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Similarities and differences in coatings for magnesium-based stents and orthopaedic implants

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Abstract

Magnesium (Mg)-based biodegradable materials are promising candidates for the new generation of implantable medical devices, particularly cardiovascular stents and orthopaedic implants. Mg-based cardiovascular stents represent the most innovative stent technology to date. However, these products still do not fully meet clinical requirements with regards to fast degradation rates, late restenosis, and thrombosis. Thus various surface coatings have been introduced to protect Mg-based stents from rapid corrosion and to improve biocompatibility. Similarly, different coatings have been used for orthopaedic implants, e.g., plates and pins for bone fracture fixation or as an interference screw for tendon-bone or ligament-bone insertion, to improve biocompatibility and corrosion resistance. Metal coatings, nanoporous inorganic coatings and permanent polymers have been proved to enhance corrosion resistance; however, inflammation and foreign body reactions have also been reported. By contrast, biodegradable polymers are more biocompatible in general and are favoured over permanent materials. Drugs are also loaded with biodegradable polymers to improve their performance. The key similarities and differences in coatings for Mg-based stents and orthopaedic implants are summarized.

Keywords

Biocompatibility; Biodegradable materials; Coatings; Drug elution; Magnesium alloys

Introduction

Magnesium (Mg) is one of the lightest metals, exhibiting good mechanical properties, biodegradability, and biocompatibility [1,2], and has thus received great attention in the field of percutaneous coronary intervention (PCI) [3] and orthopaedic applications [4,5]. The main applications of Mg-based implantable medical devices currently include cardiovascular

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Conflicts of interest

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stents, bone fixation plates and pins, and screws for tendon-bone or ligament-bone insertions. The nature of their biodegradability makes Mg alloys look promising in implant applications because there is no need for secondary surgery to remove the implants [6]. Unfortunately, due to low corrosion resistance, many problems including hydrogen elution and decreasing mechanical strength prior to the healing of the surgical regions have also arisen during in vivo studies [7,8].

To prevent rapid corrosion, various surface modification techniques have been used [9,10]. Among them, the application of coatings has been documented as one of the most effective [11]. In addition to corrosion prevention, coatings can also provide a drug reservoir for Mg-based biomedical implants. Many coating technologies have been developed for Mg alloys, including inorganic coatings, metal coatings, metallic oxide coatings, metallic hydroxide coatings, chemical conversion coatings, nanoporous inorganic coatings, and polymer coatings [11–17]. This paper reviews the various coating techniques applied to Mg alloy device scaffolds and also determines the role that coatings play in stent functionality and orthopaedic implants. The differences and similarities of coatings used in stents and orthopaedic implants are also addressed.

Metal, metallic oxide, and metallic hydroxide coatings

Metal coatings

Titanium (Ti) implantation has been shown to improve the corrosion resistance of AZ91 alloy [18]. The vapour deposition of aluminium (Al) has been applied to Mg-based alloys and has been shown to decrease the degradation rate [19]. The downside of this Al deposition, however, is its low biocompatibility. Al has also shown signs of corroding in sodium chloride (NaCl) solution, an outcome that does not suggest efficiency for an implant coating material [13]. Therefore further analysis of other more effective materials is needed for a better understanding of deposited metal coatings that produce low toxicity values when implanted. Gold was also investigated as a coating for Mg alloy in another patent [20]. However, others workers have demonstrated that stents coated with gold increase the risk of restenosis [21].

Metallic oxide and metallic hydroxide coatings

A thin film of metallic oxide can provide an interface with vascular milieu for a stent as well as enhancing its biocompatibility [22]. Therefore some metallic oxides, such as titanium dioxide and zirconium oxide, were coated on stents to improve their performance. A titanium-nitrideoxide coating was investigated to reduce neointimal hyperplasia. Compared with stainless steel, two stents coated with different titanium-nitride-oxide coatings showed better biocompatibility and reduced neointimal area [23]. Another study investigated converting metallic polycrystalline oxides into an amorphous oxide to increase the corrosion resistance of stents. The results indicated that an amorphous oxide-coated stent was safer and more biocompatible [24]. Earlier research suggests that nickel (Ni)–Ti stents may have a native oxide layer. By an electropolishing, heat treatment and passivation process, the deformed native oxide layer on a Ni–Ti stent can be removed and a new uniform oxide layer will form. These processes improved the corrosion resistance of Ni–Ti stents due to the

uniformity of the oxide layer grown on the stent surface [25]. Zirconium oxide [26], iridium oxide [27], and noble metal oxides [28] have also been reported in patents as coatings for stents. Another patent reported a multilayer metal and metallic oxide coating for a stent: the inner metallic layer was a noble metal or alloy and the outer layer was iridium oxide [29].

The simplest method of generating a coating on an Mg sample is to simply expose it to the environment (air and water). This process, called passivation, exposes the sample to atmospheric humidity at a level sufficient to create a Mg hydroxide layer on the outer surface; continuing to store the sample in air creates an additional, beneficial, carbonate layer. Oxide layers usually provide better corrosion protection than hydroxide layers. The $\text{Mg}(\text{OH})_2$ layer actually increases in thickness on the implant surface over time, whereas the MgO layer stays at a relatively constant thickness, but can be increased through thermal treatment [30]. Also, alkaline solution treatment was also believed to create a layer of $\text{Mg}(\text{OH})_2$, MgCO_3 , and MgO on the surface of Mg alloys [14].

Chemical conversion coating

Chemical conversion coating involves taking the surface of the metal implant material and converting it into the desired coating via a chemical or electrochemical process. In the past, the process was performed to create chromate layers because of its ability to provide effective corrosion resistance. However harmful environmental outcomes arise from the use of chromium (Cr) in chemical conversion baths, therefore a Cr substitute must be found [31].

Metal phosphate compounds as a possible replacement were investigated. The results of Chen et al [12] suggested that the performance of these metal phosphate layers were significantly dependent on the pre-treatments used to make the layers more or less functional. For biomedical applications, research shows that two potential coating materials, fluoride-based layers and calcium phosphates, can be applied.

Zhang et al [169] explored the preparation of calcium phosphate coatings on an Mg–1.0Ca alloy using electrochemical deposition. Enhanced corrosion resistance was observed in Hank's solutions. The thickness and morphology of the coating had a significant effect on the corrosion behaviour of this Mg alloy. Another investigation showed that calcium phosphate precipitation could be controlled by an anodization and autoclaving process [33].

A MgF_2 suspension was also synthesized to prevent corrosion of the Mg alloy by Waltz et al [34] via a plasma suspension spraying process. Li et al [35] studied the corrosion resistance and cytotoxicity of MgF_2 -coated Mg–1Ca alloy by a vacuum evaporation deposition method. The results indicated that MgF_2 -coated samples had much lower degradation rate than uncoated samples. Moreover, the MgF_2 coating induced calcium phosphate deposition on Mg–1Ca alloys, which may promote bone cell growth. Pereda et al [36] attempted to inhibit the corrosion of pure Mg by fluoride treatments and their results showed that different conditions could form different films on Mg. At 0.1 M fluoride solution treatment, KMgF_3 was present on the surface, whereas an MgF_2 film was observed at 1 M fluoride solution treatment. Another study investigated the biocompatibility of fluoride-coated Mg–

Ca alloys in a subcutaneous mouse model. No visible inflammation reaction or broad proliferative effect was observed, indicating sufficient biocompatibility of fluoride-coated Mg alloys [37]. Studies from our group also showed that fluoride-coated Mg–rare earth element alloys had much better corrosion resistance, endothelial attachment, growth, and proliferation (Fig. 1).

Nanoporous inorganic coatings

Nanoporous materials have a large surface area and surface modifications at the nanoscale level can increase biocompatibility [38]. Similarly, properties of nanoporous coatings can be easily adjusted by the manipulation of surface properties based on the specific application [39].

Hydroxyapatite

Hydroxyapatite (HA) is one of the main inorganic components of bone and teeth [40,41]. HA and some calcium phosphate compounds are used as coatings because of their biocompatibility and bioactivity [42]. Various HA and calcium phosphate coatings are summarized in Table 1 [41,44,48,55,108,150–161]. Calcium phosphate combined with zoledronate was used as a bone substitute. *In vitro* experiments on an unfractured rabbit bone indicated that calcium phosphate loaded with zoledronate decreased the area resorbed compared with calcium phosphate without zoledronate [43]. Fluorine-doped hydroxyapatite (FHA) coating is porous and loose and can ensure the long stability of an Mg alloy implant. However, different electrodeposition coating processes can have an effect on the corrosion resistance of FHA. For example, FHA coatings processed by a pulse reverse current had better microstructure and corrosion resistance than coatings processed by traditional cathodic processes [44].

Micro-arc oxidation (MAO) technology is widely used in surface modification. It has also been well investigated as a coating on Mg alloys. Tang et al [45] compared the electrophoresis deposition (EPD) technique with MAO on Mg alloys to develop surface coatings for orthopaedic applications. Both *in vitro* and *in vivo* tests indicated that the EPD technique produced better corrosion resistance than MAO. Another study explored the effect of MAO coatings on Mg–Ca alloys. MAO treatment enhanced the corrosion resistance and biocompatibility of the Mg–Ca alloy and the corrosion resistance increased with voltage [46]. Some researchers are trying to apply MAO technology to HA coatings. The role that the MAO usually plays is to create a porous coating and then HA or another calcium phosphate based coating is adhered to the MAO coating. A three-layer coating was used to delay the corrosion behaviour of Mg alloy AZ91. The inner layer was an MgF₂ conversion coating and the intermediate layer was produced by MAO with nanostructured hydroxyapatite as the outer layer. Such coated alloys had enhanced corrosion resistance as well as good cell adhesion *in vitro* [47]. Gao et al [48] developed a two-layer HA coating to enhance Mg alloy corrosion resistance and biocompatibility. The inner layer of coating was produced by MAO technology with the HA coating adhered to it as an outer layer. Electrochemical tests showed that the corrosion potential of coated Mg alloys increased by

161 mV. Only one layer of MAO coating was necessary to protect pure Mg and the coated Mg had superior corrosion resistance to pure Mg [49].

Because of structural and constituted similarities, most HA and calcium phosphate compound coatings have been applied in orthopaedics. Mg has been associated with the mineralization of calcified bones and teeth [50]. Moreover, research has shown that Mg ions can improve bone cell adhesion on the surface of implants [51] and HA can promote bone cell adhesion and proliferation [52,53]. Also, the mechanical properties of Mg alloys are more similar to those of bone than other alloys, thus decreasing stress-shielding effects [7]. Therefore, HA-coated Mg alloys are ideal biomaterials for orthopaedic applications and have been widely investigated to prove this idea [8,51,54,55]. HA coatings applied to cardiovascular stents have also been reported. Costa et al [56] studied HA coatings on stainless-steel stents loaded with low-dose sirolimus. Clinical trials demonstrated the antiproliferative effect and biocompatibility of HA. No patient had obvious neointimal hyperplasia during the trial. Another study of drug-eluting stents with HA coatings was conducted to evaluate platelet activation and deposition. The results showed that in an *ex vivo* model, a cobalt–Cr alloy coated with HA did not increase platelet reactivity and adhesion in human blood compared with a bare metal stent, demonstrating the biocompatibility of HA [57]. However, some work has indicated that calcium phosphate might cause vascular calcification and cell mineralization [58–61].

Sol–gel processed coatings

Sol–gel application is a process in which inorganic precursors undergo various reactions to form a three-dimensional molecular network [62]. Sol–gel coatings can form a dense barrier to protect corrosive metal substrates and can be used to synthesize coatings with controlled properties [63]. Several attempts to produce inorganic coatings by the sol–gel method have been reported. Different sol–gel films were coated on Mg alloys, including titanium dioxide [64] and a methyltriethoxysilane–tetraethoxysilane mixture [65]; both showed good corrosion resistance.

Polymer coatings

Polymer coatings can be used to enhance corrosion resistance and the abrasion and wear properties of Mg alloys [66]. Polymer coatings can also provide mechanical support or serve as a drug vehicle for controlled release [67].

Natural polymers

Compared with synthesized polymers, natural polymers have much higher biocompatibility [68]. Some natural polymers, such as collagen [69–71] and chitosan [72–76] have been used as coatings for stents and demonstrated to have good biocompatibility. Collagen coatings have also been used in orthopaedic implants for bone regeneration [77]. A novel tripolymer composed of collagen, RGD (Arg–Gly–Asp) peptide, and chondroitin sulfate was produced to coat Ti implants to enhance bone healing [78]. Chitosan is also a widely used coating for orthopaedic tissue-engineering materials [79,80]. Some peptides, such as GFOGER (glycine-phenylalanine- hydroxyproline-glycine-glutamate-arginine), have also been

investigated in orthopaedic tissue healing or bone repair [81,82]. However, both collagen and chitosan may cause an immunological response [83] and activate complement and blood coagulation [84]. Another natural polymer, bacterial cellulose (BC), because of its high mechanical strength, high water content, and good biocompatibility [85], has been widely used in vascular grafts or as a vascular replacement [86–89], in wound healing [90] and in tissue-engineering scaffolds [91,92]. Composites formed by BC mixed with other substances, e.g., poly(vinyl alcohol), as a coating for stents was reported in a patent [93]. BC was also used as a tablet coating for a drug-release system [94]. Moreover, as a biodegradable coating, the end degradable product of BC is glucose, which is non-toxic to the body. These studies suggest that BC has a great potential as a biodegradable coating for drug-eluting stents (DES) and orthopaedic implant applications; more work is needed to explore such possibilities.

Synthesized polymers

Most polymer coatings in cardiovascular and orthopaedic applications are synthesized polymers. This is a result of the easily altered properties of synthesized polymers through the manipulation of the synthesis condition or other modifications. For polymers to be used as coatings in these applications, the prevention of rapid corrosion with good biocompatibility and controlled drug release are of great interest. Table 2 [9,104,113,121,163–168] summarizes the synthesized polymers used for Mg and Mg alloy coatings.

Synthesized polymers used in DES and orthopaedic implants can be permanent or biodegradable. Permanent polymers can allow controlled drug release and remain after the drug is completely released [95,96]. Polymer properties affecting DES performance are summarized in Fig. 2 [112]. The polymers used in the first and second generations of DES are permanent. They can reduce angiographic restenosis and demonstrate effectiveness in PCI. However, tests show that they will cause late stent thrombosis [97]. Moreover, long-stay polymers can cause inflammatory reactions [98]. To solve the problems that permanent polymers introduce, various kinds of biodegradable polymers, such as poly-L-lactic acid (PLLA) [99] and poly(lactide-co-glycolide) (PLGA) [100,101], were synthesized and tested; both had good chemical properties, low immunogenicity and toxicity, and predictable biodegradation kinetics [102].

PLLA is a common biodegradable polymer with good mechanical properties and biocompatibility. Moreover, the end biodegradable product can be removed by body fluids and then metabolized by the liver and kidneys [103]. Xu and Yamamoto [104] compared PLLA with another biodegradable polymer, poly(ϵ -caprolactone) (PCL) as a coating to protect Mg. The results showed that PLLA had a better adhesion strength with Mg substrates than PCL and that more cells were more proliferative on PLLA. Interestingly, the early performance of PLLA-coated DES was similar to a bare metal stent, though the long-term performance was not studied [105]. *In vitro* dynamic degradation of pure Mg with PLLA and PCL coatings showed that PCL had better corrosion resistance in modified simulated body fluid solution than PLLA [9]. Wong et al [106] reported a polymer fabricated by PCL and dichloromethane to enhance the performance of AZ91 alloy in orthopaedic applications.

The results demonstrated improved corrosion resistance and good cell biocompatibility. Gollwitzer et al [107] showed that a PLLA coating for orthopaedic implants based on three different alloys had good stability. Abdal-hay et al [108] studied an HA-doped PLLA coating with respect to the bioactivity and corrosion behaviour of AZ 31 alloy as an orthopaedic implant; the coated samples showed a better biocompatibility and bending strength.

PLGA has been used in drug-delivery systems [109,110] and in tissue engineering for decades [102,111]. It can be hydrolysed *in vivo* by breaking ester linkages into lactic and glycolic acids, which are non-toxic [112]. *In vitro* degradation tests on PLGA as a coating for Mg–6Zn alloy indicated that it corroded slower and was more suitable for cell attachment than bare Mg–6Zn alloy [113]. Another study compared *in vitro* degradation with *in vivo* changes for PLGA-coated DES. The coating degradation rate was similar in both *in vitro* and *in vivo* tests. However, polymer degradation in a real vascular bed may give different results [114]. Ostrowski et al [115] used various concentrations of PLGA to control the thickness of coatings in orthopaedic applications. Although PLLA and PLGA were well investigated and demonstrated acceptable biocompatibility, some tests reported foreign body reactions with PLLA [116,117] and PLGA [118].

Poly(ether imide) (PEI) has good mechanical properties and is stable at high temperatures and has therefore been explored as a coating for Mg alloys. da Conceicao and coworkers [119,120] and Scharnagl et al [121] studied PEI as a coating for the Mg alloy AZ31. Thin layers of PEI showed high resistance to corrosion when exposed to a 3.5% NaCl solution. This could be due to the formation of Mg polyamate, which increased the corrosion impedance of the PEI coating.

Coatings and biocompatibility

Although coatings can usually enhance the corrosion resistance of Mg-based implants, sometimes the coating material itself may cause a chronic inflammatory response, especially for permanent polymer coatings [122]. A coating with good biocompatibility should not produce obvious foreign body reactions, blood coagulation, nor inflammation [123]. The physical and chemical properties of coatings determine their biocompatibility. Surface properties such as surface ligands [32], molecular chirality [124], surface patterns [125], surface roughness [126], and chemical coatings [127,128] can regulate cell behaviour significantly, thus having an effect on biocompatibility. Moreover, composites formed by combining coatings and other chemicals could enhance biocompatibility. For example, BC combined with gelatin has a better bioactivity and biocompatibility than BC alone [129]. Composite coatings produced by the sol–gel process showed a higher compatibility than coatings produced by MAO [130]. In DES, drugs of the “limus” family [57,95,99,131] and paclitaxel [95,132,133] can help inhibit smooth muscle cell proliferation. Another approach to improve the *in vivo* performance of stents is to promote endothelialization. Vascular endothelial growth factor can be loaded on to coatings to simulate endothelialization [98,123]. In orthopaedic implants, antibiotics are loaded on to coatings to reduce inflammation and infection [134,135].

Coatings for controlled drug release

In addition to enhanced biocompatibility and corrosion resistance, coatings can also be used to control the release rate of drugs. Some inorganic coatings, such as aluminium oxide, have been applied in drug-delivery systems. Aluminium oxide mixed with PLLA and PMMA (polymethyl methacrylate) has been investigated as a coating for drug release [112,136]. Nanoporous aluminium oxide, as a drug carrier, has also been reported [137,138]. A chitosan- and PLGA-coated titanium oxide nanotube to control drug release and enhance osteoblast adhesion was explored. Depending on the thickness of the polymers, reduced burst release (from 77% to >20%) and extended overall release (from 4 days to 30 days) were observed [139]. Kikuchi and Okano [140] reviewed pulsatile control of drug release using hydrogels. Coatings can provide a reservoir for drugs and controlled drug release. Sustained drug release is essential in preventing an inflammation response and reducing late restenosis. The drug release kinetics of various DES samples was similar. Many DES samples had a burst release at an early stage (24–36 hours) and then a sustained release for at least 30 days, followed by reduced neointimal hyperplasia and restenosis [112,141]. It was found that the morphology of the coating surface had no effect on the amount of drug released [142]. PLLA, a widely used biodegradable polymer coating in DES, is also a good candidate for controlled drug release. Some factors, such as the solvent removal rate [143], the matrix coated on PLLA [144], and microsphere processing parameters [145], were explored for a PLLA microsphere. Copolymers of PLGA and mPEG [monomethoxy poly(ethylene glycol)] nanoparticles was also investigated for polymer degradation and drug release [146].

The most common mechanisms of drug release are diffusion and degradation [147,148]. For diffusion, the coating acts as a rate control membrane. Degradation-controlled drug release is based on the degradation of the polymer that covered the drug reservoir. It has been shown that porosity and size had effects on the drug release mechanisms of PLGA [149].

Similarities and differences in the coatings used in stents and orthopaedic implants

The main purpose of the coatings used in Mg-based implants is to prevent rapid corrosion and improve the biocompatibility of the implants. Most surface modification methods can be used in both applications. However, the surface modification methods may vary because of the different cell types the coatings may interface with. For stents, biodegradable polymers with good biocompatibility and ideal controlled drug release profiles are of great interest. Although some biodegradable polymers have been reported in orthopaedic applications, the most commonly investigated coatings are still HA and calcium phosphate compounds because of their structural and constituted similarities to bone. In fact, HA-coated Mg alloys have been well studied and display good biocompatibility in orthopaedic applications. However, they may not be a good choice for DES because of potential vascular calcification. Drug-eluting orthopaedic implants based on Mg alloys have not been well explored to date. The differences and similarities in coatings for orthopaedic implants and stents are summarized in Fig. 3.

Conclusion

Mg-based biomaterials have a great potential in cardiovascular and orthopaedic applications due to their biodegradability, biocompatibility, and appropriate mechanical properties. However, they also have the limitation of low corrosion resistance and suboptimal biocompatibility. Coating technology is one of the leading approaches used to overcome these problems.

Surface coatings played an important role in the development of stents. Stent technology emerged in the 1980s and developed rapidly from bare metal stents to coated DES stents. Mg-based stents represent the latest generation of biodegradable stents and offer appealing features in clinical applications. There have been several clinical trials with promising outcomes on such Mg-based stents. Coatings on Mg-based stents can vary from metal and inorganic coatings to biodegradable coatings. Among these, biodegradable polymer coatings with drug-eluting features might be a better choice because of their advanced biocompatibility and capability to reduce late restenosis compared with other coatings. In the future design of coatings for Mg-based stents, novel biodegradable polymers or copolymers should be explored to further enhance biocompatibility with sustained control of drug release. Moreover, new drugs that can inhibit smooth muscle cell proliferation and reduce neointimal hyperplasia while promoting endothelialization are preferred.

In orthopaedic applications, HA and calcium phosphate compounds have many advantages over other coatings, such as structural and constituted similarity, and promoting bone cell adhesion and proliferation. There are fewer reports on orthopaedic implants with drug-eluting features. It would be interesting to use drug-eluting orthopaedic implants with controlled release to achieve an even better healing process.

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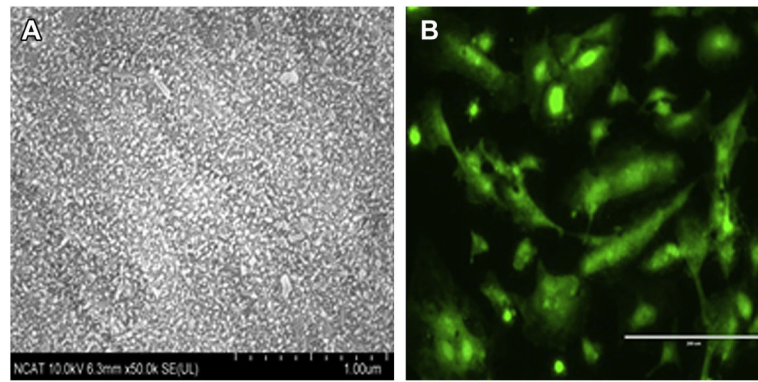


Figure 1.
(A) Scanning electron microscopy image of fluoride coating morphologies on a magnesium alloy; scale bar = 10.0 μm . (B) Endothelialization on the same magnesium alloy surface coated with fluoride; scale bar = 10.0 μm .

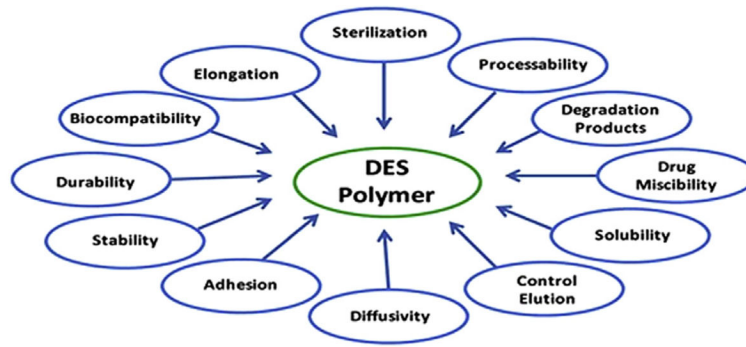


Figure 2. Polymer properties affecting drug-eluting stent (DES) performance [112].

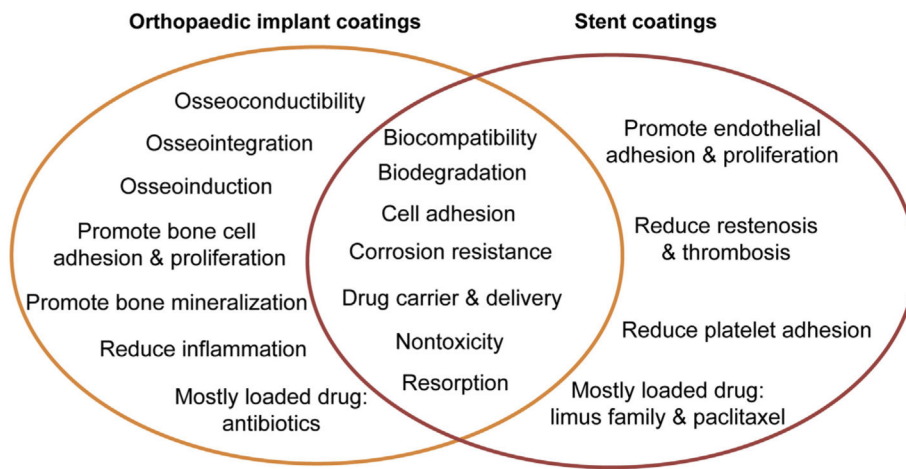


Figure 3. Differences and similarities: coating purposes and functions for stents and orthopaedic implants.

Table 1

Hydroxyapatite and calcium phosphate coated magnesium and magnesium alloys.

Reference	Mg/Mg alloy	HA/calcium phosphate-related compounds	<i>In vitro/in vivo</i> tests	Results
Chen et al. [150]	Mg	HA-Mg(OH) ₂	Electrochemical and immersion tests	Corrosion not completely stopped, but moderated rapid corrosion
Bornapour et al. [151]	Mg-0.5Sr	HA and Mg(OH) ₂ (formed by degradation in SBF)	Immersion tests, cytotoxicity evaluation, <i>in vivo</i> test in dog	Formation of an Sr-substituted HA layer in SBF; no thrombosis during 3-week implantation
Wen et al. [152]	AZ31	HA	Electrochemical test, immersion test	Alkaline-treated HA more stable; Ca-P-Mg deposition inhibited further corrosion
Zhang et al. [153]	Mg-Al, Mg-Ca	Calcium phosphate	Electrochemical test, immersion test	Coated samples had a higher free corrosion potential, lower corrosion current densities, and lower hydrogen elution rate
Jamesh et al. [154]	CP-Mg	HA	Potentiodynamic polarization tests, EIS studies	Three-fold charge transfer resistance increase in coated CP-Mg; improved corrosion-protective ability
Wu et al. [155]	AZ91D	Calcium phosphate/chitosan	Immersion test in PBS	Percentage of Ca(OH) ₂ in deposited layers influenced conversion rate and composition
Hiromoto and Tomozawa [156]	AZ31	HA	Immersion test, polarization test	Reduced Mg ²⁺ ion release and corrosion current density
Abdal-hay [108]	AZ31	HA-PLLA	<i>In vitro</i> degradation test, electrochemical corrosion test, mechanical properties test, cell viability assay	Improved performance for high corrosion rate
Feng and Han [157]	ZK60A	Calcium polyphosphate	Immersion test, electrochemical test	Enhanced corrosion resistance
Xu et al. [55]	Mg-Mn-Zn	Calcium phosphate	<i>In vitro</i> cell test, <i>in vivo</i> study	Enhanced cytocompatibility
Gao et al. [48]	Mg-Zn-Ca	Nano HA	Bonding strength test, electrochemical test, immersion test	Corrosion current density of coated alloys decreased; good corrosion resistance
Bakhsheshi-Rad et al. [158]	Mg-Ca-Zn	Nano-HA/MgF ₂ ; DCPD/MgF ₂	Electrochemical test, immersion test	Enhanced polarization resistance and corrosion potential of coated alloys
Meng et al. [44] Wang et al. [159]	Mg-Zn-Ca Mg-Zn-Ca	Fluorine-doped HA Ca-deficient HA	Electrochemical test, immersion test Coating adhesion test, electrochemical test, SSRT test	PRC coating higher corrosion resistance, lower corrosion rate, compared with TED coating. Increased E_{corr} value of coated alloys; delayed corrosion of coated alloys
Rojaee et al. [47]	AZ91	Nano HA	<i>In vitro</i> bioactivity evaluation, electrochemical test	Higher corrosion resistance of coated alloys

Reference	Mg/Mg alloy	HA/calcium phosphate-related compounds	<i>In vitro/in vivo</i> tests	Results
Jo et al. [160]	Mg	HA, MgF ₂	Immersion test, <i>in vitro</i> cell test, <i>in vivo</i> test	Improved corrosion resistance and bioactivity of coated Mg
Zhang et al. [41]	AZ91D	Calcium phosphate/chitosan	Scratch test, immersion test	Optimized fabrication parameters; enhanced corrosion protection
Niu et al. [161]	Mg–Nd–Zn–Zr	Brushite	Immersion test, electrochemical test, cytotoxicity evaluation, <i>in vitro</i> cell adhesion test, haemolysis test, <i>in vivo</i> test	Enhanced corrosion test; reduced haemolysis; produced less gas; good surface bioactivity

DCPD = dicalcium phosphate dehydrate; EIS = electrochemical impedance spectroscopy; HA = hydroxyapatite; PBS = phosphate-buffered solution; PLLA = poly-L-lactic acid; PRC = pulse reverse current; SBF = simulated body fluid; SSRT = slow strain rate tensile; TED = traditional cathodic process.

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Table 2

Synthesized polymer coatings for magnesium and magnesium alloys.

Reference	Mg/Mg alloys	Polymers
Xu and Yamamoto [104]	Mg	PLLA, PCL
Chen et al. [9]	Mg	PLLA, PCL
Li et al. [113]	Mg-6Zn	PLGA
Lu et al. [162]	AZ81	PLLA, PLGA
Zomorodian et al. [163]	AZ31	PEI, diethylene triamine, HA
Scharnagl et al. [121]	AZ31	PEI
Truong et al. [164]	Mg-Mn alloy	Polypyrrole
Yfantis et al. [165]	AZ31	Polyacrylic-polypyrrole
Wang et al. [166]	Mg-Zn-Mn	PTMC
Liu et al. [167]	WE43	Chitosan, PSS, polyelectrolyte
Adden [168]	Mg + rare earth elements	Polyphosphazene

PLLA = poly-L-lactic acid; PCL = poly(ϵ -caprolactone); PLGA = poly(lactide-co-glycolide); PEI = poly(ether imide); PTMC = poly(1,3-trimethylene carbonate); PSS = poly(styrene sulfonate).