodegradable alloys for fracture fixation due to their mechanical properties are close to those of bone. Currently, available Mg or its alloys are confronted with challenges in passing regulatory biosafety tests prior to clinical trials due to its fast degradation and associated degradation products. The degradation of Mg is accompanied by the release of Mg ions, the rise of pH and osmolality in surrounding environments. According to the standard of ISO 10993 Part 13, the pH value shall be appropriate to the site of intended use maintaining in an appropriate range. Approaches to overcome these challenges include the selection of adequate alloying elements, proper surface treatment techniques and control of the degradation rate of Mg or its alloys developed as orthopedic implants. To date, Mg or its alloy-based bone implants have not yet been widely used in clinical applications as medical implants. This review critically summarized published methods to improve the corrosion resistance of Mg and its alloys. The current progress on in vitro cytotoxicity and in vivo biocompatibility properties of these metals was also reviewed. This review aimed to provide a reference for further research and development (R&D) of biodegradable Mg and its alloys with regard to the evaluation of their corrosion process and biocompatibility and facilitation of their translation to clinical applications.

Keywords: magnesium alloy; biocompatibility; corrosion; bone implant

Introduction
Bone defects often result from orthopedic trauma, infection, bone tumor and osteonecrosis [1]. Bone defect repair, especially that in long bone with full functional reconstruction, remains a big challenge in orthopedic clinics [2–6]. It needs suitable bone substitutes and fixation devices to provide an ideal environment for bone regeneration. Autogenous bone grafts, i.e. bones obtained from the same patient, have been considered the gold standard in routine clinics, but shortcomings associated with secondary surgery [2], donor shortage and donor site complication still remain a major concern [7, 8]. Allogeneic bone grafts, i.e. bone tissues obtained from a deceased donor, are also a popular approach for bone defect repair. Nevertheless, pathogen transfer and immune rejection limit...
their clinical applications [9, 10]. Artificial materials or bone substitutes, such as biodegradable polymers, metals, ceramics, and bioactive glasses, are widely developed in bone fracture fixation and defect repair in both orthopedics and dentistry. Qin and colleagues [2, 11] developed a novel Mg-based porous composite scaffold for fracture fixation. The porous composite scaffold has a mixed matrix Polymer Material (poly(lactic-co-glycolic acid) (PLGA)) and Ceramic material, (tricalcium phosphate (TCP)). Especially, the PLGA/TCP/10% Mg scaffolds have the effect of inhibiting bacterial adhesion and considerable antibacterial ability and good cytocompatibility [11]. On the other hand, metals are the most promising materials to be developed as fixation devices or implants because of their superior mechanical properties, especially for load-bearing skeletal sites than ceramics or polymeric materials [12–16].

Table 1 summarizes the comparison of density, elastic modulus and compressive yield strength of natural bone and various metal implants. The physical and mechanical properties of Mg demonstrate closer mechanical properties to those of natural bone compared with other commercial implants [15–22]. Thus, Mg and its alloys attract considerable attention for their potential in medical applications because of their distinct features and in vivo biodegradable characteristics [23, 24]. Metallic Mg was first prepared by Sir Humphry Davy as early as in 1808 [24]. In the same year, Davy [25] also prepared metallic Mg by making the amalgam of Mg using mercury and distilling of the mercury electrolytically. Mg is the most abundant element, second only to Na in the hydrosphere (sea water: Na = 450 mM, Mg and Cl = 50 mM, and Ca and K =10 mM) and the fourth most abundant cation in living organisms (human body: Ca > K > Na > Mg) [26]. It exerts a large variety of biological functions. Mg is abundant in the human body, and bone tissue stores approximately half of the total physiological Mg [15]. This element is also vital to metabolism processes in almost all enzymatic systems involved in DNA processing as an essential cofactor, establishing the standard methods for testing the dynamic equilibrium through the reaction of Equation (4) [32]. The chloride ion concentration increases, and the equilibrium Equation (4) changes to the formation of MgCl2. Therefore, the corrosion of Mg alloys exits the formation and dissolution of oxide layer containing Mg(OH)2 [31]. The corrosion properties can be tested in vitro. The in vitro corrosion properties can be evaluated via immersion and electrochemical tests, whereas in vivo corrosion properties can be assessed using animal models [15]. To date, published studies establishing the standard methods for testing the in vitro and in vivo biocorrosion rates are available [33].

| Alloy      | Density (g/cm³) | Elastic modulus (GPa) | Yield strength (MPa) | Fracture toughness (MPam1/2) | Refs. |
|------------|----------------|-----------------------|----------------------|-----------------------------|-------|
| Human Cortical bone | 1.80–2.10 | 3–20                  | 130–193              | 3–6                         | [15, 16] |
| Mg         | 1.74–2.00      | 41–45                 | 65–100               | 15–40                       | [15]    |
| AZ91       | 1.81           | 45                    | 160                  | N/A                         | [17]    |
| WE43       | 1.84           | 44                    | 170                  | N/A                         | [18]    |
| Mg–6Zn     | N/A            | 42.3                  | 169.5                | N/A                         | [19]    |
| Mg–1Ca–Zn  | N/A            | 45.3                  | 67                   | N/A                         | [20]    |
| Ti alloy   | 4.40–4.50      | 110–117               | 758–1117             | 55–115                      | [15, 21] |
| Ti6Al4V    | 4.40           | 115                   | 900                  | N/A                         | [12]    |
| Co–Cr alloy| 8.30–9.20      | 230                   | 450–1000             | N/A                         | [15]    |
| XLPE       | 0.47–1.26      | 0.005–0.69            | 20                   | N/A                         | [12]    |
| Synthetic-HA| 3.10           | 73–117                | 600                  | 0.7                         | [22]    |

Optimization of corrosion resistances of Mg and its alloys

Corrosion rate

The corrosion behavior of Mg or its alloys is mainly governed by the characteristic of the surface film. The following equations are the main corrosion reactions on pure Mg [31]:

\[
\text{Mg} \rightarrow \text{Mg}^{2+} + 2e^- \quad \text{(anodic reaction)} \tag{1}
\]

\[
2\text{H}_2\text{O} + 2e^- \rightarrow \text{H}_2 + 2\text{OH}^- \quad \text{(anodic reaction)} \tag{2}
\]

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

\[
\text{Mg}^{2+} + 2\text{Cl}^- \leftrightarrow \text{MgCl}_2 \quad \tag{4}
\]

On the corrosion surface of Mg, Mg(OH)2 is the main oxide layer, which is not compact. Hence, the solution can infiltrate the film, causing the pitting corrosion on the alloy surface. Specifically, chloride ions can readily break the thermodynamic equilibrium Equation (3), which is the dynamic equilibrium, through the reaction of Equation (4) [32]. The chloride ion concentration increases, and the equilibrium Equation (4) changes to the formation of MgCl2. Therefore, the corrosion of Mg alloys exits the formation and dissolution of oxide layer containing Mg(OH)2 [31].

The corrosion properties can be tested in vitro and in vivo. The in vitro corrosion properties can be evaluated via immersion and electrochemical tests, whereas in vivo corrosion properties can be assessed using animal models [15]. To date, published studies establishing the standard methods for testing the in vitro and in vivo biocorrosion rates are available [33].

Alloying treatments

The performance of Mg metal may be improved by alloying so that the Mg-based metallic materials could be used to design fixation
implants for clinical applications [15, 34–36]. Secondary phase is important to improve the mechanical properties and corrosion properties of Mg alloys [32, 37]. Based on research of literatures, many kinds of Mg-based metals with novel structure have been specially developed for the biomedical applications. A significant number of research showed that grain refinement after alloying (Fig. 1) and further treatment could affect the morphology and distribution of the primary or secondary phase, and the second phase could influence the anodic and cathodic polarization behaviors in electrochemical test [15, 36, 38]. Subsequently, the yield strength (YS), ultimate tensile strength (UTS), elongation and corrosion properties of materials could be affected by alloying and further treatments, namely, hot rolling, hot extrusion, and forging process with various forging speeds.

Jeong et al. [38] evaluated the effect of Ca content (Fig. 1) and indirect extrusion on the mechanical properties and corrosion properties of the Mg–Ca alloys. The results showed that all of the materials have almost equated grains, and grain size tends to decrease with increasing amount of Ca. Increasing the Ca content may decrease corrosion resistance for as-cast Mg–Ca alloys. Nevertheless, anodic reaction is decelerated after extrusion, thus resulting in more significant improvement of corrosion resistance compared with the as-cast counterparts (Fig. 2). Similarly, Li et al. [32] selected calcium as alloying element to develop binary Mg–xCa (x = 1–3 wt.%) alloys and proved that hot rolling or as-extrusion improves the corrosion resistance of the Mg–Ca alloy in simulated body fluid (SBF) (Fig. 2). For as-cast Mg–Ca alloy, the YS, UTS, tensile ductility, and elongation properties decrease with increasing Ca content. Decreasing grain size could enhance the hardness value and plastic deformation ability of alloys, but reduce the tensile ductility.

The degradation of Mg in vivo occurs in hydrogen evolution reaction [15, 26, 39–42]. A large amount of hydrogen can cause inflammation and tissue necrosis, thereby causing discomfort and extended treatment period to the patient [15]. Immersion test showed that the average hydrogen evolution rate is 0.040 ml/cm²/h in as-extruded Mg–1Ca alloy, which is much less than that of as-cast Mg–1Ca alloy (0.136 ml/cm²/h). Potentiodynamic polarization curves were measured for freshly prepared specimens in a standard three-electrode glass cell with a standard scan rate of 0.2–0.5 mV/s [43–45]. The cathodic branch provided an extensive linear Tafel region, the evaluated icorr value is the corresponding corrosion rate [45]. Figure 2 shows the polarization curves of different alloys. The cathodic polarization current of hydrogen evolution reaction is higher in Mg–1Ca and Mg–2Ca alloys. As-rolled and as-extruded Mg–1Ca alloy samples showed higher breakdown potentials than other alloys, which indicate that the surface films of as-rolled and as-extruded Mg–1Ca alloy samples are more protective than those on the as-cast Mg–xCa alloy samples. Harandi et al. [46] showed that forging process does not provide the expected corrosion resistance of Mg–Ca alloy developed as bone implants for clinical applications.

Table 2 presents the electrochemical data of Mg and Mg-based alloys derived from the polarization test reported in the literature.

**Figure 1.** SEM Micrographs of the as-cast mg–x ca alloys: (a) the as-cast mg–0.4 ca alloys, (b) the as-cast mg–1 ca alloys, (c) the as-cast mg–2 ca alloys, and (d) the EDS analysis results of the different regions of the as-cast mg–3 ca alloys (permission obtained from jeong et al. [38])

**Figure 2.** Potentiodynamic polarization curves of as-cast mg–1Ca, mg–2Ca, and mg–3Ca alloys, and as-rolled and as-extruded mg–1Ca alloy samples in simulated body fluid (SBF) (Li et al. [13])
Table 2. Electrochemical data of Mg and its alloys derived from polarization tests

| Specimen Treatment | Treatment | $E_{corr}$ (V) | $I_{corr}$ (μA/cm$^2$) | $V_{corr}$ (mm/yr) | Solution | Refs. |
|--------------------|-----------|----------------|------------------------|-------------------|----------|-------|
| Mg                 | as-cast   | -1.886         | 86.06                  | 1.94              | SBF      | [47]  |
|                    | as-rolled | -1.796         | 37.24                  | 0.84              |          |       |
| Mg–1Ag             | as-cast   | -1.764         | 360.20                 | 8.12              | SBF      | [47]  |
|                    | as-rolled | -1.708         | 53.95                  | 1.22              |          |       |
| Mg–1Zn             | as-cast   | -1.822         | 67.30                  | 1.52              | SBF      | [47]  |
|                    | as-rolled | -1.805         | 40.78                  | 0.92              |          |       |
| Mg–1Ag             | as-cast   | -1.609         | 10.47                  | 0.24              |          |       |
|                    | as-rolled | -1.549         | 7.55                   | 0.17              |          |       |
| Mg–1Ca             | As-cast   | -1.900         | –                      | 12.56             | SBF      | [38]  |
|                    | As-extruded | -1.73        | –                      | 1.74              |          |       |
|                    | As-forged 250/65 | -1.98 | 3.71                   | 1.9              | SBF      | [48]  |
| Mg–1.25Ca          | As-cast   | -2.016         | 0.227                  | 1.97              | Kokubo   | [49]  |
| Mg–2.5Ca           | As-cast   | -2.016         | 0.307                  | 2.12              |          |       |
| Mg–1Y              | as-cast   | -1.703         | 140                    | 3.16              | SBF      | [47]  |
|                    | as-rolled | -1.848         | 73.06                  | 1.65              |          |       |
| Mg–7Y–0.2Zn        | as-cast   | -1.649         | 227                    | 5.187             | SBF      | [50]  |
|                    | Microwire$^a$ | -1.587 | 188                    | 4.296             |          |       |
|                    | Microwire$^b$ | -1.509 | 31                     | 0.708             |          |       |
|                    | Microwire$^c$ | -1.508 | 16                     | 0.366             |          |       |

$^a$Mg–7Y–0.2Zn microwire is achieved with an extraction rate of 20 m/s.
$^b$Mg–7Y–0.2Zn microwire is achieved with an extraction rate of 30 m/s.
$^c$Mg–7Y–0.2Zn microwire is achieved with an extraction rate of 40 m/s.

Purnama et al. [51] reported the critical value of degradation in plants (0.5 mm/y). Gu et al. [52] developed the binary Mg–1 wt.% X alloys to screen the acceptable alloying element for biomedical Mg alloy design. Table 2 shows that the corrosion resistance potential of as-cast Mg alloys could be improved by adding the elements Ag, Y and Zn [47]. Moreover, as-cast Mg–1Zn alloy exhibits higher positive corrosion resistance potential than pure Mg in SBF, whereas it shows negative potential compared with pure Mg in Hank’s solution [47]. After hot rolling, experimental alloys in Table 2 exhibit low corrosion resistance. Meanwhile, soak medium and follow-up treatments have a significant impact on the corrosion resistance of materials [53].

Many kinds of publications Mg-based alloys (Mg–Ca, Mg–Zn, Mg–Ag, Mg–Al, Mg–Sr, Mg–RE, Mg–Zr and so on) have been researched aiming at the feasibility for biomedical application. Among these alloying elements, Aluminum (Al) has the maximum solid solubility of 12.7% of the weight percentage (12.7 wt.%) which is the most commonly used alloying element in Mg alloys. Zirconium (Zr) could significantly refine the grains for Mg alloys. However, Zr could not be used with Al or Mn, concurrently. Otherwise, Al or Mn would form a kind of stable solid solution with Zr. According to literature studies, in order to better improving the mechanical and degradation properties of Mg-based alloys, the contents of alloying elements Ca and Zr should be no more than one percent of the weight percentage (1 wt.%), Sr and Zn should be no more than 2 and 4 wt.%, respectively.

**Surface treatments**

To slow down the corrosion rate of Mg or Mg-based alloys and improve the biocompatibility and maintain the mechanical properties, various surface treatment methods were developed and estimated to regulate the corrosion rate of Mg or Mg alloy [54]. According to the standard of enhancing corrosion resistance and desirable biocompatibility in references reported, we studied fluoride treatments, organic and polymer coatings and Ca–P coatings in details [55–59]. Table 3 shows the summary of different surface treatment methodologies are useful to minimize the corrosion of Mg and Mg alloys.

Fluoride treatments

Fluorine is an important component of the human skeleton and teeth [87]. Fluoride treatments are extensively reported with findings on enhanced corrosion resistance of Mg and its alloys [9, 58, 67, 88–93]. Li et al. [87] used vacuum evaporation deposition method to coat Mg–1Ca alloy with MgF2 to decrease corrosion rate and enhance biocompatibility. The immersion and electrochemical tests showed that the corrosion rate of Mg–1Ca alloy is significantly reduced when coated with MgF2. Cell culture experiments demonstrated that Mg63 and MC3T3-E1 cells adhere and proliferate well on the surface of MgF2-coated Mg–1Ca alloy after 72 h in the culture medium, and few cells are observed on the uncoated Mg–1Ca alloy samples. This result implies that MgF2 coating shows beneficial effects on cell responses and improve the corrosion resistance of Mg-based alloys, which is considered a surface modification method for the research and development of Mg-based alloys [87, 94].

For bone implant applications, fluoride-coated alloys were also studied by Andreas et al. [9], who developed MgF2-coated Mg–Ca to improve degradation kinetics. Five probes of Mg–Ca alloys (Ca = 0.4, 0.6, 0.8, 1.2 and 2.0 wt.%) were prepared, and the electrochemical test was conducted on different specimens to measure the corrosion properties of the Mg–Ca alloys. The uncoated Mg–Ca alloys corrode rapidly after immersion in medium with the massive gas formation, and samples added with Ca contents (0.6–0.8 wt.%) corrode the slowest. The hydrogen formation increase is an indicator of corrosion at high Ca concentrations, which reveals that the degradation kinetics are decreased more by MgF2-coated Mg–Ca.
alloys than with available Mg-based alloys [7]. Witte et al. [25] developed MgF2-coated LAE442 Mg alloy, and the results showed no elevated fluoride concentration in the adjacent bone, which reduces the in vivo corrosion rate of alloy plates. Yan et al. [58] reported a fluoride coating on the surface of AZ31B alloy, and the electrochemical and immersion tests were investigated. It showed that the fluoride coating significantly causes the corrosion of AZ31B alloy.

### Organic and polymer coatings

In order to effectively improving the corrosion resistance of Mg or Mg-based alloys, kinds of organic barrier coatings have been studied [95]. However, this coating is technically limited by coating organic barrier on to Mg or Mg-based alloys because of the poor adhesion between organic chemicals and metals [96]. Ng et al. [96] prepared CH3 (CH2)16COOH–Mg coating, and CH3 (CH2)16COOH is the main component of fat with natural non-toxicity and biocompatibility. The coating was achieved by hydrothermally treating the Mg surface to form Mg(OH)2 layer, which produces anchorage. Subsequently, CH3(CH2)16COOH is coated on the Mg surface via the chemical bone. The long-term corrosion properties are evaluated through the immersion tests. The CH3(CH2)16COOH coating could effectively enhance four-order magnitude corrosion resistance properties in the first stage of corrosion and decrease to about 40-fold in the long-term, which facilitates the need of bone growth mechanical strength.

The polymer coatings prepared through different methods are widely used. Abdulla et al. [7] prepared hydroxyapatite/poly(e-caprolactone) (nHAp/PCL) hybrid nanocomposite film coatings on AM50 substrates to control the corrosion rate and improve the biocompatibility of the Mg alloy through the dip-coating technique. The corrosion test results showed that the nHAp/PCL-coated Mg alloy has good corrosion resistance in SBF medium. Additionally, the cell culture results showed that the composite film is effective for the enhancement of cell adhesion, proliferation, and rapid formation of uniform CaP nanoparticles on the nHAp/PCL-coated Mg alloy surfaces, which could be used as potential bone implant material. Abdalla et al. [97] also prepared poly(vinyl acetate) (PVAc) coating on the Mg-based alloy AM50 by dip-coating, and evaluating the corrosion rate and biocompatibility. The immersion test showed that the corrosion rate of coated alloys is stabilized with the porous morphology of PVAc, and the untreated sample undergoes severe localized corrosion. Ping et al. [98] designed a novel coating on the WE42 substrate by the micro-arc technique. Through the method, Ping et al. obtained a biocompatible oxidation/poly(L-lactic acid) (MAO/PLLA) composite coating to control the corrosion rate. And electrochemical impedance spectroscopy test was performed. MAO/PLLA composite coating could decrease the corrosive rate as an effective physical barrier, which prevents the surface layer of the WE42 substrate from being exposed to corrosive ions [14, 98, 99]. Wong et al. [57] prepared PCL, and dichloromethane membrane deposited on the AZ91 alloy. The electrochemical corrosion properties were analyzed in SBF at pH 7.4 using potentiostat (Versa Stat II EG&G), and immersion tests were conducted [57]. The in vitro and in vivo results showed that adding polymer-coating on alloys could produce numbers of pores to reduce the corrosion rate of implant [57]. The immersion tests showed that the slow release rate of Mg ions of membrane coating AZ91 alloy would be applied widely [57].

### Ca–P coatings

Further efforts and experiment methods are designed to reduce the corrosion rate of Mg-based alloys for implant application effectively, which could match the degradation with the growth of new bone above the samples [55, 56, 100, 101]. HA (Ca10(PO4)6(OH)2) resembles the chemical and structure of mineralized bone [102]. Hence, HA coatings are widely applied to the modification of Mg-based alloys to improve the complexity of coating processes.

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**Table 3. Summary of different surface treatment techniques for Mg or its alloys developed for medical applications**

| Substrate          | Surface modification method     | Main layer structure                      | Thickness | Refs                  |
|--------------------|---------------------------------|------------------------------------------|-----------|-----------------------|
| Mechanical method  | AZ31B                           | Severe plastic deformation process, severe plasticity burning, and cryogenic machining | nanocrystalline grain structure 3.4 mm/burning 15 μm/machining | [13, 34, 38, 48] |
| Physical method    | Mg–3Nd–0.2Zn–0.4Zr/Mg–Y–RE/AZ91 | Oxygen plasma immersion ion, Al–O dual ion, and titanium ion implantation | including O and Zn ion implantation Several nm of the modified layer | [47, 49, 50, 60, 61] |
|                    | AZ31                            | Ion-beam assisted deposition             | carbon nitride (CN) coating/HA high-purity Mg coating/ diamond-like carbon film/SiC film | [62, 63] |
|                    | AZ91/WE43                       | Physical vapor deposition, Plasma-enhanced chemical vapor deposition | –         | [64–66] |
| Chemical conversion coating | LAE442/pure Mg/ AZ31B | Fluoride treatment                        | MgF2 3–200 μm | [58, 67, 68] |
|                    | pure Mg/Mg–Ca alloy/AZ31        | Alkali heat treatment                    | Mg(OH)2/MgO 100 μm | [69–72] |
| Electrochemical treatment | Mg–Ca alloy/pure Mg/AZ91      | Anodic oxidation/MAO                      | MgO and others <20 μm | [73–76] |
|                    | Mg–Zn–Ca                       | Electrode-position                      | Ca-defHA/FHA and brushite hydroxyapatite 10–20 μm | [77–79] |
|                    | AZ31B/Highly pure Mg/Extruded Mg–Mn–Zn/AZ91 | Biomimetic deposition                   | HA–Mg(OH)2/CA-P-based compound 300 μm | [43, 44, 80, 81] |
| Sol–gel            | AZ31/Mg4Y/Mg/6Zn/2AZ81/WE42    | Organic and polymer coating              | PLGA/PPLA/PCL/silane-epoxy-coating/β-TCP 2–70 μm | [47, 82–86] |
Ye et al. [103] developed 1 wt.% nanosized coating HA particles on Mg–2.9Zn–0.7Zr alloy. The corrosion properties in SBF and the in vitro cytocompatibility of the coating alloy were evaluated. The results showed that the corrosion resistance of composite is more favorable compared with that of Mg–2.9Zn–0.7Zr [103]. Witte et al. [104] and Ye et al. [105] developed a composite based on AZ91D reinforced with HA particles and prepared with a novel mesoporous HA (meso-HA) coatings on AZ31. The corrosion properties of the coating alloys were evaluated via the immersion tests and electrochemistry; the results showed that the composite with 20% HA and meso-HA has a potential to improve the corrosion resistance of Mg-based alloys [104, 105]. However, other studies reported that HA coating does not demonstrate long-term stability because of its fragile flakes or unstable amorphous. Yang et al. [106] designed the Ca–P coating through three methods, and obtained the coatings of brushite CaHPO4 -2H2O(DCPD), Ca10(P04)6(OH)2(HA) and Ca5(P04)3(OH)1-xFx(FHA), that were coated through electrodeposition on the surface of Mg–Zn alloy [80, 106]. The long-term corrosion resistance of each coating layer was evaluated through XRD. FHA coatings have the larger stack density than the DCPD and HA coatings, lower solubility products, and closely packed organization, which exhibited the best corrosion resistance compared with others [79].

More methods were tested to improve the non-stability of HA coatings. Huan et al. [80] developed bioactive glass which contained SiO2, Na2O, CaO, P2O5 composites with ZK30 as the reinforcement. Immersion tests were evaluated in the lowest limitative essential medium with Earle’s balanced salts at 37°C. Coating alloy composites with 5 and 10% BG, which could enhance the stability of coating layer during the primary stage of the corrosion and dissolution of BG particles, as well as induce calcium and phosphate ion deposition on the alloy surface, thus achieving the improvement of the corrosion resistance [107].

**Biocompatibility of Mg and its alloys as orthopedic implants**

Each implant material that should be developed and investigated for human application must be biocompatible, i.e. non-toxic or carcinogenic and tolerated by the body without causing inflammation or further injury [108]. Mg and its alloys are considered attractive metallic materials for the development of potential medical implants; biocompatibility is the most essential aspect for consideration [15, 39, 109, 110]. To ensure the biocompatibility of Mg and its alloys, in vitro degradation processes and clinical studies focusing on bone response are necessary. The rapid degradation of pure Mg implants in vivo accompanied with the generation and accumulating of large amounts of hydrogen beneath the skin. Thus, non-toxic Mg-based alloys are fabricated for the reduction of corrosion rate [15]. Biodegradable Mg alloys are regarded promising metal for long-bone fracture fixation. In 1907, Lambotte studied the potential of Mg for medical application. However, The rapid degradation of pure Mg in vivo and production of a large amount of gas beneath the skin caused the experiment failed [15].

In 1944, Troitskii and Tstirin reported 34 cases with various fractures cured by a Mg–Cd alloy developed into plates and screws [15]. Their research showed that the implants of Mg–Cd alloy promote the development of hard callous in the fracture repair. Only 9 out of 34 cases were unsuccessful because of infection or gas cysts, yet without distinct inflammatory reaction and deviant serum level of magnesium in all patients [15]. These implants could maintain the mechanical integrity for 40–60 days, and these implants were completely resorbed after 10–12 months; furthermore, using a subcutaneous needle drew off hydrogen gas efficaciously during the corrosion procedure [15, 39].

Witte et al. [25, 111] prepared rods with four different Mg alloys (AZ31, AZ91, WE43, and LAE442) and used degradable polymer as the control for implantation into femoral shaft of guinea pigs. Mg alloy implants are degraded with varying rates in vivo, mainly influenced by the alloy elements’ composition and the bone mass surrounding the implants [100, 112, 113]. Finally, quadruplet Mg implants are degraded completely in 18 weeks. Increased bone area was observed at weeks 6 and 18 on the Mg implants [15, 25, 111]. LAE442 shows the slowest rate of corrosion among the alloys used, and WE43 is rich in calcium and phosphorous. These examples supported the potential of Mg-based alloys as biodegradable, biologically compatible, and possibly biologically active orthopedic implants [111].

Zheng et al. [32] studied biomedical binary Mg–xCa (x=1–3 wt.%) alloy. Cytotoxicity evaluation was performed using L-929 cells, and the results showed that Mg–1Ca have good cytocompatibility, and the survival rate of cells is better than that of control by culturing in the extraction medium of the Mg–1Ca alloy. Furthermore, the surface of Mg–1Ca alloy deposited a constituents of a mixture of Mg(OH)2 and HA during the in vitro and in vivo corrosion reactions [32]. Through the analysis of the above, it suggested that Mg–1Ca alloy has good biocompatibility as a potential biodegradable implant material.

Gu et al. [52, 114] developed the binary alloys Mg–1X (wt.%) with nine kinds of elements, namely, including Al, Ag, In, Mn, Si, Sn, Y, Zn and Zr and Mg–XSr (1–4 wt.%) to study the corrosion resistance of Mg alloys, and they observed the cytotoxicity of Mg alloys. The cytotoxicity tests indicated that Mg–1Ca alloy extracts have no significant reduction in the cell viability of fibroblasts; and it is same to Mg–1Y and Mg–1Zn alloy in the cell viability of osteoblasts [52]. The in vitro cell culture results showed that the as-rolled Mg–1Sr and Mg–2Sr alloys had good cytotoxicity, showing Grade 1 cytotoxicity according to the regulation of ISO 10993-5 and increased alkaline phosphatase(ALP) expression [114]. ALP is deemed to a kind of membrane enzyme generally being used as a marker of osteoblastic differentiation [22]. The in vivo tests exhibited that the Sr releasing from the as-rolled Mg–2Sr alloy implanted is safety, as well as the promotion of bone mineralization and new bone formation [114].

Alani et al. [115] evaluated the compatibility of Mg-based implants and found that the nanostructured HA (nHA) coating on polished Mg substrates is a critical step for achieving good compatibility. The result of the cell culture indicated that the nHA-coated Mg specimens could significantly improve the adhesion of bone marrow stem cells [115].

Recent studies have proven that Mg-based alloys, as bone implants, are biocompatible and non-toxic for bone healing, indicating their potential application on orthopedics. However, the corrosion rate of Mg or Mg-based alloys is considerably fast to match bone healing, which commonly takes at least 12 weeks [111]. Further investigation on decreasing the corrosion rate is still essential for studying Mg and its alloys [116–118].

Finally, the most recent proof-of-concept study on an innovative hybrid system with conventional permanent metal and bioactive and degradable Mg implant for enhancement of fracture repair have been reported with novel biological mechanisms involved in neuronal pathways [115, 119]. This would be a new direction for safe
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transformation of Mg or its alloy-based orthopedics implants for clinical applications.

Conclusion and perspective
Biodegradable Mg and its alloys attract considerable attention because of their potential applications in orthopedics as bone implants and eventually without implant removal surgery. Meanwhile, as the developing of a variety of conventional scaffold fabrication techniques, Mg-scaffolds have obtained in-depth research for bone defect repair. However, Mg in vivo has low corrosion resistance. Thus, alloying and surface coatings are used to increase the corrosion resistance of Mg alloys, which aims to develop commercial Mg or Mg-based alloy implants to facilitate their translation to clinical applications.

A significant number of research showed that the performance of Mg metal might be improved by alloying and further treatment so that the Mg-based metallic materials could be used to design fixation implants for clinical applications. Through affecting the solid/liquid interface instability, alloying and further treatment could affect the morphology and distribution of the primary or secondary phase, and then improve the yield strength, UTS, elongation and corrosion properties of materials.

Literature analysis shows that various surface coating techniques have been tested for Mg and its alloys to decrease corrosion rate. Nevertheless, most of the coatings disappear along with implantation over time, though they can delay the onset of corrosion. Numerous factors should be considered, e.g. coating morphology, surface chemistry and adhesion, on their use as biomedical implants in future research. Most of the Mg alloys do not have superior corrosion resistance in vivo that match the physiological environment.

Mechanical demands may vary at different skeletal sites; thus, effective coating methods must be developed to maintain the corrosion resistance of Mg or Mg-based alloys. Consequently, concerns on rapid corrosion, which induces local accumulation of hydrogen and fast increase of local pH value, are reduced. In the future, the cooperation of researchers and clinicians is essential to develop knowledge- and experience-based design of Mg or Mg-based orthopedic bone implants, which are a promising option for current permanent metal implants or biodegradable implants made of polymers. The historical reviews should encourage researchers and clinicians to study the corrosion process and biocompatibility, as well as explore the complete characterization for clinical use.

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