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Chemism of Networking and Biological Functions of Different Types of Phosphate Cements

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SUMMARY

This article provides an overview of calcium phosphate systems used in different formulations of cement mixtures. Chemism of reactions that occur in contact of these systems with water medium shows diversity and specificity of each of selected types of mixtures. As it can be clearly seen from reactions that occur between components of cement mixtures, highly active calcium deficient hydroxyapatite is always an end product in all reactions. This makes these systems extremely biocompatible and suitable for use in dentistry from the standpoint of chemical and biological degradability.

Keywords: apatite cements; brushite cements; phosphate cements; chemism; hydroxyapatite

INTRODUCTION

Hydroxyapatite is an important biomaterial due to its resemblance to apatite mineral contained in natural teeth and bones [1]. Calcium phosphate cements (CPC) have been developed because of their ability to adjust to a given model and form hydroxyapatite during the process of biological maturation in body [2]. So far, there have been developed a few different types of phosphate cements [3]. CPC powder usually consists of tetrakalcium phosphate (TTCP), $Ca_4(PO_4)_2O$, or tricalcium phosphate, β-$Ca_3(PO_4)_2$ and anhydrous dicalcium phosphate (DCPA), $CaHPO_4$. In order to obtain corresponding cement paste, component powders are mixed with water leading to the formation of hydroxyapatite [4]. CPC exhibit an excellent biocompatibility and osteoconductivity. Moreover they are easily absorbed creating new bone [4]. First cements based on phosphate components were applied in human clinical practice in 1996 for the repair of craniofacial defects [4]. Since then they have been proved useful for a variety of dental indications, such as a root canal filling etc. Composites that contain CPC and various polymers (resin) may be applied for pulp capping and restoration of damaged cavity walls. They are suitable for the initiation of dentine remineralization process in *in vitro* conditions [5]. However, in combination with biopolymers, such as chitosan, they build strong and flexible composites that can be used for the repair of periodontal bone [6].

The only drawback of CPC is the preparation just before use where powder and liquid must be mixed to form the cement paste which hardens very quickly and may be problematic during its incorporation into defect. The preparation of mixture immediately before use has other serious drawbacks [7] such as increasing time of surgery. However, if mixing and preparation are not satisfactory, some additional problems related to instruments and materials sterilization and maintaining sterile environment may appear. To operate in such conditions, mixing components is usually improvised giving the paste that does not have satisfactory rheological characteristics, or the amount of paste at a given moment is not sufficient to fill the present craniofacial defects. These difficulties have triggered the development of finished CPC, where the CPC powder is mixed with non-aqueous medium, miscible with water (alcohol) under well-controlled conditions. The advantage of this waterless paste is that it does not harden in a tool that is used for application; it only hardens by hydration in contact with aqueous environment. When the paste in non aqueous solution comes in contact with saline, it changes non-aqueous solution with water causing the paste hardening. At the same time, the setting time becomes longer with inadequate strength of hardened cement paste [7]. Longer setting time causes some clinical problems due to instability of cement paste to maintain a desired shape during its networking and provide satisfactory mechanical properties. Therefore, it is necessary to find more favorable formulations of cement mixtures, and use various additives to accelerate setting and increase strength. It is important to note that some formulations of these mixtures show high level of cytotoxicity and can cause cell death in *in vitro* conditions. Consequently, ideal cements should be non-toxic, have good mechanical properties and harden quickly. Such cements in addition to basic components usually contain different types of additives and gel agents with diverse biological properties that have significant effects on reducing setting time of cements and viability of osteoblastic cells, both *in vitro* and *in vivo*.

For better review of all the features related to formulations of cement mixtures based on phosphate

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systems, this article gives formulations of various cement mixtures, specific reactions that occur in the process of their hydration and networking, as well as their chemism that results in the formation of calcium deficient hydroxyapatite important for biological compatibility of these systems [8].

PHOSPHATE CEMENTS AND CHEMICAL REACTIONS CHARACTERISTIC FOR THEIR NETWORKING

Chemical reactions that occur during networking of calcium orthophosphate cements depend on their composition; however, there are two main types of reactions. The first type occurs by classical rules of acid-base reactions, where relatively acidic calcium orthophosphates react with relatively alkaline orthophosphate producing almost neutral compounds. The first cement that was designed by Brown and Chow is typical example of such cement, where TTCP (alkaline phosphate) reacts with anhydride DCP (weakly acidic phosphate) in aqueous suspension, precipitating poorly crystalline hydroxyapatite (low alkaline phosphate) [8-10]:

$$2Ca_4(PO_4)_2O + 2CaHPO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2 \quad (1)$$

Earlier view was that this reaction gives stoichiometric hydroxyapatite as product. Following studies have found that first formed nuclei were stoichiometric hydroxyapatite that further formed calcium deficient hydroxyapatite. These studies have been confirmed by other researchers. Hydroxyapatite formation by reaction (1) leads to release of acidic or alkaline by-products. pH of cement liquid phase is about 7.5 for TTCP and dicalcium phosphate dihydrate, while pH for TTCP and dicalcium phosphate anhydrous is about 8. The influence of CaO/P ionic relation of TTCP on the properties of TTCP - DCP cement was also the subject of various studies.

In addition to these types of cements, cements based on β-TCP (almost neutral phosphate) and monocalcium phosphate monohydrate (acidic phosphate) that form dicalcium phosphate dihydrate (low alkaline phosphate) have been studied [8, 11]:

$$\beta\text{-}Ca_3(PO_4)_2 + Ca(H_2PO_4)_2\cdot H_2O + 7H_2O \rightarrow 4CaHPO_4\cdot 2H_2O \quad (2)$$

If orthophosphoric acid or anhydrous monocalcium phosphate (instead of monocalcium phosphate monohydrate) and α-TCP (instead of β-TCP or calcium deficient hydroxyapatite) are used, different types of reactions are possible such as [8, 11]:

$$Ca_9(HPO_4)(PO_4)_5(OH) + 3H_3PO_4 + 17H_2O \rightarrow 9CaHPO_4\cdot 2H_2O \quad (3)$$

Suitable formulations for cement pastes are mixtures of amorphous calcium phosphate with α-TCP or dicalcium phosphate dihydrate, anhydrous dicalcium phosphate and α-TCP, oktakalcijum phosphate and TTCP and partially crystallized calcium orthophosphate and anhydrous dicalcium phosphate.

Another type of networking reaction is hydrolysis reaction of metastable calcium orthophosphate in aqueous medium. In such reaction Ca/P ratio is the same at the beginning and at the end of the reaction. Such components are used as mono phase (mono components) of cement mixture. These types of cements consist of amorphous calcium phosphate, or α-TCP or β-TCP or nanocrystalline or γ-irradiated TTCP and aqueous medium as a second phase, where recrystallization and formation of calcium deficient hydroxyapatite happens in all cases, according to the following reactions [8, 11-13]:

$$Ca_xH_y(PO_4)_z\cdot nH_2O + H_2O \rightarrow Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x} + nH_2O, \quad (4)$$

$$3(\alpha\text{- or }\beta\text{-})Ca_3(PO_4)_2 + H_2O \rightarrow Ca_9(HPO4)(PO_4)_5(OH), \quad (5)$$

$$3Ca_4(PO_4)_2O + 3H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5(OH) + 3Ca(OH)_2. \quad (6)$$

In all reactions, addition of small amounts of low crystallized hydroxyapatite (about 2%) accelerates kinetics of a given reaction. Monophasic cements containing K^+ and Na^+ within the structure of calcium deficient hydroxyapatite (with Ca/P ratio of about 1.64) harden and network after mixing with sodium citrate and sodium orthophosphate. After networking, this mixture provides weak cement (compressive strength of about 15 MPa) composed of ion-substituised calcium-deficient hydroxyapatite, similar to bone mineral. Self-networking cement can be formed from thermally disassembled hydroxyapatite. Hydration process of calcium orthophosphate cements is slightly exothermic and runs in 5 stages: initiation period, induction period, accelerating period, deceleration period and termination period. Heat release during solidification process of calcium orthophosphate is low. This is very good because there is no danger of damaging surrounding tissue. The process of cement solidification is initially controlled by dissolution of reactants (during the first 4 hours) and then by diffusion through the layer of reaction product of calcium deficient hydroxyapatite [8, 11, 12, 13].

Networking of calcium orthophosphate cements occurs most frequently during first 6 hours through the conversion of 80% of reactants into the final product. The volume of cement during networking is almost constant. After hardening the cement is transformed into brittle ceramics with tensile strength that is 5 to 20 times lower than compressive strength. Therefore, these cements are commonly used with metal implants or in places that are not exposed to heavy loading (craniofacial region). All these observations are valuable only for *in vitro* networking of cements. In *in vivo* conditions, formation of carbonate hydroxyapatite is favored as compared to non-carbonated calcium deficient hydroxyapatite.

APATITE CEMENTS

Apatite cements precipitate in poorly crystallized hydroxyapatite and/or calcium deficient hydroxyapatite as the end product of networking reaction. Due to the presence of carbonates, apatite cements such as Norian SRS® and Biocement D® form non-stoichiometric carbonate apatites or dalit as end products, the chemical formula $[Ca_{8.8}(HPO4)_{0.7}(PO_4)_{4.5}(CO_3)_{0.7}(OH)_{1.3}]$. Calcium deficient hydroxyapatite and carbonate hydroxyapatite formed in aqueous medium have low crystallinity and are similar to biological apatite of bones and teeth. These qualities are essential for their good absorption *in vivo* [8, 14].

Conventional apatite cements contain TCP and/or TTCP, while monocomponent calcium deficient hydroxyapatite cements contain sodium. Reactivity of apatite cements on the basis of TCP varies depending on the fraction of crystalline tricalcium phosphate phase, its crystallinity and particle size. Generally, high reactivity was observed in less stable phases (increasing from β-TCP, α-TCP to amorphous calcium phosphate). It increases with decreasing particle size. One characteristic of cements is the weak link among crystals (calcium deficient hydroxyapatite or carbonated hydroxyapatite), therefore crystals can be easily separated from cement volume, especially after their partial dissolution. When this happens, osteoclasts and other cells can readily digest apatite crystals.

Immediately after implantation, cement is exposed to blood and other body fluids, which delays its setting time. Internal setting time for apatite cement is between 15 and 20 minutes (for the cement composition by Brown and Chow). This may lead to procedural complications. During that time, the amount of liquid should be reduced to a minimum. Therefore, apatite cements are tractable pastes that are difficult to inject. Networking time can be reduced by adding additives to the fluid phase. Such additives are phosphoric acid, monocalcium phosphate monohydrate and other soluble orthophosphates. These additives facilitate dissolution of solid phase by reducing the pH of the solution. In such cases, the setting time is 10-15 min [8, 14-16].

Influence of soluble orthophosphates (such as Na_2HPO_4 or NaH_2PO_4) on the setting time of apatite cements is explained by dissolution of dicalcium phosphate anhydrate and formation of calcium deficient hydroxyapatite during networking, avoiding the formation of calcium deficient hydroxyapatite in early stage (Figure 1).

Particle size, temperature of liquid phase and initial presence of hydroxyapatite germs in solid phase affect the time of linking. Reducing the particle size strongly affects reduction of initial and terminal binding, accelerates solidification and hydration kinetics during cement hardening. Specific surface area has similar effects (with increasing area the speed of binding increase and vice versa).

Relationship between the particle size of starting calcium orthophosphates and mechanical properties of hardened cements have not been precisely defined, although in some formulations a significant increase in compressive strength was observed. However, results are controversial and depend on many factors; therefore, they vary from author to author. The only certain thing is that all these cements are brittle and cannot be used in areas exposed to loading. Networking process of most apatite cements occurs in accordance with equations (1-6) in conditions close to physiological pH. For the precipitation of Norian SRS® and Cementek® dominant reactions are reactions of calcium deficient hydroxyapatite or carbonated hydroxyapatite precipitation, through the following steps [8, 9]:

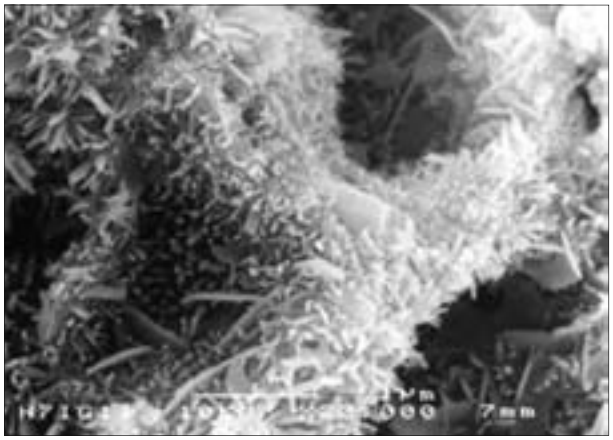

Figure 1. SEM: Microstructure of apatite calcium phosphate cements after setting; micro and nano dimensional structural elements with needle crystals can be observed.
Slika 1. SEM: mikrostruktura apatitnog kalcijum-fosfatnog cementa posle vezivanja; uočavaju se mikrodimenzionirani i nanodimenzionirani elementi strukture s igličastim kristalima

$$\alpha\text{-}Ca3(PO_4)_2 + Ca(H_2PO_4)_2{\cdot}H_2O + 7H_2O \rightarrow 4CaHPO_4{\cdot}2H_2O \quad (7)$$

$$5.2CaHPO_4{\cdot}2H_2O + 3.6CaCO_3 \rightarrow Ca_{8.8}(HPO_4)_{0.7}(PO_4)_{4.5}(CO_3)_{0.7}(OH)_{1.3} + 2.9CO_2 + 12H_2 \quad (8)$$

Initial chemical reaction is fast and causes the formation of dicalcium phosphate dihydrate whereas networking of the cement paste is secondary reaction. The second step in which dicalcium phosphate dihydrate reacts is slower and takes place over several hours with a lag of unreacted $\alpha\text{-}Ca_3(PO_4)_2$ and $CaCO_3$ according to the equation (8). This step is conditional for the cement hardening. Similar two-step mechanism of hardening is also present in cements that contain monocalcium phosphate monohydrate and CaO.

In the first step, monocalcium phosphate monohydrate reacts with CaO giving dicalcium phosphate dihydrate that in the second step reacts slowly giving calcium deficient hydroxyapatite with the remnants of CaO. Networking mechanism was investigated on three component mixtures TTCP, β-TCP and monocalcium phosphate monohydrate in appropriate proportions to satisfy the ratio of Ca/P = 1.67. At the beginning of the process there were chemical reactions [8, 10]:

$$Ca(H_2PO_4)_2{\cdot}H_2O + \beta\text{-}Ca_3(PO_4)_2 + 7H_2O \rightarrow 4CaHPO_4{\cdot}2H_2O \quad (9)$$

and

$$Ca_4(PO_4)_2O + 2H_3PO_4 + 7H_2O \rightarrow 4CaHPO_4 \cdot 2H_2O \quad (10)$$

First reaction of formation of dicalcium phosphate dihydrate corresponds to crosslinking stage. Thereafter TTCP reacts with previously created dicalcium phosphate dihydrate and β-TCP giving calcium deficient hydroxyapatite, according to the reactions [8]:

$$2Ca_4(PO_4)_2O + 2CaHPO_4 \cdot 2H_2O \rightarrow Ca_{10-x}(HPO_4)_x (PO_4)_{6-x}(OH)_{2-x} + xCa(OH)_2 + (4 - x)H_2O \quad (11)$$

and

$$2Ca_4(PO_4)_2O + 4\beta\text{-}Ca_3(PO_4)_2 + (2+2x)H_2O \rightarrow 2Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x} + 2xCa(OH)_2 \quad (12)$$

Formation of calcium deficient hydroxyapatite is very slow and corresponds to solidification stage. Although octa-calcium phosphate is not registered, its formation as an intermediate phase has been observed in some studies. According to some studies octa-calcium phosphate, as an intermediate phase, is formed faster than calcium deficient hydroxyapatite, being its precursor.

BRUSHITE CEMENTS

Brushite cements have dicalcium phosphate dihydrate as main product, resulting from crosslinking reactions given in equations (1 and 2). Several formulations are known (β-TCP and monocalcium phosphate monohydrate, β-TCP and $H_3PO_4$and TTCP, monocalcium phosphate monohydrate and CaO). All brushite cements are based on acid-base reactions. Dicalcium phosphate dihydrate precipitates at pH ≤ 6, meaning that brushite crosslinking is happening in acidic conditions. Formulation H_3PO_4 and β-TCP have advantages over the formulation β-TCP and monocalcium phosphate monohydrate due to: i) easier and faster preparation, ii) better control of chemical composition and reactivity, iii) improved physical and chemical properties, such as longer networking and greater tensile strength due to better homogeneity of cement mixture [8, 19, 20].

As solubility of calcium phosphate decreases with increasing alkalinity, the time for networking of brushite cements depends on solubility of basic phase. If this phase is more soluble, crosslinking is faster. The time needed for crosslinking of a combination of monocalcium phosphate monohydrate and alkyl calcium phosphate is shorter starting from hydroxyapatite (a few minutes), via β-TCP (30-60 s) to α-TCP (a few seconds). However, hardening takes much longer (a day). Additives that inhibit crystal growth of dicalcium phosphate dihydrate are successfully used to increase the time needed for networking of mixtures of monocalcium phosphate monohydrate and β-TCP.

Unlike apatite cements, brushite cements may be in the liquid form, however, they are crosslinked very fast. They are also biocompatible and bioresorptive. Due to better solubility of dicalcium phosphate dihydrate as compared to calcium deficient hydroxyapatite and metastability of dicalcium phosphate dihydrate under physiological conditions, brushite cements degrade faster than apatite cements. They are quickly resorbed *in vivo* and have low strength. Short time for networking and low mechanical strength are main reasons why this cement is rarely clinically applied. The use of sodium citrate and citric acid as networking inhibitors provide workable and less viscous pastes of brushite cements. Similar effect can be achieved by adding hondrotoin 4-sulfate and glycolic acid. Cements containing orthophosphoric acid as starting reactant also show better workability. Crosslinking reaction in such cases can be described by chemical reaction [8, 20, 21]:

$$3.7\beta\text{-}Ca_3(PO_4)_2 + H_3PO_4 + 27.8H_2O \rightarrow 3CaHPO_4 \cdot 2H_2O + 2.7\beta\text{-}Ca_3(PO_4)_2 + 21H_2O \quad (13)$$

Some studies have shown that brushite cements can cause tissue inflammation in the first week after *in vivo* implantation. Such tissue reaction is related to the process of partial transformation of dicalcium phosphate dihydrate into calcium deficient hydroxyapatite, which leads to release of phosphoric acid, according to the reaction [8, 21]:

$$(10 - x)CaHPO_4 \cdot 2H_2O \rightarrow Ca_{10-x}(HPO_4)_x(PO_4)_{6-x} (OH)_{2-x} + (4 - x)H_3PO_4 + (18 - x)H_2O \quad (14)$$

Transformation of dicalcium phosphate dihydrate in calcium deficient hydroxyapatite occurs through two successive processes: dissolution process and precipitation process. It can be slowed with the addition of magnesium ions to the cement paste reducing the possibility of inflammation. Reaction (13) indicates that an excess of acid released in the reaction (14), can be compensated by reaction of (13) using β-TCP. Implantation of previously crosslinked brushite material is third option, because solid material is more tolerant as an implant than a paste.

According to some studies, linear velocity of brushite cements degradation is about 0.25 mm per week. This rapid degradation can lead to formation of immature bone. Addition of β-TCP granules to cement paste solves this problem because β-TCP acts as a bone anchor and enhances the formation of mature bone [19, 20, 21].

RHEOLOGICAL PROPERTIES OF PHOSPHATE CEMENTS

It is well known how to control viscosity of calcium phosphate pastes. They belong to the group of so-called non-Newtonian fluids, in terms of viscosity of fluid shear. Cement pastes possess transient properties, which mean that their viscosity is function of shear stress and time. Calcium phosphate pastes are thixotropic. In addition to particle size (which increasing size reduces viscosity), additives added to cement composites, such as citrate ions and polyacrylic acid, reduce viscosity and cohesion by reducing interaction between the particles.

Networking time is the time for reaching mechanical stability of the cement paste. This time can be experimentally determined using the method of Gillmor's pin or Vikat's test. It is now an open topic for numerous studies. Besides networking time of cement pastes, a special significance has cement solidification rate and its dependence on particle size of the system, addition of nucleation phase or dissolving an appropriate additive (accelerator or retarder) in cement mixture etc. [22].

BIOLOGICAL PROPERTIES OF PHOSPHATE CEMENTS

The current strategy to repair bone defects is based on using bone substituent, which is quickly absorbed creating a new, mature bone (Figure 2). This problem is not related just to chemistry but also to geometry of bone substituent which should be optimized. Especially important are bone substituents in which cells and blood vessels could be easily introduced. Therefore, they must have pores larger than 50 μm. To solve this problem, cement pastes are combined with very soluble solids, hydrophobic liquids or gas bubbles. Unfortunately, gas created macropores are not linked, which limits the success of this strategy. In other approaches pastes are combined with hydrogels such as sodium alginate, dextran, sodium hyaluronate, hydroxypropylmethyl cellulose, etc. The content of hydrogel as solid matter is very low (a few percent), therefore, cells can easily penetrate hydrogel parts between the granules. Another important parameter is particle size of ceramic bone substitute in the paste [23].

Biological response to a paste that contains nano and micrometer particles is different from response to a paste with millimeter particles. Particles less than 5 μm can cause damage. Therefore, caution is needed when using such particles. In the last decade, there has been a great research on high-resorptive bone substituents. Some of these materials, such as β-TCP are resorbed differently from gypsum and brushite that are resorbed by simple dissolution. Under conditions of thermodynamic equilibrium, the solution obtained by dissolution of gypsum has about 10 times more calcium ions than serum bodily fluid. On the other hand, serum does not contain sulfate ions. The result of gypsum dissolution is rapid bone growth which is complicated by the presence of fibrous tissue in defective centers.

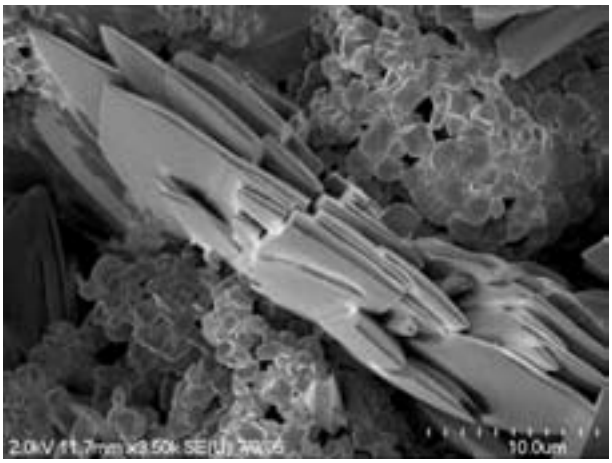

Figure 2. SEM: Calcium phosphate cement replacing damaged bone tissue
Slika 2. SEM: Kalcijum-fosfatni cement kao zamena za oštećeno koštano tkivo

Brushite is less soluble than plaster. In physiological fluids it is poorly soluble. By dissolution brushite loses its mechanical strength very quickly, transforming its center in apatite. Also, there is a resulting fibrous part between bone and resorbed cement. However, this part disappears when apatite remains in the block of cement paste. As apatite is alkaline compound, its precipitation makes surrounding medium acidic. Such cement (Brown and Chow cement) provokes *in vivo* reaction characteristic for brushite cement when implanted in large quantity. The use of fast resorbing cements leads to rapid transformation of bone defects in mature bone but has risks of negative biological response and/or very rapid disappearance from implanted defects [8, 24].

CONCLUSION

Phosphate cements show great diversity in terms of chemism of reactions that lead to hardening through their hydration. They are very resorbable, therefore, they can be used as bone replacement materials. Their disadvantages are primarily related to sometimes too rapid resorption of material and lack of adequate mechanical support to the system in which they are used as implants. Their application in tooth fillings, repairing damaged teeth walls, dentin reparations even in *in vivo* conditions is very interesting and valuable. Combination with different types of polymers and additives can significantly improve some of their characteristics, such as setting time and mechanical strength, which makes them very interesting for applications in various fields of dentistry.

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Hemizmi umrežavanja i biološke funkcije različitih vrsta fosfatnog cementa

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KRATAK SADRŽAJ

U radu je dat pregled kalcijum-fosfatnih sistema koji se koriste u različitim formulacijama cementnih mešavina. Hemizmi reakcija koje se javljaju pri kontaktu takvih sistema s vodenom sredinom pokazuju raznovrsnost i specifičnost svake izabrane mešavine. Kao što se jasno vidi iz reakcija koje se odigravaju između komponenata cementnih mešavina, uvek se kao krajnji proizvod u svim reakcijama pojavljuje visokoaktivni hidroksiapatit s nedostatkom kalcijuma. To čini ove sisteme izuzetno biokompatibilnim i, sa stanovišta hemijske i biološke degradibilnosti, pogodnim za primenu u stomatologiji.

Ključner ečі: apatitni cement; brušitni cement; fosfatni cement; hemizam; hidroksiapatit

UVOD

Hidroksiapatit (HAp) je veoma važan biomaterijal zbog svoje izuzetne sličnosti s apatitnim mineralom sadržanim u prirodnim zubima i kostima [1]. Kalcijum-fosfatni tipovi cementa (CPC) su razvijeni zbog sposobnosti da se prilagode datom modelu i da tokom procesa biološkog sazrevanja u organizmu formiraju HAp [2]. Dosad je razvijeno nekoliko različitih vrsta fosfatnog cementa [3]. CPC prah najčešće se sastoji od tetrakalcijum-fosfata (TTCP) [$Ca_4(PO_4)_2O$], odnosno trikalcijum-fosfata [β-$Ca_3(PO_4)_2$] i bezvodnog dikalcijum-fosfata (DCPA) [$CaHPO_4$], pri čemu se komponentni prahovi, da bi se dobila odgovarajuća cementna pasta, mešaju s vodom, nakon čega dolazi do stvaranja HAp [4]. Vrste CPC pokazuju odličnu biokompatibilnost i osteokonduktivnost. Uz to oni se lako resorbuju stvarajući pri tome novu kost [4]. Prve recepture cementa zasnovanog na fosfatnim komponentama primenjene su u humanoj kliničkoj praksi 1996. godine za popravku kraniofacijalnih oštećenja [4]. Otada do danas CPC su se pokazali veoma pogodnim za različite dentalne indikacije, kao što je punjenje kanala korena zuba i sl. Kompoziti koji uključuju u svoju recepturu CPC i različite vrste polimera (smola) mogu se primeniti za prekrivanje zubne pulpe i popunu oštećenih zidova zuba. Veoma su pogodni i za stimulisanje procesa remineralizacije dentina u uslovima *in vitro* [5], dok u kombinaciji sa biopolimerima, kao što je hitozan, grade veoma čvrste i fleksibilne kompozite koji mogu da se primene za parodontalnu reparaciju kosti [6].

Jedini nedostatak CPC je što je neophodno da se pre upotrebe (na licu mesta) prah i tečna komponenta savršeno izmešaju, da bi se formirala cementna pasta koja veoma brzo stvrdnjava, što može da uzrokuje poteškoće pri njenoj primeni. Priprema smese neposredno pre upotrebe ima i svoje ozbiljne nedostatke [7], jer povećava vreme hirurške intervencije, a ako se tome još doda da ni samo mešanje i priprema ponekad nisu zadovoljavajući, onda dolazi do dodatnih problema u vezi sa sterilizacijom materijala i instrumenata, te održavanja neophodnog sterilnog okruženja. Za rad u takvim uslovima mešanje komponenata obično se improvizuje, što može da dovede do toga da dobijena pasta nema zadovoljavajuće reološke osobine, kao i da količina paste u datom trenutku nije zadovoljavajuća za popunu kraniofacijalnih oštećenja. Ove poteškoće podstakle su razvoj gotovih vrsta CPC, kod kojih se CPC prah meša s nevodenim medijumom, koji je mešljiv sa vodom (alkohol), u dobro kontrolisanim uslovima. Prednost ovakve bezvodne paste je u tome što ona ne očvršćava u alatu kojim se nanosi, s obzirom na to da CPC očvršćava hidratacijom jedino u kontaktu s vodenim okruženjem. Pasta u nevodenom rastvoru dovodi se potom u kontakt s fiziološkim rastvorom, unutar kojeg se izmenjuje nevodeni rastvor s vodom, usled čega pasta očvršćava. Pri tom dolazi do povećanja vremena vezivanja, uz nezadovoljavajuću čvrstoću očvrsle cementne paste [7]. Dugo vreme vezivanja uslovljava i odgovarajuće kliničke probleme zbog nestabilnosti cementne paste da tokom svog umrežavanja održi željeni oblik i obezbedi mehaničke osobine samom uzorku. Zbog toga su neophodni iznalaženje pogodnijih formulacija cementnih mešavina, uz primenu različitih dodataka, koji ubrzavaju vezivanje i povećavaju čvrstoću. Važno je istaći da neke formulacije takvih mešavina pokazuju visok nivo citotoksičnosti i mogu izazvati ćelijsku smrt u uslovima *in vitro*. Zbog svega navedenog, idealno bi bilo da se razviju tipovi cementa koji imaju dobre mehaničke osobine i očvršćavaju brzo, a da pri tom nisu toksični. Takve vrste cementa, pored osnovnih komponenata, najčešće sadrže različite tipove aditiva i gelirajućih agensa, koji pokazuju najrazličitija biološka svojstva i bitno utiču na smanjenje vremena vezivanja cementa i vijabilnost osteoblastnih ćelija kada se nađu u odgovarajućem *in vivo* ili *in vitro* okruženju.

Radi boljeg pregleda svih mogućnosti u vezi s formulisanjem osnovnog sastava cementnih mešavina na osnovama fosfatnih sistema, u radu su, pored raznovrsnih polaznih formulacija cementnih mešavina, date i specifične reakcije koje se događaju u procesu njihove hidratacije i umrežavanja i njihovi hemizmi, čiji je rezultat nastanak hidroksiapatita s nedostatkom kalcijuma (engl. *calcium-deficient hydroxyapatite – CDHAp*), što je izuzetno važno sa stanovišta biološke kompatibilnosti takvih sistema [8].

FOSFATNI CEMENTI I HEMIJSKE REAKCIJE TIPIČNE ZA NJIHOVO UMREŽAVANJE

Hemijske reakcije koje se događaju tokom umrežavanja kalcijum-ortofosfatnih vrsta cementa zavise od njihovog sastava, a sve se u osnovi svode na dva glavna tipa reakcija. Prvi tip se dešava prema klasičnim pravilima kiselo-baznih reakcija, u ko-

jima relativno kiseli kalcijum-ortofosfati reaguju s relativno baznim ortofosfatima proizvodeći približno neutralna jedinjenja. Prvi cement koji su dizajnirali Braun (*Brown*) i Čou (*Chow*) tipičan je primer takvog cementa, u kojem TTCP (bazni fosfat) reaguje s anhidridom DCP (slabo kiseli fosfat) u vodenoj suspenziji, precipitirajući u slabo kristalni HAp (slabo bazni fosfat) [8, 9, 10]:

$$2Ca_4(PO_4)_2O + 2CaHPO_4 \rightarrow Ca_{10}(PO_4)_6(OH)_2 \quad (1)$$

Ranije se smatralo da takva reakcija daje kao proizvod stehiometrijski HAp. Istraživanja koja su potom sledila pokazala su da prvo nastaju nukleusi gotovo stehiometrijskog HAp, da bi pri daljem rastu ovih nukleusa nastao oblik CDHAp. Takvi nalazi dobili su potvrdu i u istraživanjima mnogih drugih autora. Formiranje HAp prema reakciji (1) vodi ka otpuštanju ili baznih ili kiselih nusproizvoda. Vrednost pH tečne faze cementa je oko 7.5 za TTCP i dikalcijumfosfat-dihidrat, dok je pH oko 8 za TTCP i anhidrovani dikalcijumfosfat. Uticaj Ca/P jonskog odnosa TTCP na osobine TTCP-DCP cementa bio je takođe predmet nekih istraživanja.

Pored takvih vrsta cementa, istraživani su i tipovi cementa na osnovi β-TCP (gotovo neutralan fosfat) i monokalcijumfosfat-monohidrata (kiseli fosfat), da bi nastao dikalcijumfosfat-dihidrat (slabo bazni fosfat) [8, 11]:

$$\beta\text{-}Ca_3(PO_4)_2 + Ca(H_2PO_4)_2{\cdot}H_2O + 7H_2O \rightarrow 4CaHPO_4{\cdot}2H_2O \quad (2)$$

Ako se kao reagujuće komponente koriste ortofosforna kiselina ili anhidrovani monokalcijum-fosfat (umesto monokalcijumfosfat-monohidrata) i α-TCP (umesto β-TCP ili CDHAp), tada su mogući različiti tipovi reakcija, kao što je i ova [8, 11]:

$$Ca_9(HPO_4)(PO_4)_5(OH) + 3H_3PO_4 + 17H_2O \rightarrow 9CaHPO_4{\cdot}2H_2O \quad (3)$$

Kao pogodne formulacije za cementne paste koriste se i smese amorfnog kalcijum-fosfata sa α-TCP ili dikalcijumfosfat-dihidratom, anhidrovanog dikalcijum fosfata i α-TCP, oktakalcijum-fosfata i TTCP i delimično iskristalisanog kalcijum-ortofosfata i anhidrovanog dikalcijum-fosfata.

Drugi tip reakcija umrežavanja čine reakcije hidrolize metastabilnih kalcijum-ortofosfata u vodenoj sredini. Kod takvih reakcija Ca/P odnos isti je i na početku i na kraju reakcije. Takve komponente koriste se kao monofaze (monokomponente) cementne smese. Takve vrste cementa se sastoje od amorfnog kalcijumfosfata, ili α-TCP ili β-TCP, ili nanokristalnog ili γ-ozračenog TTCP i vodenog medijuma kao druge faze, u kojem dolazi do rekristalizacije i nastajanja CDHAp, u svim navedenim slučajevima, sledeći reakcije date jednačinama [8, 11, 12, 13]:

$$Ca_xH_y(PO_4)_z{\cdot}nH_2O + H_2O \rightarrow Ca_{10\text{-}x}(HPO_4)_x(PO_4)_{6\text{-}x}(OH)_{2\text{-}x} + nH_2O, \quad (4)$$

$$3(\alpha\text{- ili }\beta\text{-})Ca_3(PO_4)_2 + H_2O \rightarrow Ca_9(HPO4)(PO_4)_5(OH), \quad (5)$$

$$3Ca_4(PO_4)_2O + 3H_2O \rightarrow Ca_9(HPO_4)(PO_4)_5(OH) + 3Ca(OH)_2. \quad (6)$$

U svim reakcijama dodatak male količine slabo iskristilisanog HAp (oko 2%) veoma ubrzava kinetiku date reakcije. Monofazni cementi koji sadrže K^+ i Na^+ unutar strukture CDHAp (sa Ca/P odnosom oko 1,64) umrežavaju i otvrdnjavaju pri mešanju s rastvorom natrijum-citrata i natrijum-ortofosfata. Posle umrežavanja ova smesa daje slab cement (pritisne čvrstoće oko 15 MPa) koji je sastavljen od jonski supstituisanog CDHAp, koji je sličan mineralu kosti. Samoumrežavajući cement može se napraviti i iz termički razloženog HAp. Hidratacioni proces kalcijum-ortofosfatnih vrsta cementa je blago egzoterman i protiče u pet stadijuma: inicijacioni period, indukcioni period, akceleracioni period, period usporenja i terminacioni period. Brzina oslobađanja toplote tokom procesa očvršćavanja kalcijum-ortofosfata je niska. To je veoma dobro jer nema opasnosti za oštećenje okolnih tkiva. Proces očvršćavanja cementa je u početku kontrolisan rastvaranjem reaktanata (tokom prva četiri sata) i potom difuzijom kroz sloj nastalog proizvoda reakcije CDHAp [8, 11, 12, 13].

Umrežavanje kalcijum-ortofosfatnih vrsta cementa dešava se najčešće tokom prvih šest sati kroz konverziju 80% reaktanata u finalni proizvod. Zapremina cementa tokom umrežavanja je skoro stalna. Posle očvršćavanja cement se transformiše u krtu keramiku sa zateznom čvrstoćom koja je od pet do dvadeset puta manja od pritisne čvrstoće. Zbog toga se takve vrste cementa najčešće koriste zajedno s metalnim implantatima ili na mestima koja nisu izložena opterećenju (kraniofacijalna regija). Sva ova zapažanja su vredna samo u uslovima umrežavanja cementa *in vitro*. U uslovima *in vivo* najčešće je nastajanje karbonatnih HAp u odnosu na nekarbonatni CDHAp.

VRSTE APATITNOG CEMENTA

Tipovi apatitnog cementa precipitiraju u slabo kristalisani HAp i/ili CDHAp kao krajnji proizvod reakcije umrežavanja. Zbog zastupljenosti karbonata, vrste apatitnog cementa kao što su *Norian SRS®* i *Biocement D®* kao krajnje proizvode formiraju nestehiometrijske karbonatne apatite ili dalit, hemijske formule $Ca_{8.8}(HPO4)_{0.7}(PO_4)_{4.5}(CO_3)_{0.7}(OH)_{1.3}$. CDHAp i karbonatni HAp nastali u vodenoj sredini imaju slab kristalinitet i slični su biološkom apatitu kostiju i zuba. Ove osobine su bitne za njihovu veoma dobru resorpciju u uslovima *in vivo* [8, 14].

Konvencionalne vrste apatitnog cementa sadrže TCP i/ili TTCP, dok monokomponentne vrste cementa CDHAp sadrže natrijum. Reaktivnost apatitnog cementa na osnovi TCP varira kao funkcija udela kristalne trikalcijumfosfatne faze, njenog kristaliniteta i veličine čestica. Generalno, visoka reaktivnost uočena je kod manje stabilnih faza (raste od β-TCP, preko α-TCP, ka amorfnom kalcijum-fosfatu). Ona raste i sa smanjenjem veličine čestica. Odlika cementa je slaba veza među kristalima (CDHAp ili karbonatnog HAp), tako da se kristali mogu lako odvojiti iz cementne zapremine, posebno nakon delimičnog njihovog rastvaranja. Kad se to dogodi, osteoklasti i druge ćelije mogu lako da svare apatitne kristale.

Neposredno nakon implantacije svaka vrsta cementa je izložena delovanju krvi i drugih telesnih tečnosti, što odlaže vreme njegovog vezivanja. Unutrašnje vreme vezivanja za tipove apatitnog cementa je između 15 i 20 minuta (za vrste cementa sastava prema Braunu i Čou), što može da dovede do proceduralnih komplikacija. Za to vreme količina tečnosti treba da je svedena na minimum. Zbog toga, apatitni cement je lako obradiva pasta koju je teško ubrizgati. Vreme umrežavanja može se smanjiti i

aditivima u tečnoj fazi. To su fosforna kiselina, monokalcijum-fosfat-monohidrat i drugi rastvorni ortofosfati. Oni pospešuju rastvaranje čvrste faze smanjenjem pH rastvora. U takvim slučajevima vreme vezivanja je 10–15 minuta [8, 14, 15, 16].

Uticaj rastvornih ortofosfata (kao što su Na_2HPO_4 ili NaH_2PO_4) na vreme vezivanja svih vrsta apatitnog cementa objašnjava se rastvaranjem anhidritnog dikalcijum-fosfata i formiranjem CDHAp tokom umrežavanja, uz izbegavanje formiranja CDHAp u ranoj fazi (Slika 1).

Veličina čestica, temperatura tečne faze i inicijalno prisustvo HAp klica u čvrstoj fazi takođe utiču na vreme umrežavanja. Smanjenje veličine čestica veoma utiče na smanjenje vremena polaznog i krajnjeg vezivanja, ubrzanje očvršćavanja i hidratacionu kinetiku pri očvršćavanju cementa. Na sličan način utiče i specifična površina (s njenim povećanjem raste i brzina vezivanja, i obrnuto).

Veza između veličine čestica polaznih kalcijum-ortofosfata i mehaničkih osobina očvrslog cementa nije precizno utvrđena, mada je kod nekih formulacija primećeno znatno povećanje kompresivne čvrstoće. Ipak, podaci su oprečni i zavise od mnogih faktora, tako da variraju od autora do autora. Jedino što je izvesno jeste da su sve vrste apatitnog cementa krte i ne mogu se koristiti na mestima koja su izložena opterećenju. Proces umrežavanja većine tipova apatitnog cementa dešava se u skladu s jednačinama (1-6) u uslovima bliskim fiziološkom pH. Kod precipitacije *Norian SRS*® i *Cementek*® dominantne su reakcije precipitacije u CDHAp ili u karbonatni HAp, kroz sledeće korake [8, 9]:

$$\alpha\text{-}Ca3(PO_4)_2 + Ca(H_2PO_4)_2{\cdot}H_2O + 7H_2O \rightarrow 4CaHPO_4{\cdot}2H_2O, \quad (7)$$

$$5.2CaHPO_4{\cdot}2H_2O + 3.6CaCO_3 \rightarrow Ca_{8.8}(HPO_4)_{0.7}(PO_4)_{4.5}(CO_3)_{0.7}(OH)_{1.3} + 2.9CO_2 + 12H_2O \quad (8)$$

Polazna hemijska reakcija je vrlo brza i uslovljava nastajanje dikalcijumfosfat-dihidrata i veoma brzo umrežavanje cementne paste. Drugi korak u kojem reaguje dikalcijumfosfat-dihidrat je sporiji i odvija se tokom nekoliko sati uz zaostajanje dela neizreagovanog $\alpha\text{-}Ca_3(PO_4)_2$ i $CaCO_3$ saglasno jednačini (8). Taj korak uslovljava očvršćavanje cementa. Sličan dvostepeni mehanizam očvršćavanja zapaža se i kod tipova cementa koji sadrži monokalcijumfosfat-monohidrat i CaO.

U prvom koraku monokalcijumfosfat-monohidrat reaguje sa CaO, dajući dikalcijumfosfat-dihidrat, koji u drugom koraku reaguje mnogo sporije dajući CDHAp sa ostacima CaO. Mehanizam umrežavanja istraživan je i na trikomponentnim smesama TTCP, β-TCP i monokalcijumfosfat-monohidrata u odgovarajućoj proporciji, da bi se zadovoljio uslov Ca/P=1,67. Odmah na početku procesa došlo je do hemijskih reakcija [8, 10]:

$$Ca(H_2PO_4)_2{\cdot}H_2O + \beta\text{-}Ca_3(PO_4)_2 + 7H_2O \rightarrow 4CaHPO_4{\cdot}2H_2O \quad (9)$$

i

$$Ca_4(PO_4)_2O + 2H_3PO_4 + 7H_2O \rightarrow 4CaHPO_4{\cdot}2H_2O \quad (10)$$

Stadijumu umrežavanja odgovara prva reakcija nastajanja dikalcijumfosfat-dihidrata. Posle toga TTCP reaguje s prethodno nastalim dikalcijumfosfat-dihidratom i β-TCP dajući CDHAp, saglasno reakcijama [8]:

$$2Ca_4(PO_4)_2O + 2CaHPO_4{\cdot}2H_2O \rightarrow Ca_{10\text{-}x}(HPO_4)_x(PO_4)_{6\text{-}x}(OH)_{2\text{-}x} + xCa(OH)_2 + (4 - x)H_2O \quad (11)$$

i

$$2Ca_4(PO_4)_2O + 4\beta\text{-}Ca_3(PO_4)_2 + (2+2x)H_2O \rightarrow 2Ca_{10\text{-}x}(HPO_4)_x(PO_4)_{6\text{-}x}(OH)_{2\text{-}x} + 2xCa(OH)_2 \quad (12)$$

Reakcija nastajanja CDHAp je vrlo spora i odgovara stadijumu očvršćavanja. Iako oktakalcijum-fosfat nije registrovan, njegovo formiranje kao srednje faze uočeno je u nekim istraživanjima. On se, naime, brže formira nego CDHAp, prethodeći mu tako.

VRSTE BRUŠITNOG CEMENTA

Tipovi brušitnog cementa su oni u kojima je glavni proizvod dikalcijumfosfat-dihidrat, koji nastaje reakcijama umrežavanja datim jednačinama (1 i 2). Nekoliko formulacija takvih vrsta cementa je poznato (β-TCP i monokalcijumfosfat-monohidrat, β-TCP i H_3PO_4 i TTCP, monokalcijumfosfat-monohidrat i CaO). Svi tipovi brušitnog cementa zasnivaju se na kiselo-baznim reakcijama. Dikalcijumfosfat-dihidrat precipituje pri vrednosti pH od najviše 6, tako da brušit umrežava u kiselim uslovima. Formulacija H_3PO_4 i β-TCP-a ima prednosti u odnosu na formulaciju β-TCP i monokalcijumfosfat-monohidrata zbog: 1) lakše i brže pripreme; 2) bolje kontrole hemijskog sastava i reaktivnosti; 3) poboljšanih fizičko-hemijskih osobina, kao što su duže umrežavanje i veća zatezna čvrstoća usled bolje homogenosti cementne smese [8, 19, 20].

Kako se rastvorljivost kalcijum-ortofosfata smanjuje s povećanjem baziciteta, vreme umrežavanja brušitnog cementa zavisi od rastvorljivosti osnovne faze, tako da većoj rastvorljivosti te faze odgovara brže umrežavanje cementa. Vreme umrežavanja za kombinaciju monokalcijumfosfat-monohidrata i baznih kalcijum-fosfata povećava se u nizu od HAp (nekoliko minuta), preko β-TCP-a (30–60 sekundi), do α-TCP (nekoliko sekundi). Samo očvršćavanje i pored ovako brzog umrežavanja traje mnogo duže (dan). Aditivi koji sprečavaju rast kristala dikalcijumfosfat-dihidrata uspešno se koriste da bi se povećalo vreme umrežavanja smesa monokalcijumfosfat-monohidrata i β-TCP.

Za razliku od apatitnog cementa, tipovi brušitnog cementa mogu biti u polazu tečni, da bi se potom brzo umrežili. Izrazito su biokompatibilni i bioresorbilni. Zahvaljujući boljoj rastvorljivosti dikalcijumfosfat-dihidrata u poređenju sa CDHAp i metastabilnosti dikalcijumfosfat-dihidrata pod fiziološkim uslovima, brušitni cement brže degradira od apatitnog. Brzo se resorbuje u uslovima *in vivo* i ima veoma slabu čvrstoću. Kratko vreme umrežavanja i niska mehanička čvrstoća su glavni razlozi što se ovaj cement šire klinički ne primenjuje. Primenom natrijum-citrata i limunske kiseline kao usporivača umrežavanja dobijaju se više obradive i manje viskozne paste brušitnog cementa. Sličan efekat postiže se dodatkom hondrotoin-4-sulfata i glikolne kiseline. Vrste cementa koje sadrže ortofosfornu kiselinu kao polazni reaktant takođe pokazuju bolju obradivost. Reakcija umrežavanja u takvim slučajevima može se opisati hemijskom reakcijom [8, 20, 21]:

$$3.7\beta\text{-}Ca_3(PO_4)_2 + H_3PO_4 + 27.8H_2O \rightarrow 3CaHPO_4{\cdot}\,2H_2O + 2.7\beta\text{-}Ca_3(PO_4)_2 + 21H_2O \quad (13)$$

Neka istraživanja su pokazala da brušitni cement može da izazove zapaljenje tkiva u prvoj nedelji nakon implantacije *in vivo*. Takva reakcija tkiva vezana je za proces delimične transformacije dikalcijumfosfat-dihidrata u CDHAp, pri čemu dolazi do oslobađanja fosforne kiseline, saglasno reakciji [8, 21]:

$$(10 - x)CaHPO_4 \cdot 2H_2O \rightarrow Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x} + (4 - x)H_3PO_4 + (18 - x)H_2O \quad (14)$$

Transformacija dikalcijumfosfat-dihidrata u CDHAp odvija se kroz dva sukcesivna procesa: proces rastvaranja i proces precipitacije. Ona može biti usporena sa dodatkom magnezijumovih jona cementnoj pasti, koji smanjuju mogućnost upale. Reakcija (13) pokazuje kako je moguće višak kiseline oslobođen u reakciji (14) kompenzovati reakcijom (13) pomoću β-TCP. Implantacija prethodno umreženog brušitnog materijala je treća opcija, zato što je čvrsti materijal tolerantniji kao implantat nego pasta.

Prema nekim istraživanjima, za brušitni cement linearna brzina razgradnje je oko 0,25 mm nedeljno. Ova brza degradacija može da vodi formiranju nezrele kosti. Dodatak β-TCP granula cementnoj pasti rešava ovaj problem, jer β-TCP deluje kao koštano sidro (anker) i pospešuje stvaranje zrele kosti [19, 20, 21].

REOLOŠKE OSOBINE FOSFATNOG CEMENTA

Relativno je poznato kako se kontroliše viskoznost kalcijumfosfatnih pasti. One pripadaju grupi tzv. nenjutnovskih fluida, sa stanovišta zavisnosti viskoznosti od sile smicanja. Cementne paste imaju tzv. tranzijentne osobine, što znači da je njihova viskoznost funkcija napona smicanja i vremena. Kalcijum-fosfatne paste su tiksotropne. Pored veličine čestica (čiji rast smanjuje viskoznost) i aditivi koji su dodati cementnim kompozitima, kao što su citratni joni i poliakrilna kiselina, takođe utiču na viskoznost i koheziju, smanjujući ih usled smanjenja interakcije među česticama.

Vreme umrežavanja je vreme postizanja mehaničke stabilnosti cementne paste. To vreme se može eksperimentalno odrediti korišćenjem metode Gilmorove (*Gillmor*) igle ili Vikatovog (*Vikat*) testa. To je i sada otvorena tema brojnih istraživanja. Pored vremena umrežavanja za cementne paste, poseban značaj ima brzina očvršćavanja cementa i njena zavisnost od veličine čestica sistema, dodatka nukleacione faze ili rastvaranja odgovarajućeg aditiva (ubrzivača ili usporivača vezivanja) u cementnoj smesi itd. [22].

BIOLOŠKE OSOBINE FOSFATNOG CEMENTA

Sadašnja strategija popravke koštanih oštećenja u osnovi je vezana za primenu koštanih supstituenta, koji se brzo resorbuju formirajući novu, zrelu kost (Slika 2). Ovaj problem nije samo problem hemije, već i geometrije koštanog supstituenta koju treba optimizovati. Posebno su važni koštani supstituenti u koje je lako uvesti ćelije i krvne sudove. Zbog toga oni treba da poseduju pore koje su veće od 50 μm. Da bi se rešio taj problem, cementne paste su kombinovane s veoma rastvornim čvrstim supstancama, hidrofobnim tečnostima ili mehurovima gasa. Nažalost, makropore stvorene gasom nisu povezane, što ograničava uspeh takve strategije. U drugim pristupima paste se kombinuju s hidrogelovima, kao što su natrijum-alginat, dekstran, natrijum-hijaluronat, hidroksipropilmetil celuloza itd. Sadržaj hidrogela kao čvrste materije je vrlo nizak (nekoliko procenata), tako da ćelije mogu lako da prodru u hidrogelne delove između granula. Drugi važan parametar je veličina keramičkih čestica koštanog supstituenta u pasti [23].

Biološki odgovor na paste koje sadrže nanometarske i mikrometarske čestice je drugačiji od odgovora kad postoje veće milimetarske čestice. Čestice manje od 5 μm mogu da prouzrokuju oštećenja. Zato treba biti oprezan kada se koriste takve čestice. Poslednje decenije aktuelna su istraživanja visokoresorbilnih koštanih supstituenata. Neki od ovih materijala, kao što je β-TCP, resorbuju se drugačije od gipsa i brušita, koji se resorbuju prostim rastvaranjem. U uslovima termodinamičke ravnoteže, rastvor dobijen rastvaranjem gipsa ima oko deset puta više kalcijuma nego serum telesne tečnosti. Serum uz to ne sadrži sulfatne jone. Kao rezultat rastvaranja gipsa dolazi do veoma brzog rasta kosti, koji je komplikovan fibroznim tkivom u oštećenim centrima.

U poređenju sa gipsom, brušit je za jedan red veličine manje rastvoran. U fiziološkim tečnostima on je slabo rastvoran. Pri rastvaranju brušit veoma brzo gubi svoju mehaničku čvrstoću, transformišući se u centru u apatit. Takođe, nastaje fibrozni deo između kostiju i resorbujućeg cementa. Ipak, taj deo iščezava kada apatit ostane u bloku cementne paste. Kako je apatit bazno jedinjenje, njegova precipitacija čini kiselijim okolni medijum. Takav cement izaziva reakciju u uslovima *in vivo* koja je tipična za brušitni cement kada se implantira u velikoj količini. Korišćenje brzoresorbujućih vrsta cementa vodi brzoj transformaciji koštanih oštećenja u zrelu kost, ali nosi i rizike negativnog biološkog odgovora i/ili veoma brzog iščezavanja iz implantirane zapremine oštećenja [8, 24].

ZAKLJUČAK

Fosfatni cement pokazuje izuzetnu raznovrsnost sa stanovišta hemizama reakcija koje vode njegovom očvršćavanju kroz procese hidratacije. On je i vrlo resorbilan, pa se zbog toga može koristiti kao zamena za kost. Njegove loše osobine vezane su prvenstveno za ponekad isuviše brzu resorpciju materijala i za nedovoljno adekvatnu mehaničku podršku sistemu kod kojeg se koristi kao implantat. Njegova primena kod ispuna zuba, reparacije oštećenih zidova zuba, reparacije dentina čak i u uslovima *in vivo* veoma je dragocena. Kombinacijom s različitim vrstama polimera i aditiva neke njegove osobine, kao što su brzina vezivanja i mehanička čvrstoća, mogu da se bitno unaprede, što ga čini veoma zanimljivim za primenu u različitim oblastima stomatologije.

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