REVIEW ARTICLE

Recent Progress of Sol-gel Coating of Pure Magnesium in Biomedical Applications. A Review

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ABSTRACT

Magnesium (Mg) has attracted great attention as a possible biomedical implant due to its appropriate mechanical property, good biocompatibility, and lightweight. However, fast and uneven degradation has been a significant problem of pure Mg. The goal of this review was to investigate the current state of the art in the corrosion resistance and load-bearing capacities of osteopromotive biomaterials created by altering Mg surface coating with Hydroxyapatite (HA) ceramics. Initially, the osteopromotive characteristics of magnesium and also the magnesium corrosion behaviour in the human body's microenvironment were discussed. Following that, the different HA sol-gel coating methods in modifying the surface and corrosion behaviour of Mg were established. It was proposed that the optimal HA coating is about 5 to 6 µm as a corrosion barrier, which may also be improved by heat treatment at temperatures ranging from 300˚C to 450˚C. Finally, the strategies of HA sol-gel surface modification to improve the apatite formed and their degradation issue to promote healing in orthopaedic high load-bearing skeletal sites were elucidated.

Keywords: Pure mg, Sol-gel, Surface modification, Hydroxyapatite, Implant

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INTRODUCTION

Significant demand for clinical orthopaedic implants for fracture fixation and age-related bone diseases exist due to the worldwide growing ageing population. An increased risk of degenerative disorders of bone, such as osteoarthritis and osteoporosis occur with ageing. Traditionally inert metals, including 316L stainless steel, titanium alloy (Ti) and cobalt-chromium (Co-Cr) alloys, have remained as the officially approved devices to be used in supporting and fixing replacement surgery of these bone diseases (1-3). However, these metals implants may have some limitations, mostly if they stay in the body for a longer period. It may cause long-term physical irritation, chronic inflammation, and release of toxic particles (4, 5). Furthermore, the high value of Young's modulus for those metallic biomaterials is not matched with skeletal bone tissue, resulting in "stress shielding effects" and toxicity. It attributes to mechanical instability and leads to implant loosening and failure (5, 6).

Nowadays, the application of Magnesium (Mg) that may combat this problem and replace the current metallic implants in the market is extensively studied. Yin et al. (7) classified Mg as a biodegradable material that can dissolve when exposed to aqueous substances. Furthermore, biodegradable materials are easily absorbed, excreted, and thus a secondary surgery is not needed to remove the biodegradable implants after the healing process (5). Moreover, it offers an osteopromotive effect and enhances the healing performance rate of host tissues. Pure Mg has greater strength than the skeletal bone, and Young's modulus is closely like compact bone. This feature reduces the stress shielding effect during weight-bearing at the implant and bone interface. The comparison of the mechanical properties of skeleton bone and pure magnesium is summarized in Table I. The elastic modulus and fracture toughness of the pure Mg remaining higher than the bone, attributed to less deformation, and buckled elastically under axial loading.

Table I : Properties of skeleton bone and pure magnesium (8)

Properties	Skeletal Bone	Magnesium
Density	1.8-2.0	1.74-2.0
Tensile Strength (MPa)	130-180	60-100
Elastic Modulus(GPa)	3-20	41-45
Fracture Toughness ($MPaM^{1/2}$)	3-6	15-40

The naturally found Mg in bone tissue is essential for stabilising nucleic acids and proteins in human metabolism. The adult human body naturally requires approximately 1,000mg of Mg and contains 24g–30g of Mg^{2+} to maintain the biological functions. Meanwhile, 60% of Mg are bound to the bone (9). To maintain adult health, the recommended dietary allowance (RDA) suggests that the daily allowance need of Mg supplement is between 310 mg and 420 mg (8, 10, 11). Mg also acts as a cofactor for almost 300 enzymes to regulate biochemical reactions in the body systems, such as synthesis of protein, nervous system, blood glucose control, and blood pressure regulation (12).

The aim of this study is to review the biocompatibility and corrosion behaviour of pure Mg coating with hydroxyapatite by using the sol-gel technique. Furthermore, the technique to improve the corrosion behaviour of pure Mg is being evaluated. The apatite forming ability of Mg coating performance with hydroxyapatite in simulated body fluid (SBF) is also discussed. The study finally evaluates improvements of pure Mg implant in basic, translational, and clinical research as a pioneer in fixing fractures and bone diseases in elders.

OSTEOPROMOTIVE PROPERTIES OF MAGNESIUM

Referring to Table II, various *in vivo* animal study models like rabbits, rats, and goats were utilised to observe the degradation, bone growth, and periosteum process between the metallic Mg implants and osseous tissue. Here, Wang et al. (8) and Cheng et al. (13) found that trabecular bone quality improved when Mg screw was implanted and a higher concentration of Mg ions ($>15x10^{-3}$) mmol/L was found around the bone. The study stated that the fusion of growth cells decreased and enhanced osteoclastogenesis of the bone. Chaya et al. (14) and Tian et al. (15) evaluated fibrocartilage growth performance on the long bone of rabbits by using Mg screws. The callus at the bone to implant contact and fracture gap was reported to be significantly improved. High tensile strength occurred when the Mg plates bonded with the ulna of the rabbit. Furthermore, Ferraro et al. (16) studied knee stability in large animal models by using metallic rings. The ends of an anterior cruciate (ACL) ligament of a goat were joined with a solid Mg link, and the device had successfully repaired and stabilised the joint. Jahn et al. (17) showed that over 70% of rat bone marrow cavity diameter increased after 133 days of pin implantation, which was fabricated by

Table II : *In vivo* animal model studies on Pure Mg

Ref	Year	Designed Implant	Surgeries	*In Vivo* Animal	Degradation Rate	Result
Han et al. (19)	2015	Screw	Femoral Intracondylar	Rabbit	≈30% volume loss after 24 weeks	Improved healing of fractures
Chaya et al. (14)	2015	Screw and Plates	Ulna	Rabbit	0.40±0.04 mm	The bony structure around Mg implant improved
Cheng et al. (13)	2016	Interference Screw	ACL	Rabbit	≈30% volume loss after 12 weeks	Enhanced fibrocartilage growth at the ten-don-bone interface
Zhang et al. (18)	2016	Pins	Femoral	Rat	N/A	Speedy fracture healing
Farraro et al. (16)	2016	Rings	Suture	Goat	More than 93% of loss of volume in 12 weeks	No reaction from foreign bodies and gas formation
Jahn et al. (17)	2016	Pin	Femoral Fracture	Rat	Complete degrade after 133 days	Callus formed at the fracture gap
Tian et al. (15)	2018	Screws	Tibial	Rabbit	N/A	Enhanced fracture gap callus growth
Wang et al. (8)	2020	Interference Screw	ACL	Rabbit	≈10% volume loss after 16 weeks	Increased of tendon by rapid mineralization

using Mg-Silver (Mg-Ag). It proved that the Mg-based metal was suitable as a biomedical implant. Zhang et al. (18) described that Mg as a biomedical implant could enhance fracture healing without any toxicity in organs. The high corrosion rate and low biological activity of pure Mg implants are challenges that require address before they are used in clinical applications.

MAGNESIUM CORROSION BEHAVIOUR

In general, the human body blood pH value lies between 7.35 and 7.45. Even small changes in pH value led to severe adverse effects on the skeletal system. In general, the natural magnesium stored in the human body may facilitate the stimulatory growth of new bone tissues (20). However, pure Mg may corrode easily under the physiological condition of the aqueous human body. Equation (1) represents the typical chemical reaction of Mg ions in a microenvironment that corresponds to the production of acidic magnesium hydroxide $Mg(OH)_2$ and diatomic hydrogen (H_2) gas (8).

$$H_2O + Mg \rightarrow Mg(OH)_2 + H_2 \quad (1)$$

Based on Equation (1), $Mg(OH)_2$ is the main intermediate product that is leached from the surface of Mg, which would degrade into Mg2+ and OH- gradually (21). In addition, in the complex human body environment, an inorganic salt degrades the Mg and increases the Mg^{2+} ion. The severe disintegration of Mg^{2+} induces alkalisation near the implant surface which leads to an alkaline poisoning effect (4). This eventually results in haemolysis of red blood cells (4, 22).

The fast corrosion of Mg also correlates to the release of H_2 gas. H_2 gas at the implant surface eventually forms a bubble and accumulates in the locality of an implant (23). In addition, Mg is the most active in the metal reactivity series, whereby it has the lowest potential standard of -2.37V (24) and easily oxidises to galvanic corrosion when reacts with a higher concentration of H_2 (24). When pure Mg is in contact with other metals, such as Al, Zn, and Ca, the H_2 gas evolves from the outer surface of these alloys, leading to external galvanic corrosion. This hydrogen evolution process can cause the separation of tissues between implants and the periosteum of bone (25, 26).

In contrast, internal galvanic corrosion activates the H_2 due to the appearance of grains or impurities on pure Mg. These impurities increase the degradation of Mg, correspond to the depositions of gas and detached particles on the exterior of the Mg implant, leading to the development of cavities (24). The H_2 gas volume in the human body must be lower than 0.01ml/cm^2 per day to prevent deterioration of the Mg implant (8). The delay in healing at fracture surfaces attributes to necrosis and death of bone tissue.

The degradation and appearance of cavities on the exterior of Mg can impair the integration of the Mg implant after implantation and increase the fracture gap after surgeries, as illustrated in Fig. 1(a). The gap that forms between the implant and bone delays callus formation. A callus is a bony and cartilaginous tissue that appears on the surface of hard bone during remodelling and protects the bone against excessive pressure and friction. It can be divided into two groups, which are soft and hard callus. The delay in callus formation increases the fracture gap and expends the healing time shown in Fig. 1(b). Fig. 1(b) demonstrates the x-ray image represents a "cloud" like callus formation which occurs during indirect bone healing. Generally, the healing time and callus formation should be two months after implantation(8). The extension of healing duration impairs the mechanical strength of Mg implant and leads to implant loosening (12, 27).

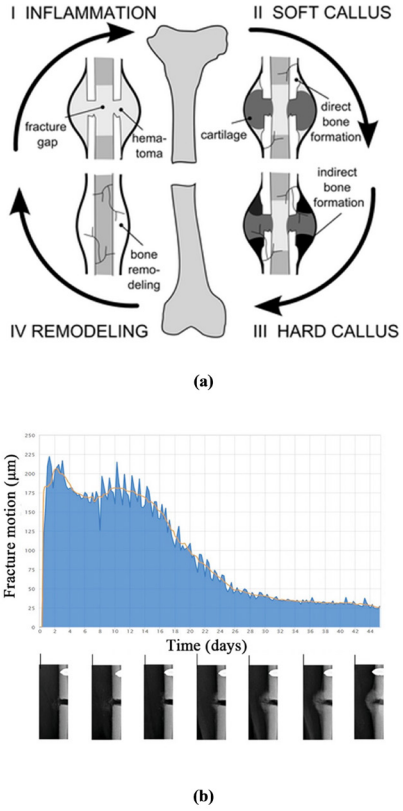

Fig. 1 : (a) Fracture gap and bone remodelling process (28) and (b) healing duration in the presence of mechanical loading (8).

The pure Mg should have sufficient mechanical properties to support the fractured bone during the early bone remodelling process and callus formation. So it is crucial to optimise pure Mg to match the bone remodelling process of the broken bone.

However, the entire surface Mg has mechanical strength inadequate to provide early support in a high load-bearing skeletal system, as reported by (17). Surface modification technologies of pure Mg may pioneer an era in developing Mg-based implant suitable in high load-bearing capabilities and functional movement of skeletal sites (10, 29).

To overcome this issue, many researchers explored possible methods to improve magnesium-based implants. These included the usage of organic or inorganic coatings on the surface of Mg metal. The protective coating was an effective method in controlling the degradation rate of Mg-based implants. Metallic Mg's layering can be prepared through a mechanical, physical or chemical process (22). Hydroxyapatite (HA) was chosen as a coating on a pure Mg implant to enhance the bioactivity and corrosion resistance. Incorporating HA is well known to impart bioactivity of pure Mg as HA is a type of bioceramic coating that has a similar crystalline composition of calcium phosphate of the human bone and tooth (30). HA promotes bone growth and accelerates bone tissue formation and reduces the healing duration as in Fig. 1(b). HA can also degrade by solution-driven after being implanted in the human body and is replaced with new lamellar bone (6). Amaravathy et al. (31) reported that HA/TiO_2 coating deposited on pure Mg improved growth cell on implant. HA with a molecular formula of $Ca_{10}(PO_4)6(OH)_2$ is the most extensively used material for skeletal tissue engineering, as the bone tissue comprises 70% of mass HA and 30% of mass collagen type 1 (32). The coating layer of HA on pure Mg acts as a barrier for corrosion between the human microenvironment and implant, without affecting the properties of the implant (33). The calcium component in HA reduces Mg tendency to corrode due to HA solubility in the body environment (30, 32).

Yang et al. (34) found that the decrease in corrosion was more than twice of magnitude for Mg covered with HA. The study reported on the refinement of in vitro corrosion and increment in cytocompatibility properties. The higher the HA bioceramic coating, the lower the risk of implant fatigue and failure in the aqueous environment of the human body (33). However, HA has brittle nature in the higher durable metallic alloy (25). HA possesses relatively low chemical permanence in the sintering process and dissipates after sintering metallic alloy (33, 35). Nevertheless, the composition of pure HA differs from human bone and long-term bone stability (32). Single HA coating can cause low bonding strength and implant instability (26). In this study, with prominent wear resistance and high adhesion to pure Mg substrate, sol-gel is a notable technology for forming HA coating on pure Mg. Sol-gel is a coating method on pure Mg with HA to enhance anti-corrosion property, bioactivity and bone-implant contact (26). The ability to incorporate HA on pure Mg presents the evolutions of functional biomaterial design.

FUNDAMENTAL OF HYDROXYAPATITE SOL-GEL COATING TECHNIQUE ON THE MAGNESIUM SURFACE

Many attempts have been made to improve the corrosion resistance through the depositions of metallic films on the Mg surface (31, 36-43). There is plasma spray coating, chemical vapour deposition (CVD), sol-gel process and laser pulse. Here, a method called the hydroxyapatite sol-gel process is commonly promoted to stick small molecules and powder catalysts on solid materials (44). This wet chemical coating is specially designed to obtain an appropriate barrier between the Mg plate and substrate, which is attributed to improving the corrosion resistance for a long time and is suitable for orthopaedic implants (23). HA is produced by the hydrolysis of the calcium nitrate ($Ca(NO_3)_24H_2O$) addition of ammonium phosphate ($(NH_4)_2HPO_4$). Niu et al. (33) and Tang et al. (36) layered HA composite coating on the Micro-arc oxidation (MOA) treated surface of AZ31 Mg alloy (MAO/HA) via dip-coating sol-gel technique. Both studies demonstrated an improvement in bonding strength between the HA/Mg. Besides, the HA coating also reduced the hydrogen embrittlement and enhanced, provide a corrosion barrier than the uncoated Mg alloy. Furthermore, Niu et al. (33) found that the hydrogen evolution rate for AZ31-HA increased rapidly after two days of immersion in SBF due to the HA coating that was leaching the surface exposing the Mg to the corrosive environment. In contrast, less hydrogen was evolved for AZ31-MAO-HA after immersion for 12 days. Zhu et al. (34) layered a HA that hybridized with hydroxyethyl cellulose (AHEC) on AZ31 Mg with the sol-gel spin coating method. The sample was rotated at 2000 rpm. They found that the coating could reduce the degradation rate in the potentio dynamic polarization tests. The surface of the sample's surface was made up of porous and uniform flake-like crystals that encouraged osteoblast growth in the in vitro MC3T3-E1 cell. Nevertheless, cracks were noticed on the surface of the implant due to the H_2O released on the samples. Guo et al. (35) fabricated titania (TiO_2) coating on the HA-coated Mg alloy by a sol-gel method. The coating morphology and corrosion resistance were determined by various HA sol-gel dipping durations.

It was of Mg and recommended that the 15 times coating exhibit the optimum coating morphology, corrosion resistance and surface biomineralization. They also reported that *E. coli* and *S.aureus* bacterial concentration consolidations were lower as compared to the uncoated groups. The antibacterial tests indicate that the composite coating possessed an excellent antibacterial property mainly against *E. coli* and *S.aureus*.

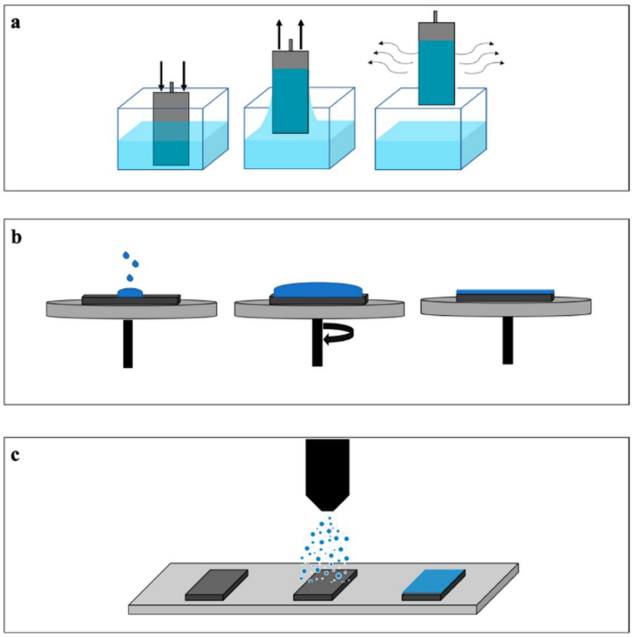

Fig. 2 : Schematic diagram of a) dip, b) spin, and c) spray coating of hydroxyapatite sol-gel method (29).

Fig. 2 shows a couple of deposition powder molecules in hydroxyapatite sol-gel methods, such as dip coating, spin coating, and spray coating produce deposition powder molecules. Therefore, the dip-coating in Fig. 2(a) samples were soaked in HA sol for 120min. The sample surface and chemical interaction between substrate and sol were formed. The spin coating process in Fig. 2(b) was begun with the HA sol covering the Mg surface and spinning at a speed range of 3,000 to 5,000 rpm to an axis perpendicular to the coating area. The centrifugal forces caused the liquid to flow radially outwards and the thin film HA was bonded on the substrate surface.

Spray coating in Fig. 2(c) occurs from compressed gas or the pressurised sol. The nozzle is used to load the HA droplets on the sample. The spray coating method is most commonly utilised in industrial applications since it has the shortest production time. However, the nozzle tips can be easily clogged due to the evaporation of solvents (29).

HYDROXYAPATITE SOL-GEL COATING ON MG SURFACE APPLICATIONS

Several studies have been conducted to evaluate the HA behaviour in the simulated body fluid (SBF). The bone-like appetite forming ability of the Mg-3Zn-HA was assessed using the SBF technique by Dubey et al. (45). The SBF has a closely similar ions concentration as blood plasma and the bone-bonding ability of Mg-3Zn-HA was evaluated based on the capacity of appetite formed on the surface. Mg-3Zn-HA was prepared by using the probe sonication method and was soaked in SBF for 3 days, 7 days and 14 days. The result showed that the amount of appetite formed increased with the immersion period. The HA formed an amorphous Mg which promoted the apatite layer on the implant. However, cracks and pit were formed, which was caused by the localised build-up of Cl- and reacted with $Mg(OH_2)$ by-product from the SBF corrosive nature. These problems were the main damage to the HA-pure Mg that can lead to the corrosion of the implant.

Several studies were conducted to evaluate the HA behaviour in the simulated body fluid. Niu et al. (36) used HA coating of method sol-gel dip-coating technique on the AZ31 type of Mg-based. The result showed stabilised alkalisation behaviour and improved corrosion. It was due to the reduction of H_2 evolution rate and decreased corrosion current densities in the AZ31-Mg. This test was conducted in the simulated body fluid. The coating delayed the corrosion process initiation by Mg, and further reduced the corrosion process. Zhu et al. (37) soaked the sol-gel samples in SBF for 180s before corrosion electrochemical measurement. The cracks and pits became smaller after the immersion with dense HA particles on the substrate. Xu et al. (46) demonstrated after the immersion in SBF for 7 days, there were some cracks developed on the HA coating. This is due to SBF being absorbed into the pores of the HA and Mg during the immersions, resulting in a loose corrosion product layer of $Mg(OH)_2$ with minor CaP precipitates from the HA by-product. Amaravathy et al. (29) discovered that covering the sample with HA using the sol-gel dip-coating technique improved the contact angle and immersed it in SBF liquid. The H_2 evolution indicated that the coating could delay the entry of corrosive metal ions in the human microenvironment had a greater calcium/ phosphate (Ca/P) ratio, resulting in increased bioactivity and bone formation. Also, a mechanical test revealed that the bonding strength between the HA and Mg implants utilising the sol-gel technique was improved.

Also, Tosun et al. (47) improved the dip-coating sol-gel method through two additional steps in ($Ca(NO_3)_24H_2O$) hydrolysis in an acidic-based medium. The hydrolysis of this precursor began with the ($Ca(NO_3)_24H_2O$) dissolving in methanol (CH_3OH). This CH_3OH acted as a homogenising agent since the precursors were not liquified in water. Followed by the addition of ($(NH_4)_2HPO_4$), the study found improvement of sol-gel HA-Mg in the mechanical and corrosion properties as compared to uncoated Mg. Rojaee et al. (38) sintered the HA powder at a temperature ranging 400°C and 600°C before coating with Mg using an electrochemical sol-gel technique. They found that an increase in crystallinity of HA nanopowder was caused by the increased sintering temperature. The HA coating on the surface of Mg however shown a rougher surface, provides good biological fixation to the surrounding tissue. The corrosion current density of the coated sample was 2.83±0.04 μA/cm^2, which indicates a lower corrosion rate. Fan et al (41) evaluated the combination between prepared a HA–methylcellulose composite coating on the surface of AZ31Mg using a sol-gel technique. They found that the optimum composite coating was around 60 μm improved the biodegradation property of the sample effectively. However, after 48h of immersion, there were cracks formed on the surface of the HA implant, nevertheless, HA coating showed a corrosion current of 5.6704 x10^{-5} A/cm^2. To slow down the degradation of Mg and improve the bioactivity, Tang et al. (42) evaluated the effect of depositing the HA particle on the AZ31 Mg alloy. The coatings were created by immersing the coupon into the HA solution at a rate of 3 cm/min and ageing it for 30 minutes at 60°C before heating it to 200°C and 400°C for 30 minutes. The bonding strength of a coating improved from 8.7 MPa (room temperature) to 20.5 MPa after 400°C of heat treatment. However, cracks formed on the surface of the HA coating caused by the elimination of water and organic content. Shen et al. (43), also conducted a similar work by using a bioglass–ceramic coatings on magnesium alloy through sol–gel dip-coating. The samples were then heated at the temperature range of 350–500°C., thus leading to the highest bond strength of 27.0 MPa for the sample heat-treated at 450°C. The dense coating matrix provided good protection for the underlying sample by establishing high interfacial adhesion between HA and Mg.

The corrosion resistance of Mg that coated by HA precursor using phosphate-buffered saline (PBS) was also evaluated by Cabeza et al. (48). The Mg samples were immersed in the PBS solution that consisted of sodium chloride (NaCl), potassium chloride (KCl) and potassium phosphate (KH_2PO_4) for 24h at pH 7.4 to restrain the additions of H_2 ions. After 122 hours of exposure, the pH value increased steadily from 7.4 to 9.2. However, in the first 5 hours, H_2 levels increased and then plateaued. After 24 hours of immersion, the volume of H2 emitted from Mg coated with HA precursor was reduced. The corrosion rates were found to be stable and moderate. The reduction corrosion rate was related to phosphate deposition on the $Mg(OH)_2$ surface as a result of the barrier between implant and solution.

CONCLUSION

Pure Mg implants are currently developed and applied in various medical trials attributed to their biocompatibility and non-toxicity with compact bone. Pure Mg has appropriate Young's modulus to the skeletal bone and can form bone-implant contact by improving a fracture fixation. Mg is easy to corrode. Numerous in vivo animal model studies have validated that beneficiary results of pure Mg on bone remodelling can revolutionise the treatment of bone disease or fracture in patients. The findings are summarised below: -

- The Mg has a high tendency to corrode in the human microenvironment corresponds to the production of $Mg(OH)_2$ and H_2 gas.
- The corrosion resistance of Mg can be improved by deposition of HA on the implant as HA has the same crystallinity structure of anatomical bone and promotes callus development at fracture locations.
- The ideal sol-gel HA coating works as a barrier to prevent corrosion of the sample was around 5 to 6 μm.
- The bonding strength between HA and Mg samples can be enhanced by heat treatment at temperatures ranging from 300°C to 450°C.
- The H2 evolution rate of the Mg sample coated with HA was 0.5mm/years, indicating better corrosion resistance.

By identifying the chemical, physical, and biological limitations of pure Mg, appropriate Mg-based implants shall be expanded for numerous clinical indications apart from fracture fixation. This study has established translational potentials and the application of pure Mg orthopaedic implants to enhance patients' well-being from fracture fixation and osteoplasty. Currently, the sol-gel generated bioglass–ceramic HA coating may push biodegradable Mg beyond its existing limit in bone tissue engineering due to its favourable bond strength and strong corrosion resistance

ACKNOWLEDGEMENTS

The authors would like to express their appreciation to the Ministry of Higher Education (MOHE) for Fundamental Research Grant (FRGS) Scheme FRGS/1/2020/TK0/UTM/02/59 and Universiti Teknologi Malaysia for supporting this research through the Geran Universiti Penyelidik (GUP) UTMFR Scheme Q.K.130000.2656.21H13, and Tier 2 Scheme Q.K.130000.2656.17J66.

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