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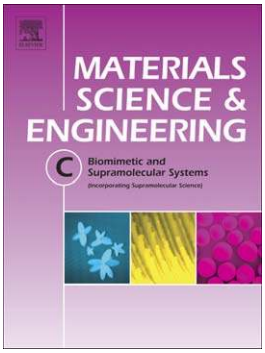

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Biodegradable Magnesium Alloys for Orthopaedic Applications: A Review on Corrosion, Biocompatibility and Surface Modifications

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Abstract

Magnesium (Mg) and its alloys have been extensively explored as potential biodegradable implant materials for orthopaedic applications (e.g. Fracture fixation). However, the rapid corrosion of Mg based alloys in physiological conditions has delayed their introduction for therapeutic applications to date. The present review focuses on corrosion, biocompatibility and surface modifications of biodegradable Mg alloys for orthopaedic applications. Initially, the corrosion behaviour of Mg alloys and the effect of alloying elements on corrosion and biocompatibility is discussed. Furthermore, the influence of polymeric deposit coatings, namely sol-gel, synthetic aliphatic polyesters and natural polymers on corrosion and biological performance of Mg and its alloy for orthopaedic applications are presented. It was found that inclusion of alloying elements such as Al, Mn, Ca, Zn and rare earth elements provides improved corrosion resistance to Mg alloys. It has been also observed that sol-gel and synthetic aliphatic polyesters based coatings exhibit improved corrosion resistance as compared to natural polymers, which has higher biocompatibility due to their biomimetic nature. It is concluded that, surface modification is a promising approach to improve the performance of Mg-based biomaterials for orthopaedic applications.

1 Introduction

Metallic orthopaedic implants have been used for the replacement and/or regeneration of damaged hard tissues [1]. Metallic implants are preferred for their high mechanical strength and toughness which make them superior to polymer and polymer-ceramic composites [2]. Orthopaedic metallic implants can be broadly classified into permanent (e.g knee or hip prostheses) and temporary biodegradable implants (e.g. Screws, pins, etc.) [2]. Metals such as stainless steel, titanium and cobalt-chromium alloys have been employed as permanent implants [3, 4]. However, there are some problems associated with the use of permanent metallic implants [5-7]. The first such problem includes incompatibility of mechanical properties of metallic alloys and natural bone; for example, metal alloys have greater elastic modulus to that of bone [8, 9]. Under *in vivo* conditions, the mechanical mismatch between bone and implants leads to clinical phenomena called stress shielding [10, 11]. In stress shielding, the implant carries much of the bulk load and the surrounding bone tissue experiences a reduced load stress. This triggers the resorption of surrounding bone tissue [11]. To address this problem, permanent metallic alloys such as Co-Cr-Mo and Ti-6Al-4V have been manufactured into porous forms to reduce the modulus mismatch with natural bone [12]. A number of techniques are available to produce a porous metallic structure (fully porous metals or surface treatments) such as sintered metal powders, gas injection to metal melt, plasma spraying, use of foaming agents etc. [12]. However, development of porous metallic implants suffers from limitations such as brittleness, impurity of phases and limited control over the size, shape and distribution of porosity [13]. This limiting their orthopaedic applications. The second problem associated with permanent implants is mechanical wear and corrosion associated with the long term implantation in the body. This results in the release of toxic metal ions (chromium, nickel, cobalt etc.) in the body which can trigger the undesirable immune responses, thereby reducing the biocompatibility of metallic implants.

[14]. Such drawbacks have compelled researchers and clinicians to look at biodegradable implants, which once used, only remain for an appropriate time to fix the damage.

Biodegradable metals have several advantages when used in orthopaedic fracture fixation (e.g. Screws, pins, etc.) [8]. The mechanical properties of Mg and its alloys such as Young's modulus of elasticity (E= 41-45 GPa) and density (1.74-1.84 g/cm^3) are known to be similar that of bone (E= 15-25 GPa and density= 1.8-2.1 g/cm^3). This is lower than other biodegradable materials such as Iron-Manganese (Fe-Mn) and Zinc (Zn) based alloys [2]. Furthermore, Mg ions are common metabolites in the body with a daily consumption range of 250-300 mg/day and are naturally stored in the bones [15]. Therefore, amongst biodegradable metals, the biocompatibility and the resemblance of mechanical properties of Mg and its alloys with bone makes it suitable for orthopaedic applications.

Ceramics which are inorganic non-metallic materials that have been employed in hard tissue engineering applications, are collectively known as Bioceramics [16]. Bioceramics possess desirable properties for biomedical applications such as (i) thermo-chemically stable, (ii) good wear resistant and (iii) are easily mouldable. Additionally, they are biocompatible, non-toxic and non-immunogenic [17, 18]. However, bioceramics like hydroxyapatite (HAP) are brittle and possess low tensile strength when compared to Mg based alloys [18]. Ceramics have been used commercially in various applications like coatings for implants, maxillofacial reconstruction and drug delivery devices [19-21].

Polymeric materials have been employed for tissue engineering applications due to their ductility, biocompatibility and biodegradable nature. Polymers are composed of small repeating monomers which give the polymer its characteristic properties. The degree of cross linking of monomers determines the physiochemical nature of polymers [24]. In general, polymeric materials are broadly classified into synthetic and natural polymers.

Synthetic polymers such as aliphatic poly-ester (poly lactic acid, poly glycolic acid, poly co-(lactic-co-glycolic acid)) can be synthesized in controlled conditions to regulate properties such as molecular weight and derivatization. These advantages of synthetic aliphatic polyesters enable their use in biomedical applications. Natural polymers such as collagen and protein based gels, hyaluronic based derivatives, polysaccharide chitosan and heparin based scaffolds have been successfully used in various tissue engineering applications [22]. Natural polymers share properties similar to materials in the body and thus may encourage expeditious tissue healing by directing cell adhesion and function. Both classes of polymer can be chemically modified to produce tuneable scaffold and biomedical implants with controlled degradation rates. [23]. Moreover, several reports showed that the by-products of biodegradable polymers are highly biocompatible [24]. These polymers can be engineered into various shapes and sizes, such as disk, rod, pellets, plates, films and fibres as required. Some applications include biodegradable sutures, bone grafting materials, pins, screw and load bearing orthopaedic devices [25]. Despite possessing many desirable properties, polymers have low mechanical strength when compared to bioceramics and metal implants, thereby hindering their applications in hard tissue engineering. Therefore polymers have been largely employed in soft tissue engineering and low-load bearing medical devices [25]. Comparatively, Mg and its alloys have advantages over polymers due mechanical strength similar to bone.

From the above discussion, it can be observed that Mg based alloys have mechanical properties (density, yield strength, tensile strength, elongation to break and elastic modulus) similar to that of natural bone as compared to other biodegradable alloys, permanent implants, ceramics and polymers as showed in Table 1. Despite many advantages, the major limitation of Mg based alloys as biomedical materials is their high corrosion rate [26]. Corrosion results in the formation of H_2 gas; which, if rapidly absorbed can lead to balloon

effect *in vivo* [27]. Additionally, shift in alkaline pH in the region surrounding the corroding surface is also a concern for biomedical applications [28].

There are some strategies to improve the corrosion behaviour and biocompatibility:

a) Optimising the composition and microstructure, including grain size, crystalline structure phase and texture of the base metal through the development of manufacture process/methods.
b) To improve the corrosion behaviour and biocompatibility of Mg based implants through protective polymer deposit coatings on Mg and its alloys.

2 Corrosion behaviour of Mg and its alloys

The usual degradation of biomedical metals is through the corrosion process. Generally, the corrosion process involves electrochemical reactions to produce oxides, hydroxides and H_2 gas species. In physiological conditions, the corrosion reactions of biodegradable metals including Mg and its alloys, involve the following anodic dissolution of metals and cathodic reduction reactions [8].

$$M \rightarrow M^{n+} + ne^{-} \text{ (anodic reaction)} \quad \text{Eq-1}$$

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

$$M^{n+} + nOH^{-} \rightarrow M(OH)_n \text{ (overall product formation)} \quad \text{Eq-3}$$

In general, immediately after contact with moisture/ body fluids, Mg is oxidised to form cations following an anodic reaction (Eq-1). The generated electrons are consumed for reduction of water corresponding to cathodic reactions (Eq-2). These reactions occur randomly over an entire surface, where galvanic couples form due to differences in electrochemical potential between the metal matrix and intermetallic phases or with organic molecules adsorbed on the surface that lead to the dissolution of biodegradable Mg and its

alloys [29]. Furthermore, physiological conditions are highly corrosive environment to Mg and its alloys such as dissolved oxygen, proteins and electrolyte ions (chloride and hydroxide ions) [30]. In these environments, pure Mg is susceptible to corrosion due to its high electrochemical potential, which results into the migration of ions from the metal surface to the surrounding fluid. These electrochemical reactions result in the formation of hydroxide layer (M $(OH)_n$) on the surface of Mg and its alloys (Eq-3). When this metal oxide covers over the entire surface, it acts as a passive layer or kinetic barrier which prevents the further migration of ions or chemical reactions across the metal surface [30]. However, this layer is slightly soluble and susceptible to breakdown, particularly in the presence of chloride ions, that subsequently lead to the pitting corrosion (Eqn-4) [31].

$$Mg(OH)_2 + 2Cl^- \rightarrow MgCl_2 + 2OH^- \text{..... Eq-4}$$

Additionally, the corrosion of Mg and its alloys produce H_2 gas. Initially, the rapid formation of H_2 gas bubble subcutaneously occurs due to the enriched chloride environment, which can disappear after the initial weeks following surgery [27]. Song *et al*., postulated that hydrogen release rate of 0.01 $ml.cm^{-2}.day^{-1}$ can be tolerated by the body and does not pose a serious threat [32]. The corrosion in body fluids is influenced by various factors such as pH, concentration and types of ions, protein adsorption on orthopaedic implant and influence of the biochemical activities of surrounding tissues [33-35]. The details of corrosion rates of Mg and its alloys under *in vitro* and *in vivo* conditions are given in Table 2. Typical forms of Mg corrosion encountered in physiological conditions are discussed in below sections:

2.1 Galvanic corrosion

Galvanic corrosion takes place when two dissimilar metals with different electrochemical potential come in contact with each other in the presence of an electrolyte [1]. The less noble metal acts as anode which corrodes rapidly producing by-products around the contact site

[36]. Galvanic corrosion of Mg is the primary issue for orthopaedic applications. In the galvanic series, Mg is the most active metal, and always an active anode, if it made contact with other metals acting as higher potential (cathode) [36, 37]. Consequently, Mg alloy implant is preferentially corroded. The even galvanic attack can also result from the presence of impurities or intermetallic elements in the Mg matrix.

2.2 Intergranular corrosion

Intergranular corrosion (IGC) occurs at the grain boundaries due to the precipitation of secondary phases [37]. For conventional metals alloys, a secondary phase is more active than the interior of grain, thereby causing corrosion [28]. For example, some Aluminium (Al) and stainless steel alloys are susceptible to IGC [28]. However, it is argued that Mg alloys suffer this corrosion or not [37]. Song *et al*, explained that this type of intergranular corrosion does not occur in some Mg alloys [38]. This arises as the intergranular phase distributed along the grain boundary is more corrosion resistant than the Mg alloy matrix. Sometime, it has been observed that matrix adjacent to grain boundaries corroded severely for some Mg alloy with Zr as a grain refiner [28]. But, this is not real interganullar corrosion, as intergranular (secondary) phases are still intact. Ghali *et al*., demonstrated the IGC attack in AE81 alloy [39]. When the grain boundaries with low Al concentration corrode at a faster rate than that in Al rich regions, as can also be seen in other Mg-Al alloys. Another study showed the AZ80 Mg alloy IGC in 3.5% NaCl for 1 hr [37]. Where aging resulted in the decrease concentration of Al in α-matrix in AZ80 which forms a poor protective oxide film on the surface and leading to breakdown [38]. As a result, the attack at α-matrix commenced next to β-phase in aged AZ80. Therefore, it could be observed that concentration of Al along the grain boundaries affects the IGC of Mg alloys.

2.3 Pitting corrosion

Pitting is a form of localized corrosion and associated with the breakdown of passivation layer in aggressive environment [36]. It is a serious form of corrosion when compared to other corrosion, since the surface pits are difficult to observe due to the presence of corrosion product [39]. The pits are highly corrosive, small and perforate the metal matrix. In general, after initial nucleation on the surface, impurities in the Mg alloy microstructure assist in further corrosion due to the galvanic differences in materials [40]. Moreover, the combination of chloride environment of body fluids and Mg ions from anodic dissolution species further accelerate the growth of the pit [40]. Once the pitting initiates, Mg component can be corroded in very short period of time, which in the case of orthopaedic applications would reduce the load bearing capacity of implants. Additionally, pitting increases the localised stress, which has the potential to form cracks [1]. The development of stress corrosion cracking (SCC) and metal fatigue cracks in the pits can lead to the implant failure under normal loading conditions.

3 Factors affecting the corrosion resistance of Mg and its alloy

3.1 Buffer systems and Inorganic Ions

In the physiological conditions, several buffers are involved to maintain the pH at neutral condition. The commonly used corrosion prototype medium is simulated body fluid (SBF) which consists of buffers such as HEPES, Tris–HCl and HCO_3^-/CO_2, which significantly affects the corrosion of Mg and its alloys [35]. The HEPES and Tris-HCl regulate the change in the pH by consuming the OH^- ions, and affect the formation of corrosion product, consequently accelerate the dissolution of Mg, as shown in Eqn-3. The HCO_3^-/CO_2 imparts buffering system in the human body which not only utilise OH^- ions, but also induce the

precipitation of $MgCO_3$ which contributes the protection against corrosion by developing the passivation layer on Mg [36].

Furthermore, the presence of inorganic ions in the body fluids influences the degradation of Mg and its alloys primarily by two manners: (a) the abundance of Cl^- ions in physiological conditions, is aggressive in the removal of passivation layer from the surface and leading to pitting corrosion and (b) the presence of HPO_4^{2-}/ PO_4^{2-}, HCO_3^-/CO_3^{2-} anions and Ca^{2+} ions form calcium phosphate and carbonate salt precipitate which protect the erosion of passivation layer on Mg and its alloys, thereby preventing the emergence of pitting corrosion [46].

3.2 Mechanical stress

The attractive high strength of biodegradable Mg alloys as compared to biodegradable polymers, which makes them promising for load bearing orthopaedic applications. Potential biodegradable biomedical devices would be exposed to the complex stress environment *in vivo*, depending upon the implantation site, and would be expected to function under various mechanical stresses, including fluid shear stress, compression etc.

Gu *et al.,* showed the increase in corrosion rate of as-extruded WE43 alloy and as-cast AZ91D under compression and cyclic loads [41]. The corrosion of these two alloys increased more than 10 times under applied loads when compared to unstressed equivalents [42]. Furthermore, the flow of electrolytes also influenced the corrosion rate of Mg based biomaterials. In case of Mg based biomaterials, the flow may produce fluid shear stress, which could help the deposition of corrosion product layer or, on the other hand, remove the locally generated OH^- ions, thus affecting the corrosion behaviour [42, 43]. For instance, Leversque *et al.*, reported that relatively low shear stress (0.88 and 4.4 Pa) slow down the

corrosion rate of AM60B alloy in the static Hanks' solution, whereas higher shear stress (8.8 Pa) enhance the rate [151].

Furthermore, time dependent changes in the integrity of the mechanical properties of metal under prolonged mechanical stress is also a crucial factor [44]. Adequate mechanical strength of metal implant is required to assist the healing and is important for post-operative recovery. As the degradation of biomaterial proceeds; the degeneration of mechanical integrity is expected. The mechanical loads can accelerate this process because of both corrosion and stress that lead to stress corrosion cracking (SCC) and corrosion fatigue, thereby causing implant failure [45]. The cyclic stress develops the formation of microscopic cracks on the surface and also damages the protective passive layer, while the chloride environment in body fluids further significantly increases crack growth rate [46]. When the loading stress exceeds the threshold of SCC, the crack grows to a critical size, resulting in the fracture of the metallic implant. This infers that the environment can significantly reduce the fatigue limit of Mg alloys over an implantation period, producing considerable shorter failure times of implants.

4 Effects of alloying element on mechanical and corrosion properties

The Mg based biodegradable substrates can be divided into four major groups: (a) pure Mg, (b) Al containing alloys (AZ91, AZ31, LAE422, AM60 etc.) (c) Rare earth elements (AE21, WE43 etc.), and (d) Al free alloys (WE43, MgCa 0.8, MgZn6 etc.). These alloying elements improves the mechanical and physical properties of Mg alloys for orthopaedic applications by: (a) optimising grain size, (b) improve corrosion resistance, (c) providing mechanical strength by the formation of intermetallic states and (d) eases the manufacture process of Mg alloys [1]. The composition of some Mg based alloys are given in Table 3. In this section, the

effects of some important alloying elements on the mechanical properties and corrosion behaviours of Mg alloys are also discussed.

As an alloying element, Al is commonly used for modifying the mechanical and corrosion properties of Mg alloys [47]. Addition of Al (1-5%) lead to the reduction of grain size, while content greater than 5% does not affect the grain size [48]. Generally, Al dissolves partly in Mg solid solutions and precipitate as $Mg_{17}Al_{12}$ secondary phases along the grain boundaries [47]. The as-cast Mg-Al alloys show α- Mg matrix and β-phases mainly consisting of $Mg_{17}Al_{12}$ phases [49]. In the presence of electrolytes, these phases show different electrode potentials. The $Mg_{17}Al_{12}$ phase exhibits a passive behaviour, acting as a cathode with respect to the α-phase of Mg matrix, thereby accelerating the corrosion of the alloy [49]. However, the inert nature of $Mg_{17}Al_{12}$ phase can itself act as a corrosion barrier, thereby reducing the corrosion in AZ91D alloys [50]. Song *et al.,* suggested that if β-phase volume fraction is higher and distributed along the grain boundary, it might act as a corrosion barrier surrounding the α-Mg matrix thereby reducing the corrosion rates [51].

Calcium (Ca) acts as a grain refining agent in Mg alloys, stabilising the grain size at levels up to 0.5% Ca content and decreases slightly with further addition [52]. Li *et al*, studied the Mg-Ca binary alloys with increasing concentration of Ca from 0.5% to 20% [52]. The increase in Ca addition resulted in a high content of Mg_2Ca secondary phase distribution towards grain boundaries. The Mg_2Ca secondary phase is brittle reducing the ductility of Mg-Ca alloys with increase in Ca concentration. This also influences the corrosion properties of Mg alloys. A high volume fraction of the Mg_2Ca secondary phase reduces the corrosion resistance of Mg-Ca alloys due to the formation of micro-galvanic cells [53]. Therefore, it can be observed that the excessive Ca concentration accelerates the corrosion of Mg-Ca alloys, and the optimum Ca concentration should be ≤1% [52].

Manganese (Mn) is commonly used as a secondary element in Mg alloys. It has been claimed that the grain size decreases with increasing Mn content in Mg-Al-Mn alloy, but at levels above 0.4% this effect ceases [49, 15]. It has also been reported that Mn addition can improve the tensile strength and fatigue life of extruded AZ31, AZ61 and AZ21 alloys [49]. Song et al, suggested that Mn improve the corrosion resistance in Al containing Mg alloys by transforming the Iron (Fe) and other impurities into harmless intermetallic compounds [51]. However, the excessive addition of Mn reduces the corrosion resistance of Mg-Al alloys due to the formation of a large amount of Mn-containing Mg-Al intermetallic phases which can be prone to galvanic effects.

Similarly to Mn, Zinc (Zn) has the ability to transform impurities such as Iron (Fe), Copper (Cu) and Nickel (Ni) into harmless intermetallic compounds, thereby reducing their corrosion enhancement effect [51]. It has been reported that the addition of Zn is associated with the grain refinement and formation of secondary phases, thus influencing the mechanical and corrosion properties of Mg alloys [49, 55]. Yin *et al.* showed that the addition of 3% Zn in Mg-Zn-Mn alloys forms Mg-Zn secondary phases which precipitate out of the Mg-matrix, thus improving the strength through a dispersion strengthening mechanism [54]. Song *et al.* also studied the effect of Zn alloying on corrosion behaviour of Mg alloys [55]. It was found that micro-galvanic effects dominate the corrosion behaviour of Mg-Zn alloys, thereby restricting Zn to levels less than 5%. Above 5% addition results in the formation of high volume fraction of Mg-Zn secondary phases which act as cathodes, accelerating the corrosion of α- Mg matrix around the Mg–Zn phases in Mg alloys.

Lithium (Li) can alter the lattice structure from hexagonal close-packed (h.c.p.) to body-centred-cubic (b.c.c.) crystal structure in Mg alloys [56]. Therefore, it can be employed to enhance the ductility and formability of Mg alloys [49]. Li is more reactive than Mg and has a pronounced effect on the corrosion behaviour of Mg alloys. Li content below 9% in pure

Mg is beneficent to corrosion resistance, whereas excess addition of Li is detrimental to the corrosion resistance [57, 58].

Rare-earth elements (REEs) are a group of seventeen elements, including fifteen lanthanides, scandium (Sc) and yttrium (Y). They are normally added to Mg alloys as master alloys or hardeners and can improve the strength and corrosion resistance by both solid solution and precipitation hardening [56]. The REEs can be classified into two groups (i) High solubility group (yttrium (Y), gadolinium (Gd), terbium (Tb), dysprosium (Dy), holmium (Ho), erbium (Er), thulium (Tm), ytterbium (Yb), and lutetium(Lu)) and (ii) limited solubility group (neodymium (Nd), lanthanum (La), cerium (Ce), praseodymium (Pr), samarium (Sm), europium (Eu)) [56]. For example, Y has a high solid-solution solubility in Mg and is often introduced along with other rare earth elements to improve creep and corrosion resistance [33].Moreover, most of REEs form intermetallic phases with Mg and Al which have a pronounced effect on the strength and corrosion of Mg alloys [59]. Several REE-doped Mg alloys such as WE43, Mg-5Gd, LAE442 and Mg-4Y have been investigated [33]. In WE43, main precipitated phases are $Mg_{12}YNd$ and $Mg_{14}YNd$ [60]. For Mg-Gd alloy, Mg_5Gd intermetallic phases can precipitate both in grains and at grain boundaries. In Mg-Al-REE systems, the REE tend to form intermetallic phases with Al as $Al_{12}REE$ and $Al_{11}REE_3$ improving strength and corrosion resistance [60]. Furthermore, the REE elements with limited solubility tend to form inter-metallic phases early during the solidification process [56]; for example, Ce aggregate at solid-liquid interfaces during solidification in Mg-Al-Ce alloys. During solidification, Al-Ce secondary phases form and segregate along the grain boundaries, effectively blocking the sliding of boundaries during deformation [49]. Al-Ce particles also influence the corrosion rate in Mg-Al-Ce alloys. Higher content of Ce in alloys leads to $Al_{11}Ce_3$ particles forming a network surrounding the Mg matrix acting as a micro-galvanic cathode and thus delaying the corrosion of the Mg alloys due to a very small

potential difference [61]. Additionally, Al-Ce phase exhibits passivation in a wide range of pH, which further retards the corrosion of Mg alloys [49].

The characteristic impurities in Mg alloys are copper (Cu), nickel (Ni), iron (Fe) and beryllium (Be). Typically, Cu is limited to 100-300 ppm, Ni should not exceed 20-50 ppm and Fe and Be are limited to 35-50 ppm and 5 ppm respectively [56]. These impurities should be strictly controlled under toxic limits for biomedical applications.

5 Pathophysiology and toxicology of alloying elements used for biodegradable Mg based orthopaedic implants

The released metallic ions resulting from the corrosion of biodegradable Mg alloys may induce systemic toxicity to human, as well as localised toxicity to the peri-implant cells. Table 4 summarises the pathophysiology and toxicology of Mg and the common alloying elements. Generally, toxic element ions released in the body could be tolerated at very low concentration below its threshold level, while the excess release in the body will have adverse effects [62]. As Mg is the most abundant element present in the body, it shows very low toxicity, however in-depth biological studies are still required. Therefore, the amount of alloying element utilised for the manufacture of Mg based biomedical implants need to be optimised with respect to corrosion rates and the physiological environment at implant sites. It is essential that biomedical implants should be designed to control the localised release of metal ions below threshold levels, since the concentration of released metal ions into tissues influenced by various factors like (a) interfacial space between the metal and implants, (b) fluid flow shear stresses between the biomedical implant and bone, (c) variation in pH and (d) local blood supply [63].

The biological effects of released metal ions from biodegradable medical implants affect the cells of the surrounding tissue. Table 4 summarises the toxic dose at 50% cell viability

(TD50) of bone related cells (MC3T3E1 and MG63 cell lines). From Table 4, the alloying elements are divided into mild, moderate and sever toxic elements [64]. The mild toxic elements include Mg, Ca, Li, Al and Zr. However, some reports showed that mild toxic element like Al (500 nM) at very low concentration induces bone related cells proliferation [65]. Moderate toxic element includes Y, whereas Zn, Ni, Cu and Mn are severe toxic elements. Thus, moderate toxic or mild toxic elements should only be used to significantly improve the corrosion resistance to make the clinically feasible Mg based alloy orthopaedic implants [64, 65]. Additionally, other strategies such as polymer deposit coatings on Mg based substrates have also been employed to prevent its rapid degradation, thereby facilitating the controlled exposure of these metal ions into the body.

6 Effect of polymeric deposit coatings on Mg alloys degradation and biocompatibility

In general, the healing process of bone consists of three phases; inflammatory, reparative and remodelling. In inflammatory phase, the immune system of the body responds against the foreign body, i.e. metallic implant fixed in the body [66]. In reparative phase, integration of the implant with new bone and regeneration of tissue takes place. Remodelling phase is one of the longest phases in the healing process. For regeneration of bone, this process takes a minimum 12 weeks, and unfortunately most of the Mg based orthopaedic implant can degrade within this period [8]. Therefore, there is a need to increase corrosion resistance of Mg based alloys.

A potential method for enhancing the corrosion resistance of Mg alloy without altering the bulk properties of material is through protective polymeric deposit coatings. Typically, the bulk properties of Mg regulate the mechanical integrity, but the surface properties play important roles in various physio-chemical processes like interaction of body fluids, adhesion of biomolecules and cells with biomedical implants, which initiate the corrosion process [8].

Therefore, the coating should be biocompatible, but also degrade at a slower rate than that of Mg and its alloys. Polymeric deposit coatings are attractive, since they possess good biocompatibility with the body and have a range of degradation rates. This section discusses the role of deposit coatings (sol-gel, synthetic aliphatic-polyesters and natural polymers) in improving the corrosion resistance and biocompatibility of Mg alloys.

6.1 Sol-gel coatings

The sol-gel process involves the creation of an oxide network through progressive reactions of the precursor solution in a liquid medium. Basically, there are two methods of sol-gel preparation (a) inorganic and (b) organic [67]. The inorganic method involves evolution of network formation through the gelation of suspended colloidal particles of size 1-1000 nm in continuous liquid phase [68]. The organic method generally involves the solution of monomeric metal or metalloid alkaloid precursor in alcohol or organic solvent [69]. In general, sol-gel formation occurs in four stages (a) hydrolysis, (b) condensation and polymerisation of monomers to form chains and particles, (c) particle growth and (d) agglomeration of the polymer structures followed by the network formation throughout in liquid medium which increases the viscosity to form a gel [70]. In fact, hydrolysis and condensation reaction starts simultaneously, once the hydrolysis reaction has been initiated [67]. These reactions yield by-product such as water and alcohol. These processes are influenced by initial reaction conditions such as, pH, molar ratio of water to precursor solution, temperature and solvent composition [71].

According to available literature, silane based sol-gel coatings have been used widely as an anti-corrosive and biocompatible coatings on Mg alloy for orthopaedic applications. There are several reasons using silane as anti-corrosive coatings such as (a) hydrophobic Si-O-Si

network (b) lower susceptibility to galvanic reactions with Mg, (c) greater adhesive properties, (d) easily chemically modifiable and (e) less cytotoxic in nature [72].

Gaur *et al*., reported the *in vitro* investigation of biodegradable composite silane coatings of diethylphosphatoethyltriethoxysilane (DEPETES) and bis-[3-(triethoxysilyl)propyl] tetrasulfide (BTESPT) for corrosion resistance of Mg-6Zn-Ca alloy in the simulated body fluid (SBF) [73]. Initially, the Mg alloy was pre-treated in alkaline conditions to generate a passivation layer, followed by coating with different volume ratios of DEPETES: BTESPT (1:1 to 1:4) and curing at 120 ºC for 1 hr. The corrosion resistance was evaluated by EIS (Electrochemical Impedance Spectroscopy) and polarisation studies. Samples coated with DEPETES: BTESPT (1:4) showed a near six fold increase in corrosion resistance as compared to bare Mg alloy in SBF. The corrosion protection of composite coating was attributed to highly dense Si-O-Si network formation. Similarly, Khramov *et al*., demonstrated the corrosion resistant sol-gel coatings with hybrid inorganic-organic phosphonate silane on AZ31B Mg alloy [74]. These coatings were prepared by mixing of diethylphosphonato-ethyl-triethoxy-silane (PHS) and tetraethoxy-silane (TEOS) with various molar ratios (PHS: TEOS- 1:1 to 1:4), and evaluated for corrosion resistance in Harrison solution by using EIS and potentiodynamic polarisation studies. The sample coated with PHS: TEOS 1:4 showed greater corrosion resistance as compared to bare and TEOS coated AZ31B Mg alloy respectively. This enhancement in corrosion was attributed to the chemical reaction of phosphonate functionalities with the surface of the alloy, resulting in improved hydrolytically stable P-O-Mg bonds.

In addition to silane coatings, other metal based precursors sol-gel coatings have been used as a surface modification for preventing corrosion of Mg alloys. For example, Shi *et al*., showed that the titania coating on pure Mg implant was compatible with PEO (Plasma Electrolytic Oxidation) treated surface covers all the surface area (including pores) [75]. Furthermore,

Lalk *et al*., developed biodegradable Mg sponges coated with bioactive glass using the sol-gel method [76]. This coating was predominantly composed of calcium phosphate and silica containing phosphate. The corrosion resistance was determined by soaking in DMEM medium (Dulbecco's Modified Eagle's Medium), and found to be stable for 3 days. However, enhanced corrosion resistance was not observed for a longer duration due to the development of defects in the coating. Additionally, osteoblast cells (MC3T3E1) showed good biocompatibility as compared to uncoated surface. Furthermore, Ishizaki *et al*., developed a corrosion resistant super hydrophobic surface on Mg alloys with cerium oxide film and fluroalkylsilane molecules (Figure 1) [77]. It was demonstrated that the super hydrophobic coating (advancing and receding contact angles are 153.2º and 146.6º respectively) enhanced the corrosion resistance with more than one fold as compared to bare Mg alloy in 5 % w/v NaCl.

6.2 Synthetic aliphatic polyester coatings

In general, biocompatible polymeric implants for orthopaedic applications have not been found suitable due to poor mechanical properties [1, 78]. Therefore, such polymers are generally deposited as anticorrosive coatings on orthopaedic implant. Usually, these polymeric materials enhance the corrosion resistance of Mg based metals by isolating the device from the fluidic and corrosive environment of the body [1, 24]. The biocompatible properties of polymers are critical because their presence at the interface of implant and body environment which could elicit the immunological response. Therefore, selecting the appropriate polymer coating is crucial in improving the corrosion resistance and biocompatibility of orthopaedic metals, including Mg and its alloys.

There are several advantages of polymers as they can be easily modified chemically, physically and mechanically, enabling their use in a wide range of biomedical applications

[82-84]. Polymers applied as coatings on Mg based biomaterials for orthopaedic applications showed in Table 5, which enlist the degraded products and corrosion behaviour of polymer coatings.

Synthetic aliphatic polyesters such as poly lactic acid (PLA), poly-co-lactic-glycolic acid (PLGA), polycaprolactone (PCL), polyethyleneimine (PEI) and many other polymers have been used in various biomedical applications [79]. These polymeric materials are attractive coatings on Mg and its alloys to control the initial rate of degradation, as their degradation rate is based on their molecular weight [79]. In particular, lactic and glycolic acid based polymers such as PLA and PGA, have been studied extensively as corrosion resistant coatings for orthopaedic applications. Similarly, a significant work has been carried out in co-polymers of lactide and glycolide i.e PLGA [80]. A co-polymer of 50% lactide and glycolide degrades faster as compared to corresponding homo-polymer. PCL also degrades slower than PLA [81]. The polymeric deposit coatings on orthopaedic Mg devices can also enhance the mechanical strength, with nontoxic degradation products enabling osteoinductive and osteogenic environments [82-84]. However, many of the currently available polymers does not fulfil the requirement, and would require chemical modifications, if they are to be applied for such applications. This section discusses the corrosion resistance and biocompatibility of selected aliphatic polyester based polymers coating on Mg and its alloys.

6.2.1 Poly lactic acid

Biodegradable polymers such as poly lactic acid (PLA) have been explored extensively for biomedical application. PLA is highly biocompatible, semi crystalline and hydrophobic in nature [24]. It undergoes hydrolytic degradation and the by-products such as lactic acid is easily metabolised in the body without exhibiting any toxicity. However, the major drawback of the PLA as a load bearing implant for orthopaedic applications is that it possesses poor

mechanical properties as compared to bone [1]. On the other hand, it can be used as an anti-corrosion coating on Mg alloys to slow down the hydrolytic degradation rate and the evolution of H_2 gas [85]. However, it is depended on the concentration of PLA and the application technique [86].

Chen *et al*., studied the corrosion resistance properties of PLA coated on pure Mg in SBF. They reported bulging in the coating due to underlying accumulation of H_2 gas, leading to the rapid destruction of Mg substrate [87]. This effect was attributed to SBF penetration through defects in the coating which initiated corrosion. Interestingly, Alabbasi *et al*, proposed the inappropriate use of pure Mg as a substrate for dip coating with PLA [88]. They explained that pure Mg is highly vulnerable to corrosion in SBF; and as consequence corrosion begins rapidly upon permeation of SBF through defects in the coating. Secondly, the dip coating resulted in non-uniform thick PLA coating with poor adhesion, thereby showing poor corrosion resistance. In order to show the utility of PLA in enhancing the corrosion resistance, Alabbasi *et al.,* employed the spin coating technique for uniform coating of PLA on AZ91D Mg alloy. It has been shown that the corrosion resistance increases with concentration and uniformity in thickness of PLA coating on AZ91D Mg alloy. Therefore, it could be observed that selection appropriate coating techniques (dip coating, spin coating and spray coating) play an important role in studying the efficiency of polymer coating in preventing the corrosion of Mg and its alloys.

Zeng *et al*., reported the coating of PLA on MAO (micro-arc oxidation) treated Mg-1.21Li-1.12Ca-1.0Y alloy [86]. The corrosion resistance was evaluated by EIS and polarisation studies. It was observed that the MAO/PLA composite imparts corrosion resistance to the alloy within the physiological pH range of 7.5- 7.8. The results indicated that PLA/MAO composite coating can become a promising biomedical coating. Similarly Shi *et al*.,

demonstrated the utility of PLA for improving the corrosion resistance of MAO treated AZ31 Mg alloy in SBF [85]. Here, layer by layer PLA coating was prepared in PLA-chloroform solution. The corrosion resistance of PLA coated MAO/AZ31 alloy was compared with MAO/AZ31 and both PLA and AZ31 alloy in SBF for 24 hrs. The PLA/MAO alloy was 100 and 38 times more corrosion resistant than untreated bare AZ31 and MAO treated equivalents respectively. This result was broadly attributed to mechanical interlocking of PLA coating with MAO treated alloy as compared to other samples.

Furthermore, porous calcium silicate (WT) has been considered as a potential bioactive material for bone tissue engineering. However, insufficient mechanical strength and high degradation rates have limited their biological applications. Wu *et al*., modify the porous calcium silicate with poly D,L-lactic acid (PDLLA) to improve the mechanical properties [89]. It was observed that PDLLA-modified WT (WTPL) scaffolds maintained a more uniform, continuous inner network, pore size, porosity and interconnectivity of the original materials when compared to WT sample alone. As a result of this combination, the compressive strength, modulus and percentage strain of the WTPL scaffold were increased significantly when compared to WT alone. Moreover, PDLLA modification also improved the spreading, adhesion and viability of human bone-derived cells. Hence, it could be proposed that the intrinsic properties of PLA can be exploited for potential application for bone tissue regeneration.

6.2.2 Poly (lactic-co-glycolic) acid

PLGA (Poly(lactic-co-glycolic)acid)) co-polymers are FDA approved for clinical applications, mainly due to their excellent biocompatibility [24]. They are hydrolytically and enzymatically (trypsin or lysozyme) degraded into glycolic and lactic acid which are easily assimilated by metabolic pathways [90]. The physical, mechanical and chemical properties of PLGA can be engineered by altering the ratio of the two-co-monomers. Several compositions

of co-polymer of glycolic acid and lactic acid have been investigated. These co-polymers are usually two types (a) (l) LA/GA (b) (dl) LA/GA. The composition of (l) LA/GA ranges of 20 to 70 % and of 0 to 70% for (dl) LA/GA are amorphous in nature [91]. Reed *et al*., showed that (l) LA/GA co-polymers are more resistant to hydrolysis [92]. The LA/GA (30/70) has the higher water absorption capacity and more susceptible to hydrolysis, while the LA/GA (50/50) co-polymer is most unstable with respect hydrolysis. These advantages of PLGA have been exploited for important applications such as corrosion protection and drug delivery.

Ostrowaski *et al*., reported on the corrosion and biocompatibility properties of the PLGA coating of varying thickness on AZ31and MgY4 alloy for orthopaedic applications [93]. In their study, two coatings of different thickness 1.6 μm and 41.8 μm were prepared on AZ31 alloy, whereas 1.6 μm and 62.1 μm thick coatings were deposited on MgY4 alloy. The corrosion resistance was measured using EIS and potential dynamic methods in SBF. It was observed that corrosion decreased with increased PLGA thickness. An improvement in corrosion resistance was observed for only 3 days, thereafter did not maintain a reduction in corrosion rate. The topographical analysis showed that the entrapped gas in the coating caused the detachment of coatings from the alloy surface. The biocompatibility studies showed enhanced adhesion and proliferation of osteoblast cells. Furthermore, a separate study was carried out using pre-treatment of AZ31 alloy and composition of PLGA. The alloy was pre-treated to form Mg $(OH)_2$ layer and subjected to dip coating with PCL and PLGA with varying composition (75/25 and 50/50). The corrosion measurements showed that PCL offered the greatest resistance, followed by PLGA (50/50) and PLGA (75/25) when compared to an uncoated alloy for 1 week in culture medium. Additionally, these coatings were biocompatible with good adhesion, proliferation and differentiation of MC3T3E1 osteoblast cells and human mesenchyme stem cells.

Furthermore, Chen *et al*., exploited the existing regular application of PLGA in drug delivery for enhancing the corrosion resistance of Mg alloys [94]. Instead of employing a drug loaded PLGA coating, an active PLGA coating was fabricated loaded with inhibitor benzotriazole (BTA) through an electrospray process, which is capable of inhibiting corrosion of Mg alloys. Principally, it has shown that rapid response of PLGA particle to both water and pH change, which lead to instant release of BTA to self-healing the protective functionality, and prevent further corrosion.

Li *et al*, studied the corrosion and cell adhesion efficacies of PLGA coating on Mg-6Zn alloy (Figure 2a and b) [95]. The Mg-6Zn alloy was coated with different concentrations of PLGA to enhance the corrosion resistance in 0.9% NaCl solution. The corrosion resistance was evaluated by using EIS and potentiodynamic polarisation studies. A significant anticorrosive activity was observed with 2% PLGA, but not 4% PLGA. However, both substrates showed better corrosion resistance when compared to bare alloy by a factor over 100. The decrease in corrosion inhibition with higher concentration of PLGA was attributed to thick coating (76 μm) and poor adhesion with Mg alloy. Furthermore, PLGA substrate showed good adhesion for MC3T3E1 osteoblast cells (Figure 2b). Hence, PLGA co-polymer properties can be exploited to prevent the corrosion of Mg based alloys for orthopaedic implants

6.2.3 Poly caprolactone

Poly caprolactone (PCL) is the most studied polymer in the family of polylactones [24]. The glass transition temperature is -60 ºC and melting point is between 59 ºC to 63 ºC. It degrades slower than PLA, and is useful for drug delivery as wells as anti-corrosive coatings. The homopolymer PCL has a degradation time about 24 to 36 months. The rate of hydrolysis can be altered by co-polymerising with other polymers like valerolactones, dl-lactide etc [24]. For example, co-polymers with epsilon caprolactone and dl-lactide have been synthesised to yield polymeric material with a higher degradation rate (e.g. biodegradable sutures). PCL is

considered to be a nontoxic biodegradable material and suitable as a protective coating on Mg based alloy for orthopaedic applications.

Park *et al*., studied the varying thickness of PCL for controlled corrosion of Mg for orthopaedic applications [96]. Their report studied the layer by layer coating of PCL using dip coating with progressive increase in average thickness from 2.8 to 13 μm on pure Mg. The degradation rate was measured by evolution of hydrogen gas in Hanks' solution for 14 days. It was observed that the rate of degradation decreases with increases in coating thickness. However, the high absorption of water was observed in the early stages, damaging the coating by decreasing the adhesion of the film on pure Mg. Furthermore, Li *et al*., combined the MAO treatment of pure Mg coatings of PCL polymer to improve its corrosion resistance [97]. A uniform PCL coating was prepared on MAO/Mg and corrosion resistance measurements were evaluated using potentiodynamic polarisation and immersion test in Hanks' solution for 7 days. Results indicated the significant corrosion resistance of porous MAO/Mg/PCL (4-7 %w/v) substrate when compared to an uncoated MAO/Mg sample. Thus, pre-treated Mg with PCL coating could be good alternative for orthopaedic. Similarly, Degner *et al*. demonstrated the corrosion resistance of PCL coated pure Mg in DMEM (corrosive medium) for one month at 37 ºC through electrochemical investigations [98]. It was shown that with increases in the concentration of PCL (2.5 to 7.5 %w/v) the corrosion resistance increases 10 folds. Hence, it can be observed that PCL could act as a potential protective coating to prevent the corrosion of Mg based alloys for orthopaedic applications

6.2.4 Polyethylenimine

Polyethylenimine (PEI) is a polymer that consists of repeating amine group with two carbon spacers with melting point of 73-75 ºC [26]. In general, PEI has been applied in polymer composite coatings because of its positively charged nature, thereby not only acting as binder but also enhancing the corrosion resistance of biodegradable metals. Cai *et al*., reported the

fabrication of anti-corrosive layer-by-layer coating composed of polyethylene imine (PEI), polystyrene sulfonate (PSS) and 8-hydroxyquinoline (8HQ) on AZ91D Mg alloys [99]. The corrosion resistance of the coating on the alloy was studied by electrochemical measurements which showed the corrosion resistance for 4 days in mSBF (modified-SBF). Further, biocompatibility of coating was evaluated by studying the alkaline phosphatase activity of osteoblast cells, which indicated the higher osteo-differentiation when compared to uncoated Mg alloys. Although the number of studies on PEI is limited, but it shows promise as a potential protective coating for Mg and its alloys for orthopaedic applications.

6.3 Natural polymers coatings

Natural polymers such as collagen, chitosan, stearic acid and serum albumin have been studied as coatings on the surface of Mg and its alloys for anti-corrosive as well as biocompatible properties [100, 101]. In comparison to sol-gel and synthetic poly-esters, natural polymers exhibit excellent biocompatibility due to their biomimetic nature [101]. For example, extracellular cell matrix (ECM) components possess cell specific domains such as RGD (Arg-gly-Asp) sequence which help in cell attachment [101]. Therefore, natural polymer based coatings on implanted material enhance the interactions between the implant surface and surrounding tissue matrix, thereby expediting the regeneration of tissues [22]. These polymers can also use for surface modifications, hydrogel scaffold synthesis and housing drugs for delivery [102]. Currently, the corrosion resistance of biopolymer is poor when compared to sol-gel and synthetic-polyester based coatings, and improvement would require in depth research work. The list of natural polymers coated on Mg and its alloys to study the corrosion resistance is given in Table 5. This section reviews the surface modifications of Mg and its alloys by natural polymers coatings to improve the corrosion resistance and biocompatibility.

6.3.1 Collagen coatings

Collagen is the major component of extracellular materials of bone matrix. Many reports have demonstrated that collagen type-I provides a favourable surface for cell adhesion, functions and cell proliferation of bone related-cells [103]. It is expected that a collagen coating on Mg and its alloy may be suitable for corrosion resistance, although very few reports are available.

Wang *et al*, studied the corrosion resistance and biocompatibility of Poly(L-lactic acid)/hydroxyapatite/ collagen composite coatings on AZ31 Mg alloys for orthopaedic applications [104]. They found that natural polymers like collagen degrades too fast to provide any corrosion resistance to Mg, whereas PLLA degrades through an autocatalytic effect resulting in a localised excessive acidic environment, where its hydrophobicity hampers the cell compatibility. In this disadvantages of composite of Hydroxy apatite (HAP)/collagen and PLLA have been offset by considering their respective advantages; Firstly, affinity of biomimetic apatite with collagen and their biocompatibility with body fluid is favourable; secondly, the porous architecture created by collagen/HAP enhances the wettability of PLLA, thereby benefiting the adhesion, cell proliferation and differentiation. It was shown that with increasing the mass ratio of PLLA/HA/C (C: collagen) the corrosion resistance increased as compared to bare Mg and PLLA coated alloy. Likewise, the overall change in pH was controlled with PLLA/HAC when compared to bare Mg AZ91 alloy.

6.3.2 Chitosan coatings

Chitosan coating is generally non-toxic and can play an important function as an adhesive basal matrix for growing cells during peri-implant healing process and also enhances the corrosion resistance of biodegradable metal [105]. Gu *et al.*, studied the surface modification of the Mg-1Ca alloy by chitosan to slow down the corrosion in SBF [106]. Different layers of chitosan with varied molecular weight were dip coated on the Mg-1Ca alloy. It was shown

that coatings produced by 1.5×10^5 and 2.7×10^5 molecular weight chitosan exhibited a smooth surface, whereas holes and defects were seen in coatings produced by 1.0×10^4 and 6.0×10^5 molecular weight equivalents. The alloy with six layers of chitosan (with molecular weight 2.7×10^5) was found to be smooth and intact in contrast to surface with one, three or nine layers of chitosan coatings. The lower corrosion of Mg-1Ca alloy in terms of change in pH and hydrogen evolution gas was observed with six layers produced by 2.7×10^5 molecular weight chitosan.

Bai *et al*., studied the corrosion of MAO/Mg-Zn-Ca Magnesium alloy coated with a chitosan/Mg composite *in vitro* condition [107]. Coatings were prepared by MAO/Mg-Zn-Ca alloy followed by dip coating in a chitosan solution. The corrosion study was evaluated by anodic polarisation in SBF. It was observed that anticorrosion performance increased significantly through composite coatings, however a single layer of chitosan coating provided limited corrosion enhancement. The corrosion studies showed nearly 3 fold increase in corrosion resistance with composite coatings when compared to bare alloy. Similarly, Liu *et al.*, demonstrated the enhanced corrosion resistance of a WE43 Mg alloys, through layer-by-layer coating of chitosan and polystyrene polymers following MAO treatment [108]. Potentiodynamic polarisation and hydrogen evolution measurements showed significant improvement in the corrosion resistance of chitosan/polystyrene polymer coated MAO/WE43 alloy in SBF [108].

6.3.3 Serum albumin coating

Serum albumins are the most abundant proteins present in the circulatory system of various organisms [109]. They play as a major role in maintaining osmotic blood pressure, drug disposition and efficacy [110]. However, the anti-corrosive and biocompatibility properties of the serum albumin coating on Mg alloys have not been widely explored. Liu *et al.,* showed

that adsorption of bovine serum albumin (BSA) on AZ91 Mg alloy decreases the cathodic current and enhance the corrosion resistance in SBF [111]. It was observed that corrosion resistance increases with an increase in BSA concentration due to their blocking effect of the protein adsorbed layer which can suppresses the dissolution of AZ91 Mg alloys. In another study, Killian *et al*., presented an innovative method to cover the pure Mg with BSA via silane coupling chemistry [112]. They used ascorbic acid as a linker and 3-aminopropyltriethoxy silane (APTES) as a coupling agent for grafting BSA onto a pure Mg substrate with Mg samples directly steeped in albumin solution used as controls. It was observed that APTES-albumin-Mg sample was smoother with fewer defects than the steeped equivalent, as a result in less prone to corrosion. After being treated with SBF for 3 days, the surface of the steeped sample exhibited larger pits because of localised corrosion. The hydrogen gas evolution decreased from 0.12 ml/cm^2/day for the polished Mg samples to 0.075 ml/cm^2/day after APTES-albumin treated Mg. This indicated that albumin coatings attached through silane linker enhanced the alloy corrosion resistance and is a useful method for preparing other protein based biocompatible coatings on Mg alloy.

In general, surface modifications with natural polymers have shown to improve the corrosion resistance and biocompatibility properties of Mg and its alloys but literature reports for orthopaedic applications are limited. This indicates that the development of these coatings is in its infancy. As natural polymers are abundant, other kinds of natural polymers such as alginate agar, cellulose, dextran, chitin, casein, chondroitin sulfate etc. offer a wealth of coating opportunities.

6.4 Osteoinductive factor loaded coatings

In an attempt to overcome the limitations of Mg and its alloy for orthopaedic applications, protective coatings loaded with bone growth stimulating factors have been employed. The synergistic prevention of corrosion with the release of osteoinductive factors for accelerated

healing at the implant site in bone are attractive [113]. However, the concept of drug eluting orthopaedic implant is relatively unexplored to date with limited literature. This contracts with drug loaded polymer coatings which have been developed extensively in biomedical devices such as cardiovascular stents, catheters etc.

Luo *et al*., reported the electrochemical deposition of conducting polymer coatings in ionic liquids on pure Mg loaded with an anti-inflammatory dexamethasone drug (Figure 3a and b) [113]. The authors argued that the ionic liquid is a highly conductive and stable, enabling the conductive polymer coatings to be electrodeposited on the Mg under mild conditions. The conducting polymer chosen (3,4-ethylenedioxythiophene) (PEDOT) was electrodeposited uniformly and improved the corrosion resistance of Mg significantly. The corrosion studies claimed a 50% decrease in current density for PEDOT coated Mg over bare Mg. Additionally, the PEDOT coating was loaded with dexamethasone during electrodeposition and sustained release of the drug was controlled through electrochemical stimulus. Hence, by employing conducting polymer coating loaded with a drug, both corrosion resistance and biocompatibility were achieved.

7 Potential challenges in surface modifications on Mg based alloys

The corrosion mechanism of Mg and its alloying elements still faces several challenges. For example, Mg-based alloys containing rare-earth metals are important structural materials, as they combine low density with high-strength properties, but have different corrosion behaviour. Furthermore, the bio-incompatibility of the alloying elements create an unfavourable environment for the bone healing process, which is considered as a big challenge in the surface modification on Mg based alloys. Therefore, it is essential to investigate the corrosion resistance together with the biocompatible properties of alloying elements which might be applied to the development of orthopaedic Mg based implants.

In the past decade, polymeric deposit coatings for the corrosion protection and biocompatibility are being investigated, and are applied in the commercial applications [114]. However, formulations of new and improved polymer which can offer enhanced corrosion resistance to Mg and its alloys still faces several challenges. The interface properties of polymeric coatings such as adhesion, delamination and the choice of base metal applied for studying the efficiency of coatings are the important factors for the quality and stability of coatings [115]. However, adhesion test for evaluating the stability and feasibility of polymer coatings have rarely been performed in the reported literature. Additionally, important parameters like pH, solvents, temperature, electrolytes, kinetics of hydrolysis, pin hole formation, crystalline temperature are all of prime importance for the overall understanding of the coating / film formation on Mg based alloys. Collectively, the above-mentioned concerns could play an important role in large scale industrial production of Mg based orthopaedic implants.

Furthermore, new polymeric material and multiple component systems might be a future of the deposit coatings on Mg based alloys. The major advantage of synthetic polyesters (e.g PLGA, PCL, PLA) and sol-gel based is the ease of chemical derivatisation [116]. This could allow the synthesis of new polymer with desired properties such as enhanced mechanical properties, low hydrolysis rate and reduced toxicity. In addition, the blend of two or more polymers with desired characteristics or layer-by-layer coating of different polymers can also be incorporated in coating systems, in order to achieve stable, anti-corrosive and biocompatible deposit coatings for orthopaedic applications.

8 Conclusions

Despite of the immense potential of biodegradable Mg alloys for orthopaedic applications, the major disadvantage is their high corrosion rate, thereby creating bio-incompatible

environment in the surrounding tissues. In order to overcome these drawbacks, strategies such as the effect of alloying elements and polymeric surface modifications of Mg and its alloys have been discussed. Based on the numerous research carried out, it is concluded that alloying elements such as Al, Ca, Mn etc., can react with Mg to form intermetallic phases which can dissolve in grain matrix or distribute along the grain boundary, thereby influencing the mechanical properties and corrosion behaviour of Mg based alloys. For some elements such as Ca and Zn, the corrosion resistance depends upon their concentration in Mg alloys. Furthermore, the biocompatibility of these alloying elements on bone related cells is an important factor, and the implant should not show cell toxicity.

Therefore, in depth investigation is required to design the corrosion resistant and biocompatible Mg based alloys for orthopaedic applications. Recent research on the effect of polymer deposit coatings on corrosion behaviour and biocompatible properties of Mg alloys shows that sol-gel and synthetic polyester based coatings have significantly improved the corrosion resistant. Numerous studies also highlighted the improvement in corrosion properties of natural polymer coatings by incorporating the synthetic polymers. Furthermore, sol-gel and synthetic poly-ester coatings have shown the capability as local drug delivery platforms, however, there are very limited studies are carried out in the area. Therefore, novel strategies need to be designed, which could exploit the multifunctional coatings for the development of potential biodegradable orthopaedic Mg based implants.

9 References

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Figures caption

Figure 1. (I) Potentiodynamic curves of (a) bare magnesium alloy, and super hydrophobic coating on magnesium alloy after immersion in 5 wt% NaCl aqueous solution for (b) 30, (c) 60, and (d) 180 min. and (II) SEM images of the sample surfaces (a) before and after immersing in 5 wt% NaCl aqueous solution for (b) 30, (c) 180, and (d) 1440 mins.(Source: Adapted from Ishikai *et al*.[77] with permission)

Figure 2. (I) Potentiodynamic studies of Mg6Zn coated and uncoated with PLGA in 0.9% NaCl (II) SEM image of cell morphology on 2% PLGA coated at different time points (a) 1 day, (b) 2 day, (c) 3 day and (d-f) cell morphology on uncoated Mg6Zn at same time points. (Source: Adapted from Li *et al* [95] with permission).

Figure 3. (a) Polarisation curves of bare Mg and Mg coated with PEDOT coating in 10 mM PBS, pH 7.4 and, (b) Electrical stimulated accumulated drug release of the PEDOT/IL/Dex/Mg. (Source: Adapted from Luo *et al.* [113] with permission).

Figure 1:

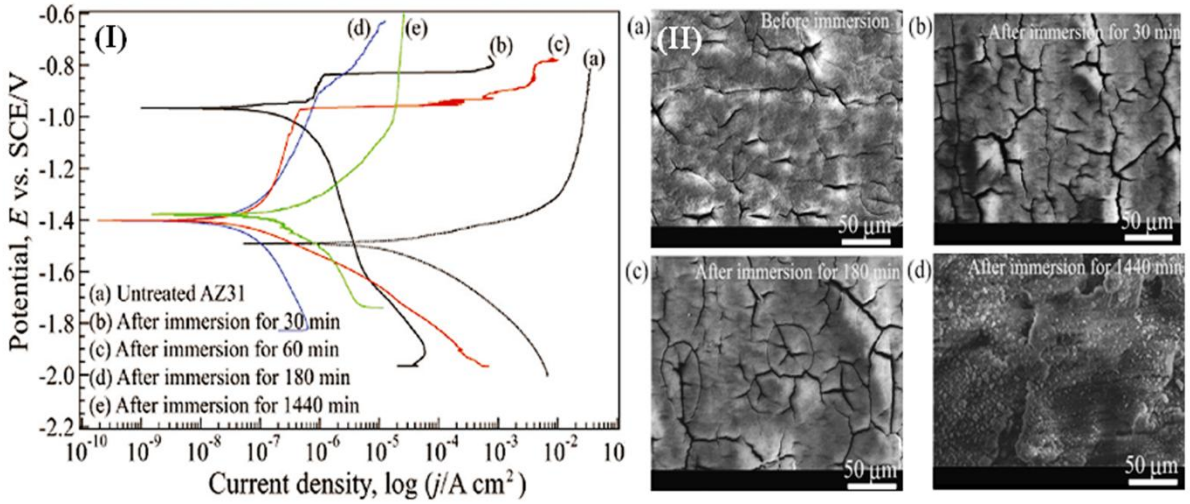
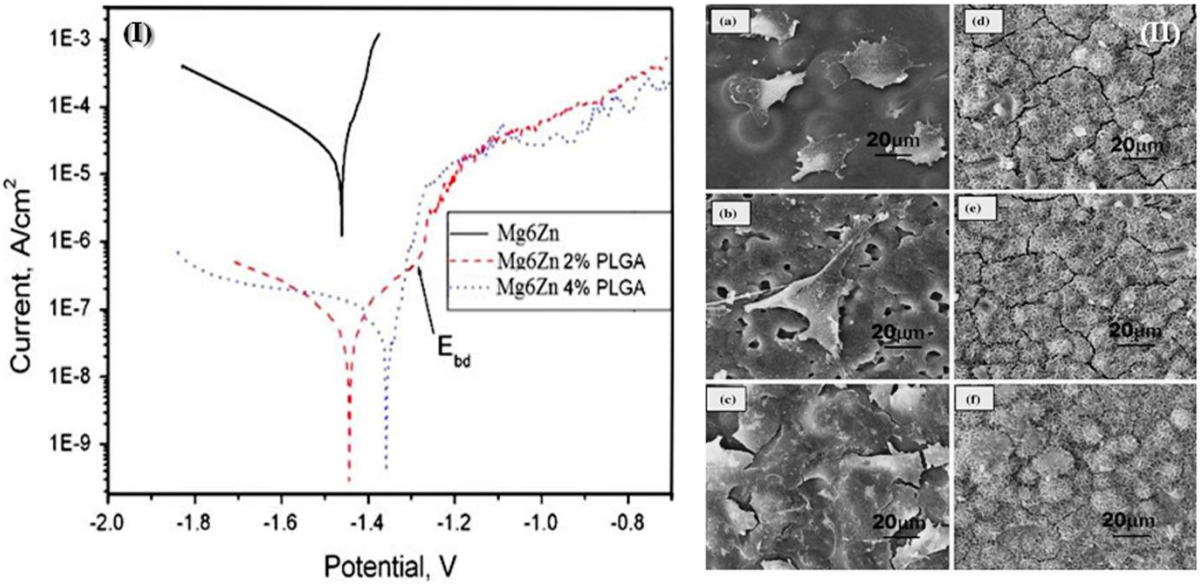


Figure 2



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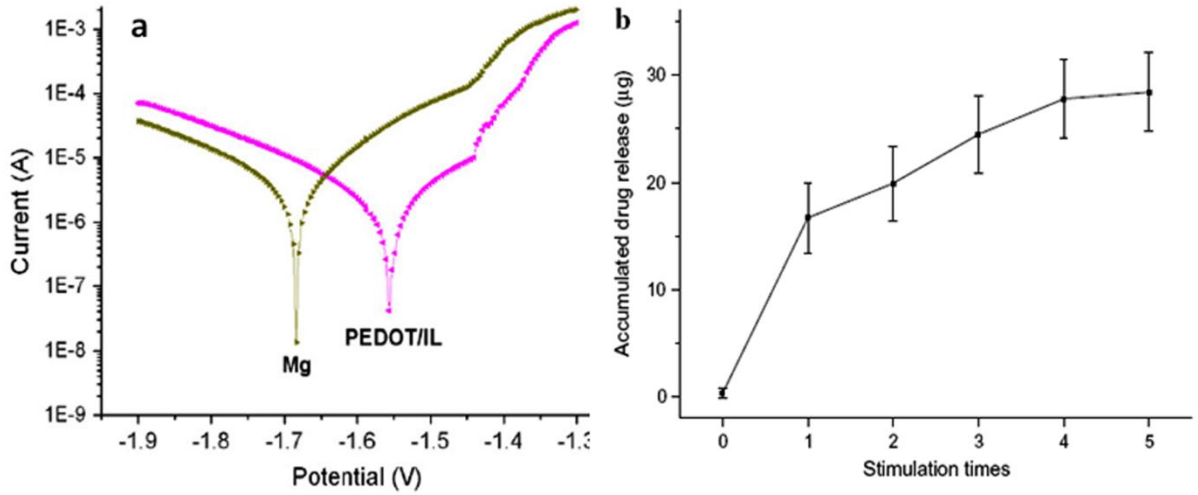

Table 1: Selected surgical metal implants/ material physical properties

Tissue/Surgical Implants		**Density (g/cm^3)**	**Yield strength (MPa)**	**Tensile strength (MPa)**	**Elongation to break (%)**	**Elastic Modulus (GPa)**	**Ref**
Bone		1.8-2.1	104-121	110-130	0.7-3	15-25	[117]
Biodegradable metal alloys							
Mg and its alloys	Pure Mg	1.74-2.0	65-100	90-190	2-10	41-45	[1]
	AZ31	1.78	185	263	15-23	45	[118], [119]
	AZ91	1.81	160	150	2.511	45	
	WE43	1.84	170	220	2-17	44.2	[120]
Fe and Mn alloys	Fe20Mn	7.73	420	700	8	207	[121]
	Fe35Mn	----	230	430	32	---	
Zn based alloys	Zn–Al–Cu	5.79	171	210	1	90	[122]
Non-degradable metal/composite implants							
Stainless Steel	SS316L	7.9	190	490	40	200	[123]
Titanium alloys	Ti-6Al-4V	4.43	880	950	14	113.8	[124]
	Ti-6Al-7Nb	4.52	800	900	10	105	
Chromium-cobalt alloys	CoCr20Ni15Mo7	7.8	240-450	450 -960	50	195 - 230	[125]
Bioceramics	Alumina Ceramics	4	---	400-580	0.12	260 – 410	[126]
	Synthetic hydroxyapetite	3.15	---	40 – 200	----	70 – 120	
Natural and synthetic polyesters							
Natural and synthetic polyesters	Collagen (Rat tail)	---	----	2.6-605	7.40-26.74	5 – 11.5	[127]
	PLGA	1.30-1.34	3.8-26.6	13.9-16.7	5.7	1.69	[128]
	PCL	1.145	8.37-14.66	68.45-102.7	22.8-28.3	281-686	[129]
	PLA (67Kda) PLA-59Kda PLA-31Kda	1.8 1.64 1.04	70 68 65	59 58 55	7.0 5.0 5.5	3750 3750 3550	[130]

Table 2: Corrosion studies of Mg and its alloys

Mg based Metals		***In vitro* degradation**			Ref	***In vivo* corrosion**					Ref.
	Duration (days)	Degradation rate (mm/yr) Unless specified	Corrosive Medium	Method/ Test		Duration of implant (days)	Degradation rate (mm/yr) Unless specified	Method /Test	Implant site	Animal	
Pure Mg	7	0.572	EBSS	Weight loss	[131]	14	0.39	Reduction in Volume	Ulnae	Rabbit	[132]
		0.728	MEM			21	0.21				
		2.185	MEMp			56	30-40%				
	14	0.468	EBSS			30	1.0 ± 0.3	Weight loss	muscle fascia	Rat	[133]
		0.676	MEM			60	0.7±0.3				
		1.483	MEMp			-	-	-	-	-	-
	21	0.382	EBSS								
		0.659	MEM								
		1.37	MEMp								
	4 8 20	Estimated 4.5 2.5 2.2	SBF	Weight loss	[134]	-	-	-	-	-	-

	3	9.1 mg/cm^2	HBSS	Weight loss	[135]						
	7	0.094 mg/cm^2									
	14	0.88	Nor's solution	Weight loss	[136]						
	6	0.57									
AZ31	3	Estimated 4 mg/cm^2	SBF	Weight loss	[137]	7	0.335	Weight loss	Subcutaneous	Rat	[131]
	7										
	15	5 mg/cm^2				14	0.335				
	20										
	25	12 mg/cm^2				21	0.223				
		16 mg/cm^2				42	1.2 mm^2	Weight loss	Femora	Guinea pig	[27]
		22 mg/cm^2									
	7	0.795	EBSS	Weight loss	[131]	126	1.6 mm^2				
		1.291	MEM								
		1.937	MEMp								
	14	0.670	EBSS	Weight loss	-	-	-	-	-	-	-
		1.018	MEM								
		1.291	MEMp								
	21	0.546	EBSS	Weight loss	-	-	-	-	-	-	
		1.192	MEM								
		0.944	MEMp								
AZ91	1	--	Nor's solution	Weight loss	[133]	126	1.3	SμCT	Femora	Guinea pig	[3]
	2	6.7				42	0.43	Area reduction			
	3	8.5									

	4	3.5				-	-	-	-	-	
	7	6	SBF27	Weight loss	[136]						
AZ91D	10 days	-0.267	Ocean water Substitute	Immersion	[138]	14	1.17	Weight loss	Subcutis	Nude mice	[139]
		5.72	1 M NaCl	Electrochemical	[140]	126	0.0003516	Vol. reduction	Femur	Guinea pig	[138]
		0.66				-	-	-	-	-	
		2.93									
	5 7 15 20 25	Estimated 4 mg/cm^2 5 mg/cm^2 6 mg/cm^2 5 mg/cm^2 4.2 mg/cm^2	SBF	Weight loss	[137]						
LAE442	10	6.9	Ocean water Substitute	Electrochemical	[138]	14	0.0134	µCT	Medullary cavity	Rabbit	[141]
		5.535		Weight loss	[142]	126	1.205 x10^{-4}	SµCT	Femora	Guinea pig	[138]
	-	-	-	-	-	365	40%	%vol. reduction	Tibia	Rabbit	[143]
						42	1.6 mm^2	Weight loss	Femora	Guinea pig	[27]
						126	1.45 mm^2				
						60	0.02 cm^3 (decreased)	Volume determination	Tibiae	Rabbit	[144]
						120	0.03 cm^3 decreased				
Mg-0.8Ca	7	0.573	EBSS	Weight loss	[131]						
		0.937	MEM								

		2.812	MEM p								
	14	0.521	EBSS								
		0.833	MEM	Weight loss	[131]	365	62%	% vol. of Reduction	Tibia	Rabbit	[143]
		1.901	MEM p			7	0.312	Weight loss	Subcutaneous	Rat	[131]
	21	0.382	EBSS	Weight loss		14	0.430				
		0.764	MEM			21	0.351				
		1.545	MEM p			60	0.02 cm^3 (Decreased)	Volume determination	Tibiae	Rabbit	[144]
						120	0.05 cm^3 (Decreased)				
WE43	0	0.79	0.01 M NaCl	Electrochemical	[145]	42	1.2 mm^2	Weight loss	Femora	Guinea pig	[27]
	-	2.91	0.2 M NaCl			126	1.0 mm^2				
	-	4.10	0.6 M NaCl			60	0.01 cm^3 (Decreased)	Volume determination	Tibiae	Rabbit	[144]
	-	5.84	1.0 M NaCl			120	0.06 cm^3 (Decreased)				
	-	6.97	2.0 M NaCl								

Table 3: Elemental compositions (%wt.) of selected Mg alloys

Magnesium alloys	Ca	Al	Mn	Zn	Li	Nd	Zr	Y	Mg	Other trace elements (% wt.)	Ref.
AZ31	-	2.4	0.4	0.8	-	-	-	-	96.7	Cu-0.008,Fe-0.003, Be-0.005	[27] [33] [146]
AZ91	-	9.0	0.13	0.5	-	-	-	-	90.37	Cu-0.003,Fe-0.014, Be-0.002	
WE43	-	-	-	-	-	2.4-3.2	0.4	3.7-4.3	92.1-93.5	-	[146]
LAE442	-	2.2	0.2	0.2	3.9	2.0	-	-	91.5	-	[27]
AM60	-	6.0	0.13	0.1	-	-	-	-	93.77	Cu-0.008,Fe-0.004, Be-0.005	[146]
MgCa0.8	0.8	-	-	-	-	-	-	-	99.2	-	[146]
Mg6Zn	6	-	-	-	-	-	-	-	94	-	[146]

Table 4: Pathophysiology of alloying elements in Mg alloy (Ref: [15], [139], [140], [54], [55]).

Elements	Effect on the alloying element	Normal amount present in human body	Pathophysiology	Toxicology	TD50 of Bone related cells (mol/L)
Mg	------	25 g	Normal blood serum level 0.73-1.06 mmol/L Required for ATP synthesis. activator of many enzymes; co-regulator of protein synthesis, stabiliser of DNA and RNA	Disorder in magnesium homeostasis leads to nausea, renal failure, impaired breathing.	73×10^{-3}
Ca	Induce Corrosion resistance in Mg-Ca alloys	1100 g	Normal serum level 0.919-0.993 mg/L Control muscle contraction, maintain homeostasis of bone, hormones and neurotransmitter release regulator	Dysregulation of calcium levels in the body leads to kidney stones, Hypoparathyrodism, cardiac unrest	$>50\times 10^{-3}$
Al	Acts as passivating element and improve corrosion resistance	<300 mg	Normal blood serum level 2.1-4.8 µg/L.	Excess amounts leads to neurotoxicity, Alzheimer's, accumulation in bone leads to decreases osteoclast viability.	$>5\times 10^{-3}$
Zn	Improves compatibility with bone by modifying yield stress and Elastic modulus. Decreases H_2 gas release	2 g	Normal blood serum level 12.4-17.4 µmol/L Essential elements for immune system.	Excessive amounts leads neurotoxic, cramps and diarrhoea	9.28×10^{-5}

Mn	Improve corrosion resistance	12 mg	Normal blood serum level < 0.8 µg/L Activator of various enzymes	Excessive amounts cause psychiatric and motor disturbances	4.59×10^{-5}
Li	Improve corrosion resistance	--	Normal blood serum level 2-4 ng/g Used in the treatment of depressive disorders	Overdose causes impaired kidney function and respiratory disorders	1.32×10^{-2}
Cu	Increase strength of Magnesium cast	--	normal blood serum level 74-131 µmol/L Involved in respiratory chain and enzyme co-factors	Causes hypotension, jaundice, melena etc.	4.15×10^{-5}
Y	Improve ductility and corrosion resistance	--	Blood serum level < 47µg	Higher concentration accumulate in liver and gall bladder	2.54×10^{-4}
Zr	Improve tensile strength, ductility and corrosion resitance	<250 mg	Low systemic toxicity	Deposited on bone and cationic form cause deposition on bone	1.64×10^{-3}

Table 5: Corrosion studies of polymers coated on Magnesium alloy

Polymers/ Composites Synthetic polyesters	Degraded products	Magnesium alloy substrate	I_{corr} ($\mu A/cm^2$, unless Indicated)	E_{corr} (V)	Corrosion Medium	Coating Method	Ref.
Poly Lactic acid	Lactic acid	PLA-AZ31	7.72	-1.57	SBF	Dip coating	[85]
		PLA-MAO-AZ31	1.83	-1.50			
		Mg-1.21Li-1.12Ca-1.0Y	1.7	--	Hanks' buffer		[147]
PLGA	d.l-lactic acid and glycolic acid	Mg Ammlite	3	-1.52	0.1 M NaCl	Electrospray	[94]
		Mg-6Zn	0.085	-1.44	0.9% NaCl	Dip coating	[95]
		AZ31-PLGA 10 %	5.20	-1.469	DMEM	Dip coating	[93]
		AZ31-PLGA 20 %	6.05	-1.45			
		Mg4Y-PLGA 10 %	8.09	-1.485			
		Mg4Y-PLGA 20 %	6.85	-1.469			
		PLGA 50:50	1.12	-1.52	DMEM	Dip coating	[148]
		PLGA 75:25	1.56	-1.44			
Poly(capro-	Caproic acid	MAO–4PCL duplex coated	0.81	−1.72	Hanks' buffer		[97]

lactone)						Dip coating	
		Mg MAO–7PCL duplex coated Mg	0.0045	−1.53			
		Mg- PCL 2.5 wt%	7	--	DMEM	Spin coating	[98]
		Mg- PCL 5 wt%	0.1	--			
		Mg- PCL 7.5 wt%	0.02	--			
		PCL-AZ91-LPM	Reduced	1.44	SBF	Spray coating	129
		PCL-AZ91-HPM		1.14			
Linear Poly-ethylene imine)	Ethylene glycol and amine	AZ91D-PEI/PSS/8HQ/PSS	24.82	-1.732	m-SBF	Spin coating	[99]
Sol-gel coatings							
DEPETES& BTESPT	-	Mg-6Zn-Ca -1(M) M-DEPETES:1BTESPT	1.20×10^{-2}	-1.39	m-SBF	Dip coating	[73]
		M-DEPETES:2BTESPT	7.24×10^{-3}	-1.35			
		M-1DEPETES:3BTESPT	2.45×10^{-3}	-1.37			
		M-1DEPETES:4BTESPT	7.59×10^{-4}	-1.38			
TiO_2	-	Mg-MAO-TiO_2	12.5	-1.93	Hanks' solution	Dip coating	[75]
Natural Polymers							
Chitosan	Glucosamine and keto-olligosacchraide	Chi/MAO/Mg–Zn–Ca-120V	14	-1.549	Na_2PO_4 + NaOH	Dip coating	[107]
		Chi/MAO/Mg–Zn–Ca-140V	0.59	-1.499	Na_2PO_4 +	Dip coating	130]

					NaOH		
		MAO-WE43-chitosan-polystyrene-LBL	2.796	-1.295	SBF	Spin coating	[101]
		AZ91E-5% chitosan	0.322	-1.562	Synthetic Sweat	Dip coating	[100]
		AZ91E-10% chitosan	0.136	-1.535			
		AZ91E-15% chitosan	0.116	1.483			
Natural polymer Composites							
HA-chitosan	CaPO4 and Glucosamine and keto-olligosacchraide	HA-5 wt.% chitosan-AZ31	15.1	-1.601	SBF	Spray coating	[131]
		HA-10 wt.% chitosan-AZ31	31.4	-1.581			
		HA-20 wt.% chitosan-AZ31	50.9	-1.586			
Stearic acid and magnesium state	Stearic acid	AZ31	4	-1.71	Hanks' solution	Dip coating	[149]
Collagen	Hydroxylysine/proline/hydroxyproline	AZ31	0.00223	-1.48	SBF	Electrospinning	[150]
			3.741	-1.460	SBF	Dip coating	

Highlights:

- The Mg based alloys are promising candidates for orthopaedic applications.
- The rapid corrosion of Mg can affect human cells, causes infection and implant failure.
- The various physiological factors and Mg alloying elements affecting the corrosion and mechanical properties of implants.
- The polymeric deposit coatings enhance the corrosion resistance and biocompatibility.