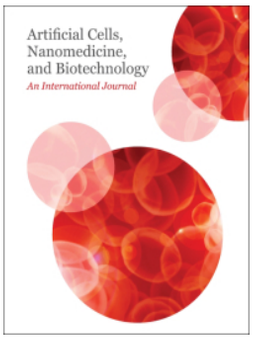

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Synthesis, characterization, biocompatibility of hydroxyapatite–natural polymers nanocomposites for dentistry applications

Jin-Hwan Chung[1], Young Kyung Kim[3], Kyo-Han Kim[1,2], Tae-Yub Kwon[1,2], Seyede Ziba Vaezmomeni[5], Mohammad Samiei[5], Marzyeh Aghazadeh[5], Soodabeh Davaran[4], Mehrdad Mahkam[5], Ghale Asadi[5] & Abolfazl Akbarzadeh[4]

[1]*Department of Medical and Biological Engineering, Graduate School, Kyungpook National University, Daegu, Republic of Korea,* [2]*Department of Dental Biomaterials, School of Dentistry, Kyungpook National University, Daegu, Republic of Korea,* [3]*Department of Conservative Dentistry, School of Dentistry, Kyungpook National University, Daegu, Republic of Korea,* [4]*Department of Medical Nanotechnology, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran, and* [5]*Department of Endodontics, Dental School, Tabriz University of Medical Sciences, Tabriz, Iran*

Abstract

Hydroxyapatite (HA), the main mineral component of bones and teeth, was synthesized by using the reaction between calcium nitrate tetrahydrate $Ca(NO_3)_2{\cdot}4H_2O$ and diammonium hydrogen phosphate $(NH_4)_2HPO_4$ (DAHP) with a chemical precipitation method. The objective of this study is to utilize novel inorganic–organic nanocomposites for biomedical applications. HA is an inorganic component (75% w) and chitosan, alginate and albumin (Egg white) are organic components of nanocomposites (25% w). Nanocomposites were prepared in deionized water solutions, at room temperature, using a mechanical and magnetic stirrer for 48 h. The microstructure and morphology of sintered n-HAP were tested at different preheating temperature and laser sintering speed with scanning electron microscopy (SEM), X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR).

Keywords: biomedical applications, hydroxyapatite, inorganic–organic nanocomposite, natural polymers

Introduction

Bone is a composite consisting of 69% hydroxyapatite (HA; inorganic component), 20% collagen type I (organic matrix) and 9% water (Tathe et al. 2010). HA $[Ca_{10}(PO_4)_6(OH)_2]$ is the main mineral component of bones, teeth and Sea corals (Ratner et al. 2004, Thamaraiselive and Rajeswari 2004). HA ceramic attracted many interest because of its excellent biocompatibility, bioactivity, osteoconductivity and osteoinductivity (Deer and Howie 1985, Wang 2003). HA particles have been used extensively for dental and bone repair and tissue engineering (Nayak 2010, Bouyer et al. 2000, Ferraz et al. 2004, Santos et al. 2004, Manuel et al. 2003, Jarcho et al. 1977, Janackovic et al. 2001, Balamurugan et al. 2006). In addition, HA has been studied as carriers of protein (Balamurugan et al. 2006, Manso et al. 2000), antibiotics and antibacterials (Brendel et al. 1992) anticancer (Takahashi et al. 1995), growth factor (Manafi and Joughehdoust 2009), etc(1). Several methods have been used for the synthesis of HA including sol–gel approach (Santos and Luklinska 2001, Montazeri and Jahandideh 2011), hydrothermal technique (Athanasiou et al. 2000, Sopyan et al. 2007, Lee 2005), electrodeposition technique (Weiner et al. 1999), precipitation technique, (Myer 2003, Teoh 2004, Yaszemski et al. 1996, Nair and Laurencin 2006, Drotleff and Lungwitz 2004) multiple emulsion technique (Wang and Li 2007), and spray drying method (Oliveiraa et al. 2006). Practically, the HA particles have been used as bone scaffolds to prove an improved bone in-growth and osseointegration (Brendel et al. 1992). However, the brittleness and low strength limited their wider applications in hard tissue implants (Lim 1999, Peppas and Mikos 1986, Bouwstra and Jungiger 1993). So composites of HA synthesis and natural polymers were prepared and used as dental and bone replacement implants. Elkady et al. have reported the synthesis of HA–polyvinyl alcohol nanocomposites and investigated the in vitro bioactivity test (Deer and Howie 1985). Kazemzadeh et al. reported the fabrication of HA–gelatin composite scaffolds for bone tissue engineering application (Thamaraiselive and Rajeswari 2004). Cui et al. have reported the preparation of nano-HA/collagen/PLA composite by biomimetic synthesis and investigated the

Correspondence: Tae-Yub Kwon, Department of Medical & Biological Engineering, Graduate School, Kyungpook National University, Daegu 700-412, South Korea. Tel/Fax: +82-53-660-6891. E-mail: zheng@keiti.re.kr; Abolfazl Akbarzadeh, Department of Medical Nanotechnology, Faculty of Advanced Medical Science, Tabriz University of Medical Sciences, Tabriz, Iran. Tel/Fax: +984113355789. E-mail: akbarzadehab@tbzmed.ac.ir; Mohammad Samiei and Marzyeh Aghazadeh, Department of Endodontics, Dental School, Tabriz University of Medical Sciences, Tabriz, Iran. Tel/Fax: +989124195987. E-mail: samiei.moh@gmail.com.

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Table I. The components of each sample.

Nanocomposite	Hydroxyapatite	Chitosan	Alginate	Albumin
S_1	75% w (3 g)	5% w (0.4 g)	0% w	20% w (0.8 g)
S_2	75% w (3 g)	15% w (0.8 g)	0% w	10% w (0.4 g)
S_3	75% w (3 g)	0% w	15% w (0.4 g)	10% w (0.8 g)
S_4	75% w (3 g)	0% w	10% w (0.8 g)	15% w (0.4 g)
S_5	75% w (3 g)	0% w	0% w	25% w (1.2 g)

in vitro and in vivo studies (Wang 2003). Reis et al. have reported the synthesis of novel HA–chitosan bilayered scaffold (Bouyer et al. 2000). Lavrynenko et al. reported the preparation of HA–chitosan composite made by a one-step co-precipitation method and investigated the in vivo study (Ferraz et al. 2004). Zargarian et al. carried out the synthesis of nanofibrous composite scaffold of PCL/HA–chitosan/PVA (Santos et al. 2004). Kalpana et al. have reported the synthesis of chitosan–polygalacturonic acid/HA nanocomposites for in vitro study (Manuel et al. 2003). Chitosan is a deacetylation derivative of chitin (Ferraz et al. 2004). Chitosan attracted many interest because of its excellent nontoxic, biodegradable, biocompatibility (Granja et al. 2004, Vijayalakshmi and Rajeswari 2006). So it has been widely used as biomaterials in pharmaceutical and medical fields such as tissue engineering scaffolding, as well as collagen (Santos et al. 2004). Alginic acid (Alg) is a natural heteropolysaccharide and a linear copolymer composed of two monomeric units, D-mannuronic acid and L-guluronic acid (Barinov et al. 2008, Kimura 2007). Alginate attracted many interest because of its excellent nontoxic, biodegradable, biocompatibility (Stamatialis and Papenburg 2008, Manso et al. 2000). So it has been widely used as biomaterials in pharmaceutical and medical fields such as tissue engineering scaffolding and drug delivery systems (Oh et al. 2006, Xuan et al. 2009).

In this work, HA–natural polymers nanocomposites were successfully synthesized. The structure and morphology of the nanocomposites were investigated by XRD, EDX, FT-IR and SEM. Finally, in vitro cytotoxicity testing on the nanocomposites was investigated.

Materials and methods

Materials

Calcium nitrate tetrahydrate ($Ca(NO_3)_2{\cdot}4H_2O$), diammonium hydrogen phosphate ($(NH_4)_2HPO_4$ (DAHP), ammonia solution (25%) and triethanolamine (TEA) were purchased from Merck (Germany). Chitosan (75% degree of deacetylation) and sodium alginate were purchased from Sigma-Aldrich (St Louis, MO). Ammonium chloride (NH_4Cl) was purchased from Fluka (Buchs, Switzerland). The infrared spectra of the nanocomposites were recorded on a Perkin Elmer 983 infrared spectrophotometer (Perkin Elmer, Boston, MA) at room temperature. X-ray powder diffraction using a Rigaku D/MAX-2400 X-ray diffractometer with Ni-filtered Cu Kα radiation and scanning electron microscopy measurements were conducted using a VEGA/TESCAN.

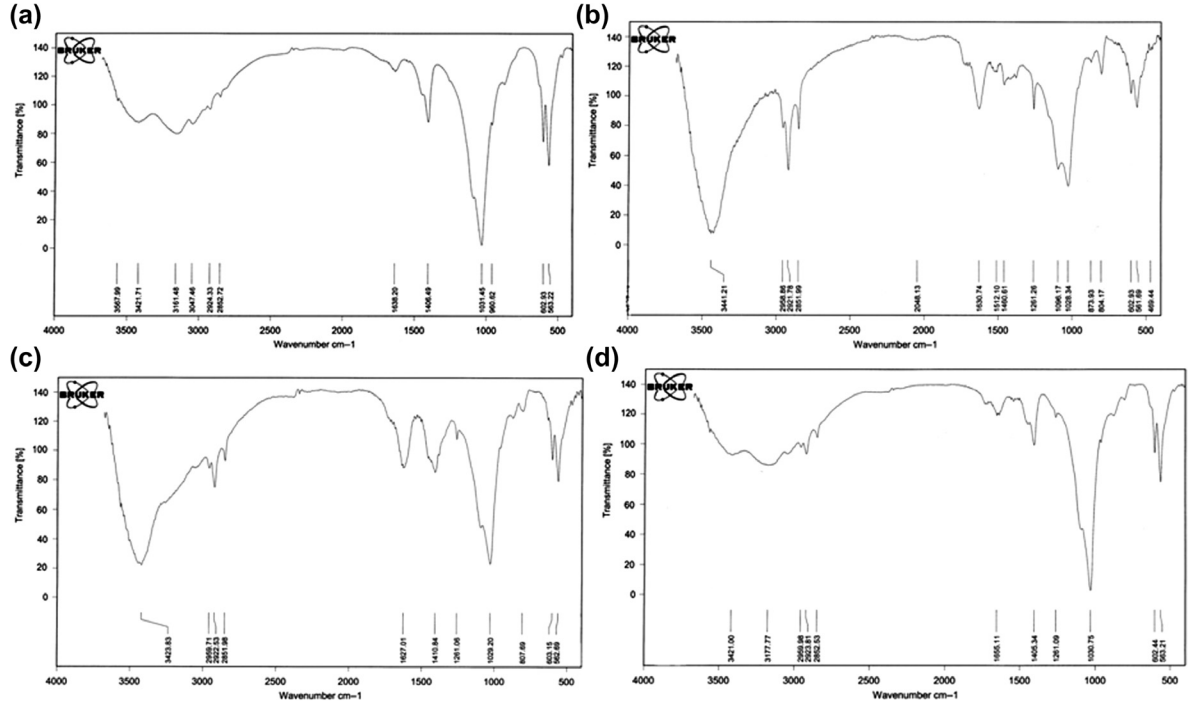

Figure 1. Fourier transform infrared spectroscopy (a) structure of HA, (b) HA/chitosan–albumin nanocomposite, (c) HA/alginate–albumin nanocomposite, and (d) HA/albumin nanocomposite.

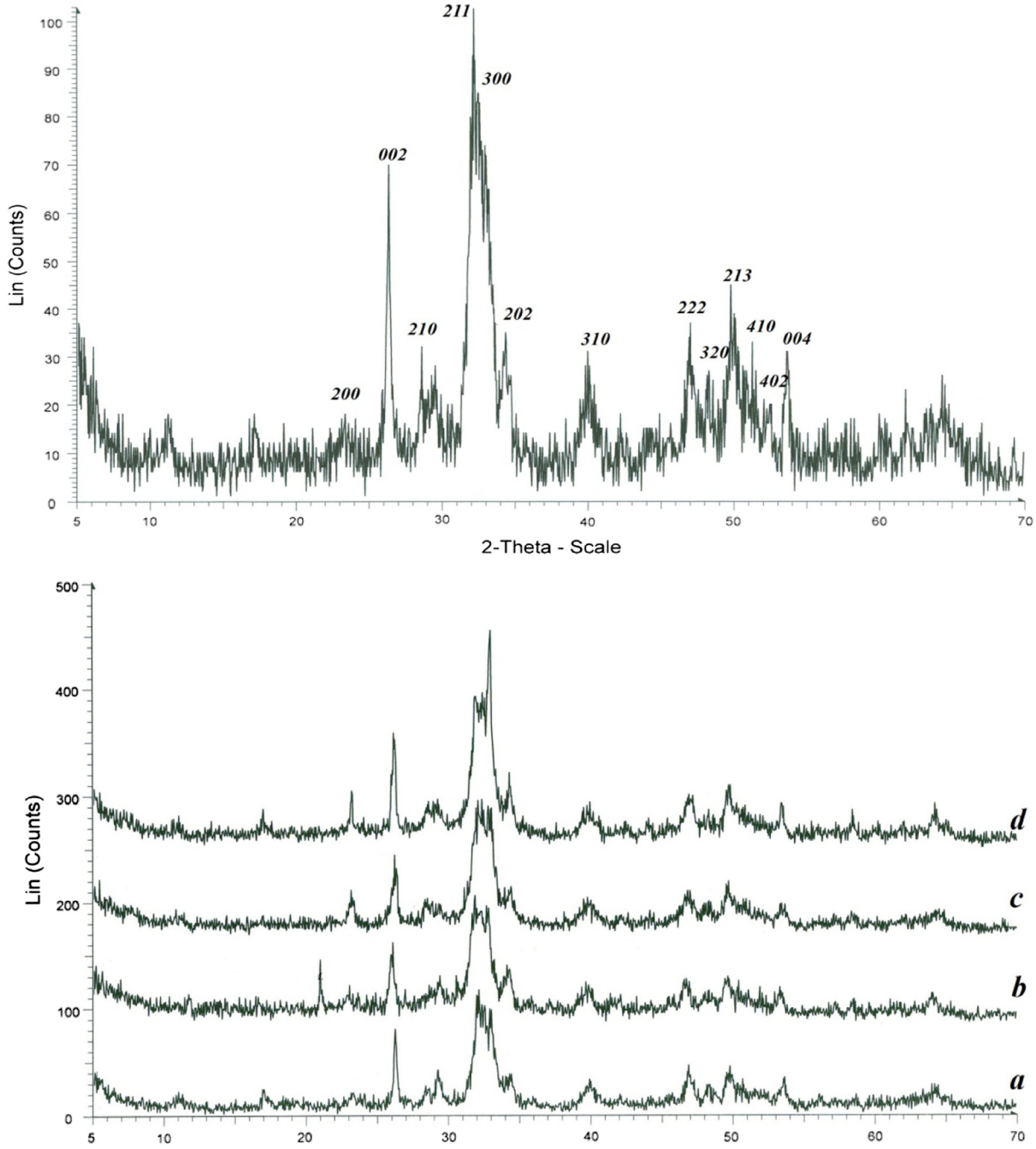

Figure 2. Shows the X-ray diffraction patterns for the pure HA (a) and HA–natural polymers nanocomposites (b–d).

Methods

Synthesis of Nano-Hydroxyapatite (n-HA)

In this work, HA nanoparticles were synthesized using a chemical precipitation method (Harris 1984, Kumar 2006). According to this method, 6.5 g of $Ca(NO_3)_2{\cdot}4H_2O$ (0.033 mol) and 4.3 g of diammonium hydrogen phosphate (0.035 mol) were dissolved in 50 and 45 mL of deionized water, respectively, with ratio Ca/P = 1.7. Triethanolamine (TEA; 1.8 g) (0.013 mol) was used in conjunction with $Ca(NO_3)_2{\cdot}4H_2O$ solution (Ca^{2+}:TEA = 1:0.6). The pH of both calcium nitrate and DAHP solutions was maintained at ~11–12. $(NH_4)_2HPO_4$ solution was added drop-wise to the mixture of $Ca(NO_3)_2{\cdot}4H_2O$ and TEA, stirred using a mechanical stirrer for 5 h. The pH of the reacting mixture was also maintained at ~11–12 by adding NH_4OH solution. A white gelatinous precipitate was formed, which was filtered by a centrifugal filtration process and washed with deionized water and NH_4Cl solution, so dried at 85°C for 20 h (Akbarzadeh et al. 2012c, Ebrahimnezhad et al. 2013, Alimirzalu et al. 2014, Hosseininasab et al. 2014, Rezaei-Sadabady et al. 2013, Nejati-Koshki et al. 2013, Ghasemali et al. 2013, Mollazade et al. 2013, Akbarzadeh et al. 2014, Akbarzadeh et al. 2013a, Ahmadi et al. 2014, Alizadeh et al. 2014c).

Preparation of HA–natural polymers nanocomposites

In this part, five samples were prepared using HA (75% w) and natural polymers (25% w) (chitosan, alginate, albu-

min) as inorganic and organic components of nanocomposites, respectively (Fuge and Saltzman 1997, Vert et al. 1991, Kaye 1989, Langer 1990).

Preparation of sample 1: 0.4 g chitosan was dissolved in 15 ml acetic acid 5% w/v solution using a magnetic stirrer at room temperature for 4 h. HA (3 g) was added slowly to the chitosan solution and stirred with a magnetic stirrer for 36 h. After creating homogeneous suspension, 0.8 g albumin was added to the suspension and stirred using mechanical and magnetic stirrer for 25 h at mentioned conditions. These conditions were established for the synthesis of other samples. Sample 2 was synthesized in the same way. However, in the synthesis of other samples was not used acetic acid solution. The resulting suspension was placed in the frozen overnight. The following Table I shows the components of each sample (Pourhassan-Moghaddam et al. 2014, Anganeh et al. 2014, Davoudi et al. 2014, Akbarzadeh et al. 2012b, Valizadeh et al. 2012, Akbarzadeh et al. 2013b, Pourhassan-Moghaddam et al. 2013, Kouhi et al. 2014, Sadat Tabatabaei Mirakabad et al. 2014, Eatemadi et al. 2014b, Abbasi et al. 2014b, 2014c).

Results and discussion

Characterization

The infrared spectra were recorded using a Fourier transform infrared spectrophotometer (FT-IR, Nicolet NEXUS 670; Thermo Scientific, Waltham, MA), and the sample and KBr were pressed to form a tablet. Powder X-ray diffraction (Rigaku D/MAX-2400 X-ray diffractometer with Ni-filtered Cu Kα radiation) was used to investigate the crystal structure of the nanocomposites. The infrared spectra of the nanocomposites were recorded on a Perkin Elmer 983 infrared spectrometer (Perkin Elmer) at room temperature. The size and shape of the nanocomposites were determined using a scanning electron microscope (VEGA/TESCAN), whereby a sample was dispersed in ethanol and a small drop was spread onto a 400 mesh copper grid.

Fourier transform infrared spectroscopy (FT-IR)

Fourier transform infrared spectroscopy was used to show the structure of HA (Figure 1a), HA/chitosan–albumin nanocomposite (Figure 1b), HA/alginate–albumin nanocomposite (Figure 1c) and HA/albumin nanocomposite (Figure 1d).

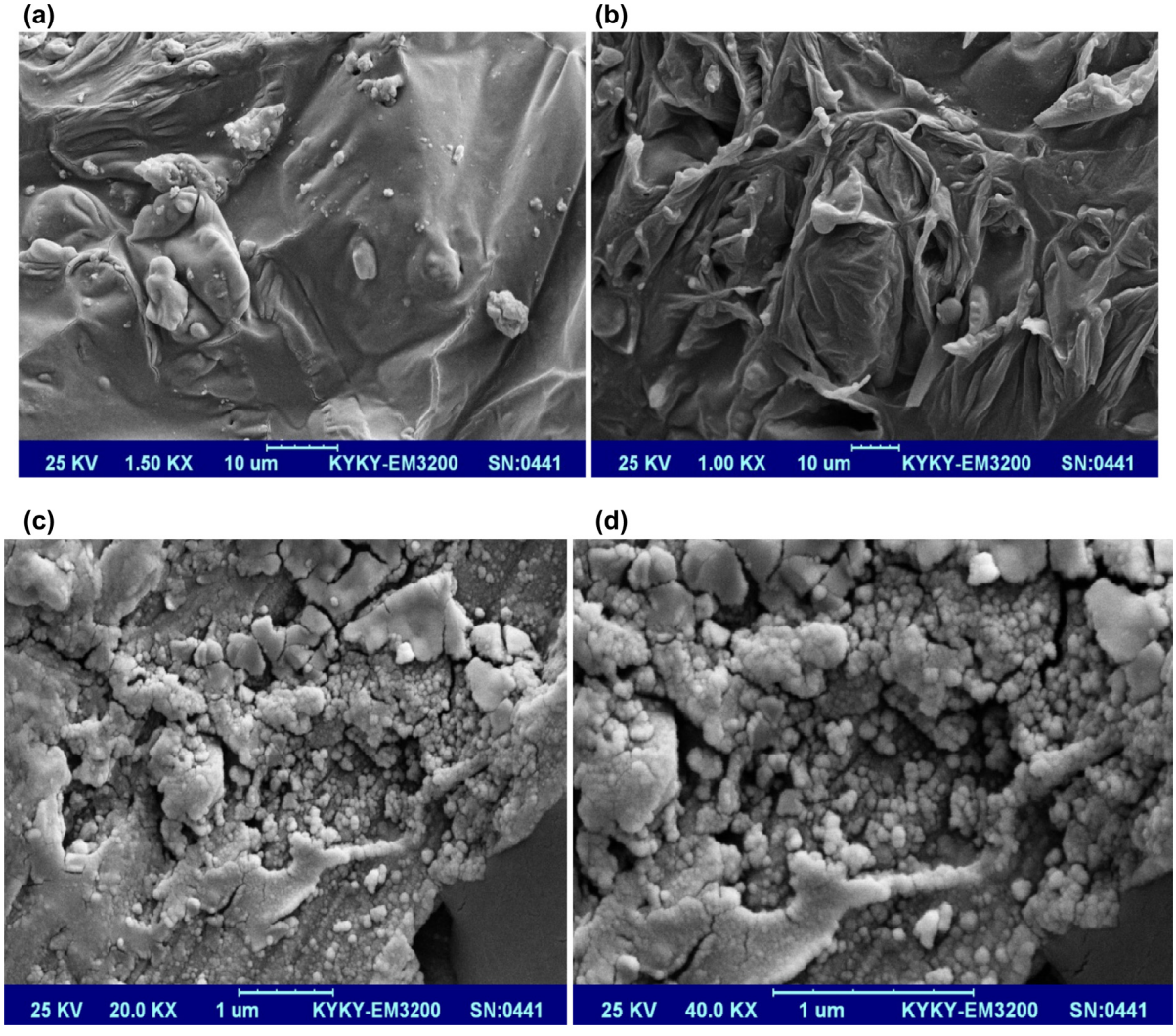

Figure 3. (a) SEM of pure hydroxyapatite, (b) hydroayapatite/chitosan–albumin, (c) hydroxyapatite/alginate–albumin, (d) hydroxyapatite/albumin.

From the infrared spectra shown in Figure 1a, the absorption peaks at 3422 cm^{-1} correspond to the stretching vibration of H–O bonds in HA. Comparing the infrared spectra in Figure 1b–d, HA–natural polymers showed absorption peak at 3440 attributable to the stretching vibrations of H–O bonds in HA and chitosan, N–H bonds in chitosan and albumin (Figure 1b), stretching vibration of H–O bonds in HA and alginate, N–H bonds in albumin (Figure 1c), stretching vibration mode of O–H bonds in HA and N–H bonds in albumin (Figure 1d). A peak at 1631 cm^{-1} (Figure 1b), 1627 cm^{-1} (Figure 1c) and 1655 cm^{-1} (Figure 1d) corresponds to stretching vibration of carbonyl groups in natural polymers. The absorption peaks at 1512–1461 cm^{-1} and 1030, 603, 563 cm^{-1} attributable to the CO_3^{-2} and PO_4^{-3} groups in HA, respectively (Figure 1a–d) (Alizadeh et al. 2014b, Nejati-Koshki et al. 2014a, Ghalhar et al. 2014, Karnoosh-Yamchi et al. 2014, Alizadeh et al. 2014a, Zohre et al. 2014).

X-ray diffraction patterns

Figure 2 shows the X-ray diffraction patterns for the pure HA (a) and HA–natural polymers nanocomposites (b–d). It can be concluded from Figure 2 that the diffraction peaks of sintered n-HAP under different preheating temperature are basically the same in position and number with that of initial n-HAP, which means n-HAP remains undecomposed after preheated and sintered (Kost and Langer 1984, Mirth 1980, Dash and Cudworth 1998). The diffraction peaks become higher and the peak (2 1 1) became narrower after sintered, which indicated that n-HAP grains have grown up and the degree of crystalline increases with the increase of preheating temperature. The results are consistent with the analysis of FT-IR and SEM. The width B of a diffraction peak is the comprehensive effects of grain size and strain broadening. So the Hall–Williamson method (Eq. (1)) was adopted to calculate grain size (Nejati-Koshki et al. 2014b, Fekri

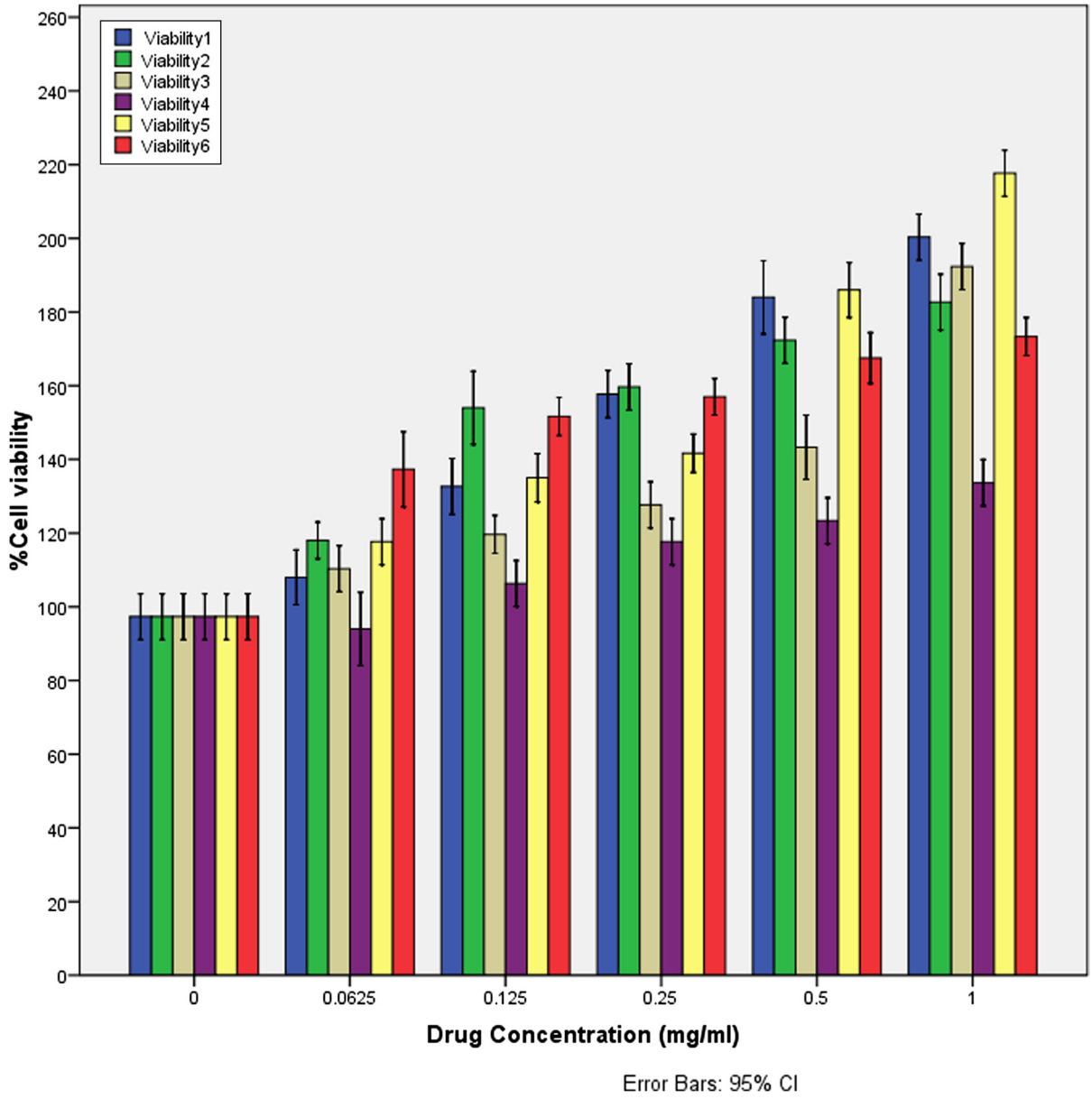

Figure 4. Cytotoxicity in the MG-63 cell line.

Aval et al. 2014, Abbasi et al. 2014a, Eatemadi et al. 2014a, Ebrahimi et al. 2014).

$$\beta_{tot}\cos\theta = C\varepsilon\sin\theta + K\lambda/L \quad (1)$$

Here β is the strain in the crystallites, D represents the size of the crystallites, the constant k is typically close to unity and ranges from 0.8 to 1.39, θ is the Bragg angle, and λ is the X-ray wavelength, which equals to 1.54056 Å (Apicella and Hopfenberg 1978, Flooladi 1978, Banker 1984, Benedtti et al. 1990).

The absorption peaks at (0 0 2), (2 1 1) and (3 0 0) are the main crystal phases of HA. The diffraction peaks of nanocomposites shows the main peaks of HA, so it can be concluded that the main crystal phases of the HA and nanocomposites were just HA. The diffraction peaks of HA became weaker than that of HA–natural polymers nanocomposites, which proved that the crystallinity of HA was lower than that of HA–natural polymers nanocomposites. The low crystallinity may lead HA to the low stability of the obtained material. On the other hand, the low crystallinity indicates that the bioactivity of the material is high, which is favorable to its nano bioeffects (Adlar et al. 1960, Lando and Morawezt 1963, Kuzuya and Kondo 1991).

Size, morphology, and core–shell structure of nanocomposites

Scanning electron micrographs of pure HA are shown in Figure 3a and HA/chitosan–albumin, HA/alginate–albumin and HA/albumin are shown in Figure 3b–d, respectively.

In vitro cytotoxicity study

The MTT assay is an important method for evaluating the cytotoxicity of biomaterials in vitro. The crystal size of HA plays a major role in bone tissue engineering for nutrient supplementation and cell attachment. A highly porous and nanocrystal structure is a prerequisite to ensure that the biological environment is conductive for cell attachment, proliferation, tissue growth and adequate nutrient flow. The cytotoxicity effects of derived HA crystals at different components were investigated by MTT assay. The HA crystals showed no cytotoxicity in the MG-63 cell line as seen in Figure 4 (Stauffer and Peppas 1992, Peppas and Khare 1993, Kaetsu et al. 1993).

In this work, we have characterized the in vitro behavior of HA–natural polymers nanocomposites for biomedical applications. n-HA was prepared with a chemical precipitation method. Ceramic matrix nanocomposites were synthesized by using hydroxyapatite as inorganic component and (chitosan, alginate and albumin) as organic components of nanocomposites. Five samples were prepared with hydrogen bonding between inorganic and organic components at room temperature, using mechanical and magnetic stirrer for 48 h, in the deionized water solution, so freeze drying at − 70°C for 24 h. Fourier transform infrared spectroscopy was used to show the structure of HA nanoparticles and HA–natural polymers nanocomposites. The X-ray powder diffraction data only showed peaks attributable to inorganic component. The size, morphology, and core–shell structure of the synthesized HA and nanocomposites were analyzed by scanning electron microscopy (Akbarzadeh et al. 2012a, Akbarzadeh et al. 2012d).

Conclusion

n-HA was synthesized by the reaction between calcium nitrate tetrahydrate and diammonium hydrogen phosphate (DAHP) solutions with a chemical precipitation method using a mechanical stirrer for 5 h, at room temperature and pH level ~11–12. The precipitating agent was TEA. Novel inorganic–organic nanocomposites were prepared by HA as inorganic component of nanocomposites (75% w) and natural polymers (chitosan, alginate and albumin) as organic components of nanocomposites (25% w). Nanocomposites were prepared at room temperature, deionized water solution, stirred with mechanical and magnetic stirrer for 48 h, so frozen at − 70°C overnight. These nanocomposites were used for in vitro cytotoxicity study. The resulting nanocomposites were characterized by X-ray powder diffraction (XRD), scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FT-IR).

Authors' contributions

JHC conceived the study and participated in its design and coordination. YKK participated in the sequence alignment and drafted the manuscript. AA, MA, SD, MM, GA, MS, KHK, and TYK helped in drafting the manuscript. All authors read and approved the final manuscript.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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