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 SiO$_2$ 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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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...
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 hydroxyapatite, 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 TiO₂. To do this, different sources of titanium were substituted for one of the common constituents of bioactive glass (SiO₂–CaO–P₂O₅). In most cases, researchers used Tetabutyl Titanate as the Ti precursor and fabricated quaternary bioactive glasses without the direct utilization of TiO₂ 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 SiO₂.

In this study, the 58S bioactive glass and a novel bioactive glass, which is synthesized by using TiO₂ 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 (HNO₃) (70%), ammonia (NH₄OH) (25%), and ethanol (C₂H₅OH) were purchased from Merck (Germany), and calcium nitrate tetrahydrate (Ca(NO₃)₂·4H₂O) as Ca source was supplied from Carlo Erba, Spain. TiO₂ 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 °C/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 SiO₂. 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-TNT); 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 CuKα radiation (λ = 1.54) with 0.032 step size over a range of 20=2=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 400–4000 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 |
|-----------------------------------------------|
|                  | SiO₂ | TiO₂ | CaO | P₂O₅ |
| 58S              | 58   |  -   | 33  |  9   |
| 58S-TNT          | 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-beers 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
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 TiO₂. 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]. The formation of these new compounds can be attributed to the reaction of titanium oxide nanotubes with functional groups of bioactive glass. As shown in this figure, the 58S-TNT15 XRD pattern has stronger TiO₂ 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. 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]. 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 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 titamate (CaTiSiO3) and calcium titmate (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

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چکیده
کامپوزیت‌های شیشه‌زیست‌فعال جدیدی با روش سل-ژل از طریق کلسیم درصد وزنی، سیلیس و جایگزین آن با 15 درصد وزنی از نانولوله‌های اکسید تیتانیوم سنتز شدند. هدف از این مطالعه در بررسی و گسترش کاربرد این دسته از مواد به عنوان کامپوزیت‌های شیشه‌زیست‌فعال در زندگی مصنوعی است. این اکسید‌های شیشه‌زیست‌فعال جدیدی، از طریق کاهش درصد وزنی سیلیس و جایگزینی آن با 15 درصد وزنی از نانولوله‌های اکسید تیتانیوم سنتز شدند. نانولوله‌های اکسید تیتانیوم به محلول اضافه می‌شود. به طور کامل، کامپوزیت‌های شیشه‌زیست‌فعال را در دو مرحله مختلف در فرآیند سنتز اضافه می‌کنیم. از اکسید تیتانیوم و نانولوله‌های اکسید تیتانیوم به کمک مادون قرمز (FTIR) و آنالیز اشعه اکسیوراکس (XRD) تجزیه و تحلیل شدند. بر اساس نتایج SEM، مرحله ای که در آن نانولوله‌های اکسید تیتانیوم به محلول اضافه می‌شود، به طور کامل مورفولوژی کامپوزیت را تغییر داده است. آزمون زیست‌فعالی شبیه‌سازی شده بدن برای بازه‌های 14 و 28 روزه و با توجه به شکل لایه‌های نانولوله‌های اکسید تیتانیوم از نمونه 58S ابداعی بیشتر داشته است. با توجه به پیک‌های XRD در زاویه‌های 10-15 و 31-35 درجه مشخص شد که میزان نانولوله‌های اکسید تیتانیوم از نمونه 58S به معنی کامپوزیت‌های شیشه‌زیست‌فعال 58S بهتر است. بیشتری را نشان داده است. به علاوه، ویژگی‌های فیزیکی و شیمیایی کامپوزیت‌های شیشه‌زیست‌فعال را ارزیابی کردند و نتایجی داشتند که این اکسید‌های شیشه‌زیست‌فعال در مقایسه با بیوگلس بهتر گزارش شد.