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Degradable Biomaterials for Temporary Medical Implants

Ahmad Kafrawi Nasution and Hendra Hermawan

Abstract Degradable biomaterials bring possibilities to fabricate medical implants that function for a determined period related to clinical events such as healing. They can be made on the basis of polymers, ceramics and metals. These metals, which are expected to corrode gradually in vivo with an appropriate host response and then dissolve completely upon fulfilling the mission to assist with tissue healing, are known as biodegradable metals. They constitute a novel class of bioactive biomaterials which supports the healing process of temporary clinical problems. Three classes of metals have been explored: magnesium-, zinc- and iron-based alloys. Three targeted applications are envisaged: orthopaedic, cardiovascular and pediatric implants. Three levels of investigations have been conducted: in vitro, in vivo and clinical trials. Discussion on standardization has been initiated since 2013 with representatives from ISO, DIN and ASTM and drafts of comprehensive standards are now under preparation. The field of biodegradable metals is exciting and witnessing more development in the future including new advanced alloys and new real breakthrough that leads to its clinical translation. This chapter starts with a discussion on biodegradable polymers to gain important lessons learned for advancing the research in biodegradable metals, the new emerging research interest in the forefront of biomaterials loaded with full of great expectations.

Keywords Biodegradable · Biomaterials · Corrosion · Metals · Polymers

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1 Introduction

Biomaterials have been widely used to make implants or devices to replace a part or a function of the body in a reliable, safe, physiologically acceptable and economic manner (Park and Lakes 2007). Examples of such implants are artificial heart valves, coronary artery stents, total hip replacement, bone plate and screw, and dental implants (Geetha et al. 2009). Biomaterials can be defined as natural or synthetic materials engineered to interact with biological systems that are used for medical treatment (Ulery et al. 2011). The development of the first medical device is based on the principles of medical and scientific acceptable for human use in the late 1940s and early 1950s (Ratner et al. 2013). The diversity of biomaterials in used today is the result of great advancement in materials technology since nearly 40 years ago (Hoffman 1996). Basically, as detailed in Table 1, they can be classified as metals, ceramics, polymers and their composites with 70–80 % of implants were made of metals (Niinomi et al. 2012).

The development of biomaterials is made possible thanks to strong interdisciplinary collaboration among clinicians, engineers, chemists, physicists and biologists as the key players (Ratner et al. 2013). Advanced biomaterials development requires the input of knowledge from diverse areas with the ultimate goal to achieve the true biological interaction between the materials and the human body (Vallet-Regí 2010; Ulery et al. 2011). This chapter starts with an overview on the currently used biomaterials then focuses further review on biodegradable polymers. The main objective is to gain some lessons from the currently used biomaterials, especially biodegradable polymers, for advancing the research in biodegradable metals, the new emerging research interest in the forefront of biomaterials loaded with full of great expectations.

Table 1 Biomaterials commonly used for biomedical applications

Materials	Applications	Advantages	Disadvantages
Metals: stainless steel, Co-Cr alloys, Ti alloys, Mg alloys, etc.	Load bearing implants, joint replacement, cardiovascular stents, dental implants, etc.	Though, strong, ductile	Non bioactive
Ceramics: alumina, bioglass, calcium phosphate, zirconia, etc.	Orthopaedic and dental implants	Bioactive, inert	Brittle, not resilient
Polymers: polyethylene, polyesters, nylon, polylactide, etc.	Blood vessel grafts, hip sockets, sutures, etc.	Bioactive, resilient	Lack of strength for load bearing implants
Composites: amalgam, fiber-reinforced bone cement, etc.	Dental filling, resin bone cement, etc.	Tailor made	Relatively difficult to make

2 Overview on Currently Used Biomaterials

Hundreds of type of metals for implants have been clinically used, but in general they can be grouped into: (1) stainless steel alloys; (2) Co-Cr alloys; (3) Ti and its alloys; and (4) precious alloys. These metallic biomaterials are always attractive due to their nature in offering structural function and inertness, the two key features that most implants need. However, as the medical science progresses and the demand for better implants increases, nowadays it is desirable that an implant also possesses bioactivities or biofunctionalities like blood compatibility and bone conductivity. Therefore, the surface of metals are often modified, for examples: in order to provide bone conductivity metal surface has been coated with hydroxyapatite (Habibovic et al. 2002), or with poly(ethylene terephthalate) to improve blood compatibility (Lahann et al. 1999). Today, development on metallic biomaterials includes those composed of nontoxic and allergy-free elements such as Ni-free stainless steel (Yang and Ren 2010) and biodegradable metals which are targeted for temporary implants (Hermawan and Mantovani 2009).

One important lesson we can learn from inert metallic biomaterials is their high strength and ductility. Mechanical properties of 316L stainless steel are often viewed as the standard reference in developing new metallic biomaterials. This also applies to biodegradable metals to ensure that the mechanical function of a specific implant, such as coronary stent, remains the same despite its material is changed from 316L stainless steel to biodegradable iron (Fe) or magnesium (Mg) alloys. Although designed to be corrosion resistant, aggressive physiological environment, that is not only corrosive but also introduces mechanical loading (static and dynamic), contributes to metallic implant failures such as wear. High concentrations of chloride and temperature of the human body have also found to induce localized corrosion such as pitting, crevice and fretting (Tavares et al. 2010). Figure 1 shows example of metal implant failure due to corrosion and wear.

Polymeric biomaterials offer main advantage over metals and ceramics in their ease of manufacturability to form various shapes. Basically, these biomaterials can be divided into: (1) inert polymers such as poly(methyl methacrylate), poly(amide) or nylon, poly(ethylene), etc.; and (2) absorbable polymers such as poly(glycolic acid) and poly(lactic acid), etc. Beside employed in their bulk, they are often made into thin layer or coating onto metal surfaces with tailored mechanical and physical properties. The recent development exploits absorbable polymers for use as drug delivery carriers loaded with a specific drug in the form of coating, for example drug eluting stents (Jenkins 2007).

Ceramics biomaterials provide inertness, high compressive strength and aesthetic appearance. They can be classified into: (1) inert bioceramics such as zirconia, alumina, aluminum nitrides and carbon; (2) bioactive ceramics such as hydroxyapatite, bioglass, etc.; (3) biodegradable/resorbable ceramics such as calcium aluminates, calcium phosphates, etc. The inherent surface qualities of ceramics have been exploited to make implants such as dental crowns. The high specific strength and blood compatibility of carbon makes carbon often used for

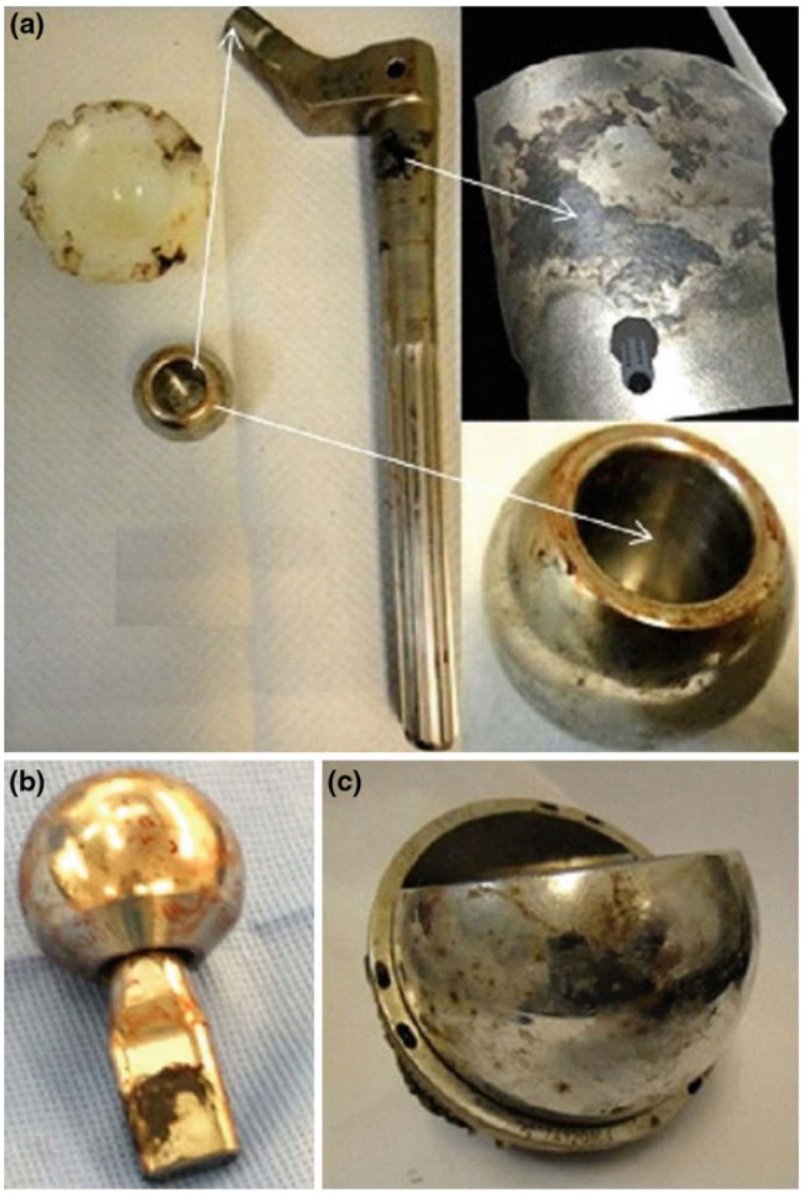


Fig. 1 Example of a component of a retrieved total hip implant revised due to adverse local tissue reaction: **a** modular implants typically provide in large crevice geometries with differential aeration that will be subjected to micromotion during loading and results result in abrasion and trigger a series of reactions in the crevice that will lead to events such as cracks, pitting and cracks, **b** corrosion at the modular neck junction, **c** corrosion debris (*black* deposits) is shown in the stem-sleeve mating interface. Adapted from Rodrigues (2014) and Tischler and Austin (2014)

heart valves leaflets. Many bioceramics have been also applied as coating onto metal surfaces including diamond like carbon, nitrides, bioglasses and hydroxyapatites (Kokubo 2008).

Composite biomaterials can be made with metals, polymers or ceramics as their matrix, and reinforced with one of these materials. Composites allow a control over material properties whereas a combination of stiff, strong, resilient but lightweight can be achieved all together. Bone is a composite of the low elastic modulus organic matrix reinforced with the high elastic modulus mineral "fibers" permeated with pores filled with liquids. Other examples include orthopaedic implants with porous structures, dental filler, and bone cement composed of reinforced poly (methyl methacrylate) and ultra-high molecular weight poly(ethylene) (Ambrosio 2009).

3 Biodegradable Polymers

The current trend shows a shift in the use of the permanent prosthetic devices for temporary therapeutic applications to biodegradable devices that can help the body to repair and regenerate damaged tissue (Nair and Laurencin 2007). Basically, the concept of biodegradable devices is providing a temporary support during the healing process of diseased tissue and degrading away thereafter, progressively. Precisely, temporary clinical problems need temporary intervention (i.e. temporary presence of implants) and this can be provided by degradable biomaterials (Li et al. 2014). Temporary support is only obtained by using implants made from degradable biomaterial (either biodegradable polymers or biodegradable metals) that allows implant to relegate biologically after fulfilling its function (Barrows 1986; Hermawan 2012). Examples of clinical problems that need temporary support for healing are narrowed arteries, fractured bones and congenital cardiovascular defects (Hermawan and Mantovani 2009). Some important properties that must be considered in the design of biodegradable biomaterials are summarized in Fig. 2.

Polymeric biomaterials has a long history of applications starting from catheters, syringes, blood contacting extra corporeal devices till matrices for drug delivery, cell encapsulation and tissue regeneration (Shastri 2003). Non-degradable polymers such as nylon, poly(methylmethacrylate), poly(ester) and poly(vinyl chloride) began to be used in the medical fieldin the mid-1940s and remain important for numbers of medical equipment till now (Griffith 2000; Hacker and Mikos 2011). They are used as a component for permanent prosthetic devices including hip implants, artificial lenses, large diameter vascular grafts and catheters. Meanwhile, degradable polymers adopted for surgery since 40 years ago as a surgical suture material and bone fixation devices (Kulkarni et al. 1971). In the last two decades there has been a development of new generations of synthetic biodegradable polymers and natural polymers specifically developed for biomedical applications.

Fig. 2 Important properties to be considered in the design of degradable biomaterials. Adapted from Lloyd (2002)

3.1 Natural Biodegradable Polymers

Natural polymers are formed in nature ranging from the growth cycle of all organisms (Chandra and Rustgi 1998). They can be considered as the first biodegradable biomaterials used clinically. In the view of regenerative medicine, natural polymers offer advantages similar to biological macro-molecules (such as tissue) and its biological environment (Mano et al. 2007). Other inherent advantages include bioactivity, the ability to receptor-binding ligands to cells, susceptibility to cell-triggered proteolytic degradation and natural remodeling. While the weakness of natural polymers including immunogenic response and the possibility of disease transmission (Puppi et al. 2010).

Most natural polymers undergo enzymatic degradation and least undergoes hydrolytic degradation. The enzymatic degradation at in vivo level varies depending on the site of implantation, the availability and concentration of enzyme (Nair and Laurencin 2007). Hydrolytically biodegradable polymers are polymers that have a hydrolytically labile chemical bond that influences the level of degradation and erosion mechanism (Griffith 2000; Ulery et al. 2011). When the rate of degradation at the interface of water-degradable devices on the entire surface is faster than the diffusion depth of the water, then this indicates surface erosion. Conversely, if the water diffusion is faster than the degradation over the entire surface and mass loss occurred throughout the bulk of the material, this is called as bulk erosion. These categorizations are extremely important in determining which material is best for a desired application, for example in drug delivery. Two most important natural polymers used in biomedical field are protein or poly(amino acid), and poly(saccharide).

Proteins are polymers with amino acid monomers joined by amide bond and are very common material in the human body. Included into proteins are collagen, poly (amino acid), elastin and elastin-like poly(peptide), albumin and fibrin. Collagen is a protein with significant amounts in human body and is the main component of the ligament, cartilage, tendon, skin and bone (Ulery et al. 2011). Collagen has been studied for medical applications due to its biocompatibility, mechanical strength and enzymatic degradability (collagenases and metalloproteinases) (Krane 2008). Collagen has a good process-ability with high solubility in acidic solution to be used as collagen sponges, tubes, sheets, powders and injectable (Matsuno et al. 2006; Bushnell et al. 2008; Choi et al. 2009; Liu et al. 2010). The majority of these studies focused on the potential use of collagen as a biomaterial for a tissue engineering scaffold, specifically in load bearing applications. Collagen was also used as composite materials (hydroxyapatite and collagen) with composition closely resemble to that of bone (Venugopal et al. 2008).

Natural poly(amino acid) is a biodegradable ionic polymers occurs naturally in three different type: poly(ε–L-lysine), poly(γ-glutamic acid), and cyanophycin (Obst and Steinbüchel 2004). This polymer has characteristic such as biocompatibility and complete biodegradability that make this material as an ideal candidate for applications in human. Poly(l-lysine) is known to have anti-bacterial, anti-viral and anti-tumour activity and is considered to be a potential candidate for developing drug carrier vehicles (Nair and Laurencin 2007). Poly(γ-glutamic acid) is capable to degrade with the presence of water and developed as drug delivery vehicles, tissue engineering scaffolds and thermo-sensitive polymers (Kishida et al. 1998). Cyanophycin, is a comb-like polypeptide isolated from cyanobacteria that contains α-amino-α-carboxy-linked L-aspartic acid residues representing the poly(α-L-aspartic acid) backbone and L-arginine residues bound to the β-carboxylic groups of aspartic acids making it a highly poly-disperse polymer (Simon 1971). Synthetic poly(amino acid) is also studied and showed high crystallinity, low degradation rate and unfavorable mechanical properties (Ulery et al. 2011). Two synthetic biomaterials derived from poly(amino acids) are poly(L-glutamic acid) with high susceptibility to degradation by lysosomal enzymes and poly(aspartic acid) that is very soluble in water and easily converted to a hydrogel by high energy radiation (Li 2002; Pitarresi et al. 2007).

Elastin is the major protein component of blood vessels and lung tissue (Ulery et al. 2011). In vivo studies showed elastin has little interaction with platelets and have limitations on the ability to obtain an immune response (Mithieux et al. 2004). With this limitation, a synthetic elastin, elastin-like poly(peptide), was developed. This artificial poly(peptide), although very flexible as elastin, has characteristic that are biocompatible and non-immunogenic (Ulery et al. 2011). It was studied as delivery vehicles for chemotherapeutics (Bidwell III et al. 2007), antibiotics (Adams et al. 2009) and proteins (Bessa et al. 2010), beside for the soft tissues engineering due to its suitable elastic behavior (Nettles et al. 2010).

Albumin is a blood protein that is soluble in water and exists nearly 50 % of the total mass of the plasma in the body. Albumin has a function as a carrier of hydrophobic fatty acids around the blood stream and maintain blood pH (Ulery et al.

2011). The solubility of albumin allowed to be processed into various forms such as fibers (Regev et al. 2010), microparticles (Okoroukwu et al. 2010) and nanoparticles (Shen et al. 2011). Albumin also has been studied as a carrier vehicle for intravenous drug/gene delivery (Chuang et al. 2002) and as coating materials for cardiovascular devices (Uchida et al. 2005).

Fibrin is a biopolymer that is similar to collagen and it is the initial biopolymer used as biomaterials. It is characterized by its excellent biocompatibility, biodegradability and inject-ability (Ulery et al. 2011). Fibrin degraded to fibrinolysis in the human body in the presence of a complex cascade of enzymes (Erin and Robert 2005). The first product resulting from fibrin is fibrin sealant used clinically for hemostasis and tissue sealing applications in various surgical procedures (Nair and Laurencin 2007).

Poly(saccharide) are macromolecules formed from many monosaccharide units joined together by glycosidic linkages (Ulery et al. 2011). By having good characteristic such as biodegradability, process-ability and bioactivity, poly(saccharide) are very promising natural biomaterials. Poly(saccharide) are divided into polysaccharides of human and non-human origins. Hyaluronic acid and chondroitin sulfate are biopolymers belongs to the poly(saccharide) of human origin. Hyaluronic acid is a linear poly(saccharide), water-soluble and forms highly viscous solutions with unique viscoelastic properties (Nair and Laurencin 2007). It has an important role in various tissues including articular cartilage, the nucleus pulposus, skin, the cervis, and the glycocalyx of endothelial cells (Nair and Laurencin 2007). Half of the total content of hyaluronic acid in the human body is found in the skin, while other sources for its isolation are rooster combs and bovine vitreous humor (Ulery et al. 2011). Hyaluronic acid can undergo degradation within the body by free radicals (Rapta et al. 2009), also via digestion by lysosomal enzymes to form mono and disaccharides, which can be further converted into ammonia, carbon dioxide and water via the Krebs cycle (Al-Assaf et al. 2003). Hyaluronic acid plays an important role in tissue repair and drug delivery applications and is very promising for numbers of regenerative therapies especially in soft tissue engineering (Ulery et al. 2011). Chondrotin sulfate is the major component of aggrecan, the most abundant glycosaminoglycan found in the proteoglycans of articular cartilage (Nair and Laurencin 2007). It can stimulate the metabolic response of cartilage tissue and has anti-inflammatory properties (Chan et al. 2005). These showed the importance of these natural polymers used in biomedical applications (Kosir et al. 2000).

Other than poly(saccharide) molecules that exists in the human body, there are a number of similar molecules derived from other sources (poly(saccharide) of non-human origin) as promising degradable polymeric biomaterials (Ulery et al. 2011). Included in this class are the cationic polymer, chitosan found in crustacean skeletons and alginate found in brown algae, both used as drug delivery vehicles.

3.2 Synthetic Biodegradable Polymers

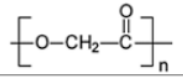
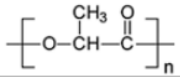
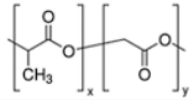
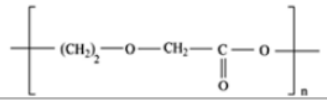
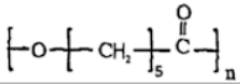
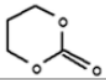
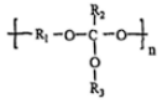
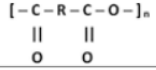
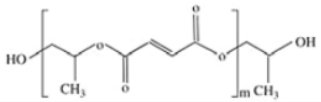
The disadvantages of natural polymers such as immunogenic response and the possibility of disease transmission (Puppi et al. 2010) has led to the development of synthetic biodegradable polymers. Among the first developed synthetic biodegradable polymers are the glycolide-based polymers, poly(glycolic acid) and poly(lactic acid), which have been used in products such as degradable sutures since 1960s and both have received approval by the FDA (Nair and Laurencin 2007). Table 2 list some of biodegradable polymers that found their application in biomedical field.

Poly(lactic acid) or PLA and poly(glycolic acid) or PGA are poly(α-ester) grade polymers which are thermoplastic and have characteristic that allows them to be degraded via hydrolytic action (Nair and Laurencin 2007). PLA is much more hydrophobic than PGA, making the rate of degradation of PLA slower (i.e. remain stable for more than 1 year) (Sinha et al. 2004) compared to PGA, which can be degraded within few weeks (Nair and Laurencin 2006). PGA are used clinically as an internal fixation device due to its higher rigidity than other degradable polymers (Tormala 1992). It has elastic modulus about 12.5 GPa (Maurus and Kaeding 2004) and very low solubility in organic solvents (Nair and Laurencin 2007). It will lose its strength within 1–2 months and loss its mass within 6–12 months (Nair and Laurencin 2007) and is broken down in vivo into glycine which can be removed through the urine (Maurus and Kaeding 2004).

PLA has chiral molecules wherein the polymerization leads to the formation of a semi-crystalline polymer and 4 different forms: poly(L-lactic acid) or PLLA, poly (D-lactic acid) or PDLA, poly(D, L-lactic acid) PDLLA which is a mixture of PLLA and PDLA, and meso-poly(lactic acid). So far, only PLLA and PDLLA have been studied extensively in biomedical research (Ulery et al. 2011) and regarded as an ideal biomaterial for load bearing applications, such as orthopedic fixation devices with high elastic modulus (about 4.8 GPa) (Middleton and Tipton 2000), while PDLLA has lower elastic modulus of 1.9 GPa (Maurus and Kaeding 2004). PLLA-based polymers replaced the non-degradable fiber (Dacron) for scaffolds materials (Wang et al. 2009). PLLA degradation rate is very low, and was reported to take between 2 and 5.6 years for the amount of resorption in vivo (Middleton and Tipton 2000). The copolymer of lactic acid and glycolic acid, poly(lactic-*co*-glycolic acid) or PLGA, degrades via hydrolytic action and its rate depends on various parameters including ratio LA:GA, molecular weight, shape and structure of the matrix. PLGA degrades in 1–2 months for a ratio of 50:50, 4–5 months for 75:25, and 5–6 months for 85:15 (Nair and Laurencin 2007).

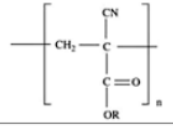
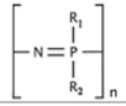
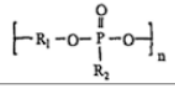
Poly(dioxanone) is a semicrystalline polymer monofilament developed commercially under the trade name of PDS and used for several orthopedic applications such as bone fixation screws (Nair and Laurencin 2007). Similar with PGA, PDS is broken into glycine which can be removed through the urine. PDS has very low elastic modulus (about 1.5 GPa) compared to PGA, and a decrease in strength within 1–2 months and loss its mass by hydrolytic degradation within 6–12 months (Maurus and Kaeding 2004).

Table 2 Some biodegradable polymers in medicine

Polymer	Chemical structure	Applications
Poly(glycolic acid)		Tissue engineering, drug delivery
Poly(lactic acid)		Tissue engineering, drug delivery
Poly(lactic-*co*-glycolic acid)		Tissue regeneration, drug delivery
Poly(dioxanone)		Orthopedic applications
Poly(caprolactone)		Tissue engineering
Poly(trimethylene carbonate)		Drug delivery, soft tissue regeneration
Poly(ortho ester)		Drug delivery
Poly(anhydride)		Drug delivery, tissue engineering
Poly(propylene fumarate)		Orthopedic applications

(continued)

Table 2 (continued)

Polymer	Chemical structure	Applications
Poly(alkyl cyanoacrylates)		Drug delivery
Poly(phosphazene)		Tissue engineering, vaccine adjuvant
Poly(phosphoester)		Drug delivery, tissue engineering

Poly(caprolactone) or PCL is a semicrystalline poly(ester) soluble in various organic solvents with slow degradation rate of about 2–3 years (Nair and Laurencin 2007). Extensive research is ongoing to develop various micro- and nano-sized drug delivery vehicles based on PCL (Sinha et al. 2004). PCL has also been extensively investigated as scaffolds for tissue engineering. PCL has low tensile strength of about 23 MPa, but has high elongation of >700 % (breakage) (Gunatillake et al. 2006).

Poly(trimethylene carbonate) or PTMC is an elastomeric aliphatic polyester with excellent flexibility. PTMC has been developed for drug delivery vehicles and soft tissue regeneration. The combination of glycolide, trimethylene carbonate and dioxane can reduce rigidity and degrades within 3–4 months (Nair and Laurencin 2007). Binding ability of amide hydrogen bonds and biodegradation given by an ester bond results the ester co-polymers with good mechanical and thermal properties. Poly(esteramide) or PEA and poly(orthoesters) or POE are thus identified as degradable polymers suitable for orthopedic applications beside for drug delivery vehicles (Gunatillake and Adhikari 2003). Preliminary in vivo studies showed that POE increased bone growth when compared with PDLGA (Andriano et al. 1999). With the addition of lactide segments as part of the polymer structure, degradation began to be achieved from 15 to hundreds of days. The degradation of the lactide segments produces carboxylic acids, which catalyze the degradation of the orthoester (Gunatillake and Adhikari 2003).

Poly(anhydride) is one of the most extensive biodegradable polymers studied with excellent biocompatibility and controlled release characteristics (Gunatillake and Adhikari 2003). In 1996, this material has been approved by the FDA as polymers for controlled drug delivery (Nair and Laurencin 2007). Mechanical properties and degradation time can vary, depending on the monomers used. Poly (anhydride) is generally classified as surface eroding polymers because of its linear mass loss during erosion (Nair and Laurencin 2007). However, research shows that the degradation is not entirely confined to the surface of the polymer matrix and additional studies tried to explain other parameters that may affect the degradation polyanhydride (Akbari et al. 1998). The good mechanical property of poly(anhydride) was combine with surface-eroding characteristic of poly(imide) resulted into poly(anhydride-*co*-imide) specifically used for orthopaedic applications (Gunatillake and Adhikari 2003). This co-polymers has significantly improvement in the mechanical properties, especially the compressive strength of about 50–60 MPa (Gunatillake and Adhikari 2003) compared with poly(anhydride). This increase is based on succinic acid trimellitylimido glycine and trimellitylimido alanine (Uhrich et al. 1995). Poly(anhydride-*co*-imide) degraded through hydrolysis of anhydride bonds, followed by the hydrolysis of imide bonds (Uhrich et al. 1997). Another approach to improve the mechanical strength of poly(anhydride) is by the inclusion of acrylic functional groups in the monomeric units to form injectable photo-cross linkable poly(anhydride) can be used for filling irregularly shaped bone defects or for soft tissue repairs and can be molded into a desired shape under physiological conditions (Nair and Laurencin 2007).

Poly(propylene fumarate) or PPF undergoes bulk erosion through hydrolysis of the ester bond and its degradation time depends on several parameters, such as molecular weight, type of cross-linker and cross-linking density (Nair and Laurencin 2007). PPF injection system was developed as a material for orthopedic implants (Temenoff and Mikos 2000). Cross-linked PPF was developed by co-polymerization with acrylic monomers such as N-vinyl pyrolidone, using different types of polymerization initiators (Gunatillake and Adhikari 2003).

Poly(phosphazene) is a remarkable macromolecules because of its versatile adaptation to a wide range of applications (Lakshmi et al. 2003) where its degradation rate can be designed from a few hours to a year by varying the chemical side groups (Nair and Laurencin 2007). The application of these polymers as a short-term medical implants are drug delivery matrices and scaffolds for tissue engineering. Although polyphosphazenes has tremendous potential as a biodegradable matrix, this material is relatively under-utilized (Lakshmi et al. 2003).

3.3 *Lesson Learned*

Figure 3 shows examples of implants made of biodegradable polymers ranging from bone related implants, such as screws and plates, till endovascular implants such as the first Igaki-Tamai stent till the most recent Abbot's bioabsorbable stent. Apart from the ease of fabrication and control of degradation, biodegradable polymers might not best suited for temporary hard tissue application such as bone, where adequate strength and elastic modulus are required. Polymeric structures are

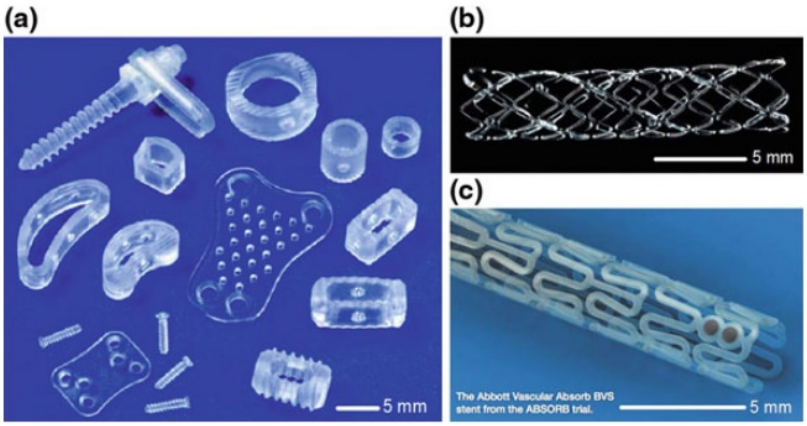


Fig. 3 Biodegradable polymer implants: **a** various spine surgical implants made of PGA and PLA (Medscape.com), **b** Igaki-Tamai stent made of PLLA (Kyoto Medical Planning, Japan), **c** bioresorbale vascular stent made of PLLA (Abbot Vascular, USA). *Note scale bars* are approximatively only

relatively weak and may not achieve sufficient level of the required strength (Yarlagadda et al. 2005; Cheung et al. 2007) and they could suddenly loss their mass and mechanical integrity due to degradation. Degradation of polymers affects the surrounding tissue by lowering the pH and releasing acidic degradation and resorption by-products which triggers inflammatory reactions (Gray et al. 1988; Therin et al. 1992; Rehm et al. 1994; Bergsma et al. 1995; James and Kohn 1996). This is a major concern in orthopaedic applications where implants with considerable bulk size are required. Release of small particles during degradation also triggers an inflammatory response (Taylor et al. 1994) and affects bone-remodeling processes (Conley Wake et al. 1998). When the capacity of the surrounding tissue to eliminate the by-products is low due to the poor vascularization or low metabolic activity, the chemical composition of the by-products may lead to local temporary disturbances (Bostman 1991).

The bioactive properties of biodegradable polymers, such as the antibacterial and anticancer properties of poly(peptide), can be further exploited to be combined with biodegradable metals to develop a strong yet bioactive temporary implants. The controllable hydrolysis of synthetic biodegradable polymers such as poly(lactic-*co*-glycolic acid) can be formulated as drug carrier and coated onto biodegradable metals to also provide a strong scaffold with pharmacologic capabilities.

4 Biodegradable Metals

More than 100 years ago, history of bone fracture fixation told us that metals were used as implants but were then abandoned because of corrosion (Uhthoff et al. 2006). At that time, metals were selected on the trial and error basis (Witte and Eliezer 2012). With the advancement in materials processing technology, the problem of corrosion can be controlled by using corrosion resistant alloys as described in the previous chapter. However, clinical reality showed that almost 10–12 % of inert metal implants were removed due to infection, exposure, pain and discomfort (Meslemani and Kellman 2012). Some cases on bone fracture fixator (bone screws) showed complications such as reactions of rejection from body (allergic) (Hallab et al. 2001; Kanerva and Förström 2001; Vos and Verhofstad 2013) that made most surgeons recommends implants removal once the bone has unified (Ochs et al. 2012; Williams et al. 2012). Indeed, implants for treating bone fractures are required only temporary during the period of tissue healing (Li et al. 2014).

The current promising solution to overcome the disadvantages of the inert (permanent) implants is the use of biodegradable ones. Presently, the choices can be taken either from biodegradable polymers or biodegradable metals with both offer each advantages and limitations. Biodegradable polymers have biomechanical limitation compared to biodegradable metals (Suuronen et al. 1992; Henderson et al. 2014). Biodegradable metals have both the strength and the ability to degrade that make them extensively studied and proposed as new temporary implant materials for vascular

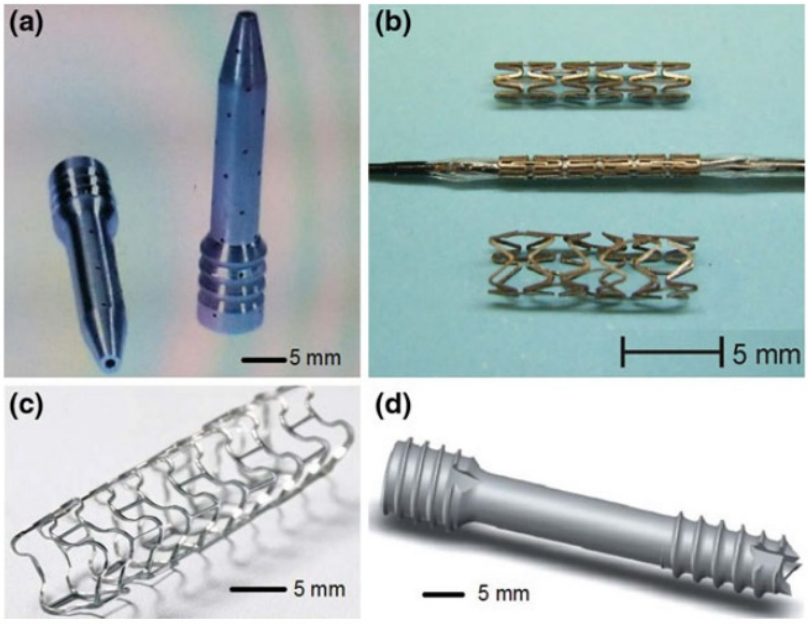


Fig. 4 Biodegradable metal implants: **a** Mg alloy cross pin (Drexel University), **b** Fe alloy stent (Laval University), **c** Mg alloy stent (Biotronik, Germany), **d** Mg alloy compression screw (Magnezix®, Syntellix, Germany). *Note scale bars* are approximative only

intervention and osteosynthesis (Hermawan 2012; Zheng et al. 2014). In the current development, variety of medical devices (or prototypes) have been made (or under research and development) from biodegradable metals including bone pins, screws and endovascular stents as shown in Fig. 4.

Based on materials science point of view, biodegradable metals can be classified as pure metals (one metallic element with impurity levels lower than the commercial tolerance limits), alloys (various microstructures and one or more alloying elements) and metal matrix composites. Up to now, Mg, Fe and zinc (Zn) are the three class of metals have been used in their pure states and as the matrix for making alloys and composites.

4.1 Basic Concept

The emergence of biodegradable metals oppose the paradigm of implant materials that they must be corrosion-resistant and inert within the body (Hermawan 2012; Zheng et al. 2014). Biodegradable metals have been defined as metals that are 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. Furthermore, the major

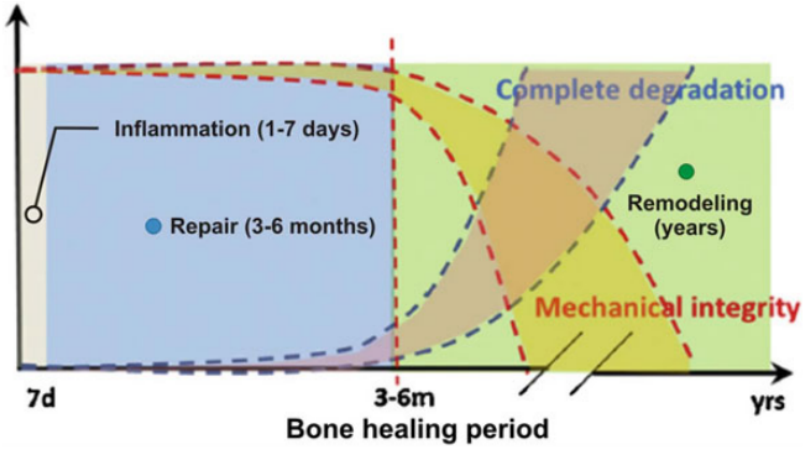


Fig. 5 Schematic diagram showing ideal behavior biodegradable metal implants for bone fracture fixation where degradation rate keeps low during 3–6 months and increases thereafter, and mechanical integrity which keeps relatively constant during 3–6 months and rapidly deteriorate thereafter. Adapted from Zheng et al. (2014)

component of biodegradable metals should be essential metallic elements that can be metabolized by the human body, and demonstrates appropriate degradation rates and mechanism (Zheng et al. 2014).

Ideal biodegradable metal implants will give the required mechanical support during the process of tissue reconstruction, and then degrade progressively with an appropriate level of tolerable degradation products in the human body (Zheng et al. 2014; Liu and Zheng 2011a, b). In the case of bone fracture, the time required to achieve hard bone union varies greatly depending on the fracture configuration and location, status of the adjacent soft tissues, and patient characteristics (Zheng et al. 2014). Figure 5 models the degradation rate and the deterioration of mechanical integrity of biodegradable metal implants to suit the bone fracture remodeling period (Zheng et al. 2014).

Similarly, for endovascular applications, the biodegradable metal implants (i.e. stent) behavior must suit the period of the vessel's healing process. It starts by inflammation period where platelet deposition and infiltration of inflammatory cells lasts for several days, followed by granulation period where endothelial cells migrate to cover the injured surface and smooth muscle cells modulate and proliferate for 1–2 weeks, finally remodeling period takes place where extracellular matrix deposits and continues for months (Zheng et al. 2014). The total healing period is not yet fully determined but some argued that the optimal mechanical integrity of a stent must be maintained within 6–12 months (Schömig et al. 1994; El-Omar et al. 2001).

Thus, the main issue is the control of degradation rate. Once implanted into the human body, biodegradable metal implants are continually exposed to extracellular tissue fluid. Their exposed surface undergoes an electrochemical dissolution of

material due to interactions with the human body environment that contains water, complex organic compounds, dissolved oxygen, anions, cations and their complex, amino acids, proteins, plasma, lymph, etc. Corrosion initiates at any site on the surface which has potential difference (electrochemical cells) created from metallurgical condition of the metals such as phase variation, grain boundaries, impurities, etc., or from geometrical condition such as crevice formation at the interface between a plate and a locking screw. Corrosion is the typical process of degradation for biodegradable metals. It's an electrochemical process where oxidation and reduction reactions occurred producing oxides, hydroxides, hydrogen gas, or other compounds. In the physiological environment, corrosion generally involve the following reactions:

$$\mathrm{M} \rightarrow \mathrm{M}^{n+} + n\mathrm{e}^{-} \quad \text{(anodic reaction)} \tag{1}$$

$$2\mathrm{H_2O} + 2\mathrm{e}^{-} \rightarrow \mathrm{H_2} + 2\mathrm{OH}^{-} \quad \text{(cathodic reaction)} \tag{2}$$

$$2\mathrm{H_2O} + \mathrm{O_2} + 4\mathrm{e}^{-} \rightarrow 4\mathrm{OH}^{-} \quad \text{(cathodic reaction)} \tag{3}$$

$$\mathrm{M}^{n+} + n\mathrm{OH}^{-} \rightarrow \mathrm{M(OH)}n \quad \text{(product formation)} \tag{4}$$

Beside affecting mechanical integrity, degradation rate also influence the local tissue response and the physiological environment (Witte and Eliezer 2012). Degradation and tissue response interact reciprocally, the implantation causes injury and the body responses to it by decreasing the pH value around the implantation site (i.e. 5.3–5.6) that may accelerate corrosion process of the implant and reduce the local oxygen concentration (Witte and Eliezer 2012). Our knowledge on this complex interaction is still very limited. One of the recommendations of the latest symposium on biodegradable metals in Italy in 2014 is to encourage more research to understand in vivo degradation behavior and to determine its relation to the in vitro degradation.

Numerous methods have been used to evaluate the corrosion behavior of biodegradable metals in the laboratory, involving either qualitative measurements of their implants into animals (in vivo) or quantitative electrochemical measurements in simulated body fluid (in vitro). These methods so far are adopted from those available for corrosion evaluation of inert metallic biomaterials. The in vitro experiments are designed to closely simulate the in vivo situation even though some important variables such as amino acids, proteins and ions at the proper temperature and pH into the simulated body fluid are often excluded to maintain reproducibility and minimize variables. Various in vitro degradation assessments are commonly used from simple mass loss experiments to more complex electrochemical methods, which each has its own unique benefits and limitations (Kirkland et al. 2012). Meanwhile, in vivo assessments used various animal models from small to bigger mammals, and different analytical tools from radiographic (X-ray, CT scan, etc.), blood analysis till histology (Dziuba et al. 2013).

4.2 Degradation Assessment Techniques

Three common assessment techniques to measure in vitro degradation rate and determine degradation mechanism of biodegradable metals are weight loss, potentiodynamic polarization and electrochemical impedance spectroscopy. Weight loss method measures degradation rate based on mass difference of specimens before and after a certain period where the specimens are usually immersed in simulated body fluid solution. The ASTM standard G31 (Standard Practice for Laboratory Immersion Corrosion Testing of Metals) is mostly referred with some modifications. This simple method typically produces accurate results when degradation layer is optimally removed and when a substantial degree of corrosion is achieved but multiple replicates are necessary to provide confidence in the results (Kirkland et al. 2012). Weight loss experiments reveal how much degradation has occurred, but they do not reveal the degradation mechanisms or explain why one alloy degrades faster than another. Figure 6 shows typical results obtained from the potentiodynamic polarization and electrochemical impedance spectroscopy techniques.

Different from the weight loss, potentiodynamic polarization method unveils the instantaneous degradation rate of a metal under a specific condition. In this electrochemical method, the metal surface is polarized by applying a range of potential and in return, the generated current is measured by a potentiostat. Generally, a three electrodes system: working, reference and counter electrodes is used and submerged in the test solution. The ASTM standard G59 (Standard Test Method for Conducting Potentiodynamic Polarization Resistance Measurements) is often referred. The working electrode comprises the specimen with a determined exposed surface area. Additionally, potentiodynamic polarization is also able to unveil degradation behavior of the metals both thermodynamically and kinetically such as passivation and activation or concentration controlled process.

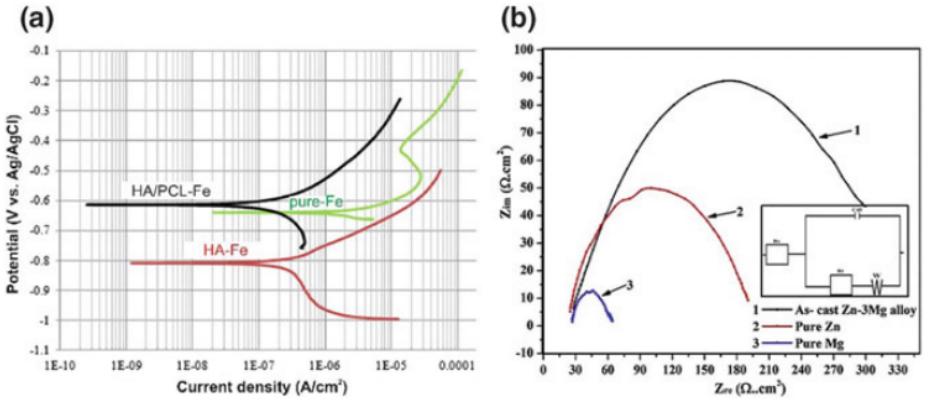


Fig. 6 Example of electrochemical corrosion test results: **a** potentiodynamic polarization curves for pure-Fe and Fe coated with hydroxyapatite (HA-Fe) and with composite of poly(caprolactone) and hydroxyapatite (HA/PCL-Fe), **b** Nyquist plots and a proposed equivalent circuit for pure Mg, pure Zn and cast Zn-3Mg alloy obtained by electrochemical impedance spectroscopy experiment. Adapted from Mohd Daud et al. (2014)

Electrochemical impedance spectroscopy is a powerful technique for unveiling information about surface characteristics of degrading metals. In this method, an AC voltage is applied onto the metal surface, normally from higher to lower frequency, followed by the generation of AC current. The two parameters are logged, analyzed and transformed by a frequency analyzer to form impedance. The experiment configuration of EIS is similar to that of potentiodynamic polarization. The ASTM standard G106 (Standard Practice for Verification of Algorithm and Equipment for Electrochemical Impedance Measurements) can be further referred. The impedance data can be presented as Nyquist and Bode plots. Some basic information can be extracted directly from the Nyquist plot are electrolyte resistance (R_e) that represents the internal solution resistance, and polarization resistance (R_p) which is the sum of the resistances caused by the electrochemical process on the working electrode surface and resistance due to the voltage drop between the working electrode and counter electrode. Combined with a cross sectional and surface analysis using microscopy and elemental analysis the characteristics of the degradation layer formed during degradation process will be optimally revealed.

4.3 Type of Biodegradable Metals

Generally, it is known that the corrosion of Mg and its alloys is considered too fast (Witte and Eliezer 2012); meanwhile, Fe and its alloys corrode relatively too slow (Witte et al. 2005). Therefore, attempts have been made to manipulate their microstructure and surface properties to control their degradation kinetics via diverse advance material processing and surface modification techniques. In addition, alternative metals have also been explored including Zn and its alloys (Murni et al. 2015; Vojtěch et al. 2011). Table 3 summarizes the mechanical and degradation properties of some metals and alloys used and proposed for biodegradable metals.

Mg and Its Alloys

History of Mg for use as an implant dated back to 1878, when it was used as ligature to stop blood vessels bleeding (Hornberger et al. 2012; Witte 2010). Abandoned due to limited mechanical properties, poor corrosion resistance and high cost of production, Mg regained its popularity as innovative biomaterial for temporary implants (Hornberger et al. 2012). It is a lightweight metal with density of 1.74 g/cm^3 and elastic modulus of ~45 GPa (Black and Kohser 2008) which are very close to those of human bones. It is also an essential element for human metabolism and can be found in bone tissue (Saris et al. 2000; Okuma 2001; Vormann 2003; Wolf and Cittadini 2003; Hartwig 2001). Biocompatibility of Mg and its alloys has been confirmed by numbers of studies both in vitro and in vivo (Heublein et al. 2003; Li et al. 2004, 2008; Witte et al. 2007a). However, their fast degradation rate limits their applications.

Basically, two factors contributing for low degradation resistance of Mg are the initial galvanic corrosion caused by second phase or impurities and the

Table 3 Mechanical and degradation properties of some biodegradable metals

Metal	Mechanical properties				Degradation rate* (mm/year)
	E (GPa)	YS (MPa)	UTS (MPa)	ε (%)	
Pure Mg (annealed)	45	30	100	7	8
Mg–Al (AZ31, extruded)		175	250	14	2.0
Mg-RE (WE43, extruded)		180	280	10	4.34
Mg-1Ca (extruded)		135	240	10	1.4
Mg-1Zn (rolled)		160	240	7	1.52
Pure Fe (annealed)	200	150	200	40	0.2
Pure Fe (electroformed annealed)		270	290	18	0.75
Fe-35Mn (PM annealed)		230	430	30	0.44
Fe-10Mn-1Pd (forged)		850	1450	10	0.42
Fe-30Mn-6Si (cast)		180	430	17	0.3
Pure Zn	100	–	20	0.3	0.5
Zn-1Mg (cast)		–	150	2	0.20
Zn-1Mg (extruded)		170	250	11	0.12
Zn-3Mg (ECAP)**		205	220	6	0.28

Note *E* elastic modulus, *YS* yield strength, *UTS* ultimate tensile strength, *ε* elongation. *Degradation data were compiled from the most similar experimental set-up (i.e. PDP method, SBF solution), but variation may occur and they may not be directly comparable. **Unpublished data. Data compiled from: Moravej et al. (2010a), Hermawan et al. (2008), Schinhammer et al. (2010), Xu et al. (2011), Liu et al. (2011), Gong et al. (2015), Dambatta et al. (2013), Gu et al. (2009) and Vojtech et al. (2011)

quasi-passive hydroxide film formed on the surface (Makar and Kruger 1993). The corrosion of Mg follows the overall reactions:

$$\mathrm{Mg} \rightarrow \mathrm{Mg}^{2+} + 2\mathrm{e}^{-} \qquad \text{(anodic reaction)} \tag{5}$$

$$2\mathrm{H_2O} + 2\mathrm{e}^{-} \rightarrow \mathrm{H_2} + 2\mathrm{OH}^{-} \qquad \text{(cathodic reaction)} \tag{2}$$

$$\mathrm{Mg} + 2\mathrm{H_2O} \rightarrow \mathrm{Mg(OH)_2} + \mathrm{H_2} \qquad \text{(overall reaction)} \tag{6}$$

The production of hydrogen (reaction 6) raises a concern as gas bubble forms when Mg is implanted in vivo (Aghion et al. 2012). New Mg-based metallic glass (Mg-Zn-Ca alloy) was developed and has not exhibited hydrogen evolution in clinical trials (Zberg et al. 2009).

In general, there are two ways to improve the corrosion resistance of Mg and its alloys: firstly, by tailoring their composition (purification and alloying) and microstructure, including grain size (Hoog et al. 2008; Wang et al. 2008) and texture (Xin et al. 2009) from base material (not only alloys) (Kaesel et al. 2005), through optimal production method (Hort et al. 2010); secondly by employing surface treatment or coating (Gray and Luan 2002) such as using ceramic, polymer

or composite layer (Hornberger et al. 2012). With the achieved improvement, variety of medical devices were proposed to be made from Mg alloys including ligature wire, pins, screws, plates and endovascular stents (Witte 2010; Henderson et al. 2014; Witte et al. 2005, 2006, 2007b, c; Kim et al. 2008; Zhang et al. 2008; Song 2007; Staiger et al. 2006; Song and Song 2007).

Pure Mg is Mg with other elements (impurities) within tolerance limit. Elements such as Fe, Cu, Ni, Co and Be are considered as impurities and their content should be limited to 35–50 ppm for Fe, 100–300 ppm for Cu, 20–50 ppm for Ni, and up to 4 ppm for Be (Witte et al. 2008; Makar and Kruger 1993). When the impurities exceed their tolerance limits, the corrosion rate will increase (Lee et al. 2009; Li and Zheng 2013). More precisely, tolerance limit for Fe was reported as 170 ppm in unalloyed as-cast Mg and 5 ppm in wrought Mg (Kraus et al. 2012; Hofstetter et al. 2015). Above this limit, Fe-rich particles are formed and thus electrochemically active cathodic sites exist and accelerate corrosive rate drastically. Addition of silicon, which is usually added to improve castability, promotes the formation and growth of Fe-rich particles and thus provokes more corrosion (Hofstetter et al. 2015). Beside by purification, the corrosion resistance of pure Mg is higher by improving the grain size through forging or rolling and heat treatment (Li and Zheng 2013). The heating temperature and the length of time of the heat treatment must be considered properly. Otherwise, it would get the opposite results (Li and Zheng 2013). Although pure Mg demonstrated the ability to stimulate new bone formation, but its mechanical properties in general is still considered insufficient for orthopedic applications (Gao et al. 2010; Huang et al. 2007) and considered unsuitable for vascular stents (Li and Zheng 2013).

Common alloying elements used in Mg for implants are Al, Mn, Zn, Ca, Li, Zr, Yand rare earth elements (RE) (Xu et al. 2007; Witte et al. 2005, 2007c; Kannan and Raman 2008; Rettig and Virtanen 2008; Qudong et al. 2001; Witte et al. 2008; Gu et al. 2009). When viewed from the alloying elements, there are two major groups of Mg alloys excluding pure: Al-containing alloys and Al-free alloys (Ren et al. 2005; Song and Song 2007; Wang et al. 2008; Witte et al. 2008). Mg alloys with Al as the main alloying element commonly form complex $Mg_{17}Al_{12}$ compound which strengthens the alloys via solid solution and precipitation strengthening mechanism (Witte et al. 2008). However, the $Mg_{17}Al_{12}$ compound has low melting point and thus cannot maintain the strength at high temperatures (Witte et al. 2008). The addition of Al decreases the liquidus and solidus lines and thus raises the alloy's castability, but adding Al more than 2 wt% may result in embrittlement (Housh and Mikucki 1990). The addition of Mn further increases the ductility and corrosion resistance as Mn binds to Fe, while addition of Zn also provide a solid solution strengthening (Mordike and Lukáč 2006) and improve castability. Calcium (Ca) can contribute to strengthen the alloys as it forms Mg_2Ca and Al_2Ca that act as precipitation and grain-boundaries strengthening but cannot be added more than 1 wt% as it will cause hot tearing during casting (Witte et al. 2008). Lithium (Li) is a unique alloying element which can change the lattice structure of the alloy from HCP into BCC (Nayeb-Hashemi and Clark 1988), but its cytocompatibility is questionable.

The current interesting alloying elements for Mg is the RE as they are found to contribute in the strengthening, raising the creep resistance, and increasing corrosion resistance (Rokhlin 2003). The RE are divided into two groups: (1) group of elements with limited solubility such as Nd, La, Ce, Pr, Sm and Eu (Mordike and Lukáč 2006), and (2) group of elements with large solubility such as Y, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu (Nayeb-Hashemi and Clark 1988). Group 1 will form initial intermetallic phases during solidification, while group 2 forms intermetallic phases complex with Mg or Al as strengthening precipitates and inhibiting the movement of dislocations at high temperatures (Witte et al. 2008). Examples of Al-containing Mg alloys are the types of AZ91, AZ31, AE21, Ca-modified AZ alloys and AE42 (Mordike and Lukáč 2006, Housh and Mikucki 1990). LAE442 alloy is a further development of AE42 with low density but with increasing ductility and corrosion resistance (Bach et al. 2003).

Examples of Al-free Mg alloys are the types of WE, MZ, WZ and Mg–Ca alloys (Witte et al. 2008). The addition of elements such as Y, Zr, Zn and RE improves creep resistance, high temperature stability and forging-ability of the alloys (Mordike and Lukáč 2006; Housh and Mikucki 1990). Currently, the Al-free alloys are the recommended types of Mg alloys for biomedical use in human (Zhang et al. 2010, 2012). In addition, the recommended alloying elements for these alloys includes Ca, Mn and Zn (Song 2007; Xu et al. 2007; Li et al. 2008)

Mg–Ca alloys became the first most studied biodegradable alloys for bone applications as Mg and Ca are two main elements that exist in human bone and beneficial for bone healing (Ilich and Kerstetter 2000; Serre et al. 1998). Their biocompatibility was tested both in vitro and in vivo where Mg-(1 wt%) Ca pins gradually degraded after 90 days and formation of new bone was evident (Li et al. 2008). Knowing that Zn is also an essential element in the human body, Mg-Zn alloys also received attentions (Tapiero and Tew 2003). The in vitro cytocompatibiliy of Mg-(6 wt%) Zn alloy was tested with fibroblast cells and showed positive results, while the in vivo test in rabbit's femoral bone showed a relatively slow degradation rate (2.32 mm/year) without any evidence of toxicity (Zhang et al. 2010; Li and Zheng 2013). Mn does not affect mechanical properties of Mg alloys, but it increases corrosion resistance and poses no toxicity (Li and Zheng 2013). Normally, Mn is also added along with Zn and form ternary Mg–Mn–Zn alloys. An in vivo study showed that after 18 weeks, Mg-1.2Mn-1Zn alloy implants did not cause an increase of serum Mg levels and renal impairment in rats (Xu et al. 2007).

Fe and Its Alloys

Fe widely involves in a large number of Fe containing enzymes and proteins in human body. It involves in the decomposition of lipid, protein and DNA damages due to its reactivity to oxygen molecules which might produce reactive species through Fenton reaction (Mueller et al. 2006). It also plays significant roles in transport, reduction of ribonucleotides and dinitrogen, storage and activation of molecular oxygen, etc. (Fontcave and Pierre 1993). The suitability of Fe as a biodegradable implant material has been tested both in vitro and in vivo in variety of cells and animal models (Waksman et al. 2008; Peuster et al. 2001a, 2003, 2006).

Even though no toxicity was observed (Peuster et al. 2001b), but the concentration of Fe ions in the body should not reach higher than 50 µg/ml as my cause toxicity and cell death (Zhu et al. 2009; Siah et al. 2005). Elastic modulus of pure Fe (211 GPa) is higher than that of pure Mg (41 GPa) and its alloys (44 GPa) or SS316L (190 GPa) (Song 2007). Obviously, Fe and its alloys possess superior mechanical properties and can meet the mechanical requirement that Mg alloys cannot provide (Hermawan et al. 2010a; Niinomi et al. 2012; Schinhammer et al. 2010). However, their slow degradation is unmatched with the tissue healing period and has become the major drawback which limit their applications (Peuster et al. 2006; Kraus et al. 2014).

Different from Mg, Fe degradation is dependent on oxygen availability. Generally, it degrades via corrosion following reactions:

$$\mathrm{Fe} \rightarrow \mathrm{Fe}^{2+} + 2\mathrm{e}^{-} \qquad \text{(anodic reaction)} \tag{7}$$

$$2\mathrm{H_2O} + \mathrm{O_2} + 4\mathrm{e}^{-} \rightarrow 4\mathrm{OH}^{-} \qquad \text{(cathodic reaction)} \tag{3}$$

$$2\mathrm{Fe} + 2\mathrm{H_2O} + \mathrm{O_2} \rightarrow 2\mathrm{Fe(OH)_2} \qquad \text{(overall reaction)} \tag{4}$$

The formation of Fe oxides have been identified as the major inhibitor for a faster degradation (Hermawan et al. 2010b; Kraus et al. 2014). Dense degradation products such as Fe-hydroxides, Fe-carbonates and Fe-phosphate layers greatly hinder oxygen transport to the fresh Fe surface (Drynda et al. 2014; Chen et al. 2014; Kraus et al. 2014). Attempts to accelerate the degradation kinetics of Fe have been explored through alloying, thermomechanical treatment and by making composite of Fe with bioceramics (Ulum et al. 2014, 2015). In the design of Fe alloys, several key points must be considered including manufacturing process (i.e. melting temperature of Fe n is higher than that of Mg which associate with cost and equipment), selection of alloying elements (Peuster et al. 2001b, 2006; Hermawan et al. 2010a) and heat treatment to control the grain size (Hermawan et al. 2010a; Moravej et al. 2010b; Niinomi et al. 2012).

Moreover, Fe is ferromagnetic in nature, therefore ideal alloying elements should change this property to make Fe alloys compatible with high magnetic field such as that generated by Magnetic Resonance Imaging (MRI) which become widely used for post-implantation monitoring and diagnostic (Hermawan et al. 2010a). Fe was made via a bottom-up electroforming process that produced finer grain sizes and preferential textures and resulted into a slight increase of corrosion rate (Moravej et al. 2011). By using surface treatment approach, Fe was also coated with micro-patterned Au disc arrays and produced a more uniform corrosion with an almost four times higher degradation rate than the uncoated ones (Cheng et al. 2015). Another attempt was by making composite of Fe with Fe_2O_3 to create more phase/grain boundaries which theoretically act as active sites for accelerating degradation (Cheng et al. 2014).

Zn and its Alloys

Zn is an important essential trace element for cell development and growth, immune and nervous system. It can be found in the bone extracellular matrix where Zn is co-deposited with calcium hydroxyapatite (McCall et al. 2000) and shows a stimulatory effect on the growth of new bone tissues (Zhang et al. 2010; Hänzi et al. 2010). The dietary intake of Zn for adult varies from 5 to 20 mg/day and its excess will be excreted by the kidney (Nriagu 2007; Fosmire 1990). The cytocompatibility of Zn alloy has been comprehensively studied where Zn-3Mg alloy extract exhibited adjustable cytotoxic effects on normal human osteoblast cells and found suitable in the view of its applications for bone implants (Murni et al. 2015). In Mg alloys, Zn is often used as a major alloying element such as Mg-Zn, Mg-Zn-Mn-Ca, Mg-Zn-Y, Mg-Gd, Mg-Zn-Si (Vojtěch et al. 2011) and positively affect the corrosion resistance and strength of Mg (Vojtěch et al. 2011).

The interest toward Zn alloys began since the work on Mg-Zn-Ca glasses (with ~50 wt% Zn) that observed a significant reduction of hydrogen evolution during in vitro and in vivo studies (Zberg et al. 2009). However, the use of Zn in the context of biodegradable implants is relatively new (Bowen et al. 2013; Vojtěch et al. 2011). Alloying Zn with Mg (<4 wt%) was reported to enhance its corrosion resistance and mechanical properties (Prosek et al. 2008). Zn alloys with up to 3 wt% Mg was recently investigated for bone fixation applications (Vojtěch et al. 2011). Zn alloys could be preferable over Mg alloys since they can be fabricated by classical routes such as die casting and hot rolling. Moreover, they have lower melting point, lower reactivity, and superior machinability compared to Mg alloys. Zn-Mg alloys were found to have a degradation rate that is slower than Mg alloys but faster than Fe alloys (Vojtěch et al. 2011). Similar to Fe, Zn degradation needs oxygen and it generally degrades via the following reactions:

$$\mathrm{Zn} \rightarrow \mathrm{Zn}^{2+} + 2\mathrm{e}^{-} \qquad \text{(anodic reaction)} \tag{8}$$

$$2\mathrm{H_2O} + \mathrm{O_2} + 4\mathrm{e}^{-} \rightarrow 4\mathrm{OH}^{-} \qquad \text{(cathodic reaction)} \tag{3}$$

$$2\mathrm{Zn} + 2\mathrm{H_2O} + \mathrm{O_2} \rightarrow 2\mathrm{Zn(OH)_2} \qquad \text{(overall reaction)} \tag{9}$$

Pure Zn has alow strength (~20 MPa) compared to Mg, but once alloyed, such as that Zn-(1–3 wt%)Mg, it can be superior to some Mg alloys (Vojtěch et al. 2011). Beside alloying, mechanical properties of Zn alloy can be further improved by (severe) plastic deformation such as extrusion, equal-channel angular pressing, high pressure torsion, drawing and forging (Zheng et al. 2014; Zhang et al. 2013). Latest report on hot extrusion of Zn–1 Mg alloy revealed a significant grain size reduction resulting into increase strength twice than that of pure Zn with a much more uniform degradation behavior (Gong et al. 2015). The cytocompatibility of Zn alloys have been comprehensively studied against various cells such as fibroblast, osteoblast and osteosarcoma, with a conclusion that the Zn alloys have potential for bone implant applications (Murni et al. 2015; Kubásek et al. 2016). However, more works have to be done on Zn alloys to confirm their suitability as biodegradable metals.

5 Perspective

The advance of our knowledge in implant-tissue interactions indicates that biomaterials should exhibit bio-functional capability while maintain a superior mechanical property. The study of innovative degradable biomaterials is one of the most interesting research topics at the forefront of biomaterials in the present days.

Biodegradable metals constitute a novel class of bioactive biomaterials which support healing process of a temporary clinical problem. They are 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. From the two recent annual symposiums on biodegradable metals for biomedical applications, 2014 in Maratea, Italy and 2013 in Umang Island, Indonesia, we witnessed many developments. Three classes of metals have been explored: Mg-, Zn- and Fe-based alloys. Three targeted applications are envisaged: orthopaedic, cardiovascular and pediatric implants. Three levels of investigations have been conducted: in vitro, in vivo and human clinical trials. Discussion on standardization has been initiated since 2013 with representatives from ISO, DIN and ASTM and a draft of comprehensive standard was now under preparation. While at least two companies have launched their biodegradable metal-based implants into the market: Swiss and Korea.

Although we can feel the high excitement, especially in the industrial side, we still observed the lack of knowledge in this field. At least, two questions remain unanswered satisfactorily: (1) interaction between metals and their degradation products with the surrounding implantation sites including the fate of the degradation products and its effects on the physiology and body functions, and (2) correlation between in vitro and in vivo studies including degradation mechanism and its kinetics that occurred differently. Over all, the field of biodegradable metals is exciting and we will witness more publications in the future reporting advanced alloys and hopefully real breakthrough that leads to the translation toward clinical practice.

In Indonesia, research on biodegradable metals was initiated by researchers at the Faculty of Veterinary Medicine, Bogor Agricultural University in collaboration with partners from Universiti Teknologi Malaysia and Laval University (Ulum et al. 2014, 2015; Nasution et al. 2015). In 2013, we have successfully brought the 5th Annual Symposium on Biodegradable Metals, which usually held in Europe, to Indonesian exotic beauty of Umang Island. In addition, with the establishment of the Indonesian Biomaterials Society in 2012, research potentials on biomaterials in Indonesia become more exposed and initiate more multidisciplinary collaborations among researchers within Indonesia and overseas.

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