# Novel nanoporous bioceramic spheres for drug delivery application: a preliminary in vitro investigation

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**Background.** Bioceramics and their composites have found myriad applications in medicine as superlative osteoalloplasts. Their potential to function as a biocompatible resorbable drug delivery system is being explored. The present study is a preliminary investigation into the efficacy of these indigenously developed nanoporous materials as vehicles for therapeutic agents. An in vitro experiment was conducted with the goal of assessing this material and comparing it with a commercially available gentamicin-loaded polymethylmethacrylate cement.
**Study Design.** The drug-eluting characteristics of gentamicin bone cement and indigenously designed nanoporous bioceramic granules were analyzed spectrophotometrically and compared. Regression analysis was done.
**Results.** The first 5 days saw the elute from both samples containing drug concentrations >100 μg/g.
**Conclusions.** Both samples exhibit a high initial-burst release, which is ideal for prophylactic purposes. Drug eluent levels for both materials were >100 μg/g, which is sufficient for bactericidal activity. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:e7-e14)

Several important factors related to bone physiology that could influence the success of a pharmacologic treatment, including heterogeneity in bone remodeling activities throughout the skeleton, differences in blood supply and local vascularization, and the "blood-bone" barrier. Osteoporosis, arthritis, and periodontal disease are common diseases of the skeleton, all of which could benefit from new therapeutic strategies. The structural qualities of bone, especially the presence of hydroxyapatite (HA) crystals in the bone mineral and the established binding of certain molecules to this mineral phase, provide unique opportunities to treat skeletal diseases using targeted drug delivery. Additional opportunities exist in targeting sites with contrasting bone surface activities, including surfaces that are inactive, forming new bone, or being resorbed.[1]

Conventional drug formulations typically provide a prompt release of drug in a bolus form. Achieving and maintaining the drug concentration within the therapeutic window necessitates a multiple dosing regimen, which is often inconvenient and encourages noncompliance from patients. There is therefore an urgent need for technology that facilitates targeted site delivery of drugs at optimal concentration. Herein lies the genesis of controlled drug-release formulations. A plethora of delivery systems are available, and polymers have been their mainstay. However, owing to denaturing of the drug within the polymer matrix causing loss of biologic activity and changes in immunogenecity, efforts to develop biocompatible systems have gained impetus.[2]

Carriers used for local delivery of therapeutic carriers used for local delivery of therapeutic agents may be broadly classified as nonbiodegradable and biodegradable. Of the former, polymethylmethacrylate (PMMA) beads impregnated with gentamicin have been a commercial success. The latter category includes collagen sponges, HA, polylactide/polyglycolide implants, and polylactate polymers. All of these systems release antibiotics at concentrations exceeding those of the minimum inhibitory concentrations (MICs) for the susceptible pathogen, without systemic toxicity. The major disadvantages of PMMA beads are the necessity for surgical removal at the completion of antibiotic release and hindrance to bony healing. Individualized chemotherapy to administer various antibiotics is not possible. This is

## Statement of Clinical Relevance

This study is a preliminary investigation into the efficacy of an indigenously developed nanoporous material as vehicle for therapeutic agents. An in vitro experiment was conducted to assess this material and to compare it with a commercial cement.

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the rationale for development of biodegradable drug delivery systems.[2]

Bioceramics and their composites have found myriad applications in medicine as superlative osteoalloplasts. Their potential to function as a biocompatible resorbable drug delivery system is being explored, and they have been used successfully as carriers for antibiotics, antimetabolites, hormones, and growth factors.

Shi et al. fabricated a mesoporous silica-HA composite for drug delivery, which showed good apatite deposition after being soaked in SBF for 7 days as well as 60% drug release. Fabrication of nanoporous HA using polyvinyl alcohol (PVA) as pore former resulted in an average porosity of 64 ± 1.4%. There were open and interconnected pores of average pore size <100 nm[3]. Seshima et al. investigated the efficacy of HA as a carrier for local administration of bisphosphonates (BPs), which currently are administered systemically. The results revealed that HA solubility depends on the sintering temperature; regulating the sintering temperature of HA as a carrier could control the concentration of released BPs; and BPs released from BP-HA composites reduced the number of osteoclasts.[4] Peter et al. suggested an HA-coated implant that releases a BP as a drug-delivery system. Zoledronate did not impair the proliferation of human osteoblasts when used at concentrations <1 μg. Murine cells can be exposed to concentrations as high as 10 μg. A concentration of 0.01% of titanium particles did not impair the proliferation of either cell line. Zoledronate affected the alkaline phosphatase activity of murine osteoblasts through a chelation phenomenon. The presence of titanium particles strongly decreased the alkaline phosphatase activity of murine osteoblasts.[5]

Mizushima et al. studied the usefulness of injectable spheric porous HA microparticles (SPHA) of average diameter 5 μm as a carrier for drugs such as interferon-alpha (IFN-α), testosterone enanthate), and cyclosporine A. Addition of human serum albumin and zinc (reinforcement) to IFN-α–adsorbed SPHA caused marked prolongation of release in vivo. SPHA seems to be useful as a biodegradable and subcutaneously injectable drug carrier.[6] Buranapanitkit et al. investigated the efficacy of local biodegradable composites composed of HA–plaster of Paris and either chitosan or alginate binder impregnated with amphotericin B. The HA composites impregnated with amphotericin B showed superior antifungal efficacy over those loaded in polymethylmethacrylate in an in vitro study.[7] Castro et al. formulated an implant formulation composed of 12% HA, 36% tricalcium phosphate, 12% poly(D,L-lactide), and 40% ciprofloxacin for use in treatment of multibacterial bone infection. The results confirmed that ciprofloxacin release is limited by its low solubility and that implant erosion and bone in growth into the implants enhance the antibiotic release.[8] Joosten et al. reported that HA cement is an effective carrier for antibiotic compounds, even in refractory infections due to methicillin-resistant *Staphylococcus aureus*.[9]

Andersson et al. synthesized HA through a sol-gel method in near–room temperature conditions. After the mineralization process, the crystal surface was coated with a mesoporous silica matrix using the templates already present in the bulk solution. The coating layer is distributed fairly homogeneously over the apatite surface, and the coating thickness is easily adjustable and dependent on the amount of added silica precursor. The hybrid material was shown to effectively induce calcium phosphate formation under in vitro conditions and simultaneously work as a carrier system for drugs.[10] Liu et al. incorporated calcium-deficient HA (CDHA) nanocrystals with bovine serum albumin (BSA), to form BSA-loaded nanocarriers via both in situ and ex situ processes. The release profile showed a bursting behavior for the nanocarrier prepared via the ex situ process, which is probably due to the desorption of BSA molecules. In contrast, for the sample synthesized via the in situ process at a higher pH level, a slower release profile without bursting behavior, owing to the dissolution of the BSA-incorporated CDHA crystal, is seen from high-resolution transmission electron microscopy, which indicates different extent of interaction between BSA and CDHA.[11] Miranda et al. evaluated alveolar ridge augmentation after surgical implantation of recombinant human bone morphogenetic protein 2 (rhBMP-2) using novel space-providing carrier technologies in the baboon (*Papio anubis*) model. The addition of rhBMP-2 resulted in an almost 2-fold increase in alveolar ridge width, including a greater percentage of trabecular bone and a higher bone density compared with control subjects. Tricalcium phosphate (TCP)/HA/absorbable collagen sponge (ACS) and alpha-BSM appear to be suitable carrier technologies for rhBMP-2. Alveolar augmentation procedures using either technology combined with rhBMP-2, rather than stand-alone therapies, may provide clinically relevant augmentation of alveolar ridge defects for placement of endosseous dental implants.[12]

Tamai devised a novel tool for articular cartilage repair, consisting of a triple composite of an interconnected porous HA (IPHA), recombinant human bone morphogenetic protein-2 (rhBMP-2), and a synthetic biodegradable polymer [poly-D,L-lactic acid/polyethylene glycol (PLA-PEG)] as a carrier for rhBMP-2. The triple composite of rhBMP-2, PLA-PEG, and IPHA promotes the repair of full-thickness articular cartilage defects within as short a period as 3 weeks in the rabbit model.[13] Thorwarth et al. conducted an in vivo study to