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Development of injectable biocomposites from hyaluronic acid and bioactive glass nano-particles obtained from different sol–gel routes

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ABSTRACT

Bioactive glass nano-powders with the same chemical composition and different particle characteristics were synthesized by acid-catalyzed (the glass is called BG1) and acid–base catalyzed (BG2) sol–gel processes. Morphological characteristics of powders were determined by TEM and BET methods. The powders were separately mixed with 3% hyaluronic acid solution to form a paste. In vitro reactivity of pastes was determined by soaking them in simulated body fluid. Rheological behaviors of paste in both rotation and oscillation modes were also measured. The results showed that BG1 particles was microporous with mean pore diameter of 1.6 nm and particle size of ~300 nm while BG2 was mesoporous with average pore diameter of 8 and 17 nm and particle size of 20–30 nm. The paste made of BG2 revealed better washout resistance and in vitro apatite formation ability than BG1. According to the rheological evaluations, both pastes exhibited shear thinning but non-thixotropic behavior, meanwhile paste of BG2 had higher viscosity than BG1. The oscillatory tests revealed that the pastes were viscoelastic materials with more viscous nature. Both pastes could be completely injected through standard syringe using low compressive load of 5–50 N. Overall, The biocomposites can potentially be used as bioactive paste for the treatment of hard and even soft tissues.

1. Introduction

Bioactive materials such as hydroxyapatite (HA) and bioactive glasses have been extensively used as substitute for defective bones and teeth [1,2]. These materials are osteoconductive, and non-toxic, non-inflammatory and non-immunogenic agents and known to be bioactive, because they are able to form a direct chemical bond with surrounding tissues.

The end-products of osteoconductive and bioactive materials are usually in the forms of porous or dense blocks, granule and moldable pastes [3–5]. The major inadequacy of bone substitutes in the form of blocks is their pre-shaped form which makes them unsuitable for implantation in defects with irregular shape. Thus it is necessary to carve these brittle materials to match them with the shape of surgical site. It is well known that brittle materials are difficult to be machined, because stresses induced by cutting tools prompt quick crack propagation leading to catastrophic fracture. Bone substitutes in the form of granules are not also integrative and can leave defect site through migration to adjacent tissues.

Making injectable biomaterials using bioactive ceramics/glasses and water-based solutions can defeat the problems of granules and blocks. The injectable pastes have also further advantages compared to conventional bioceramics. For example, they are capable to be loaded by different drugs or biological molecules with prolonged controlled release properties [6–8]. Bioactive materials in the form of paste are increasingly used for the treatment of spinal fragility fracture, cranioplasty and maxillofacial surgery, kyphoplasty, vertebroplasty, root canal sealing, orbital floor repair and even for the medication of vesicouretheral reflux in children [9–22].

Moldable and injectable bioactive pastes can be divided into two different categories regarding time-dependent changes occurring in their internal structures: Cementitious (cement-type) and non-cement type. In cement-type pastes, microstructure develops by a chemical reaction between the paste constituents leading to formation of new phase and production of a network which results in an increase in paste viscosity. Thus after elapsing a defined time (setting time), the paste sets and becomes hard. However, in non-cement pastes, there is no chemical reaction between the paste components and formation of new phases is not expected. For these pastes, viscosity may only change by physical interaction of constituents as well as drying phenomenon (evaporation of liquid phase). Calcium phosphate cements (CPCs) made of reactive calcium phosphates and aqueous solution of phosphate salts are the most well known cementitious bioactive materials. In contrast, the pastes made of non-reactive calcium phosphates (e.g. HA and β-TCP) and polymeric solutions can be introduced as non-cement pastes.

In the case of injectable pastes, the rheological properties are very important because they have to be injected without any resistance to flow and phase separation. For example, when modifying injured urethra in vesicouretheral reflux problem, a bioactive paste should travel a long path through the urethra and hence, the paste flowability is an important issue. The flowability is also important for the pastes molded

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in bone defect with complex shape, because it should flow and fill all parts of defect.

The rheological properties of cementitious paste such as calcium phosphate cements and polymethyl methacrylate (PMMA) bone cement have been discussed in literatures [23–25]. For non-cement pastes also, the rheological behavior of aqueous β-TCP suspensions was investigated by Baroud et al. [26] and Bohner et al. [27], separately. For both types of pastes, the role of some parameters such as powder to liquid ratio, particle size and distribution of solid phase and viscosity of mixing liquid on the flow behaviors has been discussed.

Bioactive glass materials are important alternatives for bone treatment as filler or scaffold. They are chemically bonded to bone and even soft tissues through the apatite layer precipitated on their surfaces after subjecting to body fluids. Bioactive glasses that prepared by sol–gel process yield high specific surface area and thus superior bioactivity. Another preference of bioactive glass materials, compared to calcium phosphates such as hydroxyapatite and tricalcium phosphate is the presence of Si element in their composition. Si contributes in bone mineralization and gene activation when released as silicate ions. The accelerating effect of silicate ions on proliferation and activity of osteoblastic cells has been proved elsewhere [28].

Bioactive glass powder can be mixed with a viscous polymeric solution to form an injectable paste for hard and soft tissue applications. In vitro bioactivity and rheological properties of the prepared paste can be strongly influenced by varying physical parameters of glass particles such as morphology and pore size distribution. These morphological discrepancies can originate from the different processes of the sol–gel route.

In previous years, limited studies have been done on bioactive glass pastes and development of these materials is fascinating. There are only a few papers that focused on the augmentation of soft tissue using bioglass pastes [29,30]. Chitosan hydrogel/nano-bioactive glass mixtures were also developed by Couto et al. and the rheological properties of the produced pastes were evaluated [31].

In this study, injectable biocomposites are developed based on sol–gel-derived bioactive glass nano-particles and hyaluronic acid (HAc) solution. Also, the goal of this paper is to investigate how bioactivity and rheological properties of these non-cement pastes can be influenced by changing morphological properties of glass part which originates from little modification of sol–gel process. HAc was selected as source of polymeric solution because of its excellent biocompatibility, viscoelastic characteristic and modifying effect on handling properties of pastes [32]. Also, it has been proved that HAc participates in the production of extracellular matrix [33].

2. Materials and methods

2.1. Synthesis of nano-bioactive glass powders

Fig. 1 shows a schematic diagram of bioactive glass powder production (based on $64SiO_2-31CaO-5P_2O_5$ system [34]) by sol–gel process through different pathways: A single step acid-catalyzed process (Fig. 1a) in which the produced bioglass is called BG1 and a two-step acid–base sol–gel processing method (Fig. 1b) in which the product is called BG2. Briefly, for the synthesis of BG1 bioglass, tetraethyl orthosilicate (TEOS) and triethyl phosphate (TEP) were introduced into a 0.1 M nitric acid solution and stirred for 1 h at room temperature for acid hydrolysis calcium nitrate which was then added to the TEOS solution and mixed 30 min to react completely. After the final addition, the mixture was stirred for 1 h for completion of the hydrolysis process. The solution was poured into a Teflon container, kept sealed at 25 °C for 10 days until the gel was formed. The product was dried at 70 °C and then 120 °C for 1 and 2 days, respectively and finally, heated at 700 °C for 3 h to eliminate the residual nitrate and organic substances. For BG2 glass, the precursors' mixing and sol-forming

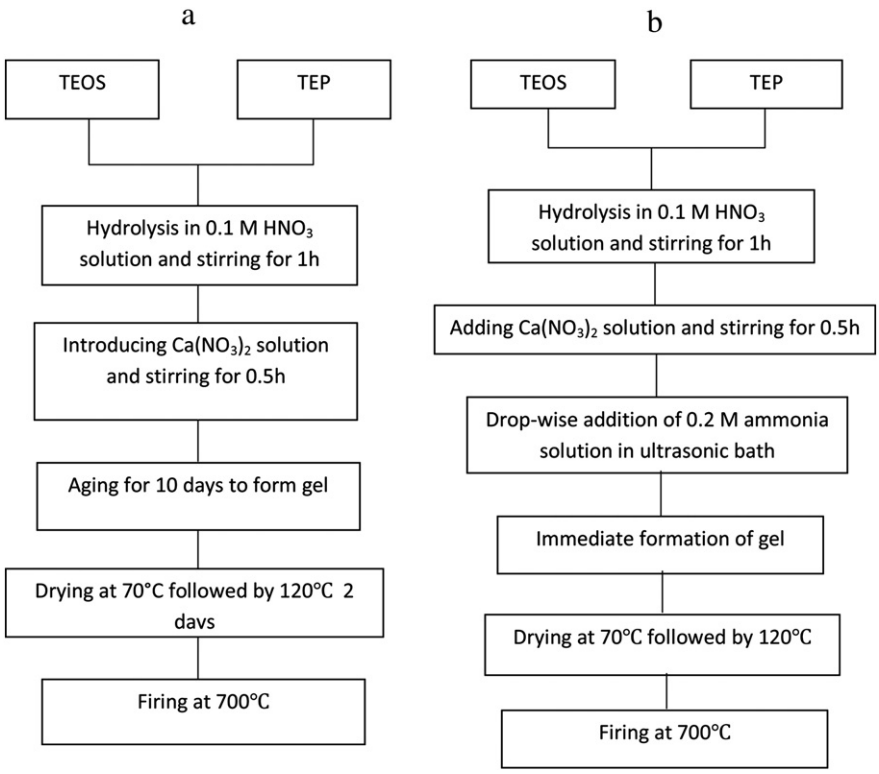

Fig. 1. A schematic diagram of bioactive glass powder production: (a) acidic catalyzed sol–gel (BG1) and (b) acid–base catalyzed sol–gel (BG2).