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Review

Calcium phosphate ceramic systems in growth factor and drug delivery for bone tissue engineering: A review

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ABSTRACT

Calcium phosphates (CaPs) are the most widely used bone substitutes in bone tissue engineering due to their compositional similarities to bone mineral and excellent biocompatibility. In recent years, CaPs, especially hydroxyapatite and tricalcium phosphate, have attracted significant interest in simultaneous use as bone substitute and drug delivery vehicle, adding a new dimension to their application. CaPs are more biocompatible than many other ceramic and inorganic nanoparticles. Their biocompatibility and variable stoichiometry, thus surface charge density, functionality, and dissolution properties, make them suitable for both drug and growth factor delivery. CaP matrices and scaffolds have been reported to act as delivery vehicles for growth factors and drugs in bone tissue engineering. Local drug delivery in musculoskeletal disorder treatments can address some of the critical issues more effectively and efficiently than the systemic delivery. CaPs are used as coatings on metallic implants, CaP cements, and custom designed scaffolds to treat musculoskeletal disorders. This review highlights some of the current drug and growth factor delivery approaches and critical issues using CaP particles, coatings, cements, and scaffolds towards orthopedic and dental applications.

1. Introduction

Musculoskeletal diseases or disorders such as arthritis, osteoporosis, osteonecrosis, bone fracture, bone tumor, trauma due to sports, war and/or road traffic injuries, back pain and other spinal disorders cost society over $250 billion annually in the USA, and affects hundreds of millions of people across the world. It is estimated that around 10 million Americans have osteoporosis, and about 34 million are at risk of getting this disease. Osteoporosis caused 2 million fractures costing over $19 billion in 2005, and this is expected to rise to 3 million fractures by 2025, costing over $25 billion per year [1]. For load-bearing implants, over 200,000 hip replacements are performed each year in the USA, and this number is increasing steadily due to increased life expectancy [2]. More and more younger patients are in need of total hip replacement (THR) due to increased daily life activities or a more active lifestyle. Thus, the American Academy of Orthopedic Surgeons (AAOS) has categorized musculoskeletal conditions as the number one reason why patients visit a doctor [3]. Considering the tremendous impact of musculoskeletal conditions on our population and economy, the years 2000–10 had been proclaimed as the Bone and Joint Decade globally; and the years 2002–11 have been marked as Bone and Joint Decade in the USA [4]. The purpose of Bone and Joint Decade is to increase the awareness and advance the understanding of musculoskeletal disorders through prevention, education and research to improve the quality of life for people with musculoskeletal disorders.

A sharp rise in musculoskeletal diseases and disorders often demands a drug treatment at the specific surgery/injury/defect site. In bone tissue engineering, the term "drug" is not limited to only therapeutic agents such as antibiotic, anticancer, anti-inflammatory. The scope of the term "drug" has grown over the last few decades to include growth factors, bioactive proteins, enzymes, and non-viral genes (DNAs, RNAs). Different growth factors, bioactive biomolecules, and drugs are used in bone tissue engineering to induce osteoinductivity in the implanted biomaterials to accelerate the healing process to address various musculoskeletal disorders. Thus, the application of drugs in bone tissue engineering is very wide and a rapidly growing research field of interest.

To be used as a drug carrier, the potential substance must have the ability to incorporate a drug either physically or chemically, retain the drug until it reaches the specific target site, be gradually degraded, and deliver the drug in a controlled manner over time [5]. All these criteria are well met by calcium phosphates (CaPs), and as a result, these materials are promising candidates for drug delivery applications. CaPs are widely used in bone tissue engineering for hard tissues such as teeth or bone replacement, augmentation, and/or regeneration due to their excellent bioactivity and compositional similarities to bone mineral [6–10]. Table 1

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Table 1
Typical compositional values of inorganic phase of adult human calcified tissues (Copyright (2002) John Wiley and Sons. Reprinted from Ref. [11] with permission).

Composition	Enamel	Dentin	Bone	Hydroxyapatite (HA)
Calcium [wt.%]	36.5	35.1	34.8	39.6
Phosphorus (as P) [wt.%]	17.7	16.9	15.2	18.5
Ca/P (molar ratio)	1.63	1.61	1.71	1.67
Sodium [wt.%]	0.5	0.6	0.9	–
Magnesium [wt.%]	0.44	1.23	0.72	–
Potassium [wt.%]	0.08	0.05	0.03	–
Carbonate (as CO_3^{2-}) [wt.%]	3.5	5.6	7.4	–
Fluoride [wt.%]	0.01	0.06	0.03	–
Chloride [wt.%]	0.30	0.01	0.13	–
Pyrophosphate,(as $P_2O_7^{-4}$) [wt.%]	0.022	0.10	0.07	–
Total inorganic [wt.%]	97	70	65	100
Total organic [wt.%]	1.5	20	25	–
Water [wt.%]	1.5	10	10	–
Ignition products (800 °C)	β-TCP + HA	β-TCP + HA	HA + CaO	HA

Table 2
Organic component of bone and their functions in bone mineralization (Copyright (2002) American Chemical Society. Reprinted from Ref. [14] with permission).

Name	Functions
Collagen	Structural protein found in many tissues
Bone sialoprotein (BSP)	Acid protein with poly(glutamic acid) run and RGD binds calcium
Osteonectin (ON) and osteopontin (OP)	Glycoproteins that may either nucleate or block HA mineralization
Chondroitin sulfate (ChS) and keratan sulfate	Large molecular weight, sulfated glycosaminoglycans that are found in cartilage and bone tissues
Osteocalcin (OC)	Inhibits bone formation; does not appear to affect HA mineralization
Biglycan and decorin	Proteoglycans that bind to type I collagen and are involved in assembly of bone matrix
Thrombospondin and fibronectin	Matrix glycoproteins that bind to integrins and ECM components (collagen, fibrin, etc.)

[11] shows the typical composition of the inorganic phase of adult human calcified tissues. Dynamic and highly vascularized bone tissue can be viewed as a composite made from biopolymer (mainly collagen) and bioceramic (CaP). CaP, in the form of carbonated apatite, is the principal mineral content (~69%) of natural bone. The organic matrix (~22%) consisted of proteins, type I collagen (90% of the organic matrix) with some non-collagenous proteins (e.g., proteoglycans), lipids and osteogenic factors (i.e., growth factors, such as bone morphogenetic proteins (BMPs) and vascular endothelial growth factors (VEGFs)) [7,12,13]. The remaining 9% is represented by water. Table 2 [14] shows the organic components of bone and their functions in bone mineralization. Osteoinductivity, a very important property of bone, allows bone to repair and regenerate itself. Though osteoconductive, CaP biomaterials are not osteoinductive [15]. However, it has been shown that osteoinductivity to CaP biomaterials can be introduced by combining these materials with growth factors, bioactive proteins, or osteogenic drugs [16–21].

Versatility, excellent bioactivity, compositional similarities to bone mineral, and tailorable biodegradability of CaPs over other ceramics are some of the reasons that CaP systems are increasingly being explored as drug delivery systems (DDSs) for numerous applications in nanomedicine, orthopedics and dentistry. Drug delivery approaches from CaP systems in the form of nanoparticles, coatings, cements and scaffolds have been discussed in this review. In dimensional perspectives, we can consider CaP coating as a two-dimensional construct, whereas calcium phosphate cement (CPC) and CaP scaffolds can be considered as three-dimensional (3-D) constructs. Fig. 1 shows the approaches for CaPs in drug delivery applications, and some common terms and their meanings are presented in Table 3 [10,14,22,23].

2. Categories of calcium phosphates (CaPs)

Depending on temperature, impurities, and the presence of water, CaPs can exist in different phases [1,24]. Exciting features of CaPs are their excellent bioactivity and biodegradability. All CaPs do not have similar bioactivity, and also do not degrade at the same rate. Bioactivity and degradation behavior generally depend on the Ca/P ratio, crystallinity and phase purity. Regardless of Ca/P ratio, phase and crystallinity, CaPs are relatively insoluble at physiological pH 7.4; however, they have increasingly high solubility in acidic environments, i.e., below pH 6.5 [25–27]. Among all CaPs, the most acidic and soluble CaP is monocalcium phosphate monohydrate (MCPM). Monocalcium phosphate (MCP) is the anhydrous form of MCPM, and is obtained by heating MCPM above 100 °C. Both MCPM and MCP are not biocompatible due to their highly acidic nature and high solubility. Bioactive calcium-deficient hydroxyapatite (CDHA), sometimes called precipitated hydroxyapatite (PHA), has a very complex chemical structure. The Ca/P ratio in CDHA is generally between 1.50 and 1.67, but a Ca/P ratio outside this ratio is also possible. Bone apatite is similar to CDHA except for the presence of carbonate (CO_3^{2-}) and trace elements, for instance, Na^+, K^+, Mg^{2+}, Sr^{2+}, Zn^{2+} [7,9]. Amorphous calcium phosphate (ACP) is similar to CDHA, while octacalcium phosphate (OCP) and tetracalcium phosphate (TTCP) can be synthesized at a higher temperature than other CaPs. Among various CaPs, HA and β-TCP are the most commonly used phases because of their osteogenic property and the ability to form strong bonds with host bone tissues. Solubility of β-TCP is much higher than HA, and thus β-TCP is termed a bioresorbable ceramic [28,29]. Development of biphasic calcium phosphate (BCP)-based biomaterials consisting of HA and β-TCP [30–32] are also of interest to control the degradation properties. Table 4 [10,11,24,33,34] presents a list of different CaPs and their properties.

Apart from different phases, sizes, fabrication and formulation techniques, from an application point of view, CaPs can be categorized as nanoparticles (NPs), coatings, scaffolds and cements. Drug loading and release processes can vary depending on whether it is a NP, coating, scaffold or cement. In this paper, we have reviewed drug delivery approaches from CaP nanoparticles, coatings, scaffolds and cements along with the associated concerns.

3. Calcium phosphate nanoparticles (CaP NPs) in drug delivery

Nanoparticle-based drug delivery systems are a rapidly growing field of interest for effective targeted drug delivery application.

ID	Title	Pages
1213	Calcium phosphate ceramic systems in growth factor and drug delivery for bone tissue engineering: A review	21