Chapter 10

Drug Delivery Systems in Bone Regeneration and Implant Dentistry

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1. Introduction

Bone regeneration is a complex, well-orchestrated physiological process involving a number of cell types and intracellular and extracellular molecular signaling pathways [1]. Bone grafts provide a structural framework for clot development, maturation and remodeling that supports bone formation in osseous defects. These materials must possess biocompatibility and osteoconductivity, as well as the properties that support osteogenesis. The ideal characteristics of a bone graft are that it must be nontoxic, non-antigenic, resistant to infection, easily adaptable, readily and sufficiently available to stimulate new attachment and able to trigger osteogenesis [2].

Osseous defects in the oral cavity have been successfully managed with a variety of biological and synthetic materials, including autografts, allografts, xenografts and alloplastic materials. Although autografts are unequivocally accepted as the gold standard, donor site morbidity and limitations on the quantity of bone that can be harvested demand that clinicians seek alternatives [3]. In light of the immunological and disease transfer risks from allogeneic bone, research has focused extensively on developing alloplastic bone substitutes that are predominantly based on ceramics, such as calcium phosphates (CaP), calcium sulfates, and bioactive glasses [4]. In general, these ceramic materials are renowned for their osteoconductive and bioactive properties [5]. The most commonly used ceramics are the CaP-based ceramics hydroxyapatite (HA) and beta tricalcium phosphate [6].

Considering engineered grafts, the most important factor is to prepare a three-dimensional structure consisting of biodegradable material, generally called a scaffold [7]. The nature and

structure of the scaffold should support cell proliferation and differentiation, accelerating the process of tissue regeneration. Furthermore, the growth factor providing a scaffold to an injury site should enhance progenitors, causing inflammatory cells to migrate and activate the healing process [8, 9]. However, among the basic challenges for scaffold implantation is to control infection due to bacterial load, which can create immune problems and finally result in implant rejection. To overcome implant-related infection and bacterial load on the scaffold, antibiotic drug incorporation and its controlled release have been suggested as a promising strategy [10]. Bone is among the few tissues of the human body that has high endogenous healing capacity. Various concepts for local drug delivery to bone have been developed in recent decades to overcome such healing deficits.

Several methods are used for drug loading and release from scaffolds. However, the basic aim for drug release is to reduce infections and bacterial load to the site of implant, but if the drug is released too quickly, there could be a chance of infection because the entire drug has drained from the scaffold in the initial time itself. Similarly, if there is too much delay to drug release, infection can set in further, making it more difficult to manage the healing of wounds. Hence, better options for drug release would incorporate higher antibiotic release at the initial time and sustained release at an effective rate to inhibit the risk of infection from bacteria in the scaffold at an effective level [11]. Different techniques have been used for drug loading to the scaffold, and controlled release has been studied. One of the simplest strategies is the application of biodegradable polymer coatings loaded with specific drugs onto the scaffold structure. The other methods reported for coating the drug-loaded polymer have included solvent casting, thermally induced phase separation, evaporation, freeze drying and foam coating. Among these methods, an interesting approach for drug loading and release consists of combining drug-loaded microspheres with a macroporous scaffold `matrix' [12-15].

In a recent study, a biodegradable nanoporous bioceramic system was used as a highly bioresorbable matrix for drug delivery. This study emphasized the efficacy of hydroxyapatite-based material having interconnected nanoporosity as a vehicle for a therapeutic agent. An in vitro experiment was conducted with the goal of assessing this material and comparing it with commercially available gentamicin-loaded PMMA cement. It was found that the nanoporous bioceramic granules could act as antibiotic carriers, exhibiting a high initial burst effect followed by sustained low-level release for 3 weeks. It was very effective, confirming that the concentration of drug eluted was greater than that needed to maintain bactericidal levels [16].

In addition to the above-mentioned technique, magnetic nanoparticle-incorporated materials have also been used as a bone regeneration scaffold, and they are schematically represented in figure 3 [17]. To obtain homogenous dispersion of magnetic particle loading and surfactant, a porous structure generated by ceramic crystals, the in-situ method was followed. Further, it was made to a specific shape, and the specific drug was loaded via dip loading or other methods. The drug-loaded scaffold was placed at the defective site in the presence of a magnetic field (MF), which facilitated easy drug release from the scaffold, helping to protect it from bacterial colonization, and the MF stimulated the scaffold for cell proliferation. Recently released in vitro results support MF-induced bone regeneration [18-20].

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Engineered biomaterials combined with growth factors, such as bone morphogenetic protein-2 (BMP-2), have been demonstrated to constitute an effective approach in bone tissue engineering because they can act both as a scaffold and as a drug delivery system to promote bone repair and regeneration. Despite the substantial progress made in developing porous materials as bone substitutes, the realization of synthetic structure able to harness fully bone's capability of regenerating and remodeling itself and to mimic the complicated physiochemical attributes of bone continues to present challenges.

In the following sections of this chapter, the materials and drug delivery techniques used to enhance bone regeneration and to control infection are discussed. The methods to enhance the surface of titanium implants to promote osseointegration are also detailed.

2. Bone regeneration materials

2.1. Calcium phosphate ceramics

The calcium phosphates have been widely studied due to their biocompatibility, tailorable bioabsorbability and bioactivity. Calcium phosphates have been used as novel delivery carriers for antibiotics, anti-inflammatory agents, analgesics, anticancer drugs, growth factors, proteins and genes [21, 22]. Furthermore, they can be synthesized using simple methods, and these drugs can easily be incorporated via different routes, such as wet chemical processes, solid state reactions, hydrothermal and micelle-mediated processes, etc. [23, 24]. Most of the polymeric systems show an acidic nature, and their degradation by-products can alter drug activity. The major advantages of CaPs, compared with other biodegradable polymeric systems, is that the degradation ions are Ca^{2+} and PO_4^{3-} ions, which already exist in the body in higher concentrations [25].

Nanotechnology-derived calcium phosphates have also successfully maintained a sustained and steady drug release over time. Calcium phosphate scaffolds not only provide initial structural integrity for bone cells but also direct their proliferation and differentiation and assist in the ultimate assembly of new tissue. Therefore, ceramic nanoscaffolds are usually 3-D and porous, although in some cases they consist of 2-D coatings or films. They mimic the in vivo environment of cells more completely than nanoparticles.

Therefore, most drug-eluted ceramic nanoscaffolds serve multiple functions, such as drug delivery, directing cell growth or tissue generation, and mechanical support. Indeed, the mechanical support provided by ceramic scaffolds far exceeds that provided by polymeric scaffolds. Studies have shown that drug-release kinetics could be further controlled by tailoring calcium phosphate nanoparticle grain size, surface area and calcium-to-phosphorus ratios [26]. Hollow silica nanospheres have been fabricated into well-controlled shapes and sizes using self-templating molecules [20]. For example, studies have shown that hollow silica nanospheres were capable of entrapping an eight-fold greater quantity of drug species than solid silica nanospheres. Time-delayed multiple-stage release profiles were also possible with these hollow silica nanospheres [27].

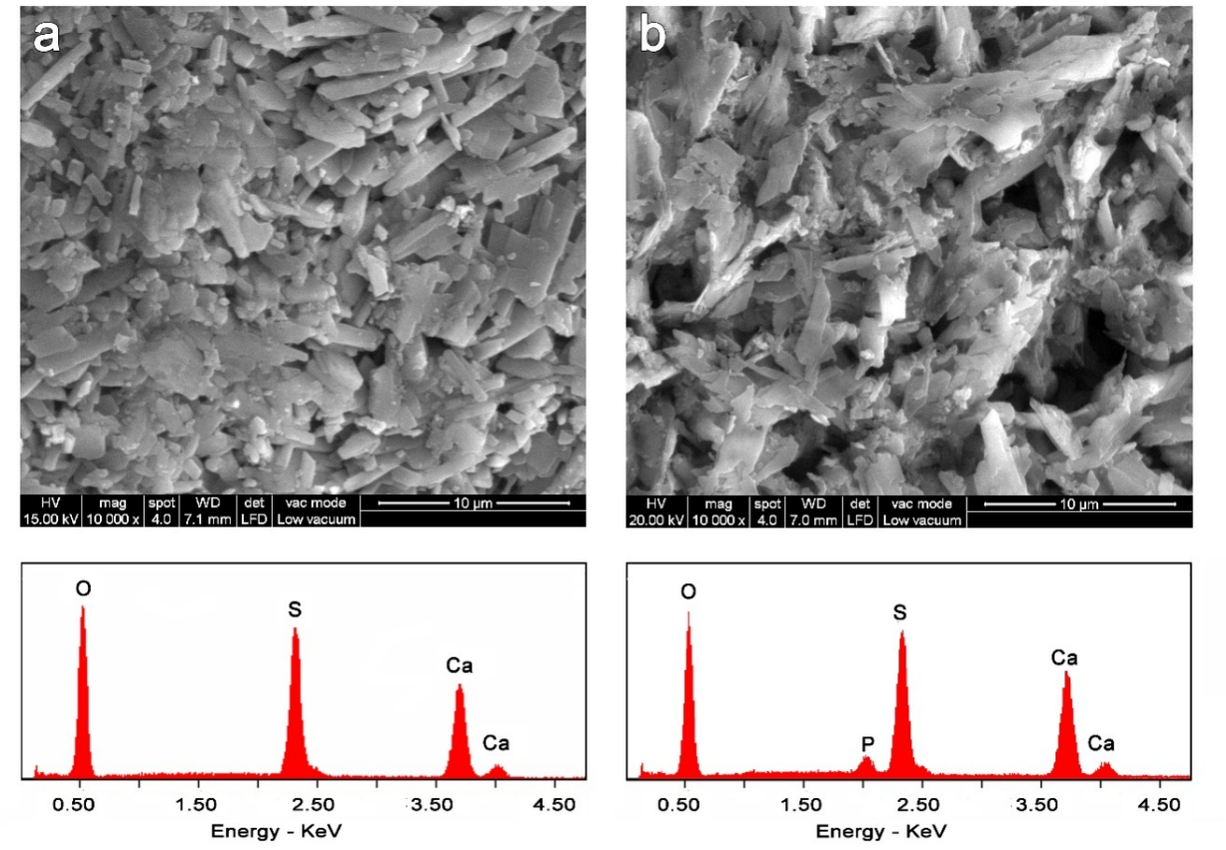

Figure 1. The micromorphology (SEM) of calcium sulfate-phosphate injectable cement. **a)** The set cement surface of unmodified low-dimensional medical grade calcium sulfate (crystal sizes less than 5 microns). **b)** The phosphate-containing material, which inhabits very small crystal formations grown into folding sheets. Energy dispersive (EDS) data, corresponding to the samples, are shown below each. The phosphorous content in the second sample is evident, whereas no separate phosphate phase appeared in XRD. The phosphate content resides as a substitution in the calcium sulfate crystals.

2.2. Porous spherical hydroxyapatite granules for drug delivery

Calcium phosphate-based bioceramics, such as hydroxyapatite (HA), are known for their excellent biocompatibility due to their similarity in composition to the apatite found in natural bone [28]. Various forms of HA bone grafts, such as dense and porous blocks, dense and porous granules, and powder forms, are available as bone substitutes [29]. The porous matrices enable cell migration and provide favorable conditions for nutrient transport, tissue infiltration, and vascularization [30, 31]. The spherically shaped particles are suitable for implantation as injectable bone cements, and the inter-granular space promotes cell migration and the growth of extracellular matrix [32, 33].

Porous HA is produced using methods such as ceramic slip foaming [34], positive replication of reticulated foam scaffolds [35], burnout of sacrificial porogens, such as polymer beads [3], and techniques that exploit naturally occurring porous calcium-based structures, such as the hydrothermal conversion of either coral or bone [36, 37]. Porous spherical HA granules can be

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used for drug delivery systems. The various pore and channel structures of spherical granules were obtained by adjusting the ratio of water to HA powder and the amount of sodium chloride (NaCl). Earlier studies focused on the use of anti-inflammatory or anti-bacterial drug release from HA, to control inflammation and infection at the site of implantation [38]. Currently, several drugs have been found to enhance bone formation, and the loading of HA with these drugs and agents could be a very effective method for enhancing bone formation at the site of implantation [39, 40]. Research is under way to control the drug release rate using the complex micro-channel structures of HA granules [41].

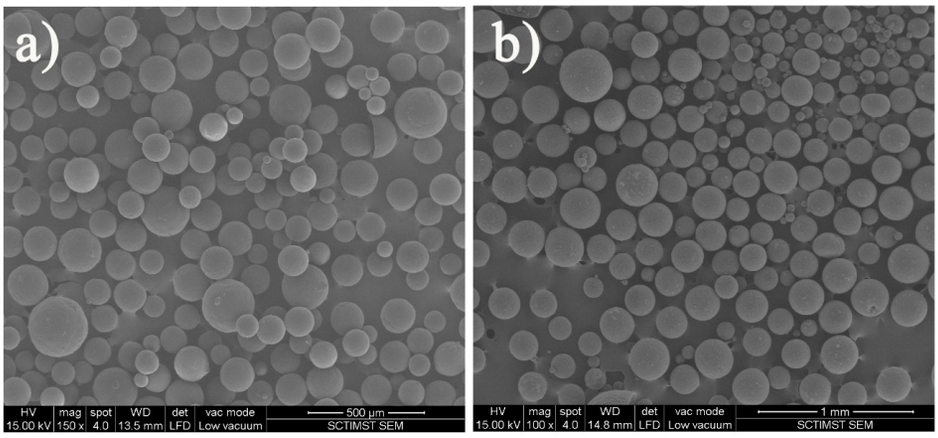

Figure 2. Scanning electron microscopic images of: a) polycaprolactone polymer microspheres; and b) magnetic hydroxyapatite-loaded polycaproctone polymer microspheres.

2.3. Demineralized bone matrix

Bone void fillers, such as demineralized bone matrix (DBM), offer a broad range of materials, structures and delivery systems to use in bone grafting procedures. Allogenic DBM possesses osteoinductive properties and could serve as an ideal drug delivery device for prophylactic treatment in a variety of different anatomical locations [42, 43]. The use of DBM would allow for the release of the entire quantity of antibiotic as the material is being remodeled.

2.4. Carriers and delivery systems for growth factors

Growth factors (GFs), such as bone morphogenetic protein, transforming growth factor-beta, fibroblast growth factor, platelet-derived growth factor, and insulin-like growth factor, are proteins secreted by cells that act on the appropriate target cell or cells to perform specific actions. A variety of so-called bone-graft substitutes, including demineralized bone matrix, calcium phosphate-containing preparations and Bioglass (BG), are also potential carriers for recombinant proteins [44]. Bioglass and calcium phosphate-based materials, such as hydroxyapatite, coralline hydroxyapatite, and tricalcium phosphate, have been shown to be biocompatible and to provide osteoconductive scaffolds that could potentially be combined with GFs to enhance bone repair [45].

Demineralized bone matrix preparations are particularly attractive as potential carriers for growth factors because they are osteoconductive and can have some osteoinductive potential as well. The disadvantages of these materials include poor handling characteristics and concerns about their overall bio-resorbability, as well as limited potential for remodeling and an unclear understanding of their effects on bone strength [46]. Recombinant bone morphogenetic protein (BMP) has been used to enhance the bone regeneration in graft and implant osseointegration in dentistry [47]. Recombinant human BMP-2 (rhBMP-2) has been shown to be effective in bone regeneration [48].

Among surface modification techniques, coating the implant surface with bone stimulating agents, such as GFs, is very promising. The most commonly used GFs include bone morphogenetic proteins (BMP-2), TGF-β1, platelet-derived growth factor, insulin-like growth factor and combinations [47, 49]. The actual mechanisms of GF combinations are not fully understood. From early reported studies, after implantation, both GFs (TGF-β and BMP) could directly increase the local pool of osteoprogenitor cells by stimulating their migration [50]. The circulation of pathways acts as a source of osteoprogenitor cells throughout ectopic BMP-induced bone regeneration. Similarly, the presence of both TGF-β1 and BMP-7 cooperatively interact to increase angiogenesis and vascular invasion after their co-administration increased vessel constitution [51]. The results demonstrated that the presence of GF associated with implant surfaces improved bone regeneration, vascular invasion and angiogenesis. Research is under way to optimize the carrier properties and the characteristics of the GF and its dose to maximize the regeneration potential.

2.5. Nanoscaffolds

The application of nanotechnology for drug delivery and the use of nanometer scale materials has helped to develop innovative approaches in this field. At this scale, materials display different physicochemical properties due to their small size, surface structure and high surface area. The nanoparticles based ceramic scaffolds have also demonstrated great potential for controlled drug delivery and is currently a fast growing research area. The ceramic nanoscaffolds have several advantages such as high porosity, high volume-to-area ratios, high surface area, high structural stability and long degradation times. These properties make them potent systems for controlled release of drugs. At the implantation sites drugs/chemical agents are applied for decreasing infection, reducing inflammation, and increasing bone growth on titanium surfaces. The nanotubular titania and calcium phosphate-based nanoscaffolds have showed good potential for drug and growth factor delivery.

2.6. Magnetic nanoparticles (FE-hydroxyapatite)

Superparamagnetic nanoparticles (MNPs) have been progressively explored for their potential in biomedical applications and in particular as contrast agents for diagnostic imaging, for magnetic drug delivery and, more recently, for tissue engineering applications [52-54]. MNPs have been used for biomedical applications, such as in hyperthermia [55], as a contrast agent for diagnostic imaging [56], for magnetic drug delivery [57, 58] [13], and for cell mechanosensitive receptor manipulation to induce cell differentiation [59].

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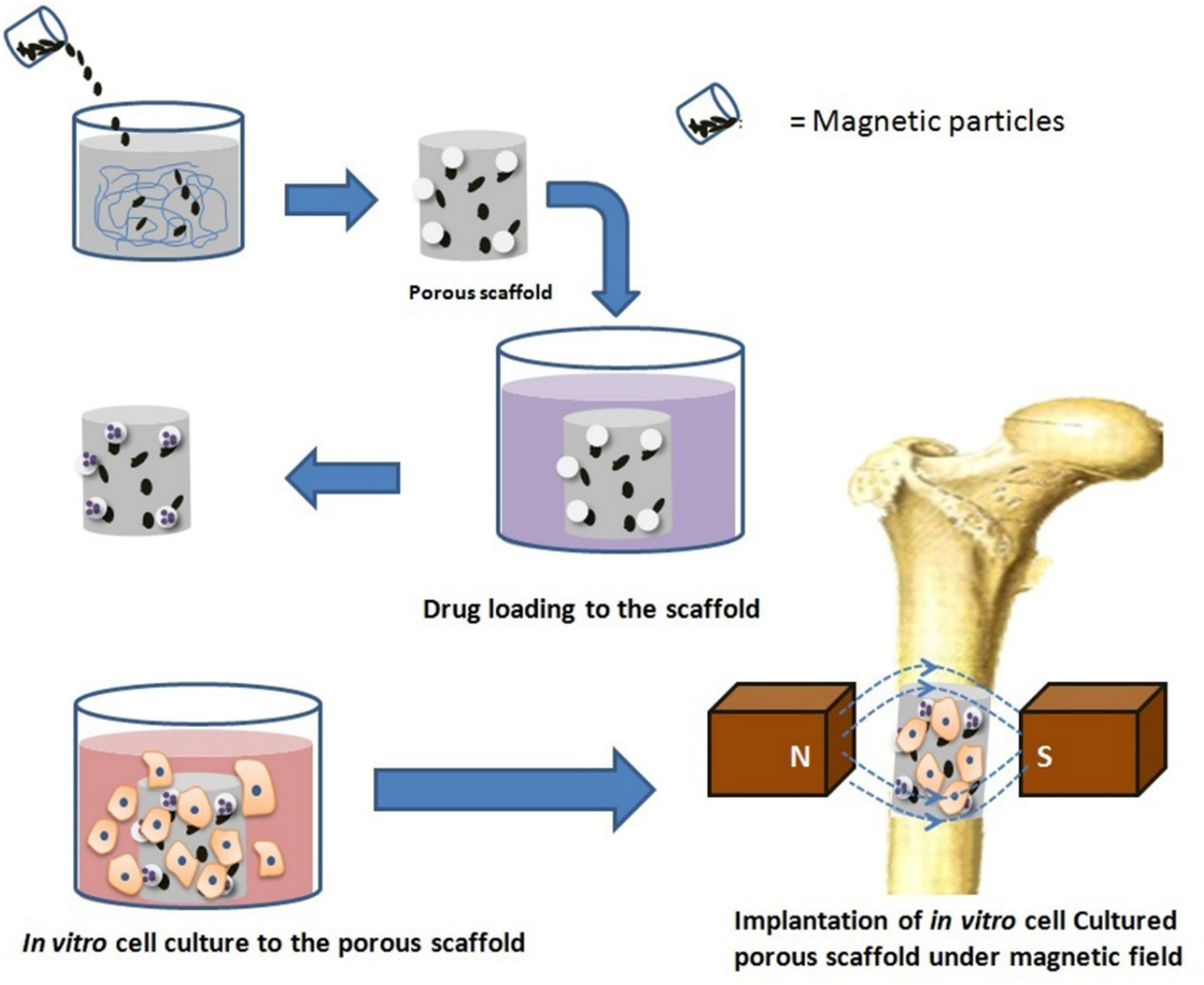

Figure 3. Schematic presentation of engineered magnetic scaffold preparation and implantation.

The most popular MNPs used in medicine and biotechnology are iron oxide-based phases, but their potential as a tissue engineering scaffold has not yet been fully assessed [60]. Although Fe is a vital element in the human body, its concentration within hard tissue is low, and its presence into the body scarcely affects bone remodeling [61]. In contrast, the biocompatibility and bioactivity of HA are already well established [62-64], and, in fact, more than 60% of the currently available bone graft substitutes involve calcium phosphate-based materials [65]. Hence, a Fe-HA phase endowed with superparamagnetic ability could be used as an active scaffold for bone and osteochondral regeneration or as a nontoxic, biodegradable, magnetic nanocarrier [17, 66, 67].

2.7. Chitosan hydroxy apatite

Chitosan is considered an appropriate functional material for biomedical applications because of its high biocompatibility, biodegradability, non-antigenicity and adsorption properties [68, 69]. The mechanical and biological properties of chitosan scaffolds could be improved by the incorporation of bioceramics, such as HA, β-tricalcium phosphate and calcium phosphate

biomaterials, such as gelatin alginate, or inorganic material, such as wollastonite [70, 71]. Chitosan scaffolds are osteoconductive and can enhance bone formation both in vitro and in vivo [72]. Currently, the development of chitosan-nanohydroxyapatite (nHA) composites through in situ hybridization by ionic diffusion processes, freezing and lyophilization, stepwise co-precipitation, and mineralization via double diffusion are being undertaken successfully [73-75].

3. Surface functionalization of titanium implants

The long-term success of dental implants also depends on the complex **biointegration** of these alloplastic materials, determined by the responses of the different surrounding host tissues. The osteoinductivity of calcium phosphate coatings has attracted significant interest, using various coating techniques, including plasma spraying, magnetron sputtering, electrophoretic deposition, hot isostatic pressing, sol-gel deposition, pulsed laser deposition, ion beam dynamic mixing deposition, electrospray deposition, biomimetic deposition, and electrolytic deposition [76]. Non-ceramic implant coating is also used, allowing for drug incorporation during the coating process. The currently available techniques can be broadly divided into three categories, including hydrogel coatings, layer-by-layer coatings, and immobilization. Techniques such as 'dip-coating' methods and 'layer-by-layer' (LbL) coating techniques are used for the incorporation of BMP-2 and TGF-β1 to the implant surface [77].

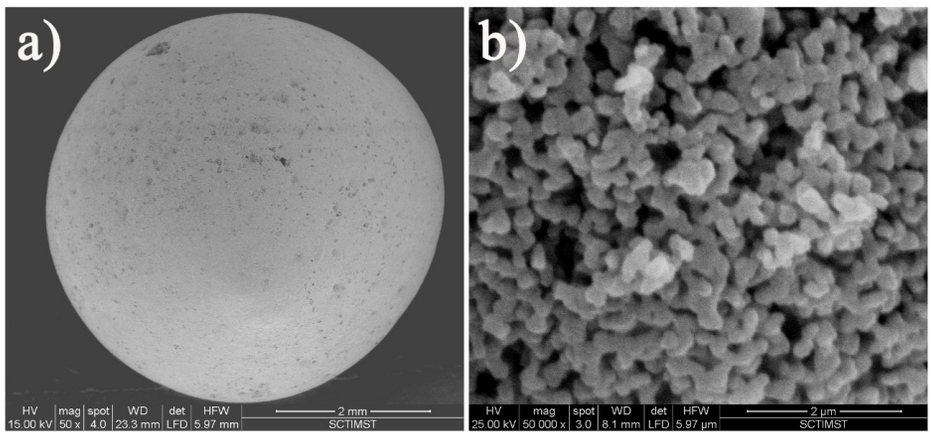

Figure 4. a) Scanning electron microscopic pictures of HAP microspheres; b) high-resolution SEM picture showing interconnected nanopores.

3.1. Nanotubular titanium surface

Nanotubular titania structures can be readily fabricated via direct anodization of titanium implants into an electrochemical cell that uses the titanium as an anode and platinum as a cathode in the presence of fluorine-based electrolytes [78, 79]. Penicillin-based antibiotics could

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be loaded to the nanotubular titania as a drug delivery platform by co-precipitating the drug and calcium phosphate crystals onto the nanostructures [80, 81].

Anodic oxidation has many advantages for surface modification, such as its ability to fabricate porous TiO_2 films through dielectric breakdown, the changeability of the crystalline structure and the chemical composition of the oxide film depending on the fabrication conditions, and it has been suggested to provide storage room for the delivery of GFs, such as rhBMP-2, to enhance osseointegration [82, 83]. In vitro studies have suggested that a dose response could be produced with appropriate period of delivery of the GF to the cells [84].

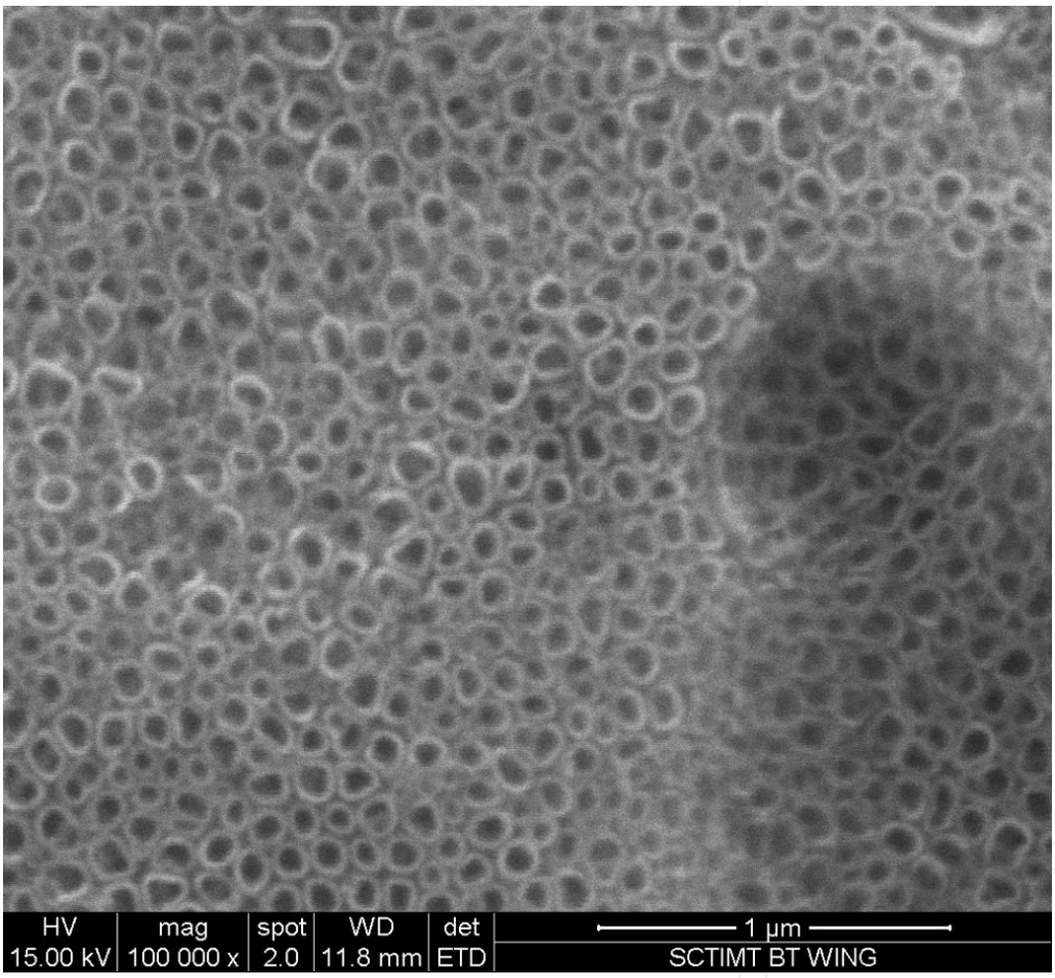

Figure 5. Scanning electron microscopic image of an anodized titanium implant surface showing uniform nano-tubules of titanium oxide throughout the surface.

3.2. Hydroxyapatite

Coating of titanium implant surfaces with HA has shown better integration with bone. HA can be coated to the surface by plasma spraying, sputtering, pulse laser deposition and electrostatic multilayer assemblies, fabricated using the layer-by-layer technique [85]. HA coatings enhance new bone formation on implant surfaces with a line-to-line fit, in areas with

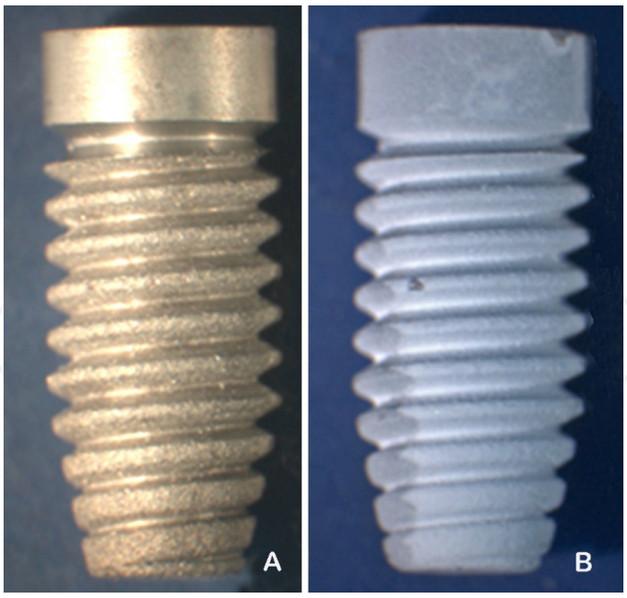

Figure 6. a) An anodized titanium implant; b) An anodized titanium implant coated with hydroxyapatite.

gaps of 1-2 mm between the coated implant and the surrounding bone. The coating also helps to prevent the formation of fibrous tissue that would normally result due to the micro-movements of an uncoated titanium implant [86].

HA coatings have been used as a method for the delivery of GFs, bioactive molecules, and DNA [85, 87, 88]. HA coatings augmented with bone morphogenetic protein-7 (BMP-7), placed on segmental femoral diaphyseal replacement prostheses, improved bone ingrowth in a canine extra-cortical bone-bridging model. Titanium alloy plasma-sprayed porous HA coatings, infiltrated with collagen, recombinant human bone morphogenetic protein (rhBMP-2) and RGD peptide, improved mesenchymal stem cell (MSC) adhesion, proliferation and differentiation in vitro and increased bone formation in ectopic muscle and intra-osseous locations in vivo [85].

Another group used hydroxyapatite nanoparticles complexed with chitosan into nanoscale non-degradable electrostatic multilayers, which were capped with a degradable poly(b-amino ester)-based film incorporating physiological amounts of rhBMP-2 [89]. Plasmid DNA, bound to calcium phosphate coatings deposited on poly-lactide-co-glycolide (PLG), was shown to be released in vitro according to the properties of the mineral and solution environment [87]. These methods of delivery of bioactive molecules extended the function of HA as a coating to enhance new bone formation around implants.

3.3. Antibiotics: Surface tethering of antibiotics

The initial adhesion and colonization of bacteria to an implant surface are considered to play key roles in the pathogenesis of infections related to biomaterials [90]. Two recent strategies are: (1) coating implants with antibiotics; and (2) covalently attaching antimicrobial molecules onto the implant surface. The objective of these bioactive surfaces is to disrupt the colonization

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Figure 7. Hydroxyapatite-coated titanium implant.

of the microbes or to prevent bacterial adhesion to the implant and subsequent development of biofilm [91]. Hydrophilic surfaces have been shown to be less prone to become infected with microorganisms than hydrophobic surfaces [92]. The topical application of antibiotics on the implant surface might be more efficient because bacteria are killed locally directly upon binding, before the formation of biofilm. Local delivery of antibiotics has long been applied in bone cements used to repair orthopedic and dental implants [93].

Antibiotics such as gentamicin are incorporated into the cement, which slowly releases the drugs after setting *in situ*. Local delivery can prevent adhesion and growth of significant numbers of bacteria. HA coatings are frequently applied to dental implants to stimulate osseointegration and to accelerate bone formation. Antibiotics can be co-precipitated on titanium surfaces to obtain drug-releasing surface coatings. Studies have shown that antibiotics with optimal calcium-chelating properties had long lasting antimicrobial properties [94, 95]. Alt et al [96] demonstrated that both gentamicin-hydroxyapatite and gentamicin-RGD (arginine-glycineaspartate)-HA coatings could release antibiotics for up to twenty-four hours without inhibiting new bone formation. Erythromycin-impregnated strontium-doped calcium polyphosphate (SCPP) was found to inhibit bacterial growth completely for up to 14 days [97]

Nanoporous implants are suitable for the incorporation of antibiotics to obtain controlled release of drugs [98]. Nanostructured surfaces play a major role in advanced biomedical implant design because these surfaces have been studied for their enhanced bioactive properties, as well as their antagonistic behavior toward bacterial colonization. To maintain sustained drug elution properties and better bone bonding ability, significant efforts have been undertaken to develop bioactive hollow nanostructures on implant surfaces [99]. In this context, one of the implant titania nanotubular surfaces created via anodization showed enhanced bioactivity, conjugated with the capacity to store diverse compounds and control their elution. The anodization technique could create porous structures with controlled sizes of three-dimensional networks on metallic surfaces [100].

Anodization followed by HA coating was adopted as a surface modification technique to make drug-loadable Ti implants for dental applications. Self-organized titania nano-tubes were grown on titanium substrate as drug-carrying vehicles by coating HA ceramic using laser deposition. Nanostructured surfaces were achieved on titanium via anodization in a glycerol-NH_4F electrolyte system, followed by annealing. The nano-tubules were then capped with HA deposited with pulsed laser ablation. HA-coated polished titanium, nano-structured titanium and hydroxyapatite coated nano-structured titanium were analyzed for their drug-carrying capacity using gentamicin sulfate. The ceramic-coated anodized substrates were found to be most efficient among the aforementioned three compounds in controlled delivery for longer than 160 h, with drug content of 0.5 $\mu g/cm^2$, compared to the anodized substrate, which delivered the whole drug within 140 h. It was thus evident that laser deposition facilitated the controlled release of drug, compared to the anodized and bare substrates. This study proposed the application of laser deposition of bioceramics, such as HA, over nano-structured titanium for drug-eluting metallic implants [101].

3.4. Tan-Ag coatings

Due to the risk of the development of antibiotic resistance associated with antibiotic-loaded coatings, non-antibiotic agents in the coating have been used as alternatives. Among the various dopants, silver nanoparticles are among the most popular agents used due to their inhibition of bacterial adhesion, broad anti-bacterial spectrum, long lasting anti-bacterial effects, and propensity for being less prone to the development of resistance. Ag and Cu are known to be efficient antibacterial agents because of their specific antimicrobial activity and the nontoxicity of active Ag and Cu ions to human cells [102, 103]. Sputter coating of Ag, along with HA, resulted in an antibacterial-bioactive coating, which inhibited bacterial attachment without cytotoxic effects [104]. TaN-Ag nano-composite coating of titanium dental implants also showed significant antibacterial properties without any cytotoxic effects. Hence, it could be concluded that coating of titanium implants with materials having antimicrobial properties might be useful in preventing infection [105].

3.5. Bisphosphonate

Bisphosphonates (BPs) constitute a group of drugs that inhibit osteoclast action and the resorption of bone, and they are used to treat metabolic diseases such as osteoporosis, Paget's

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disease, hypercalcemia of malignancy and multiple myeloma [106]. The nitrogen-containing BPs are more potent, and they accumulate in maximum concentrations in the matrix and osteoclasts [107]. BPs have a high affinity for bone minerals and bind strongly to HA, resulting in selective uptake to the target organ and high local concentrations in bone, particularly at sites of active bone remodeling. The BPs have similar chemical structures to pyrophosphate, but their chemical stability is greater. In pyrophosphates, the phosphate group is bonded through phosphoanhydride bond (P-O-P), whereas in BP, P is bonded through a germinal carbon atom (P-C-P); hence, these bonds are resistant to hydrolysis under acidic conditions [108]. The affinity of BP to Ca^{2+} ions helps to target specific bony sites, and BP can be coupled with a gamma-emitting radioisotope, such as technetium, for simultaneous bone scanning [109]. BPs inhibit osteoclast differentiation, reduce their activity, and induce their apoptosis [110]. The nitrogen-containing BPs bind to and inhibit farnesyl pyrophosphate synthase (FPPS), a key enzyme of the mevalonate pathway, thereby preventing the prenylation and activation of small GTPases, which are essential for the bone-resorption activity and survival of osteoclasts [111].

Systemic and local delivery of BPs improved the osseointegration of dental implants in osteoporotic animal models [112-116]. Improved osseointegration and the mechanical stability of titanium implants were reported in ovariectomized rats supplemented with alendronate [112]. Kurth et al [113] showed enhanced integration of HA-coated titanium implants via the administration of ibandronate to osteoporotic rats. Similar observations of enhanced osseointegration have been reported in other studies via the local release of BPs (pamidronate and zoledronic acid) from the surface coatings of implants [115, 116]. An experimental study in an ovariectomized rabbit model showed that systemic zoledronic acid (ZA) administration improved the osseointegration of titanium implants [117].

3.6. Simvastatin

Statins are prescribed to decrease cholesterol biosynthesis by the liver, thereby reducing serum cholesterol concentrations and lowering the risk of heart attack. A liposoluble statin, simvastatin, could induce the expression of bone morphogenetic protein (BMP) 2 mRNA and, as a result, promote bone formation on the calvaria of mice following daily subcutaneous injections [118, 119]. Another study showed that the topical application of statins to alveolar bone increased bone formation and concurrently suppressed osteoclast activity at the bone healing sites [120]. Yang et al [119] demonstrated that simvastatin-loaded porous titanium surface potently increased ALP activity and the extracellular accumulation of proteins, such as osteocalcin and type I collagen, in mouse preosteoblast MC3T3-E1 cells. Du et al [121] demonstrated that administration of simvastatin resulted in significant improvement in the osseointegration of titanium implants in osteoporotic rats. This finding could be attributed to the increased expression of bone morphogenic protein 2, which stimulates osteoblast differentiation [118]. Statins are known to enhance the expression of VEGF (vascular endothelial growth factor), a bone anabolic factor, in osteoblasts and to regulate osteoblast function by increasing the expression of bone sialoprotein (BSP), osteocalcin (OCN), and type I collagen (COL-I), as well as suppressing the gene expression of collagenases, such as matrix metallo-

proteinase (MMP)-1 and MMP-13 [122, 123]. Thus the competitive inhibition of simvastatin interferes with the malevonate pathway, leading to decreased protein prenylation, which is necessary for normal osteoclast function [118].

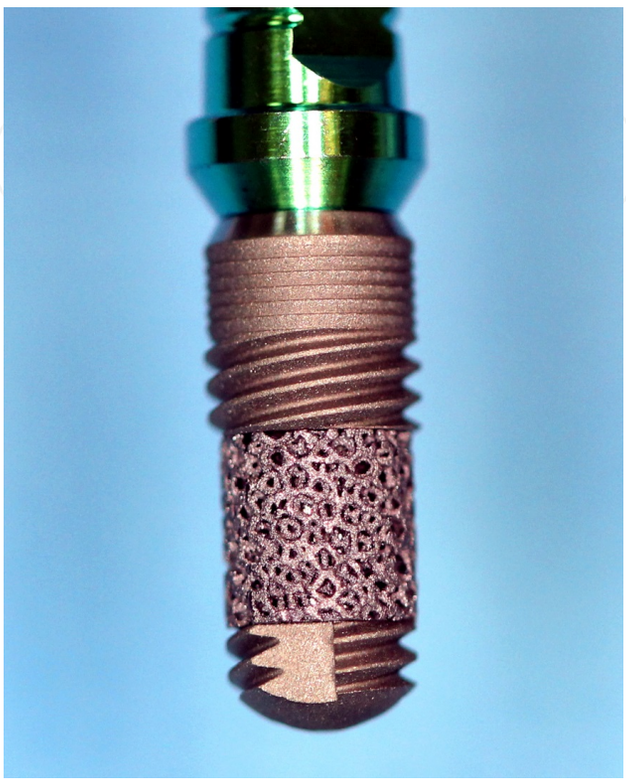

Figure 8. A trabecular implant that could be used to load drugs.

3.7. Calcitonin

Calcitonin (CT), produced by the C-cells of thyroid tissue, has been reported to stimulate hard tissue formation [124]. It acts on bone tissue via the suppression of osteolysis and the induction of Ca^{2+} release. It was reported that CT inhibited osteoclastic bone resorption by binding to specific cell surface receptors [125]. This hormone favors bone formation, inhibits osteoclastic activity and prevents osteopenia [126-128]. In vitro and in vivo studies have shown that this hormone stimulates the growth of bone tissue [40, 129, 130]. Calcitonin also showed increases in the amount and rate of bone formation, as observed in rat calvaria and extraction sockets in dogs [131].

3.8. Pantaprazole

A class of substituted benzimidazoles known as proton pump inhibitors (PPIs) have been shown to promote bone regeneration and peri-implant healing. Examples of these drugs include omeprazole and pantoprazole, which are employed clinically in the treatment of gastroesophageal reflux disorder (GERD). PPI-loaded calcium phosphate cements demon-

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strated not only inherent biocompatibility and osteoconductivity but also the ability to retard bone resorption through a drug delivery mechanism [132, 133]. Pantoprazole-loaded calcium phosphate cements inhibited osteoclastic resorption without interfering with the peri-implant bone resorption rate in a study performed rat femoral condyles [134]. Another advantage of the addition of omeprazole is that it inhibits osteoclastic acidification, which help to inhibit bone resorption and increases the lifespan of osteoclasts [135]. The drugs were dissolved in dimethyl sulfoxide to the desired concentration and were added to the liquid phase of the calcium phosphate.

4. Conclusions

Drug delivery systems (DDS) targeting specific organs and tissues and their bioavailability at specific sites have become critical issue in modern medicine. Local drug delivery systems in bone could be used to promote regeneration, prevent infection, or treat post-surgical pain. The quest for new bone scaffold materials to overcome the shortcomings of existing materials, such as ceramics and polymers, is undertaken to overcome the limited mechanical properties required for temporary bone substitutes. Mixing of polymers, natural or synthetic, and inorganic components, such as HA, TCP and BG, might help to develop better composite scaffolds that combine the advantages of both biodegradable polymers and bioactive ceramics [136].

If DDS are used in combination with implants, the coating strategies should allow for the choice of a drug or combination of drugs and their doses, localization and release due to intra-operative considerations. HA coatings on titanium implants themselves provide an osteoconductive and an osteoinductive approach for the enhancement of bone formation. These biological properties could be augmented further by adding growth factors and other molecules to produce a truly osteoinductive platform.

Proteins or glycosaminoglycans, such as collagen and chondroitin sulfate, provide a biomimetic coating on the surface of an implant, which can improve osseointegration [137]. Biomolecules such as GFs are also widely used for implant coatings, to modulate cellular functions, such as decreasing inflammation, enhancing stem cell differentiation, inducing blood vessel formation, or acting as chemoattractants for circulating osteoprogenitors [138, 139]. Although the implant materials available for the reconstruction of craniofacial bone defects have shown favorable results in most craniofacial and dental applications, the presence of complications related to infection and poor osseointegration still represent challenges in the biomedical field.

The current trend in the field of bone repair indicates that the tissue engineering field is moving toward the development of biomaterials with improved surfaces that will stimulate bone formation and avoid infections through the incorporation of surface modification techniques and antibacterial coatings and agents, as well as the incorporation of GFs, stem cells and other pharmacological drugs.

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