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Review

Current Challenges and Innovative Developments in Hydroxyapatite-Based Coatings on Metallic Materials for Bone Implantation: A Review

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Abstract: Biomaterials are in use for the replacement and reconstruction of several tissues and organs as treatment and enhancement. Metallic, organic, and composites are some of the common materials currently in practice. Metallic materials contribute a big share of their mechanical strength and resistance to corrosion properties, while organic polymeric materials stand high due to their biocompatibility, biodegradability, and natural availability. To enhance the biocompatibility of these metals and alloys, coatings are frequently applied. Organic polymeric materials and ceramics are extensively utilized for this purpose due to their outstanding characteristics of biocompatibility and biodegradability. Hydroxyapatite (HAp) is the material from the ceramic class which is an ultimate candidate for coating on these metals for biomedical applications. HAp possesses similar chemical and structural characteristics to normal human bone. Due to the bioactivity and biocompatibility of HAp, it is used for bone implants for regenerating bone tissues. This review covers an extensive study of the development of HAp coatings specifically for the orthopaedic applications that include different coating techniques and the process parameters of these coating techniques. Additionally, the future direction and challenges have been also discussed briefly in this review, including the coating of HAp in combination with other calcium magnesium phosphates that occur naturally in human bone.

Keywords: hydroxyapatite; coating techniques; metallic biomaterials; current challenges; innovative method

1. Introduction

Titanium, stainless steel 316L, nickel-titanium, magnesium, and cobalt based metal alloys are broadly applied as orthopedic implants [1]. This is because of their higher mechanical strength, stability with wear, and corrosion resistance properties. The mechanical properties, advantages, and disadvantages associated with metallic implants are as shown in Table 1. On the other hand, all these metals or alloys, except magnesium, are considered biologically inert materials. Magnesium based alloys are considered to be as bioactive, biodegradable, and biotolerant for tissue engineering [2]. These metals and alloys are normally shaped as fracture plates, bones, hip nails, pins, wires, joint caps, and screws [3]. These implants are placed to hold the bones in place and help to promote osseointegration with bone tissue. Implants, used for tissue support, must be biocompatible and give clues to host cells to start a quick natural cell healing process [4]. Coatings on biomedical

implants are considered as a promising technique to enhance the implant-tissue interactions and promote their biocompatibility and biofuctionality without altering the material's properties [5,6]. Hydroxyapatite (HAp), calcium phosphate salts, and bio-active glasses are frequently used as a coating material. These materials come under the class of ceramics and possess superior chemical compatibility with physiological medium and stiff tissues, such as bones and teeth [7]. Additionally, these materials except bioactive glass show chemical and structural similarity with biological apatite [8,9]. There are different methods for the synthesis of HAp and the most common method is using pre-cursor hydrated calcium phosphate compound [10]. Werner was the first to name HAp in 1786 as a mineral. HAp is present abundantly on earth as a naturally occurring phosphatic compound. HAp has a very close link with natural bone in terms of composition and chemical formula. It is crystalline in nature with a density of 3.22 g/cm^3. Each unit cell of HAp consists of Ca, PO_4, and OH ions which are closely packed to form the apatite structure [11]. Carbonated calcium-deficient HAp is a major part of dental enamel and dentin [12]. Hydroxyapatite contains calcium and phosphorus in a molar ratio of 1.67. This solid apatite is mainly stable due to calcium phosphate salt at ambient conditions and a wide range of pH ranging from 4 to 12. The HAp properties vary greatly with the change of chemical composition, crystallinity, size, and shape of the HAp crystals [13,14]. HAp nanoparticles possess excellent mechanical properties along with higher activity and resorb ability in comparison with bulk HAp [15]. This is because of the higher surface energy possesses by HAp nanoparticles [16]. These and other important properties make HAp the most important candidate for the coating of orthopedic implants.

Table 1. Mechanicalproperties, advantage and disadvantage of metallic implants [17,18].

Metals	Density (g/cm^3)	Elastic Modulus (Gpa)	Advantage	Disadvantage
Stainless steel 316 L	8	193	• Good corrosion and wear resistance	• High Elastic modulus • Hinder bone regeneration due to high modulus
Titanium (Ti-6Al-4V)	4.4	110	• Higher biocompatibility and osseointegration in comparison to others • Excellent tensile strength, fracture toughness, and fatigue stress	• Cytotoxic due to the presence of V and Al • Low corrosion and wear properties as compared to other metals but superior than Mg • Higher in cost
Co-Cr alloys	9.2	210	• Highest strength among all the metallic implants	• Cytotoxic due to Co, Cr, and Ni • Low corrosion, wear and friction resistance
Mg	1.74	41–45	• Posseses similar properties like natural bone • Minimize stress shielding effect • Easy to synthesize into complex shapes • Light weight to support for load bearing applications • Mg^{2+} ions essential for human metabolism &provide stimulatory effects for bone regeneration	• Very low corrosion resistance • Release of hydrogen gas • Premature loss of mechanical strength

HAp can be coated on metallic implants using various coating techniques [19]. The non-bioactivity factor of metals can be easily compensated by using HAp. The metallic implant with HAp coating supports new bone development due to strong interface between the coating and host tissue [20]. Additionally, HAp coating also acts as a corrosion control film against aggressive body fluids. This HAp film also retards the dissolution rate of metallic ions thus minimizing chances of leaching [21]. Several coating methods are available for the deposition of HAp on metallic implants. These methods include sol-gel, dip coating, electrochemical deposition, chemical vapor deposition, thermal spraying, radio frequency (RF) magnetron sputtering, micro-arc oxidation (MAO), high-velocity suspension flame spraying (HVSFS), plasma spraying, and pulsed laser deposition (PLD) [22]. Thermal spray coating is the most efficient and commonly applied nowadays on metallic implants due to its uniform coating layer on the metal surfaces [23].

The major concern during the coating process of HAp is the poor binding of HAp on the metallic surface. This is due to the low adhesive bond between metallic load-bearing sites and HAp film [24]. HAp film linkage on the metallic surface starts to reduce and suddenly fails, due to the poor crystalline nature of HAp [25]. This failure results in the discharge of metallic ions as the metal surface starts to expose against the body environment [26]. To enhance the adhesion of HAp films, surface modifying agents are required, which assist in the formation of durable film over the metallic surface. HAp is the major inorganic ingredient of hard tissues (bones) and has been applied in biomedical applications for the last 50 years due to its biocompatibility. On the other hand, previously reported studies revealed that HAp offers the properties of ceramics that are brittle and unable to withstand load [27]. As a result of previous studies, HAp was selected as a bioactive coating material for enhancement of mechanical properties. This coating supports the damaged tissue to heal quickly due to its bioactivity [28]. Few research studies have been carried out using a mixer of HAp and other mineral compounds to form composite materials with better mechanical strength [29]. Witte et al. developed a metallic composite using AZ91 magnesium alloy with HAp particle as reinforced filler in a metallic matrix [30]. Mechanical properties of composite materials are highly dependent on HAp particle size. The chitosan (CS) blend with HAp is also examined for biomedical applications. The majority of the research has been carried out to check the adhesive bond between HAp/CS film and metallic surface. The HAp/CS film is much stronger as compared to a single HAp film. The composite coating offers more bioactivity and biocompatibility than HAp film due to the presence of active agent calcium silicate which generates porosity with HAp on film surface [31].

The pros and cons of different techniques used for HAp coating on metallic bio-implants are depicted in Table 2. Conversely, this detailed article covers the regularly used technologies for HAp coating. These coating methods include sol-gel, dip coating, electrodeposition, plasma spraying, chemical vapor deposition, and pulsed laser deposition. This review thoroughly explains the raw materials, coating methods, thickness, and process parameters used in the above-said coating techniques.

Table 2. Pros and Cons of Different Coating Techniques.

Methods	Coating Layer Thickness	Pros	Cons	References
Sol-Gel	<1 µm	• Mild reaction conditions • Cheap method • Smooth coating layer • Higher purity of coating film • Easily process complicated structures	• Few reactions need closed environment • Requires costly chemicals	[32–38]

Table 2. *Cont.*

Methods	Coating Layer Thickness	Pros	Cons	References
Dip coating	0.05–15 mm	• Cheap • Easy to apply • Easily process for complicated structures • Uniform Coating Layer	• Requires high finishing temperature • High temperature damages coating film	[39–47]
Electro-chemical deposition	0.05–0.5 mm	• Economical process • Easy process for complicated substrates • Uniformity of coating film	• Weak bonding between HAp film and metallic surface	[48–51]
Electro-phoretic deposition	0.1–2.0 mm	• Uniformity of coating layer • Easy coating process for complicated substrate • Coating rate is high	• Post treatment of coating at higher temperature • Cracks develop at low temperatures	[52–55]
Bio-mimetic coating	<30 µm	• Lower reaction temperature • Easily process complex shapes	• Time taking process • Needs constant pH system • Require solution makeup	[56]
Plasma spraying	<20 µm	• Low-cost process • Fast coating • Smooth coating layer • Interconnected pores for multilayer coatings	• HAp film density fluctuates that effects uniformity • Expensive Equipment • Higher processing temperatures initiates grains formation • Poor bonding of HAp film and metal surface	[57–64]
Sputter coating	0.5–3 µm	• Thick HAp coating layer • Best for flat substrates • Good bonding of HAp film and metal surface	• Lengthy coating process • Expensive method • Unable to process difficult shapes • Amorphous coating layer	[59,65]
High-velocity suspension flame spraying (HVSFS)	≤50 µm	• Uniform coating layer • Economical process • No post treatment required • Nanometric Porosity	• Requires higher temperatures	[66–68]
Pulsed laser deposition	0.05–5 µm	• Versatile method(dense or porous)/(Crystalline or amphorphous) • Uniform coating	• Costly process • Pre-treatment of sample required • Line of sight technique	[69–71]
Hot iso-static pressing	0.2–2.0 mm	• Uniformity of coating • Processes all shapes(substrates)	• Expensive process • Requires high temperature	[72,73]
Flame spraying	100–250 µm	• Most economical among all thermal spraying techniques • Easily adaptable • Porous coating	• Requires post treatment • Crack develop at lower temperatures • Microstructure consists of melted particles	[74,75]

2. Theory of Adhesive Bond

The functionality and strength of coating layers on metallic substrate depend upon two fundamental characteristics i.e., cohesion and adhesion [76]. Adhesion is attractive force between various layers that hold the two surfaces. This force resists the applied stress to separate the two surfaces. Cohesion is the internal attractive force between molecules of a coating film. This force is responsible for holding the coating film bonded together as shown in Figure 1 below. The adhesion and cohesion forces between adhesive and metallic substrate are seen in Figure 1A,B respectively.

Figure 1. (**A**) adhesion and (**B**) cohesion forces between the adhesive layer and substrate [77].

The adhesive force between metallic substrate and adhesive is classified into three types (i) specific adhesion, (ii) mechanical force, and (iii) efficient adhesion [78,79]. The specific adhesion arises due to the presence of attractive forces between dissimilar molecules whereas mechanical adhesion is associated with forces present due to penetration of adhesive inside the microstructures of a substrate. At the same time, specific adhesion and mechanical adhesion combine to yield adhesion that holds the substrate and coating layer. The efficiency of this adhesion is dependent upon adhesive and cohesive forces. The adhesive layer failure results due to the breakage of the bond between the adhesive layer and substrate [80].

Theory behind Adhesion

Adhesives are non-metallic compounds used to bind two surfaces that hold them together and counter their separation. The application of adhesive offers several advantages, including stress distributions, ease in processing, aesthetic, and low processing costs. This adhesive penetrates down through micro-channels of a substrate and joins the two surfaces with strong binding force [81]. When different surfaces are bind with the help of adhesives, many other forces also act on these layers. These forces include physical adsorption, mechanical interlocking, and chemical forces. Adhesives are classified into two major classes named reactive and non-reactive adhesives. In the reactive class, the adhesive reacts with the surface molecules and forms a hard layer. The adhesive layer sticks to the surface of the substrate due to hydrogen bonding between substrate and adhesive. This transfer of hydrogen gives rise to electrostatic forces of attraction which are associated with the progression of Van der Waals forces between the molecules. The coating material and substrate are chemically interlinked with each other. The strength of these chemical bonds is very high, which resists the deterioration of coating against the external environment. The rough surface enhances the interfacial area for better contact between adhesive and substrate. To obtain maximum results from adhesive, the adhesive must possess wetting properties so that it can completely wet the surface. After application, it completely dries out and boosts its strength so that it shares and transmits the load between the adjacent layers [81–83].

3. Existing Challenges in Coating for Metallic Biomaterials

The adhesion of adhesive on the substrate will decide the surface and mechanical properties of metals used for biomedical applications. The improper coating on the substrate due to variation in process parameters increases the chances of sudden collapse when used as the bone supporting implants [84,85]. The poor coating layers will exfoliate and create serious effects during the tissue healing process. The coating pieces will leave the surface due to poor strength and affect the surrounding body parts [86,87]. The coating on metallic substratesis widely used to make it bio-compatible and bio-active. The crystalline nature of HAp offers better mechanical behavior against load and stress. Stability of HAp film is the biggest challenge in these coating implants. The complete degradation of the HAp occurred within the period of 4–5 years by natural cell mechanism with assistance of body environment like pH, water content and osteoclast cells. In vivo degradation of HAp can be started by dissolution or cell mediation. The speed of degradation also depends upon the chemical properties of HAp, Ca/P ratio, crystal size, crystallinity and porosity [88]. After this time, the malfunction (dissolution) can take place starting from the surface and penetrates down to the metallic substrate. Thus, stable HAp film will provide a reliable metallic implant for load-bearing applications. Operational difficulties during the

coating process also create problems for successful HAp coating with uniformity on metallic implants. The porosity and development of cracks on the coating surface is also an issue for the biomedical implant. Porosity is a very important parameter to judge the quality of ceramic coatings on biomedical implants. The porosity in coating layers dictates its bioactivity for biomedical implants. HAp offers more bioactivity and biocompatibility due to the presence of active agents calcium and phosphate which are in a similar ratio with human bone minerals [89,90]. Further enhancement of adhesive strength can be achieved by increasing the surface roughness and pores. For the further enhancement of bioactivity, the porous implants coated with HAp provide dual benefits. These implants have Young's Modulus closer to that of bone addressing the stress shielding effect and the increased surface area coated with Hap for good osseointegration [91,92]. A stress shielding effect arises when the modulus of the implant is greater than the young's modulus of bone. The support of the implant to the damaged bone is reduced as a result of this phenomenon. Due to this, the loads are taken up by the implant and shielded from going to the damaged bones [93]. According to Wolff's law, a bone developed its structure depending upon the force applied to it. The area of bone which experiences higher load will result in increasing bone density and vice versa. The decrease in bone mass results in the loosening of the implant [94]. Porous coating for bone regeneration allows the migration and proliferation of osteoblasts cells as well as vascularization. Additionally, the pores on the surface facilitate better mechanical interlocking between implant and bone. This interlocking provides higher mechanical stability which also reduces stress shielding [88]. Most pores are open and interconnected with each other. In vivo tests have shown that the pores facilitate cell migration, tissue growth, and transport of waste products [95].

4. Coating Methods

4.1. Sol-Gel and Dip Coating

Up till now, a lot of research work has been carried out using sol-gels and their application on metallic implants using the dip-coating technique. The coatings obtained by this technique possess the highest adhesion strength among all available technologies [42,96,97]. The success of the sol-gel method is due to the possibility of fabricating a wide range of materials, giving them a controlled porous microstructure [92]. The precursor mostly used for sol-gel preparation includes both calcium and phosphate-based salts. The universal solvent water and ethanol are commonly utilized for sol-gel synthesis [98–100]. Organic phosphorus compounds are dissolved in ethanol whereas in most of the cases, water is employed during sol synthesis [101,102]. The phosphorus solutions are mixed slowly with the calcium salt solutions drop wise [103,104]. Calcium nitrate salt is mostly utilized as a calcium source in HAp. Both solutions prepared separately are mixed and heated at various reaction temperatures. The sol-gel suspensions are prepared with the help of evaporation of excessive solvent present in the solution mixture. After evaporation of the solvent, the viscosity of the mixture increases to give a thick solution [105].

The apatite phase formation and nature of sol-gel are highly dependent on the type of salts used containing calcium and phosphorus and operating temperature. After evaporation, aging, drying and high-temperature calcination process are being applied to form sol-gel.

The sol-gel technique is well accepted and widely used due to its simplicity and cost-effectiveness. The superiority of this process over others is that it is capable to coat shapes with difficult geometrical symmetries. Additionally, it can offer greater coating strength along with higher adhesion [96,106,107]. The dip-coating technique is coupled with sol-gel to create a uniform coating layer on metallic bio-implants. Dip coating technique comprises of three-unit operations starting from (i) dipping step; (ii) removal step; (iii) drying period as shown in Figure 2.

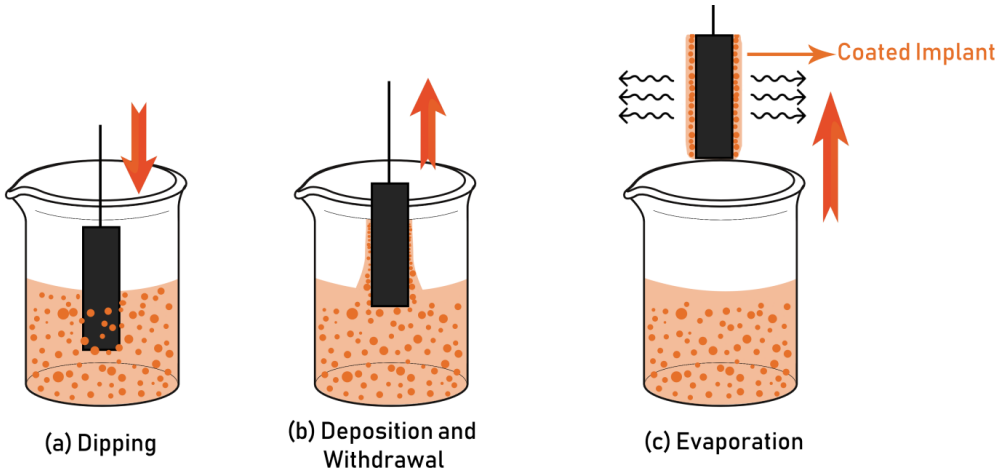

Figure 2. Schematic of Dip coating Process.

Dip coating possesses several characteristics including ease in processing, uniform coating layers, lower operating temperatures, cost-effective and process complex assemblies [108,109]. In this technique, the metallic substrate is immersed in the prepared HAp solution ata constant speed. After a fixed time interval of dipping the metallic substrate, pull out of the coating solution. The coating thickness is a function of speed, concentration of sol-gel, number of dips, and time of dipping. This method has good control over HAp film thickness [110,111]. HApcan be used single as well as with other polymers by making different blends. Several researchers used poly-(ε-caprolactone) (PCL) with a wide range of compositions ranging from 0–50 wt % with HAp. After preparation of coating solution, the metallic substrate is immersed in the HAp/PCL blend for 5 times at a rate of 200 mm/min [111]. Application of PCL promotes pore formation on the coating surface which enhances osseointegration that requires during the bone healing process. The research study shows that a 30/70 blend of PCL/HAp on Ti6Al4V metallic implant created a thick layer with even uniformity of 184 µm. On examination, the growth of cracks on the exterior layer of HAp were reduced which enhanced the adhesive force between metallic implant and HAp coating. The amount of cracks is directly linked with wear and corrosion resistance of metallic implant. Fewer the cracks greater will be the wear and corrosion resistance of implant. These cracks promote leaching of metals ions especially nickel and chromium into body thus cause harmful effects inside body including development of tumor and cancers [112–114]. After dip coating of synthesized HAp, heat treatment of coated implant is done for curing and to enhance its strength & density [113,115]. Heating of synthesized HAp at higher temperatures favored the removal of water content and promotes the formation of apatite structure within the coating layer. Various studies reported that the temperature of heat treatment ranging from 25–400 °C to maintain the surface textures and avoid the destruction of HAp structure [116–118]. Another research was carried out using 316 L stainless steel as an implant material. After application of <1 µm thick HAp coating, the material properties were enhanced. The annealing temperature of the coating ranged from 375–400 °C [36]. The coating on the implant possesses a bonding strength of 44 MPa upon testing. Further enhancement of adhesive strength can be achieved by increasing the surface roughness and pores. The combined arrangements of sol-gel and dip coating techniques are extensively used due to their simplicity, compatibility, and low cost to prepare bio-compatible implants. By comparing factors including coating time and shapes limitations is less for dip coating. Coating time is very less while dip coating can process irregular geometries. Another major advantage of this process is its mild operating conditions during coating. Moreover, sol gel and dip coating techniques yield uniform& thick HAp layer and better Ca/P ratio (1.67–1.76) in comparison to all available processes. Table 3 shows different raw materials and operating parameters used for the synthesis of sol-gels.

Table 3. Literature related to Sol-gel HAp Coating.

Sr.No	Precursor for Sols and Other Materials	Solvent	Implant Metal	Operating Conditions	Outcome	Year	References
1	Triethylphosphite and calcium nitrate	Water	Stainless steel 316 L	• Drying of coating at 80 °C for 15 min • Annealed at 375 °C, 400 °C, and 500 °C in air • Dipping speed 5 cm/min.	• Annealing at 500 °C for 15 min leads to development of nano crystals and micro-cracks. • Nano-cracks behave like natural bio-crystals	2002	[36]
2	Titanium propoxide, Di-ethanolamine, Calcium nitrate, tetrahydrate and Triethylphosphite	Water and ethanol	Titanium	• Temperatures of 400–500 °C. • Thicknesses of 800 and 200 nm.	• Enhancement of bioactivity and osteoconductivity of Ti Implant	2004	[119]
3	Calcium nitrate tetra-hydrate, Tri-ammonium phosphate tri-hydrate and Gelatine	Water	Titanium	• Reaction at room temperature • pH 6.0–7.8. • Annealed at 460–750 °C in argon media	• Bioactivity increases after application of coating	2005	[37]
4	Calcium Nitrate, Strontium Nitrate and Phosphoruspenta oxide	Ethanol	Titanium	• Dipping Speed of 8 cm/min. • 15 min drying at 150 °C • 15 min firing at 700 °C	• 10% SrHAp coating yields enhanced osseointegration compared to HA. • The bone area ratio and bone-to-implant • contact increased by 70.9% and 49.9%	2010	[41]
5	Triethylphosphite and Calcium nitrate	Water, Acetone, Ethanol	Nickel-Titanium Alloy	• Dipping time rinsed 5 min • Withdrawn speed of 20 mm/min • Drying at 80 °C • Annealing in air at 450 °C for 2 h.	• Rate of Ni ion release decreases through the Hap coatings	2011	[42]
6	Calcium nitrate Tetra hydrate, phosphorous penta oxide	Ethanol	Magnesium AZ91	• Reaction Temperature at 26 °C for 5 h • Withdrawn speed 0.1 mm/s • Drying at 60 °C for 24 h • Calcination and sintering at 400 °C for 6 h	• HAp coating stabilizes alkalization behavior • Improved corrosion resistance	2013	[44]
7	HAp Nano-particle	-	Titanium	• Heat treatment at 550 °C for 5 min in air • Nanoparticle stabilization at pH = 9	• Nano HAp coating has higher impact on earlier healing periods • Micro structures are more influential at completely healed stages	2013	[43]
8	Titanium isopropoxide, Calcium acetate monohydrate,1,2-ethandiol, poly vinyl alcohol, Triethanol amine and ortho phosphoric acid	Water	Titanium	• Reaction temperature 65 °C • Initial heat treatment at 650 °C for 5 h • Coated samples annealing at 650 °C for 5 h	• Increasing HAp layers enhances hydrophilicity • Initial heat treatment enhances HAp layer adhesion	2016	[120]

4.2. Biomimetic Deposition

The biomimetic method constitutes of mimicking natural building processes of bone. In this way, HAp can be used to enhance the osseointegration of natural bone and coated artificial implant [121,122]. The biomimetic coating process promotes the adhesion and proliferation of osteoblast cells, as it mimics the properties of natural bone tissues. A biomimetic method like other chemical coating processes needs the presence of hydroxyl groups on the surface of the implant. This functional group can easily attach with the pre-treatment step using acid or alkali. These functional groups on the substrate surface facilitated the CaP nucleation process with succeeding crystallization to promote apatite formation. The biomimetic coating processes occurred at normal conditions of pH and temperature [123–126]. Figure 3 below shows a biomimetic coating in SBF. Table 4 shows different raw materials and operating parameters used during the biomimetic coating.

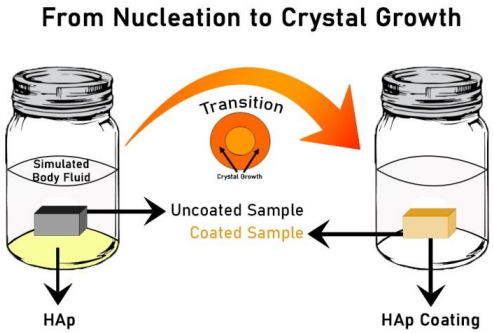

Figure 3. Biomimetic coating using HAp in Simulated body fluid (SBF).

Table 4. Raw materials and operating parameters for biomimetic coating.

Sr.No	Coating Material	Solvent	Implant Metal	Operating Conditions	Outcome	Year	References
1	Calcium phosphate, Tobramycin	Water	Titanium alloy	• 37 °C • 24 h • pH 5 or 7.3	• Coating containing antibiotics prevent post-surgical infections.	2002	[124]
2	Calcium phosphate	Water, Human blood plasma (HBP), Simulated body fluid (SBF)	Titanium and tantalum	• Temperature37 °C • 24 h • Stirring rate 250 rpm • pH7.1	• Biomimetic coating facilitated rapid bone formation around the implant • Reducing recovery time after surgery.	2004	[127]
3	Calcium phosphate, $CaO–SiO_2$ based glass	Water, Simulated body fluid (SBF)	Titanium	• Method-1 the metallic sample was placed on glass particles and soaked in SBF at 37 °C in a glass container for 6 days. The sample was immersed thereafter in SBF for 10 days • In method-2, the sample was directly immersed in SBF solution at 37 °C and examined up to 13 days.	• Thickness of coating was found to increase with the increase in immersion time. • The use of glass did not help the formation of apatite • The coating obtained by this method was also not uniform.	2005	[125]
4	Sodium hydroxide, Calcium phosphate,	Water	Titanium	• Surface activationin 10 M NaOH • Room temperature • Voltage of 10 V • Time 30 min. • pH > 7	• Coating thickness50µm was achieved • Coating promote bone in growth	2008	[128]
5	Hydroxyapatite and tri-calcium phosphate	Water	Titanium alloy	• Mix the solution well for 2 h • Stirring speed 700 rpm • Temperature 37 °C	• An adequate and uniform hydroxyapatite coating on pure titanium substrates in a shorter period of time • Coating promotes osseointegration.	2015	[129]

4.3. Chemical Vapor Deposition

Chemical vapor deposition (CVD) is a coating technique that uses volatile precursors to coat pre-heated substrates via reaction or decomposition on the surface as shown in the Figure 4 [130,131]. CVD is widely used to coat metal implants with HAp and calcium phosphate-based coating [132]. The most promising feature of CVD is that it can control the crystal phases and micro-structures formation during coating. Additionally, it can able to coat complex metallic shapes with uniform coating [131]. Table 5 below shows different raw materials and operating parameters applied during CVD.

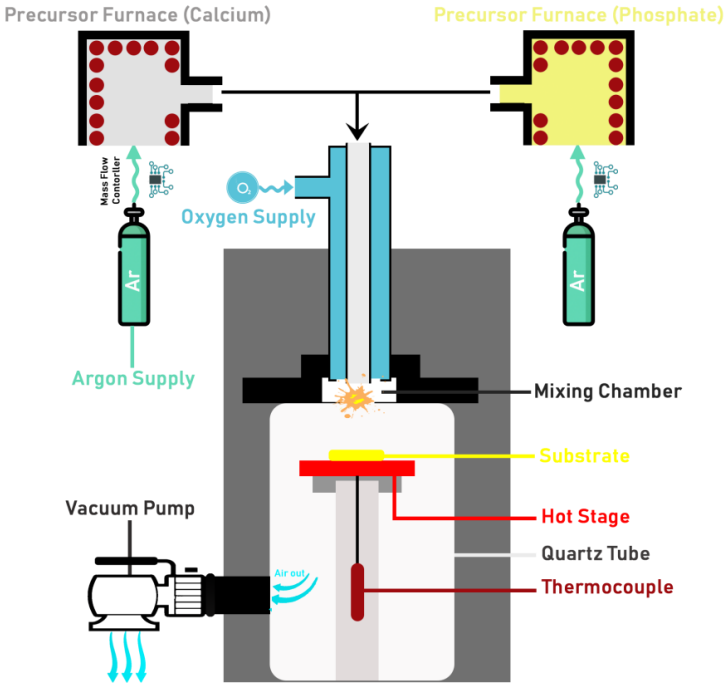

Figure 4. Schematic of HAp coating using Chemical Vapor Deposition (CVD).

Table 5. Material and operating parameters for CVD.

Sr.No	Precursor	Carrier Gas	Implant Metal	Operating Conditions	Outcome	Year	References
1	Calcium diketonate and tri-methyl phosphate	Oxygen	Titanium	• Temperatures from 500 °C to 650 °C • Pressure 10 Torr • Growth rate 15 nm/min • Thickness range from 0.1–1 micrometer	• HAp coatings with Ca/P ratio of −1.67 were amorphous. • Coatings with Ca/P ratio of 1.5 ± 0.5 and 1.0 ± 0.5 were crystalline. • Coatings were very dense and free of cracks.	1998	[133]
2	Fluorine-containing carbonated hydroxyapatite, 2,2,6,6,-tetramethy lheptane-3,5-dione	Argon	Titanium	• Substrate temperature 600 °C • Post heat treatment in air at 800 °C for 3 h	• The coating has a cauliflower-like agglomerated structure and composition with some similarities to human bone mineral	2004	[134]
3	Calcium dipivaloylmethanate and Titanium di(i-propoxy)bis (dipivaloylmethanate)	Argon	Titanium	• Pressure 0.8 kPa • Deposition temperature 873–1073 K • Deposition time 0.3–0.9 ks	• The coating was affected by substrate temperature	2007	[135]
4	Bis-dipivaloy lmethanocalcium and Triphenyl Phosphate	Argon	Titanium	• Pressure 800 Pa • Deposition temperature 973 K	• HAp-coated excellent mechanical biocompatibility	2010	[136]

4.4. Electro-Chemical Deposition

The most commercially adopted coating technique is Electro-chemical deposition for biomaterials [113]. Electro-chemical deposition uses charges associated with two-electrode systems i.e., anode and cathode as shown in Figure 5. The effectiveness of this process is the combination of both anodic and cathodic coating. A single coating layer by anodic deposition is unable to meet the requirement of small-sized structures on the surface of metallic implant. To minimize the defects cathodic deposition is mostly applied on a commercial scale for coating bio-implants [137,138]. Two operational methods come under the umbrella of electro-chemical deposition, i.e., (1) the electrophoretic procedure (EPD), and (2) the electrolytic procedure (ELD). EPD uses suspended ceramic particles whereas ELD utilizes metallic salts from saturated salts solution. Titanium implants are mostly employed in coating process using ELD or EPD techniques [139,140]. Applied voltage and deposition time are important factors in this type of coating [141]. The process starts after HAp precursor salts are dissolved in water which acts as an electrolyte [142,143]. One of the salient features of this method is the capacity to produce thick uniform coating along with high production rates [144–146]. Lower operating temperature is mostly used during process whereas energy consumptions are normally on higher side due to involvement of electricity. Many researchers worked on the electro-chemical deposition of HAp on metal implants as tabulated in Table 6. By this technique, a homogenized layer of HAp formed on the metal surface with higher force of adhesion.

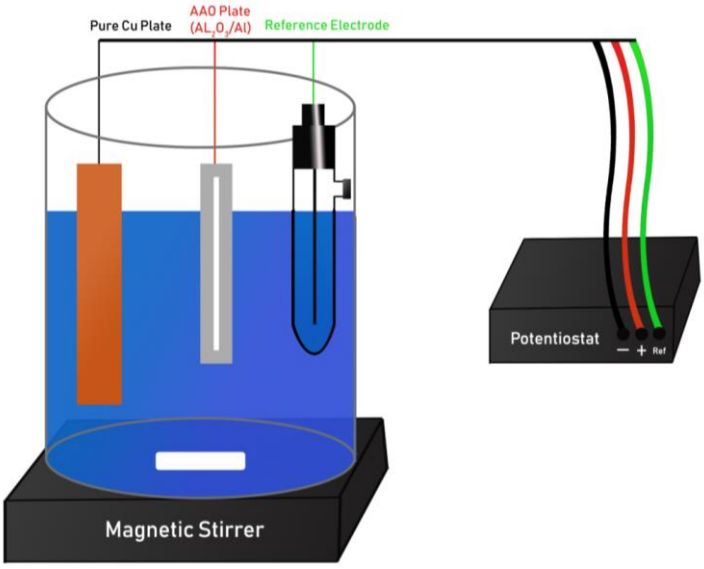

Figure 5. Schematic of Electro-chemical deposition Process.

Table 6. Research Studies related to Electro-Chemical Deposition.

Sr.No	Electrolyte and Other Chemicals	Solvent	Implant Metal	Operating Conditions	Outcome	Year	References
1	Calcium nitrate, Ammonium di hydrogen phosphate, Sodiumnitrate, Hydrogen peroxide, Zirconium oxide	Water, Ammonia, Nitric acid	Nickel -Titanium	• pH 6.0 at 25 °C • NiTi as the anode and graphite plate as the cathode. • Current density at 0.5 mA/cm^2 for 40 min • Temperature at 65 °C. • Drying at room temperature in air	• Zirconia enhances bonding strength between coating and substrate. • Corrosion resistance of NiTi increased 60 times after coating in body fluid at 37 °C.	2010	[50]

Table 6. *Cont.*

Sr.No	Electrolyte and Other Chemicals	Solvent	Implant Metal	Operating Conditions	Outcome	Year	References
2	Calcium nitrate and Sodium hydrogen phosphate and Tris-hydroxy-methyl -amino-methane	De-ionized water	Cobalt -Chromium -Molybdenum	• 200 nm thickness • CoCrMo as the cathode and platinum as the anode • pH at 6 • Electrolyte stirring at 250 rpm • Drying of coating at room temperature	• Strong mechanical bonding strength to the substrate as compared to other techniques.	2011	[51]
3	Calcium chloride, Ammonium di hydrogen phosphate, Sodium hydroxide	Distilled water	Titanium	• pH at 6.0 • Temperature at 80 °C for 30 min • Ti as cathode, Pt as anode and Ag/AgCl as reference electrode	• The coated implant was bioactive when in contact with SBF	2012	[147]
4	Calcium nitrate, Ammonium di hydrogen phosphate, Titanium nano tubes	Distilled water	Titanium	• pH of electrolyte at 7.2 • Titanium as cathode and Platinum as an anode • Electro-deposition of HAp at potential, −2.5 V for 10 min • Temperature 80 °C	• TiO2 nano-tubes improved adhesion of HAp • Bones tissue growth also increases	2014	[148]
5	Calcium nitrate, Ammonium di hydrogen phosphate	Distilled water	Magnesium	• Applied voltages were 90, 100, 110 and 120 V. • Time intervals 20, 30, 40 and 60 min • Temperature 80 °C. • Drying in autoclave at 140 °C for 4 h	• Corrosion resistance increases after coating of HAp • HAp enhances bioactivity in SBF	2015	[149]
6	Calcium nitrate, Ammonium di hydrogen phosphate	Distilled water	Ti6Al4V Alloy	• Cathode was Ti6Al4V and anode was a platinum plate • Temperature 90 °C • Deposition time 60 min • g Current densities were 1.25, 1.87, 2.50, 3.12 and 3.61 mA/cm^2.	• HAp coating increase bioactivity.	2016	[142]
7	Calcium nitrate, Ammonium di hydrogen phosphate	Ultra purewater	Pure titanium	• Cathode was titanium and platinum was anode • pH maintained at 5 • Coating temperatures 50 °C and 75 °C • Drying at room temperature in a desicator.	• Higher temperature favored thick coating with superior wet ability	2018	[150]

The researchers recently used reinforced material along with HAp to increase the mechanical properties of metallic biomaterials. These reinforced substances including zirconia oxide (ZrO_2), carbon nanotubes (CNTs), and titanium oxide (TiO_2) [53,151–154]. The block diagram of electro -chemical deposition process is shown in Figure 6.HAp nanoparticles coating also applied which yielded better results as compared to pure HAp coating. The strength of HAp coating was enhanced in a research by adding single walled nano tubes (SWNT). This blend increased the coating homogeneity along with its crystallinity. The coating on metallic implant showed a defect free surface with no cracks. Furthermore, the bond strength between HAp coating and metallic implant increases from 15.3 to 25.7 MPa after blending of SWNTs [155].HAp coatings formed using electro-chemical methods were more compact and uniform due to phenomena of nucleation and growth behind the deposition. Also the coating enhanced cell attachment and proliferation on the samples thus making it an ideal candidate for orthopedic implants [156]. Process and annealing temperatures were the critical factors deciding the nature of the coating. Chemical assisted heat treatment after electrochemical deposition

increased coating density, adhesion, and bond strength [157]. Thus, electro-chemical deposition method showed a lot of potential for future bio-medical applications.

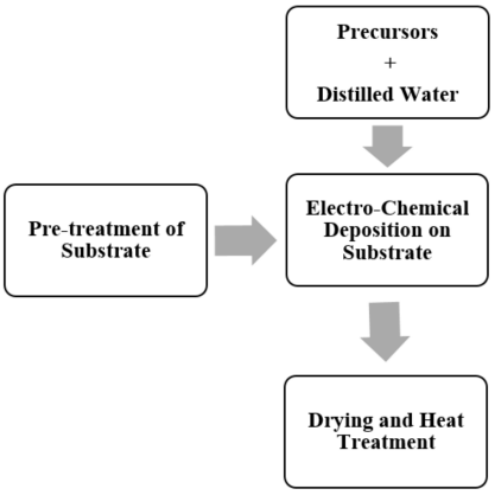

Figure 6. Block Diagram of Electro-Chemical Deposition Process.

4.5. Thermal Spraying

The thermal spray technique is gaining a lot of attention and adopted as a latest method of coating which gives excellent properties to bio-medical metallic implants. In thermal spray, precursors in the form of solution or suspension are used for coating the desired substrate to impart desired properties. Thermal spraying is classified into three sub-groups, namely flame, plasma arc, and electrical arc sprays. There are different operational approaches to carry out thermal spraying on substrates. These approaches include atmospheric plasma spraying (APS), vacuum plasma spraying (VPS), liquid plasma spraying (LPS), suspension plasma spraying (SPS), high-velocity oxy-fuel (HVOF), high-velocity suspension flame spraying (HVSFS), detonation gun spraying, and gas tunnel type plasma spraying (GTPS). All these techniques were used to coat metallic implants with HAp [158–163].

4.5.1. Plasma Spraying

Plasma spray is a commonly used technique nowadays to coat bio-active HAp on bio-medical implants [164–166]. This technique used an electric arc of high temperature and pressure for melting and showering of HAp on the metallic implants. The starting material of coating is dried HAp which is converted into plasma with the help of thermal plasma jet. After that the generated high temperature plasma contacts the surface of substrate and adheres on it as shown in Figure 7. Another type of plasma deposition includes air or vacuum spray, which is a more established technique. The HAp coating on a substrate by using this technique is stronger with superior properties. The temperature of jets varies from 10,000 K–30,000 K which decreases with a decrease in distance from the jet nozzle [167,168]. This particular technique is used for bio-active coatings on different bio-medical implant materials. The only limitation of the plasma spray process is the deformation of HAp structure due to high temperature coating operation. Sometimes high temperature operation causes reduced adhesive strength of HAp layer and metal surface [169]. The structural properties of coated HAp can be altered by using post heat treatment. The coated HAp annealed at 400 °C for 90 h. This results in the transformation of HAp structure and increased its crystallinity [170]. Higher crystalline structure favors good adhesive strength between implant and damaged tissues [171]. On the other hand, high temperature heat treatment also reduces the fatigue stresses on the surface as coating thickness decreases along with the color of coating. This post coating heat treatment at 700 °C for 1 h also enhances the purity of coating by removal of any excess water and impurities [172,173]. The metallic implants coated with HAp using plasma spray enhance the osteoconductivity due to the strong bonding

of HAp with the metal surface [174–176]. The research studies using the plasma spray technique are displayed in Table 7 below.

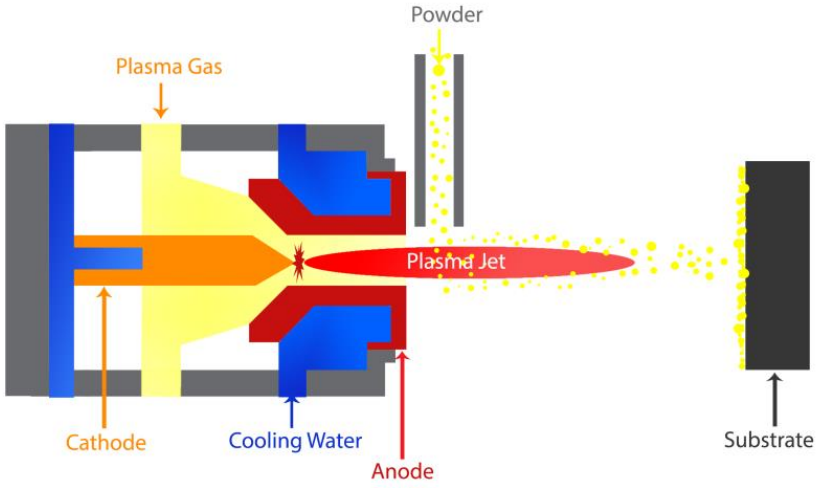

Figure 7. Plasma Spray Coating.

Table 7. Literature related to Plasma Spraying Using HAp.

Sr.No	Raw Materials	Metallic Implant	Process Conditions	Outcome	Year	References
1	HAp, Al_2O_3	Titanium	• Hap particle size 45 µm. • Current 450–750 A • Gas flow rate 33–61.4 Scfh • Powder flow rate 10–20 g/min • Spray distance 80–120 mm • Carrier gas flow rate 4.7–9.4 Scfh	• Highest coating crystallinity results at high current, low spray distance and low carrier gas flow rate.	2015	[168]
2	HAp, Al_2O_3	Titanium	• Traverse speed 38 mm/s • Spray time 35 s • Spray gun passes 15	• Osteogenic response enhances after application ofbio-active coating.	2017	[169]
3	HAp, Al_2O_3,Tri -CalciumPhosphate	Steel	• Torch speed 50, 200, and 500 mm/s • Primary plasma gas (Ar) flow rate 45 Slpm • Secondary plasma gas (H) flow rate 5 Slpm • Arc current 530 A • Standoff distance 85mm • Suspension pressure 1 bar • Suspension feed rate 25 g/min	• Hap coating thickness 28 µm. • Coatings were porous with pore size 0.2 to 6 µm	2018	[166]

4.5.2. High-Velocity Suspension Flame Spraying (HVSFS)

A high-velocity oxygen-fuel flame spray technique has been used to obtain uniformity by coating suspensions using a spray mechanism as shown in Figure 8 [177,178]. Few difficulties may encounter due to the handling of suspensions. This problem can be resolved by using axial powder injection. In this process, high-velocity suspension flame spray (HVSFS) covers the injection complications [68,179]. The coatings obtained are very dense and uniform with this technique. The salient features of this process include lower cost with high efficiency along with no post-treatment requirements [180,181]. The HVSFS process yields better coatings with uniform structure when the desired thickness is less than 50 µm [182]. The coating properties, especially the ones involving bonding strength between the substrate and coated layer produces from HVSFS techniques tend to be affected seriously due to the effect of processing parameters such as gas flow, air-fuel ratio spray distance, and electric arc current, as tabulated in Table 8. The higher thickness of coating tends to decrease the mechanical properties along with adhesive bonding of coating with the metal surface. Stresses also started to generate on the metallic surface due to the thick coating. Due to poor bonding, the coating starts to disintegrate and

exposes the metallic surface to the body fluid. This results in the discharge of metallic ions as a result of corrosion of the metallic surface after dissolution of the protective oxide film [183].

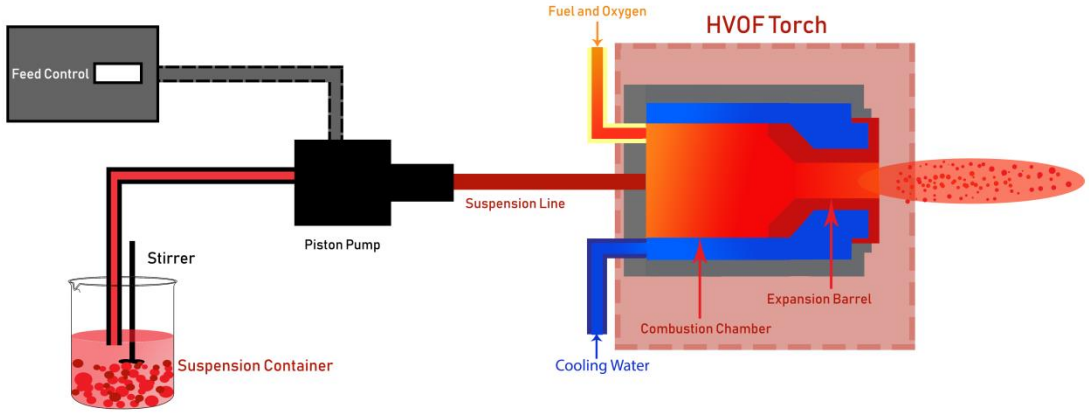

Figure 8. High velocity suspension flame spray (HVSFS).

Table 8. Recent Studies on HAp coatings Using HVSFS.

Sr.No	Coating Materials	Metallic Implant	Solvent	Process Conditions	Outcome	Year	References
1	HAp	Titanium	Water or Di-ethylene glycol (DEG)	• Low surface temperature 350 °C for Water Suspensions • High surface temperature for DEG suspensions 550–600 °C	• DEG coatings are more stable in SBF solutions than water suspension coatings • DEG coatings are more crystalline and reliable.	2011	[158]
2	HAp	-	Water or Di-ethylene glycol	• Temperature Range 357–616 °C • Torch Cycle 2–4	• HAp coatings using HVSFS are dense and more reactive than SPS due to higher calcium phosphate content.	2015	[68]
3	HAp/TiO_2	316 L Stainless Steel	Water and Iso-propanol	• Pre-heating of substrate 150–200 °C • Spray distance 100 mm • Compressed air for cooling	• Tensile strength and wear resistance of HAp/TiO2 double-layer coatings are enhanced as compared to single HAp coating.	2018	[184]

4.5.3. Pulsed Laser Deposition

Pulsed laser deposition (PLD) is a coating technology used to coat different substrates with the help of a highly accelerated beam of laser in the presence of a vacuum as shown in Figure 9. This laser beam strikes the targeted substrate with the material which we want to coat. The coating material starts to vaporize and form high-temperature plasma. This plasma strikes the target material and forms a thin layer of coating. For better coating and thin film without any defects, high vacuum atmosphere is favored. Heating of the substrate is also favored for achieving uniformity in coating [185]. PLD process has gained much attraction due to versatile coating characteristics along with a wide range of operational parameters as shown in Table 9. These parameters include uniformity, thickness, strength, crystallinity etc. [186]. The drawback of this process includes residual stresses which are associated with the failure of the coating. These residual stresses arise due to high temperature operation [187]. Another reason behind residual stresses is difference in crystal structure of HAp coating and metallic substrate. These residual stresses create defects on coating films which are unable to detect on a very thick layer (1 µm thickness). Surface roughness also plays an important role during bone healing. The coating formed during PLD is more uniform which affects the response of nearby bone tissues for tissue regeneration. The coatings formed by PLD are mostly uniform with slight micro porous structure with surface roughness ranges up to a few nanometers [188]. For minimizing

the stresses, post heat treatment operation is usually carried out. For the bio-implant, the existence of surface irregularities and porosity promote cell adhesion and proliferation due to larger surface area [189]. The response of the body towards HAp coating is affected by the particle size, texture, morphologies and surface area provided [190]. The rough surfaces of coating enhance the wetability which is required during growth and interaction with body fluids [190]. Coating surface chemistry and topography are also vital for good osseointegration [191]. The healing of damaged bone in the presence of a biomedical implant is similar to primary bone healing. At starting, blood is present which gradually transformed in to clot in between the implant and bone. This transformation is completed in the presence of phagocytic cells. If the implant is already coated with the bioactive coatings the response generated by them is fast. This response facilitated in quick bone regeneration in comparison with metallic implants without coatings. The bioactive coatings promote biological responses from the body e.g., bonding with tissues and tissue growth. Normally, there are two types of materials available. One possesses the property of osteoconductivity whereas the other offers osteoproductivity. Once these coating layers interacted with the body fluid they started to generate stimulus which facilitates in the bone growth process along the surface or away from the biomedical implant [192].

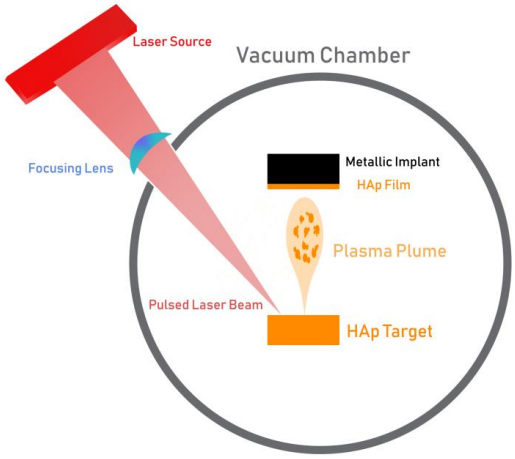

Figure 9. HAp coating using Pulsed Laser Deposition.

Table 9. Literature related to Pulsed Laser Deposition.

Sr.No	Coatings	Metallic Implant	Process Parameters	Outcomes	Year	References
1	HAp	Titanium	• Post treatment at 550 °C for 1 h • Vacuum Atmosphere • Substrate at room temperature	• Thickness 1 µm • The mechanical properties are less as compared to sputtered ones.	2004	[193]
2	HAp	Silicon(100) and Titanium	• Room Temperature • Annealed 500 °C	• Crystalline coating • Heat treatment after coating enhances mechanical properties	2005	[194]
3	HAp	Titanium	• Ambient Temperature • Pressure 10−4 to 10−1 torr of oxygen • Annealing at 290–310 °C in air.	• Purity increased after post treatment • Crystalline HAp coatings showed no dissolution in SBF.	2009	[117]
4	HAp	Titanium	• UV KrF laser λ = 248 nm and τ = 25 ns • Post treatment at 400 °C for 6 h in water vapors	• Film Thickness ranging 100 nm to 1 µm	2011	[195]
5	HAp and Silicon	Titanium	• Pulse repetition rate 5 Hz • Temperature of substrate 400 °C, 500 °C, and 750 °C • λ = 248 nm and τ = 17 ns	• Coatings were dense, crystalline, and nanostructured, which enhanced hardness • The bioactive Si-HAp coatings improved the osseointegration.	2014	[196]

4.5.4. Flame Spray Coating

Flame spraying (FS) technique was the first-ever thermal spray method developed in the year 1910. FS is the most economical and easy technique among all the thermal spray coating methods [197]. Flame spray coating started by the combustion of oxygen flame for melting the HAp powder which yields porous and composite coating on metallic surfaces as shown in Figure 10. FS possesses a lot of disadvantages in comparison to other thermal spray coating techniques. These disadvantages include a bigger size of microstructure, pore size, and cracks on the coating layer. As mentioned earlier, FS is economical with ease of operation in terms of commercial processes. The particle velocity for the process ranges from 200–300 m/s with new modernized torches. An oxygen and acetylene blend is used as a fuel to power the torch to achieve higher combustion temperatures around 2600 °C [198–201]. The flame spray method was used to deposit zinc-doped HAp on Ti-6Al-4V substrates to enhance its biocompatibility and antibacterial activity against *E. coli* [199]. Liu and coworkers deposited porous HAp coating on titanium implant using flame spraying. Wetting of metallic substrate before coating generates porous coating. The wetting method enhances the cell proliferation and differentiation of pre-osteoblast cells. The coatings developed under wet conditions contain many cracks and fissures in the range of nano-size ~100 nm [197]. Monsalve and co-workers [75] coated 316 L steel and titanium alloys with bioactive glass coating using the flame spray technique. The magnesium content present in the bioactive glass affects the crystallinity of the coating layer. The higher content favors a more crystalline coating layer that favors pores formation. Additionally, the lower thermal conductivity of titanium alloys promotes higher crystallinity in accordance with slow cooling rate. This helps to form some crystalline phases. When the coated substrate is immersed in the SBF solution, hydroxy carbonate apatite layer is formed, which confirmed its bioactivity.

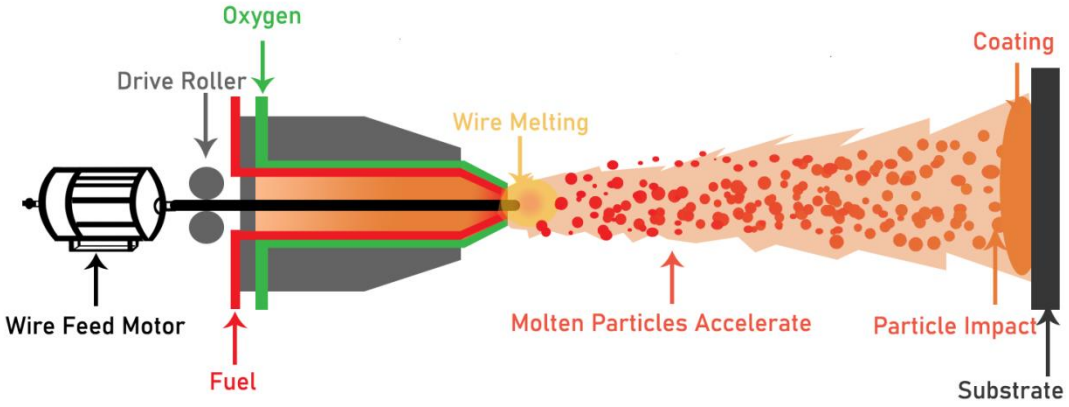

Figure 10. HAp coating using Flame Spray Technique.

5. Innovative Methods of Coating

Yuan and Golden used HAp to coat stainless steel (SS) 316 L with electro-deposition [202]. The substrates were coated with two layers to minimize the contact of the implant with body fluid. After the coating process, heat treatment was employed to samples in a vacuum at 800 °C or in presence of air at 600 °C. The benefit of bi-layer coating was to enhance uniformity with high bonding between surface and HAp along with bioactivity. Another innovative method includes the introduction of an oxide layer in between metallic implant and HAp as shown in the Figure 11. This oxide film protects the metallic surface and prevents the release of toxic ions from the top metallic layer [54,203,204]. The oxide layers covered with HAp coatings enhance the adhesion of oxide and HAp [205,206]. The metallic coating also reduces the cytotoxic effects and enhances the biological performance of the implant [206,207]. Ceramic material like Zr was also applied in between the HAp and metallic surface. This ceramic layer acted as a strong bond and worked as a composite. This type of coating was favorable for implants subjected to cyclic stresses [208]. The bond strength enhancement between metallic

implant and coating is a very important factor for the reliability of the implant. The super-high-speed (SHS) blasting method is a new and novel technique that not only enhances the bond strength but also eliminates exfoliation of HAp layers. The HAp film obtained from the SHS method yields higher adhesion strength and outstanding wetability properties [209].

Figure 11. (**A**) Oxide layer in between metallic implant and HAp and (**B**) Bi-layer Metallic oxide coating.

Another innovative technique was the combination of two coating method to produce HAp films performed by Jia et al. [210]. The researchers coupled micro arc and sol-gel processes together to form coating layers. The micro-arc improved the biocompatibility of the metallic implant, and the bioactivity was enhanced further by the sol-gel HAp coating on the anodized Ti [211].

6. Conclusions and Future Perspective

The main target of this review is to gather a broad literature bank associated with the hydroxyapatite coatings and coating methodologies for the development of biomedical implants.

HAp coatings especially nanocrystals of HAp enhance the biocompatibility of biomedical implants more which mimic the implant like natural bone. The four most commonly applied methods were discussed here with their parameters and efficiency. Thermal spray coatings are most efficient and commonly applied on metallic implants due to their uniform coating layer on the metal surfaces, in recent years. High temperature and high speed of jets permit the HAp particles to deposit the surface with the elimination of defects due to higher melting points of ceramic materials.

The coating thickness can be varied up to several microns with some carbide formation which provides porous surface and strength to coating. Sol-gel method is able to process a wide range of HAp pre-cursors in aqueous form for coating with any shape of the implant. Electro-chemical deposition also utilizes raw materials in aqueous form for coating on biomedical implant assisted by potential difference of electrochemical cell. A wide range of concentrations can be used for coating on complex shapes. The only drawback of this method is the poor conductivity of substrates which creates a hurdle in the free movement of charges. Innovative methods are also discussed here which increase the performance of implants even more in the body. Intermediate oxide layers between the metallic surface and HAp enhances the adhesion of HAp. Pre-treatments and post-treatment of HAp coating and implant surface increase the implant efficiency and makes the biomaterial more feasible for placement in the body.

Although it has been decades working and exploring HAp and its applications in biomedicine, yet there are important areas that have either not been explored well or are very rarely tested in vivo. For example, as described earlier, the adhesion strength of the HAp coating is a critical factor. Therefore, developing a coating of nanoparticles on titanium alloy implants can increase the surface area of the implant. This nanoparticle-coated titanium alloy can further be coated with HAp crystals for increased biocompatibility. The increased surface area will ultimately provide a better adhesion strength to coating keeping the biocompatibility and bioactivity factor intact. Along with this, the use of porous titanium alloys coated with HAp has also not been investigated well. These porous implants coated with HAp give dual benefits. These implants have Young's modulus closer to that of bone addressing the stress shielding effect and the increased surface area coated with HAp providing biocompatibility along with osseointegration.

Another important area that needs to be explored is the use of HAp in combination with other calcium magnesium phosphates naturally present in bones. These other phases have important functions during bone tissue healing. Whitlockite is one of the calcium magnesium phosphate that is naturally present in bone and plays an important role because of its osteogenesis properties [212,213]. Synthesis of whitlockite is a very critical process and requires extensive optimization of parameters like pH and temperature. It can therefore be the reason for not exploring the coating involving different other phases, particularly whitlockite that has not been investigated comprehensively. Following this, HAp in combination with different ions substituted whitlockite can also provide better osteogenic properties. A study has been already performed using a combination of HAp, whitlockite and chitosan which was concluded with very positive tissue healing results [214] but this along with other combinations need to explore comprehensively both in vitro and in vivo. Thus, the use of HAp coating on nanoparticle-coated titanium implants, both bulk and porous, and the use of biphasic coatings, particularly combining HAp with other available calcium magnesium phosphates, is prospective options in this area for the future.

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Nomenclature

Symbols	
HAp	Hydroxyapatite
FDA	The food and drug administration (USA)
RF	Radiofrequency
MAO	Micro-arc oxidation
CVD	Chemical vapor deposition
PLD	Pulsed laser deposition
HVSFS	High-velocity suspension flame spraying
PCL	Poly-(ε-caprolactone)
EPD	Electro-phoretic deposition
ELD	Electrolytic deposition
SBF	Simulated body fluid
FS	Flame spraying
SWNT	Single-walled nano-tubes
SLPM	Standard liters per minute
SCFH	Standard cubic feet per hour
SHS	Super-high-speed

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