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A REVIEW ON CALCIUM PYROPHOSPHATE AND OTHER RELATED PHOSPHATE NANO BIO-MATERIALS AND THEIR APPLICATIONS

Sonal R. Vasant[1] and M. J. Joshi[2]

[1]Government Engineering College, Rajkot, Gujarat, India
[2]Department of Physics, Saurashtra University, Rajkot, Gujarat, India

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Abstract. Over the past few decades, a little word with big potential has been rapidly insinuating into the world's consciousness, nano. The nano-scale structures permit the control of fundamental properties of the materials without changing their chemical structure. Living organisms can create amazing ways to produce high performance materials that involve not only creation of implants, replacing bone tissues and organs, but also synthesis of biologically active materials promoting the fullest restoration of tissues and maintenance of necessary functions of an organism. In the biomaterial research field, nowadays, a great attention is given to bone substitute materials, particularly, calcium phosphate based bio-materials play important roles in clinical applications as it possesses high bio-compatibility and excellent ability to undergo varying degrees of resorbability. These materials show a positive interaction with living tissue that includes differentiation of immature cells towards bone cells and also have chemical bonding to the bone along the interface, thought to be triggered by the adsorption of bone growth-mediating proteins at the bio-materials surface. In the present review paper an attempt is made to cover properties and applications of various phosphate nano bio-materials like calcium phosphate, calcium polyphosphate, calcium pyrophosphate etc over a time span right from 1920 to 2016. This suggests plenty of opportunities for interdisciplinary research.

1. INTRODUCTION

1959
Richard Feynman imagined a design:
Create a bot
The size of a dot.
The hope would be
Inject it into your body
Fixing your innards,
Like a micro wizard.
An exuberant vision
Or a risky decision?

The poem "Got the Bot?" is written by Alana Moe, 7th Grade Student of Memorial Middle School, Sioux Valley, South Dekot, USA. This short poem describes the nano-technology from Richard Feynman's vision to modern era with caution of risks woven with it.

Over the past few decades, a little word with big potential has been rapidly insinuating itself into the world's consciousness, that is word "nano", a popular prefix also. The term nano originates etymologically from the Greek and means "dwarf", which was first coined by Richard Feynman in 1959 [1]. Nanostructures must have at least one dimension of less than 100 nano-meters and may have two or three dimensions. The nano-scale structures permit the control of fundamental properties of the materials

Corresponding author: Sonal R. Vasant, e-mail: sonalvasant@rediffmail.com

without changing their chemical structure. The nano-particles are of great scientific interest as they are effectively a bridge between the bulk materials and the atomic or molecular structures.

Two main factors may be responsible for the changes of properties observed in nano-particles:

(i) A much greater relative surface area per unit of mass;

(ii) Predominance of quantal effects.

The first factor is responsible for the changes in reactivity, which can increase considerably as particles decrease in size. The second factor, observed in particles of a few dozen nm, explains the changes in terms of optical, electrical, mechanical, and magnetic properties.

Nano-particles that are small enough to enter human cells have the opportunity to interact (in a positive or negative sense) with the biochemical functions of the cells. In addition, nano-particles can absorb ultraviolet light and trigger chemical reactions.

The era of nano materials and nano technologies promises to be one of the major scientific developments and breakthroughs that in the not too distant future will permanently affect our everyday lives. Several of these products are already being used and many organizations foresee annual world markets, beginning in 2015, of the order of US $ 1,000 billion [2].

Researchers want to engineer various properties of nano-particles to produce new drugs, drug delivery system, clean up pollution, develop warfare armament, and improve consumer products, like dental products, sunscreen, and so on. There are several articles written by different authors [3-5] as well as several well written books are published [6-16] on nano-science, nano-technology, and nano-materials.

1.1. Bio-mineralization

In nature, amorphous phases exist extensively with readily moldable isotropic properties and of structure materials. For example, amorphous structures represent ~ 20% of approximately 60 different inorganic compounds and minerals formed by living organisms. These biologically formed minerals are often called bio-minerals, while the process of their formation is called bio-mineralization [17]. It is the process by which the living organisms can produce minerals, often to harden or stiffen existing tissues. It is a frequently used term in biology, medicine, nano-technology, astrobiology, and sometimes in geology. In this process living organism provides a chemical environment that controls the nucleation and growth of unique mineral phases. Teeth, bones, kidney stones, skeletons of algae, mussels, and magnetotactic bacteria are all examples of bio-mineralization. Calcium phosphate (CaP) materials show a positive interaction with living tissue that includes also differentiation of immature cells towards bone cells [18,19]. These materials also have chemical bonding to the bone along the interface, thought to be triggered by the adsorption of bone growth-mediating proteins at the bio-materials surface [20].

1.2. Bio-materials

A number of definitions have been developed for the term “bio-materials”. The consensus developed by experts in this field is the following: Bio-materials (or biomedical materials) are defined as synthetic or natural materials to be used to replace parts of a living system or to function in intimate contact with living tissues [21]. However, a more complicated definition has been published, “A bio-material is a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure, in human or veterinary medicine” [22]. In general, bio-materials are intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body and are now used in a number of different applications throughout the body. The major difference of bio-materials from other classes of materials is their ability to remain in a biological environment without damaging the surroundings and without being damaged in that process. Thus, bio-materials are solely associated with the health care domain and must have an interface with tissues or tissue component. A synthetic material used to make devices to replace part of a living system or to function in intimate contact with living tissue [23].

The use of bio-materials did not become practical until the advent of an aseptic surgical technique developed by Dr. J. Lister in the 1860s. Earlier surgical procedures, whether, they involved bio-materials or not, were generally unsuccessful as a result of infection. Nowadays, bio-materials in the form of implants (sutures, bone plates, joint replacements, ligaments, vascular grafts, heart valves, intraocular lenses, dental implants, etc.) and medical devices (pacemakers, biosensors, artificial hearts, blood tubes etc) are widely used to replace and/or restore the function of degenerated tissues or organs, to assist in healing, improve function, correct abnor-

malities and improve the quality of life of the patients. The various materials used in biomedical applications may be grouped into metals, ceramics, polymers and composites. The success of biomaterials in the body depends on factors such as the material properties, design, and bio-compatibility of the material used.

1.3. Bio-materials market

Currently, many materials can be found easily in the market. The global market for bio-materials was of US $44.0 billion in 2012 and is poised to grow at a CAGR (Compound Annual Growth Rate) of 15% from 2012 to reach US $88.4 billion by 2017 [24]. The global market for implantable bio-materials was US $25,277.8 million in 2012 and the market is estimated to be valued at US $33,600 million by 2019 [25], due to the need of better solution for injuries, diseases, and ageing population all over the world.

There are two main classes of ceramic bio-materials currently in use. One is derived from natural sources including coral and coral derivatives or demineralized human or bovine bone. The second is synthetic ceramics such as bio-active glasses, glass ceramics and calcium phosphates.

1.4. Bio-compatibility

Bio-compatibility is defined as acceptance of an artificial implant by the surrounding tissues and body as a whole. It is the ability of a material to perform with an appropriate host response in a specific application. “Appropriate host response” includes lack of blood clotting, resistance to bacterial colonization and normal healing.

Calcium phosphate (CaP) materials show a positive interaction with living tissue that includes also differentiation of immature cells towards bone cells [18,19]. These materials also have chemical bonding to the bone along the interface, thought to be triggered by the adsorption of bone growth-mediating proteins at the bio-materials surface [20].

1.5. CaP compounds

CaP bio-materials have been widely used in medical field in the form of powders, granules, dense porous blocks, and various composites [26]. This includes repair of periodontal defects, augmentation of alveolar bone, sinus lifts, tooth replacement, repair of large bone defects caused by tumors [27-32], as scaffolds in tissue engineering for bone or dentin regeneration [32-34], in the form of injectable cements [35,36] or as coatings on titanium and titanium alloy implants to combine the bioactivity (ability to develop strong interfacial bonding) of the CaP and the strength of the metal [37]. Each application has a need for the nano-particles to be of a particular size range.

CaPs have been used in the form of artificial bone. This material has been synthesized and used for manufacturing various forms of implants, as well as for solid or porous coatings on other implants. Extensive research on CaPs, has shown that these materials are suitable as bone substitutes due to their bio-compatible, bio-active, bio-degradable and osteo-conductive (ability to help in new bone formation) characteristics [27,38-41] and when implanted in vivo, they are non-toxic and do not induce any antigenic response [42]. The bioactivity, bio-compatibility, stability and mechanical properties of CaP materials are usually determined by its composition, structure, morphology and crystallite size [43]. However, the properties of controllable degradability, osteo-inductive and osteo-conductive abilities greatly differ among various CaP materials, which results in a large controversy on exploring qualified bone repair materials with adaptability for excellent bio properties in vivo. One common issue related to most bone repair materials is the uncontrollable degradation rate in vitro and in vivo. The exploration on adjusting degradation rate in vitro is an important part of the research on controllable degradability for bone repair materials. The degradation process of bone substitute in vivo significantly affects the bio-mineralization process on implants, because the released ions provide abundant ionic resources for surface nucleation. Thus, a controllable degradation rate of bone repair material in vitro study is meaningful because it can be adjusted to match with the mineralization rate and consequently affect osteo-induction and osteo-conduction process in vivo [44]. Recent trends in technology, however, focus on the incorporation of materials that extends the performance of CaPs to have the osteo-inductive properties or the ability to actually stimulate the new bone formation [45]. It is important to recognize that the ability to stimulate osteogenesis (bone growth) has also to couple with angiogenesis (blood vessel formation). The two processes are intricately linkedand the osteogenesis would not be possible without angiogenesis [46,47].

Being the main inorganic constituent of hard tissue, CaPs have long been attractive in hard tissue repair [48]. CaPs are preferred materials for bone-graft applications because of their similarity in composition with the bone mineral; excellent bioactivity; ability to promote cellular functions; and osteo-

conductivity [49]. These bio-materials have been widely used in medical field in the form of powders, granules, dense porous blocks and various composites [26]. There are number of articles which report the application of CaP in dentistry and orthopedics since the year 1920 [28,29,50-53].

Additionally, CaPs are the one of the widely used non-viral vectors for in vitro transfection (it is the process of deliberately introducing nucleic acids into cells) of a variety of mammalian cells due to its low toxicity, bio-degradability, ease of use, and adsorptive capacity for p-DNA [54-57]. The transfection effciency of the classical CaP method strongly depends on preparation parameters, such as pH, concentrations of calcium chloride, and DNA, temperature, the time between precipitation and transfection, cell types, as well as the skills of the researcher [57-59]. Due to the similar dimensions to the inorganic components of calcified tissues, CaPs materials in nano-size are expected to have better bioactivity compared with conventional materials [60]. The advantages of synthetic CaPs materials in nano-size again include higher bio-compatibility, good bio-degradability in situ, and excellent osteoconductive and osteo-inductive capabilities [61,62].

There are a large variety of CaPs in existence, which are distinguished by the type of the phosphate anion: ortho- $(PO_4)^{3-}$, meta- (PO^{3-}) or pyro- $(P_2O_7^{4-})$ and poly- $((PO_3)^{nn-})$. Several phases of crystallized CaPs are formed depending on temperature, partial pressure of water and impurities [63]. The quantum chemical calculations for CaP is reported by abinitio model and vibrational spectra are interpreted [64]. A series of CaP compounds is available: dicalcium phosphate [$CaHPO_4$], tri-calcium phosphate [$Ca_3(PO_4)_2$], tetra-calcium phosphate [$Ca_4(PO_4)_2O$], and hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], which differ by their chemical stoichiometry and crystallographic structure [26]. The defining factor is Ca/P ratio which lies between 1 and 2 [65]. This is summarized in Table 1.

Recently, the transfection capability of amino acid functionalized CaP nano-particles have been studied and reported that they are having the excellent bio-compatibility, biodegradability, and low immunogenicity [66]. Further, CaP facilitates DNA entry into cells without the need for toxic cationic mediators, while magnetic iron oxide allows for particle localization at a target site [67]. The CaP cements with magnetic nano-particles for bone regeneration are well reported [68]. The CaP nano-particles can be used as multi-functional tools for NIRF (near infrared fluorescence) optical imaging, PDT (photodynamic therapy) and tumor targeting as they exhibit a high therapeutic efficacy, being capable of inducing apoptosis and destroying tumor vascularization [69,70]. Wu et al. [71] have reported the development of novel self healing and anti bacterial dental composite containing CaP nano-particles. Moreover, the antimicrobial activity of the micro/nano structured biogenic silver doped CaP has been studied by Supraja et al. [72]. There are several patents reported on CaP in 2015 which includes application as body tissue repair [73], biomemitic peptide-containing compositions for deposition on magnesium alloy [74], bone cement formation containing magnetic calcium phosphate [75], method for producing CaPs [76].

Calcium polyphosphate has been investigated in the last sixty years for many applications, which include fertilizer [77], detergent [78,79] and more recently, it is being considered for various biomedical applications, including a vehicle for controlled drug release [80,81], as bone substitute [82], and as described earlier, as osteochondral substrates for tissue engineering. The proton conducting properties of CaP is explored for fuel cell application. The low methanol permeable and high proton con-

Table 1. Classification of CaP material with Ca/P ratio.

Phase	Formula	Crystal Structure	Ca/P
Tetra calcium phosphate	$Ca_4O(PO_4)_2$	Monoclinic	2.0
Hydroxyapatite (Hap)	$Ca_{10}(PO_4)6(OH)_2$	Hexagonal	1.67
Tricalcium Phosphate (TCP)	$Ca_3(PO_4)_2$	Rhombohedral	1.50
Octa calcium phosphate (OCP)	$2Ca_4(PO_4)3.5H_2O$	Monoclinic	1.33
Dicalcium Phosphate Dihydrate (DCPD)	$CaHPO_4\,2H_2O$	Triclinic	1.00
Calcium Pyrophosphate	$Ca_2P_2O_7$	Hexagonal, triclinic, monoclinic	1.00

ducting Nafion/CaP composite membrane is used for fuel cell [83]. Kasuga et al. [84] have reported the fast proton conductors from CaP hydro-gels. Moreover, the performance of fuel cell using CaP hydro-gel membrane prepared from waste materials is reported by Fukui et al. [85]. The Application of CaP nano-particles is suggested for hard tissue engineering scaffolds by Wang et al. [86].

There have been some reports on the possible use of calcium polyphosphate in the literature [53,87,88]. Because of its excellent bio-compatibility and absorption properties it has attracted more and more attention in bone tissue engineering resulting from its similar chemical structure compared with natural bone [89]. According to many reports, the size of biological apatite in biological hard tissues always possesses a range of a few to hundreds of nano-meters [90]. Currently these materials are used as a bone substitute [53], for bone screws [91], for bone crowns [92], and as a drug delivery matrix [93,94]. It has shown calcium polyphosphate implants can induce bone formation [95]. It also has non-biomedical applications, as an alternative to asbestos fibres [96], and in humidity sensors [97].

1.6. Calcium Pyrophosphate (CPP)

In chemistry, the anion, the salts and the esters of pyrophosphoric acid are called pyrophosphates. Pyrophosphates have their historical mode of formation embedded in their name. Pyrophosphates were originally prepared by heating of phosphates: the prefix pyro-is derived from Greek, means “fire” in this context. These condensed phosphates are commonly synthesized by the application of heat to orthophosphates [98, 99]. Amongst the condensed phosphates, pyrophosphate (P_2O_7), can be considered to be the smallest structure and shortest linear polyphosphate. Fig. 1 shows the molecular structure of pyrophosphate. They are essential for normal cellular functioning in virtually all living organisms. Pyrophosphatase (PPi) are very important for living body and find important place in biochemistry. Apart from this, they are good complexing agents and have many uses in industrial chemistry and also find important place in biochemistry. Mineralized tissues such as bone [100,101], dentin and enamel [102] contain substantial quantities of PPi. PPi may control the rates at which calcium and phosphate ions enter and leave the mineral phase, and may keep part of the mineral in a noncrystalline state. Due to their potential application, many researchers have synthesized either single crystal or powder of various PPi.

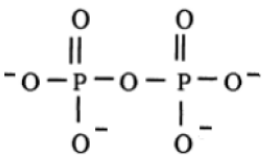

Fig. 1. Molecular structure of pyrophosphate.

The PPi are generally found in literature containing different formula groups; among these are $M^{IV}P_2O_7$ (M is tetravalent), $M^{II}P_2O_7$ (M is Divalent), and $M^{IV}M^{II}P_2O_7$ (mixed valance) [103]. Synthesis of pyrophosphate containing cations of various d-metals is of interest from the viewpoint of their possible catalytic or biological activity [104,105]. Crystalline and amorphous metal (II) pyrophosphates have long been used in many fields such as catalysts, waste water purification systems, ferro-electrics, lithium batteries, the steel and glass industries [106-110].

The scientific study of pyrophosphate salts and in particular calcium pyrophosphates (CPPs) can be divided into three periods. The first period, starting in the 1840’s, sought to understand the fundamental chemistry of ion coordination in solutions, and multiple phases of hydrated single and double salts [111]. The second period, flourished in the 1950’s and 1960’s, was directed towards identifying the chemical properties of condensed phosphates which could have superior characteristics to orthophosphate in industrial products such as fertilizer [112-114]. The third period, characterized by the study of pyrophosphates in biology, began with the identification by Fleisch and Neuman that pyrophosphate, a substance found in urine inhibited mineralization [115-117].

Calcium Pyrophosphate (CPP): $Ca_2P_2O_7$ – a shortest linear polyphosphate can be used as a bone graft material [118] and also as a mild abrasive agent in dentifrices [119,120] alike other phosphates. Abrasives are the cleaning and polishing agents in the toothpaste and generally account for about a third of its weight. Dicalcium phosphate and calcium pyrophosphate are popular materials for abrasives [121]. The CPP can be hydrolyzed slowly to the ortho monomolecular form and the rate increases with acidic pH and temperature. It is biodegradable to the ortho monomolecular form in body fluids, assisted by P-O-P splitting body enzymes, so that calcium and phosphate are supplied to the body

sera. In turn, the body sera supply calcium and phosphate back to the implant in the formation of normal body bone tissue as a replacement for the absorbed CPP [122]. The mineral CPP is one of the intermediate product in bio-mineralization process. In bone, CPP can regulate the onset of calcification and can act as a trigger mechanism to promote mineralization. It can also alter the rate of crystal growth and dissolution [123]. However, physical chemical investigations of growth and dissolution of CPP crystals are scarce [124]. In view of this suggested benefits several studies focus on the use of CPP as coating material for dental and orthopedic implants. In addition, the results of an in vitro osteoblasts cell culture and in vivo animal study demonstrated that pyrophosphate is bio compatible with bone cells and has a great potential as an in vivo biodegradable bone substitute [110]. Sintered dicalcium pyrophosphate (SDCP), a synthetic compound, has been proven to be more bio-compatible to bone tissue than hydroxyapatite [110]. Altogether, the deposition of CPPD (calcium pyrophosphate dihydrate) crystals is responsible for the diseases like pseudo-gout, an acute arthritic attack with pain and inammation of joints [125-129] and Coffin Lowry Syndrome (CLS), a heritable disorder characterized by pronounced mental retardation and vertebrae abnormalities [130,131]. The CPP constitute a wide family, which, to our knowledge, has been little explored, although their bio-compatibility is well established. CPP in crystalline form using gel growth technique have been studied by Parekh [132,133].

Calcium pyrophosphate hydrate (CPP, $Ca_2P_2O_7{\cdot}nH_2O$) and calcium orthophosphate compounds (including apatite, octacalcium phosphate, etc.) are among the most prevalent pathological calcifications in joints. Even though only two dihydrate crystalline forms of CPP (CPPD) have been detected in vivo (monoclinic and triclinic CPPD), the investigations of other hydrated forms such as tetrahydrated or amorphous CPP are relevant to a further understanding of the physico-chemistry of those phases of biological interest. It is worth noting that CPP crystals are particularly involved in several kinds of arthritis, including osteoarthritis, a degenerative joint disorder affecting 80% of the population over 75 [134]. The two different CPPD crystalline phases viz. monoclinic and triclinic calcium pyrophosphate dihydrate (CPPD), referred to as *m*-CPPD and *t*-CPPD, respectively [135], are associated with a high inammatory potential, according to in vivo studies, which is probably due to their interaction with cell membranes [136]. The pathogenic features of CPPD deposition disease in primary metabolic disorders and its relationship to PPi (pyrophosphatase-PPi-a potent, physiologic inhibitor of the nucleation and propagation of BCP crystals) metabolism and chondrocyte differentiation is reported in detail by Terkeltaub [137].

1.7. Crystal structure of calcium pyrophosphate

Fig. 2 shows the crystal structure of triclinic dihydrate of calcium pyrophosphate (t-CPPD). This is a view down the [1 0 0] direction and illustrates the probable configuration of atoms at the surface of the most prominent crystal face. Hydrogen bonding is indicated by dotted lines and “triads” of terminal pyrophos phate oxygens at the surface. The most prominent feature of the surface of the triclinic form of CPPD is the series of “triads” of negatively charged pyrophosphate oxygens. The centers of the calcium atoms lie farther below the surface than the centers of the oxygen atoms. Since the oxygen atoms have a much larger van der Waals radius than the calcium atoms, the result is that the calcium atoms lie in pockets and the partially covered by the oxygen atoms [138].

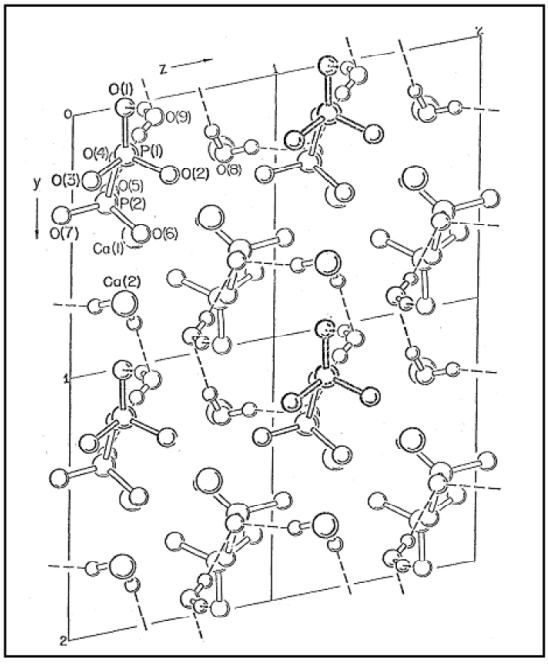

Fig. 2. Crystal structure of t-CPPD,reprinted with permission from: N. L. Davis (PhD Thesis, California Institute of Technology, USA, 1977), © 2015 California Institute of Technology.

The pyrophosphate molecules are reported to have a very high flexibility with two characteristic configurations, staggered or eclipsed [139]. Similar to pyrosilicates, pyroarsenates or pyrogermanates, the crystals of pyrophosphate compounds of the composition $X_2P_2O_7$, with an ionic radius of X less than 0.97 Å (X = Mg, Mn, Fe, Co, Ni, Cu, Zn), are isostructural with thortveitite ($Sc_2Si_2O_7$), with the P-O-P bond angle varying from 140 to 180° and O-P·····P-O pseudo-torsion angle of 60° (staggered conformation) and the YO_4 (Y = P, Si, As, Ge) tetrahedra showing a very low degree of distortion. For an ionic radius greater than 0.97 Å (X = Ca, Sr, Ba) or for hydrates, pyrophosphate molecules usually have the same configuration as the dichromate structure, with a P-OP angle of approximately 120-135°, and OP·····O pseudo-torsion angle of 0-30° (eclipsed conformation) and distorted YO_4 (Y = P, Si, As, Ge) tetrahedra [140]. The structures of several divalent metal ion pyrophosphates $M^{II}P_2O_7$ (M is Divalent) show either a bent P-O-P group in the anion [141, 142] and/or considerable disorder at the central oxygen atom at the ion [143]. The structures of CaPs are mainly determined by single crystal X-ray diffraction (XRD) [144-146]. The biological response of b-CPP for new bone formation is quite similar to that of the hydroxyapatite [147]. Fig. 3a represents the structure of β-CPP viewed along c-axis including the cell contents between approximately *z* = 0 and *z* =0.20 only. The complete coordination shells around the four independent calcium ions are shown only once; these shells contain some oxygen atoms which are either above or below the general level [148]. Fig. 3b depicts the structure of α-CPP projected onto the *xy* plane, where the large circles represent oxygen atoms, the small circles represent phosphorus atoms and the medium-sized circles represent the cations. The decimal numbers represent the *z* coordinates of the atom. The broken bonds are to oxygen atoms a unit cell length away [143].

Structures of both β- and α-CPP contain pyro groups, P_2O_7, which consist of two corner-shared PO_4 tetrahedra with P-O-P angles of 130° for the α phase and angles of 131° and 135° for the phase β. In α-CPP, the Ca ions coordinates with eight oxygen atoms and the chains of edge-shared Ca polyhedral form sheets parallel and perpendicular to the *ac* plane. The coordination number of Ca in β-CPP are seven, eight and nine; each pyrophosphate group is linked by commonly shared Ca atoms forming infinite pyrophosphate-Ca chelate-like chains which is represented in Fig. 4 [149].

Recently, the crystal structure of m-CPPM (monoclinic calcium pyrophosphate monohydrate) is reported and shown in Fig. 5 [150]. The molecular structure of m-CPPM, showing the atom-numbering scheme and symmetry-equivalent atoms. The

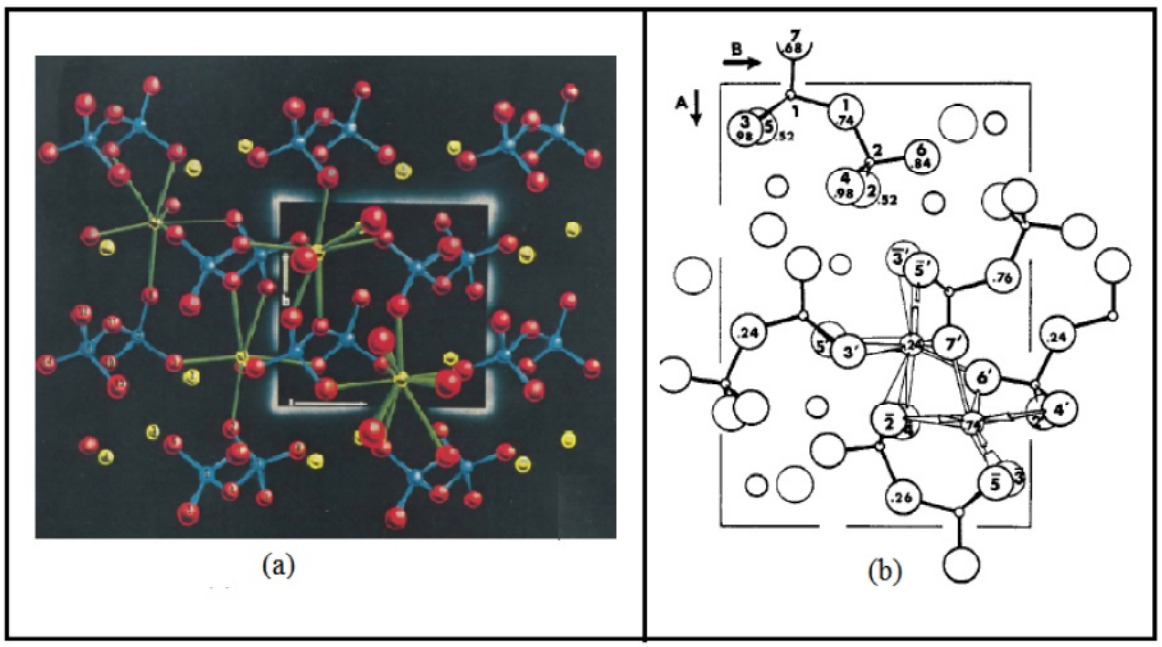

Fig. 3. Crystal structure of (a) β-CPP (reprinted with permission from: N. C. Webb // Acta Crystallogr. 21 (1966) 942; © 1966 International Union of Crystallography) and (b) α-CPP (reprinted with permission from C. Calvo // Can. J. Chem. 43 (1965) 436 © 1965 Canadian Science Publishing).

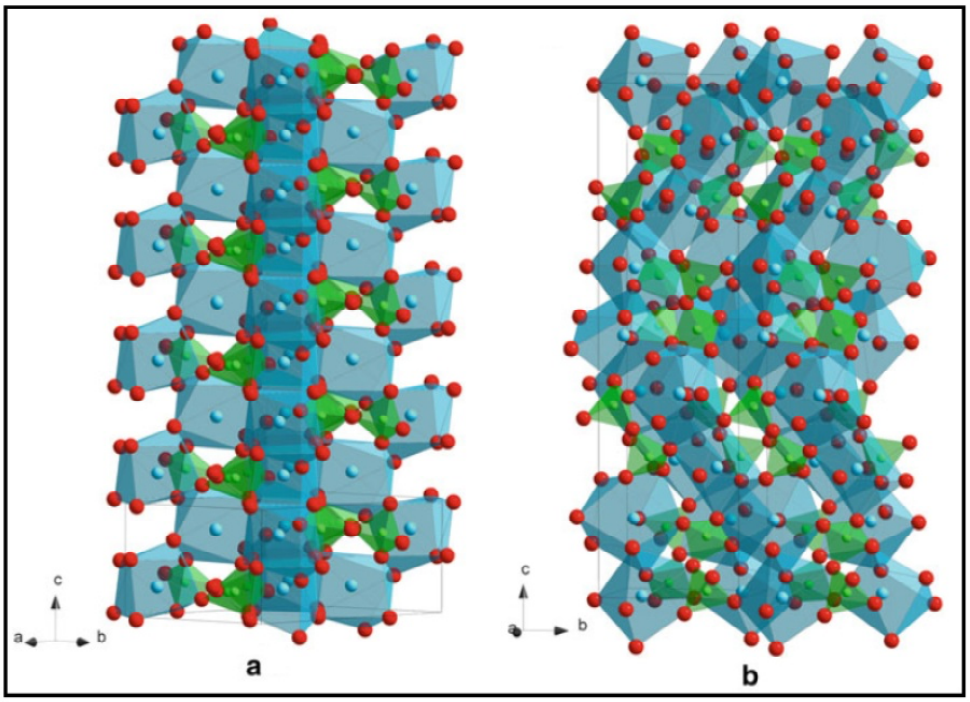

Fig. 4. Crystal structure of β-CPP and α-CPP, reprinted with permission from: T. Goto and H. Katsui // Interface Oral Science (New York: Springer,2014); © 2014 Springer.

displacement ellipsoids are drawn at the 50% probability level, except for H atoms, which are represented by 20% probability spheres.

2. SYNTHESIS METHODS

There are various techniques reported in the literature for the synthesis crystalline CPP, which include precipitation method [124], wet chemical process [132] and gel growth technique [132]. In this single diffusion gel growth technique sodium pyrophosphate solution was mixed with sodium meta-silicate solution of 1.05 specific gravity and this was acidified by 2 N acetic acid in such a manner that pH was within 4.5-5. After setting the gel calcium nitrate tetra hydrate solution was poured without disturbing the gel. Good quality, transparent, spherical granule type crystals were obtained. The CPP crystals show birefringent properties and can be viewed under polarized microscope. The monoclinic CPPD crystals were synthesized using physical methods by Winternitz et al. [151].

Altogether various techniques are reported in the literature for the synthesis of nano-sized CPP, which include wet precipitation method [152], solid state reaction [153], thermal decomposition of dicalcium phosphate dihydrate (DCPD, brushite, $CaHPO_4 2H_2O$) or dicalcium phosphate (DCP, monetite, $CaHPO_4$) [154] and glass crystallization [155].

Many methods have been employed to synthesize metal doped CaP based materials such as: hydrothermal treatment [156,157], chemical precipitation [156,158,159], sol-gel [160-162], solid-state reaction [163] and solution-reaction system [164].

3. CHARACTERIZATION OF CaP COMPOUNDS

Apart from basic characterizations like powder XRD, FT-IR and TEM, various techniques have been employed for bulk as well as nano-structured CaP compounds, for example, thermal stability of bulk CPP was studied by Thermogravimetric Analysis (TGA) [133,165] and nano-structured CPP [166,167] and dielectric study of bulk CPP was carried out by Bian [153] and Parekh [132] and Vasant and Joshi carried out for nano-CPP [167]. In order to explore better applications of CPP, the doping of different ions is reported by various authors, viz, Zn ion doped by Masala [168] and Vasant [169] and Mn ion doped by Masala [170].

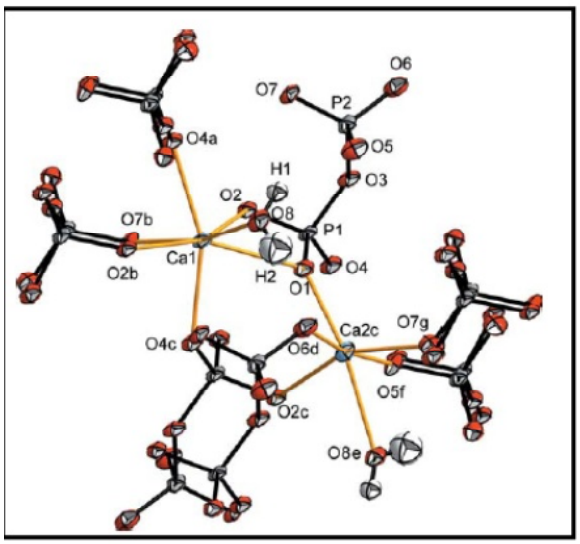

Fig. 5. Molecular structure of m-CPPM, reprinted with permission from: P. Gras, N. Ratel-Ramond, S. Teychene, C. Rey, E. Elkaim, B. Biscans, S. Sarda and C. Combes // Acta Cryst. C: Struct. Chem. 70 (2014) 862, © 2014 International Union of Crystallography.

4. SOME RECENT DEVELOPMENTS

By carefully reviewing the literature the present author has come across some interesting publications on CaP bulk and nano-particles. It is a mammoth task to cover all research publications, but a humble attempt is made to cover some important ones. It has been found that most of the studies are related to medical science for treatment or detection of disease or aliment.

As CPP is found to be responsible for pseudogout and other arthropathies. The attempt was made to grow CPP crystals in gel medium to study growth inhibition using three different herbal extracts viz *Rotula aquatica root*, *boerhaavia diffusa root,* and *commiphora wightii*. The growth inhibition was carried out by measuring the number of crystals grown and total diffusion length in gel column. All three extracts had given good results in terms of less number of crystals grown and less diffusion length in the gel the column with comparison to pure calcium nitrate solution, altogether, *commiphora wightii* showed the best results [132].

The photodynamic therapy (PDT) of tumor causes skin photo-sensitivity as a result of unspecific accumulation behavior of the photosensitizers. The PDT of tumors was improved by CaP nano-particles conjugated with (i) Temporfin as photosensitizer, (ii) the RGDfk peptide for favored tumor targeting, and (iii) the fluorescent dye molecule DY862-NHS for enabling near IR-uorescent optical imaging in vivo [69]. Earlier Ganesan et al. [171] have reported that the CaP nano-particles colloidally stabilized by surface functionalization with 5, 10, 15, 20- tetrakis (4-phosphonoxyphenyl) porphine (P-TPPP) as bio-compatible fluorescing agents or for the delivery of fluorescing molecules. Also, the surface functionalization of CaP nano-particles is achieved by Mostaghaci et al. [66] using N-(2-aminoethyl)-3-aminopropyltrimethoxysilane to achieve disperse CaP nano-particles with positive surface charges capable of transfection. These CaP nano-particles is used for delivering nucleotides into living tissues or cells. Nano tetracalcium phosphate coating on titanium substrate is recently studied and corrosion parameters have been evaluated in simulated body fluids [172]. Further, the length controlled synthesis of calcium phosphate nano-rod and nano-wire for intracellular protein delivery is reported by Das and Jana [173].

Calcification is the detrimental process in vascular aging and in diseases such as atherosclerosis and arthritis. In particular, small CaP crystal deposition associated with inamation and atherosclerotic plaque destabilization. Dautova et al. [174] have reported that CaP particles caused human vascular smooth muscle cell (VSMC) death. The CaP particles functionalized with protein fetuin-A is less toxic than naked CaP particles.

CaP nano-particles find applications in cancer treatment. The efficiency of CaP composite nanoparticles in targeting Ehrlich Ascites carcinoma cells transplanted in mice is reported by Abdel-Gawad et al. [175]. The mode of action of nano-CaP in vivo is studied by histopathological examination, which shows complete recovery of cancer cells in the thigh muscle after three months. Also, the preparation of optimized lipid-coated CaP nano-particles is investigated by Tang et al. [176] for enhanced in vitro gene delivery to breast cancer cells.

Recently some applications of CPP as catalyst are reported. Non-stoichiometric CPP is found as highly efficient and selective catalyst for dehydration of lactic acid to acrylic acid. The non-stoichiometric CPP with Ca/P ratio from 1.02 to 0.76 is studied and the ratio 0.76 is found to be the most efficient with 100% lactic acid conversion and 78% acrylic acid selectivity at 375 °C. Apart from this, the chitosan/CPP hybride micro-owers exhibit high efficiency in dye adsorption and enzymatic catalysis [177]. Abrouki et al. [178] have carried out the experimental design-based response surface meth-

odology optimization for the synthesis of β-mercapto carbonyl derivatives as anti-micro bacterial drug catalyzed by CPP.

CaP nano-particles are used as a carrier of drug, protein, marker dye, etc. It has been found that CaP nano-particles carrying bone morphogenetic protein-Y plasmid DNA induce an osteogenic response in MC3T3-E1 pre-osteoblast cells [179]. Also, magnetic iron oxide doped tricalcium phosphate nano-particles have been designed by Puddu et al. [67]. as transfection vehicles.

The novel self-healing and anti-bacterial dental composite containing CaP nano-particles is developed by Wu et al. [71]. They used DMAHDM (dyemethylaminohexadecylmethacrylate) for the antibacterial function.

The interactions of nano CaP with stem cells are recently discussed by Wang et al. [180]. The interaction is taking place in several manners, such as, (i) the nano-CaP supports stem cells attachment/proliferation, (ii) the influence of nano CaP surface pattern on cell alignment, (iii) the superiority of nano-CaP to the conventional CaP for bone regeneration, (iv) the combination of stem cells with nano-CaP accelerates bone regeneration and (v) the cell micro-encapsulations in nano-CaP scaffolds. These interactions are important from tissue engineering point of view.

5. CONCLUDING REMARKS

In this small review of CaP compounds, an attempt is made to cover as much time span as possible right from 1920 to 2016. Extensive and exhaustive research has been carried out to understand their physical, chemical and structural properties. Various applications have been identified and last few years of literature survey indicates more trend towards bio-medical applications of CaPs and their nano-particles. This leads to synthesize various doped, structurally as well as morphologically modified and functionallized bulk materials and also nano-particles. This further suggests that plenty of opportunities are available for inter-disciplinary research.

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