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FABRICATION AND EVALUATION OF THE MECHANICAL PROPERTIES OF REINFORCED BIODEGRADABLE MAGNESIUM SCAFFOLDS USING THE SPACE HOLDER METHOD

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ABSTRACT

INTRODUCTION: Magnesium metallic biomaterials have drawn attention as a promising bone substitute material because they can degrade spontaneously and have mechanical properties similar to those of bone. Despite that, rapid degradation is a major disadvantage of magnesium. Therefore, different approaches such as reinforcing magnesium with other phases have been developed to overcome this problem.

OBJECTIVE: The aim of this study was to fabricate magnesium (Mg) scaffolds alloyed with zinc (Zn) and different concentrations of hydroxyapatite (HA) using powder metallurgy route, then porosity assessment, characterization and evaluation of the mechanical properties of these composites.

METHODS: Magnesium (Mg), zinc (Zn), hydroxyapatite (HA) and ammonium bicarbonate space holding agent powder particles were mixed. Mixtures were divided into 3 groups according to the hydroxyapatite percentage: Group A (Mg-4%Zn-0%HA), group B (Mg-4%Zn-5%HA) and group C (Mg-4%Zn-7.5%HA). To fabricate the scaffolds, powder metallurgy route was used. Porosity assessment and characterization using Scanning Electron Microscope (SEM) were done. Testing of mechanical properties was done.

RESULTS: Porosity assessment and SEM characterization showed that the scaffolds were highly porous with group B having the highest percentage of porosity. Mechanical testing showed that the specimens of group A had the highest strength and elastic modulus among all specimens and scaffolds of group C had higher values of strength and elastic modulus than group B.

CONCLUSION: This work showed that fabrication of magnesium scaffolds alloyed with other elements using powder metallurgy route is feasible and the obtained scaffolds were found to be potential scaffold materials for bone tissue engineering.

KEYWORDS: Scaffolds, Biodegradable metals, Magnesium composites, Powder metallurgy.

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INTRODUCTION

A great number of people every year experience the incidence of bone defects which are repaired using grafting techniques such as autografts and allografts. However, the many problems of these techniques made researchers shift towards using biomaterials as scaffolds for bone tissue engineering[(1)].

There are certain requirements that must be fulfilled by bone scaffolds such as mimicking the natural extra-cellular matrix, being osteoconductive, biodegradable, biocompatible and having good mechanical properties. Another important requirement is porosity and a pore diameter of 100 to 500 μm has been found to be an optimum pore size for bone scaffolds[(2-4)].

Many biomaterials such as ceramics, polymers and metals can be used to fabricate scaffolds. Polymers and ceramics have many advantages such as the ease of processability, being biodegradable and biocompatible, while ceramics have been found to be bio-inert, have high corrosion resistance and superior mechanical properties compared to polymers. However, these materials have some limitations such as brittleness of ceramics, low corrosion resistance and poor mechanical characteristics of polymers that restrict their use as bone scaffold materials[(2, 5, 6)].

In light of the problems mentioned above, metallic biomaterials gained more attention as bone scaffold materials[7]. Some of the commonly used metals are stainless steel, cobalt and titanium-based alloys. Their fundamental issue is that they cause stress shielding of bone because of having an elastic modulus that is much higher than that of the bone. Besides, they are not biodegradable and have to be removed through a second surgical procedure[2, 8].

The aforementioned drawbacks can be overcome by using biodegradable metals. Iron (Fe), Zinc (Zn) and Magnesium (Mg) are examples of these biodegradable metals. Fe and Zn are not frequently used because of the high density and slow degradation of Fe and poor mechanical properties of Zn[9].

Mg is an important element for many physiological processes in the body. Because of its mechanical and physical properties that have been found to be close to those of bone, Mg has a great potential to be used in orthopedic applications. Moreover, Mg biomaterials do not require a second surgery to be removed thanks to their spontaneous biodegradation in physiological environments. Also, Mg ions resulting from degradation do not have negative side effects making Mg highly biocompatible[10]. As a result, Mg can be used as fixation devices or porous scaffolds to encourage bone formation[2].

Regardless of these previously mentioned outstanding features, pure Mg has an extremely fast degradation rate in chloride containing biological fluids which is considered a major challenge regarding the use of Mg as bone substitute material as this fast degradation is accompanied by evolution of hydrogen gas which negatively affect the healing and affects the local pH. Moreover, this rapid degradation can cause the implant to lose its integrity and deteriorate. So, it's crucial to develop strategies to control Mg corrosion and optimize its mechanical and biological characteristics[11, 12].

A successful method that has been proposed is alloying and reinforcing Mg with suitable elements like aluminum, manganese, zinc, ceramic reinforcing particles, etc.[13]. It should be taken into consideration that these elements need to be eliminated from the body without causing any harmful toxic side effects[8]. Zinc which is an essential nutrient for the body has been found to be a safe choice for biomedical applications. Also, hydroxyapatite (HA) can be used to control degradation, improve the mechanical properties and improve bioactivity of scaffolds because hydroxyapatite is a bioactive, osteoconductive mineral that has the same structure as natural bone; therefore, it can induce precipitation of calcium phosphate crystals and growth of bone-like apatite on the surfaces of scaffolds[8, 10, 14].

Many techniques have been employed to fabricate porous magnesium scaffolds, for example, casting, melt foaming, powder metallurgy, solid free-form process and additive manufacturing technique[5, 15]. A successful one is the powder metallurgy route or the space holder method in which spacers are used and responsible for creation of pores. The amount, size and shape of these particles are the primary factors that need to be considered to have scaffolds with optimum pore characteristics and sufficient mechanical properties[13].

Carbamide (urea) and ammonium bicarbonate are the most frequently used space holding agents. Pores are generated in place of these particles after their removal through thermal decomposition. Temperatures needed for thermal degradation of ammonium bicarbonate are lower than those needed for urea so ammonium bicarbonate is more preferred to be used[13].

This work aimed at using space holder method and ammonium bicarbonate spacer particles to fabricate Mg-Zn-HA scaffolds. Pressing of mixtures of the powder particles to obtain green compacts and a two-step sintering process were carried out. The null hypothesis of this study proposes that there is no significant difference in the porosity and mechanical properties of the scaffolds fabricated using different concentrations of hydroxyapatite as a reinforcing agent.

MATERIALS AND METHODS

1. Samples' preparation

1.1 Synthesis of hydroxyapatite

Hydroxyapatite was synthesized using wet-chemical precipitation method. This technique involved adding a solution of 0.5 M calcium nitrate tetrahydrate (Alfa Aesar, Germany) to a solution of 0.3 M ammonium phosphate dibasic (Alfa Aesar, Germany) at a 1:1 ratio to obtain Ca:P ratio of 1.67. Ammonia was added gradually to raise the pH of the solution to 10 which was checked using a pH meter (HQ411D, Hach, USA). The solution was stirred for 3 hours with magnetic stirrer (F91T, Falc, Italy). The powder was sintered at 500°C in a muffle furnace (HD-105 150, Hobersal, Spain) and ground using mortar and pestle to obtain the hydroxyapatite powder[16]. The size of the obtained hydroxyapatite powder was in the range of 26.9 to 49.8 nm.

1.2 Fabrication of the scaffolds

To synthesize the magnesium composites, magnesium powder (SDFCL Sd Fine Chem Limited, India, average particle size 100 μm), zinc powder (SDFCL Sd Fine Chem Limited, India, average particle size ≤ 45 μm) and ammonium bicarbonate powder (PIOCHEM, Egypt) were used.

1.2.1 Mixing of the powder particles

Powder particles were weighed and mixed according to the following compositions: group A (Mg-4%Zn), group B (Mg-4%Zn-5%HA) and group C (Mg-4%Zn-7.5%HA). The used volume percentage of ammonium bicarbonate spacer was 40% in all groups. Mixing was done in a ball mill (Insmart M-780, India) at 360 rpm for 2 hours (milling for 30 minutes followed by a 30-minute rest period) using 20 mm diameter stainless steel balls with 1:9 ball to powder ratio to obtain homogenous distribution and dispersion of the alloying elements.

1.2.2 Pressing of the mixed powder particles to form green compacts

Pressing was done using hydraulic press (GS25011 Specac Manual Hydraulic Press, UK) at a pressure of 680 MPa and holding time for 5 minutes. Dimensions of the green compacts were 13 mm in diameter and 9 mm in thickness. A green compact is the pre-sintered form of the specimen formed after the pressing step and is composed of the compressed powder particles.

1.2.3 Sintering of the green compacts

Sintering was carried out in two stages. In the first stage, the samples were heated at 130°C for 2 hours in a vacuum furnace (OVA031.XX3.5 Fistreem Vacuum Oven, UK) under argon gas to remove the spacer particles. Afterwards, the samples were heated at 550°C for a dwell time of 2 hours in a tubular furnace (Carbolite Tube Furnace, Germany) under a highly pure argon gas to increase metal particles fusion[17].

2. Characterization and evaluation of the sintered composites

2.1 Porosity assessment

Porosity percentage was determined using a method called modified liquid displacement method. This was done by immersing the scaffolds in a 5 mL measuring barrel containing ethanol for 10 min. Then, porosity was calculated using this equation: Porosity (%) = ((M2−M3−Ms) / (M1−134 M3)) x 100% where M1 is the initial mass of the ethanol-filled bottle, MS is the mass of the dry scaffold, M2 is the mass of the scaffold submerged in the bottle filled with ethanol, and M3 is the mass of the bottle after removal of the scaffold[18].

2.2 Microstructure characterization

Microstructure was observed using scanning electron microscope (SEM) (JSM-5, JEOL, Japan)[19].

2.3 Mechanical testing

Universal testing machine (UTM) (5ST, Tinuis Olsen, England) was used to measure compressive strength and elastic modulus on cylindrical specimens according to ASTM E9-89a. The dimensions of the cylinders were 8 mm × 12 mm and 0.5 mm/min crosshead speed was used[14].

3. Statistical analysis

The normality of the data was confirmed through Shapiro-Wilk test and examination of Q-Q plots. Descriptive statistics of mean and standard deviation (SD) were utilized for data presentation. One-way ANOVA was employed to evaluate the impact of varying concentrations of hydroxyapatite (HA) on mechanical parameters such as compressive stress, elastic modulus and porosity. Post-hoc pairwise comparisons were carried out, and p values adjustments were made using the Bonferroni method. All tests were two tailed and the significance level was set at p value ≤ 0.05. Data were analyzed using origin software (OriginPro, Version 2024, OriginLab Corporation, USA).

RESULTS

Porosity assessment

Regarding the percentage of porosity shown in the table 1, it has been found that incorporation of hydroxyapatite as a reinforcing phase in groups B and C resulted in marked increase in the porosity compared to specimens of group A which had zero percentage of hydroxyapatite. Also, it should be highlighted that scaffolds of group B have the highest percentage of porosity among all scaffolds. Statistical analysis (Tables 2 and 3, Figure 1A) showed that incorporation of different concentrations of hydroxyapatite has affected the porosity significantly (P < 0.0001*).

Table 1 Compressive strength, elastic modulus and porosity percentage of the scaffolds

Group	Ultimate compressive strength (MPa) ± SD	Elastic modulus (MPa) ± SD	Porosity (%) ± SD
A	11.05 ± 2.40	466.27 ± 10.16	91.7 ± 3.16
B	4.51 ± 2.46	405.77 ± 4.61	99.9 ± 3.87
C	6.67 ± 2.39	462.43 ± 4.87	98.9 ± 4.68

Table 2: One-way ANOVA for compressive strength,

Test	Mean square	F test	*P*
Compressive strength	166.55	36.07	<0.0001*
Elastic modulus	17213.37	348.41	<0.0001*
Porosity	300.20	17.96	<0.0001*

elastic modulus, and porosity of study groups

*Statistically significant difference (P < 0.05)

Microstructure characterization

After sintering, the microstructure and surface morphology of the fabricated scaffolds were examined using SEM and can be observed in the SEM images (Figure 2). A lot of pores that are irregular can be seen in these images. In terms of the morphological features, some of these pores were found to be circular in shape and others were oval. In terms of pore sizes and diameters, various pore diameters were identified (Figure 3). Some of these pores were found to have a 50 µm to 500 µm size range and are called the interconnected macropores and others had a size of ≤ 50 µm and are called micropores.

Mechanical testing

Upon observing the results obtained from the compressive strength testing (Table 1, Figure 4), it was found that compressive strength values decreased significantly in groups B and C compared to the control group A. Scaffolds of group A were found to have the highest strength and elastic modulus among all groups although specimens of group A were not reinforced with hydroxyapatite. Moreover, it should be pointed out that scaffolds of group C turned out to have higher strength and elastic modulus than scaffolds of group B. The one-way ANOVA (Tables 2 and 3, Figure 1B and figure 1C) showed that hydroxyapatite reinforcement at different concentrations had significant effect on the compressive strength ($P < 0.0001$*) and elastic modulus ($P < 0.0001$*) of the scaffolds.

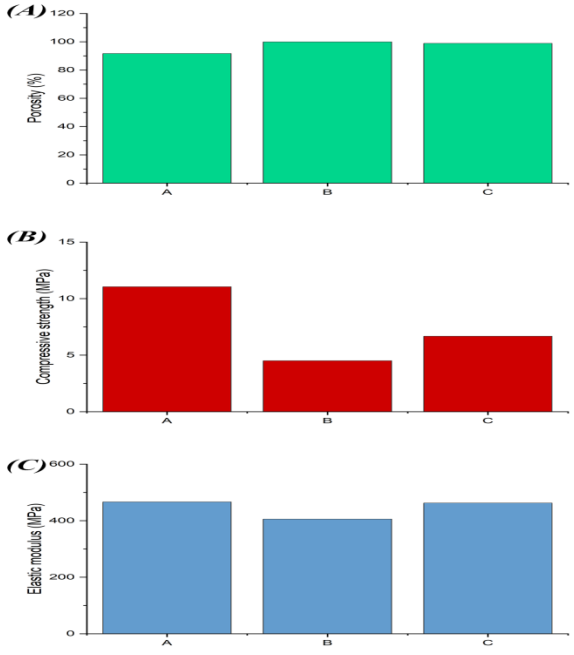

Figure 1: Graphical illustration in the form of bar charts of the data obtained from the statistical analysis of: (A) porosity (%), (B) compressive strength (MPa) and (C) elastic modulus (MPa) of the scaffolds.

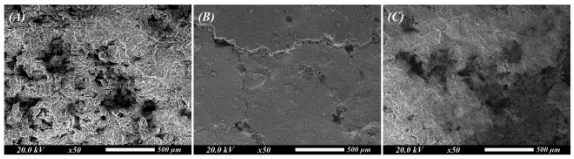

Figure 2: The SEM pictures of scaffolds of groups A, B and C at x50 magnification showing the surface morphology of the scaffolds.

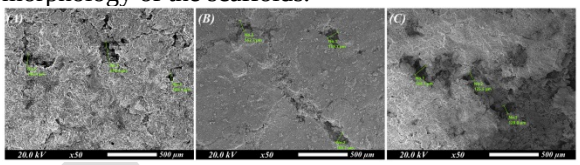

Figure 3: SEM images of the porous scaffolds showing the pore size range of groups A, B and C.

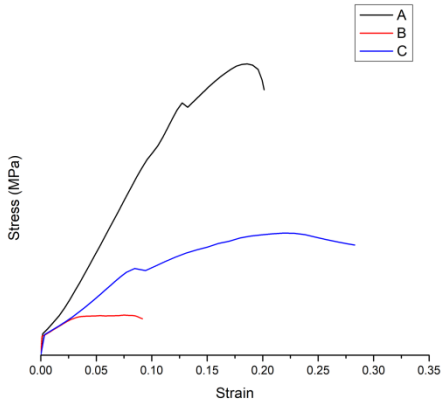

Figure 4: Stress-strain curves showing the compressive strength of the scaffolds.

Table 3: Pairwise comparisons between groups regarding compressive strength, elastic modulus, and porosity

Group	Compared with	*P*		
		Compressive strength	Elastic modulus	Porosity
A	B	<0.0001*	<0.0001*	<0.0001*
	C	<0.0001*	0.43	<0.0001*
B	C	0.03*	<0.0001*	1

*Statistically significant difference ($P < 0.05$)

DISCUSSION

In this study, porous magnesium scaffolds were fabricated and were alloyed with zinc and reinforced with hydroxyapatite at different concentrations. The aim was to study the effect of adding these elements at different concentrations on the porosity, microstructure and mechanical characteristics of these scaffolds. The null hypothesis was rejected because according to the statistical analysis, significant

difference was found in the porosity and mechanical properties of the scaffolds fabricated using different concentrations of hydroxyapatite as a reinforcing agent ($P < 0.0001$*) and this is shown in table 2 and was mentioned in the results section.

The calculated percentage of porosity shown in table 1 represent the pore spaces in each of the fabricated scaffolds. Groups B and C that were reinforced with hydroxyapatite were found to have higher porosity percentage than A. An explanation for why hydroxyapatite addition is responsible for increasing the percentage of porosity can be that the sintering and melting temperatures of hydroxyapatite and magnesium differ from each other with the Mg having very low melting temperatures (~200°C) compared to the high melting temperature of hydroxyapatite (~1100°C). This difference makes it difficult for Mg and hydroxyapatite particles to coalesce together at the 550°C sintering temperatures used in this study which is considered low compared to the high melting temperature of hydroxyapatite. Therefore, defective sintering occurs at the Mg-hydroxyapatite interface leading to inadequate densification and high porosity[20]. In addition, the cold pressing step of the mixed powder particles can be another reason for the high percentage of porosity. The mechanism by which this step can lead to increase in porosity is that pressing leads to the formation of many fresh points of contact between the powder particles causing the space holding particles to fuse together; thus, after the decomposition of those fused spacers, generation of merging pores that are interconnected occurs and this increases the interconnectivity and amount of porosity[21, 22]. Based on these explanations, it can be concluded that the reason for the scaffolds of groups B and C to have high percentage of porosity is the coupled effect of being reinforced with hydroxyapatite and the pressing step. It should be pointed out that the high porosity in these groups is beneficial to the function of the scaffolds in the process of bone regeneration because porosity with a pore diameter ranging from 100 to 500 μm such as the scaffolds fabricated in our study is needed to facilitate penetration, angiogenesis and transport of nutrients and waste through the pores[2, 3]. Also, it has been found that high porosity can enhance the mechanical interlocking between the scaffold and the surrounding tissue increasing the stability of the scaffold[23].

Microstructure characterization was done to view the surface morphology of the scaffolds using SEM. Upon observing the SEM images (Figure 2), it has been established that the formed pores are irregular in shape with some being oval and others being circular. This has been found to resemble the morphological features of the ammonium bicarbonate that have been used in this work to generate pores.

There are several ways by which the pores can be formed, hence explaining the formation of pores with different diameters (Figure 3). Macropores are found to be formed in place of the space holder particles used during the fabrication process of the scaffolds as upon heating of the ammonium bicarbonate in the vacuum furnace, they disintegrate and are replaced with macropores[24]. Another important explanation for the formation of this kind of pores is the pressing step that has been found to be responsible for the formation of interconnected merging macropores as was previously mentioned in the section of porosity analysis. The pore sizes found in the size range of these interconnected macropores is the ideal diameter needed for adhesion and proliferation of osteoblasts, hence facilitate regeneration of new mineralized bone after the scaffold implantation[25].

Regarding the micropores, the reason for their formation can be attributed to incomplete and imperfect compaction caused by the irregular shapes of the metallic powder particles which can lead to the formation of minimal cavities and, as a result, the formation of this kind of pores[24].

Concerning the mechanical properties, scaffolds of group A have been found to have the highest values of compressive strength and Young's modulus owing to the effect of adding 4% Zn as an alloying element as it leads to formation of Mg-Zn intermetallic phases which increase the strength by the mechanism of dispersion strengthening[2]. However, this finding of group A having the highest strength values despite not being reinforced with hydroxyapatite does not agree with other research[14, 26]. According to this previous research[14, 26], it has been established that adding a certain amount of hydroxyapatite can lead to improvement in the mechanical characteristics of the scaffolds and increase in their strength and elastic modulus. This can be attributed to the effect the hydroxyapatite has on the microstructure of the scaffolds because hydroxyapatite reinforcement can lead to refinement of the scaffolds' grains[19]. In addition, hydroxyapatite is known for being stiff and for having high elastic modulus because of being a ceramic material, so it has the ability to improve the stiffness of the scaffolds. However, in this work, specimens of groups B and C showed decrease in their compressive strength and Young's modulus. Reasonable justifications have been found and can explain these findings. One of these explanations is the brittle nature of this ceramic material. Also, the high melting temperature of hydroxyapatite which does not allow the hydroxyapatite particles to properly interact with the metal particles at low sintering temperatures will cause a lot of the

hydroxyapatite particles to aggregate and will not be homogenously distributed, which then act as stress concentrators and weaken the composites[8]. Another possible reason for this drop in the strength of groups B and C is the pore characteristics in terms of percentage, configuration and size as pores can be zones of stress concentration resulting in a lot of cracks nucleation and propagation when the scaffolds are subjected to compressive stresses[19, 27]. So, scaffolds that have high percentage of large pores and non-uniform pore distribution will have high susceptibility to stress concentration and will exhibit poor mechanical properties and the scaffolds fabricated for this study have these features[27, 28]. Also, the incorporated hydroxyapatite in the scaffolds of groups B and C that participates in increasing the amount and interconnectivity of pores is another justification for why the mechanical properties are inferior in these groups compared to group A. However, it should be emphasized that there is not much decrease in the elastic modulus of groups B and C compared to that of group A proving the positive effect that the hydroxyapatite has on the stiffness of the scaffolds.

It should be highlighted that the mechanical characteristics of the scaffolds in this work are found to be similar and are close to the mechanical characteristics of cancellous bone which has 0.2–80 MPa compressive strength and 10-2000 MPa (0.01–2 GPa) elastic modulus[19].

CONCLUSION

Powder metallurgy route has been found to be a successful and efficient method that can be used to fabricate porous magnesium scaffolds. It was found that the amount of reinforcing phases is an important factor that need to be considered in order to have scaffolds with good characteristics that meet the clinical needs of bone substitutes as group A was found to have the highest strength among all groups but the reinforced groups B and C were weaker. But nevertheless, scaffolds fabricated in this work were found to be highly porous with pore dimensions compatible with what the bone forming cells need to adhere, differentiate and regenerate bone. Also, their mechanical properties made them suitable to be used as bone scaffolds in regions of cancellous bone.

It is recommended to perform a cytotoxicity test to determine the biological characteristics and evaluate the interaction of these scaffolds with cells. Moreover, their bioactivity needs to be evaluated.

Conflict of interest

The authors declare that they have no conflict of interest

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