

Review

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Review

Bioactive Calcium Phosphate Coatings for Bone Implant Applications: A Review

Richard Drevet ^{1,*}, Joël Fauré ² and Hicham Benhayoune ²

¹ Department of Physical Electronics, Masaryk University, Kotlářská 2, CZ-61137 Brno, Czech Republic

² Institut de Thermique, Mécanique et Matériaux (ITheMM), EA 7548, Université de Reims Champagne-Ardenne (URCA), Bât.6, Moulin de la Housse, BP 1039, 51687 Reims Cedex 2, France ; joel.faire@univ-reims.fr ; hicham.benhayoune@univ-reims.fr

* Correspondence: drevet@mail.muni.cz or richarddrevet@yahoo.fr

Abstract: This review article deals with the design of bioactive calcium phosphate coatings deposited on metallic substrates to produce bone implants. The bioceramic coating properties are used to create a strong bonding between the bone implants and the surrounding bone tissue. They provide a fast response after implantation and increase the lifespan of the implant in the body environment. The first part of the article describes the different compounds belonging to the calcium phosphate family and their main properties for applications in biomaterials science. The calcium to phosphorus atomic ratio (Ca/P)_{at} and the solubility (K_s) of these compounds define their behavior in a physiological environment. Hydroxyapatite is the gold standard among calcium phosphate materials, but other chemical compositions/stoichiometries have also been studied for their interesting properties. The second part reviews the most usual deposition processes to produce bioactive calcium phosphate coatings for bone implant applications. Plasma spraying is the main industrial process, but magnetron sputtering, pulsed laser deposition, electrospray deposition, electrophoretic deposition, and electrodeposition are also widely studied in academic and industrial research. The last part describes the main physicochemical properties of calcium phosphate coatings and their impact on the bioactivity of bone implants in a physiological environment.

Keywords: biomaterials; coatings; calcium phosphates; hydroxyapatite; bone implant; biocompatibility; bioactivity; hard tissue repair

1. Introduction

The ageing of the world population induces an increasing clinical demand for skeletal repair [1–6]. In particular, orthopedic and dental surgeries require metallic bone implants made of titanium alloys [7–16], iron-based alloys and stainless steel [17–21], or CoCr alloys [22–28]. The mechanical properties of these alloys are appropriate for load-bearing applications, and they are biocompatible with the body environment. According to the International Union of Pure and Applied Chemistry (IUPAC), biocompatibility is the *ability of a material to be in contact with a biological system without producing an adverse effect* [29–34]. Surface modification of these metallic bone implants with a coating is however necessary to make them bioactive in the body environment. Bioactivity is the *property of materials to develop a direct, adherent, and strong bonding with the bone tissue* [35–40]. Among the bioactive materials, calcium phosphates are the most usual in industry and academic research. They are ceramic materials with a chemical composition like that of bone mineral, the inorganic component of our bones [41–47]. Inside the body, their bioactivity confers long-term stability to the metallic bone implant. They prevent bone anchorage failure and delay revision surgery [48–52]. Several methods can be used to produce calcium phosphate coatings on metallic bone implants such as plasma spraying, magnetron sputtering, pulsed laser deposition, electrospray deposition, electrophoretic deposition, and electrodeposition [53]. Among them, plasma spraying is the main industrial process, extensively used since the 1970s to coat metallic bone implants [54]. Other deposition processes have been developed for decades, and their advantages and drawbacks are nowadays well-established. The properties of a calcium phosphate coating depend on the process used to produce it, and on the

experimental conditions and deposition parameters as well. They are of great importance because the modification of the coating properties may influence the surface bioactivity of the bone implant in a physiological environment.

After a presentation of the bioceramic compounds belonging to the calcium phosphate family, this review article describes the main deposition methods used to produce calcium phosphate coatings. The specific coating properties associated with each deposition process are reviewed. The last part describes the way the physicochemical properties of calcium phosphate coatings influence the bioactivity of the bone implant inside the body.

2. Calcium Phosphates

Calcium phosphate bioceramics are materials made of calcium ions (Ca^{2+}) and phosphate ions (H_2PO_4^- , HPO_4^{2-} , or PO_4^{3-}). Several compounds belong to this family, with different stoichiometries and different phosphate species. They are specifically identified in biomaterials science by their calcium to phosphorus atomic ratio $(\text{Ca/P})_{\text{at}}$ (Table 1).

Table 1. Calcium phosphates described in the literature as coatings for bone implants.

calcium phosphate	abbreviation	chemical formulae	$(\text{Ca/P})_{\text{at}}$	solubility [-log K_s]	references
tetracalcium phosphate	TTCP	$\text{Ca}_4(\text{PO}_4)_2\text{O}_2$	2.00	38.0-44.0	[55-57]
hydroxyapatite	HAP	$\text{Ca}_{10}(\text{PO}_4)_6\text{OH}_2$	1.67	116.8	[58-60]
α -tricalcium phosphate	α -TCP	$\alpha - \text{Ca}_3(\text{PO}_4)_2$	1.50	25.5	[61-63]
β -tricalcium phosphate	β -TCP	$\beta - \text{Ca}_3(\text{PO}_4)_2$	1.50	28.9	[64-66]
calcium-deficient apatite	Ca-def apatite	$\text{Ca}_{10-x}(\text{HPO}_4)_x(\text{PO}_4)_{6-x}(\text{OH})_{2-x}$ with $0 < x < 2$	1.34-1.66	85.1	[67-69]
octacalcium phosphate	OCP	$\text{Ca}_8(\text{HPO}_4)_2(\text{PO}_4)_4 \cdot 5\text{H}_2\text{O}$	1.33	96.6	[70-72]
calcium pyrophosphate	CPP	$\text{Ca}_2\text{P}_2\text{O}_7$	1.00	18.5	[73-75]
dicalcium phosphate anhydrous, aka monetite	DCPA	CaHPO_4	1.00	6.9	[76-78]
dicalcium phosphate dihydrate, aka brushite	DCPD	$\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$	1.00	6.6	[79-81]
monocalcium phosphate anhydrous	MCPA	$\text{Ca}(\text{H}_2\text{PO}_4)_2$	0.50	1.1	[82-84]
monocalcium phosphate monohydrate	MCPM	$\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$	0.50	1.1	[85-87]

The stoichiometry of a calcium phosphate coating affects its solubility in a physiological environment which is the first step involved in the bioactivity process after implantation (Figure 1).

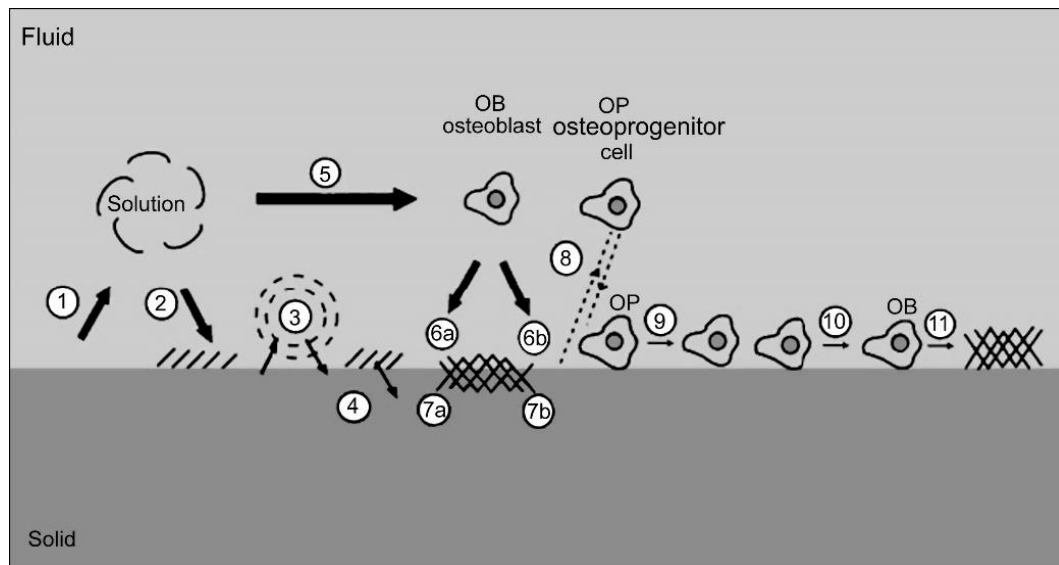


Figure 1. Schematic diagram of the events at the interface between a bioactive calcium phosphate coating (solid) and the surrounding physiological environment: (1) partial dissolution of the calcium phosphate coating; (2) precipitation from the solution; (3) ion exchange and structural rearrangement at the bioceramic/tissue interface; (4) interdiffusion from the surface boundary layer into the bioceramics; (5) solution-mediated effects on cellular activity; (6) deposition of either the mineral phase (a) or the organic phase (b) without integration into the bioceramic surface; (7) deposition with integration into the bioceramics; (8) chemotaxis to the bioceramic surface; (9) cell attachment and proliferation; (10) cell differentiation; (11) extracellular matrix formation. Reprinted with permission from Ref. [88].

The partial dissolution of the calcium phosphate coating in contact with the physiological environment induces ionic releases. The local concentrations of calcium and phosphate ions increase up to supersaturation which triggers the precipitation of biological apatite at the interface between the implant and the surrounding bone tissues [30,31,35–38]. After these first chemical steps, the biological steps start, involving bone cell attachment, proliferation, and differentiation. In the last step of the bioactivity process, the bone cells trigger the formation of the extracellular matrix (ECM) which is a three-dimensional network of macromolecules and minerals, such as collagen, enzymes, glycoproteins, and apatite [88–90]. The function of the extracellular matrix is to provide structural and biochemical support to the surrounding bone cells to promote their development [91]. Due to the bioactivity of the calcium phosphate coatings, bone-like apatite is formed at the interface between the bone implant and the bone tissue. This bone-like apatite layer is a direct, adherent, and strong bonding that results in the long-term stability of the bone implant inside the human body [92]. However, the success of the bioactivity process is related to several properties of the calcium phosphate coating and not only to the stoichiometry and solubility of the bioceramic material. The choice of the process and the experimental deposition conditions may influence many physicochemical properties of the calcium phosphate coating, and consequently the bioactivity process.

3. Deposition Methods

3.1. Plasma Spraying (PS)

Plasma spraying is the most widespread industrial process because it is remarkably efficient at producing large quantities of bioceramic coatings on metallic bone implants with good reproducibility. A calcium phosphate powder (generally hydroxyapatite) is injected into a plasma jet the temperature of which is thousands of degrees [93,94]. At this high temperature, the grains of powder are molten or partly molten. The plasma jet directs the molten powder toward the bone

implant surface where the steps of accumulation, cooling down, and solidification produce a coating (Figure 2).

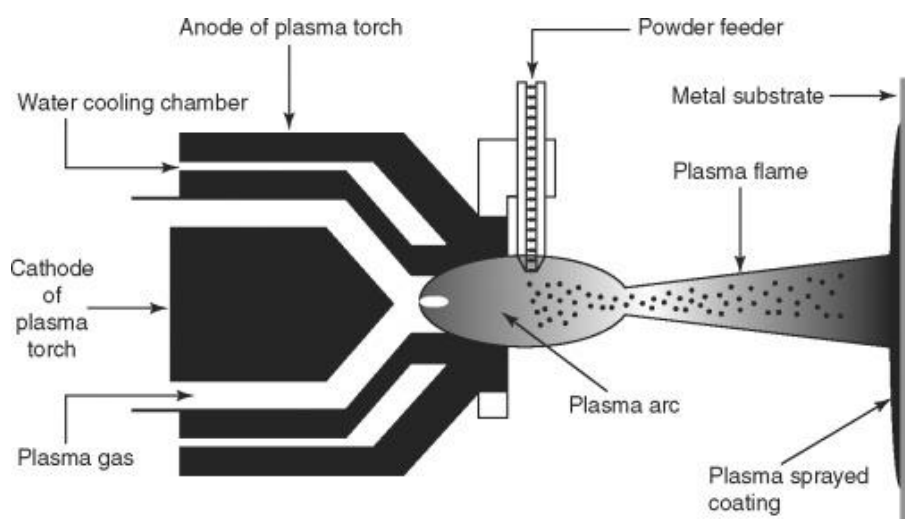
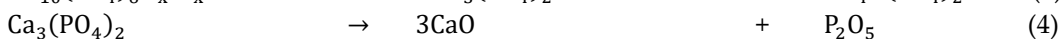
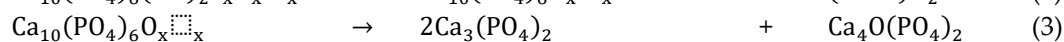
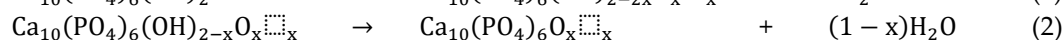
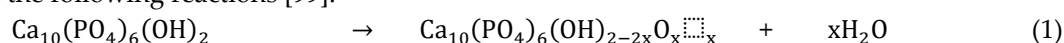


Figure 2. Schematic diagram of plasma spray deposition of calcium phosphate coatings. Reprinted with permission from Ref. [95].

However, the high temperatures of the process result in several issues. The calcium phosphate particles melt incongruently, locally resulting in structural modifications, uncontrolled phase changes, and chemical decompositions. These modifications produce a coating whose physicochemical and biological properties differ from those of the initial powder [96–98]. The thermal decomposition of hydroxyapatite within a plasma is comprehensively described by Heimann's works from the following reactions [99]:



As a function of the experimental parameters, these five reactions may occur during plasma spray deposition, where $\Box_x$ refers to lattice vacancies in the crystal structure of the calcium phosphate compound. The resulting bioceramic coating contains a mixture of oxyhydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_{2-2x}\text{O}_x\Box_x$), oxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{O}_x\Box_x$), tricalcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$), tetracalcium phosphate ($\text{Ca}_4\text{O}(\text{PO}_4)_2$), phosphorous pentoxide (P_2O_5), and calcium oxide (CaO) instead of pure hydroxyapatite as initially expected. All these additional phases affect the physicochemical properties of the coatings. Moreover, plasma spray deposition produces coatings with interconnected pores and cracks caused by imperfect melting of the particles, the insufficient flow of molten droplets in contact with the substrate, rapid solidification rate, and poor interlayer bonding [100,101]. The high temperature of the plasma induces a local melt-quenching of the particles that results in the amorphization of the bioceramics. The control of the chemical composition and structural properties of plasma sprayed calcium phosphate coatings is difficult. They are made of several phases in several crystalline states, resulting in a highly heterogeneous bioactive behavior in a physiological environment. Nonetheless, the process is efficient to reach industrial objectives, i.e., the production of large quantities of coatings at a low cost. The mechanical properties of the coatings are also satisfying, especially their hardness and long-term stability in normal storage conditions. The adhesion to the metallic substrate is generally high enough, even if many research works are still trying to find solutions to improve it more [102]. Adhesion is a key property of industrial calcium phosphate coatings whose value is standardized for the biomedical market (see section 4.5.).

Because plasma spraying has advantages and drawbacks, the study of alternative processes to produce calcium phosphate coatings for bone implant applications remains a major research topic for academic and industrial biomedical research.

3.2. Magnetron Sputtering (MS)

Magnetron sputtering of a calcium phosphate target is an alternative solution to produce bioactive calcium phosphate coatings on bone implants. Magnetron sputtering is a physical vapor deposition (PVD) process. A deposition chamber at room temperature is evacuated to high vacuum to remove all potential contaminants. After the base pressure has been reached, a working gas is injected inside the chamber, usually a noble gas such as argon. The resulting pressure is typically around 1 Pa. Plasma is then ignited from this noble gas by applying a voltage between the cathode connected to the target and the anode connected to the deposition chamber as electrical ground (Figure 3). The voltage necessary to start a discharge in a gas between two electrodes as a function of pressure and gap length is given by Paschen's law [103,104]. The process requires plasma ignition and a self-sustained discharge. Plasma contains high-energy ions that collide with the atoms of the target with enough energy to eject and transport them toward the surface of the bone implant to progressively form a coating [105].

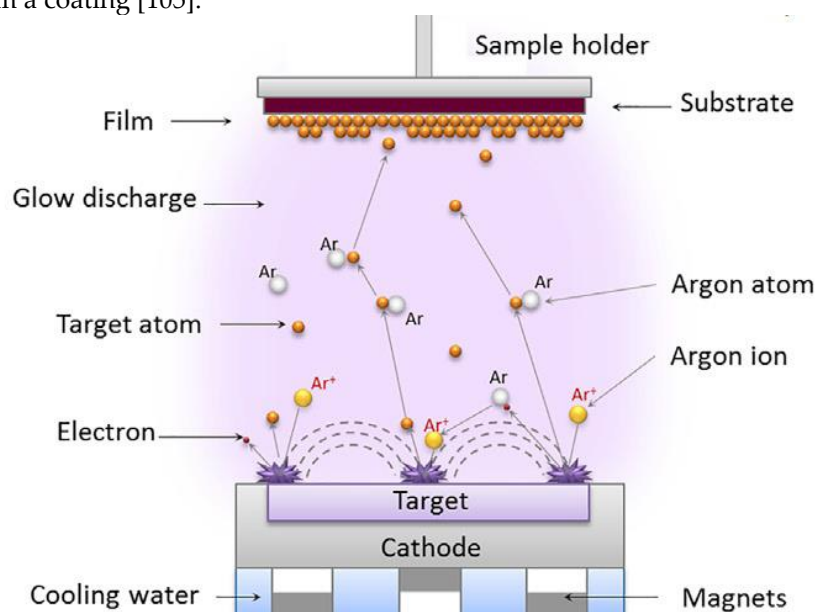


Figure 3. Schematic diagram of magnetron sputtering deposition of calcium phosphate coatings. Reprinted with permission from Ref. [105].

Direct current (DC) magnetron sputtering cannot be used to sputter insulating materials such as bioceramics because of the charge accumulation within the target during the process. Pulsed-DC or radio frequency (RF) magnetron sputtering are alternative solutions to deposit insulating materials [106–108]. They produce dense, uniform, and adherent calcium phosphate coatings. However, the different elements of a multicomponent target have different sputtering behaviors. The elemental stoichiometry of the deposited coating usually differs from that of the target. The experimental parameters of the process can be used to modify some properties of the deposited calcium phosphate coatings such as stoichiometry, morphology, and structure, resulting in different bioactive behaviors [109–111].

3.3. Pulsed Laser Deposition (PLD)

Pulsed laser deposition is another PVD process carried out in a vacuum chamber [112–114]. The ablation of a calcium phosphate target hit by a high-power laser produces a plasma plume made of ejected atoms, ions, and electrons (Figure 4). In contact with the substrate, the ejected material nucleates and grows to form a surface coating.

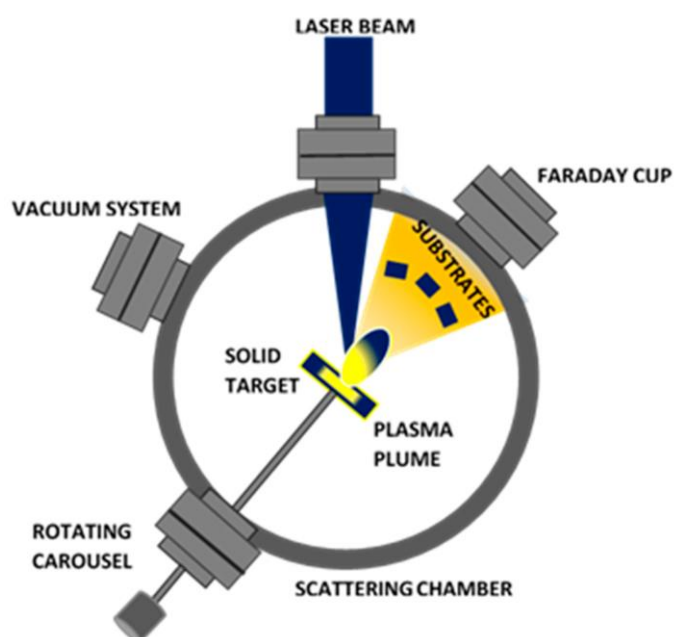


Figure 4. Schematic diagram of pulsed laser deposition of calcium phosphate coatings. Reprinted with permission from Ref. [115].

The efficiency of the process mainly depends on the laser properties such as wavelength, energy density, fluence, and pulse width. Pulsed laser deposition produces uniform and adherent thin coatings at a high deposition rate. However, as observed for magnetron sputtering, the elemental stoichiometry of the target and that of the deposited coating are not the same. The physicochemical and biological properties of the coating are impacted by the experimental conditions of the process [116–118].

3.4. Electrospray Deposition (ESD)

Electrospray deposition requires a precursor solution containing calcium and phosphate ions, or a suspension of calcium phosphate particles. The solution is sprayed by using a syringe through a nozzle that is connected to high voltage (Figure 5).

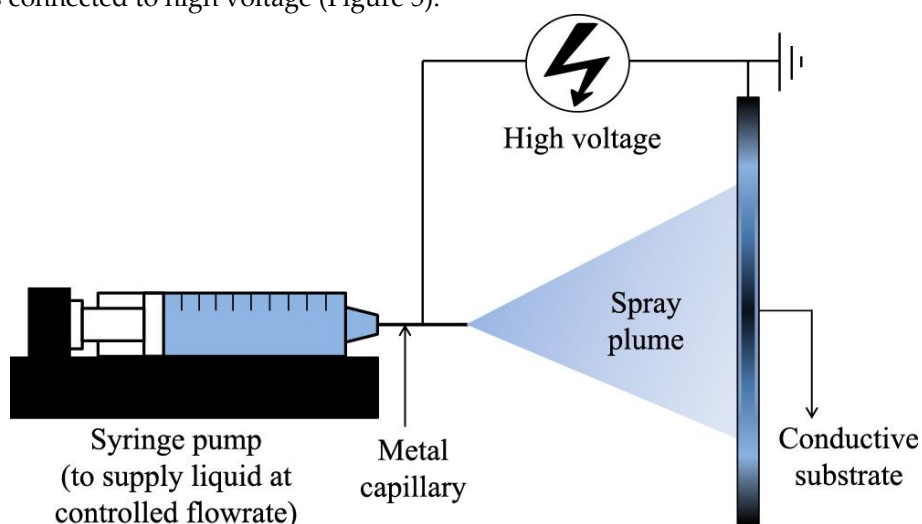


Figure 5. Schematic diagram of electrospray deposition of calcium phosphate coatings. Reprinted and adapted with permission from Ref. [119].

The droplets coming out of the tip of the nozzle are electrically charged. They travel toward the bone implant surface that is grounded and heated. In contact with the substrate, the droplets lose their surface charge and dry, progressively producing the bioactive coating (Figure 6).

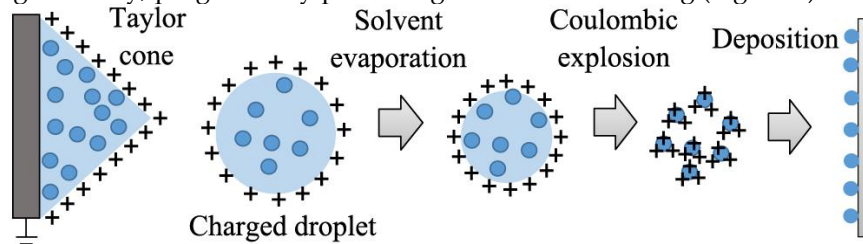


Figure 6. Schematic diagram of the droplets on their way from the tip of the needle to the substrate during the electrospray deposition process. Reprinted and adapted with permission from Ref. [119].

The morphological and structural properties of the coatings are impacted by the process parameters [120–124].

3.5. Electrophoretic Deposition (EPD)

Electrophoretic deposition occurs by the migration of calcium phosphate particles of a colloidal suspension [125–127]. In a solution, typically water or ethanol, the calcium phosphate particles carry a positive or negative surface charge due to electrostatic interactions with the ionic species of the solution. This surface charge induces the formation of a diffuse double layer containing anions and cations (Figure 7).

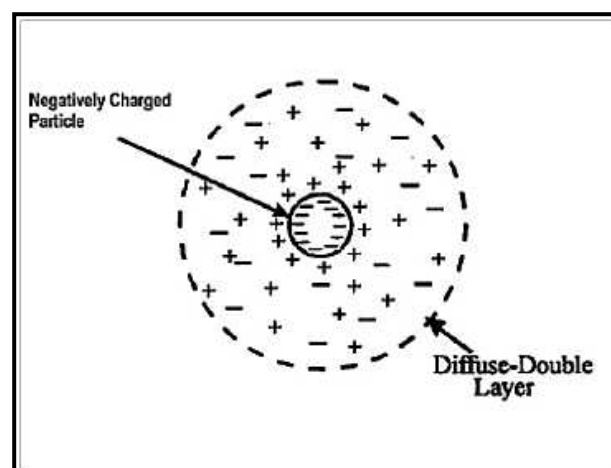


Figure 7. Model of the electric double layer of a negative particle in a solution. Reprinted with permission from Ref. [128].

The potential difference between the solution and the interface of the two layers is called zeta potential (ζ). This surface potential impacts the stability of colloidal dispersions by inducing electrostatic interactions between the particles of the suspension [128–134]. Thanks to zeta potential, the particles can be set in motion in the solution under the influence of an electric field between two conductive electrodes connected to a generator. If the particles are positively charged, they move through the liquid toward the cathode (cathodic EPD in Figure 8a). If the particles are negatively charged, they move toward the anode (anodic EPD in Figure 8b).

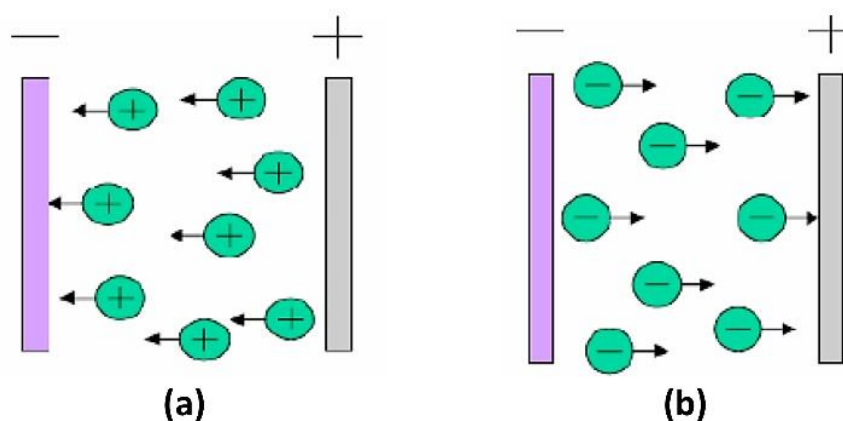


Figure 8. Schematic diagram of (a) cathodic EPD and (b) anodic EPD. Reprinted with permission from Ref. [128].

When a particle reaches the surface of an electrode, the size of the double layer is reduced (Figure 9a), promoting the progressive accumulation and coagulation of particles to form a calcium phosphate coating (Figure 9b).

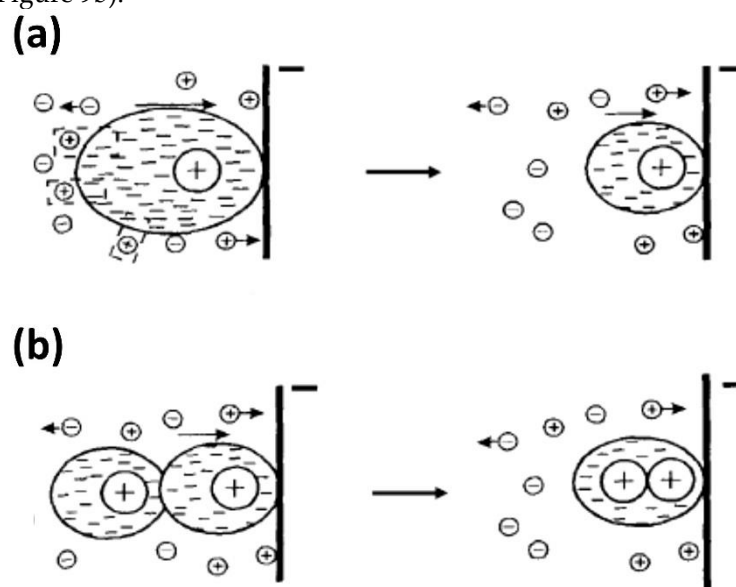


Figure 9. EPD coating formation model: (a) size reduction of the double layer, (b) coagulation of particles. Reprinted with permission from Ref. [134].

The main parameters for the success of the EPD process are the pH and the stability of the suspension, the dielectric constant (ϵ) and the viscosity (η) of the solvent, the average particle size, the substrate conductivity, the voltage, the distance between the electrodes, and the deposition time. Post-deposition thermal annealing is required to evaporate the solvent and to improve the cohesive and adhesive properties of the coating [135,136].

3.6. Electrodeposition (ELD)

Electrodeposition of calcium phosphate coatings requires two electrodes immersed in an electrolytic solution of calcium and phosphate ions. They are connected to a generator. The cathode is the negative electrode, and the anode is the positive electrode (Figure 10) [137–142].

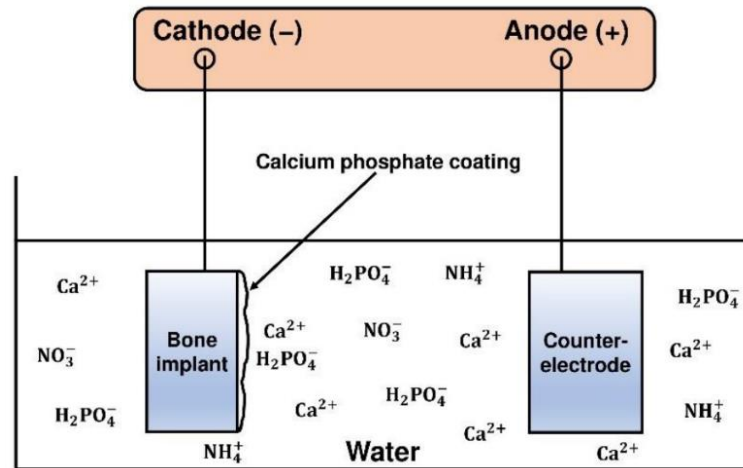


Figure 10. Schematic diagram of electrodeposition of calcium phosphate coatings. Reprinted with permission from Ref. [140].

Electrochemical reactions occur at both electrode-electrolyte interfaces. The reduction of water, the solvent of the solution, takes place at the cathode surface as follows:



If the solution is acidic, the reduction of protons may also occur at the cathode surface:



The resulting local pH variation triggers the precipitation of a calcium phosphate coating (Figure 11) [143–148].

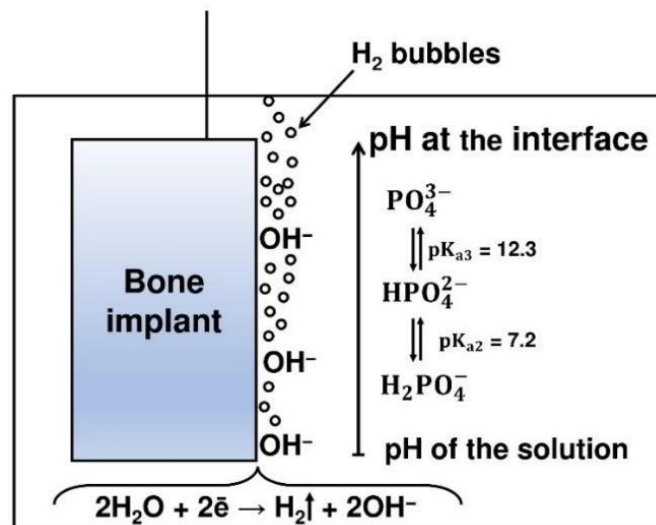


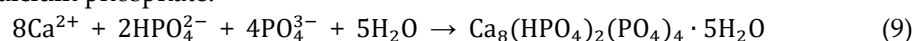
Figure 11. Schematic diagram of the cathode-electrolyte interface during electrodeposition. Reprinted with permission from Ref. [140].

The chemical composition and the stoichiometry of the precipitated coating depend on the pH value at the cathode which is impacted by the process parameters. The following phases can be obtained:

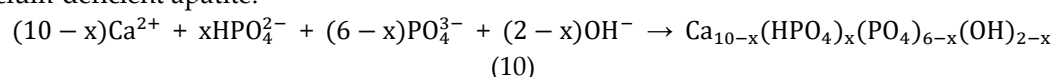
- dicalcium phosphate dihydrate (brushite):



- octacalcium phosphate:

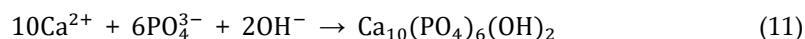


- calcium-deficient apatite:



with $0 < x < 2$

- hydroxyapatite:



The first experiments typically used direct current but pulsed current electrodeposition became more usual in the most recent years. The break times are used to reduce the negative effect of H_2 bubbles and to homogenize the electrolyte concentrations [149–153]. Ionic substitution of the electrodeposited calcium phosphate coating can be easily obtained by modifying the electrolyte composition. Due to the low temperature of the process, the addition of organic components (polymers, proteins, drugs, etc.) is also possible to improve the biological and mechanical performances of the electrodeposited coating [154–156].

4. Main Properties Impacting the Bioactivity of Calcium Phosphate Coatings

In addition to stoichiometry and solubility, several physicochemical properties impact the bioactivity of calcium phosphate coatings immersed in a physiological environment. Crystallinity, morphology, roughness, wettability, adhesion, and ionic substitution are the most important ones.

4.1. Crystallinity

The crystallinity of calcium phosphate coatings impacts their solubility in a physiological environment. The more crystallized, the more stable the coating is in solution [157–159]. Crystallinity can be controlled by post-deposition thermal annealing. The international standard ISO 13779-2 recommends a degree of crystallinity higher than 45 % for the biomedical market of bone implants [160]. However, as a function of the annealing temperature, several phases can form in addition to the calcium phosphate phases [161,162]. To maintain a low level of toxicity, the quantity of secondary phases (for example CaO) in the calcium phosphate coatings must be less than 5 wt.% [160]. The methods to determine the crystallinity of calcium phosphate coatings and the quantity of secondary phases are comprehensively detailed in the international standard ISO 13779-3 [163].

4.2. Morphology

The surface morphology of calcium phosphate coatings impacts the bone cells' attachment, growth, proliferation, and differentiation [164,165]. As a function of the deposition process and the experimental conditions, the surface morphology of the coatings can change [166,167]. Smooth surfaces are more efficient for bone cells attachment than sharp morphologies [168]. According to Cairns *et al.*, a regular smooth topography significantly promotes osteocalcin expression and alkaline phosphatase activity in comparison with sharp surfaces made of needles [169]. Osteocalcin and alkaline phosphatase are growth factors involved in the bone formation process by supporting bone cell growth [170].

4.3. Roughness

Bioactivity is a surface phenomenon impacted by the roughness of materials. High roughness of more than $2\text{ }\mu\text{m}$ is not appropriate because the long distances between valleys and peaks prevent the formation of osteoblastic pseudopodia required for bone cell adhesion [171–173]. Calcium phosphate coatings with roughness values in the range of 0.5 to $1\text{ }\mu\text{m}$ are generally described to be the most interesting to promote bone cell activity [174–176].

4.4. Wettability

Surface wettability is a key property of calcium phosphate coatings because the bioactivity processes occur in a liquid medium. Contact angle (θ) measurements are used to quantify the wetting behavior of a drop of physiological solution deposited on the coating surface [177–179]. As a function of the contact angle value, the surface is qualified as hydrophilic or hydrophobic (Figure 12).

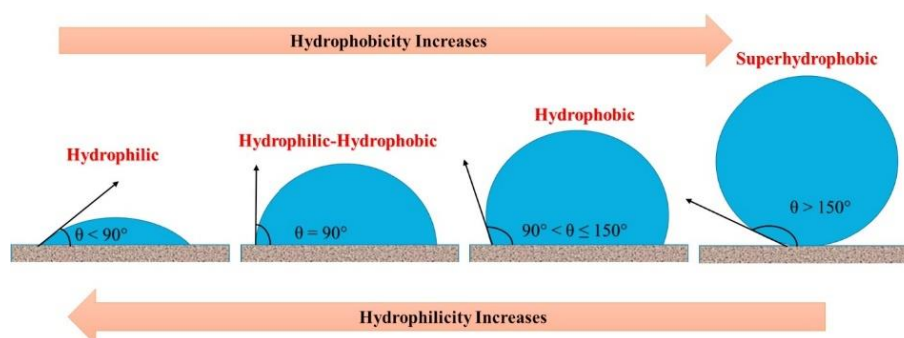


Figure 12. Surface wettability as a function of the contact angle measurement. Reprinted with permission from Ref. [180].

Biomaterials with hydrophilic surfaces are more interesting to promote chemical and biological interactions with the physiological environment [181,182].

4.5. Adhesion

Adhesion of calcium phosphate coatings is the main mechanical property for the biomedical market [102,183–187]. The value is determined by tensile adhesion measurements according to the international standard ISO 13779-4 [188].

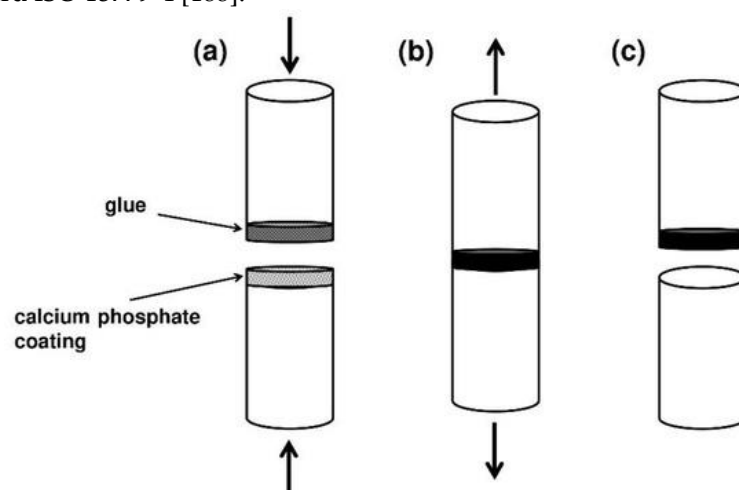


Figure 13. Schematic diagram of the standardized measurement of tensile adhesion. Reprinted with permission from Ref. [140].

The measurement requires a Ti6Al4V cylinder (25 mm in diameter and 25 mm in height) with one surface coated with calcium phosphate. The coated surface is pasted to another Ti6Al4V cylinder using adhesive glue (Figure 13a). The entire system is introduced inside a standard tensile machine where an increasing load is applied (Figure 13b) until the separation of the coating by breaking the interface with the initially coated cylinder (Figure 13c). Five measurements are necessary to obtain an average adhesion value. The bone implant industry requires adhesion values higher than 15 MPa [188].

4.6. Ionic Substitution for Biological Enhancement

The bioactivity and biological properties of calcium phosphate coatings can be improved by ionic substitution [189–199]. The objective is to release the substituting ions in the physiological environment after implantation, taking advantage of the dissolution process (see Section 2). Several ionic substitutions are described in the literature, using monovalent cations, divalent cations, trivalent cations, or anions. They are used for various biological or chemical effects described in Table 2.

Table 2. Ions used as substituents in calcium phosphate coatings.

Ions	Biological / Chemical effect	References
monovalent cations		
Ag ⁺	antibacterial activity	[200-202]
K ⁺	osteogenesis	[203-205]
Li ⁺	osteogenesis	[206-208]
Na ⁺	osteogenesis	[209-211]
divalent cations		
Co ²⁺	angiogenesis	[212-214]
Cu ²⁺	antibacterial activity	[215-217]
Mg ²⁺	osteogenesis	[218-220]
Mn ²⁺	osteogenesis	[221-223]
Sr ²⁺	osteogenesis	[224-227]
Zn ²⁺	osteogenesis/antibacterial/anti-inflammatory	[228-230]
trivalent cations		
Bi ³⁺	anticancer/antibacterial	[231-233]
Ce ³⁺	antibacterial	[234-237]
Er ³⁺	photoluminescence	[238-240]
Eu ³⁺	photoluminescence	[241-243]
Fe ³⁺	osteogenesis/anticancer/antibacterial	[244-246]
Ga ³⁺	anticancer/antibacterial	[247-249]
Tb ³⁺	photoluminescence	[250-251]
anions		
Cl ⁻	osteogenesis	[252-254]
CO ₃ ²⁻	osteogenesis	[255-257]
F ⁻	antibacterial	[258-260]
SeO ₃ ²⁻ /SeO ₄ ²⁻	anticancer/antibacterial	[261-263]
SiO ₄ ⁴⁻	osteogenesis	[264-266]

A few percent of these ions are generally used to produce substituted calcium phosphate coatings. Multi-substitution with several substituting ions is also described in the literature with the objective to cumulate the positive effects on the biological properties of bone implants [267–281].

5. Conclusions

This article reviewed the calcium phosphate compounds that are used as coatings to make the surface of metallic bone implants bioactive. The link between stoichiometry, solubility, and bioactivity of calcium phosphate coatings was explained. The main processes used in industry and academic research to design calcium phosphate coatings were described. Plasma spraying is historically the first industrial process, but interesting alternative methods were also described. The stoichiometry and the physicochemical properties of the calcium phosphate coatings depend on the deposition process and the experimental conditions used to produce it. The impact of the properties of the coating on bioactivity was described. Finally, the ionic substitution of calcium phosphate coatings was reviewed from the literature, including the biological enhancements provided by the ionic substitution.

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