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Effects of alloying elements on the corrosion behavior and biocompatibility of biodegradable magnesium alloys: a review

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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.

Received 9th December 2013
Accepted 21st January 2014

DOI: 10.1039/c3tb21746a

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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, excellent biocompatibility and 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.

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They degrade *in vivo* and are replaced by new bone tissue, which eliminates the need for 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 principal drawback of Mg alloys in biomedical applications is their rapid corrosion rate in an 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 investigation has been carried out on the composition design[6] and post-treatment[7,8] of biodegradable Mg alloys. In particular, the composition design provides a 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 the changes in the structure and phase distribution.[6] As a biodegradable material, the metallic ions released from Mg alloys must have minimal deleterious effects and it is preferred if they can also promote tissue healing and stimulate metabolism.[9,10] However, metallic ions in many cases are not perfectly biocompatible and affect tissue healing.[10,11] 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 dates 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 which have 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.

Currently, the Mg alloys considered for use as biodegradable implant materials are mainly existing commercial Mg alloys that were originally developed for their applications in the

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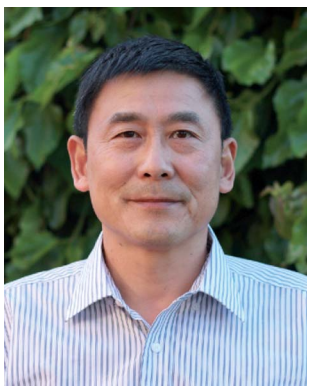

Dr Yuncang Li received his BSc degree from Peking University and PhD degree from Deakin University. Dr Li's research interest includes the development of metallic biomaterials, and amorphous and nanostructured materials. He is currently a senior research fellow at Deakin University working on titanium based shape memory alloys, biodegradable Mg alloys and surface modification of metallic biomaterials.

Table 1 Recent research of Mg alloys as biodegradable biomaterials

Mg alloys	Compositions[a]	*In vitro*/*in vivo* model	Ref.
AE21	2% Al, 1% REEs (Ce, Pr, Nd)	EIS in 0.1 M NaCl solution, stent in the coronary artery of pigs	18 and 19
		EIS in 0.1 M NaCl solution	20 and 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 sizes 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 and 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 and 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 and 92
ZK30	3% Zn, 0.6% Zr	Hank's solution, cytotoxicity by rabbit bone marrow stromal cells	36
		Cell 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)	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 cell 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 nude mice	39
MgZn	6% Zn	EIS, PPC and immersion tests in SBF, cytotoxicity by L929 cell culture, rabbits	40 and 41
	1% Zn	Human bone marrow stromal cell 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 cell culture/3 month old mice	73
	0.5–1.5% Sr	HUVEC cells/dog femoral artery	72

Table 1 (*Contd.*)

Mg alloys	Compositions[a]	*In vitro*/*in vivo* model	Ref.
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 cell culture, hemolysis test/rabbits	56

[a] Balance of Mg; %: wt%, unless specified otherwise; EIS: electrochemical impedance spectroscopy; PPC: potential polarization curve.

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, causes adverse reactions with body tissues.[33]

The effects 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, mechanical properties and biocompatibility *in vitro* and *in vivo* have been extensively investigated. However, when Zn and Mn are the principal alloying elements, they show high cytotoxicity, which leads to genotoxicity and suppression of 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 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 effects of Sr on bones, muscles and heart have been studied systemically,[79–81] and it 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]

Although 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 the 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 of -2.38 V_{nhe} of all engineering metals.[84] However, the actual corrosion potential of Mg varies depending upon other factors such as the environment and surface status. Song[16,23] found that the corrosion potential of Mg in dilute chloride solutions is usually -1.7 V_{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 always work in the particular environment of the human body. Fig. 1 presents a schematic illustration of a 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

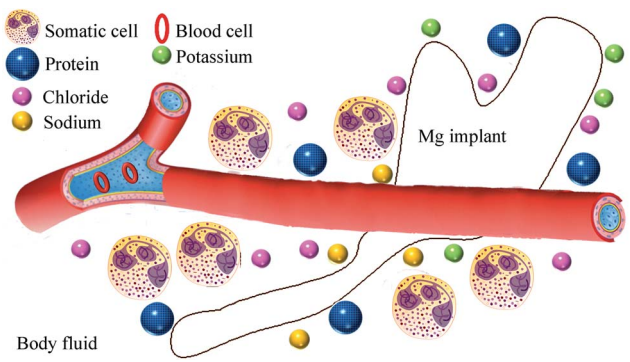

Fig. 1 Schematic illustration of a Mg implant in a physiological environment.

electrochemical corrosion measurements, biocompatibility assessments, hemolysis testing, *etc.*, in simulated body fluid (SBF) prior to *in vivo* tests, with the aim of providing basic information for biomedical applications.

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 addition of 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] Nevertheless, proteins contain 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 remains neutral; this value changes from 2.0 to 8.0 depending on the location in the human body and as a result of traumas such as injury, surgery, diseases, *etc.* In relation to experiments *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 a 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 of 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 the 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 the 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 a 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 films due to the mismatch between Mg oxide and the underlying Mg metal substrate. However, some studies also reported that the corrosion resistance deteriorates as the grain size decreases.[19,56,91,92] Minárik *et al.*[19] found that AE21 alloys with a smaller grain size showed 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 Fig. 2. In their study, the grain sizes of

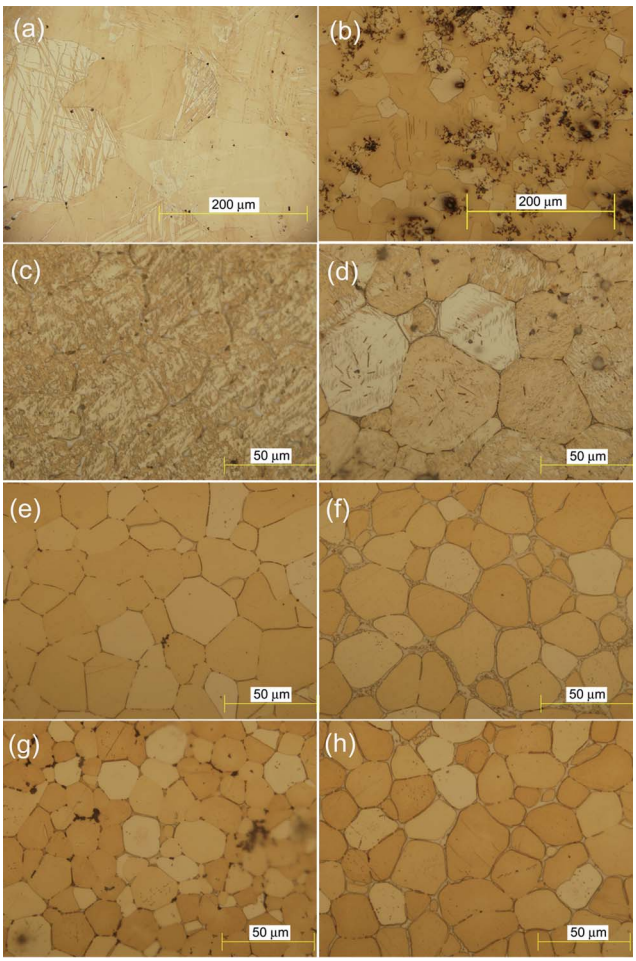

Fig. 2 Microstructures of Mg–Zr–Sr alloys: (a) Mg; (b) Mg–5Zr; (c) Mg–1Zr–2Sr; (d) Mg–1Zr–5Sr; (e) Mg–2Zr–2Sr; (f) Mg–2Zr–5Sr; (g) Mg–5Zr–2Sr; (h) Mg–5Zr–5Sr. Reproduced from data published in ref. 56.

Mg–*x*Zr–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 the corrosion of Mg alloys.

3.3 Secondary phase and galvanic corrosion

Mg is chemically reactive and can react with other alloying elements to form secondary 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 Fig. 2, the grain boundaries of Mg–2Zr–5Sr become rougher and broader with increasing Sr addition from 2 to 5%, which indicated that more secondary 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 the secondary phase which was determined by the concentration of the alloying elements in Mg alloys. Fig. 3 shows the volume fraction of secondary phases as a function of the addition of rare earth elements lanthanum (La), cerium (Ce) and neodymium (Nd) in Mg–REE alloys.[94] It can be seen that the volume percent of the secondary phases increased with the increasing concentrations of REE alloying elements. The volume fraction of the secondary phase of $Mg_{12}La$ was 30% with an addition of 5% La and that of Mg_3Nd was 10% with an addition of 3.5% Nd. The secondary phases exhibited a continuous network along the grain boundaries in alloys with a higher content of alloying elements, and they tended to be thermodynamically more stable than the Mg matrix, leading to an acceleration in the cathodic reaction and inhibition in the anodic reaction in the polarization test.

A high Zn content in alloys such as Mg–Zn alloys is associated with an appreciable amount of the secondary 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 the Mg_xZn_y phase and Mg matrix, thus accelerating the corrosion of the Mg matrix. A bio-corrosion model at the alloy–SBF interface was illustrated to show the influence of the secondary phase on the corrosion of Mg alloys, as shown in Fig. 4. When alloys were immersed in SBF, the surface was attacked by ions such as chloride, phosphate anion, *etc.* The internal secondary phase such as $Mg_{17}Sr_2$ and $Mg_{12}Ce$ acted as a cathode.[97] The degradation of the Mg matrix accelerated due to the coupled galvanic effects between the Mg matrix and secondary phase. Secondary phases in Mg alloys possess different electrochemical potentials. If the secondary phases have a higher positive potential than that of the Mg matrix, there will be many galvanic cells that

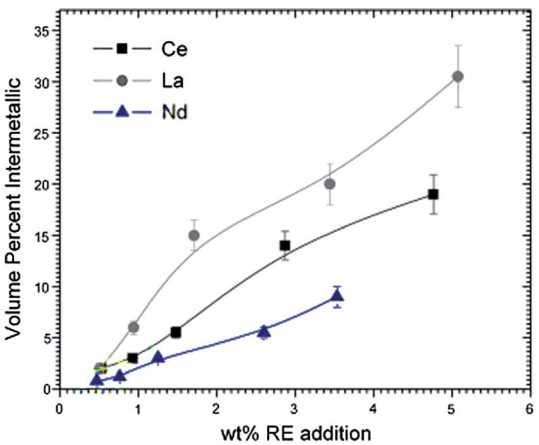

Fig. 3 Volume fraction of secondary phases with the addition of La, Ce and Nd in Mg–REEs alloys. Reproduced from data published in ref. 94.

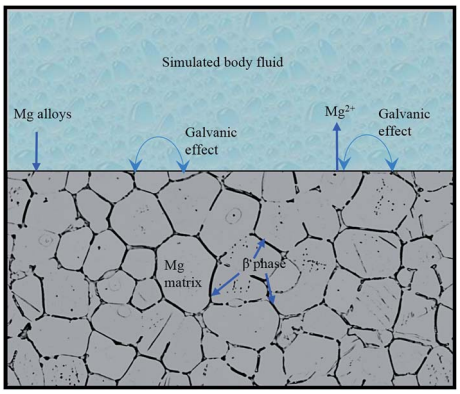

Fig. 4 Galvanic effect between the Mg matrix and secondary phase resulted in accelerated corrosion of Mg alloys.

further influence the corrosion behavior of Mg alloys. Furthermore, secondary phases may have a complicated influence on the corrosion of Mg alloys particularly for that of ternary alloys with addition of multiple elements 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 the 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 the $Mg_{17}Sr_2$ 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 secondary phases significantly affect the corrosion behavior of Mg alloys.

3.4 Surface layer

The corrosion of Mg alloys in an aqueous environment has been generally considered as an electrochemical reaction with water 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 protection 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. They 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 a Mg–Sr alloy after immersion in SBF for 3 days. This layer has been proved to improve the bioactivity 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 the partially protective layer on the surface of the alloy, which slows down the corrosion process.

4. Effects of alloying elements on the corrosion behavior of Mg alloys

The most common alloying elements of Mg alloys are Al, Ca, Li, 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 Gd and Y on the corrosion of Mg alloys are still not well understood and there are disputed conclusions regarding their influence on the corrosion behavior. Overall, further studies are needed to elucidate the effects of alloying elements on the properties of Mg alloys from the view of the corrosion mechanism in order to provide the comprehensive insight required to develop new Mg alloys alloyed with elements beneficial to corrosion resistance.

4.1 Effect of Al on the corrosion behavior of Mg alloys

Al is the most commonly used alloying element of Mg alloys for 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 the 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 secondary phase of $Mg_{17}Al_{12}$ along grain boundaries in the form of a continuous network[103] or lamellar growth.[75] The as-cast Mg–Al alloy exhibits an α-Mg matrix and a β phase mainly consisting of an $Mg_{17}Al_{12}$ phase and a eutectic Mg phase along the dendrite boundaries. When the temperature is decreased from the 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 in an increase in the yield strength of the Mg alloy. During the 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 secondary 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 a higher fraction volume and is distributed as a network along the grain boundaries, it might act as a 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 the corrosion behavior of Mg alloys

Ca is essential for living organisms and is a major component of the human bone, presenting in the form of hydroxyapatite (HA). In particular, it has a low density of 1.55 g cm^{-3}, which gives the Mg–Ca alloy an advantage because of its similar density to that of bone.[59] Ca shows a 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 Ca addition resulted in a high content of the secondary phase of Mg_2Ca, distributed along the grain boundaries. The secondary 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 secondary phase significantly influences the corrosion behavior of Mg alloys. A high volume fraction of the secondary phase of Mg_2Ca causes a decrease in the corrosion resistance of the Mg–Ca alloy 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 the corrosion behavior of Mg alloys

Mg–Li alloys are remarkably malleable and ultralight due to the alloying element 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 a pronounced influence on the corrosion resistance. Li concentration in pure Mg below 9% is beneficial to the corrosion resistance; however, increasing Li addition significantly accelerates the corrosion rate which is

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

Elements	Effects on the microstructure	Effects on mechanical properties	Effect on corrosion resistance	References
Al	Refinement of grain size; reaction with Mg to form the $Mg_{17}Al_{12}$ phase; high Al concentration leads to a network distribution of $Mg_{17}Al_{12}$ along grain boundaries	Enhances castability and hardness; increases yield strength at a concentration above 3%; significantly improves ultimate yield strength and ductility at a concentration below 6%	A network distribution of $Mg_{17}Al_{12}$ in Mg alloys enhances corrosion resistance; however, the coupled micro-galvanic effects between the $Mg_{17}Al_{12}$ phase and Mg matrix at the same time increase the corrosion rate	2, 18–32, 75, 91, 97 and 101–109
Ca	Reduction of the grain size with the addition of Ca below 15% in binary Mg–Ca alloys; formation of Mg–Ca phases distributed along the grain boundaries	Increases elasticity; compressive yield strength; ultimate strength and hardness with increasing Ca content less than 20%; increases the creep properties at a concentration less than 0.3%; deteriorates ductility at a concentration from 0.5 to 15%	Excessive addition of Ca in pure Mg deteriorates corrosion resistance; Ca concentration in Mg alloys should be less than 1%	45, 48, 54, 55, 58, 59, 61, 64–67, 101 and 110
Li	Slightly decreases the grain size; Mg–Li phases with a bcc structure distribute along grain boundaries	Increases deformability with high addition (>11%) by forming bcc structural phases; decreases the strength significantly	Enhances corrosion resistance at a concentration below 9% in pure Mg; accelerates the corrosion rate significantly with higher Li addition	13, 30, 34, 86, 101, 111, 112 and 114
Mn	Significant grain refining at low Mn concentration in Mg–Al based alloys; removes impurities by forming new phases with Fe and other heavy metals	Slightly increases the yield strength; decreases the ultimate yield strength and elongation for binary Mg–Mn alloys; the effect on mechanical properties is dependent on the composition of Mg alloys; rarely used in pure Mg	Enhances corrosion resistance by reducing impurities with a small quantity of Mn addition	5, 43–45, 68, 101 and 115–119
Zn	No obvious effect on grain refining with the addition below 5% for binary Mg–Zn alloys; reacts with Mg to form a secondary phase and distributes along grain boundaries; usually used with Al in Mg alloys	Enhances the tensile strength; excellent solid solution strengthening and aging strengthening; deteriorates castability at high concentrations; reduces the influences of Ni and Fe	Inhibits the harmful effects of Fe and Ni impurities on the corrosion; enhances the corrosion resistance of Mg alloys at a content below 5%	5, 40, 41, 43–48, 63, 68, 95, 96, 101 and 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 the stable Al–Zr phase that deteriorates the mechanical properties	Slightly increases the ultimate compressive strength with increasing Zn concentration; significantly enhances the ductility, elongation and ultimate yield strength of Mg alloys with a small amount of addition in binary Mg–Zr alloys; usually used with Zn in Mg alloys	Small amounts of Zr addition (less than 2%) enhances the corrosion resistance; otherwise significantly deteriorates the corrosion resistance	36, 52, 53, 56, 57, 101, 102, 124, 125 and 128
Sr	Refinement of grain size; leads to rough boundaries with excessive addition; reacts with Mg to form Mg–Sr phases that distribute along grain boundaries	Increases the tensile strength with the Sr addition below 2%; decreases ultimate strain and ultimate compressive strength due to the superabundant compounds in grain boundaries	The influence on corrosion depends on the fraction volume of $Mg_{17}Sr_2$ phases in Mg alloys, optimal content less 2%	56, 64, 72–75 and 130

Table 2 (*Contd.*)

Elements	Effects on the microstructure	Effects on mechanical properties	Effect on corrosion resistance	References
Ce	Excellent grain refining for pure Mg and AZ alloys; Mg–Ce phases isolate the Mg matrix and reduce the grain size; Al–Ce phases distribute along grain boundaries; excessive Ce addition to Mg leads to the formation of brittle Mg–Ce phases distributing along grain boundaries	Enhances tensile strength and tensile yield strength with the addition of Ce below 6% for binary Mg–Ce alloys; however tensile yield strength remains stable and tensile strength decreases with increasing addition of Ce after T6 treatment; deteriorates the elongation of Mg alloys with excessive addition of Ce; deteriorates creep resistance; enhances the tensile strength of AZ alloys with 1% Ce addition	Formation of the $Al_{11}Ce_3$ phase surrounding the Mg matrix in AZ alloys, suppressive galvanic effects and thus enhancement of corrosion resistance; however, increasing addition of Ce deteriorates the corrosion resistance of binary Mg–Ce alloys due to the galvanic effect	113, 127, 129–137, 140 and 143
Er	Exhibits low solubility in solid Mg; forms stable Mg–Er phases; Er addition to Mg–Al alloys leads to the formation of an Al–Er phase; excellent grain refining in ZK alloys	Improves tensile strength and tensile yield strength with the increasing addition of Er to pure Mg; however it decreases the elongation of Mg–Er alloys	Enhances the corrosion resistance of AZ alloys; Mg–Al–Er phases surround the Mg matrix; enhances the stability of the $Mg(OH)_2$ layer and thus reduces corrosion resistance	113 and 138–144
Gd	Refinement of grain size; Gd atoms replace Mg atoms to form a random substitutional solid solution	Enhance tensile strength and tensile yield strength with the increasing addition of Gd; improve the elongation of Mg–Gd alloys with the addition of Gd below 6%	No consensus. Influence on corrosion depends on the composition and Gd content in Mg alloys	113, 128, 141 and 145–151
La	Has a relatively low solubility in Mg compared with other rare earth elements; reacts with Al to form rod-like Al–La phases that refine the grain size of AZ alloys	Enhances tensile strength, yield strength and creep resistance of binary Mg–La alloys; deteriorates the elongation of Mg alloys with excessive addition of La; reduces dendrite arm spacing and slightly improves the tensile strength and age hardening response of Mg–Al–La alloys due to the formation of Al–La phases	Refinement of $Mg_{17}La_2$ phases leading to a finer microstructure for Mg–La alloys with La addition below 1%, which results in uniform corrosion; La oxide combined with $Mg(OH)_2$ enhances corrosion resistance	113, 129, 131 and 152–154
Nd	Refinement of the grain size of Mg alloys with increasing Nd content	Nd atoms replace Mg atoms thereby enhancing the tensile strength and tensile yield strength at a Nd content less than 6%; deteriorates elongation and creep resistance of Mg alloys with excessive addition of Nd	Addition to pure Mg effectively enhances corrosion resistance; the $Mg_{12}Nd$ phase suppresses the galvanic effect; the Nd_2O_3 layer combined with $Mg(OH)_2$ inhibits corrosion	113, 133, 155 and 156
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 enhances tensile strength and tensile yield strength with increasing addition of Y in pure Mg; improves elongation with the Y concentration below 3%; excessive addition of Y deteriorates elongation	Influence on corrosion resistance under debate; depends on the composition of Mg alloys; reduces corrosion resistance of binary Mg–Y alloys with a concentration >2%	38, 46, 49, 61, 93, 113, 154 and 158–161

[a] %: wt%, unless specified otherwise.

detrimental to the corrosion resistance of Mg alloys.[112–114] Thus, exploiting 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 content. When Mn addition reaches 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 to 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 of the formation of a large amount of Mn-containing intermetallic 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–*x*Mn 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 secondary 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 secondary phase of a 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 would 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 secondary 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] This investigation suggests that the actual effects of Zn addition on the corrosion resistance depend on the composition of Mg alloys. Different Zn-containing phases may be formed in Mg alloys with the addition of multiple elements, leading to the varied influence on the corrosion.

4.4 Effect of Zr and Sr on the corrosion behavior of Mg alloys

Although Zr has a relatively low solubility in the Mg matrix, it can significantly inhibit the growth of crystal grains during 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 the 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 a Zr–Mg double oxyhydroxide enriched with Zr cations. This Zr–Mg double oxyhydroxide acts as a barrier inhibiting the corrosion of Mg–Zr alloys.

Sr does not show an obvious grain refining effect of Mg–*x*Zr–*y*Sr alloys (x, $y \leq 5\%$), but it significantly enhances 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 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 $Mg_{17}Sr_2$ secondary 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; also, 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 the corrosion behavior of Mg alloys

REEs are originally isolated as oxides from rare minerals, defined as a group of seventeen chemical elements in the periodic table, including the fifteen lanthanides, scandium (Sc) and yttrium (Y). They tend to appear in the same ore deposits and show similar chemical features.[126] In recent studies, some REEs in Mg alloying elements showed encouraging functions, such as enhancing the

corrosion resistance, and improving the mechanical properties and electrochemical behavior as a result of the grain refinement and formation of secondary 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 and distribute along grain boundaries, and thus decrease the grain size effectively. In Mg–Al–Ce alloys, Ce particles aggregate at the solid–liquid interface 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 form and distribute along grain boundaries, and they can effectively block the sliding of the boundaries 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 delay 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 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 the 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 found 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 the 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 the 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 that the secondary phase of Mg_5Gd in Mg–Gd alloys is 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–*x*Gd–3Y–0.4Zr alloys ($x = 6$, 8, 10 and 12%) in a 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–*x*Gd–3Y–0.4Zr alloys was affected by the secondary phase and corrosion products on the surface. The high volume fraction of the secondary phase of Mg_5Gd in the Mg alloys acts as the barrier that inhibits corrosion, a function similar to that of the secondary 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 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 has 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 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 secondary phases of $Mg_{12}Nd$ and $Mg_{41}Nd_5$ formed and isolated the Mg matrix, resulting in reduction in the grain size and enhancement of 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 the 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

and thus effectively blocked the sliding. Moreover, the difference in the 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–*x*Nd ($x = 0$, 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 micro-galvanic corrosion and suppress the cathodic process. They also indicated that a protective layer composed of Al_2O_3 and Nd_2O_3 in 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–*x*Nd ($x = 1$ and 2%).[156] It can be seen that the corrosion in Mg alloys containing Nd is significantly affected by the secondary 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–*x*Nd ($x = 0$, 1, 2, 4 and 6%) and their conclusions were different from those above. Their results indicated that 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 as that of 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 similar to that of 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 $R_{Mg} = 1.6 \times 10^{-10}$ 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 behavior of the binary Mg–*x*Y ($x = 0.25$, 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 Y added. The corrosion resistance was improved as more Y was added, provided the Y content was below 2.5% in Mg–*x*Y ($x = 0.25$ 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–*x*Y ($x = 5$ 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 containing Mg alloy exhibited a higher corrosion rate. Liu *et al.*[93] studied the corrosion behavior of binary Mg–*x*Y ($x = 2$, 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 volume fraction of intermetallic phases increased with Y addition, which deteriorated the corrosion resistance of Mg alloys due to the accelerated micro-galvanic effect. 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 in large quantities or traces of addition were extensively studied. The addition of the alloying elements affects the microstructures and therefore influences 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–REE phases or Mg–REE 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–REE based alloys because they will contribute significantly to the alloy properties. Additionally, there are some concerns with the addition 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 by 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 the 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 are insufficient data concerning the electrochemical and corrosion properties of binary Mg–REE alloys.[163] Further research on binary and tertiary Mg–REE 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 secondary 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 secondary 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.* degradation rate) to maintain mechanical integrity during healing and excellent biocompatibility making it harmless to host tissues. After implantation, the Mg alloy implant would directly come in contact with 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 are 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 is investigated based on the 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 application process, this ideality is not always attained. 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 corrosion resistance, medical research has found that accumulation of Al in the brain may harm the 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 lymphocyte 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 permit a much larger amount of Al than in the diet, possibly as high as 12–71 mg kg^{-1} per day.[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 is present at a level of 0.919–0.993 mg L^{-1} in the normal blood serum.[173,174] The recommended Ca dietary allowance for adults is approximately 1000 mg per day.[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 the formation of an insoluble corrosion product on the surface. Kirkland *et al.* suggested that the insoluble "chalk like" product could become problematic to 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 the 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 sensory hair cells, auditory nerve fibers and spiral ganglion neurons in three rats isolated

from birth. In this study it was shown that the sensory hair cells were vulnerable to Mn toxicity. Disservice was observed with Mn absorption as low as 10 μM. Preponderant 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 a modest level of Mn.[187] It was also found that the neurotoxicity also presented on the induction factor of a disease with similar properties to those of Parkinson's disease.[185] Considering these findings for the toxicity of Mn, it would be wise to be cautious in the use of 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 the dietary allowance for Zn as 11 mg per day for men and 8 mg per day for women, so the corresponding burden of Zn is approximately 0.16 mg kg^{-1} per day for men and 0.13 mg kg^{-1} per day for women.[189] There have been many studies on the negative consequences of an overdose of Zn intake on growth, development and health.[190–193] The divalent metal can lead to neurological disorders.[188,194] Zn cation acts as a mediated inhibitor of neurotrophins, and can even lead to cell death,[195] so Zn accumulation in the 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 the body in the form of an alloying element in Mg alloys, the toxicity could be seen as possibly impairing the immune function.[194] Thus, the possible complications of using those alloys with 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 a high dose through oral administration (2250 mg kg^{-1} per day) 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} per day, 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 traditional, less biocompatible alloying elements in Mg alloys such as Al, Zn, 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 *in 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-substituted 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–REE alloys contain more alloying elements than their designations.[5,206] Almost any REE-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 alloys 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 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

Table 3 Biocompatibilities of some alloying elements used in Mg alloys[a]

Elements	Description	Method	LD_{50} of salts	Biocompatibility	References
Al	Harmful to the intelligence and causes neuropathological relevance; risk factor for the development of Alzheimer's disease; leads to lymphocyte and inconspicuous muscle fiber damage	Oral	230 mg kg^{-1} (rats)	−	33 and 168–170
Ca	Presence of Ca^{2+} in HA; essential element of the human body; normal blood serum level 0.919–0.993 mg L^{-1}; metabolic disorder may induce kidney stones and arthritis	Oral	1940 mg kg^{-1} (rats)	=	172, 174, 176 and 178
Li	Lithium toxicity presents 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 for a disease with similar properties to Parkinson's disease; toxic dosage 10 μM	Oral	1484 mg kg^{-1} (rats)	−	183–187
Zn	Essential trace element; optimally promotive factor for the recovery of acrodermatitis enteropathica; a co-factor for enzymes; normal blood serum level 0.81–1.137 mg L^{-1}; induces embryonic motor neuron death	Oral	186–623 mg kg^{-1} (mice and rats)	=	189, 190, 193 and 195
Zr	Zr is a biocompatible alloying element in MgZrSr and MgZrCa alloys. Zr oxide is non-toxic in the animal studies using mice and rats. However, Zr should be used with scrutiny depending on the applied dosage	Oral	990–2290 mg kg^{-1} (rats)	=	196–198
Sr	Promotes osteoblast maturation; maintains bone formation; diminishes bone resorption; increases bone trabecular volume	Oral	2900 mg kg^{-1} (mice)	+	200–202 and 217
Ce	Significantly disturbs the brain, lung, liver and kidney of mice at even low concentration; high concentrations of Ce may damage DNA and cause apoptosis and endomyocardial fibrosis	Oral	500 mg kg^{-1} (mice)	−	69, 212 and 220
Er	Er chlorides produce nodules with foreign body giant cells; Er is moderately to highly toxic causing writhing, ataxia, labored respiration, walking on the toes with arched back and sedation	Oral Intravenous	6200 mg kg^{-1} (rats) 535 mg kg^{-1} (rats)	−	222 and 223
Gd	Higher inflammatory responses on TNF-alpha, and leads to the apoptosis of MG63 cells at high concentrations; Gd accumulation in tissue is linked to nephrogenic systemic fibrosis and kidney failure; rats that 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 and 225
La	Increased blood eosinocyte, decreased body weight, causes 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 the brain	Intravenous	150–625 mg kg^{-1} (mice)	−	70, 214 and 219
Nd	Chronic exposure to Nd exhibits a depressant action and produces death due to cardiovascular collapse coupled with respiratory paralysis; exhibits cytotoxic effects and induces apoptosis in certain cancer cells	Intravenous Oral	600 mg kg^{-1} (rats, mice) 2750 mg kg^{-1} (rats)	−	71, 208, 219 and 221
Y	Increases blood eosinocyte, decreases body weight, causes eosinophil infiltration in the submucosa; gets distributed to plasma in the blood and leads to acute hepatic injury at a dose of 1 mg kg^{-1} for 144 days in rats	Oral	350–500 mg kg^{-1} (rats)	−	215, 218 and 226

[a] Positive influences (+), negative influences (−) and intermediate influences (=).

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 basis 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 is not

only dependent 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 REE 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 the 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 REE-containing salts such as chloride REEs or nitrate REEs *via* intravenous injection, inhalation and orally.[208,212,213] Ogawa *et al.*[214–216] 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 $\leq$5%.[56]

Ca is the most abundant element in the human body, presenting in the form of the 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 lead to the formation of a large volume of the secondary 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 degradation 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 the serum of humans could induce bipolar disorder, and with 20 mg L^{-1} Li in the 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 the human body, and tends to accumulate primarily in the bone, liver, heart and lung.[220] Nd has been classified as a light REE and exhibits similar toxicity to La and Ce.[71,208,219,221] Although Er belongs to the group of REEs with large ionic radii, it is moderately 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" used in alloying, 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 indicate that these elements should be absolutely excluded from 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

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 the human body presents in the form of HA in the skeleton. Acceptable biocompatibility can be achieved 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, excellent biocompatibility can be achieved 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 used cautiously in biomedical applications. The optimal content should be ≤1%
Zn		Excessive addition to Mg decreases the corrosion resistance significantly. Overdose of Zn absorption leads to negative consequences. The optimal content should be ≤5% in Mg alloys
Gd	Possibly a 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 the Y-containing secondary phase accelerates the micro-galvanic corrosion. A concentration of 2.5 mol% Y^{3+} doped in HA shows excellent biocompatibility

conditional Mg alloying elements and REEs on the corrosion resistance and biocompatibility of Mg alloys for biomedical applications. Table 4 summarizes the limitations of some of the potential alloying elements. The 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 the 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 acceptable responses when the concentration of 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 corrosion. The role of Gd in the corrosion of Mg alloys mainly depends on its content in the Mg alloys. As for 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 secondary 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 challenging to fully understand the corrosion mechanism of Mg alloys with complicated compositions such as Mg–Y and Mg–Gd based alloys. In addition, the structure and phase distribution vary depending on the fabrication and post-treatment, such that Mg alloys with the same composition or those 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 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 the alloying elements described in Section 5. However, it outlines that these elements can exert negative impacts on the human body, and reminds researchers the relative potential risks of common alloying elements and REEs in the design of biodegradable Mg alloys. This topic is still open to debate. Which element favors 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.

Acknowledgements

The authors acknowledge financial support for this research through the Australia–India Strategic Research Fund (AISRF, BF030031).

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