Materials Research Express

**PAPER**

Preparation of nano spherical bioglass by alkali-catalyzed mixed template

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**Keywords:** nano bioactive glasses, nanosphere, alkali-catalyzed, double template

**Abstract**

Nano bioactive glasses (NBGs) were fabricated by alkali-catalyzed sol-gel combined with self-assembly template technique using ammonia and dodecylamine as dual-alkali catalysts. Its effect of the addition of cetyltrimethyl ammonium bromide (CTAB) in NBGs on its morphology and bioactivity were characterized. It is found that the incorporation of CTAB can adjust the diameter of particles from 23 nm to 48 nm and the NBGs can induce hydroxyapatite deposition on the surface. With the increase of CTAB, the size of particle decreased while its mineralization activity in vitro was enhanced. Thus, this study provides an available method to synthesize spherical nano bioglass with controllable particle size.

**1. Introduction**

Bioactive glasses (BGs) are synthetic biomaterials [1]. BGs can facilitate apatite layer formation at the interface between material and tissue, which is correlated with the bone binding reaction and osteoconductivity [2]. The first bioactive glass with the quaternary system NaO–CaO–P2O5–SiO2 was obtained by melt-quenching method and showed excellent bioactivity and biocompatibility [3]. Comparing to high temperature procedure in the former method, the sol-gel technique is an relatively advantageous one for preparing bioactive glass at the room temperature. However, the BGs derived from conventional sol-gel method are uncontrollable on morphology, pore structure and particle size [4–6]. It was reported that highly ordered mesopore structure and tunable morphology in BG can enhance the bioactivity in vitro [7–10], for which numerous studies added an appropriate surfactant to improve the sol-gel technique for the synthesis of BG. The mechanism is that the surfactant acts as a template [11–13] in the process. The templates either have a specific morphology and structure or have capable of forming a particular one by self-assembly. As introduced into the reaction system, the template hydrolyzes in solution to form micelle firstly. The precursor materials then combined with it. Finally, BGs can be obtained with the morphology similar to the template after heat treatment [14]. Tsigkou et al. [15] found that it is accessible to induce mutually independent and highly branched polymer chains by using an alkaline catalyst in synthesis which assemble to form the monodisperse spherical bioactive glass particles. Moreover, bioactive glasses derived from selecting ammonia or dodecylamine as a single catalyst in the process tend to be micro-nano (87 ~ 1500 nm) in size [16–18]. Virtually, particle size below 100 nm contributes to improving bioactivity.

In this study, on the basis of 60 S [19], we developed alkali-catalyzed mixed template method in which NH3·H2O and DDA were double catalysts, CTAB and P123 were selected as templates to synthesize nano bioactive glasses. The bioactivity of the derived BGs were evaluated after soaked in simulated body fluid (SBF) solution.

**2. Materials and methods**

**2.1. Materials**

Absolute ethanol and ammonia solution were purchased from Shanxi Tongjie Chemical Reagent Co., Ltd and Yantai Shuangshuang Chemical Co., Ltd respectively. The deionized water was home-made by laboratory.
Cetyltrimethyl ammonium bromide (CTAB), nonionic triblock copolymer EO20PO70EO20 (P123), Dodecylamine (DDA), calcium nitrate tetrahydrate (CN), triethylphosphate (TEP) and tetraethyl orthosilicate (TEOS) were obtained from Shanghai Macklin Biochemical Co., Ltd. which were analytical grade reagents.

2.2. Synthesis of bioactive glass nanoparticles
Nano spherical bioglass was fabricated by alkali-catalyzed sol-gel combined with self-assembly template method. The specific process was as follows: 0.5 g P123 was added in a solution mixed 80 ml absolute ethanol with 10 ml deionized water after which the mixture was stirred at 35 °C for 12 h. CTAB with certain weigh and 0.1 g DDA were added sequentially at an interval of 10 min. Then 0.335 ml ammonia (28 wt% NH3) was added to the solution. 2.23 ml TEOS and 0.23 ml TEP were added in sequence with an interval of 30 min. In the procedure above, the magnetic stirrer worked continuously. After dissolved in 10 ml of deionized water, the solution containing 1.417 g CN was dropwise added to the system. White suspension was obtained after 6 h stirring. The suspension was centrifuged at a high speed to obtain the white gel precipitate which then was rinsed three times with absolute ethanol and deionized water. Next, the precipitate was dried in a constant temperature at 60 °C for 24 h to obtain dry powders. Eventually, NBGs were fabricated by undergoing heat treatment at 650 °C for 3 h. The corresponding addition of raw materials in the synthesis of four group of derived samples named as NBG-1, NBG-2, NBG-3 and NBG-4 according to the difference among the addition of CTAB were presented in Table 1.

### Table 1. The addition of reagents in the synthesis.

| Sample  | DDA g⁻¹ | NH₃·H₂O/(mol·l⁻¹) | P123 g⁻¹ | CTAB g⁻¹ |
|---------|---------|-------------------|----------|----------|
| NBG-1   | 0.1     | 0.05              | 0.5      | 0.01     |
| NBG-2   | 0.1     | 0.05              | 0.5      | 0.02     |
| NBG-3   | 0.1     | 0.05              | 0.5      | 0.03     |
| NBG-4   | 0.1     | 0.05              | 0.5      | 0.04     |

2.3. Characterization of samples
The phase compositions of obtained samples were characterized by x-ray diffraction (XRD, Rigaku, Samart-lab, Tokyo, Japan) using Cu Kα radiation (λ = 1.5406 Å). Field emission scanning electron microscope (FE-SEM, Merlin Compact, Carl Zeiss NTS GmbH, Jena, Germany) equipped with energy disperse spectroscopy (EDS, X-Max®), Oxford, UK) was used to observe the morphology and element distribution of samples. Transmission electron microscopy (TEM, JEM-2100, JOEL, Japan) was used to observe morphology as well. Moreover, the samples were analyzed with Fourier-transform infrared spectrometer (FTIR, VERTEX70, Bruker, Germany).

2.4. Bioactivity evaluation in vitro
The samples were immersed in SBF at 37 °C for 7, 14 and 28 days to evaluated bioactivity in vitro. The ratio of the sample weight to the volume of SBF was 10 mg·ml⁻¹. The SBF was prepared according to Kokubo [20] which was selected at 1.5 times of the standard solution in the test and was replaced every three days. After soaked for 7 d, 14 d and 28 d respectively, samples were removed from the SBF solution, washed with absolute ethanol and deionized water and then dried at 60 °C. The differences in phase composition, structure and morphology of the samples before and after immersion were detected using XRD, SEM-EDS and FTIR.

3. Results and discussion

3.1. Characterization of synthesized bioactive glasses
XRD patterns of the bioglasses with different addition of CTAB are shown in Figure 1. The XRD patterns of all samples were similar with broad peaks appearing around 15°–35°, which exhibited the typical amorphous structure of bioglass. The formation of wide diffraction peaks seems to be related to the long-range disordered and short-range ordered arrangement of amorphous materials [21].

The SEM and TEM images of obtained bioactive glass are presented in Figure 2. It can be seen that with the amount of CTAB from 0.01 to 0.04 g, the morphology of obtained sample particles were the same as sphere while the average diameters increased: the NBG-1 was 23.7 ± 3 nm (Figure 2(a)), NBG-2 was 30.4 nm ± 5 nm (Figure 2(b)), NBG-3 was about 41.4 ± 15 nm (Figure 2(c)), and NBG-4 was around 48.1 ± 21 nm (Figure 2(d)). Obviously, the diameters of four groups were less than 100 nm. By contrast, the spherical particles of the latter two groups of samples appeared to be non-uniform and agglomerated with poor dispersibility. Combining the
analysis above, we concluded that the incorporation of CTAB can adjust the diameter of particles from 23 nm to 48 nm, that is, the amount of CTAB significantly influence the diameter of nano spherical bioglasses.

The FTIR spectra of obtained NBGs is shown in figure 3. Based on the scientific reports [22, 23], the two vibration peaks observed at 475 and 1103 cm\(^{-1}\) are correlated with symmetric stretching and asymmetric stretching modes of Si–O–Si group respectively while the band at 803 cm\(^{-1}\) corresponds to symmetric stretching vibration of Si–O group. The absorption band aroused from O–H group at 1635 cm\(^{-1}\) and 3421 cm\(^{-1}\) is related to adsorption water [24].

![Figure 1. XRD patterns of obtained bioactive glasses.](image)

![Figure 2. SEM and TEM images of bioactive glasses prepared with different addition of CTAB. (a) NBG-1; (b) NBG-2; (c) NBG-3; (d) NBG-4.](image)
3.2. Characterization of bioglasses after immersed in SBF

The bioactivity of the obtained NBGs is generally evaluated after the samples immersed in SBF solution. Figure 4 shows the XRD patterns of NBGs powders immersed in SBF for 7, 14 and 28 days. For NBG-1 (figure 4(a)) and NBG-2 (figure 4(b)), a peak appeared at 32° after 7 days of immersion and additional weak peaks at 26°, 39°, 46°, 49° and 53° appeared after 28 days of immersion which are characteristic crystalline diffraction peaks of hydroxyapatite (HA). It can be inferred that HA was deposited on the surface of the spherical particles. Simultaneously, diffraction peaks at 29°, 36°, 39°, 43°, 47.5° and 48.5° confirmed that well-defined calcium carbonate phase arose during the early immersion. Compared with NBG-1, there existed a minor peak around 60° for NBG-2 after 14 days which was related to calcium carbonate phase as well. After further immersion for 28 days, HA was the dominant deposition which covered CaCO3 phase on the surface of NBG-2, so that the peak around 60° seemed to disappear.

After immersion for 7 days, only one peak of apatite appeared at 32° for NBG-3 sample (figure 4(c)) without peaks corresponding to calcite. It was exhibited that typical diffraction peaks of apatite and calcite coexisted after 14 days. Additional diffraction peaks related with HA was discovered after further immersion. Conversely, the intensity of diffraction peaks linked to calcium carbonate phase faded after 28 days of immersion.

There was no diffraction peaks of calcite for NBG-4 (figure 4(d)) during the whole immersion in SBF. The apatite phase started to appear after 7 days of immersion. With the increase of immersion time, the intensity of the peaks linked to HA was enhanced, that is, the crystallinity of apatite was gradually higher.

In order to compare formation rates and amount of deposited apatite among NBG-1, NBG-2, NBG-3 and NBG-4, XRD patterns of the samples for the same time of immersion including 7 days in SBF, the characteristic peaks of apatite at 32° existed in all patterns of NBGs. The intensity of the peak at 32° faded with the increased addition of CTAB in the early immersion. In addition, NBG-1 and NBG-2 had crystalline peaks at 2θ = 23°, 29°, 36°, 39°, 43°, 47.5° and 48.5° related to calcium carbonate phase. Compared 28 days of immersion in SBF among NBGs, an accessorial peak of apatite appeared after 7 days of immersion and additional weak peaks at 26°1 corresponding to P–O stretching vibration were detected in spectra of NBG-4 after 14 days, that is, the existence of CO32− groups which was attributed to the presence of calcite [27, 28]. After 28 days in SBF, the band related to P–O at 964 cm⁻¹ was detected for NBG-4 (figure 5(d)). The intensity of the bands aroused from CO32− tended to decreased for samples except for NBG-4 while the intensity of bands associated to vibrations of PO43− group increased which was in accord with the analysis of XRD patterns. That is, there was traces of calcium carbonate but eventually the resultant apatite covered it. The absorption peak at 1635 cm⁻¹ corresponded to the O–H stretch vibration of the adsorbed water, while the absorption peak at 3421 cm⁻¹ corresponded to the O–H stretching vibration of the
Si–OH group for all samples. The high content of water was due to the presence of nucleophilic groups, such as P-OH and Ca-OH, which favored the adsorption of water in humid condition [29].

Comparing the spectra of peaks appeared for immersion of 7 days among samples (figure 5(e)), it can be inferred that intensity of bands associated to vibrations of P-O increased with the particle size decreased. As the reaction continued to 28 days, the intensity of the shoulder peaks of all samples enhanced (figure 5(f)), indicating that the bioactive glass of four different addition of CTAB had superior mineralization activity in vitro.

The SEM images of obtained NBGs after immersion was showed in figure 6. Compared with relatively smooth surface morphology before immersion. After soaked in SBF solution for 7 days, the surface of all samples changed significantly, and new sediment was generated which existed in the surface of NBGs and the gaps.
among the spherical particles. Deposit formed in the gap may be correlative to the silicon hydroxyl group on the surface of the material. When the curvature was positive (the surface of the spherical particles), hydrogen bond was generated difficultly and the combination between hydroxyl group and material surface weakened for which the number of Si-OH group decreased, leading to the reduction of nucleation site of HA. When the curvature was negative (within the porosity), the situation was the opposite [30]. The XRD patterns and FTIR spectra demonstrated that the deposit contained calcite and apatite and the former was the principal phase in the early immersion. After 14 days in SBF, the scaly-like apatite particles were deposited on the surface of NBGs. After 28 days of incubation in SBF, massive apatite occurred on all samples and the amount of apatite deposited on NBG-1 and NBG-2 was more than that on NBG-3 and NBG-4. In addition, the crystallinity of induced apatite was the same case.

**Figure 5.** FTIR spectra of NBG-1 (a), NBG-2 (b), NBG-3 (c), NBG-4 (d) after soaking in SBF for different times and of four samples soaked in SBF for 7d (e) and 28d (f).
The deposit was ulteriorly verified due to high-intensity peaks of C, Ca and P elements identified by EDS analysis. The precipitation containing rich Ca and P elements deposited on bioglasses and glass-ceramics was commonly reported which was considered as the feature of bioactive materials [31]. High carbon combining low phosphorus content of deposit revealed that the precipitate was dominantly calcite with a small amount of apatite after immersion for 7 and 14 days. The content of phosphorus in 28 days was higher than that in the early immersion. Combing the analysis of XRD patterns, it was concluded that the apatite covered calcite and turned into the dominant phase in the late.

3.3. Discussion

The formation mechanism of NBGs spherical particles was visually clarified in figure 7. In the solution with NH₃·H₂O and DDA as double catalysts, a certain amount of CTAB template forms spherical micelles with small diameter. On the other hand, the alkaline catalysts accelerate the hydrolysis rate of the precursor materials after which considerable silicates equipped with negative charges are generated [32]. DDA is more than a catalyst which has the function of a template in synthesis as well [33]. DDA adsorbs inorganic components through hydrogen bonding and the negatively charged silicates are deposited on the surface of spherical micelles formed by CTAB via electrostatic interaction. Subsequently, the hydrolysis and condensation reactions will occur under
the further catalysis of DDA. As the negative charges on the outer surface of the micelles constantly accumulate, the electrostatic repulsion among the silicates in the solution gradually increases \[34\]. When the negatives charges reach saturation, the silicate cannot be deposited and spherical particles are generated \[35\]. Furthermore, certain concentration of P123 dissolving in solution contributes to altering the pore structure, because the polarity can reduce assembly between anions and cations substances and the nonionic surfactant can coat the silica-CTAB composite due to weak interaction between hydrophilic groups of ionic and nonionic materials. As is known, the spherical particle size no longer increases when the concentration of CTAB reaches the critical value. Thus, P123 covers the nanoparticles \[35, 36\]. Finally, we successfully obtained NBGs spherical particles with diameters below 50 nm via a simple ternary surfactant system.

According to Mami \[29\] research, it was found that in the early immersion in SBF, a series of reactions occurred: high release of Ca\(^{2+}\), limited dissolution of the bioglasses and absorption of phosphorus from solution by the bioglasses. The bioglasses continuously released calcium ions in SBF solution for ion exchange, and the Ca\(^{2+}\) eventually participated in the formation of HA and calcium carbonate precipitation. Calcite precipitation is formed due to lack of control in the early immersion, but the volume of the deposition increased slightly over time so that massive HA generated in the late immersion covered the calcite to be the dominant phase.

4. Conclusion

In this study, nano bioactive glasses were fabricated by alkali-catalyzed sol-gel combined with self-assembly template technique using ammonia and dodecylamine as dual-alkali catalysts in which CTAB and P123 were selected as templates to regulate the particle size and morphology. We studied the morphology and bioactivity \textit{in vitro} of the NBGs with different addition of CTAB. It is found that the incorporation of CTAB can adjust the diameter of particles from 23 nm to 48 nm. The bioactivity evaluation of NBGs manifested that the generated NBGs can induce HA on the surface. Specifically, the formation of calcite inhibited the generation of hydroxyapatite in the early immersion, but the apatite covered calcite and turned into the dominant phase in the late. In addition, with the increase of CTAB, the sizes of particles decrease while the mineralization activity \textit{in vitro} is enhanced due to improvement on the formation rate of hydroxyapatite. Thus, this study provides an available method to synthesize spherical nano bioglass with adjustable particle size. The impact on the biological activity and metabolic situation \textit{in vivo} for the derived NBGs should be depicted for further study which is necessary for bioglasses to serve as bone repair material.

Acknowledgments

This work was financially supported by the Henan province university science and technology innovation team (19IRTSTHN027), the Education Department of Henan Province Basic Research Program, China (Grant No. 19A430015, 19B430004).

Declaration

The research content and procedure of this experiment are carried out in strict accordance with the international and national ethical medical on biomedical research.
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