Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Pelagia Research Library

Advances in Applied Science Research, 2016, 7(2):66-69

Pelagia Research Library

ISSN: 0976-8610
CODEN (USA): AASRFC

Fabrication Methods of group 2 doped calcium substituted hydroxyapatite for application as biomaterial

Ravinder Kumar[1*], A. P. Singh[2] and Kanchan Lata Singh[3]

[1]I. K. Gujral Punjab Technical University, Kapurthala, Punjab, India
[2]Punjab Technical University, Kapurthala, Punjab, India
[3]D. A. V. Institute of Engineering and Technology, Kabir Nagar, Jalandhar, Punjab, India

---

ABSTRACT

In today's world HAp has gained popularity as a potential biomaterial for dental and orthopedic applications. Replacement of some of Ca^{2+} ions by some other ions of group 2 modifies biological and load bearing properties. Many methods are available for synthesizing these doped HAp samples characterized by particle size in nanometer range with each method having its own advantages. This review paper gives an insight into the methods like mechanochemical method, solution combustion synthesis, sol-gel method, aqueous precipitation method, hydrothermal method.

Keywords: Hydroxyapatite, doped hydroxyapatite, Osteoporosis, Osteoblasts, Osteoclasts Solution Combustion method.

INTRODUCTION

In 21st Century, Synthetic Hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, HAp due to its close resemblance with the mineral part of human bone and excellent biocompatibility, osteoconductivity and unique bioactivity emerged as a potential biomedical material for being used in dental implants, drug delivery system, maxillofacial surgery and orthopedic applications[1-4]. HAp based ceramics when implanted in human body shows superior fixation to the surrounding tissues because of formation of a fibrous tissue-free layer on its surface[5-6]. HAp powder having particle size in nanodimensions possess greater surface area and thus shows improved bioactivity, densification, sinterability and mechanical properties[7-10]. Poor mechanical strength and low degradation rate limited the load-bearing application of HAp[11-12].

Substitution of some of the Ca^{2+} ions with other cations of group 2 like Mg^{2+}, Sr^{2+} and Ba^{2+} bring a change in biological and mechanical properties[13-16] and modification in lattice parameters and crystallinity although there is no change in hexagonal system of apatite. Mg is the fourth most abundant cation in human body (0·44 – 1·23 wt%) and its concentration in bone is 0·55 wt%[17]. Mg promotes bone formation[18] and reduces the risk factors for osteoporosis in homosapians[19]. Mg incorporation in HAp catalyses osteoblast proliferation but its deficiency causes significant decrease of osteoblastic and osteoclastic activities and makes bone fragile[20-21]. Sr is a bone seeking trace element and 98% of its total content in the body is in the skelton[22]. Sr doping in HAp makes HAp phase stable against any phase transformation as well as crystal growth during high temperature sintering while making implant materials[23]. HAp bone cement containing Sr has advantage of being biocompatible and has better bioactivity and faster biodegradable rate than Sr free HAp bone cement[24]. Sr as strontium renelate when administrated reduces the risk of fracture in patients of Osteoporosis which is characterized by low bone mass and thus increased chances of fracture on bending or falling[25-27]. Bone formation and bone growth are influenced by Sr positively and it reduces unwanted bone resorption both in vivo and in vitro[28-30]. Partial substitution of Sr for Ca in HAp promotes osteoblast differentiation in both normal and osteopenic cells[31]. The increased solubility of Sr substituted HAp as compared to that of unsubstituted HAp is found to increase the number and activity of bone forming Osteoblasts and decreases the number and the activity of bone resorbing osteoclasts in vitro[32-33]. *Sr-HAp has the capacity of improving osteointegration*[34]. Sr has the ability of preventing bone loss[35] and increasing the bone volume[36]. Barium apatite is used in RCT as a filling material because of its good mechanical properties[37].

MATERIALS AND METHODS

Several fabrication methods like mechanochemical method in dry state, solution combustion synthesis, sol-gel method and aqueous precipitation method/wet chemical precipitation method are available.

1. Mechanochemical method in dry state[38]

$Ca(OH)_2$, $(NH_4)_2HPO_4$ and $Mg(OH)_2$ in (Ca + Mg)/ P ratio of 1·67 were ball milled using zirconia balls (power : ball mass ratio as 1 : 5) for 15h at rotating speed of 370 rpm.

$$(10 - x)\ Ca(OH)_2 + x\ Mg(OH)_2 + 6\ (NH_4)_2\ HPO_4 \longrightarrow Ca_{10-x}\ Mg_x\ (PO_4)_6(OH)_2 + 12\ NH_4OH + (6 - x)\ H_2O$$

With increase of Mg^{2+} ion concentration, the peak broadening and decrease of intensity was observed which indicates the substitution of Mg^{2+} in HAp structure.

This method has the advantage of simplicity and reproducibility suitable for mass production.

2. Solution combustion synthesis[39]

A wet paste containing required amounts of calcium acetate, diammonium phosphate and strontium salt (Ca + Sr/P ratio of 1·67) with adjustment of its pH to 7·4 by the addition of tris hydroxyl methylamino methane was obtained. Urea was added as a fuel for combustion which gets decomposed to HCNO and NH_3 on heating above 300ºC. This gaseous mixture spontaneously ignites at 500ºC in aqueous medium and raises the local temperature of the solution. This solution was kept in a crucible at 500ºC for 30 min in muffle furnace for combustion to occur. Finally the spongy mass obtained was crushed to get fine powder. Sr-HAp nanorods were seen in TEM study which may be suitable for drug delivery systems because of higher activity.

M. Kavitha et. al. concluded that Sr addition increases the lattice parameters of HAp lattice and stabilizes the HAp phase by suppressing the phase transformation and crystal growth during calcination at high temperature.

This method has the advantage of cheap raw materials, simple preparation process, chemical homogeneity of synthesized powder due to intimate blending of the constituents and self sustaining reaction[40].

3. Sol-gel method

For Mg-HAp, Mg and Ca precursors were first mixed in absolute ethanol and vigorously stirred. This solution was added drop-wise into phosphorus containing precursor solution in absolute ethanol while stirring vigorously. The formed sol was aged until a gel is obtained which is dried and ground to fine powder.

The (Ca + Mg)/P ratio was kept at 1·67. Abinaya R. et. al.[41] used $Mg(NO_3)_2 \cdot 6H_2O$, $Ca(NO_3)_2 \cdot 4H_2O$ and $NH_4H_2PO_4$ as precursors. They observed that the intensity of hydroxyl and phosphate peak in FTIR decreases with Mg concentration. The decrease in crystal size was observed with increase in Mg concentration from 0·3 M to 0·5 M. The relative intensity of X-ray diffraction peaks were decreased as the magnesium content increases. A. Gozalian et. al.[42] used $Mg(NO_3)_2 \cdot 6H_2O$, $Ca(NO_3)_2 \cdot 4H_2O$ and triethyl phosphite as precursors. They found that the presence of magnesium shifted the transformation temperature of β-TCP to α-TCP to higher degree.

For Sr–HAp, C.M. Mardziah et. al.[43] dissolved Ca and Sr nitrates in distilled water in separate beakers and stirred. These solutions were poured into the ammonium and EDTA mixture solution and then diammonium hydrogen phosphate and urea were subsequently added. This clear solution mixture was the refluxed at 100ºC while stirring. The gel obtained was dried in ambient air and the resultant solid gel was crushed into fine powder.

Sol-gel process has advantage of producing products of higher purity and more homogeneous composition[44].

4. Aqueous precipitation method/Wet chemical precipitation

This method involves dropwise addition of one reagent to another with constant gentle stirring. The resultant suspension obtained was aged under atmospheric pressure or washed, filtered, dried and grinded into a powder.

Valentina Aina et. al.[45] prepared Mg substituted HAp by adding phosphoric acid solution dropwise to a mixture solution of $Ca(OH)_2$ and $MgC\ell_2 \cdot 6H_2O$ [(Ca + Mg)/P = 1·667] with constant stirring and pH was maintained above 10·5 by adding ammonia solution. The solution was stirred for further 2h and aged for overnight and the product was filtered and dried in ambient conditions.

C. Capuccini et. al.[46] prepared Sr-substituted hydoxyapatite by dropwise addition of $(NH_4)_2HPO_4$ solution at pH 10 adjusted with NH_4OH to a mixture solution of $Ca(NO_3)_2 \cdot 4H_2O$ and $Sr(NO_3)_2$ with appropriate amounts in N_2 atmosphere. The solution is kept for 5h at 90ºC with stirring then centrifuged to give the product which is repeatedly washed with CO_2-free distilled water and dried at 37ºC overnight. They observed broader X-ray diffraction peaks.

Declan J. Curran et. al.[47] prepared Sr-HAp powder [(Ca + Sr)/P = 1·667] by first dissolving $Ca(NO_3)_2 \cdot 4H_2O$ in 600 mL water and added 10mL NH_4OH with constant stirring then adding $Sr(NO_3)_2 \cdot 4H_2O$ and the mixture was constantly stirred. To this, they added dropwise $(NH_4)_2HPO_4$ in water solution made basic by adding 25 mL of NH_4OH. The solution was aged for 1 hr and precipitate were allowed to stand for 2h at room temperature and washed with distilled water thrice. The precipitate were filtered out and dried at 85ºC for 20h. They studied the effect of Sr-doping in HAp on the density and porosity of the samples sintered at 1200ºC using both conventional and microwave sintering. They found that microwave sintered sample density is higher than conventionally sintered sample.

Arghavan Farzadi et.al.[48] prepared Mg-doped HAp by dropwise addition of an aqueous diammonium hydrogen phosphate solution into a basic solution consisting of $MgC\ell_2 \cdot 6H_2O$ and $Ca(NO_3)_2 \cdot 4H_2O$ with Mg/Ca molar ratio of 0·18 for 3h. The pH of the suspension was adjusted to 11 and stirred for 2h. The resulting precipitates were centrifuged and washed thrice using distilled water. The sample was dried at 70ºC overnight and calcined at 900ºC for 1h. Degree of crystallinity and the size of crystals of the doped HAp sample decreases due to incorporation of Mg ions in the host lattice. The lattice parameter 'c' is decreased while lattice parameter 'a' is increased with Mg substitution.

Adriana Bigi et.al.[49] synthesized calcium-strontium hydroxyapatite solid solutions in the whole range of composition by direct synthesis in an aqueous medium using $Ca(NO_3)_2 \cdot 4H_2O$, $Sr(NO_3)_2$ and $(NH_4)_2HPO_4$ solution using same procedure. They found that a linear variation in the cell parameters and in the infrared absorption bands is noticed with increasing Sr concentration. The surface area of 60 m^2/g for Ca–HAp increases slightly on increasing χ_{Sr} [Sr/(Ca + Sr)] upto about 0·3 and then decreases when $\chi_{Sr} > 0{\cdot}5$ reaching a minimum value of 26 m^2/g for Sr–HAp.

M.D. O' Donnel et. al.[50] found that lattice parameters, unit cell volume and density increases linearly with strontium addition because of substitution of larger and heavier Sr in place of Ca. Sr has a slight preference for entering the Ca(II) site (6 to 12%) in the mixed apatites and this preference increases as the Sr content increases.

Joice Terra et. al.[51] shows a preference for the Ca1 site at low Sr concentration but for higher Sr concentration occupation of the Ca2 site is progressively preferred.

5. Hydrothermal method[41]

It is simply a chemical precipitation technique in which the aging step is carried out at a higher temperature above the boiling point of water inside an autoclave or pressure vessel. This method has the advantage of producing highly crystalline nanoparticles. $Ca(NO_3)_2 \cdot 4H_2O$ and $Mg(NO_3)_2 \cdot 6H_2O$ were prepared in double distilled water with adjustment of pH at 11 using liquid NH_3. The mixture was stirred for 1 hour at room temperature. This mixture solution was added dropwise to the solution of $(NH_4)_2\ HPO_4$ and adjustment of pH at 11 was done using liquid NH_3 and then stirred vigourously for 2h to produce white precipitate. The precipitate was then kept in a teflon coated autoclave at 150ºC for 5h, filtered, washed repeatedly with double distilled water and dried in an air oven at 100ºC. They found that Mg-HAp prepared by hydrothermal route was more bioactive than sol-gel route as the calculated crystal size though this route was lower than that obtained through sol-gel route.

CONCLUSION

It can be concluded that HAp with doping of group 2 elements can be synthesized by various methods like mechanochemical method, solution combustion synthesis, sol-gel method, aqueous precipitation method, hydrochemical method etc. Many scientists and researchers are trying to develop group 2 doped HAp with optimum properties for use in various biomedical fields. We hope that with their everlasting efforts, they will be able to synthesize many novel and cost effective methodologies in the near future.

REFERENCES

[1] M. Vallet-Regi, J.M. Gonzalez-Colbet, *Prog. Solid Stat Chem*. 32 (**2004**)1-31
[2] Zhou H, Lee J. *Acta Biomater*. **2011**; 7: 2769-81.
[3] Hutmacher DW, Schantz JT, Lam CXF, Tan KC, Lim TC, *J Tissue Eng Regenerat Med* **2007** ; 1 : 245-60.
[4] A.K. Dash, G.C. Cudworth, *J. Pharmacol. Toxicol. Method* 40 (**1998**) 1-12.
[5] Habibovic P, Kruyt MC, Juhl MV, Clyens S, Martinetti R, Dolcini L, et. al. *J. Orthop Res* **2008**; 26 : 1363-70.
[6] Rabiee S, Moztarzadeh F, Solati-Hashjin M. *J. Mol struct* **2010** : 969 : 172-5
[7] Dorozhkin SV *Acta Biomater* **2010** ;6:715-34.
[8] Stupp SI, Ciegler GW, *J. Biomed Mater Res* **1992** ; 26 :169-83.
[9] Eriksson M, Liu Y, Hu J, Gao L, Nygren M, Shen Z. *J Eur Ceram Soc* **2011** : 31 ; 1533-40.
[10] Bose S, Dasgupta S, Tarafder S, Bandyopadhyay A. *Acta Biomater* **2010** ; 6 : 3782-90.
[11] M. Khrami, S. Hesarki, T. Ebadzadeh, S. Farhangdoust and A. Zamanian, *Key Engineering Materials*, Vol. 493-494 pp 231-235, Oct.**2011**
[12] B. Nasiri-Tabrizi, P. Honarmandi, R. Ebrahimi-Kahrizsangi and P. Honarmandi. *Mater. Lett.* 63 : 543-546 (**2009**).
[13] T.W.Kim, H.S. Lee, D.H. Kim, H.H. Jin, K.H. Hwange, J.K. Lee, H.C. Park, S.Y. Yoon. *Mater. Res. Bull.* 47(9)(**2012**) 2506-2512
[14] Arghavan Farzadi, Farhad Bakshi, Mehran Solati-Hashim, Mitra Asadi-Eydivand, Noor-Azuan abu Osman. *Ceramics International* 40 (**2014**) 6021 6029
[15] De Lima IR, Alves GG, Soriano CA, Campaneli AP, Gasparoto TH, Ramos E S Jr, de Sena LA, Rossi AM, Granjeiro JM. *J. Biomed Mater Res A*. **2011** ; 98A : 351-8.
[16] J. Kolmas, A. Jaklewicz, A. Zima, M. Bucko, Z.Paszkiewicz, J. Lis, A. Slosarczyk, W. Kolodziejski. *J. Mol. Struct*. 987 (1-3) (**2011**) 40-50.
[17] D. Laurencin, N. Almora-Barrios, N.H. de Leeuw, C. Gervais, C. Bonhomme, F. Mauri, W. Chrzanowski, J.C. Knowles, R.J. NewPort, A. Wong, Z.Gan, M.E. Smith, *Biomaterials* 32(7) (**2011**) 1826-1837.
[18] I. Cacciotti, A. Bianco, M. Lombardi, L. Montanaro; *J. Eur, Ceram, Soc*. 29(14) (**2009**) 2969-2978.
[19] Qi G, Zhang S, Khor KA, Lye SW, Zeng X, Weng W, Liu C, Venkatraman SS, Ma LL. *Appl Surf Sci.* **2008**; 255 : 304-7.
[20] Salima ziani, Samira Meski and Hafit khireddine. *International Journal of Applied Ceramic Technology*, Vol. 11, No.PP 83-91, **2014**.
[21] S. Adzila, M.C. Murad, I. Sopyan, *Rec. Pat. Mater. Sci* (**2012**) 18-47.
[22] Verberckmoes SC, Behets GJ, Oste L, Bervoets AR, Lamberts LV, Drakopoulos M et. al. *Calcified Tissue International :* **2004**; 75(5) : 405-415.
[23] C.M. Mardziah, I. Sopyan, S. Ramesh, *Trends Biomater. Artif. Organs* 23 (**2009**) 105-113.
[24] Guo DG, Xu KW, Han Y, Zhao XY. *J Biomed Mater Res* **2008**; 86A(4) : 947-58.
[25] Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector T D, et. al. *N. Engl J Med* **2004**; 350 (5) : 459-68.
[26] Ammann P. *Osteoporos Int* **2005** ; 16 : S11-S15.
[27] Marie P J. *Osteoporos Int*. **2005**; 16 : S7 - S-10.

[28] S.G. Dahl, P. Allain, P.J. Marie, Y. Mauras, G. Boivin, P. Ammann, Y. Tsouderous, P.D. Delmas, C. Christiansen, *Bone* 28 (**2001**) 446.
[29] Pors Nielsen S. *Bone* **2004** ; 35(3): 583-8.
[30] Buehler J, Chappuis P, Saffer J L, Tsouderos Y, Vignery A. *Bone* **2001**; 29: 176-9.
[31] E. Boanini, P. Torricelli, M. Fini, A. Bigi, *J. Mater. Sci. Mater. Med*. 22 (**2011**) 2079-2088.
[32] Capuccini C, Sima F, Boanini E, Ristoseu C. Bracci B, etal. *Acta Biomater* **2008**; 4 : 1885-1893.
[33] C. Capuccini, P. Torricelli, E. Boanini, M. Gazzano, R. Giardino, A. Bigi. J. *Biomed Mater Res* 89A: 594-600, **2009**.
[34] G.X. Ni, W.W. Lu, B Xu, K.Y.Chiu, C. Yang, Z.Y.Li, W.M. Lam, K.D.K. Luk, *Biomaterials* 27 (**2006**) 5127.
[35] Hott M, Deloffre P, Tsouderos Y, Marie PJ, *Bone* **2003**; 33: 115-23.
[36] Blake GM, Fogelman I. *J. Bone Miner Res* **2005**; 20 : 1901- 4.
[37] S. Shibata, Y. Doi, Y. Takezawa, N. Wakamatsu, T. Horiguchi, H. Kamemizul, Y. Moriwaki, F. Kubo and Y. Haeuchi, *Dent. Mater. J. ens*. 8, 77 (**1989**).
[38] S. Adzila, S. Ramesh, I. Sopyan, C.Y. Tan, M. Hamdi and W.D. Teng ; *Applied Mechanics and Materials* Vol. 372 (**2013**) pp. 62-65.
[39] M. Kavitha, R. Subramanian, R. Narayan, V. Udhayabanu. *Powder Technology* 253 (**2014**) 129-137.
[40] Samir Kumar Ghosh, Sujit Kumar Roy, Biswanath Kundu, Someswar Dutta, Debabrata Basu. *Materials science and engineering B* 176 (**2011**) 14-21.
[41] Abinaya R, Subha B, Adhilakshmi A and Ravichandran K. *International Journal of innovative Research in Science and Engineering* ISSN (Online) 2347-3207.
[42] A. Gozalian, A. Behnamghader, M. Daliri, A. Moshkforoush. *Scientia Iranica F* (**2011**) 18(6), 1614-1622.
[43] C.M. Mardziah, I. Sopyan and S. Ramesh. *Trends Biomater. Artif. Organs*. Vol 23(2) pp 105-113 (**2009**).
[44] Kalita, S.J. Bhardwaj. A. and Bhatt, H.A. *Mater, Sci. Eng* c. 27 pp 441-449 (**2007**).
[45] Valentina Aina, Gigliola Lusvardi, Basil Annaz, Iain R. Gibson, Flora E. Imrie, Gianluca Malavasi, Ledi Menabue, Giuseppina Cerrato, Gianmario Martra. *J Mater Sci : Mater Med* (**2012**) 23 : 2867-2879.
[46] C. Capuccini, P. Torricelli, E.Boanini, M. Gazzano, R.Giardino, A.Bigi. *J. Biomed Mater Res* 89A : 594-600, **2009**.
[47] Declan J. Curran, Thomas J. Fleming, Mark R. Towler, Stuart Hampshire. *Journal of the mechanical behaviour of biomedical materials* 4(**2011**) 2063-2073.
[48] Arghavan Farzadi, Farhad Bakhshi, Mehran Solati-Hashjin, Mitra Asadi-Eydivand, Noor Azuan Abu Osman. *Ceramics International* 40 (**2014**) 6021-6029.
[49] Adriana Bigi, Elisa Boanini, Chiara Capuccini, Massimo Gazzano : *Inorganica Chimica Acta* 360 (**2007**) 1009-1016.
[50] M.D. O'Donnell, Y. Fredholm, A. de Rouffignac, R.G. Hill. *Acta Biomaterialia* 4(**2008**) 1455-1464.
[51] Joice Terra, Erico Rodrigues Dourado, Jean-Guillaume Eon, Donald E. Ellis, Gabriela Gonzalez and Alexandre Malta Rossi. *Phys. Chem. Chem. Phys*., **2009**, 11, 568-577.