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Effects of Alloying Elements on the Corrosion Behavior and Biocompatibility of Biodegradable Magnesium Alloys: A Review

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Abstract

Magnesium (Mg) based alloys have been extensively considered for their use as biodegradable implant materials. However, controlling their corrosion rate in the physiological environment of the human body is still a significant challenge. One of the most effective approaches to address this challenge is to carefully select alloying compositions with enhanced corrosion resistance and mechanical properties when designing the Mg alloys. This paper comprehensively reviews research progress on the development of Mg alloys as biodegradable implant materials, highlighting the effects of alloying elements including aluminum (Al), calcium (Ca), lithium (Li), manganese (Mn), zinc (Zn), zirconium (Zr), strontium (Sr) and rare earth elements (REEs) on the corrosion resistance and biocompatibility of Mg alloys, from the viewpoint of the design and utilization of Mg biomaterials. The REEs covered in this review include cerium (Ce), erbium (Er), lanthanum (La), gadolinium (Gd), neodymium (Nd) and yttrium (Y). The effects of alloying elements on the microstructure, corrosion behavior and biocompatibility of Mg alloys have been critically summarized based on specific aspects of the physiological environment, namely the electrochemical effect and the biological behavior.

Keywords: Magnesium alloys, alloying elements, biodegradable, corrosion, biocompatibility

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1. Introduction

Magnesium (Mg) alloys are receiving increasing attention as promising biodegradable materials for orthopedic applications because of their similar mechanical properties to natural bone, their excellent biocompatibility and their lower densities compared to other metallic biomaterials [1, 2]. Unlike other metallic biomaterials such as titanium alloys, stainless steels and cobalt-chromium based alloys; Mg alloys exhibit an elastic modulus similar to that of human bone, which prevents the stress shielding effect on the human bone [3]. As degradable biomaterials, Mg and Mg alloys serve as implants temporarily after implantation. They degrade in vivo and are replaced by new bone tissue, which eliminates the need of a revision surgery to remove the implant from human body as in the case of a stainless steel implant after implantation for 15 - 20 years [4]. This significantly decreases the medical costs and further torment to the patient.

The principle drawback of Mg alloys in biomedical applications is their rapid corrosion rate in electrolytic aqueous environment, leading to detrimental interactions with biological organisms [5]. Thus, it is crucial to improve the corrosion resistance of Mg alloys for their potential biomedical applications [1]. To achieve this, extensive investigations have been carried out on the composition design [6] and post-treatment [7, 8] for biodegradable Mg alloys. In particular, the composition design provides scientific basis for the development of biodegradable Mg alloys. One of the most effective approaches to the composition design is to carefully select alloying elements of Mg alloys with enhanced corrosion resistance and mechanical properties. Elements included within the Mg matrix may create different mechanical and physical properties due to in the changes of structure and phases distribution [6]. As a biodegradable material, the metallic ions released from Mg alloys must be minimal deleterious effects; and it is preferred if they can also promote the tissue healing and stimulate metabolism [9, 10]. However, metallic ions in many cases are not perfectly biocompatible and affect tissue healing [10, 11]. A rapid degradation of Mg alloys also results in a quick loss of mechanical integrity that can lead to a collapse of the implant before the tissue is sufficiently healed [12]. The release of metallic ions through corrosion may also lead to inflammatory cascades and reduce biocompatibility if alloying elements are cytotoxic [10, 11]. Furthermore, the hydrogen gas that is produced quickly in the corrosion process of Mg alloys can lead to adverse host tissue reactions to the implants. This work reviews the research progress on the development of Mg alloys for implant biomaterials and highlights the effects of commonly used Mg alloying elements including Al, Li, Mn, Zn, Zr, Ca, Sr and REEs on the microstructure, mechanical properties, corrosion behavior and biocompatibility of biodegradable Mg alloys, in order to provide the fundamental knowledge in the design of biodegradable Mg alloys. In the standard designation of Mg alloys, the first two letters identify the two most important alloying elements in the alloy using the following code: A-Al, L-Li, M-Mn, Z-Zn, K-Zr, RE-rare earth [13]. This review also provides new insights into the approaches being used to improve the corrosion resistance and biocompatibility of biomedical Mg alloys.

2. Biodegradable Mg alloys

Mg exhibits non-toxicity and can even stimulate hard tissue recovery after implantation in the human body [1]. This makes Mg and some of its alloys promising candidates for biodegradable implant applications. However, current Mg alloys degrade rapidly in the electrolytic environment of the human body, resulting in the quick deterioration of the mechanical integrity of the Mg alloy implant and, hence, inadequate mechanical properties of the implant before the host tissue is sufficiently healed [14]. The mechanical properties of Mg alloys in a physiological environment are influenced by the corrosion rate because corrosion results in a gradual loss in both the structural integrity and the mass of the Mg alloys [11]. Therefore, it is imperative to design new Mg alloys with enhanced corrosion resistance for biomedical applications. Another concern of Mg alloy implants is the production of hydrogen gas after implantation in vivo due to corrosion [15, 16]. The rapid corrosion process of Mg alloys in a physiological environment is accompanied by the release of a large amount of hydrogen gas, which may cause serious adverse effects in the human body.

The first application of biodegradable Mg implant can date back to the beginning of the 20th century [15]. As early as 1906, Lambotte [17] applied pure Mg as a biodegradable implant material to fix a bone fracture. Recent decades have seen studies on Mg and its alloys as bio-implant materials become a booming research area. A large number of existing and newly developed Mg alloys have been considered for their potential use as biodegradable implants, as listed in Table 1.

Table 1 Recent research of Mg alloys as biodegradable biomaterials

Mg alloys	Compositions*	In vitro/in vivo model	Refs
AE21	2% Al, 1% REEs (Ce, Pr, Nd)	EIS in 0.1 M NaCl solution, stent in coronary artery of pigs	18, 19
		EIS in 0.1 M NaCl solution	20, 21
AZ21	2% Al, 1% Zn	Rat stromal cells, weight loss in culture media	22
		EIS, PPC and H_2 evolution in 1 M NaCl solution	23
AZ31	3% Al, 1% Zn	Degradation rate and bone formation in guinea pigs	11
		EIS and PPC with different grain size in phosphate buffer, SBF and NaCl solutions	24-26
AZ31B	2.94% Al, 1.06% Zn, 0.48% Mn	pH, degradation rate in rabbits and Hank’s solution	27
	3% Al, 1% Zn	Degradation in VX2 tumor tissue and muscle tissue of rabbits	28
		EIS and PPC in 3.5% NaCl solution	29
AZ91, AZ91D	9% Al, 1% Zn	PPC in a borax-phosphate buffer solution, degradation rate and bone response in guinea pigs	11, 30
		PPC in SBF	31
		H_2 evolution, weight loss and PPC in Hank’s solution	32

		Rabbits	2
LAE442	4% Li, 4% Al, REEs (1% Ce, 0.4% La, 0.3% Nd, 0.1% Pr)	PPC in a borax-phosphate buffer solution, degradation rate and bone formation in guinea pigs	11, 30
		Blood analysis and histopathology, degradation in rabbits	34
WE	4% Y, REEs (2.1% Nd, 0.2% Ce, 0.2% Dy, 1% La)	Degradation rate and bone response in guinea pigs	11
		Coronary artery of minipigs	35
	5% Y, REEs (2.89% Nd, 0.72% Gd)	H_2 evolution, weight loss and PPC in Hank’s solution	36
ZE41	4.7% Zn, REEs (1.06% Ce, 0.1% Gd, 0.52% La, 0.1% Nd, 0.13% Pr, 0.13% Y)	H_2 evolution, weight loss and PPC in 0.1 M NaCl and Hank’s solutions	32, 37, 92
ZK30	3% Zn, 0.6% Zr	Hank’s solution, cytotoxicity by rabbit bone marrow stromal cells	36
		Cells culture medium	50
		H_2 evolution and mass loss in medium with Earle’s balanced salts, cytotoxicity by rat bone marrow stromal cells	51
ZK60	6% Zn, 0.6% Zr	Hank’s solution, cytotoxicity by rat bone marrow stromal cells	36
		PPC in Hank’s solution and culture medium; murine fibroblast cells (L-929) and human osteosarcoma cells (MG63) cells	52
		Immersion test in Hank’s solution; Chinese hamster cells	53
MgCa	0.8%Ca	Rabbits, degradation analysis by micro-computed tomography	58
	1 - 3 % Ca	PPC in SBF, cytotoxicity by L929 cells culture	59
	5 - 10% Ca	Adult male Sprague-Dawley rats	60
	0.5 - 20 % Ca	Immersion test in SBF, cytotoxicity by SaOS2 osteoblast-like cells	61
Mg-Y	8% Y	PPC in 3.5% NaCl solution	38
	4% Y	EIS and PPC in SBF, subcutaneous tissue of the nude mice	39
MgZn	6% Zn	EIS, PPC and immersion tests in SBF, cytotoxicity by L929 cells culture, rabbits	40, 41
	1% Zn	Human bone marrow stromal cells culture, rabbits	42
Mg1%X	X = Al, Ag, In, Mn, Si, Sn, Y, Zn, Zr	Hank’s solution and SBF, L929, MC3T3-E1, ECV304 and VSMC cells	5
MgZnMn	1.2% Mn, 1.0% Zn	The femora of the rats, blood test, serum creatinine, uric acid	43
	4% Zn, 1% Mn	Composition (phases and microstructure)	44
MgZnX	2% Zn, 0.2% X (X = Ca, Mn, Si)	Ringer’s physiological solution	45
MgZnY	1, 2% Y, 2% Zn, 0.25% Ca, 0.15% Mn	EIS and PPC in SBF, human umbilical vein endothelial cells / pigs	46
	7% Y, 0.5% Zn	Immersion tests in SBF and Hank’s solution, EIS and PPC in SBF	49
MgBiX	5% Bi, X = 1% Ca, 1% Si	Hank’s solution/ rabbits	62

MgCaZn	66%Zn, 30%Ca; 70%Zn, 25%Ca	SBF; cytotoxicity by L929 and MG63 cells	47
	2% Zn, 0.2 % Ca	PPC and EIS immersion in Ringer's physiological solution	45
	10 - 30%Zn, 1% Ca	PPC in SBF, cytotoxicity by L929 and MG63	63
MgCaY	1%Ca, 1%Y	SBF, cytotoxicity by SaOS2 osteoblast-like cells	61
MgCaSr	0.5 - 7% Ca, 0.5 - 3.5% Sr	Hank's solution, mouse osteoblastic cells	64
MgCaZr	0.5, 1% Zr, 0.5, 1% Ca	Immersion tests in SBF, osteoblast-like SaOS2 cells	54
		Immersion tests in SBF, osteoblast-like cells	55
MgSr	1 - 4% Sr	Immersion tests in Hank's solution, EIS and PPC in SBF; MG63 cells culture/3 month old mice	73
	0.5 - 1.5% Sr	HUVEC cells/dog femoral artery	72
MgSrZn	2 – 4% Zn, 0.5% Sr	HUVEC cells/dog femoral artery	72
	4% Zn, 0.15%～1.5% Sr	Immersion tests in cell culture media, cytotoxicity by H9 human embryonic stem cells	77
MgSrZr	≤ 5% Zr, ≤ 5% Sr	PPC in SBF, osteoblast-like SaOS2 cells culture, hemolysis test/rabbits	56

*Balance of Mg; %: wt%, unless specified otherwise; EIS: Electrochemical impedance spectroscopy; PPC: potential polarization curve.

Currently, the Mg alloys considered to be used as biodegradable implant materials are mainly existing commercial Mg alloys that were originally developed for their applications in the transportation industry [13]. Mg alloys such as AE21 [18-21], AZ21 [22, 23], AZ31[11, 24-26], AZ31B [27-29], AZ91 and AZ91D [2, 11, 30-32] exhibit excellent mechanical properties and reasonable corrosion resistance. However, all of these Mg alloys contain Al, which has been reported to be cytotoxic and over time, cause adverse reactions with body tissues [33].

The effect of other alloying elements, such as REEs [11, 30, 32, 34-39], Zn [5, 40-49], Zr [36, 50-57], Ca [45, 47, 48, 54, 55, 57-67] and Mn [43-45, 68] on the degradation behavior, the mechanical properties and biocompatibility in vitro and in vivo have been extensively investigated. However, when Zn and Mn are the principle alloying elements, they show high cytotoxicity, which leads to genotoxicity and the suppression of the cell viability [5, 32]. Some REEs such as cerium (Ce) [69], lanthanum (La) [70] and neodymium (Nd) [71]exhibit potential cytotoxicity. High contents of Ca and Zr in Mg alloys could result in a poor corrosion resistance [55, 56, 59]. It is essential that an ideal biodegradable implant material has an appropriate degradation rate and excellent biocompatibility. Therefore, new alloying elements for biodegradable Mg alloys, such as Sr, have been investigated recently [56, 64, 72-77]. It has been reported that Sr promotes bone cell growth and is of benefit to postmenopausal osteoporosis as it increases bone formation [78, 79]. The effect of Sr on bones, muscles and the heart have been studied systemically [79-81], and is already considered to be a promising element and therefore introduced into new Mg alloys for biomedical applications [82, 83]. New Mg alloys such as Mg-Sr [72-74] and Mg-Zr-Sr [56] have been developed that take into consideration the biocompatible benefits of Sr and Zr. It has been demonstrated that an appropriate amount of Sr and Zr can improve the mechanical properties, corrosion behavior and biocompatibility of Mg alloys [56].

Despite significant progresses have been achieved in the research of biodegradable Mg alloys, there are still very limited Mg-based implants in clinical applications [35]. New Mg alloys with enhanced corrosion resistance and excellent biocompatibilities are highly desirable for biomedical applications. When designing an Mg alloy for degradable implants, reducing the degradation rate and improving biocompatibility are important factors to be considered in future research directions. Understanding the corrosion mechanism and its effect on the biocompatibility of Mg alloys is a precondition for the development of biodegradable Mg alloys for biomedical applications.

3. Factors influencing Mg corrosion

Mg is susceptible to the physiological environment due to the lowest standard potential $-2.38V_{nhe}$ of all engineering metals [84]. However, the actual corrosion potential of Mg varies dependent upon other factors such as environment and surface status. Song [81] found that the corrosion potential of Mg in dilute chloride solutions is usually $-1.7V_{nhe}$, and the surface film of $Mg(OH)_2$ largely determines the corrosion kinetics of Mg. Hence to meet the requirements for implant applications, it is vital to understand the factors that affect the corrosion rate of Mg alloys.

3.1. Physiological environment

It has been known that the corrosion behavior of materials always refers to some specific environments. In the case of biodegradable implants, they are always working in the particular environment of human body. Figure 1 presents a schematic illustration of Mg implant in a physiological environment. After implantation, Mg alloy implants are exposed to an environment which consists of blood, protein and other constituents of the body fluid such as chloride, phosphate, bicarbonate ions, cations (Na^+, K^+, Ca^{2+}, Mg^{2+} etc.), organic substances of low-molecular-weight species, relatively high molecular-weight polymeric components, as well as dissolved oxygen. This physiological environment makes an extremely complex corrosive medium [85]. Consequently, experiments on Mg alloys were mainly carried out in vitro using different methods, such as electrochemical corrosion measurements, biocompatibility assessments and hemolysis testing etc. in simulated body fluid (SBF) prior to in vivo tests, with the aim of providing basic information for biomedical applications.

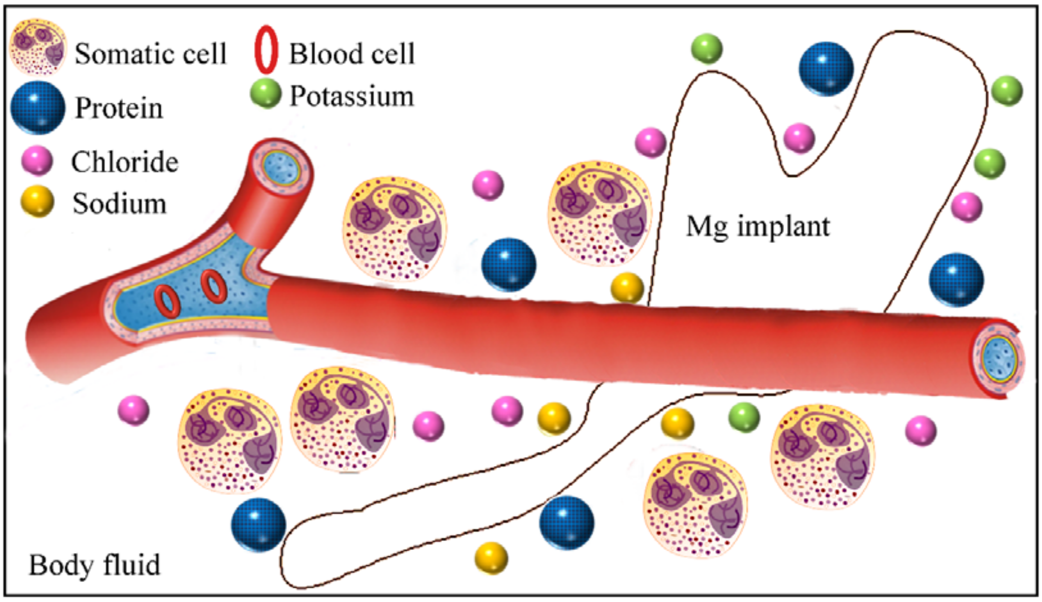

Fig. 1 Schematic illustration of Mg implant in a physiological environment

The physiological environment significantly affects the experimental results of corrosion behavior and biocompatibility. Corrosion of Mg alloys exhibits different corrosion parameters in different SBFs [86]. It has been reported that adding an albumin into the SBF could influence the corrosion rate of Mg alloys, because a protein layer adheres to the Mg alloy surface and acts as a barrier between the material and physiological environment [87]. But nevertheless, protein contains various metal cations that accelerate the corrosion rate to some extent [67, 88]. Changes in the pH values also significantly influence the corrosion of the reactive materials such as Mg alloys although the pH of the intercellular fluid usually maintains at neural, this value changes from 2.0-8.0 depending on the location in the human body and as a result of trauma such as injury, surgery, diseases, etc. In relation to the experiment in vitro, it is critical to maintain the pH value as it will typically exceed the physiological range before any significant information is provided. This is due to the increasing OH^- in the experimental solution that leads to non-realistic environment, and will have a significant impact on the corrosion rate [8].Therefore, it is important to take these factors into consideration in interpreting the results from corrosion experiments.

3.2. Microstructure and surface properties

It is well known that the corrosion behavior of Mg alloys is significantly influenced by the microstructure, such as grain size, boundary and phase distribution. Grain refinements lead to changes in the density of grain boundaries and distribution, which alter the mechanical properties and also influence the corrosion behavior of Mg alloys. Izumi et al. [89] studied the influence of grain size on corrosion behavior of Mg-Zn-Y alloys that were prepared by rapid solidification at different cooling rates. They indicated that the corrosion of Mg-Zn-Y alloys depended on the grain size. A decrease in the grain size retarded the occurrence of filiform corrosion, attributing to the grain refinement and the formation of a supersaturated solid solution of single α-Mg phase in the alloys. Compared to hot-extruded AZ31B alloys, the fine-grained AZ31B alloys exhibited a higher corrosion resistance [90]. One of the explanations for the enhanced corrosion resistance with finer grains is that grain refinement may help to relieve the stress on surface film due to the mismatch between Mg oxide and underlying Mg metal substrate. However, there are some studies also reported that the corrosion resistance deteriorates as the grain size decreases [19, 56, 91, 92].

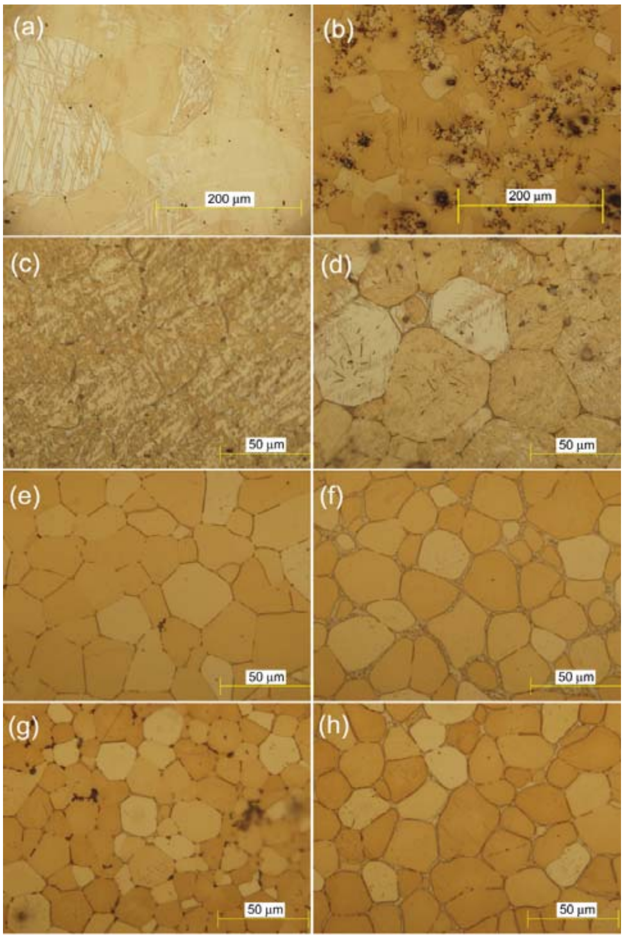

Fig. 2 Microstructures of Mg-Zr-Sr alloys: (a) Mg; (b) Mg-5Zr; (c) Mg-1Zr–2Sr; (d) Mg-1Zr-5Sr; (e) Mg-2Zr-2Sr; (f) Mg-2Zr-5Sr; (g) Mg-5Zr-2Sr; (h) Mg-5Zr-5Sr. Reproduced from data published in Ref. 56.

Minarik et al. [19] found that AE21 alloys with smaller grain size showed the deteriorative corrosion resistance after treatment of equal channel angular pressing (ECAP). A similar decrease in corrosion resistance was observed in the pure Mg after strain-induced grain refinement [91]. Li et al. [56] investigated the corrosion behavior of Mg-Zr-Sr alloys with various grain sizes. The microstructures of the Mg alloys with different contents of Zr and Sr are shown in Figure 2. In their study, the grain sizes of Mg-xZr-2Sr alloys (x=1, 2 and 5 wt%, hereafter, unless specified otherwise) decreased with increasing Zr addition (Fig. 2c, e and g), but the corrosion resistance in SBF decreased. It can be concluded that the corrosion resistance decreased with decreasing grain size in the Mg alloys.

These studies indicated that the mechanism by which grain size influences the corrosion behavior of Mg alloys is still under debate. Further studies are needed to achieve an in-depth understanding of the effect of grain size on corrosion of Mg alloys.

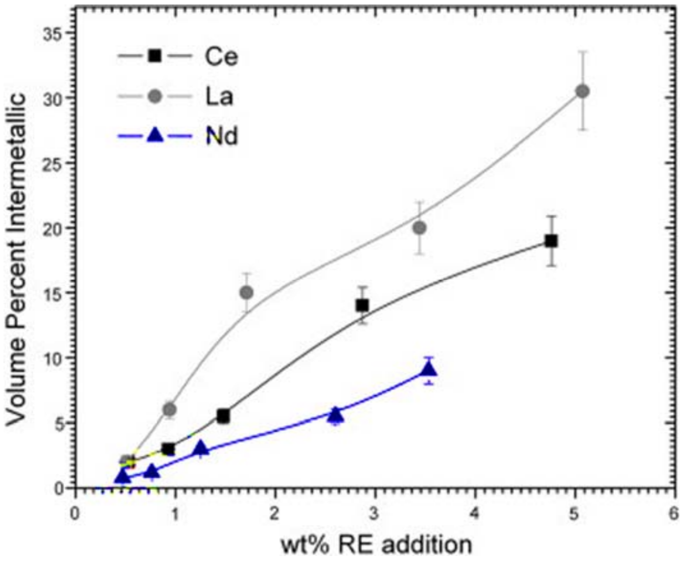

Fig. 3 Volume fraction of secondary phases with the addition of La, Ce and Nd in Mg-REEs alloys. Reproduced from data published in Ref. 94.

3.3. Second phase and galvanic corrosion

Mg is chemically reactive and can react with other alloying elements to form second phases (intermetallic compounds), which precipitate along the grain boundaries and segregate the Mg grains. These phases have a pronounced influence on the properties of Mg alloys. For example, as can be seen from Figure 2 that the grain boundaries of Mg-2Zr-5Sr become rougher and broader with increasing Sr addition from 2 to 5 %, which indicated more second phases formed and distributed along grain boundaries. Li et al. [56] found that with increasing addition of Sr in Mg-Zr-Sr alloys, the compressive yield strength increased while the corrosion resistance decreased compared with other alloys. In fact, many studies [47, 64, 93] revealed that the properties such as corrosion behavior, mechanical properties etc. in many cases depended on the volume fraction of secondary phase which was determined by the alloying elements concentration in Mg alloys. Figure 3 shows the volume fraction of second phases as a function of the addition of rare earth elements lanthanum (La), cerium (Ce) and neodymium (Nd) in Mg-REEs alloys [94]. It can be seen that the volume percent of the second phases increased with the increasing concentrations of REE alloying elements. The volume fraction of the second phase of $Mg_{12}La$ was 30 % at an addition of 5 % La and 10 % of Mg_3Nd at an addition of 3.5 % Nd. The second phases exhibited a continuous network along the grain boundaries in the high alloying elements content alloys, and they tended to be thermodynamically stable than the Mg matrix, leading to an acceleration in the cathodic reaction and inhibition in the anodic reaction in the polarization test.

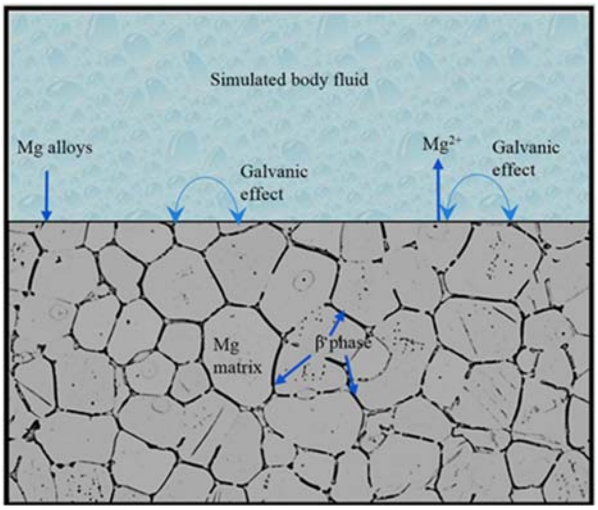

Fig. 4 Galvanic effect between Mg matrix and second phase resulted in accelerated corrosion of Mg alloys.

A high Zn content in alloys such as Mg-Zn alloys is associated with an appreciable amount of second phase, which is Mg_xZn_y [95] that precipitated along the grain boundaries. Song et al. [96] found that the volume of Mg_xZn_y increased with increasing Zn concentration, and the Mg_xZn_y phase acts as the cathode in the micro-galvanic system between Mg_xZn_y phase and Mg matrix, thus accelerated the corrosion of Mg matrix. A bio-corrosion model at the alloy/SBF interface was illustrated to show the influence of second phase on the corrosion of Mg alloys, as shown in Figure 4. When alloys were immersed in SBF, the surface was attacked by the ions such as chloride, phosphate anion etc. The internal second phase such as $Mg_{17}Sr_2$ and $Mg_{12}Ce$ acted as a cathode [97]. The degradation of Mg matrix accelerated due to the coupled galvanic effects between Mg matrix and second phase. Second phases in Mg alloys possess different electrochemical potentials. If the second phases have higher positive potential than that of Mg matrix, there will be many galvanic cells that further influence the corrosion behavior of Mg alloys. Furthermore, second phases may have complicated influence on the corrosion of Mg alloys particularly for that of ternary alloys with multiple elements additions such as Mg-Al-Sr alloys [75]. The Mg alloy used consisted of Sr-containing phases, such as AlSr, Al_4Sr and $Mg_{17}Sr_2$, formed by a reaction of Sr with Al and Mg. This was expected to result in a decrease in the amount of $Mg_{17}Al_{12}$ in the Mg alloy, leading to an enhancement in the corrosion resistance of the Mg alloy in the simulated body fluid. However, with the increase in the Sr added, a limb growth of $Mg_{17}Sr_2$ phase was observed for the Mg-Al-1.5%Sr alloy that resulted in a decrease in the corrosion resistance compared to that of the Mg-Al-1%Sr alloy. Overall, it can be concluded that the volume fraction, distribution and electrical potential of the second phases significantly affect the corrosion behavior of Mg alloys.

3.4. Surface layer

The corrosion of Mg alloys in aqueous environment has been generally considered as an electrochemical reaction with water in producing oxidation products MgO and $Mg(OH)_2$. Song et al reported that the surface layer mainly composed of $Mg(OH)_2$, as MgO can react slowly with water to form $Mg(OH)_2$, which can provide some protections for Mg alloys, restarting further corrosion [84]. Zhu et al. [98] investigated the relationship between $Mg(OH)_2$ and the corrosion rate of AZ31 alloy when immersed in Hank's solution for 31 days. It showed that at the initial corrosion stage, an $Mg(OH)_2$ layer grows on the surface of the Mg alloy, which effectively decreases the corrosion rate in Hank's solution. However, when the immersion time was prolonged, Cl^- attacked the $Mg(OH)_2$ layer and reduced the layer thickness gradually. Some tiny cracks appeared on the film after 7 days immersion, which indicated the occurrence of pitting corrosion. This study indicated that although the $Mg(OH)_2$ layer would eventually be damaged, it was still able to provide short-term protection. Bornapour et al. [74] found that Sr-hydroxyapatite (HA) formed on the surface of Mg-Sr alloy after immersion in SBF for 3 days. This layer has been proved to improve the bio-activity and bio-corrosion resistance of the Mg alloy [99, 100]. These results revealed that the corrosion of Mg alloys always leads to the formation of reaction products of the metal ions and environment on the surface of the alloy, which slows down the corrosion process.

4. Effects of alloying elements on corrosion behaviors of Mg alloys

The most common alloying elements of Mg alloys are Al, Ca, Li and Mn etc. These alloying elements can react with Mg or among each other to form intermetallic phases. These intermetallic phases distribute along the grain boundaries or dissolve in the Mg matrix, influencing the microstructure, mechanical properties and corrosion behavior, as listed in Table 2. It can be seen that some elements such as Mn, Er, Ce, La and Nd improve the corrosion resistance of Mg alloys. For some other elements such as Ca, Zn, Zr and Sr, their influence on the corrosion resistance depends on the content of the element: when the content is high, the corrosion resistance deteriorates, whilst when the content is low, they slow the corrosion rate of the Mg alloys. The corrosion resistance of Mg alloys is always reduced in the presence of the element Li. The effects of the elements of Gd and Y on the corrosion of Mg alloys are still not well understood and there are disputed conclusions regarding their influence on corrosion behavior. Overall, further studies are needed to elucidate the effects of alloying elements on the properties of Mg alloys from the view of corrosion mechanism in order to provide the comprehensive insight required to develop new Mg alloys alloyed with elements beneficial to corrosion resistance.

Table 2 Influence of alloying elements on the microstructure, mechanical properties and corrosion resistance of Mg alloys

Elements	Effects on microstructure	Effects on mechanical properties	Effect on corrosion resistance	References
Al	Refining grain size; reacting with Mg to form $Mg_{17}Al_{12}$ phase; high Al concentration leading to a network distribution of $Mg_{17}Al_{12}$ along grain boundaries	Enhancing castability and hardness; increasing yield strength at a concentration above 3%; significantly improving ultimate yield strength and ductility at a concentration below 6%	A network distribution of $Mg_{17}Al_{12}$ in Mg alloys enhancing corrosion resistance; however, the coupled micro-galvanic effects between $Mg_{17}Al_{12}$ phase and Mg matrix at the same time increasing corrosion rate	2, 18-32, 75, 91, 97, 101-109
Ca	Reducing the grain size with the addition of Ca below 15% in binary Mg-Ca alloys; forming Mg-Ca phases distributed along the grain boundaries	Increasing elasticity; compressive yield strength; ultimate strength and hardness with the increasing Ca content less than 20%; increasing the creep properties at a concentration less than 0.3%; deteriorating the ductility at the concentration from 0.5 to 15%	Excessive addition of Ca in pure Mg deteriorating corrosion resistance; Ca concentration in Mg alloys should be less than 1%	45, 48, 54, 55, 58, 59, 61, 64-67, 101, 110
Li	Slightly decreasing the grain size; Mg-Li phases with bcc structure distributing along grain boundaries	Increasing deformability with high addition (> 11%) by forming the bcc structural phases; decreasing strength significantly	Enhancing corrosion resistance at a concentration below 9% in pure Mg; accelerating corrosion rate significantly with higher Li addition	13, 30, 34, 86, 101, 111, 112, 114
Mn	Significant grain refining at low Mn concentration in Mg-Al based alloys; removing impurities by forming new phases with Fe and other heavy metals	Slightly increasing yield strength; decreasing ultimate yield strength and elongation for binary Mg-Mn alloys; the effect on mechanical properties dependent on the composition of Mg alloys; rarely being used in pure Mg	Enhancing corrosion resistance by reducing impurities with a small quantity of Mn addition	5, 43-45, 68, 101, 115-119
Zn	No obvious effect on grain refining with the addition below 5% for binary Mg-Zn alloy; reacting with Mg to form second phase and distributing along grain boundaries; usually being used with Al in Mg alloys	Enhancing tensile strength; excellent solid solution strengthening and aging strengthening; deteriorating castability at high concentration; reducing the influences of Ni and Fe	Inhibiting the harmful effects of Fe and Ni impurities on the corrosion; enhancing the corrosion resistance of Mg alloys at a content below 5%	5, 40, 41, 43-48, 63, 68, 95, 96, 101, 120-123
Zr	Excellent grain refining; extremely low solid solubility in pure Mg; using with Al in Mg alloys should be avoided due to the formation of stable Al-Zr phase that deteriorates the	Slightly increasing ultimate compressive strength with the increasing Zn concentration; significantly enhancing ductility, elongation and ultimate yield strength of Mg alloys with small amount of addition for binary Mg-Zr alloys; usually	Small amounts of Zr addition (less than 2%) enhancing the corrosion resistance; otherwise significantly deteriorating the corrosion resistance	36, 52, 53, 56, 57, 101, 102, 124, 125, 128

	mechanical properties	being used with Zn in Mg alloys		
Sr	Refining grain size; leading to rough boundaries with excessive addition; reacting with Mg to form Mg-Sr phases that distribute along grain boundaries	Increasing tensile strength with the Sr addition below 2%; decreasing ultimate strain and ultimate compressive strength due to the superabundant compounds in grain boundaries	The influence on corrosion depending on the fraction volume of $Mg_{17}Sr_2$ phases in Mg alloys, optimal content less 2%	56, 64, 72-75, 130
Ce	Excellent grain refining for pure Mg and AZ alloys; Mg-Ce phases isolating Mg matrix and reducing grain size; Al-Ce phases distributing along grain boundaries; excessive Ce addition to Mg leading to the formation of brittle Mg-Ce phases distributing along grain boundaries	Enhancing tensile strength and tensile yield strength with the addition of Ce below 6% for binary Mg-Ce alloys; however tensile yield strength remaining stable and tensile strength decreasing with increasing addition of Ce after T6 treatment; deteriorating elongation of Mg alloys with excessive addition of Ce; deteriorating creep resistance; enhancing tensile strength of AZ alloys with 1% Ce addition	Forming $Al_{11}Ce_3$ phase surrounding Mg matrix in AZ alloys, suppressive galvanic effects and thus enhancing corrosion resistance; however, increasing addition of Ce deteriorating corrosion resistance of binary Mg-Ce alloys due to galvanic effect	113, 127, 129-137, 140, 143
Er	Exhibiting low solubility in solid Mg; forming stable Mg-Er phases; Er addition to Mg-Al alloys leading to the formation of Al-Er phase; excellent grain refining in ZK alloys	Improving tensile strength and tensile yield strength with the increasing addition of Er to pure Mg; however decreasing elongation of Mg-Er alloys	Enhancing corrosion resistance of AZ alloys; Mg-Al-Er phases surrounding the Mg matrix; enhancing stability of $Mg(OH)_2$ layer and thus reducing corrosion resistance	113, 138-144
Gd	Refining grain size; Gd atoms replacing Mg atoms to form a random substitutional solid solution	Enhancing tensile strength and tensile yield strength with the increasing addition of Gd; improving the elongation of Mg-Gd alloys with the addition of Gd below 6%	No consensus. Influence on corrosion depending on the composition and Gd content in Mg alloys	113, 128, 141, 145-151
La	Having a relatively low solubility in Mg compared with other rare earth elements; reacting with Al to form rod-like Al-La phases that refining grain size of AZ alloys	Enhancing tensile strength, yield strength and creep resistance of binary Mg-La alloys; deteriorating elongation of Mg alloys with excessive addition of La; reducing dendrite arm spacing and slightly improving tensile strength and age hardening response of Mg-Al-La alloys due to the formation of Al-La phases	Refining $Mg_{17}La_2$ phases leading to finer microstructure for Mg-La alloys with the La addition below 1%, which resulting in uniform corrosion; La oxide combined with $Mg(OH)_2$ enhancing corrosion resistance	113, 129, 131, 152-154
Nd	Refining grain size of Mg alloys with increasing Nd content	Nd atoms replacing Mg atoms so that enhancing tensile strength and tensile yield strength at a Nd content less than 6%; deteriorating elongation and creep	Addition to pure Mg effectively enhancing corrosion resistance; $Mg_{12}Nd$ phase suppressing galvanic effect; Nd_2O_3 layer	113, 133, 155, 156

		resistance of Mg alloys with excessive addition of Nd	combined $Mg(OH)_2$ inhibiting corrosion	
Y	Excellent grain refining; relatively high solid solubility in Mg; always used with other REEs to enhance creep resistance of Mg alloys due to the formation of Y-rich phases	Significantly enhancing tensile strength and tensile yield strength with increasing addition of Y in pure Mg; improving elongation with the Y concentration below 3%; excessive addition of Y deteriorating elongation	Influence on corrosion resistance under debate; depending on the composition of Mg alloys; reducing corrosion resistance of binary Mg-Y alloys with the concentration > 2%	38, 46, 49, 61, 93, 113, 154, 158-161

*%: wt%, unless specified otherwise

4.1 Effect of Al on corrosion behaviors of Mg alloys

Al is the most commonly used alloying element of Mg alloys in modifying the mechanical properties and corrosion resistance [23, 24, 32, 101]. The addition of Al leads to significant grain refinement. Adding small amounts of Al (1- 5 %) results in a transition to equiaxed grains and a significant reduction in grain size. Increasing Al content to above 5 % does not further affect the grain size [102]. In general, Al is partly dissolved in the Mg solid solution and partly precipitated as the second phase of $Mg_{17}Al_{12}$ along grain boundaries in a form of a continuous network [103] or lamellar growth [75]. The as-cast Mg-Al alloy exhibits α-Mg matrix and β phase mainly consisting of $Mg_{17}Al_{12}$ phase and eutectic Mg phase along the dendrite boundaries. With the decreased temperature from eutectic point, the eutectic α phase has a tendency to transform into a lamellar α+β microstructure. Cao et al. [104] found that the yield strength of as-cast Mg-Al alloys is mainly determined by the grain size and the dendrite arm spacing. The $Mg_{17}Al_{12}$ phases increase with increasing Al content, and show a net-shaped distribution when the content of Al is above 3 %, resulting an increase in the yield strength of the Mg alloy. During a tensile test, the $Mg_{17}Al_{12}$ phase will be broken before any plastic deformation can occur. A typical AZ91D alloy consists of an Mg matrix (α phase) with a large fraction of the segregating second phase $Mg_{17}Al_{12}$ (β phase) along grain boundaries [105]. These phases have different electrode potentials. When they make contact in an electrolyte, the $Mg_{17}Al_{12}$ phase exhibits a passive behavior, acting as the cathode with respect to the α-phase of the Mg matrix, which accelerates the corrosion of the Mg alloy. However, due to the inert behavior, the $Mg_{17}Al_{12}$ phase itself acts as a corrosion barrier, reducing the corrosion of the AZ91D alloys [103, 106-109]. Song et al. [97] investigated the corrosion behavior of both the α phase and the β phase in the AZ91 alloy. They suggested that if the β phase possesses the higher fraction volume and is distributed as a network along the grain boundaries, it might act as the barrier surrounding the α-Mg matrix, thus reducing the corrosion of the Mg alloy. Once the network of the β phases breaks down after a deformation process, or is destroyed and distributed discontinuously in the Mg matrix, the action as a barrier is undermined, resulting in accelerated corrosion [103, 109].

4.2 Effect of Ca on corrosion behaviors of Mg alloys

Ca is essential for living organisms and is a major component in human bone, presenting in the form of hydroxyapatite (HA). In particular, it has a low density 1.55 g cm^{-3}, which gives the Mg-Ca alloy an advantage because of its similar density to bone [59]. Ca shows great grain refining effect on Mg alloys. The grain size reaches a stable level with the addition of 0.5 % Ca, and decreases slightly with any further addition of Ca [61]. As a result of these characteristics, Ca has been introduced to Mg alloys in the expectation that the mechanical properties, corrosion resistance and biocompatibility of the Mg alloys will be improved [58, 59, 61]. Li et al. [61] investigated the binary Mg-Ca alloys with various Ca concentrations ranging from 0.5 to 20 % for biomedical applications. An increase in the Ca addition resulted in a high content of the second phase of Mg_2Ca, distributed along the grain boundaries. The second phase of Mg_2Ca is brittle and as a result, the ductility of Mg-Ca alloys deteriorates with increasing Ca concentration. The Mg-Ca alloy exhibited a limited ultimate strain under a compression of 1.7 % with the addition of 20 % Ca. The increasing volume fraction of the second phase significantly influences the corrosion behavior of Mg alloys. A high volume fraction of the second phase of Mg_2Ca causes the corrosion resistance of the Mg-Ca alloy to be depraved due to the formation of micro-galvanic cells [110]. It can be concluded that the addition of excessive Ca accelerates the corrosion of Mg-Ca alloys, and that the optimum concentration of Ca should be $\leq$ 1.0 % [59, 61]. It also indicated that a mixture of $Mg(OH)_2$ and an HA protective layer precipitated on the surface could inhibit further corrosion of the Mg-Ca alloys [59].

4.3 Effect of Li, Mn and Zn on corrosion behaviors of Mg alloys

Mg-Li alloys are remarkably malleable and ultralight due to the alloying element of Li, which is the lightest metal [111]. According to the Mg-Li phase diagram, a large content of Li can be alloyed into Mg [13, 101]. Li can react with Mg to form Mg-Li phases, which enhance the deformability of binary Mg-Li alloys. Li possesses higher activity than Mg, and it has pronounced influence on the corrosion resistance. Li concentration in pure Mg below 9 % is beneficial to the corrosion resistance; however, with the increasing Li addition, it significantly accelerated corrosion rate which is detrimental to the corrosion resistance of Mg alloys [112-114]. Thus, by means of the excellent enhancement of corrosion resistance of Al and some REEs, Li is usually used in combination with Al [86] and REEs [34] in order to minimize the deterioration effect on the corrosion of Li.

Mn is a widely used alloying element in Mg alloys (see Table 1). The grain size of the Mg-Al-Mn alloy decreases with increasing Mn. When Mn additions reach 0.4 % or more, the grain size remains constant [13]. It has been reported that the addition of Mn in Mg alloys can refine the grain size, improve the tensile strength and enhance the fatigue life of extruded AZ61 [115], AZ31[116] and AZ21[117] alloys. Mn does not react with Mg, but Mn-based intermetallic particles can be formed when there is a high Mn content in Mg alloys, thus influencing the fatigue properties, as the nucleation of fatigue attack occurs easily at microstructural inhomogeneities [118]. Song et al. [97] suggested that Mn itself does not improve the corrosion resistance, although it is usually added to some Mg alloys, especially for the AZ series alloys. The role of the Mn addition in the AZ series alloys is considered to be the transformation of iron (Fe) and other impurities into harmless intermetallic compounds. However, a high concentration of Mn causes deterioration in the corrosion resistance of Mg-Al alloys because the formation of a large amount of Mn-containing intermetallic in Mn-Al phases. The produced intermetallic accelerates the corrosion of the Mg matrix due to the galvanic effects. Gu et al. [5] studied the corrosion behavior of binary Mg-Mn alloys in SBF and Hank’s solution using hydrogen evolution and potentiodynamic polarization. Nam et al. [119] investigated the corrosion behavior of Mg-5Al-xMn alloys with various amounts of Mn. Both studies suggested that 1 % of Mn addition is beneficial as it enhances the corrosion resistance of Mg-Mn alloys.

Similar to Mn, Zn can also transform impurities such as Fe and Ni, affecting the corrosion of Mg alloys into harmless intermetallic compounds [97]. There has been considerable research into the corrosion of Mg-Al-Zn alloys, and it has been found that the addition of Zn is associated with the formation of second phases and grain refinement, thus influencing the mechanical properties and corrosion behavior of Mg alloys [36, 95, 96, 120, 121]. Yin et al. [122] found that when the Zn content reaches 3 % in Mg-Zn-Mn alloys, a second phase of Mg-Zn intermetallic compound will precipitate from the Mg matrix, which improves the strength through a dispersion strengthening mechanism. However, the elongation decreases due to the increased dislocation density and substructure. Zn has also been used in various ternary Mg-Zn-X (X: Ca, Si, Zr) alloys [45, 47, 123]. These studies showed that the corrosion resistance of Mg alloys will be enhanced by the addition of Zn. There is also an opinion that excessive Zn addition is detrimental to the corrosion resistance of Mg alloys. Song et al. [96] investigated the effects of the addition of Zn on the corrosion behavior of Mg alloys in a 3.5 % NaCl solution. They found that the micro-galvanic effect played the dominating role in the corrosion of Mg-Zn alloys. The volume fractions of Mg-Zn second phases increased with the addition of excessive Zn. The high volume fraction of the Mg-Zn phases acted as cathodes, accelerating the corrosion of the α Mg matrix around the Mg-Zn phases. The optimal content of Zn in Mg alloys should be less than 5.0 % based on their studies [96]. These investigations suggested the actual effects of Zn additions on the corrosion resistance depends on the composition of Mg alloys. Different Zn-containing phases may formed in Mg alloys with multiple elements additions, leading to the varied influence on the corrosion.

4.4 Effect of Zr and Sr on corrosion behaviors of Mg alloys

Although Zr has a relatively low solubility in Mg matrix, it can significantly inhibit the growth of crystal grain in solidification because the undissolved Zr particles act as the nucleation sites during solidification, leading to extremely fine-equiaxed grains with a distinct hexagonal shape [102]. Zr itself has excellent corrosion resistance to alkalis, acids, salt water and other agents, and it has been utilized as an alloying element in Mg alloys combined with other popular alloying elements such as Zn to refine grain size and enhance the corrosion resistance [53, 124]. Another unique property of Zr, making it attractive, is the protective effect of its oxide film [125]. The films formed on binary Mg-Zr alloys after immersion in a borate buffer solution are composed of Zr-Mg double oxyhydroxide enriched with Zr cations. This Zr-Mg double oxyhydroxide acts as a barrier to inhibit the corrosion of Mg-Zr alloys.

Sr does not show an obvious grain refining effect of the Mg-xZr-ySr alloys (x, y $\leq$ 5 %), but it significantly enhance the osteoblastic activity and bone formation in vivo [56]. As such, Sr has been considered as a promising biocompatible alloying element of Mg alloys [56, 72-74]. Li et al. [56] comprehensively investigated the Mg-Zr-Sr alloys for biomedical applications both in vitro and in vivo. They demonstrated that the addition of excessive Sr (> 2 %) in Mg-Zr-Sr alloys resulted in rough boundaries distributed by a fine $Mg_{17}Sr_2$ second phase. This $Mg_{17}Sr_2$ phase may cause galvanic effects in the Mg-Zr-Sr alloys, leading to accelerated corrosion of the Mg matrix. Nam et al. [75] studied the combined effects of Sr and Al on the corrosion behavior of Mg alloys with various Sr contents. Their results indicated that the addition of Sr to a base material of Mg-5Al alloy had a significant influence on grain boundaries, corrosion resistance and surface film. The formation of the $Mg_{17}Al_{12}$ phase at the grain boundaries was inhibited by the precipitation of Mg-Sr and Al-Sr phases; and the Sr addition was beneficial to the formation of an $Al(OH)_3$ protective film on the surface of the Mg alloy. Bornapour et al. [74] found that a Sr-HA layer, formed on the surface of the binary Mg-Sr alloy after immersion in SBF, enhanced the corrosion resistance. Li et al. [56] demonstrated that the Sr addition should be 2 % or less, which ensures a significantly reduced corrosion rate of the Mg-Zr-Sr and Mg-Sr alloys.

4.5 Effects of rare earth elements (REEs) on corrosion behaviors of Mg alloys

REEs are originally isolated as oxides from rare minerals, defined as a group of seventeen chemical elements in the periodic table, especially the fifteen lanthanides with scandium (Sc) and yttrium (Y) as they tend to deposit in the lanthanides and show similar chemical features [126]. In recent studies, some REEs in Mg alloying elements showed encouraging functions, such as enhancing corrosion resistance, and improving the mechanical properties and electrochemical behavior as a result of the grain refinement and formation of second phases [34, 86, 127-130].

The addition of Ce is generally believed to have a beneficial effect on the corrosion of Mg alloys [113, 131, 132], particularly for commercial Mg-Zn-Zr alloys (ZK alloys) [133] and Mg-Al-Zn (AZ) alloys [134-136]. In the case of ZK alloys, $Mg_{12}Ce$ and $Mg_{17}Ce_2$ phases precipitate distribute along grain boundaries, and thus decrease the grain size effectively. In Mg-Al-Ce alloys, Ce particles aggregate at the interface of solid-liquid during solidification, leading to a reduction in the atomic diffusion rate. As such, the growth of Mg matrix grains is inhibited. During solidification, Al-Ce phases formed and distributed along grain boundaries, and they can block the boundaries sliding effectively during deformation. The Al-Ce particles also show pronounced effects on the corrosion of Mg-Al-Ce alloys. When the alloy contains a high Ce content, $Al_{11}Ce_3$ acicular particles act as a micro-galvanic cathode relative to the Mg matrix, and form a network surrounding the Mg matrix, and thus, delays the corrosion of Mg alloys. In this micro-galvanic system, the potential difference between the Al-Ce phase and Mg matrix is relatively small, and the Al-Ce phase shows passivation in a wide range of pH, which further retards the corrosion of Mg alloys. Liu et al. [137] also suggested that the decreased corrosion rate of Mg alloys with the Ce addition may be due to the suppressive micro-galvanic corrosion in AZ91Ce alloys.

Similar to other REEs, erbium (Er) has also been used in Mg alloys to enhance the corrosion resistance and mechanical properties [138-141]. According to the binary Mg-Er phase diagram, the equilibrium solid solubility of Er in the Mg matrix is 17.24 at% at the eutectic temperature [113]. Er can be dissolved in Mg during the solidification process, which reduces the axial ratio. The reduction of the axial ratio contributes to the diversification of the deformation modes in Mg-Er alloys, and thus improves the elongation. Wang et al. found that Er had an excellent grain refinement effect for Mg-Zn-Zr (ZK) alloys because the formation of Mg-Zn-Er phase distributed along grain boundaries which also enhanced the strength [142]. Rosalbino et al. [143, 144] suggested that the presence of Er combined with Al is an effective method to improve the corrosion resistance of Mg alloys because of its excellent synergistic effect. Er shows relatively high chemical activity with the formation of two types of Mg-Al-Er phases ($Mg_{95}Al_3Er_2$ and $Mg_{95}Al_2Er_3$) in Mg-Al-Er alloys, and these phases surround the Mg matrix, inhibiting the corrosion of Mg alloys due to the enhanced passivation [144]. It also has been maintained that the enhanced corrosion resistance of Mg-Al-Er alloys may be ascribed to the incorporation of Er solute in the hexagonal $Mg(OH)_2$ lattice by the substitution of Mg cation, leading to an increase in the volume ratio of Er in Mg alloys, which reduces the potential cleavage and avoids ionic diffusion paths [143].

Gd has been widely used in Mg alloys such as AM-Gd and AZ-Gd [145], Mg-Y-Gd [146], Mg-Sn-Ca [147], Mg-Zn-Gd [148] and Mg-Ho [149]alloys. The high solid solution of Gd in Mg matrix plays an important role in the strengthening of Mg alloys. The atoms of the Gd element can replace Mg atoms to form a random substitutional solid solution, and thus generate stresses [113]. These stresses block the slip plane, and thereby improve the yield strength [150]. Hort et al. [151] reported that Gd has a pronounced influence on the corrosion resistance of Mg alloys. They suggested the second phase of Mg_5Gd in Mg-Gd alloys are nobler compared to the matrix and that a high volume fraction of Mg_5Gd phases would accelerate the dissolution of the Mg matrix. However, when the Gd content remains below 10 %, some Mg_5Gd phases dissolve into the matrix, leading to an enhancement in the corrosion resistance, and the galvanic effects rapidly fade away [151]. Chang et al. [128] investigated the corrosion behavior of Mg-xGd-3Y-0.4Zr alloys (x = 6, 8, 10 and 12 %) in peak-aged condition and found that the corrosion resistance decreased as the addition of Gd increased from 6 to 10 %, then increased as the Gd addition increased from 10 to 12 %. They further suggested that the corrosion of Mg-xGd-3Y-0.4Zr alloys was affected by the second phase and corrosion products on the surface. The high volume fraction of the second phase of Mg_5Gd in the Mg alloys acts as the barrier to inhibit corrosion, a function similar to that of the second phase of $Mg_{17}Al_{12}$ in AZ alloys. The corrosion mechanism of Gd-containing Mg alloys is still not well understood, although it is clear that the addition of Gd significantly affects the corrosion behavior of Mg alloys. In practical applications, the composition design and method of manufacturing Mg-Gd alloys should be taken into consideration when adding Gd.

At present, lanthanum (La) is an abundant rare earth element. It has been considered as a substitute for other precious REEs such as praseodymium (Pr) and neodymium (Nd). La has an excellent effect in the strengthening and enhancing creep resistance due to the ability to form solid solutions in Mg and their decomposition with precipitation of the La-rich disperse phase [113], and have been widely used in AZ alloys [152]. Zhang et al. [153] found that Mg alloys with Al and La additions consisted of various phases such as $Al_{11}La_3$ and Al_2La, depending on the concentrations of alloying elements. Both $Al_{11}La_3$ and Al_2La phases were distributed along the grain boundaries and these phases occupied a large area of the grain boundary, simultaneously blocking grain boundary sliding and dislocation motion in the vicinity of the grain boundary, and thus leading to the improvement of the tensile property of Mg-Al-La alloys. Yamasaki et al. [154] reported a nano-scale $Mg_{17}La_2$ phase that formed in Mg-Zn-La alloys. The phase dispersed in the Mg matrix homogeneously during in solidification, which resulted in a fine microstructure, leading to uniform and mild corrosion of the Mg alloys. Furthermore, La containing Mg alloys always had a protective layer containing $Mg(OH)_2$ and La oxide, which enhanced the corrosion resistance [153, 154].

Similar to Ce, Nd has been widely used in Mg-Zn-Zr based alloys and Mg-Al based alloys to improve the corrosion resistance and mechanical properties. Wu et al. [133] indicated that the second phases of $Mg_{12}Nd$ and $Mg_{41}Nd_5$ formed and isolated the Mg matrix, resulting in the reduction in grain size and enhanced the tensile strength of Mg alloys. It has been reported that the addition of Nd from 1 to 6 % in Mg-Al alloys further reduced grain size, and enhanced the tensile properties and corrosion [155]. In Mg-Al-Nd alloys, Nd can suppress the formation of the $Mg_{17}Al_{12}$ phase, and large amounts of thermally stable Al_2Nd and $Al_{11}Nd_3$ formed along grain boundaries thus effectively block the sliding. Moreover, the difference in atomic radius between Mg and Nd is relatively large and, therefore, Nd atoms can replace the positions of Mg atoms, resulting in a further obstacle to dislocation movement. Liu et al. [156] investigated the effects of the addition of Nd on the corrosion behavior of Mg-5Al-0.4Mn-xNd (x = 0, 1, 2 and 4 %) alloys in NaCl solution. In this study, Mg-5Al-0.4Mn-1Nd and Mg-5Al-0.4Mn-2Nd alloys exhibited better corrosion resistance, compared to the alloy (Mg-5Al-0.4Mn-4Nd) containing a higher level of Nd. The better corrosion resistance was attributed to the intermetallic precipitates with Nd, which behave as less noble cathodes in the micro-galvanic corrosion and suppress the cathodic process. They also indicated that a protective layer composed of Al_2O_3 and Nd_2O_3 at Mg-5Al-0.4Mn-1Nd in the proper ratio formed on the surface acts as an excellent barrier to corrosion, and enhances the corrosion resistance of Mg-5Al-0.4Mn-xNd (x = 1 and 2 %) [156]. It can be seen that the corrosion in Mg alloys containing Nd is significantly affected by the second phases along the grain boundaries. However, Zhang et al. [155] investigated the effects of Nd on the microstructure, mechanical properties and corrosion behavior of a die-cast Mg-4Al-0.4Mn-xNd (x = 0, 1, 2, 4 and 6 %) and their conclusions were different to those above. Their results indicated that the Nd significantly refined the grain size and substantially enhanced both the tensile properties and corrosion resistance, and that the alloy with the addition of 6 % Nd exhibited the best tensile properties and corrosion behavior.

Yttrium (Y) is a particularly interesting alloying element for Mg alloys because it has the same electrochemical potential -2.372 V with Mg. Y exhibits a hexagonal close packed (hcp) lattice, the same crystal structure as Mg, as well as very close lattice parameters and an atomic radius with Mg ($a_{Mg} = 0.323 \times 10^{-9}$ m, $c_{Mg} = 0.520 \times 10^{-9}$ m, $a_{Y} = 0.365 \times 10^{-9}$ m and $c_Y = 0.573 \times 10^{-9}$ m; $R_Y = 1.82 \times 10^{-10}$ m and R_{Mg} = 1.:6x 10^{-10} m) [157]. Thus it can always act as the nuclei of Mg-Y alloys during the solidification, resulting in substantial grain refining [154, 158], and therefore enhances the tensile strength [159, 160]. Zhang et al. [158] investigated the corrosion behaviors of the binary Mg-xY (x = 0.25, 2.5, 5, 8 and 15 %) alloys and found that the effect of Y on the corrosion of the Mg-Y alloys altered with concentrations of the Y addition. The corrosion resistance was improved as more Y was added, providing the Y content was below 2.5 % in Mg-xY (x = 0.25 and 2.5 %). The corrosion modes altered to pitting corrosion with any further increase in Y due to the discontinuous distribution of the $Mg_{24}Y_5$ phases along the grain boundaries in Mg-xY (x = 5 and 8 %). These $Mg_{24}Y_5$ phases caused galvanic effects. By further increasing the Y content to 15 %, a continuous network of $Mg_{24}Y_5$ phases formed along the grain boundaries, resulting in improved corrosion resistance in Mg15Y. However, Li et al. [61] compared the corrosion resistance of Mg-1Ca and Mg-1Ca-1Y alloys and indicated that the latter Y contained Mg alloy exhibited a higher corrosion rate. Liu et al. [93] studied the corrosion behavior of binary Mg-xY (x= 2, 3, 4, 5, 5.5, 6 and 7 %) alloys in 0.1 M NaCl and 0.1 M

Na_2SO_4 and found that the Mg-Y alloys showed significantly different corrosion behavior. In 0.1 M NaCl, the Cl^- gradually deteriorated the surface layer, and the matrix was easily exposed to the NaCl solution. The intermetallic containing increased Y deteriorated the corrosion resistance of Mg alloys due to the accelerated micro-galvanic. While the corrosion rate decreased when the Y content increased over 3 %, this could be attributed to a Y-containing protective surface layer. Hänzi et al. [161] attempted different types of heat treatments on an Mg-Y-RE alloy (WE43: Y content 3.7 - 4.3 %) to create different surface conditions and investigated the influence of different surfaces on the in vitro degradation behavior of the Mg alloy. They suggested that a solution of heat-treated WE43 showed improved degradation resistance as reflected by the comparably low maximal degradation rate. On the other hand, oxidized WE43 showed a decreased initial degradation rate that was ascribed to the protective effect of the surface film consisting of oxides of MgO and Y_2O_3. Once the surface film was penetrated or removed, degradation accelerated until the deposition of corrosion products slowed further degradation.

The properties of Mg alloys alloyed with various elements including some frequently used elements and rare earth elements at large quantities or traces of addition were extensively studied. The addition of the alloying elements affects the microstructures; therefore influence the mechanical properties and corrosion behavior of Mg alloys. Alloying elements such as Li and Y change the density and grain boundaries due to the formation of secondary phases. It has been demonstrated that some alloying elements such as Zr and Ca can improve the corrosion resistance; however there is always an optimal concentration of alloying elements in Mg alloys. Exceeded addition of these alloying elements inevitably leads to negative effects. Rare earth elements resulted in the formation of Mg-REEs phases or Mg-REEs based phases. It has been found that many different phases such as Mg_{12}REEs, Mg_3REES or Mg_2REEs may form under certain conditions in the process of fabrication [13]. Therefore, it is important to identify which of these phases formed in each of the Mg-REEs based alloys because they will contribute significantly to the alloy properties. Additionally, there are some concerns with the additions of rare earth elements. Due to the similar chemical properties and high processing cost, a specific rare earth element is difficult to purify. When rare earth elements are added to Mg alloys, it is assumed that they behave in the same way and all rare earth elements are denoted the symbol REEs [162]. In some studies, the investigated REEs may contain more than one component. This is not ideal in the case when one of REEs is the major alloying element in Mg alloys. Furthermore, most studies on the influence of REEs on the corrosion of Mg alloys were based on Mg-Al or Mg-Zn-Zr series of Mg alloys, and there is insufficient data concerning the electrochemical and corrosion properties of binary Mg-REEs alloy [163]. Further research on binary and tertiary Mg-REEs alloys is needed to identify the optimal Mg alloy compositions that meet the mechanical and biological requirements.

Based on these studies, it can be summarized that the effects of the addition of various alloying elements on the corrosion mechanism of Mg alloys depend on factors that include the grain size, the matrix with different solid solutions, the surface layer and the second phases that may cause micro-galvanic effects (discontinuous along grain boundaries) or act as a barrier inhibiting corrosion (continuous network along grain boundaries). The concentration of the alloying elements also significantly influences the corrosion of Mg alloys because it affects the volume fraction and distribution of the second phases.

5. Concern of biocompatibility in alloying of Mg

An orthopedic Mg implant is any matter, structure, or surface that interacts with biological tissues, and it should possess biomechanical compatibility with natural bone, an appropriate corrosion rate (i.e. degrading rate) to maintain mechanical integrity during healing and excellent biocompatibility making it harmless to host tissues. After implantation, the Mg alloy implant would directly contact the organics or tissues. The degradation of Mg alloys in vivo is a reaction between metals and a physiological environment such as proteins, cations and anions. In many cases, the biocompatibility of Mg alloys is determined by the alloying elements. Therefore, it is vital to select the Mg alloying elements that are essential for the human body. It has been known that approximately 96 % of the human body is comprised of oxygen, carbon, hydrogen and nitrogen, which present in the form of water and proteins [164]. The remaining mass of the body (approximately 4 %) largely exists either in the bone and tooth as minerals (Ca, Mg and P) or in the body fluid and blood as electrolytes (Na, K and Cl), which are considered to be macroelements [165]. In addition, there are some elements such as barium, beryllium, boron, cesium, chromium, cobalt, copper, iodine, iron, lithium, molybdenum, nickel, selenium, strontium, tungsten and zinc, which exit in the human body in low concentrations. These elements are referred to as trace elements [164], [166]. Among these, Ca, Li, Sr and Zn have been utilized as the alloying elements for biodegradable Mg alloys.

In this section the biological performance of Mg alloys with these elements and containing the other commonly used alloying elements such as Al, Mn and Zr, and REEs for biodegradable Mg alloy implant materials are investigated based on abundant literature in order to provide fundamental information for the early stage of implant development, especially for the selection of alloying elements. An ideal Mg implant material must be non-toxic and not cause any inflammatory and immunogenic responses. The Mg alloys should have minimal deleterious effects and these should be short term as much as possible. However, in the actual applications process, this ideality is not always attained, and Mg alloys should have minimal deleterious effects and these should be short term as much as possible. As a result, it is crucial to ensure that the composition of Mg alloys does not impose a significant hazard to the human body.

5.1. The effect of commonly used alloying elements

Although Al is the most widely used element for Mg alloys such as AZ21, AZ91D and AZ31, due to its excellent effects on the refining of the microstructure and enhancement of the corrosion resistance, medical research has found that an accumulation of Al in the brain may harm intelligence and cause neuropathologically relevant issues [167]. It is also a risk ingredient for the development of Alzheimer's disease [168]. Al accumulation in tissues increases with age, and there is more aggregation of β-amyloid peptide formed with the increment of Al concentration, which is a factor leading to the formation of pathologic lesions in Alzheimer's disease [167]. Furthermore, Al has a significant impact on immunology, and vaccines containing Al may lead to lymphocytes and inconspicuous muscle fiber damage [169]. The total body burden of Al in healthy adults is 30-50 mg and the safe dose of Al containing medications can take a much larger amount of Al than in the diet, possibly as high as 12-71 mg kg^{-1} day^{-1} [170]. Adverse effects may be seen if the dose is exceeded in humans [33].

Ca is the most abundant element in the human body, occurring in the form of Ca^{2+}, presenting in the mineral HA in the skeleton [171]. Thus, Mg alloys with the addition of Ca have attracted much attention for biomedical applications. Mg-Ca alloys with a Ca content of less than 1.2 % have excellent biocompatibility, as reflected by results showing that incubation of dendritic cells with the degradation media of the Mg alloys over 6 days had no influence on cell viability [65]. Jung et al. [66] reported that needle-type calcium phosphates similar to HA formed at the interface of Ca-containing implants and biological tissue, providing a progressive biological environment for bone mineralization. Ca also plays an important role in bone disease and soft tissue calcification [172]. In general, Ca has a level of 0.919-0.993 mg L^{-1} in normal blood serum [173, 174]. The recommended Ca dietary allowance for adults is approximately 1000 mg day^{-1} [175]. A disturbance of Ca cation in the human body may lead to severe pathological conditions, such as hypercalcemia and hypocalcemia [171, 176]. Furthermore, vascular calcifications, caused by an excess of calcium and phosphate absorption, are the major factors of cardiovascular disease associated with kidney disease [177, 178]. Another concern of Mg-Ca alloys is formation of an insoluble corrosion product on the surface. Kirkland et al. suggested that the insoluble "chalk like" product that could be problematic in the human body if large amounts are formed[179].

Since Li was discovered, it has attracted a great deal of attention, due to its potential toxicity [180]. Li has numerous effects in humans and in other organisms as it inhibits the functioning of multiple enzymes in the body [181]. James et al. [182] reported that Li was a teratogenic hazard to the cardiovascular system of the human body, as they found that when Li was given to mice and rats they could produce skeletal and craniofacial defects. Aral et al. [181] investigated the toxicity of Li to humans and found that doses of Li (10 mg L^{-1} in serum) in humans induced bipolar disorder, and at 20 mg L^{-1} Li in serum there is a risk of death. These studies further indicated that Li has specific toxicity presenting with several features: acute abnormalities from Li poisoning and chronic changes such as nephrogenic diabetes insipidus, epithelial cell disease, and chronic kidney disease.

Mn is an essential trace element for physiological processes, and it is a necessary element for the immune system and a variety of enzymes [183]. However, Mn toxicity such as cytotoxicity and neurotoxicity has also been reported [183-186]. Ding et al. [184] assessed the cytotoxicity of Mn on the sensory hair cells, auditory nerve fibers and spiral ganglion neurons in three rats isolated from birth. In this study, the sensory hair cells were vulnerable to Mn toxicity. Disservice was observed with Mn absorption as low as 10 micro molar. The preponderance of clinical and basic research concerning the toxic actions of Mn has primarily focused on central nervous system effects [184]. In a recent report, the abnormal verbal and visual memory functions of a 10 year old boy were aggravated with excessive exposure to well water containing modest level of Mn [187]. It was also found that the neurotoxicity also presented on the induction factor of a disease with the similar properties to Parkinson's disease [185]. Considering these findings for the toxicity of Mn, it would be wise to be cautious in the use Mn as the alloying element in Mg alloys for biomedical applications.

Zn is also a trace element in the human body and a co-factor for optional enzymes in bone and cartilage [188]. The U.S. Department of Health and Human Services recommended dietary allowance for Zn is 11 mg day^{-1} for men and 8 mg day^{-1} for women, so the corresponding burden of Zn is approximately 0.16 mg kg^{-1} day^{-1} for men and 0.13 mg kg^{-1} day^{-1} for women [189]. There have been many studies into the negative consequences of overdose Zn intake on growth, development and health [190-193]. The divalent metals can lead to neurological disorders [188, 194]. Zn cation acts as a mediated inhibition of neurotrophins, and can even lead to cell death [195], so Zn accumulation in human body may induce embryonic motor neuron death and affect mature motor neurons [195]. A normal Zn concentration maintains body health. However, if a large amount of Zn was implanted into a body in the form of an alloying element in Mg alloys, the toxicity could be seen as possibly impairing immune function [194]. Thus, the possible complications of using those alloys with a Zn addition must be known, and it is critical that the concentration of the alloying element addition in the Mg alloys be controlled.

Zr has been used in Mg alloys as an effective alloying element to improve corrosion resistance and grain refinement [36, 52]. A recent study on the biocompatibility of Mg-Zr-Sr alloys showed that Mg alloys with an addition of Zr up to 5 % exhibited excellent biocompatibility and no adverse effect was observed after implantation into rabbits [56]. The good biocompatibility of Zr in Mg alloys was supported by another study on the Mg-Zr-Ca alloys, which indicated that an Mg alloy with an addition of 1 % Zr and 1 % Ca exhibited promising compressive strength, good corrosion resistance and excellent biocompatibility[55, 57]. Yamamoto et al. [196] investigated the cytotoxicity evaluation of 43 metal salts including $ZrCl_4$ using murine fibroblasts and osteoblastic cells and found that Zr^{4+} had relatively low cytotoxicity. Although it was reported that high oral administration (2250 mg kg^{-1} day^{-1}) of an aqueous solution of Zr oxychloride to mice induced chromosomal abnormalities in bone marrow cells [197]. Delongeas et al. [198] revealed that Zr oxychloride did not influence the growth curve after repeated administration of a dose of 230 mg kg^{-1} day^{-1}, and Zr oxide has been found to be non-toxic in animal studies using mice and rats. These findings indicate that Zr is promising in alloying biodegradable Mg alloys but scrutiny is still vital since the biocompatibility of Zr depends on the applied dosage and Zr ions formed in the usage.

In order to develop new implants with improved biocompatibility, researchers have been pursuing more biocompatible elements to replace those traditional, less biocompatible alloying elements in Mg alloys such as Al, Zn and Mn etc. It has been reported that Sr can reanimate bone cells and benefit postmenopausal osteoporosis as it can increase bone formation [199-202]. Sr is a plant growth stimulant, possessing similar functions to Ca [199]. Sr has been introduced into Mg alloys for biomedical applications [56, 64, 72, 73] on account of these advantages. The biocompatibilities of binary Mg-Sr alloys with various amounts of Sr content were studied in vitro and in vivo [73, 74]. An Mg alloy with the addition of 2 % Sr showed promoted bone mineralization without inducing any significant adverse effects. Novel Mg-Zr-Sr alloys with improved corrosion resistance, mechanical properties and biocompatibility have been successfully manufactured and investigated in vivo and vitro [56]. The findings have indicated that the addition of Sr in Mg alloys leads to an improvement of in vivo biocompatibility, especially for the promotion of bone formation. Research conducted by Bornapour et al. [74] showed that a Sr-substitute HA layer, known to improve cell growth and tissue healing around bone implants, presented at the interface between the alloy matrix and the corrosion products, after implantation of the binary Mg-Sr alloys into a rabbit.

5.2. Rare earth elements (REEs)

Recent studies have illustrated that REEs in Mg alloys show many desirable advantages, such as improved corrosion resistance and electrochemical behavior, and enhanced mechanical properties [130, 203-205]. In most cases, standard Mg-REEs alloys contain more alloying elements than their designations [5, 206]. Almost any REEs-containing Mg alloy contains more than one trace REE, such as LAE (containing Li, Al and REEs) [34, 86] and WE (containing Y and other REEs) [11, 53, 207]. In vivo degradation directly links the alloying elements of Mg alloys to the released metal ions and the corrosion products. The effects of REEs on the biological behavior of Mg alloy are crucial in implant applications and should be investigated thoroughly. In this section, some widely used and promising REEs are discussed, as shown in Table 3, to provide a fundamental basis on which to choose alloying elements.

To date, REEs-containing Mg alloys are the most successful of the developed Mg alloys for biomedical applications. WE43, for example, has been successfully used in a biomedical application [35]. It is well known that alloying elements come into direct contact with cells and react with tissues after an Mg alloy is implanted in vivo. Whether an element is retained by the cells, or whether the element triggers a reaction, depends on the physical

Table 3 Biocompatibilities of some alloying elements used in Mg alloys.

Elements	**Description**	**Method**	**LD50 of salts**	**Biocompatibility**	**References**
Al	Harm to intelligence and causing neuropathological relevance; risk factor of the development of Alzheimer's disease; leading to the lymphocytes and inconspicuous muscle fiber damage	Oral	230 mg kg^{-1} (rats)	-	33, 168-170
Ca	Presence of Ca^{2+} in HA; essential element of human body; normal blood serum level 0.919-0.993 mg L^{-1}; metabolic disorder may induce the kidney stones and arthritis	Oral	1940 mg kg^{-1} (rats)	=	172, 174, 176, 178
Li	Lithium toxicity presenting with several features: acute abnormalities from lithium poisoning and chronic changes such as nephrogenic diabetes insipidus, epithelial cell disease, and chronic kidney disease	Oral	525 mg kg^{-1} (rats)	-	180-182
Mn	Essential trace element; neurotoxic; factor of a disease with the similar properties to Parkinson; toxic dosage 10 micromolar	Oral	1484 mg kg^{-1} (rats)	-	183-187
Zn	Essential trace element; optimally promotive factor of the recovery of acrodermatitis enteropathica; a co-factor for enzymes; normal blood serum level 0.81-1.137 mg L^{-1}; induce embryonic motor neuron death	Oral	186-623 mg kg^{-1} (mice and rats)	=	189, 190, 193, 195
Zr	Zr is biocompatible alloying element in MgZrSr and MgZrCa alloys. The Zr oxide is non-toxic in the animal studies using mouse and rats. However, Zr should be used with scrutiny depending on the applied dosage	Oral	990-2290 mg kg^{-1} (rats)	=	196-198
Sr	Promoting osteoblast maturation; maintaining bone formation; diminishing bone resorption; increasing bone trabecular volume	Oral	2900 mg kg^{-1} (mice)	+	200-202, 217
Ce	Significant disturbing the brain, lung, liver and kidney of mice although little Ce containing cerium absorption; high concentrations of Ce may damage DNA and apoptosis; Ce may form stable bonds with	Oral	500 mg kg^{-1} (mice)	-	69, 212, 220

	endomyocarial fibrosis				
Er	Er chlorides produced nodules with foreign body giant cells; Er is moderately to highly toxic including writhing, ataxia, labored respiration, walking on the toes with arched back and sedation	Oral	6200 mg kg^{-1} (rats)	-	222, 223
		Intravenous	535 mg kg^{-1} rats)		
Gd	Higher inflammatory responses on TNF-alpha, and led to the apoptosis of MG63 cells with high concentration; Gd accumulation in tissue is linked to nephrogenic systemic fibrosis and kidney failure; rats received Gd chloride showed liver damage; 1% Gd chloride caused perinuclear vacuolization of the parenchymal cells of the liver.	Oral	585 mg kg^{-1} (rats)	=	206, 224, 225
La	Increased blood eosinocyte, dreased body weight, casued eosinophil infiltration in the submucosa; chronic exposure to La could damage the learning ability attributed to the disturbance of the homeostasis of trace elements, enzymes and neurotransmitter systems in brain	Intravenous	150-625 mg kg^{-1} (mice)	-	70, 214, 219
Nd	Chronic exposure to Nd exhibited a depressant action and produced death by cardiovascular collapse coupled with respiratory paralysis; exhibited cytotoxic effects and induce apoptosis in certain cancer cells.	Intravenous	600 mg kg^{-1} (rats, mice)	-	71, 208, 219, 221
		Oral	2750 mg kg^{-1} (rats)		
Y	Increased blood eosinocyte, dreased body weight, casued eosinophil infiltration in the submucosa; distributed to plasma in the blood and led to acute hepatic injury with the dose 1mg kg^{-1} with 144 days on rats	Oral	350-500 mg kg^{-1} (rats)	-	215, 218, 226

*Positive influences (+), negative influences (-) and intermediate influences (=)

and chemical properties of the element [206] and the ionic size of alloying elements [208]. Thus, cell culture in vitro seems to be an effective experimental approach to determine the impacts produced by the alloying element. Feyerabend et al. [206] have comprehensively investigated the short-term effects on various cells of some REEs, including Y, Nd, Dy, Pr, Gd, La, Ce and Eu. They suggested that La and Ce showed the worst biocompatibility with the highest cytotoxicity on cells, whereas the highly soluble Dy and Gd seem to be more suitable. Nakamura et al. [208] suggested that REEs can be chemically classified into three groups on the principle of their ionic radii: (i) light REEs: La, Ce and Pr, (ii) medium REEs: Nd, Pm, Sm, Eu and Gd, and (iii) heavy REEs: Tb, Dy, Ho, Er, Tm and Yb. The light REEs, Ce and Pr, usually induce severe hepatotoxicity, including symptoms of fatty liver and jaundice; medium REEs are mainly distributed into the spleen and lungs [208]. Longerich et al. [209] investigated the effect of Y and Ce on the behavior of humans and reported that concentrations of Y and Ce in the drinking water of mothers with neural tube defect infants were higher than in the mothers of normal infants, indicating that the absorption of REES are dependent not only on the concentration but also the size of the elements. Basar et al. [210] investigated the biocompatibility of HA doped with Y^{3+} (2.5, 5 and 7.5 mol %) and F^- (2.5 mol %) ions based on the cellular response of the control group with pure HA and found that HA doped with 2.5 mol % Y^{3+} had the highest cell density compared with other Y-containing HA. The cell proliferation on 2.5 Y-HA was close to that of the control group. Loos et al. [211] investigated the biocompatibilities of an absorbable Mg stent with Y and some REEs additives in vivo and in vitro, and indicated that Mg alloys without Al but containing small amounts of Y and REEs would be appropriate for biomedical applications. These studies indicated that Y is a particularly disputed alloying element, and it is essential to further investigate the effect of an addition of Y in Mg alloys on biocompatibility.

Other studies on the toxicity of REEs, besides the cell culture, were predominantly performed on small animals by administering REEs-containing salts such as chloride REEs or nitrate REEs via intravenous injection, inhalation and orally [208, 212, 213]. Ogawa et al. [214-216] c conducted a series of studies on the short-term effects of elements La, Y and Eu on rats fed with hydrated chloride. By comparing the responses of these three REEs with different oral doses of 0, 40, 200 and 1000 mg kg^{-1} for 28 successive days, results indicated that the biological effects of Y were very similar to those of La except for the accumulating patterns and volumes, while Eu showed an obvious irritation effect as hyperkeratosis of the forestomach and eosinocyte infiltration of stomach submucosa were found in both males and females receiving a dose of 1000 mg kg^{-1} $EuCl_3$-$6H_2O$.

5.3. Classification of Mg alloying elements

Based on the characteristics of alloying elements that affect the microstructure, mechanical property, corrosion resistance, and biocompatibility of an Mg alloy, alloying elements such as Al, Ca, Mn, Zn, Zr, Sr and REEs can be classified into five categories:

(a) Bio-functional elements (Sr and Ca): Sr has been reported as an osteoinductive element [199, 201]. It triggers the formation of new osteoblasts and promotes rapid integration of the graft [217]. Furthermore, it is a biocompatible element that improves the mechanical properties and enhances the corrosion resistance of Mg alloys when the addition of Sr is ≤ 5 % [56].

Ca is the most abundant element in the human body, presenting in the form of mineral HA in the skeleton. However, the disturbance of Ca cation in the human body may lead to severe pathological conditions. Ca addition to Mg alloys should be limited to less than 1 % because higher Ca content in Mg alloys will form a large volume of the second phase of Mg_2Ca, which reduces the corrosion resistance of Mg alloys [59, 61].

(b) Biocompatible element (Zr): Zr is an effective alloying element to improve the corrosion resistance and grain refinement of Mg alloys. This is essential in order to decrease the degrading rate of Mg alloys in vivo. Recent studies have indicated that the addition of Zr to Mg alloys should be limited to less than 5 % [56].

(c) Essential trace elements (Mn and Zn): Mn and Zn are essential trace elements for the human body and they are usually used in Mg-Al alloys such as the AZ series. The crucial issue when using Mn and Zn as Mg alloying elements is concentration control. To date, there has been no systematic research to define the concentration limits of Mn and Zn in biodegradable Mg alloys. Further research is needed to identify the optimal concentrations of Mn and Zn in Mg alloys for the optimal combination of corrosion resistance, mechanical properties, biocompatibility and biodegradability that is acceptable for load-bearing implant applications.

(d) Toxic elements which should be avoid: Al, Li, Ce, Er, La, and Nd. Diseases could be caused by the accumulation of Al in the human body [89, 169, 218]. Li is toxic to humans. A dose of 10 mg L^{-1} Li in serum on humans could induce bipolar disorder, and with 20 mg L^{-1} Li in serum there is a risk of death [181]. La [206, 214] and Ce [206, 208, 219] showed a lower value of LD_{50}. Ce shows toxicological effects on human body, and tends to accumulate primarily in the bone, liver, heart and lung [220]. Nd has been classified as light REEs and exhibits similar toxicity to La and Ce [71, 208, 219, 221]. Although Er belongs to the group of large ionic radii, it is moderate to highly toxic, causing writhing, ataxia, labored respiration, walking on the toes with arched back, and sedation [222, 223].

(e) No consensus was reached on the biocompatibility of Gd and Y. Although Gd [206] and Y [210, 211] were considered as potential alloying elements in Mg alloys for biomedical applications, the toxicity of Gd appeared to be apparent as even 1 % Gd chloride caused perinuclear vacuolization of the parenchymal cells of the liver [224], and Gd may affect bone quality and health [225]. Y showed obvious toxicity due to the increased blood eosinocyte and caused eosinophil infiltration in the submucosa [215, 218, 226]. Further research is needed to clarify the effects of Gd and Y and their concentrations on the microstructure, mechanical properties, corrosion resistance and biocompatibility of Mg alloys.

The classification provides suggestions for the early stage of implant development and the selection of alloying elements. In reality, some of the alleged “toxic elements” alloying elements such as Li, La, Ce and Nd have been successfully applied in commercial Mg alloys for biomedical applications [35], and the perceived toxicity does not indicates that these elements are absolutely exclusive for biomedical applications. There is no absolutely harmful or beneficial substance, and even pure water can kill at a sufficiently high dose [227]. Thus the associated toxicity is determined by the dose of alloying elements. For instance, despite Sr being classified as a bio-functional element, excessive Sr addition in Mg alloys deteriorates the corrosion resistance, and impairs the biocompatibility.

6. Summary

To date, the majority of commercial Mg alloys have been designed for engineering, aerospace and military applications and they are not necessarily biocompatible and suitable for use as biodegradable implant materials. A new research direction lies in developing new Mg alloys, alloying with non-toxic elements that can simultaneously improve the corrosion resistance and mechanical properties and offer bio-functions such as osteoinductivity etc. This review mainly analysed the effect of conditional Mg alloying elements and REEs on the corrosion resistance and biocompatibility of Mg alloys for biomedical applications. Table 4 summarized the limitation of some of the potential alloying elements. Bio-functional element Sr has excellent biocompatibility and osteoinductivity, which triggers the formation of new osteoblasts and accelerates the healing of the graft. Furthermore, it improves the mechanical properties and enhances the corrosion resistance of Mg alloys when the addition of Sr is ≤ 5 %. Ca is the most abundant element in the human body, and exhibits significant functions in the growth and health of human bone. However, the disturbance of Ca cation in the human body may induce severe pathological consequences. The optimal Ca addition to Mg alloys should be limited to less than 1 %. The essential trace elements Mn and Zn exhibit adverse effects on biocompatibility, yet they can still achieve

Table 4 Recommended alloying elements for biodegradable Mg alloys in biomedical applications

Elements	Category	Characteristics and recommended concentration (wt.%, unless specified otherwise)
Ca	Biofunctional element	The most abundant element in human body presents in the form of HA in the skeleton. Achieving acceptable biocompatibility when Ca addition to Mg alloys is ≤ 1%
Sr		Excellent biocompatibility, excessive addition in Mg alloys accelerates the corrosion rate, ≤ 2% addition in Mg alloys improves corrosion resistance
Zr	Biocompatible element	Excellent grain refinement, biocompatible element; high content in Mg alloys may lead to toxic influence, achieving excellent biocompatibility with the addition of ≤ 5% Zr
Mn	Essential trace element	A high concentration of Mn deteriorates the corrosion of Mg alloys, and induces cytotoxicity and neurotoxicity. It should be cautious to use Mn for biomedical applications. The optimal content should be ≤ 1%
Zn		Excessive addition in Mg decreases the corrosion resistance significantly. Overdose Zn absorption leads to negative consequences. The optimal content should be ≤ 5% in Mg alloys
Gd	Possibly biocompatible element	Disputed effects on corrosion, it shows accepted biocompatibility with the addition of ≤ 1% to Mg
Y		No consensus on the corrosion and biocompatibility, Y-containing surface layer decreases the corrosion rate; however Y-containing second phase accelerates the micro-galvanic corrosion. The concentration 2.5 mol. % Y^{3+} doped on HA shows excellent biocompatibility

acceptable responses when the element is controlled. Zr is completely biocompatible, exhibits a great grain refining effect and improves the corrosion resistance of Mg alloys to a remarkable extent. However, the addition of Zr to Mg should be less than 5 %, because a higher content of Zr may lead to severely reduced corrosion resistance. Rare earth elements might be of benefit to the corrosion of Mg alloys but the concentrations should be strictly controlled. Specifically, Li, Ce, Er, La and Nd are toxic and should be excluded for Mg alloy implant materials. There is no consensus on the influence of Gd and Y on the corrosion. The performance of Gd on the corrosion of Mg alloys mainly depends on the content in the Mg alloys. As to Mg alloys containing Y, the corrosion is determined by the balance of the Y contained in the surface layer and the micro-galvanic effects between the Mg matrix and the second phase of $Mg_{24}Y_5$. The composition of Mg-Gd and Mg-Y alloys and their contents should be carefully considered.

7. Suggestion

From the aspect of corrosion mechanism, this review summarized the influence of the most commonly used alloying elements and REEs on the corrosion of Mg alloys based on an extensive survey of work accomplished over a period of 10 years. Though it has been known that some alloying elements are beneficial to the corrosion resistance, it is still a challenging to fully understand the corrosion mechanism of Mg alloys with complicated composition such as Mg-Y and Mg-Gd based alloys. In addition, the structure and phases distribution varies depending on the fabrication and post-treatment, such that Mg alloys with the same composition or selected from different parts of master alloys may show different corrosion behavior.

Yuen and Ip [227] summarized the toxicological information from the Agency for Toxic Substances and Disease Registry (ATSDR) of the US Department of Health and Human Services and the UK Food Standards Agency (FSA), and they recommended the threshold implant mass equation for biomedical implants with commonly used alloying elements such as Al, Mn and Zn. Nevertheless, for some elements such as Zr and REEs, this equation is not reliable due to the lack of sufficient information, despite of the great deal of work that has been carried out on the toxicity assessment of alloying elements. This review does not give the exactly accurate toxicity in quantitative analysis for these alloying elements described in section 5. However, it outlines that the negative impacts of these elements can exert on human body, and reminds researchers the relatively potential risks of common alloying elements and REEs in design of biodegradable Mg alloys. This topic is still open to debate. Which element is in favor of corrosion? What is the optimal concentration considering the biocompatibility? These questions impel further studies of such elements to be carried out in the future to ensure the safe usage of these elements in degradable Mg alloys.

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