COMBINED COMPUTATIONAL STUDY OF MECHANICAL AND TRANSPORT BEHAVIOR OF A POROUS HYDROXYAPATITE-BASED CERAMIC BIOMATERIAL

Gabriele Dubini (1,2), Pasquale Vena (1,2), Roberto Contro (1,2)

(1) Department of Structural Engineering
Politecnico di Milano, Milan, Italy

(2) Laboratory of Biological Structure Mechanics,
Politecnico di Milano, Milan, Italy

INTRODUCTION

The conventional method of supplying a patient with pharmacological substances (such as antibiotics, chemotherapy agents, hormones, insulin, steroids, etc.) has been through either injection or oral ingestion. Generally speaking, both methods suffer from being very poorly selective, so that collateral damage can occur to healthy tissues and organs, different from the intended target. In addition, high drug doses are required to achieve the desired effects which can exalt toxic side effects, while the substance release is usually a quick burst in time. A recent, alternative approach is based on the use of implantable delivery tools, able to release the active pharmacological substance in a controlled way, long-active and more stable in time. They can also be manufactured from resorbable materials with a microporous structure, to be incorporated into the tissues.

Use of such delivery tools appears very promising in the treatment of bone diseases, for instance rheumatism, bone tumors and osteoporosis. Indeed, the solid structure can be used as a filler in the gap created by the surgery and later incorporated in the bone tissue during the healing process. Among the materials able to be loaded with pharmacological substances to the scope are: hydroxyapatite, tricalcium phosphate and alumina. Several in vitro and in vivo studies have been carried out on these materials [1], mainly aiming at determining the optimal structure porosity as well as the kinetics of the drug release.

In this work a numerical model study is presented. With reference to a three-dimensional, idealized sample of a bone delivery tool, structural and drug release analyses were performed.

MATERIALS AND METHODS

A computational model of a bone graft substitute used as a drug delivery system was developed. Drug release kinetics was investigated using the commercial FEM code FIDAP (Fluent Inc., Lebanon, NH, USA), while mechanical behavior simulations were carried out with ABAQUS code (Hibbit, Karlsson & Sorensen, Pawtucket, RI, USA). Gambit (Fluent Inc., Lebanon, NH, USA) was used for solid modeling and mesh generation.

A hydroxyapatite (HA) cylindrical drug delivery device was considered in this study. The device diameter and length were 10 mm. The drug considered was hydrocortisone Na-succinate, a steroidal antinflammatory drug.

Drug release study

Computational models of drug delivery were based on the main assumption that pure diffusion occurs both in the porous matrix and the solvent (water) in the in vitro experiments as well as in bone tissue in the clinical application. Advective contribution to drug transport was not considered and species concentration equation was solved [2]. Three-dimensional models were developed including the effects of: i) desorption and ii) solubility limit on drug release. Transient species concentration equation was written in the form:

$$\frac{\partial c}{\partial t} = D\nabla^2 c + q_c \qquad (1)$$

where c is the species concentration, D is the mass diffusion coefficient for drug in the porous material and in the solvent (in vitro experiments) and in bone and q_c is a source term.

These models required to develop Fortran subroutines yielding the q_c source term for the FIDAP solver. Solute desorption from matrix walls is governed by physico-chemical parameters depending on matrix and drug nature. It was modeled by means of a phenomenological correlation between the drug mass dissolved in solution at each time step, its initial concentration and the matrix porosity. Drug dissolution was modeled by means of the mass source qc, whose value was computed time step by time step through correlation based on experimental data. Solubility limit was implemented after Higuchi [3].

Once established that simulations of drug release fit in vitro results, the model was applied to a conceptual clinical application: bone graft for drug release implanted in different locations in the human femur.

Figure 1. Investigated locations (1 to 4, from left to right) for HA graft implants in the femur model.

This part of the work used the Standardized Femur (SF) geometry based on statistical data about human femurs (Pacific Research Lab, USA) and studied drug release from graft implanted in bone at four different femur locations (center-lateral, lateral-proximal, medial-proximal and center-medial, Fig.1). For each configuration a geometry composed of a graft and a volume of bone interested by drug release around it was studied. The examined volume of bone tissue was such that drug release occurs in suitable time for the specific clinical application (see also Fig.2).

Bone tissue properties were prescribed element by element to predict the different drug distributions out of the graft in relation to its position in the femur. Bone density distribution in a human femur was obtained through the elaboration of CT scans available in the Visible Human Dataset (VHD). A relation through each pixel gray level and the local effective diffusivity was established. As spongy bone density varies between 30% and 95%, the darkest gray in the whole images was set to correspond to the effective diffusivity for a 95% porous graft, while the white was set to correspond to the compact bone diffusion coefficient.

Mechanical behavior study

The structural analysis was carried out to verify the graft mechanical strength for different values of porosity and implant positions. A two-material model for mechanical analysis was developed on the Standardized Femur geometry. The spongy bone (elastic modulus 700 MPa, Poisson ratio 0.3) and the compact bone (elastic modulus 17200 MPa, Poisson ratio 0.3) materials were considered. Four different implant locations were studied, which correspond to those used in the drug delivery study. The load and constraint conditions generally used for the in vitro simulations of monopodalic rest were applied to the femur-graft system. Linear elastic simulations were carried out for different values of graft porosity with elastic properties referred to porous HA in the literature. The Tsai-Wu criterion was adopted to verify the graft strength, which is suitable to porous ceramic materials in complex stress conditions [4].

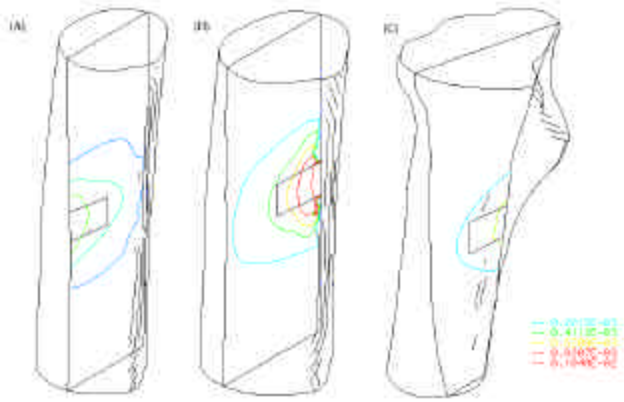

Figure 2. Drug concentration contour maps for three locations of HA graft implants in the femur model.

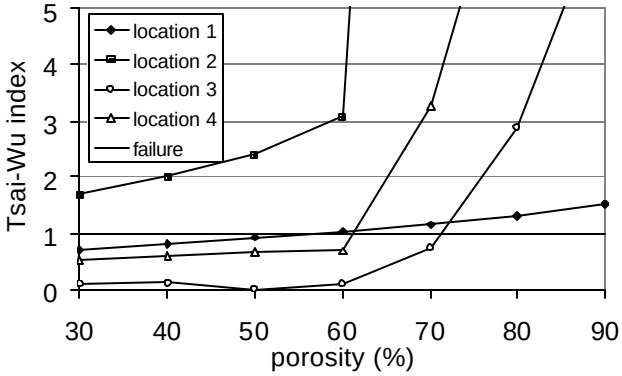

Figure 3. Strength analysis of HA graft implants in different locations in the femur model.

RESULTS

Figure 2 shows three contour maps of drug concentration for three locations of HA graft implants in the human femur model.

Figure 3 shows the results from the strength analyses of the porous grafts implanted in bone. A graft with less than 50% porosity implanted in position 1 can support the specific physiological loads while every graft porosity led to failure for position 2. Position 3 and 4, in monopodalic rest conditions, grant graft integrity for porosity lower than 60% and 70% respectively. However, low porosity and high stiffness grafts withstanding the physiological loads could turn out unsuitable for implantation if they induce stress shielding in the surrounding bone tissue. This problem is being currently addressed.

CONCLUSIONS

The reported results are part of a study on suitable HA grafts which aims at designing and manufacturing multifunctional materials able to exhibit a broad range of controllable properties for specific biomedical applications.

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