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Review

Recent research and development in titanium alloys for biomedical applications and healthcare goods

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Abstract

Nb, Ta and Zr are the favorable non-toxic alloying elements for titanium alloys for biomedical applications. Low rigidity titanium alloys composed of non-toxic elements are getting much attention. The advantage of low rigidity titanium alloy for the healing of bone fracture and the remodeling of bone is successfully proved by fracture model made in tibia of rabbit. Ni-free super elastic and shape memory titanium alloys for biomedical applications are energetically developed. Titanium alloys for not only implants, but also dental products like crowns, dentures, etc. are also getting much attention in dentistry. Development of investment materials suitable for titanium alloys with high melting point is desired in dental precision castings. Bioactive surface modifications of titanium alloys for biomedical applications are very important for achieving further developed biocompatibility. Low cost titanium alloys for healthcare goods, like general wheel chairs, etc. has been recently proposed.

Keywords: Titanium alloy; Low rigidity; Super elastic; Shape memory; Bioactive surface modification; Dental precision casting; Healthcare goods

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Contents

1. Introduction

Since the population ratio of the aged people is rapidly growing, the number of the aged people demanding replacing failed tissue with artificial instruments made of biomaterials is increasing. In particular, the amount of usage of instruments for replacing failed hard tissues such as artificial hip joints, dental implants, etc. is increasing among the aged people. Metallic biomaterials are the most suitable for replacing failed hard tissue up to now. Main metallic biomaterials are stainless steels, Co based alloys, titanium and its alloys. Recently, titanium alloys are getting much attention for biomaterials because they have excellent specific strength and corrosion resistance, no allergic problems and the best biocompatibility among metallic biomaterials. Pure titanium and Ti–6Al–4V are still the most widely used ones for biomedical applications among the titanium alloys. They occupy almost of the market of titanium biomaterials. However, these are basically developed as structural materials mainly for aerospace structures. Therefore, the development of titanium alloys targeted for

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biomedical applications are highly required. Then the research and development on titanium alloys composed of non-toxic elements were started, and are under development with the increasing continuing in common [1–3]. The titanium alloys composed of non-toxic elements that have been developed in the early stage are mainly $\alpha + \beta$ type ones. Recently, mechanical biocompatibility of biomaterials is regarded as important factor, and therefore the research and development of β types titanium alloys, which are advantageous from that point, are increasing [1,4,5].

Among these research and development, very recently, the possibility for the developments of new titanium alloys for biomedical applications, which show super elasticity, is growing, and the research and of shape memory titanium alloys composed of non-toxic elements for biomedical applications are also attracting attentions [6–11]. The super elastic or shape memory characteristics are expected to develop new applications of metallic materials not only in medical fields but also in general fields. The super elastic characteristics of some titanium alloys [12,13] are appeared to be difficult to understand through conventional mechanisms, and therefore such super elastic characteristics of titanium alloys are also very interesting from the point of view of the material science.

The research and development of bioactive surface modifications for improving the biocompatibility of titanium alloys are also increasingly done [14,15] because the titanium alloys are grouped into bioinert materials by judging from the point of view of patterns of osteogenesis as shown in Table 1 [16].

Furthermore, the direct or indirect evaluation of biocompatibility using animals [17] or cells [18,19], and evaluations of mechanical performance [20–22] such as fatigue, fretting fatigue, fracture toughness, etc. are also energetically done.

In the aged society, demand for healthcare goods such as wheel chairs, artificial limbs and legs, etc. are also increasing [23,24]. Titanium alloys are also getting much attention in the field of healthcare goods, and the research and development of low cost titanium alloys for healthcare goods [23] are recently started.

Table 1
Biocompatibility of various biomaterials judged by patterns of osteogenesis

Pattern of osteogenesis	Biomaterials	
Intervend osteoginisis	Stainless steel, Co–Cr alloy, PMMA	Biotolerant materials
Contact osteogenesis	Titanium, titanium alloys, carbon, alumina, zirconia, titania, TiN, Si_3N_4	Bioinert materials
Bonding osteogenesis	Bioglass, ceravital, tricalcium phosphate, hydroxyapatite, A–W glass ceramic	Bioactive materials

Since the new developments in titanium alloys for biomedical and healthcare goods as stated above are appearing, the selected topics of research and development in titanium alloys for biomedical and healthcare goods including the examples stated above will be described in this paper.

2. Trend of selection of alloying elements in titanium alloys for biomedical titanium alloys

Research and development of titanium alloys for biomedical applications from the beginning were started fairly recently. In that case, the elements, which are judged to be non-toxic and non-allergic through the reported data of cell viability for pure metals [25], polarization resistance (corrosion resistance) and tissue compatibility of pure metals and representative metallic biomaterials [26], and allergic properties of pure metals [27], are selected as alloying elements for titanium. As a result, Nb, Ta and Zr are selected as the safest alloying elements to titanium. In addition to these elements, Mo and Sn are selected as safer elements for living body.

The titanium alloys reported recently as biomaterials are Ti–Zr system, Ti–Mo system, Ti–Ta system, Ti–Ta–Zr system, Ti–Nb–Hf system, Ti–Nb–Zr system, Ti–Nb–Sn system, Ti–Nb–Ta–Zr system, Ti–Fe–Ta system, Ti–Mo–Zr–Sn system, Ti–Sn–Nb–Ta system, Ti–Mo–Zr–Fe system, Ti–Mo–Nb–Si system, Ti–Mo–Ga system, Ti–Mo–Ge system, Ti–Mo–Al system alloys and so on [6–11,28]. Many of these alloys contain fairly a large amount of Nb, Ta, Zr, Mo and/or Sn. See the references to understand the details of alloy compositions of these alloys.

3. Low rigidity titanium alloys for biomedical titanium alloys

Many of the titanium alloys for biomedical applications stated above are β types alloys, which have been designed with targeting low rigidity. Main metallic biomaterials are stainless steels, Co–Cr system alloys and titanium alloys as stated above. Here the comparison of Young's moduli of cortical bone, $\alpha + \beta$ type Ti–6Al–4V, 316L stainless steel and Co–Cr–Mo alloy are shown in Fig. 1 [29]. The Young's moduli of 316L stainless steel and Co–Cr–Mo alloy are much greater than that of cortical bone. The Young's moduli of biomaterials have been said to be desirable to be equal to that of cortical bone because if the Young's moduli of biomaterials are much greater than that of cortical bone, bone resorption occurs. The Young's modulus of $\alpha + \beta$ type titanium alloy, Ti–6Al–4V that is the most widely used titanium alloy for biomedical applications, is much lower than those of stainless steel and Co based alloy. However, its Young's modulus is still much greater than that of cortical bone. The Young's moduli

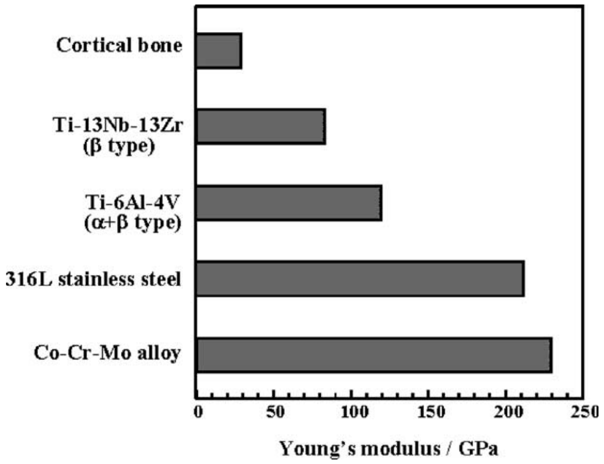


Fig. 1. Comparison of Young's modulus of cortical bone, β type Ti–13Nb–13Zr, α + β type Ti–6Al–4V, 316L stainless steel and Co–Cr–Mo alloy for biomedical applications.

of β type titanium alloys are known to be smaller than those of α or α + β type titanium alloys. Then the low rigidity can be obtained in β type titanium alloys. In addition, β type titanium alloys show excellent cold workability and high strength. Therefore, the research and development of low rigidity β type titanium alloys are getting much attention.

Young's moduli of several representative β type titanium alloys and a representative α + β type titanium alloy, Ti–6Al–4V ELI for biomedical applications are shown in Table 2 [30–32]. The Young's moduli of β type titanium alloys are recognized to be much smaller than that of α + β type titanium alloy, Ti–6Al–4V ELI. The Young's moduli increase with the precipitation of α phase or β phase by aging treatment in β type titanium alloys [33,34]. Therefore the Young's modulus trends to increase with increasing strength by aging treatment in β type titanium alloys. However, on the other hand, the Young's modulus can be controlled by aging treatment in β type titanium alloys.

Table 2
Young's moduli of representative β type titanium alloys and Ti–6Al–4V for biomedical applications

Material	Alloy type	Young's modulus (GPa)
Ti–6Al–4V (annealed)	α + β	113
Ti–6Al–4V ELI (WQ)	α + β	118
Ti–13Nb–13Zr	β	
WQ		64–77
WQ + aged		81
AC		83
WQ + 50–75% CW		44–51
Ti–12Mo–6Zr–2Fe	β	74–85
Ti–29Nb–13Ta–4.6Zr	β	
WQ		63
WQ + aged at 673 K for 3.6 ks		97
WQ + CW		62

WQ: water quenching after solution treatment; AC: air cooling after solution treatment; CW: cold working.

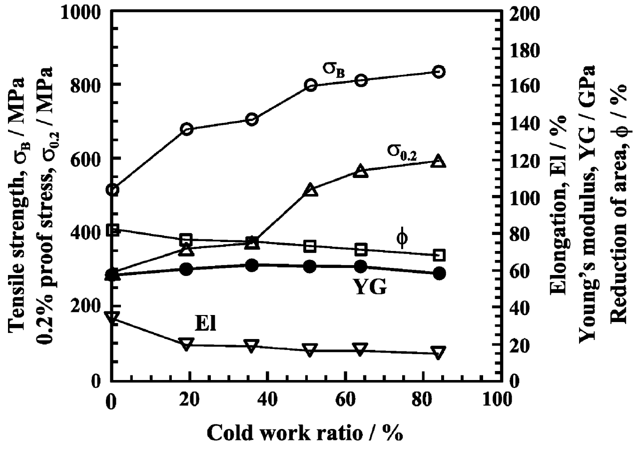


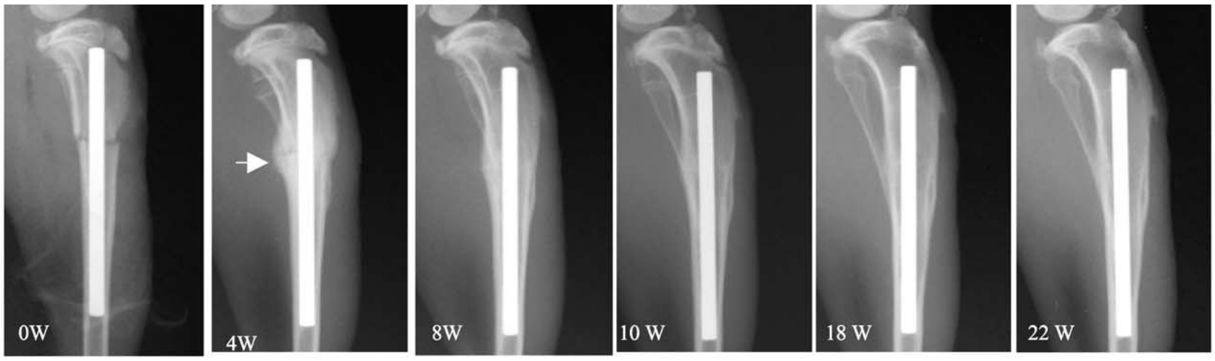
Fig. 2. Tensile properties and Young's modulus of Ti–29Nb–13Ta–4.6Zr as a function of cold work ratio; σ_B : tensile strength, $\sigma_{0.2}$: 0.2% proof stress, El: elongation, YG: Young's modulus, ϕ : reduction of area.

The strength of β type titanium alloys can be increased with keeping Young's modulus low by cold working after solution treatment because high ratio cold working is possible in β type titanium alloys. Tensile properties and Young's modulus of Ti–29Nb–13Ta–4.6Zr for biomedical applications are shown in Fig. 2 [35] as a function of cold work ratio. Strength such as tensile strength and 0.2% stress increase with increasing cold work ratio. The strength of Ti–29Nb–13Ta–4.6Zr cold worked by 84% is nearly equal to that of Ti–6Al–4V ELI. On the other hand, Young's modulus is constant to be low value regardless of cold work ratio. The ductility such as elongation and reduction of area are a little lowered at low cold work ratio by around 20%, but at higher cold work ratio over 20%, ductility is nearly constant to be high.

4. Mechanical biocompatibility of low rigidity titanium alloys for biomedical applications

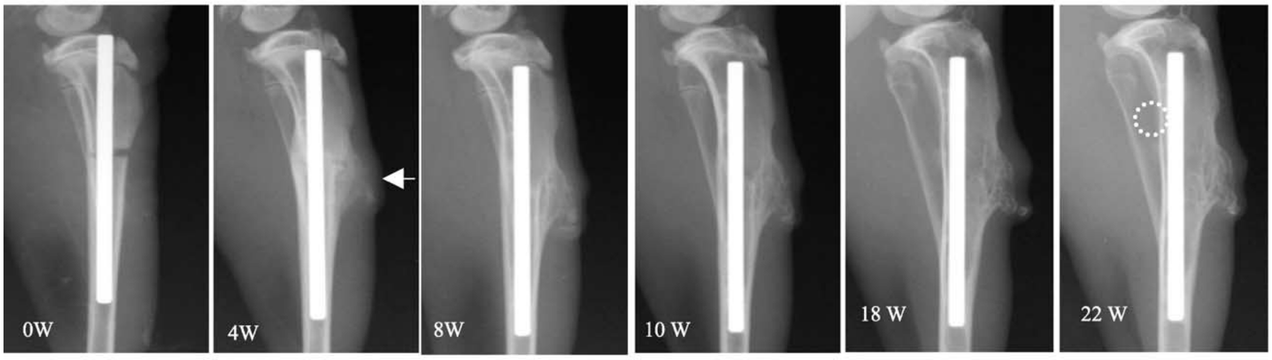
In order to confirm the advantage of low rigidity for bone healing and remodeling, using rabbits, experimental tibial fracture was induced in tibia by oscillating saw at just below the tibial tuberosity. Intramedullary rod made of low rigidity Ti–29Nb–13Ta–4.6Zr, Ti–6Al–4V ELI or SUS 316L stainless steel was inserted into the intramedullary canal to fix the fracture. Bone healing, remodeling and atrophy was observed by X-ray transmission image every 2 weeks up to 24 weeks. The results are shown in Fig. 3 [17,36].

The outline of fracture callus was very smooth with bone remodeling in Ti–29Nb–13Ta–4.6Zr. Similar phenomenon was observed at 8 weeks in Ti–6Al–4V ELI and SUS 316L. In Ti–29Nb–13Ta–4.6Zr, the amount of the fracture callus was relatively small, and gradually decreased from 6 weeks, and then there were no traces of fracture at 10 weeks after the fixation. After 10 weeks, no changes could be observed up to 18 weeks. However, a little atrophic change



(a) Ti-29Nb-13Ta-4.6Zr

(b) Ti-6Al-4V ELI



(c) SUS 316L

Fig. 3. Healing process of bone fracture from 0 to 22 weeks after surgery observed by X-ray. Arrow and dotted round mark show callus formation and atrophic change, respectively.

was observed at the posterior tibial bone after 20 weeks. In Ti–6Al–4V ELI, the callus formation and the bone remodeling were almost similar to those in Ti–29Nb–13Ta–4.6Zr, but slower as compared with Ti–29Nb–13Ta–4.6Zr. A little atrophic change was seemed to be observed at 18 weeks. In SUS 316L stainless steel, a large amount of the fracture callus was observed, and remains up to the end of the succeeding period. Bone atrophy seemed to be occurring at the posterior proximal tibial bone at 10 weeks, and became obvious every 2 weeks. The posterior tibial bone became to be very thin at 24 weeks. Therefore, low rigidity titanium alloy, Ti–29Nb–13Ta–4.6Zr, is found to improve the load transmission issue of the current metal implants with the high rigidity.

5. Super elastic and shape memory titanium alloys for biomedical applications

Only Ti–Ni has been put into wide practical use as super elastic and shape memory alloy. Formerly, shape memory alloy, Ti–Ni, was tried to apply to implants [38]. However, since Ti–Ni contains a large amount of Ni, which causes allergy at high rate as shown in Fig. 4 [37], the usage of Ti–Ni shape memory alloys is restricted. However, Ti–Ni is recently getting much attention for applying to stents or catheters where super elastic characteristics or shape memory effect is very advantageous. However, the risk of metallic allergy is still high in Ti–Ni because Ni content is very high.

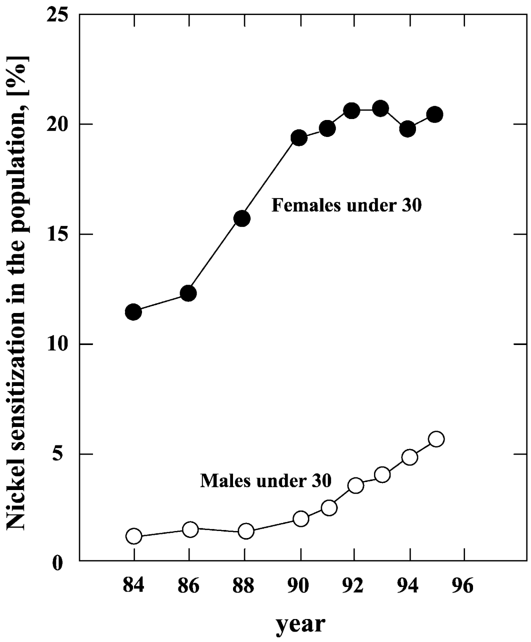


Fig. 4. Frequency of nickel sensitization in the population in Europe.

Therefore, the research and development of Ni-free super elastic and shape memory titanium alloys composed of non-toxic elements for biomedical applications are increasing.

Gum metal (a brand name) [12] is a super elastic titanium alloy that is recently getting much attention. Gum metal is a β type titanium, and shows a Young's modulus of 40 GPa at minimum and an elastic strain of 2.5%. Gum metal has been put into practical use for glass frames. Gum metal has been developed not for biomedical applications, but for general carrying goods [38]. However, the chemical composition of gum metal is very similar to that of Ti–Nb–Ta–Zr system alloy for biomedical applications mentioned above [1,39]. Therefore, gum metal has the potential to be used for biomedical applications if the chemical composition is suitably modified. The deformation mechanism of gum metal has been reported to be not related to dislocations or twins, and is unknown one. Gum metal is also very interesting from the point of view of science. The super elastic behavior has been actually observed in Ti–29Nb–13Ta–4.6Zr for biomedical applications as shown in Fig. 5 [40], and it is reported that the density of dislocations after deformation of this alloy is very low [41]. Ti–29Nb–13Ta–4.6Zr has been also put into practical use for glass frames as a brand name of bio-titan [42].

Ti–Nb–Sn system alloy is developing as Ni-free shape memory titanium alloy for biomedical applications. Its martensite transformation temperature (Ms point) decreases with increasing the amount of Nb or Sn, and the shape memory effect is recognized when the alloy is deformed below austenite transformation temperature (Af point) similar to the case of Ti–Ni shape memory alloy. It has been reported that an elastic strain of 3.5% is obtained at the composition of Ti–18 at.%Nb–4 at.%Sn [6]. The research and development of Ti–Mo–Ga system alloy [7], Ti–Mo–Ge system alloy [8] or Ti–Mo–Al system alloy [9], Ti–Ta system alloy [10], Ti–Ta–Zr system alloy [11], Ti–Sc–Mo system alloy [12] as shape memory titanium alloys for biomedical applications are also noticeable. They are all β type titanium alloys.

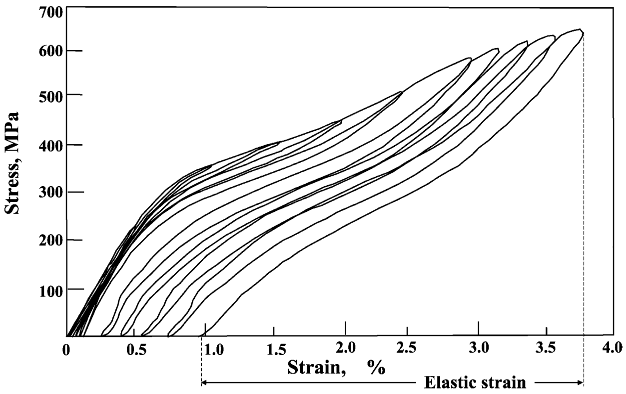


Fig. 5. Tensile loaded–unloaded curves of cold extruded Ti–29Nb–13Ta–4.6Zr wire; elastic strain: 2.7%.

6. Titanium alloys for dental applications

Titanium and its alloy are also getting much attention in dental applications. Nowadays, the cost of Ag–Pd–Au–Cu alloy, which is the most popular dental alloy in Japan, is significantly increased because of increasing cost of Pd. Titanium alloy is expected as an alternative candidate to Ag–Pd–Au–Cu alloy. This fact enhances the attention to titanium and its alloys for dental applications.

Titanium alloys for dental applications should also have excellent biocompatibility, and are sort of biomaterials. The representative dental titanium alloys reported and their mechanical properties are shown in Table 3 [43,44].

Table 3
Titanium alloys for dental applications and their mechanical properties

Alloy	Process	Tensile strength (MPa)	Yield strength (MPa)	Elongation (%)	Vickers hardness
Ti–20Cr–0.2Si	Casting	874	669	6	318
Ti–25Pd–5Cr	Casting	880	659	5	261
Ti–13Cu–4.5Ni	Casting	703	–	2.1	–
Ti–6Al–4V	Casting	976	847	5.1	–
Ti–6Al–4V	Super plastic forming	954	729	10	346
Ti–6Al–7Nb	Casting	933	817	7.1	–
Ti–Ni	Casting	470	–	8	190

Some alloys have very different chemical compositions from those for implants. Pure titanium and Ti–6Al–4V are the main materials in the dental field as well as in the surgical field. Ti–6Al–7Nb, which has been developed for surgical implants, is also attractive for dental applications [45,46].

The casting process is dominant in dental applications. Especially the elongation is very low although the strength is kept to be high. Therefore, development in elongation without reducing strength is investigated in cast titanium alloys. Hydrogenation and dehydrogenation processing, that is, thermochemical processing followed by post heat treatment [46], heat treatments like α-β solution treatment, β solution treatment, broken-up structure, etc. [47] are effective for improving elongation without reducing strength in cast titanium alloys.

Recently, Ti–40Zr [48], Ti–5Al–13Ta [49] and Ti–43.1 at.%Zr–10.2 at.%Al–3.6 at.%V [50] have been proposed.

Titanium alloys are very reactive and have relatively higher melting point comparing with other dental alloys like Au based alloys and Ag based alloys. Therefore, the low melting point titanium alloys and low reactive mold materials are desired for dental precision castings. In dental precision casting, alumina based and magnesia based mold materials are mainly used [51]. Magnesia based mold material is more suitable for dental precision casting of titanium alloys comparing with alumina based mold materials [45]. Calcia based mold material is also reported to be suitable for dental precision casting [52,53]. However, calcia based mold material is said to have difficulty in treatment.

7. Bioactive surface modification of titanium alloys for biomedical applications

Titanium alloys show the greatest biocompatibility among metallic materials for biomedical applications. However, they are grouped into bioinert materials as well as ceramics like alumina, zirconia, etc. judging from the pattern of osteogenesis as already stated before, and its biocompatibility is inferior to that of phosphate calcium (CaP) or hydroxyapatite (HAP: Ca(PO$_4$)$_3$OH), which is grouped into bioactive materials. Therefore, bioactive surface treatment (bioactive surface modification) is in general applied to titanium alloys for biomedical applications in order to improve their biocompatibility further. In that case, phosphate calcium type ceramics such as phosphate calcium (CaP), TCP(β-Ca$_3$(PO$_4$)$_2$), CCP(β-Ca$_2$P$_2$O$_7$), etc. and hydroxyapatite are mainly coated on the surface of titanium alloy. In general, formation of hydroxyapatite is finally targeted.

The bioactive surface treatment processes are in general divided into dry process and wet process. There are various dry and wet processes [14].

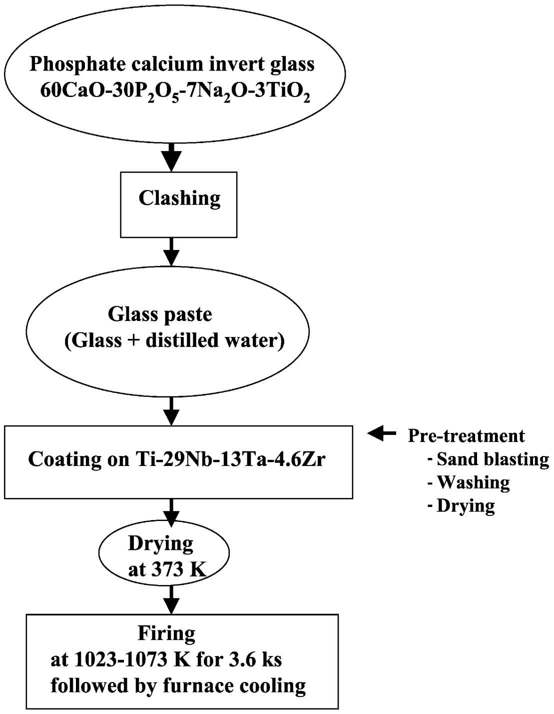


Fig. 6. Schematic explanation of coating of phosphate calcium crystallized glass on Ti–29Nb–13Ta–4.6Zr.

Dry processes are divided into direct HAP forming methods and indirect HAP forming methods. The formers are for example plasma spray method, ion plating [54], RF magnetron sputtering [55], pulse laser deposition method [56,57], ion beam dynamic mixing method [58], super plastic joining method [59], etc. where HAP are formed directly on titanium alloy surface. The latter are for example calcium ion implantation [60] where calcium ions are implanted into biomedical titanium alloys, calcium ion mixing method [14] where Ca is sputtered on the surface of

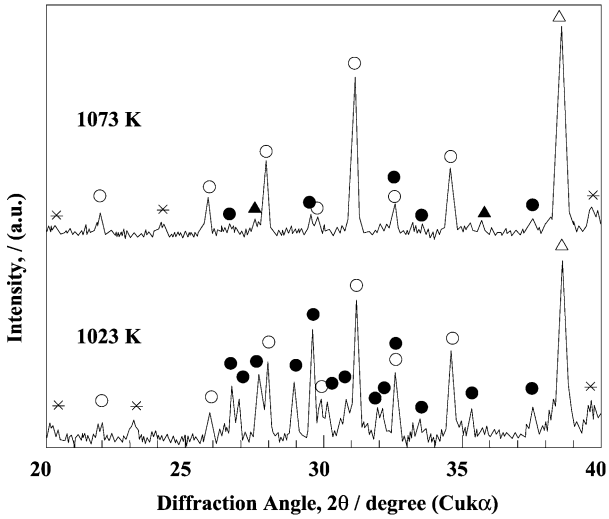


Fig. 7. X-ray diffraction patterns of coating layers on the specimens prepared by heating at 1023 and 1073 K for 3.6 ks in air; ○: TCP, ●: CPP, ▲: β-Ti, and ∗ : unknown phase.

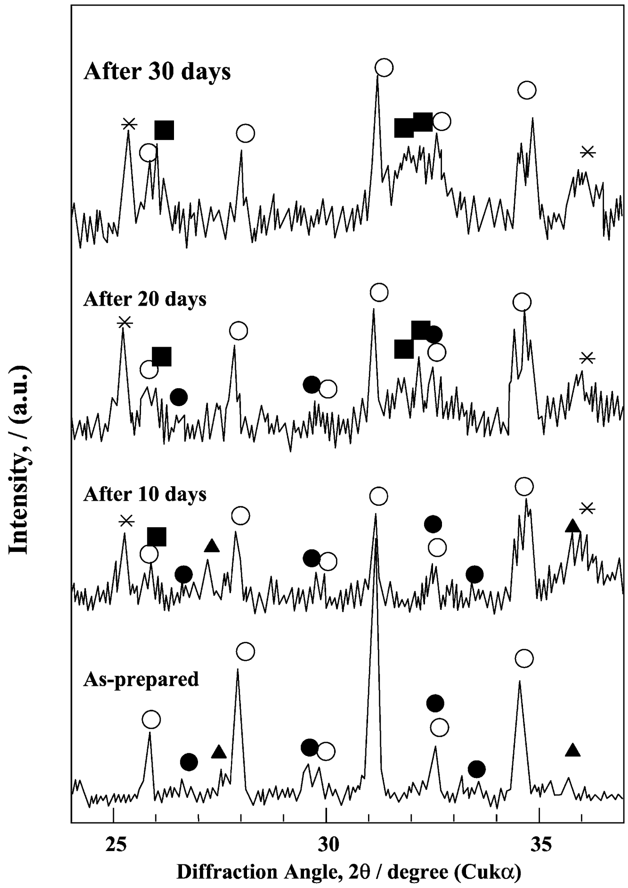


Fig. 8. X-ray diffraction pattern of the surface of the glass-ceramic layer coated on the alloy before or after soaking in SBF for 10, 20 or 30 days; ■: HA, ○: TCP, ●: CPP, ▲: TiO_2, and ∗ : unknown phase.

biomedical titanium alloys followed by Ar ion implantation, etc. CaP precipitation is enhanced on the surface of biomedical titanium alloys conducted with these treatments when they are implanted into living body.

Wet processes are also divided into direct HAP forming methods and indirect HAP forming methods. The formers are for example electrochemical treatment [61], etc. The latter are for example alkali treatment [62] where the biomedical titanium alloy is immersed into NaOH solution and heated followed by immersing the alloy into living body liquid.

There is an another interesting method [15] (Fig. 6 [63]) where the powder of calcium phosphate invert glass mixed with distilled water is coated on the surface of the titanium alloy followed by heating at around 1073 K, and then phosphate calcium type ceramics precipitate. Fig. 7 shows the X-ray profiles of the surface of Ti–29Nb–13Ta–4.6Zr conducted in this method. Bioactive β-TCP and β-CCP are formed by heating glass coated Ti–29Nb–13Ta–4.6Zr at 1073 K for 3.6 ks. Furthermore, HAP is formed by immersing that in simulated body liquid, SBF as shown in Fig. 8 [63]. This processing is more advantageous for the oxidation resistant titanium alloys containing a large amount of Nb and Ta such as Ti–29Nb–13Ta–4.6Zr.

8. Titanium alloys for healthcare goods

Main metallic materials used for healthcare goods such as wheel chairs, artificial limbs, artificial legs, etc. are steels, aluminum alloys and titanium alloys. Nowadays titanium

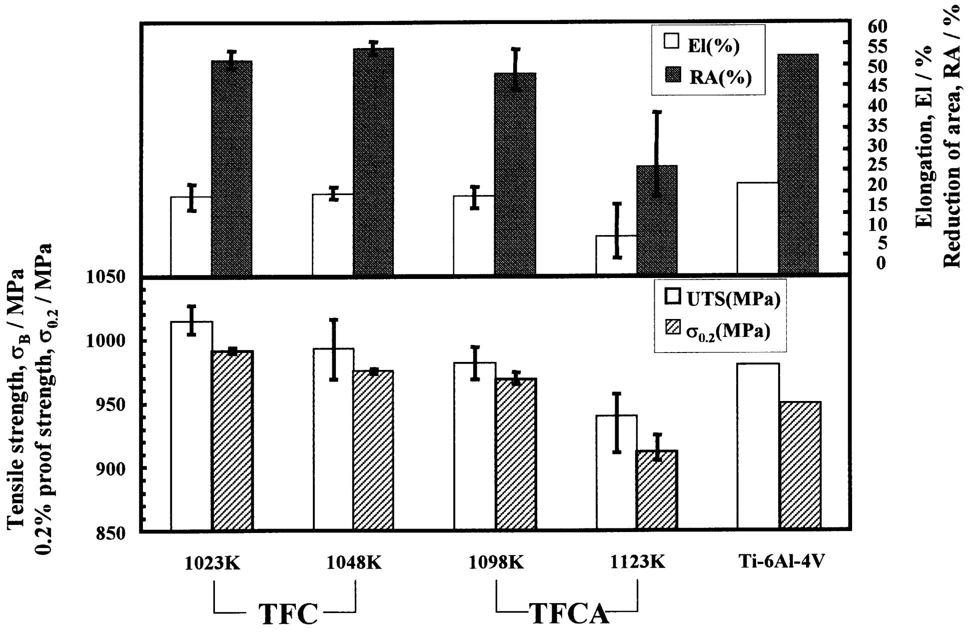


Fig. 9. Tensile properties of TFC and TFCA as a function of solution treatment temperature comparing with tensile properties of Ti–6Al–4V.

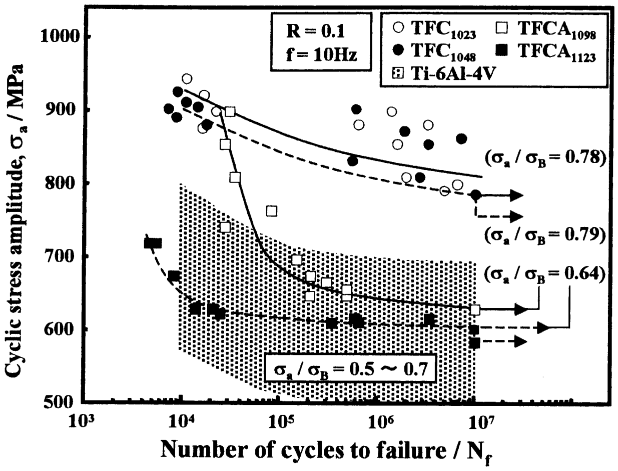


Fig. 10. Fatigue strength (S–N curve) of TFC, TFCA and Ti–6Al–4V. The numbers subscribed to TFC and TFCA are solution treatment temperatures. R and σ_s/σ_B where σ_s and σ_B are fatigue limit and ultimate tensile stress are stress ratio and fatigue ratio.

and its alloys are also getting much attention in the field of healthcare goods. Titanium and its alloys are well known to have been used for wheel chairs for sports, which are basketball wheel chairs, racing wheel chairs, etc. On the other hand, the usage of titanium and its alloys for general wheel chairs is limited because of the cost. However, the usage of titanium and its alloys are expected to expand because of excellent biocompatibility and sensitivity such as touch feeling. Recently the research and development of low cost titanium alloys for healthcare goods with focusing on wheel chairs have been started. The examples of the representative alloys are Ti–4.2Fe–6.9Cr (TFC) and Ti–4.0Fe–6.7Cr–3.0Al (TFCA) [23]. Their costs are reported to be lower than that of pure titanium because low cost ferro-Cr or recycled titanium containing Fe can be used. The tensile properties and fatigue of both alloys are excellent as shown in Figs. 9 and 10 [24]. Since both alloys have high strength, the weight of a certain wheel chair frame made of these alloys is calculated to be 50% of pure titanium. Therefore, by taking the cost of materials account into, fairly a large amount of cost reduction of wheel chair can be expected to be achieved. However, in the present state, since development of the forming processes of both alloys are not completed, the processing cost cannot be estimated.

Although the materials for healthcare are not used in the living body, biocompatibility such as allergic problems, etc. should be considered because the aged people whose immune abilities are in general lowered, are considered to have a lot of chances to use them. Fig. 11 [24] shows comparison of cell viability of filtrated extracts and non-filtrated extracts of TFC, TFCA, pure titanium and Ti–6Al–4V after extracting for 7 days or 14 days evaluated through MTT method. In both non-filtrated and filtrated extracts, cell viabilities of TFC and TFCA are greater than those of pure titanium and Ti–6Al–4V. The developments of TFC and TFCA for healthcare goods are highly expected in future.

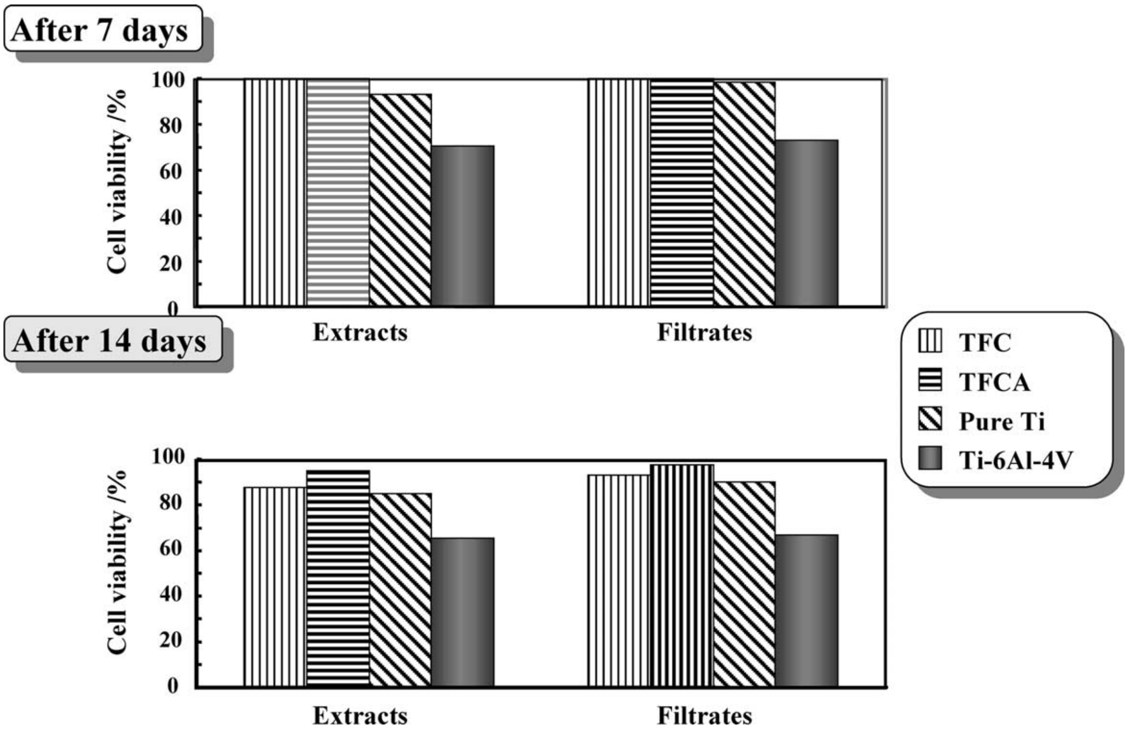


Fig. 11. Comparison of cell viability of filtrated extracts and non-filtrated extracts of TFC, TFCA, pure titanium and Ti–6Al–4V after 7 days or 14 days.

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