PARTICLE SIZE EFFECT OF METASTABLE CALCIUM PHOSPHATES ON CRUSHING STRENGTH OF SELF-SETTING BIOACTIVE CALCIUM PHOSPHATE CEMENT

Makoto OTSUKA,*,[a] Yoshihisa MATSUDA,[a] Yoshiko SUWA,[b] Jeffrey L. FOX,[c] and William I. HIGUCHI [c]

Kobe Women's College of Pharmacy,[a] Kobe 658, Kyoritsu Ceramic Materials Co.,[b] Nagoya 455, Japan, and Department of Pharmaceutics,[c] University of Utah, Salt Lake City, Utah 8112, U.S.A.

The resistance to crushing after a self-setting bioactive calcium phosphate cement, consisting of various particle sizes of tetracalcium phosphate (TECP), dicalcium phosphate dihydrate (DCPD) and hydroxyapatite (HAP), had hardened was tested after setting at 37°C, 100% RH. X-ray diffraction suggested that the cement containing fine particles of DCPD and TECP was completely transformed to HAP, but that containing larger particles was not. Since particle size of both DCPD and TECP affected the dissolution rate, the crystal growth of HAP during cement formation depended on the specific surface area (Sw) of the raw materials. The crushing strength of the cement after hardening increased with an increase of its Sw.

KEYWORDS hydroxyapatite; self-setting calcium phosphate cement; particle size effect; crushing strength; specific surface area

When used in implanted artificial hard tissue, hydroxyapatite (HAP, $Ca_{10}(PO_4)_6(OH)_2$) has a high affinity for natural hard tissue *in situ* and can be molded to fill spaces created by physical damage to the bones and/or teeth.[1,2] Brown and Chou[3] reported that a bioactive self-setting calcium phosphate cement was molded to fill the space created by the absence of bone as an artificial hard tissue. From a pharmaceutical perspective, Otsuka *et al.*[4] investigated a system for delivering antibiotics using a self-setting calcium phosphate cement. However, in practical applications, the calcium phosphate cement does not have adequate mechanical strength after setting, which is the most serious problem of this system. Therefore, in this study, in order to improve the mechanical strength of self-setting calcium phosphate cement for use as a drug delivery system, we investigated the effect of the particle size of metastable calcium phosphates as raw materials on the crushing strength of the cement.

MATERIALS AND METHODS

Production of the Self-Setting Calcium Phosphate Cement System

The calcium phosphate cement powder[3,5] consisted of an equilmolar mixture of various particle sizes of tetracalcium phosphate (TTCP, $Ca_4(PO_4)_2O$) (1.1-13.1 μm) and dicalcium phosphate dihydrate (DCPD, $CaHPO_4\ 2H_2O$) (0.52-3.33 μm), and 40% HAP seed

crystals. The cement powder (1 g) was mixed and kneaded with 0.50 ml, 20 mM H_3PO_4. The paste was poured into a mold 6-mm in diameter and 12-mm in thickness (Japan Industrial Scale), and stored at 37°C and 100% RH for 24 h.

Characterization The X-ray powder diffraction profiles of the cements were measured with an X-ray diffractometer (Target, Cu; 35 kV, 15 mA). The specific surface area (Sw) was measured with a gas adsorption apparatus using BET gas adsorption.

RESULTS AND DISCUSSION

Characterization of Self-Setting Calcium Phosphate Cement

The results of X-ray diffractometry suggested that the cement containing fine particles of DCPD and TECP completely transformed to HAP, but that containing larger particles did not. Since particle size of both DCPD and TECP affected the dissolution rate, the crystal growth of HAP during cement formation depended on the Sw of raw materials.

Effect of Metastable Calcium Phosphates Particle Size on the Crushing Strength of Self-Setting Calcium Phosphate Cement

Figure 1 shows the relationships between the diameter of DCPD or TECP and the crushing strength of self-setting calcium phosphate cement. The crushing strength of the cements containing smaller DCPD particles (Sw=4.93 m^2/g) increased with increasing of TECP Sw, but that of the cements containing larger DCPD particles (Sw=0.760 m^2/g) did not. The Sw of DCPD affected the crushing strength of fixed self-setting calcium phosphate cement as follows: The crushing strength of all cements increased with increasing of the Sw of DCPD, and that of the cements containing the smallest TECP particles (Sw=1.71 m^2/g) was the hardest. All cements containing the largest TECP particle powder had significantly low mechanical strength, which increased with decrease of the diameter of the TECP particle. However, the best mechanical strength was not the cement formulation of the finest TECP and DCPD powders. In general, the nucleation and crystal growth processes during the cement setting were derived from the degree of supersaturation, which depended on the dissolution rate of the metastable calcium phosphates. At the initial stage of cement setting, the dissolution rate of the metastable substance is generally considered to be diffusion-controlled, given by the Noyes-Whitney equation (eq. 1)[6] as follows:

$$dC/dt = k\,S/V\,(Cs - C) \qquad \text{eq. 1}$$

where k is the rate constant per unit area, S is the available surface area, V is the solvent volume, Cs is the solubility, and C is the solute concentration.

The dissolution rate of the metastable form of calcium phosphate was controlled by the solubility and surface area of the solid. Therefore, after dissolution of the metastable form, the concentration reached supersaturation, after which the stable

form of the crystal grew. Since the solubility of TECP was much higher than that of DCPD, the Sw of TECP affected the crushing strength more than that of DCPD.

Relationship between the Crushing Strength and the Specific Surface Area of the Cement after Setting

Figure 2 shows the relationship between the crushing strength and the Sw of the cements after setting. The crushing strength of the cement increased with increase of the Sw, and the relationship was linear. The results indicated that the Sw of the cement increased with the crystal growth, and became rod-type crystals, as reported by LeGeros et al.[7] The harder cement contained the fine particles, because the contact area between the particles was larger. Fine particles arise from highly supersaturated mother liquid, because the driving force of the nucleation rate is supersaturation. The supersaturation depended on the Sw of TECP or DCPD in this cement system, as discussed in the previous section.

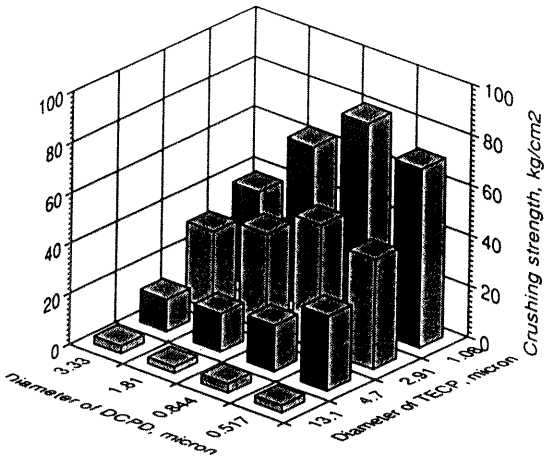

Fig. 1. Effect of the Particle Size of DCPD and TECP on Crushing Strength of Self-Ssetting Calcium Phosphate Cement

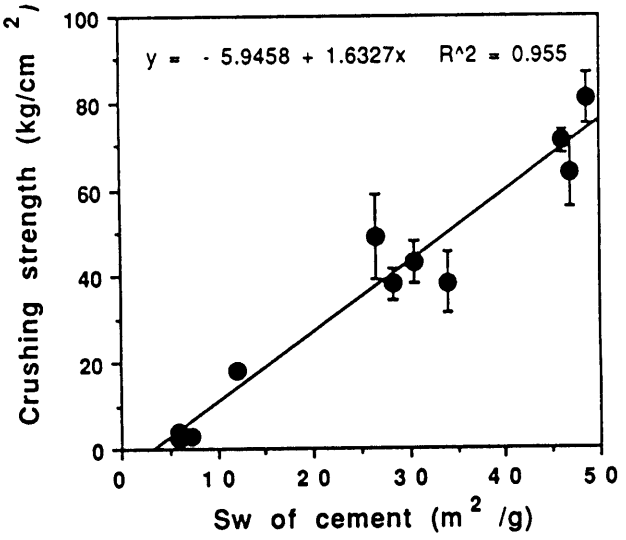

Fig. 2 Relationship between the Crushing Strength and the Specific Surface Area of Self-Setting Calcium Phosphate Cement

REFERENCES

1) H. Aoki, "Science and medical applications of hydroxyapatite", p.137-163 , Takayama Press., Tokyo, 1991.
2) T. Tabata, M. Ogiso, J. Dent., **18,** 337 (1983).
3) W. E. Brown, C. L. Chow, U.S. Patent 4,612,053, (1986).
4) M. Otsuka, Y. Matsuda, D. Yu, J. Wong, J. L. Fox, W. I. Higuchi, Chem. Pharm. Bull., **38,** 3500, (1990).
5) Y. Doi, Y. Takezawa, S. Shibata, N. Wakamatsu, H. Kamemizu, T. Goto, M. Iijima, Y. Moriwaki, K. Uno, F. Kubo, Y. Haeuchi, J. Jpn. Dent. Mat. Dev., **6,** 53, (1987).
6) A. Noyes, W.Whitney, J. Am. Chem. Soc., **19,** 930, (1897).
7) R. Z. LeGeros, J. P. LeGeros, W. P. Shirra, Advances in X-ray Analysis, **14,** 57, (1971).

(Received July 5, 1993)