

# Surface Modification and Coatings for Controlling the Degradation and Bioactivity of Magnesium Alloys for Medical Applications



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**Keywords** Magnesium · Coating · Surface modification · Degradation · Biomedical implant · Degradable metal · Anodization · Micro-arc oxidation · Calcium phosphate · Polymer · Dip coating · Spin coating · Bioactive factor

## 1 Introduction

### 1.1 *Magnesium and the Current Orthopedic Materials*

Coated magnesium (Mg) alloys possess many desirable properties that will enable them to supplement the current generation of orthopedic biomaterials. The most common orthopedic implants are generally made from non-degradable alloys such as titanium (Ti), stainless steel, and cobalt-chromium alloys. These alloys have extremely high mechanical strength and fracture toughness, enabling them to withstand the forces that moving bodies exert on them. They are also biocompatible and non-degradable. Orthopedic implants made from these non-degradable alloys have improved the quality of life for millions of patients for decades, and will likely continue to do so for many more years. However, applications that only require implants temporarily may be better served by Mg alloys.

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## ***1.2 There Is No Such Thing as Permanent Implants***

Non-degradable implants are not permanent. Various phenomena will require their revisions; especially with younger and more active patients. A common challenge with non-degradable implants is encapsulation within fibrous tissue [1]. Encapsulation is the body's response to foreign objects and impedes osteointegration, which is the formation of a direct bone/implant interface without non-bone tissue in-between. The long term success of orthopedic implants hinges upon their osteointegration [2]. Another challenge is the release of wear debris from biomaterials, which can stimulate immune responses and is a major cause for implant revision [3]. Around 5% of internal fixators become infected [4], which may necessitate removal of those implants [5]. Other reasons for removing implants are pain, swelling, and sub-cutaneous prominence [6]. Non-degradable implants have more opportunities to encounter complications because they reside in the body for long periods of time.

## ***1.3 Why Use Biodegradable Implants?***

Certain applications only require implants temporarily. Leaving implants in the body permanently might cause future complications [4], but surgical removal of implants always increases patient morbidity and medical costs [7]. The consequences of surgical removal of implants can include refracture of bone, nerve damage, and infection [6]. Due to these consequences there is still debate among physicians about when non-degradable implants should be surgically removed [7].

Biodegradable implants are a promising alternative that could perform their function for the desired time period, and then be replaced with new healthy tissue as they degrade. The new healthy tissue would no longer need the implant for support after a certain timeframe. This would prevent both the foreign body complications and the need for removal surgery that often accompany non-degradable implants.

Mg is one of the front-runners in the search for new biodegradable materials for implant applications. Much of the research is focused upon orthopedic implants such as screws [8–10]. Other diverse implant applications for Mg include: coronary stents [11], securing myocardial grafts [12], ureteral stents [13], intestinal anastomosis rings [14], extraluminal tracheal stents [15], microclips for laryngeal microsurgery [16], and nerve guidance conduits [17]. The reasons for the interest in Mg for such diverse applications are its excellent mechanical and biological properties.

## ***1.4 The Advantages of Magnesium***

Many of the challenges with the established biomaterials arise because of the differences between their mechanical properties and natural tissue. The most common metallic biomaterials (e.g. Ti) have a much higher elastic modulus than bone,

which causes stress shielding [18]. Ceramic biomaterials are brittle, making them vulnerable to breakage [19]. Many polymeric biomaterials have insufficient mechanical properties, limiting the support they provide in load bearing applications [20]. Mg alloys have the advantage of possessing mechanical properties similar to cortical bone [21, 22], which enables Mg to be used for load bearing applications while minimizing stress-shielding. Implants made from Mg alloys slowly lose mass and volume until they are gone from the body without the need for removal surgery (Table 1).

Mg also has many advantageous biological properties. Mg degradation products are non-toxic and rapidly cleared from the body [23]. Mg degradation products can also increase cell proliferation and osteogenic differentiation [24]. Mg is osteoconductive and improves bone growth on implants in vivo [25, 26]. Mg implants can have better osteointegration than Ti implants [27]. Another advantage of Mg implants is that some are not encapsulated [28, 29], although this is not always the case [30]. A Ca rich mineral phase is deposited upon Mg orthopedic implants after implantation [31], which helps increase mineral apposition rates of surrounding bone tissue [9, 32, 33]. Mg inhibits osteolysis induced by wear particles [34]. Mg ion release may prevent some forms of osteoporosis [35]. Mg can protect against bone cancer [36] and nerve damage [37]. Mg degradation can be bacteriocidal due to the increased pH [38, 39]; its bacteriocidal activities can be improved in alloys such as those containing silver (Ag) [40]. These desirable properties make Mg alloys attractive choices for orthopedic implant applications.

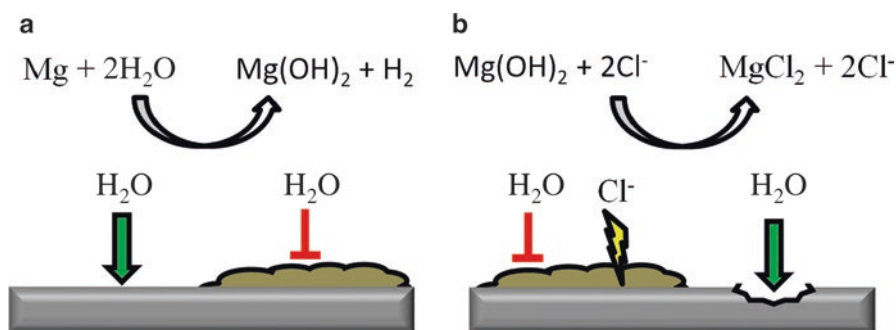
## 1.5 The Challenges of Magnesium

Despite the many advantages of Mg alloys, there are still challenges that must be resolved before the clinical translation of Mg based implants. Most of these challenges are the result of excessively rapid Mg degradation in vivo [10, 41], which causes undesirable physical and chemical changes. Rapid degradation of Mg implants reduces their mechanical properties too early and may lead to a catastrophic mechanical failure. Eroding Mg surfaces are unstable and may limit cell adhesion. Additionally, rapidly degrading surfaces recede from neighboring tissue, creating a gap that can impair tissue ingrowth [42].

Galvanic reactions cause Mg degradation [43–45]. Mg is almost always the anode in galvanic couples and forms a Mg hydroxide ( $Mg(OH)_2$ ) passivation layer at the surface of the alloy. The passivation layer acts as a barrier against electrolyte, which limits the rate of further Mg degradation reactions (Fig. 1a). The protection provided by the passivation layer is limited by its inherent porosity, looseness, and vulnerability to aggressive ions [46]. Aggressive ions such as chloride ( $Cl^-$ ) are common in body fluids and can convert the passivation layer into the much more soluble  $MgCl_2$ , which is then dissolved [47–49]. Dissolution of the passivation layer enables further Mg degradation reactions to occur (Fig. 1b). The location where Mg is implanted in the body influences its degradation rate; Mg tends to degrade more quickly in the soft tissue or bone marrow than in cortical bone [2–5]. This can cause

**Table 1** Mg implants lose mass and volume in vivo

Sample loss		Coating	Implant	Animal model	Body location	6 weeks	8 weeks	12 weeks	24 weeks
Alloy		None	2 × 7 mm screw	Rabbit	Tibia	20% volume [70]			
Mg		HA	2 × 7 mm screw	Rabbit	Tibia	5.28% volume [70]			
Mg-Y-Nd based on WE43		None	60 × 6 × 1.5 mm plate	Pig	Nasal bone		0.33% volume [218]	5% mass [53]	13% mass [53]
Mg-Y-Nd based on WE43		MAO	60 × 6 × 1.5 mm plate	Pig	Nasal bone			6% mass [53]	14% mass [53]
AZ91		None	3 × 6 mm rod	Rabbit	Greater trochanter		0.33% volume [218]		
AZ91		Low porosity PCL	3 × 6 mm rod	Rabbit	Greater trochanter		0% volume [218]		
AZ91		High porosity PCL	3 × 6 mm rod	Rabbit	Greater trochanter		0.05% volume [218]		
MgCa0.8		None	4 × 6 mm screw	Rabbit	Tibia	3.31 ± 1.60% mass [9]	4.27 ± 1.05% mass [9]		
AZ91		None	3 × 6 mm rod	Rabbit	Greater trochanter		25 mg/cm <sup>2</sup> [219]		
AZ91		MAO	3 × 6 mm rod	Rabbit	Greater trochanter		16 mg/cm <sup>2</sup> [219]		
Mg-3Zn-0.8Zr		None	3 × 10 mm rod	Rabbit	Femur			37.02% volume [89]	
Mg-3Zn-0.8Zr		CaP	3 × 10 mm rod	Rabbit	Femur			22.67% volume [89]	
Mg-3Zn-0.8Zr		MgF2	3 × 10 mm rod	Rabbit	Femur			23.85% volume [89]	



**Fig. 1** (a) Mg degradation forms a passivation layer at the surface of the substrate, slowing further degradation. (b)  $\text{Cl}^-$  solubilizes the passivation layer and enables further degradation to occur unimpeded

the thread and head of screws to dissolve faster than the shaft [9], and could help explain why degradation rates differ between *in vivo* and *in vitro* tests [50–53].

The dissolution of Mg alloys releases Mg ions, hydrogen gas ( $\text{H}_2$ ), and hydroxide ions ( $\text{OH}^-$ ) [47]. Mg ions have low toxicity and are rapidly excreted by the kidneys. Diffusion and fluid transport remove  $\text{H}_2$  from the implant site; but if Mg degradation is too rapid then  $\text{H}_2$  evolution may exceed the  $\text{H}_2$  clearance rate. Accumulation of  $\text{H}_2$  may form subcutaneous gas bubbles [9, 32], create a gap between implant and bone [54], and may also delaminate some coatings from Mg substrates [55]. The most frequently problematic degradation product is  $\text{OH}^-$ , which can significantly increase the pH surrounding a Mg implant. The cytotoxicity exhibited by Mg alloy degradation is often caused by the alkaline pH and not the high Mg ion concentration [23]. Excessively rapid Mg degradation can also cause significant hemolysis (Table 2). Controlling the degradation rate of Mg will resolve many of these challenges.

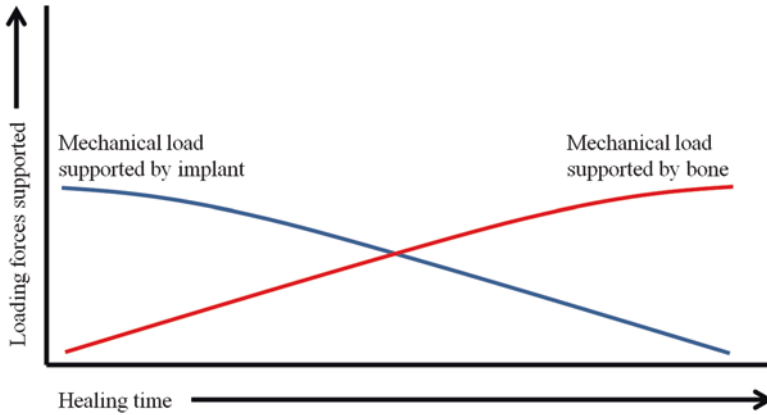
The degradation rate of implants should be tailored to match the growth rate of bone tissue [56–58]. Excessively fast degradation rates can create a gap between implant and bone or lead to insufficient support or premature mechanical failure. Excessively slow degradation rates can lead the body forming an empty bone socket instead of replacing the implant with bone tissue [59, 60]. If the degradation rate and bioactivity are tightly controlled, the biodegradable implants will be replaced with ingrowing natural tissue as they degrade. As time passes, the role of supporting loading forces will be transferred from the implant to the tissue (Fig. 2). The transfer of the mechanical support role has profound implications upon bone remodeling processes, which can lead to healthier bone tissue. If the degradation rate is controlled, Mg screws can be clinically equivalent to Ti screws over the short term [22].

**Table 2** Effect of Mg alloy and coating upon hemolysis rates

Alloy	Coating	Hemolysis rate (%)
WE42	None	50.37 ± 0.42 [220]
WE42	MAO	3.67 ± 0.47 [220]
WE42	MAO/PLLA	1.79 ± 0.67 [220]
Mg-4.0Zn-1.0Ca-0.6Zr	None	4.12 [72]
Mg-4.0Zn-1.0Ca-0.6Zr	HA	4.35 [72]
AZ31	None	90 [221]
AZ31	CaP	4.3 [221]
316 L SS	None	0.26 ± 0.14 [222]
MgZnMn	None	2.41 ± 0.24 [222]
MgZnMn	PCL	0.01 ± 0.17 [222]
MgZnMn	PTMC	0.04 ± 0.14 [222]
AZ31	None	93.290 ± 0.782 [208]
AZ31	MAO	23.419 ± 1.565 [208]
AZ31	MAO/PLLA	0.806 ± 0.771 [208]
ZK60	None	28.78 [223]
ZK60	MAO	1.04 [223]

## 1.6 Coatings Can Address Many Challenges

Coatings and surface modifications can decouple Mg degradation rates from bulk Mg properties. The coated surfaces initially act as barriers protecting the underlying Mg substrates, but coating degradation gradually reduces their effectiveness as barriers. The slow initial Mg degradation can enable implants to retain their mechanical properties for support applications, while the delayed and more rapid degradation minimizes the implants interference with longer term healing processes. Another advantage of coatings is that they may perform multiple functions, such as increasing the bioactivity of implants. Osteoconductive materials, particles, drugs, and growth



**Fig. 2** An idealized plot showing the transfer of support functions from a biodegradable orthopedic implant to neighboring bone tissue. The increased loading forces upon the bone tissue will cause remodeling processes to strengthen the bone

factors may be incorporated into coatings to improve surface bioactivity. The success or failure of implants is often determined by their initial contact with host cells and tissue. Thus, it is critical to engineer coatings to not just control the bulk substrate degradation rate, but also to improve surface bioactivity.

## 2 Substrate Preparations

The properties of Mg substrates will obviously affect their degradation, bioactivity, and interactions with coatings. Thus alloy bulk composition is a major means of controlling Mg implants [32]. Substrate bulk structure also plays a role; solid substrates provide more mechanical strength, but porous substrates may have better coating and cell adhesion and the pores can be filled with bioactive materials [61, 62].

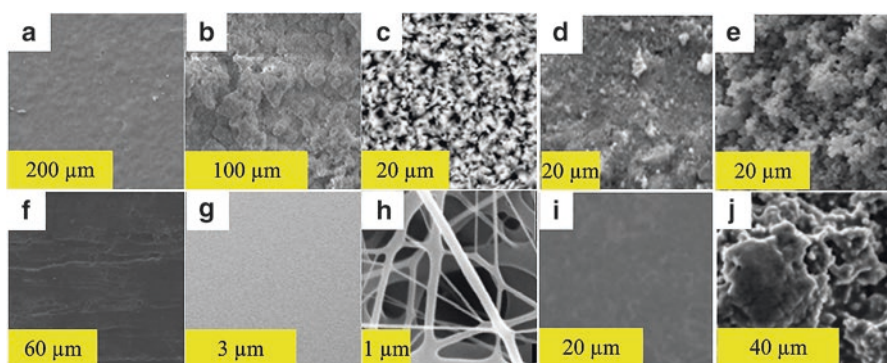
The surfaces of metallic substrates must be prepared for coating processes in order to achieve the best results. The surface roughness of substrates affects their degradation [63, 64], coating adhesion strength, cell adhesion, and bone volume/tissue volume ratio (BV/TV) in vivo [65]. Sandblasted Mg surfaces degrade faster than threaded surfaces, which in turn degrade faster than smooth Mg surfaces [66]. An appropriately rough surface provides a larger surface area for binding and can form mechanical interlocks with coatings. Some preparation processes can alter the chemistry of the surface, which may alter the surface's affinity for the coating. Different surface preparations have varying effects with different coatings [67, 68]. On unclean surfaces, coatings may bond to grease or particulates instead of the surface, which will weaken the coatings adhesion to those surfaces. Surfaces should be clean and have appropriate roughness in order to ensure strong coating adhesion.

### 3 Structure and Physical Properties of Coatings

The composition and processing routes of coatings determines their structure and physical properties (Fig. 3) [55, 69–76]. This in turn determines the barrier mechanisms and effectiveness of coatings (Table 3). Oxide and ceramic coatings are made of impermeable materials, but have cracks and pores that allow the passage of electrolyte. In addition, many oxide and ceramic coatings are susceptible to the same aggressive ions that attack Mg; leading to pitting, undermining, and eventually dissolution of the coating (Fig. 4a). Polymer coatings on the other hand are permeable to electrolyte and aggressive ions, but significantly reduce their diffusion which limits Mg degradation rates (Fig. 4b). It is not desirable to have completely impermeable coatings because then the Mg implants would be non-degradable like Ti. The rate of electrolyte transport through coatings must be tailored so that Mg substrates degrade at a similar rate as tissue growth.

Thicker coatings tend to slow Mg degradation more effectively than thinner coatings of the same quality, but thicker coatings often have more defects that allow electrolyte and aggressive ions to bypass the coating and directly attack the underlying Mg substrate. It has been observed that moderately thick coatings with fewer defects can provide superior protection when compared to thicker coatings with numerous defects.

Porous coatings generally permit more electrolyte and aggressive ions to reach underlying Mg substrates than solid coatings. However, the pores can promote physical interlocking between multiple layer coatings. Porous surfaces can also improve cell adhesion and integration with tissue if in an appropriate range, but an inappropriate pore size can inhibit bioactivity of surfaces. For example, nanoporous PCL can elicit foreign body response and lower BV/TV than microporous PCL [52].

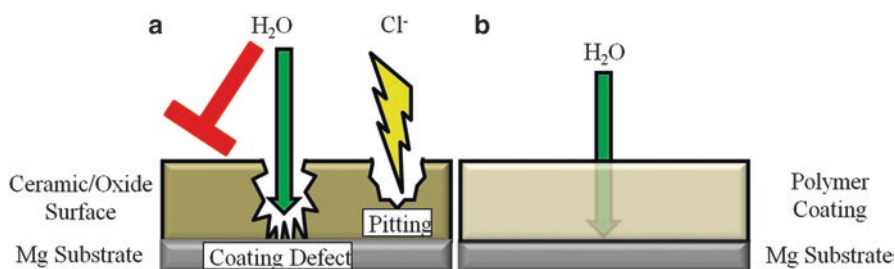


**Fig. 3** SEM images of coatings deposited by various methods from the literature. HA coatings deposited by (a) sol-gel [70], (b) biomimetic [71], (c) hydrothermal [72], (d) electrophoretic [73], and (e) electrochemical processes [74]. Polymer coatings deposited by (f) dip [75], (g) spin [56], (h) electrospin [76], (i) electrophoretic [77], and (j) electrochemical deposition processes [78]



**Table 3** Comparison of the different coating methods

Coating method	Coating materials	Barrier mechanism	Unique properties
Alkaline heat treatment	Metal oxide	Impermeable except for cracks and pores	Simple, less compact
Anodization	Metal oxide		
MAO	Ceramic		Very compact barrier, but brittle
Sol-gel	CaP, metal oxide		
Biomimetic	CaP, metal oxide		
Hydrothermal	CaP, metal oxide		Simple, less control over CaP properties
Dip coating	Polymer		
Spin coating	Polymer	Simple, inhomogeneous structure	
Electrospinning	Polymer		Simple, can only coat one face, wastes large amount of coating material
Electrophoretic deposition	CaP, metal oxide, polymers	Depends upon material	Extremely porous structure
Electrochemical deposition	CaP, metal oxide, polymers		Deposits pre-made coating materials
		Depends upon material	Creates and deposits coating material simultaneously



**Fig. 4** (a) Surface modifications form dense barriers that prevent electrolyte from reaching the underlying Mg substrate. Electrolyte can still penetrate the surface through cracks and other defects. Many of these surface modifications are slowly undermined by  $\text{Cl}^-$ , reducing their barrier properties over time. (b) Polymer matrices are permeable to electrolyte but significantly reduce the diffusion rates; thus limiting Mg degradation

Delamination is frequently encountered with coatings for Mg substrates due to the unstable Mg surface and  $\text{H}_2$  evolution. Delamination can lead to rapid Mg degradation and its associated consequences, dislodging or movement of implants, and the departure of fragments from the implant site. Controlling the rate of electrolyte diffusion through coatings will minimize delamination by improving surface stability and limiting  $\text{H}_2$  evolution. Coating design can be optimized to mitigate delamination as well; thinner coatings [77] and low molecular weight polymers [78] tend to resist delamination more effectively. Maintaining a relatively stable but slowly eroding Mg surface is critical to the function of Mg implants.

## 4 Surface Modification of Magnesium

Surface modifications transform the surfaces of Mg substrates into substances with increased degradation resistance. This differs from deposition coating processes in that the raw materials for the new surface come from the original Mg substrate. The modified surface is generally much more stable than the Mg substrate and acts as barrier against electrolyte and aggressive ions. Mg surfaces can be modified through numerous methods.

### 4.1 Chemical Surface Modification

The simplest means of creating protective coatings on Mg substrates is passivation, which is the oxidation of Mg to form a barrier oxide or hydroxide barrier layer. Mg forms passivation layers through chemical reactions in most environments, but alkalinity and heat can create even thicker and more protective barrier layers [72, 79–82]. The surfaces of alkaline heat treated substrates often have better cell adhesion [79, 82] and implant/tissue interface strength [83] than polished substrates. The parameters of the alkaline baths and the heat treatments control the thickness, structure, and composition of the oxide layer formed [80]. Alkaline baths without heat treatments tend to create loose and porous barrier layers that are susceptible to aggressive ions. Heat treatments can densify the oxide barrier layer so that it resists attacks by aggressive ions and significantly reduces the Mg degradation rate in physiological fluids [79, 80]. Chemical surface modifications significantly reduce Mg degradation rates, but like many other impermeable barriers they are also impaired by the presence of pores and cracks [84].

The chemical composition of the alkaline bath can be used to tailor the chemical composition of the Mg surface. Some alkaline bath compositions can create surface layers that promote more calcium phosphate (CaP) deposition and may therefore improve osteoconductivity [80]. Incorporating silicon (Si) or strontium phosphates into the surface can improve the protectiveness and durability of the passivation layers [83, 85, 86]. Silicates can enhance mineralization activity of osteoblasts [87] and improve the mechanical strength of bone/implant interfaces [83]. Some species of silicates, like akermanite, have better bioactivity than  $\beta$ -tricalcium phosphate ( $\beta$ -TCP) [88]. These properties have attracted much interest in Si as a dopant for coatings. Silicates surfaces may be formed through surface modifications or deposition.

Not all chemical surface modifications occur at alkaline pH; fluoridation [84, 89–91] occurs at highly acidic pH. Fluoridation may have additional benefits beyond controlling Mg degradation. The *in vivo* bioactivity of fluoridated surfaces may be comparable to hydroxyapatite (HA) coatings [61, 89] and superior to collagen coatings [91]. In some cases, and fluoridated surfaces may even have intrinsic anti-bacterial properties [90].

## 4.2 Anodization

Anodization is an electrochemical process that creates protective amorphous oxide barriers [92–94]. Greater potential, current, and anodization time generally increase the thickness of the barrier layer; but too much will create cracks in the surface. The cracks undermine the effectiveness of anodized surfaces as barriers. Certain bath compositions are also more prone to sparking, which increases pore formation in the surface. Additionally, the temperature of the electrolytic bath [92] and the composition of the Mg alloy substrate [93] can influence the properties of the anodized surface. Anodized surfaces are more protective if their degradation products have low solubility and strong adherence to their substrate [94].

## 4.3 Micro-Arc Oxidation

Micro-arc oxidation (MAO) is a surface modification process related to anodization, but uses higher potentials over shorter times to create ceramic surfaces instead of amorphous oxide surfaces. The ceramic nature of MAO surfaces can provide greater degradation resistance, hardness, crystallinity, and bioactivity than anodized surfaces [95, 96]. The potential during MAO exceeds the breakdown potential of the substrate, creating localized plasma reactions. These plasma reactions can create regions of high heat and pressure that can cause melting, flowing, sintering, annealing, and rapid cooling. The composition of the electrolytic bath can influence the surface composition, surface morphology and roughness, porosity, types of deposits formed during immersion, and the degradation rate [97]. Larger currents for longer times will increase the thickness of MAO surfaces, but may also increase degradation rates due to crack formation [98].

MAO surfaces generally have several layers; a porous outer layer, a compact inner layer, and finally the surface of the substrate [95]. The majority of degradation resistance comes from the compact inner layer [99]. The increased surface roughness of the porous outer layer can improve cell adhesion [100]. However, electrolyte and aggressive ions can enter the pores and cracks to react with Mg [101], causing degradation products to accumulate at the coating/substrate interface and lift the MAO surface off of the Mg substrate [102]. The brittleness of MAO surfaces [103] can exacerbate the damage caused by localized degradation.

## 5 Deposited Coatings

Deposited coatings are made from materials foreign to the Mg substrates, and may be deposited through numerous methods. Such coatings have a vast range of barrier, mechanical, and biological properties; enabling them to be fine-tuned for specific applications.

## 5.1 Calcium Phosphate Coatings

Materials derived from CaP are highly osteoconductive because they mimic the mineral content of bone. However, the role of CaP alone is limited in orthopedic applications due to its inherent brittleness. Coatings can take advantage of the superb osteoconductivity of CaP while the underlying Mg substrates provide the mechanical support needed in orthopedic applications.

The phase of CaP that most closely mimics the mineral content of bone and has the greatest osteoconductivity is hydroxyapatite (HA). It is also the slowest dissolving phase, which improves the barrier properties of coatings. Another frequently investigated phase of CaP is  $\beta$ -tricalcium phosphate ( $\beta$ -TCP), which is osteoconductive and known to induce macrophage activity that is beneficial to implant integration [104]. CaP coatings can increase CaP deposition in simulated body fluid (SBF), which suggests improved osteoconductivity [105]. Incorporation of Si into the CaP coating can further increase CaP deposition [106]. Nano-scale HA (nHA) has even better osteoconductivity than microscale HA [107], but may also provide less protection from degradation to underlying Mg substrates [108]. Rod shaped HA crystals may have better bioactivity than flake shaped HA crystals; such as increased cell proliferation and ALP activity [109]. Mesoporous HA structure can ameliorate damage from residual stress, reduce penetration of electrolyte, and reduce Mg corrosion rate [110]. The wide range of properties for CaP can be fine-tuned for specific applications.

CaP coatings can be deposited through numerous methods such as: plasma spray, sol-gel, chemical deposition [69, 70, 111, 112], biomimetic deposition [69, 113], electrophoretic deposition [71], and electrochemical deposition [72, 106] (Fig. 3). There are two general strategies for depositing CaP coatings: (1) synthesizing CaP first and then depositing it onto the substrate; and (2) synthesizing CaP and depositing it onto the substrate simultaneously. The first strategy offers the most control over the properties of CaP, but requires multiple steps. Furthermore, the properties of the CaP that were painstakingly fine-tuned may be altered during the deposition process. High temperature coating processes such as plasma spray can change the phase of CaP [114], alter the crystallinity of CaP [114], or increase the grain size of CaP. Alternatively, low temperature coating processes often create less adherent coatings without subsequent heat treatment [72]. The second strategy for depositing CaP coatings is often simpler, but provides less control over the properties of CaP in the coating.

Many CaP coatings have weak adhesion strength to their substrates. CaP and metallic substrates have very different thermal expansion coefficients, which can damage the coating or coating/substrate interface initially during high temperature coating processes and sintering, or gradually when the implant is exposed to temperature changes and loading cycles in vivo. Both of these challenges are exacerbated by the inherent brittleness of CaP. A potential resolution is the incorporation of CaP into composites with flexible materials, such as polymers.

## 5.2 *Polymer Coatings*

### 5.2.1 *Commonly Used Polymer Coatings*

Polymers can be divided into two major categories: natural and synthetic. Natural polymers are derived from natural sources while synthetic polymers are manufactured artificially. The advantage of natural polymers is that they often have good bioactivity. The disadvantages of natural polymers are that they have less consistency between different production runs and that they are more likely to carry microbial contamination. Many synthetic polymers are the opposite case. The advantages of synthetic polymers are that they have greater consistency between different production runs and less risk of microbial contamination. A disadvantage of synthetic polymers is that they frequently lack the bioactivity exhibited by some natural polymers.

Examples of natural polymers include chitosan, alginate, collagen, and protein. Chitosan coatings have been investigated for controlling the degradation rate Mg alloys [115–119]. Chitosan is the deacetylated derivative of chitin, which is commercially obtained from crustaceans (i.e., crabs and shrimp). Chitosan is more soluble than chitin, which is important for processing because both polymers thermally degrade before melting [120]. Chitosan has several unique advantages over other polymers: its insolubility above pH 7 may help further protect Mg substrates [117], it can promote bone growth [121], and it has intrinsic antibacterial properties [122–124]. Chitosan is degraded enzymatically in vivo [125].

Alginate is a polysaccharide that can be used as a coating material for controlling Mg degradation [126, 127]. An advantage of alginate is that it is commercially produced by bacteria or algae; which enables the production to occur in an industrial setting and may prevent issues associated with harvesting organisms outside of an industrial setting (i.e., risk of microbial contamination and inconsistency between different production runs). Another advantage is that water is a solvent of alginate, which makes it easier to embed coatings with pharmaceuticals. Finally, alginate can protect implants from the immune system, which may be beneficial for some niche applications. A disadvantage of alginate coating materials is their poor cell adhesion [128]. This challenge may be addressed through the covalent attachment of biological recognition sites (i.e., RGD) to alginate polymers [129] or dispersion of bioactive materials such as HA within the alginate matrix [126].

Other natural polymer or protein based coatings used to control Mg degradation include: collagen [91, 130], albumin [131], phytic acid [132–134], and other proteins or peptides [135]. Coatings derived from natural proteins can significantly increase bioactivity, especially when the coating proteins are native to the physiological region where the implant is placed. Most proteins carry greater risks of immune responses, although collagen tends to have low antigenicity [136]. Many protein coatings also face more costly mass production, batch to batch variability, and risk of microbial contamination. The immunological and logistical challenges associated with natural polymers can make the readily manufactured and customized synthetic polymers an attractive alternative.

Examples of common synthetic polymers include polyesters such as poly lactic acid (PLA), polyglycolic acid (PGA), and polycaprolactone (PCL). The degradation products of these polyesters are natural metabolites, which improves their biocompatibility and clearance. The polyesters degrade primarily by hydrolysis of their ester bonds by water molecules, though enzyme catalyzed degradation may play a role in vivo.

PLA can be produced as a semicrystalline isomer (PLLA) or an amorphous isomer (PDLA). PLLA is more common in nature [137] and more easily metabolized [138], so it is used more frequently than PDLA. PLLA is one of the most commonly used polymers for orthopedic implants because of its high mechanical strength and low immunogenicity. PLA has an additional methyl group that increases its hydrophobicity and sterically blocks hydrolysis of its ester bonds. These properties enable PLLA coatings to provide significant protection to Mg [78, 139, 140]. However, PLLA is brittle, which limits its use as a load bearing material. It also has limited thermal stability at high temperatures which may complicate the use of some processing routes [137]. Additionally, PLLA also has an excessively long degradation time and low bioactivity, which can lead to poor bone ingrowth at the implant site [59, 60, 141]. The impaired bone ingrowth may be exhibited by empty bone sockets outlining the original implant site after degradation [60, 142, 143].

PGA was investigated as an orthopedic biomaterial in its own right because of its good mechanical properties, but is now mainly used in copolymers. It is insoluble in most organic solvents because of its highly crystalline structure, which limits the compatible processing methods [138]. An increased occurrence of osteolysis from PGA implants has also been observed in some studies [144], while others have shown an inhibition of osteogenesis by PGA [145]. PGA sutures are also more inflammatory than PLA sutures [146].

PLA and PGA are frequently combined in the copolymer poly(lactic-co-glycolic acid) (PLGA) to address their individual challenges. PLGA is one of the most commonly used polymers for implants due to its physical properties, biocompatibility, and it is approved by the FDA for certain applications [147, 148]. PLGA is less brittle than PLLA and is soluble in many organic solvents. The degradation rate [149] and water absorption [150] of PLGA can be tailored by altering the PLA:PGA ratio. PLGA coatings have been used to control Mg degradation [55, 151, 152], but may delaminate due to H<sub>2</sub> evolution [55]. PLGA also has mediocre cell adhesion [153, 154], which limits bone growth into the implant site. Finally, both PLA and PGA release acidic degradation products which can lower the pH of the local environment.

PCL is another common polyester coating material for Mg [78, 139, 155–157], and one of the earliest biodegradable polymers used for implants in general [158]. PCL coatings can increase the volume of bone growth on Mg substrates [157]. The low melting temperature makes PCL especially easy to process, especially with embedded pharmaceuticals or proteins that are vulnerable to heat or organic solvents. This makes PCL a good choice when drugs or bioactive factors are

incorporated into the coating. However, PCL has an excessively long degradation time and mediocre cell adhesion.

Polyester coatings can chemically interact with Mg substrates during degradation; although the published results are contradictory. Acidic polymer degradation products may attack the Mg substrate while the alkaline Mg degradation products attack the polymers. Additionally,  $\text{Mg}(\text{OH})_2$  in the passivation layer may catalyze polymer hydrolysis; which has been observed as a positive feedback loop for degradation [73]. Contrarily, it has also been observed that dispersed  $\text{Mg}(\text{OH})_2$  particles may reduce polymer degradation by stabilizing the pH microclimate and disrupting autocatalyzation of polymer degradation reactions [159]. These contradictory results may be due to differences in experimental design.

### 5.2.2 Overview of Polymer Properties

One of the greatest strengths of polymers as a class of coating materials is their versatility (Table 4). Polymers possess a vast range of physical, chemical, and biological properties, although polymers alone often have insufficient mechanical properties for many support applications. Numerous methods exist to deposit polymer coatings including dip [73, 152], spin [55, 160], electrospin [74, 161], electrophoretic [75, 162], and electrochemical [76] deposition processes (Fig. 3). The deposition method controls the structure of the coatings; some methods create solid coatings while others create porous coatings. Finally, a large body of knowledge surrounds polymers, their use as biomaterials, and the means to tailor their properties.

Many of a polymer's physical properties are inter-related; and so altering one property will also alter others. Molecular weight ( $M_w$ ) influences the viscosity of solutions/melts, the mechanical properties of the polymer matrix [163], the coating adhesion strength [78], polymer degradation rates [164], and degradation rates of underlying Mg substrates [139]. The  $M_w$  decreases during degradation, until it is small enough to allow monomers or short polymer chains to be dissolved. A lower  $M_w$  can also lead to more autocatalysis of degradation reactions for some polymers because the number of reactive end groups increases. The glass transition temperature ( $T_g$ ) determines the temperature at which the polymer becomes rubbery and more susceptible to many physical processes; and is influenced by the  $M_w$ . The  $T_g$  is often reduced concurrently with  $M_w$  during degradation, which can make the coating more vulnerable. Both the  $M_w$  and  $T_g$  affect the crystallinity of polymers, which influences degradation rates, water permeability [165–167], and bioactivity [168]. A more crystalline polymer is generally a more effective barrier to water, but in some cases increased crystallinity is accompanied by crack and void formation that increases water permeability [169]. The interactions between all of the polymer coatings properties must be balanced in order to ensure that Mg implants degrade at the desired rate.

**Table 4** Summary of polymer properties

Polymers	Polymer origin	Degradation mechanism	Degradation time	Degradation products	Bioactivity	Solvent	Melt processing
Chitosan	Natural	Enzymatic	~4 months	Cleared by phagocytosis	Osteoconductive, antibacterial	Dilute acids	Poor thermal stability
Alginate	Natural	Dissolution of ionic bridges	~2 weeks->6 months	Slow clearance of polymer chains	Very poor, immunoprotective	Water	
PLLA	Synthetic	Hydrolysis	~2 years	Acidic metabolites	Low	Organic solvents	High $T_m$
PGA	Synthetic	Hydrolysis	~1 year	Acidic metabolites	Low	Poor solubility	High $T_m$
PLGA	Synthetic	Hydrolysis	~5 months	Acidic metabolites	Low	Organic solvents	High $T_m$
PCL	Synthetic	Hydrolysis	~3 years	Acidic, cleared by phagocytosis	Low	Organic solvents	Low $T_m$



### 5.2.3 Methods of Depositing Polymer Coatings

Many processes are used to deposit polymer coatings, and each process has its own idiosyncrasies. The coating process used affects the coating structure, and therefore water transport to underlying substrates. Some processes have better compatibility with certain materials and applications than other processes. A thorough understanding of coating materials and processes is necessary for the creation of reliable protective coatings.

Solvents are commonly used for the processing of polymers. The advantage of using solvents to liquefy polymers is that very little heat is needed; which is useful when polymers thermally degrade while melting, for copolymers whose constituents have different melting points, or when viscosity must be controlled. The disadvantages of solvent processing routes are that some polymers have low solubility, the solvents can denature drugs or proteins within the polymer, solvent residues can impair bioactivity, and potential vapor hazards during coating processes.

Different solvents can create polymer matrices with vastly different structures [170]. The choice of solvent impacts the thickness, porosity, and crystallinity of coatings. Solvents with slower evaporation rates can increase the crystallinity of coatings because the polymer chains have more time to form crystals [171]. The size, frequency, and interconnectivity of pores in solvent cast coatings is also heavily influenced by the choice of solvent [170].

Other coating processes liquefy the polymers with high temperatures instead of solvents. Heating polymers above their  $T_m$  enables them to be extruded, molded, or dipped onto substrates. Annealing is a process related to melting that can further reduce water absorption by polymer coatings by increasing their crystallinity. During annealing, the coatings are heated above the polymers  $T_g$  but below the  $T_m$ , causing the polymer chains to align in a more crystalline arrangement. Excessively high annealing temperatures or long annealing times can lead to crack and void formation, undermining the barrier properties of the coating despite the increased crystallinity.

#### Dip Coating

Dip coating is the simplest coating process, wastes very little material, and is able to cover complex geometries. It is applied by dipping substrates into a solution/melt. When the coated substrate is withdrawn from the solution/melt, most of the coating material remains in place, but the pull of gravity can increase inhomogeneity (Fig. 3) [73]. The thickness and structure of dip coatings are influenced by solvent evaporation rate, viscosity, coating material concentration, immersion time, and withdrawal speed from the solution or melt.

## Spin Coating

Spin coating is another simple coating method with greater homogeneity and control of coating structure than dip coating (Fig. 3) [55]. After the solution/melt is deposited on the substrate, centripetal force removes excess solution/melt to create a uniform coating. The thickness and structure of spin coatings are influenced by the amount of coating material added, solution/melt viscosity, evaporation rate, and substrate roughness. Limitations of spin coating are that it can only be used on flat surfaces and is extremely wasteful of coating materials.

## Electrospinning

Electrospun coatings have the advantage of exquisite control over the thickness of the coating and the fibers within the coating. The fibrous structure is similar to the structure of the extracellular matrix of some tissues (Fig. 3) [74], which may improve interactions with cells. However; electrospun coatings are extremely porous and may exhibit increased water transport processes [172] with a concomitant increase in Mg degradation, although this is not always the case [130]. Finally, the electrospinning process is more complicated than dip or spin coating.

During electrospinning, a potential is applied to a polymer solution/melt at the tip of a syringe. A strong enough potential will overcome the viscosity and surface tension of the solution/melt, and the polymer will form a fiber that is pulled towards the substrate. The mechanical strength of electrospun fibers may be inversely proportional to fiber diameter because the thicker fibers may contain less organized nanofibers [171]. The fiber structure may be controlled through the operating parameters or solution composition.

Key operating parameters of electrospinning are potential, flow rate, distance, and time. The operating parameters can have significant effects upon fiber morphology and crystallinity [173]. The parameters of the solution/melt are also important; key properties include concentration, viscosity, surface tension, evaporation rate, and conductivity. Some solvents are better suited for the electrospinning process; in general a better solvent will be associated with smooth fiber morphology instead of the “beads on a string” morphology. The latter morphology is observed due to a transition between electrospinning and electrospraying [174]. The choice of solvent also affects the fiber diameter, crystallinity, and presence of holes within the fiber. It is generally more desirable that the solvents have lower viscosity and higher conductivity. Operating conditions can be modified to compensate for solvents that are less suited for electrospinning.

## Electrodeposition

Electric potential can be used to coat Mg substrates with a variety of materials, and has two general approaches. Electrophoretic deposition is the use of electric potential to transport pre-made coating materials to the substrate and then bind them

to that substrate. Electrochemical deposition on the other hand is the use of electric potential to transport coating material precursors to the substrate where they will react to form the final coating material and bind to the substrate. The key parameters of electrodeposition are the potential, current, time, electrolyte, concentration of coating materials in the electrolyte, charge of polymers or particles, and the mobility of the polymers or particles. Electrodeposition can be used to coat Mg with a variety of materials including ceramics [72, 106], polymers [17, 76], ceramic/polymer microspheres [175], and others. However; electrodeposited coatings are often not as homogenous as other methods such as spin coating (Fig. 3) [17, 55], and ensuring homogeneity can be especially difficult for composite coating materials whose constituents have different charges or degrees of mobility under an electric field. Another challenge is that H<sub>2</sub> gas evolving during electrodeposition can create void spaces in the coating. These challenges may be addressed by tailoring the operating parameters and electrolyte bath composition.

## 6 Composite Coatings

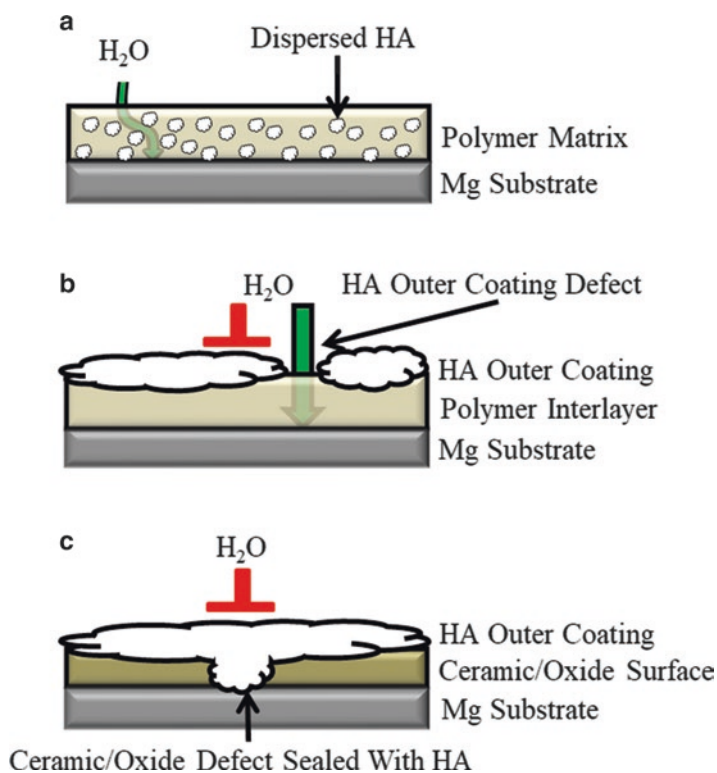
Natural bone is a composite material; the unique mechanical and biological properties of bone are enabled by the interplay between the mineral content and the collagenous matrix. No single material possesses the physical and biological properties needed to mimic bone tissue and support injured bones. Thus, composite materials are needed for orthopedic applications.

### 6.1 Hydroxyapatite Composite Coatings

One of the most frequently investigated composite coatings for orthopedic implants is HA particles dispersed within polymer matrices. The polymer matrix provides a flexible interface between HA and Mg that mitigates the thermal expansion coefficient mismatch. Nano-scale particle size and good dispersion of HA particles throughout the polymer matrix improve both the mechanical strength and the bioactivity of the composite material [176–182]. Cell adhesion and mechanical strength of PLGA matrices both increase with increasing HA content until they plateau at around 30 wt.% HA. Increasing HA content beyond 30 wt.% in PLGA matrices has only marginal effect upon cell adhesion, but increases brittleness [178, 179]. The incorporation of HA has been shown to significantly improve cell adhesion to chitosan [115], alginate [126], PLA [183, 184], PLGA [185], and PCL [186]. This improvement is not limited to just cell adhesion; improved protein secretion and alkaline phosphatase (ALP) activity are often observed as well [187]. HA composites also improve bone ingrowth at the implant sites in vivo; CaP/PLLA interference screws did not leave behind the empty screw holes [188, 189] in bone tissue that were observed with pure PLLA screws [143, 190].

HA particles have profound effects upon diffusion and uptake of electrolyte in polymer matrices. HA particles increase water uptake by polymer matrices [147], but still tend to improve barrier properties of coatings [55]. Electrolyte diffusion through particle/polymer composites is reduced by the filler effect; which is caused by particles increasing the tortuosity of routes taken by diffusing electrolyte or by particles increasing the local rigidity of the polymer matrix surrounding them [191] (Fig. 5a).

Alternatively, polymer interlayers can be used to ameliorate the thermal expansion coefficient mismatch between HA and Mg (Fig. 5b). A flexible and elastic interlayer can minimize cracking of the outer HA coating during repeated loading and temperature changes [156]. The combination of coating layers also requires electrolyte to bypass to different barrier mechanisms. Electrolyte must enter through cracks, pores, and voids in the impermeable outer coating. Then the electrolyte must diffuse through the permeable polymer interlayer, but at a significantly reduced diffusion rate that limits Mg degradation reactions.



**Fig. 5** Composite coatings utilize synergy between different materials. (a) Polymer matrix binds HA particles to Mg substrate, provides a flexible interface, and exhibits a filler effect. (b) Polymer inter-layer provides a flexible interface between HA coating and Mg substrate, and acts as an additional barrier. (c) HA outer coating seals defects in inner coating and prevent aggressive ions from reaching ceramic/oxide surface

Polymers are not the only coating matrix that can hold HA particles, MAO surfaces can accomplish this feat as well. HA can be incorporated into MAO surfaces by adding HA particles [98, 192] or HA chemical pre-cursors [193] to the electrolyte during a one-step HA/MAO coating process. This process creates a MAO surface with HA particles dispersed inside it. The HA particles are not always distributed homogeneously throughout the surface, some processes may concentrate the HA particles in the outer region of the coating [98]. Increasing the HA concentration in the electrolyte can increase the HA concentration in the MAO surface [98]. Ultrasonication can increase corrosion resistance and Ca/P ratio of HA/MAO coatings [194]. The high temperatures during the MAO coating process can convert HA to  $\beta$ -TCP [192]. Alternatively, HA/MAO coatings can be created using a two-step coating process. First the MAO surface is created on the Mg substrate, and then HA is deposited onto the MAO surface by sol-gel deposition [105, 195, 196], electrochemical deposition [197–199], electrophoretic deposition, or other means. The combination of HA and MAO is beneficial because it can address some of the major challenges of both coating types. The HA can prevent aggressive ions from reaching and attacking the MAO surface, and can seal cracks and pores in the MAO surface (Fig. 5c). Conversely, the porosity of MAO surfaces provides many opportunities for mechanical interlocks with HA coatings, which can significantly increase the often poor adhesion strength of HA coatings. Furthermore, bone-like CaP is often deposited on HA/MAO coatings during immersion [98, 105]. Other materials can be deposited atop MAO surfaces; silicates [200–203] and polymers are common choices.

## 6.2 *Polymer Coatings and Surface Modifications*

Polymers and polymer composites are also used as outer coating layers on top of modified Mg surfaces [204–212]. The polymer coatings seal pores and cracks in the underlying modified surfaces [205, 209–211], and reduce the diffusion of aggressive ions to that surface. The underlying modified surface is generally an impermeable barrier with the exception of those cracks and pores, and a reduced diffusion of aggressive ions promotes stability of the modified surface. This synergistically improves the barrier properties of the composite coating. Outer polymer coatings can improve the hemocompatibility of modified surfaces [207, 208], but outer coating layers with poor bioactivity may promote encapsulation of the implant [213]. For this reason, the outer coating layer must have both good barrier and biological properties.

## 7 **Incorporation of Bioactive Factors into Coatings**

Proteins and other bioactive factors can be attached to the surface of coatings to control interactions with cells and tissue. Attaching heparin to coatings can improve hemocompatibility, increase umbilical vein endothelial cells (HUVEC)

proliferation and inhibit human umbilical artery smooth muscle cells (HUASMC) adhesion [212]. Preferential control over which cells adhere to and proliferate on a surface can improve the biological outcome of implants, such as promoting endothelialization of stents.

Coatings can store and release drugs at a controlled rate [215–217]. Common examples of these drugs include growth factors to improve healing at the wound site and antibiotics to prevent colonization of the implant. Storing drugs within coatings can resolve three major challenges facing drug use: (1) transporting drugs to the target site, (2) achieving a therapeutic dose at the target site while minimizing the dose outside the target site, and (3) maintaining a constant dose at the target site over time. Polymers, CaP, and other nanoparticles have long been used for controlled storage and release of drugs [218], enabling this technology to be easily translated to coatings.

## 8 Summary

Coatings have great potential to control Mg degradation and bioactivity because their wide range of physical and biological properties enables them to be tailored to specific functions, and decouple surface properties from bulk properties. A well-controlled Mg degradation rate will prevent many of the challenges associated with rapid degradation (i.e., catastrophic mechanical failure, local alkalization, H<sub>2</sub> gas bubbles, swelling) and slow degradation (i.e., empty bone sockets). Ideally, functional natural tissue will replace the biodegradable Mg implants over time. The clinical translation of Mg derived implants will lead to improved patient outcome and lower medical costs by preventing the complications associated with the current generation of non-degradable implants.

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