HOSTED BY

ELSEVIER

CrossMark

Available online at www.sciencedirect.com

ScienceDirect

Progress in Natural Science: Materials International 24 (2014) 414–422

Progress in Natural Science Materials International

www.elsevier.com/locate/pnsmi
www.sciencedirect.com

REVIEW

Progress of biodegradable metals

Huafang Li[a], Yufeng Zheng[a,*], Ling Qin[b]

[a]Department of Materials Science and Engineering, College of Engineering, Peking University, Beijing 100871, China
[b]Department of Orthopedics & Traumatology, The Chinese University of HongKong, Shatin, Hongkong, China

Received 2 July 2014; accepted 1 September 2014
Available online 30 October 2014

Abstract

Biodegradable metals (BMs) are metals and alloys expected to corrode gradually *in vivo*, with an appropriate host response elicited by released corrosion products, then dissolve completely upon fulfilling the mission to assist with tissue healing with no implant residues. In the present review article, three classes of BMs have been systematically reviewed, including Mg-based, Fe-based and Zn-based BMs. Among the three BM systems, Mg-based BMs, which now have several systems reported the successful of clinical trial results, are considered the vanguards and main force. Fe-based BMs, with pure iron and Fe–Mn based alloys as the most promising, are still on the animal test stage. Zn-based BMs, supposed to have the degradation rate between the fast Mg-based BMs and the slow Fe-based BMs, are a rising star with only several reports and need much further research. The future research and development direction for the BMs are proposed, based on the clinical requirements on controllable degradation rate, prolonged mechanical stability and excellent biocompatibility, by optimization of alloy composition design, regulation on microstructure and mechanical properties, and following surface modification.

Keywords: Biodegradable metals; Magnesium; Iron; Zinc; Biocompatibility

1. Introduction

With the development of society and the improvement of living standards, the expectation for a better quality of life has been increasing. Researchers have to develop new materials and technologies in order to provide implants with higher clinical performance. In practical clinic applications, some specific clinical problems (such as bone fracture and vessel blockages) need only temporary support for tissue healing process. This temporary support can only be provided by an implant made of degradable biomaterials which allow the implant to progressively degrade after fulfilling its function. The concept of biodegradation has been known in medical applications for a long time, such as the use of biodegradable polymer sutures. However, implants that degrade, especially those made of metals and alloys, can be considered as a novel concept which actually breaks the established paradigm of "metallic biomaterials must be corrosion-resistant"[1].

The definition of biodegradable metals (BMs) had been given as follows: BMs are metals expected to corrode gradually *in vivo*, with an appropriate host response elicited by released corrosion products, then dissolve completely upon fulfilling the mission to assist with tissue healing with no implant residues. Therefore, the major component of BMs should be essential metallic elements that can be metabolized by the human body, and demonstrate appropriate degradation rates and modes in the human body [2].

*Corresponding author. Tel./fax: +86 10 62767411.
E-mail address: yfzheng@pku.edu.cn (Y. Zheng).
Peer review under responsibility of Chinese Materials Research Society.

http://dx.doi.org/10.1016/j.pnsc.2014.08.014

Till now, the newly-developed BMs include three main body systems: Mg-based BMs [3–9] (pure Mg, Mg–Ca alloys, Mg–Zn alloys, Mg–Sr alloys, Mg–RE alloys, Mg-based bulk metallic glasses (BMGs), etc.), Fe-based BMs [10–13] (pure Fe, Fe–Mn alloys, Fe–W alloys etc.), Zn-based BMs [14–17] (pure Zn, Zn–Mg alloys and Zn-based bulk metallic glasses) and other BMs (Ca-based [18–21] and Sr-based BMGs [22–24], etc.). Fig. 1 shows the research status of the three main body BM systems: Mg-based BMs [4,7,9,25–42], Fe-based BMs [12,13,43–49], and Zn-based BMs [15–17,50–52]. It is quite clear that among these BMs, Mg-based BMs [3–9] are the research's vanguard and main force with hundreds of publications on the *in vitro* cytoxicity, animal testing and clinical trails, Fe-based BMs [10–13] are reported in tens of publications on alloy design and several animal testing as potential vascular stent, Zn-based BMs [14–17] are referred with less than ten publications but seems to be a rising star in the family of biodegradable metals.

2. Mg-based BMs

Mg based BMs are attractive for biodegradable implants because of their good mechanical properties and biocompatibilities. Promising Mg alloying systems including Mg–Ca, Mg–Sr, Mg–Zn, Mg–Si, Mg–Sn, Mg–Mn, Mg–RE and Mg–Ag have been developed [3–9]. The microstructures, mechanical properties, degradation behavior, ion release, in vitro and in vivo animal biocompatibility studies and clinical trials have been widely explored in order to evaluate their feasibility for biomedical purposes.

2.1. Mechanical properties

Fig. 2 shows the tensile properties of magnesium alloys, including pure Mg [30], Mg–Zn–Mn [53], Mg–Ca [4], Mg–Sr [7], Mg–Si [30], Mg–Zr [30], AZ91D [54], AZ31 [54], LAE442 [54], WE43 [54].

It is quite clear that magnesium alloys have a large range of ultimate tensile strength (UTS) and elongation to failure (EL), from 86.8 to 300 MPa and from 3% to 30%, respectively. Alloying and processing history have great effect on the mechanical properties of magnesium alloys. Adding Sn, Si, Zr and Zn can improve both the UTS and EL [30], while Ca, Sr and Mn will deteriorate their ductility to some extent [4,7,30]. Processing deformation (including hot rolling, hot extruding, and ECAP) also contribute to the strength and elongation of magnesium alloys [4,7,32].

2.2. Corrosion behavior

Although the reported inspiring results indicated that Mg-based BMs may be possible alternatives for permanent biomaterials. However, Mg-based BMs have rapid degradation rates in body fluids. The rapid degradation rate would result in the loss of mechanical integrity in a short period which can limit its application as an implant material. To control the biodegradation rate of Mg-base BMs, selection on alloying elements, microstructural adjustment and surface modification methods have been applied.

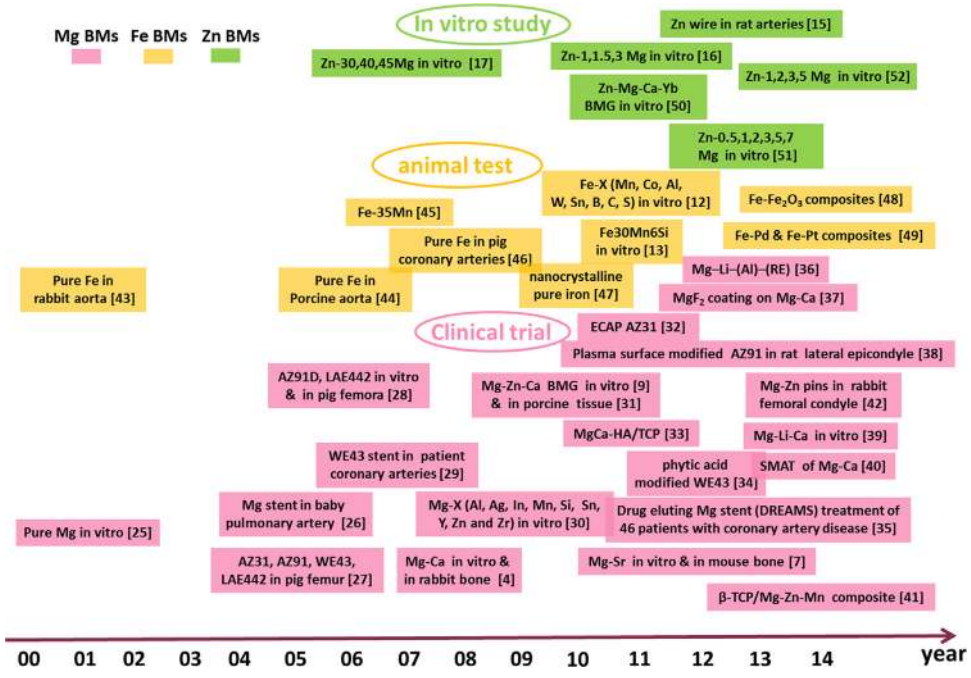

Fig. 1. Research status of the three BM systems: Mg-based BMs [4,7,9,25–42], Fe-based BMs [12,13,43–49], and Zn-based BMs [15–17,50–52].

(1) Addition of the alloying elements. WE43, ZW21 and WZ21 containing Zn, Y, Ca RE (rare earth metal) and Mn as alloying elements showed fine and even microstructures with grain sizes smaller than 10 μm, which generated exceptional plasticity of 17% and 20% at ambient temperature [55–57]. These WE43, ZW21 and WZ21 alloys also exhibited fairly homogeneous degradation behavior in physiologically simulated solutions and a higher corrosion resistance than that of ZQ30 alloy magnesium alloys [55,56]. *In vitro* cell tests indicated good cytocompatibility. Animal implantation studies of WZ21 alloy disc specimens revealed a promising *in vivo* performance of the alloy [56].

(2) Slowing down the biodegradation rate by surface coatings. HA coatings were produced on AZ91D in a two-step process, which was shown to slow down the corrosion process in SBF [58]. PCL coatings were developed on AZ91 samples. Polarization and immersion tests in SBF were carried out, which showed that the polymer coating reduced the degradation rate, which was controlled by the degree of porosity. A two-step coating process was introduced for WE42 alloy, and corrosion studies using polarization and EIS methods in Hank's solution showed increased corrosion resistance after coating [59].

(3) Composited with other degradable biomaterials. Adding ZnO into Mg-based BM matrix to form composites is proved to improve the tensile strength, surface hardness, and corrosion resistance [60].

(4) Microstructural refinement. Ultrafine-grained structure of Mg-based BMs obtained by rapid solidification (RS) [61] or severe plastic deformation techniques (SPD), such as the equal channel angular pressing (ECAP) [62], high pressure torsion (HPT) [63], or cyclic extrusion and compression (CEC) [64] are favorable for mechanical properties and corrosion resistance. The grain size of Mg–3Ca alloy was refined to 200–500 nm by rapid solidification (RS) and the grain size decreased with increasing cooling rate. In comparison with the as-cast Mg–3Ca alloy, the Mg–3Ca alloy with ultrafine-grained structure processed by RS exhibited dramatically reduced degradation rate from 21 mm/yr to 0.36–1.43 mm/yr (the higher the RS speed, the lower the degradation rate) and exhibited more uniform corrosion morphology on the surface [65]. The as-CECed Mg–Nd–Zn–Zr alloy exhibited fine grain size (about 1 μm) and largely improved tensile properties (71% and 154% higher YS and elongation than the as-extruded Mg–Nd–Zn–Zr alloy). The degradation rate was slowed down after CEC process [66]. Similarly, the ultrafine-grained Mg–Zn–Ca alloy prepared by the HPT process demonstrated improved corrosion resistance compared to its as-extruded counterpart [63].

(5) Glassy structure. Compared with conventional crystalline pure Mg and Mg alloys, Mg-based BMGs with amorphous microstructure have been found to have higher corrosion resistance, higher strength and lower elastic modulus due to the single structure without defects of grain boundary. Zberg et al. [31] and Gu et al. [9] have studied the corrosion behavior, cellular response and tissue response of Mg–Zn–Ca BMGs and the results demonstrated that Mg–Zn–Ca BMGs present more uniform corrosion morphology compared with conventional crystalline Mg alloys and has much lower corrosion rates, and show higher cell viabilities than conventional crystalline pure Mg. In addition, the *in vivo* study indicated that no tissue-imprinted hydrogen gas cavities have formed in the histological preparations of the Mg–Zn–Ca BMG samples and no inflammatory reaction was observed [31]. To make the final medical devices such as woven stent of Mg-based BMGs, Zberg et al. [67] produced wires with very good surface quality via a melt-extraction setup which show extended homogeneous plastic deformation in tensile tests. A significantly improved ductility of Mg-based BMGs under bending and tensile loading through minor alloying with rare-earth element ytterbium (Yb) was done by Yu et al. [68], and the achieved plastic strain was about 0.5% after adding 2% and 4% Yb into MgZnCa glasses. Additionally the in vitro biocompatibility of Mg-based BMGs was also improved by Yb-alloying as confirmed by indirect cytotoxicity and direct cell adhesion, extension and proliferation assays [68].

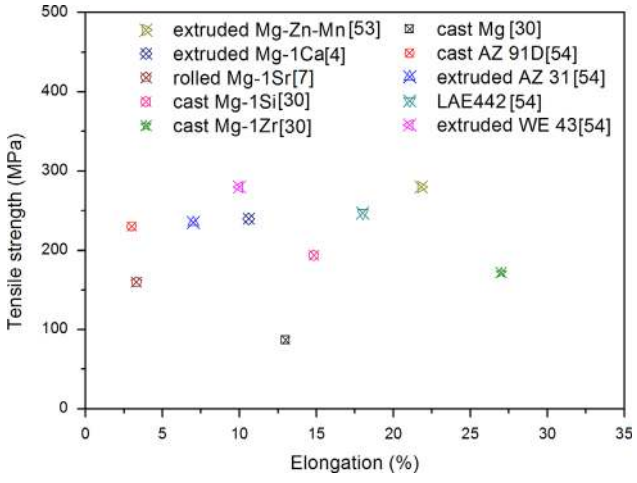

Fig. 2. Tensile properties of magnesium alloys: pure Mg [30], Mg–Zn–Mn [53], Mg–Ca [4], Mg–Sr [7], Mg–Si [30], Mg–Zr [30], AZ91D [54], AZ31 [54], LAE442 [54], WE43 [54].

2.3. Clinical trials

In 2005, Zartner et al. [26] reported that they have successfully rescued the life of a preterm baby from an extremely severe clinical congenital heart disease via implanting a biodegradable Mg stent in the left pulmonary artery of the baby. The follow-up procedure showed the complete degradation occurred during 5 months and no in-stent obstruction or neointimal hypertrophy could be observed [26]. WE43 stents were implanted into the coronary arteries of 63 patients. Angiography at 4 months showed an increased diameter stenosis of 17.0%. After serial intravascular ultrasound examinations, only small remnants of

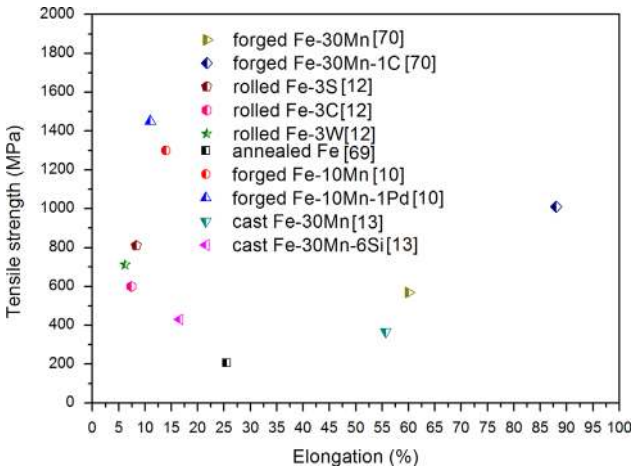

Fig. 3. Tensile properties of iron alloys: pure Fe [69], Fe–3C [12], Fe–3S [12], Fe–3W [12], Fe–10Mn [10], Fe–10Mn–1Pd [10], Fe–30Mn (forged) [70], Fe–30Mn (cast)[13], Fe–30Mn–1C [70], Fe–30Mn–6Si [13].

the original struts were visible, well embedded into the intima. Neointimal growth and negative remodeling were the main operating mechanisms of restenosis [29]. Drug-eluting Mg-based scaffold (DREAMS) was implanted into 46 symptomatic patients with de-novo coronary lesions and clinical follow-up was scheduled at 1, 6, 12, 24, and 36 months. Two of 46 (4%) patients had target lesion failure at 6 months (both clinically driven target lesion revascularizations), which rose to three of 43 (7%) at 12 months (one periprocedural target vessel myocardial infarction occurred during angiography at the 12 month follow-up visit). No cardiac death or scaffold thrombosis was noted [35].

3. Fe-based BMs

3.1. Mechanical properties

Fig. 3 summarized the mechanical properties of Fe-based BMs including pure Fe [69], Fe–3C [12], Fe–3S [12], Fe–3W [12], Fe–10Mn [10], Fe–10Mn–1Pd [10], Fe–30Mn (forged) [70], Fe–30Mn (cast)[13], Fe–30Mn–1C [70], Fe–30Mn–6Si [13].

From Fig. 3 we can see that Fe-based BMs have high strength (up to 1450 MPa) and high ductility (up to 80% elongation) thus make them favored candidates for biodegradable stents. The high strength can be helpful in making stents with thinner struts. The high ductility can be helpful during the implantation of stent when the stent is plastically deformed.

3.2. Biocompatibility evaluations

Up to now, there is no clinical report about Fe-based stents. Several animal tests have been reported and the main results are listed below.

Peuster et al. firstly implanted pure Fe into descending aorta of New Zealand white rabbits [43] and minipigs [44] as bio-
degradable stent. The results showed no significant evidence of inflammatory response or neointimal proliferation, and organ examination did not reveal any systemic toxicity. There was also a maintained stent patency and no adverse events during a 6–18 month follow-up. Besides, the stents maintained their mechanical properties during the implantation without any failure. However, their results demonstrated that faster degradation rate is desirable for iron and further studies have to focus on the modification of the composition and design of the stent to expedite the degradation process [43,44]. The suggested mechanisms were either using iron-based alloys with a more pronounced corrosion rate or increasing the surface of the stent along with reduction of the strut thickness and modification of the stent design [71].

3.3. Acceleration on biodegradation rate

Based on these above *in vivo* test results, following investigations have been performed in order to accelerate the degradation rate of Fe-based BMs while still maintaining their mechanical properties. On the one hand, Mn, Pd, W, Sn, B, C, S, Si, etc. were introduced into Fe as alloying elements [12,13]. The corrosion rate of Fe30Mn6Si alloy was higher than that of Fe30Mn alloy. Fe30Mn6Si alloy showed to inhibit the metabolic activity of human endothelial cells (ECV304) and rodent VSMC to a higher extend compared to pure iron [13]. The alloying elements, including Mn, Co, W, B, C, and S were found to improve the yield and ultimate strength of iron, whereas the alloying element Sn led to a severe reduction in the mechanical properties [12].

Microstructure adjustment is another factor that has been employed to modify the corrosion rate of Fe BMs. Generally, the corrosion of electroformed iron is higher. The smaller grains of electroformed iron provide higher grain boundary area and are more susceptible to the corrosive attack. The high density of microstructural defects in electroformed iron is another reason for the higher corrosion rate [72]. The corrosion mechanism of electroformed iron appeared to be uniform as no localized attack was observed after the degradation testing. Besides, electroformed iron has no inhibition to cell metabolic activity of primary rat SMCs compared to 316L SS [72].

4. Zn-based BMs

4.1. Unique advantages of Zn-based BMs

Zinc is an essential element for human beings, and it is the second most abundant transition metal element in human body [73]. Zinc serves as a cofactor in all six classes of enzymes [74] as well as several classes of regulatory proteins

Table 1
Comparison of the corrosion rates of the Mg-, Fe- and Zn-based BMs.

Alloy system		State	*In vitro* (mm/year)		*In vivo* (mm/year)	References
			Electrochemical test	Immersion test		
Mg BMs	**Mg**		0.20	0.10 ± 0.07		[76]
	Mg–6Zn	Extruded	0.16	0.07 ± 0.02	2.32 ± 0.11	[76]
	Mg–1Ca	Cast		12.56	1.27	[4]
	LAE442	Cast	6.9	5.535	0.46 ± 0.11	[28,77]
	Mg–10Gd	Cast		1.25 ± 0.2		[8]
	Mg–8Y	Cast	2.17 ± 0.23			[78]
	Mg–0.8Ca	Extruded			0.39 ± 0.1	[79]
	Mg–2Sr	Rolled	0.87 ± 0.08	0.37 ± 0.05	1.01 ± 0.07	[7]
Fe BMs	**Fe**	Cast	0.105	0.012		[12]
	Fe–2W	SPS	0.075	0.026		[80]
	Fe–0.5CNT	SPS	0.099	0.048		[80]
	Fe–Mn	Cast	0.105	0.0018		[12]
	Fe–W	Cast	0.151	0.016		[12]
Zn BMs	**Zn**	Cast		0.08	0.02	[16]
	Zn–1Mg	Cast		0.09		[16]

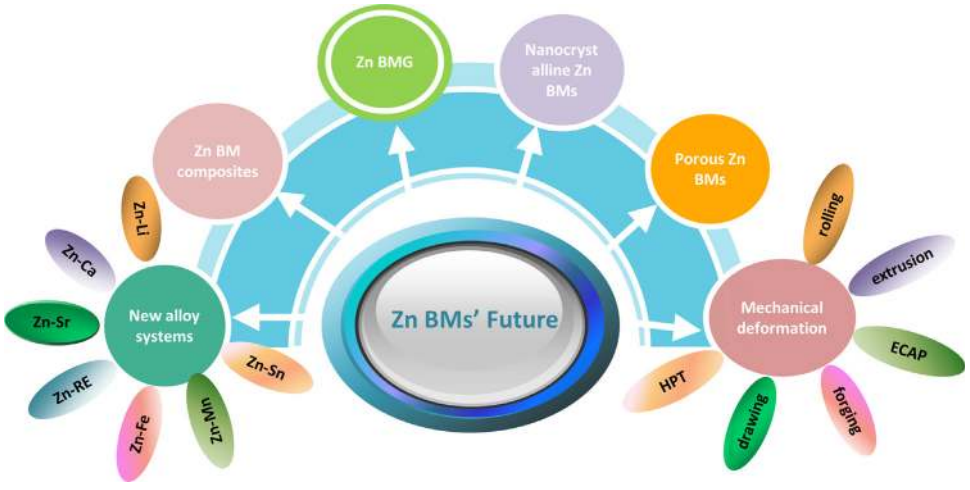

Fig. 4. Future research directions of Zn-based BMs.

[75]. Zinc has been widely used as an alloying element in Mg-based BMs.

According to the standard electrode potential, i.e. Mg (-2.37V) < Zn (-0.763V) < Fe(-0.440V) (vs. SHE), which means that Zn has a corrosion rate faster than Fe, but slower than Mg. Table 1 summarizes the corrosion rates of the Mg-, Fe-, and Zn-based BMs. Considering Mg-based BMs need decreased degradation rate while the Fe-based BMs need enhanced degradation rate, Zn-based BMs are believed to be the next rising stars in the BM family.

4.2. Research status of Zn-based BMs

At present, there is only 1 scientific paper reported the *in vivo* results on Zn-based BMs. Pure zinc wires were placed into the arteries of rats and they degraded at a rate just below 0.2 mm per year—the "magic" value for bioabsorbable stents—for the first three months. After that, the corrosion accelerated, so the implant would not remain in the artery for too long. Moreover, the rats' arteries appeared healthy when the wires were removed, with tissue firmly grasping the implant [15].

4.3. Future research directions of Zn-based BMs

One drawback of pure Zn as potential biodegradable metal lies in that pure Zn has quite low strength and plasticity (UTS < 20 MPa and EL < 30% for the as cast pure Zn [16]). In order to modify the mechanical properties of pure Zn,

adding alloying elements, microstructural adjustment, etc., would be the appropriate ways, as illustrated in Fig. 4.

4.3.1. Choosing appropriate alloying elements and form new Zn-based BMs

Mg was chosen as the alloying element and formed Zn–Mg binary alloys by casting method. The as cast Zn–Mg binary alloys were found to have greatly-enhanced microhardness, tensile strength, elongation compared with pure Zn [16,17,81]. Besides the reported Zn–Mg BMs, the essential nutrient Ca, Sr, Sn, Fe and other alloying elements RE, Li, Mn, Si which commonly applied as alloying elements in biomedical Mg-based and Fe-based BMs can be considered as the potential alloying elements when developing new Zn-based BMs.

4.3.2. Hot/cold working

Mechanical deformation is another effective mean to improve the mechanical and corrosion properties of BMs [2,4,61]. Rolling (hot/cold), extrusion, equal-channel angular pressing (ECAP), high pressure torsion (HPT), drawing, forging are the most commonly-used process methods for BMs' properties enhancement. It has been reported that these severe plastic deformation methods have dramatically improved the mechanical strength [82–85], elongation [82,83,85], vickers' hardness [86–88], corrosion behavior [86,89–91], biocompatibility [92] of BMs. Clearly these are adoptable and promising techniques for Zn-based BMs in the future.

4.3.3. Zn-based nanocrystalline and BMGs

It is well known that the mechanical properties, corrosion behaviors and biocompatibility of metallic alloys are strongly influenced by alloying elements as well as by the microstructure. Materials with amorphous, nano- or quasicrystalline structure [93] that exhibit very promising physical, mechanical and chemical properties, e.g. high corrosion resistance.

In general, nanocrystallinity is assumed to improve the mechanical behavior as well as the corrosion resistance[94] of an alloy as compared to its conventional counterpart. A reason for such a behavior might be a higher diffusivity due to the high ratio of surface to volume due to the presence of large number of grain boundaries, thus improving the formation of a protective layer. Furthermore, the higher homogeneity allows a better distribution of contamination because of the increased area of grain boundaries, thus reducing local segregation[95].

It is well known that glassy alloys offer superior resistance to corrosion and vastly improved mechanical properties over their conventional counterparts. Amorphous alloys have often a corrosion resistance one to two orders of magnitude higher than polycrystalline alloys with the same alloy composition [95–97]. Zn-based BMGs were firstly developed by Jiao and co-workers in 2010 [14], and they further studied their magnetic susceptibility, mechanical properties, corrosion behavior and cytocompatibility [50] aiming to develop this new kind of Zn-based BMGs as new kind of bone repair and fixation materials. It was found that Zn-based BMG with composition of Zn38Ca32Mg12Yb18 shows much higher strength (above 600 MPa) than conventional Mg (about 200 MPa) crystalline materials, much smaller magnetic susceptibility (22.3×10^{-6}) than that of commonly used biomedical alloys, slower degradation rate than pure Mg and hardly any hydrogen is generated during the immersion time. Its compression fracture strength did not show obvious decline after immersed in Hank's solution for 30 days. Cytotoxicity test revealed that this Zn-based BMG shows good cytocompatibility to MG63 osteoblast cells.

4.3.4. Zn-based BM composites and porous BMs

Composites with enhancement phases, either metal (Fe, Mg, Ca, Ti, Zr etc.) or non-metal (HA, ZnO, Al_2O_3 etc.) can further improve the mechanical, corrosion properties and the biocompatibility of Zn-based BMs. The porous scaffold provides the necessary support for cells to proliferate and maintain their differentiated function, and its architecture defines the ultimate shape of the new bone.

5. Concluding remarks

The family of biodegradable alloys now mainly consists of three alloy systems, including Mg-based BMs as the research's main body and at the stage of clinical trial stage, the Fe-based BMs at the animal testing stage and the Zn-based BMs at initial development stage. Investigations are still ongoing in this field in order to get the optimized BMs that meet the clinical requirements, including controllable degradation rate, prolonged mechanical stability and excellent biocompatibility. These targets can be achieved through optimization of alloy composition design, microstructure and mechanical property alternation and surface modification. The following aspects are the main research in the BM area.

5.1. New alloy systems

Along with the optimization on the present Mg-based, Fe-based and Zn-based alloy systems, with the essential elements of the human body, C, H, O, N, Ca, K, Na, P, Mg, S, Si, Fe, Zn, Se, Cu, Mo, Sn, Co, Mn and Sr, as alloying elements. There will be a consideration on the adding content for each element, based on the material science (for instance, according to the phase diagram how much should be added to obtain the best microstructure and mechanical property) and the biomedicine (for example, the critical value for a certain element by daily food uptake).

5.2. Amorphous structure

Amorphous structure can bring about unique properties for materials, thus developing novel BMs with amorphous structure will make new breakthroughs. A case in point is that due to the excessively active chemical reactivity of Ca and Sr, the design and development of conventional crystalline pure Ca- and Sr- based BMs for biomedical application is infeasible. However, with amorphous structure, the Ca-based [21,50,98–100], Sr-based [22,101] BMs have been developed which dramatically slowed down the corrosion rate of their crystalline counterparts.

5.3. BM composited with macromolecules and/or ceramics

Macromolecules and/or ceramics have been used in clinics for many years and possess quite different properties compared with metals and alloys. BM composites with macromolecules and/or ceramics can combine the strengths of alloys and macromolecules and/or ceramics together.

5.4. Advanced manufacturing technology

By using 3-D printing technology, the BMs can be directly processed into scaffolds, implants, organs and other tissues which needed in clinical applications. In order to fabricate synthetic bone scaffolds, three-dimensional (3-D) porous structures have been pursued to allow for bony ingrowth, infiltration of cells and fluids, and to mimic the natural cellular structure of bone. It has been possible to create a controllable porous, interconnected architecture via 3-D printing technology. Open-cell porous Mg with controllable macroscopic architectures by 3-D printing [102]. It is found that the method is capable of replicating highly accurate porous structures (~5–12% error) with macroscopic features as fine as 0.8 mm. By using inkjet 3-D printing, a technique which generates complex, customizable parts from powders mechanically milled Fe–30Mn (wt%) powder was directly processed into scaffolds [103]. Study suggests that the printed scaffolds demonstrated tensile mechanical property values very similar to those of natural bone and it presented an estimated corrosion rate that is higher than that of pure iron, while depositing corrosion products containing bone mineral components Ca and P, indicating its promise for bone replacement. Based on these preliminary studies, we believe that 3-D printing is a promising technology for biomedical applications, and bring new opportunity for the biodegradable metals to be fabricated using this unique method.

Acknowledgements

This work was supported by the National Basic Research Program of China (973 Program) (Grant No. 2012CB619102 and 2012CB619100), National Science Fund for Distinguished Young Scholars (Grant No. 51225101), National Natural Science Foundation of China (No. 31170909), the NSFC/RGC Joint Research Scheme under Grant No. 51361165101, Beijing Municipal Science and Technology Project (Z131100005213002) and Project for Supervisor of Excellent Doctoral Dissertation of Beijing (20121000101).

References

[1] H. Hermawan, Biodegradable Metals: State of the Art, Biodegradable Metals, Springer, 2012, p. 13–22.
[2] Y.F. Zheng, X.N. Gu, F. Witte, Mat. Sci. Eng. R 77 (2014) 1–34.
[3] G. Manivasagam, S. Suwas, Mater. Sci. Tech. – Lond. 30 (2014) 515–520.
[4] Z.J. Li, X.N. Gu, S.Q. Lou, Y.F. Zheng, Biomaterials 29 (2008) 1329–1344.
[5] H. Li, Q.M. Peng, X.J. Li, K. Li, Z.S. Han, D.Q. Fang, Mater. Des. 58 (2014) 43–51.
[6] I.S. Berglund, H.S. Brar, N. Dolgova, A.P. Acharya, B.G. Keselowsky, M. Sarntinoranont, M.V. Manuel, J. Biomed. Mater. Res. B 100B (2012) 1524–1534.
[7] X.N. Gu, X.H. Xie, N. Li, Y.F. Zheng, L. Qin, Acta Biomater. 8 (2012) 2360–2374.
[8] N. Hort, Y. Huang, D. Fechner, M. Stormer, C. Blawert, F. Witte, C. Vogt, H. Drucker, R. Willumeit, K.U. Kainer, F. Feyerabend, Acta Biomater. 6 (2010) 1714–1725.
[9] X.N. Gu, Y.F. Zheng, S.P. Zhong, T.F. Xi, J.Q. Wang, W.H. Wang, Biomaterials 31 (2010) 1093–1103.
[10] M. Schinhammer, A.C. Hanzi, J.F. Loffler, P.J. Uggowitzer, Acta Biomater. 6 (2010) 1705–1713.
[11] M. Schinhammer, I. Gerber, A.C. Hanzi, P.J. Uggowitzer, Mat. Sci. Eng. C – Mater. 33 (2013) 782–789.
[12] B. Liu, Y.F. Zheng, Acta Biomater. 7 (2011) 1407–1420.
[13] B. Liu, Y.F. Zheng, L.Q. Ruan, Mater. Lett. 65 (2011) 540–543.
[14] W. Jiao, K. Zhao, X.K. Xi, D.Q. Zhao, M.X. Pan, W.H. Wang, J. Non-Cryst. Solids 356 (2010) 1867–1870.
[15] P.K. Bowen, J. Drelich, J. Goldman, Adv. Mater. 25 (2013) 2577–2582.
[16] D. Vojtech, J. Kubasek, J. Serak, P. Novak, Acta Biomater. 7 (2011) 3515–3522.
[17] X. Wang, H.M. Lu, X.L. Li, L. Li, Y.F. Zhenh, T Nonferr, Metal. Soc. 17 (2007) S122–S125.
[18] Y.B. Wang, X.H. Xie, H.F. Li, X.L. Wang, M.Z. Zhao, E.W. Zhang, Y.J. Bai, Y.F. Zheng, L. Qin, Acta Biomater. 7 (2011) 3196–3208.
[19] H.F. Li, Y.B. Wang, Y. Cheng, Y.F. Zheng, Mater. Lett. 64 (2010) 1462–1464.
[20] J.D. Cao, N.T. Kirkland, K.J. Laws, N. Birbilis, M. Ferry, Acta Biomater. 8 (2012) 2375–2383.
[21] H.F. Li, X.H. Xie, K. Zhao, Y.B. Wang, Y.F. Zheng, W.H. Wang, L. Qin, Acta Biomater. 9 (2013) 8561–8573.
[22] K. Zhao, J.F. Li, D.Q. Zhao, M.X. Pan, W.H. Wang, Scr. Mater. 61 (2009) 1091–1094.
[23] H.F. Li, K. Zhao, Y.B. Wang, Y.F. Zheng, W.H. Wang, J. Biomed. Mater. Res. B 100B (2012) 368–377.
[24] K. Zhao, W. Jiao, J. Ma, X.Q. Gao, W.H. Wang, J. Mater. Res. 27 (2012) 2593–2600.
[25] Y. Al-Abdullat, S. Tsutsumi, N. Nakajima, M. Ohta, H. Kuwahara, K. Ikeuchi, Mater. Trans. 42 (2001) 1777–1780.
[26] P. Zartner, R. Cesnjevar, H. Singer, M. Weyand, Catheter. Cardiovasc. Interv. 66 (2005) 590–594.
[27] F. Witte, V. Kaese, H. Haferkamp, E. Switzer, A. Meyer-Lindenberg, C.J. Wirth, H. Windhagen, Biomaterials 26 (2005) 3557–3563.
[28] F. Witte, J. Fischer, J. Nellesen, H.A. Crostack, V. Kaese, A. Pisch, F. Beckmann, H. Windhagen, Biomaterials 27 (2006) 1013–1018.

[29] R. Erbel, C. Di Mario, J. Bartunek, J. Bonnier, B. de Bruyne, F.R. Eberli, P. Erne, M. Haude, B. Heublein, M. Horrigan, C. Ilsley, D. Bose, J. Koolen, T.F. Luscher, N. Weissman, R. Waksman, Lancet 369 (2007) 1869–1875.
[30] X.N. Gu, Y.F. Zheng, Y. Cheng, S.P. Zhong, T.F. Xi, Biomaterials 30 (2009) 484–498.
[31] B. Zberg, P.J. Uggowitzer, J.F. Loffler, Nat. Mater. 8 (2009) 887–891.
[32] X.N. Gu, N. Li, Y.F. Zheng, F. Kang, J.T. Wang, L.Q. Ruan, Mater. Sci. Eng. B – Adv. 176 (2011) 1802–1806.
[33] X.N. Gu, X. Wang, N. Li, L. Li, Y.F. Zheng, X.G. Miao, J. Biomed. Mater. Res. B 99B (2011) 127–134.
[34] C.H. Ye, Y.F. Zheng, S.Q. Wang, T.F. Xi, Y.D. Li, Appl. Surf. Sci. 258 (2012) 3420–3427.
[35] M. Haude, R. Erbel, P. Erne, S. Verheye, H. Degen, D. Bose, P. Vermeersch, I. Wijnbergen, N. Weissman, F. Prati, R. Waksman, J. Koolen, Lancet 381 (2013) 836–844.
[36] W.R. Zhou, Y.F. Zheng, M.A. Leeflang, J. Zhou, Acta Biomater. 9 (2013) 8488–8498.
[37] N. Li, Y.D. Li, Y.B. Wang, M. Li, Y. Cheng, Y.H. Wu, Y.F. Zheng, Surf. Interface Anal. 45 (2013) 1217–1222.
[38] H.M. Wong, Y. Zhao, V. Tam, S.L. Wu, P.K. Chu, Y.F. Zheng, M.K.T. To, F.K.L. Leung, K.D.K. Luk, K.M.C. Cheung, K.W. K. Yeung, Biomaterials 34 (2013) 9863–9876.
[39] R.C. Zeng, L. Sun, Y.F. Zheng, H.Z. Cui, E.H. Han, Corros. Sci. 79 (2014) 69–82.
[40] N. Li, Y.D. Li, Y.X. Li, Y.H. Wu, Y.F. Zheng, Y. Han, Mat. Sci. Eng. C – Mater. 35 (2014) 314–321.
[41] X. Wang, P. Zhang, L. Dong, X. Ma, J. Li, Y. Zheng, Mater. Des. 54 (2014) 995–1001.
[42] P. Han, M.Y. Tan, S.X. Zhang, W.P. Ji, J.N. Li, X.N. Zhang, C.L. Zhao, Y.F. Zheng, Y.M. Chai, Int. J. Mol. Sci. 15 (2014) 2959–2970.
[43] M. Peuster, P. Wohlsein, M. Brugmann, M. Ehlerding, K. Seidler, C. Fink, H. Brauer, A. Fischer, G. Hausdorf, Heart 86 (2001) 563–569.
[44] M. Peuster, C. Hesse, T. Schloo, C. Fink, P. Beerbaum, C. von Schnakenburg, Biomaterials 27 (2006) 4955–4962.
[45] H. Hermawan, D. Dube, D. Mantovani, Adv. Mater. Res. – Switz. 15–17 (2007) 107–112.
[46] R. Waksman, R. Pakala, R. Baffour, R. Seabron, D. Hellinga, F.O. Tio, J. Interv. Cardiol. 21 (2008) 15–20.
[47] F.L. Nie, Y.F. Zheng, S.C. Wei, C. Hu, G. Yang, Biomed. Mater. 5 (2010).
[48] J. Cheng, T. Huang, Y.F. Zheng, J. Biomed. Mater. Res. A 102 (2014) 2277–2287.
[49] T. Huang, J. Cheng, Y.F. Zheng, Mat. Sci. Eng. C – Mater. 35 (2014) 43–53.
[50] W. Jiao, H.F. Li, K. Zhao, H.Y. Bai, Y.B. Wang, Y.F. Zheng, W.H. Wang, J. Non-Cryst. Solids 357 (2011) 3830–3840.
[51] D.V. Iva POSPÍŠILOVÁ, Brno, Czech Republic, EU, 2013.
[52] C.Z. Yao, Z.C. Wang, S.L. Tay, T.P. Zhu, W. Gao, J. Alloy Compd. 602 (2014) 101–107.
[53] L.P. Xu, G.N. Yu, E. Zhang, F. Pan, K. Yang, J. Biomed. Mater. Res. A 83A (2007) 703–711.
[54] F. Witte, N. Hort, C. Vogt, S. Cohen, K.U. Kainer, R. Willumeit, F. Feyerabend, Curr. Opin. Solid State Mater. Sci. 12 (2008) 63–72.
[55] A.C. Hanzi, P. Gunde, M. Schinhammer, P.J. Uggowitzer, Acta Biomater. 5 (2009) 162–171.
[56] A.C. Hanzi, I. Gerber, M. Schinhammer, J.F. Loffler, P.J. Uggowitzer, Acta Biomater. 6 (2010) 1824–1833.
[57] A.C. Hanzi, A.S. Sologubenko, P.J. Uggowitzer, Mater. Sci. Forum. 618-619 (2009) 75–82.
[58] Y.W. Song, D.Y. Shan, E.H. Han, Mater. Lett. 62 (2008) 3276–3279.
[59] X.H. Xu, P. Lu, M.Q. Guo, M.Z. Fang, Appl. Surf. Sci. 256 (2010) 2367–2371.
[60] T. Lei, W. Tang, S.H. Cai, F.F. Feng, N.F. Li, Corros. Sci. 54 (2012) 270–277.
[61] H.J. Zhang, D.F. Zhang, C.H. Ma, S.F. Guo, Mater. Lett. 92 (2013) 45–48.
[62] F.M. Lu, A.B. Ma, J.H. Jiang, D.H. Yang, Y.C. Yuan, L.Y. Zhang, J. Alloy Compd. 601 (2014) 140–145.
[63] J.H. Gao, S.K. Guan, Z.W. Ren, Y.F. Sun, S.J. Zhu, B. Wang, Mater. Lett. 65 (2011) 691–693.
[64] Q. Wu, S.J. Zhu, L.G. Wang, Q. Liu, G.C. Yue, J. Wang, S.K. Guan, J. Mech. Behav. Biomed. Mater. 8 (2012) 1–7.
[65] X.N. Gu, X.L. Li, W.R. Zhou, Y. Cheng, Y.F. Zheng, Biomed. Mater. 5 (2010).
[66] X.B. Zhang, G.Y. Yuan, Z.Z. Wang, Mater. Lett. 74 (2012) 128–131.
[67] B. Zberg, E.R. Arata, P.J. Uggowitzer, J.F. Löffler, Acta Mater. 57 (2009) 3223–3231.
[68] H.-J. Yu, J.-Q. Wang, X.-T. Shi, D.V. Louzguine-Luzgin, H.-K. Wu, J.H. Perepezko, Adv. Funct. Mater. (2013)http://dx.doi.org/ 10.1002/adfm.201203738.
[69] M. Moravej, F. Prima, M. Fiset, D. Mantovani, Acta Biomater. 6 (2010) 1726–1735.
[70] L.X. Xu WL, L.L. Tan, K. Yang, Acta Metall. Sin. 47 (2011) 1342–1347.
[71] M. Moravej, D. Mantovani, Int. J. Mol. Sci. 12 (2011) 4250–4270.
[72] M. Moravej, A. Purnama, M. Fiset, J. Couet, D. Mantovani, Acta Biomater. 6 (2010) 1843–1851.
[73] B. Vallee, Biofactors 1 (1988) 31–36.
[74] J.E. Coleman, Curr. Opin. Chem. Biol. 2 (1998) 222.
[75] J.M. Berg, Y. Shi, Science 271 (1996) 1081–1085.
[76] S.X. Zhang, X.N. Zhang, C.L. Zhao, J.A. Li, Y. Song, C.Y. Xie, H.R. Tao, Y. Zhang, Y.H. He, Y. Jiang, Y.J. Bian, Acta Biomater. 6 (2010) 626–640.
[77] F. Witte, J. Fischer, J. Nellesen, C. Vogt, J. Vogt, T. Donath, F. Beckmann, Acta Biomater. 6 (2010) 1792–1799.
[78] Q.M. Peng, Y.D. Huang, L. Zhou, N. Hort, K.U. Kainer, Biomaterials 31 (2010) 398–403.
[79] M. Thomann, C. Krause, D. Bormann, N. von der Hoh, H. Windhagen, A. Meyer-Lindenberg, Materialwiss Werkst 40 (2009) 82–87.
[80] J. Cheng, Y.F. Zheng, J. Biomed. Mater. Res. B 101B (2013) 485–497.
[81] J. Kubasek, D. Vojtech, 21st Int. Conf. Metall. Mater. (Metal 2012) (2012) 1355–1361.
[82] Y.C. Yuan, A.B. Ma, J.H. Jiang, F.M. Lu, W.W. Jian, D. Song, Y.T. T. Zhu, Mat. Sci. Eng. A – Struct. 588 (2013) 329–334.
[83] J. Zhang, C. Xin, K. Nie, W. Cheng, H. Wang, C. Xu, Mater. Sci. Eng. A 611 (2014) 108–113.
[84] F. Guo, D. Zhang, X. Yang, L. Jiang, S. Chai, F. Pan, Mater. Sci. Eng. A 607 (2014) 383–389.
[85] Q. Peng, X. Li, N. Ma, R. Liu, H. Zhang, J. Mech. Behav. Biomed. Mater. 10 (2012) 128–137.
[86] E. Mostaed, M. Hashempour, A. Fabrizi, D. Dellasega, M. Bestetti, F. Bonollo, M. Vedani, J. Mech. Behav. Biomed. Mater. 37 (2014) 307–322.
[87] H. Dong, F. Pan, B. Jiang, Y. Zeng, Mater. Des. 57 (2014) 121–127.
[88] L. Zhang, J. Zhang, Z. Leng, S. Liu, Q. Yang, R. Wu, M. Zhang, Mater. Des. 54 (2014) 256–263.
[89] S. Koleini, M.H. Idris, H. Jafari, Mater. Des. 33 (2012) 20–25.
[90] H.-Y. Ha, J.-Y. Kang, S.G. Kim, B. Kim, S.S. Park, C.D. Yim, B.S. You, Corros. Sci. 82 (2014) 369–379.
[91] X. Zhang, G. Yuan, L. Mao, J. Niu, W. Ding, Mater. Lett. 66 (2012) 209–211.
[92] X. Zhang, G. Yuan, J. Niu, P. Fu, W. Ding, J. Mech. Behav. Biomed. Mater. 9 (2012) 153–162.
[93] D. Facchini, 3 – Biomedical nanocrystalline metals and alloys: structure, properties and applications, in: T.J. Webster (Ed.), Nanomedicine, Woodhead Publishing, 2012, pp. 36–67.
[94] M. Bobby Kannan, V.S. Saji, 15 – Nanoscience and biomaterial corrosion control, in: V.S. Saji, R. Cook (Eds.), Corrosion Protection and Control Using Nanomaterials, Woodhead Publishing, 2012, pp. 375–392.
[95] D. Zander, U. Köster, Mater. Sci. Eng. A 375–377 (2004) 53–59.
[96] K. Hashimoto, T. Masumoto, Mater. Sci. Eng. 23 (1976) 285–288.
[97] K. Hashimoto, K. Osada, T. Masumoto, S. Shimodaira, Corros. Sci. 16 (1976) 71–76.
[98] J.F. Li, D.Q. Zhao, M.L. Zhang, W.H. Wang, Appl. Phys. Lett. 93 (2008) 171907.
[99] Y. Du, Y. Lu, T. Li, T. Wang, G. Zhang, Mater. Res, Innovations 15 (2011) 107–110.

[100] J.D. Cao, N.T. Kirkland, K.J. Laws, N. Birbilis, M. Ferry, Acta Biomater. 8 (2012) 2375–2383.
[101] H.F. Li, K. Zhao, Y.B. Wang, Y.F. Zheng, W.H. Wang, J. Biomed. Mater. Res. Part B: Appl. Biomater. 100B (2012) 368–377.
[102] M.P. Staiger, I. Kolbeinsson, N.T. Kirkland, T. Nguyen, G. Dias, T.B. F. Woodfield, Mater. Lett. 64 (2010) 2572–2574.
[103] D.-T. Chou, D. Wells, D. Hong, B. Lee, H. Kuhn, P.N. Kumta, Acta Biomater. 9 (2013) 8593–8603.