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A NOVEL SKELETAL DRUG DELIVERY SYSTEM FOR ANTI-BACTERIAL DRUGS USING SELF-SETTING HYDROXYAPATITE CEMENT

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To solve the problem of delivering drugs to skeletal tissue at high enough local concentrations for desirable therapeutic effects, we report a novel approach using a self-setting hydroxyapatite cement, with cephalexin and norfloxacin as model drugs. After setting, the cement was transformed into hydroxyapatite with affinity for hard bone tissue. Continuous in-vitro drug release profiles from loaded cement pellets (0.9-4.8% by weight) in phosphate buffer at pH 7.4 and 37°C followed the Higuchi equation.

KEYWORDS drug delivery system; cephalexin; norfloxacin; hydroxyapatite; self-stetting cement; controlled release

Currently, an antibiotic loaded polymer, polymethylmethacrylate (PMMA), is used as a bone cement and drug delivery system, and has had clinical success.[1] However, the toxicity of this polymer makes its application undesirable.[2] Even at low concentration the polymer can seriously suppress the phagocytic and bactericidal activity of human polymorphonuclear leukocytes. Furthermore, shrinkage during setting will leave the defect with marginal mechanical support. PMMA must also be removed before sound bone can regrow in the defect. Here we propose a patented self-setting hydroxyapatite cement,[3] $Ca_{10}(PO_4)_6(OH)_2$ (Mw = 1004.62), which has the same elementary chemical composition as bone and tooth mineral, as a new way to deliver drugs. A common problem associated with bone infection is the presence of a dead space where the infection resides. In addition there may be an area of dead bone, as in osteomyelitis, or an area from which bone is absent where a removed prosthesis has been removed. In this approach, hydroxyapatite cement can be formed in situ and molded to fill the space created by the absence of bone. It can also be used as a bonding material between bones or between a bone and a prosthesis.[4] At the same time, anti-bacterial drugs can be dispersed in the cement while it is being fixed. Once formed and bonded with bone tissue, controlled drug delivery may be achieved.

EXPERIMENTAL SECTION

Hydroxyapatite Cement The patented hydroxyapatite cement was prepared by a procedure described by Brown et al.,[3] except for the addition of hydroxyapatite seed crystals[5] and varying amounts of antibiotics. The mixed powder of hydroxyapatite cement samples are fabricated from 1.83 g of tetracalcium phosphate, $Ca_4(PO_4)_2O$ (TTCP), 0.86 g of dicalcium phosphate dihydrate, $CaHPO_4$ $2H_2O$ (DCPD), and 1.79 g of seeding hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ crystals. Various amounts of cephalexin and/or norfloxacin were mixed with 500 mg of a mixture of hydroxyapatite cement powder, and then mixed with 0.25 ml of 20 mM H_3PO_4. The mixed paste was put into the mold (diameter 13 mm), and stored at 37°C and 100% relative humidity for 24 h.

Dissolution Rate Determination The dissolution rates of all hydroxyapatite pellets with antibiotics were measured using the rotating disk method (50 rpm) in phosphate buffer (50 ml) at pH 7.4 at 37.0 ± 0.1°C. During dissolution 5-ml samples were withdrawn at suitable intervals and replaced immediately with 5 ml of buffer. The concentrations of cephalexin and norfloxacin were measured by the UV method at 262 nm.

Characterization The X-ray powder diffraction profiles of hydroxyapatite cement and drug-loaded hydroxyapatite cement samples were measured by powder X-ray diffraction analysis (XRG 250, Cu radiation, 15 mA, 35 kV, NIMS).

RESULTS AND DISCUSSION

Figure 1 shows the X-ray diffraction profiles of hydroxyapatite cement and 4.8% drug-loaded cement samples. The drug-loaded cement samples exhibited typical hydroxyapatite patterns. Mixing cephalexin and norfloxacin with the cement paste did not interfere with the fixing process in the formation of hydroxyapatite cement. All HAP cements had broader diffraction patterns than those of hydroxyapatite seed crystals. This suggests that the hydroxyapatite cement has high affinity for hard bone tissue with respect to crystallinity, after release of all loaded drugs from the hydroxyapatite cement.

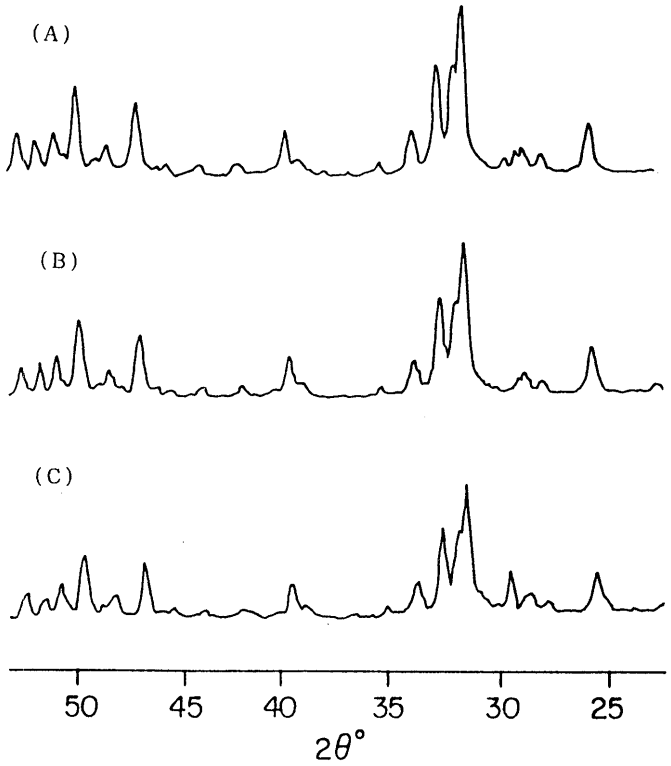

Fig. 1. X-ray Powder Diffraction Profiles of Anti-bacterial Drug-Loaded Hydroxyapatite Cement
(A) Hydroxyapatite cement;
(B)4.8% cephalexin-loaded cement;
(C) 4.8% norfloxacin-loaded cement.

Figures 2 and 3 show the patterns of anti-bacterial drug release from the hydroxyapatite cement in a phosphate buffer at pH 7.4. The release pattern of cephalexin and norfloxacin can be modeled by the Higuchi equation (eq. 1).[6]

$$M_t = (D_{eff}\, C_s\, (2C_d - \varepsilon C_s)t)^{1/2} \qquad \text{eq. 1}$$

where M_t is the amount of drug released from the cement, D_{eff} is the effective diffusivity, C_s is the solubility, C_d is the concentration of drug, and ε is the porosity.

The release rate of cephalexin from the cement depended on the amount of drug loaded. The norfloxacin-loaded cement released the anti-bacterial drug continuously for 250 h. This pattern of anti-bacterial drug release from hydroxyapatite cement may enable clinicians to achieve and maintain a therapeutic drug concentration in an infected area. Also, the neutral pH during the cement fixing process avoids stimulation of the surrounding bone by the pH of the H_3PO_4 solution.[5]

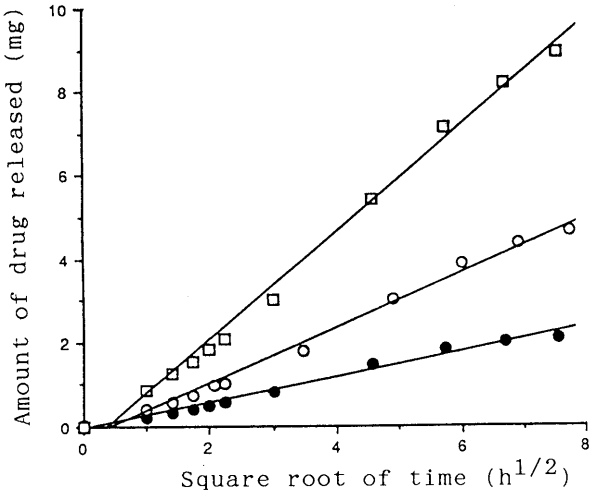

Fig. 2. Release of Cephalexin from Hydroxyapatite Cement versus Square Root of Time
(□) 4.8% drug-loaded cement; (○) 2.6%; (●) 0.9%.

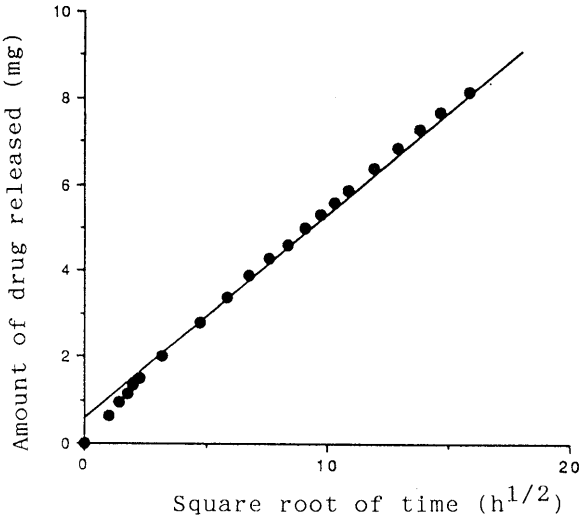

Fig. 3. Release of 4.8% Norfloxacin-Loaded Hydroxyapatite Cement versus Square Root of Time

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