Review Article

Hydroxyapatite Nanoparticle Coating on Polymer for Constructing Effective Biointeractive Interfaces

Tania Guadalupe Peñaflor Galindo, Yadong Chai, and Motohiro Tagaya

Department of Materials Science and Technology, Nagaoka University of Technology, 1603-1 Kamitomioka, Nagaoka, Niigata 940-2188, Japan

Correspondence should be addressed to Motohiro Tagaya; tagaya@mst.nagaokaut.ac.jp

Received 7 August 2018; Accepted 26 October 2018; Published 3 January 2019

Academic Editor: Paulo Cesar Morais

Copyright © 2019 Tania Guadalupe Peñaflor Galindo et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Bone is an organic-inorganic composite with the ability to regenerate itself. Thus, several studies based on artificial organic-inorganic interface sciences have been tried to develop capable materials for effective regenerative bone tissues. Hydroxyapatite nanoparticles (HAp NPs) have extensively been researched in bone tissue engineering due to the compositional and shape similarity to the mineral bone and excellent biocompatibility. However, HAp alone has low mechanical strength, which limits its applications. Therefore, HAp NPs have been deposited on the biocompatible polymer matrix, obtaining composites with the enhanced mechanical, thermal, and rheological properties and with higher biocompatibility and bioactivity. For developing new biomedical applications, polymer-HAp interfacial interactions that provide biofusion should be investigated. This paper reviewed common coating techniques for obtaining HAp NPs/polymer fusion interfaces as well as in vitro studies of interfacial interactions with proteins and cells, demonstrating better biocompatibility. Studies based on interfacial interactions between biomolecules and HAp NPs were highlighted, and how these interactions can be affected by specific protein preadsorption was also summarized.

1. Introduction

Human bone is an organic-inorganic composite having the components of collagen fibrils containing embedded and well-disposed, nanocrystalline hydroxyapatite (HAp) with 25–50 nm length and rod-like shape [1]. Bone has the ability to repair and regenerate itself for damage. Nevertheless, old age, diseases, and trauma can negatively affect bone functions, and these functions only can be restored with surgical reconstruction by the implantation of bioceramics, which is aimed at generating an environment to stimulate specific cellular responses in order to promote osteogenesis [2].

Bioceramics are biocompatible ceramics that have been used for biomedical applications in both crystalline and amorphous forms [3]. Bioceramics can be classified into three bioinert, bioactive, and resorbable or biodegradable types.

Bioinert bioceramics (e.g., titania (TiO₂) [4], and zirconia (ZrO₂) [5]) have high chemical stability as well as high mechanical strength in vivo. After the implantation into bone tissues, they act as the guideline of “contact osteogenesis” [6]. Though inert ceramics do not form a bonding with the bone [7], a thin fibrous tissue layer immediately adjacent to the surface can be formed, creating a separation between the bioimplant and the host and generating minimal tissue response and the inability of the implant to encourage bonding of natural bone by the osteoconduction process [2]. The interfacial zone thickness between the biomaterial surface and the host tissue is determined by the level of bioactivity [8, 9]. The use of bioactive materials can prevent these problems since these materials are partially soluble in water, resulting in the direct chemical bonding with bone.

Bioactive bioceramics (e.g., hydroxyapatite (HAp), tricalcium phosphate, biphasic calcium phosphates, bioactive glass, and some glass-ceramic formulations [10–12]) are osteoconductive and have the capability to form chemical bonding with living bone tissues, taken in accordance with the guideline of “bonding osteogenesis.” Generally, the mechanical strength of bioactive ceramics is lower than that of inert bioceramics.
Due to the ability of varying the calcium to phosphorus ratio (i.e., the bioactivity based on the resorption rate), it allows controlling the rate of bone growth as the bioceramic is resorbed [13, 14]. "Osteoconductive bioceramics allow attachment, proliferation, migration and phenotypic expression of bone cells, leading to the formation of new bone" [15].

Resorbable or biodegradable bioceramics (e.g., calcium phosphates like tricalcium phosphate (TCP) and carbon-contained HAp (CHAp) [16–19]), in vivo, are gradually adsorbed and replaced by endogenous bone tissue. The incorporation guideline is similar to contact osteogenesis; however, the interface between the bone and resorbable bioceramics is not stable as that of bioinert ceramics [4, 14]. These bioceramics are clinically relevant due to the controlled chemical apportionment and resorption [2]. All the chemical formulations can be produced in the forms of crystals, powders, particles, granules, scaffolds, and/or coatings [20–22].

Nanotechnology has allowed the preparation of nanostructured biomaterials, giving way to the third generation of bioceramics, focused on the enhanced bioactivity and the initial physiological trace inducing an enhanced cell to respond at the molecular level in order to regenerate tissues due to their similarity to the inorganic component of human bone tissues [1]. A nanobioceramic is defined as ceramic less than 100 nm in at least one direction [23]. Nanobioceramics are highly biocompatible, stable at a physiological environment, and corrosion-resistant and have remarkable higher specific surface area and volume ratio and contain a higher quantity of grain boundaries than the conventional counterparts, offering better surface properties such as topography, energy, roughness, and wettability which potentially favor cell response [24, 25]. Besides, they become more active with regard to dissolution and recrystallization processes [2]. Bioceramics play a crucial role, enabling the design of bioceramics that can provide better suitability to biological tissues to empower their regeneration through natural signaling pathways and using natural components such as cells, growth factors, and proteins, adjusting the interactions between the biological tissue and bioceramics.

In this paper, HAp nanoparticles (NPs) have been deposited on the biocompatible polymer matrix, obtaining composites with enhanced mechanical, thermal, and rheological properties and with higher biocompatibility and bioactivity. For developing new biomedical applications, polymer-HAp interfacial interactions that provide biofusion should be investigated. This paper reviewed common coating techniques for obtaining HAp NPs/polymer fusion interfaces as well as in vitro studies of interfacial interactions with proteins and cells, demonstrating better biocompatibility. Studies based on the interfacial interactions between biomolecules and HAp NPs were highlighted, and how these interactions can be affected by the specific protein preadsorption is also summarized.

2. Hydroxyapatite Nanoparticles

2.1. Structures and Their Properties. The inorganic component of bone and teeth is nanocrystalline HAp, which provides the toughness and ability to withstand pressure. This calcium phosphate is stacked and aligned with the organic matrix formed by collagen fibers, glycoproteins, and mucopolysaccharides for conferring the elasticity and resistance to the structure [26–28]. HAp belongs to the apatite group with a composition of $\text{M}_{10} (\text{PO}_4)_6 \text{X}_2$. The elements that can occupy $M$, $Z$, and $X$ are:

(i) $M = \text{Ca, Sr, Ba, Cd, Pb, etc.}$
(ii) $Z = \text{P, V, As, S, Si, Ge, etc.}$
(iii) $X = \text{F, Cl, OH, O, Br, etc.}$

Despite the great variety of compounds that can be prepared by substituting elements at the $M$, $Z$, and $X$ sites, the apatite compounds have a common crystal structure that is characterized by the space group $P6_3/m$ and a hexagonal system and with similar X-ray power diffraction patterns [26, 29]. The chemical formula of stoichiometric HAp is $\text{Ca}_{10} (\text{PO}_4)_6 (\text{OH})_2$, with a Ca/P ratio of 1.67 and properties including solubility, bioactivity, osseointegration, and osteoinduction [1, 24]. By changing the Ca/P ratio, several calcium phosphates can be obtained [29, 30]. Figure 1(a) shows the crystal structure of HAp projected along the $c$-axis, centered on the hexagonal $c$-axis channel. Figure 1(b) exhibits an overview of the HAp unit cell structure, indicating the negatively charged $c$-plane due to the rich content of phosphate ions and the positively charged $a$-plane due to the content of calcium ions.

The properties of HAp can significantly affect the particle composition, assembly, size, and morphology. Nanosized HAp NPs (20–80 nm) have shown to be more efficient in osteoblast adhesion and proliferation and improved mineralization [24]. Since the sizes of the microparticles are not much smaller than those of cells, the microparticles are not able to penetrate into the cell wall and will be promptly degraded by phagocytosis [2]. Among the nanoscale levels, it has been reported that HAp NPs with the size of around 20 nm are better for cell proliferation and induction of apoptosis in some cancer cells [31–33]. It was found that the spherical and rod-like shapes of HAp NPs showed remarkably less cytotoxicity as compared with the needle and plate-like shapes [34].

The obtained sizes and shapes of HAp depend strongly on the synthetic route as well as synthetic parameters [35]. HAp nanostructures of spherical shapes with the sizes of 5–200 μm, rod-like shapes with those of 5 nm–150 μm, and needle-like shapes with those of 40 nm–150 μm can be synthesized by diverse methods such as the mecanochemical method [36, 37], hydrolysis method [38, 39], sol-gel method [40–42], hydrothermal method [43], chemical precipitation method [44], emulsion method [45], and solid-state reactions [46]. Nevertheless, mecanochemical, chemical precipitation, and sol-gel methods frequently result in irregular shapes with agglomerations. In the precipitation method, chemical agents have been used as modifiers to control the sizes and morphologies. The most reported agents are (i) complex ligands such as citric acid [47, 48], ethylenediamininetetraacetic acid (EDTA) [49, 50], tartaric acid, or acetic acid [51, 52]
and (ii) organic molecules such as amino acids [53], polymers [54, 55], and surfactants like cetyltrimethylammonium bromide (CTAB) [56]. For example, CTAB has been used as a rod-like micelle template (see Figures 2(a) and 2(b)). After the addition of CTAB into the solution, bromine ions on the surfaces of the formatted micelle of CTAB are replaced quickly with phosphate ions. The precursors which reacted with phosphate ions on the surfaces of CTAB micelles formed the HAp nanostructure [57].

HAp-based nanophase materials offer excellent biocompatibility, biodegradability, and osteoconductive and osteoinductive properties [35, 58] and have been widely applied for several biomedical applications as shown in Figure 3. Among the most important biomedical applications are bone filling and medical implants [16–19], bone tissue engineering scaffolds [20], bioactive coatings, composites with antibacterial properties [17], drug delivery systems [21, 26], bioimaging and diagnosis materials [28–30], and biosensors [17]. The shapes, sizes, crystalline phases, and functional groups are responsible for the surface reactivity of HAp (i.e., biorelevant parameters).

2.2. Biomedical Applications. Several forms, shapes, and sizes of HAp have been synthesized and investigated; however, nanosized HAp exhibits enhanced bioactivity, biocompatibility, mechanical properties, and higher resorbability as compared with microsized HAp [59, 60]. The particles can be incorporated inside the cells, when the particles have the appropriate sizes and the charge are up to about 200 nm and is positive [61]. HAp NPs with crystalline sizes less than 100 nm have the ability to cross the natural barrier and interfaces of the cells and can deliver drugs in sites with difficult access sites of delivery; in addition, they have the possibility to associate and they can bind with DNA and proteins owing to the cell structure. The dynamic and energetic length scales of HAp NPs match with those exhibited by many biological processes [58]. The interfacial properties of nonstoichiometric HAp due to calcium and hydroxide ion deficiency confer higher solubility and interfacial reactivity, favoring both biomolecular adsorption and ion exchange [35]. In drug delivery systems, the hollow and porous HAp spheres showed better properties due to the higher surface areas and 3D porous architectures with nanosized channels allowing greater drug storage and a better release with higher intake capacity and better pH behavior response for drug release [62]. These NPs can form mesoporous structures with pore sizes around 4.0–14.0 nm and a surface area up to 46.5 m²/g [1]. For bone regeneration, it is attempted to synthesize chemical and crystallographic HAp NPs, which were more effective for promoting cell proliferation and cellular activity [63, 64], to obtain excellent biocompatibility and optimal mechanical properties in terms of hardness, rigidity, biorsorbability, and biodegradability [10, 11]. The cells cultured with the spherical HAp NP suspension showed better osteoblast proliferation, cell adhesion, migration, and cell-matrix interactions, suggesting that spherical HAp NPs are more hazardous than needle-like shape particles [60, 63]. In vitro studies showed that HAp NPs with a particle size of 20 nm have enhanced cell viability and proliferation of bone marrow mesenchymal stem cells and inhibited the growth of osteosarcoma cells [41]. HAp NPs with a diameter of about 50 nm showed the apoptotic action of the hepatoma cell line [44]. Bioimaging properties such as photostability, biocompatibility, and spherical shapes are necessary properties [61]. HAp NPs doped with lanthanide or europium ions are prepared by integrating into the HAp structure by ion exchange during synthesis for bioimaging applications. These NPs having crystalline sizes around 10–50 nm are included in the lattice to endow the NPs with luminescence moiety and are detected due to the fluorescence caused by an external stimulus [65–67]. This strategy is better than the use of fluorophores since it avoids inconveniences as poor stability and photobleaching [67]. For antibacterial activity applications, studies have been done by doping HAp with metals such as silver, copper, or zinc, obtaining a decrease in bacterial growth in all cases.

Figure 1: (a) Crystal structure of HAp in the top view along with the c-axis, which were centered on the hexagonal c-axis channel and (b) the overview structure to exhibit the rich phosphate and hydroxyl ions at the c-plane and the calcium ions at the a-plane (drawing using VESTA (10) from the CIF obtained from American Mineralogist Crystal Structure Database).
However, of these metals, zinc (Zn) is the less toxic metal. In the case of HAp doped with Zn, when Zn was incorporated into the structure, nanocrystals decreased in size, which favored the biocompatibility with fibroblast cells in vitro (see Figures 2(c) and 2(d)) and increased the antibacterial activity due to the bioresorbability and biodegradability properties [68]. The doping with Zn promoted the proliferation and differentiation of fibroblast cells as compared with pure HAp [58, 68]. The rod-like HAp nanocrystals showed the better biomimedical features as the bone fillers and promoted osseointegration, followed by the bone tissue regeneration, since the biological HAp in the body tissues consisted of the rod-like HAp nanocrystals. Thus, filling the bone with similar HAp NPs increases the concentration of bioactive molecules generating successful osseointegration in vivo and in vitro [69, 70]. Micrometer-scaled pores at

Figure 2: TEM images of (a) general HAp (HAp–40-Aft) NPs, (b) cationic surfactant-assisted HAp (CTAB/HAp–40-Aft) NPs, (c) zinc ion-doped HAp (0.5-Zn : HAp) NPs, and (d) zinc ion-doped CHAp (0.5-Zn : HAp) NPs. Reprinted with permission from [57], K. Shiba et al., Cryst. Growth Des. 16, 1463—1471 (2016) © 2016, American Chemical Society, and [68] T.G.P. Galindo et al., J. Nanomater. 2015, 360 (2015) © 2015, Hindawi.

Figure 3: Illustration of the various biomedical applications of HAp NPs.
around 1–10 μm and >100 μm have an important effect on bone formation. Microporosity is related with the osteoinduction process and promoted cartilage formation before osteogenesis [61], while the smaller pores (1–10 μm) induced direct osteogenesis [23]. It has been reported that pore sizes of 100 μm enhanced cell spreading and migration, whereas pores of >300 μm promoted the formation of bone and capillaries [1, 61]. The applications of HAp NPs are remarkably influenced by their shapes, sizes, and crystallinity. Spherical HAp NPs can imitate the hierarchical features of the human bones, which enhanced the cell adhesion, proliferation, differentiation, and osseointegration in vivo [70]. The control of these parameters is the fundamental factor to determining the physicochemical properties and biological activity of HAp.

3. Biomedical Polymeric Substrates

3.1. Surface Modification. Studies on polymers applied to the medical field began in the 20th century; nonetheless, at the end of the 1950s, the use of polymers in medicine and medical applications was intensified because of their good biocompatibility, low toxicity, bioinert nature, and good mechanical properties such as strength, abrasion resistance, and flexibility [10–14]. The nature of the chemical bonds of the main chain of the polymer determines the polymer properties [71]. In the nondegradable polymers, the carbon–carbon bond is chemically and biologically stable and inert. Nevertheless, the physiochemical properties can be modified by the oxidation of the carbon backbone, changing the mechanical properties, crystallinity, hydrophobicity, weight, solubility, chemical composition, and melt and glass transition temperatures of the polymer [72–75]. Biodegradable polymers have hydrolytically unstable linkages. In the backbone of the polymers, the end group contains ester, amide, or ether bonds [76]. Functional groups frequently found in these biodegradable polymers are esters, anhydrides, orthocenters, and amides [72]. Biodegradable polymers as well as nondegradable polymers have been widely used in biomedical applications such as medical devices [73, 77], sutures [72], drug delivery systems [78–81], scaffolds for tissue engineering [82–85], implants [86–87], and organ regeneration [88, 89]. The basic properties as well as the most notorious biomedical application are listed in Table 1 for the most common biocompatible polymers, which were classified into biodegradable and nonbiodegradable types.

The chemical compositions and structures of the polymer surfaces will determine the interfacial interactions that take place between the biological media (such as proteins, cells, and tissues) and the polymer substrates [133]. In order to improve the biointeractions, specificity, biofunctionality, biorecognisability, and biocompatibility of the biomedical polymers, the several techniques have been used for modifying the surfaces (i.e., controlling the roughness, domain or ionic charge, introduction of functional sites, adsorption of molecules, or higher hydrophilicity) [133–135]. Surface modification methods can be divided in two categories. (1) Physicochemical methods alter the atoms and molecules of the polymer surface. Among the most used physicochemical methods are ion beam etching, plasma etching, corona discharge, ion beam implantation, ion exchange, UV irradiation, chemical reactions like non-specific oxidation, functional group modification, addition and derivatization of reactions, and surfactant or hydrophilic polymer immobilization [133, 134]. In contrast, (2) coating of the polymer surface with an external hydrophilic layer can be raised [136]. These methods include photografting, chemical grafting, radiation grafting, electron beam-induced grafting, plasma, gas phase deposition, silanization, gas phase deposition, laser ablation, biological methods [133, 134, 137], and patterning [135]. These treatments have been used to obtain functional groups at the surface, leading to the increase in energy, lubricity, electrical conductivity, and dyeability at the surface; improvement in hydrophilicity; introduction of surface cross-linking; and removal of contaminants or weak boundary layers [138]. Thin surface modifications which only modify the outermost molecular layer would be ideal in order not to change the mechanical and functional properties of the polymer, although the minimum thickness required depends on the length of the molecule to be incorporated [135]. The intermolecular interactions at the overlayer of the modified region will produce the surface rearrangement through the diffusion or translation of the atoms or molecules at the surface as a response of the stresses transmitted from the matrix across the interfaces [135, 139]. If the interactions between the overlayer and the substrate are not strong, or the surface modification layer is very thin, surface reversals will occur [137, 140]. Among the surface modification methods, oxygen plasma treatments have been widely used to form the reactive silanol groups on the surface of the siloxane component, which increase the hydrophilicity, wettability, characteristic, and biocompatibility at the surfaces of biomedical polymers including devices or implants [141–143].

One of the most used polymers in biomedical applications is polydimethylsiloxane (PDMS), due to the good biocompatibility, low toxicity, high flexibility, good thermal and oxidative stability, low modulus, antiadhesive nature, soft and rubbery behavior, bioinertness, transparency in the visible region, and control of free volume with the aim of accommodation of metal nanoparticles [1, 144]. Anteriorly, our group has reported the incorporation amount and state of gold nanoparticles into the PDMS by controlling the cross-linking degree during the hydrosilylation reaction (see Figure 4). The general reaction between the siloxane oligomer (liquid PDMS) and the siloxane cross-linker takes place to generate the cross-linked PDMS as shown in Figure 4(a). Figures 4(b) and 4(c) show the UV-visible adsorption spectra and photographs of gold-PDMS composite films containing 2 to 10 wt% of the cross-linker to PDMS. In gold-PDMS composite films containing low cross-linker concentration (less than 4 wt%), the aggregation of gold nanoparticles was found. For gold-PDMS composite films containing 6 wt% of the cross-linker, gold nanoparticles were dispersed in the film [145].

3.2. Surface Functionalization. The surface structure of the biocompatible polymer is able to enhance protein adsorption, and then the cells interact with the proteins, leading to
Table 1: Features of representative biomedical polymers used in vitro and in vivo. The upper and lower broken lines indicate the biodegradable and nonbiodegradable polymers.

| Polymer                        | Basic properties                                                                 | Possible biomedical applications                                                                 | References |
|-------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|------------|
| Collagen                      | Biodegradable, biocompatible, great tensile strength, and weak antigenicity. The isoelectric point is 8.26. Young’s modulus in the range from 3.7 to 11.5 GPa. Nontoxic, biodegradable, biocompatible, and antimicrobial and hydrating agent. Highly hydrophobic, insoluble in water and even most organic solvents. | Wound healing, tissue engineering, hemostatic agent, bone grafts. | [90–93] |
| Chitin                        |                                                                                  | Tissue engineering scaffolds, drug delivery, wound dressings, antibacterial coatings, and sensors | [94–97] |
| Chitosan (CS)                 |                                                                                  | Tissue engineering scaffolds, bone regeneration, angiogenesis, and wound healing                 | [98, 99] |
| Poly(ε-caprolactone) (PCL)    | Biodegradable, amphiphilic, flexible, nontoxic, and biocompatible polyester with melting point of around 60°C and a glass transition temperature of about −60°C. Biodegradable, biocompatible and with tailorable chemical and physical forms. Glass transition temperature about −73 to −23°C, Young’s modulus in the range from 0.002 to 0.003 GPa, tensile strength, and yield stress in a range from 25 to 51 MPa. High crystallinity, good mechanical properties including high tensile strength, high flexibility, good resilience, low rates of biodegradation, very high tenacity, and excellent sliding characteristics and wear resistance. Conductivity: 10⁻¹² S/m, melting point: 190–35°C, thermal conductivity: 0.25 W/(m·K). | Tissue engineering, long-term implantable devices, drug delivery systems, microencapsulation, and scaffold for tissue repair | [100–103] |
| Polyurethane elastomers (eLPU) |                                                                                  | Used in catheters, drug delivery vehicles, prosthetic implants, surgical dressings/pressure sensitive adhesives, tissue engineering scaffolds, and cardiac patches | [104–107] |
| Poly(amide) (PA)              | Semicrystalline, excellent mechanical, very stable, and chemical resistance properties. Glass temperature: 143°C, Thermal conductivity: 0.25 W/(m·K), melting point: 343°C, Young’s modulus: 3.6 GPa, tensile strength: 90–100 MPa. | Used as suture material, ligament and tendon repair, balloon of catheters, and dialysis membranes | [108–112] |
| Polyether ether ketone (PEEK) | Strong and impact-resistant, excellent water and moisture barrier material, biostable, insoluble in water, melting point: >250°C, glass transition temperature: 67–81°C, Young’s modulus: >2800–3100 MPa, tensile strength: 55–75 MPa, thermal conductivity: 0.15 to 0.24 W/m.K. | Orthopedic applications or inner lining of catheters | [113–116] |
| Poly(ethylene terephthalate) (PET) |                                                                                  | Used for membranes, vascular grafts, surgical meshes, and ligament and tendon repair | [117–119] |
| Poly(ethylene glycol) (PEG)   | Nontoxic, nonimmunogenic, nonantigenic, hydrophilic, bioreabsorbable, and biocompatible polymer. Flash point: 182–287°C. | Used as antifoiling coating on catheters, hydrogel or as pore former in dialysis membranes and drug delivery systems. | [120, 121] |
| Poly(dimethylsiloxane) (PDMS) | Hydrophobic, stable, biocompatible, bioinert, flexible, and soft rubbery behavior | Used for catheters, nucleus pulposus substitute, plastic surgery, intraocular lenses, glaucoma drainage devices, and dialysis membranes | [122–126] |
| Poliglycolic acid (PGA)       | High crystallinity (45–55%), high tensile modulus, poor solubility in organic solvents. Excellent fiber forming ability. High rate of degradation and acidic degradation products. Glass transition temperature: 35–40°C and melting point 235–230°C, tensile strength: 340–920 MPa, Young’s modulus 7–14 GPa. | Regenerative biological tissue, bone internal fixation devices, tissue engineering scaffolds, suture anchors, meniscus repair, medical devices, and drug delivery | [127–129] |
| Poly(L-lactic acid) (PLLA)    | Degradable, good tensile strength. Glass transition temperature: 50–60°C and melting point 170–190°C, tensile strength: 870–2300 MPa, Young’s modulus 10–16 GPa. | Orthopedic fixation tools, ligament and tendon repair, and vascular stents | [130–132] |
the cells forming tissues on the biomedical polymer. In this manner, it is desirable to tailor the surface of the biomedical polymer in order to provide a biocompatible physicochemical environment to guide the cells to form tissues [146–149].

These specific requirements will depend on the medical applications. For tissue engineering, it is necessary to give good biocompatibility, cell adhesion, and biodegradable properties [150]. On the other hand, for drug delivery...
systems, multiresponse properties are desirable for intelligent control of drug release [151]. A great variety of superficial physicochemical properties can be obtained through surface modification; however, to obtain specific requirements, it is necessary to functionalize polymer surfaces [146]. Surface modification can serve as the bench for surface functionalization to improve the properties [152].

Two commonly used strategies to functionalize polymers can be raised: (1) functional groups are introduced into polymer monomers. Although hydrophilic co-monomers can be inserted into the prepolymerization system by chemical functionalization, these monomers can alter the bulk properties, which is not desirable for biomedical applications [136]. (2) Functional groups are introduced into the polymer chain by the further modification of the prepared polymer [150–153]. Strategies for functionalization of biomedical polymers include topography (surface graft polymerization or thin film deposition by chemical vapor deposition (CVD) and immobilization (such as proteins, nucleic acids, and carbohydrates) [154]. It has been reported that plasma treatment allows precisely controlling the chemical functionalization and morphology of the surface of biodegradable and nonbiodegradable polymers, which results in coating with good stability and better compatibility with the biomolecules and host cells in liquid media [146, 155, 156]. Some biocompatible polymers exhibit a hydrophobic surface, which impairs the desired cellular response. Functionalization through graft polymerization has been extensively studied [157–160]. The surface graft polymerization method tailors the properties of the polymer through the direct introduction of other types of monomers on the polymeric surface without alteration of the bulk properties [153]. Hydrophobic polyurethane (PU) scaffolds were modified by grafting hydrophilic methacrylic acid (AA) monomers (under UV light), resulting in hydrophilic polyurethane methacrylic acid (PMAA) with better cell compatibility than pure polyurethane (PU) [157, 161, 162].

By plasma-enhanced CVD (PECVD), different kinds of polymeric surfaces can form different types of thin films depending on inorganic coatings such as carbon nanotubes [163], diamond-like carbon [164], ZnO [165], TiO₂ [166], and SnO₂ [167]. Diamond-like carbon (DLC) has been used as a biocompatible hard coating on biomedical polymers, showing higher flexible properties [168]. The amorphous nature of DLC allows incorporating elements like Si, F, P, Ag, and N, which improve the properties of the polymer [169–171].

3.3. Applications and Assignments. Surface-functionalized biomedical polymers are expected to show good potential properties for blood-contacting devices [172], tissue engineering applications [173], drug delivery systems [174], selective protein adsorption [175], and antibacterial applications [176]. Blood-contacting medical devices have thrombogenic complications. In order to prevent blood clotting, it is necessary to improve the biocompatibility and hemocompatibility of the polymer. Blood compatibility based on the platelet test in calcium- and phosphorous-doped DLC films on low-temperature isotropic pyrolytic carbon (LTIC) was studied. It was found that calcium- and phosphorous-doped DLC films reduced the platelet adhesion in comparison with pure LTIC, suggesting that DLC doped with calcium or phosphorus enhanced the hemocompatibility [172].

For tissue engineering, cell compatibility is necessary. Our group studied the effect of vitronectin and γ-globulin in PDMS films untreated and treated with plasma on defined culture conditions. Figure 5(a) shows the schematic representation of the plasma treatment and the contact angle before and after oxygen-plasma treatments of PDMS, demonstrating the surface modification from hydrophobic to hydrophilic surfaces after the plasma treatment. Figure 5(b) is followed by the functionalization of the surface with γ-globulin and vitronectin and the interactions with human-induced pluripotent cells (hiPSCs). It was found that γ-globulin on the untreated PDMS surfaces blocked the vitronectin adsorption, which prevents hiPSC adhesion [177]. It was reported that allylamine plasma deposition on poly(D,L-lactic acid) (PDLLA) promoted N3T3 fibroblast adhesion and proliferation. It was demonstrated that the amino groups have supported the cell attachment, obtaining better cell activity and attachment on the allylamine-deposited PDLLA scaffolds [173]. PDMS was pretreated with air plasma and subsequently amorphous titanium deposition by liquid-phase deposition (LPD) to obtain an amorphous titanium-PDMS thin film with antibacterial activity. Titanium surfaces showed better antibacterial effect for Gram-negative than for Gram-positive bacteria [176].

4. Mild Coating of Hydroxyapatite nanoparticles on Polymeric Substrates

4.1. Electrophoretic Deposition. Artificial bone is one of the most transplanted tissues. For this reason, the interest to develop new and more biocompatible inorganic-organic composites is increasing [178], not only because the physicochemical properties of the composites provide the necessary properties for bone replacement but also because human bone tissues are the nanocomposites formed by inorganic HAp (70 mass%) embedded in an organic matrix composed of collagen (30 mass%) and noncollagenous proteins [179, 180].

The objective of the incorporation of HAp into the biocompatible polymer matrix enhances the mechanical strength and provides the topographic features to improve the integrity of implants and the surrounding bone and to stimulate bone tissue ingrowth [181]. The coating methodology has the advantages to cover porous and irregularly shaped surfaces and to have control over the thickness [182]. Electrophoretic deposition (EPD) is a functional coating technique associated with the movement of charged particles in a liquid, which takes place by applying an electric field. The charged particles of the suspension can be deposited on the conductive or semiconducting substrate, creating a uniform particulate film. The film thickness depends on several factors such as viscosity, conductivity, zeta potential [183], and particle concentration in the suspension, deposition time, and applied voltage [184–186]. The coverage of some polymers with HAp has been investigated by EPD.
using AC (alternating current) or DC (direct current) in different alcoholic solvents for the biomedical applications [187]. The advantages of EPD are the possibility of uniform covering of the substrates with complex shapes, control of the microstructures, rapid deposition, simple and low-cost techniques, room temperature, and suitability of co-deposition [187–189]. A schematic representation of the electrophoretic deposition process is shown in Figure 6. In the suspension, the alcoholic solvent is adsorbed on the c-plane of HAp to generate ionic dissociation [190]. Thus, the negatively charged ethoxide ion and positively charged HAp nanocrystals were formed. Thus, the positively charged HAp nanocrystals, dispersed in the alcoholic solvent, move towards the negatively charged substrates under the influence of the applied electric field and the HAp nanocrystals are deposited on the polymer forming the dense particulate layer [191]. The EPD of the HAp-alginate and HAp-chitosan (CS) composites has been reported with the uniform coatings at the thickness of up to 60 μm [192, 193]. However, it has sought to improve the physicochemical properties of composites through co-deposition with other materials such as bioactive glass, obtaining bioactive glass-HAp-alginate and bioactive glass-HAp-CS composite coatings for biomedical applications. The film thickness in the range was up to several micrometers, although the deposit states were nonuniform because of the use of relatively larger bioglass particles [194]. The co-deposition of carbon nanotubes (CNTs) and HAp nanoparticles with crystal sizes of 20–40 nm has been investigated to obtain the microstructured HAp-CS-CNT composite coatings, indicating the enhanced, mechanical properties (hardness, elastic modulus, and adhesion strength), bioactivity, and corrosion-resistant properties [188]. The co-deposition of polyether ether ketone (PEEK) and HAp to obtain PEEK-HAp composite coatings with approximately 70 μm of thickness has been successfully obtained for the improved bioactivity [187]. The cathodic EPD of graphene (Gr), CS, and HAp on Ti substrate in ethanol suspension resulted in HAp/CS/Gr coatings with crystalline domain sizes of 42.6, 25.1, and 22.0 nm, respectively. The HAp/CS/Gr coatings showed improved morphology, thermal stability, and bioactivity by the incorporation of Gr [195]. Our group has reported EPD of HAp nanocrystals doped with zinc (Zn : HAp) on conductive silicone (Ti-silicone) to improve the biocompatibility and provide antibacterial activity. The thickness of the Zn : HAp nanocrystal layer was 20–50 nm. It was observed that there was better adhesion and spreading of the fibroblasts on the Zn : HAp film doped with 5 mol% of zinc ion (0.5-Zn : HAp) as shown in Figure 7 [196].

4.2. Biomimetic Processes. Biomineralization (or biological mineralization) is a well-regulated process, which is responsible for the controlled formation of inorganic materials from aqueous solution in living organisms [197]. The formation of inorganic biomaterials is demonstrated by the result of the combination of three physicochemical stages of supersaturation, nucleation, and crystal growth [198]. At the first stage, inorganic ions in the supersaturated body fluid start forming the nuclei [199]. The surface reactions between the nuclei develop the aggregation-based crystal growth [197]. Interactions between the aggregates and the ions in the solution generate the formation of stable clusters, followed by anisotropic crystal growth and phase transformation from amorphous calcium phosphate (ACP) to octacalcium phosphate (OCP). The next step is the transition from OCP to the well-ordered biological HAp crystals (BAp) [199–202]. The schematic representation of the biomineralization process is shown in Figure 8. In the living body, osteoblasts secrete a collagen-proteoglycan matrix. This matrix is important in controlling the mineralization [203]. Collagen can stabilize the amorphous clusters until they become HAp and orientate the formation of the HAp along the c-axis, which

Figure 6: (a) Scheme of the electrophoretic deposition (EFD) procedure with a direct current (DC) of 100 V, (b) deposition mechanism in ethanol, and (c) resultant electrophoretic deposition system at the monolayer, after ultrasonification. Reprinted with permission from [190], M. Tagaya et al., Sci. Technology Adv. Mater. 92 11 045002.1–045002.8. (2010) © 2010 IOP Publishing.
Figure 7: Silicone surface modification technique through the deposition of zinc-(Zn-) substituted HAp by EFD to achieve for providing bioactive properties to the films. Photographs of the PDMS substrates (a) before and (b) after the EPD and (c) after ultrasonication (US), indicating the maintenance of a flexible state in folding back. (d) AFM topographic images of 0.5-Zn : HAp nanocrystals electrophoretically prepared at coating voltages of 100 V in ethanol and micrographs of the biocompatible properties based on fibroblast ingrowth on the Zn-substituted HAp with the different initial Zn concentrations of (e) 0.0, (f) 2.5, (g) 5.0, and (h) 10 mol% at the culture time of 72 h. Reprinted with permission from [196], T.G.P. Galindo et al. Colloid Interface Sci. Commun. 10, 15–19 (2016) © 2016 Elsevier.

Figure 8: Scheme of the biomineralization process. (a) Ions in solution, (b) nucleation, (c) aggregation, (d) amorphous calcium phosphate—the circle shows the Posner cluster unit [Ca\textsubscript{9}(PO\textsubscript{4})\textsubscript{6}] projected on the ab plane, (e) octacalcium phosphate, projected on the ab plane, (f) hydroxyapatite projected on the ab plane, and (g) biological hydroxyapatite [199–202] (drawing using VESTA (10) from the CIF obtained from American Mineralogist Crystal Structure Database).
allows preferential binding with acidic extracellular matrix (ECM) proteins on its surface [197].

The new technology called “bioinspired growth” has been sought to emulate the natural biomineralization process in order to obtain bioactivity and mechanical properties, which can improve the biointeractions with the human bone [204]. Organic-inorganic fusion interfaces can be constructed by placing the polymer in simulated body fluid (SBF), which is a metastable solution containing supersaturated calcium (Ca\(^{2+}\)) and phosphate (PO\(_4^{3-}\)) ions. This process is a simple and inexpensive technique that can coat complex shapes [205]. Synthesis of nanocomposites with biocompatibility and similar structures to the natural bone by mineralization of nano-HAp on the assembled collagen has been reported [206]. It has been observed that the formation of HAp begins with the union between Ca\(^{2+}\) ions and negative ions on the polymer surface. The number and arrangement of the functional groups in the surface are important factors for HAp formation [207]. Higher functional groups on the polymer produce a higher HAp nucleation rate [208]. Nucleation occurs at the specific sites, and the polymer directs the nucleation [209,210]. As described above, some functional groups on the surface of polymers such as silanol groups (Si–OH) [211,212], carboxyl groups (–COOH) [213], and sulfonic groups (–SO\(_3\)H) [214] can effectively induce the formation of HAp through interactions with Ca\(^{2+}\) ions. Ca\(^{2+}\) ions are the key factor for HAp coating on polymers. The control of the deposition and growth conditions of deposited HAp can be carried out by changing the composition of the SBF solution. The thickness of the coated HAp can be controlled by the immersion time [207]. Our group has studied the biomineralization process to promote BAp growth from SBF by three different processes in Figure 9: process 1—the bare (gold (Au), Ti, and HAp) substrates induced BAp growth by immersion; process 2—the fetal bovine serum (FBS) proteins preadsorbed on the substrates showed slight BAp growth, indicating the significant inhibition of BAp growth [215]; and process 3—the BAp coating technique on tissue culture poly(styrene) through the film formation by the hybridization of BAp with the L-α-phosphatidylcholine phospholipid vesicle (PV) was achieved, obtaining a transparent HAp-PV film with stability against sterilization treatments, suggesting cell culture dish application [216].

4.3. Other Techniques. It has been observed that incorporation of HAp into the polymer matrix can enhance the mechanical properties, increase the roughness, and produce a topography that allows mimicking the nanostructure of the bone [217]. Among the most used techniques for the manufacture of HAp/biocompatible polymer composites are the solvent-solution casting method [218], plasma spraying process [219], electrospinning [220], electrochemical deposition [221], thermally induced phase separation (TIPS) also known as freeze-drying method [222], and pulsed laser deposition [223]. Calcium-deficient HAp nanocrystals (d-HAp) dispersed in N,N-dimethylformamide (DMF) were successfully deposited on PLA by the solvent-casting technique. d-HAp was homogeneously distributed on films and had similar morphology, composition, and crystalline structure to BAp. The thickness of the PLA/d-HAp nanocomposite films was about 0.1 mm. The tensile modulus of PLA/d-HAp nanocomposites was 2.77 GPa and higher as compared with that of pure PLA (1.66 GPa) [224]. The potential toxicity of the solvents is the major drawback of

![Figure 9: Scheme of the biomineralization process to promote biological apatite (BAp) growth from a simulated body fluid (SBF) by three different processes: process 1—the bare substrates induced BAp growth by immersion in SBF; process 2—the fetal bovine serum (FBS) proteins preadsorbed on the substrates showed slight BAp growth, indicating a significant inhibition of the BAp growth; and process 3—the BAp coating technique on tissue culture poly(styrene) through the film formation by the hybridization of BAp with the L-α-phosphatidylcholine phospholipid vesicle (PV) was achieved. Reprinted with permission from [215], C. Yadong et al., Cryst. Growth Des. 17, 4977—4983 (2017) © 2017, American Chemical Society [216], M. Tagaya et al. J. Phys. Chem. C,115, 22,523—22,533 (2011) © 2011, American Chemical Society.](image)
the solvent-casting technique. The fabrication of the nanofibrous (NF) gelatin/HAp composite scaffold by the TIPS technique mimicked the physical architecture and chemical composition of ECM in natural bone. NF-gelatin/apatite scaffolds showed significantly higher mechanical strength and better osteogenic differentiation, suggesting the use in bone tissue engineering [225]. This technique could present the toxicity due to the used solvents. The HAp/cellulose nanocomposite films were developed by the incorporation of HAp NPs with the particle sizes of 20-40 nm into the cellulose matrix in NaOH/urea aqueous solution and subsequent coagulation with a Na2SO4 aqueous solution. The thermal stability and tensile strength of the HAp/cellulose nanocomposite films were improved as compared with those of pure cellulose. The HAp/cellulose nanocomposite films showed excellent biocompatibility with nontoxicity [226]. These techniques to form inorganic-organic composites are more innovative, although they have the disadvantage of being more complicated and having a higher cost.

5. Polymer/Bioceramic Fusion Interfaces

5.1. Polymer/Bioceramic Cell-Interactive Interfaces. The process of bone tissue formation is called osteogenesis and is carried out by two ossification mechanisms: intramembranous (IM) and endochondral (EC) [227]. In IM ossification, mesenchymal stem cells (MSCs) derived from the neural crest are attached at the bone formation site, and then MSCs proliferate and condense into compact nodules and subsequently differentiate into osteoblasts. Osteoblasts capture the calcium, carbonate, and phosphate ions for the formation of HAp nanocrystals from the blood and deposit them in the osteoid matrix and also secrete the matrix components to promote calcification tissue. In this process, the transcription factor and morphogenic proteins are expressed [228]. EC ossification is responsible for the formation of long bones. After the condensation, MSCs differentiate into chondrocytes to form cartilage templates that will later be replaced by endochondral bone. In the growth plate, the extracellular matrix (ECM) is composed of type II, IX, X, and XI collagen, proteoglycans containing glycosaminoglycans (chondroitin sulfate), hyaluronic acid, molecular components like matrix lines, and cartilage oligomeric matrix protein, among others [228, 229]. In the HAp/polymer fusion interfaces, as mentioned in Section 4, HAp provides good osteoconductivity, bioactivity, and a biocompatible interface, while the polymer contributes a continuous and flexible structure to obtain a high surface area and high porosity composites, which allows anchoring, growth, and differentiation of cells for bone formation such as fibroblasts [230]. However, polymer/bioceramic interfacial functions for providing preferential biomolecular interactions at the nanoscale were not understood so far.

For porous composite structures, the study of the interactions between the HAp/bioinert polymer and the cells is carried out using in vitro cell culture models. One of the most important states for cell/HAp/polymer interactions, which can be called “biofusion materials,” is the characteristic of cellular adhesion [231]. It has been reported that chemical compositions, crystallinity, topographical structures, particle sizes, and surface properties can directly affect the cell adhesion, proliferation, and differentiation [232]. The topography of the composites promotes the adsorption of specific proteins, which affects the cellular characteristics. Surface roughness can induce cell adhesion and proliferation [233]. It has been demonstrated that the pore interconnectivity, pore size, and total porosity are important factors for the cellular attachment, proliferation, and nutrient diffusion. If the pores are very small, cell migration is difficult, which generates cellular encapsulation around the implanted composite. The limited diffusion of nutrients and the reuse of waste cause necrotic regions. If the pores are very large, the surface area decreases, which hinders cell adhesion. Pore size determines the number of struts and ligands available for cell adhesion [234]. In the composites, pore diameters of 186-200 μm can transport nutrients and metabolites and ingrowth of blood vessels, while pore diameters of 10-100 μm take nutrients and throw waste and ingrowth capillaries [235]. It has been reported that osteoblastic cells could be attached easily to the Hap-coated surface, allowing osteoid formation with chemical and biological interactions between the implanted composites and the bones [236], indicating the importance of HAp surface properties.

The initial attachment of human osteoblasts (HOBs) on poly(ε-caprolactone) (PCL) and PLA as the matrix for composing two HAp particles of (a) 50 μm size and sintered (HApω) and (b) submicron size (HApρ) has been studied. After the cell culture for 4 h, the cells on the PLA/HAp composites showed a higher degree of cellular spreading than the case on PCL/HAp. The cells on PLA/HApω and PCL/HApω with the rough macrotexures exhibited more elongated morphology than those on the composites with HApρ. After 24 hours, cell activity on PCL/HAp and PLA/HAp composites was remarkably higher than the case on pure polymer films. The “point exposure” of HAp provides suitable composites for controlling the cell density on implant surfaces [237]. A synthetic HAp/collagen composite with similar composition and structure of natural bone was reported. In the in vivo and in vitro studies of biological reactions, the composites were resorbed by osteoclasts through phagocytosis and also promoted the adhesion of osteoblasts to form a new bone in the surrounding [238]. Our group achieved the microstructures of HAp NPs composites with SU-8 polymer micropatterns by a nano/microfabrication technique and studied the interfacial phenomena of hepatocytes. The hepatocytes interacted and promoted cellular aggregation and then preferential adhesion on HAp NP sites. Preferential adhesion was observed by a quartz crystal microbalance with dissipation (QCM-D) technique and optical microscopy (Figure 10) [239].

5.2. Control of Cell-Protein-Hydroxyapatite Interfacial Interactions. Cell adhesion, proliferation, migration, differentiation, and survival can be modulated by ECM proteins. The ECM can influence diverse types of cells such as osteoblasts, osteoclasts, osteocytes, and bone lining cells [178]. The ECM can be constituted by several constituents like arginine-glycine-asparagine (RGD) and peptides such as...
collagen (Col), laminin, fibronectin (Fn), and vitronectin [240]. Numerous in vivo studies showed that the implanted materials are immediately covered by interstitial fluids and blood proteins, indicating the importance of adsorbed proteins for the initial interaction [241]. In particular, fibrillar proteins such as fibrinogen and vitronectin favor the adhesion and migration of cells [242]. Attachments of the cells can occur via the integrin-mediated receptor, followed by clustering of transmembrane receptors to start the signaling cascade and finally regulate the attachment and characteristics of the cells, leading to the improvement of the environment for cellular interactions (cell-cell and cell-material) [243, 244]. The way in which the proteins are adsorbed causes specific cellular reactions to the underlying physicochemical properties of the material [242]. To control the cell function, it is necessary to clarify the ECM protein adsorption because the structural organization of the proteins can result in different initial interactions with the cells [245]. The adsorption of proteins depends on surficial properties like free energy, wettability, roughness, and charge. Porous HAp improved protein adsorption and provided better viability as compared with the case by the dense HAp [235]. The water molecules from the solvents can be absorbed on the HAp surface to form the hydration layers, which has great influence on the three-dimensional arrangement of the proteins [246]. In the previous reports about hydration [247], the possible schematic representation of protein adsorption on HAp is shown in Figure 11. In the beginning, hydrated fibrinogen (Fgn) interacts with the hydration layer with possible dehydration. Then, Fgn absorption on HAp occurs, when the αC domain of the positively charged Fgn interacts with the negatively charged phosphate ions and hydroxyl groups of HAp. Because of the Fgn saturation and the Fgn-Fgn hydrophobic interactions, the adsorbed Fgn changes the conformation from “side-on” to “end-on” in Figure 11(a). The adsorption model of albumin (Ab) could be “side-on” at the initial adsorption region at the monolayer. The positively charged calcium ions on HAp effectively bond with the imidazole and carboxyl groups of Ab. Nonfreezing water could suppress the denaturalization of the adsorbed proteins, suggesting the concept of “biofusion interfaces” as shown in Figure 11(b) [247].

Several HAp/polymer/cell interactions have been studied to improve bone tissue regeneration and to control cell adhesion. HAp which bonded with insulin was incorporated in PLGA to obtain insulin-HAp/PLGA composites. In vitro studies showed better cell adhesion and differentiation with an accelerated osteogenesis on the insulin-HAp/PLGA composites as compared with the case on HAp/PLGA and pure PLGA, suggesting its possible application as an artificial bone for implantation and as scaffolds for bone tissue regeneration [248]. In vitro, the cellular response of HOBs to HAp roughness was studied. The increase in roughness increased the adhesion, proliferation, and detachment strength of the cells. The detachment strength could be due to the specific adsorption of serum proteins such as Fn. The substrates preadsorbed with Fn have resulted in high detachment strength [249]. Previously, our group investigated the interfacial phenomenon between the preadsorbed protein layer and cells on HAp and oxidized polystyrene (PSox) by the Voight-based
viscoelastic model. With the increase in cell adhesion, the interfacial layer was changed from elastic to viscose. The cells on pretreated HAp showed rough fibrous pseudopods, whereas the pseudopods on the pretreated PSox were particulate, suggesting the change in the cytoskeleton and ECM [250, 251]. Our group observed the change in the arrangement of the ECM and the cytoskeleton at the interfaces due to the interactions between the cells and the proteins. The first interfacial phenomenon was carried out by the preadsorption of Ab, Fn, and Col, followed by the adsorption in FBS, and finally the cellular adhesion of osteoblasts. Col adsorption had higher elasticity and viscosity than the cases in Fn and Ab adsorption. Fn and Col formed the viscous interfacial layer and cell adhesion to exhibit the elongated cellular shapes with fibrous pseudopods, contrary to the modification of Ab that had round shapes (Figure 12). Figure 12(a) shows the scheme of the evaluation for the effect of different preadsorbed proteins on the interfacial phenomenon during the initial adhesion between the proteins and the osteoblast-like cells by QCM-D and the confocal laser scanning microscope (CLSM). CLSM images of the cells adhered on (b) fetal bovine serum (FBS), (c) FBS-Fgn, (d) FBS-Ab, and (e) FBS-collagen adsorbed on the HAp. Reprinted with permission from [252], M. Tagaya et al. Langmuir, 27, 7645—7653 (2011), © 2011, American Chemical Society.
Figure 13(a) shows the conventional successive events on bioceramic surfaces after implantation in the animal body, and Figure 13(b) shows the possible illustration of preferential mobility for cell adhesion by fusion interfaces between bioceramics and polymers, exhibiting comfortable viscoelastic and flexible structures by the cells.

6. Conclusion and Future Perspectives

HAp NPs, biocompatible polymers, and their composites have been extensively studied in both in vitro and in vivo biomolecular interactions for various biomedical applications. HAp, due to the similarity with the inorganic component of bones and teeth, remains the most suitable biomaterial to be used for bone regeneration and replacement. In order for the bone implants to be properly attached to the bone to ensure bone regeneration, HAp/polymer fusion interfaces have been developed. HAp NPs provide good osteoconductivity, bioactivity, and biocompatible interfaces, and the polymer contributes with a continuous and flexible structure and provides support structures for cellular growth. Since the structures, chemical compositions, and surface topographies of the HAp/polymer fusion interfaces will determine the interfacial interactions with the biological medium (cells, proteins, and tissues), several methods of depositing HAp NPs on the polymer surfaces have been developed. Within these methods, “bioinspired growth” is a promising method, since it forms a HAp with a structure more similar to the biological HAp NPs in the bones, which can allow a better incorporation of osseous implants. Since cell adhesion, migration, and proliferation are strongly influenced by the preadsorbed proteins, it is necessary to develop HAp/polymer fusion interfaces that bind only with specific proteins, such as fibrillar proteins, in order to enhance the adhesion and cell growth.

The above points have revealed some of the critical events for HAp NPs to stimulate an interface in body fluid. In future, the study on biointeractive interfaces of HAp NPs deposited on the rigid and soft polymers can be useful for biomedical applications. Due to that the HAp/rigid polymer has better support and strength, it can be used for bone repair and replacement in hard tissues, while the HAp/soft polymer can be used in skin tissues that require more flexibility to preserve their functions, as is the case with tendon repair and cartilage replacement, to build blood vessels or long-term catheters. Further researches can bring significant improvements to existing experimental methods to prepare and characterize useful nanobioceramic-polymer fusion interfaces. These studies will lead to a deep understanding of nanobiointerfaces.

To overcome existing scientific challenges, mutual interactions at the nanobiointerfaces should be explored by developing novel detection techniques for biomolecular interactions [253]. Proper understanding of cell behavior during contact with implanted HAp NP films is essential for attaining adequate health and safety. In particular, the development of tissue engineering techniques requires greater consideration of cell adhesion properties, whether for the improvement of the surfaces by adsorption or grafting of specific adhesion factors or for the development of hybrid materials for autologous bone cells and materials. Therefore, bioceramic-cell fusion interface studies have great potential in informing the development of superior biomaterials.

Conflicts of Interest

There is no conflict of interest regarding the publication of this paper.
Acknowledgments

This study was supported by a grant from the Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant-in-Aid for Young Scientists (A), Grant No. 17H04954).

References

[1] H. Zhou and J. Lee, “Nanoscale hydroxyapatite particles for bone tissue engineering,” Acta Biomaterialia, vol. 7, no. 7, pp. 2769–2781, 2011.
[2] M. M. Stevens, “Biomaterials for bone tissue engineering,” Materials Today, vol. 11, no. 5, pp. 18–25, 2008.
[3] T. Thamaraiselvi and S. Rajeswari, “Biological evaluation of bioceramic materials—a review,” Trends in Biomaterials and Artificial Organs, vol. 18, pp. 9–17, 2004.
[4] J. Strnad, Z. Strnad, J. Šesták, K. Urban, and C. Povýšil, “Bio-activated titanium surface utilizable for mimetic bone implantation in dentistry—part III: surface characteristics and bone-implant contact formation,” Journal of Physics and Chemistry of Solids, vol. 68, no. 5–6, pp. 841–845, 2007.
[5] W. J. Shon, S. H. Chung, H. K. Kim, G. J. Han, B. H. Cho, and Y. S. Park, “Peri-implant bone formation of non-thermal atmospheric pressure plasma-treated zirconia implants with different surface roughness in rabbit tibiae,” Clinical Oral Implants Research, vol. 25, no. 5, pp. 573–579, 2014.
[6] E. Kon, A. Muraglia, A. Corsi et al., “Autologous bone narrow stromal cells loaded onto porous hydroxyapatite ceramic accelerate bone repair in critical-size defects of sheep long bones,” Journal of Biomedical Materials Research, vol. 49, no. 3, pp. 328–337, 2000.
[7] J. Li and G. W. Hastings, “Oxide bioceramics: inert ceramic materials in medicine and dentistry,” in Handbook of Biomaterial Properties, pp. 339–352, Springer, New York, NY, USA, 2016.
[8] J. A. Juhasz and S. M. Best, “Bioactive ceramics: processing, structures and properties,” Journal of Materials Science, vol. 47, no. 2, pp. 610–624, 2012.
[9] P. Frayssinet, “Calcium phosphates in orthopedic surgery,” in Biomechanics and Biomaterials in Orthopaedics, Chapter 9, D. G. Poitout, Ed., p. 101, Springer, London, 2004.
[10] E. Champion, “Sintering of calcium phosphate bioceramics,” Acta Biomaterialia, vol. 9, no. 4, pp. 5855–5875, 2013.
[11] S. V. Dorozhkin, “Multiphasic calcium orthophosphate (CaPO4) bioceramics and their biomedical applications,” Ceramics International, vol. 42, no. 6, pp. 6529–6554, 2016.
[12] S. V. Dorozhkin, “Calcium orthophosphates as bioceramics: state of the art,” Journal of Functional Biomaterials, vol. 1, no. 1, pp. 22–107, 2010.
[13] Y. Leng, J. Chen, and S. Qu, “TEM study of calcium phosphate precipitation on HA/TCP ceramics,” Biomaterials, vol. 24, no. 13, pp. 2125–2131, 2003.
[14] S. Bose and S. Tarefder, “Calcium phosphate ceramic systems in growth factor and drug delivery for bone tissue engineering: a review,” Acta Biomaterialia, vol. 8, no. 4, pp. 1401–1421, 2012.
[15] T. E. San, H. Jie, and A. Mamoru, Eds., Nanobioceramics for Healthcare Applications, World Scientific, 2016.
[16] T. Yamamuro, “Bioceramics,” in Biomechanics and Biomaterials in Orthopedics, Chapter 3, D. G. Poitout, Ed., pp. 22–23, Springer, London, 2004.
[17] C. B. Carter and M. G. Norton, Ceramic Materials: Science and Engineering, Springer, 2007.
[18] D. H. Kohn, Bioceramics: Standard Handbook of Biomedical Engineering and Design, Chapter 13, McGraw-Hill, 2004.
[19] S. V. Dorozhkin, “Bioceramics of calcium orthophosphates,” Biomaterials, vol. 31, no. 7, pp. 1465–1485, 2010.
[20] S. Dorozhkin, “Calcium orthophosphate based bioceramics,” Materials, vol. 6, no. 9, pp. 3840–3942, 2013.
[21] S. V. Dorozhkin, “Calcium orthophosphate deposits: preparation, properties and biomedical applications,” Materials Science and Engineering: C, vol. 55, pp. 272–326, 2015.
[22] S. V. Dorozhkin, “Calcium orthophosphate bioceramics,” Ceramics International, vol. 41, no. 10, pp. 13913–13966, 2015.
[23] B. Kundu, D. Ghosh, M. K. Sinha et al., “Doxorubicin-intercalated nano-hydroxyapatite drug-delivery system for liver cancer: an animal model,” Ceramics International, vol. 39, no. 8, pp. 9557–9566, 2013.
[24] E. Pepla, L. K. Besharat, G. Palaia, G. Tenore, and G. Migliau, “Nano-hydroxyapatite and its applications in preventive, restorative and regenerative dentistry: a review of literature,” Annali di Stomatologia, vol. 5, no. 3, pp. 108–114, 2014.
[25] M. P. Ferraz, F. J. Monteiro, and C. M. Manuel, “Hydroxyapatite nanoparticles: a review of preparation methodologies,” Journal of Applied Biomaterials and Biomechanics, vol. 2, no. 2, pp. 74–80, 2004.
[26] H. Aoki, “Science and medical applications of hydroxyapatite,” JAAS, vol. 1991, p. 214, 1991.
[27] A. Takeuchi, C. Ohtsuki, T. Miyazaki et al., “Heterogeneous nucleation of hydroxyapatite on protein: structural effect of silk sericin,” Journal of the Royal Society Interface, vol. 2, no. 4, pp. 373–378, 2005.
[28] M. Vallet-Regi and D. A. Navarrete, Nanoceramics in Clinical Use: from Materials to Applications, Chapter 1, RSC Nanoscience & Nanotechnology, 2nd edition, 2015.
[29] M. Okada and T. Matsumoto, “Synthesis and modification of apatite nanoparticles for use in dental and medical applications,” Japanese Dental Science Review, vol. 51, no. 4, pp. 85–95, 2015.
[30] M. Parent, H. Baradari, E. Champion, C. Damia, and M. Viana-Trecant, “Design of calcium phosphate ceramics for drug delivery applications in bone diseases: a review of the parameters affecting the loading and release of the therapeutic substance,” Journal of Controlled Release, vol. 252, pp. 1–17, 2017.
[31] Z. Shi, X. Huang, Y. Cai, R. Tang, and D. Yang, “Size effect of hydroxyapatite nanoparticles on proliferation and apoptosis of osteoblast-like cells,” Acta Biomaterialia, vol. 5, no. 1, pp. 338–345, 2009.
[32] Y. Yuan, C. Liu, J. Qian, J. Wang, and Y. Zhang, “Size-mediated cytotoxicity and apoptosis of hydroxyapatite nanoparticles in human hepatoma HepG2 cells,” Biomaterials, vol. 31, no. 4, pp. 730–740, 2010.
[33] X. Zhao, S. X. Ng, B. C. Heng et al., “Cytotoxicity of hydroxyapatite nanoparticles is shape and cell dependent,” Archives of Toxicology, vol. 87, no. 6, pp. 1037–1052, 2013.
[34] Y. Zhao, Y. Zhang, F. Ning, D. Guo, and Z. Xu, “Synthesis and cellular biocompatibility of two kinds of HAP with different nanocrystal morphology,” Journal of Biomedical Materials Research Part B: Applied Biomaterials, vol. 83B, no. 1, pp. 121–126, 2007.
[35] K. Lin, C. Wu, and J. Chang, “Advances in synthesis of calcium phosphate crystals with controlled size and shape,” Acta Biomaterialia, vol. 10, no. 10, pp. 4071–4102, 2014.

[36] M. Sadat-Shojai, M. T. Khorasani, E. Dinpanah-Khoshdargi, and A. Jamshidi, “Synthesis methods for nanosized hydroxyapatite with diverse structures,” Acta Biomaterialia, vol. 9, no. 8, pp. 7591–7621, 2013.

[37] B. Nasiri-Tabrizi, P. Honarmandi, R. Ebrahimi-Kahrizsangi, and P. Honarmandi, “Synthesis of nanosize single-crystal hydroxyapatite via mechanochemical method,” Materials Letters, vol. 63, no. 5, pp. 543–546, 2009.

[38] W. J. Shih, Y. F. Chen, M. C. Wang, and M. H. Hon, “Crystal growth and morphology of the nano-sized hydroxyapatite powders synthesized from CaHPO₄·2H₂O and CaCO₃ by hydrolysis method,” Journal of Crystal Growth, vol. 270, no. 1-2, pp. 211–218, 2004.

[39] A. Nakahira, K. Sakamoto, S. Yamaguchi, M. Kaneno, S. Takeda, and M. Okazaki, “Novel synthesis method of hydroxyapatite whiskers by hydrolysis of alpha-tricalcium phosphate in mixtures of water and organic solvent,” Journal of the American Ceramic Society, vol. 82, no. 8, pp. 2029–2032, 1999.

[40] W. Feng, L. Mu-Sen, L. Yu-Peng, and Q. Yong-Xin, “A simple sol–gel technique for preparing hydroxyapatite nanopowders,” Materials Letters, vol. 59, no. 8-9, pp. 916–919, 2005.

[41] A. Beganskiene, O. Dudko, R. Sirutkaitis, and R. Giraitis, “Water based sol-gel synthesis of hydroxyapatite,” Materials Science, vol. 9, pp. 383–386, 2003.

[42] A. K. Nayak, “Hydroxyapatite synthesis methodologies: an overview,” International Journal of ChemTech Research, vol. 2, pp. 903–907, 2010.

[43] J. Liu, X. Ye, H. Wang, M. Zhu, B. Wang, and H. Yan, “The influence of pH and temperature on the morphology of hydroxyapatite synthesized by hydrothermal method,” Ceramics International, vol. 29, no. 6, pp. 629–633, 2003.

[44] P. Wang, C. Li, H. Gong, X. Jiang, H. Wang, and K. Li, “Effects of synthesis conditions on the morphology of hydroxyapatite nanoparticles produced by wet chemical process,” Powder Technology, vol. 203, no. 2, pp. 315–321, 2010.

[45] S. Bose and S. K. Saha, “Synthesis and characterization of hydroxyapatite nanopowders by emulsion technique,” Chemistry of Materials, vol. 15, no. 23, pp. 4464–4469, 2003.

[46] H. Güler, G. Günçoğmaz, F. Kurtuluş, G. Çelik, and Ş. S. Gacanoğlu, “Solid state synthesis of calcium borohydroxyapatite,” Solid State Sciences, vol. 13, no. 11, pp. 1916–1920, 2011.

[47] Y. Han, S. Li, X. Wang, and X. Chen, “Synthesis and sintering of nanocrystalline hydroxyapatite powders by citric acid sol–gel combustion method,” Materials Research Bulletin, vol. 39, no. 1, pp. 25–32, 2004.

[48] A. Wang, D. Liu, H. Yin et al., “Size-controlled synthesis of hydroxyapatite nanorods by chemical precipitation in the presence of organic modifiers,” Materials Science and Engineering C, vol. 27, no. 4, pp. 865–869, 2007.

[49] R. Xin, F. Ren, and Y. Leng, “Synthesis and characterization of nano-crystalline calcium phosphates with EDTA-assisted hydrothermal method,” Materials and Design, vol. 31, no. 4, pp. 1691–1694, 2010.

[50] D. S. Seo and J. K. Lee, “Synthesis of hydroxyapatite whiskers through dissolution–recrystallization process using EDTA,” Journal of Crystal Growth, vol. 310, no. 7-9, pp. 2162–2167, 2008.

[51] W. Wei, X. Zhang, J. Cui, and Z. Wei, “Interaction between low molecular weight organic acids and hydroxyapatite with different degrees of crystallinity,” Colloids and Surfaces A: Physicochemical and Engineering Aspects, vol. 392, no. 1, pp. 67–75, 2011.

[52] Y. J. Wang, J. H. Chen, Y. X. Cui, S. Q. Wang, and D. M. Zhou, “Effects of low-molecular-weight organic acids on Cu (II) adsorption onto hydroxyapatite nanoparticles,” Journal of Hazardous Materials, vol. 162, no. 2-3, pp. 1135–1140, 2009.

[53] G. Zhang, Z. Shen, M. Liu et al., “Synthesis and characterization of mesoporous ceria with hierarchical nanoarchitecture controlled by amino acids,” The Journal of Physical Chemistry B, vol. 110, no. 51, pp. 25782–25790, 2006.

[54] A. Wang, H. Yin, D. Liu et al., “Effects of organic modifiers on the size-controlled synthesis of hydroxyapatite nanorods,” Applied Surface Science, vol. 253, no. 6, pp. 3311–3316, 2007.

[55] Y. T. Huang, M. Imura, Y. Nemoto, C. H. Cheng, and Y. Yamauchi, “Block-copolymer-assisted synthesis of hydroxyapatite nanoparticles with high surface area and uniform size,” Science and Technology of Advanced Materials, vol. 12, no. 4, article 045005, 2011.

[56] L. Yan, Y. Li, Z. X. Deng, J. Zhuang, and X. Sun, “Surfactant-assisted hydrothermal synthesis of hydroxyapatite nanorods,” International Journal of Inorganic Materials, vol. 3, no. 7, pp. 633–637, 2001.

[57] K. Shiba, S. Motozuka, T. Yamaguchi et al., “Effect of cationic surfactant micelles on hydroxyapatite nanocrystal formation: an investigation into the inorganic–organic interfacial interactions,” Crystal Growth & Design, vol. 16, no. 3, pp. 1463–1471, 2016.

[58] F. Ridi, I. Meazzini, B. Castrolflorio, M. Bonini, D. Berti, and P. Baglioni, “Functional calcium phosphate composites in nanomedicine,” Advances in Colloid and Interface Science, vol. 244, pp. 281–295, 2017.

[59] T. G. P. Galindo, T. Kataoka, and M. Tagaya, “Morphogenesis of Zn-substituted stoichiometric and carbonate hydroxyapatite nanoparticles and their cytotoxicity in fibroblasts,” Journal of Nanomaterials, vol. 2015, Article ID 376045, 8 pages, 2015.

[60] N. Tran and T. J. Webster, “Nanotechnology for bone materials,” Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, vol. 1, no. 3, pp. 336–351, 2009.

[61] S. V. Dorozhkin, “Nanosized and nanocrystalline calcium orthophosphates,” Acta Biomaterialia, vol. 6, no. 3, pp. 715–734, 2010.

[62] E. Engel, A. Michiardi, M. Navarro, D. Lacroix, and J. A. Planell, “Nanotechnology in regenerative medicine: the materials side,” Trends in Biotechnology, vol. 26, no. 1, pp. 39–47, 2008.

[63] V. Karageorgiou and D. Kaplan, “Porosity of 3D biomaterial scaffolds and osteogenesis,” Biomaterials, vol. 26, no. 27, pp. 5474–5491, 2005.

[64] W. Wang and K. W. K. Yeung, “Bone grafts and biomaterials substitutes for bone defect repair: a review,” Bioactive Materials, vol. 2, no. 4, pp. 224–247, 2017.

[65] R. A. Perez, S. J. Seo, J. E. Won et al., “Therapeutically relevant aspects in bone repair and regeneration,” Materials Today, vol. 18, no. 10, pp. 573–589, 2015.
[66] K. Deshmukh, M. M. Shaik, S. R. Ramanan, and M. Kowshik, “Self-activated fluorescent hydroxyapatite nanoparticles: a promising agent for bioimaging and biolabeling,” ACS Biomaterials Science & Engineering, vol. 2, no. 8, pp. 1257–1264, 2016.

[67] C. Rosticher, B. Viana, T. Maldiney, C. Richard, and C. Chanéal, “Persistent luminescence of Eu, Mn, Dy doped calcium phosphates for in-vivo optical imaging,” Journal of Luminescence, vol. 170, pp. 460–466, 2016.

[68] C. Zhang, J. Yang, Z. Quan et al., “Hydroxyapatite nano- and microcrystals with multiform morphologies: controllable synthesis and luminescence properties,” Crystal Growth & Design, vol. 9, no. 6, pp. 2725–2733, 2009.

[69] A. L. Rosa, M. M. Beloti, P. T. Oliveira, and R. Van Noort, “Osteointegration and osteoconductivity of hydroxyapatite of different microporosities,” Journal of Materials Science: Materials in Medicine, vol. 13, no. 11, pp. 1071–1075, 2002.

[70] U. Joos, H. P. Wiesmann, T. Szuwart, and U. Meyer, “Mineralization at the interface of implants,” International Journal of Oral and Maxillofacial Surgery, vol. 35, no. 9, pp. 783–790, 2006.

[71] L. S. Nair and C. T. Laurencin, “Biodegradable polymers as biomaterials,” Progress in Polymer Science, vol. 32, no. 8–9, pp. 762–798, 2007.

[72] J. C. Middleton and A. J. Tipton, “Synthetic biodegradable polymers as orthopedic devices,” Biomaterials, vol. 21, no. 23, pp. 2335–2346, 2000.

[73] L. G. Griffith, “Polymeric biomaterials,” Acta Materialia, vol. 48, no. 1, pp. 263–277, 2000.

[74] A. S. Hoffman, “Surface modification of polymers: physical, chemical, mechanical and biological methods,” in Macromolecular Symposia, vol. 101, pp. 443–454, Hüthig & Wepf Verlag, Basel, 1996.

[75] J. M. Goddard and J. H. Hotchkiss, “Polymer surface modification for the attachment of bioactive compounds,” Progress in Polymer Science, vol. 32, no. 7, pp. 698–725, 2007.

[76] B. D. Ulery, L. S. Nair, and C. T. Laurencin, “Biomedical applications of biodegradable polymers,” Journal of Polymer Science Part B: Polymer Physics, vol. 49, no. 12, pp. 832–864, 2011.

[77] A. J. R. Lasprilla, G. A. R. Martinez, B. H. Lunelli, A. L. Jardini, and R. M. Filho, “Poly-lactic acid synthesis for application in biomedical devices—a review,” Biotechnology Advances, vol. 30, no. 1, pp. 321–328, 2012.

[78] Y. Lu and S. C. Chen, “Micro and nano-fabrication of biodegradable polymers for drug delivery,” Advanced Drug Delivery Reviews, vol. 56, no. 11, pp. 1621–1633, 2004.

[79] K. S. Soppimuth, T. M. Aminabhavi, A. R. Kulkarni, and W. E. Rudzinski, “Biodegradable polymeric nanoparticles as drug delivery devices,” Journal of Controlled Release, vol. 70, no. 1-2, pp. 1–20, 2001.

[80] K. E. Uhrich, S. M. Cannizzaro, R. S. Langer, and K. M. Shakesheff, “Polymeric systems for controlled drug release,” Chemical Reviews, vol. 99, no. 11, pp. 3181–3198, 1999.

[81] A. K. Bajpai, S. K. Shukla, S. Bhanu, and S. Kankane, “Responsive polymers in controlled drug delivery,” Progress in Polymer Science, vol. 33, no. 11, pp. 1088–1118, 2008.

[82] B. Dhandayuthapani, Y. Yoshida, T. Maekawa, and D. S. Kumar, “Polymeric scaffolds in tissue engineering application: a review,” International Journal of Polymer Science, vol. 2011, Article ID 290602, 19 pages, 2011.

[83] F. J. O’Brien, “Biomaterials & scaffolds for tissue engineering,” Materials Today, vol. 14, no. 3, pp. 88–95, 2011.

[84] S. Bose, M. Roy, and A. Bandypadhyay, “Recent advances in bone tissue engineering scaffolds,” Trends in Biotechnology, vol. 30, no. 10, pp. 546–554, 2012.

[85] S. Stratton, N. B. Shelke, K. Hoshino, S. Rudraiah, and S. G. Kumbar, “Bioactive polymeric scaffolds for tissue engineering,” Bioactive Materials, vol. 1, no. 2, pp. 93–108, 2016.

[86] A. U. Daniels, M. K. O. Chang, K. P. Andriano, and J. Heller, “Mechanical properties of biodegradable polymers and composites proposed for internal fixation of bone,” Journal of Applied Biomaterials, vol. 1, no. 1, pp. 57–78, 1990.

[87] G. O. Hofmann, “Biodegradable implants in traumatology: a review on the state-of-the-art,” Archives of Orthopaedic and Trauma Surgery, vol. 114, no. 3, pp. 123–132, 1995.

[88] B. L. Seal, T. C. Otero, and A. Panitch, “Polymeric biomaterials for tissue and organ regeneration,” Materials Science & Engineering R: Reports, vol. 34, no. 4–5, pp. 147–230, 2001.

[89] L. Zhang and T. J. Webster, “Nanotechnology and biomaterials: promises for improved tissue regeneration,” Nano Today, vol. 4, no. 1, pp. 66–80, 2009.

[90] B. P. Kanungo and L. J. Gibson, “Density–property relationships in collagen–glycosaminoglycan scaffolds,” Acta Biomaterialia, vol. 6, no. 2, pp. 344–353, 2010.

[91] S. J. Lee, G. J. Lim, J. W. Lee, A. Atala, and J. J. Yoo, “In vitro evaluation of a poly (lactide-co-glycolide)–collagen composite scaffold for bone regeneration,” Biomaterials, vol. 27, no. 18, pp. 3466–3472, 2006.

[92] M. P. E. Wengel, L. Bozec, M. A. Horton, and P. Mesquida, “Mechanical properties of collagen fibrils,” Biophysical Journal, vol. 93, no. 4, pp. 1255–1263, 2007.

[93] M. Okuda, M. Takeguchi, M. Tagaya et al., “Elemental distribution analysis of type I collagen fibril in tilapia fish scale with energy-filtered transmission electron microscope,” Micron, vol. 40, no. 5-6, pp. 665–668, 2009.

[94] W. Arbia, L. Arbia, L. Adour, and A. Amrane, “Chitin extraction from crustacean shells using biological methods—a review,” Food Technology and Biotechnology, vol. 51, pp. 12–25, 2013.

[95] R. Jayakumar, M. Prabaharan, S. V. Nair, and H. Tamura, “Novel chitin and chitosan nanofibers in biomedical applications,” Biotechnology Advances, vol. 28, no. 1, pp. 142–150, 2010.

[96] S. Islam, M. A. R. Bhuiyan, and M. N. Islam, “Chitin and chitosan: structure, properties and applications in biomedical engineering,” Journal of Polymers and the Environment, vol. 25, no. 3, pp. 854–866, 2017.

[97] T. Freier, R. Montenegro, H. Shan Koh, and M. S. Shoichet, “Chitin-based tubes for tissue engineering in the nervous system,” Biomaterials, vol. 26, no. 22, pp. 4624–4632, 2005.

[98] C. Ji and J. Shi, “Thermal-crosslinked porous chitosan scaffolds for soft tissue engineering applications,” Materials Science and Engineering: C, vol. 33, no. 7, pp. 3780–3785, 2013.

[99] M. Cheng, W. Cao, Y. Gao, Y. Gong, N. Zhao, and X. Zhang, “Studies on nerve cell affinity of biodegradable modified chitosan films,” Journal of Biomaterials Science, Polymer, vol. 14, no. 10, pp. 1155–1167, 2003.

[100] B. Lepoittevin, M. Devalkenaere, N. Pantoustier et al., “Poly (ε-caprolactone)/clay nanocomposites prepared by melt intercalation: mechanical, thermal and rheological properties,” Polymer, vol. 43, no. 14, pp. 4017–4023, 2002.
M. F. Ashby and D. R. H. Jones, Materials Data Book, Cambridge University Engineering Department, 2003.

P. Krol, C. Zhang, N. Abbasi, S. M. Hashemi, M. Salehi et al., "Compressive properties of commercially available polyurethane foams as mechanical models for osteoporotic human cancellous bone," BMC Musculoskeletal Disorders, vol. 9, no. 1, pp. 137–137.7, 2008.

C. Zhang, "Elastic degradable polyurethanes for biomedical applications," All Theses, vol. 381, pp. 1–89, 2006.

L. Verbel, S. Dadaksh, M. Van den Eynde, J. P. Kruth, B. Goderis, and P. Van Puystvelde, "Characterization of polyamide powders for determination of laser sintering processability," European Polymer Journal, vol. 75, pp. 163–174, 2016.

E. Parodi, L. E. Govaert, and G. W. M. Peters, "Glass transition temperature versus structure of polyamide 6: a flash-DSC study," Thermochimica Acta, vol. 657, pp. 110–122, 2017.

H. Klinkmann and J. Vienken, "Membranes for dialysis," Nephrology, Dialysis, Transplantation, vol. 10, Supplement 3, pp. 39–454, 1995.

I. Capparell, "Suture materials: a review," Clinical Materials, vol. 4, no. 1, pp. 3–12, 1989.

M. H. Mohammed, W. M. Banks, D. Hayward, J. J. Ligget, R. A. Pethrick, and B. Thomson, "Physical properties of poly (ether ether ketone) exposed to simulated severe oilfield service conditions," Polymer Degradation and Stability, vol. 98, no. 6, pp. 1264–1270, 2013.

K. A. Laux, A. Jean-Fulcrand, H. J. Sue, T. Bremner, and J. S. Wong, "The influence of surface properties on sliding contact temperature and friction for polyetheretherketone (PEEK)," Polymer, vol. 103, pp. 397–404, 2016.

L. Pruitt and J. Furmanski, "Polymeric biomaterials for load-bearing medical devices," JOM, vol. 61, no. 9, pp. 14–20, 2009.

S. M. Kurtz and J. N. Devine, "PEEK biomaterials in trauma, orthopedic, and spinal implants," Biomaterials, vol. 28, no. 32, pp. 4845–4869, 2007.

L. E. Amborski and D. W. Flierl, "Physical properties of polyethylene terephthalate films," Journal of Industrial and Engineering Chemistry, vol. 45, no. 10, pp. 2290–2295, 1953.

Y. Bin, K. Oishi, K. Yoshida, and M. Matsuo, "Mechanical properties of poly (ethylene terephthalate) estimated in terms of orientation distribution of crystallites and amorphous chain segments under simultaneous biaxially stretching," Polymer Journal, vol. 36, no. 11, pp. 888–898, 2004.

R. Y. Kannan, H. J. Salacinski, P. E. Butler, G. Hamilton, and A. M. Seifalian, "Current status of prosthetic bypass grafts: a review," Journal of Biomedical Materials Research Part B: Applied Biomaterials, vol. 74B, no. 1, pp. 570–581, 2005.

U. G. Longo, A. Lambert, N. Maffulli, and V. Denaro, "Tendon augmentation grafts: a systematic review," British Medical Bulletin, vol. 94, no. 1, pp. 165–188, 2010.

T. Billiet, M. Vandenhaute, J. Schelhout, S. van Vlierberge, and P. Dubreul, "A review of trends and limitations in hydrogel-rapid prototyping for tissue engineering," Biomaterials, vol. 33, no. 26, pp. 6020–6041, 2012.

M. Grotli, C. H. Gotfredsen, J. Rademann et al., "Physical properties of poly (ethylene glycol)(PEG)-based resins for combinatorial solid phase organic chemistry: a comparison of PEG-cross-linked and PEG-grafted resins," Journal of Combinatorial Chemistry, vol. 2, no. 2, pp. 108–119, 2000.

D. Campoccia, L. Montanaro, and C. R. Arciola, "A review of the biomaterials technologies for infection-resistant surfaces," Biomaterials, vol. 34, no. 34, pp. 8533–8554, 2013.

M. H. Wu, "Simple poly (dimethylsiloxane) surface modification to control cell adhesion," Surface and Interface Analysis, vol. 41, no. 1, pp. 11–16, 2009.

Q. Tu, J. C. Wang, R. Liu et al., "Antifouling properties of poly (dimethylsiloxane) surfaces modified with quaternized poly (dimethylaminoethyl methacrylate)," Colloids and Surfaces B: Biointerfaces, vol. 102, pp. 361–370, 2013.

K. McLaughlin, B. Jones, R. Mactier, and C. Porteus, "Long-term vascular access for hemodialysis using silicon dual-lumen catheters with guidewire replacement of catheters for technique salvage," American Journal of Kidney Diseases, vol. 29, no. 4, pp. 553–559, 1997.

G. Lewis, "Nucleus pulposus replacement and regeneration/repair technologies: present status and future prospects," Journal of Biomedical Materials Research Part B: Applied Biomaterials, vol. 100B, no. 6, pp. 1702–1720, 2012.

S. Wu, X. Liu, K. W. K. Yeung, C. Liu, and X. Yang, "Biometric porous scaffolds for bone tissue engineering," Materials Science & Engineering B: Reports, vol. 80, pp. 1–36, 2014.

B. H. Chew and J. D. Denstedt, "Technology insight: novel ureteral stent materials and designs," Nature Clinical Practice Urology, vol. 1, no. 1, pp. 44–48, 2004.

Y. Ikada and H. Tsuji, "Biodegradable polymers for medical and ecological applications," Macromolecular Rapid Communications, vol. 21, no. 3, pp. 117–132, 2000.

B. J. R. F. Bolland, J. M. Kanczler, P. J. Ginty et al., "The application of human bone marrow stromal cells and poly (dl-lactic acid) as a biological bone graft extender in impaction bone grafting," Biomaterials, vol. 29, no. 22, pp. 3221–3227, 2008.

H. Mehboob and S. H. Chang, "Application of composites to orthopedic prostheses for effective bone healing: a review," Composite Structures, vol. 118, pp. 328–341, 2014.

L. Lu, S. J. Peter, M. D. Lyman et al., "In vitro and in vivo degradation of porous poly (DL-lactic-co-glycolic acid) foams," Biomaterials, vol. 21, no. 18, pp. 1837–1845, 2000.

P. Kingshott, G. Andersson, S. L. McArthur, and H. J. Griesser, "Surface modification and chemical surface
analysis of biomaterials,” *Current Opinion in Chemical Biology*, vol. 15, no. 5, pp. 667–676, 2011.

[134] A. S. Hoffman, “Surface modification of polymers,” *Chinese Journal of Polymer Science*, vol. 13, pp. 195–203, 1995.

[135] B. D. Ratner, “Surface modification of polymers: chemical, biological and surface analytical challenges,” *Biosensors & Bioelectronics*, vol. 10, no. 9-10, pp. 797–804, 1995.

[136] R. Song, X. Hu, P. Guan et al., “Surface modification of imprinted polymer microspheres with ultrathin hydrophilic shells to improve selective recognition of glutathione in aqueous media,” *Materials Science and Engineering: C*, vol. 60, pp. 1–6, 2016.

[137] D. Falconnet, G. Csucs, H. Michelle Grandin, and M. Textor, “Surface engineering approaches to micropattern surfaces for cell-based assays,” *Biomaterials*, vol. 27, no. 16, pp. 3044–3063, 2006.

[138] R. Ogaki, M. Alexander, and P. Kingshott, “Chemical patterning in biointerface science,” *Materials Today*, vol. 13, no. 4, pp. 22–35, 2010.

[139] C. M. Chan, T. M. Ko, and H. Hiraoka, “Polymer surface modification by plasmas and photons,” *Surface Science Reports*, vol. 24, no. 1-2, pp. 1–54, 1996.

[140] P. K. Chu, J. Y. Chen, L. P. Wang, and N. Huang, “Plasma--surface modification of biomaterials,” *Materials Science and Engineering: R: Reports*, vol. 36, no. 5-6, pp. 143–206, 2002.

[141] C. Oehr, “Plasma surface modification of polymers for biomedical use,” *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*, vol. 208, pp. 40–47, 2003.

[142] E. M. Liston, L. Martinu, and M. R. Wertheimer, “Plasma surface modification of polymers for improved adhesion: a critical review,” *Journal of Adhesion Science and Technology*, vol. 7, no. 10, pp. 1091–1127, 1993.

[143] Q. F. Wei, W. D. Gao, D. Y. Hou, and X. Q. Wang, “Surface modification of polymer nanofibres by plasma treatment,” *Applied Surface Science*, vol. 245, no. 1-4, pp. 16–20, 2005.

[144] H. Dong and T. Bell, “State-of-the-art overview: ion beam surface modification of polymers towards improving tribological properties,” *Surface and Coatings Technology*, vol. 111, no. 1, pp. 29–40, 1999.

[145] M. Tagaya and M. Nakagawa, “Incorporation of decanethiol-passivated gold nanoparticles into cross-linked poly (dimethylsiloxane) films,” *Smart Materials Research*, vol. 2011, Article ID 390273, 7 pages, 2011.

[146] I. Armentano, M. Dottori, E. Fortunati, S. Mattioli, and J. M. Kenny, “Biodegradable polymer matrix nanocomposites for tissue engineering: a review,” *Polymer Degradation and Stability*, vol. 95, no. 11, pp. 2126–2140, 2010.

[147] L. Minati, C. Migliaretti, L. Lunelli, G. Viero, M. Dalla Serra, and G. Speranza, “Plasma assisted surface treatments of biomaterials,” *Biophysical Chemistry*, vol. 229, pp. 151–164, 2017.

[148] B. Gupta, C. Plummer, I. Bisson, P. Frey, and J. Hilborn, “Plasma-induced graft polymerization of acrylic acid onto poly (ethylene terephthalate) films: characterization and human smooth muscle cell growth on grafted films,” *Biomaterials*, vol. 23, no. 3, pp. 863–871, 2002.

[149] S. D. Lee, G. H. Hsiue, P. C. T. Chang, and C. Y. Kao, “Plasma-induced grafted polymerization of acrylic acid and subsequent grafting of collagen onto polymer film as biomaterials,” *Biomaterials*, vol. 17, no. 16, pp. 1599–1608, 1996.

[150] H. Tian, Z. Tang, X. Zhuang, X. Chen, and X. Jing, “Biodegradable synthetic polymers: preparation, functionalization and biomedical application,” *Progress in Polymer Science*, vol. 37, no. 2, pp. 237–280, 2012.

[151] L. Cen, K. G. Neoh, and E. T. Kang, “Surface functionalization technique for conferring antibacterial properties to polymeric and cellulosic surfaces,” *Langmuir*, vol. 19, no. 24, pp. 10295–10303, 2003.

[152] K. Bazaka, M. V. Jacob, R. J. Crawford, and E. P. Ivanova, “Plasma-assisted surface modification of organic biopolymers to prevent bacterial attachment,” *Acta Biomaterialia*, vol. 7, no. 5, pp. 2015–2028, 2011.

[153] S. Yoshida, K. Hagiwara, T. Hasebe, and A. Hotta, “Surface modification of polymers by plasma treatments for the enhancement of biocompatibility and controlled drug release,” *Surface and Coatings Technology*, vol. 233, pp. 99–107, 2013.

[154] Q. P. Pham, U. Sharma, and A. G. Mikos, “Electrospinning of polymeric nanofibers for tissue engineering applications: a review,” *Tissue Engineering*, vol. 12, no. 5, pp. 1197–1211, 2006.

[155] S. Cheruthuruthakatt, M. Černák, P. Slaviček, and J. Havel, “Gas plasmas and plasma modified materials in medicine,” *Journal of Applied Biomedicine*, vol. 8, no. 2, pp. 55–66, 2010.

[156] D. G. Petlin, S. I. Tverdokhlebov, and Y. G. Anissimov, “Plasma treatment as an efficient tool for controlled drug release from polymeric materials: a review,” *Journal of Controlled Release*, vol. 266, pp. 57–74, 2017.

[157] R. Bitar, P. Cools, N. de Geyter, and R. Morent, “Acrylic acid plasma polymerization for biomedical use,” *Applied Surface Science*, vol. 448, pp. 168–185, 2018.

[158] L. Bacakova, E. Filova, M. Parizek, T. Ruml, and V. Svorcik, “Modulation of cell adhesion, proliferation and differentiation on materials designed for body implants,” *Biotecnology Advances*, vol. 29, no. 6, pp. 739–767, 2011.

[159] S. Morita and A. Takasu, “Adhesion control of human umbilical vein endothelial cells using clickable poly (2-oxazoline)-grafted biosynthesized extracellular matrix protein,” *Polymer*, vol. 136, pp. 194–204, 2018.

[160] P. N. Le, C. K. Huynh, and N. Q. Tran, “Advances in thermosensitive polymer-grafted platforms for biomedical applications,” *Materials Science and Engineering: C*, vol. 92, pp. 1016–1030, 2018.

[161] H. S. Choi, Y. S. Kim, Y. Zhang, S. Tang, S. W. Myung, and B. C. Shin, “Plasma-induced graft co-polymerization of acrylic acid onto the polyurethane surface,” *Surface and Coatings Technology*, vol. 182, no. 1, pp. 55–64, 2004.

[162] S. H. S. H. Hsu and W. C. Chen, “Improved cell adhesion by plasma-induced grafting of L-lactide onto polyurethane surface,” *Biomaterials*, vol. 21, no. 4, pp. 359–367, 2000.

[163] X. L. Xie, Y. W. Mai, and X. P. Zhou, “Dispersion and alignment of carbon nanotubes in polymer matrix: a review,” *Materials Science & Engineering R: Reports*, vol. 49, no. 4, pp. 89–112, 2005.

[164] M. H. Ahmed, J. A. Byrne, and J. McLaughlin, “Evaluation of glycine adsorption on diamond like carbon (DLC) and fluorinated DLC deposited by plasma-enhanced chemical vapour deposition (PECVD),” *Surface and Coatings Technology*, vol. 209, pp. 8–14, 2012.

[165] Z. Y. Xiao, Y. C. Liu, D. X. Zhao et al., “Optical property of hexagonal nanocrystalline zno film on Si substrate prepared...
by plasma-enhanced CVD,” *Journal of Luminescence*, vol. 122-123, pp. 822–824, 2007.

[166] J. C. Shearer, M. J. Fisher, D. Hoogeland, and E. R. Fisher, “Composite SiO$_2$/TiO$_2$ and amine polymer/TiO$_2$ nanoparticles produced using plasma-enhanced chemical vapor deposition,” *Applied Surface Science*, vol. 256, no. 7, pp. 2081–2091, 2010.

[167] A. Grüniger, A. Bieder, A. Sonnenfeld, P. R. von Rohr, U. Müller, and R. Hauert, “Influence of film structure and composition on diffusion barrier performance of SiOx thin films deposited by PECVD,” *Surface and Coatings Technology*, vol. 200, no. 14-15, pp. 4564–4571, 2006.

[168] S. Nagashima, T. Hasebe, D. Tsuya et al., “Controlled formation of wrinkled diamond-like carbon (DLC) film on grooved poly (dimethylsiloxane) substrate,” *Diamond and Related Materials*, vol. 22, pp. 48–51, 2012.

[169] M. C. Vasudev, K. D. Anderson, T. J. Bunning, V. V. Tsukruk, and R. R. Naik, “Exploration of plasma-enhanced chemical vapor deposition as a method for thin-film fabrication with biological applications,” *ACS Applied Materials & Interfaces*, vol. 5, no. 10, pp. 3983–3994, 2013.

[170] L. Martinu, O. Zabeida, and J. E. Klemberg-Sapieha, “Plasma-enhanced chemical vapor deposition of functional coatings,” in *Handbook of Deposition Technologies for Films and Coatings*, pp. 392–465, William Andrew, 2010.

[171] M. Allen, B. Myer, and N. Rushton, “In vitro and in vivo investigations into the biocompatibility of diamond-like carbon (DLC) coatings for orthopedic applications,” *Journal of Biomedical Materials Research*, vol. 58, no. 3, pp. 319–328, 2001.

[172] T. Hasebe, S. Yohena, A. Kamijo et al., “Fluorine doping into diamond-like carbon coatings inhibits protein adsorption and platelet activation,” *Journal of Biomedical Materials Research, Part A*, vol. 83, no. 4, pp. 1192–1199, 2007.

[173] J. A. Barry, M. M. G. Silva, K. M. Shakesheff, S. M. Howdle, and M. R. Alexander, “Using plasma deposits to promote cell population of the porous interior of three-dimensional poly(D,L-lactic acid) tissue-engineering scaffolds,” *Advanced Functional Materials*, vol. 15, no. 7, pp. 1134–1140, 2005.

[174] K. Tanaka, M. Kogoma, and Y. Ogawa, “Fluorinated polymer coatings on PLGA microcapsules for drug delivery system using atmospheric pressure glow plasma,” *Thin Solid Films*, vol. 506-507, pp. 159–162, 2006.

[175] G. M. L. Messina, C. Satriano, and G. Marletta, “A multitechnique study of preferential protein adsorption on hydrophobic and hydrophilic plasma-modified polymer surfaces,” *Colloids and Surfaces, B: Biointerfaces*, vol. 70, no. 1, pp. 76–83, 2009.

[176] O. Girshievitz, Y. Nitzan, and C. N. Sukenik, “Solution–deposited amorphous titanium dioxide on silicone rubber: a conformal, crack-free antibacterial coating,” *Chemistry of Materials*, vol. 20, no. 4, pp. 1390–1396, 2008.

[177] R. Yamada, K. Hattori, S. Tachikawa et al., “Control of adhesion of human induced pluripotent stem cells to plasma-patterned polydimethylsiloxane coated with vitronectin and γ-globulin,” *Journal of Bioscience and Bioengineering*, vol. 118, no. 3, pp. 315–322, 2014.

[178] L. Roseti, V. Parisi, M. Petretta et al., “Scaffolds for bone tissue engineering: state of the art and new perspectives,” *Materials Science and Engineering: C*, vol. 78, pp. 1246–1262, 2017.

[179] G. Chiara, F. Letizia, F. Lorenzo et al., “Nanostructured biomaterials for tissue engineered bone tissue reconstruction,” *International Journal of Molecular Sciences*, vol. 13, no. 1, pp. 737–757, 2012.

[180] J. Venkatesan, I. Bhatnagar, P. Manivasagan, K. H. Kang, and S. K. Kim, “Alginic composites for bone tissue engineering: a review,” *International Journal of Biological Macromolecules*, vol. 72, pp. 269–281, 2015.

[181] M. Swetha, K. Sahithi, A. Moorthi, N. Srinivasan, K. Ramasamy, and N. Selvamurugan, “Biocomposites containing natural polymers and hydroxyapatite for bone tissue engineering,” *International Journal of Biological Macromolecules*, vol. 47, no. 1, pp. 1–4, 2010.

[182] S. Oh, N. Oh, M. Appleford, and J. L. Ong, “Bioceramics for tissue engineering applications—a review,” *American Journal of Biochemistry and Biotechnology*, vol. 2, pp. 49–56, 2006.

[183] L. Cordero-Arias and A. R. Boccaccini, “Electrophoretic deposition of chondroitin sulfate-chitosan/bioactive glass composite coatings with multilayer design,” *Surface and Coatings Technology*, vol. 315, pp. 417–425, 2017.

[184] M. W. Losey, J. J. Kelly, N. D. Badgayan, S. K. Sahu, and P. S. Rama-Sreenkath, “Electrodeposition,” in *Reference Module in Materials Science and Engineering*, vol. 13, S. Hashimi, Ed., pp. 1–20, Elsevier, Oxford, 2017.

[185] G. Vargas, A. Muñoz, J. Méndez, M. Méndez, and P. Mondragón, “Deposición electroeróforética de una porcelana dental sobre acero inoxidable austenítico 304,” *Boletín de la Sociedad Española de Cerámica y Vidrio*, vol. 42, no. 1, pp. 21–26, 2003.

[186] G. Zangari, “Electrodeposition of alloys and compounds in the era of microelectronics and energy conversion technology,” *Coatings*, vol. 5, no. 2, pp. 195–218, 2015.

[187] F. E. Bastan, M. Atiq Ur Rehman, Y. Y. Avcu, E. Avcu, F. Üstel, and A. R. Boccaccini, “Electrophoretic codeposition of PEEK-hydroxyapatite composite coatings for biomedical applications,” *Colloids and Surfaces, B: Biointerfaces*, vol. 169, pp. 176–182, 2018.

[188] M. Farrokh-Rad, T. Shahrabi, S. Mahmoudi, and S. Khanmohammadi, “Electrophoretic deposition of hydroxyapatite-chitosan–CNTs nanocomposite coatings,” *Ceramics International*, vol. 43, no. 5, pp. 4663–4669, 2017.

[189] M. Farrokh-Rad, “Electrophoretic deposition of fiber hydroxyapatite/titania nanocomposite coatings,” *Ceramics International*, vol. 44, no. 1, pp. 622–630, 2018.

[190] M. Tagaya, T. Ikoma, N. Hanagata, D. Chakarov, B. Kasemo, and I. Zhitomirsky, “Reusable hydroxyapatite nanocrystal sensors inorganic coatings for biomedical applications,” Electrodeposition of nanocomposites,” *International Journal of Nanoscience*, vol. 4, no. 3, pp. 218–224, 2010.

[191] X. Pang and I. Zhitomirsky, “Electrodeposition of nanocomposite organic–inorganic coatings for biomedical applications,” *International Journal of Nanoscience*, vol. 4, no. 3, pp. 409–418, 2005.

[192] X. Pang and I. Zhitomirsky, “Electrophoretic deposition of composite hydroxyapatite–chitosan coatings,” *Materials Characterization*, vol. 58, no. 4, pp. 339–348, 2007.

[193] D. Zhitomirsky, J. A. Roether, A. R. Boccaccini, and I. Zhitomirsky, “Electrophoretic deposition of bioactive
glass/polymer composite coatings with and without HA nanoparticle inclusions for biomedical applications,” *Journal of Materials Processing Technology*, vol. 209, no. 4, pp. 1853–1860, 2009.

[195] M. Došić, S. Eraković, A. Janković et al., “In vitro investigation of electrophoretically deposited bioactive hydroxyapatite/chitosan coatings reinforced by graphene,” *Journal of Industrial and Engineering Chemistry*, vol. 47, pp. 336–347, 2017.

[196] T. G. P. Galindo, T. Kataoka, S. Fuji, M. Okuda, and M. Tagaya, “Preparation of nanocrystalline zinc-substituted hydroxyapatite films and their biological properties,” *Colloid and Interface Science Communications*, vol. 10-11, pp. 15–19, 2016.

[197] J. F. Banfield, S. A. Welch, H. Zhang, T. T. Ebert, and R. L. Penn, “Aggregation-based crystal growth and microstructure development in natural iron oxhydroxide biomineralization products,” *Science*, vol. 289, no. 5480, pp. 751–754, 2000.

[198] M. Vallet-Regí and D. A. Navarrete, *Nanoceramics in Clinical Use: from Materials to Applications*. Chapter 1, vol. 39, RSC Nanoscience & Nanotechnology, 2nd edition, 2015.

[199] F. J. Cuisinier, “Bone mineralization,” *Current Opinion in Solid State and Materials Science*, vol. 1, no. 3, pp. 436–439, 1996.

[200] K. Onuma and A. Ito, “Cluster growth model for hydroxyapatite,” *Chemistry of Materials*, vol. 10, no. 11, pp. 3346–3351, 1998.

[201] G. Treboux, P. Layrolle, N. Kanazaki, K. Onuma, and A. Ito, “Symmetry of Posner’s cluster,” *Journal of the American Chemical Society*, vol. 122, no. 34, pp. 8323-8324, 2000.

[202] G. Treboux, P. Layrolle, N. Kanazaki, K. Onuma, and A. Ito, “Existence of Posner’s cluster in vacuum,” *The Journal of Physical Chemistry A*, vol. 104, no. 21, pp. 5111–5114, 2000.

[203] Y. V. Shih and S. Varghese, “Tissue engineered bone mimetics to study bone disorders ex vivo: role of bioinspired materials,” *Biomaterials*, pp. 1–15, 2018.

[204] H. Ozawa, K. Hoshi, and N. Amizu, “Current concepts of bone biomineralization,” *Journal of Oral Biosciences*, vol. 50, no. 1, pp. 1–14, 2008.

[205] N. H. Saddiqi, D. Patra, and S. Seeger, “Hydroxyapatite biomineralization on functionalized silicone nanofilaments,” *Colloid and Interface Science Communications*, vol. 16, pp. 1–5, 2017.

[206] J. Song, V. Malathong, and C. R. Bertozzi, “Mineralization of synthetic polymer scaffolds: a bottom-up approach for the development of artificial bone,” *Journal of the American Chemical Society*, vol. 127, no. 10, pp. 3366–3372, 2005.

[207] C. Ohitsuki, M. Kamitakahara, and T. Miyazaki, “Coating bone-like apatite onto organic substrates using solutions mimicking body fluid,” *Journal of Tissue Engineering and Regenerative Medicine*, vol. 1, no. 1, pp. 33–38, 2007.

[208] H. W. Huh, L. Zhao, and S. Y. Kim, “Biomimeralized biomimetic organic/inorganic hybrid hydrogels based on hydroxyapatite and poloxamer,” *Carbohydrate Polymers*, vol. 126, pp. 130–140, 2015.

[209] S. Mann, “Molecular recognition in biomineralization,” *Nature*, vol. 332, no. 6160, pp. 119–124, 1988.

[210] S. Mann, “Molecular tectons in biomineralization and biomimetic materials chemistry,” *Nature*, vol. 365, no. 6446, pp. 499–505, 1993.

[211] K. Hosoya, C. Ohtsuki, T. Kawai et al., “A novel covalently crosslinked gel of alginate and silane with the ability to form bone-like apatite,” *Journal of Biomedical Materials Research*, vol. 71A, no. 4, pp. 596–601, 2004.

[212] T. Miyazaki, C. Ohtsuki, and M. Tanihara, “Synthesis of bioactive organic–inorganic nanohybrid for bone repair through sol–gel processing,” *Journal of Nanoscience and Nanotechnology*, vol. 3, no. 6, pp. 511–515, 2003.

[213] T. Miyazaki, C. Ohtsuki, Y. Akioka et al., “Apatite deposition on polyaacrylamide films containing carboxyl group in a biomimetic solution,” *Journal of Materials Science: Materials in Medicine*, vol. 14, no. 7, pp. 569–574, 2003.

[214] T. Kawai, C. Ohtsuki, M. Kamitakahara et al., “A comparative study of apatite deposition on polyaacrylamide films containing different functional groups under a biomimetic condition,” *Journal of the Ceramic Society of Japan*, vol. 113, no. 1321, pp. 588–592, 2005.

[215] Y. Chai, T. Yamaguchi, and M. Tagaya, “Fabrication of phospholipid vesicle-interacted calcium phosphate films with sterilization stability,” *Crystal Growth & Design*, vol. 17, no. 9, pp. 4977–4983, 2017.

[216] M. Tagaya, T. Ikoma, M. Takeguchi, N. Hanaga, and J. Tanaka, “Interfacial serum protein effect on biological apatite growth,” *Journal of Physical Chemistry C*, vol. 115, no. 45, pp. 22523–22533, 2011.

[217] X. Liu, L. A. Smith, J. Hu, and P. X. Ma, “Biomimetic nanofibrous gelatin/apatite composite scaffolds for bone tissue engineering,” *Biomaterials*, vol. 30, no. 12, pp. 2252–2258, 2009.

[218] S. H. Kim, B. K. Lim, F. Sun et al., “Preparation of high flexible composite film of hydroxyapatite and chitosan,” *Polymer Bulletin*, vol. 62, no. 1, pp. 111–118, 2009.

[219] G. M. Wu, W. D. Hsiao, and S. F. Kung, “Investigation of hydroxyapatite coated polyether ether ketone composites by gas plasma sprays,” *Surface and Coatings Technology*, vol. 203, no. 17-18, pp. 2755–2758, 2009.

[220] F. Sun, H. Zhou, and J. Lee, “Various preparation methods of highly porous hydroxyapatite/polymer nanoscale biocomposites for bone regeneration,” *Acta Biomaterialia*, vol. 7, no. 11, pp. 3813–3828, 2011.

[221] J. Redepenning, G. Venkataraman, J. Chen, and N. Stafford, “Electrochemical preparation of chitosan/hydroxyapatite composite coatings on titanium substrates,” *Journal of Biomedical Materials Research Part A*, vol. 66, no. 2, pp. 411–416, 2003.

[222] J. Liuyun, L. Yubao, and X. Chengdong, “Preparation and biological properties of a novel composite scaffold of nano-hydroxyapatite/chitosan/carboxymethyl cellulose for bone tissue engineering,” *Journal of Biomedical Science*, vol. 16, no. 1, pp. 65, 2009.

[223] W. Y. Zhou, M. Wang, W. L. Cheung, and W. Y. Ip, “Selective laser sintering of poly (L-Lactide)/carbonated hydroxyapatite nanocomposite porous scaffolds for bone tissue engineering. Chapter 9,” in *Tissue Engineering*, pp. 179–204, InTech, 2010.

[224] X. Deng, J. Hao, and C. Wang, “Preparation and mechanical properties of nanocomposites of poly (D, L-lactide) with Ca-deficient hydroxyapatite nanocrystals,” *Biomaterials*, vol. 22, no. 21, pp. 2867–2873, 2001.

[225] S. Tjahbakhsh and F. Hajjali, “A comprehensive study on the fabrication and properties of biocomposites of poly (lactic acid)/ceramics for bone tissue engineering,” *Materials Science and Engineering: C*, vol. 70, Part 1, pp. 897–912, 2017.
[226] M. He, C. Chang, N. Peng, and L. Zhang, "Structure and properties of hydroxyapatite/cellulose nanocomposite films," *Carbohydrate Polymers*, vol. 87, no. 4, pp. 2512–2518, 2012.

[227] N. Gusić, A. Ivković, J. VaFaye et al., "Nano-technoloy and bone regeneration: a mini-review," *International Orthopaedics*, vol. 38, no. 9, pp. 1877–1884, 2014.

[228] N. López-Serna, *Biología del Desarrollo. Cuaderno de Trabajo. Chapter 13*, McGraw-Hill, New York, 2012.

[229] A. D. Berendsen and B. R. Olsen, "Bone development," *Bone*, vol. 80, pp. 14–18, 2015.

[230] P. X. Ma, "Biomimetic materials for tissue engineering," *Advanced Drug Delivery Reviews*, vol. 60, no. 2, pp. 184–198, 2008.

[231] M. Maltioli-Belmonte, G. Giavaresi, G. Biagini et al., "Tailoring biomaterial compatibility: in vivo tissue response versus in vitro cell behavior," *The International Journal of Artificial Organs*, vol. 26, no. 12, pp. 1077–1085, 2003.

[232] C. Gao, S. Peng, P. Feng, and C. Shuai, "Bone biomaterials and interactions with stem cells," *Bone Research*, vol. 5, article 17059, 2017.

[233] J. Costa-Rodrigues, A. Fernandes, M. A. Lopes, and M. H. Fernandes, "Hydroxyapatite surface roughness: complex modulation of the osteoclastogenesis of human precursor cells," *Acta Biomaterialia*, vol. 8, no. 3, pp. 1137–1145, 2012.

[234] C. M. Murphy, F. J. O’Brien, D. G. Little, and A. Schindeler, "Cell-scaffold interactions in the bone tissue engineering triad," *European Cells & Materials*, vol. 26, pp. 120–122, 2013.

[235] L. Cerroni, R. Filocamo, M. Fabbri, C. Piconi, S. Caropreso, and S. G. Condo, "Growth of osteoblast-like cells on porous hydroxyapatite ceramics: an in vitro study," *Biomolecular Engineering*, vol. 19, no. 2–6, pp. 119–124, 2002.

[236] A. Haider, S. Haider, S. S. Han, and I. K. Kang, "Recent advances in the synthesis, functionalization and biomedical applications of hydroxyapatite: a review," *RSC Advances*, vol. 7, no. 13, pp. 7442–7458, 2017.

[237] S. C. Rizzi, D. J. Heath, A. G. A. Coombes, N. Bock, M. Textor, and S. Downes, "Biodegradable polymer/hydroxyapatite composites: surface analysis and initial attachment of human osteoblasts," *Journal of Biomedical Materials Research*, vol. 55, no. 4, pp. 475–486, 2001.

[238] M. Kikuchi, S. Itoh, S. Ichinose, K. Shinomiya, and J. Tanaka, "Self-organization mechanism in a bone-like hydroxyapatite/collagen nanocomposite synthesized in vitro and its biological reaction in vivo," *Biomaterials*, vol. 22, no. 13, pp. 1705–1711, 2001.

[239] M. Tagaya, T. Yamazaki, D. Tsuya, Y. Sugimoto, N. Hanagata, and T. Ikoma, "Nano/microstructural effect of hydroxyapatite nanocrystals on hepatocyte cell aggregation and adhesion," *Macromolecular Bioscience*, vol. 11, no. 11, pp. 1586–1593, 2011.

[240] M. Tagaya, T. Yamazaki, S. Migita, N. Hanagata, and T. Ikoma, "Hepatocyte adhesion behavior on modified hydroxyapatite nanocrystals with quartz crystal microbalance," *Bioceramics Development and Applications*, vol. 1, pp. 1–4, 2011.

[241] V. Guarino, V. Benfenati, I. Cruz-Maya, A. I. Borraчерo-Conejo, R. Zamboni, and L. Ambrosio, "Bioinspired scaffolds for bone and neural tissue and interface engineering," in *Functional 3D Tissue Engineering Scaffolds*, pp. 51–74, Woodhead Publishing, 2018.
