CONTRIBUTIONS ON BIODEGRADABILITY OF Mg-Ca ALLOYS FOR ORTHOPEDIC IMPLANTS

Horatiu MOLDOVAN [1,2], Elisa PLOPEANU[3], Gheorghe DAN[4], Marius VASILESCU[5], Mircea DOBRESCU[6], Claudia MILEA[7], Kamel EARAR[8], Daniela GHEORGHITA[9]

Given their biodegradability, magnesium (Mg) and magnesium-based alloys are nowadays in the center of attention. This aspect is closely related to degradation time, mechanical properties and local physiology of the environment in which the material is implanted. All these parameters are important as uncontrolled degradation can cause premature implant failure and consequently, more complications. Other important properties such as light weight and high strength made magnesium-based alloys to be very interesting for various applications. Extensive research has been conducted on the effects of composition, surface modification and structure on the degradation behavior. With important applications in orthopedic implants and cardiovascular stents, magnesium-based alloys open the way to a new generation of biodegradable metallic implants. This paper presents our experimental research on the biodegradability of Mg-Ca alloys for orthopedic implants with focus on the factors that influence the degradation process such as surface conditions, microstructure and alloying elements with reference to structure and composition of an elaborated Mg-0.8Ca alloy.

Keywords: magnesium alloys, biodegradable implants, corrosion.

[1] Conf., Faculty of Medicine, Titu Maiorescu University, Bucharest, Romania

[2] Department Chief, Department of Cardiovascular Surgery, Sanador Hospital, Bucharest, Romania

[3] PhD std., Faculty of Materials Science and Engineering, University POLITEHNICA of Bucharest, Romania

[4] Conf., Faculty of Materials Science and Engineering, University POLITEHNICA of Bucharest, Romania

[5] Conf., Faculty of Materials Science and Engineering, University POLITEHNICA of Bucharest, Romania a

[6] Conf., Faculty of Materials Science and Engineering, University POLITEHNICA of Bucharest, Romania

[7] PhD std., Faculty of Materials Science and Engineering, University POLITEHNICA of Bucharest, Romania

[8] Professor, Dunarea de Jos University of Galati, Medicine and Pharmacy Faculty, Galati, Romania.

[9] PhD std., Faculty of Materials Science and Engineering, University POLITEHNICA of Bucharest, Romania

1. Introduction

1.1. Biodegradation process for metallic implants

The classical approach in the case of metallic biomaterials is focused on creating an ideal implant that is inert. Thus, it would not influence and in the same time it would not be influenced by the physiological medium in which it is implanted. This sounds like the optimum way to avoid a series of adverse reactions such as inflammatory responses and even bacterial infections [1]. The relevance of the interaction between biomaterials and human tissues is essential for the bio functionality of implants used in various clinical specializations like cardiovascular surgery [2-5], orthopedics [6-11], dentistry [12-15], neurosurgery [16,17], and other surgery [18-23].

However, in the last years, a new class of biodegradable metals is changing the perspective. An increasing interest in biodegradable implants brought magnesium in the spotlight due to its degradation properties. The main advantage of biodegradable metals is that after implantation, the material is absorbed by the body and a removal surgery is no longer needed [24, 25]. These implants are intended to provide the necessary mechanical support and act like a scaffold for the cell growth. Therefore, controlling the degradation rate is a crucial step in creating a biodegradable implant as a higher degradation rate affects the mechanical integrity, resulting in implant failure [25-27].

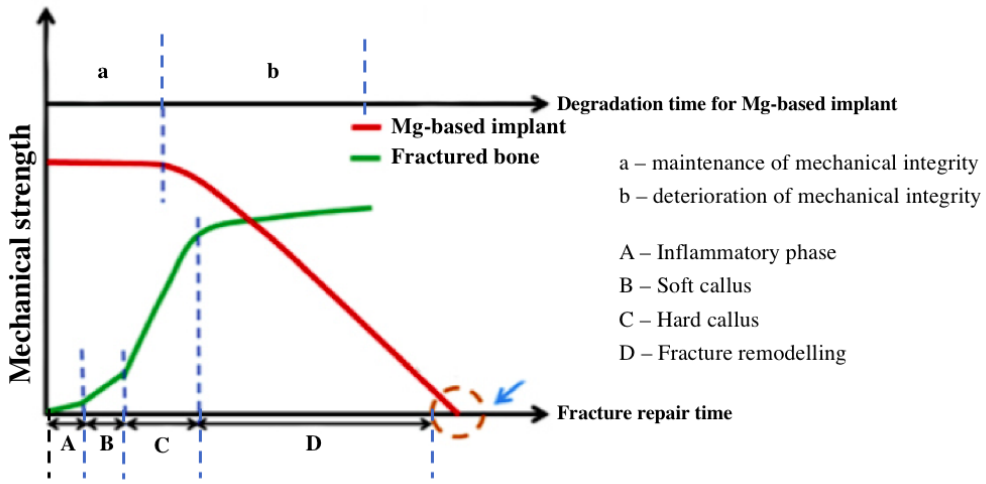


Fig. 1. Optimal degradation rate of Mg-based implant in fracture healing [27]

The optimal relationship between the degradation time of an Mg-based implant and the healing time of a fractured bone is represented in Fig.1 [28]. As shown in the scheme, in order for the bone fracture to heal properly, the implant must maintain its most of the mechanical integrity until at least half of the hard callus is formed, having a gradual degradation from the moment it is implanted until it is metabolized by the body, completely disappearing. However, it must keep a slower rate of degradation until the bone starts to heal and have an accelerated degradation once the bone is strong enough to sustain a part of the mechanical load [28,29].

Biodegradation is a complex process that implies many other factors starting from the production process of the alloy to local pH of implantation site [24-28]. A scheme representing the main influencing factors is presented in Fig. 2 [28].

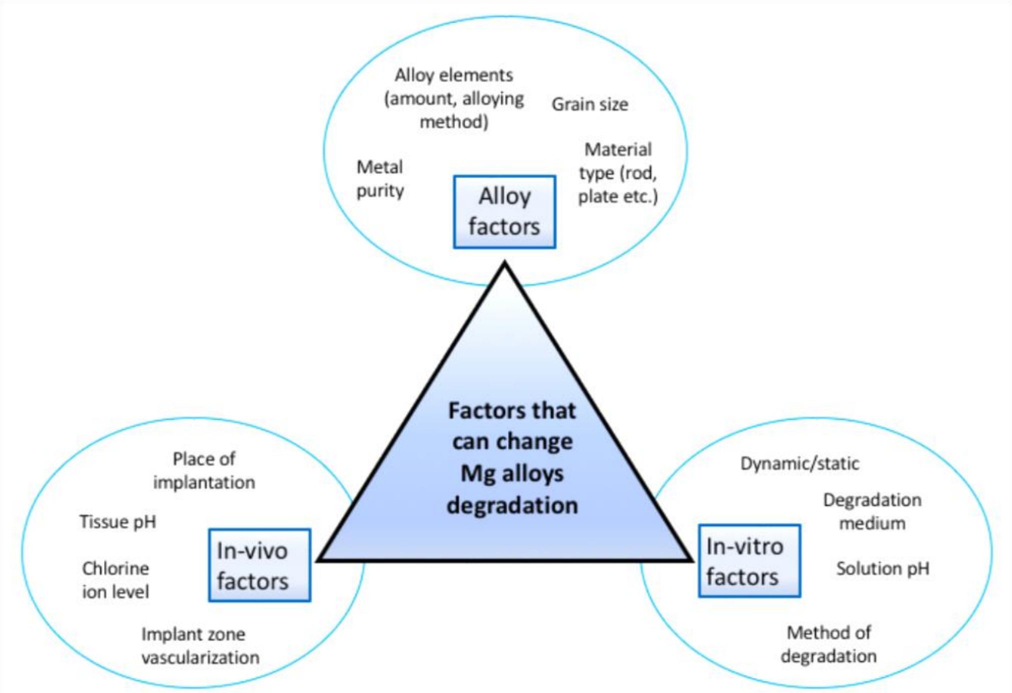


Fig. 2. Factors that affect Mg alloys rate of degradation [28]

1.2. Mg alloy development strategy

Even though magnesium is a biodegradable metal, its high corrosion rate makes it inadequate to be used as a stand-alone biomaterial. Alloying is a general method used for improving the properties of a pure metal. Mostly used as Mg alloying elements are Al, Zn, Mn, Ca, Li, Zr and rare earth (RE) elements [25,29,30].

Commercial Mg alloys which have been under investigation for diverse engineering applications (automobile, aerospace, etc.) are currently under investigation as biomaterials for their desirable properties in medical applications such as strength and ductility. Being originally intended for industrial usage, toxic elements such as Al and RE are widespread in commercial Mg alloys. Since the presence of toxic elements is not suitable for medical applications, new kinds of Mg based alloys have been developed. Some characteristic impurities found in Mg alloys are represented by iron (Fe), copper (Cu), nickel (Ni) and beryllium (Be), the last two being elements that should be avoided due to their toxicity when referring to alloys with medical applications [25,31,32]. Table 1 presents some representative Mg alloys tested by various groups for potential medical applications [25,28,31].

Table 1

Chemical composition of some representative Mg alloys tested for medical applications [25,28,31]

Family	Representative alloys
Pure Mg	>99%Mg
Mg-Ca	Mg-xCa (x=0.8, 1, 2, 3, 4)
Mg-Zn	Mg-xZn (x=1, 3)
Mg-Mn	Mg-1Mn
Mg-Zn-Ca	Mg-1Zn-1Ca
Mg-Zn-Mn	Mg-1Mn-1Zn
Mg-RE	AE44
	LAE442
	WZ21
	AZ91/AZ91D
	ZE41
	Mg-2.5Zn-0.5Y
	AZ21
	AZ31
	AZ61/AZ63
	Mg–10Gd–0.5Zr
	Mg–10Gd–0.5Zr–1.2Ca

Depending on the alloying elements selected, and also on the production process, Mg alloys gain different microstructural aspects as well as properties. The most used alloying element when it comes to Mg alloys is aluminium (Al). It was found that the presence of Al forms an oxide film (Al_2O_3) on the surface of metal conferring a higher resistance to corrosion. However, when referring to medical applications, the neurotoxicity of this element represents a huge drawback, Al not being recommended as an alloying element [25]. When using Zn as an alloying element for Mg, the corroding effect of impurities like Fe and Ni is removed, Mg-Zn alloys having therefore, a higher resistance to corrosion. To increase ductility and remove the harmful effects of Fe, manganese (Mn) is the preferred alloying element. The only element that can change the structure of Mg alloys from hexagonal close packed to body-centered cubic is lithium (Li). This aspect improves properties such as ductility and plasticity.

Numerous studies have been conducted in order to assess biological responses induced by Mg based alloys [28, 32, 33, 34]. Binary (Mg-Ag, Mg-Zn, Mg-Ca, etc.) ternary and quaternary series alloys (Mg-Zn-Mn, Mg-Al-Zn, Mg-Nd-Zn-Zr, etc.) have been tested in order to develop better properties. Fig. 3 presents a scheme of Mg-based alloys development [34].

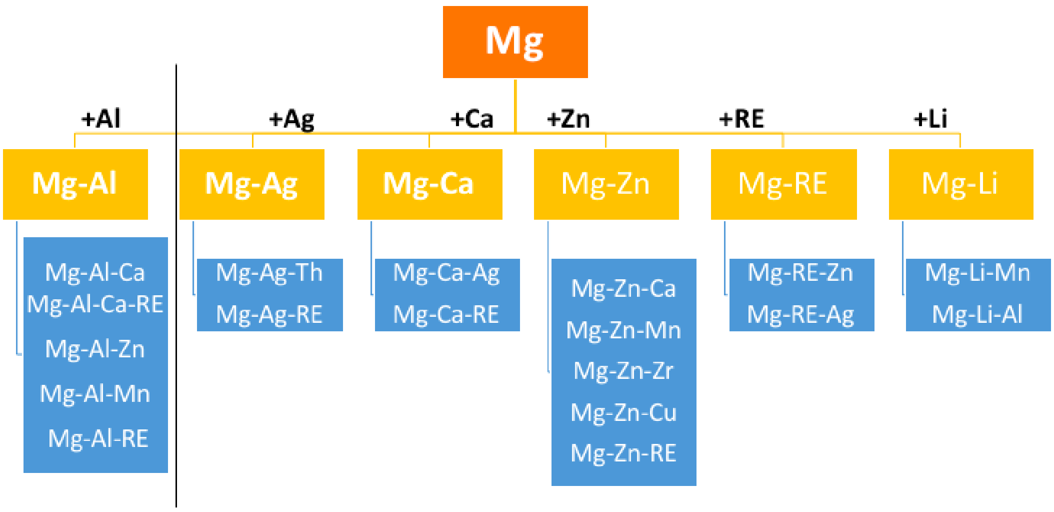


Fig. 3. Scheme of Mg-based alloys development [34]

Most alloying elements are improving corrosion resistance but they have also a critical limit due to their solubility in Mg. Further addition of an alloying element beyond the critical limit can lead to opposite effects such as loss of corrosion resistance and deterioration. An eloquent example is calcium (Ca) that is an effective grain refiner in alloys based on Mg. When more than 1 wt.% content of Ca is present in Mg-based alloys, the strength and ductility decrease

[27,35]. Fig. 4 presents the atomic diameters of Mg alloying elements. This aspect is important since it is a solubility dependent factor. The elements between the dashed lines are more favourable to form a solid solution with magnesium because they have the atomic size within ±15% of Mg atomic size [36].

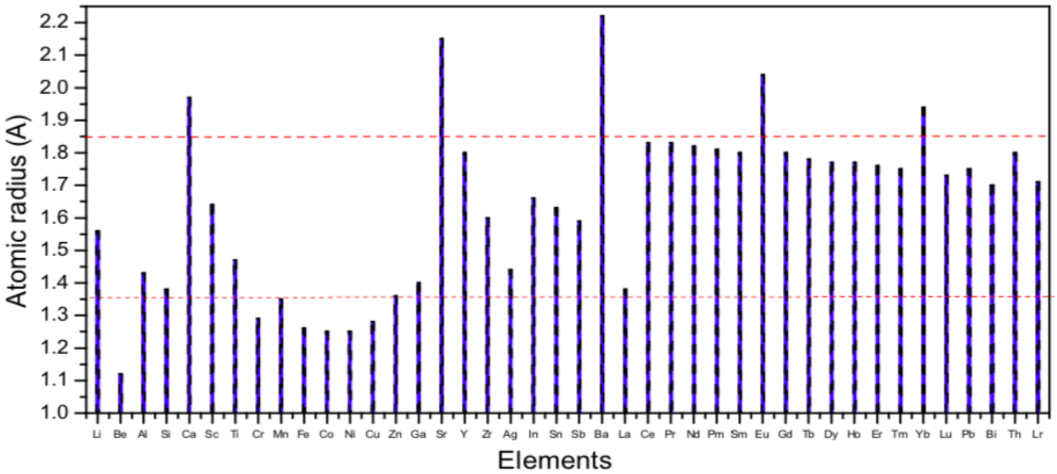


Fig. 4. Atomic diameters of Mg alloying elements [36]

New types of Mg alloys have been developed in the last years in order to meet special criteria for medical applications [27, 30, 36, 37]. In the experimental research part, aspects such as metallurgical processing, structure, and corrosion of biodegradable Mg-Ca alloys for orthopaedic implants are discussed.

2. Experimental Research

2.1. Metallurgical processing

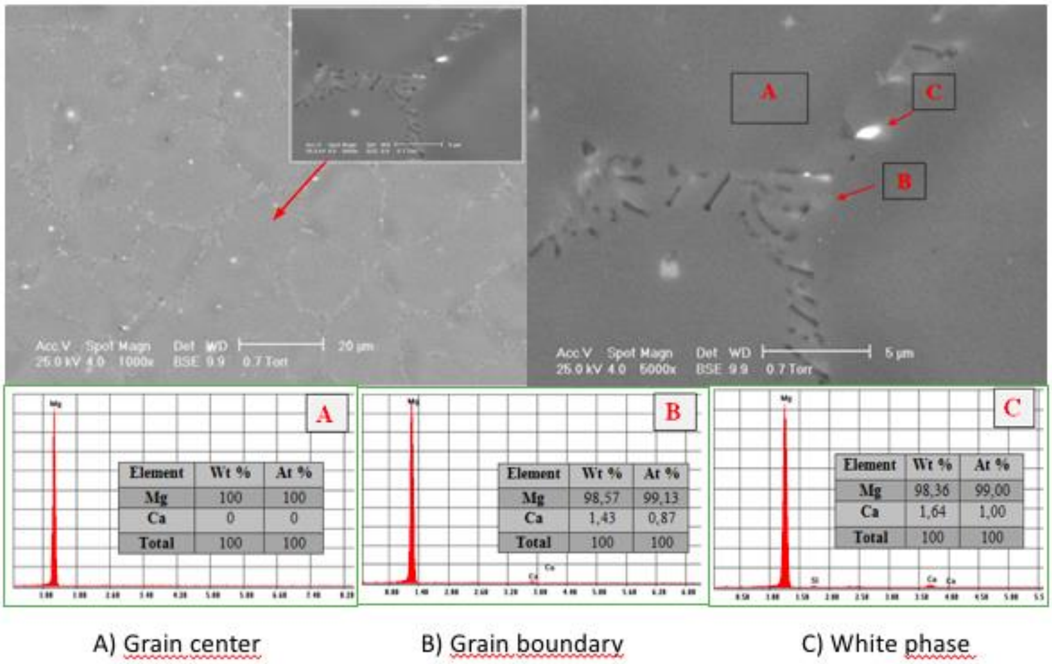
For advantages such as mass production and small series, casting appears to be the most used technological process for manufacturing Mg implants. However, segregations, inhomogeneous grains, micro- and macro porosities and precipitation shrinkage are defects that appear frequently. Before deformation, preheating is recommended in the case of wrought magnesium alloys. This process is done in order to activate additional slide systems in Mg alloys with hexagonal close-packed (h.c.p.) crystal structure and to dissolve precipitations. Grain size and distribution are influenced not only by the process, but also by the alloying elements. Areas with imperfections are more prone to corrosion and when the degradation process starts, these zones are usually first affected as the grain boundary has a different chemical composition than the grain matrix [24,31,33].

Aging and heat treatments create a single-phase microstructure containing well-distributed precipitations. Fine precipitations created after these treatments have the ability of improving corrosion resistance. Another effective way to refine grain size of Mg based alloys is mechanical pre-processing. Images with different shapes of casted Mg alloy are presented in Fig. 5.

Fig. 5. Casted Mg alloy

2.2. Microstructural characterization

In order to determine the optimal conditions for design, casting and thermo-mechanical processing of various Mg alloys for obtaining ideal properties, the knowledge of phase diagrams and thermodynamic properties of these alloys is essential. The description of the phase equilibrium diagrams for binary magnesium alloy systems offers the opportunity to determine the development of new alloys as well as estimate behaviour of the alloy when using different thermo-mechanical treatments. Also, the study of Mg binary phase diagrams with alloying elements highlights the processes that take place and the interactions between metals that will influence the final properties of the magnesium alloy [24,33,34]. From biocompatibility standpoint, calcium (Ca) is an essential element, being an important component of hard human tissues. Ca presence in Mg alloys is benefit for bone tissue healing through concomitant release of both Mg and Ca ions. Besides biocompatibility, Ca addition in Mg alloys can lead to grain refinement and improved creep resistance, in the same time it hardens through precipitation, conferring a higher mechanical resistance [33]. However, inadequate mechanical properties and low corrosion resistance of Mg-Ca alloys are big drawbacks. Structural characteristics of an experimental Mg-0.8Ca alloy were investigated using Scanning Electron Microscopy (SEM) technique and Energy-dispersive Xray spectroscopy (EDS) being shown in fig. 6. In the case of Mg-0.8Ca, secondary phase with lamellar aspect is continuously distributed at grain boundaries. EDS results show the existence of lamellar eutectic aspect formed of Mg and Ca that confirms the existence of Mg_2Ca phase. Microstructure investigations of Mg-Ca alloys indicate the presence of a primary Mg phase with eutectic format along grain boundaries. Grain boundaries are rich in Ca and suggest that Mg_2Ca phase precipitated along these limits.



Element	Wt %	At %
Mg	100	100
Ca	0	0
Total	100	100

Element	Wt %	At %
Mg	98,57	99,13
Ca	1,43	0,87
Total	100	100

Element	Wt %	At %
Mg	98,36	99,00
Ca	1,64	1,00
Total	100	100

Fig. 6. Microstructural and compositional aspects of MgCa0.8 alloy by SEM (top), respectively EDX (bottom)

3. In vitro corrosion

3.1. Immersion test

The corrosion phenomena occurring in binary Mg-Ca alloys, potentially usable in implantology, has been studied by several research groups [30-38]. Li et al. published in 2008 the first complex study of these binary alloys, taking into account several binary Mg-Ca alloys with different percentages of calcium [32]. Calcium was selected as an alloying element for the development of Mg-Ca binary alloys since it represents an important component of human harsh tissues, being an essential element in biochemical processes. Also, its low density (1.55 g / cm3) allows alloys in the Mg-Ca system to reach a density similar to that of bone tissue [33].

The immersion test and electrochemical method are common techniques used to determine the in vitro corrosion rate. The chosen medium and the environmental conditions in which the experiment takes place must imitate the human physiological conditions. Although initially it was thought that the complex environment in the body would induce a corrosion rate higher that in vitro, studies have shown the opposite, as Witte observes in his experiments on AZ91 and LAE442 Mg alloys [34]. Wen et al. [35] studied the degradation rate of AZ61, AZ31 and AZ91D concluding after an immersion time of 24h in m-SBF (Simulated Body Fluid) that the degradation rate was 3-8 mm/yr. After a prolonged immersion period (24d), the high degradation rate that was estimated after 24h slowed down, reaching 1.32mm/yr for AZ61, 2 mm/yr for AZ31 and 1.23mm/yr in the case of AZ91D.

Yang et al. [36] analysed the importance of calcium phosphate coating applied to AZ31 alloy after an immersion test of 48h in supersaturated calcification solution (SCS), reporting a slower degradation rate. An immersion test was performed on Mg-0.8Ca alloy. Fig. 7 shown the macro-morphology of the samples after immersion test in 3 different immersion solutions: phosphate buffered solution (PBS), Hanks' Balanced Salt Solution (HBSS) and Dulbecco Modified Eagle Medium supplemented with fetal bovine serum (DMEM + 10% FBS).

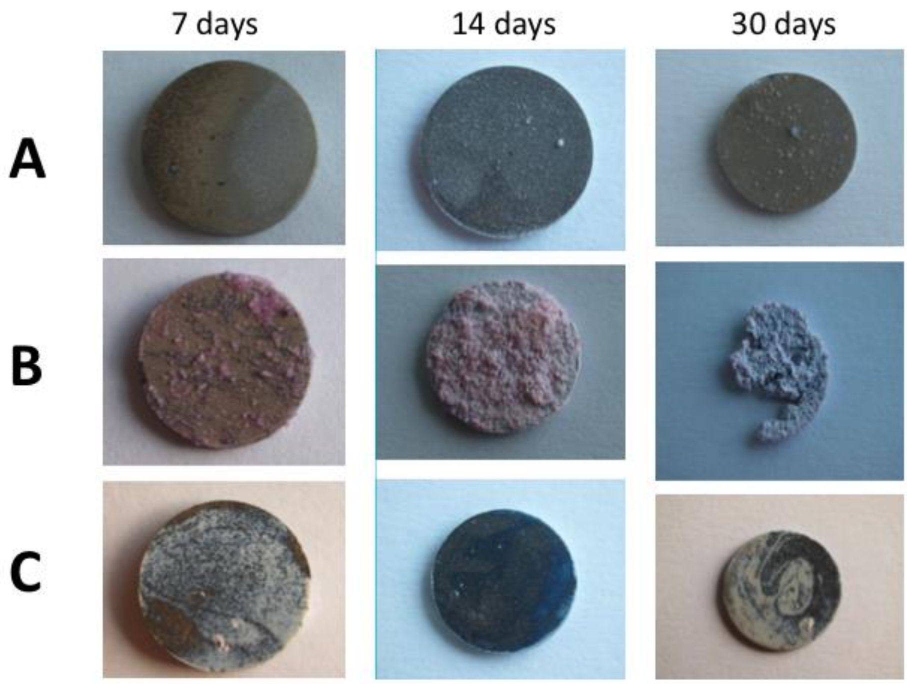


Fig. 7. Surface macro-morphologies of MgCa0.8 alloy after different days of immersion in various testing medium: A-PBS, B-HBSS, C-DMEM+10%FBS

3.2. Hydrogen release

If large volumes of hydrogen bubbles are formed in a short period of time, important problems leading to blood flow blockage or tissue separation that is precursor to necrosis in the close vicinity of the implant can interfere. Mg corrosion products are harmless for the human body but other issues such as fast release of hydrogen and higher rate of implant degradation are serious matters to be taken into account as well as the potential risk of inflammation due to loss of mechanical integrity of the implant before healing due to accelerated degradation of Mg implant [31,36,37].

Inside the human body, Mg degrades in conformity with equation (2), releasing hydrogen (H) bubbles. Also, as a result of reactions (3) and (4) Mg hydroxide is formed [26,37]. The hydrogen volume generated is useful when calculating the amount of degraded Mg alloy and therefore, the corrosion rate of the biomaterial.

3.3. Electrochemical method

Corrosion represents an electrochemical process that describes the flow of the electron between anode and cathode. While low resistance to corrosion of Mg and its alloys represents a big issue for automobile industry applications, this fact makes them attractive for biodegradable implants used for bone fracture fixation [24,29,38]. Mg corrosion rate in aqueous solutions is pH dependent. While Mg degrades at a lower value of pH level of approx. 11.5, it forms a passive film of $Mg(OH)_2$ at a higher pH level value. Mg has a very low standard electrode potential, having a value of -2.37 V, aspect that conducts to a higher sensitivity than most of metals. It can be said that Mg has a low corrosion resistance, this aspect being more relevant in the case of chlorine solutions and thus, actively dissolved at human pH (7.2-7.4). To determine the corrosion resistance by electrochemical methods, corrosion tests were performed at the temperature of the human body (37 ± 0.5 ° C) in Dulbecco's Modified Eagle's Medium (DMEM) and Simulated Body Fluid (SBF).

Table 2.

The main parameters of the corrosion process in DMEM

No.	Sample	E_{oc} (V)	E_{corr} (V)	i_{corr} ($\mu A/cm^2$)	CR (mm/yr)	β_c (mV)	β_a (mV)	Rp ($k\Omega x cm^2$)	P_e (%)
1	Mg-Ca	-1,498	-1,411	50,811	1,168	280,342	165,827	0,89	-

Table 3.

The main parameters of the corrosion process in SBF

No.	Sample	E_{oc} (V)	E_{corr} (V)	i_{corr} ($\mu A/cm^2$)	CR (mm/yr)	β_c (mV)	β_a (mV)	Rp ($k\Omega xcm^2$)	P_e (%)
1	Mg-Ca	-1,867	-1,857	576,046	13,247	404,321	350,555	0,14	-

If we take into account the value of the corrosion potential (Ecorr), it is considered that the more electropositive the value of Ecorr is, the better corrosion behaviour it shows, meaning that the corrosion process is inhibited. It is known that a high polarization resistance reveals good corrosion behaviour of a material, and a low value of this parameter has worse corrosion behaviour [37,38].

The variations of open circuit potential (Eoc) recorded in both environments (DMEM and SBF) are shown in Fig. 8, while the Tafel curves are presented in Fig. 9.

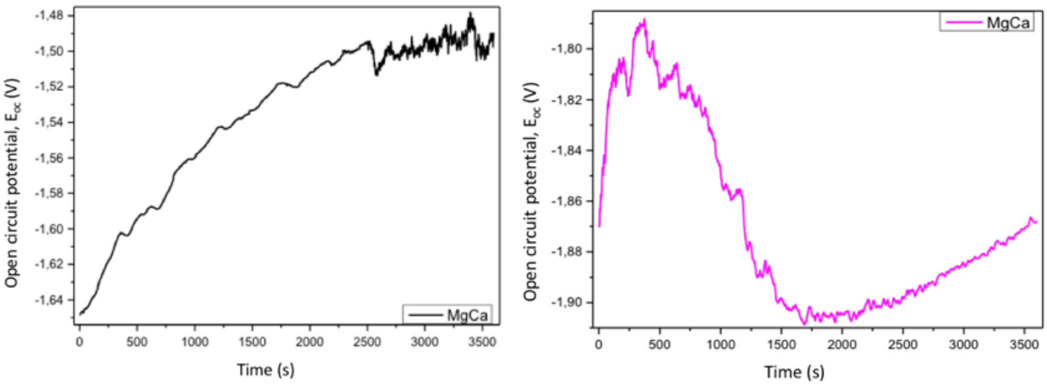


Fig. 8. Evolution of open-circuit potential (Eoc) for Mg0,8Ca alloy: left-DMEM and right-SBF

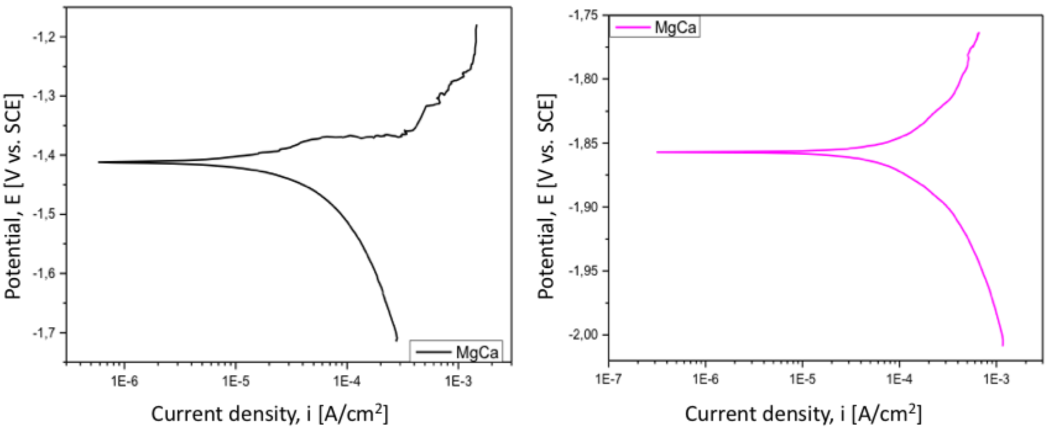


Fig.9 Tafel curves for the Mg09.8Ca alloy: left-DMEM and right-SBF

Images of scanning electron microscopy (SEM) after the determination of corrosion resistance by electrochemical methods on Mg0.8Ca alloy in SBF as well as in DMEM are shown in Fig. 10.

In the same time, EDS investigations after the determination of corrosion resistance by electrochemical methods of Mg0.8Ca alloy in SBF and DMEM show the presence of higher amount of Ca at the surface samples after using SBF as testing medium.

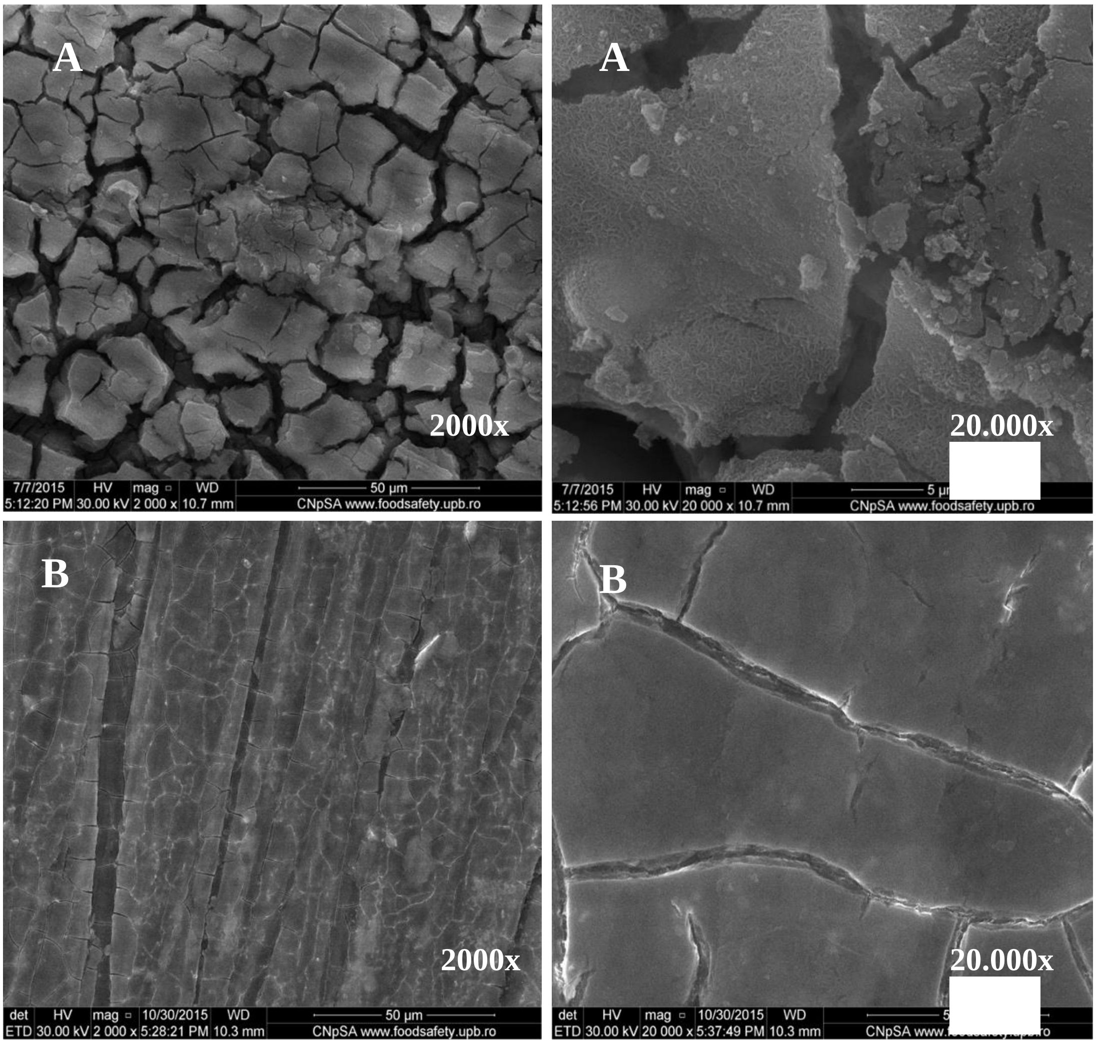


Fig. 10. SEM images after corrosion resistance determination by electrochemical methods on Mg0.8Ca alloy in different medium: A-SBF and B-DMEM

4. Cytotoxicity evaluation

The primary considerations when using alloying elements are the mechanical properties and when these materials are intended for medical applications, degradation rate and biocompatibility are other factors that must be carefully taken in consideration. They are primordial factors because a material can have the desired mechanical strength but lack biocompatibility, being toxic for human body and therefore useless in such applications.

This aspect intensifies in the case of biodegradable implants as the compounds of the material have to be metabolized by the body. Large amounts of elements that are in the composition of implanted material can be released by the corrosion process and lead to cytotoxicity. However, the amount of elements released during a time period is closely correlated with the dissolution rate [39].

Typically, biocompatibility evaluation is performed in two ways. One of the ways is by seeding cells directly on the samples but this approach is not preferred due to high corrosion in the early stage that changes the surface of the material. The other way of performing this evaluation is by indirect immersion tests that imply exposing the samples to a suitable solution and then using the extracted test solution for cell cultures. In the case of Mg and its alloys, the second approach is mainly preferred [40].

5. *In vivo* corrosion - clinical aspects

Implants are recognized in the body as a foreign body. In the case of biodegradable implants, they must meet special requirements because the substances from which the implant is made of will be released in the body through degradation process. In vivo studies represent a necessary stage in research, required to certify the results obtained through in vitro studies. T

The biocompatibility of an implant depends on a multitude of factors, such as its composition, the type of degradation, the surface properties of the implant that influences the interface between the implant and adjacent tissues, the implant site and the surgical technique used [40].

The present in vivo study, performed on laboratory animals, respectively rabbits, aimed the assessing of biocompatibility of a Mg-0.8Ca binary alloy.

Parallelepiped Mg-0.8Ca implants before implantation, during the implantation surgery as well as radiography of the implantation site and aspect of the sample after removal are presented in fig. 11.

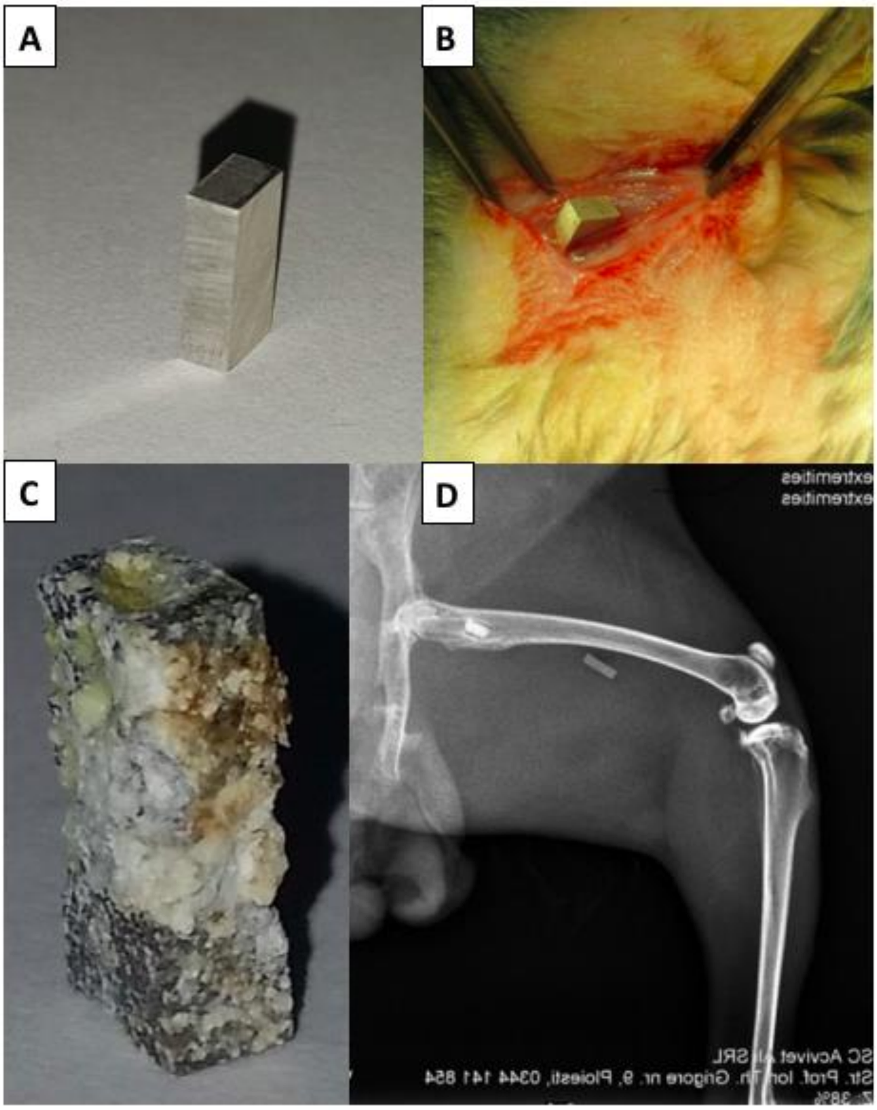


Fig. 11. Aspects depicted during implantation test in rabbits for the Mg-0.8Ca alloy: (A) specimen before implantation, (B) specimen during the implantation procedure, (C) macroscopically aspect of the specimen after removal from rabbit tibia; and (D) radiological aspect of the specimen during implantation.

6. Conclusions

Biodegradable magnesium alloys have several advantages over the biodegradable materials used today, such as polymeric, bioceramic and composite materials, particularly due to superior mechanical properties. However, rapid degradation of magnesium alloys due to corrosion in the human environment could limit clinical applications because a degradation rate that is too high leads to premature deterioration of functionality of the implant in the human body.

Due to its presence in the composition of bone tissue and its role in metabolic processes, magnesium has stimulating effects on the formation and growth of new bone tissue. An effective way to improve the microstructural characteristics of casted magnesium alloys in order to obtain superior properties is to obtain a fine microstructure by application of thermal treatments or plastic deformations. If the choice of magnesium alloy for biomedical applications meets the toxicity criteria of its chemical elements, corrosion products of magnesium alloys are harmless to the human body. However, other problems remain, such as hydrogen emission or too high corrosion rate, with potential risk of inflammation due to loss of mechanical integrity of the implant before healing.

At present there are several technological possibilities to adapt the corrosion rate of magnesium, both by using alloying elements and by depositing layers. It can be said that studies and researches on biocompatible and biodegradable coatings for magnesium and magnesium alloys with the intention of reducing and controlling corrosion rate in human or simulated environments as well as increasing their initial biocompatibility represent a topic of great relevance. The phenomena that are taking place are not fully elucidated and each contribution in this area will add to the development of this study direction on biodegradable magnesium alloys.

Acknowledgement

„This work was supported by a grant of the Romanian Ministery of Research and Innovation, CCCDI – UEFISCDI, project number PN-III-P1-1.2-PCCDI-2017-0239 / 60PCCDI 2018, within PNCDI III".

R E F E R E N C E S

[1]. *L.J. Liu, M. Schlesinger*, Corrosion of magnesium and its alloys, Corrosion Science **51** (2009), 1733-1737.

[2]. *R. Jurcut, O. Savu, B.A, Popescu, et al.,* Primary Cardiac Leiomyosarcoma When Valvular Disease Becomes a Vascular Surgical Emergency, Circulation, **121(21)** (2010), E415-E418.

[3]. *V.S. Costache, H. Moldovan, C. Arsenescu, et al.,* Aortic valve surgery of the 21st century: sutureless AVR versus TAVI, Minerva Cardioangiologica, **66(2)** (2018), 191-197.

[4]. *F. Golgovici, M. Prodana, G.R. Pandelea-Dobrovicescu,* About Electrochemical Stability of a Co-Cr Alloy used as Stents Material in Medicine, UNIVERSITY POLITEHNICA OF

BUCHAREST SCIENTIFIC BULLETIN SERIES B-CHEMISTRY AND MATERIALS SCIENCE, **80(1)** (2018), 219-230.

[5]. *F. Miculescu, D. Bojin, L.T. Ciocan, I.A. Antoniac, M. Miculescu, N. Miculescu,* Experimental Researches on Biomaterial-Tissue Interface Interactions, Journal of Optoelectronics and Advanced Materials, **9(11)** (2007), 3303-3306.

[6]. *H.R.C. Benea, K. Earar, W. Lattanzi, et al*., Collagen Scaffold and Lipoaspirate Fluid - derived Stem Cells for the Treatment of Cartilage Defects in a Rabbit Model, Rev. Chim., **69(2)** (2018), 515-520.

[7]. *C. Luta, M. Soare, A.C. Mocanu, et al.,* Comprehensive Nondestructive Testing of Implants for Orthopedic Applications, UNIVERSITY POLITEHNICA OF BUCHAREST SCIENTIFIC BULLETIN SERIES B-CHEMISTRY AND MATERIALS SCIENCE, **80(3)** (2018), 159-174.

[8]. *P. Botez, P. Sirbu, L. Simion, et al.* Application of a biphasic macroporous synthetic bone substitutes CERAFORM(A(R)): clinical and histological results, European Journal of Orthopaedic Surgery and Traumatology, **19(6)**, 387-395.

[9]. *A. Maidaniuc, F. Miculescu, A.C. Mocanu, et al.,* Sinterability Study of Bovine-Derived Hydroxyapatite and Silver Microcomposites, UNIVERSITY POLITEHNICA OF BUCHAREST SCIENTIFIC BULLETIN SERIES B-CHEMISTRY AND MATERIALS SCIENCE, **79(1)** (2017), 145-154.

[10]. *H. Benea, Horea, G. Tomoaia, O. Soritau, et al.*, A Review on the Reconstruction of Articular Cartilage Using Collagen Scaffolds, Romanian Biotechnological Letters, **21(4)** 2016, 11720-11728.

[11]. *B. Ghiban,* Fractographic Evaluation of the Metallic Materials for Medical Applications, UNIVERSITY POLITEHNICA OF BUCHAREST SCIENTIFIC BULLETIN SERIES B-CHEMISTRY AND MATERIALS SCIENCE, **79(3)** (2017), 103-112.

[12]. *E. Craciunescu, C. Sinescu, M.L. Negrutiu, et al.,* Shear bond strength tests of zirconia veneering ceramics after chipping repair, Journal Of Adhesion Science And Technology, **30(6)** (2016), 666-676

[13]. *S.I. Voicu, A. Dobrica, S. Sava, et al.,* Cationic surfactants-controlled geometry and dimensions of polymeric membrane pores By: Journal Of Optoelectronics And Advanced Materials, **14(11-12)** (2012), 923-928.

[14]. *M. Ionita, L.E. Crica, S.I. Voicu, et al.,* Fabrication of cellulose triacetate/graphene oxide porous membrane, Polymers For Advanced Technologies, **27(3)** (2016), 350-357.

[15]. *S.I. Voicu, C.M. Ninciuleanu, O. Muhulet, et al.,* Cellulose acetate membranes with controlled porosity and their use for the separation of aminoacids and proteins, Journal Of Optoelectronics And Advanced Materials, **16(7-8)** (2014), 903-908.

[16]. *M. Rivis, M. Pricop, S. Talpos, et al.,* Influence of the Bone Cements Processing on the Mechanical Properties in Cranioplasty, Rev. Chim., **69(4)** (2018), 990-993.

[17]. *D.C. Voinescu, A.G. Mohan, A.A. Marinescu, et al.,* Multum in parvo, Romanian Journal Of Morphology And Embryology, **58(1)** (2017), 297-300.

[18]. *C.I. Mavrodin, G. Pariza, D. Ion, et al.,* Abdominal Compartment Syndrome - A Major Complication of Large Incisional Hernia Surgery, Chirurgia, **108(3)** (2013), 414-417.

[19]. *K. Earar, S. Gradinaru, G. Pariza, et al.,* Effect of the Sterilization Procedures of Different Surgical Meshes for Abdominal Surgery, Rev. Chim., **68(8)** (2017), 1868-1873.

[20]. *M.M. Mitache, C. Curutiu, E. Rusu, et al.,* Urinary Tract Infections in Patients with Type 1 and Type 2 Diabetes: Etiology, Resistance to Antibacterial Chemicals and Virulence Features, Rev. Chim., **68(3)** (2017), 566-569.

[21]. *E. Rusu, I. Sarbu, C. Cristescu, et al.* Highlighting the Antimicrobial Activity of Organic Compounds Isolated from Some Strains of Lactic Acid Bacteria, Rev. Chim, **67(12)** (2016), 2417-2421.

[22]. *E. Rusu, I. Sarbu, M. Mitache, et al.*, Ultrastructural Changes of Candida albicans Species Induced by the Presence of Sodium Diclofenac, Rev. Chim., **68(11)** (2017), 2566-2569.
[23]. *I.V. Antoniac, M. Burcea, R.D. Ionescu, et al.*, IOL's Opacification: A Complex Analysis Based on the Clinical Aspects, Biomaterials Used and Surface Characterization of Explanted IOL's, Mat. Plast., **52(1)** (2015), 109-112.
[24]. *A. I. Bita, A. Antoniac, C. Cotrut et al.* In vitro Degradation and Corrosion Evaluation of Mg-Ca Alloys for Biomedical Applications, Journal of Optoelectronics and Advanced Materials, **18** (2016), 394-398.
[25]. *F. Witte*, The history of biodegradable magnesium implants: A review. Acta Biomaterialia, **6** **(**2010**)**, 1680-1692.
[26]. *G. Song*, Control of biodegradation of biocompatible magnesium alloys. Corros. Sci., **49** (2007), 1696–1701.
[27]. *N.T. Kirkland, N. Birbilis, J. Walker, T. Woodfield, G.J. Dias, M.P. Staiger*, In vitro dissolution of magnesium-calcium binary alloys: Clarifying the unique role of calcium additions in bioresorbable magnesium implant alloys. J. Biomed. Mater. Res. B., **95** (2010), 91–100.
[28]. *N.T. Kirkland, J. Lespagnol, N. Birbilis, M.P. Staiger*, A survey of bio-corrosion rates of magnesium alloys. Corrosion Sci. **52** (2010), 287–291.
[29]. *B. Denkena, A. Lucas*, Biocompatible magnesium alloys as absorbable implant materials—Adjusted surface and subsurface properties by machining processes. Ann. CIRP, **56** (2007), 113–116.
[30]. *L. Yang, E.L. Zhang,* Biocorrosion behavior of magnesium alloy in different simulated fluids for biomedical application. Mater. Sci. Eng. C, **29** (2009), 1691–1696.
[31]. *W.D. Mueller, M.L. Nascimento, M.F.L. de Mele*, Critical discussion of the results from different corrosion studies of Mg and Mg alloys for biomaterial applications. Acta Biomater., **6** (2010), 1749–55.
[32]. *Z. Li, X. Gu, S. Lou, Y. Zheng*, The development of binary Mg–Ca alloys for use as biodegradable materials within bone. Biomaterials, **29** (2008), 1329-44.
[33]. *A.I. Bita, G.E. Stan, M. Niculescu, et al.,* Adhesion evaluation of different bioceramic coatings on Mg-Ca alloys for biomedical applications. Journal of Adhesion Science and Technology, **30** (2016), 1968-1983.
[34]. *F. Witte, J. Fischer, J. Nellesen, H.A. Crostackl, V. Kaese, A. Pisch, et al.,* In vitro and in vivo corrosion measurements of magnesium alloys. Biomaterials, **27** (2006), 1013–1018.
[35]. *Z. Wen, C. Wu, C. Dai, F. Yang, Z. Wen, C. Wu, C. Dai, F. Yang, F,* Corrosion behaviors of Mg and its alloys with different Al contents in a modified simulated body fluid. Journal of Alloys and Compounds, **488** (2009), 392–399.
[36]. *J.X. Yang, F.Z. Cui, Q.S. Yin, Zhang, Y.T.; X.M. Wang*, Characterization and degradation study of calcium phosphate coating on magnesium alloy bone implant. IEEE Transactions on Plasma Science, **37** (2009), 1161–1168.
[37]. *J.V. Rau, I. Antoniac, M. Fosca, et al.*, Glass-ceramic coated Mg-Ca alloys for biomedical implant applications. Materials Science and Engineering C, **64** (2016), 362-369.
[38]. *G.L. Song, A. Atrens*, Corrosion Mechanisms of Magnesium Alloys. Adv. Eng. Mater., **1** (1999), 11–33.

[39]. *T. Kraus, S.F. Fischerauer, A.C. Hanzi, P.J. Uggowitzer, J.F. Loffler, A.M. Weinberg*, Magnesium alloys for temporary implants in osteosynthesis: In vivo studies of their degradation and interaction with bone. Acta Biomater., **8** (2012), 1230–1238.
[40]. *R. Montoya*, *C. Iglesias*, *M. Escudero*, *M. García-Alonso*, Modeling in vivo corrosion of AZ31 as temporary biodegradable implants. Experimental validation in rats. Mater. Sci. Eng. C Mater. Biol. Appl., **41** (2014), 127–133.