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Synthesis and characterization of hydroxyapatite-based nanocomposites by the functionalization of hydroxyapatite nanoparticles with phosphonic acids

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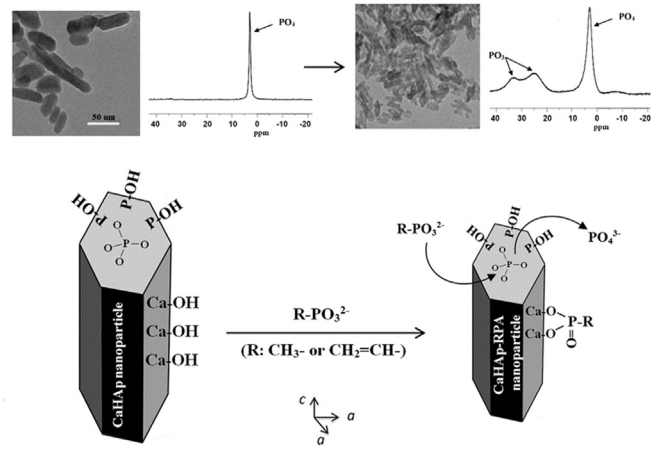
HIGHLIGHTS

- New hydroxyapatite-phosphonate composites were prepared by hydrothermal method using methylphosphonic and vinylphosphonic acids.
- The functionalization of hydroxyapatite nanoparticles with phosphonates is confirmed by several techniques.
- X-ray powder analysis shows the conservation of unique crystalline phase of hydroxyapatite after phosphonic acids reacting.
- MPA exhibited a greater affinity for hydroxyapatite structure compared to VPA.
- TEM observations revealed nanosized crystallites and indicated that the texture surface was changed by the grafting.

GRAPHICAL ABSTRACT



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ABSTRACT

Understanding phosphonates-CaHAp structure interaction and its role in the control of CaHAp particles properties is of interest for the development of biomaterials able for repairing the skeletal system. In this work, the direct synthesis by hydrothermal method of calcium hydroxyapatite (CaHAp)-phosphonic acids (PA) nanocomposites was carried out in the presence of increasing contents of methylphosphonic (MPA) and vinylphosphonic (VPA) acids in the solution. The new CaHAp-PA composite formation was confirmed by IR, Raman and NMR-MAS spectroscopy, and by chemical and thermal analyses. PA amount in composites increased with their added content and MPA showed a greater affinity for CaHAp. A part of PA substituted phosphate groups in CaHAp structure and another was grafted on its surface *via* Ca-OH sites. X-ray powder diffraction showed that the presence of the PA did not inhibit CaHAp nucleation, but reduced the growth of their crystals and affected their crystallinity. TEM observations revealed nanosized

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crystallites and confirmed the dimension reduction, which is in agreement with the increase of the surface area up to 250 $m^2 g^{-1}$. Taken together, the characteristics of the obtained CaHAp-PA nanocomposites suggest their usefulness for the preparation of biomaterials for bone replacement.

1. Introduction

Calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$, CaHAp] is the major inorganic component of bones and teeth, and is widely studied due to its excellent biocompatibility and bioactivity. It is well known that CaHAp has high reactivity with many organic molecules such as amino acids [1], carboxylic acids [2], organosilanes [3], methacrylates [4], bisphosphonates [5,6], alcohols [7] and polymers [8]... This high reactivity is mainly due to the presence of two active sites ≡Ca—OH and ≡P—OH on its surface as well as to the high capacity of CaHAp to incorporate substituents in its structure [9,10]. Therefore, the interaction of organic molecules with CaHAp has received great interest in many fields, in particular biology (biomineralization, biomaterials, biochemistry and biosensors) [11–14].

Several studies have paid attention to the modification of CaHAp with various organic substances for the regulation of its surface chemical and physical properties (hydrophilicity, hydrophobicity, surface roughness...), as well as structural properties of its particles (crystalline order, crystal growth...). The addition of aspartic and glutamic acids during wet-state synthesis induces morphological changes in CaHAp nanoparticles through the inhibition of crystal growth by preferential adsorption of the added amino acids onto CaHAp surface [15]. The modification of CaHAp nanoparticle surface with the polycaprolactone graft is also described [16]. The research showed that grafted polycaprolactone on CaHAp surface enhanced the colloidal stability, and the CaHAp could be well dispersed in organic solvents. The possibility to synthesize CaHAp particles containing phenyl and alkyl phosphonic acids was also demonstrated [17,18]. Studies showed that the phosphonate introduced into the apatite lattice has a strong effect on its specific surface area and porosity. Grafting of oleylphosphate molecules to the surface of CaHAp particles carried out by a co-precipitation method was succeeded [19], making the particles more hydrophobic. Other studies were devoted to the morphological control of CaHAp crystal growth, for example, through a polymeric route using calcium nitrate and phenyldichlorophosphine as starting materials enabling the formation of hydroxyapatite layers [20].

Phosphonic acids such as methyl and terbutylphosphonic acids [18], phenylphosphonic acid [17], phosphonoformic acid [21], *tert*-butyl phosphonic and 2-carboxyletylphosphonic acids [22] were among the well-used organic molecules for the functionalization of CaHAp nanoparticles. Phosphonates have important applications in the biomineralization process, most importantly to control the remodeling of bone in the treatment of osteoporosis and other diseases of bone metabolism [23–26]. The various biological uses of phosphonate function are driven by their four combined features, namely tetrahedral geometry, their ability to form electrostatic interactions and hydrogen-bonds, as well as their capacity to accommodate diverse metal ions [27].

Understanding how the phosphonates interact with CaHAp structure and clarifying their role in the control of the properties of the CaHAp particles is of interest for the development of biomaterials suitable to repair the skeletal system as well as for a better elucidation of the natural processes. To this aim, we carried out a structural, morphological and chemical investigation of CaHAp nanoparticles synthesized by hydrothermal method in the presence of increasing amounts of methylphosphonic acid (MPA) and vinylphosphonic acid (VPA).

2. Experimental

2.1. Synthesis and functionalization of CaHAp nanoparticles

The synthesis of pure CaHAp nanoparticles was carried out in aqueous medium using the hydrothermal method [22]. Twenty milliliters of ammonium dihydrogen phosphate solution (0.25 M) was mixed at stirring with 11.2 mL of calcium nitrate solution (0.75 M). The pH of the mixture was maintained at 10 by the addition of ammonium hydroxide solution (NH_4OH) under nitrogen gas. The resulting mixture was treated in an autoclave (50 mL) at 120 °C for 15 h. After filtration and washing with hot water, the obtained precipitate was dried at 100 °C overnight.

The functionalization of CaHAp nanoparticles with MPA and VPA was obtained according to the same above procedure except for the phosphate solution (0.25 M), it was prepared by mixing MPA or VPA (P_{org}) and ammonium dihydrogen phosphate (P_{inorg}) with atomic ratios P_{org}/P_{inorg}: 0%, 10%, 20% and 30%. The new products were CaHAp, CaHAp-$(RPA)_{10}$, CaHAp-$(RPA)_{20}$ and CaHAp-$(RPA)_{30}$, respectively (R = M or V).

2.2. Characterization techniques

X-ray diffraction (XRD) powder patterns were collected on a Panalytical X'Pert PRO MPD diffractometer (Cukα radiation, 40 kV, 30 mA, step size of 2θ = 0.05°). The lattice parameters were calculated by the EXPO program. The crystallite sizes were calculated using the Debye-Scherrer equation: $D = K\lambda/(\beta_{1/2}\cos\theta)$ [28], where λ is the wavelength of monochromatic X-ray beam (λ = 1.5418 Å for CuKα radiation), θ is the diffraction angle (°), K is a fixed constant equal to 0.9 for apatite crystallites and $\beta_{1/2}$ is line width at half maximum of a given reflection (rad). Infrared measurements (ATR-FTIR) were carried out on a Brucker IFS 66 V spectrometer (400–4000 cm^{-1}). The spectral resolution was 2 cm^{-1} and 64 scans were co-added for each spectrum. Measurements were performed using an attenuated total reflectance (ATR) device equipped with a diamond crystal allowing single reflection. Raman spectra (FTR) were acquired using a Horiba LabRAM 800 HR spectrometer equipped with a He-Ne (632.8 nm) laser. The laser was focused on the sample with a 5 μm confocal hole using the 100X objective. The ^{31}P MAS NMR measurements of the cross-polarization ($^1H \rightarrow {}^{31}P$ CP) were realized using a Bruker Avance 800 (rotor 3.2 mm, spinning rate 15 KHz). ^{13}C and ^1H MAS NMR spectra were recorded on a Bruker Avance 500 spectrometer (rotor 4 mm, spinning rate 7 KHz) and a Bruker Avance 300 spectrometer (rotor 4 mm, spinning rate 10 KHz), respectively. Solution-state ^{31}P NMR spectra were recorded in D_2O using Bruker Avance 300 spectrometer (121.4 MHz). The calcium and phosphorus contents were obtained by ICP-OES on a Horiba Jobin Yvon Model Activa. The analysis of carbon was made using a Perkin Elmer CHN Analyzer. Thermal analysis experiments were performed in the air flow at a heating rate of 10°/min in a Pt crucible with SETARAM SETSYS 1750 equipment. Specific surface area (S_{BET}) were determined by Brunauer–Emmett–Teller (BET) method (adsorptive gas N_2) using