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Research article

Interaction of Ti-6Al-7Nb alloy with simulated body fluid; a preliminary biocompatibility investigation

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Abstract

The current study aims to investigate the interaction of Ti-6Al-7Nb with simulated body fluid (SBF) in order to apply a preliminary biocompatibility investigation of this novel biomedical alloy, promising for orthopedic applications. Results of the static immersion tests conducted in SBF at body temperature demonstrated that Ca-P rich structures form on the Ti-6Al-7Nb alloy surfaces and the oxide layer formation-dissolution cycle reaches a stable state during immersion. Ion release levels were mostly below critical values except for the initial Al ion release level, which indicated the need for the presence of a stable protective layer on the alloy surface. The second set of static immersion experiments conducted in densified SBF demonstrated that, such a protective layer can rapidly form by biomimetic coating if followed by a preliminary surface treatment. Overall, Ti-6Al-7Nb alloys layers exhibit promising biocompatibility for orthopedic applications, especially with the presence of a stable protective layer.

Keywords: *Biomedical alloy; biomimetic coating; ion release; simulated body fluid; Ti-6Al-7Nb*

1. Introduction

Biomaterials have become an important material class that contribute to improving life quality. Among the many applications of biomaterials, orthopedic implants, which can replace or support bone tissue, are commonly needed due to various reasons such as bone and joint disorders, large and complex fractures, and bone tissue losses (Bauer et al., 2013; Behera, 2021). For orthopedic implant applications, usually metallic biomaterials are preferred, mainly owing to their mechanical properties as well as their biocompatibility (Bauer et al., 2013). Stainless steel, Cobalt-Chromium (Co-Cr) alloys, and Titanium (Ti) and Ti alloys, which are included in this group, are widely used biomaterials for bone tissue applications such as hip and knee implants, dental implants as well as bone screws and plates (Manam et al., 2017; Hazwani et al., 2022).

Among these biomedical alloys, Ti and its alloys (e.g. Ti-6Al-4V) have been favored over the recent years owing to their lower density which enables the manufacturing of low weight implants (Hazwani et al., 2022). Superior mechanical properties, corrosion resistance, and elastic modulus close to that of the bone tissue constitute other advantages of Ti and Ti alloys. Especially, the TiO_2 layer, which naturally forms on Ti alloys, provide remarkable corrosion resistance for these alloys. The chemical stability of the oxide layer on Ti enables chemical inertness, corrosion and erosion resistance as well as improved biocompatibility (Mahyudin et al., 2016; Hazwani et al., 2022). Moreover, this passive oxide layer provides protection against ion release from the alloy to the surrounding tissue and supports osseointegration by favoring the formation of hydroxyapatite like calcium-phosphate (Ca-P) rich structures on the surface of implant (Gedikoglu et al., 2021).

Owing to the aforementioned advantages, Ti and its alloys are preferred for many biomedical applications. Commercial grade Ti (Cp-Ti) is generally used in dental implants, while Ti-6Al-4V alloy is preferred for orthopedic applications such as hip and knee implants due to its superior mechanical properties (Toker et al., 2019). Ti-6Al-4V alloy is an α/β Ti alloy in which

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the α phase is stabilized by Aluminum (Al) and the β phase by Vanadium (V). Despite its advantages, the potential release of Al and V elements from Ti-6Al-4V alloy might cause some undesired effects for the patient (Mahyudin et al., 2016; Gedikoglu et al., 2021). Specifically, V element was shown to cause adverse reactions for the patient in long term use such as Alzheimer's disease, bone and nerve softening in addition to toxicity at cellular level (Toker et al., 2019; Badhe et al., 2021; Wei et al., 2023). On the other hand, Al element ion release above certain values may also cause various disorders such as changes in blood pressure, heart failure, parkinsonism including mild to severe symptoms in the body. Moreover, in the case of excessive Al ion release, this metal may accumulate in the kidney and damage different cells (Badhe et al., 2021). Therefore, the release of V and Al ions may cause significant health problems if they surround the tissues (Tuten et al., 2019).

Due to the aforementioned issues, β-Titanium alloys are being developed as an alternative by adding alloying elements such as Molybdenum (Mo), Tantalum (Ta), Zirconium (Zr), Tin (Sn) and Niobium (Nb) that can stabilize the β phase. These alloying elements, which can replace V, exhibit lower or no toxic effect when compared to V element; while maintaining the other properties (Bocchetta et al., 2021). Among these, Nb becomes prominent as an element that does not exhibit toxicity while contributes to high corrosion resistance (Fellah et al., 2014). Therefore, through the replacement of V with Nb, Ti-6Al-7Nb alloy has been developed as an alternative material to Ti-6Al-4V alloy for biomedical applications which exhibits as good mechanical properties while not causing toxic effects (Liu et al., 2013).

There are still various ongoing studies investigating the mechanical properties and biocompatibility of Ti-6Al-7Nb alloys to be used for biomedical purposes (Cingi and Cimenoglu, 2010; Fellah et al., 2014; Izmir et al., 2019). When exploring the biocompatibility of potential biomaterials, especially biomedical alloys, investigating the relationship between corrosion resistance and oxide layer formation of the metal in the body fluid environment is of utmost importance as metals are materials prone to corrosion. Specifically, it is crucial to examine the biomedical alloys' behavior in a synthetic body fluid environment at a pH value and ion concentration similar to the body part in which they will be used, especially for evaluating their corrosion resistance in the specific corrosive body environment and determining the possible corrosion reactions and toxic ion release behaviors (Yilmaz et al., 2020). Therefore, *ex situ* tests focusing on the correlation between corrosion, ion release and formation-dissolution cycle of the protective oxide layer of the metal in a simulated body fluid environment are important methods for understanding the preliminary biocompatibility response of metallic biomaterials (Toker et al., 2014; Toker and Canadinc, 2014; Gurel et.al, 2022; Li et al, 2023; Ozdemir et.al, 2023).

While there are few studies focusing on testing the biocompatibility of Ti-6Al-7Nb in synthetic body fluid environment, they are mostly focused on the bioactivity of this alloy and most of the studies on Ti-6Al-7Nb alloys for biomedical applications are focused on their mechanical properties. Specifically, studies investigating the various aspects of the biocompatibility of this novel alloy via static immersion tests where the corrosion–ion release relationship is investigated are relatively limited. Moreover, since Al, is a critical element for tissues due to the aforementioned reasons and is one of the constituents of Ti-6Al-7Nb alloy, it is especially crucial to investigate the ion release behavior of this alloy for potential biomedical applications. With this motivation, in the current study, the *ex situ* biocompatibility of Ti-6Al-7Nb alloy in synthetic body fluid environment is investigated as a function time. Specifically, the ion release behavior over time is examined in relation to the formation and dissolution of the oxide layer and Ca-P structures, which are important markers for osseointegration. The purpose of this study is to provide a preliminary biocompatibility investigation of the novel Ti-6Al-7Nb alloy for biomedical, specifically for orthopedic applications, via *ex situ* methods.

2. Materials and methods

The elemental composition of the Ti-6Al-7Nb alloy used in the study are given in Table 1 as weight percentage (%) value of each element (Titanium Ti-6Al-7Nb Data, 2022). The Ti-6Al-7Nb samples were in cylindrical geometry with a radius of 1 cm and height of 3 mm.

Table 1
The elemental composition of the Ti-6Al-7Nb alloy used in the study.

Element	Composition (weight %)
Titanium (Ti)	85.41-87.41
Aluminum (Al)	5.50-6.50
Niobium (Nb)	6.50-7.50
Iron (Fe)	max. 0.25
Oxygen (O)	max. 0.20
Carbon (C)	max. 0.08
Nitrogen (N)	max. 0.05
Hydrogen (H)	max. 0.009

In order to investigate of the behavior of Ti-6Al-7Nb alloy in the body fluid environment, the samples were statically immersed in a simulated body fluid (SBF) solution, which mimicked human blood plasma in terms of its pH and ionic content. The SBF solution was prepared according to the Kokubo protocol with the chemical content specified in Table 2 and the pH of the solution was fixed at 7.4 (Yilmaz et al., 2020).

Table 2
Chemical content of the SBF solution prepared for the static immersion experiments.

Adding order	Chemical	Amount (g/L)
1	NaCl	8
2	$NaHCO_3$	0.35
3	KCl	0.224
4	$K_2HO_4.3H_2O$	0.228
5	$MgCl_2.6H_2O$	0.304
6	HCl	40 ml
7	$CaCl_2$	0.278
8	Na_2SO_4	0.07
9	$(CH_2OH)_3CNH_2$	6.056

Surfaces of the Ti-6Al-7Nb samples were prepared by grinding and polishing prior to the static immersion experiments. Following surface preparation, the samples were placed in separate tubes where each sample was subjected to the SBF solution with a ratio of 1/10 of sample surface area (mm^2)/body fluid (ml) according to the Kokubo protocol. The sealed tubes containing alloys samples immersed in SBF solution were placed in a water bath where the body temperature environment of 37°C was provided. The immersion experiment was applied for different time periods of 1, 7, 14, 21 and 30 days in order to investigate the ion release, passive oxide layer dissolution-reformation behavior as well as Ca-P rich precipitate formation on the Ti-6Al-7Nb samples in SBF as a function of time. At the end of each immersion period, the surfaces of the samples retrieved from the solutions were examined by scanning electron microscopy (SEM) (FE-SEM, Hitachi Regulus 8,230, Hitachi High-Tech Co., Tokyo, Japan,) coupled with Energy-Dispersive X-Ray Spectroscopy (EDX) (Ultim Extreme EDX instrument, Oxford Instruments, High Wycombe, UK) for the chemical analysis of the structures formed on the sample surfaces during static immersion. EDX analyses were conducted using both point and area spectrums at an accelerating voltage of 10kV and 10mm working distance. Potential ion release from the Ti-6Al-7Nb alloys into the SBF solutions were analysed via Inductively Coupled Plasma-Mass Spectrometer (ICP-MS) (ICP-MS, Thermo Fisher Scientific, iCAP RQ, MA, USA).

Finally, in order to test the biomimetic coating capability of the tested alloys, static immersion experiment was applied in a 3-times densified SBF (3X SBF) solution where the amount of each ingredient in the solution was multiplied by three. The immersion in 3X SBF was applied for periods of 1 and 7 days. For the sample-area/fluid ratio, Kokubo protocol was followed as in the procedure applied for the initial static immersion experiments. In order to prevent precipitate formation in the densified SBF environment, the 3X SBF solutions were renewed every two days. Following the immersion in the densified SBF solutions for 1 and 7 days, the samples were retrieved and analysed via SEM and EDX for the detection and elemental analysis of the newly formed structures, especially Ca-P products.

3. Results and discussion

3.1. Ex situ tests in SBF

The TiAlNb samples, which were immersed in SBF for 1, 7, 14, 21 and 30 days were retrieved from the fluids at the end of each immersion period and both the samples and fluids were thoroughly investigated. The initial examinations revealed that there were no significant changes on the pH values of the SBF solutions after the alloys were retrieved from the fluids following the determined immersion periods, which indicate the stability of the SBF solutions throughout the experiments.

The selected SEM images of the sample surfaces following immersion in SBF for 1, 7, 14, 21 and 30 days together with the control sample are given in Fig. 1. The initial visual observations from the SEM images indicate the formation of new structures starting from the 1st day of immersion in comparison to the control sample. The intensity and distribution of the new structures on the sample surfaces exhibit slight differences among the different immersion periods. These differences are due to the expected new structure formation-dissolution cycle that occurs throughout the immersion (Toker and Canadinc, 2014; Toker et al., 2014; Gurel et al., 2022; Li et al., 2023; Ozdemir et al., 2023).

The results of the EDX analyses obtained from the different areas of each sample paired with the corresponding SEM image are also provided in Fig. 2. Three or four different areas were examined via EDX on each of the samples, which were selected among the regions where formation of new structures was detected. In the EDX analysis of these selected regions, special attention was paid to Ca, P and O; as the changes in O signal are representative of the formation and dissolution of the protective oxide layer on the alloy surface while Ca-P signals are important in terms of providing information about the bone tissue formation tendency of the surface.

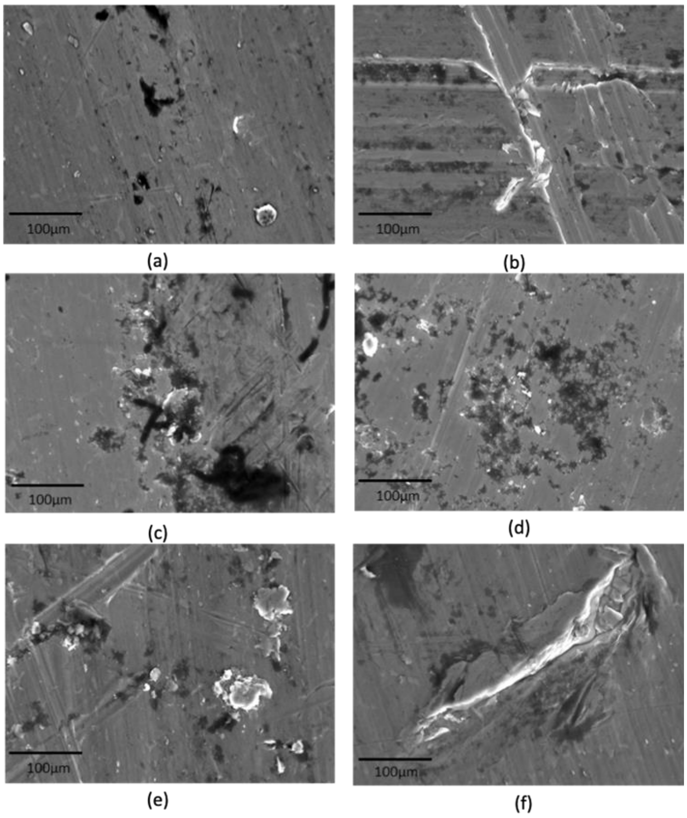

Fig. 1. SEM images of the Ti-6Al-7Nb sample surfaces; (a) control sample, (b) sample immersed in SBF for 1-day (c) sample immersed in SBF for 7 days, (d) sample immersed in SBF for 14 days, (e) sample immersed in SBF for 21 days, (f) sample immersed in SBF for 30 days.

In order to make a quantitative comparison, the maximum O, Ca and P levels measured on each surface were noted and organized as a graph of element weight percent vs. immersion period (Fig. 3 and Fig. 4.).

It is known that during the interaction of the implant materials with bodily fluids, the protective oxide layer goes into a continuous cycle of dissolution and reformation, which affects the ion release from the metal into the fluid (Toker et al., 2014). For the current samples, the change in O levels with respect to time exhibits a steady increase from the 1st day of immersion up to the 14th day, becomes stable around 21 days and followed by a decrease approaching to 30 days. Since this behavior is strongly correlated to the ion release behavior, it is important to examine this trend in relation with the ion release rates over time. The measured ion release levels of Al and Ti elements at each immersion period is provided as parts-per-billion (ppb), ie μg lt^{-1} in Fig. 5. According to this figure, the most striking observation is the sudden Al release on the 1st day immersion. This sudden increase is stabilized at the 7th day of immersion, followed by a slight decrease on the 14th day and afterwards the Al release levels fell below detectable levels. On the other hand, the detected Ti ion release levels over time are relatively low and close to each other. In terms of the critical levels of the ions, it is stated that the safe range in the body for the Ti element in the body is <1 ppb, and for the Al element is <5 ppb (Sahin et al., 2015). The current results exhibit that risky ion release levels

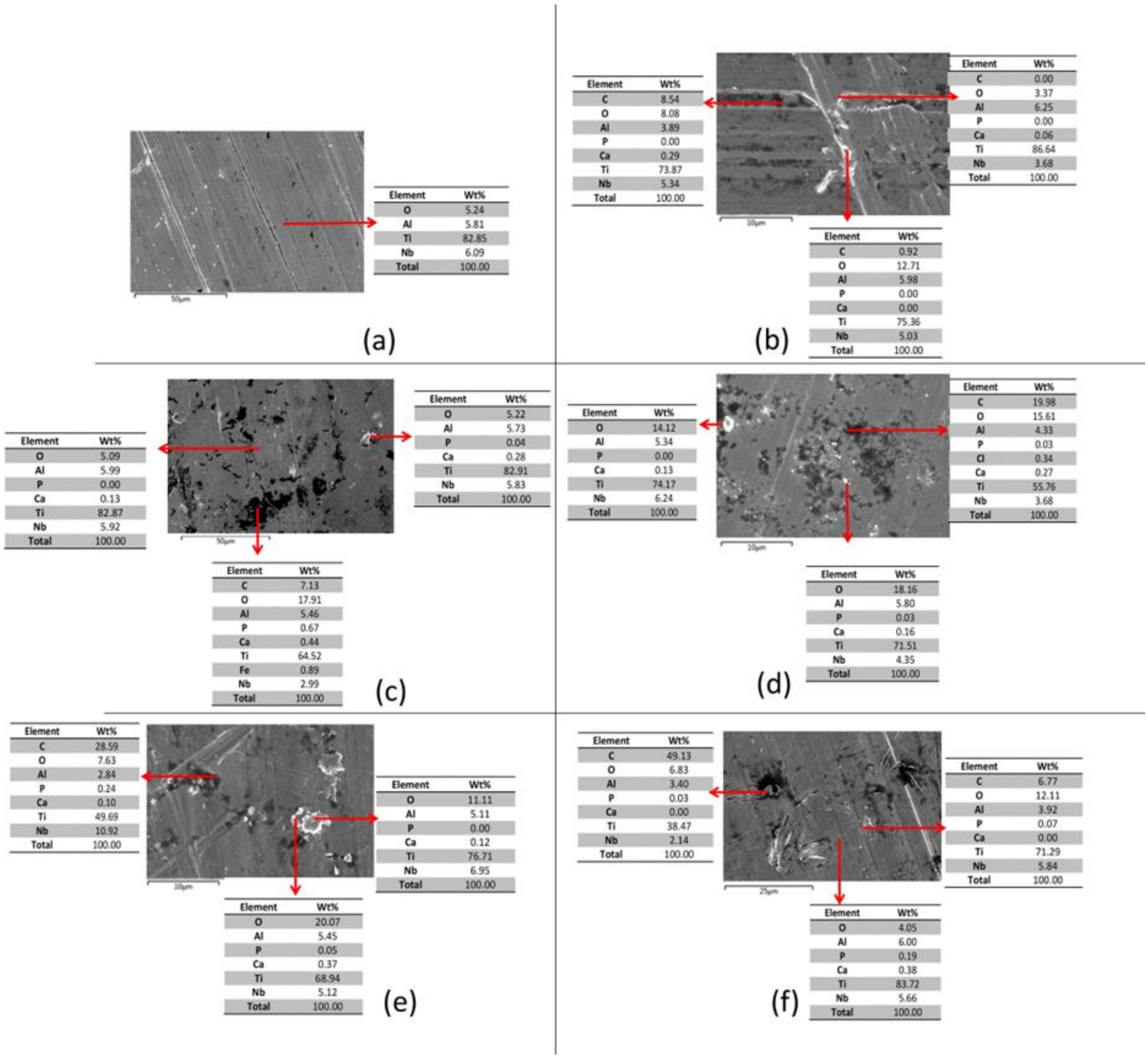

Fig. 2. EDX analysis results from selected areas of the Ti-6Al-7Nb sample surfaces; (a) control sample, (b) sample immersed in SBF for 1day (c) sample immersed in SBF for 7 days, (d) sample immersed in SBF for 14 days, (e) sample immersed in SBF for 21 days, (f) sample immersed in SBF for 30 days.

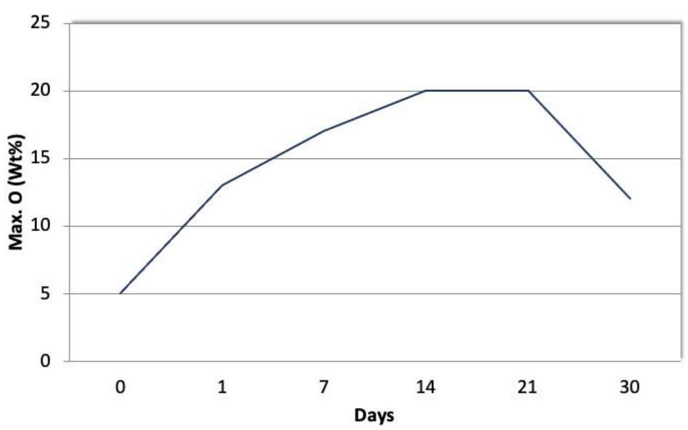

Fig. 3. The maximum O level measured on each sample surface throughout the different immersion periods. (Since the comparisons were based on the max O level observed on each sample, no standard deviation data was provided).

were observed for Al element, only on the 1st day of immersion while the measured Al ion release levels on the other days are much lower than the critically risky values (Sahin et al., 2015).

Although O signal is slightly higher as compared to the control sample on the 1st day of immersion, it can be argued that the oxide layer is not sufficiently protective at this stage. Literature shows that, as the thickness of the oxide layer increases, the potential of crack formation within the oxide layer also increases, inducing higher ion release levels (Toker et al., 2014), which explains the observed result. However, the drastic decrease in the ion release levels and the steady state behavior following this decrease can indicate that oxide layer thickness reaches a protective level past the 1st day of immersion and preserves its protective nature despite the slight fluctuations in thickness over time. Therefore, it can be argued that, for this promising alloy, application of a process to ensure the stability of the oxide layer for the safety during initial interaction with bodily fluids is essential.

The changes in Ca and P levels detected by the EDX analyses were also recorded as a function of time since these observations are indicative for osseointegration which is the ability of bone tissue formation on the implant surface (Toker et al., 2020). Specifically, formation of Ca-P rich structures on the implant surface plays a supporting role in bone tissue formation by providing a surface where bone cells can adhere and multiply

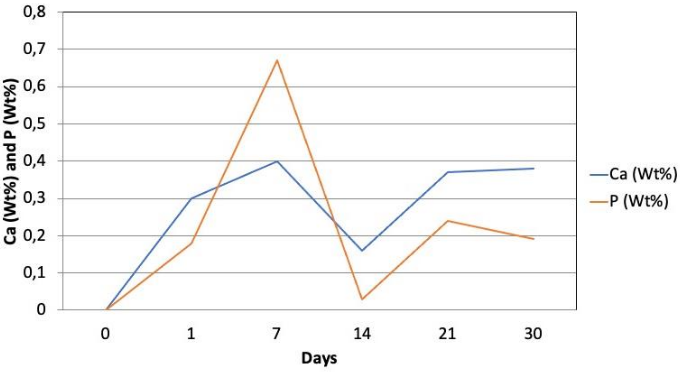

Fig. 4. The maximum Ca and P levels measured on each sample surface throughout the different immersion periods. (Since the comparisons were based on the max Ca and P levels observed on each sample, no standard deviation data was provided).

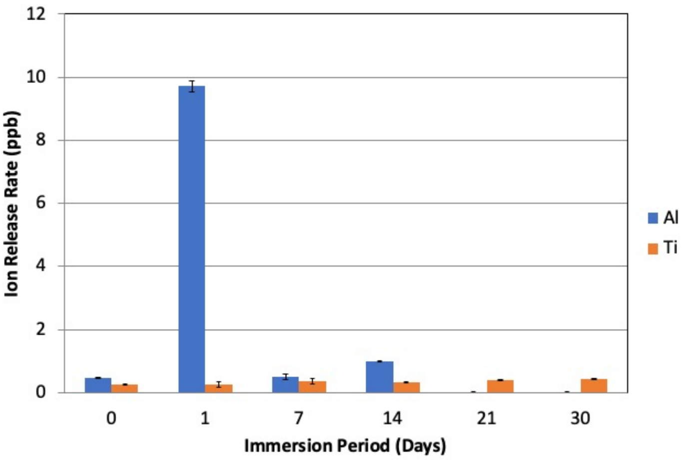

Fig. 5. The Al and Ti ion release levels at each immersion period (ppb: parts per billion). (Average value of the three measurements taken from each sample is provided with the error bar corresponding to the standard deviation).

in a healthy way and therefore play a critical role in terms of the biocompatibility of the implant material (Yilmaz et al., 2014). According to Fig. 4, significant increases are observed in both Ca and P signals from the 1st day up to the 7th day, which is followed by a decrease on the 14th day. Afterwards, both signals re-increase on the 21st day and remain stable until the end of the immersion period of 30 days. This fluctuating behavior of the time dependent Ca-P structure formation on the alloy surface can again be correlated to the dynamic dissolution and reformation cycle in corrosive body fluid environment over time (Toker et al., 2014; Ozdemir et.al, 2023). An important observation for the Ca-P structure formation behavior which exhibits similarity to that of oxide layer formation is the significant increase from the 1st day of immersion up to 7 days. Based on this similarity in the new structure formation over time, it can be suggested without any special surface treatment, bioactivity of the TiAlNb alloy increases and reaches a more optimum level for oxide and Ca-P rich structure formation following initial immersion. Although, this behavior may be considered promising for the overall biocompatibility of the alloy, the high ion release level of Al observed on the 1st day of immersion indicates that a stable layer should be present on the alloy surface prior to implantation. In other words, despite the relatively biocompatible components in this alloy, presence of a protective layer on the implant surface, in addition to the naturally formed passive TiO_2 layer, is still required to prevent Al ion release.

3.2. Determination of biomimetic coating capability in densified SBF

For orthopedic implant materials, usually hydroxyapatite-based coatings are used as protective layers, which also supports the bone formation ability of the implant with its chemical resemblance to the actual bone tissue. Among the commonly applied methods for hydroxyapatite coating, a simple and effective method is biomimetic coating, where the metal surface is subjected to a densified simulated body fluid environment (Yilmaz et al., 2014; Sarikayak et al., 2021).

For the current study, in order to test the biomimetic coating capability of the tested alloys, static immersion procedure was applied in a 3-times densified SBF solution for the immersion periods of 1 and 7 days. The reason 1 and 7 days were selected as biomimetic coating periods was based on the observations of the initial static immersion tests, where significant changes in new product formation occurred between 1 and 7 days. Both the visual observations from the SEM images and the quantitative results from the EDX analyses indicate that, biomimetic coating does not start on the 1st day of immersion (Fig. 6 and Fig. 7).

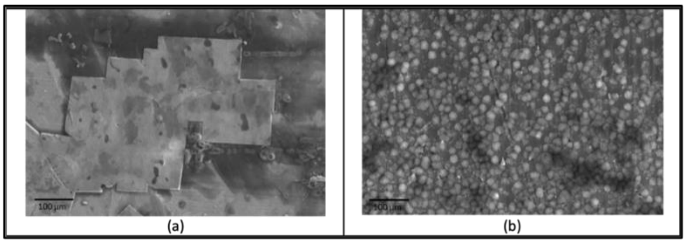

Fig. 6. SEM images of the sample surfaces following immersion in 3X SBF for (a) 1 day and (b) 7 days.

Specifically, following the 1st day of immersion in 3X SBF, formation of salt like precipitates rich in Na are observed, however Ca and P formation does not start yet. It is known that the formation of Na rich structures, specifically sodium titanate structures are favorable for the adhesion of Ca-P based structures (Sarikayak et al., 2021). As expected, Ca-P rich structure formation are prevalent on the alloy surface on the 7th day of immersion. The observed structures are widespread throughout the alloy surface and significant Ca and P signals are detected from these structures (Fig. 6 and Fig. 7). Normally, preliminary surface processing is necessary to achieve such rich Ca-P based structure formation (Hazwani et al., 2022; Wei et al., 2023). These findings indicate that, without any specific surface processing, such as alkaline procedures which are commonly applied prior to biomimetic coating, the TiAlNb alloy surface can be successfully coated with the biomimetic method in 7 days. However, in order to prevent any potential ion release, which may occur on the early stages of implantation, biomimetic coating procedure should be applied following a preliminary surface process such as alkaline treatment.

Overall, the findings of the current study support the opinions regarding the promising biocompatibility of the novel TiAlNb alloy for biomedical applications. However, in order to ensure the safe use of this alloy as orthopedic implant materials, presence of a stable protective layer is required, especially at the early stages of implantation. In that manner, results of the

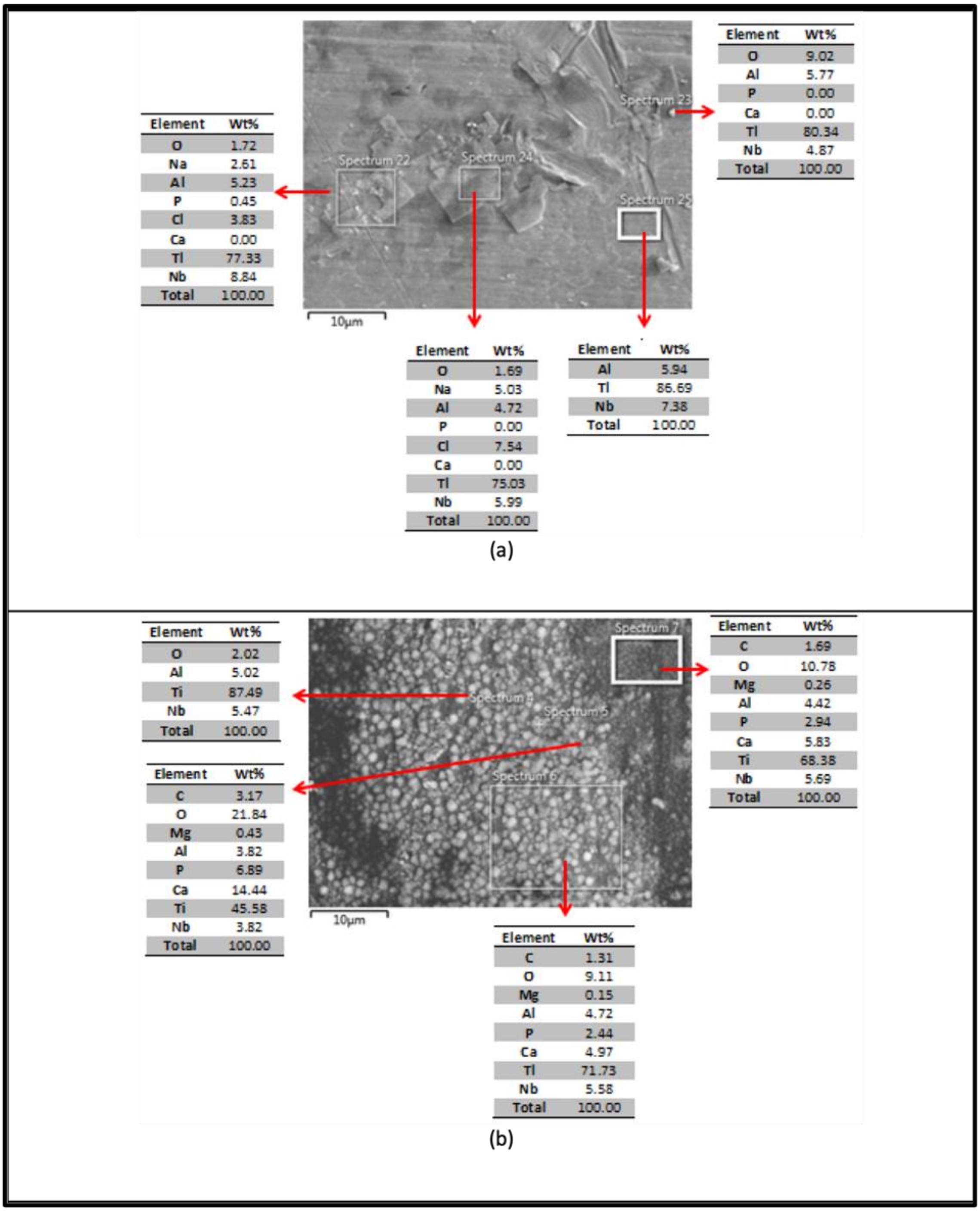

Fig. 7. EDX analysis results from the selected areas of sample surfaces following immersion in 3X SBF for (a) 1 day and (b) 7 days.

biomimetic coating test of this study indicate that, such a layer can be rapidly achieved by biomimetic coating applied a in densified simulated body fluid environment followed by the application of a preliminary surface treatment.

4. Conclusion

In the current study, it was aimed to systematically investigate the *ex situ* biocompatibility of Ti-6Al-7Nb, a promising alloy for biomedical applications. Results of the static immersion experiments conducted in synthetic body fluid environment indicated that even the untreated alloy surface is favorable the formation of Ca-P rich structures, starting from the early periods of immersion which is important for osseointegration. The oxide layer formation-dissolution cycle over time, which is important in terms of affecting ion release, was observed to reach a stable state around the 14th day of immersion. Although majority of the measured ion release levels were much lower than critically toxic or allergic values, the Al ion release level at the 1st day of immersion was above critical levels. This result indicated the need for the presence of a stable protective layer before implantation.

Findings of the static immersion in densified SBF part of the study, which aimed at the testing the biomimetic coating ability of the alloy exhibited that, formation of such a protective layer can be rapidly achieved by biomimetic coating applied in densified SBF environment. As compared to commonly used biomedical alloys whose bioactivity can be enhanced over complex surface treatments, rapid biomimetic capability of the tested TiAlNb alloy is another positive indication for its biocompatibility (Hazwani et al., 2022; Wei et.al., 2023). Overall, the findings *ex situ* biocompatibility tests of the current study indicate that novel TiAlNb alloys are promising materials for biomedical applications, however in order to ensure their safe use in orthopedic implant applications, presence of a stable protective layer is required, prior to implantation.

Conflict of interest: The authors declare that they have no conflict of interests.

Informed consent: The authors declare that this manuscript did not involve human or animal participants and informed consent was not collected.

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