NEW SKELETAL DRUG DELIVERY SYSTEM CONTAINING ANTIBIOTICS USING SELF-SETTING BIOACTIVE GLASS CEMENT

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A novel device containing cephalexin as a model drug using a self-setting bioactive cement basing on CaO-SiO_2-P_2O_5 glass was investigated. Glass powders contained 5% cephalexin powder hardened within 5 min after being mixed with a phosphate buffer. After hardening, *in vitro* drug release from homogeneous or heterogeneous drug-loaded cement pellets in a simulated body fluid at pH 7.25 and 37°C continued for more than 2 weeks.

KEYWORDS drug delivery system; biomaterial; cephalexin; calcium phosphate glass; crystalline transformation; hydroxyapatite; self-setting cement; controlled release

For use in implanting artificial hard tissue, several novel materials have a high affinity to hard tissue and can be molded to fill spaces created by physical injury to bones or teeth.[1] Kokubo *et al.*[2] developed a novel bioactive bone cement based on CaO-SiO_2-P_2O_5 glass and reported its physicochemical properties and transformation mechanism. The cement hardened within 5 min in the human body, and had sufficient mechanical strength and high bioactivity in humans.[3, 4] Therefore, it seems that the bioactive bone cement is suitable as the base for a drug delivery system to solve the problem for delivering drugs to skeletal tissue[5] at a local concentration high enough for desirable therapeutic effects. We reported previously on a drug delivery system for antibiotics[6] using patented self-setting hydroxyapatite cement containing tetracalcium phosphate and dicalcium phosphate,[7] as a novel administration route. In the present study, we investigated the pharmaceutical properties of bioactive bone cement as a novel drug delivery system and its *in vitro* drug release properties.

EXPERIMENTAL SECTION

Bioactive Glass Cement System Bioactive glass consisting of CaO (47.1), SiO_2 (35.8), P_2O_5 (17.1), and CaF_2 (0.75) by weight were prepared by heating at 1500-1600°C for 4 h, and

the mixing solution was obtained to dissolve 60.1 g of $(NH_4)_2HPO_4$ and 5.0 g of $NH_4H_2PO_4$ in 100 ml of distilled water according to the methods reported previously.[2)]

Procedures for Cement Forming The homogeneous system was prepared as follows: Bioactive glass cement powder, 500 mg, was mixed with 0.250 g of the mixing solution for 1 min; then 25 mg of the drug was mixed with the paste. The mixed paste was placed in a mold (diameter: 13 mm) and stored at 37°C and 100% relative humidity for 24 h. In contrast, the heterogeneous system consisted of a double-layer pellet in which the upper pellet (8 mm in diameter) was compressed at 1000 kg/cm^2 containing 25 mg of hydroxyapatite and 25 mg of the drug and the lower was a hardened cement (500 mg and 13 mm diameter) without drug. Samples were fixed to a holder with bees wax, so that only one face of the cement surface was exposed.

Dissolution Test The dissolution rates of the drug from all bioactive cement pellets containing antibiotics were measured using the rotating disk method (50 rpm) in 50 ml of the simulated body fluid (SBF)[2)] containing 2.5 mM of Ca^{2+} and 4.2 mM HPO_4^{2+} at pH 7.25 at 37.0 $\pm$ 0.1°C. During the release test all the dissolution media were replaced with fresh SBF at suitable time intervals. The concentrations of cephalexin were measured spectrophotometrically at 262 nm.

RESULTS AND DISCUSSION

The X-ray diffraction profiles of bioactive bone cement bulk powder showed a halo pattern, suggesting that the sample was in a glass state. After drug release test the cement samples hardened for 10 days exhibited characteristic peaks at 26° and 32° attributable to hydroxyapatite. This suggested that the cement paste with cephalexin did not interfere with the setting process in the formation of bioactive bone cement.

Figure 1 shows the drug release profiles from 5% drug-loaded homogeneous and heterogeneous bioactive bone cement systems in SBF at pH 7.25 and 37°C. In the drug release profile of the homogeneous drug-load cement, the initial release was very rapid and the amount released increased immediately up to 32% (8.0 mg), indicating a burst effect, but the release became very slow after 24 h, and continued over the long term. After 14-days, the cement pellet had decreased about 5% in volume. In the drug release profile of the heterogeneous system, the amount released after 24 h was 18% (4.5 mg), suggesting that the initial release rate decreased, and the release continued for more than 2 weeks. The heterogeneous system of the hardened cement soaked in SBF at 37°C for 7 days had no drug release at 0-20 h, and was very slow after 100 h because the cement was shrunken in SBF before the drug release test and had low porosity.

Figure 2 shows the effect of drug load on the release rate of drug from the bioactive glass cements. Since the cement shrank due to crystalline transformation at the initial drug release test, all drug release profiles showed characteristic rapidly decreasing

release rate at initial dissolution, followed by slower long-term release except for that of the heterogeneous system after soaking of the cement. The drug release rate of heterogeneous system after soaking increased with the elapse of time, and after 180 h it reached a constant level at around 7×10^{-4} mg/hcm^2. After 150 h, the drug release followed zero order mechanism. This result suggested that the burst effect of this delivery system was caused by cement shrinkage due to the crystalline transformation.

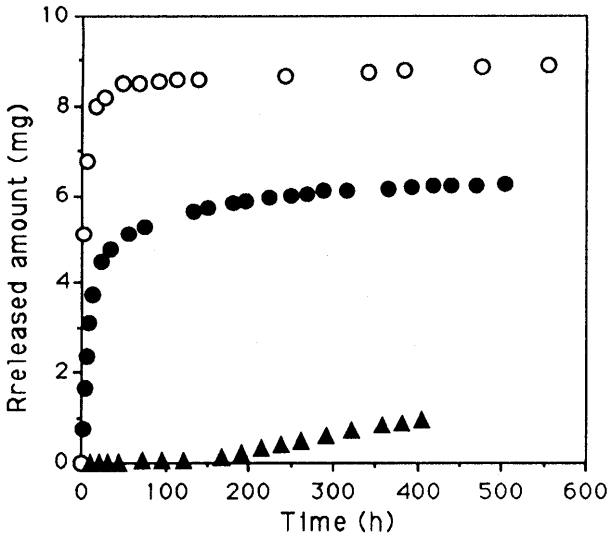

Fig. 1. Drug Release Profiles for Various Kinds of Bioactive Bone Cement Containing 5% Cephalxin

○, homogeneous system; ●, heterogeneous system; ▲, after soaking system.

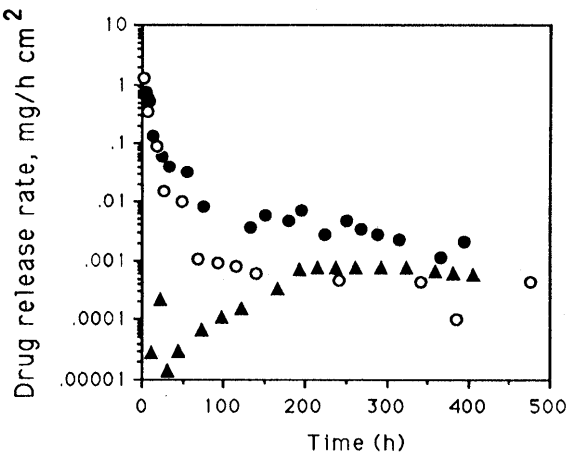

Fig. 2. Relation between Drug Release Rate of Bioactive Bone Cement and Time

○, homogeneous system; ●, heterogeneous system; ▲, after soaking system.

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