Topical Notions About in Vivo Analysis for Degradable Biomaterials with Utility in Human Body

B Istrate¹, T Vololeniuc¹, C Munteanu¹* and Ș Lupescu¹

¹ Department of Mechanical Engineering Mechatronics and Robotics, Faculty of Mechanical Engineering, "Gheorghe Asachi", Technical University, Iasi, Romania

E-mail: cornelmun@gmail.com

Abstract. Based on the biodegradable biomaterial development, there are numerous studies demonstrating partial or total aspects that have ultimately led to their use in many fields, especially in medicine. This study summarizes the latest information on the development of degradable biomaterials based on magnesium, especially used in vivo tissue compatibility assessment. The biomaterial compatibility assessment combines with the development of medical devices, this study following evolutionary parameters and integration of implants for human use. One of the most important parameters is the efficiency with which the medical device works near to the maximum potential. In conclusion, our study aims to broadly present the in vivo analysis of biodegradable biomaterials based on magnesium.

1. Introduction

Biodegradable materials are non-toxic, non-carcinogenic, non-immunogenic, and non-teratogenic alloys with adequate physical and mechanical properties that, after implantation into a living organism, will gradually degrade, performing regular biological functions and dissolving to complete the mission, to heal tissues, preferably without leaving a metallic residue. The study, research and development of biodegradable materials is necessary to enhance their performance, improve their function, develop the release of bioactive compounds, and achieve tissue regeneration [1-3].

2. The interaction clinical response

Regarding the clinical response, among all the biomaterials used, those based on magnesium are considered to be the avant-garde of use in research studies and therapeutic medical applications, due to certain properties and functions that are closer to biological ones. A major pillar in the development and implementation of vascular and orthopedic applications, the two main areas of investigation associated with the development of magnesium materials and alloys, is the in vivo assessment of the compatibility of biomaterials and medical devices with tissues, a branch that has begun to be developed in recent years [4, 5]. Magnesium-based biomaterials have amazing advantages over stainless steel, titanium or Co-Cr-Ni alloys, which leave metallic residues resulting from in vivo abrasion with toxic effects that can cause hypersensitivity, local inflammation or tissue necrosis [1, 4, 6]. Magnesium alloy has chemically active properties and is susceptible to degradation in the physiological environment after implantation without causing toxic and secondary effects [3, 7, 8].
The researchers made a comparison of the most used elements in the medical implant industry, namely magnesium, iron and zinc (these are considered biodegradable base materials for use in the medical industry), and found that, from the point of view of the main properties, magnesium meets all the criteria to be considered a good biodegradable material (Table 1) [6].

**Table 1.** Mechanical parameters and degradation rate of pure Fe, Zn, and Mg used for medical applications (compare the stainless steel).

| Material       | Yield strength (MPa) | Tensile strength (MPa) | Elongation (%) | In vivo degradation rate (mm year$^{-1}$) |
|----------------|----------------------|------------------------|----------------|-----------------------------------------|
| Pure Fe: annealed | 150                  | 200                    | 40             | 0.16                                    |
| Pure Zn: as cast    | 17                   | 20                     | 0.2            | 0.2                                     |
| Pure Mg: as cast    | 20                   | 86                     | 13             | 407                                     |

2.1. **Magnesium physiology**

Magnesium is an essential nutrient for life, and it is, regarding abundance in the human body, the fourth element and the most common divalent intracellular cation. The human body contains approximately 25 grams of magnesium (70 kg average adult body) of which about 65% is found in the bones and teeth, and the rest is distributed into blood, body fluids, organs and other tissues. Once in the body, it is decomposed and released to form independent atoms of magnesium or "ions". Like other vitamins and minerals, the role of magnesium is mainly regulating and is involved in more than 300 enzymatic reactions that help the body to function properly [1, 6, 9]. In addition to its importance in reactions involving ATP, Mg plays roles in protein and nucleic acid synthesis, mitochondrial activity and integrity, ion channel modulation, plasma membrane stabilization and translation processes, and many other cellular functions. Due to the importance of this element, homeostasis as well as the potential pathological effects of a possible mineral imbalance should be studied closely before the human body is exposed to an excess of Mg as a result of its use as a biomaterial [4, 9].

Magnesium homeostasis is effectively maintained by the combination of intestinal absorption, renal excretion and bone use as a magnesium deposit. Exposure to degradable material may cause disruption to these systems causing discontinuation of homeostasis and pathological ailment due to an excess of deposits that may be clinically manifested as hypermagnesemia. Acute destruction of muscle tissue can also lead to an excess of magnesium [4, 9]. To date, studies have not demonstrated that hypomagnesaemia can be associated with the implantation of magnesium-based biomaterials.

3. **Biocompatibility**

To serve as an in-vivo biomaterial, one of its primordial properties referring to the development of biodegradable materials is biocompatibility. This is the ability of the material to come into contact with living tissue so that it does not produce toxic and allergic side effects and its level of adaptability to the biological environment is as high as possible [2, 4, 10].

3.1. **In vitro methods for the analysis of biocompatibility**

In vitro tests for biocompatibility assessment provide information on general toxicity, avoiding in vivo implantation of potentially toxic materials. However, in vitro techniques can not reproduce the complex environment that a biomaterial will exhibit when implanted in a physiological environment, requiring the use of in vivo investigations. There are many techniques that are associated with identifying the tissue reaction, the area where the implant is in direct contact with the biomaterial, but below we will only list the most commonly used.

Investigating intramedullary or I.O., intramodal magnesium based biomass is a technique that relies on the use of histological techniques and can be used to indicate inflammation,
neovascularization and follow-up of new bone formation [11, 12]. This technique can be supplemented by following the microscopic aspect (tissue response to implants) Another standard and widely accepted technique for initial in vivo investigations is the implantation of magnesium-based biomaterials in a subcutaneous or intramuscular environment with several specific benefits: the implant can be easy removed and evaluated for corrosion behavior, and tissue interacts much better with a possible hydrogen gas production. Several other investigations have used similar techniques to analyze soft tissue reaction in magnesium implants by specifically removing the muscle and connective tissue covering but these techniques are time consuming, costly and require the use of antibodies for a wide range of antigens to provide a complete picture of the tissue reaction that is taking place [4, 13].

4. Degradability
By comparing with other metallic materials, magnesium-based materials and alloys exhibit high bioactivity and low density, thus favoring degradability in the physiological environment and influencing success as biomaterials. For single-phase materials, degradation is typically located, resulting in the formation of concavities on the surface of the material [8, 10, 14]. The presence of a secondary phase, due to impurities, causes a galvanic degradation. The lack of generalized degradation is an important factor in the use of magnesium as a biomaterial, because extended degradability surfaces cause mechanical properties to change. On the other side of the barrier, using a magnetically degraded magnesium biomaterial could lead to the production of gaseous hydrogen in the implant medium and an increase in the local pH that could cause significant effects on surrounding tissues [4, 8, 10, 14, 15].

4.1. In vivo methods for the analysis of degradability
Techniques used for assessing the degradability of magnesium after in vivo implantation are much less compared to in vitro methods, mainly aiming at measuring the physical reduction in material size due to degradation. The most used analysis is to measure the remaining volume of the implanted material using micro-computerized tomography (μ-CT), a non-destructive technique that does not affect the implant and surrounding tissue, and then allows for other analyzes such as new bone growth or osteointegrity [4].

Another method used for analyzing material degradability is measuring the weight loss of the implant. The technique offers direct comparative data on weight loss obtained from in vitro studies but has many major drawbacks: the biomaterial has to be removed and the implant-tissue interface can not be investigated and the shear forces required to mechanically remove an implant are likely to deteriorate the tissue that surrounded the material, eliminating the potential for tissue analysis [4].

Another quantitative method used to assess degradation of magnesium in vivo is to analyze the surface of the remaining transverse section of implants in two-dimensional sections. These results are then compared to the original size of the implant, indicating the degradation. This technique is generally associated with the transverse sections of the implant that is cut with the associated surrounding tissue, allowing for a specific biocompatibility analysis [4, 12, 15]. In particular, the degradability of magnesium materials and alloys could compromise the mechanical integrity of the implant, thus requiring in-depth studies of the behavior of each material. But some studies state that the magnesium used as a candidate material meets many of the desired requirements, and in terms of manufacturing processes and initial degradability rates it is indicated to have an excellent potential.

4.2. Alloying with other materials
It is known that magnesium has a low strength under casting with a high rate of degradation [4], and the consolidation of the properties can be achieved by suitable alloying and machining conditions with
elements that are, in turn, degradable and biocompatible. These elements improve the mechanical properties by hardening the solid solution with the closed hexagonal structure, curing the precipitations and refining the granules. Aligning with other elements can inhibit early weight loss, healing, bone thickening, and inflammation, and magnesium alloy surfaces can reduce the rate of degradation until the healing period. The addition of Sn, Si, Zr and Zn can improve maximum traction resistance and elongation at failure, while combining with Ca, Sr and Mn will cause acceleration of degradation [1, 4, 16-19].

| Pro | Characteristics | Details |
|-----|-----------------|---------|
|     | Low density     | Low     |
|     | High specific   | High    |
|     | strength        |         |
|     | High damping    | High    |
|     | capacity        |         |
|     | Machinability   | High    |
|     | and dimensional |
|     | accuracy        |         |
|     | Stress shielding | Less    |
|     | Biocompatibility | Good    |
|     | Degradation     | Good    |
|     | Elastic modulus | Low     |
|     | Degradation     | Rapid   |
|     | Hydrogen        | High    |
|     | evolution       |         |

| Contrary | Characteristics | Details |
|----------|-----------------|---------|
|          | Low density     |         |
|          | High specific   |         |
|          | strength        |         |
|          | High damping    |         |
|          | capacity        |         |
|          | Machinability   |         |
|          | and dimensional |
|          | accuracy        |         |
|          | Stress shielding |         |
|          | Biocompatibility |         |
|          | Degradation     |         |
|          | Elastic modulus |         |
|          | Degradation     |         |
|          | Hydrogen        |         |
|          | evolution       |         |

Table 2. Major key benefits and drawbacks of Mg [1].

| Characteristics | Details |
|----------------|---------|
| Low density    | Mg density (1.738 g/cm³) is close to that of cortical bone (1.75–2.1 g/cm³); |
| High specific  | Strength-to-weight ratio of approximately 130 kNm/kg; |
| strength       |         |
| High damping   | Mg has the ability to absorb energy of any metal can be used for load bearing applications; |
| capacity       |         |
| Machinability  | Mg is the easiest structural metal to machine, and stable final dimensions are easy to achieve. Consequently, complex shapes are easily producible, which is crucial for the often intricate shapes that are required for medical applications; |
| and dimensional |
| accuracy       |         |
| Stress shielding| Stress-shielding-related problems can be greatly reduced for many orthopaedic implants as Mg density is very close to that of bone; |
| Biocompatibility| Mg is considered biocompatible and has been shown to increase the rate of bone formation; |
| Degradation    | Corrosion of Mg in the body would eventually result in complete degradation and it would be beneficial for patients have temporary exposure to an implant in the body. |
| Elastic modulus| Lower elastic modulus of Mg may be beneficial with respect to stress shielding and it is vital to ensure that any implant is designed to sustain its load without deformation; |
| Degradation    | Mg implants are intended to completely degrade, but at a slow rate to the pace of bone remodelling; |
| Hydrogen       | The released H2 gas accumulates at the surrounding soft tissues at severe degradation rate. The hydrogen evolution rates for various Mg alloys containing Zn, Al and Mn are reported as 0.01 ml/cm²/day |

There are studies that have tracked alloying magnesium with aluminum but have not shown concretely whether it increases / decreases the compatibility and degradability of magnesium used in medical applications. Also included in this category are rare elements such as lanthanum, lutetium, scandium and yttrium.
Manganese is an essential element that plays an important role in the metabolic cycle of lipids, amino acids and carbohydrates. In the magnesium alloy, manganese is mainly used to increase ductility. Recently, magnesium-manganese alloys have attracted considerable attention due to their high damping capacity (about 80%), which can help suppress vibrations generated during motion and stress at the implant-bone interface [4].

Alloying elements can significantly improve the mechanical properties, control the rate of degradation, and influence the biological response to the magnesium alloy. But it is difficult to choose the best alloy and, to do this, we need more in vitro and in vivo experiments such as clinical investigations [16, 20-25].

5. Other properties that can cause biodegradability
Magnesium elastic modulus (41 ~ 45 GPa) is closest to that of natural bone (3 ~ 20 GPa) compared to other elements used to make bioresorbable materials, inducing stress protection and increasing secondary bone fracture [4].

Other properties that define good biodegradable material are yield strength, elastic modulus and maximum traction resistance for load applications (Table 1), low weight, good wear resistance and osteointegration [1].

6. Conclusions
Since the beginning of the 20th century, magnesium and its alloys have been applied in many clinical cases but are not widely used due to uncontrollable degradability. The latter has led to numerous failures, as well as to clinical complications. From the studies conducted, there is a way to improve biodegradable implants, namely adding elements by making alloys to meet both the biodegradability criterion and biocompatibility. There are multiple alloys created with improvement properties, but their biological effect as well as long-term clinical outcomes are not yet well established. This study seeks clarification on the use of magnesium-based biomaterials in the use of implants so that both researchers and physicians benefit from avant-garde materials that will allow less invasive and less costly surgical interventions.

7. References
[1] Radha R, Sreekanth D 2017 Journal of Magnesium and Alloys5(3) 286-312
[2] Buddy D, Ratneret al. 2013 Biomaterials Science: An Introduction to Materials in Medicine; Third Edition; Academic Press, Elsevier; II.3.4.; p. 609-615
[3] Prakasam M et al. 2017 Journal of fundamental biomaterials8 44
[4] Walker J et al. 2014 Journal of Biomedical Materials Research102(6) 1316-1331
[5] Mao L et al. 2017 Scientific Reports7 46343
[6] Li H, Zheng Y, Qin L 2014 Progress in Natural Science: Materials International24(5) 414-422
[7] Hou L et al. 2014 Progress in Natural Science: Materials International24(5) 466-471
[8] Shimizu Y et al. 2009 Interface Oral Health Science 318-320
[9] Allan R, Mara N 2012 Acute Med11 3-7
[10] Yufeng Z 2016 Magnesium alloys as degradable biomaterials CRC Press p. 46-48
[11] Razavi Met al. 2015 Journal of Materials Science: Materials in Medicine26 184
[12] Cheng J 2014 Research of Magnesium-based Alloys for Medical Applications 2nd International Conference on Education Technology and Information System; Atlantis Press p. 631-635
[13] Mehrban N, Bowen J 2016 Elsevier 81 110
[14] Witte F et al. 2006 Biomaterials27(7) 1013-1018
[15] Li L et al. 2017 Regenerative Biomaterials4(2) 129–137
[16] Pogorelov M et al. 2017 Interv Med Appl Sci.9(1) 27–38
[17] Persaud-Sharma D, McGregor A 2012 J Biomim Biomater Tissue Eng.12 25–39
[18] Trinca L C, Fintananiu M, Solcan C, Trofin A E, Burtan L, Acatrinei D M, Stanciu S, Istrate B and Munteanu C 2015 Appl. Surf. Sci. 352 140–50

[19] Istrate B, Munteanu C, Matei M, Oprisan B, Chicet D and Earar K 2016 Influence of ZrO 2-Y 2 O 3 and ZrO 2-CaO coatings on microstructural and mechanical properties on Mg-1.3Ca-5.5Zr biodegradable alloy IOP Conference Series: Materials Science and Engineering 133 12010

[20] Zhang E, Xu L, Pan F, Yu G, Yang L, Yang K 2009 Biomaterials 30 (8) 1512–1523

[21] Minciuna M G and Vizureanu P 2013 Metalurgia International 18(6) 123-126

[22] Minciuna M G, Vizureanu P, Geanta V, Voiculescu I, Sandu A V, Achitei D C, Vitalariu A M 2015 Revista de chimie 66(6) 891-894

[23] Hanganu S C, Armencia A O, Grigoras S, Hanganu L C and Vizureanu P 2010 Materiale Plastice 47 357-378

[24] Bălătuță M S, Vizureanu P, Mareci D, Burtan L C, Chiruță C and Trincă L C 2016 Materials and Corrosion-Werkstoffe und Korrosion 67(12) 1314-1320

[25] Stoleriu S, Iovan G, Pancu G, Georgeescu A, Sandu A V and Andrian S 2014 Materiale Plastice 51 162-166