THE DESIGN CRITERIA FOR BIODEGRADABLE MAGNESIUM ALLOY IMPLANTS

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DOI: 10.17973/MMSJ.2018_12_201867

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Magnesium (Mg) and its alloys posse's great potential for the application of biodegradable medical implants. However, the extensive applications of Mg-based alloys are still inhibited mainly by their high degradation rates and consequent loss in mechanical integrity. Using suitable alloying elements mechanical strength and corrosion resistance of Mg-alloys can be enhanced but cytotoxicity and long term inflammatory consequences of these elements are the major concern. Further modifying the surface characteristics of Mg-alloy through various surface coating, machining, mechanical working, etc., corrosion behaviour can be manipulated. Metal matrix composites reinforced by nano-particles are very promising materials, suitable for a large number of applications. These composites consist of a metal matrix filled with nano-particles featuring physical and mechanical properties very different from those of the matrix. The nano-particles can improve the base material in terms of wear resistance, damping properties and mechanical strength. This review paper summarises the various challenges and opportunities in design and development of biodegradable Mg alloy implants.

KEYWORDS

design criteria, magnesium alloys, magnesium composite, biocompatibility, mechanical integrity, biomaterials, orthopaedics, manufacturing processes.

1 INTRODUCTION

In the present time of third generation biomaterial development, a new strategy of tissue engineering and regeneration is adopted by researchers, when the biomaterials are being created to act as temporary structure, that enables them degrade in biological media and allow surrounding tissue to proliferate and integrate with the implant and eventually replace it [Kumara 2017]. The biodegradable implant would be the one of matching corrosion rate with bone healing rate, mechanical properties sufficient to provide the required support during healing period, degrades completely in the body when the target bone is completely healed. Furthermore, the resultant by-products of the degradation process should be non-toxic; capable of being consumed or absorbed by the human body [Chen 2015, Purnama 2010, StJohn 2005]. Biodegradable medical implant for orthopaedic and vascular applications, require an integrated approach involving appropriate composition selection, design of implant geometry with combined set of properties such as mechanical, corrosion, biocompatibility and a suitable manufacturing technique. Recently, biodegradable metallic materials have gained growing interest and are intensively investigated [Panda 2017].Magnesium (Mg) and its alloys have been advocated as potential candidates to serve this purpose for obvious reasons [Janz 2007, Janz 2009, Yang 2011]. The density (1.74 g/cm3) and Young's modulus (42 GPa) of Mg are much closer to those of bone than stainless steels or Ti alloys [Chen 2015, Gu 2010]. The properties are of great importance as high mechanical strength reduces the amount of implant material needed for a given applied load and reducing the elastic modulus mismatch alleviates stress-shielding effects between bone and the implant material.

Thanks to these desirable physical and mechanical properties, Mg and Mg alloys are endowed with great potential as ideal temporary implant materials. However, the rapid degradation in the physiological environment hampers its clinical use. Therefore, one of the most exigent problems concerning Mg and Mg alloys is the unpredictable corrosion behavior in vivo, where numerous ions are present in the body fluids (e.g. Na, K, Ca, Mg, HCO3, Cl, HPO4 and SO4) that make metallic corrosion very hard to predict or define.Thus, to compensate or even improve the antimicrobial activity of the Mg alloy, the elements having antimicrobial property should be chosen as alloy or coating compositions to enhance the corrosion resistance of Mg alloy. [Lock 2014, Pandova 2014, Pandova 2016, Prislupcak 2014, Seitz 2014, Zaborowski 2007, Zhao 2015].

A substantial number of scientific publications regarding the degradation of Mg and its alloys have reported a large range of results due to the different materials, methods and experimental conditions selected. To the best of our knowledge there has not been a systematic approach, or agreement on the experimental conditions necessary [Zhao 2015, Panda 2013, Mordike 2001]. The research is underway to tailor the degradation rate of magnesium to match the healing of bones through alloying and composite technology.

Metal matrix composites (MMC) have been reported to show significant improvement in mechanical properties [Wentian 2014] when compared to non-reinforced monolithic metal. MMC reinforced by nanoparticles (NPs) are very promising materials, suitable for a large number of applications. These composites consist of a metal matrix filled with NPs featuring physical and mechanical properties very different from those of the matrix. The NPs can improve the base material in terms of wear resistance, damping properties and mechanical strength.

Physicochemical characteristics of nanoparticles and engineered nanomaterials including size, shape, chemical composition, physiochemical stability, crystal structure, surface area, surface energy, and surface roughness generally influence the corrosion resistance and good biocompatibility of the Mg-based implants. Mg-based MMC have shown improved specific mechanical properties and low density [Ratna Sunil 2014]. The improvement in mechanical properties of magnesium is influenced by the processing technique, the type and amount of nanoparticles added. Today information on magnesium alloys nanomaterials is scarce. Innovative use of nanosized particles, hollow balloons, shape memory alloy (SMA) fibers, and other engineered reinforcements has made it possible to develop next-generation MMCs.This compels the researchers to evaluate the role of these properties in determining associated corrosion rates and localized corrosion modes issues. Reckoning with this fact, in this paper, issues pertaining to the the design criteria of biodegradable magnesium alloy implants.

The aim of this work is to review recommendations assessment the main potential applications of this new class of materials.

2 GENERAL: MAJOR RECENT ADVANCES

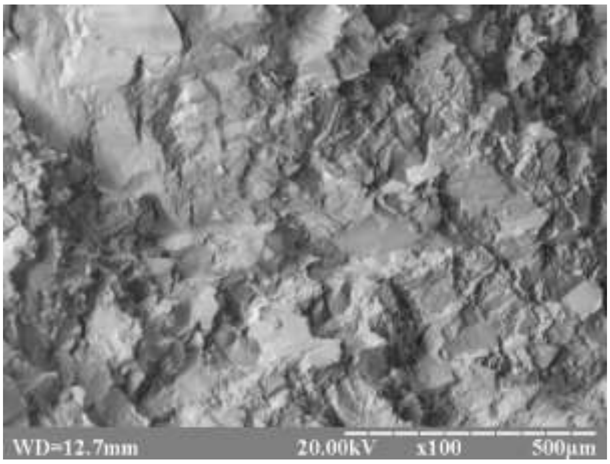
2.1 Assessment of biodegradable materials for medical applications

A review of current regulation relating to medical devices

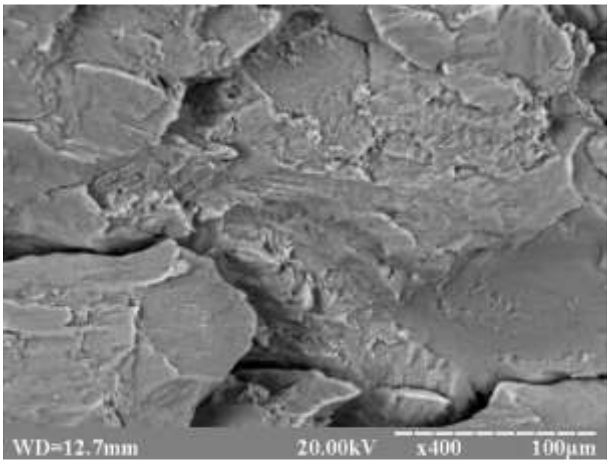
Biomaterials alone or in combination with electronic devices are used to replace a part or a function of the body in a safe, reliably economical, and physiologically acceptable manner. Current regulation for medical devices is based on several European directives, the main ones are listed below: Directive 90/385/EC relating to active implantable medical devices (AIMD) and Directive 93/42/EC relating to medical devices (recently revised and consolidated by Directive 2007/47/EC22b) and Directive 98/79/EC relating to *in-vitro* diagnostic medical devices. These directives are based on the premise that the medical device manufacturer is responsible for risk management. Thus, to launch medical devices on the European market, manufacturers must ensure that the devices comply with the essential safety requirements listed in Appendix I of these European Directives by providing evidence in terms of efficacy and safety of the device in order to minimize the risks associated with the use of such devices by patients and users. Therefore, it is of great importance, in particular, to alter and improve the intrinsic corrosion behavior of Mg-based alloys for biomedical applications. Approaches to overcome these challenges include the selection of adequate alloying elements, proper surface treatment techniques and control of the degradation rate of Mg or its alloys [Li 2008, Long 2017, Peng 2015 , Wan 2008]. It can be seen that most of the commercial alloys are multicomponent [Yanga 2008]. Relevant parts of the body that biodegradable materials are applicable for clinical application include cortical/cancellous bone, dentin and enamel, cartilage, and ligament, tendon and fascia. Generally, it is important to match the stiffness of the targeted body part to avoid harmful effects like stress shielding. In stress shielding due to much higher stiffness of the implanted device compared to the surrounding tissue, areas adjacent to the implanted biodegradable device tend to heal well but at the expense of regions further away from the implanted device. The higher stiffness of the implanted device points toward adjacent areas preferentially conducting higher levels of mechanical stress compared to regions further away from the implanted device.

The advantages Mg-based materials possess include apparent non-toxicity, biocompatibility, mechanical compatibility with bone, and biodegradability in the body. Concerning good biological behaviour, Mg is an essential element for the human body. Being the fourth most abundant cation in the human body, Mg^{2+} is stored mainly in bone tissue. Mg^{2+} is the direct corrosion product of magnesium, is absorbed by the human body easily, and can be excreted in urine [Muralidharan 2015]. Mg also has Young's modulus similar or close to that of bone (20–40 GPa), compared with titanium (Ti) alloys (about 110 GPa), stainless steel (SS) alloys (about 200 GPa) and cobalt (Co) based alloys (about 230 GPa). This generally mitigates or minimizes the stress shielding effect induced by serious mismatch in modulus between natural bone and metal implant. The density of Mg (1.74 g/cc) is also close to those of natural bone (1.8–2.1 g/cc), compared with Ti alloys (4.42 g/cc for Ti–6Al-4V), SS alloys (about 7.8 g/cc), biodegradable polymers (about 1 g/cc for PLLA) and hydroxyapatite (3.16 g/cc) [Mohammad Mezbahul-Islam 2014].

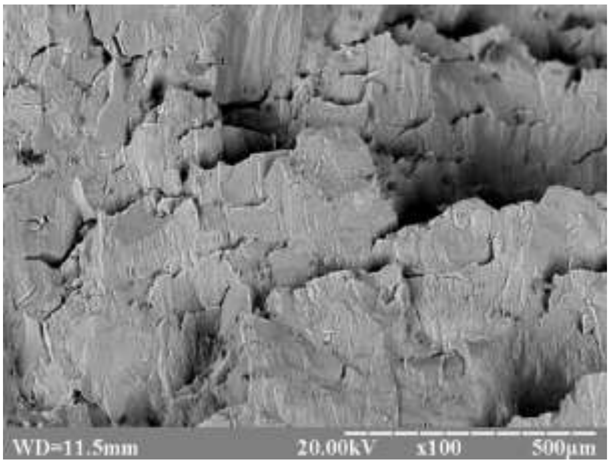
Fig. 1 shows the micrographs of the surface and the cross section of the samples obtained by our group with a flake-like microstructure on the surface (Fig. 1 a, bSEM morphology of Mg at 4 weeks).



a)



b)

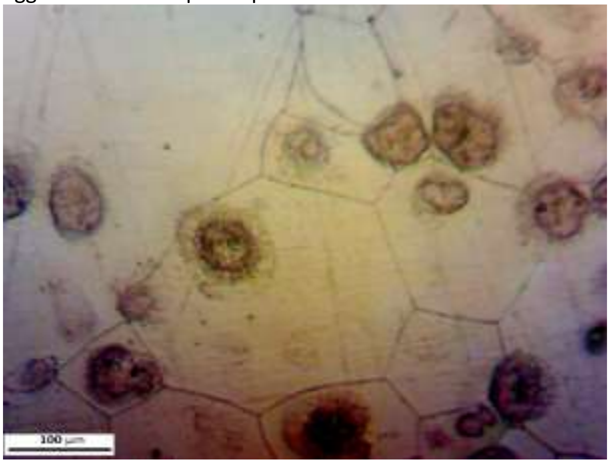


c)

Figure 1 Morphology of (a) surface and (b) cross section of Mg-alloy (wt. fraction: Al (0.013 %), Zn (0.24 %), Nd (2.09 %), Zr (0.49 %) balance Mg), c)morphology of Mg at 24 weeks post-operation

According to EDX-data, the roughly spherical IMP particles contain Mg, Zn, Zr and Nd, while only Mg and Zn were found in the rod- and plate-like particles.

The optical images of the Mg–Al–Zn–Nd–Zr alloy are shown in Fig. 2. It was revealed more dark-colored phases with a lower particle size and a semi-ideal distribution. The above results reveal that alloying with Zn, Zr and Nd formed agglomerated composite particles.



a)

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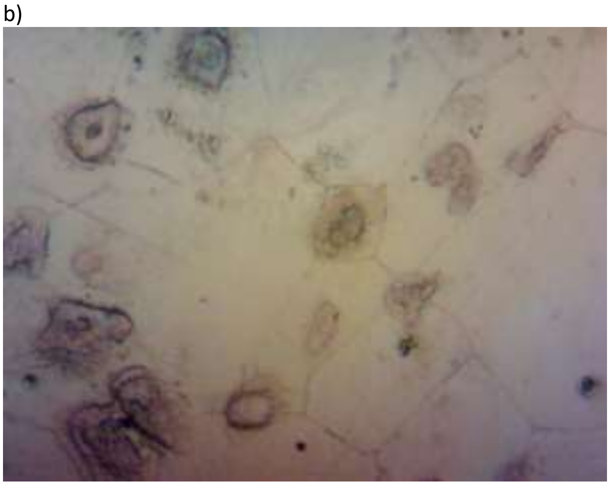

c)

Figure 2. The optical microscopy images of the Mg–Al–Zn–Nd–Zr alloy. The form inter-metallic phases that can enhance thestrength: a)rolling, b) extrusion, c) as-cast alloys.

Mg-based implants demonstrated a high susceptibility to stress corrosion cracking (SCC) in ionic solution due to the dual effect of corrosion and mechanical stress of surrounding tissues, therefore, probability of collapse of these implants is high.The influence of different mechanical processing operations like rolling (a), extrusion (b), heat treatment during fabrication has the potential to greatly influence surface and microstructural properties and hence affect the performance of Mg-alloy. Using rolling and extrusion process, reduced grain size and definite orientation helps to improve the strength, ductility and corrosion resistance of Mg-alloys. Figure 2 shows the grain size reduction in micro-tubes made of ZM21 after hot indirect extrusion, two pass, three pass and four pass drawing. It was found that randomly shaped grains in the as-cast alloys (c) are changed to equiaxial ones after extruding procedure. Figure 2 shows the microstructure.

The nature of reaction between the carrier agent and molten magnesium is very significant. During an exothermic reaction, the greater amount of heat generated would be expected to aid the reinforcement releasing process, while endothermic reactions negatively affect this process. Therefore, by utilization of smaller composite reinforcement powders Zn, Zr and Nd and using a carrier agent resulting in an exothermic reaction with the molten magnesium, the method could be more successful.

The degradation of Mg is accompanied by the release of Mg ions, the rise of pH and osmolality in surrounding environments. According to the standard of ISO 10993 Part 13, the pH value shall be appropriate to the site of intended use maintaining in an appropriate range.

2.2 Corrosion behaviour

Magnesium alloys corrode/degrade in aqueous materials by several different oxidation-reduction reactions which are influenced by the alloying elements. Generally, the corrosion of magnesium in water will yield magnesium-hydroxide and hydrogen gas evolution. The following equations are the main corrosion reactions on pure Mg [Peng Q. 2013]:

Anodic reaction: $Mg \rightarrow Mg^{2+} + 2e^-$ (1)

Cathodic reaction: $2H_2O + 2e^- \rightarrow H_2\uparrow + 2OH^-$ (2)

$Mg^{2+} + 2OH^- \rightarrow Mg(OH)_2\downarrow$ (3)

If phosphate and calcium ions are available, than Mg^{2+}may aid in the precipitation of calcium phosphate:

$PO_4^{3-} + Ca^{2+} + Mg^{2+} \rightarrow Mg_xCa_y(PO_4)$ (4)

$Mg(OH)_2$ forms a stable protective layer on the surface of magnesium implants in high pH (>11.5) environments, but lower pH (<11.5) will facilitate corrosion of magnesium alloys in aqueous solution.

In order to define the processing conditions for making various Mg-based alloys and subsequent treatments to obtain the optimum mechanical properties, knowledge of the phase diagram and thermodynamic properties of these alloys is essential. In addition, phase relations and phase stability under given conditions can be better understood through computational thermodynamic modeling. Precise description of the binary systems provides an opportunity to approach the phase equilibria aspects of alloy development and track of individual alloys during heat treatment or solidification by calculating the phase distributions and compositions.

3 METAL MATRIX COMPOSITES REINFORCED BY NANO-PARTICLES

3.1 Specific features of the nanoscale

In the emerging field of nanotechnology, a goal is to make nanostructures or nano-arrays with special properties with respect to those of bulk or single particle species. Metal matrix composites reinforced with NPs, also called Metal Matrix nano-Composites (MMnCs), are being investigated worldwide in recent years, owing to their promising properties suitable for a large number of functional and structural applications. The reduced size of the reinforcement phase down to the nano-scale is such that interaction of particles with dislocations becomes of significant importance and, when added to other strengthening effects typically found in conventional MMC, results in a remarkable improvement of mechanical properties [Casati 2014]. Particle size is expected to influence three important groups of basic properties in any material. A number of processing routes are available for the synthesis of nano-reinforced MMC based either on solid sintering or on liquid processing. Several methods have been proposed for the preparation of Mg-based MMC, including squeeze casting, stir casting and powder metallurgy.

Consolidation of powder, generally preceded by high-energy ball milling, is carried out both by conventional technique (HIP, forging or CIP followed by heat treatment) or alternative methods, firstly by ECAP or hot extrusion. Indeed, among the liquid processes, promising results were achieved by ultrasonic assisted casting. For composites prepared by the conventional liquid metallurgy route, severe aggregation of nanoparticles frequently occurs even when mechanical stirring is applied before casting. This is due to poor wettability and high viscosity generated in the molten metal owing to high surface-to-volume ratio of the nano-sized ceramic particles. The density of NPs do not play an important role in the production process of nanocomposites. Such small particles are supposed to float on the top of the molten bath even if their density is relatively higher than that of the liquid matrix. This issue was indeed of paramount importance in micron-sized particle reinforced composites but it is felt that in nano-reinforced materials, other effects such as those induced by extensive surface tension play a much more important role.

The high mechanical resistance of MMnCs is the result of several strengthening mechanism contributions, namely: Hall-Petch strengthening due to grain refinement, Orowan strengthening due to the presence of nanoparticles, increased dislocation density and formation of internal thermal stresses due to coefficient of thermal expansion mismatch between reinforcements and matrix, work hardening due to elastic modulus mismatch between reinforcements and matrix and effective load transfer from the matrix to the stiff and hard particles. Given the large proportion of atoms on the surface of a nanoobject, the crystalline network is subject to constraints, which lead to deformities and re-arrangement of the atoms. This configuration therefore alters the phenomena appearing on the external surface, essentially adsorption, absorption and the binding of external chemical species. This specific chemical reactivity of nanoparticles is therefore widely used in chemical catalysis and also in biological applications. The presence of nanostructures on surfaces also determines protein adsorption on these materials. The adsorption of proteins on nano-objects, which is influenced by the properties of the latter, can alter their overall size and surface charge. These factors are therefore likely to impact upon the internalization of nano-objects in cells, cell response and their distribution in the body.

The thermodynamic instability at the surface of nano-objects makes the latter highly reactive. Increased surface energy and the high dispersion rate specific to nanoparticles contribute to the agglomeration and aggregation phenomena often observed with these materials. Such behaviour has been documented and investigated in the colloidal studies. The growing importance of surface free energy and stress with decreasing particle size must be considered: changes in thermodynamic stability associate with size can induce modification of cell parameters and/or structural transformations and in extreme cases the nanoparticle can disappear due to interactions with its surrounding environment and a high surface free energy. In order to display mechanical or structural stability, a nanoparticle must have a low surface free energy. As a consequence of this requirement, phases that have a low stability in magnesium alloys can become very stable in nanostructures.

In recent years, studies have revealed that the addition of nano-reinforcements such as oxides (Al_2O_3 [Luo 2012b, Berglund 2012, Zhang 2014], TiO_2 [Song 2007, Luo 2012a, Panda 2016b], Y_2O_3 [Luo 2012b], ZnO [Berglund. 2012] and ZrO_2 [Zhang 2014]), carbides (SiC [Novakova-Marcincinova 2014b], B_4C [Cao 2006] and TiC [Sun, Rad 2012]), nitrides (BN [Friedrich HE.2006], AlN [Novakova-Marcincinova 2013] and TiN [Schmid-Fetzer 2012, Rad 2012]), borides (TiB_2 [Koike 2003b, Wu 2002, Panda 2016b], SiB_6 and ZrB_2 [Zhang 2012, Zhang 2014, Panda 2016b]), CNT [Niu 2013, Gibson. 2010, Panda 2016a] and graphene [StJohn 2005, Janz 2009], helped to simultaneously improve the yield strength and ductility of magnesium. In these studies, a small volume fraction of approximately 1 to 2 volume percent of nano-size reinforcements have been shown to produce results comparable or even superior to that of MMCs containing a much higher volume fraction of micron size reinforcements.

The addition of ceramic reinforcements such as Al_2O_3, Y_2O_3, ZrO_2, ZnO, TiO_2, B_4C, SiC, TiC, AlN, BN, TiN, TiB_2 and CNT typically improves yield strength and ductility of magnesium. The addition of metallic reinforcements such as Cu and Ti improves strength but the ductility may be reduced. A hybrid combination of metallic and ceramic reinforcements can improve both strength and ductility for hybrid microwave sintered nanocomposites. Also, the improvement in yield strength for magnesium nanocomposites with approximately $1-2$ vol% of nanoparticles are comparable with magnesium alloys composites reinforced with higher volume fraction (> 10 vol% of micron size particles) and the ductility of nanocomposites are significantly better. The addition of nanoparticles were able to improve the compressive strength of magnesium. Compressive strength of magnesium was increased due to grain refinement by the addition of nanoparticles which reduced the twinning activity.

Alani et al. [Mordike, B. 2001] evaluated the compatibility of Mg-based implants and found that the nanostructured HA (nHA) coating on polished Mg substrates is a critical step for achieving good compatibility.

However, the Mg-based MMCs prepared in these reports suffer from several problems, including phase separation caused by inhomogeneous reinforced fibre distributions [**Chyba! Záložka není definována.**], large and uncontrolled pores inside the material and large grain size. Such MMCs characteristics degrade their performance as a structural material.

Several methods have been explored to produce nanocrystalline or amorphous Mg. One of the most common methods is rapid solidification, which requires rapid cooling of the alloy melt to avoid crystal nucleation and growth. Several Mg alloys with small (< 1 µm) grain size have been produced by rapid solidification and powder metallurgy methods, including Mg-Cu-Y, Mg- Al-Ge, Mg-Al-Si, Mg-Ni-Nd. However, strict requirements regarding the composition of Mg-based metallic glasses limit freedom in terms of the design of novel nanocrystalline or amorphous alloys for having the desired density and mechanical properties. Another method of producing small grains involves the severe plastic deformation of metal alloys. The disadvantages of these techniques include the limited grain size obtained (commonly > 100 nm), long processing time and high energy consumption. These can be achieved with the addition of biocompatible nanoparticles such as Ti [Mordike 2001], TiO_2 [Peng 2013, Novakova-Marcincinova 2014a], TiC [Yang 2011, Zhao 2015, Kuric 2016] and fluorapatite and hydroxyapatite (HA) or carbonate-HA (CO_3^{2-}-HA).

The risk to man of any given nanomaterials is the combination of the intrinsic hazard of the product and human exposure to this product. According to current studies [Gibson 2010, Guan 2014], though still scarce and sometimes contradictory, it is generally admitted that the toxicity of a nanoscale particle would differ from its conventional counterpart; which does not necessarily mean that the nanomaterial is more toxic.

Detected either directly in the blood or indirectly, nanomaterials can be opsonized, recognized by the reticulo-endothelial system and subjected to phagocytosis by macrophages in order to eliminate them from circulation. They were then distributed in various organs such as spleen, liver and kidney. They could also be detected in the heart, lungs or bone marrow. Translocation to the Central Nervous System was also possible. Enzymes such as proteases or metallothioneins in the organs could be involved in the metabolism of metallic nano-objects. Surface functionalisation of nanomaterials is particularly important here because it affects biodistribution and kinetics.

Firstly, when a nanomaterial is exposed to a biological medium, its behavior is determined by various factors and does not depend solely on its intrinsic characteristics. In fact, on coming into contact with a biological environment, nano-objects are immediately covered with a dynamic protein "corona" of variable composition [StJohn 2005, Janz 2007, Janz 2009, Yang 2011, Novakova-Marcincinova 2017, Barfield. 2012, Hiromoto 2015, Seitz 2005, J.M. 2014, Zhao 2015, Kuric 2017].

4 CONCLUSIONS

In order to prevent or minimise cytotoxicity or adverse tissue reactions from implant materials, it is advisable to use the alloying elements that exist in the human body or have shown beneficial effects on tissue regeneration and healing such as calcium (Ca), zinc (Zn), strontium (Sr) and zirconium (Zr). Therefore, only the most important alloying elements which improve the performance of Mg alloys for biodegradable implants are discussed. Nanotechnologies are genuinely important tools for the future of medicine, improving existing instruments and creating new medical devices that are more intelligent, more effective and more biocompatible. The development of nanotechnologies brings many hopes in terms of new diagnostic and treatment applications but also raises issues concerning potential harmful biological effects, which have not been fully elucidated. Reinforcement at nano-length scale in magnesium has the capability to enhance tensile, compressive, wear, high temperature and fatigue properties over traditional magnesium composites containing micron-size particles. Most of these properties are fundamental properties that are required to qualify a material for engineering or biomedical applications. The capability of some of the nanoparticles to simultaneously increasing strength and/or ductility of magnesium ensures higher damage tolerance for any given application. The successful extension of these materiali as implant materiali, however, will depend on their degradation behaviours in the human body where much research is required.

ACKNOWLEDGMENTS

The authors would like to thank the KEGA grant agency for supporting research work and co-financing the project KEGA: 004TUKE-4/2017.

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