



Titanium Dioxide Nanotubes Incorporated Bioactive Glass Nanocomposites: Synthesis, Characterization, Bioactivity Evaluation and Drug Loading

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ABSTRACT

Nano bioactive glasses are known as suitable alternatives to repair the damaged bone tissues. In this research, novel sol-gel derived bioactive glass composites were synthesized through a reduction in the common weight percent of SiO₂ substituted by 15 wt% of titanium dioxide nanotubes (TNTs) at two different steps by the synthetic procedure. The morphology, crystalline structure, and functional groups of the composites were evaluated through scanning electron microscopy (SEM), X-ray diffraction (XRD) and Fourier transform infrared (FTIR) analyses. Based on the SEM images, the step in which TNTs were added to the solution completely changed the morphology of the composite. Bioactivity tests were carried out by soaking the samples in the simulated body fluid (SBF) at the intervals of 14 and 28 days followed by the investigation of hydroxyapatite (HA) layer formation on the surface of the samples. According to XRD peaks at 2-theta angle of around 31 and 40 degrees, it was found that the presence of titanium dioxide nanotubes improved bioactivity after 14 days of immersion and both 58S-TNT composites were more bioactive than 58S bioglass, while 58S bioactive glass possessed more intense peaks of HA after 28 days of immersion in SBF. Furthermore, the drug loading characteristic of the prepared composites was examined and the results showed that the addition of nanotubes improved the drug loading performance of bioactive composites containing TNTs up to 70% compared to the 58S bioglass with 37% drug loading.

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NOMENCLATURE

°C	Degree celcius	M	Molar concentration
λ	Wavelength	wt%	Weight percent
\$	U.S Dollar	kV	Kilovolt
°	Degree	θ	diffraction angle (in X-Ray Diffraction)

1. INTRODUCTION

Tissue engineering is an interdisciplinary field involving life sciences, medicine, material sciences, and engineering [1]. The development of practical substitutes for damaged tissues is the main purpose of tissue engineering. The global market of tissue engineering and cell therapy was appraised in 2014 at about \$15 billion. Tissue engineering and regenerative medicine solutions can also be used for any tissue, although the levels of complexity of targets are different [2].

Bone tissue engineering is a complex and dynamic process that begins by transferring and utilizing osteogenic cells after proliferation, differentiation, matrix formation, and bone regeneration [3]. As a tissue or a critical organ in the human body, the bone not only plays an essential role in protecting the organs within the body but also causes the stability of the body and provides the mineral reserves of the body [4].

Natural bone is a composite material consisting of organic and mineral substances. Organic substances mainly include collagen fibers that cause bone hardness. In contrast, minerals mainly include calcium and

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phosphorus in the form of hydroxyapatite crystals and, along with them, sodium, potassium, magnesium, fluoride, chlorine, carbonate, and some elements in small quantities such as silicon, strontium, iron, and zinc are the cause of bone strength [5].

Unlike some tissues, the bones have the potential to regenerate and repair against injury. However, when the demand for bone regeneration is more than average potentials, such as extensive bone defects that are caused after trauma, infection, and tumor removal or skeletal abnormalities, bone grafting is required [6]. Bone grafting, which can be used as an autograft [7], allograft [8], or xenograft [9], is applied when a part of the bone is destroyed. It is required to fill the gaps after injuries and accidents or after tumor removal. However, the use of the above methods is limited due to the lack of connective tissues for all patients, as well as the likelihood of recoil by the immune system. There is also the possibility of infection and disease transmission from the donor person to the patient. Bone tissue engineering is looking for methods to replace the damaged bone tissue of the human body by combining the cells of living organisms in an artificial or natural substance. This strategy introduces a good solution for the treatment of diseases and injuries of bone tissue. Alternative materials used in bone tissue engineering can be classified into polymers, including natural and synthetic polymers, ceramics including calcium phosphates and bioactive glasses, metals, and composites [10].

Bioglass is a material with high biocompatibility which has significant osteoconductivity, osteoinductivity, and controllable biodegradability. Bioglass, which is a material with high biocompatibility, remarkable osteoconductivity, significant osteoinductivity, and controllable biodegradability, was originally developed by Larry Hench. In an aqueous environment, this material can form hydroxycarbonate apatite, which is similar to biological minerals, and thus was widely used in the regeneration of bone and tissue engineering [11, 12].

Typically, glass is made through melting or the sol-gel method. In the melting method, the bioactive glass can be obtained by melting a mixture of raw materials and then cooling [13]. The sol-gel method is a wet chemical process for producing materials such as bioactive glass, using materials such as silicate compounds and metal ions. This process mainly involves hydrolysis, condensation of raw materials, drying, and calcination [14, 15]. By controlling the process parameters, it is possible to control properties such as morphology and composition [16]. The results of in vitro and in vivo tests indicate the superiority of sol-gel bioglass to melt-driven bioglass in bioactivity [17]. For the synthesis of bioactive glass by the sol-gel method, mostly, tetraethyl orthosilicate (TEOS) is used as a source of silica. Also, water or ethanol is used as a solvent

[18]. The sol-gel method, according to the catalyst used in synthesis, can be divided into two acid and base catalytic methods that can affect the properties of the resulting materials. Metal ions can be added during the hydrolysis and condensation of tetraethyl orthosilicate, or after the formation of silicon-oxide nanoparticles. After drying and calcination of resulting nanoparticles, the bioactive glass is obtained. For particle shaping or dispersion improvement, it is possible to add other organic material during synthesis to the solution [18].

To ensure the effectiveness and safety of bone tissue substitutes, they should be tested in vitro and in vivo before testing in the human body. To avoid the high cost of in vivo tests, several types of in vitro tests are used to predict the in-vitro bioactivity of bioceramics. The purpose of in vitro bioactivity tests is to select the most appropriate biomaterial to continue its development [19, 20].

Currently, the most common in vitro bioactivity test is the soaking of the ceramics in the simulated body fluid [21]. In this method, the hydroxyapatite layer is formed on the surface of the bioactive material, after immersion in the simulated fluid of the bodies' plasma. Materials that a layer of hydroxyapatite is formed on their surface after immersion in simulated body fluids, but they are not implanted in the body, are known as in vitro bioactive [19]. Simulated body fluid which proposed by Kokubo et al. [22] is an ionic solution, which is similar to human plasma and is fixed in the physiological acidity by Tris Buffer. The formation of a layer of hydroxyapatite on the surface of bioactive glass is a sign of readiness for transplantation into living bone tissue [23]. The composition of the glass, the particle size, and finally their surface area are known as the factors that have the greatest impact on the formation of the hydroxyapatite layer and bone graft [18].

One of the fundamental challenges of implantation is controlling the infection caused by the bacterial load, which can create immune problems and eventually lead to the rejection of the implant [24]. To overcome the implant-related infection and the bacterial load on the implant, an incorporation combination of antibiotic drugs is recommended [25].

However, there are some limitations to the application of common medicinal drugs like toxicity in non-objective tissues, low efficiency, biological distribution, absence of selectivity, and overdose of medication [26]. To overcome these abovementioned restrictions and to reduce the side effects of medications, the local delivery of the drugs to bone tissue was considered as a suitable candidate [27]. Local delivery of medication to the desired tissues not only maintains the healthy cells unaffected but also provides the optimal amount of generally expensive related drugs with no drug dilution throughout the body, which results in bioavailability optimization of drugs [28].

The fabrication of nanostructures with physical properties such as pore size, pore volume and suitable surface area will improve the adsorption of guest particles such as drugs on the nanostructures [29]. Tetracycline (TC) is an effective antibiotic that is widely used in the treatment of infectious diseases. There is a very high tendency for TC towards calcified tissues like bone and teeth [30].

To enhance the bioactivity of bioactive glasses, some groups of researchers impregnated various types of metal oxides such as TiO_2 . To do this, different sources of titanium were substituted for one of the common constituents of bioactive glass ($\text{SiO}_2\text{-CaO-P}_2\text{O}_5$). In most cases, researchers used Tetrabutyl Titanate as the Ti precursor and fabricated quaternary bioactive glasses without the direct utilization of TiO_2 particles [31, 32]. During the last decades, it has been proven that titania nanotubes (TNT) have desirable properties such as biocompatibility, high surface area, controllable pores size, chemical stability, mechanical strength, excellent accretion to bone tissue, and ability to promote hydroxyapatite growth [33, 34]. To the best of our knowledge, no research reported the application of titanium oxide nanoparticles directly in the common structure of 58S bioactive glass by decreasing the weight percent of SiO_2 .

In this study, the 58S bioactive glass and a novel bioactive glass, which is synthesized by using TiO_2 nanotubes as one of the raw materials in the synthesis of bioglass, were produced by the sol-gel method. Furthermore, functional groups, phase structures, and bioactivity of samples, as well as tetracycline loading on the glasses, were investigated.

2. EXPERIMENTAL

2.1. Materials The chemicals used in this study was tetraethyl orthosilicate (TEOS) as Si source, triethyl phosphate (TEP) as a P source, nitric acid (HNO_3) (70%), ammonia (NH_4OH) (25%), and ethanol ($\text{C}_2\text{H}_5\text{OH}$) were purchased from Merck (Germany), and calcium nitrate tetrahydrate ($\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$) as Ca source was supplied from Carlo Erba, Spain. TiO_2 nanotubes (TNT) were purchased from Day Petronic Company (Iran), and tetracycline hydrochloride was purchased from Razak Laboratory Company (Iran).

2.2. Glass Preparation The 58S bioactive glass was prepared by a quick alkali-mediated sol-gel method as described in a previous publication [35, 36]. Briefly, 21.6 ml of tetraethyl orthosilicate, 13.9 ml of deionized water, and 2.8 ml of nitric acid were dissolved in 50 ml of ethanol. This solution was stirred at room temperature for 30 minutes to complete the hydrolysis of tetraethyl orthosilicate. After this stage, 2.2 ml of triethyl phosphate

was added to the previous solution and stirred for 20 minutes. Next, 14.04 g of calcium-nitrate was added to the solution and stirred for 20 minutes. The 2 M ammonia solution was then added dropwise to the solution, so that the viscosity of the solution increased slowly, and the solution became a gel. Ammonia was used as an accelerating agent in the gelation process. The resulting gel was then placed in an oven at 60°C for one day for drying the gel and evaporating the alcoholic and water compounds, and the gel was obtained in a powder form. Subsequently, The resulting powder was placed in a furnace with a temperature of 600°C for 2 hours at the $3^\circ\text{C}/\text{min}$ to remove its nitrate compounds (sample code: 58S).

For the synthesis of novel modified bioactive glass with titanium dioxide nanotubes, the synthesis method was similar to the 58S biglass synthesis, while 15 wt% of titanium dioxide nanotubes were incorporated into the solution by reducing the weight percent of SiO_2 . In other words, the amount of used TEOS was reduced to 16.02 ml and instead, 0.755 g of titanium dioxide nanotube was added to the solution. Moreover, for better evaluation of the TNTs role in the modified bioactive glasses, TNTs were added to the solution in two different steps:

1. after hydrolysis step of TEOS (sample code: 58S-15TNT);
2. before ammonia solution addition (sample code: 58S-TNT15).

The weight percent composition of the synthesized nanocomposites as well as the nanotube addition step are presented in Table 1.

2.3. Characterization The X-ray diffraction (XRD) analysis of powdered bioactive glasses was performed on Inel EQUINOX 3000 diffractometer using $\text{CuK}\alpha$ radiation ($\lambda = 1.54$) with 0.032 step size over a range of $20 < 2\theta < 60$. The Fourier transform infrared spectroscopy (FT-IR) absorption spectra of the samples were recorded with an ABB Bomem MB Series spectrometer at room temperature in the $400\text{-}4000\text{ cm}^{-1}$ range with a resolution of 4 cm^{-1} and 25 scans per minute. The morphologies of prepared samples were investigated using KYKY EM3200 scanning electron microscope (SEM) operating at the accelerating voltage of 30 kV. Before SEM analysis, the samples were covered with gold.

TABLE 1. Compositions of bioactive nanocomposites

	SiO_2	TiO_2	CaO	P_2O_5
58S	58	-	33	9
58S-15TNT	43	15	33	9
58S-TNT15	43	15	33	9

2. 4. Bioactivity Evaluation

The *in vitro* bioactivity of samples was investigated by immersion of the samples in the simulated body fluid (SBF). The composition of the simulated body fluid is according to the method proposed by Kokubo et al. [22]. Powders were immersed in the simulated body fluid and were placed in an incubator at 37 °C for 14 and 28 days. The mass of powder per volume of SBF was 25 mg/ml. Also, to maintain the concentration of ions in the solution, the previous solution was replaced by the fresh simulated body fluid. Finally, the powders were dried in an oven at 60 °C and then were analyzed by XRD, FTIR, and SEM.

2. 5. Drug Loading

Drug loading analysis was carried out using the immersion of samples in the drug solution. Initially, 2000 mg/ml drug solution was prepared by mixing of tetracycline hydrochloride and deionized water for 5 minutes. The bioglass powders were added to the drug solution with 10 mg/ml concentration and stirred at room temperature for one day using a magnetic stirrer. Afterward, the absorbance of the dissolved solution was determined by Unico 2100 UV-Vis spectrometer at 383 nm [37] after the solution was centrifugated. Using the calibration curve, the concentration of the soluble drug was calculated after the loading process. This concentration is related to the residual drug in the loading solution, and the decrease in the drug concentration is assigned to the drug adsorption by the bioglass powders.

The calibration curve of Tetracycline concentration was determined at room temperature by plotting absorbance versus different concentrations of tetracycline hydrochloride solution including 18.75, 37.5, 50, 75, 100, 125, 150, 200 ppm. The calibration curve was obtained based on the Lambert-Beer's law.

3. RESULTS AND DISCUSSION

3. 1. Phase Structure Analysis

Figure 1 shows the scanning electron microscopy (SEM) images of the prepared samples. As shown in the SEM picture of 58S bioactive glass, this synthesized material possessed spherical nanoparticles, while the addition of titanium dioxide had a significant effect on the morphology of the composites. Moreover, the step in which titanium dioxide nanotubes were added to the solution completely changed the composite morphology. In other words, the SEM picture of 58S-15TNT composite shows that titanium dioxide nanotubes were impregnated through the composite surface with no considerable spherical particles, while the 58S-TNT15 SEM image displays that needle-like titanium dioxide nanotubes were formed on the spherical bioactive glass composite.

XRD patterns for 58S, 58S-15TNT, and 58S-TNT15 samples are shown in Figure 2. There are no obvious

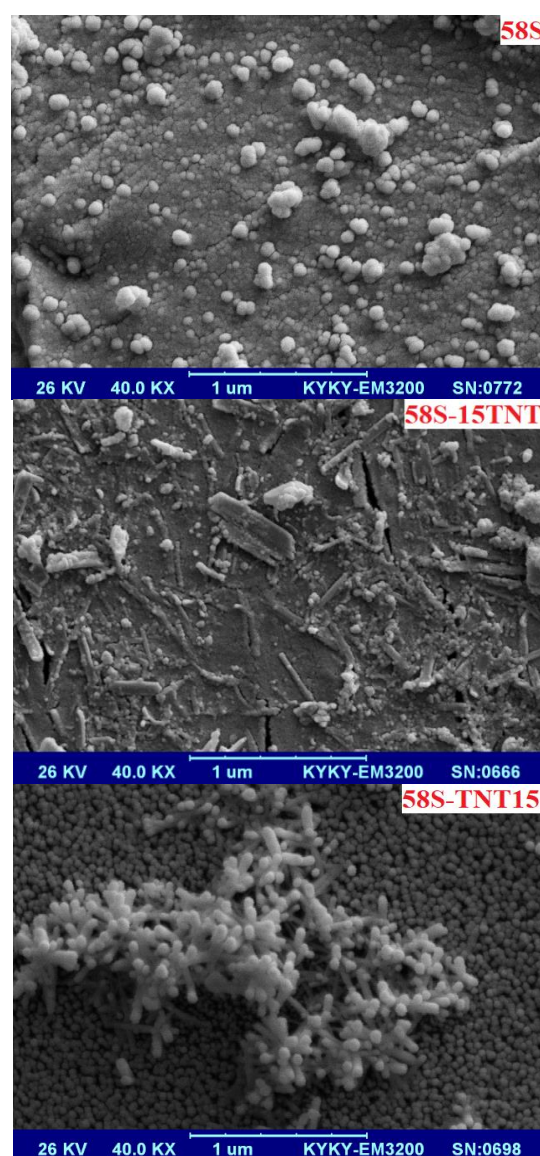


Figure 1. SEM images of 58S, 58S-15TNT, and 58S-TNT15

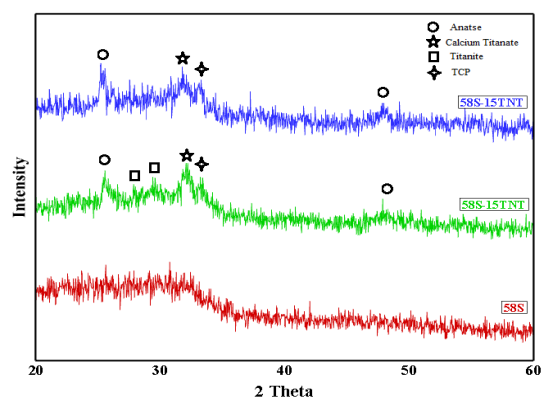


Figure 2. XRD spectra of 58S, 58S-15TNT, and 58S-TNT15

peaks in the 58S XRD pattern, which indicates that this bioglass was amorphous. By incorporation of titanium dioxide nanotubes in the bioactive composites, two characteristic peaks of this material appeared at approximate angles of 25° and 48° , which represents the presence of anatase TiO_2 . The peak appeared at an approximate angle of 34° may be due to tricalcium phosphate [38]. A peak created around an angle of 32.5° , is related to the formation of calcium titanate phase.

Also, two peaks shown at about angles of 27° and 29° correspond to the titanite [39, 40]. The formation of these new compounds can be attributed to the reaction of titanium dioxide nanotubes with functional groups of bioactive glass. As shown in this figure, the 58S-TNT15 XRD pattern has stronger TiO_2 peaks compared to that of 58S-15TNT. This may be due to the weaker interaction between TNTs and the functional groups involved in the synthesis of 58S-15TNT biocomposite due to the step of TNTs addition. In addition, the lack of calcium titanium silicate phase in the XRD pattern of the 58S-TNT15 sample confirms this finding.

Figure 3 shows the FTIR absorption spectra of the 58S, 58S-15TNT, and 58S-TNT15 bioglasses. The band at 468 cm^{-1} is attributed to Si-O-Si bending vibration, while the peak at 1099 cm^{-1} is ascribed to Si-O-Si asymmetric stretching vibration [41]. Due to the addition of TNTs, a band appeared at around 940 cm^{-1} , which can be assigned to Si-O stretching vibration in Si-O-Ti groups [42].

3. 2. In Vitro Bioactivity Figure 4 shows XRD patterns of 58S, 58S-15TNT, and 58S-TNT15 samples after immersion in SBF for 14 and 28 days. Two weak peaks observed at approximate angles of 31.5° and 40° in 58S XRD pattern indicates the onset of hydroxyapatite formation after 14 days of immersion [43]. At an around angle of 35° , a new peak was generated that may be due to the formation of tricalcium phosphate [38].

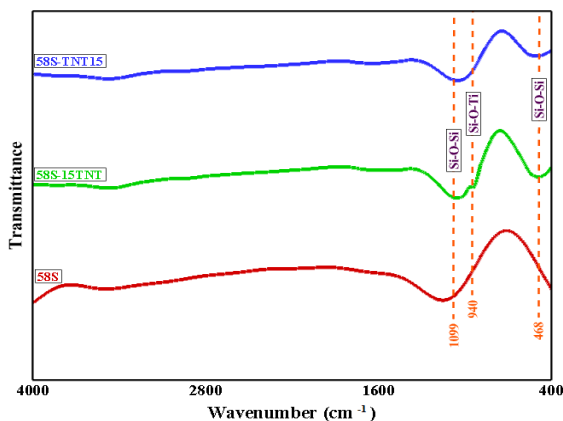


Figure 3. FTIR spectra of 58S, 58S-15TNT, and 58S-TNT15

Furthermore, the peak observed for all samples at an about angle of 30° can be assigned to wollastonite formation [44].

Due to the increase in the number of peaks related to hydroxyapatite as well as their intensity after 28 days of immersion in SBF compared to 14 days, it can be concluded that increasing the soaking time enhanced the formation of hydroxyapatite and subsequently the bioactivity of samples. Furthermore, based on the intensity of hydroxyapatite peaks at 31.5° and 40° shown in the XRD patterns of composites containing titanium dioxide nanotubes, it can be understood that the presence of titanium dioxide nanotubes improved the bioactivity after 14 days of immersion and both 58S-TNT composites were more bioactive than 58S bioglass. Although the 58S-15TNT sample was the more bioactive sample after 14 days of soaking in SBF, 58S bioactive glass possessed more intense peaks of HA after 28 days of immersion in SBF.

Figure 5 shows the FTIR absorption spectra of the 58S, 58S-15TNT, and 58S-TNT15 composites after 14 and 28 days of immersion in SBF. The peaks at 567 cm^{-1} and 604 cm^{-1} can be assigned to the bending mode of the O-P-O bond [43]. Another peak that appeared at 961

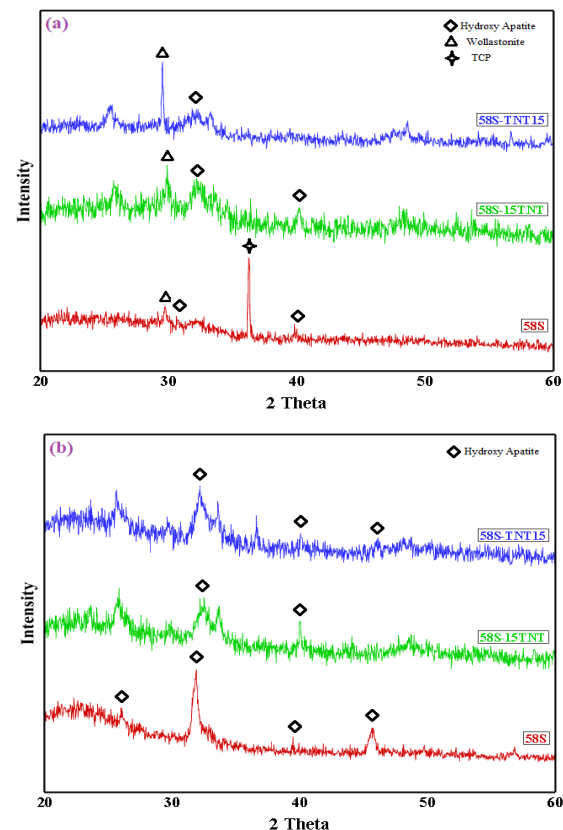


Figure 4. XRD patterns of 58S, 58S-15TNT, and 58S-TNT15 samples after a) 14 and b) 28 days of immersion in SBF

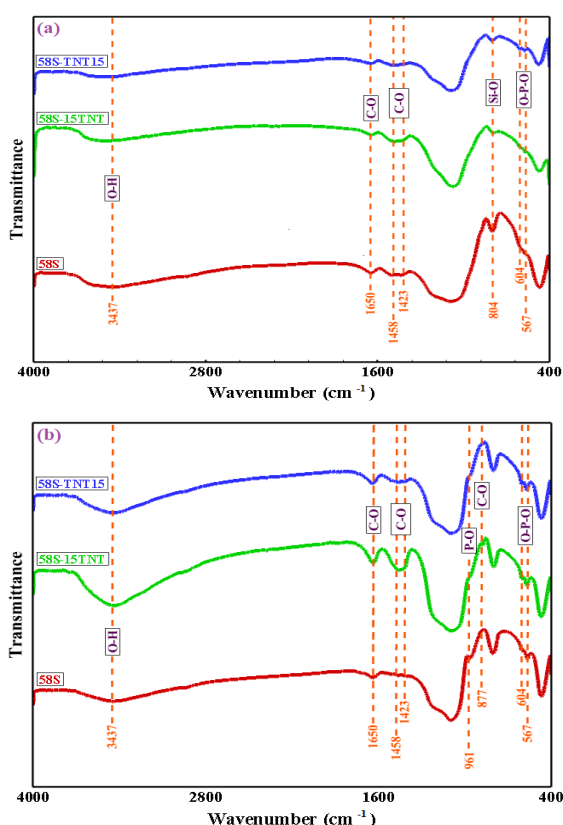


Figure 5. FTIR spectra of 58S, 58S-15TNT, and 58S-TNT15 samples after a) 14 and b) 28 days of immersion in SBF

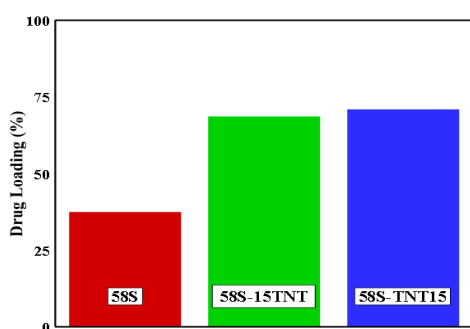


Figure 6. TC loading capacity on of 58S, 58S-15TNT, and 58S-TNT15 samples

cm^{-1} is attributed to the symmetric stretching mode of the P-O bond of the phosphate group [43]. The peak that appeared at 877 cm^{-1} corresponds to the symmetric vibrational.

C-O [45]. A new peak appeared at 961 cm^{-1} is assigned to P-O stretching vibration. The peak at 1650 cm^{-1} can be ascribed to the vibration of CO_3^{2-} and the twin peaks located at 1423 cm^{-1} and 1458 cm^{-1} can be

attributed to C-O asymmetric stretching vibration due to the presence of CO_3^{2-} in site PO_4^{3-} [43, 46]. The peak at 3437 cm^{-1} could be ascribed to O-H bond [47].

According to the peaks shown in the FTIR spectra of the composite containing titanium dioxide nanotubes, it can be perceived that the intensity of peaks present in the FTIR spectrum of 58S-15TNT is higher than that of the 58S-TNT15 sample, which again confirms better bioactivity of 58S-15TNT.

3. 3. Drug Loading The drug loading performance of each sample is shown in Figure 6. As shown in this bar chart, with an addition of the TNT to the structure of 58 base bioglass, the drug loading capacity of samples increased more than 2 times. The dominant mechanism of drug loading on the bioactive nanocomposites is adsorption in which the active sites of the composites are occupied by tetracycline particles during the process [48]. The composites containing titanium dioxide nanotubes showed a higher value of tetracycline loading compared to 58S bioactive glass due to a better adsorption capacity of TNTs present in the matrix of nanocomposites [49]. The slightly better performance of 58S-TNT15 in comparison with 58S-15TNT may be attributed to its higher surface area due to the presence of needle-like titanium dioxide nanotubes formed on the spherical bioactive glass composite as shown in the SEM picture of the final product.

3. 4. Comparison of the Results As described in this study, navel nano bioactive nanocomposites were synthesized by the incorporation of titanium dioxide nanotubes into the bioglass structure. As mentioned in the introduction section, The literature review in this area shows that no research reported the direct substitution of SiO_2 with titanium dioxide nanotubes in the bioglass composition. Based on the results obtained in this study, it is clear that the presence of titanium dioxide nanotubes resulted in better bioactivity of samples after 14 days of soaking in the SBF solution compared to 58S bioglass. However, Ni et al. [30] investigated the effect of adding TiO_2 to a bioactive glass compound. They reported that the addition of TiO_2 reduced the rate of hydroxyapatite formation, but this effect diminished in a long time and did not affect the growth of the apatite layer after long periods of soaking. Moreover, Heidari et al. [32] assessed the replacement of CaO with TiO_2 in 45S5 bioactive glass synthesized by sol-method. They reported that despite the slowdown of hydroxyapatite formation in the early days in titanium-containing samples, the bioactivity results were almost the same over the 14 days. Therefore, it is worth mentioning that direct utilization of titanium dioxide nanotubes as a titanium precursor, applied in this study, was more effective in increasing the bioactivity of the composites than other titanium sources such as Tetrabutyl Titanate used by other researchers.

4. CONCLUSION

In this study, novel sol-gel derived modified bioactive glasses incorporated by titanium dioxide nanotubes were synthesized by reducing the amount of SiO₂ present in the structure of common 58S. According to the SEM images of the modified bioglasses, it was found that the addition of TiO₂ nanotubes caused a change in the morphology of samples and also new crystalline phases such as titanite (CaTiSiO₅) and calcium titanate (CaTiO₃) were generated. Comparing XRD and FTIR patterns of the modified samples before and after in vitro bioactivity tests revealed that the hydroxyapatite was formed on both composites containing titanium dioxide nanotubes. However, there was a decrease in the bioactivity behavior of the modified bioglasses compared to 58S base bioglass after 28 days of immersion in simulated body fluid. Moreover, the 58S-15TNT composite showed better bioactivity than the 58S-TNT15 sample after 28 days of soaking in SBF. The results of drug loading on the modified bioglasses also indicated that the presence of titanium dioxide nanotubes in the structure of bioactive composites was effective and these composites possessed better drug loading performance due to an increase in the tetracycline loading. Therefore, TNT incorporated bioactive composites have the potential for extensive research in the regeneration of bone defects and local drug delivery.

5. REFERENCES

- Chiu, L. L. Y., Chu, Z., Radisic, M., Mozafari, M., "Tissue Engineering, Reference Module in Materials Science and Materials Engineering", Elsevier, (2017).
- Hasan, A., "Tissue Engineering for Artificial Organs: Regenerative Medicine, Smart Diagnostics and Personalized Medicine", Vol. 2, Wiley, Weinheim, (2017).
- T. Gong, J. Xie, J. Liao, T. Zhang, S. Lin, Y. Lin, "Nanomaterials and bone regeneration", *Bone Research*, Vol. 3, (2015), 1-7. doi: [10.1038/boneres.2015.29](https://doi.org/10.1038/boneres.2015.29)
- Maksimkin, A.V., Senatov, F.S., Anisimova, N.Y., Kiselevskiy, M.V., Zalepugin, D.Y., Chernyshova, I.V., Tilkunova, N.A. and Kaloshkin, S.D., "Multilayer porous UHMWPE scaffolds for bone defects replacement", *Materials Science and Engineering: C*, Vol. 73, (2017), 366-372. doi: [10.1016/j.msec.2016.12.104](https://doi.org/10.1016/j.msec.2016.12.104)
- Gao, C., Peng, S., Feng, P. and Shuai, C., "Bone biomaterials and interactions with stem cells", *Bone Research*, Vol. 5, (2017), 1-33. doi: [10.1038/boneres.2017.59](https://doi.org/10.1038/boneres.2017.59)
- Kim, T., See, C.W., Li, X. and Zhu, D., "Orthopedic implants and devices for bone fractures and defects: Past, present and perspective", *Engineered Regeneration*, Vol. 1, (2020), 6-18. doi: [10.1016/j.engreg.2020.05.003](https://doi.org/10.1016/j.engreg.2020.05.003)
- Shin, S. Y., Rios, H. F. Giannobile, W. V., Oh, T. -J., "Stem Cell Biology and Tissue Engineering in Dental Sciences", in: Vishwakarma, A., Sharpe, P., Shi, S., Ramalingam, M. (Ed.), Academic Press, Boston, (2015), 459-469, (Chapter 36).
- Yoshida, R., Baron, S., Rodner, C. and Ferreira, J., "Biologics in Orthopaedic Surgery", in: Mazzocca, A. D., Lindsay A. D. (Ed.), Elsevier, Philadelphia, (2019), 135-139, (Chapter 13).
- Shibuya, N. and Jupiter, D.C., "Bone graft substitute: Allograft and xenograft", *Clinics in Podiatric Medicine and Surgery*, Vol. 32, No. 1, (2015), 21-34. doi: [10.1016/j.cpm.2014.09.011](https://doi.org/10.1016/j.cpm.2014.09.011)
- Nikolova, M.P. and Chavali, M.S., "Recent advances in biomaterials for 3D scaffolds: A review", *Bioactive Materials*, Vol. 4, (2019), 271-292. doi: [10.1016/j.bioactmat.2019.10.005](https://doi.org/10.1016/j.bioactmat.2019.10.005)
- Diaz-Rodriguez, P., Sánchez, M. and Landin, M., "Drug-loaded biomimetic ceramics for tissue engineering", *Pharmaceutics*, Vol. 10, No. 4, (2018), 272. doi: [10.3390/pharmaceutics10040272](https://doi.org/10.3390/pharmaceutics10040272)
- Bargavi, P., Ramya, R., Chitra, S., Vijayakumari, S., Riju Chandran, R., Durgalakshmi, D., Rajashree, P. and Balakumar, S., "Bioactive, degradable and multi-functional three-dimensional membranous scaffolds of bioglass and alginate composites for tissue regenerative applications", *Biomaterials Science*, Vol. 8, No. 14, (2020), 4003-4025. doi: [10.1039/D0BM00714E](https://doi.org/10.1039/D0BM00714E)
- Kaur, G., Pickrell, G., Sriranganathan, N., Kumar, V. and Homa, D., "Review and the state of the art: Sol-gel and melt quenched bioactive glasses for tissue engineering", *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, Vol. 104, No. 6, (2016), 1248-1275. doi: [10.1002/jbm.b.33443](https://doi.org/10.1002/jbm.b.33443)
- Rabiee, S.M., Nazparvar, N., Azizian, M., Vashae, D. and Tayebi, L., "Effect of ion substitution on properties of bioactive glasses: A review", *Ceramics International*, Vol. 41, No. 6, (2015), 7241-7251. doi: [10.1016/j.ceramint.2015.02.140](https://doi.org/10.1016/j.ceramint.2015.02.140)
- Derhambakhsh, M., Novinrooz, J. and Tohidi, S.H., "Preparation and study of molecular structure of copper ions doped in a silica xerogel matrix", *International Journal of Engineering, Transactions A: Basics*, Vol. 19, No. 1, (2006), 53-60.
- Zheng, K. and Boccaccini, A.R., "Sol-gel processing of bioactive glass nanoparticles: A review", *Adv Colloid Interface Sci*, Vol. 249, (2017), 363-373. doi: [10.1016/j.cis.2017.03.008](https://doi.org/10.1016/j.cis.2017.03.008)
- Nabian, N., Delavar, M., Rabiee, S.M. and Jahanshahi, M., "Quenched/unquenched nano bioactive glass-ceramics: Synthesis and in vitro bioactivity evaluation in ringer's solution with BSA", *Chemical Industry and Chemical Engineering Quarterly*, Vol. 19, No. 2, (2013), 231-239. doi: [10.2298/CICEQ120323057N](https://doi.org/10.2298/CICEQ120323057N)
- Vichery, C. and Nedelec, J.-M., "Bioactive glass nanoparticles: From synthesis to materials design for biomedical applications", *Materials*, Vol. 9, No. 4, (2016), 288. doi: [10.3390/ma9040288](https://doi.org/10.3390/ma9040288)
- Salinas, A.J. and Vallet-Regí, M., "Bioactive ceramics: From bone grafts to tissue engineering", *RSC Advances*, Vol. 3, No. 28, (2013), 11116-11131. doi: [10.1039/C3RA00166K](https://doi.org/10.1039/C3RA00166K)
- Wu, C. and Xiao, Y., "Article commentary: Evaluation of the in vitro bioactivity of bioceramics", *Bone and Tissue Regeneration Insights*, Vol. 2, (2009), 25-29. doi: [10.4137/BTRL.S3188](https://doi.org/10.4137/BTRL.S3188)
- Saebnoori, e. and vali, I., "Surface activation of niti alloy by using electrochemical process for biomimetic deposition of hydroxyapatite coating", *International Journal of Engineering, Transactions A: Basics*, Vol. 27, No. 10, (2014), 1627-1634. doi: [10.5829/idosi.ije.2014.27.10a.17](https://doi.org/10.5829/idosi.ije.2014.27.10a.17)
- Kokubo, T. and Takadama, H., "How useful is SBF in predicting in vivo bone bioactivity?", *Biomaterials*, Vol. 27, No. 15, (2006), 2907-2915. doi: [10.1016/j.biomaterials.2006.01.017](https://doi.org/10.1016/j.biomaterials.2006.01.017)
- Sorrell, C.C., Saeri, M.R., Ehsani, N., Afshar, A. and Ghorbani, M., "Interface characterization of plasma sprayed hydroxyapatite coat on Ti 6Al 4V ", *International Journal of Engineering, Transactions B: Applications*, Vol. 15, No. 2, (2002), 173-182.
- Abbaspour, S. and Sadmezhaad, S.K., "Loading drug on nanostructured Ti6Al4V-HA for implant applications", *International Journal of Engineering, Transactions B: Applications*, Vol. 31, No. 8, (2018), 1159-1165. doi: [10.5829/ije.2018.31.08b.01](https://doi.org/10.5829/ije.2018.31.08b.01)
- Turkyilmaz, I., "Current concepts in dental implantology, IntechOpen, (2015).

26. Rubiana, M.M. and Luciano, P.S., "Drug delivery systems: Past, present, and future", *Current Drug Targets*, Vol. 5, No. 5, (2004), 449-455. doi: [10.2174/1389450043345407](https://doi.org/10.2174/1389450043345407)
27. Porter, J.R., Ruckh, T.T. and Popat, K.C., "Bone tissue engineering: A review in bone biomimetics and drug delivery strategies", *Biotechnology Progress*, Vol. 25, No. 6, (2009), 1539-1560. doi: [10.1002/btpr.246](https://doi.org/10.1002/btpr.246)
28. Wu, P. and Grainger, D.W., "Drug/device combinations for local drug therapies and infection prophylaxis", *Biomaterials*, Vol. 27, No. 11, (2006), 2450-2467. doi: [10.1016/j.biomaterials.2005.11.031](https://doi.org/10.1016/j.biomaterials.2005.11.031)
29. Bavnhøj, C.G., Knopp, M.M., Madsen, C.M. and Löbmann, K., "The role interplay between mesoporous silica pore volume and surface area and their effect on drug loading capacity", *International Journal of Pharmaceutics: X*, Vol. 1, (2019), 100008. doi: [10.1016/j.ijpx.2019.100008](https://doi.org/10.1016/j.ijpx.2019.100008)
40. Seok, H., Kim, S.-G., Kweon, H., Jo, Y.-Y., Lee, K.-G., Kang, T.Y., Chae, W.-S., Min, S.-K., Ahn, J.-H., Park, J.-W. and Choi, D.-J., "Comparison of different concentrations of tetracycline-loaded silk fibroin membranes on the guided bone regeneration in the rat calvarial defect model", *Tissue Engineering and Regenerative Medicine*, Vol. 11, No. 6, (2014), 476-482. doi: [10.1007/s13770-014-9057-3](https://doi.org/10.1007/s13770-014-9057-3)
31. Ni, S., Du, R. and Ni, S., "The influence of Na and Ti on the in vitro degradation and bioactivity in 58S sol-gel bioactive glass", *Advances in Materials Science and Engineering*, Vol. 2012, No., (2012), 730810. doi: [10.1155/2012/730810](https://doi.org/10.1155/2012/730810)
32. Heidari, S., Hooshmand, T., Yekta, B.E., Tarlani, A., Noshiri, N. and Tahri, M., "Effect of addition of titanium on structural, mechanical and biological properties of 45S5 glass-ceramic", *Ceramics International*, Vol. 44, No. 10, (2018), 11682-11692. doi: [10.1016/j.ceramint.2018.03.245](https://doi.org/10.1016/j.ceramint.2018.03.245)
33. Aw, M.S., Khalid, K.A., Gulati, K., Atkins, G.J., Pivonka, P., Findlay, D.M. and Losic, D., "Characterization of drug-release kinetics in trabecular bone from titania nanotube implants", *International Journal of Nanomedicine*, Vol. 7, (2012), 4883-4892. doi: [10.2147/IJN.S33655](https://doi.org/10.2147/IJN.S33655)
34. Hassanzadeh Nemati, N., Ghasempour, E. and Zamanian, A., "Effect of dual releasing of β -glycerophosphate and dexamethasone from Ti nanostructured surface for using in orthopedic applications", *International Journal of Engineering, Transactions A: Basics*, Vol. 32, No. 10, (2019), 1337-1344. doi: [10.5829/ije.2019.32.10a.01](https://doi.org/10.5829/ije.2019.32.10a.01)
35. Xia, W. and Chang, J., "Preparation and characterization of nano-bioactive-glasses (NBG) by a quick alkali-mediated sol-gel method", *Materials Letters*, Vol. 61, No. 14, (2007), 3251-3253. doi: [10.1016/j.matlet.2006.11.048](https://doi.org/10.1016/j.matlet.2006.11.048)
36. Taghian Dehaghani, M. and Ahmadian, M., "Fracture mechanism of CoCrMo porous nano-composite prepared by powder metallurgy route", *International Journal of Engineering, Transactions A: Basics*, Vol. 31, No. 1, (2018), 19-24. doi: [10.5829/ije.2018.31.01a.03](https://doi.org/10.5829/ije.2018.31.01a.03)
37. Andrade, A.L., Souza, D.M., Vasconcellos, W.A., Ferreira, R.V. and Domingues, R.Z., "Tetracycline and/or hydrocortisone incorporation and release by bioactive glasses compounds", *Journal of Non-Crystalline Solids*, Vol. 355, No. 13, (2009), 811-816. doi: [10.1016/j.jnoncrsol.2009.01.015](https://doi.org/10.1016/j.jnoncrsol.2009.01.015)
38. Gallinetti, S., Canal, C., Ginebra, M.-P. and Ferreira, J., "Development and characterization of biphasic hydroxyapatite/ β -TCP cements", *Journal of the American Ceramic Society. American Ceramic Society*, Vol. 97, No. 4, (2014), 1065-1073. doi: [10.1111/jace.12861](https://doi.org/10.1111/jace.12861)
39. Hu, W., Liu, H., Hao, H., Yao, Z., Cao, M., Wang, Z. and Song, Z., "Influence of TiO₂ additive on the microwave dielectric properties of α -CaSiO₃-Al₂O₃ ceramics", *Ceramics International*, Vol. 41, (2015), 510-514. doi: [10.1016/j.ceramint.2015.03.138](https://doi.org/10.1016/j.ceramint.2015.03.138)
40. Zhu, W., Jiang, H., Sun, S., Jia, S. and Liu, Y., "Effect of TiO₂ content on the crystallization behavior and properties of CaO-Al₂O₃-SiO₂ glass ceramic fillers for high temperature joining application", *Journal of Alloys and Compounds*, Vol. 732, (2018), 141-148. doi: [10.1016/j.jallcom.2017.10.166](https://doi.org/10.1016/j.jallcom.2017.10.166)
41. Letaief, N., Lucas-Girot, A., Oudadesse, H., Dorbez-Sridi, R. and Boullay, P., "Investigation of the surfactant type effect on characteristics and bioactivity of new mesoporous bioactive glass in the ternary system SiO₂-CaO-P₂O₅: Structural, textural and reactivity studies", *Microporous and Mesoporous Materials*, Vol. 195, (2014), 102-111. doi: [10.1016/j.micromeso.2014.03.035](https://doi.org/10.1016/j.micromeso.2014.03.035)
42. Taloş, F., Senilä, M., Frentiu, T. and Simon, S., "Effect of titanium ions on the ion release rate and uptake at the interface of silica based Xerogels with simulated body fluid", *Corrosion Science*, Vol. 72, (2013), 41-46. doi: [10.1016/j.corsci.2013.03.003](https://doi.org/10.1016/j.corsci.2013.03.003)
43. Mezahi, F.Z., Oudadesse, H., Harabi, A., Lucas-Girot, A., Le Gal, Y., Chaair, H. and Cathelineau, G., "Dissolution kinetic and structural behaviour of natural Hydroxyapatite vs. Thermal treatment", *Journal of Thermal Analysis and Calorimetry*, Vol. 95, No. 1, (2008), 21-29. doi: [10.1007/s10973-008-9065-4](https://doi.org/10.1007/s10973-008-9065-4)
44. Mokhtari, H., Ghasemi, Z., Kharaziha, M., Karimzadeh, F. and Alihosseini, F., "Chitosan-58S bioactive glass nanocomposite coatings on TiO₂ nanotube: Structural and biological properties", *Applied Surface Science*, Vol. 441, (2018), 138-149. doi: [10.1016/j.apsusc.2018.01.314](https://doi.org/10.1016/j.apsusc.2018.01.314)
45. Sossa, P.A.F., Giraldo, B.S., Garcia, B.C.G., Parra, E.R. and Arango, P.J.A., "Comparative study between natural and synthetic hydroxyapatite: Structural, morphological and bioactivity properties", *Matéria (Rio de Janeiro)*, Vol. 23, No. 4, (2018). doi: [10.1590/s1517-707620180004.0551](https://doi.org/10.1590/s1517-707620180004.0551)
46. Chen, J., Zeng, L., Chen, X., Liao, T. and Zheng, J., "Preparation and characterization of bioactive glass tablets and evaluation of bioactivity and cytotoxicity in vitro", *Bioactive Materials*, Vol. 3, No. 3, (2018), 315-321. doi: [10.1016/j.bioactmat.2017.11.004](https://doi.org/10.1016/j.bioactmat.2017.11.004)
47. Nabian, N., Jahanshahi, M. and Rabiee, S.M., "Synthesis of nano-bioactive glass-ceramic powders and its in vitro bioactivity study in bovine serum albumin protein", *Journal of Molecular Structure*, Vol. 998, No. 1, (2011), 37-41. doi: [10.1016/j.molstruc.2011.05.002](https://doi.org/10.1016/j.molstruc.2011.05.002)
48. Zhao, L., Yan, X., Zhou, X., Zhou, L., Wang, H., Tang, J. and Yu, C., "Mesoporous bioactive glasses for controlled drug release", *Microporous and Mesoporous Materials*, Vol. 109, No. 1, (2008), 210-215. doi: [10.1016/j.micromeso.2007.04.041](https://doi.org/10.1016/j.micromeso.2007.04.041)
49. Delavar, M., Bakeri, G., Hosseini, M. and Nabian, N., "Fabrication and characterization of polyvinyl chloride mixed matrix membranes containing high aspect ratio anatase titania and hydrous manganese oxide nanoparticle for efficient removal of heavy metal ions: Competitive removal study", *The Canadian Journal of Chemical Engineering*, Vol. 98, No. 7, (2020), 1558-1579. doi: [10.1002/cjce.23725](https://doi.org/10.1002/cjce.23725)

Persian Abstract

چکیده

کامپوزیت‌های شیشه زیست‌فعال جدیدی با روش سل-ژل، از طریق کاهش درصد وزنی سیلیس و جایگزینی آن با ۱۵ درصد وزنی از نانولوله‌های اکسید تیتانیوم سنتز شده‌اند که این مواد در دو مرحله متفاوت در فرآیند سنتز اضافه شده‌اند. خواص زیست‌فعالی، مورفولوژی، ساختار کریستالی، گروه‌های عاملی کامپوزیت‌ها از طریق میکرو سکوپ الکترون روبشی (SEM) و آنالیزهای پراش اشعه ایکس (XRD) و تبدیل فوریه مادون قرمز (FTIR) مورد ارزیابی قرار گرفتند. بر اساس تصاویر SEM، مرحله‌ای که در آن نانولوله‌های اکسید تیتانیوم به محلول اضافه می‌شود، به طور کامل مورفولوژی کامپوزیت را تغییر داده است. آزمون زیست‌فعالی بیرون‌تنی با غوطه‌ور کردن نمونه‌ها در مایع شبیه سازی شده بدن برای بازه‌های ۱۴ و ۲۸ روزه و با توجه به تشکیل لایه هیدروکسی‌آپاتیت روی سطح نمونه‌ها انجام شد. با توجه به پیک‌های XRD در زاویه دو تتا حدود ۳۱ و ۴۰ درجه، مشخص گردید حضور نانولوله‌های اکسید تیتانیوم منجر به بهبود زیست‌فعالی نمونه‌ها بعد از ۱۴ روز گردیده است و هر دو کامپوزیت حاوی نانولوله‌های اکسید تیتانیوم از نمونه 58S زیست‌فعالی بیشتری داشته‌اند، در حالیکه بعد از ۲۸ روز غوطه‌وری در SBF، شیشه زیست‌فعال 58S پیک‌های هیدروکسی‌آپاتیت با شدت بیشتری را نشان داده است. به علاوه، ویژگی بارگذاری دارو کامپوزیت‌های تهیه‌شده ارزیابی شدند و نتایج مربوطه نشان دادند که اضافه نمودن نانولوله‌ها در مقایسه با بیوگلس 58S با بارگذاری داروی ۳۷ درصد، عملکرد کامپوزیت‌های زیست‌فعال حاوی نانولوله‌های اکسید تیتانیوم را تا ۷۰ درصد بهبود بخشیده است.