TOPICAL REVIEW

Titanium and titanium based alloy prepared by spark plasma sintering method for biomedical implant applications—a review

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Keywords: titanium, spark plasma sintering, biomedical implant, powder metallurgy

Abstract

Titanium has been widely used in biomedical implant applications due to its excellent mechanical properties and biocompatibility. However, manufacturing titanium was quite challenging due to the need for high temperature while having high reactivity. Therefore, spark plasma sintering (SPS) is proposed as an advance rapid sintering technique which allows the fabrication of bulk and porous titanium for biomedical application. This review aims to explore the recent status of titanium alloys prepared by the SPS method. There are two common approaches of titanium development by the SPS method, develop a bulk titanium alloy, or develop porous titanium. The development of titanium for biomedical implant application was done by improving biocompatibility alloy and repair some unsatisfactory mechanical properties. Some low toxicity of titanium alloys (Aluminum free and Vanadium free) had been studied such as Ti–Nb, Ti–Zr, Ti–Ag, Ti–Mg, Ti–Nb–Zr, Ti–Nb–Cu, Ti–Nb–Zr–Ta, etc. SPS was shown to increase the mechanical properties of titanium alloys. However, porous titanium alloys prepared by SPS had gained much attention since it may produce titanium with lower elastic modulus in such a short time. Low elastic modulus is preferable for implant material because it can reduce the risk of implant failure due to the stress-shielding effect. Besides mechanical properties, some corrosion resistance and the biocompatibility of titanium are also reviewed in this paper.

1. Introduction

In recent, metallic biomaterials have been developed to fulfill specific requirements to be used in various applications such as dental and orthopedics, drug delivery, tissue engineering, or cardiovascular devices [1, 2]. Biomaterials are generally accepted as biocompatible materials that support or replace a part of an organ or tissue of the biological system [3]. It is commonly known that the sufficient mechanical properties, biocompatibility, high wear resistance, also corrosion resistance in the biological environment are the requirement for biomedical implant applications [2]. Metals have better mechanical strength than polymers and highly tougher than most bioceramics which makes metallic biomaterials play an important role in the reconstruction of failed hard tissue [4]. Commonly used metallic biomaterials are cobalt-chromium (Co–Cr) alloys, stainless steel, and titanium (Ti) and its alloys. Among them, titanium and its alloys showed the excellent properties which make it the most commonly used biomaterial in implant application, such as good biocompatibility [5], specific mechanical strength (high mechanical properties compared to the density), lower elastic modulus (Ti-based alloy: 53–110 GPa, Stainless Steel: 190–210 GPa, Co–Cr alloy: 210–253 GPa; closer to human bones: 4–30 GPa) [2], and high corrosion resistance [1, 4, 6, 7]. More details on the mechanical properties of the bone are shown in table 1.

For implant materials, lower elastic modulus is preferable for bone replacement hence the higher stiffness of the implant would prevent the stress-transfer processing in the bone. This condition would lead to the bone resorption around the implant and resulted in the implant loosening, which called as ‘stress shielding effect’.
The biocompatibility is a term to describe that the material is non-toxic and acceptable in the human body. Likewise, high wear and corrosion resistance were important to reduce the risk of allergic or toxicity related to the released of metal ions after implantation in the human body. Further, implant materials also need to have an osseointegration properties which means the implant surface can be integrated with the bone and tissue [2].

For orthopedic implant materials, pure titanium was previously developed, but then Ti6Al4V was started to become more popular hence it offered higher strength and preferable mechanical properties. But some concerns during the healing process compared to bulk material was further showed up because Vanadium (V) may induce an allergic reaction and Aluminum (Al) was susceptible to cause Alzheimer’s disease. Therefore, there is an increasing trend to develop high strength Ti alloy without Al and V for the medical implants [9]. Accordingly, the non-V alloy was developed such as Ti–6Al–7Nb and Ti–5Al–2.5Fe [6, 10].

Table 1. Mechanical properties of cortical bone and cancellous bone [6, 8].

|                         | Elastic modulus (GPa) | Yield strength (MPa) | Compressive strength | Elongation (%) |
|-------------------------|-----------------------|----------------------|----------------------|----------------|
| Cortical Bone           | 7–30                  | 120–160              | 100–230              | 0.55–0.94      |
| Cancellous Bone         | 0.3–4                 | 1.75                 | 2–12                 | 0.78           |

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Aside from the consideration of non-toxic alloying, the improvement of titanium performance such as lowering elastic modulus (to be closer to human bone), balancing strength/ductility, fatigue strength, fracture toughness and wear resistance, increasing anti-bacterial, and corrosion resistance has gained a lot of interest [11–13]. Lowering the elastic modulus has led to enormous research related to titanium such as developing beta titanium or porous structure [4, 14–16]. Beta titanium can be produced by the addition of β-stabilizing elements such as Mo, V, Ta, Nb, Fe, Mn, Cr, Co, Ni, Cu, Si, H [17]. Hereafter, more alloying system was developed such as Ti-Mo [18], Ti-13Nb–13Zr [19–21], Ti–Nb–Ta–Zr [22, 23]. These β–Ti alloys were attractive because not only offered non-toxic alloys but also has lower elastic modulus which can reduce the stress shielding effect of the implant. Later on, the porous structure of titanium was developed because it can reduce elastic modulus much closer to human bone. Porous structure also gives better osseointegration because it allows bone tissue ingrowth during the healing process compared to bulk material [8]. Furthermore, there was a rising concern to develop antibacterial properties of titanium hence some failed implant related to the postoperative infection. Ti-based implant with antibacterial properties would reduce the risk of bacteria attachment which lead the biofilm formation. Some Ti inorganic antibacterial agents such as Cu and Ag are added as the alloying element to form Ti–Ag [13, 24], Ti–Cu [25, 26], or Ti–Nb–Cu [27].

Lower elastic modulus is important hence it can reduce the stress shielding effect which leads to bone resorption and implant failure [10]. For hard tissue replacement, low modulus Ti alloys can be used as an artificial hip joint, bone plates, or spinal fixation rod [4]. Meanwhile, porous Ti can be used for spinal fusion devices [28–30], acetabular cup in hip prosthesis [31, 32], fracture plate, or dental implant [33]. The elastic modulus of the commonly used biomedical alloys being compared with human bone is shown in figure 1.

Titanium and its alloys had been produced using arc melting and casting techniques [41–44] or powder metallurgy [39, 45–47]. However, titanium high melting point (1668 °C), high chemical reactivity (with O2, N2, H2, etc) especially in higher temperature, and low machinability makes titanium powder metallurgy was
considered as a favorable method than the conventional casting method [48–50]. Furthermore, when titanium is alloyed with other elements that has a high difference in melting temperature, powder metallurgy combined with mechanical alloying offered better homogeneity [51]. Currently, there is an increasing interest in applying rapid sintering such as spark plasma sintering (SPS) to fabricate the enormous type of titanium alloys with a fine-grained microstructure to achieve excellent mechanical properties [52–56]. By applying SPS, high pressure is given to a compact powder during sintering therefore the densification is enhanced, lowering the sintering temperature and holding time. This process also proved to reduce the grain growth rate, resulting in excellent mechanical properties [57]. SPS is commonly used to create relatively high-density alloys, nevertheless, SPS also could be used to fabricate porous structure titanium, depending on its specific biomedical application. Currently, there are two common approaches in manufacturing porous titanium using SPS, which is applying the partial sintering method, or space holder-assisted in the SPS method [47, 58, 59].

It is important to note that alloying type, particle size, mixing process, and sintering parameter would affect the microstructure of titanium and also its densification process. In the present review, the role of spark plasma sintering in the fabrication of titanium and its alloy for biomedical application is explored. There are two common approaches in manufacturing titanium for biomedical application, by developing bulk/non-porous titanium alloy, or porous titanium alloy. Mechanical properties, corrosion resistance, and biocompatibility of the resulted titanium and its alloys are evaluated. The schematic representation of this paper is depicted in figure 2.

1.1. SPS principle

SPS is also known as the field-assisted sintering technique (FAST), which is a technology that utilizes the Joule heating effect through an electric current to get densification [60]. This method includes a relatively easy procedure, which is fulfilling the mold with powder material, followed by pressing the compact while increasing the temperature to sinter the powder. The schematic process of SPS can be seen in figure 3. Compared to conventional PM, the rapid sintering process in SPS and the results of a smooth size process are the advantages of this method [52].

In the SPS, several parameters can be adjusted such as the holding time, temperature gradient, pressure, pulse duration, pulse current, and also voltage [62]. Compared to conventional sintering, relatively lower sintering temperature, shorter holding time, and faster cooling during the whole process can be achieved by SPS.
Moreover, the heating rate of the SPS can reach several hundred °C min⁻¹. Hence, SPS can be used for tailoring specified microstructure based on the powder sintering mechanism [6].

2. Processing of Titanium and Its Alloy (Bulk/non porous) using SPS Method

To date, beside CP-Ti (α–Ti) and Ti–6Al–4V (α + β Ti), there is an increasing interest in developing the β titanium. The addition of β stabilizing agents such as Niobium, Tantalum, Molybdenum, and Zirconium are considered safer for biomedical implant compared to Aluminum and Vanadium. However, these rare elements were expensive, accordingly, the recent development of β titanium are including low-cost alloying elements such as Fe, Mn, Sn, and Cr [1, 11]. It is expected that the new titanium alloy may have preferable mechanical and biocompatible properties but low in cost. Further, there is also a growing interest in developing antibacterial properties of titanium by the addition of an antibacterial element. Therefore, beside binary Ti alloy (Ti–Nb [63, 64], Ti–Zr [65], Ti–Ag [13], etc), ternary alloy system (Ti–Nb–Zr [20, 51, 66, 67], Ti–Nb–Ag [68], Ti–Nb–Cu [27], etc), and even quaternary alloy system (Ti–Nb–Zr–Ta [23, 56], Ti–Nb–Zr–Fe [69], etc) are also been developed. Some studies of fabricating β titanium using spark plasma sintering are shown in table 2.

2.1. PTi

An earlier study on the fabricating CP-Ti by SPS method was conducted by Eriksson et al in 2005 [70] which focused on the densification and what the cause was. The sintering process was applied up to 950 °C (no holding time, 50 MPa), while the heating rate was varied from 25 °C min⁻¹ up to 200 °C min⁻¹. It mentioned that the particle deformation contributed more to the densification mainly in the α phase region. Further, Zadra et al [71] investigated the use of SPS for fabricating CP-Ti grade 1 and grade 3. From this study, to get a good microstructure, chemical, and mechanical properties of the Titanium required the temperature sintering to be at least 900 °C. Afterward, Pascu et al [75] developed Ti alloy using SPS for biomedical application. TiH₂ was used as the starting powder. The microstructure of the SPS samples shows the lamellar structure of α + β. Sintering process at 1000 °C for 10 min resulted in a finer lamellar structure, meanwhile, the sintering process at 1100 °C for 20 min resulted in a nearly bimodal structure. Furthermore, the porosity would be lower at a higher temperature and longer holding time. On the other hand, the sintering process through conventional sintering (classic sintering) under argon revealed the formation of TiO₂, indicated the oxidation process occurred. The microstructure of the resulted Ti alloy was shown in figure 4.

2.2. Ti-6Al-4V

Crosby et al [72] developed Ti-6Al-4V for the core of functionally graded implant material. The milling process and the SPS process were shown to reduce the sintering temperature while enhancing the densification of the Ti–6Al–4V alloy. It showed that 99% of dense alloy can be achieved by a sintering temperature of 740 °C on the SPS due to the applied pressure of 50 MPa and the intrinsic joule effect at the SPS process. While the conventional sintering required a temperature sintering of 1200 °C for 2 h sintering to reach 99% dense alloy.

While Long et al [73] fabricated ultrafine-grained of Ti–6Al–4V using mechanical milling for 5 to 50 h combined with the SPS. The sintering was conducted at 850 °C for 4 min, the heating rate of 100 °C min⁻¹, and 50 MPa pressure. The microstructure of the as-sintered alloy showed equiaxed α + β phases (size of 0.51–0.89 μm) and α phase (size of 2%–8% μm). The sample with 10 h milling time has 1260 MPa compressive yield strength, 1663 MPa ultimate compressive strength, and 20% ductility.

2.3. Ti-Nb

Ti-Nb alloys have been proposed as better biomaterials because of their excellent biocompatibility [10, 64]. Kalita, et al [63] studied microstructure, mechanical properties, and the superelasticity of Ti-xNb (14,20, and 26 at.%). The Ti powder (150 mesh) and Nb powder (300 mesh) was used the starting powder. Mechanical alloying was done using a planetary ball mill (150 rpm for 30 h) under argon atmosphere. The alloys were then sintered at 1300 °C for 60 min (50 MPa pressure) under Argon atmosphere. Microstructure examination showed the undissolved Nb particles and also α - phase precipitation at the grain boundary of the β phase. Thus, to enhance the homogeneity of the alloy, additional annealing at 1250 °C for 24 h was performed. The addition of Nb content would reduce the Yield strength due to the reduction of the α phase (949 MPa to 656 MPa). Further, the mechanical properties of the alloy were insignificantly improved by heat treatment. In this study, the heat-treated Ti-14Nb alloy showed superelastic behavior, a 3% maximum recoverable strain was reached.

Meanwhile, Sharma et al [64] prepared Ti-Nb (Ti-40 wt% Nb) alloy using TiH₂ as the starting powder. Compare to the ductile elemental Ti powder, TiH₂ was brittle and possibly increase the strength of mechanically alloyed powder. It was shown that the dehydrogenation temperature was decreased. SPS was done under pressure of 50 MPa, varied temperature sintering (950, 1100, and 1250 °C) for 30 min Microstructure
Table 2. Example of Titanium and Ti-based Alloys (Non Porous) Fabrication via SPS.

| No | Alloy system | Processing route | Mechanical properties | Other properties and comments | References |
|----|--------------|------------------|-----------------------|-------------------------------|------------|
|    |              |                  | Hardness (HV) | Compressive yield strength | Elastic modulus (GPa) |                       |                      |
|    |              |                  | —           | —                            | —             | Comparison of SPS and Hot Press Conventional. Densification and Microstructure were studied. | [70]                |
| 1  | CP-Ti        | Sintering at 950 °C, no holding time | 130–150 (Grade 1) | 380–450 (Grade 1) | 320–350 (Grade 1) | —                      | [71]                |
|    |              | (Pressure 50 MPa, heating rate varied) | 190–240 (Grade 3) | 600–750 (Grade 3) | 500–600 (Grade 3) | Densification enhancement can be done through SPS, in comparison with conventional (radiant heat) and microwave sintering. | [72]                |
| 2  | CP-Ti        | Ti powder grade 1 and grade 3. Sintering at 750 °C–1150 °C, 5 min (min) holding time (Pressure 60 MPa, heating rate not shown) | 380–450 | 500–600 | Microstructure and morphology of grain after milling, microstructure, chemical composition, and mechanical properties after sintering were observed. | [73]                |
| 3  | Ti-Nb        | Ti-6Al-4V (spherical, 45–250 μm). Milling: 1–4 h (h) using stearic acid as process control agent (PCA). Sintering under vacuum: pressure 50 MPa, heating rate 100 °C min⁻¹. | 949–656 | — | Optimum milling time 30 h. Microstructure and mechanical properties were observed. | [63]                |
| 4  | Ti-Nb        | Ti-6Al-4V powder. Milling: 5–50 h. Sintering at 850 °C for 4 min (Pressure 50 MPa, heating rate 100 °C min⁻¹) | 1663–1750 | 1260–1361 | The use of TiH₂ increased the strength. Thermal analysis, microstructure, and mechanical properties (hardness) were observed. | [64]                |
| 5  | Ti-Nb        | Ti and x Nb (x = 14, 20, and 26%at) milled for 30 h (150 rpm). Sintering: 1300 °C for 30 min under 35 MPa pressure in Argon atmosphere. Followed by annealing at 1250 °C for 24 h. | 460–530 | — | TiH₂ was shown to better than ductile Ti. Thermal analysis, phase and microstructure, and hardness were observed. | [74]                |
| 6  | Ti-Nb        | TiH₂-Nb (Ti-40 wt.% Nb) milled for 30–300 min (200 rpm). Sintering 950 °C–1250 °C, pressure: 50 MPa, holding time 30 min | 470–530 (A) | — | — | — | — |
| 7  | Ti-Nb-Sn     | TiH₂-Nb-Sn (Ti-25Nb-15Sn, in wt%) milled for 72 ks and 180 ks (200 rpm). Sintering: temperature and pressure was programmed to simultaneously, hold for 1.8 ks | 520–560 (B) | 1140–1619 | 43.91–58.01 | Microstructure examination showed Ti-Nb-Cu phase and Ti₂Cu phase. High compressive strength, yield strength, and also low elastic modulus were observed. Antimicrobial testing also showed a good result. | [27]                |

520–560 (B)
| No | Alloy system | Processing route | Mechanical properties | Other properties and comments | References |
|----|--------------|------------------|-----------------------|-------------------------------|------------|
|    |              |                  | Hardness (HV) | Compressive strength | Elastic modulus (GPa) |                             |            |
| 9  | Ti-Nb-Zr    | Ti-20at%Nb-13at%Zr (<45 μm) milled for 10 h (300 rpm). Sintering at 800 °C–1200 °C, pressure 50 MPa, heating rate 100 °C min⁻¹, holding time 10 min | 620–660 | — | — | Nanostructured grain of non-toxic near β Ti alloy. Densification, microstructure, and hardness were observed. | [67] |
| 10 | Ti-13Nb-13Zr | Ti-13Nb-13Zr (in wt%) milled for 2 h (300 rpm) followed by additional mechanical alloy (time varied, 400 rpm). Sintering at 700 °C–900 °C | 273–356 | — | — | Phases, microstructure, mechanical (hardness and compressive strength) properties, and electrochemical properties were observed. Highly dense alloy can be produced in a low sintering temperature. | [20] |
| 11 | Ti-Nb-Zr    | Ti-24Nb-2Zr (at%) milled for 24 h (350 rpm). Sintering at 850 °C–1200 °C. Heat treatment: 850 °C for 1 h followed by water quench. | 280–450 | 1000–1250 | — | Density, microstructure and mechanical properties were observed. Heat treatment was used to make sure homogeneity | [66] |
| 12 | Ti-Nb-Ta-Zr | Ti-xNb-yZr-20Ta (x = 30, 35; y = 5, 7 all in wt%). milled for 60 h (300 rpm). Sintering at 1100 °C, 5 min, pressure: 50 MPa. | 173–608 | — | 60–149 | Different effect of alloying element on the microstructure, phase transformation, and mechanical properties were observed. High corrosion in the NaCl solution | [23] |
| 13 | Ti-Mg       | Ti-xMg (x = 5, 10, and 15 wt%) milled for 4–30 h using zinc stearate as PCA. First heated to 600 °C for 180 s at a pressure of 796 MPa then further heated to 800 °C, holding time 30 s. | — | 1500–1800 | 36–50 | Different effect of alloying element on the microstructure, phase transformation, and mechanical properties were observed. Further, corrosion resistance and also biocompatibility were studied. | [15] |
| 14 | Ti-Mn       | Ti (2–12 wt%) Mn milled for varied hours in hexane (PCA). Sintering at 500 °C–800 °C (pressure 50 MPa, heating rate 100 °C min⁻¹). | 2.4–5.28 (GPa) | — | 83.3–122 | Microstructure and phase, mechanical properties (hardness, elasticity, and ductility), also cytotoxicity was observed. | [9] |
| 15 | Ti-Ag       | Ti-Ag (0, 1, 3, 5 wt%). milled. Sintering at 900 °C 10 min. Heating rate 100 °C min⁻¹, pressure 50 MPa. Followed by acid etching with a mixture of 40 wt% HF and HNO₃ | — | — | — | Surface feature, antibacterial activity, and biocompatibility were studied. | [13] |
| 16 | Ti-30 Zr    | Ti-30Zr (in at%) milled for 8 h, 200 rpm. Sintering at 900 °C, pressure 50 MPa. Heating rate was varied (140 °C–350 °C min⁻¹) | 950–1040 | — | — | The sintering kinetics and densification were studied. Microstructure, phase transformation, and microhardness were evaluated. | [65] |
examination showed that a fine-grained heterogeneous phase consisted of $\alpha$, $\beta$, and unreacted Nb was observed at the sintering temperature of 950°C and 1100°C. While at the sintering temperature of 1250°C, coarse-grained and almost homogeneous $\beta$ phases were shown. Hardness testing of the specimens showed that increasing sintering temperature would increase the mechanical strength which may be a result of embrittlement of the $\beta$ phase due to hydrogen entrapment in the as-sintered alloy.

Continuing his previous research, Sharma et al. [52] developed a two-step sintering process in fabricating Ti-Nb alloy. A combination of Ti powder, TiH$_2$ powder, and Nb powder was used as the starting material. The first heating was to dehydrogenate the compact (800°C for 7.2 ks), while the second heating was to sinter the compact (1200°C for 1.8 ks, 50 MPa pressure). Unlike the one-step sintering, this two-step SPS contributes to the nearly completed $\beta$ phases with the equiaxed grain. Increasing TiH$_2$ content corresponded to the finer grain

![Figure 4. SEM microstructure aspects of Ti material(a). processed by SPS route at 1.000°C for 10 min. (b) processed by SPS route at 1.300°C for 20 min. (c) by classic sintering at 1.150°C for 120 min [73], [73] (2013)© 2021 Springer Nature Switzerland AG. Part of Springer Nature.). With permission of Springer. Pascu, C.I., Gingu, O., Rotaru, P. et al. Bulk titanium for structural and biomedical applications obtaining by spark plasma sintering (SPS) from titanium hydride powder. J Therm Anal Calorim 113, 849–857 (2013).](https://doi.org/10.1007/s10973-012-2824-2.)
structure which showed the increase of mechanical properties (hardness and yield strength) and also higher ductility.

2.4. Ti–Nb–Sn
Instead of using elemental Ti as the raw material, Sharma [74] used the brittle TiH2 to fabricate beta Ti-25Nb-11Sn using mechanical alloying and the SPS method. Mechanical alloying was shown to lower the dehydrogenation temperature of the hydride powder. Free pore and high-density alloy had been produced in this study. The microstructure of the bulk alloy showed $\beta + \alpha''$ phases and $\beta + \alpha$ phases. A longer duration of mechanical alloying (180 ks) was shown to give higher hardness than the shorter duration of mechanical alloying (72 ks).

2.5. Ti–Nb–Cu
The addition of Cu element to Ti-40Nb alloy would increase antimicrobial property as studied by He, et al [27]. Ti, Nb, and Cu powder were used as the starting materials. The microstructure of the $\beta$ Ti–Nb–Cu phase and Ti$_2$Cu phase were shown as the result of the mechanical alloying and SPS method. High mechanical properties were achieved from Ti–Nb–Cu (higher than 5 wt%) alloy such compressive strength of 1693 MPa, yield strength of 1140–1619 MPa, the low elastic modulus of 43–58 GPa, and large plastic strain over 18.5%. Anti-microbial properties against bacteria ($E. coli$ and $S. aureus$) were shown to be increased, therefore Ti–40Nb–Cu is a promising material for hard tissue replacement.

2.6. Ti-Nb-Zr
Hussein 2015 [67] fabricated nanostructure Ti-20Nb-13Zr (at.%) alloy (near $\beta$). The sintering process was done at 800 °C–1200 °C for 10 min (heating rate constant: 100 C min$^{-1}$). To reach nearly full density, the temperature of sintering should be 1200 °C. Microstructure examination showed a duplex structure (equiaxed grain) with the $\alpha$ phase surrounding the $\beta$-Ti (as seen in figure 5). The highest microhardness was 660 HV which is higher than other literature. Hussein et al [51] also studied the influence of processing parameters on the resulted mechanical strength and also corrosion resistance under simulated body fluid (SBF) medium. In this study, the maximum hardness was 584 HV, and the relative density was 97.9%. Further, the corrosion testing of the alloys was showing good corrosion resistance.

While Kong et al [20] fabricated Ti-13Nb-13Zr alloy via mechanical alloying and SPS. This study examined the microstructure, mechanical properties, and also corrosion behavior. It was shown that finer grain microstructure ($\beta$ and $\alpha$, with $\alpha''$ dispersion) can be formed even at the low sintering temperature. The as-sintered alloy could reach 1790 MPa compressive strength and hardness of 356 HV. In addition, corrosion properties in the Ringer’s solution showed good corrosion resistance. On the other hand, Ti–24Nb–2Zr (at%) alloy was also examined to be a biomedical application material by Qiang Li et al [66]. The sintering process at 850 °C for 10 min in the SPS resulted in a similar density with the arc melt alloy specimen. The microstructure
showed a single $\beta$ phase. Followed by an hour heat treatment at 850 °C, the phases were distributed more evenly. Sintering at 1100 and 1200 °C were considered optimum for fabricating Titanium as biomedical material.

### 2.7. Ti–Nb–Zr–Ta

Development of beta titanium with Zr, Nb, Mo, Hf, or Ta alloying element was shown to increase the strength while reducing the elastic modulus and also has biocompatibility properties [23]. The quaternary system Ti–Nb–Zr–Ta was considered as the promising orthopedic implant material due to its good corrosion resistance and has a lower elastic modulus. Therefore, it reduced the risk of delamination of the bone and the implant [10, 76].

Mavros, et al [23] researched Ti-xNb-5Zr-20Ta (x = 30, 35; all in wt%) using mechanical alloying (300 rpm, 60 h) and the SPS (1100 °C, 5 min, 50 MPa pressure). The fabricated TNTZ alloys had $\beta$-phase with low content of $\alpha$-phase as a result of Nb, Ta, and Zr addition as a $\beta$ stabilizing agent. Compared to the conventionally sintered alloy, the mechanically alloyed and SPS specimens had higher hardness because of the refined grained structure as reached by mechanical alloying and SPS process.

### 2.8. Ti–Zr

In the SPS processing, the heating rate is one of the important parameters during titanium fabrication as studied by Chavez, et al [65]. The microstructure showed the equiaxed martensitic precipitation in the $\alpha$ matrix would dominate the phase of Ti-30Zr alloy. Increasing the heat-rate to 200 °C min$^{-1}$ would slightly increase the resulted grain size.

### 2.9. Ti–Mg

Liu, et al [15] prepared Ti–Mg alloys using mechanical alloying and SPS. Compared to other Ti alloy, Ti–Mg was shown to have a lower elastic modulus (35–60 GPa) but has a quite high compressive strength (1500–1800 MPa). Microstructure examination showed the existence of pure Ti, Mg, and also Mg oxides. Further, the addition of elemental Mg showed good biocompatibility and bioactivity. Corrosion resistance would be decreased by the increasing Mg content but the corrosion resistance of Ti–Mg was shown to be acceptable.

### 2.10. Ti–Mn

As another alternative to Ti–6Al–4V alloy, Ti–Mn was developed using the mechanical alloying and SPS method [9]. Microstructure examination showed an $\alpha + \beta$ structure. Hardness and elastic modulus were increased by the increase of Mn content. However, from the cytotoxicity testing, it was shown that Mn content should be limited to below 8 wt.% in Ti to be used as biomedical materials.

### 2.11. Ti–Ag

Lei, et al [13] developed Ti-Ag (0,1,3,5 wt.%.) alloy via SPS method followed by acid etching. Ti and Ar starting powder were milled for 3 h then sintered at 900 °C for 10 min (50 MPa pressure, heating rate 100 °C min$^{-1}$). The as-sintered alloys were treated with HF and HNO$_3$. It was observed that Ti-Ag with higher Ag contents has increasing antibacterial properties. Besides, Ti-Ag alloys were shown to have a good biocompatible property.

### 2.12. Ti–Zr

Zr was also used as an alloying element for Ti due to its biocompatibility property. Chavez, et al [65] prepared Ti-30Zr (at.%) using the mechanical alloying and SPS method. It was shown that the densification process (reached 99.7% relative density) would be occurred even at a lower temperature compared to the conventional sintering technique. Microstructure examination showed the formation of $\alpha''$ and $\omega$ phases without further post-treatment. Meanwhile, the resulted hardness was around 950–1040 HV due to the effect of SPS and the formation of precipitation phases.

### 3. Processing of porous Ti and Ti alloys using SPS method

Spark plasma sintering was able to produce a relatively high-density material due to the combination usage of pressure and pulsed direct current. But recently, it was shown that SPS can be also used to fabricate porous material and it was previously reviewed in other literature [47, 58]. To create a porous structure, two common methods can be chosen. The first method is partially sintering loose powders or fiber (low sintering temperature or pressure during consolidation). The benefit of this method is the time, energy, and cost-saving and reduce the possibility of contamination because no intermediate materials are involved in this method. The second method is using a temporary secondary material that can be removed from the sample (space holder). The benefit of this method is a wide range of porosity can be achieved but this method is more complex and required a longer time [77]. The examples of Porous Titanium and its alloy which fabricated using SPS was shown in table 3.
Table 3. Examples of porous titanium production using SPS.

| No | Materials/alloy | Method | Sintering temperature (°C) | Sintering pressure (MPa) | Sintering time (minutes) | Porosity | Compressive strength | Elastic modulus | Yield strength | Other properties and comments | References |
|----|----------------|--------|---------------------------|-------------------------|-------------------------|----------|---------------------|----------------|---------------|-----------------------------|------------|
| 1  | Ti             | Partial Sintering | 570                     | 25                      | 30                      | 32.90    | 90.10               | 15.5           | —             | Hardness 79.6 HV             | [78]       |
| 2  | Ti             | Partial Sintering | 900–1300                | 0–10                    | 10                      | 5–39.2   | —                   | 9–93.2         | —             | Biocompatibility in vitro showed good results. Followed by immersion in the SBF to increase bioactivity. | [79]       |
| 3  | Ti             | Partial Sintering | 600–700                 | 20–30                   | 3–10                    | 27       | 233                 | 18–20          | —             | Good Biocompatibility in vitro showed good results. Followed by immersion in the SBF to increase bioactivity. | [80]       |
| 4  | Ti-6Al-4V      | Partial Sintering | 600–700                 | 20–30                   | 3–10                    | 31–32    | 113–125             | 16–18          | —             | Compressive cycle stress-strain showed the recoverable strain ratio of porous Ti after five cycles could reach more than 70% at the pre-strain of 2%. | [81]       |
| 5  | Ti-5Al-2.5Fe   | Partial Sintering | 750–850                 | 5                       | 5                       | 28.4–29.1| 240–300             | —              | —             | Good Biocompatibility            | [59]       |
| 6  | Ti             | Space Holder     | 1000–1200               | (precompact 300 MPa) Pressureless | 5                       | 38–56    | 61–287              | 6.1–11.2       | —             | Compressive cycle stress-strain showed the recoverable strain ratio of porous Ti after five cycles could reach more than 70% at the pre-strain of 2%. | [81]       |
| 7  | Ti             | Space Holder     | 600–700                 | 30                      | 0–20                    | 50–70    | 20–100              | 2.6–8.5        | Yield strength 8.1–68 MPa  | Lower porosity is suggested for further study | [82]       |
| 8  | Ti             | Space Holder     | 550–800                 | 30–50                   | 3–8                     | 30–70    | 6.2–36.1            | 27.2–94.2 Mpa (Plateau stress) | —             |                           | —                     | [83]       |
| 9  | Ti6Al4V        | Space Holder     | 700–725                 | 30–60                   | *not mentioned          | 33–44    | 79–124              | 20–45          | —             |                           | —                     | [84]       |
| 10 | Ti6Al4V        | Space Holder     | 700–1100                | 50 + Pressureless        | 8 + 5                   | 44.7–70 | 9.5–33              | 110.278.0 MPA  | In vitro evaluation on the human osteoblast cell line MG-63 showed good biocompatibility | [85]       |
| No. | Materials/ alloy | Method | Sintering temperature (°C) | Sintering pressure (MPa) | Sintering time (minutes) | Porosity | Compressive strength | Elastic modulus | Yield strength | Other properties and comments | References |
|-----|------------------|--------|-----------------------------|--------------------------|-------------------------|----------|---------------------|---------------|---------------|-----------------------------|------------|
| 11  | Ti               | Space Holder | NaCl \(\text{NH}_4\text{HCO}_3\) and TiH\(_2\) | 1000 | Pressureless | 5 | 53 | — | 40 | — | — | [54] |
| 12  | Ti-5Mn           | Space Holder | NaCl \(\text{NH}_4\text{HCO}_3\) and TiH\(_2\) | 950–1100 | Pressureless | 5 | 56–21 | — | 35–51.8 | — | — | [54] |
| 13  | Ti-Nb            | Space Holder | NaCl \(\text{NH}_4\text{HCO}_3\) | 950 | (precompact 700 MPa) | 5 | 13.4–61.2 | 326–452 | 18.4–27.3 | — | In vitro evaluation in the Rat bone marrow mesenchymal stem cells (rBMSCs) showed good biocompatibility | [86] |
| 14  | Ti-Nb-Zr         | Space Holder | NaCl \(\text{NH}_4\text{HCO}_3\) | 850 | 30 | *not mentioned | 19–22 | 900–1166 | 45.3–52.9 | — | In vitro evaluation in human osteoblast cell line showed good biocompatibility | [87] |
| 15  | Ti-2Cu-4Ca       | Space Holder | NaCl \(\text{NH}_4\text{HCO}_3\) | 900–1100 | (precompact 300 Mpa) | 5 | 38–48 | 206–325 | 6.2–12.2 | — | In vitro evaluation showed high bioactivity on osteoblast cell | [88] |
3.1. Fabrication of porous titanium using partial sintering

Sakamoto 2008 [78] studied porous titania using spherical powder CP-Ti (particle size average 100 μm) prepared by spark plasma sintering. The powders were pre-compacted (20 MPa) followed by sintering in SPS (pressure 25 MPa, temperature 570 °C, holding time 30 min) under a vacuum of 4 Pa. The resulted porous Ti has 33% porosity, the elastic modulus of 15.5 GPa, and the compressive strength of 90 MPa. The micrograph of porous Ti is displayed in figure 6.

In recent research, Yamanoglu, et al [59] used pressureless SPS to fabricate porous Ti5Al2.5Fe using pre-alloyed powder as the starting materials. The resulted porous Ti5Al2.5Fe was found to have good biocompatibility properties after in-vitro testing in the simulated body fluid (SBF). Further, Titanium-Niobium-Zirconium-Tantalum (TNZT) alloy was developed to be a biomaterial because it may have a lower elastic modulus than Ti–6Al–4V but maintain the corrosion resistance performance [4]. Rechtin, et al [77] developed partial densification SPS for fabricating porous TNTZ alloy. Correlation between the relative density of the specimen and the sintering temperature, pressure, holding time, and also the initial particle size was observed in this study.

3.2. Fabrication of porous titanium using space holder-assist SPS method

Even though partial sintering SPS can produce a porous structure, but the porosity would be limited, therefore powder metallurgy using a space holder is an alternative method to produce a higher range of porous structure [89]. Similar to conventional sintering, some space holder has been used to create porous titanium. NaCl and NH₄HCO₃ are commonly used in titanium porous processing.

Hasebe, et al [82] studied porous Ti through space holder-assist of the SPS method. This study was conducted to see the effect of spaceholder particle size, temperature sintering, and holding time. Ti powder (45 μm) and NaCl powder (106–214 μm and 214–425 μm) were used as the starting powder to form Ti/NaCl composite (50% vol). After mixing, the powders were sintered in the SPS. Sintering temperature was varied (500 °C–700 °C), holding time was also varied (0–20 min), but the pressure was kept at the 30 MPa. After sintering, the porous Ti was produced by leaching in the Aqua DM at 50 °C 10 min. Microstructure and mechanical properties examination showed that 700 C and 20 min sintering would give the optimum porous specimen. The resulted porosity was opened and also interconnected, and showed a reduction of elastic modulus by the increasing porosity.

Later on, Makena et al [89] has been successfully developed porous titanium using NaCl. The process consists of mixing Ti powder with the NaCl as the space holder and PEG as the binder followed by sintering at 500 °C–650 °C for 10 min under the pressure of 30 MPa. After the sintering process, NaCl was dissolved in deionized water at a different temperature to remove the excess of salt and create a highly interconnected porous Ti. However, the strength of the resulted porous Ti was inadequate, therefore post-treatment in a vacuum (10–4 mbar) furnace at 1200 °C for 1 h was conducted respectively [90].

Following their previous study, Makena et al [90] studied more on the sintering temperature effect on the pore morphology and the mechanical properties. XRD analysis (figure 7) showed an indication of β phase formation and also TiO₂ which may result from the chemical reaction with the binder, PEG (polyethylene glycol). The porosity in the porous Ti varied from 61%–54% as influenced by the sintering temperature. The microstructure of the titanium foam is depicted in figure 8. The optimum porous Ti was the specimen sintered at 650 °C, having a compressive strength of 123 MPa and the elastic modulus of 8.1 GPa.

Beside pure Ti, SPS has been successfully prepared other alloying systems of porous Ti such as Ti–6Al–4V [84, 85], Ti–5Mn [34], Ti–Nb [86], Ti–Nb–Zr [87], and also antibacterial alloys Ti–2Cu–4Ca [88].

Zhang 2017 [88] developed porous Ti–2Cu–4Ca using the NH₄HCO₃ space holder and SPS method. The addition of Cu and Ca were intended to increase the osseointegration and also antibacterial properties of the
titanium. The schematic fabrication method, image of the porous Ti-2Cu-4Ca, and the XRD analysis were shown in figure 9.

The titanium alloys had interconnected pores with the total porosity higher than 43% and having the average pore size of 460 μm. From the mechanical testing, the elastic modulus was 6.2–12.2 GPa (similar to human bone), and the compressive strength was 206–325 MPa (close to the human bone). In vitro testing showed that porous Ti-2Cu-4Ca has good biocompatibility as indicated by the cell growth inside the pores.

4. Mechanical properties, corrosion resistance, and biocompatibility of titanium and its alloy prepared by SPS method

4.1. Effect of SPS on the mechanical properties of bulk titanium alloys

The mechanical properties of the biomaterial would determine the long-term success of the implant. When the implant failed to give adequate support for the bone or the elastic mismatch occurred, it is called biomechanical incompatibility [2]. By far, evaluation of the mechanical properties of titanium alloy prepared by SPS was usually from hardness or compression properties of the resulted alloy. The appropriate hardness of titanium during cyclic load provides a higher service period of the orthopedic implant. As influenced by the alloying element and also the processing parameter, the mechanical properties of some titanium alloys were summarized and shown in figures 10–12.

From figure 10, despite the alloying element and the processing parameter, SPS processing to prepare Ti alloy was able to produce material with higher hardness than CP-Ti. Much higher hardness property of Ti-Zr was caused by the solid strengthening effect and also the formation of metastable phases and also intermetallic precipitation [65]. Meanwhile, from figures 11 and 12, it can be seen that other alloying systems may have comparable compressive properties in comparison to Ti-6Al-4V. As a consequence, other alloying systems can be developed as a promising substitute for Ti6Al4V.

Unfortunately, the elastic modulus was not always studied in the aforementioned preparation of Ti alloys. Low modulus alloy was shown in some studies such as Ti-Nb-Cu (43.9–58 GPa) [27], Ti-Mg (36–50 GPa) [15], and Ti-Nb-Zr-Ta (60–149 GPa) [23]. Further observation on the elastic modulus should also be conducted in the near future hence lower elastic modulus would reduce the risk of implant failure due to the elastic mismatch.

4.2. Effect of SPS on the mechanical properties of porous Ti alloys

As it was previously mentioned, the mechanical properties of the titanium implant should provide sufficient strength and has similar elastic modulus with bone. It is generally accepted that porosity would affect mechanical properties. Therefore, the challenge of the porous titanium fabrication would be tailoring porous titanium while maintaining the mechanical properties. Despite the different method (space holder or pressureless, and all the SPS parameter processing), mechanical properties of porous Ti alloy is depicted in figures 13(a) and (b).
For porous Ti and Ti alloys, elastic modulus and compressive strength are the common mechanical properties used in the evaluation. From figure 13(a) it can be seen that porous Ti fabricated by SPS has a wide range. It shows that porous Ti could be tailored to fit a specific biomedical application via the SPS method, as it is also seen in the porous Ti–6Al–4V. The elastic modulus for human cortical bone is around 7–30 GPa, while the elastic modulus for cancellous bone is around 0.2–2 GPa [6]. While from figure 13(b) it can be seen that the compressive strength of porous Ti alloy could be much higher than the porous Ti. This could be influenced by the nano grained size microstructure as a result of mechanical alloying and spark plasma sintering. From the fabrication of porous Ti–Nb–Zr, the longer milling time and the reduction of space holder content would in line with the increased mechanical strength [87]. As a comparison, the compressive strength of human cortical bone is around 100–230 MPa, while the compressive strength of the cancellous bone is 2–12 MPa [6].

4.3. Corrosion resistance and biocompatibility of titanium alloys prepared by SPS

For biomedical applications, the corrosion resistance of titanium and its alloys is also important criteria. The corrosion resistance of the implant is crucial since contact with corrosive body fluid cannot be avoided during implantation. The high corrosion resistance of biomedical implant would prevent the metal ion-release which may induce inflammation or allergic reaction and provide a long service period for more than 30 years [91]. Titanium is known as highly corrosion material since it can form an oxide layer to protect itself. However, in the case of the aggressive environment, the protective oxide layer may be unstable and further reduce the life of the
Figure 9. (a) SPS processing of porous Ti-2Cu-4Ca, (b) cross section image of the porous Ti-2Cu-4Ca, and (c) XRD pattern of the porous Ti-2Cu-4Ca sintered at 1000 C. Reprinted with permission from [88]. Copyright (2017), Elsevier.

Figure 10. Hardness Property of Ti alloys prepared by SPS, compiled from references [6, 20, 23, 27, 64–67, 71, 74].

Figure 11. Compressive Yield of Ti alloys prepared by SPS, compiled from references [5, 15, 20, 27, 66, 73].
titanium implant. Just like the mechanical properties, the corrosion properties of the titanium are also influenced by the alloying element and also the microstructure of the alloy. However, information on the corrosion behavior for titanium fabricated by SPS was still limited and should be studied more.

Corrosion properties were studied by Mahundla et al [53]. In this research, Ti-34Nb-25Zr (TNZ) alloy was prepared by the mechanical alloying and also SPS method, for a comparison, CP-Ti and Ti-6Al-4V were also studied. The microstructure of the specimens is shown in figure 14.

Corrosion testing was done in the SBF solution (Hank’s, 0.9 wt.% NaCl, and E-MEM + 10% FBS). From this
study, the TNZ alloys showed good corrosion resistance in the entire solution. Further, corrosion behaviors were also observed in Ti-Mg alloy by potentiodynamic polarization tests and the electrochemical impedance spectroscopy (EIS) test in the simulated body fluid solution [15]. Ti-Mg was shown to have lower corrosion resistance by the increasing content of Mg but still show good corrosion resistance. A summary of the corrosion behavior of titanium alloy prepared by the SPS method is shown in Table 4.
Table 4. Summary of SPS processing method on corrosion properties.

| No | Materials/Alloy          | Electrochemical testing                          | Electrolyte solution          | Findings                                                                                                                                                                                                 | References         |
|----|--------------------------|--------------------------------------------------|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| 1  | Ti-Nb-Ta-Zr (TNTZ)       | Cyclic potentiodynamic polarization             | NaCl                          | Tafel extrapolation of cathodic curve, for the Alloys (varied in between 0.4–0.7 μA/cm²).                                                                                                                  | Mavros [23]        |
| 2  | Ti-Mg                    | Potentiodynamic polarization and Electrochemical Impedance Spectroscopy (EIS) test | SBF                           | Increasing Mg content reduced corrosion resistance but still showed good corrosion resistance. High Ecorr and Icorr (53.7–85.9 μA/cm²). All Nyquist plots possess a similar behavior that is characterized by an incomplete and large depressed semicircle indicating a capacitive response of a passive film. | Liu [15]           |
| 3  | Ti-13Nb-13Zr             | Open Circuit Potential (OCP), Potentiodynamic Polarization, EIS test | Ringer’s Solution              | Ti and TNZ-900 exhibit OCP values of 96.5 mV and 145 mV respectively. (Icorr) of TNZ-900 (∼2.42 μA/cm²), smaller than pure Ti (∼3 μA/cm²). The higher Rct value obtained for TNZ-900 indicates the formation of a stable passive film on its surface, demonstrating a nobler electrochemical behavior than pure Ti. | Kong [20]          |
| 4  | Ti-35Nb-25Zr             | OCP, Potentiodynamic polarization (immersion for 4 h) | Hank’s solution, 0.9%NaCl, E-MEM + FBS | Ecorr values for TNZ alloy in Hank’s, 0.9 wt% NaCl and E-MEM + 10%FBS solutions were about −202 mV, −251 mV and −171 mV, respectively. The measured Icorr values were ∼1.66 nA/cm² in hank’s solution, which is lower than that in 0.9 wt% NaCl (∼4.20 nA/cm²) and E-MEM + 10% FBS solution (∼3.19 nA/cm²). | Mahundla [53]      |
4.4. Biocompatibility of titanium alloys prepared by SPS

Applying biomaterial as the orthopedic implant means that the material should not be toxic to the human body and would not lead to any inflammatory or allergic reaction. Therefore, biocompatibility is evaluated by the reaction of the human body to the implantation which would be influenced by the toxicity level of the material and the degradation process of the material in the body [2]. It was mentioned by Zhang, et al [11], Ti, Nb, Mo, Ta, Zr, Au, W, and Sn are highly biocompatible but Al, V, Cr, Ni, etc are considered toxic to the human body. Another consideration related to the field of the orthopedic implant, the material is expected to have osseointegration, an interaction process between the implant and the human body which promotes the bone ingrowth which leads to bone healing. Porous titanium is expected to have better osseointegration [8]. Similar to the corrosion properties, the research related to the biocompatibility of titanium alloy prepared by spark plasma sintering is still limited.

Liu, et al [15] studied biocompatibility of the low modulus Ti-Mg alloy which prepared by the SPS method via direct and indirect method using murine fibroblast cells (NIH-3T3). It was shown that the cell proliferation rates are higher than 90% which showed the biocompatibility of Ti-Mg alloys. Further, the morphologies of cells on the surface of Ti-Mg are almost similar and showed a good spreading. Hence, the Ti-Mg alloy prepared by the SPS method showed good biocompatibility. Cytotoxicity evaluation for Ti-Mg alloy is shown in figure 15.

A summary on the biocompatibility evaluation of titanium alloy prepared by SPS method is tabulated in table 5.

5. Conclusions and future work

This article briefly reviews the recent development of titanium alloys for biomedical implant applications manufactured by the SPS method. It was shown that SPS is a powerful tool that can reduce the time processing of titanium and its alloy compared to conventional powder sintering or to the conventional casting processing. Combined with mechanical alloying, the SPS method can be used to produce a finer grain structure having higher mechanical properties. The development of the alloying system in the titanium is feasible and could be explored more. The hardness, compressive yield, and also compressive strength of bulk titanium alloy would be
| No | Materials/Alloy | Biocompatibility Test | Cell line/implantation | Findings | References |
|----|----------------|-----------------------|------------------------|----------|------------|
| 1  | CP Ti          | *In vitro*            | Fibroblast like (L-929) and osteoblast like (MG-63) | The viability of cells cultured with the diluted extract solutions was almost the same compared to that of the control. Porous Ti has no toxicity | Oh [79] |
| 2  | Ti-Mg          | *In vitro* (direct and indirect) | Murine Fibroblast Cell (NIH 3T3) | All the cell proliferation rates from each group are higher than 90%. The good spreading as well as proliferation of the cells were shown on the Ti–Mg alloys | Liu [15] |
| 3  | Ti-Ag          | *In vitro*            | Newborn mouse calvaria-derived MC3T3-E1 subclone 14 pre-osteoblastic cells (MC3T3-E1) | Viability and proliferation of MC3T3-E1 cells was shown a good result. While from ALP production, the acid etching treatment had no influence on cell differentiation. Excellent cytocompatibility without cytotoxicity. | Lei [13] |
| 4  | Ti-Mn          | *In vitro*            | The human osteoblastic cells MG-63 (osteosarcoma cell line) | The Ti2Mn, Ti5Mn, and Ti8Mn alloys all exhibit acceptable cytotoxicity and cell proliferation of the human osteoblasts. | Zhang [9] |
| 5  | Ti-Nb          | *In vitro*            | rat bone marrow stem cells (rBMSCs). | Cell morphology, MTS assay and live cell fluorescence imaging showed that Ti–40Nb alloys promote cell adhesion and cell proliferation. Optimum 30% pore | Hao [86] |
| 6  | Ti-Nb-Zr       | *In vitro*            | Human osteoblast (HOB) cells | The biocompatibility of porous TNZ alloys was similar to that of Ti-6Al-4V extra low interstitial alloy. | Kim [87] |
| 7  | Ti-2Cu-4Ca     | *In vitro*            | Osteoblasts of rats (ROS1728) | The porous Ti-2Cu-4Ca showed no toxicity to osteoblast by supporting cell proliferation on the surface, indicating the good bioactivity of the alloy. | Zhang [88] |
comparable with the currently most commonly used titanium implant, CP-Ti or Ti6Al4V alloy. However, the fabrication of low modulus bulk titanium alloy seems to remain a challenge. Accordingly, further heat treatment process might be needed to create a low modulus bulk titanium alloy.

Meanwhile, it was shown that the low modulus of titanium alloy can be fabricated through developing porous alloy using SPS. Designing a specific porosity should be obtained to achieve sufficient strength and provide a similar elastic modulus with the bone. For preparing porous titanium and titanium alloys, there are two commonly approach in SPS processing, by partial sintering method or assisted with space holder. SPS parameter processing should be optimized in order to create a specific porous titanium alloy. However, it is noteworthy that the porosity of the partial sintering method would be more limited than the assisted space holder method, but the space holder method would have a risk of contamination that should be taken care of. Besides mechanical properties, the corrosion properties and biocompatibility of porous titanium also need to be studied more since the information was still lacking. Corrosion properties and biocompatibility are influenced by the alloying element and the microstructure of the alloy which depend on the processing parameter such as sintering temperature, heating rate, and holding time. SPS of porous titanium is shown to be a promising technique to be researched in order to improve the performance of titanium in biomedical implant applications. Further, there is also an increasing interest to develop antibacterial properties of titanium which can improve the service life of titanium in a biomedical implant application.

Acknowledgments

The author would like to thank the Ministry of Research and Technology/National Research and Innovation Agency of Republic Indonesia for their financial support through the program of Doctoral Dissertation (PDD) research grant with the contract number of 8/AMD/E1/KP.PTNBH/2020 and 332/PKS/R/UI/2020 dated on 11th May 2020, and addendum contract of number NKB-3011/UN2.RST/HKP.05.00/2020.

Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

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References

[1] Kaur M and Singh K 2019 Materials Science and Engineering: C 102 844–62
[2] Geetha M, Singh A K, Asokamani R and Gogia A K 2009 Prog. Mater Sci. 54 397–425
[3] Chen Q and Thouas G A 2015 Materials Science and Engineering: R: Reports 87 1–57
[4] Niinomi M, Nakai M and Hieda J 2012 Acta Biomaterialia. 8 5888–903
[5] Mohamed S and Shamaz B 2015 Int. J. Dent. Oral Health 1 1–15
[6] Liu Y, Yang C, Zhao H, Qiu S, Li X and Li Y 2014 Materials 7 1709–800
[7] Kirmanidou Y, Sidra M, Drosou M-E, Bennani V, Bakopoulou A, Tsouknidas A, Michailidis N and Michalakis K 2016 Bio. Med. Research International 2016 2908570
[8] Palka K and Pokrowiecki I 2018 Adv. Eng. Mater. 20 1700648
[9] Zhang F, Weidmann A, Nebe J B, Beck U and Burkel E 2010 Journal of Biomedical Materials Research Part B: Applied Biomaterials. 94 406–13
[10] Niinomi M 2003 Science Technology of Advanced Materials 4 445
[11] Zhang L-C and Chen L-Y 2019 Adv. Eng. Mater. 21 1401215
[12] Niinomi M 2018 Titanium spinal-fixation implants Titanium in Medical and Dental Applications. (Amsterdam: Elsevier) pp 347–369
[13] Lei Z, Zhang H, Zhang E, You L, Ma X and Bai X 2018 Materials Science and Engineering: C 92 121–31
[14] Arifivianto B, Leeflang M and Zhou J 2016 Mater. Charact. 121 48–60
[15] Liu Y et al 2015 Materials Science and Engineering: C 56 241–50
[16] Mohammed M T, Khan Z A and Siddiquee A N 2014 Int. J. Chem. Mol. Nucl. Mater. Metall. Eng. 8 726–31
[17] Liu X, Chen S, Tsoi J K H and Matinlinna J P 2017 Regenerative Biomaterials 4 315–23
[18] Liu Y, Wei W-F, Zhou K-C, Chen L-F and Tang H-P 2003 Journal of Central South University of Technology 10 81–6
[19] Henriques V A R, Cairo C A A, Silva C R M and Bressiani J C 2005 Mater. Sci. Forum 498–499 40–8
[20] Kong Q, Lai X, An X, Feng W, Lu C, Wu J, Wu G, Wu L and Wang Q 2020 Materials Today Communications 23 101130
[21] Seramak T, Zielinski A, Serbinski W and Zasinska K 2019 Materials Manufacturing Processes. 34 915–20
[22] Sakaguchi N, Mitsu N, Akahori T, Saito T and Furuta T 2004 Mater. Sci. Forum 449–452 1269–72
[23] Mavros N, Larimian T, Esquivel J, Gupta R K, Contieri R and Borkar T 2019 Materials & Design 183 108163
[24] Chen M, Zhang E and Zhang L 2016 Materials Science and Engineering: C 62 350–60
[25] Dong R, Zhu W, Zhao C, Zhang Y and Ren F 2018 Metallurgical and Materials Transactions A 49 6147–60
[26] Liu J, Li F, Liu C, Wang H, Ren B, Yang K and Zhang E 2014 Materials Science and Engineering: C 35 392–400
[27] He Y, Zhang Y, Jiang Y and Zhou H 2017 Mater. Res. 32 2510–20
[28] Rao P J, Pelletier M H, Walsh W R and Mobbs R J 2014 Orthop. Surg. 6 81–9
[29] Fujibayashi S, Takekoto M, Neo M, Matsuishi T, Kobuko T, Doi K, Ito T, Shimizu A and Nakamura T 2011 Eur. Spine J. 20 1486–95
[30] McGilvray K C, Easley J, Seim H B, Regan D, Berven S H, Hsu W K, Mroz T E and Puttlitz C M 2018 The Spine Journal 18 1250–60
[31] Nazari Q, Josa K, Pivec R, Harwin S F, Delamont R E and Mont M A 2013 Orthopica 36 e390–4
[32] Levine B 2008 Adv. Eng. Mater. 10 788–92
[33] de Vasconcellos L M R, Cairo C, de Vasconcellos L, de Alencastro Graça M, do Prado R and Carvalho Y 2012 Biomedial Engineering: Technical Applications in Medicine 1st edn (Rijeka: InTech) 47–74
[34] Niinomi M 1998 Materials Science and Engineering: A 243 231–6
[35] Zhao X, Niinomi M, Nakai M and Hieda J 2012 Acta Metallurgica 58 1990–77
[36] Hao Y, Li S J, Sun S Y and Yang R 2006 Materials Science and Engineering: A 441 112–8
[37] Ehtemam-Haghighi S, Liu Y, Cao G and Zhang L C 2016 Materials & Design 97 279–86
[38] Li X, Ye S, Yuan X and Yu P 2019 J. Alloys Compd. 772 968–77
[39] Nazari K A, Nouri A and Hilditch T 2015 Materials & Design, 88 1164–74
[40] Jha N, Mondal D P, Dutta Majumdar J, Badkul A, Jha A K and Khare A K 2013 Materials & Design 47 810–9
[41] Senopati G, Sutowo C, Kartika I and Suharno B 2019 Materials Today: Proceedings 13 2224–8
[42] Zhang L B, Wang K Z, Xu L J, Xiao S L and Chen Y Y 2015 Transactions of Nonferrous Metals Society of China 25 2214–20
[43] Oliveira N T C and Guastaldì A C 2008 Corros. Sci. 50 938–45
[44] Watanabe K, Miyakawa O, Takada Y, Okuno O and Okabe T 2003 Biomaterials 24 1737–43
[45] Abakumov G, Duz V, Ivanishin O, Moxxon V and Savvakin D 2012 High performance titanium powder metallurgy components produced from hydrogenated titanium powder by low cost blended elemental approach Tr-2011: Proc. of the 12th World Conf. on Titanium (Beijing) (Science Press)
[46] Aritovianto B and Zhou J 2014 Materials 5 3588–622
[47] Dudina D V, Bokhonov B B and Oleksy E A J M 2019 Materials 12 541
[48] Shon J H, Song I B, Cho K S, Park Y I, Hong K J, Park N K and Oh M H 2014 International Journal of Precision Engineering and Manufacturing 15 643–7
[49] Dunand D C 2004 Adv. Eng. Mater. 6 369–76
[50] Niknam S A, Khettabi R and Songvene G 2014 Machinability and machining of titanium alloys: a review Machining of Titanium Alloys (Berlin: Springer) pp 1–30
[51] Hussein M A, Suryanarayana C, Arumugam M K and Al-Aqeeli N 2015 Materials & Design 83 344–51
[52] Sharma B, Vaipai S and Ameyama K 2018 Metals 8 516
[53] Mahendla M R, Matizambuka W R, Yamamoto A, Shongwe M B and Machaka R 2020 Journal of Bio- and Tribo-Corrosion 6 38
[54] Ibrahim A, Zhang F, Ottersten E and Burkel E 2011 Materials & Design 32 146–53
[55] Molinari A, Zadra M, Vicente N Jr, Facchini I and Buccicoti F 2016 Spark plasma sintering of titanium alloys for biomedical applications Key Eng. Mater. 704 500–5
[56] Zou I M, Yang C, Long Y, Xiao Z Y and Li Y Y 2012 Powder Metall. 55 65–70
[57] Yamamoto R 2019 Powder Metallurgy Metal Ceramics 57 513–25
[58] Azariniya A, Azariniya A, Safavi M S, Farshbaf Ahmadipour M, Esmeeled Seriali M, Saeedi S, Saquei M, Yamanooglu R, Soltaheinjead M and Madaah Hosseini H R 2020 Critical Reviews in Solid State Materials Sciences 45 22–65
[59] Yamanooglu R, Gulsy N, Oleksy E and Gulsy H 2016 Journal of Alloys and Compounds 680 654–8
[60] Fang Z Z, Paramore J D, Sun P, Chandran K R, Zhang Y, Xia Y, Cao F, Koopman M and Free M 2018 Int. Mater. Rev. 63 407–59
[61] Guillon O, Gonzalez-Julian J, Dargatz B, Kessel T, Schierning G, Rathel J and Herrmann M 2014 Advanced Engineering Materials 16 1086–92
[62] Sahel N, Iqbal Z, Khalil A, Hakeem A S, Al Aqeeli N, Laosu T, Al-Qutub A and Kirchner R 2012 Journal of Nanomaterials 2012 983470
[63] Kalita D, Rogal L, Czeppe T, Wójcik A, Kolano-Burian A, Zachwieja P, Kania B and Dutkiewicza T 2020 J. Mater. Eng. Perform. 29 1445–52
[64] Sharma B, Vaipai S K and Ameyama K 2016 J. Alloys Compd. 656 978–86
[65] Chávez J, Olmos L, Jimenez O, Alvarado-Hernández F, Flores-Zúñiga H, Camargo-García J-P and Guevara-Martínez S J 2020 Journal of Materials Research and Technology 9 9328–40
[66] Li Q, Ma G H, Liu X Y, Tu Z K and Pan D 2017 Key Eng. Mater. 727 136–42
[67] Hussein M A, Suryanarayana C and Al-Aqeeli N 2015 Materials & Design 87 693–700
[68] Wen M, Wen G, Hodgson P and Li Y 2014 Materials & Design (1980–2015) 56 629–34
[69] Li Q, Yuan X, Li J, Wang P, Nakai M, Niinomi M, Nakano T, Chiba A, Liu X and Pan D 2019 Materials Transactions 60 1763–8 ME201913
[70] Eriksson M, Shen Z and Nygren M 2005 Powder Metall. 48 231–6
[71] Zadra M, Casari F, Girardinli I and Molinari A 2008 Powder Metall. 51 59–65
[72] Crosby K, Shaw L I, Estournes C, Chevallier G, Filllet A W and Imam M A 2014 Powder Metall. 57 147–54
[73] Long Y, Zhang H, Wang T, Huang X, Li Y, Wu J and Chen H 2013 Materials Science and Engineering: A 585 408–14
[74] Sharma B, Vaipai S K and Ameyama K 2016 Materials Transactions 57 1440–6
[75] Pasco C I, Gingo O, Rotaru P, Vida-Simiti I, Harabor A and Lupu N 2013 J. Therm. Anal. Calorim. 113 849–57
[76] Brazlovski V, Prikoshon S, Gauthier M, Inaeckyan K, Dubinskys S, Petruchik M and Filonov M 2011 Materials Science and Engineering: C 31 643–57
[77] Rechting J, Torresani E, Ivano E and Oleksy E 2018 Materials 11 181
[78] Sakamoto Y, Moriyama S, Endo M and Kawakami Y 2008 Mechanical property of porous titanium produced by spark plasma sintering Key Eng. Mater. 385–387 637–40
[79] Oh I H, Son H T, Kang C S, Lee J S, Cho J I, Bae J C, Lee B T and Song H Y 2007 Mater. Sci. Forum. 539 635–40
[80] Kon M, Hirasaka L M and Asakura K 2004 J. Bio- Med. Res. 68B 88–93
[81] Zhang L, Zhang Y, Jiang Y and Zhou R 2015 Vacuum A 122 167–94
[82] Hasebe T, Kobayashi E, Tezuka H and Sato T 2013 Jpn. J. Appl. Phys. 52 (1S)01AE03
[83] Zhang F, Ottersten E and Burkel E 2010 Adv. Eng. Mater. 12 863–72
[84] Lantang Y S F, Kobayashi E, Tezuka H and Sato T 2014 *Materials Transactions* **55** 1428–33
[85] Quan Y, Zhang F, Rebl H, Nebe B, Keöller O and Burkel E 2013 *Materials Science and Engineering: A* **565** 118–25
[86] Hao D, Lei Z, Yuqin Z, Zongyu Z and Fei H 2019 *Materials Research Express.* **6** 1065f3
[87] Kim D G, Woo K D, Kang D S, Lee T and Lee M H 2015 *Mater. Res. Innovations.* **19** (supp1) S1-301–S1-304
[88] Zhang L, He Z Y, Tan J, Calin M, Prashanth K G, Sarac B, Volker B, Jiang Y H, Zhou R and Eckert J 2017 *J. Alloys Compd.* **727** 338–45
[89] Makena I M, Shongwe M B, Machaka R and Matizamhuka W R 2019 *Int J Adv Manuf Technol.* **104** 2301–11
[90] Makena I M, Shongwe M B, Machaka R and Masete M S 2020 *SN Applied Sciences* **2** 516
[91] Manam N S, Harun W S W, Shri D N A, Ghani S A C, Kurniaawan T, Ismail M H and Ibrahim M H I 2017 *J. Alloys Compd.* **701** 698–715