Synthesis of Superparamagnetic Hydroxyapatite Core-Shell Nanostructure by a Rapid Sol-Gel Route

A. H. M. Yusoff,* M. N. Salimi, and M. F. Jamlos
School of Bioprocess Engineering, Universiti Malaysia Perlis, 02600 Arau, Perlis, Malaysia
(Received 15 July 2017; Accepted 19 September 2017; Published 30 November 2017)

Magnetic transportation of therapeutic agents to the infected site in the body promises a superb platform for cancer treatment. To increase the safety profile and to stay clear from the agglomeration issue, core shell structure of magnetite-hydroxyapatite (Fe₃O₄-HAp) nanoparticles was developed. Fe₃O₄ as the core was synthesised by co-precipitation method which then coated with HAp layer through the sol-gel technique to maintain its high crystalline property. Optimum process parameters were applied during the fabrication process to yield small nanocomposites. The results show that HAp retained its phase purity and molecular structure even with the addition of Fe₃O₄ as analysed by XRD and FTIR. The FESEM and TEM micrographs show a magnificent monodispersed distribution of functionalised Fe₃O₄-HAp nanoparticles with the size of around 36 nm. EDXRF result confirmed the Ca/P ratio of 1.63, close to the value of main inorganic material of human bones (HAp) and possessed the superparamagnetic properties with saturation magnetisation of 23.274 emu/g as displayed by VSM curves. Thus, the dual affinity of the magnetic Fe₃O₄ and excellent biocompatibility HAp offer a synergetic effect as the drug or gene delivery vehicle to stealthy localize in infection site. [DOI: 10.1380/ejssnt.2017.121]

Keywords: Nanoparticles; Nanostructure fabrication; Magnetic; Iron oxide

I. INTRODUCTION

Ultra-small size of magnetic nanoparticles possesses an outstanding property, namely superparamagnetism that is strictly dominated by its size. Once the size is formed in nanometer scale, the particles are said to have a single-domain particles, also known as superparamagnets. At superparamagnetic state, particles exhibits paramagnetic behavior when the external magnetic field is applied. The particles no longer show magnetic interaction after the external magnetic field is removed [1]. They retain no residual magnetism that leaves them survive as an individual particle without bringing out the agglomeration problem after the field removal. Such unique magnetism property that unremarkably possesses by the magnetite (Fe₃O₄) nanoparticles gives them a superior ability over other nanoparticles. Magnetically driven ability attribute by every single particle enables its application in various fields particularly in biomedicine such as magnetically assisted drug and gene delivery [2, 3], contrast agents for magnetic resonance imaging (MRI) [4, 5] and as heat mediator for hyperthermia therapy [6]. Yet, these nanoparticles exhibit several biological challenges such as poor access into the target tissue, unwanted immunogenicity and negative binding to nucleic acids for the magnetofection. Therefore, the surface modification of Fe₃O₄ nanoparticles is one of the efficient ways to encounter those problems. The surface modification through core-shell-like structure is the easiest way to fabricate where the Fe₃O₄ nanoparticles is made as a core and subsequently enveloped by another material either polymeric materials [7, 8], silica [9], or gold [10] layer. However, the coating can vanish under extreme condition [11] and also due to safety issues [12].

Among the variety of coating materials, inorganic hydroxyapatite (HAp) coating offers a great potential to form a nanocomplex with Fe₃O₄ nanoparticles. The similar chemical structure to the inorganic component of bone matrix makes them a perfect candidate for nano drug and gene delivery system [13]. The potential of nanoscale HAp to kill and inhibit the spread of cancer cells determines their success and high performance as therapeutic agent carrier [14, 15]. HAp preserves a great safety profile when administered intravenously due to their well-known properties; excellent biocompatibility and slow biodegradability [16-17]. As for gene transfection, nucleic acids such as bare DNA and RNA are incapable to passively penetrating the cell membranes. Therefore, the modified Fe₃O₄ surface growing with a uniform HAp coating layer helps in promoting adherence of nucleic acids. An efficient delivery of nucleic acid into the cell nucleus is assured by the pH-dependent dissolution of HAp. HAp dissolution is accelerated in low pH media which normally found in endolysosomes resulting in a release of their cargo into mluign zones or cell organelles [18]. Moreover, their excellent protection to the nucleic acid from cytoplasmic environment has drawn this nanoparticles a favourable attention as a non-viral gene therapy [19]. Herein, the ultimate goal is to improve the bioavailability at the specific site of the body after administration. Thus, HAp coating shell con-joint with magnetic Fe₃O₄ core is the ideal combination to precisely retain the nanocomplexes at the treatment site for a long time and concurrently provides a low side effect to health tissue.

Of all the available methods for HAp coating, the prepa-rate from sol-gel is the most widely used technique. It involves low temperature, no pH adjustment and it is a simple low cost method to obtain pure HAp powder [20]. But it is obvious that this technique is a time-consuming method for ageing and drying process resulting in a total period of more than three days [21, 22]. Hsi-Chin et al. [23] obtained HAp powder by applying a rapid drying process using freeze drying method. However, the method required a minimum of 10 h of ageing for a highly crystalline product. On the other hand, in some cases, the magnetization curve shows a transition of superparamagnetism Fe₃O₄ cores into paramagnetic-like [24] or ferromagnetic [25] behavior nanocomplexes after the coating with ceramic nanoparticles due to the non-magnetic cal-

* Corresponding author: huzaifah.usm@gmail.com
Sol-gel method involves several essential stages for high purity HAp production. The first stage is mixing the precursors. The gelation stage takes place after making the stable sol where a cross-linking of the sol particles occurs to form a 3-dimensional network. This gelation reaction mitigates the problems associated with precipitation method which produces inhomogeneous size since the cross-linking of particles begins once the particles reach their critical size. Despite the formed gel, a numerous number of cluster of sol particles has not reacted completely. The reaction continues to form a continuous network during the aging stage. The next stage is drying where the entrapped solvent inside the gel is removed to strengthen the network. Lastly, sintering stage eliminates the porous structure and completes the reaction. Amorphous state of HAp is noticed in the as-dried gel which owes to the incomplete reaction between the precursors [26]. Thus, the thermal treatment process is the crucial step to crystallize the as-dried gel and transform to a stable thermodynamic phase [27]. However, the parameters used at each stage play a vital role to provide a continuous structure and produce a high quality of HAp. The present article reports a convenient way for Fe₃O₄-HAp core shell structure that involves a very short mixing, gelation and ageing process. Fe₃O₄ was prepared through co-precipitation method and subsequently HAp layer was employed using optimum processing parameter through the sol-gel approach. This research also focused on the rapid drying process up to only 1 h to complete the whole process which 150 to 200 times faster than conventional ageing and oven drying. A non-alkoxide-based gel without any catalyst was produced using inexpensive precursor.

II. METHODOLOGY

A. Materials

All chemical reagents employed in this work were of analytical grade and used without further purification. Iron (III) chloride (FeCl₃, 98% pure, anhydrous), iron (II) chloride (FeCl₂ • 4H₂O, 99%) and sodium hydroxide (NaOH) were obtained from Acros Organics. Meanwhile, calcium nitrate tetrahydrate [Ca(NO₃)₂ • 4H₂O], phosphorus pentoxide (P₂O₅) and absolute ethanol were obtained from Sigma-Aldrich UK. Deionised water was employed in all experiments.

B. Preparation of magnetite (Fe₃O₄) nanoparticles

Magnetite nanoparticles were prepared by co-precipitation method with iron (III) chloride (FeCl₃) and iron (II) chloride (FeCl₂ • 4H₂O) at a ratio of 2:1. Both iron precursors were dissolved in treated deionised water and allowed to mix for 30 min before heated up to reflux. Five milliliters of sodium hydroxide (NaOH) was added into the mixture once the temperature of the solution reached 70°C. The overall reaction process was performed under continuous aeration of nitrogen gas to provide an oxygen-free environment. The black precipitate was separated by centrifugation at 3,000 rpm for 15 min and washed with deionized water for several times. The prepared samples was then dried overnight under vacuum oven for further characterization.

C. Preparation of hydroxyapatite coated Fe₃O₄ nanoparticles (Fe₃O₄-HAp nanoparticles)

Hydroxyapatite coating was employed by sol-gel technique according to our previous study [28]. Optimum processing parameters from this literature were applied for coating process. The reaction is as follows:

\[
10Ca(NO_3)_2 \cdot 4H_2O + 3P_2O_5 
\rightarrow Ca_{10}(PO_4)_6(OH)_2 + 29H_2O + 20HNO_3 \quad (1)
\]

In brief, the stoichiometric amounts of calcium nitrate tetrahydrate and phosphorus pentoxide were dissolved in a separate ethanol solution with the molar ratio of 10:6. The freshly prepared Fe₃O₄ nanoparticles suspension was added dropwise into 30 mM of Ca(NO₃)₂ • 4H₂O under sonication. Then, 100 mM of P₂O₅ solution was added into the mixture and the reaction mixture was stirred for 1 h at 500 rpm using an overhead stirrer. The solution was then fixed at 200 rpm and the solution slowly transformed into gel after 1 h. Afterwards, the system was allowed to undergo ageing process for 1 h. The as-formed gel was dried using a rotary evaporator at 50 mbar with a water bath temperature of 60°C for 1 h before sintered at a temperature of 800°C with a heating rate of 5°C/min. Finally, the sintered sample was ground using a pestle and mortar. All the experiments were done at ambient temperature.

D. Particle characterisation of fabricated Fe₃O₄ nanoparticles and Fe₃O₄-HAp nanoparticles

FTIR analysis was conducted using PerkinElmer Spectrum 400. A certain amount of KBr and sample powder were mixed in the ratio of 10:1 and was pressed down to ensure contact. Infrared spectra in the wavenumber range of 400–4000 cm⁻¹ were collected with 2 cm⁻¹ resolution and 64 scans. The crystal structure and crystallite size were obtained using Shimadzu XRD-6000 diffractometer with monochromatic Cu Kα (λ = 1.5406 Å) radiation in the 2θ range of 20° to 80° at a scan rate of 1°/min. The Scherrer’s equation was used to calculate the crystallite size [29]:

\[
X_D = \frac{0.9λ}{FWHM \cos θ} \quad (2)
\]

where \(X_D\) is the crystallite size (nm), \(λ\) is the wavelength of X-ray beam, FWHM is the full width at half maximum for the diffraction peak under consideration (rad) and θ is the diffraction angle (°). The diffraction peak at 35.4° and 26° were chosen for the calculation of crystallite size of Fe₃O₄ nanoparticles and HAp nanoparticles, respectively.

122 http://www.sssj.org/ejssnt (J-Stage: http://www.jstage.jst.go.jp/browse/ejssnt/)
The determination of average particle size, morphology and particles distribution of as-prepared sample was carried out by field emission scanning electron microscopy (FESEM, JEOL JSM 6460LA). A small amount of particles were dispersed in ethanol and sonicated for at least 15 min and one small drop was placed on a glass cover slip. The particles were left to dry at ambient temperature and coated with a thin platinum film using JFC 1600 instrument to enhance the resolution. The same purpose also done using transmission electron microscopy (TEM, Philips: model CM 12) operated at 200 kV. The sample was dispersed in ethanol and sonicated prior transfer to the copper grid for analysis.

The quantitative analysis was determined by energy dispersive X-ray fluorescence spectrometer (EDXRF, Minupal PW 4030) to identify the calcium (Ca), phosphorus (P) and iron (Fe) content in the powder. The samples were measured using rhodium Ka at 30 kV and 1.0 mA. The acquired values were later expressed in terms of Ca/P ratio. The magnetic property was studied using a Lakeshore 7404 vibrating sample magnetometer (VSM) in atmospheric air at room temperature. The mass magnetisation (M) is defined as the magnetic moment m per total mass of sample measured.

### III. RESULTS AND DISCUSSION

The encapsulation of HAp around the magnetite surface was confirmed by FTIR spectroscopy. The phosphate, carbonyl, hydroxide and Fe-O bond absorption peaks are obviously seen in Fig. 1. The sharp bands at around 567 cm$^{-1}$ and 602 cm$^{-1}$ are corresponded to the bending vibration of phosphate (PO$_4^{3-}$, O–P–O) [30] while the strong bands at 960 cm$^{-1}$, 1036 cm$^{-1}$ and 1100 cm$^{-1}$ are denoted to the stretching vibration of phosphate (PO$_4^{3-}$, P–O) [31]. The stretching mode bands of the lattice OH$^-$ are demonstrated at 474 cm$^{-1}$, 632 cm$^{-1}$ and 3573 cm$^{-1}$.

Substitution of carbonate ions in the HAp lattice can occur due to the reaction of the apatite structure with the atmospheric CO$_2$ during preparation process [32]. Basically, two different types of the stretching modes of carbonyl group (CO$^-$) are reported where both types of substitution differ in the site of ions substitution [33, 34]. Type A substitution involves the substitution of carbonate ions for hydroxyl ions which commonly have the absorption peaks at 1550 cm$^{-1}$, 1457 cm$^{-1}$ and 880 cm$^{-1}$. The absorption peaks at 1462 cm$^{-1}$, 1418 cm$^{-1}$ and 876 cm$^{-1}$ are shown in type B substitution which involves the substitution of carbonate ions with phosphate ions [33, 34]. In our study, the carbonyl absorption peaks are in agreement with the type B substitution. The formation of such carbonated hydroxyapatite in a way mimics the chemical composition of hard tissue that contains 2.3 to 8 wt% of carbonate [35, 36] and thus improved the solubility in vitro and in vivo tests [37].

No absorption band that corresponds to the interaction between Fe$_3$O$_4$ nanoparticles and HAp coating layer, indicating that Fe$_3$O$_4$ nanoparticles was enclosed firmly under HAp layer and existed as an integral part. The absorption peaks for Fe–O stretching vibration that normally shown at 590 cm$^{-1}$ are not clearly identified since the peaks are hindered with phosphate’s peaks.

XRD characterisation was employed to further verify the presence of Fe$_3$O$_4$. The XRD pattern analysis shows the existence of Fe$_3$O$_4$ core under HAp layer as shown in Fig. 2. The Fe$_3$O$_4$ and HAp pattern peak was in well agreement with the PDF 19-0629 and PDF 09-0432, respectively. Six characteristic peaks that correspond to cubic inverse spinel structure of pure Fe$_3$O$_4$ nanoparticles marked by 220, 311, 400, 422, 511 and 440 peaks are observed in the Fe$_3$O$_4$–HAp nanoparticles revealing the enclosed Fe$_3$O$_4$ nanoparticles. However, due to the very small size of Fe$_3$O$_4$ nanoparticles resulted these peaks to have relatively low intensity value and the HAp diffraction peaks position has disturbed the Fe$_3$O$_4$’s peaks from appear well and noticeable in the consolidated sample. Additionally, all crucial characteristic peaks of HAp are also clearly observed which further confirmed the formation of Fe$_3$O$_4$–HAp nanoparticles.

The powder exhibited distinct and sharp peaks of diffraction peaks, suggesting a high degree of crystallinity. The incorporation of Fe$_3$O$_4$ nanoparticles did not influence the crystallinity of HAp coating layer since the calculated crystallinity of 90.22% was obtained. Furthermore, the enclosed Fe$_3$O$_4$ did not change the phase and crystal structure of both particles because no tertiary phase was detected. The pH of the reaction significantly affected the feature of the end product. The recorded pH of reaction was reduced from initial pH of 9 to 7.7 during the ageing period. The solution exhibited a slightly alkaline solution that yielded monophasic HAp layer instead of a biphasic mixture of HAp and tri-calcium phosphate (TCP). It is reported that the acidic solution prompts to a calcium-deficient HAp and leads to a biphasic product as a result of the presence of hydrogenophosphate ions in the lattice [38]. Whereas, pH of greater than 7.5 provides the OH groups to enter the apatite lattice and contributes
to yield pure HAp [39]. Thus, according to the observed stretching bands and characteristics peaks shown in FTIR and XRD results, the homogenous and single phase of carbonated HAp coating layer that is close to biological apatite was obtained and no extraneous phases were noticed.

The crystallite size of HAp shell determined by Scherrer’s equation showed a large particle size of 30 nm, indicating that the growth of HAp layer completely surrounded the Fe$_3$O$_4$ core as the calculated crystallite size of Fe$_3$O$_4$ was 17 nm. The clear micrograph and measurable size of powder was shown by FESEM (Fig. 3). The bare Fe$_3$O$_4$ nanoparticles revealed a monodispersed particle size of about 21 nm with spherical shape. In the consolidated samples, the Fe$_3$O$_4$ nanoparticles are inside the HAp shell forming the core-shell structure and no Fe$_3$O$_4$ nanoparticles residuals are observed outside the shells. The nearly spherical shape of Fe$_3$O$_4$-HAp nanoparticles improved the size of particles to approximately 36 nm, suggesting that Fe$_3$O$_4$ surface was successfully enclosed within the HAp shell. The well coating features shown by the HAp layer on Fe$_3$O$_4$ nanoparticles minimize the agglomeration issue, thereby reducing the possibility of emboli formation within the cardiovascular system for in vivo applications. Sophisticated observation of core shell structure are shown by TEM micrographs (Fig. 4). The structural morphology of spherical core of Fe$_3$O$_4$ with size of about 11.76 nm and the irregular HAp shell structure with the average particle diameter of 48.26 nm were agreed with XRD and FESEM analysis. Also, the particle comprise of single crystal due to the close comparison between XRD results and TEM micrographs. Based on many studies, nanoparticles size of 25–50 nm is the optimum range to avoid RES sequestering and to have a superior cellular uptake [40–44]. Here, the size obtained demonstrated that the nanoparticles size is in this ideal range and has a potential for effective drug and gene transportation. Furthermore, the Fe$_3$O$_4$ particles retain their single particles without any aggregation despite in HAp shell structure indicated that the particles do not preserve any magnetic memory. The zero resistance of ferromagnetic material to be demagnetized and wipe out the magnetic memory is exclusively possessed by superparamagnetic particles alone.

The EDXRF spectra generated show that Ca, P and Fe are the major elements found in the nanocomposites. The concentration of Ca and P of the Fe$_3$O$_4$-HAp nanoparticles are 47.7 wt% and 29.2 wt%, respectively and therefore giving the Ca:P atomic ratios of 1.63. The close agreement with the theoretical value of stoichiometric HAp of 1.67 shows that the nanocomposites simulate the natural bioapatite. The chemically mimic to the tissue structure marks its superiority as a safe vehicle for intracellular delivery and provides protection to the therapeutic agent from enzymatic degradation [45]. Furthermore, the presence of 22.88 wt% of Fe verified the incorporation of Fe$_3$O$_4$ phase in HAp matrix. This is in line with the results shown earlier.

The magnetic property of bare Fe$_3$O$_4$ nanoparticles and Fe$_3$O$_4$-HAp nanoparticles was studied at room temperature (300 K) ranging from −10,000 to 10,000 G. The effect of magnetization curves on consolidation process of
the as-prepared powders is observed in Fig. 5. Generally, the magnetic property of both nanoparticles displayed a superparamagnetic characteristic where no hysteresis loop was developed. The superparamagnetism of the nanoparticles is wholly attributed from Fe$^{2+}$ content that occupies the octahedral sites of the inverse-spinel structure [46] which the superparamagnetism behaviour was acquired due to their small size effect. In agreement to the literature, Fe$_3$O$_4$ particles below 50 nm size exhibited a single magnetic domain which they possessed no magnetic property after the magnetic field was removed [47–49]. The as-prepared Fe$_3$O$_4$ core surpassed the threshold size where both sample experienced superparamagnetism property. The presented magnetisation curve of bare Fe$_3$O$_4$ nanoparticles has the saturation magnetisation ($M_s$) of 30.431 emu/g and negligible coercivity and magnetic remanence. The magnetic property is clearly related with particle size. The difference of $M_s$ compared to the bulk Fe$_3$O$_4$ ($M_s = 84$ emu/g and $H_c = 500$ to 800 Oe) owes to the increase of spin canting effect and thermal fluctuation as the particle size was reduced [50]. The $M_s$ value shifted down to 23.274 emu/g after Fe$_3$O$_4$ nanoparticles were coated with diamagnetic HAp. The resultant coating with diamagnetic HAp layer lessened the magnetic domain, correspondingly lowered the $M_s$ value than that of Fe$_3$O$_4$ nanoparticles. However, the rapid fabrication of HAp shell has no effect on the superparamagnetic behavior, keeping its potential as a safe non-viral agent and effectively delivers the therapeutic agents to the affected sites using the external magnetic source. Such remarkable physical property is not exhibited in pure HAp.

### IV. CONCLUSION

The current study details the fabrication of magnetic core-shell structure under an optimized sol-gel method. Consolidating Fe$_3$O$_4$ nanoparticles and HAp coating layer into one body created novel structures, resulted in minor changes in the morphology and also the physical behaviour. Introducing Fe$_3$O$_4$ nanoparticles as a core still retained the chemical structure of HAp without losing its superparamagnetic property. The elemental analysis demonstrated high bioactive Ca-P composition resemblance to human bone and tooth minerals surrounding the magnetic core that was expected to shelter the incompatible core from reticuloendothelial system clearance. Furthermore, in conjunction with magnetic delivery to the particular site could enhance the drug delivery and magnetofection efficiency, minimising time for cellular uptake and attaining a deep penetration process. These appealing characteristics provide considerable interest as a potential candidate for invulnerable agent in medical applications.

[1] C. P. Bean and J. D. Livingston, J. Appl. Phys. 30, S120 (1959).
[2] H. W. Child, P. A. Del Pino, J. M. De La Fuente, A. S. Hursthouse, D. Stirling, M. Mullen, G. M. McPhee, C. Nixon, V. Jayawarna, and C. C. Berry, ACS Nano 5, 7910 (2011).
[3] J. W. Park, K. H. Bae, C. Kim, and T. G. Park, Biomacromolecules 12, 457 (2011).
[4] P. Zou, Y. Yu, Y. A. Wang, Y. Zhong, A. Welton, C. Galban, S. Wang, and D. Sun, Mol. Pharmaceutics 7, 1974 (2010).
[5] R. Chen, H. Yu, Z.-Y. Jia, Q.-L. Yao, and G.-J. Teng, Int. J. Nanomedicine 6, 511 (2011).
[6] F. Gazeau, M. Levy, and C. Wilhelm, Nanomedicine (London, U. K.) 3, 831 (2008).
[7] J. Wang, B. Zhang, L. Wang, M. Wang, and F. Gao, Mater. Sci. Eng. C 48, 416 (2015).
[8] G. Li, L. Cao, Z. Zhou, Z. Chen, Y. Huang, and Y. Zhao, Colloids Surf. B 128, 379 (2015).
[9] N. Mahmood, O. Hezcko, A. Lancok, and S.-P. Hannula, J. Magn. Magn. Mater. 353, 15 (2014).
[10] A. Majouga, M. Sokolksy-Papkov, A. Kuznetsov, D. Lebedev, M. Efremova, E. Beloglazkina, P. Rudakovskaya, M. Veselov, N. Zykov, Y. Golovin, N. Klyachko, and A. Kabanov, Colloids Surf. B 125, 104 (2015).
[11] C. Altavilla and E. Ciliberto, Inorganic nanoparticles: Synthesis, Applications, and Perspectives (CRC Press, Boca Raton, FL, 2011).
[12] S. Guo and L. Huang, Biotechnol. Adv. 32, 778 (2014).
[13] G. K. Lim, J. Wang, S. C. Ng, C. H. Chew, and L. M. Gan, Biomaterials, 18, 1433 (1997).
[14] F. Yang, C. Jin, S. Subedi, C. L. Lee, Q. Wang, Y. Jiang, J. Li, Y. Di, and, D. Fu, Cancer Treat. Rev. 38, 566 (2012).
[15] J. Li, Y. Yin, F. Yao, L. Zhang, and K. Yao, Mater. Lett. 62, 3220 (2008).
[16] S. Wang, X. Wang, H. Xu, H. Abe, Z. Tan, Y. Zhao, J. Guo, M. Naito, H. Ichikawa, and Y. Fukumori, Adv. Powder Technol. 21, 268 (2010).
[17] Y.-H. Yang, C.-H. Liu, Y.-H. Liang, F.-H. Lin, and K. C.-W. Wu, J. Mater. Chem. B 1, 2447 (2013).
[18] V. Uskokovic and D. P. Uskokovic, J. Biomed. Mater. Res. B, Appl. Biomater. 96, 152 (2011).
[19] C. M. Wiethoff and C. R. Middaugh, J. Pharm. Sci. 92, 203 (2003).
[20] W. Feng, L. Mu-sen, L. Yu-peng, and Q. Yong-xin, Mater. Lett. 59, 916 (2005).
[21] M. Ajeesh, B. F. Francis, J. Annie, and P. R. Harikrishna Varma, J. Mater. Sci: Mater. Med. 21, 1427 (2010).

http://www.sssj.org/ejssnt (J-Stage: http://www.jstage.jst.go.jp/browse/ejssnt/)
[22] E. B. Ansar, M. Ajeesh, Y. Yokogawa, W. Wunderlich, and H. Varma, J. Am. Ceram. Soc. 95, 2695 (2012).

[23] H.-C. Wu, T.-W. Wang, J.-S. Sun, W.-H. Wang, and F.-H. Lin, Nanotechnology 18, 165601 (2007).

[24] C.-H. Hou, S.-M. Hou, Y.-T. Li, and F.-H. Lin, Biomaterials 30, 4700 (2009).

[25] H. Yang, Q. Liu, S. Masse, H. Zhang, L. Li, and T. Coradin, Chem. Eng. J. 275, 152 (2015).

[26] M. H. Fathi and A. Hanifi, Mater. Lett. 61, 3978 (2007).

[27] A. C. Pierre, Introduction to Sol-Gel Processing (Kluwer Academic Publishers, Boston, 1998).

[28] Y. M. Yusoff, M. N. A. Salimi, and A. Anuar, AIP Conf. Proc. 1660, 070054 (2015).

[29] R. Jenkins and R. L. Snyder, Introduction to X-Ray Powder Diffractionometry (John Wiley & Sons, Inc., 1996).

[30] S. J. Joris and C. H. Amberg, J. Phys. Chem. 75, 3172 (1971).

[31] J. Liu, X. Ye, H. Wang, M. Zhu, B. Wang, and H. Yan, Ceram. Int. 29, 629 (2003).

[32] I. R. Gibson and W. Bonfield, J. Biomed. Mater. Res. 59, 697 (2002).

[33] M. H. Fathi, A. Hanifi, and V. Mortazavi, J. Mater. Process. Technol. 202, 536 (2008).

[34] A. Krajewski, M. Mazzocchi, P. L. Buldini, A. Ravaglioli, A. Tinti, P. Taddei, and C. Fagnano, J. Mol. Struct. 744-747, 221 (2005).

[35] A. Bigi, G. Cojazzi, S. Panzavolta, A. Ripamonti, N. Roveri, M. Romanelli, K. Noris Suarez, and L. Moro, J. Inorg. Biochem. 68, 45 (1997).

[36] F. C. M. Driessens, Bull. Soc. Chim. Belg. 89, 663 (1980).

[37] R. Z. LeGeros, Monogr. Oral Sci. 15, 1 (1991).

[38] R. N. Correia, M. C. F. Magalhães, P. A. A. P. Marques, and A. M. R. Senos, J. Mater. Sci.: Mater. Med. 7, 501 (1996).

[39] B. A. Ben-Arafa, I. M. M. Salvador, J. M. Ferreira, and R. C. Pullar, Mater. Sci. Eng. C 70, 796 (2017).

[40] F. Osaki, T. Kanamori, S. Sando, T. Sera, and Y. Aoyama, J. Am. Chem. Soc. 126, 6520 (2004).

[41] V. Jeannot, S. Mazzaferro, L. Lavaud, L. Vanwonterghem, M. Henry, M. Arboléas, J. Vollaire, V. Josserland, J.-L. Coll, S. Lecommandoux, C. Schatz, and A. Hurbin, Nanomedicine: Nanotechnology, Biology and Medicine 12, 921 (2016).

[42] T. Nakai, T. Kanamori, S. Sando, and Y. Aoyama, J. Am. Chem. Soc. 125, 8465 (2003).

[43] B. D. Chithrani, A. A. Ghazani, and W. C. W. Chan, Nano Lett. 6, 662 (2006).

[44] W. Jiang, B. Y. S. Kim, J. T. Rutka, and W. C. Chan, Nature Nanotech. 3, 145 (2008).

[45] S. Bisht, G. Bhakta, S. Mitra, and A. Maitra, Int. J. Pharm. 288, 157 (2005).

[46] S. Alibeigi and M. R. Vaezi, Chem. Eng. Technol. 31, 1591 (2008).

[47] D. J. Dunlop, J. Geophys. Res. 78, 1780 (1973).

[48] S. Mohapatra, N. Pramanik, S. Mukherjee, S. K. Ghosh, and P. Pramanik, J. Mater. Sci. 42, 7566 (2007).

[49] C. T. Yavuz, J. T. Mayo, W. W. Yu, A. Prakash, J. C. Fulkner, S. Yean, L. Cong, H. J. Shipley, A. Kan, M. Tomson, D. Natelson, and V. L. Colvin, Science 314, 964 (2006).

[50] B. H. Kim, N. Lee, H. Kim, K. An, Y. I. Park, Y. Choi, K. Shin, Y. Lee, S. G. Kwon, H. B. Na, J.-G. Park, T.-Y. Ahn, Y.-W. Kim, W. K. Moon, S. H. Choi, and T. Hyeon, J. Am. Chem. Soc. 133, 12624 (2011).