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Novel Magnesium Alloys Developed for Biomedical Application: A Review

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Prof. Yufeng Zheng's research is concerned with development of new kind of biomedical metallic materials, including biodegradable magnesium alloys and iron-based alloys, β-Ti alloys with low elastic modulus, nickel-free Ti-based shape memory alloys, nanocrystalline metals and alloys and bulk metallic glasses, and their medical devices in dentistry, orthopedics and interventional therapy. He has published over 230 SCI journal papers since 1998, with the citation of over 3100 times and h-index of 26. He edited 7 books and book chapters, and owned 27 Chinese Invention Patents. He was granted with over 30 projects including the National Basic Research Program of China and the National Science Fund for Distinguished Young Scholars. He served as a member of the editorial board of Journal of Biomedical Materials Research Part B-Applied Biomaterials (Wiley), the associate editor board of Materials Letters (Elsevier), the editor board of Journal of Materials Science & Technology (Elsevier) and Acta Metallurgica Sinica (English Letters) (Springer).

There is an increasing interest in the development of magnesium alloys both for industrial and biomedical applications. Industrial interest in magnesium alloys is based on strong demand of weight reduction of transportation vehicles for better fuel efficiency, so higher strength, and better ductility and corrosion resistance are required. Nevertheless, biomedical magnesium alloys require appropriate mechanical properties, suitable degradation rate in physiological environment, and what is most important, biosafety to human body. Rather than simply apply commercial magnesium alloys to biomedical field, new alloys should be designed from the point of view of nutriology and toxicology. This article provides a review of state-of-the-art of magnesium alloy implants and devices for orthopedic, cardiovascular and tissue engineering applications. Advances in new alloy design, novel structure design and surface modification are overviewed. The factors that influence the corrosion behavior of magnesium alloys are discussed and the strategy in the future development of biomedical magnesium alloys is proposed.

KEY WORDS: Biomaterials; Magnesium alloys; Biodegradation; Mechanical property; Biocompatibility

1. Introduction

Magnesium alloys for biomedical applications are in spotlight recently. They have advantages over traditional metallic materials, ceramics and biodegradable polymers. For mechanical properties, metals are more suitable for load-bearing applications compared with ceramics or polymer because of their high mechanical strength as well as high fracture toughness. The densities of magnesium (1.738 g/cm^3) and magnesium alloys (1.75−1.85 g/cm^3) are very similar to that of human cortical bone (1.75 g/cm^3), while the density of biomedical titanium alloy Ti6Al4V is 4.47 g/cm^3[1]. For biocompatibility, magnesium ions are present in large amount in the human body and involved in many metabolic reactions and biological mechanisms. The human body usually contains magnesium approximately 35 g per 70 kg body weight and the daily demand for magnesium is about 375 mg[2]. Magnesium alloys are promising candidates for orthopedic and cardiovascular implants and have attracted increasing attention since there is no requirement for a secondary removal surgery.

Potential of commercial magnesium alloys as biodegradable implant materials were evaluated. Witte et al.[3] investigated *in vivo* corrosion of 4 magnesium alloys and found that the corrosion layer of all the alloys displayed an accumulation of biological calcium phosphates and all alloys increased the newly formed bone compared to the polymer. According to this study, LAE442 exhibited the lowest corrosion rate, while AZ31, AZ91 and WE43 were found to degrade at similar rates[3]. Gao et al.[4] reported that ZK60 alloy lost 3.1% of its original mass after

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soaking in a simulated body fluid (SBF) for 242 h, while the mass loss of Mg−5.6Zn−0.55Zr−0.9Y alloy was merely 1.7%, indicating that the addition of the alloying element Y improves the corrosion resistance of ZK60 alloy. Heublein et al.[5] implanted 20 AE21 stents into coronary arteries of 11 domestic pigs. The main limit of the AE21 stents was that their degradation occurred faster than expected as the loss of mechanical integrity occurred between 35 and 56 days after implantation. Then Mario et al.[6] and Peeters et al.[7] reported the results of animal experiment and first clinical study of Lekton Magic coronary stent (Biotronik, Bulach, Switzerland) made from WE43 magnesium alloy, respectively. Based on this Lekton Magic coronary stent, Biotronik Company developed 3 generations of absorbable metal stent (AMS): (1) Studies on clinical implantation of 71 AMS-1 magnesium stents in the coronary arteries of 63 patients showed that the AMS stents can achieve an immediate angiographic result similar to that of other metal stents, and can be safely degraded after 4 months[8]; (2) AMS-2 with new alloy design and stent design maintains longer stent integrity in animal; (3) AMS-3 stent is a Mg alloy stent coated with a fast-degradable polymer carrier with an anti-proliferative drug. The first animal trial in porcine model showed promising results in terms of safety and efficacy compared to bare AMS Mg stent[9].

Although commercial magnesium alloys containing aluminum and/or rare earth elements exhibit good mechanical properties and corrosion resistance, they are not suitable for biomedical applications in consideration of toxicity. Aluminum is well known as a neurotoxicant. The accumulation of Al has been suggested to be associated with various neurological disorders[10]. Severe hepatotoxicity has been detected after the administration of cerium, praseodymium and yttrium[11]. To guarantee the biosafety of biodegradable materials, researchers have developed new type of magnesium alloys, choosing element with no toxicity or low toxicity as alloying elements.

This article reviews the progress and development on biomedical magnesium alloys, mainly on pure Mg, Mg−Ca-based, Mg−Zn-based, Mg−Si-based, Mg−Sr-based and Mg−RE-based alloys. We also discussed novel structure design and surface modification, and proposed the unsolved scientific problems for the future development of biodegradable magnesium alloys.

2. Purification and Alloying Design of Magnesium for Biomedical Application

Purification and alloying are two strategies to obtain magnesium-based biomaterials with proper properties. Mechanical properties of currently investigated biodegradable magnesium and magnesium alloys are shown in Fig. 1. Fig. 2 shows their corrosion rate and hydrogen evolution rate. Hemolysis rate and effect of magnesium alloy extract on cell viability are summarized in Fig. 3 and Table 1, respectively.

2.1. Pure Mg

Due to the high chemical activity of magnesium, any of the alloying elements or impurities in its pure form or intermetallic phase will increase the galvanic corrosion of magnesium and magnesium alloys. The magnesium matrix acts in any case as a cathode of the micro galvanic cell and gets dissolved[12]. Song[13] and Ren et al.[14] found that purification remarkably slow down the corrosion rate of pure magnesium. The corrosion resistance of pure magnesium is relevant to the tolerance limits of impurities. When the impurity concentration exceeds the tolerance limit, the corrosion rate is greatly accelerated. The most harmful impurities to pure magnesium are Fe, Cu and Ni, with a tolerance limit of 170×10^{-6}, 1000×10^{-6} and 5×10^{-6}, respectively[15]. The tolerance limits are influenced by the method of manufacture as well as the presence of a third element. Lee et al.[16] claimed that the corrosion behavior of pure magnesium depends on the content ratio of impurities, such as Fe/Mn ratio, rather than their content values. Grain refinement through forging or rolling can also enhance the corrosion resistance of pure magnesium. Heat treatment with different temperatures and durations may have contrary effects. Ren et al.[14] reported that the corrosion rate of as-forged high-purity magnesium is increased after heat treatment at 773 K for 10 h, which is caused by the coarsening of grains. However, Kuwahara et al.[17] found that the MgO layer formed in the heat-treated process at 803 K for 25 h enhances the precipitation of magnesium apatite HBSS(+) solution, so that the corrosion rate of 3N−Mg is decreased.

Due to the high hydrogen evolution rate[2] and high hemolysis rate (as-cast ∼57%, as-rolled ∼25%[18]), pure Mg may not be a proper material for biodegradable vascular stents. For orthopedic applications, although pure Mg shows the ability of inducing the formation of new bone[19,20], the poor mechanical property is a concern.

2.2. Mg−Ca-based alloys

Calcium is a major component in human bone and is essential in chemical signaling with cells[21]. Moreover, magnesium is necessary for the calcium incorporation into the bone[22], which might be expected to be beneficial to the bone healing with the co-releasing of Mg and Ca ions.

Ca is also beneficial to grain refinement of magnesium alloys. The solubility limit of Ca in Mg is 1.34 wt%[23]. The Mg−Ca alloys are mainly composed of α(Mg) phase and Mg_2Ca phase[24]. With increasing Ca content, more and coarser Mg_2Ca phase precipitates along grain boundaries, weakening both the mechanical property and corrosion resistance of as-cast Mg−Ca alloy[24,25]. After hot rolling or hot extrusion, coarse Mg_2Ca phase turns into smaller particles and the grain size is refined, contributing to improved mechanical properties and corrosion resistance[24]. Referring to Drynda et al.[26], the strength of as-extruded binary Mg−Ca alloys increases with Ca content but the ductility decreases. Gu et al.[27] found that the rapid solidified Mg−3Ca alloy ribbons showed much finer grain features, better corrosion resistance and improved cell reaction than the as-cast Mg−3Ca alloy ingot. *In vitro* cytotoxicity test indicated that Mg−1Ca alloy does not induce toxicity to L929 cells[24]. Mg−1Ca alloy pins gradually degraded *in vivo* within 90 days and new bone formed[24]. Moreover, in the study carried out by Krause et al.[28], as-extruded Mg−0.8Ca alloy maintained more than half of their initial volume after being implanted into rabbit tibiae for 6 months.

2.3. Mg−Zn-based alloys

Zn exists in all human body tissues and is one of the most abundant nutritionally essential elements in the human body[29]. Zn is a common alloying element in magnesium alloys with the

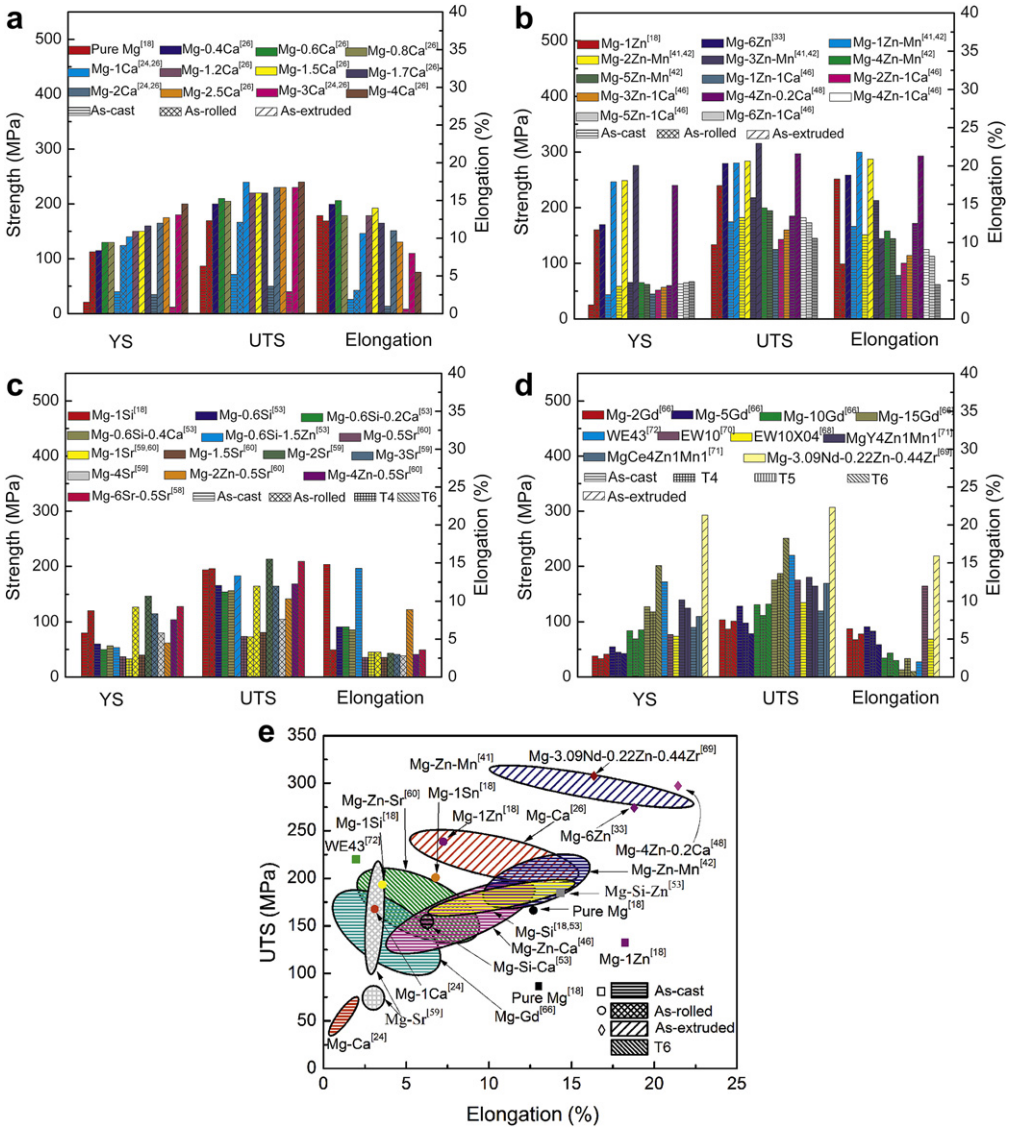

Fig. 1 Mechanical properties of pure Mg and Mg−Ca-based alloys[18,24,26] (a), Mg−Zn-based alloys[18,33,41,42,46,48] (b), Mg−Si-based and Mg−Sr-based alloys[18,53,59,60] (c), Mg−RE-based alloys[66,68−72] (d) and comparison of mechanical properties of these alloy systems (e).

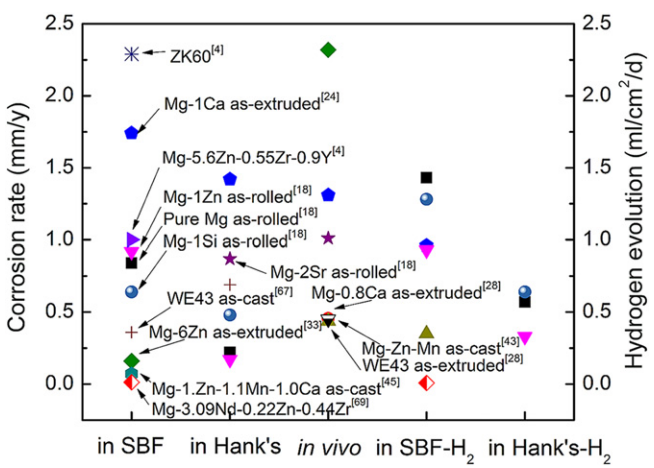

Fig. 2 Corrosion rate and hydrogen evolution rate of several kinds of magnesium alloys[4,18,24,28,33,43,45,67,69].

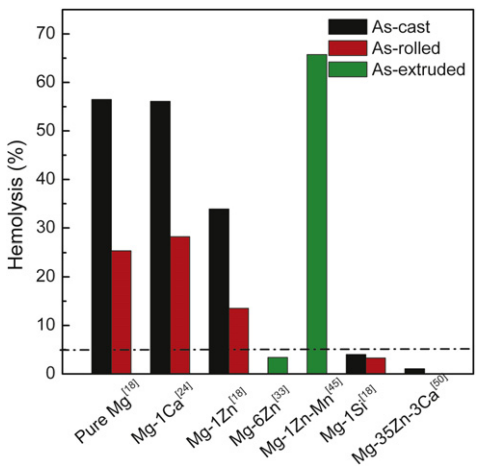

Fig. 3 Hemolysis rate of several kinds of magnesium alloys[18,24,33,45,50].

Table 1 Cell viability of several cell lines cultured in magnesium and its alloys extracts

Materials	Working history	Cell line	Culture time (d)	Cell viability (%)	Ref.
Pure Mg	As-cast	L929	4	65.7	[18]
	As-cast	NIH3T3	7	90.6	[18]
	As-cast	MC3T3-E1	7	87.5	[18]
	As-cast	ECV304	7	76.8	[18]
	As-cast	VSMC	7	93.6	[18]
Mg−1Ca	As-cast	L929	4	81.8	[24]
Mg−3Ca	As-cast	L929	4	~55	[27]
	RS15	L929	4	~90	[27]
	RS30	L929	4	~100	[27]
	RS45	L929	4	~105	[27]
Mg−1Zn	As-cast	L929	4	111.8	[18]
	As-cast	NIH3T3	7	114.1	[18]
	As-cast	MC3T3-E1	7	112.7	[18]
	As-cast	ECV304	7	98.9	[18]
	As-cast	VSMC	7	110.6	[18]
Mg−6Zn	As-extruded	L929	4	~100	[33]
Mg−1Zn−Mn	As-extruded	L929	3	100	[45]
Mg−1Zn−1Ca	As-cast	L929	7	~75	[46]
Mg−2Zn−1Ca	As-cast	L929	7	~70	[46]
Mg−3Zn−1Ca	As-cast	L929	7	~72	[46]
Mg−1Si	As-cast	L929	4	88.3	[18]
	As-cast	NIH3T3	7	102.4	[18]
	As-cast	MC3T3-E1	7	119.0	[18]
	As-cast	ECV304	7	80.5	[18]
	As-cast	VSMC	7	95.1	[18]
Mg−1Sr	As-rolled	MG63	5	~84	[59]
Mg−2Sr	As-rolled	MG63	5	~80	[59]
Mg−3Sr	As-rolled	MG63	5	~68	[59]
Mg−4Sr	As-rolled	MG63	5	~50	[59]

solubility limit of 6.2 wt%[23] and can effectively improve mechanical properties of magnesium. Various kinds of Mg−Zn based alloys were studied.

2.3.1. Mg−Zn binary alloys. Zhang et al.[30−33] investigated an extruded Mg−6Zn alloy as a biodegradable material. This alloy consists of a uniform single phase after solid solution treatment and hot working, so galvanic corrosion is avoided[33]. The mechanical properties of the Mg−6Zn alloy is believed to be suitable for implant applications[33]. The *in vitro* cytotoxicity of Mg−6Zn to L929 cells was found to be Grade 0−1 and the hemolysis rate is 3.4%[30,33], indicating the Mg−6Zn alloy exhibits good biocompatibility *in vitro*. The Mg−6Zn alloy rods were implanted into the femoral shaft of rabbits and gradually absorbed *in vivo* at degradation rate about 2.32 mm/y with newly formed bone surrounding the implant[33]. The viscera histology examination and the biochemical measurements proved that the degradation of Mg−Zn alloy did not harm the important organs[32,33]. In Fig. 2, it is noticeable that the corrosion rate of the Mg−6Zn alloy *in vivo* is one order of magnitude higher than that *in vitro*, and is higher than other Mg alloys.

2.3.2. Mg−Zn−Zr, Mg−Zn−Y and Mg−Zn−Zr−Y alloys. The addition of Y into magnesium alloys increases the solubility of the matrix due to its high solubility (8.0 wt%[23]) in Mg, which enables the harmful elements to dissolve into the matrix and therefore slows down the corrosion rate[4]. Zr is usually used as a grain refiner in magnesium alloys[34]. Zr shows good biocompatibility and osseointegration both *in vitro* and *in vivo*, even outperforming titanium[35,36].

Zhang et al.[37] investigated the influence of Y content on tensile properties and corrosion resistance of Mg−Zn−Y alloys with low Zn content (1.73−1.98 wt%). The results showed that both tensile strength and elongation increase with increasing Y content, due to that the I-phase (Mg_3Zn_6Y) has better strengthening effect than the W-phase ($Mg_3Zn_3Y_2$). The alloys with a single secondary phase showed a better corrosion resistance than those with two secondary phases. ZW21 and WZ21 alloys are found to perform good cytocompatibility both *in vitro* and *in vivo* with homogeneous degradation and only limited gas formation being observed *in vivo*[38]. Gao et al.[4] found after 242 h soaking in SBF, the mass loss of Mg−5.6Zn−0.55Zr−0.9Y alloy was merely 1.7%, while that of Mg−5.4Zn−0.55Zr (ZK60) was 3.1%, but still larger than that of pure Mg.

2.3.3. Mg−Zn−Mn alloys. Manganese has no toxic effect except after extreme occupational exposure[39]. It plays a primary role in the activation of multiple enzyme system[39]. Mn does not affect the mechanical property of magnesium alloy, but can improve their corrosion resistance by removing iron and other heavy-metal elements into relatively harmless intermetallic compounds[23].

Zhang et al.[40−42] investigated the effect of Zn content on microstructure, mechanical properties and corrosion behavior of Mg−Zn−Mn alloy. When the Zn content increases from 0 to 3 wt%, the grain size decreases from 12 to 4 μm and the mechanical properties increase remarkably. When the Zn content is more than 3 wt%, the grain size stops decreasing, so the strength cannot be improved any more and the elongation decreases significantly. The best anti-corrosion property is obtained with 1 wt% Zn while further increase of Zn content deteriorates the corrosion property. *In vivo* study showed that after 18 weeks, about 54% as-cast Mg−Mn−Zn (Mg−1.2Mn−1.0Zn, in wt%) implant had degraded but the degradation of magnesium did not cause any increase in serum magnesium content or any disorders of the kidney after 15-weeks postimplantation[43]. More degradation phenomena of implant (Mg−1.0Zn−0.8Mn, in wt%, as-extruded) were observed in the marrow channel than in the cortical bone[44].

2.3.4. Mg−Zn−Ca alloys. Similar to Mg−Zn−Mn alloys, Mg−Zn−Ca ternary alloys with medium Zn content (~4 wt%) exhibit the best mechanical properties[46] and their corrosion resistance decreases with increasing Zn content[46,47]. An as-extruded Mg−4Zn−0.2Ca alloy prepared by Sun et al.[48] exhibited excellent mechanical integrity during *in vitro* degradation. After 30 days immersion in SBF solutions, the values of the yield strength, the ultimate tensile strength, the elongation and the elastic modulus of the alloy were degraded to 160 MPa, 220 MPa, 8.5% and 40 GPa, respectively, which are still enough for bone fixing[48]. Gao et al.[49] found the corrosion current density of Mg−2Zn−0.24Ca alloy after high-pressure torsion decreased remarkably from 5.3×10^{-4} to 3.3×10^{-6} A/cm^2 due to the homogeneous distribution of the nano-sized second phase.

2.4. Mg−Si-based alloys

The average intake of silicon ranges from about 20 to 50 mg/day with the lower values for animal-based diets and higher values for plant-based diets[51]. A trace amount of Si has been

reported to be essential in mammals[13] and may be important for the growth and development of bone and connective tissue[52].

Mg−1Si alloy shows a low ductility due to the presence of coarse Mg_2Si, since there is almost no solubility for Si in Mg[18]. Zhang et al.[53] introduced Ca and Zn elements to refine and modify the morphology of Mg_2Si so as to improve the corrosion resistance and the mechanical properties. The addition of Ca can improve the corrosion resistance of Mg−Si alloys but no improvement was observed in the strength and elongation. The addition of 1.6 wt% Zn into Mg−0.6Si can obviously modify the morphology of Mg_2Si phase from course eutectic structure to a small dot or short bar shape, so the tensile strength, elongation and corrosion resistance are all improved significantly.

2.5. Mg−Sr-based alloys

Strontium, along with Ca and Mg, belongs to group IIA of the periodic table and shares similar chemical, biological and metallurgical properties. There is about 140 mg Sr in the human body and 99% of the body content of Sr is located in the bones[54]. Indeed, because of the bone formation stimulation effect of Sr, oral administration of Sr salts is used in the treatment of osteoporotic patients to increase bone mass and reduce the incidence of fractures[55,56]. From the materials science point of view, proper addition of Sr can refine the grain size of magnesium alloys[57] and enhance the corrosion resistance[58].

Gu et al.[59] prepared hot rolled Mg−Sr binary alloys with a Sr content ranging from 1 to 4 wt% and found Mg−2Sr alloy exhibited the highest strength and the slowest corrosion rate. The *in vivo* results showed that the degrading as-rolled Mg−2Sr alloy promoted bone mineralization and peri-implant new bone formation without inducing any significant adverse effects[60]. Brar et al.[60] and Berglund et al.[61] developed Mg−Zn−Sr and Mg−Ca−Sr ternary alloys, respectively, both of which suggest that the presence of higher amount of secondary intermetallic phases leads to poorer corrosion resistance.

2.6. Mg−RE-based alloys

Rare earth elements in magnesium alloying are predominantly used for strengthening and to improve the corrosion resistance[62]. Rare earth elements contain totally 17 elements, *i.e.* scandium (Sc), yttrium (Y), lanthanum (La), cerium (Ce), praseodymium (Pr), neodymium (Nd), europium (Eu), gadolinium (Gd), terbium (Tb), dysprosium (Dy), holmium (Ho), erbium (Er), thulium (Tm), ytterbium (Yb), lutetium (Lu) and promethium (Pm). They are introduced into magnesium alloys by master alloys or so-called hardeners that contain mainly 1 or 2 rare earth elements and almost all other rare earth elements in smaller amounts. In the ASTM nomenclature of magnesium alloys, rare earth elements are collectively represented by E, except that yttrium is specially represented by W.

Drynda et al.[63] cultured human vascular smooth muscle cells (VSMCs) with trivalent chlorides of 16 rare earth elements (radioelement Pm was not included) and found that rare earth metals at low concentration exhibit no major adverse effects on the proliferation of VSMCs but lead to the upregulation of inflammatory genes at high concentrations[51]. Feyerabend et al.[64] recommended that for rare earth elements with high solid solubility in magnesium, Gd and Dy are more suitable than Y, while Eu, Nd and Pr are suitable elements with low solubility in magnesium. La and Ce should be used cautiously because they are highly cytotoxic.

Currently invented Mg−RE-based alloys for biomedical usage include Mg−Y[65], Mg−Gd[66], WE43[3,67,68] and so on. Among them, WE43 alloy is mostly intensively investigated for its excellent mechanical properties and corrosion resistance. Zhang et al.[69] prepared a new type of Mg−Nd−Zn−Zr alloy (denoted as JDBM), which outperforms WE43 on mechanical properties and corrosion resistance.

Although magnesium-based alloys in orthopedic applications are still in preclinical trials, magnesium-based cardiovascular stents have already entered clinical trials in patients with peripheral arterial obstructions and coronary artery disease. Magnesium alloys investigated for cardiovascular application are mainly Mg−RE-based alloys as mentioned in the introduction section. However, the biosafety of rare earth elements is still under concern.

2.7. Comprehensive comments on currently investigated magnesium alloys

2.7.1. Mechanical property. As illustrated in Fig. 1(e), magnesium alloys exhibit a large range of ultimate tensile strength and elongation. The mechanical properties can be adjusted by alloying or processing. Moreover, mechanical integrity during degradation is as important as initial strength. Ideal biodegradable magnesium alloy devices should be able to compromise their degradation and mechanical integrity during implantation. Theoretically, the degradation should begin at a very slow rate to maintain optimal mechanical integrity so as to provide sufficient time for the tissue to heal. Thereafter, the degradation progresses at a relatively higher rate while the mechanical integrity decreases. For magnesium alloy coronary stents, they are expected to maintain their mechanical integrity for a period of 6−12 months for the vessel remodeling process to be completed and totally degraded in 12−24 months[73]. For orthopedic biomaterials, it needs 3−4 months from fracture callus formation to new bone formation and eventually solid bone healing restoring most of the bone's original strength[74]. Unfortunately, most of the currently researched magnesium alloys degrade too fast and the strength drops sharply at the initial stage of degradation[33].

2.7.2. Degradation rate. Fig. 3 shows the *in vitro* corrosion rate, hydrogen evolution rate and *in vivo* corrosion rate of currently studied magnesium alloys. It can be seen that Mg−Mn−Zn[43], Mg−0.8Ca[28] and WE43[28] alloys show the lowest *in vivo* corrosion rate. However, as 54% Mg−Mn−Zn alloy implants degraded *in vivo* after 18 weeks[43], the residue may not provide sufficient mechanical property for fracture fixation. Due to the degradation, the applied force at fracture of Mg−0.8Ca and WE43 in three-point bending test reduced 35.43% and 22.04% after 3 months implantation, respectively[28].

2.7.3. Biocompatibility. Table 1 summarizes the cell viability of several cell lines cultured in magnesium alloy extracts. According to ISO 10993-5:2009, the reduction of cell viability by more than 30% is considered a cytotoxic effect. So in Table 1 only as-cast pure Mg and Mg−3Ca alloy have a cytotoxic effect on L929 cells. Additionally, only Mg−6Zn, Mg−1Si and WE43 alloys exhibit hemolysis rate less than 5%, while most of magnesium alloys are severely hemolytic, as shown in Fig. 3.

Table 2 Mechanical properties and biocompatibility of some porous magnesium and its alloys scaffolds

Composition	Method	Porosity (%)	Average pore size (μm)	Compression strength (MPa)	*E* (GPa)	Biocompatibility	Ref.
Mg (≥99.9%)	P/M	35	250	17	1.8	–	[77]
		41	250	~15	~1.1	–	[77]
		45	250	~13	~0.8	–	[77]
		55	250	~12	~0.8	–	[77]
		45	73	16	1.3	–	[77]
		45	168	~14	~0.8	–	[77]
		45	412	~11	~0.7	–	[77]
β-TCP coated Mg (99.99%)	Laser perforation	42.61	500	12.02	0.63	UMR106 cells were well adhered and proliferated	[79]
		50.34	500	9.05	0.46	–	[79]
		50.89	500	8.36	0.41	–	[79]
Mg (99.9%)	GASAR	28	170	23.9	–	L929, 5 d, viability ~80%	[81]
AZ91	Negative salt-pattern molding cast	25	–	~7	–	Though degraded very fast, it caused no significant harm to the neighboring tissues; promote both bone formation and resorption	[82−84]

3. Strategy for Property Adjustment of Biomedical Magnesium Alloys

Besides alloying and processing, there are other approaches that can further adjust properties of magnesium-based biomaterials to realize diverse function and meet the requirement of different implant location. Mechanical properties can be controlled through structure design. Surface treatment is an effective strategy to regulate the degradation rate and the surface properties.

3.1. Development of Novel Structure

3.1.1. Porous structure. Various kinds of techniques, such as powder metallurgy (P/M)[75−78], laser perforation[79,80] and metal/gas eutectic unidirectional solidification method (GASAR process)[81] and negative salt-pattern molding process[82−84], were employed to fabricate porous magnesium scaffold or foam for tissue engineering or drug deliver application. Mechanical properties and biocompatibility of some porous magnesium scaffolds are given in Table 2. The configuration of 4 porous magnesium scaffolds is shown in Fig. 4.

Wen et al.[75−77] investigated porous magnesium processed by powder metallurgy technology with the porosity of 35%−55% and the pore size of approximately 70−400 μm. Results indicated that the Young's modulus and stress increased with decreasing porosity and pore size, while the mechanical properties of porous magnesium were in the range of those of natural cancellous bone. Aghion et al.[78] developed a magnesium foam for drug delivery using powder metallurgy technology. They

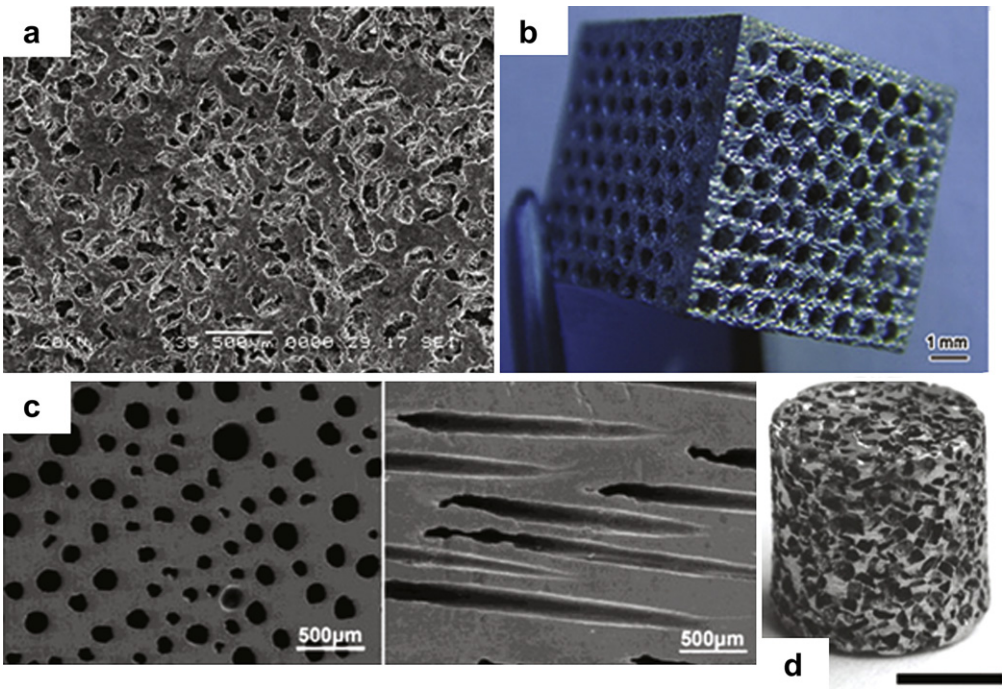

Fig. 4 Configuration of porous magnesium scaffold prepared by powder metallurgy[77] (a), laser perforation[79] (b), GASAR[81] (c) and negative salt-pattern molding cast (scale bar = 2000 μm)[84] (d).

concluded that the release profile of gentamicin from magnesium foam with 10% and 25% spacer in PBS solution is in according with common dissolution kinetics of an active ingredient from polymeric drug delivery systems. Open porous AZ91 scaffolds, cast in a negative salt-pattern molding process, were found to react *in vivo* with an appropriate inflammatory host response and induce extended peri-implant bone remodeling with a good biocompatibility, even though the scaffolds degraded rapidly *in vivo* due to the large surface area[82−84]. Tan et al.[80] designed three-dimensional honeycomb-structured magnesium scaffolds with interconnected pores of accurately controlled pore size and porosity by laser perforation technique. Using orthogonal arrays and the finite element method (FEM), they found that the magnesium scaffold with porosity of 70%, pore size of 300 μm and pore arrangements angle of 90° performed the best compression behavior. Moreover, this porous magnesium coated with β-tricalcium phosphate showed the improved biocompatibility with the human osteosarcoma cells (UMRl06) well adhered and proliferated on the materials surface[79]. Gu et al.[81] prepared lotus-type porous pure magnesium using a metal/gas eutectic unidirectional solidification method (GASAR process). Although the compressive yield strength of porous pure magnesium is lower than the compact one ((23.9 ± 4.9) MPa *vs* (110.3 ± 8.5) MPa) before immersion test, the porous pure Mg exhibits slower decay in compressive yield strength with the extending of immersion period in SBF.

3.1.2. Composite. Magnesium metal matrix composites (MMCs) have gained great interest for their adjustable mechanical properties and corrosion properties (Table 3). In consideration of biocompatibility, reinforcements in magnesium MMCs are usually HA[85−90], FA[91], calcium polyphosphate[92], calcium[91] and so on. Two conventional techniques for fabricating magnesium MMCs are powder metallurgy (P/M)[85,87,88,91−93] and stirring cast method[86,87,89]. Besides that, Gu et al.[94] proposed a novel Mg−Ca-based composite by melt infiltration method using the HA/TCP scaffold as porous preform.

The amount, distribution and size of the reinforcements are of major importance for mechanical and corrosive properties of magnesium MMCs. Because the reinforcements in magnesium

Table 3 Mechanical properties, corrosion rates and biocompatibility of currently investigated magnesium metal matrix composites

Composition	Method	Mechanical properties				Corrosion rate (mm/y)	Cell viability	Ref.
Mg/10HA	P/M	117.3	171.6	6.7	–	1.36	L929, 4 d, ~95%	[85]
Mg/20HA	P/M	105.8	146.9	4.3	58	1.38/~62	L929, 4 d, ~85%	[85, 88]
Mg/30HA	P/M	71.7	92.1	2.6	–	1.43	L929, 4 d, ~65%	[85]
Mg/40HA	P/M	–	68	–	65	~40	–	[88]
Mg/5HAP	Stirring cast	122.3	171.1	–	–	–	–	[87]
Mg/10HAP	Stirring cast	137.0	146.4	–	–	–	–	[87]
Mg/15HAP	Stirring cast	129.6	136.7	0.3	–	–	–	[87]
ZM61/15HAP	Stirring cast	225.5	225.5	0.3	–	–	–	[82]
AZ91D/20HA	P/M	264.3	–	–	40	1.25A	RAW264.7, 2 d, ~100%; MG63, 2 d, ~225%; HBDC, 3 d, ~130%	[89]
Mg−Zn−Zr/HA	Stirring cast	–	–	–	–	0.75	Exhibits better cytocompatibility than Mg−Zn−Zr alloy	[90]
AZ91/10FA	P/M	116.5c	–	5.78	34.1	1.671R	–	[91]
AZ91/20FA	P/M	123.2c	–	5.32	37.5	0.052R	–	[91]
AZ91/30FA	P/M	112.4	–	4.51	42.3	0.008R	–	[91]
ZK60/10CPPp	P/M	~215	~230	–	38	0.002	–	[92]
ZK60/20CPPp	P/M	~210	~220	–	39	0.002	–	[92]
ZK60/30CPPp	P/M	~195	~200	–	38	0.002	–	[92]
Mg/1Ca	P/M	147.78	217.28	14.36	–	–	L929, 4 d, ~95%	[93]
Mg/5Ca	P/M	183.32	202.72	9.03	–	–	L929, 4 d, ~90%	[93]
Mg/10Ca	P/M	119.63	200.25	7.74	–	–	L929, 4 d, ~60%	[93]
HA/TCP-MgCa	Liquid metal infiltration	128.7c	–	13.5	–	0.34	L929, 5 d, ~55% (100% extract); MG63, 5 d, ~60% (100% extract); L929, 5 d, ~95% (50% extract); MG63, 5 d, ~95% (50% extract); L929, 5 d, ~95% (10% extract); MG63, 5 d, ~90% (10% extract)	[94]

Notes: c—the mechanical properties were obtained from compression test; A—the corrosion test was conducted in artificial sea water; R—the corrosion test was conducted in Ringer solution; Other corrosion tests were conducted in SBF.

MMCs are usually hard and brittle, in general, the MMCs exhibit improved compression strength but reduced tensile strength and elongation than the master alloys. The corrosion resistance of MMCs could be either better or worse than the master alloy. Witte et al.[89] claimed that HA particles can stabilize the corrosion rate of AZ91D-HA MMC and exhibit more uniform corrosion attack in artificial sea water and cell solutions mainly due to the uniform passive layer formed on the MMC. However, Gu et al.[85] found that the corrosion rate of Mg/HA composites is larger than that of bulk pure Mg and increased with increasing HA content, which could be explained by that there are more anodic sites forming galvanic coupling in the MMC.

In general, magnesium MMCs with less than 20 wt% and homogenously distributed reinforcements are desirable.

3.1.3. Glassy state. Magnesium-based bulk metallic glasses (BMGs) are designed by taking advantage of their uniform corrosion behavior resulted from single-phase structure and chemical homogeneity. Zberg et al.[95] reported Zn-rich magnesium-based BMGs $Mg_{60+x}Zn_{35-x}Ca_5$ ($0 \leq x \leq 7$) without clinically observable hydrogen evolution *in vivo*. Gu et al.[96] found $Mg_{66}Zn_{30}Ca_4$ exhibited a decreased corrosion rate, uniform corrosion morphology and improved cytocompatibility, with MG63 cell well adhered and growth on its surface.

3.2. Control of the degradation rate of magnesium alloys by surface modification techniques

In order to slow down the corrosion rate of magnesium alloys, as well as to maintain their mechanical integrity and to improve their biocompatibility, various surface modifications have been developed. Table 4 summaries *in vitro* and *in vivo* corrosion rate and biocompatibility of surface modified magnesium alloys.

3.2.1. Anodic oxidation & microarc oxidation (MAO) coatings. Hiromoto et al.[97] investigated the anodization treatment of pure Mg and found that porous films, which showed local corrosion, were formed at 7 and 100 V, and non-porous films were formed at 2 and 20 V. Guo et al.[98] reported that magnesium oxide film on AZ31B magnesium alloy synthesized by anodic oxidation technique at a constant current can efficiently delay the degradation process of AZ31B magnesium alloy, as well as reduce the mutagenesis and hemolytic reactions. Zhang et al.[99] reported an improvement in the corrosion and wear resistance of AZ91D alloy in Hank's solution after MAO treatment. Yao et al.[100] introduced Ca and P into a ceramic coating on MAO-treated AZ91D alloy and found that the coating reduced the corrosion current density by two orders of magnitude. Gu et al.[101] suggested that MAO showed beneficial effects on the corrosion resistance, and thus improved the cell adhesion to the Mg−Ca alloy.

3.2.2. Calcium phosphate coatings. Calcium phosphate coatings are the most widely studied coatings for biomedical magnesium alloys for orthopedic applications because of their excellent biocompatibility, nontoxicity, bioactivity, bone inductivity, and stability. Many surface coating techniques, such as chemical immersion, alkali-heat treatment and electrodeposition, were developed to synthesize many kinds of calcium phosphate coatings.

Chemical immersion method is a low cost and simple technique suitable for preparing calcium phosphate coatings, such as brushite (dicalcium phosphate dihydrate, DCPD)[103−105] and hydroxyapatite (HA)[106,107], on substrates of multiple materials and various shapes. All the coatings can induce bone-like apatite deposition on the surface, leading to good bioactivity both *in vitro* and *in vivo*.

Alkali-heat treatment is also a simple and effective surface modification method for metallic biomaterials. Li et al.[1] reported that alkali-heat treatment could enhance the corrosion resistance of pure Mg and no signs of morphological changes on cells or inhibitory effect on cell growth were detected in cytotoxicity tests. Gu et al.[109] used different alkaline solutions to alkali-heat treat an Mg−Ca alloy and found the corrosion rate of samples followed the ranking order $NaHCO_3$ heated $<Na_2HPO_4$ heated $<Na_2CO_3$ heated, while none of the alkali-heat treated Mg−Ca alloys induced toxicity to L929 cells.

DCPD, HA and fluoridated hydroxyapatite (FHA) coatings have been prepared by electrodeposition technique[110−116]. Song et al.[111] electrodeposited DCPD and FHA layers onto a Mg−6Zn alloy. The DCPD coating was subsequently alkali-heat treated to form HA. They found all the coatings can significantly decrease the degradation rate of Mg alloy and both the HA and FHA coating can promote the nucleation of osteoconductive minerals, whereas the FHA coating is the most stable one[110]. Further study indicated that the bioactive FHA coated Mg−6Zn alloy presented more stimulation effects to human bone marrow stromal cells (hBMSC) proliferation as well as differentiation[111].

3.2.3. Fluorinated coatings. Fluoride treatments have been extensively reported to improve the corrosion resistance of Mg and its alloys in industrial application[119−121]. Recent studies indicated that they could also be used to degrade cytotoxicity of implants[122] and promote osseointegration in the early phase of healing following implant installation[123]. Yan et al.[124] successfully prepared a fluoridated coating on AZ31B magnesium alloy, which could maintain the mechanical property of the alloy for as long as 45 days in SBF. Witte et al.[125] found that MgF_2 coating could reduce *in vivo* corrosion rate of LAE442 alloy with no elevated fluoride concentration in the adjacent bone. Drynda et al.[26] developed fluoride-coated magnesium−calcium alloys that exhibit improved mechanical features, decreased degradation kinetics and good biocompatibility toward vascular cells. However, another study demonstrated that the MgF_2 coating could not decrease the corrosion rate or maintain the mechanical strength sufficiently[126].

3.2.4. Polymer coatings. Some biodegradable polymers coatings on magnesium alloy have been investigated. Wong et al.[128] reported a biodegradable polymer-based porous membrane on AZ91 magnesium alloy made of polycaprolactone and dichloromethane, which can significantly control the corrosion rate, maintain the mechanical property and promote more new bone forming *in vivo*. Gu et al.[129] studied the influence of molecular weight and layer numbers of chitosan coating on the corrosion resistance of Mg−Ca alloy. They concluded that the six-layer coating prepared by chitosan with a molecular of 2.7×10^5 had a smooth and intact surface morphology, suggesting the slowest corrosion rate of Mg−Ca alloy in SBF. Li et al.[130] adopted a poly(lactic-co-glycolic acid) (PLGA) coating on Mg−6Zn alloy and the coated alloy showed improved corrosion resistance and enhanced cell attachment than the bare one.

3.2.5. Other treatments. There are many other methods to coat or modify the surface of magnesium alloys, such as heat-stearic acid treatment[132], ion-beam assisted deposition (IBAD)[133,134], magnetron sputtering[135], ion implantation[136,137], laser shock peening[138], laser surface melting[139], and the list is still increasing.

Table 4 A summary of *in vitro* and *in vivo* corrosion rate and biocompatibility of surface modified magnesium and its alloys

Alloy	Working history	Coating	Method	V_{corr} *in vitro* (mm/y)			V_{corr} *in vitro* ($ml/cm^2/d$)		V_{corr} *in vivo* (mm/y)	Biocompatibility		Ref.
				SBF	Hank's	0.9% NaCl	SBF	Hank's		*In vivo*	*In vivo*	
Mg	As-cast		$NaHCO_3$—$MgCO_3$ alkali-heat treatment	–	–	–	–	–	–	No inhibitory effects on marrow cells growth No signs of cellular lysis	–	[1]
	As-cast	β-TCP	Na_2HPO_4 alkali-heat treatment	–	–	–	–	–	–	MG63, 10 d, viability ~ 80%	–	[108]
	As-cast	Stearic acid	Heat-self-assembled monolayer	–	–	–	–	–	–	No inhibitory effects on marrow cells growth; hemolysis is 0	New bone mineralizes obviously on the interface and the osteoclast cells array orderly	[19, 127]
Mg—0.8Ca	As-extruded	MgF_2	Fluoride treatment	–	–	–	–	–	0.302	After 10 d smooth muscle and endothelial cells around the alloys were still alive, whereas colonization of the surfaces was only observed for smooth muscle cells	New bone formed	[26, 126]
Mg—1Ca	As-cast		Na_2HPO_4 alkali-heat treatment	2.08	–	–	0.7	–	–	No obvious toxicity to L929 cells	–	[109]
	As-cast		Na_2CO_3 alkali-heat treatment	2.27	–	–	0.86	–	–	No obvious toxicity to L929 cells	–	[109]
	As-cast		NaHCO3 alkali-heat treatment	2.29	–	–	0.48	–	–	No obvious toxicity to L929 cells	–	[109]
	As-cast	DCPD	Electrodeposition	–	0.17	–	–	–	–	–	–	[115]
	As-extruded	DCPD	Electrodeposition	–	0.14	–	–	–	–	–	–	[116]
	As-extruded	Chitosan		–	–	–	0.312—0.686	7	–	–	–	[129]
Mg—6Zn	As-extruded	DCPD	Electrodeposition	–	–	1.9×10^{-3} -2.2×10^{-3}	~0.07	–	–	–	–	[110]
	As-extruded	HA	Electrodeposition	–	–	–	~0.06	–	–	–	–	[110]
	As-extruded	FHA	Electrodeposition	–	–	–	~0.02	–	–	Present more stimulation effects to hBMSCs proliferation and differentiation; can up-regulate main osteogenic genes after 21 d of culture	–	[110, 111]
	As-extruded	PLGA	Dipping	0.68—1.18	–	–	–	–	–	Significantly enhanced ability of	–	[130]

(*Continued on next page*)

Table 4 (*continued*)

Alloy	Working history	Coating	Method	V_{corr} *in vitro* (mm/y)			V_{corr} *in vitro* (ml/cm^2/d)		V_{corr} *in vivo* (mm/y)	Biocompatibility *In vivo*	Biocompatibility *In vivo*	Ref.
				SBF	Hank's	0.9% NaCl	SBF	Hank's				
Mg−Mn−Zn	As-extruded	DCPD		–	–	0.09 −0.30	–	–	–	MC3T3 cell attachment Better surface cytocompatibility than naked Mg−Mn−Zn and pure Ti	Significantly improved osteoconductivity and osteogenesis in the early first 4 weeks	[104, 105]
Mg−Zn−Ca	As-cast	Ca-deficient HA	Electrodeposition	0.56	–	–	–	–	–	–		[113]
AZ31	As-cast	HA	IBAD	–	–	–	–	–	–	–	–	[134]
	As-cast	Ca−P	Electrodeposition and alkali-heat treatment	–	–	–	–	–	–	Hemolysis is 2.5%	New bone formed; slighter inflammation than the bare alloy	[117]
	As-cast	C−N	IBAD	–	–	–	–	–	–	–	–	[131]
		CeO2\ MgO	Rare earth conversion	–	–	0.03	–	–	–	Good anti-clotting property equivalent to that of 316L stainless steel	–	[141]
	As-cast	MgO	Anodic oxidation	–	–	–	–	–	–	Does not affect the proliferation and the bone formation of osteoblast; hemolysis is 4.3%	–	[98]
	As-extruded	DCPD	Electrodeposition	–	0.06	–	–	–	–	–	–	[116]
	As-extruded	MgF_2	Fluoride treatment	–	2.26	–	–	0.0011	–	–	–	[118]
AZ91	As-cast		MAO	3.4×10^{-3} -7.1×10^{-4}	$4.34/4.6 \times 10^{-3}$	0.09	–	–	–	–	–	[99, 102, 103, 118]
	As-cast		Laser surface melting	0.17	–	–	–	–	–	–	–	[139]
	As-cast	α-Si:H	Magnetron sputtering	0.08	–	–	–	–	–	hFOB1.19 cells attach well on the coating and proliferate normally	–	[135]
WE43		Chitosan		–	0.05	–	–	–	–	–	–	[131]
LAE442	As-extruded	MgF_2	Fluoride treatment	–	–	–	–	–	0.77	–	In direct bone contact and without a fibrous capsule:no elevated fluoride concentration in the adjacent bone	[125]

4. Environmental Factors Influencing Corrosion Behavior of Magnesium

It is very important to understand corrosion mechanism of magnesium implants *in vivo* and set up a reliable *in vitro* test bench to estimate the *in vivo* degradation process. However, previous results of *in vitro* and *in vivo* study are in poor correlation between the observed corrosion rates. Magnesium alloys display dramatically faster degradation *in vitro*[140]. In order to improve the accuracy of *in vitro* prediction, we should fully understand the factors that influence *in vivo* degradation of magnesium implants.

4.1. Chemical composition of corrosion media

It is widely accepted that the degradation of magnesium and its alloys strongly depends on the composition of corrosion media. The corrosion of magnesium alloy in solutions proceeds by following reactions:

$$Mg \rightarrow Mg^{2+} + 2e^{-}$$

$$2H_2O + 2e^{-} \rightarrow H_2 + 2OH^{-}$$

$$Mg^{2+} + 2OH^{-} \rightarrow Mg(OH)_2$$

According to the above reactions, $Mg(OH)_2$ formed on the surface of the magnesium sample. Chloride ion is known to be detrimental to corrosion resistance of magnesium. The chloride ions can transform $Mg(OH)_2$ into more soluble $MgCl_2$. A lot of investigations have proven that high chloride concentration will accelerate the transform reaction of $Mg(OH)_2$ to $MgCl_2$ and promote the dissolution of magnesium alloy. Sulfate ions also attack magnesium[142]. It is reported that calcium ions are only precipitated together with phosphates on the surface, but phosphates can be deposited without calcium[143]. Phosphate ions can retard the corrosion rate effectively and delay the emergence of pitting corrosion[142].

Currently used artificial biological fluid for *in vitro* test are quite diversiform, such as NaCl solution, Hank's solution, SBF, artificial plasma (AP), Dulbecco's modified Eagle's medium (DMEM) and so on. SBF and Hank's solution are more aggressive than AP[144,145] mainly due to the higher chloride concentration. Hank's solution is more aggressive than DMEM[146], which may also be explained by the higher chloride concentration and the lower hydrocarbonate concentration. It is important to realize that chloride concentration of all above solutions is higher than that in human plasma.

Albumin and amino acid added in biological fluid can form an absorbed layer on the surface of magnesium alloy[146−148]. The absorbed layer can either promote or weaken the corrosion resistance of magnesium alloys depending on the composition of corrosion layer[146,147].

The corrosion of Mg and its alloys is also markedly affected by the presence of different buffers. Both Tris−HCl[149] and HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)[150] promote corrosion of magnesium. $NaHCO_3$ is a buffer present in human body. Hydrocarbonate ions promote the dissolution of magnesium during early immersion but induce rapid surface passivation due to precipitation of magnesium carbonate, which totally suppresses pitting corrosion[142].

4.2. Solution volume/surface area ratio

Yang and Zhang[145] found low solution volume/surface area (SV/SA) ratio resulted in a high pH, which resisted the corrosion. But when the ratio was high enough, 6.7 for example, the influence was negligible. They suggest that Hank's solution with a high SV/SA ratio, such as 6.7, and Hank's solution with a low SV/SA ratio, such as 0.67, should be selected to simulate the *in vivo* degradation behavior of magnesium bone screw in a bone marrow cavity and magnesium plant and screw in cortical bone or muscle tissue, respectively. SBP solution with a high SV/SA ratio, *e.g.* 6.7, should be chosen to simulate the degradation of magnesium stent in artery.

4.3. Flow

To understand the corrosion behavior of magnesium stents in a blood vessel, it is necessary to take the influence of flow into consideration. Hiromoto et al.[151] found that the existence of flow prevented the accumulation of the corrosion product and promoted uniform corrosion, leading to an increase of the anodic current density and a decrease of the impedance. Levesque et al.[152] reported that when the stress applied by the flow is low, it protects the surface from localized corrosion, while when it is very high, in addition to high uniform corrosion, some localized corrosion also occurs[152].

5. Concluding Remarks

Development of biodegradable magnesium implants has revolutionized the concept of metallic biomaterials. A qualified magnesium alloy implant should be one of matching corrosion rate with tissue healing rate, sufficient mechanical properties and acceptable biocompatibility. It is challenging but still promising to obtain such new kind of biodegradable metallic implants or devices. Mechanical properties strongly depend on the grain size, the solubility of alloying elements and the size, amount and distribution of the second phase. So the composition of the alloy, the heat-treatment and processing technique should be carefully designed. Emerging processing technique such as severe plastic deformation (SPD) can be adopted to fabricate magnesium alloys with ultra-fine grain and excellent mechanical properties. Because of the low plastic deformation ability of magnesium, one difficulty in fabrication of magnesium-based cardiovascular stents is the drawing of minitubes from which the stents are cut. Electroforming is reported to be used to produce fine grain biodegradable iron stent minitubes directly on a cylindrical mandrel[153]. We hope new technique for the fabrication of magnesium minitubes will also emerge. Moreover, the influence of manufacturing process on the implants surface, such as turning, cutting, laser cutting and electro discharge machining, should be investigated. In order to produce magnesium alloy implants with controllable degradation rate and prolonged mechanical stability, coating is indispensable. In many cases, a single layer of coating cannot sufficiently insulate the substrate from the surrounding solution. Thus, composite coatings with two or more layers fabricated by combined different techniques might be a promising solution. It is necessary to reach a uniform criterion to evaluate the biomedical properties of magnesium alloy and establish a reliable *in vitro* test bench to estimate the *in vivo* degradation process. There are some questions need to be solved in the future, such as influence of local pH change on adjacent tissue, metabolic pathway of hydrogen gas and

insoluble second phase particles, *etc*. Furthermore, Ren et al.[154] found magnesium-based implants show antibacterial function due to the increase of pH value. This function is clinically valuable since infections associated with surgical implants are currently becoming a serious issue. Besides orthopedic and cardiovascular implants, biodegradable magnesium can be used for many other applications. A novel magnesium-based bioabsorbable microclip for laryngeal microsurgery[155] and a magnesium wire that can meet the requirements of a resorbable suture[156] are reported recently. In a word, the development of magnesium-based implants or devices is an area wide open for exploration and innovation.

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