Biocompatibility and degradation study of magnesium alloys: a review

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Abstract

Metallic materials like stainless steel, Co-based and Ti alloys are being used as biomedical implants. The problem of stress shielding and metal ion releases exhibits with these metals, which affects biocompatibility and corrosion behaviour of implants. Also, the secondary removal surgery is one of the biggest reasons behind the exposure of the body to the toxic contents. This leads to the development of biodegradable metallic biomaterials which eliminates secondary surgery to remove the implant. Magnesium (Mg) as a trace element of human body possesses excellent properties to be a biodegradable medical implant like low density and young's modulus, good biocompatibility and Osseo-integration, also it is non-toxic in body fluids. Magnesium alloys also having good mechanical properties reliable to bear body loads. In this review, the effects of alloying elements and surface treatment such as coating on corrosion behaviour of Mg alloys are summarized which describes the degradation rate and biocompatibility. This study reveals that the degradation rate can be controlled by reducing the corrosion rate with the help of proper alloying and surface coatings and the biocompatibility can be improved as well.

Keywords: Alloying, biocompatibility, biodegradation, coating, Mg alloys

Introduction

The development of new biomaterial requires the creation of healthier, reliable and cheaper alternatives that are required to fulfil the critical therapeutic requirement for human injured or ill tissues. To allow for healing, broken bones must remain firmly fixed to prevent micro-movements even under the impact of substantial forces. The implant must be highly biocompatible as inflammatory diseases can irritate bone repair. In load-bearing applications, metallic implants are favoured due to their superior strength and fracture toughness. The metallic biomaterial's currently approved and commonly used includes stainless steel, titanium alloys, cobalt chromium alloys and iron alloys. These have good resistance to corrosion to ensure body's long-term structural stability. Such implants, however, may be causing permanent physical irritation, chronic inflammatory responses or releasing toxic elements if they remain in the body for a long time[1]. In addition, as compared to the biological tissue which they replace, the materials exhibit distinct mechanical properties. One of the biggest problems is difference between elastic modulus of traditional implant and the fractured bone tissue which induces stress shielding in the bone, interferes with bone turnover, contributes to bone loss and likely leads to secondary bone fracture [2]. Also these traditional materials are non-degradable. A second surgery is required to remove implants for short-term applications, like bone fracture fixation or scaffolds that helps to support bones during healing. This second surgery raises discomfort, risk of recovery and medical costs for the patients. The development of biodegradable implants for the treatment of complex bone fractures has thus become one of the focus areas of research into biomedical materials. Such implants should degrade at a rate that is conducive to tissue healing, preferably decreased strength and stiffness, in line with the increase in tissue load-carrying capacity and preserve mechanical integrity until the tissue is completely healed [3].

Magnesium (Mg) as biodegradable implant

A successful biodegradable implant is one that correlates between corrosion rate and bone healing rate, mechanical properties are sufficient to give necessary support during healing period, degrades completely in the body environment when the implanted bone is completely healed. The mechanical properties of magnesium (Mg) and its alloys thereof are similar to human bones. In the body environment, Mg is an essential non-toxic factor and degrades completely [4]. Mg and its alloys have been identified as a new class of biodegradable metallic materials and growing attention has been given to orthopedic applications as a possible matrix material [5]. For temporary implant applications such as bone plates and screws in orthopedics, and stents in cardiovascular implant logy they attracted special interest for various reasons:

i Particularly because of its corrosion susceptibility in aqueous solutions, Mg and its alloys have a natural biodegradability in particular if they contain chloride ions. Mg alloy implants degrade more rapidly in physiological conditions compared to Fe and its alloys [6].

ii Mg has excellent biocompatibility. Mg ions (Mg^{2+}) released during implantation and degradation are used in daily metabolism, and no critical toxic limits or side effects for Mg^{2+} ions have been reported to date [7].

iii In comparison to the elastic modulus of traditional metallic materials such as stainless steel (~200 GPa), cobalt-based alloys (~230 GPa) and titanium alloys (~115 GPa), the elastic modulus of Mg (40–45 GPa) matches with the modulus of natural bone (3–20 GPa), thus reducing the stress shielding effect [8].

iv Mg alloys are remarkably lighter weights with density varying from 1.74 g/cm^3 to 2.0 g/cm^3, which is much smaller than that of, for example, biomedical titanium alloys (4.4–4.5 g/cm^3) and similar to that of natural bone (1.8–2.1 g/cm^3) [9].

Magnesium degradability and biocompatibility in body environment

Corrosion of Mg and its alloys in aqueous solution is an electrochemical phenomenon and degradation mechanism of Mg in aqueous solution is:

$$Mg\,(s) + 2H_2O\,(l) \longrightarrow Mg(OH)_2\,(s) + H_2\,(g)$$

which produces hydrogen and magnesium hydroxide. A soluble magnesium hydroxide film forms a marginally effective protective layer to the Mg surface that prevents corrosion in body fluids. If the chlorides presents in a concentration above 30 mmol/L in the corrosion medium, magnesium hydroxide is converted into magnesium chloride ($MgCl_2$):

$$Mg(OH)_2 \text{ layer:} \quad Mg(OH)_2 + 2Cl^- \longrightarrow MgCl_2 + 2(OH)^-$$

The highest concentration of chlorides (~150 mmol/L) is found in physiological environments, which results in production of highly soluble magnesium chloride that reduce the effective protection from more corrosion. As the Mg alloy surface has to expose to this kind of physiological environment again and again, this increases the corrosion rate. Many methods to calculate the corrosion rate are shown in table 1. The pH value of media that surrounded Mg surface increases with the generation of H_2 and OH^-. In addition to a number of inorganic materials, body fluids contain organic elements like bio-molecules, proteins, cells, and even bacteria, which may adsorb or adhere to the Mg surface and thereby influence the dissolution behaviour. Proteins and other organic molecules that present in blood create a protective coating on Mg implants surface, which slows down corrosion. With time proteins may first inhibit and then accelerate degradation rate of Mg alloys [10].

New Mg alloys with reduced corrosion rate and better mechanical strength are needed because of rapid degradation of pure Mg alloy, for this various alloying elements like Zn, Ca, Al, Zr, Sr, Li, Sn and Rare Earth (RE) are being used to develop new Mg alloys. Cell viability or biocompatibility is adversely affected by high concentration of Mg2+, OH– and ions of alloying elements, which are released due to rapid degradation of Mg alloy implants. One of the useful methods to check the cell/biomaterial interactions is cell culture [11], [12]. If the cell viability reduces by more than 30%, then, according to ISO 10993-5:2009, it is considered as a cytotoxic effects.

Table 1: Various methods to calculate corrosion rate [13]

Weight Loss	Volume Loss	Ion Release Rate	Hydrogen Evaluation Rate	Potentiodynamic Polarization
$CR = 8.76 \times 10^4 \Delta W / At\rho$ Here, **ΔW** is weight loss, **t** is exposure time, **ρ** is material standard density, **A** is the original surface area	$CR = 8.76 \times 10^4 \Delta v / At$ here, **ΔV** means volume loss, **t** is exposure time of sample in solution, **A** is the original surface area	$CR = cV/St$ here, **c** is the concentration of ion released, **t** is exposure time of sample in solution, **S** is the original surface area in contact with corrosive media, **V** means the volume of immersion solution	$PV = nRT$ here, **P** means atmospheric pressure (Pa), **T** is temperature (K), **V** is the volume of H_2, **R** is the universal gas constant (J/mol.K), **n** stands for the amount of gas (mol)	$CR = K (I_{corr}/\rho) m_e$ here, **I_{corr}/ρ**means current density, **m_e** is equivalent mass, **K** is 3.273×10^{-3} mm g/(μAcm a)

Magnesium degradation and biocompatibility

High corrosion or degradation rates, hydrogen gas evolution, poor mechanical integrity and toxicity of the alloy elements that affect the functionality of Mg alloy implants are the major challenges for Mg alloy implants. Although the performance of biodegradable implants with Mg-alloy is difficult, controlled composition and metallurgy of the Mg implant alloy, surface treatments, mechanical working, optimised geometry and implant design can be improved. Mainly the challenges are inclusion of Poor mechanical Integrity, Hydrogen evolution rate, fast degradation, biocompatibility , low ductility etc whereas with these many opportunities for Mg-alloy implants are lies with the mechanical work on implant and samples, alloying may improve their characteristics, surface treatment can enhance the properties and moreover with the selection of proper machining with its optimization parameters [11] .

Performance of Mg-alloy based biodegradable implants can be improved through suitable alloying with controlled composition, mechanical working, modifying the surface characteristics and optimal machining process. Alloying plays the most important role in biodegradation, biocompatibility and mechanical properties of biomedical magnesium alloys [14]. In the past decade, a substantial amount of *in vitro* and *in vivo* work has been carried out on considerable novel magnesium alloys, such as Mg–Ca, Mg–Zn–Ca, Mg–Mn–Zn and Mg–Nd–Zn–Zr, for the purpose of biomedical applications[15], [16]. In Mg alloys, the use of alloys such as alloys, Al, Ca, Li, Mn, Y, Zn, Zr and RE will dramatically increase the alloy's physical and mechanical properties. It is advisable to use the alloy elements in the human body or showed positive results on regeneration and treatment of the tissues such as calcium, zinc (Zn), strontium (Sr) and zirconium (Zr) to prevent or minimise cytotoxicity or adverse reactions of tissues in implant materials [17].

The effect of essential and most keen alloying nutritional elements with their properties such as calcium (Ca), zinc (Zn), manganese (Mn), strontium (Sr) zirconium (Zr) is described in Table-2 and 3.

Table 2- Effect of alloying elements in biodegradable Mg alloys [2]**,** [18]

Alloying element	Role
Calcium (Ca)	Bones contain 99.5% of the total calcium in human body. It improves corrosion resistance and Grain refinement; maintain necessary level of bone mass to support the structures of the body.
Zinc (Zn)	More than 85% of Zn is present in the muscles and bones. It improves yield stress, reduces hydrogen gas evolution during bio-corrosion and helps to overcome the harmful corrosive effect of iron and nickel impurities that might be present in the magnesium alloy.
Manganese (Mn)	It is beneficial for healthy bone structure, bone metabolism and helps to create enzymes for the bone formation. It helps in grain refinement and improvement in tensile strength and corrosion

	resistance of Mg.
Strontium (Sr)	Strontium is an important element in the human body helps in increasing bone mass and reduces the incidence of fractures. It also improves corrosion resistance and grain refinement.
Tin (Sn)	Tin can encourage the synthesis of proteins and nucleic acids, which are crucial for the growth of bone. It improves compressive strength and corrosion resistance.
Silver (Ag)	Silver improves tensile strength of Mg alloys. It also helps in improving Antibacterial effect. But silver has less corrosion resistance.
Rare Earth elements (REE's)	REE's are yttrium (Y), lanthanum (La), gadolinium (Gd), neodymium (Nd) etc. Yttrium (Y) addition results in increasing ductility but decreases corrosion resistance and biocompatibility. Neodymium (Nd) improves cell adhesion and improves biocompatibility. Lanthanum (La) and Gadolium (Gd) improves the corrosion resistance of Mg alloys.

Table 3: Properties of some biodegradable alloying elements [19], [20]

Elements	Quantity in human beings	Level of blood serum	Quantity in human blood	Quantity in human bone	Daily allowance
Mg	25 g	0.73-1.06 mM	900 µmol/L	1.7 mg/g	0.7 g
Mn	12 mg	< 0.8 µg/l	5.67 µg/l	Nil	4 mg
Ca	1100 g	0.919-0.993 mM	1300 µmol/L	353.3 mg/g	0.8 g
Zn	2 g	12.4-17.4 µM	6.42 mg/L	67 mg/Kg	15 mg
Si	1-2 g	9.5 µmol/L	< 44 µg/g	Nil	< 204 mg
Zr	< 250 mg	Nil	Nil	Nil	3.5 mg
Fe	4-5 g	5.0-17.6 g/l	45-50 mg/cm^3	91 mg/Kg	10-20 mg
Li	Nil	2-4 ng/g	0.004 µmol/L	Nil	Nil
Sr	0.3 g	0.17 mg	3 µmol/L	0.287 mg/g	2 mg
Y	Nil	< 4.7 µg	Nil	Nil	Nil
REE's	Nil	Nil	Nil	Nil	Nil

Recently, a modification of the surface has proved to enhance the corrosion efficiency of Mg alloy implants by a method that offers resilient barriers against the body [15]. Compared to alloy design, multifunctional surfaces are less expensive, versatile and possible toxic alloy elements are removed. For biologically degradable Mg-based implants, it is simply the objective of surface modification to regulate their degradation and increase their biocompatibility of surface areas, but not to permanently alter surface properties, which could lead to a loss of tissue degradation or toxicity.

Biocompatibility:

Implants of mg alloy degrades rapidly due to which OH-, Mg2+ and alloying element ions are exposed with fast concentration that oppositely effects the biocompatibility or viability of the cell. Interaction of biomaterial or a cell determined by the cell culture method [21]. As per ISO10993-5:2009, if the viability of the cell decreases greater than 30% than it is counted as cytotoxic effect [22]. If the alloying elements are added in uncontrollable concentration or out of adequate limit than it causes toxicity and disturb the ordinary molecular functions of proteins, DNA and enzymes [23]. So, it's essential to obtain the requirement of implantation materials which should be non-toxic in the environment of the human body[24]. Different effects caused in corrosion response due to the existence of extra amount of mg. In the formation of bone mg plays an important role. The interfacial power of implants increased as a result of the existence of mg in Hap (hydroxyapatite) along with aluminium oxide (Al_2O_3). Mg is contemplated as non-toxic and biocompatible [25], [26].

The bulk of bone mineral make up by the biological apatite which is an important factor in the formation of new bone and in the formation of biological apatite magnesium plays an essential role [27], [28].Mg is also known for its positive effect on the bone strength and gentleness [29]. For the purpose of implantation, mg must have good mechanical properties, corrosion resistance and should be non-toxic. Due to these conditions less numbers of compatible elements remain which gives corrosion or mechanical profits when alloyed with magnesium. Two elements may be the most biocompatible are Zinc (zn) and calcium (ca) [30].

Surface Treatment:

Biodegradability of Mg and its alloys makes it a promising candidate for implants, but low corrosion resistance and rapid degradation rate are still the bottlenecks in its use as biomedical material. It is because Mg is more prone to corrosion in chlorine-containing fluids; and body fluids are similar to these. Recently surface treatment has been quoted as a cost effective approach to optimize corrosion resistance along with biodegradability and biocompatibility [31], [32]. A number of coating techniques are developed to achieve desired characteristics of Mg alloys and are also currently in service. Various coating preparation techniques for Mg alloys are shown in Table 4.

Table 4: Classification of Coatings according to the preparation method [33]

Physical Coatings	Chemical Coatings	Mechanical Coatings	Biological Coatings
Magnetron sputtering	Chemical Conversion	Shot Peening	Bio-mineralization
Laser Cladding	Micro Arc Oxidation (MAO)	Friction or Attrition	Molecular Recognition
	Mechanical Attrition Enhanced Electro-less Plating		
Electric Field Assisted Chemical			

Conversion			
Electron Beam	Thermal Treatment		
Ion Implant	Electro Deposition		
Diffusion Treatment	Layer-by-layer Assembly		
	Electro-less Plating		

On the ground of the chemical nature and atomic structure of materials used, coatings can be categorized as metallic, polymer, ceramic and composite coatings as shown in Table 5.

Table 5: Classification of Coatings according to the materials used [34]

Type	Material	Coatings
Metallic Coatings	Titanium	Titanium oxide, Titanium dioxide (TiO_2)
	Zinc	Zinc oxide (ZnO), Zinc fluoride (ZnF_2)
	Calcium	Calcium oxide (CaO), Calcium fluoride (CaF_2), $Ca_3(PO_4)_2$
	Magnesium	Magnesium oxide (MgO), Magnesium fluoride (MgF_2)
	Rare Earth Elements (REEs)	Cerium (Ce conversion coating), Neodymium (Nd diffusion coating), Lanthanum (La coating), Niobium (Nb coating)
Polymer Coatings	Synthetic Polymers	PLA (Poly lactic acid), PCL (Polycaprolactone) PLGA [Poly(lactic-*co*-glycolic acid)] PLLA (Poly-l-lactic acid) PCUU [Poly (carbonate-urethane) urea] PEUU [Poly (ether-urethane) urea]
	Natural Polymers	Chitosan, Alginate, Collagen, Chitin
Ceramic Coatings	Hydroxyapatite (HA)	Strontium doped HA, Nanostructured HA, Micro-arc oxidation nanostructured HA
	X-phosphate films	Calcium phosphate (Ca-P), Zinc phosphate (Zn-P), Zinc-calcium phosphate (Zn-Ca-P), Magnesium phosphate (Mg-P), Strontium phosphate (Sr-P)
	Bio-glass	Mesoporous 45S5 bioglass-ceramic, Bioglass ceramic cement (BGCC)
Composite Coatings	Composed of any two materials;	Combined calcium phosphate and calcium silicate

	composite + composite	
	polymer + polymer	Chitosan and Poly(styrene sulfonate)polyelectrolyte Multi-layers,
	Polymer + composite	Hydrothermal deposited calcium phosphate and polyarcylic acid

Discussion and findings

From the literature review, it is summarized that biodegradable magnesium alloys have great potential to be used as orthopedic implants and biomedical applications. These alloys have good biocompatibility, low cytotoxicity and high osseo-integration along with excellent mechanical properties (low density, high specific strength, and modulus of elasticity comparable to that of bone). Despite these characteristics magnesium alloys has poor strength in as cast condition with high degradation rate. The corrosion rate of these alloys is also uncertain. Due to high degradation rate and corrosion it degrades before complete healing. A result of this leads to loss of mechanical properties and biocompatibility. With suitable alloying and surface treatment such as coating the performance of biodegradable Mg-alloy implants can be improved. The use of trace human elements or elements that exists in the human body is beneficial for tissue regeneration and healing. These elements like Ca, Zn, Mn, Sr and Zr etc. are also non-toxic in body environments

Summary and conclusion:

Mg has proved to be an excellent choice for biomedical applications because it possesses properties similar to human bone, degraded completely in physiological environment, high biocompatibility and helps in bone formation. Mg also avoids the need for a second surgery to remove implants in orthopaedics through complete degradation in body fluids. Still with these benefits Mg and its alloys are not being used successfully in biomedical applications yet, because of its fast corrosion or degradation rate, which gives rise to hydrogen evolution rate and deteriorates mechanical properties. Alloying and surface coating are methods being used by researchers to overcome these problems. Alloying of Mg with non-toxic and trace elements help in improving corrosion and mechanical properties offering reasonable biocompatibility. Surface coating slows down the degradation rate of Mg alloys and facilitates increased mechanical properties and maintains implants till proper healing.

Alloying of Mg with Al has widely been studied by researchers, which improves mechanical strength and corrosion resistance of Mg implants but it is toxic in nature. To prevent this toxicity Mg and Al can be alloyed with other elements which help in maintaining corrosion and mechanical properties without sacrificing biocompatibility. Ca, Zn and Mn help in tissue regeneration and bone healing as they are human trace elements. Some elements increase cell viability and biocompatibility when alloyed with Mg; such as Sr and Zr. Alloying with REEs also improves mechanical properties like ductility and strength of Mg but their biocompatibility is still questionable, so further research is needed.

Surface treatment is an impressive technique to control the rapid loss of mechanical properties, hydric bubble concentricity, corrosion rate, etc. manufacturing methods straight impact sub-surface and surface properties of the bi-metallic materials and also impact the fatigue life and the bio functionality of the bio-medical implants. Surface coating is another promising method to control corrosion rate and mechanical properties. The coating helps to improve the surface structure of Mg alloys which minimizes the degradation rate and in a result reduces the loss of mechanical properties. A number of coating techniques like chemical conversion coating, MAO, ECD, ion implantation etc. is being used presently. But the need of an optimized degradation rate is still there because the coating degraded in physiological environment and makes Mg to expose in body fluids, this leads to excessive hydrogen evolution. Phosphate coating like Ca-P, Zn-P and Ca-Zn-P coatings are widely used for Mg alloys. The combination of alloying and surface coating could be an excellent option for biomedical implants because alloying tackle the hydrogen evolution, corrosion problems and enhance biocompatibility; then coating helps to control the degradation rate of Mg alloys.

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