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Research Paper

Development and effect of different bioactive silicate glass scaffolds: In vitro evaluation for use as a bone drug delivery system

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ABSTRACT

Local drug delivery systems to bone have attracted appreciable attention due to their efficacy to improve drug delivery, healing and regeneration. In this paper, development and characterization of new formulations of bioactive glass into a porous scaffold has been reported for its suitability to act as a drug delivery system in the management of bone infections, in vitro. Two new glass compositions based on SiO_2–Na_2O–ZnO–CaO–MgO–P_2O_5 system (BGZ and MBG) have been developed which after thorough chemical and phase evaluation, studied for acellular static in vitro bioactivity in SBF. Porous scaffolds made of these glasses have been fabricated and characterized thoroughly for bioactivity study, SEM, XRD, in vitro cytotoxicity, MTT assay and wound healing assay using human osteocarcoma cells. Finally, gatifloxacin was loaded into the porous scaffold by vacuum infiltration method and in vitro drug release kinetics have been studied with varying parameters including dissolution medium (PBS and SBF) and with/without impregnation chitosan. Suitable model has also been proposed for the kinetics. 63–66% porous and 5–50 μm almost unimodal porous MBG and BGZ bioactive glass scaffolds were capable of releasing drugs successfully for 43 days at concentrations to treat orthopedic infections. In addition, it was also observed that the release of drug followed Peppas–Korsmeyer release pattern based on Fickian diffusion, while 0.5–1% chitosan coating on the scaffolds decreased the burst release and overall release of drug. The results also indicated that MBG based scaffolds were bioactive, biocompatible, noncytotoxic and exhibited excellent wound healing potential while BGZ was mildly cytotoxic with moderate wound healing potential. These results strongly suggest that MBG scaffolds appear to be a suitable bone drug delivery system in orthopedic infections treatment and as bone void fillers, but BGZ should be handled with caution or studied elaborately in detail further to ascertain and confirm the cytotoxic nature and wound healing potential of this glass.

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1. Introduction

From the beginning of this decade, local drug delivery systems to bone have attracted appreciable attention due to their efficacy in improving drug delivery, healing and regeneration (Cartmell, 2009). Considerable effort has been exerted to develop biologically acceptable materials and carrier systems to locally deliver drug in bone (Luo and Prestwich, 2001). Bioceramic materials are a class of biomaterials that can both chemically bond with bone and act as a drug carrier in prolonged-release drug delivery systems (Soundrapandian et al., 2009). Bioactive glasses and related silicate glass-ceramics constitute a much-preferred subgroup of bioceramics due to their high bioactivity and their ability to activate genes in osteoblast cells that stimulate new bone formation (Yunos et al., 2008). Considerable success has also been reported in the fabrication of bioactive glass scaffolds and their application (Gadre and Gouma, 2006).

Irrespective of the success in the development of drugs, devices and surgeries, orthopedic surgeries fail at an embarrassing rate due to infection. The prevention of post-surgical infection remains a major challenge due to difficulties in making conventionally administered antibiotics effectively available at the site. Physiological barriers that limit the supply, pathological conditions that escalate the demand, i.e., the concentration of the drug [10 times the minimum inhibitory concentration (MIC) for antibiotics], and the period of treatment (4–6 weeks) constitute the prime reasons for failure (Soundrapandian et al., 2007). Local drug delivery systems provide higher concentrations of drugs at the required site than those achieved with parenteral application (Kundu et al., 2010b; Nandi et al., 2009a) and are hence considered an area of potential future in orthopedic infection eradication.

The potential use of bioactive glass material as a drug delivery system has not been studied in great detail. Previous studies have mainly focused on biopolymers (Yagmurlu et al., 1999; Zhang et al., 1994a, 1994b), which were found to not be ideal for bone repair (because they do not chemically bond with bone) beyond drug delivery. In some of the studies, mesoporous bioactive glass materials have been studied for use as a drug delivery system (Domingues et al., 2004), but the effect of different cations and anions available in the composition has not been studied in detail. Moreover, their effect on long-term drug elution kinetics, particularly for the treatment of osteomyelitis, has also not been examined. Inorganic–organic composites have also been tested for this purpose, but with limited success (Arcos et al., 2001). In this paper, we present the development and characterization of new formulations of bioactive glass into a porous scaffold and their suitability to act as a drug delivery system in the management of bone infections in vitro.

2. Materials and methods

2.1. Preparation and characterization of different glass compositions

Two new glass compositions based on a SiO_2–Na_2O–ZnO–CaO–MgO–P_2O_5 system (hereafter referred to as BGZ and MBG) were prepared from reagent grade quartz (SiO_2), calcium carbonate ($CaCO_3$), light magnesium carbonate ($MgCO_3$), dry soda ash (Na_2CO_3), di-ammonium hydrogen ortho-phosphate [$(NH_4)_2HPO_4$] and zinc oxide (ZnO) using a conventional glass melting procedure. All raw materials were of analytical grade and sourced from S.D. Fine-Chem, India. Briefly, the raw materials were melted in air in a platinum crucible at 1400 °C for 30 min., and the molten glass was quenched (Kundu et al., 2011). The glass frits resulting from the quenching operation were powdered in a planetary ball mill, sieved and stored in an airtight container until further use. Table 1 presents the compositions of both glasses (assessed via thorough conventional chemical analysis). A differential thermal analysis (DTA) and a derivative differential thermal analysis (DDTA) were conducted using a DTA (STA 449C, Netzsch, Germany) to determine the thermal profiles of the glass powders. Scans were conducted between 40 and 850 °C heated at a rate of 5 °C/min. Profiles were collected over three repeats with a sample mass of 5 ± 0.5 mg. Fourier transformed infrared (FTIR) transmittance spectra were recorded at wave numbers ranging from 4000 to 400 cm^{-1} using a Spectrum 100 instrument (Spectrum 100, PerkinElmer, USA) with a resolution of 2 cm^{-1} to confirm the functional groups present. Potassium bromide (KBr) pelleted discs that consisted of approximately 2 mg of sample and 200 mg of KBr were employed. The X ray diffraction (XRD) patterns of powdered glass was recorded at a diffraction angle of 20–60° (2θ) using a X'Pert Pro (Phillips Analytical, Netherlands) X ray diffractometer with Cu $K_{\alpha 1}$ radiation ($\lambda = 1.5406$ Å) at a scan speed of 2° min^{-1}.

2.2. Preparation of porous bioactive glass scaffolds and their characterization

The respective glass powders were first mixed with an equal quantity of porogen (naphthalene). The resultant mix was compacted at 150 MPa in a cold-isostatic press (EPSI, Belgium). Subsequently, specimens of required dimensions (φ 8 mm) were sliced with a low speed saw (Isomet, Buehler, USA). The naphthalene was evaporated from the samples via very slow drying up to 80 °C, followed by sintering at approximately 725 °C on a Pt–Rh plate for 6 min. The samples were finally stored in a vacuum desiccator until further use. The porosity of the blocks was measured using water displacement method (Archimedes' principle), and the pore size distribution was measured using a mercury porosimeter (PM60, Quantachrome, USA) with an applied pressure ranging from 0 to 3000 psi.

Table 1 – Compositions of the glasses.

Composition	BGZ (mol%)	MBG (mol%)
SiO_2	55.9	58
Na_2O	11.8	12
CaO	16.14	18
P_2O_5	2.5	7
ZnO	1.24	2.4
MgO	9.93	2.6
K_2O	2.5	–

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