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Drug delivery system using bioactive bone cement consisting of Bis-GMA resin and bioactive glass ceramics

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A novel drug delivery system containing cephalexin (CEX) as a model drug using a new bioactive bone cement consisting of bisphenol-α-glycidyl methacrylate (Bis-GMA) resin and apatite- and wollastonite-containing glass-ceramic (A-W GC) powder was investigated. *In vitro* drug release rate increased with increasing mixing CEX amount. The drug release rate increased with increasing of lactose amount, since it was considered that dissolution media penetrated inside the cement through the voids, and dissolved lactose, and then, the void increase with increase of amount of lactose. The drug release rate increased also with increasing mixing A-W GC powder amount.

1. INTRODUCTION

Polymethylmethacrylate (PMMA) cements have been used with clinical success as an artificial bone filler cement for the stabilization of prostheses. Therefore, Salvati et al[1] developed an antibiotic loaded bone cement based on PMMA is currently used as a combination bone filler and drug delivery system for fixing non-bioactive prostheses to the surrounding bone, and has had clinical success. However, this cement has several clinical problems for long-term application. One of the most serious of these is its nonadhesiveness with bone surfaces. Another problem is that PMMA has considerably weaker mechanical properties than bone cortex.[2]

We have investigated self-setting apatitic cements[3,4] for use in drug delivery systems for antibiotics,[5] polypeptides[6] and anti-inflammatory drugs,[7,8] as a new way to deliver these agents to bone. However, hydroxyapatite is brittle and has poor strength characteristics, limiting its use as an implant in loaded area.[9]

On the other hand, Kokubo *et al*, have developed a new bioactive bone cement consisting of bisphenol-α-glycidyl methacrylate (Bis-GMA) resin and apatite- and wollastonite-containing glass-ceramic (A-W GC) powder, which was demonstrated previously to form a chemical bond with living bone through an apatite layer.[10] We, therefore, used a bioactive bone cement as the basis of a drug delivery system for skeletal tissue, and reported the *in vitro* drug release rate from this type of cement.

2. EXPERIMENTALS

2.1. Materials

Modified A-W GC bulk powder: Particles of A-W GC were provided by Nippon Electric Glass Co., Ltd. (Japan). The material contained 38% oxyfluoroapatite[$Ca_{10}(PO_4)_6(O, F_2)$], 34% β-wollastonite ($CaO \cdot SiO_2$), and 28% MgO-CaO-SiO_2 glass matrix. The average diameter of the particles was 5 μm. This powder was sifted into a 1.0% aqueous solution of γ-methacryloxy propyl trimethoxy silane (Chisso Co., Ltd. Japan) and mixed with a magnetic stirrer on a hot plate for 1 h. This slurry was dried at about 120℃, and then benzoyl peroxide, 0.4% per unit weight of the treated powder, was added.

Bis-GMA/ TEGDMA resin: The Bis-GMA resin was prepared from equal weights of Bis-GMA and trietylene-glycol dimethacrylate (TEGDMA) (Shin-Nakamura Chemical Industry, Wakayama, Japan). N,N-Dimethyl-p-toluidine, 0.2% per unit

weight of resin, was dissolved into the mixture. Bulk CEX powder (lot No. Y172) was obtained from Yamaguchi Pharm. Co., Japan. All other chemicals were of analytical grade.

2.2. Preparation of bioactive bone cement

The weight ratio of the A-W GC powder against to resin were 50, 70 and 80%. CEX powder (1, 2 and 5%) were carefully mixed with A-W GC powder, then 50, 30 and 20% of the resin were added and stirred for 1 min. The unpolymerized composite was placed in a Teflon mold (15 mm diameter, 2 mm thickness), and stored at room temperature for 5 min. The hardened cement pellet was coated with silicon rubber, so that only one face of the pellet surface was exposed.

2.3. Mechanical strength of the cement

The A-W GC powder with or without drug and lactose was mixed with the resin as described above. The mixed paste was placed in a mold (6 mm diameter, 12 mm long), and stored at room temperature for 5 min. The compressive strength of the hardened cement was measured using an accurate compression/tension testing machine (Autograph model IS-5000, Shimadzu Co.) at a compression speed of 0.5 mm/min.

2.4. *In vitro* drug release test

The drug release rates from all bioactive bone cement pellets containing CEX were measured as follows: A sample cement was placed in 15 ml of simulated body fluid (SBF)[10] comprised of 142 mM Na^+, 5.0 mM K^+, 1.5 mM Mg^{2+}, 147.8 mM Cl^-, 2.5 mM Ca^{2+}, 4.2 mM HCO_3^-, 0.5 mM SO_4^{2-}, 1.0 mM HPO_4^{2+} (pH 7.25) in a 50 ml capped test tube at 37.0±0.1℃. During the release test, the entire dissolution medium was replaced with fresh buffer at various intervals. The concentrations of CEX were measured spectrophotometrically (W 160A, Shimadzu Co., Kyoto, Japan) at 245 nm. Each value represented an average of three runs.

3. RESULTS AND DISCUSSION

3.1. Effect of CEX concentration on drug release from the bioactive bone cement

In general, the drug release from the matrix tablet follows the Higuchi equation (Eq. 1).

$$M_t = AM_0\sqrt{\frac{D_i\varepsilon C_s(2C_d - C_s)t}{\tau}} \quad \text{(Eq. 1)}$$

where M_t is the amount of drug released from the cement at time t, M_0 is the total amount of drug, A is the surface area of the tablet, Di is the diffusivity of the drug, C_s is the solubility, C_d is the concentration of drug, τ is the tortuosity and ε is the porosity.

Figure 1 shows Higuchi plots of 1, 2 and 5% CEX-loaded bioactive bone cement systems.

In vitro CEX release profiles of all drug loaded cements in SBF are linear at initial drug release stage on the Higuchi plot. The initial CEX release rate from the cement increased with increase of the drug concentration, indicating that the drug release followed Higuchi equation (Eq. 1). However, the drug release profiles was bended at latter stage of the release test. This may suggest that the geometrical structure of the cements changed during the drug release test.

3.2. Effect of lactose addition on CEX release from the bioactive bone cement

Figure 2 shows the effect of lactose addition on Higuchi plot for CEX release profiles from 5% drug-loaded bioactive bone cement systems in SBF at pH 7.25 and 37℃. The drug release rates from the cements depended on the amount of lactose amount. After 2 weeks, the total drug released from their system containing 0, 2 and 10% lactose were about 5.4, 6.2 and 8.8%, respectively, and continued for a long term (over 2 weeks). The drug release rate increased with increasing of lactose amount, since it was considered that dissolution media penetrated inside the cement through the voids, and dissolved lactose, and then, the void increase with increase of amount of lactose. All of the drug release profiles followed the Higuchi

equation at the initial stage, but at the latter stage, their didn't follow it. As hydroxyapatite was precipitated out on the cement surface, the drug release rate decreased by inhibition of precipitated layer.

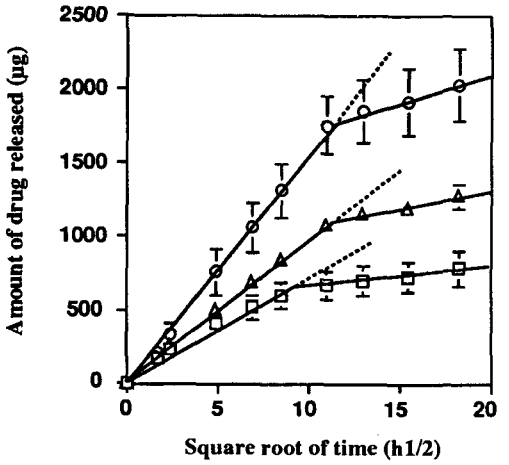

Fig. 1. In vitro CEX release profiles from bioactive bone cement
□, 1%; △, 2%; ○, 5%.

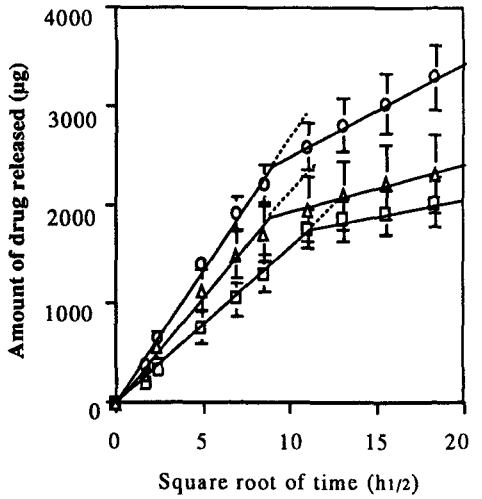

Fig. 2. Amount released of CEX from 5% CEX and 0, 2, 10% lactose contained bioactive bone cement
○, lactose 10%; △, lactose 2%; □, lactose 0%

3.3. Effect of A-W GC powder amount on CEX release from the bioactive bone cement

Figure 3 shows the effect of A- W GC powder amount on Higuchi plot for CEX release profiles from 5% drug-loaded bioactive bone cement systems in SBF at pH 7.25 and 37°C. After 2 weeks, the total drug released from their system containing 50, 70 and 80% A-W GC powder were about 1.7, 2.2 and 2.4%, respectively, indicating that CEX release rates from the cements depended on mixing A-W GC powder amount, and those continued for a long term (over 2 weeks). Since CEX released from the pores between the ceramics powder and resin and the pore volume increased with increase of the ceramic amount, it seems that the drug release rate increased also with increasing mixing A-W GC powder amount. All of the drug release profiles followed the Higuchi equation at the initial stage, but at the latter stage, because their didn't follow it by increasiing of outer precipitated layer on surface of the cement.

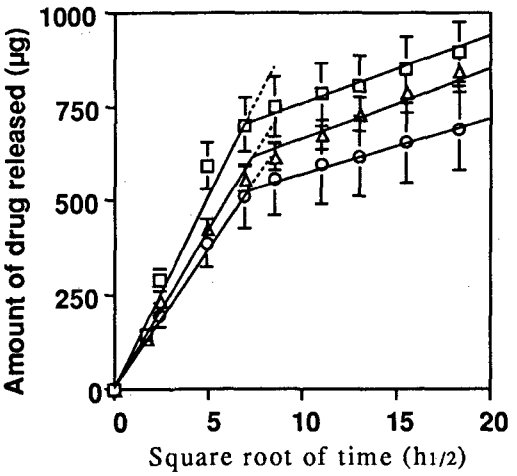

Fig. 3. Effect of A-W GC powder amount on CEX released from bioactive bone cement.
○, 50% A-W GC; △, 70%; □, 80%.

4. CONCLUSION

These results suggest that the CEX release rate from bioactive bone cement could be controlled with amount of drug, lactose and/or A-W GC powder. Therefore, this cements can be represent an effective delivery system for the local application of antibiotics to a specific area in bone.

5. Acknowledgments

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