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Effects of Organic Additives on the Morphology of Various Calcium Phosphates Prepared via Solution and Emulsion Methods

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Abstract. Dicalcium phosphate anhydrous (DCPA) and dicalcium phosphate dihydrate (DCPD) particles were prepared through the reaction between calcium nitrate and dipotassium hydrogen phosphate in a solution and a multiple emulsion. Organic compounds were added into the phosphate solution with the aim of modifying the morphology. Large parallelogrammic particles of DCPD were obtained with no additive. By adding 2-aminoethanol, the product was changed to rhombic in shape and reduced to one-twentieth in size, and the phase was DCPA. In the multiple emulsion, microspheres composed of DCPA were prepared. They were constructed by flaky, primary particles. The crystalline phase and morphology were affected by the concentrations of surfactants in the oil and outer aqueous phases.

1. Introduction

Calcium phosphates, *e. g.* hydroxyapatite (HAp), tricalcium phosphate (TCP), dicalcium phosphate anhydrous (DCPA), dicalcium phosphate dihydrate (DCPD), and so on, are so good in biocompatibility that they are applied to biomaterials. Microspheres made of these compounds are expected to be used as a microcarrier for drug delivery system. Calcium phosphates can be synthesized in a variety of morphology, which varies with synthesizing methods and conditions [1−3]. The authors have prepared microspherical HAp in a multiple emulsion, or a W/O/W dispersion [4]. The construction of the multiple emulsion is illustrated in Figure 1. The interface between the oil phase and the inner aqueous phase is hereafter referred to as an inner interface. It is understood that as calcium ions in the outer aqueous phase diffuse through the oil phase to reach the inner interface, they react with hydrogen phosphate ions to produce calcium phosphate compound. If the reaction site is limited at the inner interface, the morphology of the product can be sustained the morphology of the inner

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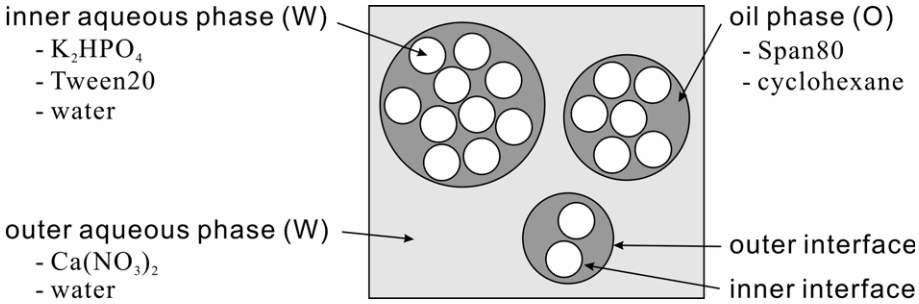

Figure 1. Construction of the multiple emulsion.

interface to form a microsphere. In this study, first, the effects of organic additives on the morphology of DCPA and DCPD synthesized via solution method were investigated. Dodecylphosphoric acid (DPA), polyacrylic amide (PAAm), dodecyltrimethylammonium bromide (DTMA), and 2-aminoethanol (AE) were used as organic additives. Second, the effects of sorbitan monooleate (Span80) of an oil-soluble surfactant and polyoxyethylene(20) sorbitan monolaulate (Tween20) of a water-soluble surfactant on the morphology of microspheres produced via an emulsion method were investigated.

2. Experimental

2.1. Solution method

DPA, PAAm(molecular weight: 600,000–1,000,000), DTMA or AE was dissolved at 2 wt% in 0.3 mol/kg dipotassium hydrogen phosphate (K_2HPO_4) aqueous solution, and then the pH was adjusted at 6 with nitric acid. 0.3 mol/kg calcium nitrate ($Ca(NO_3)_2$) aqueous solution was added dropwise at 3 mL/min. Stirring was kept for 3 h at 303 K. The product obtained was washed, freeze-dried, and characterized by X-ray powder diffraction (XRD) and scanning electron microscopy (SEM).

2.2. Emulsion method

0.3 mol/kg K_2HPO_4 solution at a pH of 6 was used as an inner aqueous phase. In some runs, AE was added at 2 wt% in it. Span80 was dissolved at 0.5–10 wt% in cyclohexane to prepare an oil phase. The inner aqueous phase of 0.3 in volume fraction and the oil phase were mixed and agitated at 12,000 rpm to prepare a W/O emulsion. Tween20 was dissolved at 0.01–1 wt% in 0.3 mol/kg $Ca(NO_3)_2$ solution to prepare an outer aqueous phase. The W/O emulsion of 0.3 in volume fraction was mixed to the outer aqueous phase having been stirred at 300 rpm to make a W/O/W emulsion. Stirring was kept for 3 h at 303 K.

3. Results and discussion

3.1. Solution method

The product obtained with no organic additive was single phase DCPD. The morphology was large, plate-like, parallelograms of 30–100 μm in long axis, 20–30 μm in short axis and ~500 nm in

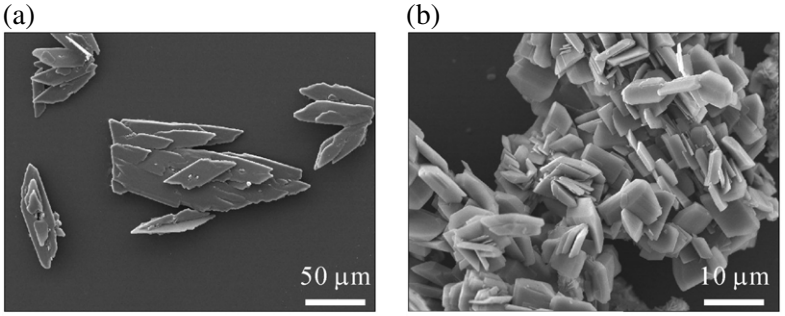

Figure 2. SEM micrographs of the products prepared via the solution method.
(a) No additive, (b) with AE.

Table 1. Summary of results by the solution method.

Additive	Crystalline phase	Morphology
none	DCPD	large parallelogram
DPA	DCPD	large parallelogram
PAAm	DCPD	large parallelogram, small rhombus
DTMA	DCPA	small rhombus, large parallelogram
AE	DCPA	small rhombus

thickness, as shown in Figure 2a. When DTMA or AE was added, DCPA was produced. Small, rhombic particles of less than 5 μm in both axes were observed in the product with the addition of PAAm or DTMA as well as the large parallelogrammic particles. The thickness seemed to be almost the same. By adding AE, the only rhombic particles were produced, as shown in Figure 2b. This means AE can reduce the particle growth most effectively. Table 1 lists the summary of these results. Under the condition that DCPA is produced, the tendency for particles to be smaller is recognized. The mechanism how an organic additive acts to change the formation of calcium phosphate particles in this situation is not understood at present.

3.2. Emulsion method

The crystalline phase was changed by surfactant concentrations. Figure 3a shows the XRD pattern of the products prepared in the emulsion method at a Tween20 concentration of 0.5 wt% and a Span80 concentration of 0.5 wt%. This product was identified as DCPD. SEM showed that this product was composed of large, parallelogrammic particles, similar to the results by the solution method. Figure 3b illustrates that the specimen prepared at 1 wt% were a mixture of DCPD and DCPA. Figure 4a shows that this specimen was composed of rod-like particles and microspheres. At 3wt% and more, the only DCPA was detected by XRD as shown in Figure 3c, and the only microspheres of 5–10 μm in diameter were observed by SEM as shown in Figure 4b. The comparison of results between XRD and SEM suggests that the plate-like and rod-like particles should be DCPD and the microspheres DCPA.

The condition under which almost spherical microspheres were obtained was a Tween20 concentration of 0.05 wt% and a Span80 concentration of 5 wt%. Figure 4c depicts that these microspheres were assemblages of flaky particles of 100–1000 nm in length and ~20 nm in thickness. It was confirmed that they have certain strength not to be broken by ultrasonication. Such morphology is almost the same as that of the

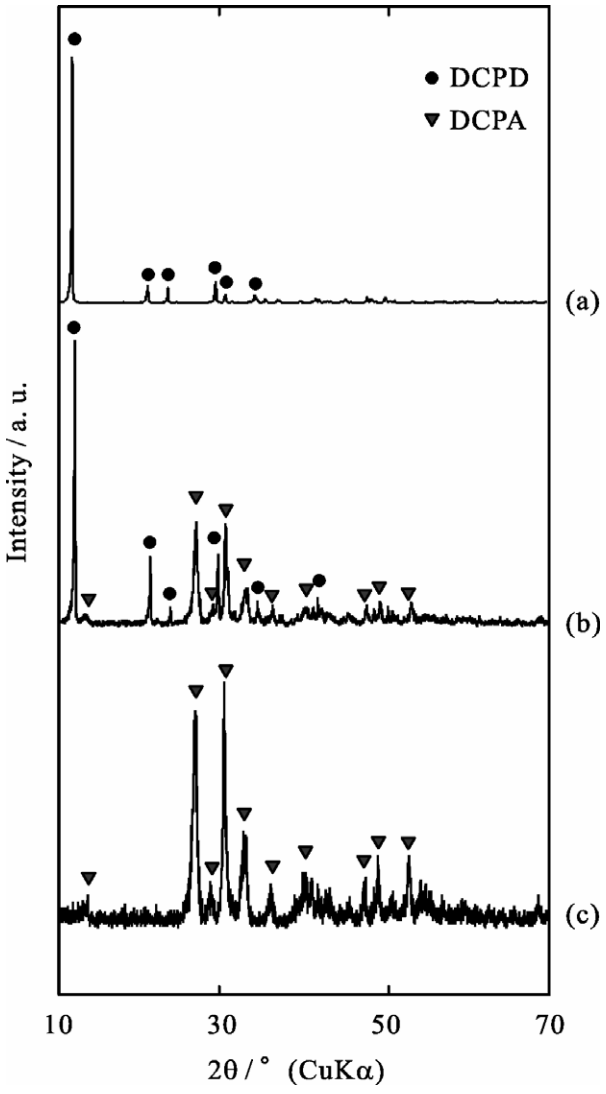

Figure 3. XRD patterns of the products prepared in the emulsion method at a Tween20 concentration of 0.5 wt% and Span80 concentrations of (a) 0.5, (b) 1, and (c) 5 wt%.

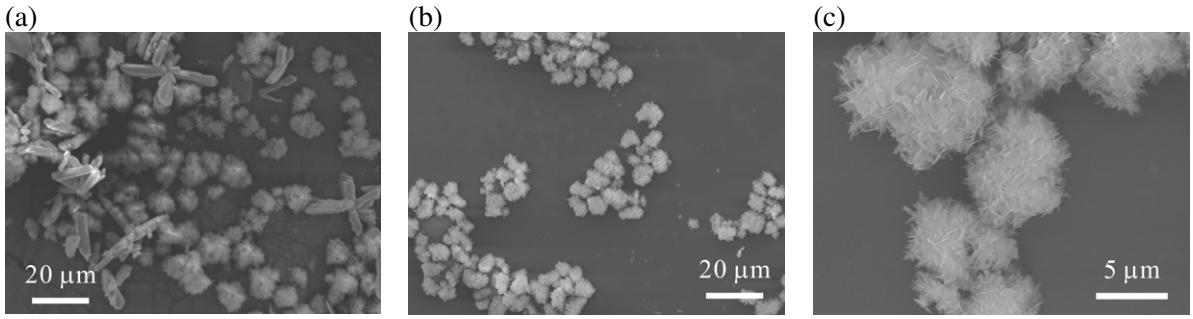

Figure 4. SEM micrographs of the products prepared via the emulsion method.
(a) Tween20 0.5 wt% and Span80 1 wt%, (b) Tween20 0.05 wt% and Span80 5 wt%,
(c) higher magnification of (b).

HAp microspheres reported in the previous paper [4]. Thus, it is confirmed that various calcium phosphates microspheres can be prepared by this emulsion method.

The addition of AE to the inner aqueous phase did not affect the morphology.

The formation mechanism of microspheres in multiple emulsion was inferred as follows. The diameter of the inner aqueous droplets and the oil droplets was 1–5 μm and 20–50 μm, respectively. The size of the microspheres was ~5 μm, almost the same as that of the inner aqueous droplets. Therefore, the formation site of the microspheres is thought to be the inner interface. Span80 molecules make their own clusters, *e.g.* dimers, trimers or micelles, and transfer to the inner interface with accompanied by part of the outer aqueous phase. Whereas calcium ions and hydrogen phosphate ions instantaneously come into contact each other in solution, the contact in emulsion system is slower due to the resistance to diffusion through the oil phase. This retardation can be thought to be the same as the action by an organic additive in the solution method. At lower Span80 concentrations, the stabilization of the inner aqueous droplets is insufficient, resulting in their escape to the outer aqueous phase. Tween20 relates to the transportation of the outer aqueous phase in cooperation with Span80. Too high concentration of these surfactants may cause unnecessarily high transfer rate. Thus, the retardation to particle growth may be reduced.

4. Conclusion

DCPA and DCPD were prepared via a solution method and an emulsion method. DCPA microspheres were produced in the multiple emulsion. The crystalline phase and morphology of them were changed with organic additives.

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