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Review Article

BIOMEDICAL APPLICATIONS OF POLYMER-COATED HYDROXYAPATITE MATERIALS

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ABSTRACT

The primary objective of this article is to present the potential biomedical applications of hydroxyapatite-based materials coated with polymers, as well as the methods used for producing such polymer coatings. Hydroxyapatite (HA) is an inorganic component of bone, distinguished by its high biocompatibility, bioactivity, and ability to integrate with bone tissue. However, its limited mechanical strength poses a barrier to broader clinical application. A solution to this issue involves coating HA with polymeric layers — both synthetic and natural — which enhances its physicochemical properties, increases resistance to compression and fracture, and enables surface functionalization. The article outlines various coating techniques, categorized into physical and chemical methods. It also discusses examples of applications for these materials, including controlled drug delivery systems, bone tissue engineering, and gene delivery. Owing to its surface modification capabilities and favorable properties, polymer-coated HA may serve as a basis for advanced implants and drug carriers. Furthermore, the article highlights the use of HA-polymer composites for coating metallic implants, which significantly improves their corrosion resistance and enhances bioactivity. The entire study is based on a review of scientific literature that identifies current trends and research directions in the development of modern HA-based biomaterials.

KEYWORDS: hydroxyapatite, polymer, coating, biomaterial

1. Introduction

Bone tissue is a natural composite composed of an inorganic mineral phase (mainly hydroxyapatite) and an organic collagen matrix arranged in a hierarchical structure from nano- to macroscale. This biphasic architecture provides bone with both hardness (mineral phase) and toughness/resilience (collagen phase) and is a major design inspiration for biomimetic HA-polymer composites [1, 2]. Unlike previous broad reviews [3—5], the present manuscript focuses specifically on polymer-coated hydroxyapatite systems, comparing coating strategies, translational readiness, and outstanding limitations to help guide future preclinical and clinical translation efforts.

Hydroxyapatite (HA) is a calcium phosphate compound that plays a key role in a wide range of medical applications. It is described by the chemical formula $Ca_{10}(PO_4)_6(OH)_2$ and constitutes the primary inorganic component of bone and teeth. This formula corresponds to stoichiometric HA with a Ca/P ratio of 1.67, which can only be obtained under specific synthetic conditions. The main component of bone tissue in living organisms is biological (or bone-derived) HA, which is characterized by a molar Ca/P ratio below 1.67 [6—8]. As a bioceramic material, it accounts for approximately 70% of the total bone mass, with the remaining portion composed of collagen (20%) and water (10%) [9, 10]. Its current popularity among researchers is attributed to its favorable physicochemical and biological properties. HA is characterized by high biocompatibility, osteoconductivity, and bioactivity, making it one of the leading materials used in bone surgery [6, 11]. Moreover, it is non-toxic and does not induce inflammatory responses [9]. Unfortunately, its poor mechanical properties significantly limit the use of dense HA to implants that are not subjected to high mechanical loads. In this context, its porous counterpart (Fig. 1) is more desirable, as it exhibits better bioresorbability and allows bone tissue to grow into the implant [11]. Over the past decade, porous ceramic biomaterials have attracted considerable attention due to their ability to support the migration of bone tissue cells into the material’s structure and to promote angiogenesis in newly formed bone [12].

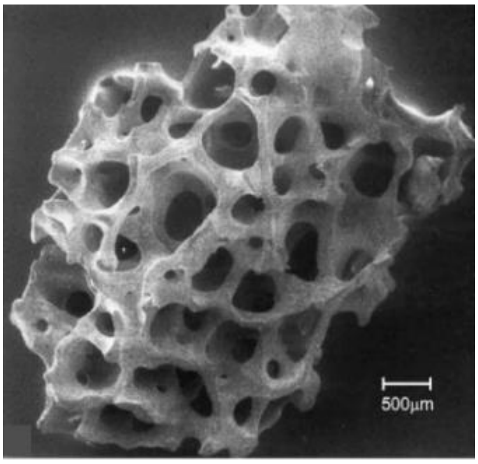

Fig. 1. SEM image of porous hydroxyapatite ceramic [11].

Polymers constitute a class of materials composed of large molecules formed by the repeated linking of smaller units known as monomers. Their diversity is influenced by factors such as chemical composition, molecular weight, and degree of solubility. Based on their origin, polymers are classified into synthetic polymers (e.g., polyethylene (PE), polylactic acid (PLA), polyglycolic acid (PGA)) and natural polymers, also referred to as biopolymers (e.g., alginate, collagen, gelatin) [13]. Additionally, semi-synthetic polymers are distinguished; these are derived from natural sources and subsequently subjected to chemical modification. A representative example is carboxymethyl cellulose [14]. Polymers obtained through synthetic processes are produced under controlled conditions, which ensures desirable and reproducible properties. An additional advantage of this group of polymers is the ability to control impurity levels during production [13]. However, their drawbacks include lower predictability in terms of biocompatibility, toxicity, and biological response. In general, synthetic polymers exhibit superior mechanical strength compared to natural polymeric compounds. Nonetheless, biopolymers are naturally occurring materials in biological environments, which makes them both biocompatible and biodegradable [15]. In recent years, natural polymers have become an attractive subject of research due to their unique properties [13]. Their biocompatibility allows them to serve as internal matrices for cell adhesion and growth. Moreover, the microstructure of biopolymers is highly organized, and they can serve as a temporary extracellular matrix, enabling effective regeneration of bone tissue and other tissues [15].

As previously mentioned, the poor mechanical properties of HA — such as low compressive strength and low fracture toughness — limit its application to small-sized granules, powders, or non-load-bearing implants. To broaden the scope of this material's use across various medical fields, its mechanical resistance must be appropriately enhanced [16]. Literature reports highlight a growing interest among researchers in natural and synthetic polymers, as well as their combinations, which is reflected in numerous studies evaluating their potential application as coating substances for HA. These coatings aim to reinforce the material or encapsulate embedded drugs [15]. The introduction of a polymeric phase appears to be a promising solution to the problem of low mechanical strength in porous ceramics, as it improves the hardness and flexibility of HA-based materials [17].

2. Materials and methods

We performed a targeted literature search in PubMed, Web of Science, ScienceDirect, and Google Scholar for articles published between 2000 and 2024 (and a few older works when necessary). Inclusion criteria: peer-reviewed original research articles and reviews in English reporting biomedical applications of polymer-coated hydroxyapatite (drug delivery, tissue engineering, coatings). Exclusion criteria: conference abstracts, patents, non-biomedical or purely computational studies. Screening was performed first by title/abstract and then by full-text. Over one hundred articles were analyzed, rejecting those that did not fit the topic, leaving about eighty. The search focused on identifying coating methods, performance metrics, and potential application examples to summarize trends in the literature.

3. Polymer coating methods

Polymeric coatings are prepared using various physical or chemical techniques. Physical methods involve the direct deposition of a polymer layer onto a material through an appropriate technical process. This category includes techniques such as spin coating, dip coating, electrospinning, and vapor deposition. In contrast, chemical coating methods rely on chemical reactions between the polymer and the substrate material. These approaches typically require preliminary chemical modification of either the polymer or the surface to be coated. The selection of a specific deposition technique depends on several factors, including the properties of the material to be coated, the desired coating thickness, and economic considerations [18].

3.1. Physical coating

The strength of physical interactions between the polymer material and the target substrate material affects the efficiency of the physical coating process. Physical deposition techniques can be divided into two groups: dry coating processes (using polymer powders) and wet coating processes (utilizing polymer solutions). The latter are better suited for coating with biopolymers, as most biopolymers are not resistant to the elevated temperatures required in dry coating processes. The absence of thermal treatment steps allows wet coating techniques to be applied on virtually any material [18]. Electrospinning, dip coating, and spin coating are the main examples of wet coating processes, which are schematically illustrated in Fig. 2.

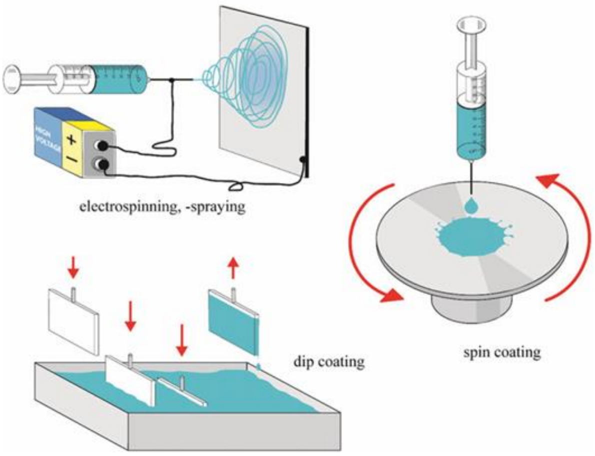

Fig. 2. Physical polymer coating methods [18].

Electrospinning is a technique that utilizes electrostatic forces to create thin fibers from a polymer solution, which are then deposited onto the material to be coated. The equipment commonly used in this method consists of at least three components: a high-voltage power supply generating an electrically charged jet, a fine capillary tube (e.g., a pipette or needle) producing fibers with diameters ranging from several tens of nanometers to a few micrometers, and the substrate material to be coated [19]. To enable this voltage-driven process, one electrode is attached to the reservoir containing the polymer solution, while the other is connected to the substrate material receiving the deposit [18]. The main advantage of this technique is its versatility, as it allows the production of fibers with a wide range of morphological structures and their assemblies in diverse configurations on the coated material [20].

Another relatively simple and cost-effective wet coating process is dip coating. This technique involves immersing and holding the material in a liquid medium to allow adsorption of polymer molecules onto the substrate material surface. Subsequently, the material is withdrawn from the solution, and the resulting wet coating dries through solvent evaporation. Using this method, uniform polymer layers can be obtained even on large materials. Furthermore, the coating thickness depends on several factors: the substrate material's surface characteristics, immersion time (typically ranging from several minutes to several hours), withdrawal speed, number of dipping cycles, polymer solution concentration and viscosity, as well as the specific conditions under which solvent evaporation occurs from the formed coating [21, 22]. The adhesion strength between the coating and the substrate material is generally low because, in dip coating, polymers bind to the substrate material primarily via passive adsorption [23]. One way to address this issue is to subject the substrate material to sandblasting prior to coating, although this treatment increases surface roughness [24]. Improved coating durability can also be achieved by using polymers with high, nonspecific adsorption strength or by exploiting hydrophobic or electrostatic interactions through careful selection of polymer-substrate pairs possessing opposite charges [25].

Spin coating is another wet deposition method used to form polymer coatings on flat materials. The coating process begins by dissolving the selected polymer in an appropriate solvent, followed by dilution of the resulting solution. This solution is then applied to the central area of the substrate material to be coated. At this stage, the substrate material may already be set into rotation, although typically at a low speed [26]. Subsequently, the rotation speed is rapidly increased, and the combined effects of centrifugal force and surface tension cause the polymer film to be uniformly distributed across the material surface. The thickness of the coating primarily depends on the spin speed, surface tension, and viscosity of the polymer solution. Although the actual volume of polymer solution required in this method is very small, a significant amount is lost due to the high rotational speed of the substrate material. This technique is not suitable for coating large samples, as it is not possible to achieve sufficiently high rotational speeds necessary to obtain a thin and uniform coating [27].

As previously mentioned, physical coating methods are distinguished by their process simplicity, which has contributed to their frequent use to date. However, polymer coatings obtained using these techniques typically exhibit unfavorable properties, such as low mechanical strength, which can be a critical issue depending on the intended application of the coated material. Good mechanical stability of the coating is especially important in applications where the final product is exposed to external mechanical stresses or when the release of individual particles from the polymer layer poses a risk to the human body by causing various side effects. For these reasons, in such application areas, it is essential to obtain coatings with high mechanical strength through the formation of covalent bonds between the polymer coating and the substrate material [18].

3.2. Chemical coating

Essentially, there are two different strategies for obtaining coatings covalently bonded to the substrate material. In the first strategy, the entire polymer molecule can be attached to the substrate material surface by creating appropriate binding sites either on the coated material, on the polymer itself, or on both. This approach is commonly referred to as the "grafting to" method. The second approach, called "grafting from," involves using small, functionalized polymerization initiator molecules that enable the formation of a high-molecular-weight polymer coating directly on the substrate material surface. Consequently, this method is limited to producing coatings where the macromolecule can be synthesized *in situ* [18].

One of the most commonly used chemical strategies for covalently bonding polymers to materials employs glutaraldehyde as a crosslinking agent (Fig. 3). This compound readily reacts with a variety of functional groups, including primary amines, thiol, phenol, and imidazole residues, which are widely present in biopolymers [28]. The high reactivity of glutaraldehyde makes polymer bindings formed with its involvement a simple and effective tool for obtaining coatings. However, creating a coating using glutaraldehyde involves the formation of its layer on the surface of the target substrate. This step is preceded by an intermediate stage, typically involving the formation of a primer layer containing (3-aminopropyl)triethoxysilane (APTES), since the primary amine group in APTES enables the attachment of the crosslinking agent through covalent bonding [29, 30]. Subsequently, the functionalized surface is incubated with the target biopolymer, which attaches itself to the glutaraldehyde via aldol condensation or Michael addition reactions [31].

The second well-established chemical method leading to the formation of polymer coatings is covalent coupling using carbodiimides (Fig. 3). This strategy is based on the formation of a covalent bond between two of the most common functional groups in natural polymers, namely carboxyl groups and primary amines. In the first step, molecules containing carboxyl groups are exposed to 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and N-hydroxysuccinimide (NHS), resulting in the formation of a reactive intermediate. Subsequently, amine groups react with the activated carboxyl groups, forming an amide bond, while the EDC/NHS byproduct is released into the solution [32, 33]. When choosing this method, one should consider the structure of the coated material, as it requires the presence of specific functional groups on its surface, i.e., primary amines or carboxyl groups. If these

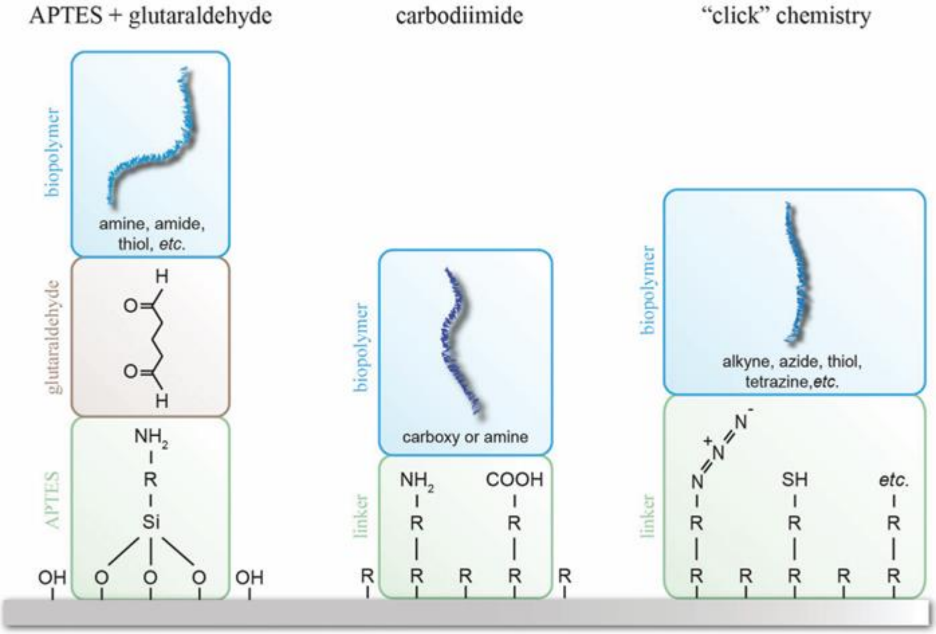

Fig. 3. Chemical polymer coating methods [18].

groups are absent, silanes (e.g., APTES) are used to introduce amine groups, and TMS-EDTA is employed to obtain carboxyl groups. These then form a primer layer enabling the formation of the polymer coating [18].

Another strategy for immobilizing biopolymers on material surfaces is the so-called "click" chemistry (Fig. 3). Click reactions constitute a group of mechanisms that, by definition, should be modular, easy to perform, and highly efficient [34]. The absence of byproduct formation is a key advantage of this concept, as toxic byproducts often pose a problematic issue in biomedical applications, especially when their presence compromises the biocompatibility of the material [35]. Typically, the click chemistry strategy also requires, as the first step, the deposition of an appropriate linking molecule on the surface of the coated substrate. This leads to the formation of a base layer containing functional groups necessary to enable the chemical reaction and the formation of the polymer coating [18].

4. Applications of polymer-coated hydroxyapatite materials

Polymer coatings are gaining increasing popularity across a wide range of applications, as they enhance the functionality of the materials they coat. They can be applied to various substrates such as metals, ceramics, polymers, or nanoparticles. In the field of biomedicine, polymer-based coatings play a fundamental role in the development of the next generation of biomaterials. Smart polymer coatings represent the latest advancement by researchers studying these materials. Various reports indicate that polymers have the ability to respond to multiple stimuli, including temperature, light, magnetic and electric fields, as well as pH [36]. In medicine, these smart polymer coatings are primarily used in drug delivery systems, where therapeutic agents are incorporated directly into the coating and then delivered to the targeted site. Besides improving the transport functions of the material, the polymer layer also contributes to increasing its hardness. Furthermore, polymer coatings are gaining popularity as a promising solution in bone tissue engineering [37].

Polymer coating is a strategy used to modify the properties of various materials, driven by the need to tailor them for specific functions in many practical applications. The advantages of polymers forming these coatings lie undoubtedly in their mechanical and elastic properties, which are comparable to those of polymers found in biological tissues [38]. Although polymer-coated HA materials show promise, important limitations remain. It was reported that they can cause inflammatory reactions in newly created tissue [39]. Certain polymers appeared to be filling HA pores, which is treated as an undesirable effect, especially in terms of bone ingrowth [40]. Polymers often exhibit poor wettability and low surface area, which reduce their bioactivity and thus hinder their standalone use as implants. Sterilization methods (autoclave, gamma, EtO, e-beam) and subsequent hydrolytic aging can alter polymer molecular weight, porosity, and mechanical strength. Polymer degradation (hydrolytic and enzymatic) and mechanical fatigue can reduce coating integrity over time. *In vivo* long-term stability and biodegradation profiles are sparsely reported. Additional challenges include nanoparticle aggregation, reproducible scale-up of coating processes, and the absence of standardized mechanical and biological testing protocols across studies [38, 41, 42].

A few HA-based products have reached clinical use (e.g., BoneSource® hydroxyapatite cement) and composite grafts such as Collagraft® have been evaluated in clinical trials, indicating translational potential for HA-containing materials [43—45]. However, most polymer-coated HA systems described in the literature remain at preclinical stages. Bridging this gap requires standardized safety testing, reproducible manufacturing, and longer-term *in vivo* studies. This article considers the latest research achievements in the field of potential applications of polymer-coated hydroxyapatite materials.

4.1. Drug carriers

In drug delivery processes, nanoscale HA appears as an attractive material due to its high loading capacity, ability to absorb and release active substances through adsorption or electrostatic interactions, as well as the possibility of tailoring its morphological structure according to specific needs [46—48]. However, systemically administered HA has limited utility because of particle aggregation and heterogeneity. It has been shown that HA nanoparticles accumulate *in vivo* and are subsequently eliminated by the liver within a short time [49, 50]. Moreover, they accumulate in the pulmonary capillaries and cause disturbances in lung surfactant function [51, 52]. Drug loading onto HA via adsorption can result in a typically undesirable phenomenon known as the initial burst release of the therapeutic agent from the material [53]. This occurrence is often related to changes in the physicochemical properties of the nanoparticles, which in turn may affect the behavior of the carrier within the living organism [54].

To address these challenges, Moore et al. developed nanoscale HA coated with a polyglycolide–polyethylene glycol copolymer (PGA-PEG) and investigated the release profile of lovastatin, used as a model compound due to its therapeutic potential in treating diseases associated with bone tissue density loss. It has been demonstrated that statins increase osteoblast activity. Such a drug delivery system, enabling controlled release, can be employed to prolong osteoblast exposure to statin drugs. Polymer coatings can bind drug molecules, modify their release profile, and mediate the interaction of HA with the biological environment. In this study, the polymer shell was formed by grafting polyglycolide onto the HA surface, followed by attaching polyethylene glycol to the chain ends of the polymer forming the first layer. The resulting hybrid material is capable of storing lovastatin molecules, which are bound to the coating via hydrophobic interactions. This method of drug binding to the polymer layer can also be applied to other hydrophobic active substances. Applying such a coating on a drug-loaded material not only influences the drug release profile but also protects it from premature degradation. Moore et al. designed the carrier so that the outer polyethylene glycol layer functions as a stabilizer in aqueous environments, reduces protein adsorption, and prolongs the circulation time of the nanocarrier *in vivo*. The inner polyglycolide layer was intended to bind lovastatin and regulate its release, while the HA core was responsible for further enhancing osteoblast activity. A 14-day drug release analysis confirmed controlled release kinetics. The study showed that the examined carrier was taken up by human osteoblasts and maintained human umbilical vein endothelial cell viability at about 70% at doses up to 500 µg/mL *in vitro*. Preliminary *in vivo* studies determining the maximum tolerated dose revealed that coated HA exhibits lower toxicity compared to its uncoated counterpart. The results suggest that the tested nanosystem may serve as a vehicle for transporting lovastatin to sites of reduced bone mineral density while ensuring controlled drug release [55].

The literature provides numerous other studies describing the use of polymer-coated HA as a carrier for therapeutic agents. Wang et al. investigated the effect of poly(lactic-co-glycolic acid) (PLGA) on the doxycycline release profile from HA microspheres and evaluated the potential use of this material as a carrier for small-molecule drugs with prolonged release. Uncoated HA exhibited a burst release effect, whereas samples with the polymer coating released the active substance steadily over 7 days [56]. The polymer degradation rate determines the total release time of the compound from the material.

Based on the study by Dubnika et al., it was demonstrated that the selection of specific polymers as well as the sequence of their deposition on the carrier influences both the active substance release time and even the morphology of drug crystals. The authors coated a porous HA material saturated with lidocaine hydrochloride using sodium alginate and chitosan in various combinations and then examined the drug release profile. All specimens included in the study had two polymer layers, and the drug molecules were introduced into the material structure either before coating or after applying the first polymer layer, depending on the sample. Changes in the morphology of lidocaine crystals were observed for each version of the specimens. Using alginate as the coating material produced rectangular, evenly dispersed crystals, whereas coating with chitosan caused the drug substance to form needle-like shapes. Comparing the lidocaine release profiles from all samples indicated that the carrier doubly coated with sodium alginate was the most promising material for drug delivery, as in this sample, drug release could be prolonged and last up to 60 hours. Much faster lidocaine release from chitosan-coated specimens was observed as early as 6 hours after the start of the release study. The unfavorable results obtained for chitosan coatings may have been caused by the good solubility of this polymer in slightly acidic solutions, with the pH likely influenced by the chemical nature of the drug [57].

Coatings on HA carriers are not always single-component. In their study, Kim et al. immersed a porous HA scaffold in a hybrid coating solution containing polycaprolactone, HA powder, and vancomycin. The aim of their work was to evaluate the potential use of the resulting material in tissue regeneration and wound healing processes. The control sample was an uncoated carrier saturated with the therapeutic agent. Vancomycin was used as a model compound due to its broad-spectrum antibacterial activity and common incorporation into prostheses to protect against staphylococcal infections. HA powder was included in the coating composition to maintain the osteoconductivity of the scaffolds. It was shown that applying the hybrid coating caused a slight modification of the pore structure within the scaffold, resulting in reduced material porosity. The coated carrier exhibited greater resistance to compressive stress compared to the control sample. Drug release from the coated scaffolds was prolonged, whereas their uncoated counterparts showed a rapid burst release of the active substance. These findings suggest expanding the application scope of polymer-coated HA scaffolds in bone tissue regeneration and the delivery of bioactive molecules to wound sites [16].

4.2. Bone tissue engineering

Bone defects may arise as a consequence of inflammatory conditions, traumatic or neoplastic changes, as well as congenital developmental abnormalities. In the process of reconstructing the missing structure, bone tissue is involved, and in cases of larger defects, bone substitutes are used. Autologous bone grafting is considered the treatment of choice for filling bone defects. However, the limited availability of bone tissue poses a challenge to performing bone grafts. In such cases, synthetic implant materials represent a viable therapeutic alternative. Among the available implant materials, hydroxyapatite is currently widely used in reconstructive surgery due to its excellent biocompatibility combined with favorable osteoconductive properties [58–60].

Control over cell adhesion is a key objective of all tissue engineering strategies. Polymers have proven to be a promising and versatile tool for achieving controlled integration of scaffolds and implants with the biological environment. Most approaches aim to improve the adhesive properties of materials used in tissue engineering or to actively induce cell migration, proliferation, and differentiation. Typical examples of biopolymers used as coatings in tissue engineering applications include polydopamine, hyaluronic acid, and chitosan, whose properties have been extensively studied in recent years [18].

Nanometric HA synthesized via chemical methods continues to be regarded as an attractive material for bone tissue engineering applications. Its properties can be enhanced through microstructural modification or by combining it with other materials [39]. Advances in nanotechnology have enabled the design of numerous hybrid, multi-component systems based on HA as the primary constituent [61]. Composite biomaterials based on nanometric HA show great potential in bone tissue repair and defect filling [39]. Literature reports indicate that coating HA particles with bioresorbable synthetic polymers, such as the copolymer of lactic and glycolic acids (PLGA), has yielded materials suitable for bone defect filling [62, 63]. Chitosan, a naturally derived polymer, possesses many physicochemical and biological properties that make it an interesting material with potential applications in bone tissue engineering when combined with HA [64, 65]. Such combinations of soft polymeric and hard mineral components are considered a promising approach toward creating materials that mimic the natural properties of bone [66].

In a study conducted by Ignatović et al., nanometric HA particles were synthesized and analyzed both *in vitro* and *in vivo*; some samples were coated solely with chitosan, while others were coated with a mixture of chitosan and PLGA. Scaffolds coated with the natural polymer exhibited the highest antimicrobial activity against all tested microbial strains; however, after bone defect regeneration, they induced an inflammatory reaction in the newly formed tissue surrounding the defect. In contrast, scaffolds coated with the dual-polymer layer showed reduced reactivity and antimicrobial activity, but their application improved the quality of the newly formed bone tissue in the defect area [39].

The development of bioactive ceramic composite materials with enhanced mechanical strength is a topic of significant interest among researchers working in the field of bone tissue engineering. Govindan et al. in their study obtained a composite scaffold composed of phosphate glass and HA with an open porous structure using a polyurethane foam method. To increase the strength of the resulting material, they applied a coating via dip-coating using solutions of natural polymers: alginate, chitosan, and gelatin. The polymer coating did not affect the interconnectivity of the pores but led to a reduction in the scaffold's porosity. Biodegradation studies showed that all analyzed samples underwent significant degradation. Among the three polymers considered in the study, gelatin provided the most beneficial properties to the material. Scaffolds coated with this polymer layer exhibited compressive strength seven times higher than that of uncoated scaffolds and did not negatively affect the material's biocompatibility. Applying a polymer coating on porous bioceramic scaffolds not only improved their mechanical properties but also enabled surface functionalization of the scaffold. Gelatin-coated samples demonstrated excellent biocompatibility with human osteoblast-like MG-63 cells. The results obtained from this study clearly indicate that the phosphate glass/HA composite scaffold coated with gelatin is a promising material for use in tissue engineering, exhibiting the most favorable properties among all samples tested [15]. According to literature reports, the presence of a gelatin layer on the surface of HA increases its corrosion resistance compared to the uncoated counterpart. Moreover, this polymer plays a key role in enhancing cell viability [67].

4.3. Gene delivery systems

Due to their specific properties, HA nanoparticles have also attracted researchers' interest as potential gene delivery systems [68]. It is known that calcium ions form ionic complexes with the phosphate groups of DNA, which facilitates transport across the cell membrane via endocytosis through ion channels [69]. It has also been demonstrated that interactions between calcium ions and negatively charged DNA or RNA molecules enhance the stability of the transported genes, while simultaneously protecting them from cytoplasmic and nuclear degradation [48].

Interestingly, microRNA (miRNA) emerges as an alternative therapeutic option for treating bone defects due to its ability to regulate the expression of genes responsible for the regeneration of damaged bone tissue by promoting a biological substitute that mimics the functions of bone cells, including their differentiation, proliferation, and apoptosis. Unfortunately, the susceptibility of miRNA to cleavage by nucleases and its poor cellular uptake remain significant challenges for its therapeutic application. Therefore, HA nanoparticles can be utilized as delivery systems that successfully transport miRNA to target cells while simultaneously enhancing bone tissue regeneration. Many researchers have investigated the correlation between HA properties — such as particle size, morphology, surface charge, and coating methods — and its capacity for bone regeneration or gene delivery. However, the potential of this material as a carrier for miRNA has not been fully appreciated and requires further investigation [68].

Conventional synthetic insecticides yield limited effectiveness due to the development of insect resistance as well as their adverse effects on non-target organisms and the environment. RNA interference (RNAi) is widely used as a tool for silencing target genes by utilizing double-stranded RNA (dsRNA). Since its discovery in the nematode *Caenorhabditis elegans*, its mechanism has been studied in other model organisms (mammals, insects, and plants) for a broad range of applications, including functional genomics, gene therapy, and pest control. Although RNA interference technology holds great promise for insect management, its practical application remains limited. A number of physiological barriers have been identified that hinder the application of this strategy for eliminating these crop pests, including the presence of endonucleases and differences in the efficacy of the technology based on the genetics and cellular biology of individual insect species. Another obstacle may be the entrapment of dsRNA molecules within endosomes, which ultimately leads to their degradation and prevents their entry into the cytoplasm, where the initial stage of RNA interference occurs. One approach to enhance the effectiveness of dsRNA is its conjugation with a nanocarrier, which is most commonly composed of coated inorganic materials such as carbon nanotubes, gold nanoparticles, or calcium phosphates, as these allow the formation of complexes of appropriate size [70].

HA is a desirable material in agricultural applications because, being a compound naturally present in bone tissues, it exhibits biocompatibility and is widely distributed in the environment [70]. Numerous studies have been conducted whose results indicate the promising efficacy of coated HA nanoparticles for the delivery of small interfering RNA (siRNA) *in vitro* [71—74]. In the study by Baddar et al., HA nanocarriers coated with polyacrylic acid were prepared using the layer-by-layer method and subsequently coated with a layer of the cationic polyamino acid — poly-L-arginine — to enable binding of the negatively charged dsRNA. The binding affinity of the nanocarriers to RNA increased with the rising mass ratio of nanoparticles to RNA. *In vitro* studies on transgenic SF9 cells derived from the moth species *Spodoptera frugiperda*, which express the firefly luciferase gene, confirmed significant gene silencing using the obtained nanocarrier transporting dsRNA, whereas "naked" dsRNA was ineffective at gene expression knockdown. Confocal microscopy revealed that dsRNA delivered via the nanocarrier was not localized within endosomes, whereas its naked counterpart appeared to be trapped inside endosomes, preventing it from fulfilling its function. Based on these results, it can be concluded that the cellular uptake of dsRNA complexed with polymer-coated HA nanocarriers leads to inhibition of the target gene expression, an effect not observed when naked dsRNA is introduced. A plausible hypothesis supporting these findings is the ability of HA to facilitate the release of dsRNA molecules from the endosome [70].

The use of HA nanoparticles as gene delivery systems is, however, associated with certain limitations. Despite exhibiting promising properties, this material is characterized by a heterogeneous structure (dependent on synthesis conditions) and a tendency to aggregate. These unfavorable phenomena play a crucial role in the transfection process, including affecting the cellular uptake of genes. Heterogeneous HA particles demonstrate variable transfection efficiency, resulting in unpredictable effects on the organism. Appropriate temperature, pH, ionic strength, and stabilizing agents, among other important parameters, are key factors in producing coated HA nanoparticles with characteristics ideal for their safe and effective use as gene carriers [48].

4.4. Hydroxyapatite coatings

Biomaterials are used in a wide range of biomedical applications, including the fixation and stabilization of fractured bones. Traditional non-degradable metals, such as titanium alloys, stainless steel, and cobalt-chromium alloys, have been widely employed due to their good mechanical properties, high corrosion resistance, and appropriate biological performance. However, compared to biodegradable metallic implants, they require an additional surgical procedure for removal from the body [75].

With advancements in tissue engineering technology, biodegradable materials are currently attracting significant attention because they are gradually replaced by the host tissue. Magnesium and its alloys are presently used as biomaterials in implant applications, as the potential corrosion of magnesium does not cause adverse side effects, and the element is non-toxic when in contact with the body's physiological fluids. Furthermore, magnesium alloys exhibit favorable mechanical properties and biocompatibility. However, rapid and uncontrolled corrosion of magnesium in physiological environments leads to hydrogen release. Although the released gas is quickly exchanged with surrounding tissues, its presence can cause defects in tissues adjacent to the magnesium-based implant, which from a clinical perspective is an undesirable phenomenon [75].

Besides alloying, surface modification methods such as the sol-gel technique, electrolytic plasma oxidation, application of conversion coatings, physical deposition, polymer coating, thermal spraying, electrodeposition, and laser cladding have been investigated as potential solutions to slow down the corrosion rate of magnesium alloys. According to the literature, polymer coatings protect the implant from rapid degradation. Polycaprolactone, being a semi-crystalline hydrophobic linear polymer, is widely used as a component of such coatings due to its good mechanical strength, flexibility, and biocompatibility. However, its use in bone tissue regeneration is limited because of low stiffness and relatively low bioactivity. To mitigate these unfavorable properties, before applying the polymer layer, the implant surface can be coated with a bioactive ceramic layer, which leads to increased osteoconductivity of the polymer without negatively affecting its mechanical properties [75].

Among all bioceramic materials used in bone tissue regeneration, HA exhibits excellent bioactivity and osteoconductivity as a coating compound. Numerous studies have been conducted to analyze the effect of bioceramic-polymer coatings on improving the corrosion resistance and bioactivity of magnesium alloys [75]. Wang et al. applied a composite coating composed of calcium hydrogen phosphate ($CaHPO_4$) and polycaprolactone to a magnesium-zinc substrate. *In vitro* studies showed that this coating slowed down the degradation of the alloy [76]. Similarly, Bakhsheshi et al. applied a dual-layer coating to a magnesium-calcium alloy, where the first layer consisted of nano-HA deposited via electrodeposition, and the outer polycaprolactone layer was applied using the dip-coating method. The obtained results indicated that the introduction of the HA layer enhanced the corrosion resistance of the magnesium-calcium alloy. A significant improvement in the compressive strength of the coated material was also observed compared to uncoated samples after ten days of immersion in simulated body fluid [75].

Table 1 Summary of common coating methods, example polymers, and typical advantages/disadvantages for biomedical applications [18].

Method	Type	Example polymers	Advantages	Disadvantages
Dip coating	Physical (wet)	Chitosan, alginate, PCL	Simple, scalable, uniform coverage	Weak adhesion without priming; thickness control limited
Spin coating	Physical (wet)	PDMS, PCL, PLA	Thin uniform films on flat substrates	Not suitable for large/porous scaffolds
Electrospinning	Physical (wet)	PCL, PLGA, collagen	Creates fibrous meshes, high surface area	Batch variability; limited for conformal coating of complex 3D parts
Grafting-to / Grafting-from	Chemical	PEGylated chains, functionalized polymers	Strong covalent attachment; tunable interface	Requires surface functionalization; more complex chemistry
EDC/NHS or glutaraldehyde crosslinking	Chemical	Chitosan, gelatin	Simple covalent coupling to amines/carboxyls	Possible cytotoxic residues; careful control required
Click chemistry	Chemical	Functionalized polymer precursors	High efficiency, minimal byproducts	Requires functional handles; may need catalysts

A similar analysis was conducted by Ji et al., who developed a functional coating based on HA saturated with gentamicin sulfate and supplemented with polycaprolactone, using a one-step hydrothermal deposition method. Their objective was to obtain an improved HA coating enriched with a polymeric component to enhance the corrosion resistance of the magnesium alloy and to incorporate a therapeutic agent with antibacterial properties. It was found that the release of gentamicin from the resulting coating occurred in a sustained manner, providing the potential implant with long-term bactericidal activity. This is a valuable feature, as infections associated with implant placement are among the most common causes of postoperative complications [77].

Research in this area was also undertaken by Taha et al., who modified the surface of a titanium implant material coated with HA by applying a layer of polymer formed through the cross-linking of cyclodextrin with polycarboxylic acid. This enhancement aimed to enable the incorporation of therapeutic agents within the implant area and ensure their sustained release at the implantation site. The researchers used two commonly applied antibiotics in orthopedic surgery — tobramycin and rifampicin — and impregnated the tested material with each drug individually or in combination. The drug content, release kinetics, and therapeutic efficacy were thoroughly analyzed. The results demonstrated that the polymer coating significantly improved the affinity of both antibiotics to the HA-coated titanium implant surface. A major advantage of impregnating the implant with a combination of both drugs is its high efficacy against *Staphylococcus aureus* and *Enterobacter cloacae*, thus overcoming the limitations associated with using a single antibiotic to treat infections caused by these two bacterial strains. The sustained antibacterial activity of the tested samples confirmed that the cyclodextrin-based polymer may serve as a promising drug delivery system, enabling the release of therapeutic agents at a constant rate [78].

5. Summary and conclusions

Synthetic nano-hydroxyapatite continues to demonstrate its value as a noteworthy material used not only in tissue engineering and drug delivery systems, but also in various other fields. Due to its limited standalone applicability resulting from unfavorable mechanical properties, numerous researchers have attempted to improve its performance. Analysis of their findings reveals that such enhancement can be achieved by coating the ceramic material with polymers. This modification improves the properties of HA on multiple levels, as evidenced by the significantly expanded range of applications of the coated compound. Applying a polymer layer enables the development of a controlled drug delivery system, offering advantages such as the use of significantly lower drug doses and targeted release at the desired site at a constant rate. Such modification of hydroxyapatite considerably enhances the safety and effectiveness of therapy. Its combination with polymers is also desirable in tissue engineering, as it allows the development of a biomaterial that mimics the natural properties of bone and improves mechanical characteristics, making it an ideal candidate for use in implant form.

The scientific literature provides numerous studies highlighting the invaluable role of polymer-coated hydroxyapatite in the delivery of genetic material; however, this area of application remains not fully explored. The most commonly used implants are those made of metals, due to their high hardness and mechanical strength. A major drawback of such implants is their low biocompatibility and limited osteointegration. These unfavorable properties can be compensated by applying a hydroxyapatite coating to the implant surface, a widely adopted strategy. It is also common practice to further coat metallic implants with a polymer layer to protect them against corrosion and rapid degradation. A summary of the most important aspects described in the manuscript is presented in

Table 1.

Key takeaways:

- Polymer-coated HA is a promising material that holds a possibility to be used in a wide range of applications.
- Polymer coatings improve HA handling, mechanical resilience, and enable controlled drug/gene release.
- Chemical grafting approaches (covalent coupling) yield more mechanically robust coatings than passive adsorption.
- Sterilization and long-term degradation are critical translational challenges that require systematic study.

Future perspectives:

- Focus on scalable, reproducible coating processes compatible with clinical manufacturing (GMP).
- Consider further investigation of the potential use of this material as a carrier of genes, as it is the least studied application area.
- Conduct standardized, long-term *in vivo* biocompatibility and degradation studies.
- Integrate smart, stimuli-responsive polymers with HA cores to enable on-demand local therapy and to enhance translational potential.

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