Preparation of Iron Doped Hydroxyapatite Microsphere by Mist Process

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Hydroxyapatite and Fe doped hydroxyapatite microsphere were prepared by mist process using $\text{Ca}(\text{NO}_3)_2$, FeCl_3 and $(\text{NH}_4)_2\text{HPO}_4$ aqueous solutions, and the effects of the preparation condition and Fe doping on the crystal phase, microstructure and other properties were investigated. From XRD analysis, obtained powders were HAp in a single phase at the Ca/P ratio from 1.5 to 2.0, independent from preparation temperature and gas flow rate. In the case of the Ca/P ratio of 1.0, obtained powder was mixed phase of HAp and $\text{Ca}_2\text{P}_2\text{O}_7$. The crystallinity of powders strongly depended on preparation temperature and flow rate of carrier gas and was enhanced with decreasing flow rate of argon and increasing preparation temperature. The SEM observation suggested that the obtained samples had a fine microsphere consisted of further smaller primary grains. The microsphere size of sample was about 1 μm , and size distribution was between 0.5 and 5 μm .

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1. Introduction

Hydroxyapatite (HAp, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) has been widely used as artificial bone and coatings of artificial implant in the medical and dental fields because HAp is chief inorganic element of hard tissue, occupying about 70%, and shows excellent biocompatibility and bioactivity.¹⁻³⁾ Since HAp also shows excellent ion exchange ability, the developments of HAp based functional materials have been performed by doping of functional elements that provide a novel properties to HAp.⁴⁻¹²⁾ For example, the doping of Fe^{3+} and SiO_4^{4-} provides a non-equilibrium of charge balance, and this electrically-charged HAp can be anticipated to use as environmental materials such as water purification and heavy metal ion removal materials.^{13,14)}

From these points of view, morphological design for HAp based materials is important in order to obtain its full functions. Especially, HAp microsphere is expected to be a good candidate for use as drug delivery system (DDS) materials and resource powder of 3D printer. Therefore, HAp based microsphere with wide particle size range from submicron to several mm have been prepared by many kinds of method such as template method, ultrasonic pyrolysis method and aerosol method, so far.¹⁵⁻¹⁸⁾

Mist process is a unique technique to obtain powder and film under the atmospheric conditions, analogous to ultrasonic pyrolysis system (USPS) and chemical transport system. Since mist process has advantages of easy-to-use device configuration and many kinds of solution can be used as a precursor, this method has attracted much attention as a safe and economical method. The principle of mist process is that a liquid precursor is atomized by ultrasonic vibrator, and mist solution is transported by carrier gas to a reaction furnace, then mist precursor thermally decomposes and reacts. Therefore, many kinds of oxides film caused by the thermal decomposition and reaction can be obtained by setting a substrate at heating area, and many studies on the preparation of ZnO , Al_2O_3 and TiO_2 have been reported, so far.¹⁹⁻²²⁾ Besides, oxides powders also can be filtered by

setting the exhaust system at the end of heating tube at the same time, and it is expected that the filtered powders had a sphere shape.

In this study, we prepared spherical Fe-doped HAp particles by mist process and investigated the effect of Fe-doping and preparation condition such as gas flow rate, the Ca/P ratio and preparation temperature on the crystal phase, microstructure and shape of particles.

2. Experimental Procedure

0.1 mol/L $\text{Ca}(\text{NO}_3)_2$, FeCl_3 and $(\text{NH}_4)_2\text{HPO}_4$ aqueous solutions were used as starting materials. The pH of Ca and Fe mixed solution was adjusted to 8 by 1.0 mol/L tris solution, and that of P solution was adjusted to 12 by 5 mol/L NaOH solution. After controlling pH, they were mixed up each other to become the ratio of Ca to P in the range from 1.0 to 2.0. The ratio of Fe changed from 0 to 5 mol% for Ca. The mixed solution was atomized by mist process apparatus. Figure 1 shows a schematic diagram of mist process apparatus. Atomized precursor undergoes drying and nucleation by passing the heated glass tube. Particles were collected by installed exhaust system at the terminal of glass tube. Argon gas was used as a carrier gas, and the flow rate of Ar was changed from 1 to 5 L/min. The preparation temperature was changed in the range from 873 to 1073 K, and the preparation time was fixed at 60 min. The detailed

Fig. 1 Schematic diagram of mist process apparatus.

Table 1 Preparation condition of Ca-P-O powder.

Precursor	
Ca(NO ₃) ₂	0.1 mol/L
(NH ₄)HPO ₄	0.1 mol/L
FeCl ₃	0.1 mol/L
Ca/P ratio	1.0, 1.5, 1.67, 2.0
Fe ratio	1, 2, 5 mol%
Gas species	
Ar	
Flow rate	1, 3, 5 L/min
Preparation temperature	873, 973, 1073 K
Preparation time	60 min

preparation conditions were listed in Table 1. The crystal phase of samples was determined by X-ray diffraction (XRD) using X-ray diffract meter at 30 kV and 15 mA. All scans were run with CuK α radiation from 10° to 60° at a speed of 4°/min. The microstructure of sample was observed by field emission scanning electron microscope (FE-SEM, S-4800, Hitachi High-Technologies, Corp.), and the average grain diameter and specific surface area were measured by BELSORP mini (BEL JAPAN, INC.) and laser diffraction particle size analyzer (SALD-2200, Shimadzu Corp.), respectively.

3. Results

Figure 2 shows XRD patterns of obtained samples prepared at different Ca/P ratio. HAp in a single phase was obtained at the Ca/P ratio of 1.67, and mixed phase of HAp and Ca₂P₂O₇ with low crystallinity was obtained at the Ca/P ratio of 1.0, and mixed phase of HAp and Ca(OH)₂ was obtained at the Ca/P ratio of 2.0, respectively.

Figure 3 shows XRD patterns of samples prepared at the Ca/P ratio of 1.67, the preparation temperature of 1073 K, gas flow rate of 3 L/min and the Fe-doping ratio from 0 to 5 mol%. Although the obtained all samples had HAp phase as a main phase, the peaks derived from Ca(OH)₂ and CaClOH phases were observed as a second phase at the Fe ratio of 2 and 5 mol%.

Figure 4 shows FT-IR spectra of samples prepared at 1073 K, Ca/P ratio of 1.67, flow rate of 3 L/min and Fe ratio of 0 mol% and 1 mol%. Both samples showed HAp in a single phase as shown in Fig. 3. Obtained spectra showed similar tendency with commercial HAp. There was the OH stretching band around 3450 cm⁻¹. The CO₃ ν 3 band was observed at around 1500 and 873 cm⁻¹, respectively. The phosphate bands were observed around 1000 and 580 cm⁻¹.

Figure 5 shows SEM images of samples prepared at the different preparation temperature and the ratio of Fe. Obtained HAp powders had microsphere shape consisted from primary particles of about 10 nm in diameter in all preparation conditions. Although a necking of particle was observed for the HAp microsphere prepared at the 873 K, it was collapsed with increasing the preparation temperature. From the observation of the fragment of HAp microsphere as shown in Fig. 5 (c), it was indicated that the obtained microsphere has a solid structure. In addition, no change in

Fig. 2 XRD patterns of samples prepared at preparation temperature of 1073 K, flow rate of Ar gas of 3 L/min, Ca/P ratio of 1.67 and different Fe ratio.

Fig. 3 XRD patterns of samples prepared at preparation temperature of 1073 K, flow rate of Ar gas of 3 L/min, Ca/P ratio of 1.67 and different Fe ratio; (a) 0 mol%, (b) 1 mol%, (c) 2 mol%, (d) 5 mol%.

the morphology was observed by Fe-doping as shown in Fig. 5 (d).

Figure 6 shows grain size distribution of Fe-doped HAp microsphere prepared at preparation temperature between 973 and 1073 K with the flow rate of 3 and 5 L/min and the Ca/P ratio of 1.67. The average grain diameter of HAp microspheres prepared at the preparation temperature of 973 K was 1.19 μ m at the flow rate of 3 L/min and 1.05 μ m at the flow rate of 5 L/min. In the case of the preparation temperature of 1073 K, the average grain diameter of HAp microsphere was 1.01 μ m at the flow rate of 3 L/min and 1.28 μ m at 5 L/min. The size distribution of samples changed depending on the flow rate of carrier gas, and the sample prepared at the flow rate of 5 L/min had slightly wider size distribution than that prepared at the flow rate of 3 L/min.

Fig. 4 FT-IR spectra of samples prepared at preparation temperature of 1073 K, flow rate of Ar gas of 3 L/min, Ca/P ratio of 1.67 and different Fe ratio; (a) Commercial HAp, (b) 0 mol%, (c) 1 mol%.

Fig. 5 SEM of samples prepared at Ca/P ratio of 1.67, flow rate of Ar gas of 3 L/min and different preparation temperature and Fe ratio; (a) 873 K and 0 mol%, (b) 973 K and 0 mol% (c) 1073 K and 0 mol%, (d) 1073 K and 5 mol%.

4. Discussion

The XRD analysis exhibits that the generation phase of sample is able to control by changing the Ca/P ratio of precursor and HAp phase were obtained in the relatively wider Ca/P ratio from 1.5 to 1.67. The similar trend was obtained in our previous report.²³⁾ Besides, the change in crystallinity was observed at the same Ca/P ratio by changing the gas flow rate and preparation temperature as shown in Fig. 2. The crystallinity of sample increased with decreasing gas flow rate and increasing preparation temperature. This means that the flight time of atomized droplets strongly affect for the crystallinity of samples, and the crystallinity of sample is able to be regulated by changing both of gas flow rate and temperature during the preparation. Generally, HAp phase is stable under basis condition, and it has a trouble of degradation behavior in a living body.

Fig. 6 Grain size distribution of HAp microsphere prepared at Ca/P ratio of 1.67, preparation temperature of 973 and 1073 K and flow rate of Ar gas of 3 and 5 L/min.

Therefore, improvement of degradability of HAp in such a condition has been conspired by elemental substitution and crystallinity control. The mist process has an advantage of crystallinity controllability by relatively simple method, and this process is enables to prepare the powders with different crystallinity by one step.

The generation of $\text{Ca}(\text{OH})_2$ phase as shown in Fig. 3 denotes that the Ca/P ratio in droplets moved to high Ca ratio site, and the generation of CaClOH phase is caused by a condensation reaction between $\text{Ca}(\text{OH})_2$ and Cl^- ion. The crystallinity of samples decreased with increasing Fe ratio, and the similar trend of Fe ratio dependency of crystallinity of HAp phase has been observed in our previous study.²⁴⁾ Although the ratio of Fe in obtained samples increased with increasing additive amount of Fe from the ICP measurement, the actual amount of Fe in the sample was lower than the targeting composition, and that of sample was 0.9, 1.6 and 2.6 mol% for the Ca of HAp, respectively. Fe-based compounds did not observed in a present study as shown in Fig. 3, and this result suggests the possibility of Fe substitution into the HAp structure. In order to investigate the substitution of Fe into HAp structure, the measurement of lattice parameter of HAp phase is efficient method. However, there were no trends depending on change in the ratio of Fe. This result is caused by the existence of CO_3^{2-} ions, which derives from the dissolved CO_2 into atomized droplets during the synthesis, into HAp structure clarified as shown in Fig. 4. It has been understood that the carbonate-substituted HAp is actually more soluble than pure HAp and increases the local concentration of calcium and phosphate ions. This local alignment of these ions are necessary for new bone formation.^{25,26)} This result suggests that the possibility to use the obtained microsphere as a scaffold of artificial implant due to an excellent biodegradability.

The SEM observation exhibits that the mist process is suitable to prepare the microsphere particles. However the necking of particle was partially observed at low preparation temperature as shown in Fig. 5 (a). It is thought that the necking of particle is mainly caused by the insufficient drying

of droplets during the preparation. Therefore, it was easily overcome by applying sufficient thermal energy to atomized droplets during transportation by regulating the gas flow rate and preparation temperature. It is generally understood that the morphology of particle changes from solid to hollow structure depending on the density of atomized droplets. In this process, the evaporation and nucleation in droplets firstly occurs by receiving a thermal energy from the external heat source. Then, precipitates move to the surface of droplets caused by the surface tension and then sintered. During that period, solid spherical powder is obtained in the case of high droplet density. In the case of low droplets density, obtained spherical powder has hollow structure due to the low amount of precipitates. Moreover, when the thickness of the wall consisted of precipitates is thin, hollow structure ruptured due to the inside pressure caused by the further evaporation of droplets. Although the solid spherical powder was obtained in a present study, there is a possibility to prepare the hollow HAp spherical powder by choosing the optimum precursor concentration.

The specific surface area of obtained microsphere using BET method was about $80\text{ m}^2/\text{g}$ at the gas flow rate of 5 L/min and preparation temperature of 1073 K , and that increased to $130\text{ m}^2/\text{g}$ at gas flow rate of 3 L/min . Similar trend was observed in the case of Fe addition. The average particle size of powders is generally estimated from the value of specific surface area. The estimated particle size showed good agreement with the SEM observation and the result of grain size distribution as shown in Fig. 6.

From these results, the mist process is proper technique to prepare the HAp-based microspheres in the particle size range from 0.5 to $5\text{ }\mu\text{m}$, and the possibility of co-substitution of CO_3^- ion with other functional elements was suggested.

5. Conclusion

HAp microsphere was prepared by mist process using 0.1 mol/L $\text{Ca}(\text{NO}_3)_2$, FeCl_3 and $(\text{NH}_4)_2\text{HPO}_4$ solutions. Obtained powders were HAp in a single phase at the Ca/P ratio between 1.5 and 1.67 in all preparation temperature and the flow rate of argon. In the cases of the Ca/P ratio of 1.0 and 2.0 , obtained powder was mixed phase of HAp and $\text{Ca}_2\text{P}_2\text{O}_7$ or $\text{Ca}(\text{OH})_2$. By addition of Fe, $\text{Ca}(\text{OH})_2$ and CaClOH phases generated and the crystallinity of sample decreased with increasing the ratio of Fe. FT-IR measurement showed the existence of CO_3^- ion into HAp structure. From the SEM observation, obtained HAp powders had fine microsphere consisted of further smaller primary grains of about several 10 nm . In addition, obtained HAp microsphere had main grain size of about $1\text{ }\mu\text{m}$ and size distribution between 0.5 and $5\text{ }\mu\text{m}$. From the BET measurement, the HAp microsphere particle had a porous structure and the specific surface area of that was $60\text{--}80\text{ m}^2/\text{g}$.

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