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Time and temperature mediated evolution of CDHA from ACP nanoparticles in deep eutectic solvents: Kinetic and thermodynamic considerations

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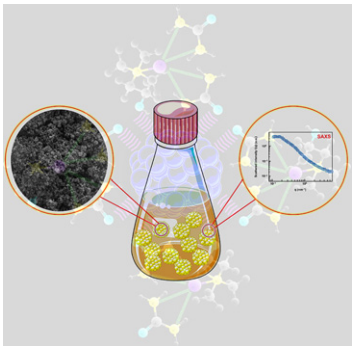
HIGHLIGHTS

- ACP and CDHA nanoparticles were synthesized in choline chloride-urea DES.
- ACP nanoparticles with diameter of 29 nm were synthesized at 25 °C after 10 min.
- CDHA nanoparticles with crystalinity of 97% were obtained at 150 °C after 24 h.
- $\Delta G_{crystal\ growth}$ increased from $3.2 \times 10^{+2}$ (at 25 °C) to $4.5 \times 10^{+2}$ KJ·mol^{-1} (at 150 °C).
- SAXS analysis revealed the electrosteric stabilization of ACP nanoparticles by DES.

GRAPHICAL ABSTRACT



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ABSTRACT

Calcium phosphate (CP) nanoparticles were synthesized in choline chloride-urea deep eutectic solvent (DES). The effect of synthesis time and temperature on crystallinity, particulate properties, and elemental/chemical purity of the CP nanoparticles were investigated by X-ray diffraction, field emission scanning electron microscopy, energy dispersive X-ray spectroscopy, and Fourier transform infra-red spectroscopy. The results confirmed the formation of amorphous calcium phosphate (ACP) nanoparticles (at 25 °C for 10 min) with spherical morphology, mean diameter of 29 nm, and high elemental-structural purity. The increase of synthesis time from 10 min to 48 h at 25 °C had no significant influence on the phase transformation of ACP nanoparticle so that the nanoparticles showed high degree of amorphization after 48 h. The crystallization of particles rapidly rose upon increase of the synthesis temperature so that the nanoparticles of calcium-deficient hydroxyapatite (CDHA) with percent crystallinity of ~97% were obtained in choline chloride-urea DES at 150 °C after 24 h. Kinetic and thermodynamic studies revealed that upon increase of temperature from 25 to 150 °C, the rate constant and Gibbs free energy for growth of CP crystals in the DES rises from 8.70×10^{-4} to 1.37×10^{-3} min^{-1} and $3.22 \times 10^{+2}$ to $4.57 \times 10^{+2}$ KJ·mol^{-1}, respectively.

1. Introduction

In recent years, calcium phosphates (CPs) have attracted a great deal of interest for hard tissue engineering. This interest seems to be driven by the excellent biocompatibility, bioresorbability and bioactivity of

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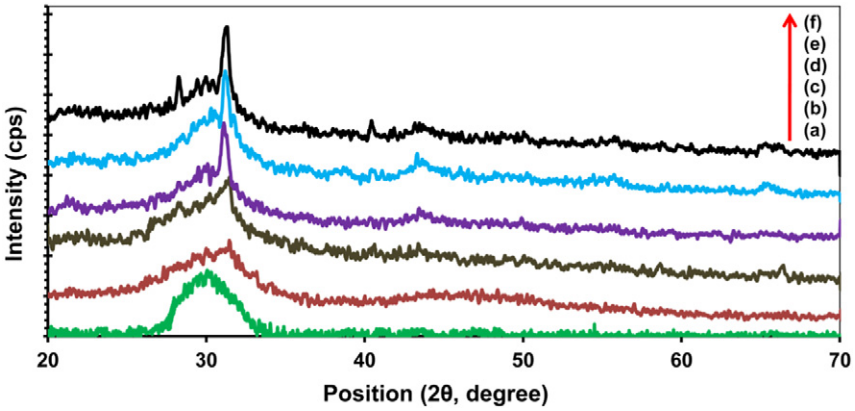

Fig. 1. XRD patterns of the CP nanoparticles synthesized at 25 °C at time intervals of 10 min (a), 1 h (b), 3 h (c), 6 h (d), 24 h, and 48 h (f).

CPs arising from their chemical and structural similarity to human hard tissues [1–4]. They exist throughout the body in the form of a non-stoichiometric, ion-substituted and calcium-deficient hydroxyapatite (CDHA, commonly referred to as "biological apatite") [5–7]. The calcium-deficient hydroxyapatites ($Ca_{10-x}(PO_4)_{6-x}(HPO_4)_x(OH)_{2-x}$, $0 \le x \le 1$) with a Ca/P molar ratio of 1.5 are of greater biological importance than stoichiometric apatite since the Ca/P ratio in bone is close to 1.5 [8].

It is well established that nanosized and nanocrystalline calcium phosphates can mimic the dimensions of the building blocks of mammalian calcified tissues. Thus, they can be utilized in biomineralization because of their improved biocompatibility and bioactivity [6]. In both biomimetic mineralization (in vitro) and biomineralization (in vivo) processes, a thermodynamically metastable phase, amorphous calcium phosphate (ACP, $Ca_9(PO_4)_6$), is formed rapidly in the initial stages of the process that finally transforms into a more stable apatite phase [9]. As one of the most frequent forms of CaP materials in biological organisms, ACP plays an important role in the formation of in vivo apatite layer analogous to bone mineral [3,6]. In addition, the promising biocompatibility and bioresorbability of ACP nanoparticles make them interesting candidates for various biomedical applications [3].

To date, several methods have been developed for the synthesis of CaP nanomaterials such as ACP and CDHA nanoparticles; of them the precipitation method [10], hydrothermal synthesis [11], sol-gel method [12], mechanochemical synthesis [13], and spray pyrolysis [14] can be mentioned. Using harsh synthesis conditions and employing poisonous and unsafe precursors, solvents and surfactants as well as the possible contamination of final CaP product with additional ions resulted from dissolution of precursors (that strongly influences the chemical, physical and biological properties of CaP) are the major challenges faced by the foregoing methods [15]. In addition, due to the inherent instability of the ACP especially in solution media, synthesis of ACP nanoparticles with high amorphization degree which remain stable for a reasonable period of time is often problematic [16].

As a continuation of our earlier works [17–19], herein we have reported a green and facile method based on choline chloride-urea deep eutectic solvent (DES) for synthesis of ACP and CDHA nanoparticles under different time-temperature conditions. As a new generation of sustainable solvents, DESs are regarded as green analogues of ionic liquid [20,21]. DESs are mostly obtained via complexation of quaternary ammonium salts (choline chloride) with hydrogen bond donors (amines, amides, alcohols and carboxylic acids [20,22]). Because of their unique properties such as high solubilizing power, high ionic conductivity, good thermal stability, low vapor pressure, green entity, biocompatibility, and ease of preparation/handling, the DESs are in the process of establishing themselves as one of the foremost choices for application in various areas of science and technology including synthesis of nanomaterials [22,23]. Our hypothesis was that due to the supramolecular structure, high thermal stability and the proper acidity required for synthesis/stabilization of ACP and CDHA, the DESs provide a suitable medium for both stabilization and conversion of ACP to CDHA. In the present study, the optimum conditions for synthesis of ACP and CDHA nanoparticles in the DES medium have been provided. To this end, the kinetics and thermodynamics of CDHA crystal growth and mechanism of ACP stabilization/transformation have been explored by X-ray diffraction (XRD), field emission scanning electron microscopy (FESEM), energy dispersive X-ray spectroscopy (EDS), Fourier transform infrared spectroscopy (FTIR), and small angle X-ray scattering (SAXS).

Table 1
Diffraction characteristics of calcium phosphate nanoparticles synthesized at 25 °C at different time intervals.

Synthesis time	Emerged crystalline peaks	Main peak intensity (cps)	Main peak position (2θ)
10 min	Amorphous	80 (Amorphous)	30° (Amorphous)
1 h	(211)	85 (211)	31.19°
3 h	(211)	91 (211)	31.28°
6 h	(210), (211)	97 (211)	31.33°
24 h	(102), (210), (211)	121 (211)	31.33°
48 h	(102), (210), (211), (310)	135 (211)	31.46°

2. Experimental

2.1. Materials

Calcium chloride anhydrous ($CaCl_2$, ≥98.0%), di-potassium hydrogen orthophosphate (K_2HPO_4, 98.0–100.5%), choline chloride ($C_5H_{14}ClNO$, 98.0–100.5%), and urea (CH_4N_2O, ≥99.0%) were obtained from Merck Chemicals (Germany) and used as received without any purification.

2.2. Preparation of deep eutectic solvents (DESs)

To obtain a homogeneous and liquid DES at room temperature, 1 mol of choline chloride was mixed with 2 mol of urea and the resulted mixture was heated up to 100 °C for 1 h until a colorless liquid was formed. The as-prepared DES was designated as CU.

2.3. Synthesis of calcium phosphate nanoparticles

Briefly, a solution (0.12 M) of anhydrous calcium phosphate, $CaCl_2$, was prepared in the as-prepared DES. Then, an aqueous solution (0.81 M) of di-potassium hydrogen phosphate, K_2HPO_4, was added to the eutectic solution containing calcium ions. The solution was stirred vigorously at temperatures of 25, 35, 55, 100, and 150 °C for different time intervals ranging from 10 min to 48 h. After the desired time, the emerged precipitates were filtered, washed five times with deionized