Chapter 2
Biodegradable Metals: State of the Art

Abstract Degradable biomaterials constitute a novel class of bioactive biomaterials which are expected to support healing process of a diseased tissue and to degrade thereafter. Two classes of metals have been proposed: magnesium- and iron-based alloys. Three targeted applications are envisaged: orthopaedic, cardiovascular and pediatric implants. Conceptually, biodegradable metals should provide a temporary support on healing process and should progressively degrade thereafter.

Keywords Biodegradable metals · Degradation · Temporary implant

2.1 Paradigm Shifted

The scientific knowledge about tissue-implant interactions, tissue engineering, as well as recent advances in biology and physiology raises a new concept of biofunctional/bioactive biomaterials. These unconventional bioactive biomaterials are expected to promote positive interactions with the physiological implantation sites. Degradable biomaterials constitute a novel class of considerably bioactive biomaterials which are expected to support healing process of a diseased tissue or organ and slowly degrading thereafter. The study of innovative degradable biomaterials is one of the most interesting research topics at the forefront of biomaterials in present days.

The advancement of materials science and engineering, especially for processing and thermomechanical treatments, allow the structural material adjustment to meet the expected properties of materials. The increasing society expectation for a better quality of life has fostered biomaterialists to develop new technologies to provide implants with higher clinical performance. The paradigm of implants must be inert and corrosion resistant has now been challenged by the advent of this new class of degradable biomaterials.

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Some specific clinical problems (disease/trauma) need only temporary support for healing. 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, such as the use of biodegradable sutures. However, implants that degrade, especially those made of metal, can be considered as a novel concept which actually breaks the established paradigm of "metallic biomaterials must be corrosion resistant".

Degradable biomaterials have been proposed from both polymers and metals. Degradable polymers for use as biomaterials have been investigated since 1988 (Stack et al. 1988). Among the polymers that have been proposed were poly(L-lactic acid) (PLLA) (Stack et al. 1988; Tamai et al. 2000), poly(lactic-*co*-glycolic acid) (PLGA) and poly(ε-caprolactone) (PCL) (van der Giessen et al. 1996).

Considering metals as degradable biomaterials is a recent idea. In term of mechanical property, metals are considered as more suitable compared to polymers for some specific applications which require high strength to bulk ratio, including for internal bone fixation screws/pins and for coronary stents.

Magnesium- and Fe-based alloys are the two classes of metals have been proposed. Several Mg-based alloys have been investigated, including Mg–Al—(Heublein et al. 2003; Levesque et al. 2003; Witte et al. 2005; Xin et al. 2007), Mg–RE (rare earth)—(Di Mario et al. 2004; Peeters et al. 2005; Witte et al. 2005; Waksman et al. 2006; Hänzi et al. 2009) and Mg–Ca—(Zhang and Yang 2008; Li et al. 2008) based alloys.

Among the Fe-based alloys have been studied, including pure Fe (Peuster et al. 2001; Peuster et al. 2006) and Fe-Mn alloys (Hermawan et al. 2008; Schinhammer et al. 2010). They were mainly proposed for cardiovascular applications.

2.2 The Concept

In general, the concept of degradable biomaterials is as simple as that, some implants might require only temporary presence for supporting the healing process of a diseased tissue. This temporary intervention (implant) is envisaged to be applied in some specific cases such as in cardiovascular, orthopaedic and paediatric field. Figure 2.1 illustrates an example of envisaged temporary implant (stent) which is implanted to open a narrowed artery.

Those envisaged temporary implants possess a similar concept but employed in different physiological environments with different specific functions. In example, temporary cardiovascular implants, i.e. stents (Fig. 2.1), should be able to open a narrowed artery and hold it open until the vessel remodels, and then they degrade and are replaced by new arterial vessel tissue. Temporary orthopaedic implants, i.e. bone fixation screws/pins, should be able to join a fractured bone and hold it tight until sufficient bone joint is formed and then degrade and are replaced by new

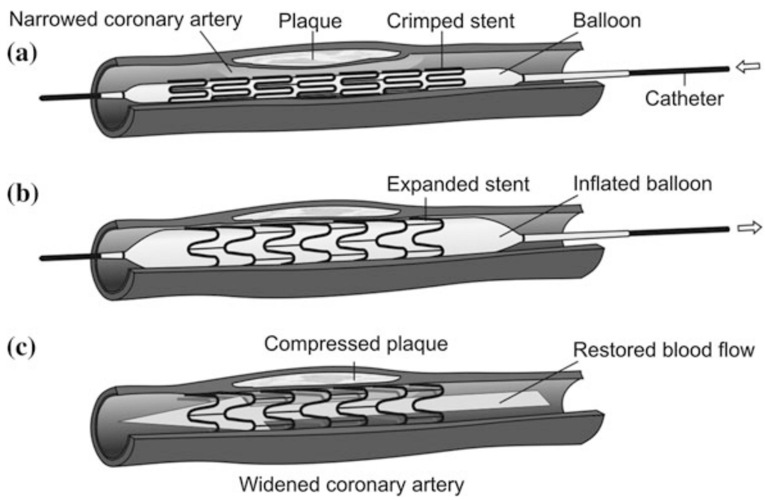

Fig. 2.1 Illustration of a coronary stent during it's: **a** delivery into a narrowed artery by a catheter, **b** expansion to open the artery, **c** restoring the blood flow. Adapted with permission from Minerva Medica (Hermawan and Mantovani 2009)

bone tissue. In paediatric, the implants should also deal with the growing implantation sites, the surrounding tissue and organ.

Ideally, biodegradable coronary stents should reach a compromise between mechanical integrity and degradation (Hermawan et al. 2010). The degradation should begin at a very slow rate to keep the stent's optimal mechanical integrity until the arterial vessel remodeling process completed which is expected in a period of 6–12 months (El-Omar et al. 2001; Schomig et al. 1994). Thereafter, while the mechanical integrity decreases, the degradation progresses. The degradation rate should be sufficient enough to do not cause an intolerable accumulation of degradation product around the implantation site and in the systemic organs. A reasonable total period for the stent to be totally degraded could be between 12 and 24 months after implantation (Serruys et al. 2006). However, this time frame is still not supported by sufficient data and evidences from the real degradation behavior in vivo, including that for orthopaedic implants.

In other words, the concept of biodegradable metals is *"providing a temporary support on healing process of a diseased tissue and progressively degrade thereafter"*. It derives two main features: (1) temporary support; and (2) degradation. Biodegradable metals are also expected to positively interact (bioactive) during the healing process. The metals, the degradation and its products are not supposed to provide adverse effect to the healing process.

Table 2.1 Mechanical properties of biodegradable metals compared to SS316L

Metal, metallurgy and its composition (wt%)	Density (g/cm^3)	Yield strength (MPa)	Tensile strength (MPa)	Young's modulus (GPa)	Ductility (%)
SS316L, annealed plate Fe, 16–18.5 Cr, 10–14 Ni, 2–3 Mo, <2 Mn, <1 Si, <0.03 C (ASTM 2003)[a]	8.00	190	490	193	40
Fe, annealed plate 99.8 Fe (Goodfellow 2010)	7.87	150	210	200	40
Fe-Mn-Pd alloy, cast + heat treatment Fe, 10.2 Mn, 0.92 Pd, 0.12 C (Schinhammer et al. 2010)	N/A	850	1450	N/A	11
Mg, annealed sheet 99.98 Mg (ASM 2005)	1.74	90	160	45	3
WE43 Mg alloy, temper T6 Mg, 3.7–4.3 Y, 2.4–4.4 Nd, 0.4–1 Zr (ASTM 2001)	1.84	170	220	44	2
Mg-Ca alloy, extruded Mg, 1 Ca (Li et al. 2008)	N/A	140	240	N/A	11

[a] Non-degradable, taken for comparison purpose. The values shown here are the minimum requirements by ASTM

2.3 Proof of Concept

2.3.1 Mechanical Support

The mechanical properties of metal are derived from its type, design and process. This includes the use of alloying elements, thermomechanical treatments and by employing new processing methods. The use of alloying elements which can form corrosion protective layer on the surface of materials; i.e. Cr for the case of stainless steel, should be avoided in order to ensure the alloys to become degradable or not corrosion resistant.

Biodegradable metals should provide an adequate mechanical support to a healing process throughout the implantation period. Even though it is still difficult to define the exact required support for specific clinical events, i.e. narrowed artery or fractured bone, it is reasonable to compare to the mechanical property of currently used corrosion-resistant metals. Table 2.1 resumes mechanical properties of Fe, Mg and their alloys compared to the known clinically proven metallic biomaterials, the SS316L.

Mechanical integrity of biodegradable metals over time can be theoretically predicted by conducting in vitro degradation tests. Kannan et al. have conducted a slow strain rate test on Mg-Al alloys allowing the measurement of mechanical properties as a function of degradation (Kannan and Raman 2008). The results showed that the elongation to fracture and ultimate tensile strength of AZ91Ca alloy in modified-simulated body fluid (SBF) decreased about 15–20 % in comparison with these properties in air.

2.3.2 *Degradation*

Biodegradable metals must degrade in the complex physiological environment of human body with matching degradation kinetics to the healing period. The degradation products should be transported and eliminated from the body and do not cause local or systemic accumulation. Table 2.2 summarizes published implantation studies of biodegradable metal intended for orthopaedic implants in animals. It briefly details the type of alloy and implant prototype, method of implantation; host, site, period and analysis, and some important findings.

The animal implantation studies showed that the proposed biodegradable metal implants were degraded under in vivo environment. In cardiovascular environment, generally the implants showed obvious sign of degradation in less than 1 month after implantation (Waksman et al. 2006, 2008). Magnesium alloy implants degrade faster than those of pure Fe, whereas Mg alloy stent completely degraded in less than 6 months (Waksman et al. 2006), meanwhile parts of pure Fe stents were still visible after a year of implantation (Peuster et al. 2001). In bone environment, Mg alloy pins degraded within 3 months and were replaced by new bone tissue (Li et al. 2008).

Absence of degradation products accumulation and signs of metal overload or metal-related organ toxicity (heart, lung, spleen, liver, kidney and para-aortic lymphatic nodes) were confirmed for Fe stents (Peuster et al. 2001, 2006). Examination of the blood has shown that the degradation of Mg implant caused only little change to the composition without disorder to liver or kidneys (Zhang et al. 2009). Similar finding showed no statistically significant differences of serum Mg before operation and at 1, 2, 3 months post-operation, suggesting the functionality of self-regulation mechanism of organism and excretion of surplus Mg from urine (Li et al. 2008).

2.4 Recent Development

Most of works on biodegradable metals covers materials development, property enhancement, degradation study and in vivo implantation of the material. There is still limited work that transformed biodegradable metals into implant or prototype. Among the developed implants are Fe-Mn alloy coronary stent (Hermawan and Mantovani 2011), WZ21 Mg alloy gastrointestinal would closure (Hänzi et al. 2011) and Mg micro-clip for laryngeal micro-surgery (Chng et al. 2012), (Fig. 2.2).

Table 2.2 Implantation of biodegradable metals in animal

Materials	Methods	Findings
Mg-Al/Y/Li/RE alloys pins (Witte et al. 2005)	Implantation on femora of 40 guinea pigs for a period up to 18 weeks, followed by radiography and histology	The corrosion layer of the rods displayed accumulation of biological Ca/P while in direct contact with the surrounding bone; subcutaneous gas bubbles formed after 1 week and disappear in 2–3 week but no adverse effect was observed
Mg-Ca alloy pins (Li et al. 2008)	Implantation on femora of: 18 New Zealand rabbits for a period up to 3 months, followed by radiography and histology	Gas bubbles formed in a week and disappear later without special treatment; the pins gradually degraded in vivo within 90 days; newly formed bone was clearly seen at month 3
Mg-Zn-Mn alloy rods (Zhang et al. 2009)	Implantation on femora of 18 rats for a period up to 26 weeks, followed by blood test and histology	No gas bubble was observed, new bone tissue formed around Mg implants after 6 weeks; higher degradation rate was found in the marrow channel than in the cortical bone tissue; little change to blood composition without disorder to liver or kidneys
Mg-0.8Ca screws (Erdmann et al. 2011)	Implantation on tibiae of 40 rabbits up to 8 weeks, followed by micro-CT and remnant analysis	The screws showed good tolerability and biomechanical properties comparable with S316L in the first 2–3 weeks post-implantation; They gradually degraded and became distinct after 6 weeks resulted in a loss of holding power; further investigation on the relation of the reduced holding power and bone healing was suggested especially with the combination of screw and plate
ZX50 and WZ21 alloys pin (Kraus et al. 2012)	Implantation on femora of 32 Sprague–Dawley rats up to 24 weeks, followed by online micro-CT monitoring and histology	ZX50 pins degraded at $\approx$1.2 % daily volume loss, WZ21 pins maintained their integrity for 4 weeks and degraded at $\sim$0.5 % volume loss per day; WZ21 generated enhanced bone neoformation with evidence for good osteoconductivity and osteoinductivity; bone recovered after complete degradation
Mg-Zn-Ca alloy rods (Chen et al. 2012)	Implantation on femur shaft of rabbits for a period up to 50 weeks, followed by radiography, micro-CT and histology	HA-composite coated rods degraded slower than the uncoated; the coated rods induced more newly formed bone tissue and faster bone response

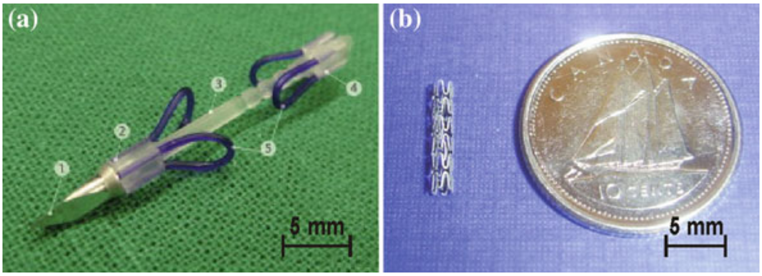

Fig. 2.2 Examples of implant prototype developed from biodegradable metals: **a** a wound closing rivet made of WZ21 Mg alloy, adapted with permission from Elsevier (Hänzi et al. 2011), **b** a coronary stent made of Fe-35Mn alloy, courtesy of Centre de recherche du CHUQ, Quebec, Canada

Fig. 2.3 Map of research groups working on biodegradable metals as of 2012

Up to now, proposed biodegradable metals can be identified as:

1. Mg-based alloys both conventionally produced through casting or by fine microstructure oriented processes;
2. Pure Fe and Fe-based alloys which were produced by casting, mechanical alloying or electrodeposition;
3. Metallic glasses which have been developed from both Mg- and Fe-based alloys.

The growing interest toward biodegradable metals was recorded in both journal database such as in the US National Library of Medicine and the National Institutes of Health (PubMed 2011) and in patent database such as the United States Patent and Trademark Office (USPTO 2011). Three consecutive international symposiums on biodegradable metals for biomedical applications were successfully held:

1. During the Thermec'2009 in Berlin, Germany, 25–29 August 2009;
2. In Maratea, Italy, 31 August-3 September 2010; and
3. During the Thermec'2011 in Quebec City, Canada, 1–5 August 2011.

It was revealed from those symposiums that the field has gained attentions from researchers around the world including from Canada, USA, Australia, Germany, Swiss, Japan, China, Mexico, and New Zealand. Figure 2.3 maps the groups working on biodegradable metals created based on their participation in the three symposiums and its publications in the special issues of Acta Biomaterialia 2010 and Materials Science and Engineering B 2011.

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