



Review

Biodegradable Mg alloys for orthopedic implants – A review

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Abstract

The last decade has seen a significant growth in the market for alloys used for implants, especially for those intended for orthopedic implants. Research into biodegradable magnesium-based alloys has made great strides in this period, so huge progress has been made in their use in the medical industry. The important factors that led to the intensification of research in this regard, were social but also economic, wanting to improve the quality of life, by reducing the use of conventionally permanent metallic implants (stainless steel, cobalt-based alloys, and titanium alloys) which involve the second implant removal surgery and other undesirable effects (stress shielding and metal ion releases), with a negative impact on the emotional and physical condition of patients, and by significantly reducing the costs for both the patient and the health system in the field of orthopedics. This paper refers to the impact and importance of biodegradable Mg alloys, reviewing the beginning of their development, the significant characteristics that make them so desirable for such applications (orthopedic implants) but also the characteristics that must be modulated (corrosion rate and mechanical properties) to arrive at the ideal product for the targeted application. It highlights, in detail, the mechanism and aspects related to the corrosion behaviour of Mg alloys, electrochemical characterization techniques / methods, as well as strategies to improve the corrosion behaviour and mechanical properties of these types of biodegradable alloys. The means of optimization, the category and the effect of the alloying elements, the design criteria, the requirements that the implants of biodegradable alloys Mg-based must meet and the aspects related to their efficiency are also presented. Finally, the potential applications in the specialized clinics, as well as the final products currently used and made by important prestigious companies in the world are approached.

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1. Introduction

Many people suffer bone fractures every year caused by accidents or diseases. Most of these fractures are too complex to be resolved by external medical treatment, which is why they must be surgically fixed by implants. Traditional methods of osteosynthesis or osteotomy use for fixing the bone, permanent metal implants, such as screws and plates made of steel or titanium alloys, which are then excised. This is especially necessary in young, growing patients. Usually,

permanent metal implants are removed after one or two years from the first operation. Trauma is generally, after heart problems, the most expensive medical treatment reaching ~ 56 billion dollars annually in the US alone [1,2]. Of these, bone fractures consume ~ \$ 32 billion, annually. Bone is the organ that undergoes the most grafts/transplants and is estimated to be over 3 million such surgeries worldwide each year. For this reason, the efficiency and quality of bone fracture treatments is both important for patients (physical and mental condition) and at the same time, it is a priority for doctors and, in general for the health system and from an economic point of view. Human bone is a living tissue, and next to the skin it could self-heal following a fracture or even trauma. Healing of bone fractures (from trauma, surgery or congenital) is a complex mechanism composed of anatomical, biological, and

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biomechanical processes, through which mechanical forces are essential for the process of bone regeneration.

Recent orthopedic surgery depends heavily on the development of biomaterials used to fix fractures and replace joints. Biomaterials contribute significantly to improving the health and well-being of mankind. Human bodies are often susceptible to painful injuries, such as sprains, dislocations, and fractures. The risk of fracture is affected by age, sex and bone strength and pre-existing conditions, except for accidents. Most fractures are caused by excessive external forces and are classified as traumatic fractures. Orthopedic biomedical materials can be implanted in or near a bone fracture to facilitate healing or to compensate for the lack or loss of bone tissue. Traditionally, in the case of permanent metal implants, once the fracture has healed, they are surgically removed.

In the case of using biodegradable implants, which dissolve in the human body, their elimination after the convalescence period of the fractured bone is no longer necessary. This ensures a considerable benefit for both patients and the public health care system in terms of costs. To fix bone fractures, temporary metal implants will increasingly replace permanent osteosynthesis materials, especially in the field of low-volume implants. These implants will temporarily take over the function of the bone for an efficient mechanical stabilization until, after a gradual degradation, they will be replaced by the newly formed bone tissue. The process of making biodegradable metal implants (Mg based) is a complex problem because it combines both engineering and medical requirements for the material [2–4].

Mg-based metal alloys are currently the new generation of biodegradable metal materials with a good osseointegration property. Compared to other metallic materials used as orthopedic implants such as titanium and titanium alloys, stainless steels or cobalt-chromium alloys, magnesium alloys are distinguished by their low elasticity, like that of human bone, which prevents the negative effect of stress-shielding in bone structure. Moreover, Mg biomaterials and their alloys are currently mainly used as temporary implants, degrading completely in the biological environment (*in vivo*), being replaced by newly formed bone, thus eliminating the need for surgical re-intervention to remove the implant, which is necessary for permanent implants after 10–15 years. This feature makes them extremely attractive for the market of biodegradable metal implants, for bone repair applications that require temporary support. However, there is a shortcoming, in the biological environment they degrade rapidly, thus requiring a rigorous control of the corrosion rate that is in accordance with the repair/healing processes of the affected bone tissue. The rapid corrosion process involves other consequences for the implant such as loss of mechanical properties, as well as for the biological environment, through toxic effects due to side reactions and accumulation of corrosion by-products. Thus, there are major implications in the medical cost of the operation, but also in the health of the patients. Therefore, in such applications it is necessary to improve the corrosion resistance of Mg alloys.

2. Brief history on Mg and Mg alloys for medical applications

The history of magnesium (Mg) began when it was first recognized as an element in 1755 by the Scottish physician and chemist Joseph Black. In 1808, the British chemist Sir Humphrey Davy isolated Mg from a mixture of magnesium (MgO) and mercury oxide (HgO). The first metallic samples of magnesium, made on an industrial scale, were marketed for use in pyrotechnic and photographic applications, around 1862 [5].

In 1878, Dr. Edward C. Huse successfully used Mg threads to stop bleeding vessels in a radial artery and varicocele surgery. After the treatment of several patients, Huse noticed that the threads degraded slowly, and the time for complete degradation was dependent on the size of the Mg thread used [5].

In 1892, the Austrian physician Erwin Payr implemented versatile clinical applications and reported progress in the field of biodegradable Mg implants [5]. Two of his publications around 1900 suggested that the water content of tissues, dissolved salts in the blood and the chemical processes of cells were responsible for Mg corrosion *in vivo* [5]. A few years later, the Belgian orthopaedist Albin Lambotte extended *in vivo* experiments performed on rabbits and dogs to human clinical studies [6]. The supplier for Payr's experiments was the Austrian company I. Rohrbeck, which produced filaments, plates, and wires of pure Mg, among other forms. However, this company was not the "pioneer" in marketing Mg products. In 1886, a German aluminium and magnesium plant built a facility to produce Mg by electrolysis of molten carnallite (MgCl₂ to KCl·6H₂O). Ten years later, Griesheim-Elektron company further developed the process and became the world's leading manufacturer until 1916 [5]. In 1937, the British company Magnesium Elektron Ltd., still in existence, began large-scale production of Mg. In the first half of the twentieth century, Mg alloys were introduced into orthopedic and traumatic surgery [5], and good biocompatibility was observed in clinical trials [7,8]; however, the rapid degradation resulted in a large amount of hydrogen accumulated as subcutaneous gas bubbles. This problem has interrupted the investigation of Mg and its use as a biomaterial in medical applications [5,9]. Soon after, a new type of stainless steel introduced in the 1920s replaced the preferred Mg alloys as orthopedic implant materials. At the same time, however, Mg and its alloys continued to be used in a wide range of structural and non-structural (non-medical) applications, including equipment for the automotive, material handling and aerospace industries [10]. Currently, Mg alloys are considered valuable for structural applications due to their low weight, good strength, and rigidity, both at room temperature and at high temperatures.

In 1948 a standardized system was adopted indicating the name of the alloy and the working temperature [10]. In general terms, the system operates by indicating the two main alloying elements, the amount of the two main alloying elements and the temperature conditions, e.g., only manufactured

(processed) or heat treated. With the advanced equipment of that time and the alloying knowledge available at that time, Mg regained its interest as a metal implant in various medical applications.

In the first half of the last century, degradable metal implants made of magnesium alloys were introduced in orthopedic and traumatic surgery.

Researchers such as Witte [5,7], Xu et al. [11,12] and Staiger et al. [13] resumed the study of Mg alloys as biodegradable implant materials. Since then, magnesium alloys with aluminium and zinc (AZ) have been among the most studied due to their commercial availability. An important result of the experiments was that these Mg alloys degrade *in vivo* depending on the composition of the alloying elements [7]. Consequently, Mg alloys have been produced with a low corrosion rate due to the addition of alloying elements including rare earths [7]. However, efforts are being made to elucidate how the local environment and the modification of the implant surface influence the corrosion mechanisms of Mg alloys, both *in vitro* and *in vivo*.

In 1945, the first two positive results of bone fracture repair/healing were reported by Znamenskii He used Mg alloy with 10% Al, and 6 months after the bone graft, the implants were not detected in the fracture area [14]. In 1972, Stroganov et al. used Mg alloy implants with additions of rare earth elements. The alloy consisted of 0.4–4 wt.% rare earth metal, 0.05–1.2 wt.% cadmium, 0.05–1.0 wt.% calcium or aluminium and 0.8 wt.% additions of manganese, silver, zirconium, or silicon. The author reported a slow degradation of this complex alloy, within 5 to 10 months, by *in vivo* tests, but there is no reference to the distribution of trace elements or various complications [15]. From 2001 to 2005, Witte et al. studied the *in vivo* degradation of Mg alloys (4 types) - with aluminium and zinc (3% Al + 1% Zn and 9% Al + 1% Zn) and, respectively, with rare earth elements (4% Y + 3% Nd, Ce and Dy, and 4% Li + 4% Al + 2% Ce, La, Nd and Pr. Microtomography showed a degradation of the alloy in 18 weeks after surgery, with a significant increase in bone formation compared to the control group (polylactide rod). The authors proved that the slowest corrosion rate was for the alloying of Mg with Li and Al as alloying elements, Moreover, the alloying elements were observed in the corrosion layer next to a layer of amorphous calcium phosphate and were not observed in adjacent bone tissue [16].

In 2015, Jingbo Wang implanted Mg-Zn-Zr alloy cylinders in the femoral condyles of Japanese white rabbits. In 24 weeks, the implant showed some corrosion, but also an increase in bone density of the surrounding compact bone. Micro-CT analysis confirmed that new bone tissue (on the surface of the residual alloy implant) grows during the 12th to 24th week after implantation. In general, the gas produced by the degradation of the Mg-Zn-Zr alloy can cause cavitation inside the bone, without affecting the osteogenesis around the Mg alloy [17].

Pan et al. developed new magnesium alloys such as Mg-2Sn-1Ca (wt.%) coded (TX21) and Mg-2Sn-1Ca-2Zn, coded (TXZ212), respectively, with high strength and ductility, pro-

duced by casting, homogenization, and indirect extrusion. They consider that these high values of resistance are due to the high value of density of the nano phases of MgSnCa, as well as to the ultrafine granulation ($\sim 0.8 \mu\text{m}$) [18]. J. Hofstetter investigated the effect of impurities on the degradation behaviour of ZX50 (Mg-5Zn-0.3Ca) high-strength Mg alloys. The author demonstrated that although in small quantities, these impurities increase the rate of degradation, predominantly in the initial testing period, and increase the susceptibility of the material to localized corrosive attack. These effects are explained based on the corrosion potential of the intermetallic phases present in the alloys [19]. Zhou et al. developed extruded alloys of the Mg-1Mn-2Zn-xNd ($x = 0.5, 1.0, 1.5 \text{ wt.}\%$) type. The experimental results showed that all Mg-1Mn-2Zn-xNd extruded alloys have a good ductility and a much higher mechanical strength than pure cast Mg, as well as natural bones. The tensile and elongation strengths of extruded alloys increase with increasing neodymium content. Compressive strength does not change significantly with increasing neodymium content. Extruded alloys have good biocompatibility and a much higher corrosion resistance than pure Mg [20]. However, the ideal Mg alloy for degradation rate, *in vivo* behaviour and satisfactory mechanical strength is not yet reported. In this context, researchers and clinicians should collaborate and realize that to achieve successful medical applications made of Mg biodegradable alloys, they need specific knowledge and meticulous/interdisciplinary approaches.

3. Characteristics of biodegradable products based on Mg

Magnesium is considered the best alloy in the 21st century, being the lightest structural metal. Lately, magnesium alloys have been intensively studied extensively worldwide. Only in the period 2000–2019, there was an increase in research on Mg alloys of 491%, so that magnesium became the most common structural metallic material in the world [21].

The density of Mg is 1.738 g/cm^3 [22] and its melting point is of approx. $650 \text{ }^\circ\text{C}$. Due to its light metal quality, magnesium is often used for products where weight is an important parameter, i.e., in the automotive and aircraft industries and the electronics sector.

Recent studies pay special attention to magnesium-based alloys for medical applications because they are lightweight materials (its density is close to that of cortical bone $1.75\text{--}2.1 \text{ g/cm}^3$) [23], have mechanical properties close to those of human bone and are biodegradable. The last aspect is extremely important for surgical applications. Although there is a considerable international effort to research and develop Mg-based alloys, corrosion rates are still difficult to control and relatively high. This causes the implant to degrade too quickly, so that its mechanical properties deteriorate before the newly formed bone can take on the necessary mechanical load, such as body weight. At the same time, the generation of hydrogen, which accompanies the process of rapid biodegradation, can be intense [24], with undesirable effects

on the body. For Mg alloys with Zn, Al, and Mn as alloying elements, the H_2 evolution rates reported in the research work [25] is $0.01 \text{ ml/cm}^2/\text{day}$.

To reduce these processes, several solutions have been proposed, such as improving the quality of the surface with the corresponding reduction of roughness, modifying the implant surface with plasma, alloying, and using new additives or new compounds, covering the implant surfaces, and using technologies that allow the modification of the microstructure of the material. It was found that inclusion of alloying elements such as Al, Mn, Ca, Zn, and rare earth elements improve the corrosion resistance of Mg alloys and the surface modification is a promising approach to improve the performance of Mg-based biomaterials for orthopedic applications [26].

It is desirable that implants made of biodegradable Mg alloys, temporarily inserted into patients' bodies, corrode completely so that patient's exposure to treatment with these implants is beneficial and short-lived. In the cast state, it was shown that pure Mg has *in vitro* degradation rate of 407 mm year^{-1} [27]. It is important that the corrosion process of the Mg implant takes place at a low speed, to allow the remodelling of the bone at the same time as its degradation.

Gas embolism is another disadvantage for Mg bioresorbable alloys because it is related to the danger that hydrogen gas released during the corrosion process of biodegradable Mg implant can penetrate the bloodstream and cause serious medical problems. In addition, as the production of hydrogen gas bubbles can impede the good connectivity of osteocytes, interfered with the initial cortical bone healing process, resulting in callus formation and cortical defects [28–33].

The most advantages of temporary magnesium alloys are the attractive biodegradability, biocompatibility, and their good mechanical properties [10,11,34,35]. The first finding [36] that proves that Mg and its alloys should have biocompatibility *in vivo* was inferred from the fact that mass gain occurs through the reaction of Mg with the constituents of the human body. The authors of the research work [34] considered Mg to be biocompatible, showing that it increases the rate of bone formation. Another advantage of Mg is its high damping capacity, having the ability to absorb the energy of any metal that can be used for load applications [25,37]. Mg is the lightest workable metal structure, and the stable final dimensions are easy to achieve [38]. Consequently, complex shapes are easy to obtain, which is essential for the often-complicated shapes that are needed for medical applications [39–41].

Compared to the biodegradable polymeric materials used in osteosynthesis, Mg has a higher resistance and a good strength to weight ratio ($\sim 130 \text{ KNm/Kg}$) [37].

Mg orthopedic implants have the elastic modulus close to that of bone while the fracture toughness of magnesium is greater than of ceramic biomaterials. However, the implant must support its load without any deformation [42].

The advantages and disadvantages of Mg alloys used as biodegradable implants are presented in Fig. 1.



Fig. 1. Characteristics of biodegradable Mg alloys: advantages and disadvantages.

Compared to permanent metal implants, the effect of stress shielding, effect that results from the difference in stiffness/Young's modulus between implant and bone and which diminishes the healing process, bone growth and implant stability, can be reduced or even avoided by using Mg-based metal implants. Young's modulus for the magnesium products (41–45 GPa) is closer to that of human bone (3–20 GPa) than to other permanent implanted materials, such as those made of stainless steel (190–205 GPa), Ti (110–117 GPa) and Co-Cr alloys (230 GPa) [43]. Moreover, in the case of the use of permanent implants, even though they are essentially passive materials and do not harm the human body, the release of toxic materials by wear can occur, which can lead to inflammatory reactions. The physical and mechanical properties for different implants in compare with the natural bone are presented in Table 1 [43,44], and their advantages and disadvantages are shown in Fig. 2.

Many of the fractures must be surgically fixed through internal bone implants, such as the orthopedic implant. Permanent commercial metal implants, in the form of screws or bone plates, are made of titanium alloys, stainless steel and cobalt-chromium. Thus, for permanent metal implants currently used in surgical practice there are currently two major challenges, the effect of stress shielding and respectively, “the surgery itself”. First, permanent metal implant materials are too rigid (Young's modulus, 100–200 GPa) compared to adjacent spongy bones (Young's Modulus, 10–30 GPa) [45]. In this situation, the internal load will be supported mainly by the metal implant whose purpose is to protect the adjacent bone tissue from the usual mechanical stresses. This “protective” effect results in several critical clinical problems, such as early weakening of the implant, deterioration of the fracture healing process and adjacent anatomical structure, and even chronic inflammation. Second, metal implants should be removed 1 or 2 years after the first surgery. Therefore, another surgery is needed with all the personal, medical, social, and economic consequences and costs. Under these conditions, biodegradable metal implants, which dissolve in the human body, are an ideal solution for major challenges related to the effect of stress shielding and, respectively, for the surgery itself.

Table 1

Physical and mechanical properties for different metal implants compared to natural bone [43,44].

Material	Density (g/cm ³)	E(GPa)	Compressive strength(MPa)	Fracture toughness(MPa•m ^{1/2})
Natural bone	1.8–2.1	3–20	130–180	3–6
Mg	1.74–2.0	41–45	65–100	15–40
Ti Alloy	4.4–4.5	110–117	758–1117	55–115
Co-Cr Alloy	8.3–9.2	230	450–1000	–
Stainless steel	7.9–8.1	189–205	170–310	50–200
HA Synthetic	3.1	73–117	600	0.7
PLA	1.25–1.29	2.2–3.3	–	–

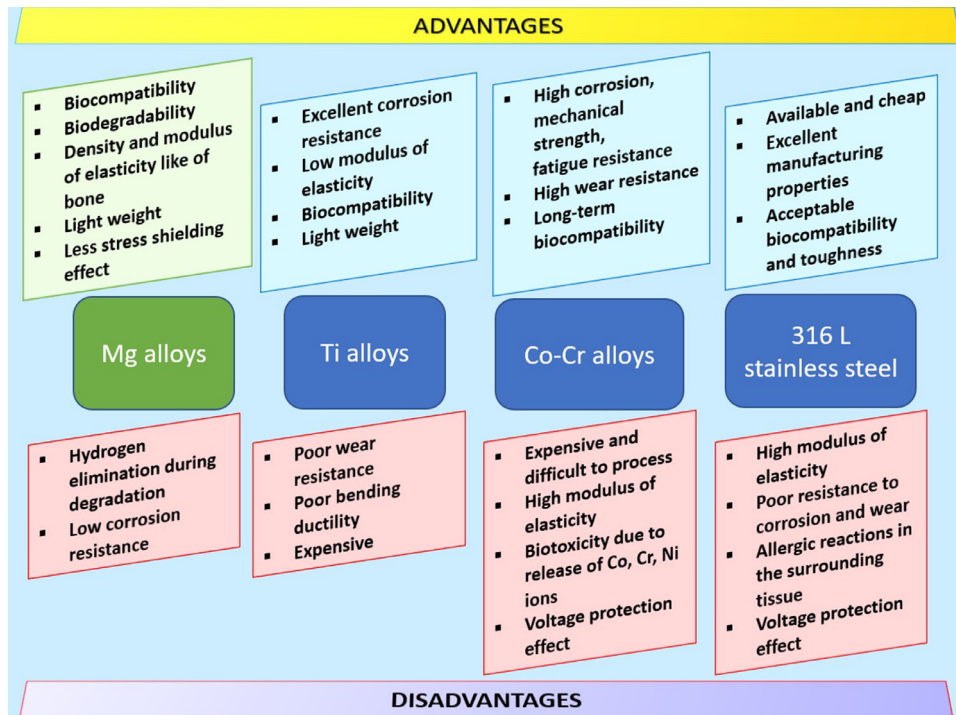


Fig. 2. Characteristics of biodegradable Mg alloys compared to other metal implants: advantages and disadvantages.

Table 2

Mechanical parameters and degradation rate for pure metals of Fe, Zn, and Mg used for medical applications, compared to steel [27].

Material	Yield Strength, [MPa]	Tensile Strength, [MPa]	Elongation [%]	Degradation rate (<i>in vitro</i> tests)[mm/an]
Hardened steel, 316 L SS	190	490	40	–
Pure Fe, hardened	150	200	40	0.16
Pure Zn, cast	17	20	0.2	0.2
Pure Mg, cast	20	86	13	407

For medical applications, as metals/biodegradable implants, three metals (iron, zinc, and magnesium) are generally used as basic elements [46]. The main characteristics compared to similar steel products are presented in Table 2.

Iron is an interesting candidate for biodegradable materials/implants due to its mechanical properties. It has a high radial resistance due to the high elasticity. This can be useful in the manufacture of thin-walled materials. Iron also has a high ductility that can be useful during implantation when the material is plastically deformed. The first biodegradable metal stent was made of Armco® iron (Fe > 99.8%) and implanted in the descending aorta of white rabbits in New Zealand in 2001 [47,48]. Surgical results showed no significant evidence

of inflammatory response and no systemic toxicity. However, due to the slow rate of biodegradation (0.16 mm/year) and the ferromagnetic nature of pure Fe, problems arose when these materials were used as implantable devices [49]. The addition of a small percentage of Mn resulted in an increase in the degradation rate to 0.44 mm/year, however, insufficient for large-scale applications.

Zinc-based alloys can also be promising candidates for biodegradable implants. The main advantages of molten Zn-based metal alloys are low melting point and reactivity. Therefore, they can be made by simple melting, gravity, or die-casting in air, or by hot forming [50]. Zinc alloys did not show local or general toxicity or other biological compati-

bility [51]. However, a major disadvantage of pure zinc (as a potential biodegradable implant) is that it has low strength and plasticity.

Magnesium, on the other hand, serves this purpose best; it plays an essential role in the body's metabolism and is eliminated from the body within a few days after degradation [51]. Because it has an extremely low potential of a standard electrode (-2.37 V), magnesium can be gradually dissolved and adsorbed after implantation in the human body. The Mg^{2+} ions produced are absorbed by the surrounding tissues or eliminated by the fluids of the human body. Magnesium alloys are biocompatible, osteoconductive and biodegradable materials used in restorative bone surgery due to biodegradation, natural bone-like elastic properties and osteosynthesis capacity.

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 [27]. For biomedical applications, these impurities must be strictly controlled so that they are below the limits of toxicity.

4. Corrosion and corrosion mechanisms for Mg alloys

For materials used in bone tissue repair or replacement, metal implants continue to play a key role in clinical surgery due to their high mechanical strength and breaking strength. They are more suitable for applications with mechanical stress, compared to ceramic or polymeric ones [52]. Furthermore, current permanent metal implants must be removed by a second surgery after the tissues have healed sufficiently, and at the same time, they may release toxic metal ions and/or particles by corrosion or wear, as the corrosion rate in the physiological environment of metal implants is so great that their degradation takes place before the end of the healing process.

In general, degradable implants have the advantage that a second implant removal operation is not necessary, thus saving costs for the health system and bringing benefits to the patient. In addition, degradable implants are also recommended in cases of paediatric surgery, a situation in which the body is still in a process of growth, and permanent implants should be changed to suit the period of growth. Moreover, the healing and remodelling process of the affected tissue is stimulated by degradable implants due to the gradual transfer of load from implant to tissue, as illustrated in Fig. 3.

The basic electrochemical character of magnesium, with a standard potential of -2375 volts leads to a low corrosion resistance. Usually, the surface of magnesium implants passivates and creates a thin layer of magnesium oxide when exposed to air, preventing further chemical reactions.

However, magnesium is significantly attacked in saline environments, such as the biological one in the human body. These characteristics mainly allow the use of Mg alloys as resorbable implants [53]. Mainly, magnesium reacts with water (abundant in body fluid) and produces hydroxide and hy-

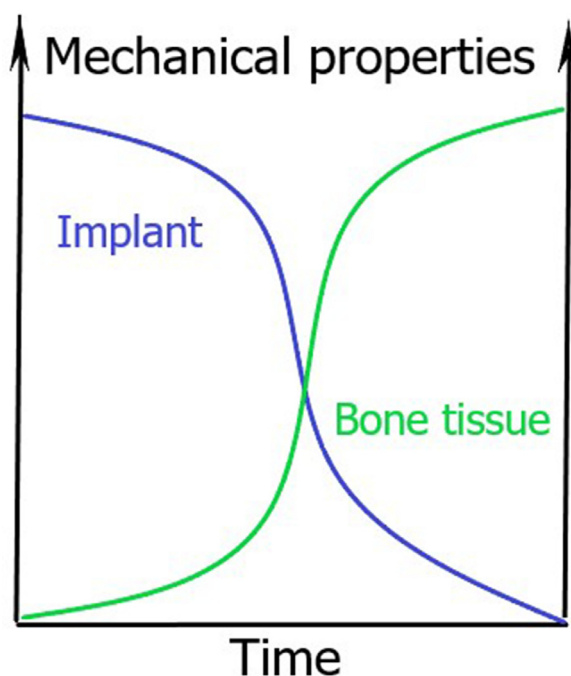
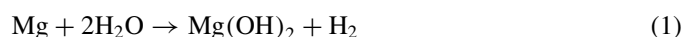


Fig. 3. The ideal diagram representing the evolution of the implant over time (reduction of mechanical strength by degradation) simultaneously with the healing process of bone fracture.

drogen according to the reaction:



In environments with high pH (> 11.5), magnesium hydroxide will act as a stable protective layer on the surface of magnesium implants, but at low pH (< 11.5) it will facilitate the corrosion of magnesium alloys in the aqueous solution [54]. Because the local pH at the implant-bone interface is approximately 7.4 or even lower, due to secondary acidosis resulting from metabolic processes and post-surgery resorption processes [7], the magnesium hydroxide layer cannot cover the implant surface. Therefore, constant exposure to the high chlorine electrolyte in the physiological system causes accelerated corrosion on the Mg implant surface *in vivo*.

Corrosion is generally an undesirable phenomenon in engineering applications, as it results in the degradation of material properties. In the field of biomedical applications, however, biodegradable implants are of considerable interest: they not only protect patients from a secondary operation to remove the permanent implant, but also eliminate the long-term negative effects on the implant. Magnesium is an attractive biodegradable material due to its high strength and biocompatibility. Its degradation, however, is accompanied by the elimination of hydrogen, which can create problems in some biomedical applications.

Hydrogen released during the degradation of the metal implant of Mg in aqueous solutions, and the increase in pH because of the corrosion process could subsequently irritate the damaged tissue. The hydrogen gas around the implant disappears over time or can be removed by a puncture, which can be “uncomfortable” rather than harmful [55]. Despite the

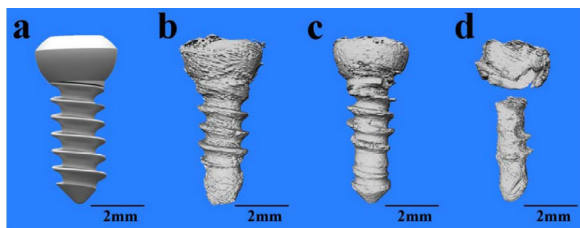


Fig. 4. Microphotography of the biodegradation process of the Mg implant in its initial state (a) and 3D images reconstructed after 1 (b), 4 (c) and 7 (d) months, after implantation [61].

relatively high degree of corrosion, magnesium has a positive influence on the biological process of bone growth [56]; as it degrades, it releases Mg ions essential for human metabolism and is known to provide stimulating effects on the generation of new bone tissue [57]. For such advantages, Mg-based materials are recommended for biodegradable orthopedic implants and vascular stents [58]. For different Mg alloys, respectively 3D structures, the biodegradation kinetics can be controlled both by the nature of the alloying metals, and by different mechanical processing and coating processes [59].

4.1. Potential negative biological effects of the corrosion process

The biodegradation process of magnesium and its alloys will increase the pH in the environment/ tissues in the immediate vicinity of the implant. If the local pH exceeds 7.8, alkaline poisoning can occur, leading to local toxic effects. During the process of biodegradation of magnesium, hydrogen is released in the form of gas bubbles, causing suspicion of tissue necrosis. At the same time, the hypothesis of gas embolization in vital organs was issued. The rapid release of ions from the alloy can lead to pathological changes in the ionogram, with negative systemic effects and influencing the function of vital organs.

The cause of corrosion processes of metal alloys, used as medical implants, was the instability of metals from a thermodynamic point of view, these having the tendency to return to the initial state of metal compounds.

The typical forms of corrosion encountered in the case of magnesium and its alloys used for medical applications are presented below, the most common being pitting corrosion and galvanic corrosion.

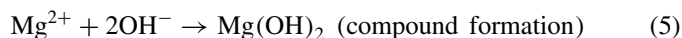
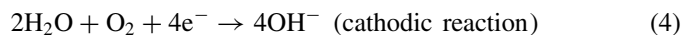
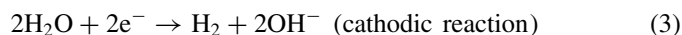
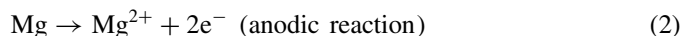
A dynamic of the corrosion process for a biodegradable implant from Mg (screw), visualized with the help of the X-ray synchrotron is presented in Fig. 4. Both the uncovered implant and the one coated with bruised ceramic compound are biocompatible, the *in vivo* degradation rate for the coated implant, after 1; 4 and 7 months, being 0.161 ± 0.075 ; 0.097 ± 0.013 , and 0.218 ± 0.030 mm/year, respectively [60,61]. Mg implants fractions (debris) can damage neighbouring biological matrix or cause inflammatory responses. An example of such fraction can be seen in Fig. 4d (screw head).

From the figure above, it is noticed that, in a first period (1 month) from the implantation, no obvious changes appear; a small volume of loss is noticed after the first 4 months after implantation and an obvious degradation (with disintegration) is noticed after 7 months, from implantation [61].

4.2. The mechanism of the corrosion process

The corrosion process of Mg and its alloys is an electrochemical process, being different in aqueous environment than in air [62,63].

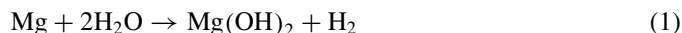
The mechanism of corrosion in the aqueous environment (like the biological environment) is described by the reactions below [[62–64].



The anodic reaction (2) generates a significant amount of H_2 , while the cathodic reaction (4) favours the formation of the hydroxide protection layer, insufficiently resistant, which, through the subsequent polarization anodic reaction, will cause its destruction [65] and thus, a high susceptibility of magnesium and Mg alloys to galvanic corrosion, with serious implications in the manufacturing technology.

The layer of magnesium hydroxide formed on the surface of magnesium alloys, in the human body, will lose its protective capacity under the influence of chlorine ions in the adjacent tissues. When the concentration of chlorides in the environment exceeds 30 mmol/L, magnesium hydroxide $\text{Mg}(\text{OH})_2$ will react with chlorine to form a water-soluble magnesium chloride, thus accelerating the corrosion process [66,67].

These processes are represented by the chemical reactions presented below:



The formation of the MgCl_2 layer on the implant surface will determine a decrease of the corrosion resistance, knowing the moderate character of the solubility of the MgCl_2 salt [66,67], although biocompatible and without obvious cytotoxic effects. On the other hand, the presence of hydroxyl ions increases the alkalinity, which, together with calcium and phosphate ions will precipitate various calcium phosphates as a protective layer on the surface [5,64,68,69].

According to the images in Figs. 5 [3] and 6 [64], the contact with the biological fluid determines the oxidation of the

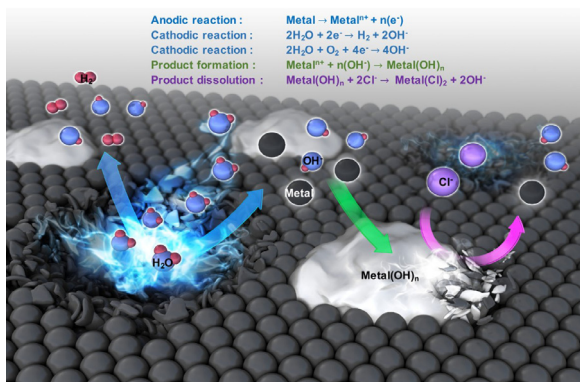
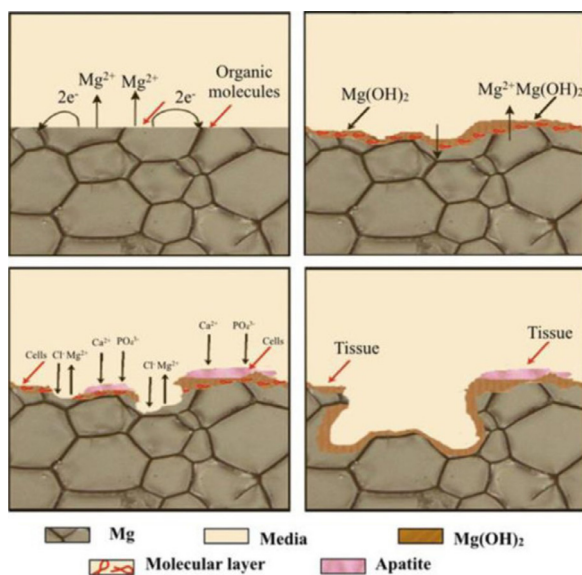


Fig. 5. Mechanism of metal degradation [3].

Fig. 6. *In vivo* degradation mechanism of Mg [64].

metal with generation of electrons, which will be consumed by cathodic reactions and the release of hydrogen gas together with the hydroxide, with the formation of the protective layer on the surface.

4.3. The stress corrosion performance

Mg-based biodegradable materials for implants must have adequate resistance to cracking or fracturing in the human body. For example, an orthopedic implant is subject to load by walking, running and normal body movements. The failure of the implants is due to the combined effect of stress loading and corrosive environment. This phenomenon, known as *stress corrosion cracking* (SCC), occurs below the yield stress [70].

The stress corrosion performance of Mg based implants is studied by many researchers [2,71–76], but many aspects are still unclear.

Generally, the initiation and the propagation of cracks induced by stress corrosion conditions is due to the action of two mechanisms, namely [71, 76–78]:

- anodic dissolution at a film-free crack tip that causes crack extension and further crack propagation, characterized by inter-granular stress corrosion cracking
- atomic hydrogen generated during the cathodic reaction of Mg alloys that can penetrate the Mg matrix and induce cracking, characterized by trans-granular stress corrosion cracking.

According to the research paper [76,77], the SCC of Mg under mechanical loading conditions causes slow and sub-critical crack growth. When the critical crack size is reached, the combination effect of the crack plus the applied load causes sudden and rapid fracture.

SCC is strongly dependent on the passive film behaviour that forms on the surface of the material during corrosion and its stability and coherence is influenced by the characteristics of the material. Chloride ions from the human body fluid can cause localized breakdown of the magnesium hydroxide (Mg(OH)₂) layer, thereby resulting pitting corrosion. The speed of deformation plays an important role in terms of behaviour at SSC by causing the film to break which allows localized dissolution or hydrogen penetration.

Other factors, such as the existence of defects and the chemical composition of the Mg alloy greatly influence the SCC susceptibility of the implants.

The authors of study [70] developed a biodegradable implant alloy based on Mg (Mg – 6% Nd – 2% Y – 0.5% Zr (EW62), by rapid solidification, and demonstrated the positive influence of this process on the improvement of the corrosion resistance, mechanical properties, and SCC behaviour.

The addition of up to 3% Nd to a Mg-5%Zn alloy [71] did not have any substantial influence on the stress corrosion susceptibility due to the surface film stability and by the fact that the secondary phases did not generate any significant detrimental micro-galvanic effect.

According to Kannan et al. [74], the rare-earth elements introduced into Mg alloys, such as EV31A with 0.48% Zn, 2.85% Nd and 0.50% Zr and balance Mg, can improve the SCC significantly. Also, the SCC resistance is dependent both on the existence of other critical elements such as Zn and Ag and on the degree of fineness of the microstructure.

5. Methods for optimizing Mg alloys for medical applications

Mainly, the optimization of a Mg alloy for implantology includes aspects related to electrochemical processes (slow and homogeneous degradation), mechanical (high strength and good ductility) but also biological performance (biocompatible, non-cytotoxic).

For a better correlation of the data obtained from the studies with the real requirements of orthopedic implants, it is necessary to test some alloys processed thermally or mechanically. Through these processes, *the refining of the alloy granulation* can be obtained, this leading to superior mechanical properties, the tensile strength being able to be improved by up to 300% [79]. At the same time, the granulation refining

process can lead to a decreased corrosion rate while maintaining mechanical properties for a longer time, and to a minimum release of hydrogen. Another method of technological development of Mg alloys is represented by *surface changes*, in this direction, hydroxyapatite (HAP) or bio-glass coatings can be considered. These will improve corrosion resistance and biocompatibility.

In practice, other modalities are used, such as, reinforcement with ceramic compounds (composites with biocompatible compounds, β -TCP, calcium polyphosphate-(CPP, HAP or hybrid HAP + β -TCP particles), mainly for biocompatibility and microstructural characteristics. Recent studies have shown that ceramic reinforcing additions can increase the mechanical and corrosion resistance properties of Mg alloys [80–83]. Tricalcium phosphate (β -TCP) is a bioactive material that has good biocompatibility and biodegradability. Moreover, the degradation of β -TCP can provide abundant elements of calcium and phosphorus, osteoblasts, favouring the formation of new bone. Nanometric β -TCP particles were added to the Mg-Zn-Zr alloys to improve the microstructure and properties of the extruded Mg-3Zn-0.8Zr alloy, and Mg-3Zn-0.8Zr/x β -TCP composites were manufactured ($x = 0, 5\%, 1.0\%$ and 1.5%). The granulation of Mg-Zn-Zr/ β -TCP composites was significantly refined. The results of the tensile tests indicate that the maximum tensile strength and elongation for the developed composites have been improved by the addition of β -TCP. The result of the electrochemical corrosion test in synthetic solutions SBF (Simulated Body Fluid), shows that properties, such as the corrosion resistance of composites has been greatly improved compared to that of the alloy. The corrosion potential of the Mg-3Zn-0.8-Zr/1.0 β -TCP composite is -1.547 V, and its current density is 1.20×10^{-6} A/cm². Instead, it is known that hydroxyapatite has a composition like that of natural bone and has a low solubility in the physiological environment. Therefore, HAP particles appear to be suitable as a reinforcing material in magnesium-based composites. In previous studies, the magnesium alloy AZ91D showed a local corrosion attack through *in vitro* and *in vivo* experiments [7,84].

In conclusion, magnesium composites reinforced with ceramic powders (β -TCP and HAP) have both improved mechanical and biological properties, which recommends them for medical applications as biodegradable implants. Such composites are already studied and characterized, the experimental results confirm the improvement of mechanical performance, corrosion, and biocompatibility [85–87]. However, it is known that the properties of composites are significantly influenced by the method of elaboration, by the characteristics of the powders and as well as by the microstructure [88]. For example, the mixture of Mg powders (with particle size: $50 \div 250 \mu\text{m}$) and HAP (with particle size: $0.2 \div 0.5 \mu\text{m}$) were used to make composites with 0, 2, 5 and 10% HA.

Another way to control the corrosion rate is to combine magnesium with various alloying metals. *Alloying* is one of the methods in which different metals can be added at different concentrations, to improve the ductility, strength, and

corrosion properties of pure Mg. Improvements in strength and corrosion are primarily related to changes in microstructural characteristics and, particularly, to a reduction in grain size compared to pure Mg. Most research investigating Mg alloys has focused on improving all these characteristics, for commercial purposes. The alloying elements can significantly improve the mechanical properties, control the corrosion rate, and influence the biological response of the Mg alloy. But it is difficult to choose the best alloy, and to do this, more *in vitro* and *in vivo* experiments and clinical investigations are needed. To avoid concerns about potential toxicity, the alloying elements of Mg should be limited to those that have already demonstrated long-term biocompatibility. In fact, the large amount of magnesium and potentially harmful alloying elements released during biodegradation can lead to cytotoxicity, and the degree of toxicity depends largely on the rate of biodegradation.

In Table 3, different types of Mg alloys, representative (tested) compositions and the main alloying elements [89] are presented.

Typical examples of Mg-Al-Zn alloys used are AZ91, AZ31 and AZ63. Compared to pure magnesium, the introduction of Al not only changes the mechanical properties, but also improves the corrosion resistance [90]. In fact, both Mg(OH)₂ and Al₂O₃ will form in a layer of corrosion products made of magnesium alloys containing Al during corrosion. Mg(OH)₂ is slightly soluble in water and can be converted to MgCl₂, soluble with chlorine ions. Unlike Mg(OH)₂, Al₂O₃ is insoluble and cannot be destroyed by chlorine ions. So, the inclusion of Al can increase the corrosion resistance of magnesium alloys. On the other hand, a too high concentration of Al is harmful to the nervous system and osteoblasts, and can be associated with specific diseases such as, dementia and Alzheimer's disease [91]. Therefore, the amount of Al released from magnesium alloys must be carefully controlled.

In vivo studies of the magnesium alloy AZ91D, showed an improved activity of osteoblasts experiments on guinea pigs. No adverse effects on MG-63 cells and human-derived cells (HBDC) were observed in the immersion extracts. Thus, Zn alloying improves the strength and malleability of magnesium alloys [92].

Zn and Ca are both biological elements, and magnesium alloys containing Zn and/or Ca, such as Mg-3%Zn, Mg-1%Zn-1%Ca and Mg-5%Ca have been proposed for the development of biodegradable implants [93,94].

In the Mg-Ca system, Mg₂Ca is the only secondary phase apart from α -Mg, distributed around the grains. In *in vitro* assays, good cell adhesion was observed on Mg-Zn, Mg-Ca, and Mg-Zn-Ca alloys, in direct cell assays [95].

Mn does not significantly affect the mechanical properties of magnesium alloys; however, it improves corrosion resistance by converting iron and other metallic elements into relatively harmless intermetallic compounds. The toxic effect of Mn in magnesium alloys on cell viability and proliferation has also been demonstrated by tests/measurements [72].

Table 3
Biodegradable magnesium alloys and alloying elements [89].

Mg alloy	Formula	Alloying elements		
Pure Mg	Mg			
Mg-Al-Zn	AZ31	3Al	1Zn	
	AZ63	6Al	3Zn	
	AZ91	9Al	1Zn	
Mg-Ca	Mg-xCa ($x = 1, 2, 3, \dots$)	xCa		
Mg-Zn-Ca	Mg-1Zn-1Ca	1Zn	1Ca	
Mg-Zn-Mn-Ca	Mg-2Zn-1.2Mn-1Ca	2Zn	1.2Mn	1Ca
Mg-Si-Ca		1Si	1Ca	
Mg-Zn	Mg-xZn ($x = 1, 3, 6, 10$)	xZn		
Mg-Zn-Mn	Mg-1Zn-1Mn	1Zn	1Mn	
Mg-Mn	Mg-1Mn	1Mn		
Mg alloys with rare elements (RE)	LAE442	4Li	4Al	2RE
	WE43	4Y	3RE	
	ZE41	4Zn	1RE	
	AE44	4Al	4RE	
	Mg-xGd ($x = 5, 10, 15, \dots$)	xGd		
	WZ21	2Y	1Zn	
	Mg-8Y	8Y		

Rare Earth Elements (REE) are a group of seventeen elements, including fifteen lanthanides, scandium (Sc) and yttrium (Y). They are commonly added to Mg alloys as main elements, or to increase the strength of Mg alloys and can improve mechanical strength and corrosion resistance by both solidifying solid solutions and hardening by precipitation [27]. Several Mg alloys doped with REE have been investigated, such as WE43, Mg-5Gd, LAE442 and Mg-4Y [96]. Rare earth elements are used in both Al and Al-free alloys to change the mechanical properties of the alloys, the resorption rate, and the biological response. A balance is needed between possible toxicity and benefits. In MgAl-REE systems, REE tend to form intermetallic phases with Al such as $Al_{12}REE$ and $Al_{11}REE_3$, improving mechanical strength and corrosion resistance [97]. Moreover, REE elements with limited solubility tend to form intermetallic phases in the early stages of the solidification process [98].

The identification of magnesium alloys is standardized worldwide by ASTM standards; each alloy is marked with letters indicating the main elements of the alloy, followed by values (usually two), rounded, of each weight, in percentage. The last letter of each identification number indicates the stage of development of the alloy.

In Table 4, the ASTM codes corresponding to the alloying elements are presented [25,99].

6. Pathophysiology and toxicology of Mg and of alloying elements used for biodegradable Mg-based orthopedic implants

Metal ions released because of corrosion of biodegradable Mg alloys may induce systemic toxicity in humans as well as local toxicity in *in vitro* tests.

Normal serum blood Mg level is between 0.73 and 1.06 mmol/L. Among the multitude of attributions for intracellular physiological functions, Mg is required for adeno-

Table 4
ASTM codes corresponding to the alloying elements [25,99].

Abbreviation	Alloying Element	Abbreviation	Alloying Element
a	aluminium	M	Manganese
B	Bismuth	N	Nickel
C	Copper	P	Lead
D	Cadmium	Q	Silver
E	Rare earths	R	Chromium
F	Iron	S	Silicon
G	Magnesium	T	Tin
H	Thorium	W	Yttrium
K	Zirconium	Y	Antimony
L	Lithium	Z	Zinc

sine triphosphate (ATP) synthesis and is activator of many enzymes. Also, is co-regulator of protein synthesis, and stabiliser of deoxyribonucleic and ribonucleic acids (DNA and RNA) [26].

The implantation of Mg could stimulate new bone growth by increased levels of Mg ions and potentially has an anti-osteoporotic activity. Experimental studies in mice have shown that Mg improves brain activity through short-term synaptic facilitation and long-term potentiation, as well as learning and memory functions [100].

Regarding the toxicological effect of Mg, the disorder in magnesium homeostatics leads to nausea, kidney failure, impaired respiration. The toxic dose at 50% cell viability (TD50) of bone related cells (MC3T3E1 and MG63 cell lines) is 73×10^{-3} mol/L [26]. Because Mg is the most abundant element in the body, it has exceptionally low toxicity, but extensive biological studies are still needed.

The amount of alloying element used to manufacture Mg-based biomedical implants needs to be optimized in terms of corrosion rates and physiological environment in the implantation areas. In general, ions of toxic elements released into the body could be tolerated at an extremely low concentration

Table 5

The effects of the alloying elements in the Mg alloy [25,26,72,100].

Alloying Element	The effect of the alloying process	Pathophysiology/toxicology
Al	Increases hardness, strength, and casting capacity (fluidity), while density increases little.	Normal blood serum level 2.1–4.8 $\mu\text{g/L}$; Established alloying element in titanium implants; Risk factor in generation of Alzheimer's disease; Can cause muscle fibre damage; Decrease osteoclast viability
Ca	Improves thermal and mechanical properties, helps refine granulation and increases elongation resistance; reduces surface stresses.	Normal serum level 0.919–0.993 mg/L ; Most abundant mineral in the human body (1–1.1 kg); Mainly stored in bone, teeth; Is tightly regulated by homeostasis of skeletal, renal, and intestinal mechanism.
Cu	Helps increase resistance to both room temperature and high temperature.	Normal blood serum level 74–131 $\mu\text{mol/L}$
Mn	Increases corrosion resistance in salt water in some aluminium-containing alloys.	Normal blood serum level <0.8 $\mu\text{g/L}$; Essential trace element; Important role in metabolic cycle of e.g., lipids, amino acids, and carbohydrates; Influences the function of the immune system, bone growth, blood clotting, cellular energy regulation and neurotransmitters; Neurotoxic in higher concentration (magnesium).
Ni	Increases both efficiency and maximum force at room temperature. It has a negative impact on elongation and corrosion resistance.	Normal blood serum level 0.05–0.23 $\mu\text{g/L}$; Strong allergenic agent which can induce metal sensitivity; Carcinogenic and genotoxic.
Sr	Increases elongation resistance (used with other elements); increase bone mass and reduce the incidence of fractures.	140 mg in the human body; Neurological disorder
Sn	Improves ductility and reduces the tendency to fracture during processing, when used with Al; Improves compressive strength and corrosion resistance	9–140 $\mu\text{g/L}$, located in higher levels in liver and less toxic; Carcinogenic
Y and Lantanides	Y- increases high temperature resistance and elongation resistance when mixed with rare earth metals; increases the fluidity of alloys when casting. Ce - Improves corrosion resistance; increases plastic deformation capacity and Mg elongation and hardening ratio; reduces deformation strength. Nd- improves the strength of the material.	<47 μg in blood serum level; Substituted for Ca^{2+} and matters when the metal ion at the active site; compound of drugs for treatment of cancer; Basic lanthanides deposited in liver; more acidic and smaller cations deposited in bone
Zn	Improves corrosion resistance when added to Mg alloys (with Ni and Fe impurities); at 2wt% or more, there is a tendency for hot cracking.	Normal blood serum level 12.4–17.4 $\mu\text{mol/L}$; Trace element; Essential for the immune system; Co-factor for specific enzymes in bone and cartilage; Neurotoxic at higher concentrations

below the critical threshold level, while excessive release into the body will have undesirable side effects [101].

It is essential that biomedical implants be designed so that the localized release of metal ions below critical threshold levels can be controlled.

Table 5 summarizes the pathophysiology and toxicology of the common alloying elements of Mg and their effects on mechanical properties [25,26,72,100].

7. Electrochemical characterization of biodegradable alloys based on Mg

Electrochemical testing is simple and reproducible but leads to acceleration of the corrosion process that does not always correlate with *in vivo* degradation [102]. For example, the rate of degradation using the immersion method for pure Mg reported by Zhang S. was 0.26 mm/year, while the electrochemical method showed a value of 2.52 mm/year [103]. The main challenge for corrosion tests is choosing the environment for the experiment. For these tests, solutions that reproduce the *in vivo* conditions, as accurately as possible, must be used. The best test media are Hank Solution, Physi-

ological Fluid (SBF), Earles Buffer (EBSS), or Minimum Essential Medium (MEM). The concentration of ions in SBF is remarkably similar to that of blood, while MEM contains glucose, amino acid and vitamins [104]. In contrast, MEM and EBSS contain a slightly lower amount of Ca and Mg, compared to blood [105]. Using different environments, a lot of valuable results can be obtained. For pure Mg, the corrosion rate measured by immersion in EBSS and reported by Walker J. was 0.39 mm/year [106], while in SBF and Hank solutions it was 1.39 mm/year and 2.05 mm/year, respectively [106]. It is also possible that the rate of Mg degradation increases from 0.25 mm/year in Hanks solution to 1.88 mm/year in SBF [107].

It is noted that not only the test methods and solutions used can influence the rate of degradation. The temperature of the experiment can significantly influence the *in vitro* degradation of the Mg alloy. Mg in its pure state, degrades twice as fast at 37 °C, compared to 200 °C. The same authors show that increasing the temperature up to 40 °C accelerates the corrosion rate by 50%, compared to 370 °C [108]. This finding presents the potential risk of expanding the corrosion of the Mg alloy after implantation, especially during inflamma-

tory processes. The influence of pH solution on Mg corrosion has been described in several publications [106,109,110]. The authors have shown that the use of a buffer system to maintain a constant pH around the material is especially important in terms of adequate experimental results. The non-buffered solution can lead to an increase in pH, to the formation of the protective layer on the surface of the alloy and to a decrease in the corrosion rate. The best buffer solution, like the *in vivo* medium, is the NaHCO₃/CO₂ buffer. It maintains the pH value in a neutral regime and the corrosion process continues [104].

To “copy” the conditions of the *in vivo* environment, a dynamic test is needed. In the static immersion test, a protective layer will form on the Mg surface because the degradation products have not been removed. The latter can lead to changes in the test environment causing corrosion to stop. Authors such as Shi et al. have shown that the degradation rate for AZ31 Mg alloy, under static conditions (0.3 mm/year), is 5 times lower than that resulted in dynamic conditions (1.5 mm/year). Moreover, the dynamic test conditions correlate very well with *in vivo* experiments (1 mm/year) [111].

7.1. In vitro evaluation methods for corrosion and biocompatibility

In vitro tests are a mandatory task in the study of the behaviour of biodegradable magnesium alloys. These must be performed in conditions as physiological as possible, like those in the human body. *In vitro* tests are classified into two main categories: tests that assess the speed and mode of corrosion and tests that assess biocompatibility and toxicity.

7.1.1. In vitro corrosion tests

In vitro corrosion tests performed to determine the corrosion rate of magnesium alloys are realized by immersing them in different media. These vary from simple media, such as saline or Ringer’s solution, to complex media that simulate the physiological conditions of the human body, with values as close as possible to pH, electrolytes, amino acids, or proteins.

The chosen environment and environmental conditions in which the experiment takes place (incubator, water bath) must mimic as accurately as possible human physiological conditions.

The evaluation of the corrosion rate must always consider the type of environment used, which has a major influence on corrosion. For example, if the medium contains chloride ions, the protective layer, Mg(OH)₂ of the magnesium alloy will dissolve rapidly, thus recording an increased rate of corrosion. On the other hand, if the environment contains proteins, they will form a protective layer, decreasing the corrosion rate.

The main corrosion media used are simple ones, such as saline, Ringer’s Solution, Simulated Body Fluid (SBF), Hank’s Solution or more complex media, which also associate organic compounds such as amino acids, or complex molecules, such as vitamins. The most used complex media include [72,79,112]:

- (1) Modified Eagle’s Medium- α (α -MEM) + 10% Fetal Bovine Serum (FBS)
- (2) Dulbecco’s Solution (Dulbecco’s Modified Eagle’s Medium - DMEM).

Alloy corrosion products must be non-toxic, easily adsorbed, dissolved in the surrounding tissue, and disposed of.

Depending on the effects that can be induced, they can be classified as toxic elements, allergic elements, and nutrients, present in fact, in the human body [113]:

- (1) toxic elements: Cd, Be, Pb, Ba, Th
- (2) allergic elements: Al, Co, V, Cr, Ni, Ce, La, Cu, Pr
- (3) nutrients: Ca, Mn, Zn, Sn, Sr.

Non-polarized corrosion tests: Non-polarized corrosion tests are the evaluation of the hydrogen release rate, evaluation of the corrosion rate by determining the weight loss and determination of pH variations [79].

Each of these tests will be presented below.

Evaluation of the hydrogen release rate. During the corrosion process of magnesium alloys, a magnesium atom will release a hydrogen molecule in the form of a gas. Pure magnesium has a H₂ release rate at 37 °C of 40 ml/cm²/day, while the rate of absorption of the human body is 2.25 ml/cm²/day, which leads to the accumulation in the form of bubbles of gas, in the tissues. The test is performed at a temperature of 37 ± 1 °C, to simulate the physiological conditions as accurately as possible. The most used corrosion medium is SBF, but other media such as saline, Ringer’s solution, or more complex solutions such as Hank’s solution and Dulbecco’s Solution can also be used. The volume of hydrogen measured during the immersion of the magnesium alloys is directly proportional to the amount of alloy dissolved by corrosion.

The calculation of the corrosion rate (CR) according to the volume of hydrogen emitted is performed according to the equation [79]:

$$CR = (8.76 \cdot 10^4 \cdot \Delta g) / (A \cdot t \cdot \rho) \quad (8)$$

where:

CR - corrosion rate, Δg - change in weight of the sample (g), A - the area of the initial surface exposed to corrosion (cm²), t - immersion time (h) and ρ - density of the alloy (g/cm³)

Between the volume of hydrogen released in 24 h ($v \cdot H$), evaluated in ml/cm²/day and the weight loss Δw , evaluated in mg/cm²/day, there is a relationship highlighted from the equation:

$$\Delta w = 1.085 \cdot v \cdot H \quad (9)$$

which means that 1 ml of hydrogen released is equal to 0.001085 g of corroded magnesium alloy [79].

Evaluation of the corrosion rate by determining the weight loss. To determine the corrosion rate, a magnesium sample, corrosion medium and a scale with micron units are required.

Corrosion media can range from simple (Ringer, SBF) to more complex solutions such as Hank or Dulbecco. The conditions under which the experiments are carried out must be as close as possible to the physiological ones, the temperature 37 °C, pH 7.4 and an atmosphere with a concentration of 5% CO₂. This method does not provide data on how the corrosion of the alloy occurs but can provide information about the speed with which the corrosion process takes place. The relationship between the mass loss rate (ΔW), expressed in mg/cm²/24 h and the average corrosion rate (P_w), expressed in mm/year, is given by the following equation [79]:

$$P_w = 2.10 \cdot \Delta W \quad (10)$$

The corrosion rate can be evaluated according to the mass loss of the sample, according to the equation [79]:

$$R = W/A \cdot t \cdot \rho \quad (11)$$

where:

R - corrosion rate, W - weight loss, A - the area exposed to corrosion of the initial sample, t - exposure time and ρ - density of exposed alloy.

Determination of pH variations. The release of hydroxide ions (OH⁻) during the corrosion process will lead to changes in the pH of the corrosion medium. The measurement of the pH in the corrosion environment is important to achieve because its value influences the corrosion rate and this, in turn, influences the hydrogen release rate. The measurements performed in the culture media showed differences between the values recorded in the immediate vicinity of the alloy sample and the values recorded at a distance from the sample.

Polarized corrosion tests: Polarized corrosion tests are the potentiodynamic polarization (PDP) measurements and the Electrochemical Impedance Spectroscopy (EIS). Each of these tests will be presented below.

The PDP method is the most widely used electrochemical method for *in vitro* evaluation of the corrosion process of magnesium alloys. This method provides data on how the corrosion process of magnesium and its alloys occurs. It provides information on the corrosion potential (E_{cor}) and the anodic and cathodic reactions that take place on the surface of the magnesium alloy, the latter being the basis of the corrosion process. At the same time, PDP measurements provides at any time, kinetic information about how the corrosion process takes place, information extracted from the intensity of the corrosion current (I_{cor}). A low value of I_{cor} represents a low corrosion rate or an increased corrosion resistance of the magnesium alloy [79].

The polarization characteristics of a sample are measured by the graphical representation of the response current as a function of the applied potential.

Because the response current varies in a range of several orders of magnitude, the representation of the potential as a function of the logarithm of the current (a semilogarithmic representation) is often used. This is known as the polarization curve, which can be anodic or cathodic, when the potential varies linearly at low speeds. Potentials more positive than

Table 6

Conventional scale for assessing corrosion resistance [116].

Resistance group	i_{cor} mA/cm ²	Stability group
Completely stable	< 0.001	4
Very stable	0.001 – 0.01	3
Stable	0.01 – 0.1	2
Low stable	0.1 – 1	1
Unstable	>1	0

E_{cor} give anodic currents, while potentials more negative than E_{cor} give cathodic currents.

A polarization curve obtained over a wider potential range can provide useful information, such as: [114,115]:

- the capacity of the sample to be spontaneously passivated in the environment of interest.
- the field of potential in which the sample remains passive.
- the mechanism of corrosion processes (passivation, localized corrosion, etc.).
- corrosion rate in the passive region [115].

Using the corrosion current density, the polarization resistance and the corrosion rate can be determined according to relations (12) and (13) [114]:

$$R_p = \frac{b_a \cdot b_c}{2.3 \cdot (b_a + b_c) \cdot i_{\text{cor}}} \quad [\Omega] \quad (12)$$

$$v_{\text{cor}} = \frac{i_{\text{cor}} \cdot A}{\rho \cdot z \cdot F} * N_{S_{\text{year}}} \quad [mm/year] \quad (13)$$

where:

R_p - polarization resistance, [Ω]; b_a , b_c - anodic and cathodic Tafel slopes, [mV/dec]; i_{cor} - corrosion current density, [mA/cm²]; v_{cor} - corrosion rate, [mm/year]; A - atomic mass, [g]; ρ - density, [g / cm³]; z - valence; F - Faraday's constant, [C]; $N_{S_{\text{year}}}$ - number of seconds in a year = 3.1536 * 10⁷.

By the method of extrapolating the Tafel lines, a series of electrochemical parameters are obtained, such as: corrosion current density, corrosion potential, polarization resistance, anodic and cathodic Tafel slopes, cathodic and anodic charge transfer coefficients, speed of corrosion.

Based on these parameters, the corrosion behaviour of the material can be estimated, and, at the same time, the material can be classified in a stability group according to Table 6 [116].

The use of the EIS can provide information about the charge transfer processes during the corrosion process, the electronic or ionic conduction in the electrolyte medium, or the charging between two layers. The EIS provides information about the surface impedance of a sample with minimal polarization. The impedance value is inversely proportional to the corrosion rate, thus being able to perform an evaluation of the corrosion process. EIS is a non-destructive process providing real-time information, while being able to identify,

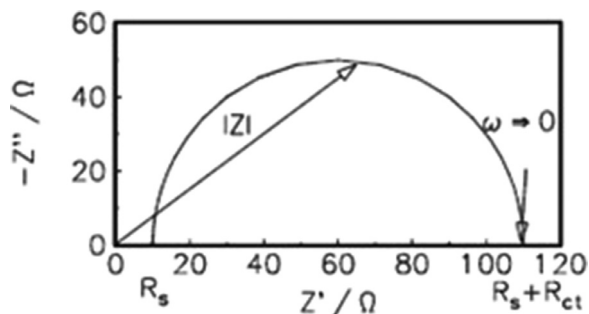


Fig. 7. Nyquist diagram [114].

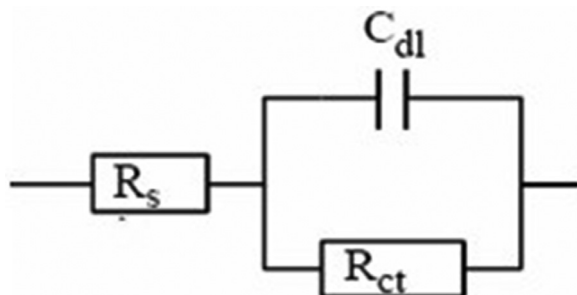


Fig. 8. Equivalent circuit [114].

individually, the layers formed on the surface of the alloys [79].

Unlike methods of investigating the electrode interface based on the application of a variation of potential or direct current (DC) to the working electrode, which lead to the electrode being taken out of steady state and tracking the system response, which is usually a transition signal, another possibility is the realization of the disturbance with the help of an alternating current (AC) signal, of small amplitude and study of the way in which the system responds to it in steady state. Methods using AC are based on the concept of impedance, given that an electrochemical cell can be assimilated with an equivalent circuit comprising resistors and capacitances.

It is generally accepted that the impedance of an interface can be represented by the parallel connection of a capacitor (electric double layer capacity) with an impedance (faradaic impedance), which depends on the electrochemical reactions that take place at the interface [114].

The Nyquist diagram, shown in Fig. 7 is known as the graph of the complex impedance plane, which corresponds to a circuit like the one shown in Fig. 8.

In Fig. 9, the data shown in the Nyquist diagram are represented in Bode format. In this diagram, the absolute impedance $|Z|$ and the phase angle of the resulting wave are represented as a function of frequency.

From the variation curve of $\log |Z|$ depending on the $\log \omega$ (Fig. 9a), the values R_p and R_s can be determined. At intermediate frequency values, the inflection point of the curve should be on a slope line -1 . From the extrapolation of this line to the y-axis ($\log |Z|$) at $\omega = 1$ or $\log \omega = 0$, the value of C_{dl} results. The graphical representation with

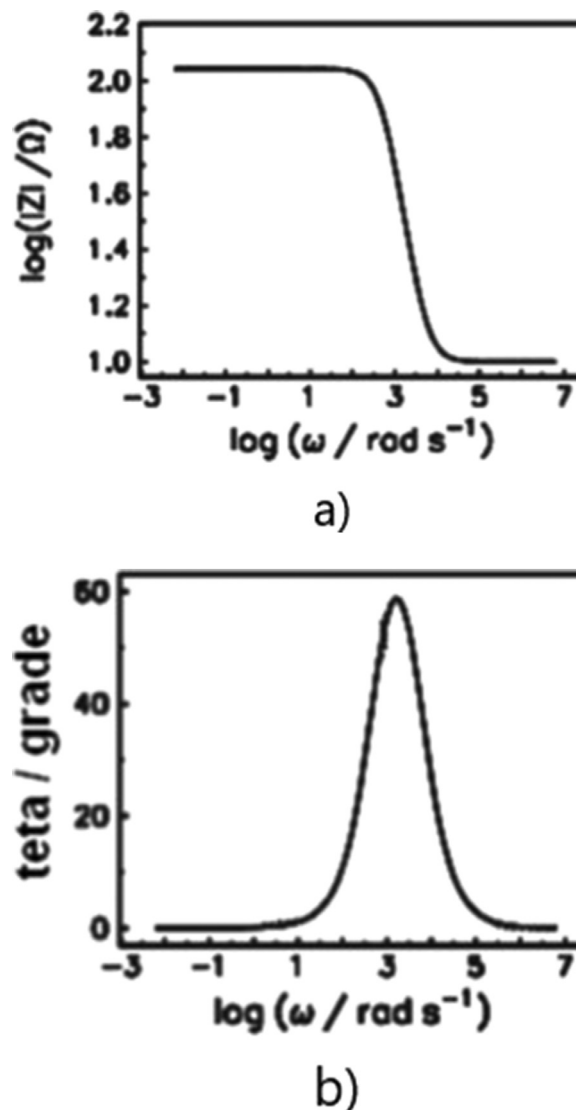


Fig. 9. (a). Bode diagram [114]. (b). Bode diagram [114].

the variation of θ (theta) depending on the $\log \omega$ (Fig. 9b) presents a maximum corresponding to $\omega^{\theta_{max}}$, expressed in rad/sec. At $\omega^{\theta_{max}}$ the phase shift of the response is maximum. At this frequency C_{dl} can be calculated.

The advantage of the Bode diagram, shown in Fig. 9, compared to the Nyquist diagram is that it avoids the long measurement times associated with low frequency R_p determinations, as the diagram allows more efficient extrapolation of data at higher frequencies. A Bode chart is preferable when a true semicircle in Nyquist format is not obtained due to data scattering. The frequency dependence of an electrochemical system is much more clearly described in a Bode diagram than in a Nyquist one [114].

7.1.2. In vitro biocompatibility tests

Cytotoxicity tests: Cytotoxicity is defined by the degree of destruction produced by the studied material in adjacent cells.

According to ISO 10,993–5: 2009, a reduction in cell viability of more than 30% is considered a cytotoxic effect.

Table 7

In vitro and *in vivo* tests of biodegradable magnesium alloys [89].

<i>In vitro</i> tests	<i>In vivo</i> tests
Immersion tests (weight gain, weight loss, corrosion ratio).	Surgical procedure.
Electrochemical tests (Tafel polarization, EIS).	Radiographic evaluation.
Volume change testing.	Fluorescence observation.
Hydrogen removal test.pH change test.	Routine pathological examination.
Cell culture (attachment, morphology, proliferation, cytocompatibility and alkaline phosphatase activity).	Immunohistochemistry.
Bioactivity tests (SEM-EDX, XRD, AAS).	Microstructural study by SEM, EDS, XPS and XRD analyses.
	Analysis of the concentration of magnesium ions in the blood.

Cytotoxicity can be studied either by *in vivo* assays, evaluating the changes produced in the tissues adjacent to the implant or by *in vitro* assays performed on cell culture lines. The cell lines used must be as similar as possible to the cells with which the implant will interact in the human body. The tests require cell cultures maintained in conditions as close as possible to physiological ones. The cultures will be prepared and maintained in a humid environment, at 37 °C and an atmosphere with a CO₂ concentration of 5% and a humidity of 95%. Depending on how they are performed, cytotoxicity tests can be of two types: direct or indirect. In the case of *direct tests*, the cell cultures are placed in direct contact with the magnesium alloy sample, which is immersed in the cell culture medium. For *indirect tests*, it is necessary to obtain an extract from the alloy sample, an extract that will be put in contact with the cell line, these being the most used tests. In current practice, the most widely used cytotoxicity tests are *the MTT colorimetric assays*, which use (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium) and *the XTT*, which uses (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide). The two tests are based on the reduction reaction of tetrazolium salts to formazan, coloured, under the action of cellular metabolism [79].

In vivo tests: To be used in human orthopedic surgery, an implant must be safe and effective. *In vivo* tests, on laboratory animals, are the level that follows the *in vitro* tests, subjecting the obtained results to validation in the context of the biological activities of a living organism. Small animals such as mice, guinea pigs or rabbits, the latter being the most used, or large animals: dogs, cats, sheep, may be used for *in vivo* testing. For bone tests it is recommended to use mature animals, in which bone growth has been completed. In Table 7 [89], the test methods and the main tests performed are briefly presented.

8. Potential biomedical applications of Mg alloys.

Current market trends

Magnesium-based screws have been used in clinical trials to heal/repair bone defects without noticeable side effects, as reported by patients [117,118]. The first commercial magnesium screws (Magnezix, Syntellix, Hannover, Germany) were available in 2013 and their disappearance was

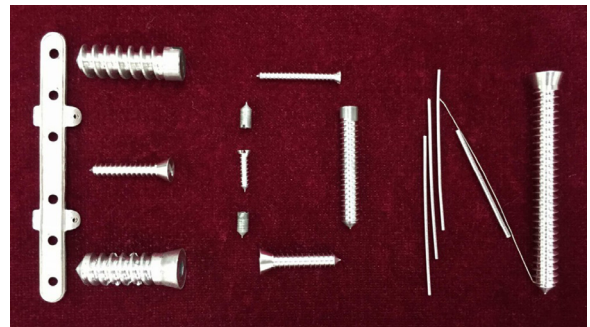


Fig. 10. Various types of biodegradable metal implants with clinical applications [4].

found one or two years after implantation [119]. Furthermore, an additional interference bolt made of MgYREZr alloy (Milagro, DePuy Mitek, Leeds, United Kingdom) was recently introduced on the market [120]. The transient appearance of radio-translucent areas around magnesium implants has been reported [121].

Vascular stents made of magnesium alloys, with low corrosion rates, have been shown to be mechanically stable for up to 6 months in animal experiments, and have finally been evaluated in clinical trials [122,123]. Drug-controlled, polymer-coated biodegradable stents made by the Swiss company Magmaris and DREAMS, Biotronik AG, 231, Bülach, have been marketed and clinically tested, demonstrating a resorption efficiency of up to 95% over a year [124]. Both orthopedic and vascular magnesium implants appear promising, but, except for small orthopedic implants, such as bolts or screws, development is still in its infancy and wider clinical applicability needs to be demonstrated [121,125]. Examples of clinical applications are shown in Fig. 10 [4].

Recently, a new type of Mg-Nd-Zn-based alloy (Jiaoda BioMg, called JDBM) was developed at Shanghai Jiao Tong University [126], using molecular dynamics simulation but also experimental results. In this series of alloys, neodymium was selected as the main alloying element along with Zn and Zr as microelements. Nd is one of the elements in the category of rare earths which, although showed some cytotoxicity, their alloys (Mg-Nd binary alloys) have shown a significant increase in mechanical properties [127] and a decrease in the process of galvanic corrosion. Zn is one of the essential nutritional elements in the human body, which increases the duc-

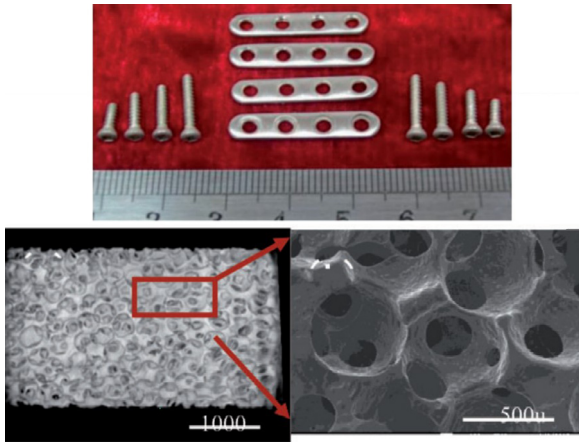


Fig. 11. Various bone implants made of JDBM-1 alloy (rods, screws, and porous 3D structures) [131].

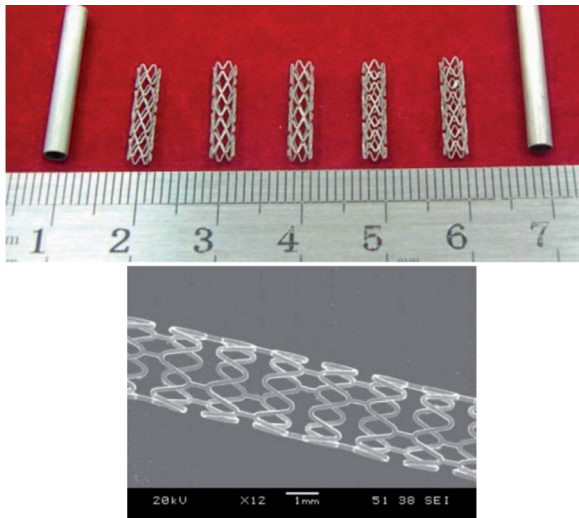


Fig. 12. Various cardiovascular stents made of JDBM-2 alloy [131].

tility and deformability of the Mg alloy. A variety of bone implants were made of JDBM-1 alloy, making bone plates, screws and even 3D porous structures for bone tissue, Fig. 11, and from the JDBM-2 alloy (with high ductility and moderate resistance), the cardiovascular stents were made, Fig. 12.

The first clinical research on magnesium alloys for medical applications found that they were too fragile, had limited mechanical properties and degraded too quickly. As a result, the use of magnesium alloys in medicine has almost been abandoned. But, under the influence of technological developments and new types of high purity magnesium alloys with superior mechanical and corrosion performance, interest in medical applications of biodegradable magnesium-based alloys, marked by the studies of Heublein et al. in the period 2000–2003 [128].

Currently, several orthopedic implants and not only magnesium-based implants are already in clinical use. As shown in Figs. 13 and 14, adsorbent metal stents (AMS) made of materials such as WE43 and modified Mg-based alloys,

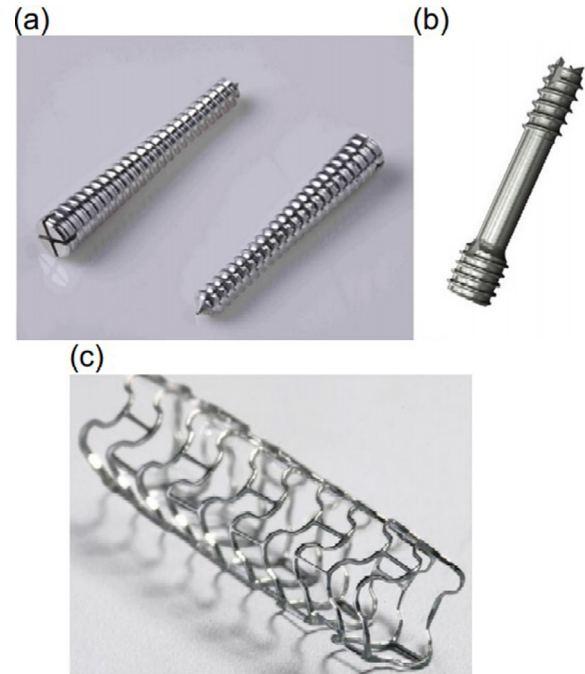


Fig. 13. Commercial implants based on Mg alloys: (a) orthopedic devices; (b) MAGNEZIX® tightening screws, Syntellix AG, Germany, (c) AMS® cardiovascular stent, Biotronik, U.S.A. [125].

and MAGNEZIX type screws, are currently used in medical applications as orthopedic devices [125,129–131].

Although remarkable progress has been made in recent years in the development of magnesium-based biodegradable alloys, a series of fundamental challenges still need to be addressed for medical applications.

The range of medical applications of Mg-based alloys is still limited due to the high rate of degradation and rapid formation (because of degradation), usually in the first week after surgery, of hydrogen gas bubbles [132,133].

Ideally, an implant made of these metals retains its mechanical integrity during the required healing period, progressively corroding, as it is shown in Fig. 15. The fundamental research of bioresorbable metals focuses in three major directions: (1) analysis of metal toxicity both *in vitro* and *in vivo*, for the biocompatibility study; (2) improving the mechanical properties of metals by designing alloys (compositional) and by metallurgical processes; (3) control of corrosion behaviour, by modifying the substrate or surface, by coating and other surface treatments.

The new resorbable metals are expected to gradually corrode *in vivo*, generating an adequate host response, and then dissolving completely by healing the tissues [102]. The family of absorbable metals includes iron, magnesium, zinc, and their alloys. In a recent publication, iron-based stents have been reported to demonstrate good long-term biocompatibility when tested on animals [134]. Magnesium alloy stents have been clinically tested in humans and have shown a desired safety profile, continuously, for 24 months,

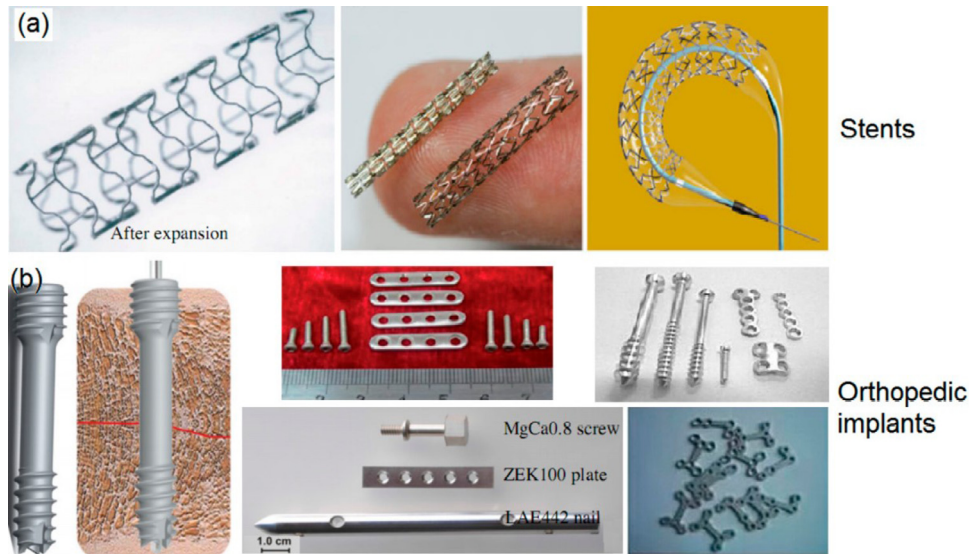


Fig. 14. Best important applications: (a) stents and (b) orthopedic implants made of Mg alloys [131].

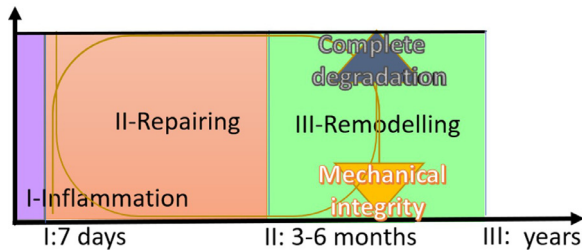


Fig. 15. Sketch, the ideal compromise between the mechanical integrity and the biodegradation rate of a biodegradable metal implant.

in which no thrombosis or cardiac death was detected [124].

It has been found that pure zinc stents show a long-term corrosion process and a biocompatibility in the vascular environments of rabbits [135]. Recently, numerous scientific articles have appeared on this field, several reviews have focused on each metal (e.g., magnesium, iron, or zinc) and specific cardiovascular or orthopedic medical applications [136].

Although several relevant standards for bioresorbable materials are underway, there are currently three published standards for bioresorbable implants and their compositions, as follows: ISO/TR 37,137: 2014: Cardiovascular biological evaluation of medical devices - Guide for absorbable implants (ISO 2014a), ISO / TS 17,137: 2014: Cardiovascular implants and extracorporeal systems (ISO 2014b) and ASTM F3036–13: Standard guide for testing absorbable stents (ASTM 2013) [137–140]. Although these standards are somewhat more general, they may be useful in assessing absorbable metal implants, requiring a more comprehensive approach to bioresorbable metals. Realizing this need, both ASTM and ISO have made collaborative efforts to develop coordinated standardized guidelines to adequately assess activities such as metallurgy, corrosion, and biocompatibility of bioresorbable

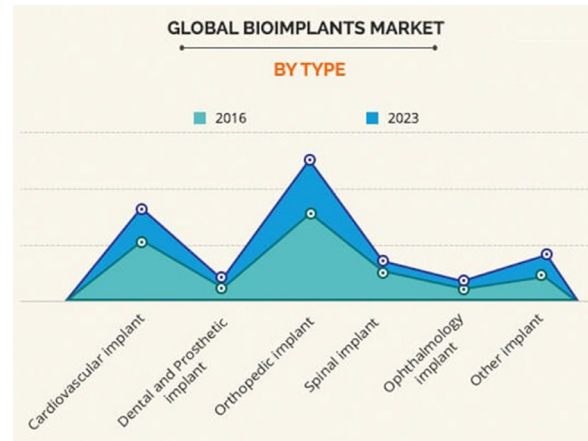


Fig. 16. Metal bioimplant market, evolution over time [143].

metals [141,142]. Once all these standards become active, they will certainly facilitate the solution of major problems, such as modern and efficient technologies to produce bioresorbable metals/alloys, both for their clinical use and for commercialization. The immediate benefits will be mainly economic, but there will also be a clear increase in the quality of life of patients.

Some of the most important companies on the international market are: aap Implantate AG; Abbott; Bausch & Lomb Incorporated; BIOTRONIK, Inc.; Edwards Lifesciences Corporation; LifeNet Health; MiMedx; Smith & Nephew Plc; Zimmer Biomet.

Bioimplants have emerged as a promising solution for a variety of conditions, such as: cardiovascular, dental, orthopedic, ophthalmology, neurological diseases, road accidents and trauma. The global metal bioimplant market was estimated at ~ \$ 78 billion for 2016, and is estimated to reach ~ \$ 124 billion by 2023, with an average increase of 6.9% for the period 2017–2023, Fig. 16, [143]. The high prevalence of cardiovascular, orthopedic, and spinal diseases, which can

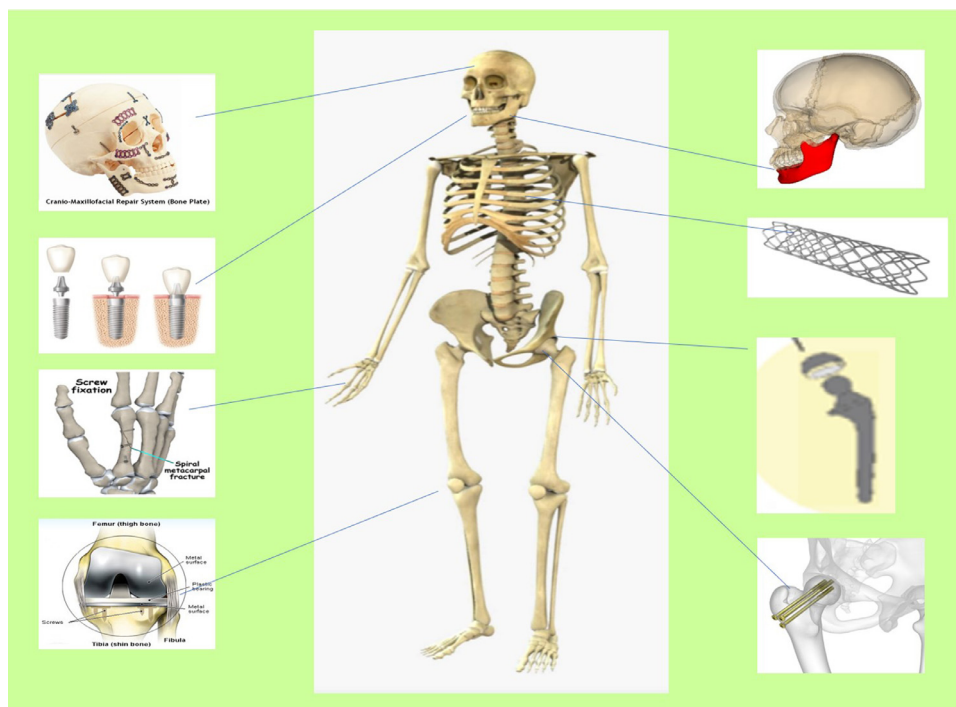


Fig. 17. Application of bioimplants in humans depending on the area affected by the disease/accident.

be treated with bioimplants, are the key factors of market growth [143]. The major factors in the growth of the implant market are the increase in the prevalence of chronic diseases, along with the rapid trend (worldwide) of an aging population.

Fig. 17 shows the application of some bioimplants in humans depending on the area affected by the disease/accident. Moreover, an increased awareness of these issues and the technological advances currently being made in the field of bioimplants, are important factors in market growth [2].

9. Mg biodegradable alloy requirements for implants

Current biodegradable implants are mainly made of resorbable polymers and bio-ceramics. However, the low mechanical strength of polymers and the fragility of ceramics often limit their application as support devices. Degradable metal implants based on magnesium or iron and their alloys have great potential as materials for temporary implants. However, biodegradable metals with better mechanical properties, good biocompatibility, non-cytotoxicity, and adequate degradation properties, harmonized with the tissue healing process are still in the research, testing and optimization phase. Recently, Mg and its alloys have been introduced as a new class of biodegradable metallic materials and have gained more and more attention as a material for orthopedic implants.

In conclusion, for many reasons, biodegradable metal alloys have attracted particular interest for applications such as temporary implants such as plates and screws in orthopedics, and stents in cardiovascular implantology:

- (i) Most importantly, Mg and its alloys have a natural biodegradation capacity due to their susceptibility to corrosion in aqueous solutions, especially if they contain chloride ions. Compared to Fe and its alloys, implants from Mg alloys degrade faster in physiological environments.
- (ii) Mg has excellent biocompatibility: Mg ions (Mg^{2+}) that are released during implantation and degradation are used in normal metabolism, and so far, no critical toxic limits or side effects have been reported for Mg^{2+} ions.
- (iii) The modulus of elasticity of Mg (40–45 GPa) fits better with that of natural bone (3–20 GPa) compared to conventional metallic materials such as stainless steel (~200 GPa), cobalt-based alloys (~230 GPa) and titanium alloys (~115 GPa), thus reducing the effect of stress shielding.
- (iv) Mg alloys are exceptionally light metals, with a density between 1.74 and 2.0 g/cm³, which is much lower than that of the biomedical titanium alloys (4.4–4.5 g/cm³) and close to that of natural bone (1.8–2.1 g/cm³) which leads to lighter implants compared to other metallic biomaterials.

10. Biodegradable implant design based on Mg alloys

Absorbable materials must have physicochemical properties consistent with the physiology of adjacent tissues. Their main requirements are the ability to be biocompatible and biodegradable. By biocompatible is meant the ability of an implant to be composed of materials that do not induce a pathological biological response from adjacent tis-

sues. Biodegradable, it represents the ability of a material to be chemically decomposed or to degrade into compounds under the action of biological factors. In the case of an orthopedic implant, it would be ideal for resorption to occur simultaneously with the bone remodelling process. Thus, an ideal resorbable implant can be characterized by the ability to biodegrade, biocompatibility, bioactivity (the ability to interact between the implant and adjacent tissue) and by mechanical properties as close as possible to human bone tissue, but strong enough to support the bone up to callus formation.

10.1. The design criteria for a biodegradable metal material

The design criteria for a biodegradable metal material must be different from permanent (inert) metal implants [144].

Regarding the design principles for metal implant materials, the following essential scientific aspects must be considered [133]:

- (i) Biocompatibility and biosafety. Elements such as Al (undesirable for medical applications due to toxicity) should be avoided in the alloying process.
- (ii) Acceptable mechanical strength and ductility. As an orthopedic implant material, a value of mechanical strength > 200 MPa, an elongation of min. 10% and a degradation rate < 0.5 mm/year in SBF at 37 °C, to guarantee an effective “life” of the implant of 90–180 days. In contrast, a higher ductility (> 20%) and a moderate resistance value are desirable for cardiovascular stents.
- (iii) Controlled biodegradation. Most Mg alloys (according to the reported data) are easily susceptible to local corrosion effects; a uniform and controllable degradation is crucial to accurately predict the “life expectancy” of the implant.

All three aspects are interrelated and necessary in the process of designing and developing Mg metal alloys, and are the “key” to achievement biodegradable, modern and high-performance metal implants.

10.2. Strategies for improving mechanical performance and degradation

Magnesium has a low strength in the casting condition with a high degradation rate. Property improvement can be achieved through appropriate alloying and processing conditions. The alloying elements in self-absorbable Mg alloys should be selected not only on the improvement of mechanical properties, but also on the consideration of degradation and biocompatibility.

It is well known that the corrosion behaviour of Mg alloys is significantly influenced by microstructure, particle size and distribution, phase distribution. The process of “refining” the granules will cause changes in density and, respectively, in the distribution and interconnection of the granules, with

implications in changing the mechanical properties and ultimately, will influence the corrosion behaviour of magnesium alloys.

Improving refining is an effective approach to improve the mechanical properties and corrosion resistance of Mg-based alloys. The consolidation of the grain size is represented by the known Hall-Petch relation:

$$\sigma_s = \sigma_0 + k \cdot d^{-1/2} \quad (14)$$

where σ_s is the yield stress, σ_0 is the friction stress for movement of dislocations on the slip plane, k is the stress coefficient and d is the average grain size [145].

Mg alloys can generally have two forms of corrosion, namely: uniform corrosion and localized corrosion [146]. Most Mg alloys contain a second phase, precipitates and/or impurities. Due to the presence of these phases, which are cathodic in relation to the α -Mg matrix, it is possible that the anodic reaction will be accelerated, and the Mg(OH)₂ protective film will be rapidly destroyed. Once the protective film is destroyed, the surrounding solution will continuously penetrate through the porous film and the Mg matrix will suffer additional and accelerated corrosion. If the second phase has a higher corrosion potential and is inhomogeneously distributed, the alloy will tend to corrode in a localized manner. Rarely, the Mg alloy may show uniform corrosion [147]. In the paper [95] it is reported that 29 out of 31 types of Mg alloys suffer from uneven corrosion. Recently, the importance of the absence of secondary phases was demonstrated again [148], by obtaining of a new material based on Mg (Mg₃Zn₁Ca₁₅Nb) by using PM method, with improved properties in terms of mechanical properties and corrosion, without having secondary phases or impurities, which is particularly important for applications in the biomedical field.

Processing conditions, such as casting, powder metallurgy and other severe processes of plastic deformation, greatly influence the phenomenon of refining and hardening of the metal matrix.

Another way to reduce and control the degradation behaviour of Mg alloys and implicitly, to improve the biocompatibility of the Mg alloy surface is to modify the surface. Many researchers have shown that by modifying the surface, by applying specific treatments, excellent results have been obtained in terms of improving the corrosion resistance of Mg implants in the body [149–151].

10.3. Practical (efficiency) characteristics of biomaterials

The efficiency of metallic biomaterials refers to the reliability in use, accessibility in manufacturing, a cost price as low as possible due to accessible raw materials, easy processing and sterilization capacity, aesthetic appearance.

For the obtaining of Mg metallic biomaterials, raw materials of medical purity are selected. Affordable manufacturing processes are chosen to ensure a mass production with appropriate dimensional accuracy. At the same time, the technology must not use toxic chemicals, which would lead to damage

of the implant. Sterilization can cause changes in the physical and tribological properties of biomaterials. Different sterilization processes are used: thermal, by irradiation with gamma radiation or electron flux, with aqueous solutions based on aldehydes and polyene oxide, by autoclaving.

11. Conclusions

It is undeniable that Mg-based metal alloys represent, at this moment, the new generation of biodegradable metal materials, with a good osseointegration property. Biodegradable implants dissolve in the human body and their elimination after the convalescence period of the fractured bone is no longer necessary. This ensures a considerable benefit for both patients and the public healthcare system in terms of costs.

There are several mandatory requirements for Mg alloys, usable as biodegradable, temporary biomaterials in orthopedics: natural biodegradation capacity, excellent biocompatibility, the modulus of elasticity as small as possible (like biological bone) and to be as light as possible.

To improve the corrosion resistance of Mg alloys for medical applications, there is still intense research in this direction. Only the use of pure or ultra-pure raw materials, selection of certain alloying elements in certain quantities, should be considered in the manufacturing process, so that they are compatible and lead to improving the mechanical properties and corrosion behaviour. The corrosion behaviour is also influenced by the application of efficient processes, such as: ultra-fast solidification, severe plastic deformation and adequate heat treatment, but also by treatment/coating the surface of materials with special corrosion resistant and biocompatible coatings with a good adhesion to the substrate.

The nature and stability of the surface film that develops on Mg alloys is critical for their stress corrosion cracking. To improve the behaviour of stress corrosion cracking (SCC), certain processes for the manufacture of implant can be applied, such as plastic deformation by extrusion, to reduce the micro-galvanic effect induced by secondary phases due to their homogeneous and uniform distribution in the matrix, but also by reduction of grain size or by applying heat treatments to determine the microstructural modifications with impact on the failure modes in Mg alloys for implants.

All these aspects are still studied methodically and in depth, to find the ideal solution for the targeted medical application.

In conclusion, the design criteria for the next generation of biodegradable Mg alloys must aim at a good combination of suitable mechanical properties, adequate corrosion behaviour and excellent bioactivity. Finally, the design of these degradable biomaterials must also consider the practical aspects and efficiency, referring to reliability in use, accessibility in manufacturing, a low-cost price, easy processing, and sterilization capacity and respectively, to the aesthetic aspect.

To achieve successful medical applications, close collaboration between researchers and doctors is needed, requiring specific interdisciplinary knowledge.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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