Bioceramics Development and Applications

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Calcium Orthophosphates ($CaPo_4$) and Dentistry

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Abstract

Dental caries, also known as tooth decay or a cavity, remains a major public health problem in the most communities even though the prevalence of disease has decreased since the introduction of fluorides for dental care. In addition, there is dental erosion, which is a chemical wear of the dental hard tissues without the involvement of bacteria. Besides, there are other dental losses, which may be of a medical (decay or periodontal disease), age (population aging), traumatic (accident) or genetic (disorders) nature. All these cases clearly indicate that biomaterials to fill dental defects appear to be necessary to fulfill customers' needs regarding the properties and the processing of the products. Bioceramics and glass-ceramics are widely used for these purposes, as dental inlays, onlays, veneers, crowns or bridges. Calcium orthophosphates ($CaPO_4$) belong to bioceramics but they have some specific advantage over other types of bioceramics due to a chemical similarity to the inorganic part of both human and mammalian bones and teeth. Therefore, $CaPO_4$ (both alone and as constituents of various formulations) are used in dentistry as both dental fillers and implantable scaffolds. This review provides brief knowledge on $CaPO_4$ and describes in details current state-of-the-art on their applications in dentistry and dentistry-related fields. Among the recognized dental specialties, $CaPO_4$ are most frequently used in periodontics; however, the majority of the publications on $CaPO_4$ in dentistry are devoted to unspecified "dental" fields.

Keywords: Biooceramics; Hydroxyapatite; Calcium orthophosphates; Caries; Dentistry; Fillers; Oral; Scaffolds

Introduction

Dental caries, also known as tooth decay or a cavity, is an infectious disease (usually bacterial in origin), which causes demineralization and destruction of teeth. If left untreated, the disease can lead to pain, tooth loss and infection. Historically, this disease is very old and it is not exclusive of the human species. Namely, evidences of dental lesions compatible with caries have been observed in creatures as old as Paleozoic fishes (570 – 250 million years), Mesozoic herbivores dinosaurs (245 – 65 million years), prehominines of the Eocene (60 – 25 million years), as well as in Miocenic (25 – 5 million years), Pliocenic (5 – 1.6 million years) and Pleistocenic animals (1.6 million – 10000 years). Nowadays caries is also detected in bears and other wild animals, as well as it is common in domestic animals [1]. Back to humans, dental caries has been detected in various epochs and societies throughout the world [2-9]. Even though in most developed countries the prevalence of the disease has decreased since the introduction of fluorides for dental care, dental caries remains a major public health problem.

Very briefly, dental caries occurs as this. As the most highly mineralized structure in vertebrate bodies, dental enamel is composed of numerous nanodimensional needle-like crystals of ion-substituted calcium orthophosphates ($CaPO_4$) with the apatitic structure (so called "biological apatite"), which are bundled in parallel ordered prisms or rods to ensure unique mechanical strength, remarkable hardness and biological protection. Nevertheless, teeth possess some porosity allowing fluids beneath their surface. Organic (mainly, lactic and acetic) acids, produced by dental plaque cariogenic bacteria (such as *Streptococcus mutans* and *Lactobacillus*) from fermentable carbohydrates of sugar or from the remaining food debris, initiate the disease. When the sufficient quantity of acids is produced, so that the solution pH drops below ~ 5.5, the acids begin to demineralize (dissolve) dental enamel and the pores become larger (Figure 1a). The dissolution increases the concentration of calcium, orthophosphate/acid orthophosphate, magnesium, carbonate/bicarbonate ions in the microenvironment of the caries lesion, leading to the formation and transformation of different types of acidic $CaPO_4$ [10-12]. Several models have been developed to simulate dental caries [13-15].

Luckily, saliva has some restorative functions, acting not only as a buffer, to reduce the acidity caused by plaque bacteria, but also as the constant source of soluble ions of calcium and orthophosphate [11-16]. Therefore, upon neutralization of the plaque acids, $CaPO_4$ complexes from saliva diffuse back into the channels between the depleted enamel rods, replenishing the supply of the dissolved ions (Figure 1b). Consequently, the surface of dental tissues is remineralized. Additional application of toothpastes, mouthwashes, mouth rinses, tooth mousses, *etc*., assists the remineralization. Thus, under normal circumstances, enamel demineralization is compensated by its remineralization. This dynamic process takes place more or less continually and equally in a favorable oral environment. However, when the demineralization exceeds the combined abilities of saliva, toothpastes, mouthwashes, mouth rinses, tooth mousses, *etc*. to remineralize, the dental tissues are progressively dissolved and finally break down, producing dental caries, which look like cavities and/or holes in the teeth [17]. An example of a cariogenic tooth is shown in Figure 2 [11]. Filling with artificial materials is a conventional treatment to repair damaged enamel. However, secondary caries frequently arise at the interfaces between the tooth and foreign materials, which always require restoration replacement [18].

In addition to dental caries, there is dental erosion, which is a chemical wear of the dental hard tissues without the involvement of bacteria. Clinical features are loss of surface structures with shallow lesions on smooth surfaces and cupping and flattening of cusps; already

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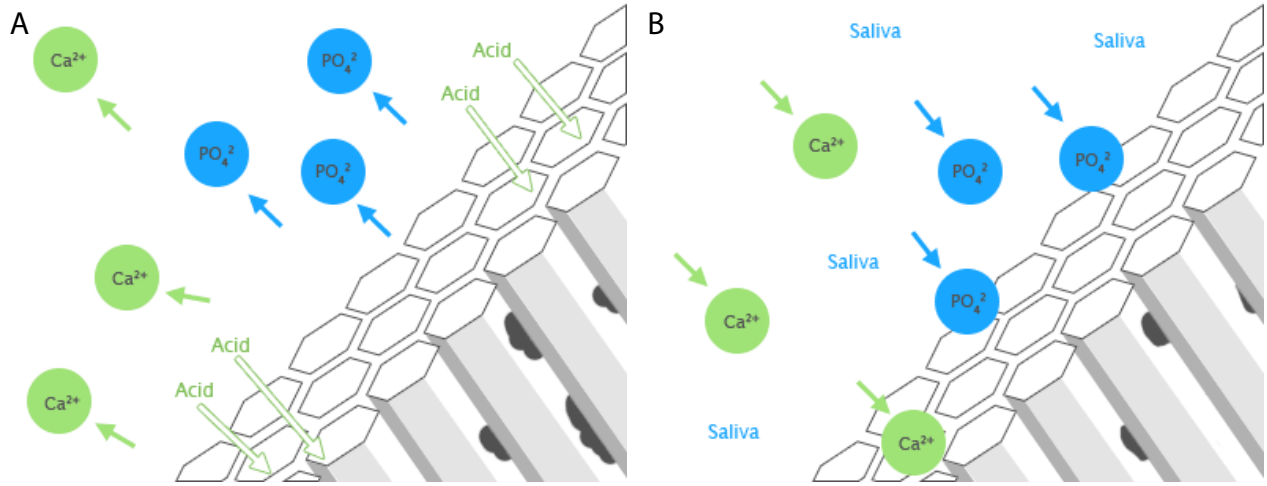


Figure 1: Schematic drawings of: (A) – demineralization and (B) – remineralization processes of dental enamel.

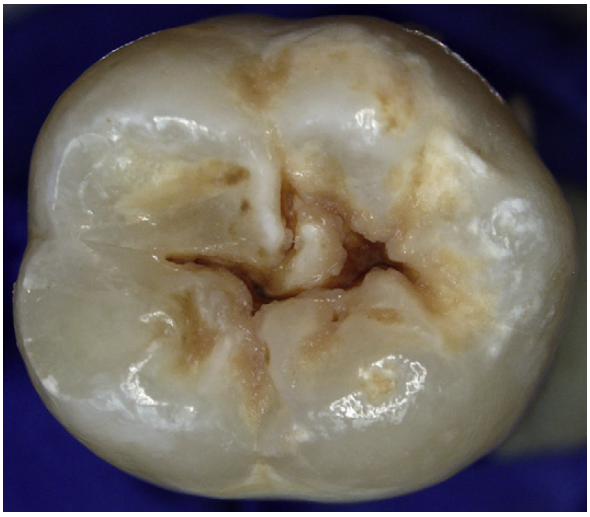


Figure 2: A small cavitated caries lesion in the occlusal surface of a mandibular molar. (Reprinted with permission from Ref. [11]).

in early stages, coronal dentine often is exposed. Frequently, acid-containing drinks and/or food cause it. The acids that cause erosion are rather strong with an average pH of ~ 2 for the colas, ~2-2.5 for citrus fruits and ~1 for gastric contents. A repeated exposure leads to surface demineralization and, therefore, softening, while the softened surface is susceptible to loss by abrasion from food or a toothbrush. Repeated cycles of acid exposure lead to smooth, cupped out cavities. Surfaces most susceptible to erosion are the palatal surfaces of maxillary anterior teeth, although, other teeth are also affected. Currently, dental erosion is considered as one of the main tooth pathologies able to cause patient discomfort after periodontal diseases and caries [12,19,20].

Besides, there are other reasons why people need restorative dental biomaterials, such as inlays, onlays, crowns, veneers or bridges. The causes may be of a medical (decay or periodontal disease), age (population aging), traumatic (accident) or genetic (disorders) nature. All these causes adversely affect masticator efficiency, language function, facial aesthetics and even the psychological health. Still other patients simply wish to change their smile to improve their appearance. Since no one wants to cover up their mouth when they smile, the demand for esthetic, tooth-colored ("invisible") restorations permanently increase [21]. Finally, there are dental abrasion and dental attrition processes. The former is defined as the mechanical removal of hard tissues by the repeated introduction of foreign bodies into the oral cavity that are in contact with the teeth, while the latter is the physiological wearing a way of dental hard tissues though tooth to tooth contact, without the intervention of foreign substances [12].

Therefore, due to their visibility, the restorative dental biomaterials are fundamentally different from those required to make artificial implants for bone replacements (reviewed in Refs. [22,23]). The greatest driving force to develop biomaterials for dental restoration is to fulfill the customers' (patients, dentists and dental technicians) needs. In addition to the esthetic requirements, pressures from the environmental regulations and public apprehension are on the verge of eliminating dental amalgam as a practical and inexpensive restorative filling material [24]. Thus, by the late of 1990's, amalgam use in several European countries was phased out. Consequently, a great challenge was and is the development of metal-free restorations with properties close to natural teeth (with respect to translucency, color and abrasive behavior) or even better mechanical properties and better durability than natural teeth [21].

Briefly, all restorative dental biomaterials must meet the following basic requirements [21]:

- They must be durable and biocompatible;
- Their optical characteristics (gloss, translucency and color, in particular) must be comparable to those of natural teeth;
- Their mechanical properties (strength and toughness) must meet the requirements of the indication range (namely, the required strength of an inlay is lower than that of a dental bridge);
- Their wear behavior must be similar to that of natural teeth.

In addition, they should be easily implantable or injectable, which is a critical requirement for any medical application.

Hence, a selecting problem of the appropriate biomaterials arises. When all material characteristics and clinical factors are considered,

bioceramics offer, perhaps, the best choice for a metal-free dentistry. Namely, bioceramics possess the excellent chemical durability, wear resistance, biocompatibility, environmental friendliness and esthetics. The bioceramic restorations can be used in situations such as treatments of primary caries where inlays can be applied without a more excessive removal of tooth structure that is associated with amalgam. Besides, bioceramic onlays or crowns can also be used in place of large amalgam restorations. However, the widespread use of all-ceramic restorations has been hindered by concerns related to marginal fracture resistance and clinical longevity. Therefore, the goal of dental bioceramics research is to produce all-ceramic dental restorative systems that utilize the known advantages of ceramic materials and minimize the existing disadvantages [25].

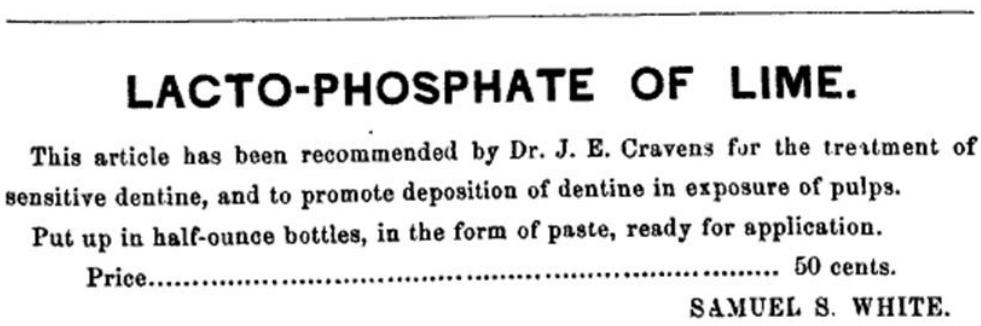
$CaPO_4$ belong to bioceramics but they have some specific advantages over other types of bioceramics due to a chemical similarity to the inorganic part of both human and mammalian bones and teeth. Due to these known similarities, dentists have been using $CaPO_4$ in clinical practice for over a century. Namely, Dr. Junius E. Cravens (1844 – 1920) from USA proffered creative concepts in pulp capping in the 1870's. He had the opinion that dentin-like material would be the best to keep the pulp vital. Therefore, Cravens used a $CaPO_4$ powder, which was mixed with lactic acid to low viscosity. The result was a soluble calcium lactic orthophosphate, which was applied onto the exposed pulp tissue [26]. This pulp-capping agent was brought to the market by the S.S. White company with the trade name "Lacto-Phosphate of Lime" (Figure 3) [27]. Besides, $CaPO_4$ appear to be the only bioceramics potentially applicable for remineralization of dental surface [28].

The available $CaPO_4$, their standard abbreviations and solubility values are listed in Table 1 [29,30]. Additional details on $CaPO_4$, their properties and applications are available in the special monographs on the subject [31-33]. The objective of this overview is to provide current state-of-the-art on $CaPO_4$ applications in dentistry and dentistry-relevant fields.

General definitions and knowledge

According to Wikipedia, the free encyclopedia: "*Dentistry* is the branch of medicine that is involved in the study, diagnosis, prevention, and treatment of diseases, disorders and conditions of the oral cavity, maxillofacial area and the adjacent and associated structures and their impact on the human body. The American Dental Association recognizes nine dental specialties: public health dentistry, endodontics, oral and maxillofacial pathology, oral and maxillofacial radiology, oral and maxillofacial surgery, orthodontics, pediatric dentistry, periodontics, prosthodontics, and general dentistry. There are other dental niches such as oral medicine, dental aesthetics, dental implantation, and orofacial pain and temporo-mandibular disorders, some of them are recognized as dental specialties in other countries. In the European Union, all member states must recognize the specialties of orthodontics and oral and maxillofacial surgery" [34].

Now it is necessary to describe briefly all dental specialties and determine in which of them $CaPO_4$ are used. According to Wikipedia: "Dental public health is involved in the assessment of dental health needs and improving the dental health of populations rather than individuals. One of the controversial subjects relating to dental public health is fluoridation of drinking water" [35]. A search in Scopus database has been performed for papers containing in the title a combination of terms (keywords) "public health dentistry" + "apatite" and "public health dentistry" + "calcium phosphate". Zero publications have been found in both cases (Table 2). Thus, this direction has nothing in common with $CaPO_4$. Endodontics (from the Greek ένδο (*endo*) "inside" and όδούς (*odous*) "tooth") deals with the tooth pulp and tissues surrounding roots of teeth. If the pulp (containing nerves, arterioles, venules, lymphatic tissue, and fibrous tissue) becomes diseased or injured, endodontic treatment is required to save the tooth [36]. The results of a similar search (Table 2) revealed that $CaPO_4$ are used rarely in endodontics. Oral and maxillofacial pathology, radiology and surgery represent "the study, diagnosis, and sometimes the treatment of oral and maxillofacial related diseases", "the study and radiologic interpretation of oral and maxillofacial diseases" and "extractions, implants, and facial surgery", respectively [37]. Only surgery appears to deal with $CaPO_4$ occasionally (Table 2). Furthermore, within these three dental specialties, one needs to differentiate between "oral" and "maxillofacial" terms. The former term is relevant to the subject of this review, while the latter one is undoubtedly irrelevant, since it deals with treatment of the surrounding bones. Various $CaPO_4$-based formulations have been proposed for reconstruction of the contour and discontinuity defects in maxillofacial surgery [38-51]; however, this subject belongs to bone grafts [22,23]. Orthodontics, formerly orthodontia (from Greek όρθός (*orthos*) "straight, or proper, or perfect" and όδούς (*odous*) "tooth") is the first specialty of dentistry that is concerned with the study and treatment of malocclusions (improper bites), which may be a result of tooth irregularity, disproportionate jaw relationships, or both [52]. $CaPO_4$ are used rarely in orthodontics (Table 2). Pediatric dentistry (formerly pedodontics (American English) or paedodontics (Commonwealth English)) is the branch of dentistry dealing with children from birth through adolescence. It places special importance in preventing tooth decay. Additionally, pediatric dentists work toward the maintenance of primary teeth (baby teeth) until they are naturally lost. It is irrelevant



LACTO-PHOSPHATE OF LIME.

This article has been recommended by Dr. J. E. Cravens for the treatment of sensitive dentine, and to promote deposition of dentine in exposure of pulps.

Put up in half-ounce bottles, in the form of paste, ready for application.

Price..... 50 cents.

SAMUEL S. WHITE.

Figure 3: An advertisement of the S.S. White Company for "Lacto-phosphate of lime" 1873. (Reprinted from Dent. Cosmos 1873, 15, 683).

to the $CaPO_4$ subject (Table 2). Periodontics (also periodontology, from Greek περί (*peri*) "around" and όδούς (*odous*) "tooth") is the specialty of dentistry that studies supporting structures of teeth, as well as diseases of periodontium (these are specialized tissues investing and supporting teeth, including cementum, periodontal ligament, alveolar bone and gingiva, characterized by the loss of support around teeth) and conditions that affect them. Although $CaPO_4$ are used in periodontics (Table 2); in fact, they are applied to treat alveolar bones, which, again, is another story [22,23]. Prosthodontics (from Greek πρόσθεση (*prosthesis*) "addition" and όδούς (*odous*) "tooth"), also known as dental prosthetics or prosthetic dentistry, is a dental specialty pertaining to the diagnosis, treatment planning, rehabilitation and maintenance of the oral function, comfort, appearance and health of patients with clinical conditions associated with missing or deficient teeth and/or oral and maxillofacial tissues using biocompatible substitutes [53]. $CaPO_4$ are used rarely in prosthodontics (Table 2). In addition, similar searches in Scopus database using key words "dental", "dentistry", "oral", "stomatology" and "caries" combined with "apatite" or "calcium phosphate" have been performed (Table 2, the bottom lines).

Brief information on current biomedical applications of $CaPO_4$

Due to a chemical similarity to the inorganic part of normal calcified tissues (bones, teeth and deer antlers) of mammals, artificially prepared $CaPO_4$ possess good biocompatibility, bioactivity and osteoconductivity [29-33]. These properties of $CaPO_4$ are extensively used in medicine for repairing or replacement of injured or damaged bones and teeth. Since the diverse biomedical applications require different formulations, configurations and/or shapes, the biomedically relevant $CaPO_4$ are produced in various physical forms, such as: powders, particles, granules, dense blocks, porous scaffolds, self-setting formulations, suspensions, non-hardening pastes, implant coatings, as well as composite components of different origin (natural, biological or synthetic) often with the specific shapes, such as implants, prostheses or prosthetic devices [22,23,29-33,54]. In view of the fact that several dental specialties deal with an invasion into (such as, bone drilling to insert an implant) and/or treatment of the surrounding bones, in principle, all the aforementioned forms, formulations, configurations and shapes of $CaPO_4$ might be applicable to the dentistry field.

$CaPO_4$ for dental caries prevention and in dentifrices

Traditionally, caries prevention strategies are focused on reducing bacterial growth, neutralizing of oral acids and teeth remineralization. Among them, only the third strategy appears to deal with the $CaPO_4$ subject. Briefly, the teeth remineralization is a process in which dissolved $CaPO_4$ minerals are returned to the molecular structure of the teeth themselves. To reduce dental caries by performing remineralization, systemic and/or topical fluoridation of water is commonly used [55]. In addition, various ions-delivering agents are used in the form of dentifrices, toothpastes, mouthwashes, mouth rinses, chewing gums, *etc*. Many of these remineralizing agents contain $CaPO_4$ [56]. This is because the focus in caries research has shifted to development of methodologies for detection of the early stages of caries lesions and non-invasive treatment of these lesions. For example, in the presence of calcium and orthophosphate ions, topical fluoride ions promote formation of FA (which is the least soluble compound among all known types of $CaPO_4$, Table 1) in dental enamel. This property of fluorides has been known since, at least, 1956 [57]. However, to form one unit cell of FA, 10 calcium and 6 orthophosphate ions are required for every 2 fluoride ions. Hence, on topical application of fluoride ions, the availability of calcium and orthophosphate ions can be the limiting factor for net enamel remineralization to occur and this is highly exacerbated under the xerostomic (*i.e.* a dry mouth) conditions [28].

Now, let me describe the applications of $CaPO_4$ in dentifrices. According to Wikipedia: "Dentifrice are agents used along with toothbrush to clean and polish natural teeth. They are supplied as paste, powder, gel or liquid form." [58]. To the best of my findings, the first publication dealing with an application of $CaPO_4$ in dentistry was related to dentifrices. It was a presentation made at the 23rd general meeting of the International Association for Dental Research (held in Chicago, IL, May 27, 1945) and the abstract of that presentation was published shortly afterwards [59]. Since then, numerous studies devoted to various applications of $CaPO_4$ in dentifrices have been published [60-96]. A number of such formulations also contains fluorides [60,61,67,68,71-74,76,81,85,94-96].

Toothpastes: $CaPO_4$-containing toothpastes were found to promote a partial remineralization of the demineralized enamel [78,79,81-83,85-88,92-95], as well as depending on the addition of other constituents they also could possess some whitening effect [75,77,96] and reduce tooth sensitivity [82,89]. For example, the polishing and whitening properties of HA-containing toothpastes were investigated in a combined study [75]. The polishing properties were evaluated by means of artificial teeth by polishing with different toothpastes, while the brightening and whitening properties were examined in volunteers using two colorimeters with two specially made fiberscope. The results revealed that addition of HA to the toothpaste did not alter its polishing properties, while it did result in a marked increase in tooth whitening. It was also found that the brightening and whitening properties increased as the amount of HA in the toothpaste increased. Thus, HA-containing toothpaste appeared to be effective at whitening teeth and whitening was not due to their polishing effect on tooth surface [75]. The whitening properties of HA-containing toothpastes were also found by other researchers [77,96].

In addition, it is worth mentioning on a randomized study with 181 children (92 boys, 89 girls) from different Japanese schools over a period of 3 years [65]. After lunch, the children brushed their teeth under supervision with a toothpaste containing 5% HA and a control group with a paste without HA. Yearly controls of the DMFT (number of decayed, missing and filled teeth due to caries) index were diagnosed as well as the caries incidence on newly erupted teeth. The DMFT index appeared to be significantly deeper in the HA-containing toothpaste group, while the incidence for caries in newly erupted teeth was significantly lower if compared to the control [65].

Besides, dentifrices containing a combination of monofluorophosphate (MFP) with a DCPD abrasive were evaluated in a variety of *in vivo* tests [67]. MFP with silicon dioxide abrasive at an equivalent fluoride concentration was used for comparison. The data indicated that DCPD was more effective than silica in preventing plaque pH drop. A toothpaste containing MFP + DCPD was significantly more effective than an MFP + silica toothpaste. In addition, a toothpaste containing ^{45}Ca radiolabeled DCPD was applied topically in rats' teeth. The results showed that ^{45}Ca was incorporated into the enamel with a concomitant reduction in enamel solubility. In a rat caries study using MFP + DCPD, matching placebo and MFP + silica, the MFP + DCPD dentifrice showed a significantly greater reduction in smooth surface caries. These dentifrices were also tested in an *in situ* human model for fluoride uptake in artificial root caries lesions where MFP + DCPD provided a significantly higher fluoride uptake than MFP + silica. A

Ca/P molar ratio	Compounds and their typical abbreviations	Chemical formula	Solubility at 25ºC, -log(K_s)	Solubility at 25ºC, g/L	pH stability range in aqueous solutions at 25°C
0.5	Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2·H_2O$	1.14	~ 18	0.0 – 2.0
0.5	Monocalcium phosphate anhydrous (MCPA or MCP)	$Ca(H_2PO_4)_2$	1.14	~ 17	[c]
1	Dicalcium phosphate dihydrate (DCPD), mineral brushite	$CaHPO_4·2H_2O$	6.59	~ 0.088	2.0 – 6.0
1	Dicalcium phosphate anhydrous (DCPA or DCP), mineral monetite	$CaHPO_4$	6.9	~ 0.048	[c]
1.33	Octacalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4·5H_2O$	96.6	~ 0.0081	5.5 – 7.0
1.5	α-Tricalcium phosphate (α-TCP)	$α\text{-}Ca_3(PO_4)_2$	25.5	~ 0.0025	[a]
1.5	β-Tricalcium phosphate (β-TCP)	$β\text{-}Ca_3(PO_4)_2$	28.9	~ 0.0005	[a]
1.2 – 2.2	Amorphous calcium phosphates (ACP)	$Ca_xH_y(PO_4)_z·nH_2O$, n = 3 – 4.5; 15 – 20% H_2O	[b]	[b]	~ 5 – 12 [d]
1.5 – 1.67	Calcium-deficient hydroxyapatite (CDHA or Ca-def HA)[e]	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$ (0<x<1)	~ 85	~ 0.0094	6.5 – 9.5
1.67	Hydroxyapatite (HA, HAp or OHAp)	$Ca_{10}(PO_4)_6(OH)_2$	116.8	~ 0.0003	9.5 – 12
1.67	Fluorapatite (FA or FAp)	$Ca_{10}(PO_4)_6F_2$	120	~ 0.0002	7 – 12
1.67	Oxyapatite (OA, OAp or OXA)[f], mineral voelckerite	$Ca_{10}(PO_4)_6O$	~ 69	~ 0.087	[a]
2	Tetracalcium phosphate (TTCP or TetCP), mineral hilgenstockite	$Ca_4(PO_4)_2O$	38 – 44	~ 0.0007	[a]

[a] These compounds cannot be precipitated from aqueous solutions.
[b] Cannot be measured precisely. However, the following values were found: 25.7 ± 0.1 (pH = 7.40), 29.9 ± 0.1 (pH = 6.00), 32.7 ± 0.1 (pH = 5.28). The comparative extent of dissolution in acidic buffer is: ACP >> α-TCP >> β-TCP > CDHA >> HA > FA.
[c] Stable at temperatures above 100°C.
[d] Always metastable.
[e] Occasionally, it is called "precipitated HA (PHA)".
[f] Existence of OA remains questionable.

Table 1: Existing calcium orthophosphates ($CaPO_4$) and their major properties [29,30].

Number of Publications			
Dental specialty	**Apatite**	**Calcium phosphate**	**Cumulative**
Public Health Dentistry	0	0	0
Endodontics	18	12	30
Oral and Maxillofacial Pathology	1	0	1
Oral and Maxillofacial Radiology	0	0	0
Oral and Maxillofacial Surgery	20	11	31
Orthodontics	9	26	35
Pediatric Dentistry	0	0	0
Periodontics	195	113	308
Prosthodontics	9	0	9
Additional keywords			
Dental	370	208	578
Dentistry	22	17	39
Oral	73	90	163
Stomatology	4	2	6
Caries	29	75	104
Total*	750	554	1304
*duplications are possible.			

Table 2: The amount of publications containing the selected keywords in their titles, found in Scopus database.

second *in situ* study in humans evaluated the same dentifrices MFP + DCPD increased salivary plaque calcium and fluoride. These results of laboratory, animal and *in situ* studies taken together indicated that the MFP + DCPD combination was the unique one in providing extra supersaturation in saliva and plaque with concomitant enhanced anticaries efficacy [67].

Thus, due to the aforementioned successful cases of $CaPO_4$ addition to toothpastes, such toothpastes are commercially produced worldwide (Table 3). As seen from the Table 3, toothpastes for both human and animals are available. One should note that HA and ACP are added to toothpastes to provide remineralization properties, while DCPD and DCPA are added to toothpastes as abrasives to provide a gentle polishing action.

To finalize this section, one should mention on the studies, in which addition of $CaPO_4$ to toothpastes did not show any positive influence on enamel and/or dentin demineralization/remineralization properties [97].

Chewing gums: Except of toothpastes, $CaPO_4$ are added to chewing gums to reduce dental caries [98-116]. In the vast majority of cases, a positive effect was noticed. Namely, to evaluate chewing gums as a vehicle to increase salivary mineral saturation levels and enhance salivation, both MCPM and the equimolar mixture of TTCP with DCPA were chosen as experimental chewing gum additives [103]. Each subject chewed a commercial sugar-free bubble gum (control) for 16 min or the same gum to which 5 wt. % of MCPM or TTCP + DCPA mixture had been added. Both experimental gums were found to increase significantly the concentrations of calcium and orthophosphate ions in saliva during the 16-minute period even more than with a previously evaluated gum that contained DCPD. The degree of saturation of tooth mineral was significantly increased by both experimental gums, with a greater increase being produced by the TTCP + DCPA gum. The MCPM gum produced a significantly greater saliva flow and a lower salivary pH than did the control and TTCP + DCPA gums. The results suggested that the experimental gums could be useful for promoting remineralization in general and for inducing salivation in xerostomic patients [103].

In other studies, both sugar-free gums (control) and casein phosphopeptide-ACP (CPP-ACP) containing gums were chewed for either 20 min periods, four times a day or 5 min periods, seven times a day. Microradiography and computer assisted densitometric image

Type of $CaPO_4$	Human or Animals	Trade name and producer (when available)
HA	Human	Active Remineralization Toothpaste (A.R.T.) (Pearlie White, Corlison, Singapore)
		ApaCare (Cumdente, Germany)
		Apadent (Sangi Co., Japan)
		Apagard Premio (Sangi Co., Japan)
		Arcticum (SPLAT-COSMETICA, Russia)
		Biorepair (Coswell, Italy)
		Coolin Bubble (Canavena Co., Korea)
		DIO (DIO Co., Korea)
		Desensibilize Nano P (FGM Produtos Odontológicos, Brasil)
		Desensin repair (Dentaid)
		Hakusanshiko (Japan)
		Janina (Janina Ultra White, UK)
		Kalident - calcuim hydroxyapatite (Kalichem, Italia)
		MAXDENT (STS Cosmetics, Bulgaria)
		Megasonex (Goldspire Group, Hong Kong)
		nanoXIM•CarePaste (FLUIDINOVA, Portugal)
		Parodontol Active (Svoboda Ltd., Russia)
		PrevDent (PrevDent International, Netherlands)
		Renamel AfterBleach (Sangi Co., Japan)
		Remin (X-PUR, Oral Science, QC, Canada)
		R.O.C.S. SENSITIVE (DRC Group, Russia)
		Sensitive Reminx (Pharma Jenistec Co., Korea)
		Triple Denta (TripleLife Co., Ltd., Korea)
		Ultracomplex (SPLAT-COSMETICA, Russia)
		UltraDEX Recalcifying and Whitening (Periproducts Ltd., UK)
		VITIS anticaries toothpaste (Dentaid)
		YP Dental (You Co., Ltd. Japan)
ACP	Human	Age Defying (Arm & Hammer, Church & Dwight Co. NJ, USA)
		Complete Care (Arm & Hammer, Church & Dwight Co. NJ, USA)
		Enamel Care (Arm & Hammer, Church & Dwight Co. NJ, USA)
		Enamel Pro (Premier Dental Products Company, USA)
		Enamelon (Premier Dental Products Company, USA)
		INNOVA (SPLAT-COSMETICA, Russia)
		MI paste (GC America, IL, USA)
		MI paste plus (GC America, IL, USA)
DCPD or DCPA	Human	All White (Dr. Collins, USA)
		Dentu-Creme Denture (Polident, GlaxoSmithKline, UK)
		Plus White (CCA Industries Inc., NJ, USA)
		Pureen (Singapore)
		Snappy Jaws (Australia)
		Supersmile (USA)
		Triple Action Whitening (Pearl Drops, Church & Dwight, NJ, USA)
		Triple Power Whitening (Pearl Drops, Church & Dwight, NJ, USA)
		VITA-MYR (NV, USA)
	Animals	Advanced Oral Care (Nylabone, NJ, USA)
		C.E.T. Enzymatic (Virbac, TX, USA)
		Colgate Cavity Protection (Colgate-Palmolive, NY, USA)
		Dental Care Kit (Sentry Petrodex, Sergeant's Pet Care Products, NE, USA)
		Dentifresh (Hatchwell, UK)
		Enzymatic toothpaste (Sentry Petrodex, Sergeant's Pet Care Products, NE, USA)
		Four Paws Pet Dental (Four Paws Products, NY, USA)
		Original (Oxyfresh, ID, USA)
		R.O.C.S. PRO Baby (DRC Group, Russia)
		VetOne (VetOne, ID, USA)
Undisclosed $CaPO_4$	Human	TriMedica Pure MSM

Table 3: Trademarks of $CaPO_4$-containing commercial toothpastes.

analysis demonstrated that, regardless the gum type and chewing duration (*e.g.*, 20 min or 5 min), the CPP-ACP nanocomplexes produced a dose-related remineralization of enamel subsurface lesions *in situ*. The gums containing 18.8 mg and 56.4 mg of the nanocomplexes, chewed for 20 min, four times per day for 14 days, increased enamel subsurface remineralization by 101% and 151%, respectively, relative to the control sugar-free gums. Microradiographs of the enamel lesions before and after remineralization showed that the CPP-ACP nanocomplexes promoted remineralization throughout the body of the lesion. Electron microprobe wavelength dispersive spectrometric analyses of sections of the remineralized enamel indicated that the mineral deposited was apatite with a higher Ca/P ratio than that in the stoichiometric HA. Acid challenge of the enamel remineralized by the CPP-ACP nanocomplexes *in situ* showed that the remineralized apatite was more resistant to acid challenge than the normal calcium-deficient carbonated tooth enamel. Thus, the clinical trials of CPP-ACP-containing sugar-free chewing gums demonstrated that these gums significantly slowed progression of caries and enhanced regression of caries compared with the control sugar-free gums [106-110].

Teeth remineralization: In general, remineralization of teeth can be defined as the process in which calcium and orthophosphate ions are supplied from a source external to teeth to promote their deposition into crystal voids in demineralized enamel, to produce net mineral gain [117]. The earliest found paper on a possibility of a remineralization phenomenon occurring in caries was published in 1912 [118], while that using $CaPO_4$ for rehardening was performed in 1961 with solutions, contained dissolved ions of calcium and orthophosphate [119], followed by the set of the studies by Silverstone [120,121] and ten Cate and Arends [122-125].

The early attempts to use $CaPO_4$ for remineralization of dental surface were unsuccessful due to their low solubility, particularly in the presence of fluoride ions. Namely, the insoluble $CaPO_4$ cannot be applied easily; they do not localize effectively at the tooth surface and require an acidic environment for solubility levels sufficient to produce ions capable to diffuse into enamel subsurface lesions. Furthermore, due to the intrinsic insolubility of $CaPO_4$ at the physiological pH values, soluble calcium and orthophosphate ions can only be used at very low concentrations. Besides, the soluble ions of calcium and orthophosphate are neither substantially incorporated into the dental plaque, nor localized at the tooth surface to produce the effective concentration gradients to drive diffusion into the subsurface enamel [28].

Nevertheless, such studies keep going. For example, a remineralization potential of HA itself for caries lesion treatment was investigated [66]. Previously demineralized enamel blocks were immersed into an aqueous solution of sludgy HA at 37°C for 55 hours, followed by 24 hours washing with synthetic saliva and another group was washed only with synthetic saliva. Artificial caries lesions were remineralized slightly by immersion into artificial saliva but significant acceleration of remineralization was observed in the sludgy HA group [66]. Positive results were also obtained in other studies [64,126-137]. Besides, remineralization of caries lesions could be performed by supersaturated solutions [138,139] and/or gels [140-147] containing dissolved ions of calcium and orthophosphate. In addition, supersaturated by $CaPO_4$ mouth rinses were found to experience a significant increase in reversals of caries in high-risk for caries patients due to xerostomia (salivary hypofunction) [148]. A remineralization potential of sport drinks, containing nano-sized HA, was also studied [149,150].

More complicated formulations, such as $CaPO_4$-loaded liposomes combined with amelogenin-inspired oligopeptides, have been also developed to promote remineralization of dental enamel [151]. Thus, $CaPO_4$ appear to be the chemicals able to reduce dental caries at the early stages. However, studies performed by using atomic force microscopy nano-indentation technique revealed that previously demineralized samples of dental enamel further exposed to remineralizing solutions did show a crystalline layer of $CaPO_4$ formed on their surface. Unfortunately, the re-precipitated deposits of $CaPO_4$ always consisted of loosely packed crystals and did not protect the underlying enamel from a subsequent acid attack. Furthermore, these surface deposits were completely removed by either a toothbrush or a short exposure to an erosive acidic solution [152-155]. In this context, it should be emphasized that the term "remineralization", which is often misused in the literature, should imply the process of mineral growth that goes hand in hand with a strengthening effect of the weakened enamel surface. Since no strengthening of an exposure to remineralizing solutions was observed, it might be considered that no "passive mineralization" was found (in spite of the real evidence of the re-precipitated surface deposits of $CaPO_4$) [152,154,155].

Further details on the remineralization attempts of teeth are available in the topical reviews [156-158].

Dentin hypersensitivity treatments: As written in Wikipedia, the free encyclopedia: dentin hypersensitivity (abbreviated to DH or DHS and also termed sensitive dentin, dentin sensitivity, cervical sensitivity and/or cervical hypersensitivity) is dental pain which is sharp in character and of short duration, arising from exposed dentin surfaces in response to stimuli, typically thermal, evaporative, tactile, osmotic, chemical or electrical and which cannot be ascribed to any other dental disease [159]. Dentin hypersensitivity is a frequently reported oral pain condition, which is mostly diagnosed at the buccal surfaces of teeth, where enamel is missing due to erosion, abrasion and/or attrition. Contrary to enamel, which is dense and contains a small amount of pores, dentine has a great number of tiny tubes ("tubules") that lead to the nerve and are filled with fluids. However, until about the third or fourth decade of life in healthy individuals, the surface of dentin is not exposed and the tubules are sealed. When a tooth loses its protection from gum recession and/or tooth enamel wear, these tubules are exposed to the outside, allowing external stimuli to reach the nerve endings. Therefore, even mild external stimuli such as hot or cold foods and beverages can cause a change in fluid movement, which causes the nerve endings to react in response, triggering a short but sharp pain (Figure 4).

Due to the aforementioned abilities of $CaPO_4$-containing formulations (section *4.3. Remineralization studies*), some types of $CaPO_4$ were found to be able to treat this disease as well [82,89,114,160-167]. For example, in sensitivity studies, a HA-containing toothpaste was compared with positive control toothpastes. That study demonstrated that the HA-containing toothpaste was similarly effective in reducing dentine hypersensitivity with pre-existing benchmark toothpastes [82]. Positive results were also obtained with both HA-containing Renamel After Bleach toothpaste [89] and an undisclosed nano-HA, potassium nitrate, sodium monoflurophosphate and antioxidants-containing toothpaste [166]. In another study, HA-treated teeth showed statistically significant reduction in hypersensitive symptoms compared to the control groups and the authors concluded that HA showed "definite potential as an effective and permanent desensitizer when used as an in-office procedure" [164]. Furthermore, a $CaPO_4$ precipitation method was once tried as a treatment for dentin hypersensitivity using vital teeth of beagle dogs. The results revealed

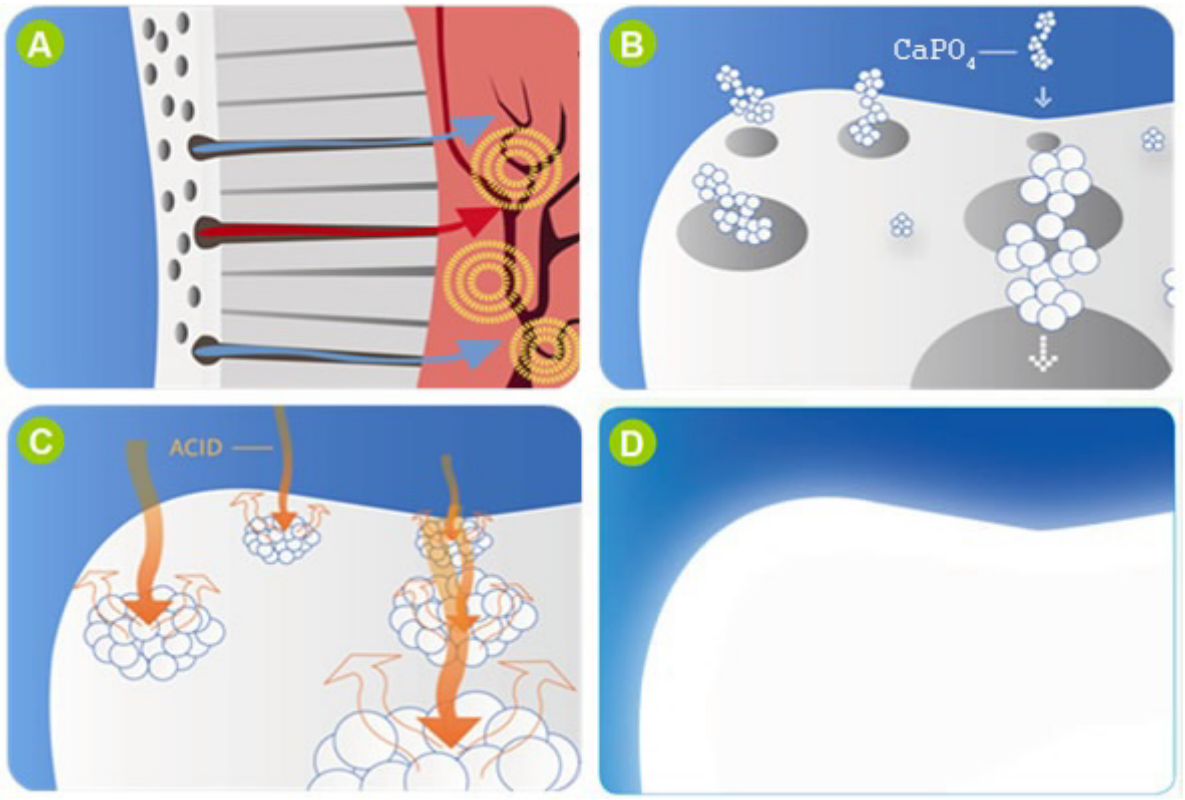


Figure 4: (A) Exposure of dentin tubules to hot and cold temperatures stimulates nerves and causes pain; (B) nano-dimentional $CaPO_4$ particles fill dentin tubules binding chemically to dental structure reducing hypersensitivity; (C) $CaPO_4$ remineralizes the tooth enamel protecting it against acid attacks from food and beverages; (D) improved smoothness and whitening due to the enamel repair.

that dentin tubules were occluded homogeneously and completely with an apatitic mineral after application of the $CaPO_4$ precipitation in vital teeth [162]. A commercial self-setting formulation TEETHMATE™ DESENSITIZER (Kuraray Noritake Dental Inc., Japan), consisting of a mixture of DCPA + TTCP + some additives, which formed CDHA precipitates upon exposure to saliva, appeared to able to occlude open dentinal tubules and, by this way, acted as an effective desensitizer compound [167].

Very schematically, the mechanism of dentin hypersensitivity and the major principles of its treatment by $CaPO_4$ are shown in Figure 4.

Clinical applications of $CaPO_4$ in dentistry

As written in introduction, dentists have been using $CaPO_4$ for over a century. However, to the best of my findings, the first available publication on decalcification of teeth as the reason of various dental pathologies was published in 1925 [168]. Furthermore, the clinical applications of $CaPO_4$ in dentistry started only in 1970-s [169]. Namely, the first application of a $CaPO_4$ (erroneously described as "TCP of HA structure") bioceramics in surgically created periodontal defects was reported in 1975 [170], followed by a publication on alveolar ridge augmentation in 1978 [171], while the use of dense HA cylinders for immediate tooth root replacement was reported in 1979 [172]. A summary on early (before 1987) studies might be found in Table 3 of Ref. [173], while Table 4 of this publication represents the various types of dental applications of $CaPO_4$ in the middle of 1980-s [31,173].

Overall, the reasons for the clinical application of $CaPO_4$ in dentistry are similar to those for their applications in bone grafting. A chemical similarity to the inorganic phases of teeth and bones appears to be the major reason. Consequently, $CaPO_4$ possess an excellent biocompatibility, biotolerance, an ability to be resorbed by both tooth- and bone-related cells, osteoconductivity, *etc*. In addition, $CaPO_4$ are less expensive than most of the inorganic fillers used today. Below, the clinical applications of $CaPO_4$ in dentistry have been classified using two ways: according to the existing $CaPO_4$, listed in Table 1, and according to the modern dental specialties, listed in Table 2.

Classification according to the existing $CaPO_4$ (Table 1)

MCPM and MCPA: Just a few studies on dental applications of MCPM and MCPA were found in databases. According to the available publications, both compounds are used in dentistry as components of self-setting formulations [174,175], including sealers [176]. For example, a commercial product EndoSequence® BC Sealer (Brasseler USA, Savannah, Georgia) is a premixed ready-to-use injectable cement paste developed for permanent root canal filling and sealing applications. It contains zirconium oxide, calcium silicates, MCPA, calcium hydroxide, filler and thickening agents. When this sealer is placed in the root canal, it absorbs water from the dentin tubules causing hydration reactions of calcium silicates. Simultaneously, MCPA reacts with calcium hydroxide to precipitate CDHA. This leads to formation of a composite network of gel-like calcium silicate hydrates, which intimately mixes with CDHA crystals and forms a hermetic seal inside the root canal [176]. In addition, MCPM and/or MCPA were tried as components of caries-inhibiting dental biocomposites, releasing ions

1	Restore (augment) alveolar ridge for better denture fit
2	Immediate tooth root replacement to prevent resorption of alveolar ridge
3	Fillers for periodontal defects or bone loss
4	Coatings for metal implants to improve bone-implant adhesion and prevent loosening of the metal implants
5	Repair of cleft palate
6	Repair of maxillofacial defects
7	Pulp capping materials

Table 4: Dental applications of $CaPO_4$ in the middle of 1980s [31,173].

of calcium and orthophosphate [175,177]. Once a MCPM-containing chewing gum was tested; it produced a significantly greater saliva flow and a lower salivary pH than the control gum did [103].

DCPD and DCPA: As seen in Table 3, DCPD and/or DCPA are often added to toothpastes as gentle polishing agents. In addition, DCPD and/or DCPA (unfortunately, the authors of the publications on the subject rarely specify which of them was used) are added to chewing gums [98-101,103,111] and other types of dentifrices [61-63,67-74,76]. Furthermore, they are used as either components or end products of various $CaPO_4$-based self-setting formulations [42,43,160,167,178-187] and root canal sealers [188]. In addition, both compounds are added to biocomposites [189-192]. For example, decreasing of DCPA particle dimensions were found to increase the Ca- and PO_4-ions releases from DCPA-based biocomposites. Therefore, such biocomposites possess both a high strength and good release of Ca- and PO_4-ions, which may provide the needed and unique combination of stress-bearing and caries-inhibiting capabilities suitable for dental applications [191]. Besides, DCPD was tried in pulpectomy [193].

OCP: Just a few publications were found on applications of OCP in dentistry and dentistry-related fields. Namely, OCP might be used as a coating [194,195], a component of biocomposites [195,196] and self-setting formulations [197,198]. In addition, OCP was tried in pulpectomy [193], as a direct pulp capping material [197] and for alveolar ridge augmentation [196,199]. Furthermore, investigations with rats revealed that implanted OCP could serve as a core for initiating bone formation and cause osteoinduction and osteoconduction in experimentally created cranial defects [200] and enhanced reparative dentine formation via induction of odontoblast differentiation [201].

ACP: Unlike OCP, ACPs appear to be very popular compounds for dental applications [28,113,115,116,161,163,202-252]. For example, two ACP-based remineralization systems have been developed and are now commercially available: a casein phosphopeptide (CPP) stabilized ACP with a trade name Recaldent™ (Cadbury Enterprises Pte Ltd., Singapore) and an unstabilized ACP with a trade name Enamelon™ (Enamelon Inc., Cranbury, NJ, USA). CPP is produced from milk protein casein and has a remarkable ability to stabilize $CaPO_4$ in solutions and substantially increase the level of $CaPO_4$ in dental plaque. Therefore, in Recaldent™ technology, it is claimed that CPP stabilizes high concentrations of calcium and orthophosphate ions, together with fluoride ions, at the tooth surface by binding to pellicle and plaque. Through the cluster sequence, CPP binds to forming nanodimensional clusters of ACP preventing their growth to the critical size required for nucleation and phase transformation. CPP-ACP nanodimensional complexes are formed as a result [253]. It is believed that these CPP-ACP nanocomplexes enter the porosities of an enamel subsurface lesion and diffuse down concentration gradients into the body of the subsurface lesion. Once present there, the nanocomplexes release the weakly bound calcium and orthophosphate ions, which would then deposit into crystal voids [117]. Due to ACPs' bioactivity, local Ca- and PO_4-enriched environments are created with supersaturation conditions favorable for the regeneration of tooth mineral lost to decay or wear. Although all the available ions are stabilized by CPP from promoting dental calculus, they are freely available to diffuse down concentration gradients into enamel subsurface lesions thereby effectively promoting remineralization *in vivo*. The Enamelon™ technology applies calcium ions (*e.g.*, calcium sulfate) and orthophosphate ions (*e.g.*, ammonium orthophosphate, sometimes in the presence of fluoride ions) separately (*e.g.*, from a dual chamber device). Therefore, as the salts mix with saliva they dissolve releasing calcium and orthophosphate ions and ACP (or F-containing ACP) forms intra-orally. In the intra-oral environment, both ACP and F-containing ACP are very unstable and rapidly transform to a more thermodynamically stable, insoluble crystalline phases, such as CDHA and a blend of CDHA + FA, respectively. It is believed that this helps rebuild tooth enamel through remineralization [71,254,255]; however, this approach may also promote dental calculus [28]. Thus, both previously prepared ACP (Recaldent™) and *in situ* precipitated ACP (Enamelon™) are used in dentistry to remineralize tooth surface. This property of ACPs is used in toothpastes (Table 3).

As seen from the available references, in dentistry ACPs are usually used as components of various biocomposites. In an acidic oral environment, such biocomposites take advantages of the ability of ACPs to release calcium and orthophosphate ions, which potentially can take part in enamel remineralization [94,106,107,109,110, 113,115,116,202-212,216,217,231,232,247,248,252,256-281]. The ACP-containing biocomposites and hybrid biomaterials can be prepared in various forms, such as crèmes [232] or nanodimensional fibers [234]. Such formulations are used mainly as anti-cariogenic and/or remineralizing agents [106,107,109,110,231,232,247,248,252,256-281], *e.g.*, in chewing gums [106,107,109,110,113,115,116], sugar confections [213], various tooth mousses [259-261], bleaching gels [264,265], mouth rinses [266], various drinks [267,268] or even in milk [272,273]. To improve cell adhesion, coatings composed of ACP and hyaluronic acid were used [222]. Finally, ultrathin freestanding ACP sheets were manufactured and tested [251].

α-TCP and β-TCP: According to the available literature, α-TCP and/or β-TCP (unfortunately, the authors of the publications on the subject not always specify which of them was used) are widely used in dentistry and dentistry-related fields. For example, they are used for augmentation of the surrounding bones [171,282-289], in maxillofacial surgery [290-293], as a component of root canal sealers [294], as implant coatings [295], as remineralization [296-299] and pulpotomy [300] agents, for dental pulp capping [301-306], to treat perforations [307,308], as endodontic plugs [309] and to fill various types of bone defects and lesions [310-318].

In addition, β-TCP could be functionalized by various organic compounds, such as sodium lauryl sulfate [297], fumaric acid [298] and some other compounds [299,319,320]. Functionalization of β-TCP served two major roles: first, it provided a barrier that prevented premature β-TCP-fluoride interactions, and second, it provided

a targeted delivery of β-TCP when applied to the teeth. Placebo-controlled clinical studies demonstrated that if compared to fluoride alone, the combination of fluoride plus functionalized β-TCP improved remineralization by building stronger, more acid-resistant mineral in both white-spot lesions as well as eroded enamel [297-299]. Once a therapy of 36 teeth with deep caries by both HA and undisclosed TCP was carried out. Repeated examinations of patients 1 and 6 months after treatment showed that both HA and TCP normalized the function of the pulp and caused remineralization of dentin in the bottom of carious cavity [321]. Furthermore, α-TCP-containing chewing gums were prepared and tested [104,105].

Apatites (HA, CDHA and FA): As seen in Table 2, apatites (HA, CDHA and FA) appear to be the most popular type of $CaPO_4$ used for dental applications. Since nanodimensional and nanocrystalline apatites are often considered as the model compounds of dental enamel due to both the chemical and phase similarities [31,32], their use in restorative dentistry offers several promising advantages, including intrinsic radio-opaque response, enhanced polishability and improved wear performance. In addition, they have hardness similar to that of natural teeth [322]. For example, nanodimensional HA particles were found to have an ability to infiltrate a demineralized collagen matrix of dentin. Afterwards, the infiltrated collagen matrix of dentin might provide a suitable scaffold for dentin remineralization, whereby the infiltrated HA particles could act as seeds within the collage matrix and, given the appropriate remineralizing environment, dentin remineralization might occur [323]. In addition, it was demonstrated that nano-sized HA particles could be self-assembled to form enamel-like structures [324]. Therefore, a localized biomimetic repair of the enamel surface could be achieved by nano-sized (~ 20 nm) HA, which were analogues to the basic building blocks of the enamel rods. This similarity resulted in a good fixation of artificial biomaterials to natural tissues. Moreover, the enamel structure became reinforced by nano-sized HA since a secondary caries was suppressed and the hardness was retained [325-327]. Furthermore, nano-sized HA could be adsorbed onto the enamel surface strongly and even be integrated into the natural enamel structure [328]. Generally, these studies also suggest that analogues of nanodimensional building blocks of biominerals should be highlighted in the entire subject of biomineralization. This strategy may have prospective applications in dentistry as it offers an easy but effective method to reconstruct tooth enamel that is suffering from mineral losses.

Normally, apatites for dental applications are prepared from the pure chemicals; however, they could also be prepared from the biological sources, such as teeth [329]. Due to the versatile applications in dentistry, apatites could be used in various formulations, configurations and/or shapes. First, apatites are added to toothpastes (Table 3). Second, apatites are used as coatings to enhance osteoinductivity of various dental implants [330-342]. For example, degradation rates of dental implants covered by 50- and 100-micron thick coatings of HA, FA and fluorhydroxylapatite (FHA) were studied [333]. The implants were inserted in dog jaws and retrieved for histological analysis after 3, 6, and 12 months. The HA and FA coatings (even of 100-micron thick) were almost totally degraded within the implantation period. In contrast, the FHA coatings did not show significant degradation during the same period [333]. The apatite coatings on titanium implants followed by bisphosphonate-immobilization appeared to be effective in the promotion of osteogenesis on surfaces of dental implants [337]. Regarding their durability, the HA-coated dental implants were found to work well in the short to medium terms (during 4 – 6 years [343], 8 – 10 years [344] and 14 years [345]); nevertheless, even longer-term clinical results are awaited with a great interest.

Third, apatites are added as components to intermediate restorative materials [346,347], glass ionomer cements (which are dental restorative materials used for filling teeth) [348-355], as well as to various dental biocomposites [356-362], dentifrices and toothpastes [64,65,70,80,84,90-96]. HA-containing glass ionomer cements are commercially produced. For example, Cavalite (Kerr Italia S.r.l.) is a light-cured cavity liner containing HA and glass ionomer powder. Furthermore, application of HA powder was found to be effective in apexogenesis of young permanent teeth of dogs [363]. In addition, an interesting approach to control dental caries by CDHA-osteopontin biocomposites was introduced [362]. Since caries is caused by acid production by bacteria in biofilms located on dental surfaces, its preventing involves a control of microorganisms producing the acids. Therefore, CDHA-osteopontin biocomposite particles were prepared to bind to bacteria in the biofilms, impede biofilms building-up without killing the microflora and release orthophosphate ions to buffer bacterial acid production if pH decreased below 6. Analysis of the results revealed that the treatment by either CDHA-osteopontin or pure osteopontin led to less biofilm formation compared to untreated controls. Thus, the anti-biofilm effect of the CDHA-osteopontin particles was ascribed to osteopontin, while CDHA was responsible for buffering effect, which kept pH always above 5.5 [362].

Forth, there are various types of self-setting apatite-forming and/or apatite-containing formulations [38-40,45-49,364-382]. For example, a cement was injected as a bone filler for gaps around oral implants placed on the medial femoral condyles of six goats and excellent bone formation around the graft material was found. Unfortunately, the degradation rate of the cement appeared to be very slow and no resorption was observed [373]. In another study, a cement was placed on artificially created periodontal defects but no significant difference was found between the cement and control. Nevertheless, the cement acted as a scaffold for bone formation and provided histocompatible healing of periodontal tissues [374]. Other investigators used cements for direct pulp capping [368,369] and compared them to calcium hydroxide. Both materials were found to be equally capable of producing a secondary dentin at ~ 24 weeks [368]. Still other investigators extracted all mandibular premolar teeth from beagles [371]. After one month of healing, alveolar bones were reduced to make space for previously fabricated $CaPO_4$ cement blocks. One more month later, 8-mm HA implants were placed in such a manner that the apical half was embedded into alveolar bones and the coronal half in the cement blocks. The investigators observed that the cement blocks were gradually replaced by bone and histopathologic features of the cement area were similar to that of natural bone. Moreover, the coronal half of the implants, previously surrounded by the cement, was firmly attached by natural bone [371]. In another study, the same researchers used fluorescent labeling analysis and electron microanalysis to measure the extent of new bone formation and elemental (Ca, P, Mg) distribution [372]. Besides, several apatite-forming and/or apatite-containing self-setting formulations were tested as root canal fillers [182,367,376] and sealers [364-366,370,375,377]. Since HA alone does not possess the self-setting abilities, to create a self-setting formulation it could be mixed with an epoxy resin [377]. To impart an antibacterial effect, an apatite-forming MCPM + CaO self-setting formulation with an excess of CaO (which after contact with water was transformed to $Ca(OH)_2$) was elaborated [176]. Finally, injectable forms of such cements can be used as adjunctive supportive agents for dental implants [380].

An interesting approach was performed in an attempt to regenerate the tooth enamel *in vitro* using thin and flexible HA sheets [383]. First, a thin HA film was deposited onto a soluble substrate by pulsed laser

deposition technique. Next, the HA film was collected as a freestanding sheet by dissolving the substrate using a solvent. HA sheets of 1 to several microns thick and up to 50 mm in diameter could be produced by this technique. Then, the HA sheet was adhered to the extracted human teeth using a $CaPO_4$-containing solution with pH of 5.5. The authors found that the HA sheet was fused with tooth enamel within approximately one week and that the HA sheet was effective for the restoration and conservation of the tooth in dental applications [383]. This approach was further developed in later studies by introducing a bit thicker (8 μm thick) HA sheets with additionally deposited a thin layer of undisclosed TCP of 500 nm thick [384,385]. One should mention that, due to a small thickness, the HA sheets are transparent (therefore, invisible) and their coloration is possible. Therefore, they could be applied in cosmetic dentistry. In addition, the HA sheets have a number of minute holes that allow liquid and air to escape from underneath to prevent their forming bubbles when it is applied onto a tooth. One problem is that it takes almost one day for an HA sheet to adhere firmly to the tooth's surface. Similar sheets from ACP were developed and tested as well [251].

More to the point, dental applications of apatites include direct pulp capping [306,386-390], dentin hypersensitivity treatments [164-166], using in endodontics [391-408], orthodontics [409-417], oral and maxillofacial surgery [290,336,418-444], orthognathic surgery [445-449], prosthodontics [450-460] and periodontics [461-478].

To conclude this section, one should mention that due to a close chemical and phase similarities between apatites and dental enamel, dissolution of apatites in acids is considered as a good model of dental caries [479].

TTCP: According to the available literature, TTCP alone is rarely used in dentistry [480,481]. In the vast majority of the cases, TTCP is combined with either other types of $CaPO_4$ (mainly DCPD or DCPA) or other chemicals to form various self-setting formulations [160,167,178,179,181,183-187], biocomposites [178,179,181,482] and root canal sealers [188] and fillings [483]. For example, a FA forming self-setting formulation consisting of solid TTCP, solid NaF and liquid H_3PO_4 was prepared and used for *in vitro* filling of big enamel carious cavities. The results revealed that the hardened formulation was tightly combined with the enamel surface due to the chemical interaction between the formulation and enamel apatite [186]. Once a TTCP-containing chewing gum was prepared and tested [103].

Biphasic and multiphasic $CaPO_4$ formulations: According to the definition, biphasic and multiphasic $CaPO_4$ formulations represent various blends of two or more individual types of $CaPO_4$, respectively, and, among them, a biphasic calcium phosphate (abbreviated as BCP) formulation, consisting of HA and β-TCP, appears to be the most popular one [23]. An injectable bone and dental substitute constituted of BCP and a hydrosoluble cellulose polymer as a carrier was developed [484]. This formulation was used for filling bone defects after tooth extractions in 11 patients. 3 years after surgery, small biopsies of the implanted areas were harvested and analyzed by using micro-computed tomography, non-decalcified histology and histomorphometry. The BCP granules appeared in direct contact with mineralized bone tissue, thereby supporting bone growth. A gradual substitution of the filler by bone tissue was observed thus preserving the height of the alveolar bone crest [485]. Similar results were obtained in another study [486]. In addition, BCP was found to be effective for healing of dental bones, osseous and/or intrabony defects [50,487-500]. For example, micro- and macroporous BCP combined with a fibrin sealant was found to be safe and effective in sinus floor elevation for dental implant placement, supporting bone regeneration [497]. Furthermore, BCP was used to fill dental root canals [501], while multiphasic $CaPO_4$ (α-TCP + HA + TTCP) were applied as direct pulp capping materials [502].

Classification according to the dental specialties

Endodontics: Generally, root canal filling materials are divided into core materials and root canal sealers. Root canal obturation consists of placing an inert filling material in the space previously occupied by pulp tissue. To achieve successful endodontic therapy, it is important to obturate the root canal system completely. Thus, the effective endodontic obturation must provide a dimensionally stable, inert fluid tight apical seal that will eliminate any portal of communication between the canal space and the surrounding periapical tissues through the apical foramen. According to the databases, the earliest publication on use of $CaPO_4$ in endodontics was published in Japanese in 1983 [391], followed by a publication in English in 1984 [392]. Several examples of endodontic applications of $CaPO_4$ are given below (Table 2).

A case of combined endodontic-periodontic lesions on a mandibular first molar was treated by intentional replantation and application of HA. Four months after the surgery, a porcelain-mental full crown restoration was completed. The 15-month follow-up examination showed that the tooth was clinically and radiographically healthy and functioned well [400]. Several types of $CaPO_4$ (DCPD, OCP, β-TCP, BCP (HA + β-TCP) and HA) in particle sizes of < 5 μm or < 150 μm were used for pulp capping teeth of pigs, rats, and dogs. All types of $CaPO_4$ showed biocompatibility. Based on these results, it was suggested that these types of $CaPO_4$ might be useful for specific clinical applications in endodontics, such as, pulp capping (microparticles of HA, β-TCP, BCP) and pulpectomy (HA, OCP, DCPD) [193]. Applicability of $CaPO_4$ in pulpotomy and pulpectomy was confirmed in other studies [300,503,504].

Bone regeneration in endodontically induced periapical lesions using HA, platelet-rich plasma and a combination of HA with platelet-rich plasma was evaluated for a period of one year with 20 systemically healthy patients [405]. To qualify, the patient had to have a tooth where non-surgical root canal therapy had failed, periapical radiolucency was present and periapical root end surgery was required. The bony defect had to be confined to the apical area, with the bone covering the entire root surface coronally, with an intact lingual cortical plate. The patients were randomly divided into 4 groups, with 5 patients each, as follows: replacement with HA, replacement with platelet-rich plasma, replacement with HA with platelet-rich plasma and a control group with no substitutes. The radiographic evaluation revealed that the HA patients showed complete bone regeneration with evidence of a trabecular pattern at the end of one year, the platelet-rich plasma patients showed complete bone regeneration at the end of 9 months, the HA with platelet-rich plasma patients showed complete bone regeneration at the end of 6 months, while the control patients showed unsatisfactory bone regeneration even after one year. Thus, HA addition to platelet-rich plasma was proven to facilitate bone regeneration [405].

An injectable bone substitute made of a suspension of BCP (HA + β-TCP) bioceramics was used to fill dental root canals after removing of canal pulp [501]. The aim of that study was to verify the ability of a $CaPO_4$ ceramic suspension to fill the apical zone of teeth both *ex vivo* and *in vivo* in a sheep model. The results showed that injection was possible with a good level of BCP granules at the end of the root dental canal with extracted tooth. The scanning electron microscopy revealed mineral formation at the apex level with mineral tissue conduction between the BCP granules; however, only one tooth showed a good

apical filling with a good sealing. The authors concluded that the sealing of the apex seemed to depend of the amount of BCP granules [501].

Furthermore, there are $CaPO_4$-containing endodontic and/or root canal sealers [188,294,364-366,370,375, 377,396,397,401,402,404,406-408,505-515]. The composition of 2 examples of such sealers (Sankin apatite root canal sealer and Capseal) are presented in Table 5 [510]. Of them, Capseal was found to result in both a higher alkalinity and a higher calcium ion releases than Sankin apatite root canal sealers [509]. The results of their application revealed that the sealers mentioned in Table 5 facilitated the periapical dentoalveolar and alveolar healing by controlling cellular mediators from periodontal ligament cells and osteoblast differentiation of precursor cells [510].

Furthermore, endodontic perforations were treated by $CaPO_4$ [307,308,393,511-516], but once a lack of complete healing was noticed [308]. Additional examples of the endodontic applications of $CaPO_4$ comprise the following cases. They can be used as components of endodontic cements [394,517] or coatings for endodontic dental implants [403], as well as serve as a root end filling material [397,399] and as endodontic endosseous implants [395]. Since $CaPO_4$ do not cause inflammation [307], they could be used as a hard plug deep inside teeth [309]. Finally yet importantly, $CaPO_4$ crowns were manufactured [518].

Oral and maxillofacial surgery: An insufficient bone volume and a poor bone density are common problems in edentulous patients with resorbed maxilla. One method that makes implant placement possible in such difficult situations is augmentation of maxillary sinus using various bone grafts [511]. Besides, there are other cases, in which bone grafts appear to be necessary for dentistry-related fields.

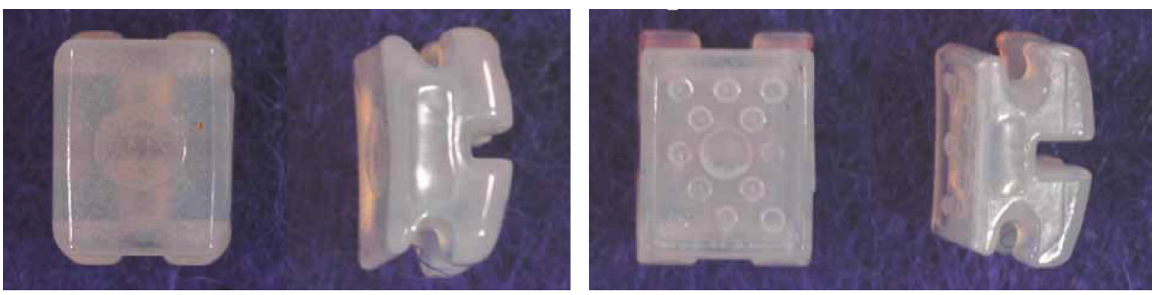
Due to these cases, $CaPO_4$ have been used in oral and maxillofacial surgery since 1980-s [290,418-427] and up to now many scientific articles have been published on the subject [38-51,291,428]. However, as written in section 2, the vast majority of the publications on this subject deals with a treatment of the surrounding bones and, thus, they fall into a category of bone substitutes, which is another story. Nevertheless, the following directions of $CaPO_4$ application in oral and maxillofacial surgery can be outlined: coatings on various types of dental implants [330-345,403,519-524], augmentation of the surrounding bones [44,196,199,283-289,336,371,287,411-437,525] and using as fillers of osseous mandible and/or jaw defects [292,369,378,438-444].

Orthodontics: According to the databases, the earliest publications on use of $CaPO_4$ in orthodontics appeared in 1989 [409-411]. Coatings of $CaPO_4$ (both HA [413] and α-TCP [295]) were successfully applied to titanium implants and the coated implants were found to be applicable as anchorage for short-term orthodontic treatment [413] and both types of coatings appeared to be effective stimulators of new bone formation [295]. In another study, HA addition to an orthodontic cement was found to have a protective action on the dental enamel near the orthodontic bands or brackets [412]. Furthermore, there are $CaPO_4$ bioceramic brackets Hyaline® (Tomy International Inc., Tokyo, Japan) (Figure 5). In addition to excellent biocompatibility, these brackets have a hardness equivalent to that of tooth enamel, which eliminates fears of dental abrasion due to the occluding tooth even when the patient has a deep-bite [526-528].

However, among all available types of $CaPO_4$ (Table 1), ACP-containing formulations are most often used in orthodontics [215,218-221,223-227,229,235,236,239-244]. For example, an efficacy of an ACP-containing orthodontic biocomposite and a resin-modified glass ionomer cement on enamel demineralization adjacent to orthodontic brackets was evaluated by a new laser fluorescence device. The authors concluded that both formulations should be recommended for any at-risk orthodontic patient to provide preventive actions and potentially remineralize subclinical enamel demineralization [215]. Similarly, ACP-containing orthodontic biocomposites were found to reduce both enamel decalcification around orthodontic brackets [225,226,239] and bacterial adherence [239]. Furthermore, ACP-containing orthodontic biocomposites were found to possess a lower but still satisfactory bond strength needed to function as orthodontic adhesives [218,219,221,222,223]. Therefore, CPP-ACP biocomposite, either alone or combined with fluoride, may safely be used as a prophylactic agent before bracket bonding [236,242]. Besides, a pretreatment by CPP-ACP, enamel microabrasion and the combination of these two methods were found to improve bonding of orthodontic brackets to demineralized enamel [242].

Brand name	Manufacturer	Components
Sankin apatite root canal sealer (I, II and III)	Sankin Kogyo, Tokyo, Japan	Powder: α-TCP and Sankin HA in type I, iodoform is added to powder in type II (30%) and type III (5%). Liquid: polyacrylic acid and water
CAPSEAL (I and II)	experimental	Powder: TTCP and DCPA, Portland cement (gray cement in type I and white cement in type II), zirconium oxide, and others. Liquid: hydroxypropyl methyl cellulose in sodium phosphate solution

Table 5: Composition of the available $CaPO_4$-containing sealer materials [510].



Hyaline Hyaline II

Figure 5: Appearances of $CaPO_4$ ceramic brackets hyaline and hyaline ii. (Reprinted with permission from Ref. [527]).

Adiaphorous results were obtained either. For example, a topical treatment of white spot lesions after debonding of orthodontic appliances with a CPP-stabilized ACP agent resulted in significantly reduced fluorescence and reduced areas of the lesions after 4 weeks; however, the improvement was not superior to the natural regression following daily use of fluoride toothpaste [227]. In addition, no clinical advantages for use of a CPP-fluoridated ACP paste supplementary to normal oral hygiene over the time span of 12 weeks were found in another study [229].

Prosthodontics: Humans have long used both natural and synthetic materials as replacements for lost teeth. For example, the earliest known dental implant was made of iron and found in a Roman male, who lived around the first or second century AD [529]. The first known tooth made from a natural material was found in a Mayan woman, estimated around 600 CE, and was made of nacre from seashells [530]. Nevertheless, despite a long history of the tooth grafts, just a few publications on prosthodontic applications of $CaPO_4$ are available (Table 2). According to the databases, the earliest publication on the subject was published in 1983 [450], followed by another publication by the same authors [451]. A 4-year study and evaluation of non-resorbable HA to augment different alveolar ridges was performed. The technique used resulted in improved contour, height, and width of the alveolar ridge. The state and health of the tissues were found to be improved with the use of HA or HA combined with bone marrow [450]. However, the study dealt with a treatment of bones but not teeth, which is another story. Similar can be said about other publications on the subject [452-459]. Furthermore, as seen from the publication dates, all these papers were published in the previous century and only one recent paper [460] has been found. Nevertheless, even this recent paper is devoted to the preparation subject with just a possibility to use the material as dental prosthesis. Thus, one can mention on the past attempts to use $CaPO_4$ in prosthetic dentistry and, since no promising results were obtained, currently $CaPO_4$ are not used in prosthodontics.

To finalize this topic, it is important to mention that one of the challenges in dental implantology is to achieve and maintain a good osseointegration, as well as an epithelial junction of gingival tissues with the implants. An intimate junction among them may prevent bacteria colonization leading to peri-implantitis, while the direct bonding may ensure a biomechanical anchoring of the artificial dental roots (Figure 6) [531]. To achieve this, the presence of sufficient bone volume is an important prerequisite for dental implant placement. However, this is not always the case. Namely, atrophic maxilla and mandible bones are less tolerant to the placement of dental implants due to their reduced height and width; hence, supplementary bone augmentation by $CaPO_4$ might be necessary [532,533]. In addition, I would like to point the readers' attention to a review on dental implants for patients with osteoporosis. According to the authors, osteoporosis is not a contraindication for the implant surgery if the accurate analysis of bone quality has been performed [534].

Periodontics (periodontology): In general, the regeneration of tissues affected by periodontal disease is a complex process; it encompasses formation of bones, cementum and periodontal ligaments [535]. According to the databases, the earliest publication on use of $CaPO_4$ in periodontics was published in 1974 [536], followed by research papers of 1975 [170] and 1977 [310] and a review of 1978 [311]. A schematic diagram of the management of periodontal defects by a bone graft technique is shown in Figure 7 [537]. However, as written in section 2, the vast majority of the publications on periodontics deals with a treatment of the surrounding bones and, thus,

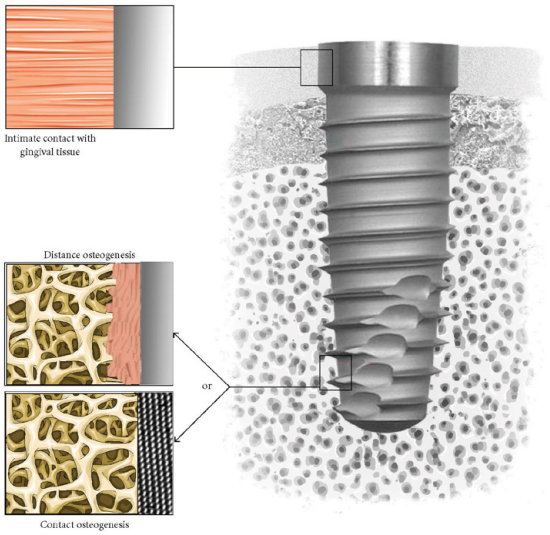


Figure 6: Tissue integration of a dental implant. Note the intimate contact with gingival tissue in the upper part and the desired contact osteogenesis in the tapered lower part rather than distance osteogenesis. (Reprinted with permission from Ref. [531]).

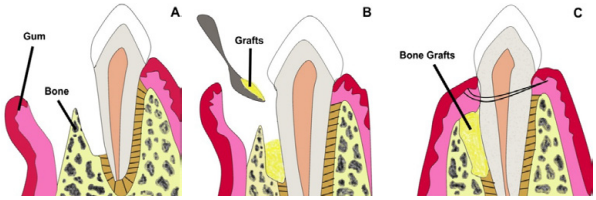


Figure 7: A schematic diagram of the management of periodontal defects by a bone graft technique. The $CaPO_4$ grafts stimulate bone growth and a new bone fills the defect, which provides a better support for a tooth. (Reprinted with permission from Ref. [537]).

they fall into a category of bone substitutes [183,282,312-320,382,461-478,490,492,495,498-500,538-546]. Nevertheless, a few examples are given below.

The post-extraction bone resorption is an increasing problem in modem dentistry. Namely, after extraction of a tooth, the bony socket heals naturally. First, it is immediately filled with coagulated blood. In a few days afterwards, the granular and fibrous tissues are organized to form a new bone tissue gradually. However, due to the tooth absence, maxilla and/or mandibular alveolar atrophies occur simultaneously. These resorptive and remodeling phenomena of the surrounding bone negatively affect the support for the adjacent teeth; the shallow ridge makes it difficult for future prosthesis retention and less bony support remains for any dental implant placement in the future. To promote healing, the socket of an extracted tooth might be filled by $CaPO_4$ bioceramics. For example, an efficacy of commercial HA granules APAFILL-G™ as a filler to prevent the resorption of alveolar bone after tooth extraction was studied [547]. After seven days, the result revealed that only one of all treated patients experienced an adverse response observed at the clinical evaluation that promptly disappeared after analgesic treatment. The rest 32 dint had adverse clinical response. Radiographically, a continuous radio-opacity between bone and the implant resorption was detected after one year the surrounding alveolar bone maintained its contour without symptoms of resorption

for the 100% of the patients [547]. In another study, two different types of HA grafting materials, biomimetic and nanocrystalline, were placed into fresh extraction sockets aiming to limit bone resorption. The surgical sites were histologically, clinically and radiographically evaluated 6 months after tooth extraction. The percentages of bone, osteoid areas [548].

Furthermore, repositioning maxillaty and mandibular bone segments in orthognathic surgery frequently creates bone gaps or continuity defects. These often require grafting to provide positional stability and bony continuity and $CaPO_4$ are used for this purpose. For example, as early as 1987, a study to evaluate the use of coralline porous HA as a bone graft substitute in orthognathic surgery [445], followed by another study in 1989 [446]. 92 consecutive patients received totally of 355 block implants to the maxilla (294), mandible (41) and midface (20). There were 202 implants positioned directly adjacent to the maxillary sinus. Complications were minimal, the most common being exposure of the implant to the oral or nasal cavity. Histological evaluation of implants that were biopsied in nine patients, four to 16 months postsurgery, revealed connective tissue ingrowth throughout the implants with approximately one-third being bone of variable maturity and two-thirds being soft tissue [445]. Similar results were obtained in another study [446]. Periodontal ligaments around extracted sockets were found to have an ability to regenerate bone on HA-coated tooth-shaped implants [341]. Positive results were also observed in another study, in which bone formation around BCP (HA + β-TCP) particles in periodontal defects of dogs were found to be more discernible if compared to healing in control [486]. In addition, the porosity of the implanted $CaPO_4$ was found to influence periodontal healing of furcation defects in dogs [293].

To increase a treatment efficiency of the periodontal defects, $CaPO_4$ might be combined with the biologically active molecules, such as hormones, growth factors, morphogenetic proteins, *etc.* [491,549-555]. For example, an application of recombinant human growth and differentiation factor-5 (rhGDF-5) lyophilized onto β-TCP granules demonstrated an effective regeneration of the artificially created periodontal defects [549,550]. Positive results were also obtained for a combination of a recombinant human platelet-derived growth factor BB (rhPDGF-BB) with β-TCP for the treatment of human intra-osseous periodontal defects [551,552]. However, a combination of an enamel matrix derivative with BCP (HA + β-TCP) resulted in no to minimal new bone formation [491]. Furthermore, a combination of human bone morphogenetic protein-2 (rhBMP-2) with a bioresorbable $CaPO_4$ cement Ceredex™ was not suggested for periodontal indications [553]. Besides, there are results indicating that the use of $CaPO_4$ after open flap procedure does not improve the clinical and radiological treatment outcomes of periodontal intrabony defects [554]. Thus, applications of $CaPO_4$ in periodontology were not always positive.

Other types of oral applications: Of patients undergoing allogeneic hematopoietic stem cell transplantation, ~ 75% or even more experience oral mucositis, which is a painful acute complication that can delay discharge, interrupt treatment and threaten life. To help the patients, rinses, supersaturated by undisclosed types of $CaPO_4$, were prepared and evaluated. Compared to the control groups, the supersaturated $CaPO_4$ rinse groups were found to have significantly lower mean measures of oral toxicity, peak mouth pain and disease course duration [556-559].

Tissue Engineering Approaches

As seen from the aforementioned, $CaPO_4$ are widely used in dentistry

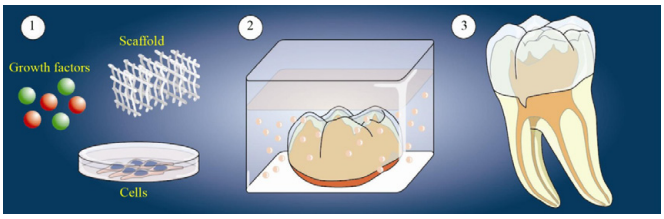


Figure 8: A schematic diagram of entire tooth regeneration from the proper combination of growth factors and cells (stem cells or progenitor cells) seeded on a $CaPO_4$ scaffold. (Adapted with permission from Ref. [570]).

to restore and/or repair various types of oral defects. However, all the previously mentioned approaches have encountered shortcomings if compare to the normal and healthy teeth and surrounding bones. Therefore, various tissue-engineering approaches to develop new strategies for tooth regeneration are attempted. The history of tissue engineering in dentistry started in 1982, when the first regeneration technology of periodontium was introduced [560]. The modern tissue engineering approaches in dentistry include combinations of cells, engineering materials and suitable biochemical and physicochemical factors to improve or replace biological functions. Finally, it will cause *in vivo* formation and growing of new functional tissues instead of reparation and/or replacement of damaged and/or missing ones by artificial materials and/or implants [561-565]. From the material point of view, there are two main approaches towards making a bioengineered tooth: scaffold-free and scaffold-based regenerations. The scaffold-free approaches, such as tissue recombination, cell pellet engineering and chimerical tooth engineering, are being developed and the correct tooth-like structures could be generated after transplantation in the sub-renal capsule [566-568]. However, with an exception of using soluble calcium- and orthophosphate-containing solutions to promote proliferation, osteogenic differentiation and mineralization of various types of dental cells [569], the scaffold-free approaches do not utilize $CaPO_4$. Therefore, in this review, scaffold-based tooth regeneration approaches are considered only. A schematic drawing of this process is shown in Figure 8 [570].

For example, it was hypothesized that dental follicle cells combined with β-TCP might become a novel therapeutic strategy to restore periodontal defects. The authors suggested isolation of dental follicle cells from a beagle dog. The isolated cells should be induced by bone morphogenetic protein-2, basic-fibroblast growth factors and dexamethasone and, then, seeded onto β-TCP bioceramics. Afterwards, the complex should be auto-implanted into the periodontal defects in the same dog to observe regeneration of periodontal tissue *in vivo* [571]. However, this was just a hypothesis. Let me describe the real investigations.

A biocompatibility of four different types of 3D scaffolds for regeneration of tooth tissues was tested [572]. The scaffolds consisted of pure poly(lactic-*co*-glycolic) acid (PLGA) or 50/50 w/w biocomposites of PLGA with HA, β-TCP or carbonate-containing HA. Afterwards, human dental pulp stem cells were seeded onto the scaffolds, followed by implantation into the mesentery or subrenal capsule of mice or rats for 4 to 5 weeks. The results showed that, while all $CaPO_4$-containing formulations were able to support effectively regeneration of the tooth tissues, the PLGA/β-TCP scaffolds appeared to be superior to the other three scaffolds for tooth tissues regeneration, especially for dentin formation [572]. Very promising results were also obtained by other researchers for β-TCP/chitosan biocomposites [573], recombinant

human transforming growth factor-beta 1 (rhTGF-β1) combined with two different bone grafts: calcified freeze-dried bone allograft and porous BCP [574] and a complex of recombinant human bone morphogenetic protein 2 (rhBMP-2)-mediated dental pulp stem cells and nano-HA/collagen/poly(L-lactide) for clinical reconstruction of periodontal bone defects [575].

In still other studies, polyglycolic acid (PGA) scaffolds were compared with β-TCP, fibrin and collagen scaffolds for their capacity to grow dental structures when seeded with tooth germs from 6-month-old minipigs. On fibrin and collagen gels, the porcine third molar tooth bud maintained its epithelial structure, resembling tooth buds, whereas on PGA and β-TCP the implanted tooth buds produced more dentin-like material [576]. Porous BCP (HA + β-TCP), powdered BCP and PGA fiber mesh were used as scaffolds and transplanted with cultured porcine dental pulp-derived cells into the backs of nude mice for 6 weeks. Although newly formed hard tissues were observed in all implants, a dentin-like hard tissue was observed when porous BCP was used [577]. Besides, incorporation of nano-sized HA into electrospun poly(ε-caprolactone)/gelatin scaffolds was found to enhance dental pulp stem cells differentiation towards an odontoblast-like phenotype both *in vitro* and *in vivo* [578]. The osteoblast marker bone sialoprotein was highly expressed on β-TCP scaffolds seeded by dental follicle cells but almost absent in differentiated dental follicle cells without β-TCP. The latter means that dental progenitor cells have to be combined with $CaPO_4$ bioceramics.

To conclude this topic, the tissue engineering approaches of dental regenerations, obviously, appear to be the most promising healing technologies and many interesting studies on a combination of $CaPO_4$ scaffolds with cells and/or growth factors are expected to appear in the near future.

Conclusion

Biologically relevant types of $CaPO_4$ are the emerging bioceramics, which are widely used in various biomedical applications, including dentistry. They have excellent biomedical properties and biological behavior because their composition and structure are similar to those of human bones and teeth. Therefore, $CaPO_4$ possess exceptional biocompatibility and unique bioactivity, which are widely used in dentistry and dentistry-related fields. For example, incorporation of $CaPO_4$ into various restorative biomaterials was found to improve mechanical properties of the biomaterials without impeding their inherent biological properties. Other examples have been described above. Nevertheless, the versatile employing strategies of $CaPO_4$ in dentistry aim to ultimately reach the same goal, namely to enhance osseointegration process of dental implants in the context of immediate loading and to augment formation of surrounding bones to guarantee a long-term success. However, still the complete understanding related to use of $CaPO_4$ in clinical dentistry is lacking and further research is needed to improve their efficacy in clinical dentistry.

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