Expert Opinion



# Drug delivery from internally implanted biomedical devices used in traumatology and in orthopedic surgery

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***Importance of the field:*** Millions of people receive annually an internal device aimed to repair or reconstruct damaged bone, and different therapeutic moieties are administered during or after surgery generally using systemic routes. The local administration of those moieties using *in situ* drug-eluting devices emerges as an alternative to minimize undesired side effects in healthy tissues, optimize the amount of drug needed, and reduce the costs.
***Areas covered in this review:*** *In vitro* and *in vivo* published evidence regarding the performance of internally implantable drug-loaded biomedical devices for traumatology and orthopedic surgery are reviewed in this article, the problems that are encountered, and the main challenges in the development of a new generation of devices.
***What the reader will gain:*** An insight of past and current efforts to control the rate of drug release from devices, as well as the requirements that future developments may fulfill, such as responding 'on demand' after biological signaling or communicating the device with the exterior.
***Take home message:*** The main drawback for proper design of devices having improved capabilities mainly remains in the lack of understanding with regards to the complex regulation of physiopathological mechanisms and the thermodynamics at the interface between the implant surface and the surrounding tissue. The potential toxicity and risk versus benefits of any new drug-eluting device need to be evaluated carefully.

**Keywords:** antibiotic, biomaterials, biomedical devices, drug delivery, implants, orthopedic surgery, traumatology

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## 1. Introduction

The obvious advantage of using *in situ* drug-eluting devices is that it is possible to deliver therapeutic dosages at target locations while minimizing systemic side effects. To this end, the device is expected to limit drug availability to that required for optimal therapeutic results through a careful control of the release of previously adsorbed or encapsulated pharmacological agents (including drugs, enzymes, proteins, genes, radioactive isotopes, bactericides, fungicides, etc). Although most drug delivery devices are of the *passive* type (where the drug release rate is governed by processes such as diffusion or dissolution), the ideal scenario is that in which *active* devices are used, and the payload is released in response to an external stimulus (availability on demand). In this case triggering would be related to a highly specific signal derived from the targeted pathology (e.g., the presence or absence of biomolecules), although less specific events can also be contemplated, including changes in temperature, pH and ionic strength. Drug delivery could



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**Article highlights.**

- Most of drug delivery devices used at present in traumatology and orthopedic surgery are designed to overcome bacterial infection and biofilm formation. Antibiotic molecules are integrated within the device or deposited on its external surface.
- Despite the fact that an ideal scenario is that in which payload is released in response to stimuli, devices in current use are passive. In those, the release of the drug is governed by molecular diffusion, which might be ineffective and might increase the risk of antimicrobial resistance. Research is now focused on finding biodegradable alternatives to acrylic bone cements and fillers to avoid the surgical removal of the implanted device.
- Safety is a key issue when designing systems releasing biological agents such as growth factors, chemotherapeutic drugs, hormones, and so on.
- There is active research on designing drug-eluting devices able to respond 'on demand' to specific biological, chemical or physical signals, and able to send feedback to the physician on the status of the payload release in a real-time manner. Microfabrication technologies will facilitate the integration of biosensors with the device.
- For any drug-eluting biomedical device, exhaustive preclinical and clinical tests are required to evaluate the significant cost differential, unwanted side effects and risk/benefit compared with the use of the same device without the drug-eluting characteristics in combination with the systemic administration of the drug.

This box summarizes key points contained in the article.



also be externally triggered when needed by using physical (e.g., light, electric or electromagnetic fields, sonic waves, heat, etc.) or chemical stimuli. Another desirable feature would be the ability to monitor in real time the release process, and to communicate wirelessly the progress of the therapy.

In addition to the release-related characteristics of the device (triggering, release rate control, communication), other characteristics of an ideal implantable drug-eluting biomedical device would be: biocompatibility, facilitated tissue integration (when needed), biodegradability or bioreabsorbability features to avoid the necessity of a second surgery to remove it, the ability to resist sterilizing techniques before implantation, stability on storage, high mechanical resistance, safety, comfort, negligible possibility of chemical or physical leaching coming from the device constituent material, short post-surgical rehabilitation after implantation, and stability of the therapeutical payload for the required therapeutic period.

In 2002, the FDA established the Office of Combination Products (OCP) to ensure the prompt assignment of combination products (drug-device, biologic-device, drug-biologic, or drug-device-biologic products) to FDA centers, the timely and effective premarket review of such combination products and their consistent and appropriate post-market regulation [1]. An updated list of guidance documents for the development of these products as well as examples of combination product approvals is available on their website. Internally implantable drug-eluting devices have found application in a variety of areas, including cardiovascular diseases, orthopedics, periodontal diseases, microbial pathologies, ophthalmology, diabetes and cancer, and have been used in the treatment of either acute or chronic diseases. Some of the biomedical drug-eluting devices now used in medical practice, undergoing clinical trials, or available for license are described in **Table 1**.

The types of drug-eluting implants used in traumatology and in orthopedic surgery include: i) antibiotic-loaded bone cements and fillers used to prevent infection (osteomyelitis) in orthopedic surgery; ii) cements loaded with osteoinductive molecules such as growth factors to favor the osseointegration of the implant; and iii) devices loaded with chemotherapeutic agents, antiestrogens or anti-inflammatories used to treat different pathologies including osteosarcomas and degenerative diseases (see **Table 1**).

The modes of controlling the release of the payload include those in which the active moiety is: i) triggered by using an external stimulus (i.e., ultrasonic waves, optically induced release using near-infrared radiation, electromagnetic radiation, temperature, electric charge, etc.) [2]; ii) triggered by using an internal stimulus (pH of the environment, a biological response, a reducing environment, etc.) [3,4]; iii) released by molecular diffusion from a stable permanent structure [5]; and iv) released by erosion and diffusion from a biodegradable structure [6].

In this paper an overview is presented of internally implantable drug-loaded biomedical devices used in traumatology and in orthopedic surgery. Externally applied drug-eluting devices (i.e., delivery from patches, dressings, insulin pumps, needles, probes, aerosols, etc.) are not discussed. Delivery from pellets, hydrogels, fibers, micro- or nanoparticles is also excluded from this paper when they are decoupled from a drug-eluting device.

## 2. Internally implanted biomedical devices: problems and challenges

In the context of this review, implants are dosage devices that are subcutaneously placed with the aid of surgery or by other methods of skin penetration (e.g., a hypodermic needle) and are designed to release drugs over a prolonged period of time [7]. Prostheses are artificial extensions that replace a missing body part or that supplement a defective body part resulting from trauma, chronic diseases, congenital disorders or tumor resection. The main function of most of the implants used in traumatology and in orthopedic surgery is to provide mechanical support. In terms of patient numbers, 4.4 million people in the US alone have received at least one internal fixation device and 800,000 new hip arthroplasties are performed annually [8,9]. Despite the great variety and

**Table 1. Some of the drug-eluting devices in use, in clinical trials or available for licensing.**

| Drug-eluting biomedical device | Targeted pathology/mechanism of action/application |
|---|---|
| Endovascular, urethral, biliar, or colon stents | An antiproliferative drug used to prevent restenosis (renarrowing of the vessel after stent implantation) following angioplasty is released from the stent coating (Cypher® (Cordis Corporation Bridgewater, NJ, USA), Taxus® (Boston Scientific Inc., Natick, MA, USA), Xience V® (Abbott Park, IL, USA), Endeavor® (Medtronic, Inc. Minneapolis, MN, USA), Axxess™ (Devax, Lake Forest, CA, USA), NX® (XTENT, Inc. Menlo Park, CA, USA), etc.) |
| Brachytherapy probes | An encapsulated radioactive isotope (Iodine-125, Palladium-103, Cesium-131, etc.) is placed in the proximity of a tumor to treat localized prostate, liver, breast, cervical cancers, sarcomas, and cancers of the head and neck<br>Also used to prevent restenosis |
| Drug-loaded orthopedic implants | Used to prevent infection in orthopedic surgery, including antibiotic-loaded bone cements and fillers loaded with gentamicine (Cobalt™ (Biomet Inc., Warsaw, IN, USA), Palacos® (Zimmer, Inc. Warsaw, IN, USA), Cemex® (Exactech, Inc. Gainesville, FL, USA), Septopal® (Biomet Inc., Warsaw, IN, USA), DePuy® (DePuy Orthopaedics, Inc. Warsaw, IN, USA), etc.) or loaded with tobramycin (e.g., Simplex® (Stryker Kalamazoo, MI, USA))<br>Used to favor the osseointegration of the implant (i.e., cements loaded with growth factors, with osteosynthetic genetic material, etc.)<br>Used to treat disc disease, acute open tibial fractures or recalcitrant non-unions of long bones and pelvis, (INFUSE® (Medtronic, Inc. Minneapolis, MN, USA) and OP-1 Bone Graft consisting on a carrier/scaffold for recombinant human bone morphogenetic proteins rhBMP-2 and rhBMP-7, respectively) [61,62]<br>Used to treat osteosarcomas loaded with chemotherapeutic agents, antiestrogens, anti-inflammatory molecules, etc |
| Bactericidal coatings (silver-containing coatings) | Based on the antimicrobial properties of silver cations against bacteria, viruses, and some eukaryotic microorganisms; used on medical and surgical equipment such as endotracheal tubes, dental filling materials, medical dressings, bandages, surgical meshes, catheters, etc |
| Microelectromechanical systems (MEMS) | Drug-loaded microchips sealed with a membrane that degrades in response to a physical or biochemical signal. The release can be triggered by diffusion, by osmotic pressure, by applying voltage or temperature (implantable rapid-drug-delivery device IRD [70], MIP™ (Debiotech S.A., Lausanne, Switzerland), etc.), or by tailoring size-specific pores [71]<br>Intracochlear delivery of neurotrophic factors [72]<br>Manually refillable device for the treatment of glaucoma [73] |
| Polymeric intracerebral implants | Biopolymeric wafers designed to deliver a chemotherapeutic drug directly into the surgical cavity created when a brain tumor is resected (e.g., Gliadel® (Eisai Co., Ltd. Tokyo, Japan))<br>DURIN™-Leuprolide (Durect Corp., Cupertino, CA, USA) product intended for the treatment of Alzheimer's disease |
| Osmotically driven miniaturized implants | Used for the palliative treatment of advanced prostatic cancer, management of endometriosis, treatment of children with central precocious puberty, uterine leiomyomata (Viadur® (ALZA Corporation, Mountain View, CA, USA),<br>the ALZET® (ALZA Corporation, Mountain View, CA, USA) osmotic pump for animal research studies, DebioSTAR™ (Debiotech S.A., Lausanne, Switzerland), etc.) |
| Periodontal devices | Used for the treatment of periodontal disease using drug-loaded non-biodegradable fibers (e.g., Actisite™ (ALZA Corporation, Mountain View, CA, USA)), or biodegradable systems (e.g., Perio-chip™ (Dexcel Pharma GmbH, Alzenau, Germany), Atridox™ (Tolmar Inc., Fort Collins, CO, USA)) |
| Ophthalmic drug delivery | Contact lenses that release a moisturizing agent into the tear film with each blink to prevent dry eyes (e.g., Focus® DAILIES® with AquaRelease™ (CIBA Vision Corp. Duluth, GA, USA))<br>Used to prevent infection by releasing antibiotics [74,75]<br>Neurotransmitter-loaded prosthetic retina for potential use in macular degeneration [76]; neurotrophin-eluting polymeric hydrogel coatings [77]<br>Drug-eluting intravitreal implants used to treat diabetic retinopathy, macular degeneration, and glaucoma (e.g., I-vation™ (SurModics Inc., Eden Prairie, MN, USA)) |
| Prosthetic arterial auto and allo-grafts | Grafts are used to replace blood vessels in aneurismal disease, advanced artherosclerosis, etc<br>Used to prevent clotting by the graft's surface: grafts are usually clotted with the patient's own blood before implantation, but it is also extends the use of adsorbed or attached anti-clotting components on the graft surface (i.e., heparine, albumin, hirudin, thrombomodulin) [78]<br>Used to prevent infection: different antibiotics are adsorbed or attached to the surface of the graft [79] (e.g., collagen-coated knitted polyester graft coated with silver acetate (InterGard Silver® (GETINGE AB, Rochester, NY, USA)) |

**Table 1. Some of the drug-eluting devices in use, in clinical trials or available for licensing (continued).**

| Drug-eluting biomedical device | Targeted pathology/mechanism of action/application |
|---|---|
| Steroid-eluting leads in pacemakers | The lead allows a pacemaker to monitor the heart and it slowly releases a steroid into the body. The pacing output from the pacemaker is sent through the lead to the heart. The steroid allows the patient's heart to pace with less energy [80], (Fineline® II Sterox (Boston Scientific Inc., Natick, MA, USA), CapSure®SP (Medtronic, Inc., Minneapolis, MN, USA), Stelid® (ELA Medical Inc., Arvada, CO, USA), etc.) |
| Pregnancy control devices or implants releasing spermicides, hormones, hormone antagonists, antimicrobials, etc | Used as prophylactic control (e.g., Cu-IUDs, cervical caps or diaphragms, polymeric rods containing capsules that release hormones such as levonorgestrel, etonogestrel, etc.)<br>Subdermal implants releasing hormone antagonists used to treat hormone-sensitive cancers of the prostate and breast and some benign gynecological disorders (Vantas™ (Endo Pharmaceuticals, Chadds Ford, PA, USA) for palliative treatment of advanced prostate cancer in men, Supprelin® LA (Endo Pharmaceuticals, Chadds Ford, PA, USA) for the treatment of children with central precocious puberty, etc.)<br>Used to prevent infection, i.e., antibiotic eluting implants (e.g., InhibiZone® (American Medical Systems Inc., Minnetonka, MI, USA) in penile implants, etc.) |



successful results of bioinert (i.e., alumina, metals, etc.) or bioactive materials (i.e., calcium phosphates) used in traumatology and orthopedic surgery, their main disadvantages are that they do not completely integrate or adapt to the host tissue. The main complications after implantation in traumatology and orthopedic surgery and their clinical solutions are shown in **Table 2**. Bacterial infections after trauma (i.e., septic arthritis) [10] or orthopedic implant surgery (i.e., prosthetic-joint infection) [11] continue to be a serious complication owing to the ability of certain adherent bacteria to form biofilms, which evade host defenses and withstand antimicrobials. Two of the most frequent pathogenic organisms involved in prostheses infections are *Staphylococcus aureus* (**Figure 1**) and *Staphylococcus epidermidis* [12].

The more commonly used antibiotics for bone and joint infection are β-lactams and lincosamides (i.e., cefuroxime, cefazoline, flucloxacilin, etc.), quinolones (i.e., ciprofloxacin, levofloxacin), which show high activity against adherent bacteria, rifampicin for the treatment of methicillin-resistant *S. aureus* (MRSA) in combination with fusidic acid, oxazolidinones (i.e., linezolid) and glycopeptides (i.e., vancomycin). The latter is one of the most widely used antibiotics in the US for the treatment of MRSA [13]. Antimicrobial peptides (i.e., Dhvar-5, human lactoferrin, etc.) have also been investigated for their application in osteomyelitis [14].

As early as in 1957, Elek and Conen demonstrated that the presence of a foreign body (silk structures) significantly reduces the number of bacteria required to produce infection in men [15]. Despite the sterility levels achieved in orthopedic operating theaters during surgical implantation and parenteral antibiotic prophylaxis, infections continue to be a major complication after implantation. Most of the staphylococcal infections originate during the implantation procedure, either from the cutaneous flora of the patient or from the hospital environment. Although less frequent, prosthesis infection also occurs by means of reactivation of previous latent chronic osteomyelitis, owing to the trauma that occurs when placing the implant, or by means of a hematogenous route during bacteriemia originating from a distant focus. The infection process begins with the bacteria traveling to the implant surface. Once there, the bacteria adhere nonspecifically to the surface first through mechanisms mainly directed by physicochemical interactions and subsequently through specific receptor–ligand interactions driven by proteins that spontaneously adsorb to the surface on implantation, providing a dynamic environment for bacteria [16]. Within minutes, bacteria upregulate the secretions of signal molecules that orchestrate a community-wide phenotypic response, through a process termed 'quorum-sensing'. This leads to the irreversible bacteria attachment to the implant surface by secretion of extracellular polymers where the bacteria become embedded, causing biofilm formation. Infections related to biofilms cannot be effectively treated with antibiotics, and usually require device removal. Antibiotics act on growing bacteria and the minimum inhibitory concentration (MIC) of antibiotics typically increases with bacteria that have reduced metabolic activity, as biofilm-forming bacteria [17]. Mechanisms to explain the antibiotic resistance of bacteria in biofilms hypothesize: i) slow or incomplete penetration of the antibiotic in the biofilm; ii) resistant phenotype from bacteria that display a protected phenotype; and iii) altered microenvironment in zones of nutrient depletion or waste product accumulation, which may antagonize antibiotic action [18]. Biofilm formation has been demonstrated not only in orthopedic surgery, but also in contact lenses, central venous catheters and needleless connectors, endotracheal tubes, intrauterine devices, mechanical heart valves, pacemakers, peritoneal dialysis catheters, tympanostomy tubes, urinary catheters and voice prostheses [19]. To prevent bacterial infections, current research follows two different strategies: the development of antiadhesive surfaces to prevent bacterial attachment; and bactericidal- and bacteriostatic-loaded implants.

**Table 2. Main complications after implantation in traumatology and orthopedic surgery, their clinical interventions, and new approaches.**

| Complications | Clinical interventions | New approaches |
|---|---|---|
| Aseptic 'loosening' | Revision surgery combined with a course of intravenous antibiotics | New materials or surface treatments with enhanced mechanical properties |
| 'Biofilm' formation | Systemic treatment with antibiotics, incision and drainage, excision, arthrodesis, debridement of the necrotic and infected area, and revision surgery that may require device removal, often complicated by tissue destruction | Antibiotic-eluting materials or devices; new synthetic surfaces and coatings that inhibit bacterial adhesion |
| Lengthy post-surgical rehabilitation | Palliative treatments | Surface modification: i) change of the physicochemical surface properties to favor integration; and ii) adsorbing bioactive moieties |
| Lack of integration or adaptation | Revision surgery | Surface modification: i) change of the physicochemical surface properties to favor integration; and ii) adsorbing bioactive moieties |



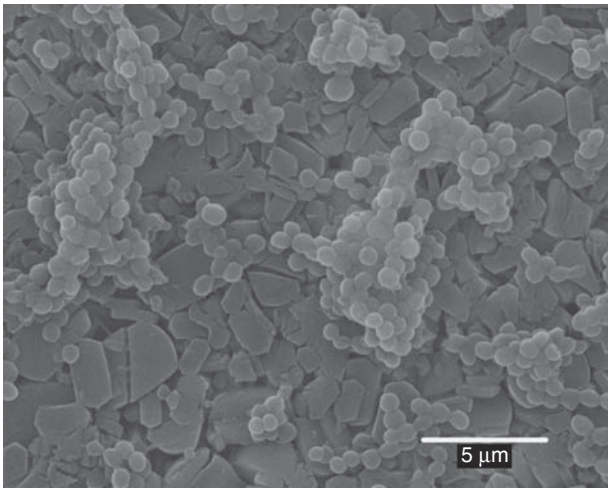


**Figure 1. Scanning electron micrograph of *S. aureus* (spherical) grown *in vitro* on the surface of a ceramic material (hexagonal aluminosilicate crystals).**

Finally, 'aseptic loosening' remains the most common long-term complication of major arthroplasties and is the main cause of implant revision surgery. Extensive localized bone resorption resulting in implant failure without signs of infection or aseptic loosening was reported in the 1970s [20,21]. At that time, the observation of bone cement debris within the periprosthetic tissue led to the term 'bone-cement disease'. However, the diverse chemistry of particles isolated from revision tissues, also from cementless prostheses, has led to the more general concept of wear-mediated osteolysis. Aseptic loosening is induced by a combination of events including the generation of wear micro- or nanoparticles caused by the material released from the implant owing to mechanical stress during long service periods (**Figure 2**), corrosion products and reactive oxygen species. On exposure to particles, resident macrophages and various other types of cell, including osteoblasts, release cytokines, chemokines and other soluble factors into the periprosthetic milieu [22]. These cellular mediators act in concert in paracrine and autocrine fashions, inducing resorption directly by stimulating precursor cells along the osteoclast lineage as well as indirectly by acting on stromal or osteoblastic cells, which ultimately results in loss of bone stock [23]. The only clinical intervention for aseptic loosening is implant revision surgery, and bone loss associated with this procedure limits the number of times that it can be performed [24,25].

## 2.1 Antibiotic release from implanted devices

Owing to the problems just discussed, perhaps the most common scenarios for drug delivery in orthopedic surgery concern fighting infections with antibiotics. Antibiotic molecules can be integrated within the device (mixed in the bone cement, adsorbed in internal or external porous structures or loaded in larger internal cavities), or deposited on its external surface. **Figure 3** provides a conceptual description of these approaches.

### *2.1.1 Antibiotic release integrated within the device*

Acrylic bone cements and fillers are used on a daily basis by orthopedic surgeons in arthroplasty (i.e., hip, knee, shoulder replacements). So far, the FDA has approved only the use of bone cement with gentamicin or tobramycin for the second surgery in a two-stage revision procedure, although antibiotic-loaded bone cements have been used worldwide for more than three decades for prophylaxis and treatment applications in orthopedics [26]. In 1970, Buchholz and Engelbrecht were the first to report the incorporation of antibiotic powders into polymethyl methacrylate (PMMA) bone cement to reduce the infection rate in arthroplasty [27].

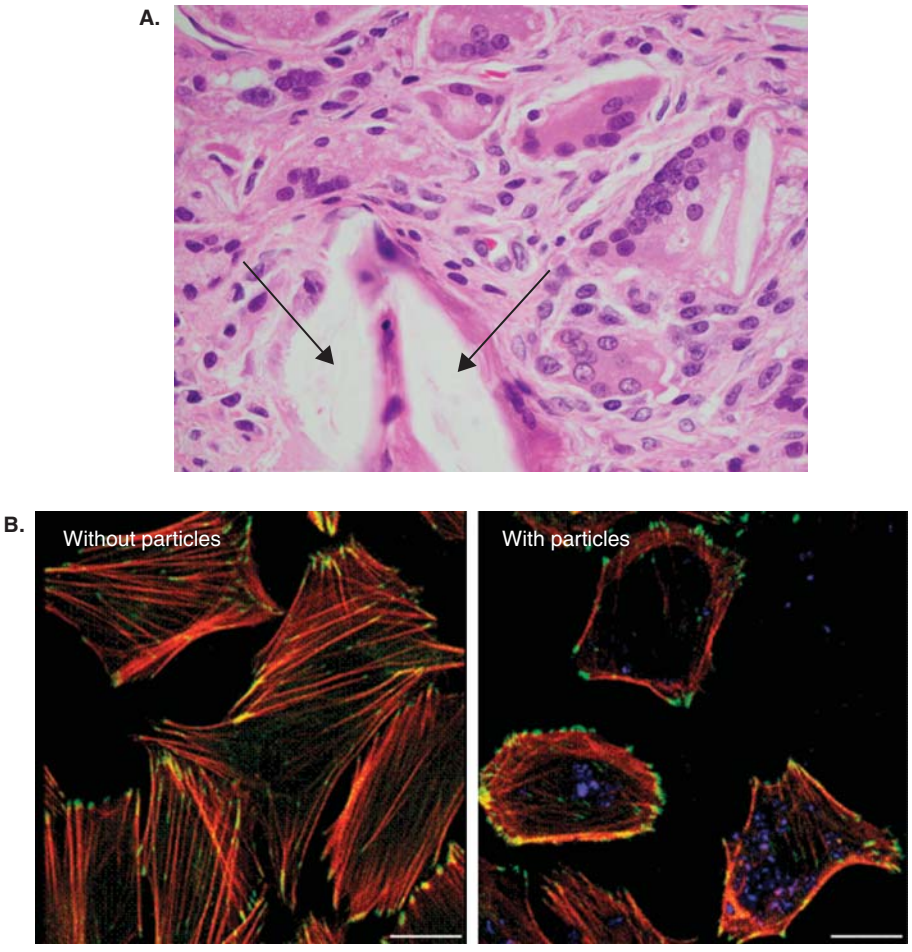


**Figure 2. A.** Periprosthetic tissue retrieved from a patient undergoing revision surgery to replace a loosened cemented hip prosthesis. Stained with hematoxylin and eosin (magnification ×500). A characteristic granulomatous reaction involving macrophage infiltrate and the presence of giant cells is observed. The bright areas marked with arrows correspond to polyethylene particles. **B.** Effect of the exposure of cultured osteoblastic cells to micrometric titanium particles. *In vitro* exposure to particles led to the disorganization of focal contacts (green) and actin filament networks (red). Bar = 25 μm.

PMMA is still the most studied material as a carrier for different drugs in orthopedic applications and it is used in two forms: that of antibiotic-impregnated bone cement applied in arthroplasty and antibiotic-impregnated beads for musculoskeletal infections [28]. There are antibiotic/cements premixed on the market, but usually the surgeon premixes a solid containing the polymer, an initiator of the polymerization, the antibiotic or drug, and other additives (i.e., contrast agents) with a liquid containing the monomer of the former polymer, a binding agent, and a stabilizer before implantation [29]. Usually the drug is premixed as a powder because as a liquid it might compromise the strength of the implant. The mixture cures in a few minutes and the drug remains entrapped in the macropores that the air bubbles and the evaporation of the volatile monomer leave after drying out. That macroporosity, in addition to the cracks and voids left after curing the cement, cannot tune the drug release in a controlled manner. In addition, only antibiotics that can withstand the heat released during the exothermic polymerization reaction can be used as additives (e.g., ampicillin is destabilized under polymerization conditions). The release of the drug is governed by molecular diffusion and the drug pharmacokinetic depends on its solubility, concentration, and on the host matrix characteristics such as surface area and porosity. The applied antibiotic concentration is usually 10 times the MIC or a concentration well above the biofilm-eradication concentration for the involved pathogen [14]. The elution of the drug typically starts with a burst, then decreases, and finally increases very slowly, attaining a steady value. In many cases, <10 wt% of the drug is released from the cement as observed during *in vitro* evaluation of gentamicin-loaded PMMA beads after 8 weeks [30]. An important disadvantage of using antibiotic-loaded PMMA beads is that a second surgery is necessary to remove them, which usually takes place a few weeks after implantation. The release of gentamicin coming from implanted gentamicin-loaded PMMA beads has been

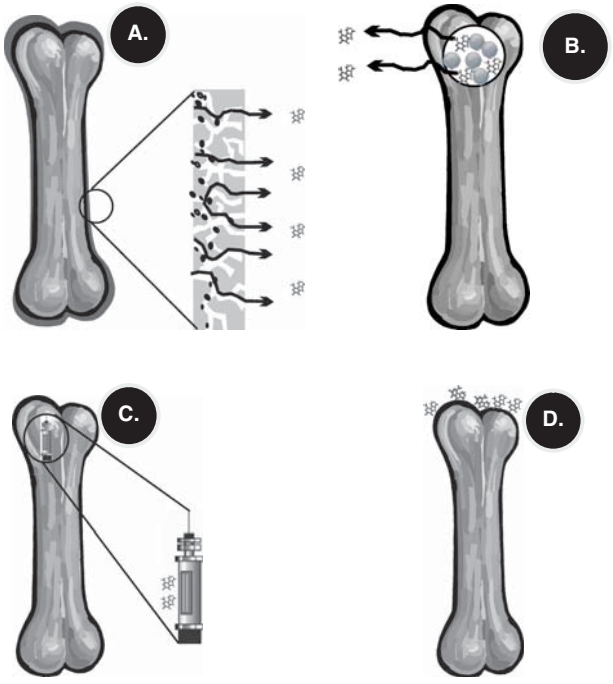


**Figure 3. Conceptual description of the different approaches for the antibiotic release from drug-eluting devices. A.** Adsorbed on internal or external porous structures. **B.** Mixed in the bone cement. **C.** Loaded in larger internal cavities or devices. **D.** Deposited on its external surface.

reported up to 5 years after implantation in a patient in whom these beads were left *in situ* [31]. Microbiological sampling of the retrieved beads raised concerns, as it disclosed a gentamicin-resistant staphylococcal strain [31]. Besides problems related to residual shrinkage stresses, the major drawback of those cements is their lack of biodegradability, which is in turn related to their hydrophobic character. For that reason the inclusion of degradable polymers in the matrix has been advocated to obtain partially degradable cements with higher hydrophilicity [32].

Most of the alternatives to solve the deficiencies of acrylic bone cements explore their replacement by biodegradable materials that will not require surgical removal when added either as monolithic structures or as microparticulate materials (**Table 3**). The use of biodegradable materials for surgical implants (vascular grafts and sutures) was first postulated by Kulkarni *et al.* in the 1960s [33]. Any biodegradable biomaterial must remain mechanically stable until bone union has been achieved, and then erode and degrade completely without leaching out cytotoxic degradation components. Research is focused at present on controlling the erosion of the polymeric matrix in order to get sustained release of the previously encapsulated drug, which could be achieved by selecting a specific polymer and controlling its interaction with the drug, by adding a crosslinker to retard the erosion or by varying the molecular mass of the polymer used. Despite their poor mechanical properties, antibiotic-loaded collagen-based sponges offer a biodegradable alternative to PMMA beads. Better results compared with PMMA beads have been demonstrated for gentamicin-loaded sponges in animal models of *S. aureus*-induced osteomyelitis. An additive effect was attained when the loaded sponges were combined with systemic antibiotic treatment [34]. Different approaches to control the release of the drug from those sponges are reviewed elsewhere [35]. The primary sources of industrial collagens are calf skin and bone, and some concern has been raised that this may increase the risk of transmissible diseases (bovine spongiform encephalopathy or transmissible spongiform encephalopathy) [36].

Bioactive inorganic materials are also commonly used as drug-eluting systems in traumatology and orthopedic surgery. Hydroxyapatite from different sources and tricalcium phosphate have been used for the controlled release of different antibiotics including fluorquinolones [37] and tobramycin [38], respectively, as well as many other antibiotics and combinations (see **Table 3**). Some of those inorganic materials are commercialized as self-supported structures or as coatings on metallic (i.e., stainless steel, titanium and its alloys, cobalt-chromium, porous tantalum) surfaces (**Figure 4**). Inorganic materials are promising alternatives to polymeric bone cements and fillers because of their high chemical stability, hydrophilic character, easy functionalization, large surface area and ability to adsorb drugs. Owing to the possibility of synthesizing ordered mesoporous silica-based structures, inorganic particulate fillers can achieve

**Table 3. Different alternatives and approaches to solve the limitations of drug-loaded acrylic bone cements.**

| Pathology | Drug-eluting device | Drug | Drug loading | Study | Ref. |
|---|---|---|---|---|---|
| Infected hip arthroplasty | Porous calcium hydroxyapatite ceramic block | Different antibiotics according to the results of bacterial cultures from the draining sinuses or preoperative joint aspirations | Volumetric as powder in the inner volume | *In vivo* | [81]* |
| Osteomyelitis | Drug-loaded acrylic bone cement aided with ultrasounds | Vancomycin | Mixing/blending | *In vivo* | [82] |
| Infected hip implant | Simplex™ Cement Spacers | Vancomycin and aztreonam | Mixing both antibiotics in combination | *In vivo* | [83]* |
| Osteomyelitis | Partially biodegradable acrylic composites (e.g., PMMA/poly caprolactone) | Vancomycin | Mixing/blending | *In vitro* | [84] |
| Osteomyelitis | Biodegradable poly(lactic acid) (PLA)/poly(glycolic acid) (PGA) copolymers | Gentamicin | Mixing/blending | *In vivo* | [85] |
| Osteomyelitis | Biodegradable PLA/PGA copolymer | Fluorquinolones (Ciprofloxacin) | By non-solvent-induced phase separation | *In vitro* and *in vivo* | [86] |
| Osteomyelitis | Blends of tricalcium phosphate, hydroxyapatite and PDLLA | Ciprofloxacin | By compression | *In vitro* and *in vivo* | [87] |
| Osteomyelitis | Biodegradable polyanhydride | Gentamicin | Melt-mixing | *In vitro* | [88] |
| Osteomyelitis | Intramedullary dispenser with a T-95 chest tube filled with PMMA | Combination therapy (vancomycin + gentamycin, vancomycin + tobramycin) | Filling of PMMA + antibiotics | *In vivo* | [89]* |
| Filling or reconstruction of bone defects | Biodegradable hydroxyapatite and calcium sulfate | Combination therapy (vancomycin + gentamycin) | Impregnation | *In vitro* | [90] |
| Osteomyelitis | Calcium sulfate pellets and demineralized bone matrix | Tobramycin | Impregnation | *In vivo* | [91] |
| Osteomyelitis | Porous β-tricalcium phosphate/PCL/PEG | Gatifloxacine | Melt-mixing | *In vivo* | [92] |
| Osteomyelitis | Calcium sulfate | Moxifloxacin | Impregnation | *In vivo* | [93] |
| Osteomyelitis | Hydroxyapatite with hydroxypropyl-β-cyclodextrin polymer | Ciprofloxacin and vancomycin | Dip-coating | *In vitro* | [94] |
| Infected hip arthroplasty | Two-stage revision with an interim temporary prosthesis | Gentamicin | Impregnation | *In vivo* | [95]* |
| Osteomyelitis | Biodegradable alginate beads | Vancomycin | Mixing | *In vitro* | [96] |
| Osteomyelitis | Biodegradable polyesters | Sulperazone® or Duocid® (Pfizer Inc., New York, NY, USA) | Mixing | *In vivo* | [97] |

*Clinical results obtained with patients.



a controlled release of the adsorbed or attached moiety (**Figure 5**) [39]; however, self-supported structures of those materials lack mechanical stability. Composite materials might combine the mechanical properties of polymeric materials with the adjustable controlled release obtained with inorganic materials (hydroxyapatites, tricalcium phosphates and mesoporous silicas). Mechanically, a well-designed composite material could simulate at best the behavior of natural bone, which is composed of an inorganic (calcium hydroxyapatite) and an organic (type I collagen and other non-collagenous proteins) matrix.

### 2.1.2 *Antibiotic release from the coating on the external surface of the device*

The antibiotic can be attached to the external surface of the device by: i) electrostatic attraction between the negatively

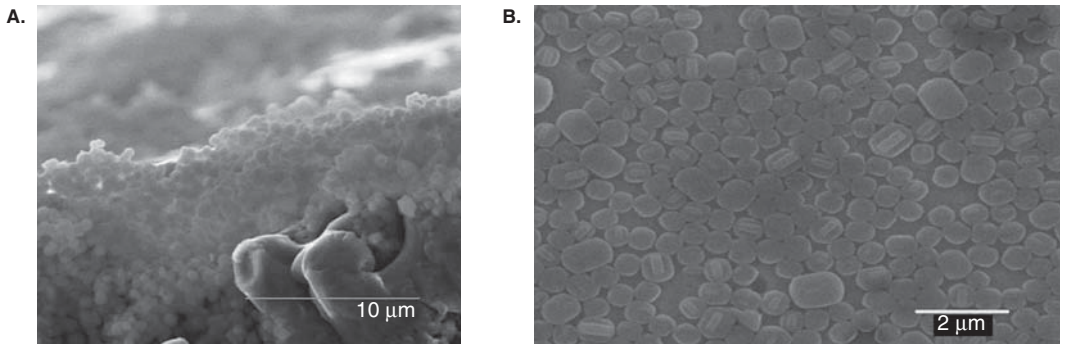


**Figure 4. A.** Mesoporous silica (MCM-48) deposited on NiTi supports. **B.** Aluminosilicate crystals coating a NiTi support.

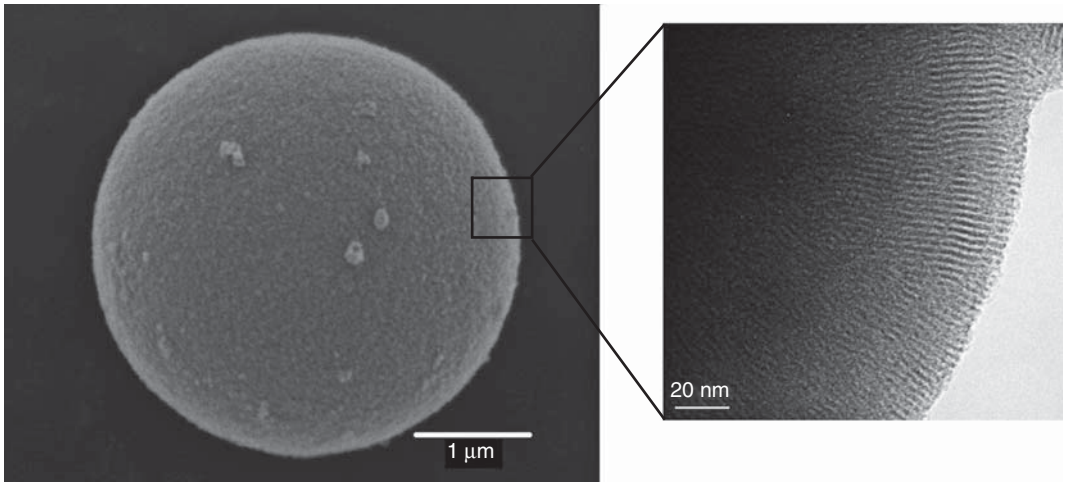


**Figure 5. Mesoporous MCM-41.** The ordered porous structure can be observed in the inset.



charged antibiotics and the positively charged devices (the positive charge is created by using cationic surfactants) [3]; or ii) covalent attachment of the antibiotic to the device using a chemical linkage that can be cleaved in the physiological environment without losing the functionality of the drug [40]. Most of the antibiotic-coated devices commercialized so far make use of the first approach.

In 1996, Price *et al.* [41] described the *in vitro* release of gentamicin from polylactic-*co*-glycolic acid copolymer-coated orthopedic implants. In 1998, Daraouiche *et al.* [42] reported the effect of intramedullary nails coated with an antiseptic combination of chlorhexidine and chloroxylenol in a rabbit model of device-related infection after fixation of an open tibial fracture. Gentamicin-poly(DL-lactide) (PDLLA)-coated commercial tibial nails have been successfully used for closed reduction and internal fixation in grade III open tibial fractures [43]. Gentamicin and vancomycin-coated PMMA nails have been postulated for the treatment of bone and intramedullary MRSA infections [27]. Orthopedic titanium-alloy pins coated with minocycline and rifampin were significantly protected during 1 week against *S. aureus* device colonization and infection in rabbits [44]. Gentamicin-loaded PDLLA coatings on titanium Kirschner wires showed a significant reduction in implant-related infection after 6 weeks of implantation in rats, compared with uncoated or PDLLA coated wires [45].

Silver-coated biomedical devices (see **Table 1**) are commercialized for many applications based on the antimicrobial properties of ionic silver. Silver can be deposited as such (metallic silver) by a variety of methods, including sputtering, electroless plating, autocatalytic growth and dip-coating of nanoparticle suspensions, or can be included in inorganic (e.g., zeolites) or organic (polymer) coatings. Silver is considered a wide spectrum antibacterial agent, and a variety of biochemical explanations have been proposed to explain its effectiveness [46-48]. However, bacterial resistance to silver has been documented [49].

There is a huge number of reports describing the antimicrobial properties of different coatings on biomedical devices or simply on biomaterials; however, in many cases

there is still a lack of convincing clinical (or even preclinical) trial data comparing the effects of antibiotic-coated and uncoated devices to assess whether the significant cost differential and the potential risk of antimicrobial resistance is justified. For example, a comparative *in vitro* and *in vivo* study on local antiseptic and antibiotic coating on osteosynthesis implants showed that the antiseptic coating led to the same reduction in infection rate as the antibiotic coating [50].

### 2.2 Other drugs and their release from the device or scaffold

As shown in **Table 1**, growth factors alone (i.e., recombinant human bone morphogenetic proteins such as rhBMP-2 and BMP-7) [51-53], cocktails of growth factors (i.e., rhBMP-2 in combination with recombinant human transforming growth factor-β2 [rhTGF-β2]) [54], hormones alone (i.e., human growth hormone) [55] or in combination with antibiotics (i.e., gentamicin and human growth hormone) [56], chemotherapeutic agents (i.e., adryamicin and doxorubicin) [57,58], anti-inflammatories (i.e., dexamethasone) [59] and vitamin E [60] have been incorporated into biomedical devices or scaffolds used in traumatology and in orthopedic surgery. In all the applications, except for the vitamin E, a controlled release is sought. In commercial applications (i.e., E-Poly™; Biomet Inc., Warsaw, IN, USA) of the latter, the antioxidant properties of vitamin E are used to prevent the formation of free radicals and consequently the oxidative degradation of the polyethylene. In this application the bioactive moiety is not meant to be released from the polymer used to manufacture the articulating surfaces of hip and knee prostheses, but is included on it to prevent its degradation and consequent decay in its mechanical properties.

In the systems described above the main challenges are to maintain the stability of the therapeutic payload by using moieties designed to avoid metabolic degradation, and to achieve a controlled release having the required pharmacokinetics. The systemic presence of active concentrations of agents such as osteoinductive factors or chemotherapeutic drugs must be avoided or minimized.

rhBMP-2 and rhBMP-7 are present in two commercially available osteoinductive composite materials for use in the management of the healing of fractures [61,62]. As currently formulated, these devices must include the BMP proteins at very high concentrations to be effective. An inherent risk with their use is the formation of ectopic bone owing to diffusion into adjacent tissues. In fact, heterotopic ossification of triceps, adjacent soft tissues and joints after using commercially available collagen sponges carrying recombinant bone morphogenetic proteins, which often required operative excision, has already been documented [63,64]. Therefore, safety is a key issue when designing new payload-releasing systems. In addition to *in vitro* evaluation, exhaustive *in vivo* preclinical tests and clinical trials should demonstrate that devices loaded with molecules having well-known cell- or tissue-specific functions lack undesired side effects.

## 3. Conclusions

Progress in the prosthesis field in the last two decades has been outstanding, with new designs and functionalities being made available, and with increasing success rates in orthopedic surgery brought about by a better control of the factors that lead to an undesired immune response, or to complications caused by bacterial colonization of the implant. The next generation of implants is likely to be endowed with much better drug release properties than those now afforded by the introduction of antibiotics in bone cement.

Different materials (porous ceramic or metallic structures with modified surfaces to facilitate integration, polymers with controlled hydrophilicity and biodegradability, new composites for scaffolding) can be used to harbor a variety of drugs and to control the pharmacokinetics of their release. Therefore, there is a clear opportunity in developing new materials with structured properties to encapsulate drugs, and interfaces that allow a controlled drug release avoiding burst release and premature degradation of the active moiety. The use of microfabrication to facilitate integration of biosensors with the device, and embedding technologies to produce biocompatible and active systems for long-term use, is still one of the main challenges for scientists in this field.

## 4. Expert opinion

The design of efficient drug-eluting devices will often have to be carried out on an *ad hoc* basis. First, specific conditions (such as the nature, size and morphology of the prosthesis) will play a key role in the complex physical and biochemical processes taking place at the interface between the implant surface and the surrounding tissue. Second, it is necessary to consider that drug release rate and duration depend on each clinical context and therefore it is not possible to work with 'universal' or standard systems. Instead, drug release systems need to be tailored to each medical scenario, taking into account factors such as the patient's metabolic conditions, the drug solubility and the dose achieved systemically and at the targeted location during treatment, as well as the clearance mechanisms, the bioavailability and the toxicity thresholds. The goal is to develop a 'personalized medicine' concept by studying the patient's status to select the most suitable drugs and to control the pharmacokinetics from the device while allowing the physician to monitor externally the efficacy of the therapy. However, with most of the pre-loaded systems used at present only limited options are available for the physician to select a specific drug or combination of drugs for each patient or their dosages. Achieving this goal will require a more sophisticated design of the drug-eluting device, with built-in triggers and release rate controls and possibly also with multiple drug reservoirs.

When looking for an antibacterial application it is necessary to consider the patient's records in antibacterial resistance and allergies. It is also necessary to identify primary and

secondary pathogens, the existence of latent bacterial infections, predisposing factors, assess the patient's compliance, and so on. It would be desirable to modulate the drug release from the device. This often involves a burst release of the antimicrobial after implantation to prevent initial colonization, followed by a steady release for extended periods of time approaching zero-order kinetics at a concentration above the MIC (to prevent the device form harboring latent bacteria that may cause antibiotic resistance) but below the toxicological threshold, which might cause unwanted side effects. Also, hospitals would be required to monitor the antibiotic resistance patterns that may be encountered after implantation of drug-eluting devices to plan future treatments in addition to keeping an updated database with the available treatment options. These would ideally be supported by comparative clinical trails where significant statistical differences between treatments could be ascertained.

For any drug-eluting biomedical device, it is necessary to evaluate the significant cost differential compared with the use of the same device (e.g., prosthesis) without the drug-eluting characteristics in combination with systemic administration of the drug and also the potential toxicity and risk/benefit of having the drug (i.e., possibility of increased antimicrobial resistance in antibiotic-eluting medical devices). The drug-eluting device should demonstrate clear medical advantages over administering both the drug and the device in their conventional separate forms. The term 'clear medical advantages' is somehow ambiguous and needs to be specified for each medical application in which a drug-eluting device is considered. As an example, the safety of drug-eluting stents was questioned by different reports describing increased stent thrombosis, myocardial infarction and death [65]. Such studies were often deemed inconclusive because of their insufficient size, the use of historical controls, a limited follow-up period, and the lack of access to original source data. This was solved by performing a pooled analysis of data from four double-blind trials in which 1748 patients were randomly assigned to receive either sirolimus-eluting stents or bare metal stents and five double-blind trials in which 3513 patients were randomly assigned to receive either paclitaxel-eluting stents or bare metal stents – revealing that stent thrombosis after 1 year was more common with both drug-eluting stents than with bare metal stents whereas no significant differences were found between drug-eluting stents and bare metal stents in the rates of death or myocardial infarction [65]. However, current research continues with the goal of obtaining completely bioresorbable drug-eluting stents, some of them already in clinical trials (i.e., ABSORB®; Abbott Park, IL, USA).

Another promising line of research involves designing drug-eluting devices that respond 'on demand' to a biological signaling and send a feedback to the physician in a real-time manner. This could be achieved by using sensors located in the proximity of the implant or built-in on the implant. However, for the near future a more realistic scenario would involve acquiring the information without the need for sophisticated new equipment, using either imaging routine techniques available in many hospitals (i.e., X-rays, contrast arthrography, TAC, utrasonography, MRI, scintigraphy, PET) or by telemetry (i.e., wireless cardiac monitors used to monitor patients following surgery). Also, the requisite of supporting electronics in the implant involves the use of long-lasting batteries. So far the actuators used in biomedical devices to release a previously encapsulated drug are based on systems that do not use batteries but instead electrochemical dissolution of gold or polymeric membranes under physiological conditions or on the melting of a membrane placed on the pore mouth of the drug reservoir by using resistive heating [66]. Alternatively, electrical power could be supplied using fuel cells powered by biological fluids. These are being actively researched, and already provide power outputs in the milliwatt range [67-69].

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## Declaration of interest

Each author certifies that he has no commercial associations (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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