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Biomimetic Porous Titanium Scaffolds for Orthopedic and Dental Applications

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1. Introduction

The development of artificial organs and implants for replacement of injured and diseased hard tissues such as bones, teeth and joints is highly desired in orthopedic surgery. Orthopedic prostheses have shown an enormous success in restoring the function and offering high quality of life to millions of individuals each year. Therefore, it is pertinent for an engineer to set out new approaches to restore the normal function of impaired hard tissues.

Over the last few decades, a large number of metals and applied materials have been developed with significant improvement in various properties in a wide range of medical applications. However, the traditional metallic bone implants are dense and often suffer from the problems of adverse reaction, biomechanical mismatch and lack of adequate space for new bone tissue to grow into the implant. Scientific advancements have been made to fabricate porous scaffolds that mimic the architecture and mechanical properties of natural bone. The porous structure provides necessary framework for the bone cells to grow into the pores and integrate with host tissue, known as osteointegration. The appropriate mechanical properties, in particular, the low elastic modulus mimicking that of bone may minimize or eliminate the stress-shielding problem. Another important approach is to develop biocompatible and corrosion resistant metallic materials to diminish or avoid adverse body reaction. Although numerous types of materials can be involved in this fast developing field, some of them are more widely used in medical applications. Amongst them, titanium and some of its alloys provide many advantages such as excellent biocompatibility, high strength-to-weight ratio, lower elastic modulus, and superior corrosion resistance, required for dental and orthopedic implants. Alloying elements, i.e. Zr, Nb, Ta, Sn, Mo and Si, would lead to superior improvement in properties of titanium for biomedical applications.

New processes have recently been developed to synthesize biomimetic porous titanium scaffolds for bone replacement through powder metallurgy. In particular, the space holder sintering method is capable of adjusting the pore shape, the porosity, and the pore size distribution, notably within the range of 200 to 500 μm as required for osteoconductive applications. The present chapter provides a review on the characteristics of porous metal scaffolds used as bone replacement as well as fabrication processes of porous titanium (Ti)

scaffolds through a space holder sintering method. Finally, surface modification of the resultant porous Ti scaffolds through a biomimetic chemical technique is reviewed, in order to ensure that the surfaces of the scaffolds fulfill the requirements for biomedical applications.

Outline:

The chapter is constructed as follows:

1. Introduction
 - 1.1 The structure and mechanical properties of bone
 - 1.2 Orthopedic metal alloys
 - 1.3 Titanium and its alloys as orthopedic biomaterials
2. Biomimetic Porous Scaffolds for Bone Tissue Engineering
 - 2.1 Characteristics of porous metal scaffolds
 - 2.1.1 Type of porous structure and porosity
 - 2.1.2 Density and porosity
 - 2.1.3 Shape and size of pores
 - 2.1.4 Mechanical properties of porous metal scaffolds
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4. Summary

1.1 The structure and mechanical properties of bone

Bone is an open cell composite material composed of a complex vascular system and a significant fraction of protein-related materials. At the architectural level, bone is made up of two types of different tissues tightly packed together. The outer shell is of dense compact or cortical bone, while the inner core is comprised of porous cellular, cancellous or trabecular bone, as shown in Figure 1. Cortical bone is highly dense and contains cylindrically organized osteons, also known as Haversian system, ranges between 10 to 500 μm . It is notable that the Haversian canal is composed of blood vessels in parallel to the long axis of the bone. These blood vessels are interconnected with vessels on the surface of the bone through perforating canals. Contrary to cortical bone, cancellous bone is highly porous, consisting of an interconnected network of trabeculae which is about 50-300 μm in diameter. These two types of bone tissues differ in porosity or density. The porosity of cortical bone is 5-10%, while in cancellous bones the porosity ranges between 75% and 90% (Burr & Martin, 1989; Choi et al., 1990; Rho et al., 1998; Parente et al., 2006).

The (wet) apparent density of cortical bone is 1.99 g/cm^3 (Currey, 1998), while this value for cancellous bone varies substantially and is typically in the range 0.05-1.0 g/cm^3 (Keaveny, 1998). The porosity of cancellous bone is the total volume that is not occupied by bone tissue and is usually filled with marrow. Although for the porosities less than 50% the distinction between the two bone tissues is fairly difficult, the change from compact to cancellous bone is usually clear and takes place over a small distance.

The fraction of cancellous bone varies in different living forms. For instance, birds flying in the sky have larger fraction of cancellous bone compared to those of animals crawling on the ground (Nakajima, 2007). The difference between the cortical bone and cancellous bone is

also manifested by histological evaluation of the tissue's microstructure. The microstructure of cortical bone is made up of regular, cylindrically shaped lamellae, whilst cancellous bone is identified by irregular, sinuous convolutions of lamellae. In addition, cancellous bone tissue is metabolically active and can be remodeled more frequently than that of cortical bone (Rho et al., 1998).

The porosity of bone can be characterized by the small pores of canaliculi and smaller lacunae and larger pores of osteons, and Volkmann's canals, as shown in Figure 1. In normal cortical bone, the size of the smaller canaliculi and vasculature channels are in the range of 1-5 μm (Ascenzi & Bonucci, 1976). In addition, bone is a reservoir for calcium in the body, containing 99% of the body's calcium. Bone mineral is mostly in the form of hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$). Biological hydroxyapatite contains carbonate ions as replacement groups in phosphate and hydroxyl sites of the hydroxyapatite structure.

The successful implantation of bone scaffolds not only needs to meet biological requirements but also demands to have adequate mechanical strength. The mechanical characteristics of bone can be defined by its interaction with other bones, joints, or muscles in the body. However, the total geometry of the bone and the distribution of the tissue favor the mechanical strength of the structure. Principally, bone is an anisotropic material and its mechanical properties vary with anatomical location and the loading direction. There is also a great variability of modulus between the longitudinal and transverse directions (Rho et al., 1998; Silva et al., 2007).

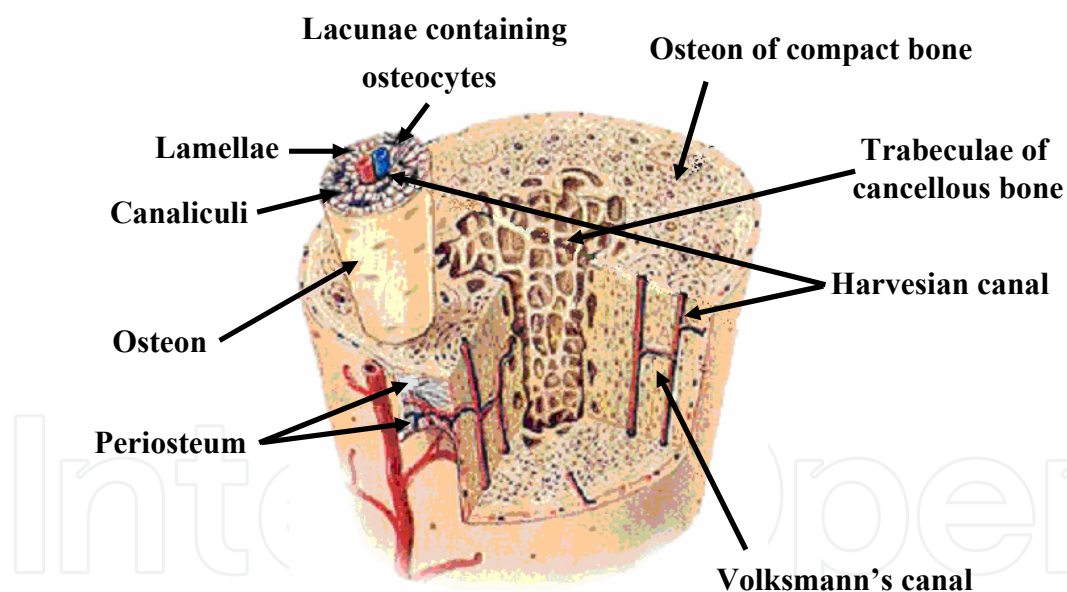


Fig. 1. The structure of bone (<http://training.seer.cancer.gov/anatomy/skeletal/tissue.html>).

It is reported that the strength of cortical bone in the longitudinal direction is about 79-151 MPa in tension and 131-224 MPa in compression (Thomson et al., 1995). However, the experiments carried out in the transverse direction show strength of 51-56 MPa in tension and 106-133 MPa in compression. The elastic moduli of compact bone range from 17 to 20 GPa in the longitudinal direction and 6 to 13 GPa in the transverse direction (Thomson et al., 1995; Veisoh & Edmondson, 2003). On the other hand, cancellous bone does not show a consistent mechanical strength and varies both longitudinally and from one bone to another.

As a result, cancellous bone exhibits much broader mechanical properties compared to those of cortical bone. The trabeculae of cancellous bone follow the lines of stress and can be realigned by changes in the direction of stress. The compression strength is reported in the range of 2-5 MPa, and the elastic modulus ranges from 0.76 to 4 GPa (Veisoh & Edmondson, 2003). In a study by Wang *et al.* (Wang *et al.*, 2007) on a dry cancellous bovine bone, the elastic modulus in the longitudinal and transverse directions were 20 ± 2 GPa and 14.7 ± 1.9 GPa, respectively.

1.2 Orthopedic metal alloys

The main goal of design and fabrication of an orthopedic biomaterial is to restore the function and mobility of the native tissue that is considered to be replaced. In order to select an ideal biomaterial for orthopedic and dental applications specific property requirements must be fulfilled. The ideal materials for hard tissue replacement should be biocompatible and bioadhesive, possess adequate mechanical properties to tolerate the applied physiological load, be corrosion/wear resistant and finally show good bioactivity to ensure sufficient bonding at the material/bone interface. The materials used in orthopedic surgery can be divided into five major classes of metals, polymers, ceramics, composites, and natural materials (Hoffman, 2004). However, this chapter focuses mainly on orthopedic metal alloys.

Compared to other biomaterials like ceramics and polymers, the metallic biomaterials offer a wider range of mechanical properties such as high strength, ductility, fracture toughness, hardness, formability, as well as corrosion resistance, and biocompatibility. These are the required properties for most load-bearing applications in fracture fixation and bone replacement (total joint arthroplasty) (Breme & Biehl, 1998a; Hallab *et al.*, 2004).

Metallic biomaterials can also be used as functional constructions such as valves and heart pacemakers (Breme & Biehl, 1998a). In view of their mechanical properties, ceramics and carbon can be highly loaded under compression stresses while polymers show a poor strength under both tensile and compression loads. However, ceramic materials are brittle and exhibit low toughness under compression loads. Taking these limitations into account, metals are preferred in most cases for structural biomedical constructions. The structural metallic biomaterials fall into two classes of low-loaded implants (e.g. plates, screws, staples) or high-loaded implants (e.g. hip and knee prostheses) (Breme & Helsen, 1998b).

However, the main concern regarding the application of bulk (dense) metallic biomaterials is their higher stiffness than that of bone. The magnitude of elastic modulus for bulk metallic implant materials surpasses that of cortical bone by far and results in a failed stress transmission from biomaterial to bone, the so-called stress-shielding effect. The stress-shielding may lead to bone resorption or even fretting, due to micro motions occurring at the bone/implant interface (Kawalec *et al.*, 1995). The idea of preparing a porous material is to bridge this biomechanical mismatch. A decrease in elastic modulus (or lowering the stiffness) would result in a higher elastic elongation of the cells in the vicinity of the implant, whereby stimulating bone formation by producing calcium (Natali & Meroi, 1989).

Metals used for implant materials must have a high corrosion resistance and should be stable in physiological environments. Although there are a few metallic elements (e.g. Cr, Co, Ni and V) possessing a relatively high corrosion resistance, they may cause adverse biological reactions (Steinemann, 1980; Okazaki *et al.*, 1998). The metallic ions of these metals may also combine with patient's proteins and trigger allergic immune response

(Kramer, 2000). In general, compared to cobalt-chromium alloys (Co-Cr) (Varma et al., 2002), and stainless steels (Winters & Nutt, 2003), titanium and some of its alloys (Ashraf Imam & Fraker, 1996) are the more suitable metallic materials used for orthopedic applications.

It is notable that the materials used for fabricating orthopedic metallic implants are mostly metal alloys rather than pure metals. In this chapter, the application of stainless steels and cobalt-chromium alloys are described briefly, whilst the characteristics of Ti and its alloys and their application in orthopedics are reviewed in more details.

Stainless steel: Stainless steels were the first reliable metals used as prosthesis in orthopedics. The basic elements in steels are iron and carbon and may usually contain chromium, nickel, and molybdenum as additional elements. The most common stainless steel in orthopedics is designated 316L. This is an austenitic steel with a low amount of carbon (0.03 wt.%). Compared to other metallic implants, stainless steels exhibit lower strength and much higher corrosion resistance, but possess greater ductility and lower production cost (Hallab et al., 2004). Their high stiffness makes them inferior to Ti in bone replacement applications (Williams, 2001).

Cobalt-chromium alloys: The two Co-Cr alloys widely used as implant materials are: (1) cobalt-chromium-molybdenum (Co-Cr-Mo), and (2) cobalt-nickel-chromium-molybdenum (Co-Ni-Cr-Mo). The possible toxicity of released Ni ions from Co-Ni-Cr alloys and also their poor frictional properties are a matter of concern in using these alloys as articulating components. Thus, Co-Cr-Mo is distinguished as the dominant class for total joint arthroplasty. However, wear debris from Co-Cr alloys have been considered as a cause of implant loosening and soft tissue adverse reaction (Browne & Gregson, 1995).

1.3 Titanium and its alloys as orthopedic biomaterials

In selecting a material for orthopedic applications, a few general criteria should be considered. The first criterion is a series of properties required for biomedical applications, such as good biocompatibility, no adverse tissue reaction with host tissue, as well as high corrosion and wear resistance. Meanwhile, an orthopedic implant should also meet the requirements of certain mechanical properties, whether the function is related to fracture fixation or total joint arthroplasty (bone replacement). In particular, an ideal orthopedic implant must exhibit an elastic modulus mimicking that of the bone selected. Secondly, the candidate material should meet the requirement of a certain processing profile, meaning that they are capable of being processed to the required shape by feasible manufacturing techniques with the minimum overall cost (Abel et al., 1994; Gasser, 2001). This requires a profound knowledge of all aspects of the implant's properties.

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-centered cubic crystal structure (bcc) referred to as β phase (Molchanova, 1965; Lütjering & Williams, 2003). 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) (Brooks, 1982).

The microstructure of Ti alloys is rather complex and depends upon the alloying elements and thermomechanical process (cold working and annealing). Depending on the type and amount of alloying elements, commercial Ti alloys are typically classified into three different categories: α , β , and $\alpha+\beta$ alloys. Some alloying elements lead to an increase in the transition temperature of Ti, referred to α stabilizing elements, whilst others lower the transition temperature known as β stabilizing elements. Most of the body-centered cubic elements (bcc) would be expected as β stabilizing elements. Amongst them, Mo, V, Nb, Ta, Mn, Fe, Cr, Co, Ni and Cu are the most common β -stabilizers. On the other hand, most of the interstitial elements (e.g. O, N, and C, except H) as well as some substitutional elements such as Al, Ga, Ge and Sn fall into the category of α -stabilizer. In addition, the final microstructure of Ti alloys can be affected by the cooling process from β phase, as this affects the $\beta\leftrightarrow\alpha$ transition temperature, as well as the obtained α grain size and shape.

Ti alloys were first used in orthopedics in the mid-1940s and have continued to gain attention because of their unique properties, including high specific strength, light weight, excellent corrosion resistance and biocompatibility. Due to the aforementioned properties, this class of materials exhibits tremendous clinical advantages in terms of reduced recovery time and rehabilitation, and improved comfort for patients (Nyberg et al., 2005a). However, for bone replacement components, the strength of pure Ti is not sufficient and Ti alloys are preferred due to their superior mechanical properties. In general, alloying elements would lead to an improvement in the properties of Ti for orthopedic applications.

Ti-6Al-4V ELI and NiTi shape memory alloys (SMA) are the most commonly used Ti alloys in orthopedic applications because of their good combination of mechanical properties and corrosion resistance (Baumgart et al., 1980; Andreasen & Fahl, 1987; Li et al., 2005). However, the possible release of toxic ions from aluminum (Al), vanadium (V) and nickel (Ni) during in vivo corrosion of the implant remains the matter of concern. Al for exceeding content of 7% at low temperature would lead to possible embrittlement and it may also cause severe neurological, e.g. Alzheimer's disease (Mjoberg B, 1997) and metabolic bone diseases, e.g. osteomalacia (Boyce et al., 1992; Zaffea et al., 2004). Similarly, V can alter the kinetics of the enzyme activity associated with the cells and results in potential cytotoxic effects and adverse tissue reactions (Zwicker et al., 1980; Woodman et al., 1984; Semlitsch et al., 1985; Pimenova & Starr, 2006). Moreover, the oxide layer of Al_2O_3 and VO_2 are less thermodynamically stable than that of TiO_2 , as their harmful debris may take place in living organism (Lewis & Shaw, 1995). Evident cytotoxic and allergic responses of Ni have also been reported (Castleman & Motzkin, 1981; McKay et al., 1996). Thus, it is necessary to develop new Ti alloys that contain non-toxic elements.

Over the last two decades, the researchers working on Ti alloys have discovered new alloys for orthopedic applications. For instance, Ti-Al-Nb and Ti-Al-Nb-Ta (Semlitsch et al., 1992; Sasaki et al., 1996), Ti-Nb-Ta-Zr (Niinomi et al., 2004), Ti-Zr-Nb (Yu et al., 2001), Ti-Zr-Nb-Ta-Pd (Okazaki et al., 1996), Ti-Sn-Nb (Nouri et al., 2008a), and Ti-Ni-Ta (Lekston & Goryczka, 2007), have been developed or used as implant biomaterials. Some of the Ti alloys developed for biomedical applications are given in Table 1.

In general, most of the Ti alloys offer appropriate mechanical properties for orthopedic applications. The torsional and axial stiffness (modulus) of Ti alloys are closer to those of bone and theoretically provide less stress shielding than those of stainless steel and Co-Cr alloys. Figure 2 presents elastic moduli of some important materials used in bone tissue engineering (Niinomi et al., 2004).

Perhaps the most unfavorable properties of Ti alloys with respect to mechanical behavior are their susceptibility to crack propagation, their relative softness and relatively poor wear and frictional properties compared to Co-Cr-Mo alloys. In terms of biocompatibility, the clinical success of Ti and its alloys is based on the presence of a passive oxide layer on their surface. The naturally occurring oxide of titanium is TiO_2 which has a thickness of 5-29 nm and can be restored quickly (milliseconds) after damage (Breme & Biehl, 1998a; Bram et al., 2006a). However, there is some disagreement about the exact oxide chemistry in pure Ti versus alloyed Ti (Brunski, 2004). A comparison between the properties of Ti with their metallic biomaterial counterparts are tabulated in Table 2.

Composition	Type
Pure Ti	α
Ti-6Al-4V ELI (ASTM F136084, F620-87)	$\alpha+\beta$
Ti-6Al-4V (ASTM F1108-88)	$\alpha+\beta$
Ti-6Al-7Nb	$\alpha+\beta$
Ti-5Al-2.5Fe	$\alpha+\beta$
Ti-5Al-3Mo-4Zr	$\alpha+\beta$
Ti-15Sn-4Nb-2Ta-0.2Pd	$\alpha+\beta$
Ti-15Zr-4Nb-2Ta-0.2Pd	$\alpha+\beta$
Ti-13Nb-13Zr	near β (low modulus)
Ti-12Mo-6Zr-2Fe	β (low modulus)
Ti-15Mo	β (low modulus)
Ti-16Nb-10Hf	β (low modulus)
Ti-15Mo-5Zr-3Al	β (low modulus)
Ti-15Mo-2.8Nb-0.2Si-0.26O	β (low modulus)
Ti-35Nb-7Zr-5Ta	β (low modulus)
Ti-29Nb-13Ta-4.6Zr	β (low modulus)
Ti-40Ta, Ti-50Ta	β (high corrosion resistance)

Table 1. Titanium alloys for biomedical applications (Niinomi et al., 2004).

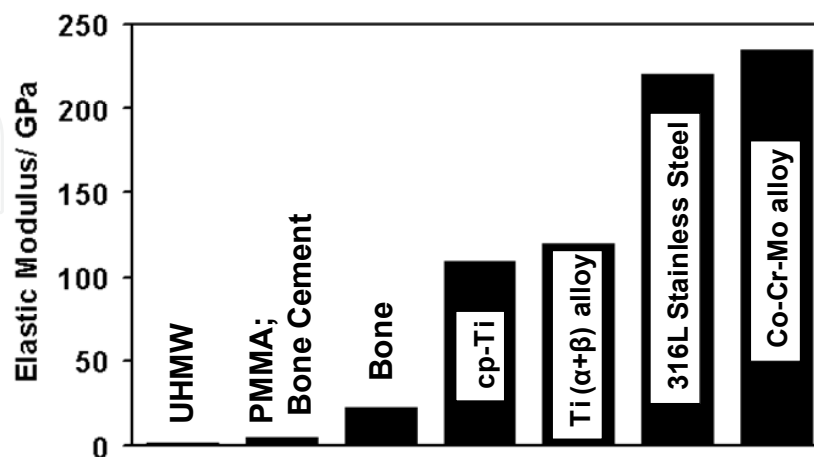


Fig. 2. Elastic modulus of some widely used orthopedic biomaterials (Niinomi et al., 2004).

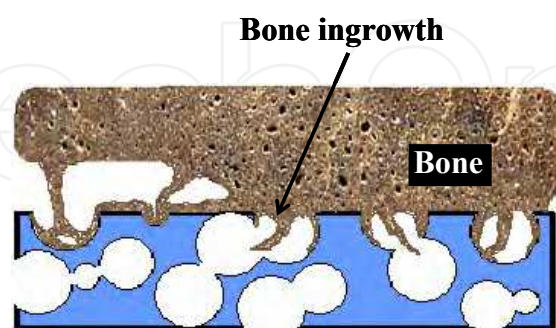
Characteristics	Stainless Steel	Cobalt-Chromium	Titanium
Stiffness	High	Medium	Low
Strength	Medium	Medium	High
Corrosion resistance	Low	Medium	High
Biocompatibility	Low	Medium	High

Table 2. Comparison between the properties of three major metallic biomaterials.

2. Biomimetic Porous Scaffolds for Bone Tissue Engineering

Bone tissue implants require not only a material with adequate composition, but also a good structure that mimics the mechanical properties and architecture of bone. Despite the great progress in manufacturing of bulk (dense) metallic implants for orthopedic applications, there are major concerns associated with their use in the human body. Two major problems are the biomechanical mismatch of stiffness between the implant and bone, as well as micromotion of the implants due to inadequate initial fixation with host tissue (Robertson et al., 1976; Cameron et al., 1978; Ryan et al., 2006). Consequently, bone surrounding the implant is subjected to negligible mechanical stress, which may result in detrimental bone resorption (Turner et al., 1986; Breme & Helsen, 1998b; Thieme et al., 2001; Thelen et al., 2004). In this situation, the bone holding the implant in place becomes weakened, causing a loosening of the device. Any approach towards solving the raised problems in providing a good load transfer and bone anchorage is of foremost importance in designing the material and structure of orthopedic implants.

Recently, a great deal of attention has been given to a new class of materials, known as porous materials. Because bone is a porous tissue material, there is a physiological rationale for the use of porous materials in its replacement. Introducing pores into a material structure reduces the stiffness values close to that of natural bone which can subsequently provide a good load transfer and stimulate the formation of new bones (Griss & Heimke, 1976). In addition, the porosity allows new bone tissue to grow into the porous structure, providing an adequate biological fixation. Figure 3 illustrates the bone growing into the open pores of an implant, creating a highly convoluted interface.



Stable Fixation

Fig. 3. The bone ingrowth into the pores of an orthopedic porous scaffold providing a stable fixation (Nouri, 2008).

Due to the anchorage of porous materials in bone, they are also considered as a preferred alternative to bone cement fixation (Oliveira et al., 2002). A number of different porous materials have been developed in the past three decades including porous ceramic, polymeric and metallic materials. Despite the excellent corrosion resistance and biocompatibility of ceramic materials, they are inherently brittle and crack easily (Breme & Helsen, 1998b; Shannon & Rush, 2005). Similarly, porous polymeric systems cannot sustain the mechanical forces present in joint replacement surgery. This leads researchers to seek for porous metal scaffolds for their appropriate mechanical properties of load-bearing applications (Breme & Helsen, 1998b). Porous Ti scaffolds possess a unique combination of properties required for orthopedic and dental applications including strength, stiffness, durability and biocompatibility.

2.1 Characteristics of porous metal scaffolds

The structure of porous metal scaffolds is extremely important for their biological and mechanical properties, and can determine their performance in orthopedic applications (Bobyne et al., 1980; Li et al., 2004a). In order to manufacture an orthopedic implant with appropriate mechanical properties and an ability to allow biological anchorage with surrounding bone tissue, the geometry of the porous structure must be taken into account (Wen et al., 2001; Banhart, 2002; Li et al., 2005).

2.1.1 Type of porous structure and porosity

The structure of porous metal scaffolds can be classified into closed cells and open cells or the combination of both, depending on the fabrication methods. Typical configurations of closed- and open cells are shown in Figure 4. In the closed-cell porous metal scaffolds, pores are surrounded by pore walls and disconnected from each other, while in open-cell porous scaffolds, pores are connected to each other through various channels such as voids, interstices, etc. Biomedical applications are challenging, as they often have requirements in both structural and functional aspects. However, for orthopedic surgery, open cells are often required since new bone tissue grows into the porosity and ensures the fixation of the implant with the surrounding host tissue (Ishizaki et al., 1998; Banhart, 2002; Shehata Aly et al., 2005). The interconnected pore networks also support the vascular system required for continuing bone development (Murray & Semple, 1981; Li et al., 2005). In view of biocompatibility, the open pores allow the access of oxygen throughout the porous structure, facilitating the formation of an important resistant passive layer (Seah et al., 1998). Porous metal scaffolds are classified into three major groups: (1) partly or fully porous-coated solid substrates, (2) fully porous body, and (3) porous metal part joined to a solid metallic part (Pilliar, 1983; Li et al., 2005; Ryan et al., 2006). However, the porosity can also be gradually changed from the surface to the centre of the sample, known as gradient porosity (Kutty et al., 2001; Zhang et al., 2007; Wen et al., 2007a).

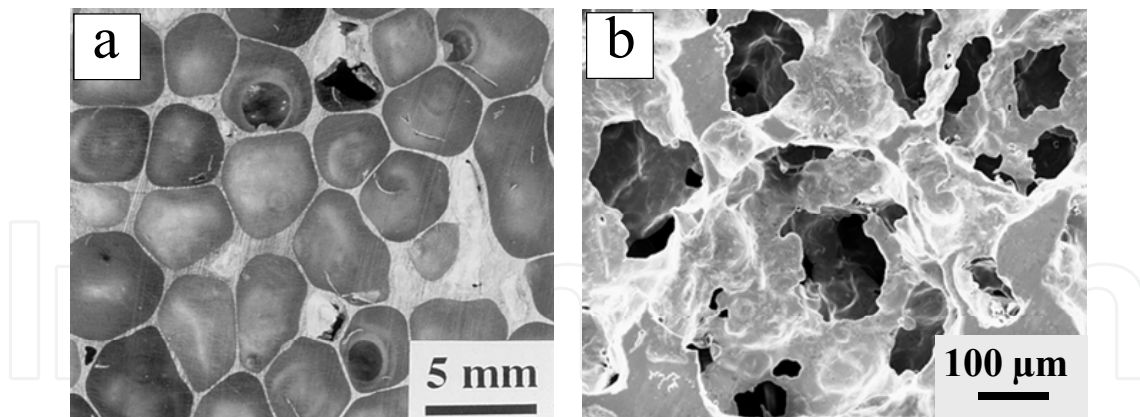


Fig. 4. Typical cell structures of (a) a closed cell aluminum foam ALPORAS (Miyoshi et al., 1999); and (b) open cell Ti-16Sn-4Nb (wt.%) scaffold (Nouri, 2008).

2.1.2 Density and porosity

The density of porous metal with an open-cellular structure is an important parameter for predicting permeability and mechanical properties. The permeability of a porous material is defined as the degree to which bone can grow into the pores and pass through it (Despois & Mortensen, 2005). By increasing the porosity, the mechanical strength is reduced and the permeability is increased (Eisenmann, 1998). However, a trade-off should be made between these two parameters to achieve a suitable implant for orthopedic applications.

In the porous metal field, the term 'relative density' is often used to describe the porous materials. It is the ratio of the density of porous metal to the density of its parent metal. The relative density of porous metals depends on the volume fraction of metal and pores. Typical porous metal scaffolds have relative densities less than 0.3 (Gibson & Ashby, 1997; Kriszt et al., 2002).

To stimulate the growth of new bone tissue into the pores, the material must have at least 60% porosity (Bram et al., 2006a). Similarly, in a study by Esen and Bor (Esen & Bor, 2007) a minimum porosity of 55% was reported for direct connectivity of macropores. These degrees of porosity would lead to an interconnected porous structure which favors the cell ingrowth to the porous space, vascularization, and transport of metabolic products. The degree of porosity is also considered to be crucial for biocompatibility. In an experiment performed by Tuchinskiy and Loutfy (Tuchinskiy & Loutfy, 2003), two materials with the same chemical composition but different porosities, were implanted in mice for a period of up to four weeks. The less porous material provoked a more vigorous foreign body reaction, and was encapsulated in a dense, highly collagenous bag with few blood vessels running through it. Consequently, the more porous material had a thinner sac with far greater vascularity.

2.1.3 Shape and size of pores

In order to increase bone growth into porous material, appropriate pore size must be provided. The pore size should be at least in the order of bone trabeculae and osteons which are tens of micrometer thick, otherwise bone ingrowth will not occur (Jasty et al., 2007). However, the optimum pore size for humans use has not been exactly defined. According to

Pilliar (Pilliar, 1987), pore size suitable for bone ingrowth is in the range of 75-250 μm ; while Elema *et al.* (Elema *et al.*, 1990) proposed that the pore size should range from 200 to 300 μm for bone tissue ingrowth in the porous samples. In general, implants with pore sizes in the range of 100 to 500 μm are suitable for bone ingrowth (Engh, 1983; Hungerford & Kenna, 1983; Bucholtz, 2002; Laptev *et al.*, 2004). Pore size from 500 μm to a millimeter would resemble a macro-structured surface rather than a three dimensionally interconnecting porous surface and theoretically would lead to loss of interface shear strength (Jasty *et al.*, 2007). It has also been suggested that the degree of interconnectivity is more important for new bone formation than the pore size itself (Kuhne *et al.*, 1994; Lu *et al.*, 1999).

The porous structure of the alloys is crucial for the growth of bone tissue and thus for improving the fixation and remodeling between the implant and the human tissue (Zhang *et al.*, 2007). However, Ayers *et al.* (Ayers *et al.*, 1999) addressed that there is no apparent correlation between pore size and bone ingrowth during the cartilaginous period of bone growth in the NiTi implant. This fact is attributed to the use of thin implants with the same thickness order as the pore size.

In addition to size, it appears that the shape of the pores will affect the extent of cell ingrowth. Goodman *et al.* (Goodman *et al.*, 1993) have reported the increase of bone ingrowth with square-shaped pores as compared with round-shaped pores. Pores with more ragged and rough surfaces also offer larger surface area for bone ingrowth (Li *et al.*, 2004a). However, depending on the various function and location of the bones in the human body, the same pore shape may not be ideal for all potential uses (Oh *et al.*, 2006).

It has been reported that the rate of bone growth into the pores can also be influenced by other factors. Bobyne *et al.* (Bobyne *et al.*, 1980) have demonstrated that ingrowth rate of bone is higher in parts placed in cancellous than in cortical bone. According to Clemow *et al.* (Clemow *et al.*, 2004), the percentage of bone growing into the surface was inversely proportional to the square root of the pore size.

2.1.4 Mechanical properties of porous metal scaffolds

One of the most important properties of porous metal scaffolds in orthopedics is their mechanical properties. Porous metals should have sufficient strength to resist stresses and physiological loadings that are imposed on them while maintaining their original size and shape. The scaffold should provide sufficient mechanical strength to support itself until the new bone tissue is completely formed into the pores.

As previously mentioned, the elastic modulus of dense metallic implants is much higher than that of natural bone. For the three most commonly used metallic orthopedic materials, the elastic modulus ranges from 55-110 GPa for Ti alloys to 205 GPa for stainless steel and 230 GPa for Co-Cr-Mo type alloys, as shown in Figure 2. However, the elastic moduli of human compact and cancellous bones are 17-20 GPa and less than 4 GPa, respectively (Gibson & Ashby, 1997; Niinomi *et al.*, 2004). Therefore, the adaptation of the elastic modulus or stiffness is one of the crucial tasks in the development of a suitable bone substitute material.

Although increased porosity and pore size facilitate bone ingrowth, it deteriorates the structural integrity of the scaffold, leading to a very low mechanical strength. The compromise in mechanical properties of the scaffold with increasing porosity sets an upper limit on the porosity and pore size (Dewidar & Lim, 2008). Thus, a trade-off must be maintained between the biomechanical properties and porosity of the material needed for

orthopedic surgery (Ryan et al., 2006; Gutierrez et al., 2008). The mechanical properties of a porous structure can be determined by various methods including compression, tensile, bending, fatigue, impact, and torsion tests. Since the compressive mechanical properties are most important for the implant applications, the present chapter summarizes only the compressive properties of porous metal materials.

Figure 5 shows a schematic compressive stress-strain curve for porous metal scaffolds with high porosity. In principle, the compressive behavior of a porous sample is characterized by three different regions. Firstly, there is a linear-elastic region which is manifested by an initial increase in stress. This initial high slope is associated with the elastic modulus (stiffness) of the porous samples. Subsequently, due to the collapse of the pores, the flow stress no longer increases with strain and there appears a wide stress plateau known as plateau or collapse region.

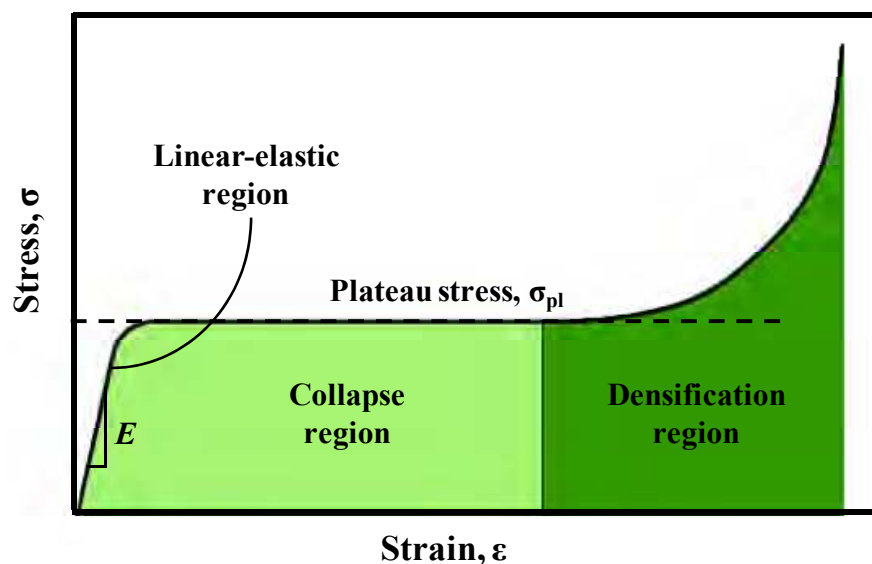


Fig. 5. A schematic illustration of compression curve of porous metal scaffolds (Nouri, 2008).

The smoothness of the plateau is highly dependent on the degree of porosity as well as the deformation behavior of the pore walls under compression. The brittle fracture of pore walls would lead to fluctuations in this region. Following the plateau region, the stress-strain curve gradually changes into a densification region where the pore walls touch each other, accompanied by a steep increase in stress (Gibson & Ashby, 1997; Banhart & Baumeister, 1998a).

2.2 Fabrication of porous titanium scaffolds through powder metallurgy

In view of the manufacturing process, Ti alloys can be classified into two groups of casting and powder metallurgy (P/M). At present, however, the fabrication of Ti-based implants through the casting method is limited to a costly, multi-step process of vacuum arc melting, hot rolling, scale removal (resulting in wasting the material), vacuum annealing, machining, and surface treatment. The casting limitations in manufacturing Ti alloys mostly arise from the high melting temperature of Ti and its affinity for oxygen (Gasser, 2001; Nyberg et al., 2005b). Moreover, as a raw material, Ti is relatively expensive compared to stainless steel

and Co-Cr alloys. The aforementioned difficulties drive the designers to search for more cost effective manufacturing methods with minimal waste production (Gasser, 2001).

The P/M process is an established method to produce Ti alloys for biomedical applications. On one hand, it reduces the cost and complexity of processing, and on the other hand, it improves the biological activity of the implant surface without compromising its structural integrity, *i.e.* its strength, fatigue resistance, and biocompatibility (Nyberg et al., 2005b). Furthermore, the P/M process is an established method for manufacturing dimensionally precise pieces finished without the need of machining work (Justino et al., 2006), which is more pronounced for Ti and its alloys due to their difficulties in machining (Kutty et al., 2001).

Powder metallurgy products are synthesized by either blending of elemental metals, or pre-alloying process. In the process of blending elemental metals, the proper proportions of elements are thoroughly mixed to obtain the alloy composition; whilst in the pre-alloying process, a homogeneous casting ingot is made into a fine alloyed powder via melting and gas atomization (Froes et al., 1980; Freese et al., 2001). Cost effectiveness of the former method offers strong potential in commercial products (Fujita et al., 1996). The metal powder from each process is cold pressed into the desired final shape and is hot sintered in vacuum. A post-sintering hot isostatic pressing (HIP) may be employed to further densify the powder-fabricated parts. Finished parts are usually annealed or heat treated, depending on the specific requirements (Freese et al., 2001). However, the high affinity of Ti and its alloys for interstitial elements like oxygen and nitrogen requires a non-oxidizing sintering environment in a high vacuum furnace as well as controlled processing media. This is due to the fact that the particle contamination hinders the particle bonding and, thus, degrades the ductility of Ti particles (Froes et al., 1980; Ryan et al., 2006; Nouri et al., 2008b).

Various processes are available for manufacturing porous metal scaffolds including casting, powder metallurgy, metallic deposition and sputter deposition (Davis & Zhen, 1983; Banhart & Baumeister, 1998b). However, to date, the choice has been between the cost and quality (Yu et al., 1998). Conventional processing of molten metal to fabricate porous metal scaffolds is suffering from limited part geometries, contamination, and limited control over the size, shape and distribution of porosities (Krishna et al., 2008). In particular, the casting method is unsuitable for manufacturing of porous Ti based scaffolds, due to the high melting temperature and the associated reactivity of Ti with oxygen and refractory materials during the melting process (Ryan et al., 2006).

The P/M method for fabricating porous metals, on the other hand, offers low cost and direct net-shaped parts with a wide range of alloys and a relatively homogeneous pore structure (Wen et al., 2001; Wen et al., 2002a; Santos et al., 2005). In addition, this method allows further control over the degree of porosity and pore size. However, depending on the method and availability of powders to be used, the P/M process could sometimes be less economic than other methods (Gasser, 2001). This is mostly pronounced when hot isostatic pressing (HIP) is involved in Ti alloy parts using pre-alloyed powder (Liu et al., 2006).

The first application of P/M technology in fabrication of porous metals for orthopedics was investigated by Hirschhorn and Reynolds, on cobalt based alloys (Hirschhorn & Reynolds, 1969). The work performed by Weber and White (Weber & White, 1972) in 1972 is also considered a pioneering study in the application of porous metals in osseointegration.

In the present chapter, due to the importance of open-cell porous implants in orthopedic surgery, the fabrication processes associated with closed-cell porous metal scaffolds are

ruled out. Based on this consideration, the P/M methods of fabricating open-cell porous materials are highlighted as follows:

1. Sintering of partially compacted or loose powder (Hirschhorn et al., 1971; Upadhyaya, 1997),
2. Space holder method (Bram et al., 2000; Wen et al., 2002a; Nouri et al., 2007a),
3. Replication (Li et al., 2002; Bansiddhi & Dunand, 2007),
4. Combustion synthesis (Li et al., 2000; Whitney et al., 2008),
5. Microwave sintering (Kutty et al., 2001).

The choice of fabrication method is usually driven by the powder characteristics, the required type of porosity and the overall cost (Eisenmann, 1998). Moreover, in order to fabricate uniform and repeatable porous structures, the sintering conditions (i.e. temperature, time and atmosphere) should be controlled precisely. More information regarding other aforementioned processes has been described in a previous study by Ryan *et al.* (Ryan et al., 2006).

2.2.1 Space holder method

A variety of methods for producing porous Ti scaffolds and other metals have been developed and commercialized. However, there are still some limitations in those methods. For instance, sintering of loose powder allows a high level of porosity to be reached, but the strength and fatigue properties of parts are lowered. Mechanical characteristics can be improved by compaction of the powder before sintering, but at the same time compaction often causes an undesirable decrease in porosity (Laptev et al., 2004). Major challenges remain in the ability to control pore morphology, pore size, porosity, product purity, and most importantly, production cost. Therefore, appropriate methods which can satisfy these requirements are desirable.

One of the most promising methods for manufacturing open porous Ti scaffolds is the P/M technique using removable space holder materials. This process can provide open porosities, which is essential for the implant bone fixation by growing the bone tissue into the pores. This method is a cost effective process, capable of adjusting the pore size distribution, pore shape, and the level of porosity by adjustment of mixing ratio of space holder and metal powder, as well as the size of space particles into a very narrow pore size distribution (Wen et al., 2001; Wen et al., 2002a; Wen et al., 2002b; Kotan & Bor, 2007).

The weight ratio of metal powder to the space holder is dependent on the predefined porosity of the final sample. The metal powders and space holder material are mixed and compacted into a green form. The compaction lends itself to better green strength to the metal powder upon removal of the space holder material during sintering process. The compaction can be uniaxial or isostatic. During the heat treatment at relatively low temperatures, the space holder is removed by decomposition, leaving the occupied spaces to become pores. Figure 5 schematically represents the space holder removal during heat treatment process. It is worth noting that fabrication of porous parts using the space holder method requires metal particles considerably smaller than the space holder particles, as seen in Figure 5 (Nouri, 2008).

After removal of the space holder the green samples are sintered at temperatures of 1100-1400 °C. The shapes and sizes of the pores are predominantly controlled by the initial shapes

and sizes of the space-holder particle. Thus, high porosity samples with spherical and angular pores in the range of 0.1-2.5 mm can be obtained (Rausch & Banhart, 2002).

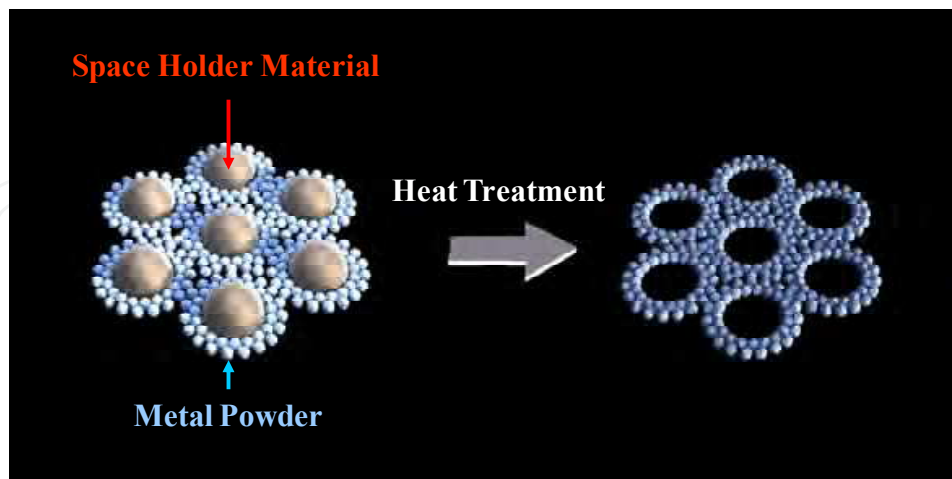


Fig. 5. Schematic illustration of the space holder method, showing a mixture consisting of metal matrix with embedded space holder material and the final metal porous structure after heat treatment (Nouri, 2008).

Several studies have already been reported about using the space holder method for manufacturing porous metallic scaffolds, in particular Ti-based materials. Esen and Bor (Esen & Bor, 2007) used magnesium (Mg) as a space holder, which was removed by slowly heating to 1200 °C and keeping for 1 h under high purity argon gas. In this experiment, Ti scaffolds with a porosity range of 45-70% and an average pore size of around 525 μm were manufactured. The yield strength and elastic moduli values of the resultant scaffolds were varying in the range 15-116 MPa and 0.42-8.80 GPa, respectively. The advantage of using Mg as space holder is its low boiling point (1107 °C) and complete immiscibility with Ti (Wheeler et al., 1983).

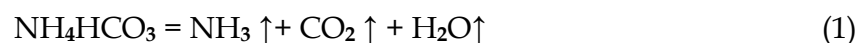
In two different experiments, Bansiddhi and Dunand distinctively used the ionic compounds of NaF (Bansiddhi & Dunand, 2007) and NaCl (Bansiddhi & Dunand, 2008) as space holder material in the mixture with shape memory NiTi powder. NiTi scaffolds consisting of 35-40% open pores with shape memory properties were fabricated by isostatic pressing at 950 and 1065 °C. The NaF and NaCl phases were then removed by water dissolution. The samples fabricated with NaCl as a space holder showed a wider range of pore size between 70 to 400 μm , compared to 240 μm for the samples with NaF. The metastable austenitic scaffold showed average stiffness of 6-12 GPa and 4-25 GPa for the porous samples made from NaF and NaCl as space holders, respectively. However, using NaCl is preferred over the NaF due to its lower cost, ease of dissolution in water and lower toxicity.

Polymer granules were used as a space holder at Fraunhofer IFAM, Bremen, Germany for synthesizing iron-based scaffolds. The polymer granules were decomposed at temperatures around 130 °C, followed by sintering in vacuum at temperatures of 1100-1250 °C. As a result, porous scaffolds with 55-80% porosity with a tensile strength range of 1.5-30.0 MPa and elastic modulus of 0.3-16.0 GPa were produced. Depending on the particle size of the granules, the resultant scaffolds exhibited average pore diameters in the range of 200-300 μm (Rausch & Banhart, 2002).

Although most of the aforementioned space holder materials have their individual merits, they also have their own limitations. The application of conventional, high-melting, organic space holders is limited by the strong reaction of Ti, stainless steel, or Ni-based alloys with the cracking products of these compounds in a temperature range of 350-600 °C. In this case, high concentrations of impurities remain in the samples. Similar problems occur if alkali salts or low-melting metals such as Mg, Sn, or Pb are used (Bram *et al.*, 2000; Buchkremer *et al.*, 2001). For instance, in the complete removal of NaCl, any residual NaCl can lead to contamination or corrosion of the base metal (Bakan, 2006). Therefore, it is important to select an appropriate space holder material which can be completely removed at low temperatures (< 200 °C) to keep the level of impurities low.

Carbamide ((NH₂)₂CO, also called urea) and ammonium hydrogen carbonate (NH₄HCO₃, also known as ammonium bicarbonate) were successfully used to produce porous samples from Ti, stainless steel (316L), and Ni-based superalloys with porosities between 60 and 80%. Depending on the shape and size distribution of the space holder, spherical and angular pores in the range of 0.1-2.5 mm were obtained. Wen *et al.* (Wen *et al.*, 2001; Wen *et al.*, 2002b; Wen *et al.*, 2006; Wen *et al.*, 2007a) and Bram *et al.* (Bram *et al.*, 2006a; Bram *et al.*, 2006b) have successfully used carbamide and ammonium hydrogen carbonate as space holder for the fabrication of porous Ti scaffolds. Successful results of using these space holders in fabricating porous materials have also been reported by other authors (Imwinkelried, 2007; Li *et al.*, 2008).

Both carbamide and ammonium hydrogen carbonate can be burnt out and then removed at temperatures below 200 °C with minimal contamination of the Ti powders. In the case of ammonium hydrogen carbonate, it can be decomposed to ammonia, carbon dioxide and water by the following reaction:



The removal process can be carried out in the air. In this respect, less exposure time of green sample during annealing is preferred (approximately 170 °C for 3 h). Low annealing temperature and longer exposure time has also been reported (80 °C for 14 h) (Bram *et al.*, 2006a). A general difficulty of this method is the removal of large quantities of organic or inorganic space holder from the sample. After heat treatment at low temperature, the porous metal scaffold is prone to collapse before the formation of strong bonding between the metal particles (Andersen & Stephani, 2002; Zhao *et al.*, 2005). Therefore, the sample after the removal of space holder must be handled with care. To achieve a sufficient stability of the compacts after removal of the space holder material, ductile metal powders with an irregular particle shape are preferred. The interlocking of adjacent powder particles enables the formation of a stable network without the need of an additional organic binder. Furthermore, the excessive size of the space holder material or the loose packing of the powder mixture may lead to a loss in interconnectivity between the powder particles, and thereby the loss of strength of the material.

Upon the removal of the space holder, the pore-space structure in the sintered material contains two types of pores: macro-pores, determined by the number and size of the space holder materials, and micro-pores, formed by particles of the metal powder or by incomplete sintering. The distribution of micro- and macro-pores in a porous Ti-16Sn-4Nb (wt.%) scaffold is depicted in Figure 6 (Nouri, 2008).

Wen *et al.* (Wen et al., 2001) synthesized an open porous Ti scaffold with a pore size distribution in the range of 200-500 μm . For the Ti scaffold with 78% porosity, the compressive strength and stiffness were 35 MPa and 5.3 GPa, respectively, showing excellent characteristics tailored for bone replacements. A wide range of strength and stiffness was reported in the Ti scaffolds with 35-80% porosity using ammonium hydrogen carbonate, suggesting that they have the adequate strength to meet the practical requirements for use as cortical and cancellous bone (Wen et al., 2002b). In another study by Niu *et al.* (Niu et al., 2009) porous Ti scaffolds with a similar pore size of 200-500 μm and porosity range of 55-75% were fabricated using carbamide. Subsequently, a plateau stress and Young's modulus were in the range of 10-35 MPa and 3.0-6.4 GPa, respectively. In an experiment conducted by Bram *et al.* (Bram et al., 2000), a plateau stress of approximately 10 and 100 MPa was reported for Ti scaffolds with porosities of 77% and 60%, respectively. Later on, the same authors produced 60% porous Ti scaffolds using different sizes of ammonium hydrogen carbonate. The result showed a stiffness of 3 GPa which is distinctively lower than the theoretical value of 18 GPa and almost independent of the size of the macropores (Bram et al., 2006a). The lower mechanical properties of the scaffold compared to the theoretical values can be attributed to the residual microporosity in the pore walls, as well as the irregular pore shape and the surface roughness of the pore walls.

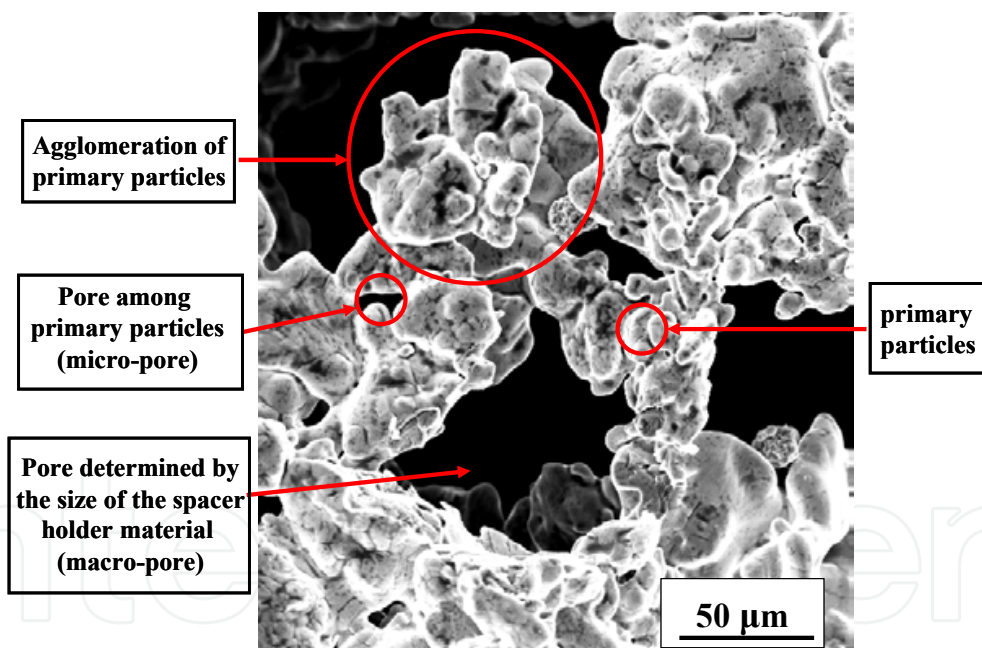


Fig. 6. SEM micrograph showing macro-pores and micro-pores in the Ti-16Sn-4Nb (wt.%) scaffold with 76% porosity (Nouri, 2008).

However, it has been reported that the mechanical properties of the porous structure can be affected by the shape of the space holder material. In an experiment performed by Jiang *et al.* (Jiang et al., 2005), open-cell Al scaffolds were synthesized using spherical- and strip-shaped carbamide particles. The scaffolds with spherical-shaped pores revealed higher compressive strength than those of the strip-shaped pores. In another experiment performed by Imwinkelried (Imwinkelried, 2007), it was found that the nonspherical space holder

particles are preferentially arranged along their elongated sides during compaction. The scaffolds obtained were anisotropic in their mechanical properties, as they were stronger perpendicular to the compaction direction, and weaker along the compaction axis. It was also found that the number of pore walls perpendicular to the compaction direction is consequently larger than those along the compaction direction, thus explaining the higher stiffness and strength.

Zhang *et al.* (Zhang *et al.*, 2007) have recently developed a method of producing gradient porosities using the space holder technique. The addition of 0%, 10%, 20% and 30% ammonium hydrogen carbonate in four layers led to an increase in porosity from 25.5% to 61.3%. For the sample with radial gradient porosities, the outside layer (about 2.5 mm thick) had a much higher porosity (60.9%) and larger pore size (433 μm) compared with the inner part which displayed a porosity of 19.5% and pore size of 84 μm .

3. Chemical Surface Modification of Porous Titanium Scaffolds

The biological performance of metallic orthopedic implants is significantly influenced by its surface properties. The surface of implant controls new bone tissue formation and long term bone-implant biological fixation. The response of bone to implants is attributable to the wide range of factors including anatomical location, the type of bone, surgical procedure, the mechanical load applied on the implant-bone system, gender and age, and, in particular, surface characteristics of the material (Williams, 1987). For this reason, extensive investigations have been attempted aiming at modifying the implant surface composition and morphology so as to optimize implant-to-bone contact and improve integration.

As previously discussed, orthopedic Ti alloys are classified as biocompatible materials; however, being bioinert materials, they do not possess the required bioactivity to bond to bone directly, resulting in a longer recovery time for bone regeneration (Anselme, 2000). Although a porous implant is capable of providing a primary stability between implant and living bone structures, when implanted into the human body, Ti alloys are generally encapsulated by soft-fibrous connective tissue. A fibrous layer intervenes between the implant and bone which reduces the stability of the implant and contribute to the loosening of the implant (Plenk, 1998; Cannas *et al.*, 2000). This phenomenon is illustrated in Figure 7 (Nouri, 2008). Apart from the biocompatibility of biomaterials, the thickness of fibrous connective tissue can also be influenced by other factors. Brunski (Brunski, 1991) has reported that the interfacial bone reaction may be affected by the anatomical location of the implant, the method of implantation, and the biomechanical performance of the implant under the load. Therefore, it is desirable to introduce a method to provoke active bone growth onto the surfaces throughout the porous structure of a Ti scaffold and therefore, maintain a stable biological fixation.

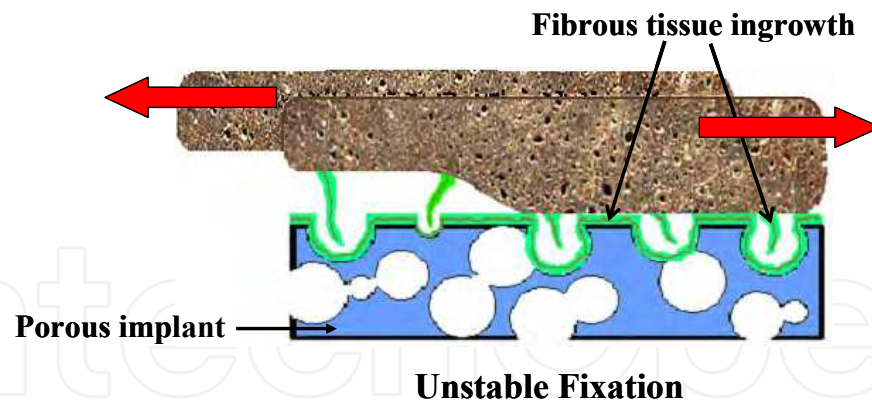


Fig. 7. The intervention of fibrous tissue with porous metallic scaffold leading to the loosening of the implant, known as unstable fixation (Nouri, 2008).

Hydroxyapatite (HA) coating on the surface of Ti implants is an effective method to enhance bioactive properties. Synthetic HA, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, is regarded as a bioactive and biocompatible material and can directly bond to bone without the occurrence of an encapsulation with fibrous tissue. Apatite is a main component of bone crystal, and also preferentially adsorbs proteins that serve as growth factors (Hench, 1991). Despite the excellent bioactivity of hydroxyapatite, its application has been limited in clinics due to its intrinsic brittleness and high modulus of elasticity.

The bioactivity of Ti implants can be improved using various surface modification technologies. These methods can be categorized into three classes: mechanical, physical and chemical. In mechanical methods, a rough or smooth surface is formed by machining (Lausmaa et al., 1990), grinding (Hignett et al., 1987), or blasting (Wennerberg et al., 1996). In the physical method, the formation of films or coating on Ti and its alloys are mostly attributed to the thermal, kinetic, and electrical energy. Thermal spraying is one of the most demanding processes of coating in this method, in which the coating materials are thermally melted into liquid droplets and coated to the substrate at a high speed (Liu et al., 2004). The surface modification of Ti implants through mechanical and physical methods lies outside the scope of this chapter and will not be discussed further.

Currently, chemical methods are attracting more attention for the lower cost, easier control and stronger adhesion between bones and implant surfaces compared to mechanical and physical methods. This method is aimed to modify the surface of metal implant materials without significantly altering the surface morphology. The chemical reactions are predominantly occurring at the interface between the metal and chemical solution, providing unique properties required in the biological environments. The most common chemical treatments are acid, hydrogen peroxide (H_2O_2), alkali treatments, sol-gel and anodic oxidation (i.e. hydrothermal treatment). In addition, the chemical method helps to achieve better and thinner hydroxyapatite coating which possesses high bonding strength and sufficient bioactivity (Kim et al., 1996). Table 3 presents various processes used in the surface modification of Ti and its alloys through the chemical methods.

Method	Modified layer	Objective
Chemical treatment		
Acidic treatment	< 10 nm of surface oxide layer	Remove oxide scales and contamination
Alkaline treatment	~ 1 μm of sodium titanate gel	Improve biocompatibility, bioactivity or bone conductivity
Hydrogen peroxide treatment	~ 5 nm of dense inner oxide and porous outer layer	Improving biocompatibility, bioactivity or bone conductivity
Sol-gel	~ 10 μm of thin film, such as calcium phosphate, TiO_2 and silica	Improve biocompatibility, bioactivity or bone conductivity
Anodic oxidation	~ 10 nm to 40 μm of TiO_2 layer, adsorption of electrolyte anions	Produce specific surface topographies, improved corrosion resistance; improve biocompatibility, bioactivity or bone conductivity

Table 3. Various chemical methods used for surface modification of Ti and its alloys (Liu et al., 2004).

Sol-gel approach, for instance, possesses many benefits, such as fine grain structure and homogeneous substrate coverage, low cost and technical simplification, and effectiveness for the coating of implants with complex shape and porous scaffold (Wen et al., 2007b; Li et al., 2009a; Xiong et al., 2009a). However, higher bonding strength of hydroxyapatite coating on the metal surface is produced when hydrothermal treatment is used as compared to sol-gel method (Liu et al., 2005). The hydrothermal treatment usually provides materials with a high degree of crystallinity and with a calcium/phosphate ratio close to that of stoichiometric hydroxyapatite (1.67). The hydroxyapatite particles in the coating layer exhibits a polygonal shape with size in the range nanometer to micrometer (Tang et al., 2005; Xiong et al., 2009b).

Acid treatment is usually used to remove oxide scales and contamination, in order to obtain clean and uniform surface finishes. Only several acids, hydrofluoric acid (HF), nitric acid (HNO_3), hydrochloric acid (HCl), and sulfuric acid (H_2SO_4) possess the capability to react with the oxide on Ti surface whilst providing very low chemical reactivity on the surface. However, the degree of acidic reaction on the surface of Ti and its alloys is dependent on the acid concentration, temperature, and processing time, which is usually kept in the range of 1-60 min (Lausmaa, 2001). The strongly etched parts may predominantly affect the extent of material removed from the surface, and thus change the surface topography. For instance, Ti alloys containing both α and β phases react differently in etching rates resulting in surface topography where β phase sticks out from the α phase, which is etched faster (Ask et al., 1988). In general, acidic treatments would lead to the formation of a thin oxide layer

(< 10 nm), predominantly TiO₂, on the surface of Ti alloys. Absorption of hydrogen into the Ti surface due to acid treatment can cause embrittlement of the surface layer.

Hydrogen peroxide treatment is based on the reaction of Ti surface with hydrogen peroxide, H₂O₂, producing Ti-peroxy gels. Titania gel coating can improve the bioactivity of Ti implants because titania gels can induce the formation of apatite when soaked in a simulated body fluid (SBF). This process may result in roughening of the surface on the submicron scale and a considerable growth in thickness of oxide layer. However, a shorter processing time gives rise to a thinner gel layer with higher porosity in submicron size. The oxide layer consists of mainly TiO₂, as well as hydroxyl groups (Pan et al., 1998; Liu et al., 2004).

The detailed process of the aforementioned chemical treatments has been described in the literature (Tengvall et al., 1989; Wen et al., 1997; Pan et al., 1998; Sittig et al., 1999; Liu et al., 2004; Yang et al., 2004). However, the focus of the present chapter is on alkaline method for surface modification of the porous Ti scaffolds.

3.1 Alkali treatment

Alkali treatment provides a novel and simple technique for modification of Ti surfaces. This method was first introduced by Kim and Kokubo (Kim et al., 1996; Kokubo et al., 1996) to enhance the bioactivity of Ti and its alloys. They found, after this simple chemical treatment, that the treated surface of Ti and its alloys, such as pure Ti, Ti-6Al-4V, Ti-6Al-2Nb-Ta and Ti-15Mo-5Zr-3Al, form a thin sodium titanate layer on their surfaces. Thus, treated materials formed a dense and uniform bonelike apatite layer on their surfaces after soaking in SBF. SBF is an electrolyte solution which reproduces the inorganic part of human blood plasma. Therefore, it can be assumed that the structure of coatings precipitated from SBF will be close to that biological apatite present in human bone (Müller & Müller, 2008). Using SBF for the formation of apatite on the surface of Ti offers a promising alternative to plasma spraying and other coating methods.

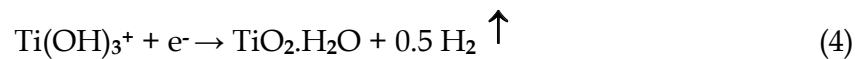
Treatment of Ti in 5-10 M NaOH at 60 °C for 24 h has been shown to produce a surface layer consisting of a sodium titanate gel (Lausmaa, 2001). The surface layers are of the order of 1 μm thick, with an irregular topography and a high degree of open porosity on the submicron scale. Subsequent heat treatments can be used for modifying the composition and structure of the surface layers.

The surface structural change of pure Ti with the alkali and heat treatments, and the mechanism of apatite formation on the treated surface in SBF have been reported in detail by Kokubo *et al.* (Kokubo et al., 2003). The mechanism of apatite formation on the surface of the porous Ti scaffold after alkali- and heat treatment process and during soaking in a SBF solution is schematically illustrated in Figure 8 (Kokubo et al., 2003; Nouri, 2008). This process is based on the induction of hydroxyl groups on the Ti surface that involves the heterogeneous nucleation and the growth of bone-like apatite layer on the surface of the porous material at physiological temperatures and pH conditions.

The structural changes during alkali treatment are described as follows. The first step is the partial dissolution of TiO₂ layer in an alkaline solution by hydroxyl groups.



The reaction is assumed to continue with hydration of Ti (Kim et al., 1996; Gil et al., 2002; Liu et al., 2004):



By proceeding the alkali treatment, more hydroxyl reacts with the hydrated TiO_2 , leading to negatively charged hydrates on the surface of the sample as follows:

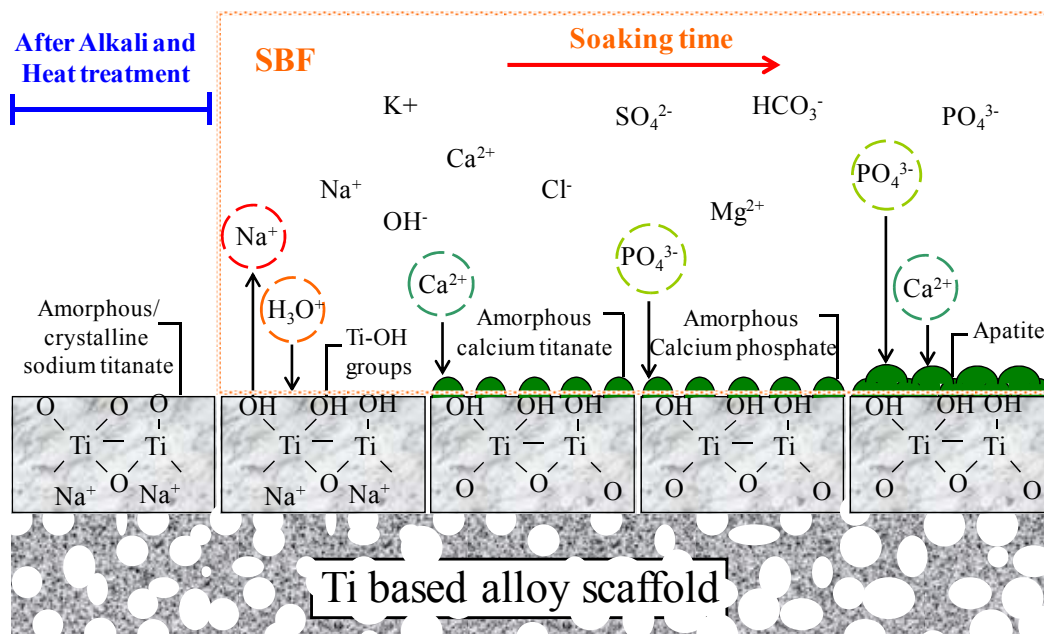
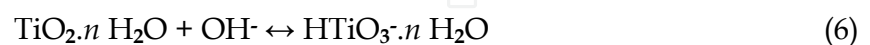
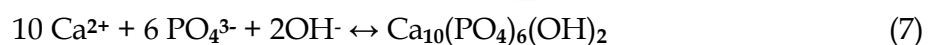


Fig. 8. A schematic illustration of the apatite formation on the surface of alkali and heat treated porous Ti based alloy scaffold soaking in SBF (Kokubo et al., 2003; Nouri, 2008).

These negatively charged species are partially dissolved into the alkaline solution to form a sodium titanate hydrogel layer. This gel layer is, however, unstable and needs to be dehydrated and densified using heat treatment to convert to a more mechanically stable layer. According to Kim *et al.* (Kim et al., 1997a), heat treatment around 600 °C results in a mechanically strong amorphous sodium titanate layer containing a small amount of crystalline sodium titanate and rutile; therefore, it induces a moderately short time for apatite nucleation. Kokubo and Takadama (Kokubo & Takadama, 2006) have shown that if a sodium titanate layer could be formed on the surface of Ti and its alloys after alkali- and heat treatment process, the following soaking in SBF can induce an apatite on the surface. As a result, the formation of apatite can provide a strong bond between the coated surface and living bone.

During the SBF soaking, sodium ions (Na^+) releases from the sample via exchange with H_3O^+ ions, resulting in the formation of a Ti-OH layer. The rate of the Na^+ ion release from the sample remarkably decreases when the surface changes from the gel to amorphous phase and then crystalline phases. The Ti-OH layer is negatively charged and can selectively combine with the positively charged Ca^{2+} through an electrostatic force and forms calcium titanate. Consequently, the positively charged surface combines with negatively charged phosphate ions (PO_4^{3-}) to form amorphous calcium phosphate. Upon the formation of the apatite nuclei, they spontaneously grow on the surface by consuming the calcium and phosphate ions from the surrounding SBF solution (Kim et al., 1996; Kim et al., 1997a; Gil et al., 2002; Liu et al., 2004). The formation of HA in SBF is according to the following equilibrium:



Apart from the hydroxide groups, the presence of titanium oxide also aids the formation of apatite on the Ti surface. Amongst the three forms of TiO_2 , known as anatase, rutile and brookite, anatase is the lower temperature phase and possesses higher activities than rutile of higher temperature phase. The reason is that anatase can provide a proper atomic arrangement in its crystal structure that suits the formation of apatite. However, the activities can be affected by other factors such as the crystallinity, impurities, lattice defect, and reaction conditions (Yoshida & Watanabe, 2005; Narayanan et al., 2008).

Kim *et al.* (Kim et al., 1997b; Kim et al., 1999) compared the bonding strength of bonelike apatite layer to Ti metal substrates pre-treated by alkali- and heat treatment at different temperatures from 500 to 800 °C. The results revealed that the heat treatment at 500 and 600 °C has the highest bonding strength. The rate of apatite formation on Ti substrate, however, decreases with increasing the temperature, especially at 800 °C. This is attributed to the lower release rate of Na^+ ion from the crystallized sodium titanate at 800 °C. Under tensile stress, the substrates heat treated at 600 °C showed higher bonding strength of the apatite to the substrates than those of heat treated at 800 °C. This is because the former introduced a smooth and graded interface structure between the apatite and the substrates while the latter had the graded interface structure disturbed by a thick Ti oxide.

The alloy composition also appeared to have an important effect on the apatite formation after alkali- and heat-treatment and soaking in SBF. Lee *et al.* (Lee et al., 2002; Lee et al., 2003) have reported better bioactivity for Ti-In-Nb-Ta alloy compared to that of Ti-6Al-4V ELI alloy in vitro. After surface modification by alkali heat treatment, porous network layers of sodium titanate ($\text{Na}_2\text{Ti}_5\text{O}_{11}$ or $\text{Na}_2\text{Ti}_6\text{O}_{13}$) were formed on both alloys surfaces. However, the finer and thinner porous layers of the former exhibited more physical stability and stronger bone-bonding strength than the coarse and thick layer of the latter.

The deposition coatings from aqueous solutions can be accelerated by several methods. Wang (Wang et al., 2003) and Yang (Yang et al., 2004) and their co-workers have demonstrated the electrodeposition of calcium phosphate by applying a current in a Ti cathode and a platinum. This method provides a perfect control over the thickness of the coating layer within a short time. Others have multiplied the concentration of calcium and phosphate ions in SBF to form a thin layer on the Ti surface. Such a procedure led to a considerable enhancement of coating rate in a very short time (2-6 h) (Habibovic et al., 2002; Tas & Bhaduri, 2004). The surface characteristics of implant material directly or indirectly

influence the way bone cells act and bone apatite nucleates. For instance, the cell response to the surface roughness of Ti and some of Ti alloys has been extensively investigated both *in vitro* and *in vivo* (Carinci et al., 2003; Li et al., 2004b; Chen et al., 2008) and there is a commonly held belief that the surface roughness of the metal substrate plays an important role in this respect. For instance, the optimum surface roughness range of 0.15-0.35 μm exhibited the improved adhesion and proliferation of human SaOS₂ osteoblast-like cells on the surface of the solid Ti6Ta4Sn alloy (Li et al., 2009b). In another study by Wang *et al.* (Wang et al., 2008; Wang et al., 2009) the better apatite induce ability was obtained for the Ti surface with a nanofiber-like structure than nanoporous or nanoplate surface structures. In addition to alkali- and heat treatments on bulk Ti and its alloys, a few experiments have been conducted on the effect of alkali- and heat treatment on the porous structures. Nishiguchi *et al.* (Nishiguchi et al., 2001) studied the effects of the alkali- and heat treatments on the bone-bonding ability of porous Ti scaffolds with a solid core and a 0.7 mm thick porous outer layer. Good clinical results were obtained by alkali- and heat treatment of such porous Ti, showing extremely high bonding shear strength in the canine femora push-out model after implantation for 4 weeks. In another study, the apatite formation was investigated on the porous Ti, with maximal pore size of approximately 250 μm and 40% porosity (Liang et al., 2003). The samples were soaked in 0.5, 1.0, 5.0, and 10.0 M NaOH aqueous solutions at 60 °C for 24 h, respectively. The results indicated no apatite nucleation on the small pores of samples soaked in 0.5 and 1.0 M NaOH solutions, whilst the apatite coating was formed on all other samples. Recently, Xiong *et al.* (Xiong et al., 2008) have conducted the alkali- and heat treatment on a porous Ti-18Nb-4Sn (at.%) scaffold using an aqueous solution of 10 M NaOH at 50 °C. A thick layer of spherical precipitate with small cracks was formed after soaking in SBF for 7 days. Nouri *et al.* (Nouri et al., 2007b) have also investigated the apatite forming ability of porous Ti alloy scaffold by soaking the porous samples in a concentrated simulated body fluid (10×SBF) from 1 to 6 h. The results indicated the deposition of bone-like apatite globules throughout the alkali- and heat treated porous Ti alloy scaffold after soaking in the 10×SBF for 1 h. Proceeding the soaking time to 6 h, a uniform layer of bone-like apatite granules deposited on the entire surface throughout the scaffold showing considerable apatite forming ability after the thermochemical treatment and soaking in a 10×SBF solution. Figure 9 depicts the morphology evolution of the apatite coating on the surface of the porous Ti alloy scaffold after the alkali- and heat treatment and soaking in a 10×SBF for 6 h.

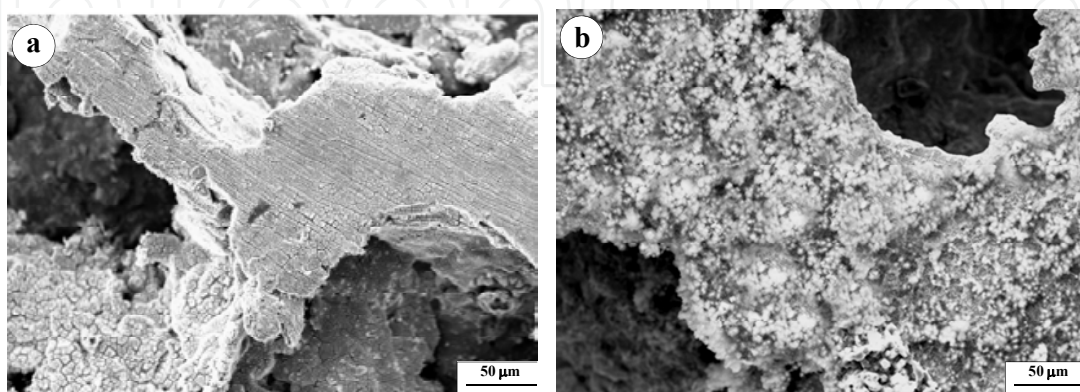


Fig. 9. SEM micrographs of the porous Ti-16Sn-4Nb (wt.%) scaffold after (a) alkali- and heat treatment and (b) soaking in the concentrated 10×SBF for 6 h (Nouri et al., 2007b).

4. Summary

This chapter presented a summary of the fabrication and characteristics of the biomimetic porous Ti scaffold for orthopedic and dental applications. In order to design and characterize an implant for orthopedic applications, a brief discussion was presented regarding the structure and mechanical properties of the natural bone. The chapter continued with the growing consensus regarding the use of Ti and its alloys for orthopedic and dental applications. Some of the issues related to porous Ti scaffolds including their physical properties, microstructure and biomedical characteristics were demonstrated and compared to their nonporous counterparts. Within the scope of the orthopedic applications, Ti alloys with biocompatible alloying elements, i.e. Zr, Nb, Ta, Sn, Mo and Si, are considered as promising candidate for bone tissue engineering.

A brief overview was also given to several potential powder metallurgical approaches for developing new advanced porous Ti alloys. In particular, the space holder method was introduced as a feasible method for fabricating biomimetic porous Ti scaffold as bone tissue replacement. This technique allows the control of pore size, pore shape and porosity in porous titanium scaffolds and the adjustment of the chemical compositions of the titanium alloys, providing excellent scaffolds for bone ingrowth. Finally, the choice of an appropriate surface technique for enhancing the bone-bonding ability of porous Ti scaffolds was discussed using the alkali- and heat treatment.

It is hoped that some basic concepts have been relayed to the reader that will provide a basis for the understanding of these biomimetic porous scaffolds in orthopedics.

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Nature's evolution has led to the introduction of highly efficient biological mechanisms. Imitating these mechanisms offers an enormous potential for the improvement of our day to day life. Ideally, by bio-inspiration we can get a better view of nature's capability while studying its models and adapting it for our benefit. This book takes us into the interesting world of biomimetics and describes various arenas where the technology is applied. The 25 chapters covered in this book disclose recent advances and new ideas in promoting the mechanism and applications of biomimetics.

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