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REVIEW ARTICLE

Current and Emerging Bioresorbable Metallic Scaffolds: An Insight into Their Development, Processing and Characterisation

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Abstract | Solid metals and their alloys have been widely used for synthesis and fabrication of the implants and stents replacing human tissues or their functions for a quite a long time. However, in recent years, the advent of bioresorbable metallic materials have played an important role in biomedical applications. Scaffolds have been utilized in tissue regeneration to facilitate the formation and growth of new tissues or organs where a balance between temporary mechanical support and mass transport (degradation and cell growth) is ideally achieved. Bioresorbable metallic scaffolds are designed to reduce adverse events related to permanent metallic implants by providing temporary mechanical support and subsequent complete resorption. In view of the importance of emerging bioresorbable biomaterials, a brief review about development, processing and characterisation of bioresorbable metallic scaffolds is presented here. Focus is placed on metals/alloys as material for scaffold preparation. First, fundamental aspects about biomaterials and metallic materials and their considerations related to scaffold development are established. Second, processing/fabrication methods of these materials are described and finally characterisation methods to establish suitability of scaffolds are presented.

Keywords: *Bioresorbable scaffold, Biodegradable metals, Biodegradable metal matrix composites*

1 Introduction

At present, around 70–80% of biomedical implants are made from metallic materials[1,2]. Metallic scaffolds have traditionally been utilised in bone tissue engineering. A stent is a device that is placed into a blood artery to prevent or relieve a blockage. It is also referred to as a specific form of metallic scaffold utilised in cardiovascular applications. They are made of non-resorbable metal mesh and remain in the body indefinitely or until removed by other surgical intervention and may even pose a hurdle if future procedures need to be performed in that place. Another issue with conventional metal implants is that after implantation, they release harmful ions as a result of corrosion with biofluids, producing allergic responses, local anaphylaxis, and inflammation[3]. To note that typical metal implants do not degrade significantly in the body's natural environment, necessitating revision surgery to remove them after the tissues have healed.

The poor mechanical characteristics of biodegradable polymers as scaffolds remain as their main limitation[4]. Polymers may lose their bulk and mechanical integrity during degradation. A scaffold with sufficient strength and Young's modulus is desirable for some hard tissue applications. Porous polymeric structures, on the other hand, are rather weak and may not reach the requisite strength[4,5].

As a result, material scientists and engineers have looked into developing new biomaterials to

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replace conventional metals and polymers. The use of biodegradable metals for biological purposes has received a lot of attention recently[6]. After an early empirical phase of biomaterials selection based on availability, design attempts were primarily focused on either achieving structural/mechanical performance or on rendering biomaterials inert and thus unrecognizable as foreign bodies by the immune system. Sutures, bone plates, joint replacements, ligaments, vascular grafts, heart valves, intraocular lenses, dental implants, and medical equipment such as pacemakers, biosensors, and so on are examples of biomaterials utilised as implants[7,8].

A bioresorbable scaffold serves similar purpose like that of a stent but is manufactured from materials that may acclimate to body conditions and further get absorbed in body[9]. Ideally, a scaffold must be porous, bioactive, and biodegradable as well as have mechanical characteristics that are compatible with biological requirements[10]. Accordingly, bioresorbable and biodegradable materials have been considered as a viable method for biomedical applications associated with bone[11] and blood vessels[12,13]. Given the requirements described above for biomaterials the following three have been the main areas of investigation in recent years:

a. Development of suitable materials.
b. Processing methods for right compositions.
c. Optimizing mechanical properties of metallic materials.

Metals' inherent strength and ductility are the primary characteristics that make them desirable for use in hard tissue applications. The use of biodegradable metal matrix composites (BMMCs) has emerged in recent years. Biodegradable metal matrix composites are also being considered as a possible scaffold material due to their outstanding mechanical characteristics and resorbability. Therefore, the present paper aims to review the current status of porous bioresorbable metals as materials for fabrication of scaffolds.

2 Metallic Materials Used for Making Scaffolds

Metallic materials used for making scaffolds can be classified into:

a. Bioresorbable metallic materials.

Magnesium Based[14]
Iron based[15]
Metal Matrix Composites[16]

Zn based scaffolds seems to be a promising candidate however they are less studied[2]b.
Non-bioresorbable/permanent materials.

Titanium Based[17]
Stainless Steel Based[18]

2.1 Mg–Based Scaffolds

Magnesium has good mechanical properties and can provide a strength-to-weight ratio that is comparable to that of stainless steel. Another virtue of magnesium-based scaffolds is the substantial resistance to platelet adhesion and aggregation owing to its electrochemical properties[19]. Mg can be considered as osteoconductive and bone growth stimulator material as suggested by many studies. Mg is largely found in bone tissue, it is an essential element to human body, and its presence is beneficial to bone growth and strength[20–22]. In simulated body fluid (SBF) immersion experiments, porous Mg has been found to have superior degradable behaviour in terms of lower pH change, slower hydrogen evolution, and slower decrement of compressive yield strength[23]. Pure Mg has a higher elastic modulus than cortical and cancellous bones, making it a better choice for bone scaffolds. Alloying and thermomechanical techniques can increase the mechanical characteristics of Mg.

Early research has demonstrated the importance of a porous structure in bone healing. Although porosity reduces a material's bulk mechanical characteristics, porous magnesium possesses strength and stiffness that are comparable to natural bone. The influence of pore size and porosity on the mechanical characteristics of porous Mg scaffolds has been studied, with findings indicating that yield, compressive, and flexural strength, as well as Young's modulus, declined as pore volume and size increased[24–26]. Cell growth and proliferation have been shown to be aided by the porous design of Mg scaffolds[27].

2.2 Fe–Based Scaffolds

Recently, Fe-based porous materials have become an emerging hot topic. Despite the fact that Fe is practically never found in natural bone, it plays a critical function in bone development. Although a quick degradation rate for Fe stents is usually desirable,[28–30] from the point of view of bone repair, fast degradation of a porous Fe scaffold is undesirable in the initial stage of implantation, as this phenomenon would lead the scaffold to disintegrate too early and result in high cytotoxicity[31].Compared to Mg (40–45 GPa) and its alloys (~45 GPa) and 316L stainless steel (190 GPa), Fe has a greater elastic modulus (211 GPa)[32,33]. There is currently a scarcity of information about Fe as a scaffolding material.

2.3 Biodegradable Metal Matrix Composite Scaffolds

Biodegradable Metal Matrix Composites' development begins with the pure metal, then alloy development. Alloying research is still ongoing to develop BMs that meet the material requirements of biomedical applications. However, alloys, once produced, have fixed properties such as degradation rate and may not offer good biocompatibility. Thus, there are additional requirements for processing techniques, such as structure design or surface modification which can further improve the properties of BMs for biomedical applications[34,35]. This leads to the development of biodegradable metal matrix composites (BMMCs) development in recent times. One such biodegradable Mg/HA/TiO_2 nanocomposite was developed by Khalajabadi et al. [16]. Pure Mg may be made more corrosion resistant and ductile by adding HA and TiO_2 elements. On the surface, a protective covering made up of MgTiO3 nanoflakes was produced, which increased the BMMC's wettability and corrosion resistance. The Mg/HA/TiO_2 nanocomposites were shown to be very cytocompatible in cell culture. In recent years, the usage of biodegradable metal matrix composites has noticeably increased. Furthermore, as the biomedical applications of biomaterials is ever expanding, multifunctional biodegradable implanted medical devices made possible by composite technology have become an inevitable part of BM development[11].

2.4 Ti Alloy–Based Scaffolds

Titanium (Ti) is a lightweight, high strength metal located in the fourth horizontal row of the periodic table, grouped with transition metals. Ti exists in two allotropic structures with different crystal lattices. At room temperature, it is characterized by the hexagonal closely packed crystal structure (hcp) known as α phase. Upon heating to temperatures over 883 °C, it transforms into the body centred cubic crystal structure (bcc) referred to as β phase[36,37]. However, the temperature of the allotropic transformation of Ti depends on the degree of purity of the metal. The properties of Ti and its alloys are relatively sensitive to even small amounts of interstitial elements (H, O, N and C)[38]. In addition, titanium forms a very stable passive layer of TiO_2 on its surface and provides superior biocompatibility. Even if the passive layer is damaged, the layer is immediately rebuilt. In the case of titanium, the nature of the oxide film that protects the metal substrate from corrosion is of particular importance and its physicochemical properties such as crystallinity, impurity segregation, etc., have been found to be quite relevant.

Further biocompatibility enhancement and lower modulus has been achieved through the introduction of second generation titanium orthopaedic alloys including Ti-15Mo-5Zr-3Al, Ti-15Zr-4Nb-2Ta-0.2Pd, Ti-12Mo-6Zr-2Fe, Ti-15Mo-3Nb-3O and Ti-29Nb-13Ta-4.6Zr. This new generation of Ti alloys is at present under development and investigation, and it does not seem to be commercialized yet. In general, porous titanium and titanium alloys exhibit good biocompatibility[39]. Ti and its alloys are not ferromagnetic and do not cause harm to the patient in magnetic resonance imaging (MRI) units. Nitinol is one of the most promising titanium implants that find various applications as it possesses a mixture of novel properties, even in a porous state, such as shape memory effect (SME), enhanced biocompatibility, super plasticity, and high damping properties[40,41].

2.5 Stainless Steel–Based Scaffolds

Trabecular bone, which is located in the core of bones, contains a large amount of interconnected and approximately equiaxed pores with a diameter of hundreds of micrometers. The high porosity of trabecular bone leads to significantly lower mechanical property values. Therefore, a scaffold material with low modulus that does not cause the stress shielding effect is needed and one such metal exhibiting those properties is Stainless Steel with 316L-Stainless Steel widely used[18,39,42,43].

3 Processing of Metallic Scaffolds

3.1 Powder Metallurgy—Space Holder Method

The space holder method has been recognized as one of the viable methods for the fabrication of metallic biomedical scaffolds. In this method,

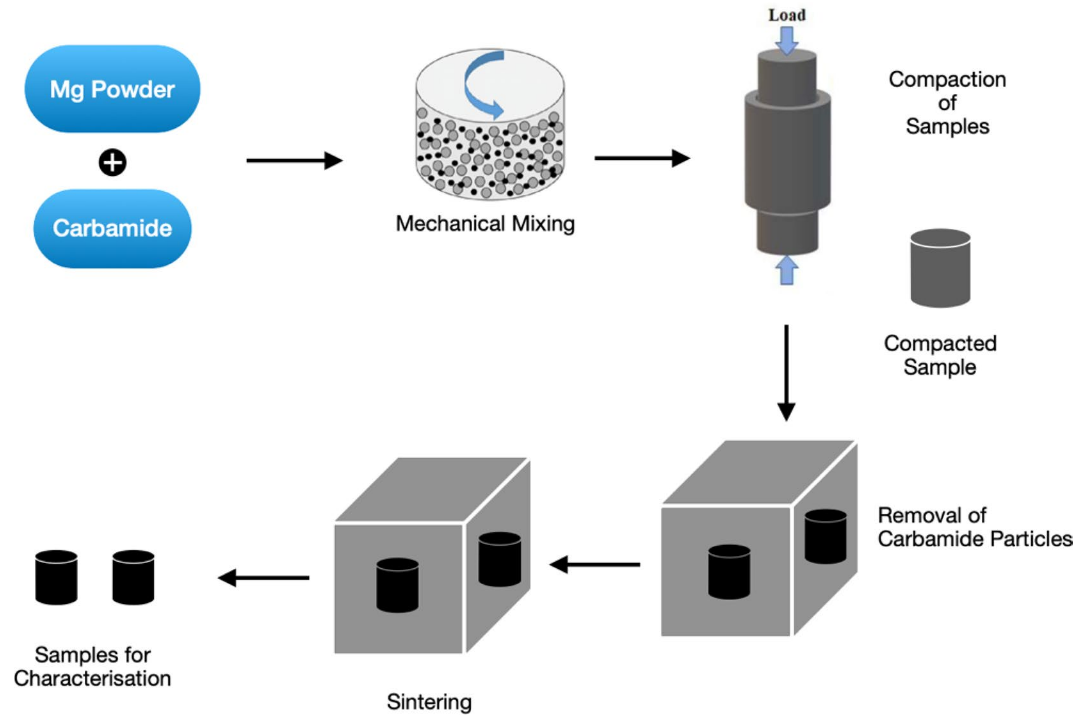

Figure: 1 Porous Mg Scaffold made by powder metallurgy technique[25].

temporary powder particles, namely space holder, are used as pore formers for scaffolds. In general, the process is split into four main steps:

a. Mixing of metal matrix powder and space-holding particles.
b. Compaction of granular materials.
c. Removal of space-holding particles.
d. Sintering of porous scaffold preform.

Figure 1 depicts the method of manufacturing a magnesium-based scaffold. The initial step is to choose the right powder, which is then combined with space-holding particles. The porous structure of a scaffold is mostly determined by the configurations of metal matrix powder particles that make up the scaffold framework. Powdered metallic materials such as titanium and magnesium are utilised. Alloy powders are also favoured for superior characteristics[24,25,44]. The morphological features of metal matrix powder particles, as well as the quality of a sintered scaffold, impact the properties of a metallic scaffold. The size of matrix powder particles affects sintering densification. The following criteria are used to choose a space-holding particle(a) biocompatibility and cytotoxicity; (b) chemical stability; (c) removal ability; (d) mechanical characteristics Reactions between space-holding particles and the binder employed in the manufacturing process should also be avoided since they can distort the shape and sizes of space-holding particles, as well as the scaffolds' macro-pore geometry. The sizes of space-holding particles must be selected, based on the desired macro-pore sizes in scaffolds. The size distribution of space-holding particles must be controlled. In most cases, a narrow distribution of space-holding particle sizes is preferred.

The initial step in scaffold manufacturing is to mix the matrix powder with space-holder. Depending on the volume percentage of space-holding particles added to the mixture, both open and closed pores can develop in scaffolds[4]. To develop uniform distribution of pores in scaffolds, uniform mixing of metallic powder and space holding particles must be ensured.

Compaction is performed after mixing to achieve a certain green strength that can keep the mixture of metal matrix powder and space holding particles intact during the subsequent steps of scaffold fabrication, i.e., space holder removal and sintering. During compaction, granular materials obtained from mixing are densified, forming the green body of scaffolds or scaffold preforms. During compaction, powder particles or granular materials rearrange themselves, fill the voids and increase packing coordination.

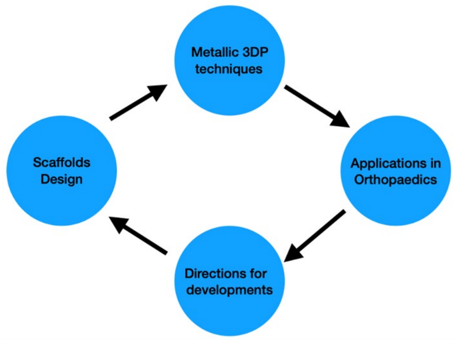

Figure 2: Scheme of metallic 3D printing techniques and design of metallic prostheses with regards to clinical applications in orthopaedics[46].

The space holder particles removal process determines the geometry of macro-pores, as well as the structural integrity and purity of scaffolds. Complete removal of space-holding particles is desired to obtain the requisite scaffold porosity and to prevent scaffolds from contamination by residual space-holding particles[45]. Space holder particle removal can be carried out by either heat treatment or leaching.

Sintering is performed at high temperatures where bonding between metal matrix particles in scaffold preforms takes place. Bonded matrix particles build up the framework of the porous structure of scaffolds. Through sintering, the final structure of metallic scaffolds can be achieved. As sintering proceeds, voids at powder particle interstices are rounded, along with densification and grain growth that occur simultaneously.

In this powder metallurgical process, the metals' pore morphology, pore size, and amount has to be precisely controlled. Ti foams and Mg foams were fabricated with an open-cellular structure in the work by Wen et al., and their pore size distribution was in the range of 200–500 um, which is specifically regulated to enhance their suitability as porous bone replacements[25].

3.2 Additive Manufacturing Method

Scaffolds made using additive manufacturing technologies are beneficial because of their unique exterior form and porous interior structure, both of which are critical for repairing large segmental bone defects. This method involves scaffold design using computer-aided design, reverse modelling, topology optimization, and mathematical modelling. Figure 2 explains a general scheme of 3D printing techniques and design of metallic scaffolds. Computer-aided design (CAD) software is used to create a three-dimensional (3D) scaffold model with the appropriate architecture. Before being converted to stereolithography (STL) files, the 3D scaffold model is split into a sequence of two-dimensional (2D) slices. An AM machine uses these STL files to create the appropriate toolpath in the 2D directions for direct creation of 2D layers. To create a 3D component, each layer is simply constructed on top of the previous.

Increasing the porosity of the scaffolds enhances the resorbability but inevitably impairs the mechanical properties so these two conflicting properties should be balanced to obtain an optimal comprehensive performance. Thus topology optimization method is used to optimize the distribution of materials in a given region based on the given load condition, constraint condition, and performance index[47]. Reverse modelling design, also known as image-based design, reconstructs bone tissue microstructure using computed tomography (CT) or magnetic resonance imaging (MRI) images of the item[48]. The CT/MRI slice pictures are subjected to a variety of analyses in this approach, with the goal of extracting essential characteristics for reconstruction.

AM techniques, include methods like selective laser sintering (SLS) and fused deposition modelling (FDM). SLS method includes a system which mainly consists of a laser, powder bed, a piston to move down in the vertical direction, and a roller to spread a new powder layer. The computer-controlled laser beam sinters the powder, while the untreated powder serves as a structural support for the scaffold being built. In FDM, the materials are heated up until it flows before extruding or squeezing out of a nozzle. The extruded fluid is subsequently deposited on the substrate with a layer-wise pattern based on the motion of the nozzle in each layer; then, a 3D scaffold is built layer by layer.

Today's AM technologies bring up previously unimaginable possibilities for creating complex designs with unique structures, and porous implants created by AM have shown tremendous promise in the orthopaedic area. Furthermore, studies have shown that personalized porous metallic implants can save surgery time and provide excellent bone defect restoration. Customized prosthesis, on the other hand, should be followed up on to determine long-term clinical results[46].

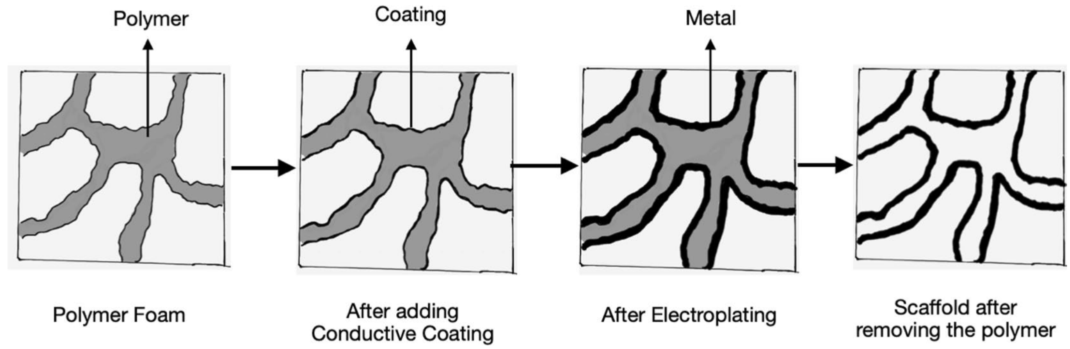

Figure 3: Electrodeposition method for making metal scaffolds.

3.3 Casting Method

Casting is a classic manufacturing technique in which a liquid substance is poured into a mould with a hollow cavity of the required shape and subsequently solidified. To finish the process, the solidified component is ejected or broken out of the mould[49]. This technique is applied to magnesium-based materials. Yamada and co-workers have reported the fabrication of open cellular magnesium foams using casting method and using polyurethane foam as a template. Briefly, polyurethane foam was heated after being filled with plaster and removed leaving a porous plaster mould. The molten magnesium was poured into the porous plaster mould heated to 873 K. Following that, water was utilised to remove the plaster mould, resulting in open cellular magnesium foams[26]. In this technique one should be careful while handling molten magnesium as it could be dangerous because it can catch fire when exposed to atmospheric gases in molten form.

3.4 Fibre Enhancement Method

Polymers are known for their biodegradability, biocompatibility, and mechanical properties. During the process of degradation, polymer will produce acid group and result in tissue inflammation while the biodegradable metal will provide an alkaline environment as a result of electrochemical corrosion. The combination of these two types of materials can be utilized to keep the pH of the degradation environment neutral and produce more biocompatible composites based on the principle of acid and alkali neutralisation. One kind of copolymer utilised in biomedical applications is poly(L-lactic acid-co-e-caprolactone) (P(LLA-CL))[50]. Using this method different materials could be electrospun in to composite nanofiber scaffolds with different mass ratios successfully. The degradation rate of P(LLA-CL) was also increased after combining them with Mg[50].

3.5 Leaching Method

The leaching technique is used to make porous Mg-calcium-phosphate (MCP), with NaCl particles and saturated NaCl solution creating macropores and micropores, respectively[51]. Pore size is regulated in the salt leaching process by employing porogens such as wax, salt, and sugars. Because of its simplicity and accessibility without the need for expensive equipment, solvent casting particle leaching is one of the most frequently explored procedures for producing polymer-based porous 3D scaffolds for bone tissue regeneration[52]. In recent times, it is also employed in fabrication of metallic scaffolds[51]. The manufacturing of scaffolds using this technology is quite simple, and the right combination of polymer type, polymer-to-salt ratio, and salt particle size allows for precise control of porosity and pore size, with direct effects on the scaffolds' mechanical characteristics[52].

3.6 Electrodeposition Method

Electrodeposition is the process of depositing metallic components on electrically conductive polymeric foam using a solution of metallic ions as shown in Fig. 3. Deposition processes begin with metals in their ionic state, which is a solution of ions in an electrolyte. During the procedure, a foamed polymer is replaced by a metal. Electro-deposition on a polymer foam requires some electrical conductivity of the initial polymer foam. This can be accomplished by dipping the polymer foam into an electrically conductive slurry made of graphite or carbon black, soaking the foam in an electroless plating solution, or sputtering a thin conductive layer onto

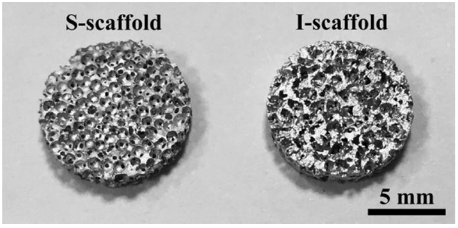

Figure 4: Optical image of Mg Scaffolds (S-Scaffold and I- Scaffold) made using template replication technique [14].

the polymer. Thermal treatment can be used to remove the polymer from the metal/polymer composite after electroplating. The result is a three-dimensional array of hollow metallic struts[53]. The advantage of electrodeposition method is that it is commercially available and can achieve a porosity of 92–95%[53].

3.7 Vapor Deposition Method

Gaseous metal or gaseous metallic compounds can also be used to make metal foams. The shape of the foam or cellular substance to be generated must be defined by a solid antecedent structure. Metal vapour can be generated in a vacuum chamber and allowed to condense on the cold precursor. The condensed metal covers the polymer precursor's surface and creates a layer of a specific thickness, which is determined by the vapour density and exposure duration[53]. Chemical reactants in a gaseous state are heated by radiation before being deposited on a polymeric precursor substrate in vapour deposition[54]. The advantage of this method is that it is commercially available and can achieve a porosity of 93–97.5%[53].

4 Processing Methods Specific to Different Metal Systems

4.1 Mg–Based Scaffolds

The synthesis of cellular materials with open or closed pores has received a lot of attention in recent years. In terms of mechanical efficiency and function, uniform and repeating designs have an advantage over random structures[55]. Powder or chip sintering (conventional, laser aided, or spark plasma), low pressure casting, or removable spacer techniques can all be used to create random cellular Mg. Processes that can be used to fabricate Mg with topologically ordered open cell structure include solid free-form process, space holder method, leaching method, replication, electrodeposition, and vapor deposition (Fig. 4).

Powder metallurgy may also be used to make Mg Scaffolds by combining Mg Powder with space holding agents. To burn off the space holding agents and sinter the material, a two-step heat treatment technique is used. Seyedraoufi et al. [56] produced a Mg-Zn alloy scaffold by blending and pressing Mg, 4wt% Zn and 6wt% Zn powders with carbamide ($CO(NH_2)_2$, 15%, 25% and 35% volume contents) with the particle size of 200–400 µm. The blended powders were pressed at 100 MPa pressure followed by a two-step heat treatment. The first step involved removing the carbamide particles by heating up to 250 °C for 4 h. The second step involved the sintering process, by heating up to 500, 550, 565 and 580 °C for 2 h.

4.2 Fe–Based Scaffolds

Porous Fe has been fabricated via several methods including solid–gas eutectic solidification process,[57,58] $CO–CO_2$ gas foaming powder metallurgy process,[59] or powder metallurgy with the use of polymer foaming agent,[60,61] or even utilising wood as template[62].

4.3 Biodegradable Metal Matrix Composite Scaffolds

Three-dimensional BMMCs are constructs of a large size in all three dimensions. There are many different methods to form a three-dimensional BMMC. The seven manufacturing techniques used to form these BMMC's are: Powder Metallurgy, Casting, Pressing, Fibre Enhancement, Microwave Assisted Processing and Three-dimensional Printing[63].

4.4 Ti Alloy–Based Scaffolds

The PM method was used to create porous titanium samples. The first material in the PM method was commercially available titanium powder (purity: 99.95 percent; powder size: below 45 lm; shape: irregular; Alfa Aesar Comp.)[4]. There were four steps to the PM process as described in earlier sections.

4.5 Stainless Steel–Based Scaffolds

Unfortunately, the fabrication of these materials with designed porosity is very difficult due to their high melting points that prevent the use of casting methods, such as foaming of a melt or casting into a removable mold. Rapid prototyping (RP) techniques are aimed at being the preferred technique for manufacturing materials with complex features like trabecular bone[17,64]. One of these processes, selective laser melting (SLM), provides for the production of materials with a very well-defined exterior form and minimal porosity, as well as materials with a practically nonporous matrix and pores with a specified shape, size, volume fraction, and interconnectivity[18].

5 Characterisation

Metallic biomaterials require metals with sufficient strength and improved corrosion resistance in the body[2]. Hence characterization of these materials is a very important aspect which needs to be considered when designing a scaffold. Light and scanning-electron microscopy may both provide useful information about material surfaces. The way materials interact with tissues and physiological fluids is influenced by the smoothness or roughness of their surfaces. The binding of protein and biochemical intermediates (lymphokines and cytokines) can be affected by smoothness or roughness, which can help define a material's biocompatibility. Materials are also evaluated using mechanical testing procedures under a range of loading circumstances (stresses and strains). Material characteristics and composition analysis is equally important for characterizing materials throughout the selection and receipt process, assessing failures and other issues, and verifying production processes[65].

The ability of implants to accomplish their intended function depends on biomaterials characterization. Mechanical strength may be particularly significant in major load-bearing circumstances, such as joint replacement, but in tiny bone defects, the chemistry and structure of the material may be more crucial for initiating the development of new bone tissue[66]. The density of a solid is a readily quantifiable attribute that is widely used to track physical changes in a sample, as a measure of sample homogeneity, and as a method of identification. The significant physical properties of a material can be identified with various test instruments[67]. Some of the properties have already been studied and hence discussed below. These properties are compiled and contrasted along some of the major bioresorbable materials.

Metallic implants have a tendency to corrode in a physiological medium that comprises ions, organic compounds, and dissolved oxygen. Corrosion causes structural damage and can produce by-products that harm biological activities. Depending on their electrode potential, metals have varying degrees of corrosiveness. While wet corrosion in the body might be a disadvantage, dry corrosion, which is a comparable electrochemical reaction with oxygen in the air, can be advantageous. Some metals generate an adhering oxide layer on their surface when exposed to air in an ambient atmosphere, which is just a few nanometers thick. Because corrosion is a surface phenomenon, this oxide layer serves as a passivating barrier, stopping metallic ions and electrons from traveling between the metal implant and bodily fluids. This prevents aqueous corrosion as well as the leaching of potentially unpleasant or poisonous ions. Because some metals, such as Al, Cr, and Ti, are highly reactive in air, they are nearly always included as alloy components to assure that an oxide layer forms[66].

Pure Mg, corrodes fast in physiological solution. This might result in the Mg implant losing its mechanical integrity before the tissue has fully recovered. Furthermore, its corrosion process creates hydrogen gas at a pace that is too fast for the host tissue to handle. Many improvements in corrosion resistance and mechanical qualities of Mg alloys have been recorded as the science and technology of Mg processing progresses[10]. To increase the mechanical qualities and corrosion resistance of magnesium, it is necessary to alloy it. Magnesium-based implants can also benefit from protective coatings and surface treatments to increase corrosion resistance and, perhaps, biological compatibility and activity[11].

The results revealed that adding phosphorus boosted compressive yield up to 11 MPa, greater than that of pure Fe of 2.4 MPa, and resulted in a Young's modulus of 2.3 GPa, which is equivalent to that of ordinary bone. The alloys showed also showed faster in vitro degradation than pure Fe but still considered slow as large fraction of material was observed during 12 months in vivo study. Nonetheless, alloying Fe with phosphorous appears to be a viable strategy to improve Fe's mechanical and degrading characteristics, particularly for bone scaffold[10].

A bioactive scaffold reacts in a controlled manner with its environment to stimulate specific biological responses where it is placed. Some of the most important design considerations are biofunctionality, biocompatibility, bioresorbability, mechanical properties, pore size and porosity.

Methods to visualize and subsequently quantify scaffold structures include the use of scanning electron microscopy (SEM),[68–70] micro-computed tomography (m-CT),[71–76] and confocal laser scanning microscopy[33]. Porosity

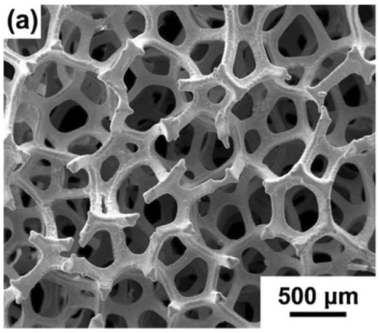

Figure 5: SEM image of 1.5 Fe-W Scaffold[15].

being the percentage of void space in a solid[77] is a morphological property independent of the material[42]. Porosity assessment via porosimetry is based on the study of the flow of gases or liquids (or both), across a porous structure. This method, therefore, is only suitable for the detection of open pores that allow fluid transport. Clearly, understanding the correlation between pore structure, porosity, and scaffold mechanical properties is crucial in the process of optimization of scaffold architecture[4,78–80]. As an example of microstructure characterization, Fig. 5 clearly illustrates the morphology of Fe Scaffold with clearly identifiable pores. Two different Mg-based scaffolds mainly S-Scaffold and I- Scaffold are used for characterisation by SEM as shown in Fig. 6 where the S-Scaffold refers to the Mg scaffolds with spherical pores and I-Scaffold refers to the Mg scaffolds with irregular polyhedral pores prepared by template replication technique[14]. The results indicate the capability of processing technique to change the morphology of the pores.

In most of the cases, compressive mechanical testing is used to measure the mechanical strength of a scaffold. Table 1 illustrates some of the important mechanical properties of metal scaffolds and a Poly Lactic Acid (PLA) which is used as a scaffold which clearly indicates that the metals can withstand more compressive load and the modulus of elasticity of the polymer is significantly lower when compared to other metals. For BMMCs, the mechanical properties, biodegradation rate, and bio compatibility can be further optimized by finding the ideal material composition and best processing techniques. The study conducted by Seyedraoufi et al. [55] found a relationship between the mechanical properties and the porosity content. At all sintering temperatures,

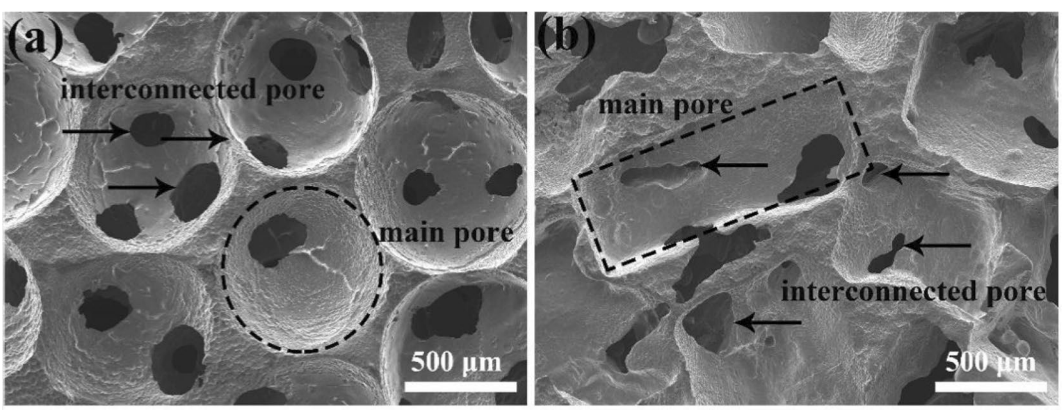

Figure 6: SEM images of Mg Scaffolds **a** S- Scaffold **b** I- Scaffold[14].

Table 1: Mechanical properties of few biomaterials.

	Density	Modulus of Elasticity (GPa)	Yield Strength (MPa)	Tensile Strength (MPa)	References
Mg	1.74	45	90	160	[81]
Fe	7.87	211.4	120–150	180–210	[81]
Ti Alloy	4.5	110	485	760	[81]
Stainless Steel	7.9	190	331	586	[81]
PLA	1.24	0.95	39	47.5	[82]
Mg BMMC	1.93	53	95	298	[83]

the compressive strength and Young's modulus of the Mg-Zn scaffolds declined as the porosity increased. Furthermore, the temperature of 550 °C was introduced as the optimal setting for the sintering process since this temperature yielded the maximum compressive strength and Young's modulus.

6 Conclusions

Biodegradable metals as tissue scaffolding materials have been viewed as viable alternatives to polymers and other hybrids for hard tissue regeneration exploiting mostly their superior mechanical properties over other materials. Biodegradable metals such as Mg and its alloys possess mechanical properties closest to native human bone and have shown encouraging results when used as tissue scaffolds. Porous Fe could also be viewed as a potential scaffold material but available data are scarce especially in its relation to bone tissue. Porous metallic scaffolds are used in tissue engineering to replace damaged hard tissues to restore its functionality. These structural scaffolds possess an imposed pore structure and interconnectivity and are designed to maintain their shape and strength. For the long-term replacement of bone defects porous metallic scaffolds offer the advantage of interfacial porosity as well as permanent structural framework. Comprehensive understanding of applications of biodegradable metals for tissue engineering scaffold is incipient. The next generation of metallic biomaterials must meet three major design criteria: (1) mechanical qualities that are biomimetic to those of host tissues; (2) porosity structure design and surface bioactivation treatment; and (3) biodegradable metal design to match tissue regeneration. Limited work has been done and much work still has to be conducted. The further direction to advance could be in finding suitable processes for making the porous structure in scaffolds from all perspectives related to biodegradable metals. Understanding the influence of porous structure to mechanical and degradation properties, and getting a good grasp on the cell regeneration and degradation product transport in the porous structure is imperative.

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Declarations

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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