Calcium Phosphate Bone Cements in Drug Delivery: Review

İlaç Verilişinde Kalsiyum Fosfat Kemik Çimentoları

Evren ALĞIN YAPAR[a]

[a]Republic of Turkey, Ministry of Health, Turkish Medicines and Medical Devices Agency, Ankara

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Yazışma Adresi/*Correspondence:*
Evren ALĞIN YAPAR
Republic of Turkey, Ministry of Health, Turkish Medicines and Medical Devices Agency, Ankara, TÜRKİYE/TURKEY
evrenalgin@yahoo.com

ABSTRACT In recent years, local drug administration has gain importance due to increase in the success in the field of orthopedic surgery. Accordingly implants has been prepared in various forms with different materials. Researches have been carried out regarding to their *in vitro* and *in vivo* performances. Between orthopedic implant applications, cement forms have been found clinically successful and calcium phosphate cements with their similarity to bone structure have gain attention in drug delivery due to their advantages such as injectability and fast setting time in low-temperatures providing that their mechanical properties develop by combination of other biomaterials. Several attempts have been made to include growth factors and morphogens within bioactive scaffolds to stimulate cellular adhesion, proliferation and differentiation, so as to promote bone regeneration. Additionally, enhancing further the functionality of these already complex cements by loading drugs into them to treat bone disorders or to act on the surrounding tissues with an adequate therapeutic concentration level and for a desired time frame is recognized as being highly beneficial. Successful researches are available with especially to antibiotics, biphosphanates, growth factors, anti-inflammatory and antimicrobial actives in the form of calcium phosphate cements and this field is promising for new applications of the future for musculoskeletal diseases and defects.

Key Words: Drug delivery systems; biocompatible materials; bone cements; calcium phosphate; orthopedics

ÖZET Son yıllarda ortopedi alanında lokal ilaç verilişi, özellikle cerrahi mühalelerin başarısını arttırması nedeniyle önem kazanmıştır. Bu doğrultuda çeşitli materyaller ile değişik formlarda implantlar hazırlanmış, *in vitro* ve *in vivo* performanslarına yönelik araştırmalar yapılmıştır. Ortopedik implant uygulamaları arasında, klinik olarak çimento formları başarılı bulunmuş ve materyal olarak kemik yapısı ile oldukça benzer kalsiyum fosfatlar, mekanik özelliklerinin diğer biyomateryaller ile geliştirilmesi kaydıyla ilaç salımında enjekte edilebilirlik, düşük sıcaklıkta hızlı sertleşme gibi avantajları nedeniyle dikkat çekmiştir. Kemik rejenerasyonu teşvik etmek amacıyla, hücre yapışması, çoğalması ve farklılaşması, uyarmak için biyolojik olarak aktif iskeleler içinde büyüme faktörleri ve morphojenlerin verilmesi amacıyla çeşitli girişimler yapılmıştır. İlaveten, kemik bozukluklarını tedavi etmek veya çevre dokularda etki etmek üzere yeterli terapötik konsantrasyon seviyesinin arzu edilen zaman dilimi içinde sağlanması amacıyla bu kompleks çimentolara ilaç yüklenerek işlevselliğinin arttırılması son derece faydalı olarak kabul edilmektedir. Başta antibiyotikler olmak üzere bifosfonatlar, büyüme faktörleri, antiinflamatuarlar ve antimikrobiyallerin kalsiyum fosfat kemik çimentosu formunda başarılı çalışmaları mevcut olup, ileriye yönelik kas ve iskelet sistemi hastalık ve defektlerinde yeni uygulamalar açısından umut vericidir.

Anahtar Kelimeler: İlaç dağıtım sistemleri; biyouyumlu materyaller; kemik çimentosu; kalsiyum fosfat; ortopedi

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In recent years drug delivery implants have gain importance for long term therapies which have some advantages like avoidance of first pass metabolism, reduce dose and side effects of active substance with fluctuations in blood levels.[1]

In orthopedic surgery osteoclasts, one of the major causes of bone lysis leading to implant failure has been clinically proved that could be effectively sponge out by decreasing the catabolic bone activity provided with bisphosphonate group drugs. Due to systemic delivery of bisphosphonate by injections could not effectively reach to peri-implant region; local drug delivery has been preferred.[2] Drug delivery orthopedic implants particulary focus on bone infections which is an important factor in the success of orthopedic implants. Drug delivery with an implant can be available either coated on an implant surface, or incorporated in a biomaterials/cement scaffold or included in beads (Figure 1). Between those approaches most of clinical orthopedic applications were performed in cements successfully.[2-5]

Several attempts have been made to include growth factors and morphogens within bioactive scaffolds to stimulate cellular adhesion, proliferation and differentiation, so as to promote bone regeneration.[6-8] In addition, enhancing further the functionality of these already complex matrices by loading drugs into them to treat bone disorders or to act on the surrounding tissues with an adequate therapeutic concentration level and for a desired time frame is recognized as being highly beneficial.[6,9-20]

Three-dimensional bioactive bone scaffolds can be fabricated by using bioceramics, biodegradable polymers and their composites. Bioactive ceramic scaffolds alone used in bone tissue engineering can serve as a delivery vehicle for drugs but the drug release patterns are difficult to control. On the other hand, biodegradable polymeric materials such as poly(lactic-co-glycolic acid) (PLGA) and poly(propylene glycol-fumerate)/methylmethacrylate can be used to control the local delivery of drugs. However, they can show impaired osteoconduction and they can provoke an adverse tissue response owing to inflammation as a consequence of acidic degradation.[6,7,21-24] Inorganic materials are promising alternatives to polymeric bone cements and fillers because of their high chemical stability, hydrophilic character, easy functionalization, large surface area and ability to adsorb drugs. Owing to the possibility of synthesizing ordered mesoporous silica-based structures, inorganic particulate fillers can achieve a controlled release of the adsorbed or attached moiety. However self-supported structures of those materials lack mechanical stability.[25,26] Composite materials might combine for improvement of mechanical properties and adjustable controlled release of drug which can be obtained with combination of polymeric and inorganic (hydroxyapatites, tricalcium phosphates and mesoporous silicas) materials. Mechanically, a well-designed composite material could simulate at best the behavior of natural bone, which is composed of an inorganic (calcium hydroxyapatite) and an organic (type I collagen and other non-collagenous proteins) matrix.[26] Thus, the smart combination of bioceramics and biodegradable polymers can not only improve the degradability of the inorganic material and alter its mechanical/physical properties, but also drug-release profiles can be controlled to a greater extent rather than pure ceramics. There is a wide range of different polymers that can be use for such applications, having different degradation rates and mechanisms, and a wide range of bioceramic/biopolymer composite scaffolds is available for bone tissue engineering.[6,7,21,26-29]

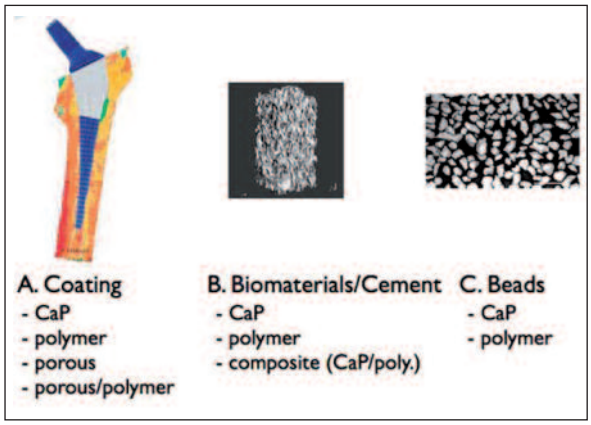

FIGURE 1: Drug delivery implant approaches A. Coating, B. Scaffold or Cement, C. Beads.[2]
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CALCIUM PHOSPHATE CEMENTS

GENERAL PROPERTIES

Calcium phosphates (CaPs) have good biocompatibility, osteoconductivity and chemical properties

make them suitable for bone-remodeling kinetics and they can be resorbed by cells. They have enough mechanical strength but they are brittle and slowly degradable.[6,30-32] Their osteoconductive properties allowed them to use in orthopedics, dental, ear, nose and throat surgeries.[33] CaPs can be in different forms such as ceramics, cements, composites and thin coatings.[33-35] Their performance can be affected by some pathological situations such as infection, irradiation, diseases etc. in terms of the substitution and/or resorption process. To prevent the undesirable results related pathological situations, CaPs preferred to combine with active molecules which represent the most current alternatives to biological bone grafts and exist in various forms such as powders, granules, ceramic, cement and coatings.[33] On the basis of composition, synthetic CaPs presently used as biomaterials are classified as presented in Table 1.

Drug delivery bone cements should be bioactive and resorbable to provide bonding to bone tissue and substitution. Moreover injectablity is desirable for ease of administration and better fitting to the bone defect. Calcium phosphate cements (CPCs) meet above mentioned needs which make them good candidates for clinical applications.[37] The CPCs was first patent by Brown and Chow in 1986.[33,38] CPCs have more advantages such as being noncytotoxic, promoting the development of osteoconductive pathways, enough mechanical strength for different applications and restore contour. Furthermore, their low-temperature setting reaction and intrinsic porosity allow for the incorporation of drugs into the cement. Fast setting time, excellent mouldability, easy manipulation and injectibility can perfectly fit the bone defect; their low temperature *in vivo* self-setting capability is important not to give harm to surrounding tissue and provide no risk of infectious diseases allow to prevent grafting failure.[33,37,39-46]

TABLE 1: Calcium phosphate types, abrreviations and mineral names.[36]

Calcium phosphates	Abbreviations	Mineral name
Monocalcium phosphate monohydrate	MCPM	–
Monocalcium phosphate	MCP	–
Dicalcium phosphate dihydrate	DCPD	Brushite
Dicalcium phosphate	DCP	Monetite
Octacalcium phosphate	OCP	–
alpha-Tricalcium phosphate	α-TCP	–
beta-Tricalcium phosphate	β -TCP	Whitelockite
Amorphous calcium phosphate	ACP	–
Calcium-deficient hydroxyapatite	CDHA	–
Carbonated apatite	CA	Dahlite
Hydroxyapatite	HA	–
Oxyapatite	OXA	–
Tetracalcium phosphate	TTCP	Hilgenstockite

CPCs are composed of an aqua/aqueous solution and CaPs or combiantions. Upon mixing of these components, dissolution and precipitation into a less soluble CaP has occurred and entanglement of the growth of crystals provided the mechanical rigidity of the cement.[36,39,46] The prepared CaPs paste can be placed into the damaged part of bone and generally hardens less than 20 min at body temperature (37°C) *in situ* and then displays limited solubility. Stability and solubility of CaPs and their combinations is the major collimator for the setting process which also dependent upon the pH value of a cement paste.[46] Various CPCs are currently commercially and many more are in experimental stages.[33]

MECHANICAL PROPERTIES

Although having many advantages, CPCs have limitations owing to their poor mechanical properties and slow *in vivo* biodegradation.[36] Mechanical properties of CPCs such as strength, setting time, porosity and swelling can be controlled by liquid-to-powder ratio, pH of the liquid phase, powder composition, chemistry, crystallinity, particle size, presence of nucleating agents in the reaction system are other important factors for mechanical properties.[36,47-52]

The current commercial CPCs remain dense after implantation and insufficient macroporosity will take advantage of 3D cell colonization and tissue ingrowth.[33] In this context, recently CPCs have been designed with polysaccharides or resorbablefibers which are supposed to develop channels suitable for bone ingrowth by dissolution of these particles or fibers.[33,53-55]

Polymers are usually added to CPC to increase the mechanical properties and control degradation.[36,56-58] Increased setting time and reduced workability are also reported with increased mechanical properties.[36,59-61] Polymeric materials such as chitosan,[62,63] alginate,[64,65] gelatin,[66-68] poly(acrylic acid),[69] polymethylmethacrylate,[70] PLGA,[71] pectin[72] have been used to improve the anti-washout and handling properties of CPCs as these materials tend to disintegrate on early contact with blood and other fluid.[36] The undesired effects of organic additives reported as delay in setting time and decrease in mechanical strength.[51] The setting reaction of CPCs can be affected or modified by adding an active molecule to the powder phase or the liquid phase which could be resulted as a change in physico-chemical and mechanical properties.[37,69,73-77] In general, in apatitic cements, antibiotics have a tendency to increase setting times and reduce the mechanical strength of the cements.[37,73-76] This decrease of mechanical strength can be attributed to different factors, such as increased porosity or to some inhibition of the setting reaction, as suggested by the presence of certain amount of reactants in the set cements when the antibiotic quantity increases. In other cases the change in the setting properties are caused by some chemical interaction with the drug, which can modify the kinetics of the dissolution-precipitation reaction and the morphology of the precipitated crystals.[37] The highly microporous structure of CPC can be obtained different liquid-to-powder ratios, after setting, allows it to incorporate drugs into its structure. More compacted cement microstructure with smaller size of pores can be obtained by decreasing the liquid-to-powder ratio.The drug can be introduced either in the liquid or the solid phase of the CPC, but the physicochemical properties of the drug or protein must be considerated for do not change during the chemical reaction and setting of CPC.[36,52,78] Studies particularly for antibiotics showed the relation between drug concentration and CPCs structure by means of incorporated drug effects on the structure of CPCs.[36,79-81] A morphological change and decrease in compressive strength of CPC with increases in tetracycline concentration was reported and referred as the strong affinity of tetracycline hydrochloride and addressed this limitation to some extent by treating tetracycline hydrochloride with CaP solution and then incorporating it into CPC.[36,80] A maximum of 7% cephalexin monohydrate was incorporated without affecting the mechanical properties of CPC and also observed an increase in setting time and decrease in crystallinity of CPC.[79] An increase in setting time was also reported due to gentamicin sulphate incorporation into the CPC matrix.[81] Drug release from CPC depends also on the intrinsic porosity, which is consequence of processing parameters.[36,78,81] Despite excellent osteoconductivity and good applicability, CPCs use in drug delivery is limited which is mostly due to the changes in the final properties of CPCs resulting from the drug incorporation, changes in the drug activity and its bioavailability.[36]

CPCs are available to use both as bone substitutes and drug carriers for treatments of different skeletal diseases and bone fracture healings. The drugs can be incorporated throughout the whole material volume of CPCs without losing activity and denaturalization by adding them into one of the two cement phases which can facilitate the release of drugs for more prolonged times. Several studies related to the application of both commercial and experimental CPCs as drug carriers for local or systemic treatments for different durations have been published.[37]

DRUG RELEASE BEHAVIORS

Release behaviors from CPCs are influenced by physico-chemical properties such as drug solubility and chemical property, microstructure, crystallinity, density and porosity of the final CPC. Changes during hydration and setting are also effective on drug-cement interactions, and degradation behavior of CPCs. If a polymer is used in the CPC matrix, drug release kinetics also depends on its solubility, molecular weight, drug-polymer interactions and degradation rate. Generally, depending on the drug release behavior, drug

delivery devices can be categorized mainly as diffusion controlled and activation controlled systems which also can be defined as i.diffusion controlled ii. chemical processes controlled, and iii. externally or electronically controlled.[1,36,41] The degradation of drug incorporated CPC matrix is usually a slower process than the drug release kinetics, thus release kinetics is generally a diffusion dominated process from the biodegradable CPCs. Degradation related release is also a simultaneous process with this diffusion.[36,82] Figure 2 illustrates the schematic of drug release from a CPC loaded with drug molecules.[36] Diffusion dominated release kinetics from a matrix can be described by the square root of time kinetics namely Higuchi law which is based on Fickian diffusion under the assumption that drug molecules are uniformly dispersed in a homogeneous matrix. For longer duration, release kinetics does not always follow the Higuchi law due to other factors such as changes in cement matrix composition.[36,69,82,83] Hydrophobic-hydrophilic interactions between drug-polymer and drug-release medium also could influence the release kinetics, which might not follow simple power laws.[36]

TREATMENT APPROACHES FOR CPCS

Biocompatibility and nonexothermic behavior of CPCs are important factors in drug corporating attemps and CPC used for antibiotic delivery gives good clinical results[33,39,84-87] except some resistance strains. Avoidance of the routine use of such drug loaded cements and restricting their use only to multiresistant strains are recommended by some clinicians.[33,88-90] On the other hand further studies clearly showed that CaP matrices are good carriers for controlling the catabolic bone remodeling drugs.[2,91-93]

CPCs can be used for local drug delivery for the treatment of different skeletal diseases such as bone tumors, osteoporosis or osteomyelitis. The types of drug-eluting implants used in traumatology and in orthopedic surgery include: **i)** antibiotic-loaded bone cements and fillers used to prevent infection (osteomyelitis) in orthopedic surgery; **ii)** cements loaded with osteoinductive molecules such as growth factors to favor the osseointegration of the implant; and **iii)** devices loaded with chemotherapeutic agents, antiestrogens or anti-inflammatories used to treat different pathologies including osteosarcomas and degenerative diseases.[26]

In this context, many kinds of drugs/active molecules, including antibiotics,[3,79,94-96] chemotherapeutics,[36,97-99] growth factors,[4,36] proteins/amino acids,[36,100,101] antimicrobial peptides (AMPs),[36,102,103] nonsteroidal analgesic and anti-inflammatory drugs (NSAIDs)[104] and bisphosphonates[90,105,106] have been incorporated into CPCs for various applications. Table 2 refers some research studies on CPCs with different drugs published in last decades.

CONCLUSION

As a conclusion development of new dosage forms by using biometerials is important in drug delivery since it is hard to develop new drug molecules. In this respect drug delivery either local or systemic via bone cements, particularly with CPCs owing to their biocompatibility, noncytotoxicity, osteoconductivity, low-temperature setting reaction and fast setting time, mouldability, easy manipulation and injectibility would make them good alternative and beneficial application in musculoskeletal diseases and defects.

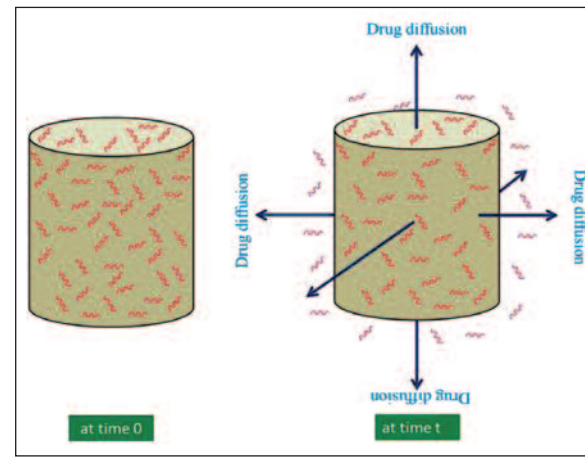

FIGURE 2: Drug delivery implant approaches A. Coating, B. Scaffold or Cement, C. Beads.[2]
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TABLE 2: Some research studies on CPCs with different drugs published between 2003 and 2013 years.

Cement Composition	Active ingredient	Group	References
Silica-CaP	Gentamicin	Antibiotic	3
HA	Bone marrow stroma cell	Stem cell	31
α-TCP,DCP,CaCO3, HA,PLGA	rhBMP-2	Growth factor	71
DCPD	Vancomycin	Antibiotic	82
Sr-substituted β-TCP	Doxycycline hyclate	Antibiotic	83
HA	Zoledronate	Bisphosphonate	91
HA:calcium sulphate mixture	Cephalexin	Antibiotic	96
α-TCP, DCP, HA	Paclitaxel	Chemothetapeutic	99
TTCP:DCPA mixture and Chitosan	rhBMP-2	Protein	100
TTCP, DCP	Gentamicin	Antibiotic	103
β-TCP	Ibuprofen	NSAIDs	104
α-TCP	Alendronate	Bisphosphonate	106
TTCP:DCPA mixture and Chitosan	human bone marrow mesenchymal stem cell (hBMSC)	Protein	107
ACP, DCPD	rhBMP-2	Growth factor	108
Sr- substituted HA	Gentamicin	Antibiotic	109
α-TCP, alginate	Rat bone mesenchymal stem cells	Protein	110
nano-hydroxyapatite/chitosan (n-HA/CS)	Berberine	Antimicrobial	111
HA	Tetracycline hydrochloride	Antibiotic	112
DCPD and TTCP	Zoledronic acid	Bisphosphonate	113

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