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Review

Drug/device combinations for local drug therapies and infection prophylaxis

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Abstract

Combination devices—those comprising drug releasing components together with functional prosthetic implants—represent a versatile, emerging clinical technology promising to provide functional improvements to implant devices in several classes. Landmark antimicrobial catheters and the drug-eluting stent have heralded the entrance, and significantly, routes to FDA approval, for these devices into clinical practice. This review describes recent strategies creating implantable combination devices. Most prominent are new combination devices representing current orthopedic and cardiovascular implants with new added capabilities from on-board or directly associated drug delivery systems are now under development. Wound coverings and implantable sensors will also benefit from this combination enhancement. Infection mitigation, a common problem with implantable devices, is a current primary focus. On-going progress in cell-based therapeutics, progenitor cell exploitation, growth factor delivery and advanced formulation strategies will provide a more general and versatile basis for advanced combination device strategies. These seek to improve tissue–device integration and functional tissue regeneration. Future combination devices might best be completely re-designed de novo to deliver multiple bioactive agents over several spatial and temporal scales to enhance prosthetic device function, instead of the current 'add-on' approach to existing implant device designs never originally intending to function in tandem with drug delivery systems.

Keywords: Combination devices; Drug delivery; Stents; Bone cement; Growth factors; Antibiotics

Contents

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1. Introduction to combination devices

Drug/medical device combination products represent an emerging new trend in implantable therapeutics. Combination devices have drawn increasing attention from both pharmaceutical and medical device companies as a strategy to overcome several long-standing clinical problems involving complications associated with device implantation. Using locally controlled drug delivery, combination products have already found applications in various areas of cardiovascular disease, diabetes, orthopedics, and cancer [1]. Drug and device combinations can be designed in coordinated strategies to elicit mutually reinforcing effects and provide, in certain circumstances, significant medical advantages over administering both the drug and the device in their conventional, separate forms. Formal regulatory recognition and development of the combination device design motif world-wide is relatively new [2], with flexible performance features and biotechnology both advancing on many contributing fronts, combination products represent a promising new opportunity for improving implanted prosthetic device performance and associated quality of life issues.

According to the US FDA's definition, "a combination device comprises two or more regulated components, i.e., drug/device, biologic/device, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; or two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products" [2]. With increasing clinical and commercial interest in combining medical devices with pharmacological agents for joint marketing, both the European union and the US FDA have recently established new policies and guidelines for these combination products [2]. FDA approval of the drug-eluting coronary stent (DES, i.e., Cordis' CYPHER™, Johnson & Johnson, USA) in 2003 opened the gate for broadly adapting similar technology to combine the device and pharma worlds that have remained largely separate to date. While combination device approvals in Europe (i.e., "CE mark") pre-date introductions elsewhere, formation of the US FDA's Office of Combination Products in 2003 recognized the need for a dedicated group to manage the regulation of combination products. Clear precedents and approval protocols should now spur significant growth in the combination products market estimated to reach $9.5 billion by 2009 according to a recent report [1]. Effective exploitation of capabilities of both medical devices and drug delivery in combination approaches requires intelligent incorporation of new technology, changes and refinement of both existing drug delivery systems and medical devices, shifts from traditional devices and drug forms, and compliance with new FDA and EU regulations [2]. Product efficacy is not as simple as a linear combination of status quo technologies in both the device and delivery arenas: neither current product has been designed or utilized with the intent of exploiting the benefits of the other, and as such cannot necessarily maximize benefit from a simple add-on combination. As combination products are currently developed in diverse medical areas, comprehensive understanding of appropriate controlled release strategies with distinct therapeutic advantages to more complex combination products is critical. This article reviews current controlled drug release techniques from local devices, especially those relevant existing first-generation combination products, as a basis for identifying needs and improving designs for next-generation products.

2. Device-based local drug release versus systemic administration

Combination devices are predicated on the principle of local controlled drug delivery from an implanted prosthetic device whose primary purpose is functional or structural replacement of host tissue. Optimal dual function (i.e., drug release and prosthetic performance) are ideally coordinated and designed to work in tandem. Hence, drug release properties from the device are not simply adjunct to device implantation, and must be thoroughly understood. Drugs are clinically administered in diverse ways, including topical (nasal, cutaneous, ocular, aural), oral, intravenous, intramuscular, subcutaneous, sublingual, and other local administration routes [3]. While many delivery strategies facilitate systemic drug bioavailability, local release seeks to provide therapeutic drug concentrations only to intended target sites for prolonged times required to produce the desired pharmacological outcome. Due to numerous acknowledged advantages (see Table 1), local

Table 1
Advantages of local drug release strategies over systemic drug therapy

1	Lower doses required
2	Greater control over toxicity and bioavailability of dose
3	Less susceptibility to promoting antibiotic resistance
4	Extended duration of release
5	Possibilities to combine local and systemic drugs with different kinetics
6	Controlled release from surfaces of combination devices directly to site
7	Avoidance of systemic drug exposure
8	Direct mitigation of device-centered infection using combination device release

drug release strategies are frequently considered to address thrombosis, osteomyelitis, periodontitis, biomedical device-related infections and other microbial pathologies, or inflammatory complications that are refractory to most conventional methods of systemic drug administration once established.

An ideal drug delivery system should (a) provide effective drug doses continually to target site, and (b) offer possibilities for continuously therapeutic drug release over prolonged periods [4]. Drug release rates and durations depend upon each clinical context, including the therapy sought, disease or pathogen, device design, tissue implant site, and drug susceptibility and clearance mechanisms. These considerations then require careful assessment of target site pharmacokinetics, effective dosage and release kinetics requirements, formulation of device design factors to enable effective drug dose delivery without impairing device performance, as well as analysis of site, side-effects and toxicity, and selection of clinically effective drugs in each context. In treating thrombosis, for example, the adherent clot or coagulation film can deter drug release from the device. In the case of implant-based infections, increased complexity associated with wound site compromised healing biology and microbial colonization, anticipated primary and secondary pathogens, tissue site drug toxicity and local metabolism, and infection susceptibility must all be considered in drug selection, dosing and release mechanisms.

Drug release properties from many current devices are currently unsatisfactory or at least, sub-optimal, primarily due to poor design, biomaterial selection, drug release mechanism, drug selections, matrix/device fabrication methods and manufacturing specific to local host implant site environmental characteristics. Additionally, drug dosing requirements for extended release regimens (e.g., months to years) cannot be readily accommodated by simply adapting known release technologies to existing medical implant designs. Many factors need to be considered for dosing strategies including therapeutic indices, bioavailability, toxicity thresholds, and efficacy in the context of the therapy sought (e.g., pro-angiogenic, anti-coagulation, anti-inflammatory, anti-fibrotic, and antimicrobial) and the tissue site. Special therapeutic conditions warrant further design considerations. For example, the release of ''sub-therapeutic'' or ''sub-inhibitory'' drug concentrations (e.g., those below the minimum therapeutic or inhibitory concentration (MTC and MIC, respectively)) from biomaterials devices into surrounding tissue or fluids might actually exacerbate infectious complications or induce resistance in wound-site bacteria [5]. Therefore, local antibiotic release profiles should ideally exhibit initial high release rates (burst release) to counter any initial elevated infection risk immediately post-surgery or implantation, followed by a long period of drug release within the therapeutically efficacious dosing zone to continually hinder latent infection [6].

3. Device-related infection

All implanted medical devices, from transient, easily inserted and retrieved contact lenses, urinary catheters and endotracheal tubes, to more permanently surgically implanted cardiac valves, embolic coils, vascular grafts, hip, knee and shoulder joints, pacemakers, coronary stents, and plastic surgery augmentation devices suffer from recognized risks of ''device-related'' or ''implant-associated'' infection [7]. This risk is both acute and chronic, with periods of latency extending the entire life of the patient. Pathogen-device colonization occurs too often, resulting in host patient morbidity and device removal, or mortality. Bacteria encounter the implant via several mechanisms: (a) exogenous pathogens from skin, surgical instrumentation or the local environment, gaining direct access to the implant site during device placement, or (b) ubiquitous, systemically circulating, non-pathogenic but opportunistic bacteria spontaneously alter their phenotype to become pathogenic at the implant site. The former event produces immediate colonization while the latter event can occur at any time post-implantation, even years after device placement (so-called ''latent infection''). The host implant site offers a continued opportunistic environment for bacterial colonization: surgical trauma instantly reduces tissue transport and perfusion, enhances inflammatory reactions, blood clotting, edema, alters homeostasis, and produces an abrupt, non-integrated biomaterial-tissue interface. All of these factors favor microbial survival and colonization of the site. In short, the implant site overcomes acute phase reactions but chronically never resolves to a true healing mode that stabilizes the site. Additionally, most implant materials and designs manifest poorly controlled, dynamic interfacial responses in physiological milieu that favor microbial surface colonization [8]. Adhesion of ubiquitous host planktonic bacteria to device surfaces through their extension of fibrils, expression of new sessile surface receptor patterns, and secretion of polysaccharide adhesins is the first step in device-site infection [9]. After surface attachment, rapid bacterial proliferation produces sister cells eventually forming resident colonies. Many pathogens, once sessile, use quorum sensing mechanisms to adapt [10,11]; some create protective, complex mucopolysaccharide barrier films known as ''biofilms'' to enhance colony stability and escape the host immune response. Once a biofilm is formed, bacteria can shed to become free satellites that migrate and attach to other, non-colonized surfaces. Through quorum signaling the biofilm structure also facilitates cell-to-cell communication, furthering phenotypic alterations, adaptation against immune response, and cross-breeding that promotes genetic exchange and antibiotic-resistance transfer processes [7]. Bacteria within a mature adherent biofilm colony are very difficult to eliminate, refractory to administered antimicrobials, host immune mechanisms and clearance. Systemization of implant-induced infection is a serious complication (sepsis). Hence, removal of the

device is often required to effectively treat the infection both locally and systemically [12].

Nosocomial infections occur in more than two million hospitalizations in the US each year, with the average hospital cost near US $15,000 [13–15]. Increased clinical use of both long-established and new innovative medical implanted devices increases every year with consequent higher infection incidence. With more extensive use of medical devices in aging populations, accompanied by serious infection problems associated with these medical devices, design and study of improved methods for direct, controlled, and local release of drugs to prevent device-related infections remains a compelling priority. Innovative, effective drug/device combination products are required for improved performance of medical devices, decreasing health care costs, avoiding systemic administration of high levels of antimicrobial drugs and reducing further risks of antibiotic-resistance.

Two main strategies have attempted to reduce incidence of device-related infections: anti-adhesive biomaterials using physicochemical surface modification methods (including non-drug containing coatings, films and ion treatments—not covered in this review), and direct incorporation of drugs into or onto the medical device [16], either immobilized or released. Depending on the intended medical device application, cost-effectiveness and usage period, drugs are combined with medical devices using different formulation methods.

4. Drug-eluting stents

Since first clinical introduction in 1977 [17], percutaneous coronary intervention (PCI) has always been limited by restenosis. As the most common therapeutic treatment for coronary artery disease (CAD), PCI procedures now number more than 1.5 million annually in the United States [18]. Deploying a rigid but compliant endovascular scaffold that prevents vessel shrinkage and recoil post-intervention (i.e., an endovascular stent) mitigates incidence of restenosis compared to balloon angioplasty alone [19,20]. The stent has produced perhaps the greatest clinical impact in combination device technology to date, generating a new billion-dollar cardiovascular device market impacting millions of patients annually. Nonetheless, vessel restenosis remains a major complication of stent placement, so-called ''in-stent restenosis'', requiring re-intervention at rates up to 50% in several patient classes, depending on the anatomical placement, pathophysiology, size and lesion complexity [21,22]. To date, most systemically administered drugs have shown disappointing results in preventing in-stent restenosis [23–25] generally attributed to poor drug bioavailability, toxicity, and insufficient drug concentration at injury sites. Substantial effort has been directed toward optimization and testing of novel drug eluting stents (DES), which represent a highly visible and successful precedent combination device clinical technology.

Sirolimus, also called rapamycin, is perhaps the most successful and extensively studied stent-released drug to date because of its demonstrated effectiveness against in-stent hyperplasia following coronary stent deployment [26]. Sirolimus is a potent inhibitor of cytokine and growth factor-mediated smooth muscle cell proliferation. Its mechanism of action is via receptor-based antagonism of the intracellular enzyme, mammalian target of rapamycin (mTOR [27]), the downstream mediator of the cell's PI3K/Akt phosphorylation signaling pathway that regulates many basic cell functions. Receptor-based inhibition of mTOR results in cell-cycle arrest in the late G1 to S phases, a potent anti-proliferative and anti-hyperplastic event [28]. Sirolimus-eluting stents have demonstrated dramatically reduced rates of restenosis compared to conventional bare metal stents in several clinical trials involving 238–1058 patients with 6–12 months follow-up time [29–32]. Following Europe's lead, FDA's approval of Cordis' CYPHER^{TM} sirolimus-eluting stent (2003) opened the gate for adapting new technology combining both device and pharmaceutical designs in the United States. The FDA-approved and CE-certified CYPHER^{TM} stent is now routinely deployed in millions of PCI cases annually throughout Europe, the Middle East, Canada, Asia-Pacific, Latin America and United States. The remarkable success of the sirolimus-eluting stent spurred substantial interest in developing improved drug-eluting stents with anti-mitotic sirolimus analogues [26]. Various immunosuppressive drugs (sirolimus, everolimus, tacrolimus, ABT-578), anti-proliferative drugs (paclitaxel, antinomycin, angiopeptin, etc.), anti-migratory drugs (batimastat) and gene therapeutic reagents (antisense and siRNA, vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (eNOS and related genes)) have been combined with stents and investigated for their local release and anti-restenotic effects [33–36]. Very recently, the FDA approved Boston Scientific's TAXUS Express^{2TM} paclitaxel-eluting coronary stent [37], touting consistently low re-vascularization rates throughout the stent, equivalent deliverability with the CYPHER^{TM} system, and immediate post-procedure magnetic resonance imaging (MRI). Such in situ device imaging capability (e.g., MRI for metallic implants) provides new detailed diagnostic information on device placement and lesion site healing. However, recent data [38] suggest that sirolimus-eluting stents exhibit superior performance in reducing incidence of stent thrombosis compared to the paclitaxel-eluting stents.

As all clinically approved cardiovascular stents to date comprise expandable metallic wire woven or etched tubular designs for endovascular placement, anti-restenotic drugs for delivery to the vascular wall can be directly adsorbed onto the stent struts or incorporated into a matrix or coating on-stent, and continually released after stent deployment. The stent directly contacts the vessel wall and protrudes into the endovascular tissue bed close to cellular agents implicated in restenosis. Hence, stent-released drugs are locally available to target smooth muscle

cells in the vessel wall with high local concentrations and minimal systemic bioavailability and toxicity. Most drug-on-stent impregnation techniques and polymer coatings are proprietary, but must be demonstrated biocompatible or at least biologically inert. Although sirolimus and paclitaxel-eluting stents demonstrate clinical effectiveness now up to 2 years after implantation [39], evidence for actual implant site healing and normal tissue homeostasis are lacking. Long-term concerns over late neo-intimal formation and stent-based thrombosis still remain in drug-eluting stent sites once drug elution is exhausted and chronic inflammatory responses dominate. Completely biodegradable drug-eluting stents may prove ideal in this regard for long-term applications if mechanical and safety concerns can be resolved, providing initial restenotic prevention while eventually resorbing completely to eliminate thrombosis risks and allow complete endoluminal healing [33,40]. Next-generation commercial drug-eluting stents will use a FDA- and EU-approved degradable polymeric coating (polylactic acid) over metallic stents for drug encapsulation and release [41]. The Champion^{TM} stent (Guidant, Santa Clara, CA) is one example currently in trials. With restriction of this absorbable polymer to the abluminal (outer) surface of each strut, drug and polymer are not exposed to flowing blood in the arterial lumen, a primary cause of current stent thrombosis with rates of 4–6% often requiring aggressive systemic anticoagulant therapy (and associated risk factors) [41]. Notably, eventual degradation of bioresorbable polymers ensures predictable systemic drug elimination over a finite time without drug retention, while reducing potential risks for late adverse events months to years after implantation [42].

Current commercial drug-eluting stents are coated with a thin (~μm) non-degradable polymer coating (e.g., polyisobutylene or polymethacrylate copolymers). These coatings are compositionally balanced for drug partitioning, solubility and release, as well as processing and endoluminal compatibility. Loaded with micrograms of drug (e.g., currently approved for paclitaxcel or sirolimus, ~140 μg/cm^2) per device, these coatings usually exhibit similar drug release kinetics: an early significant burst release (24–36 h) followed by slow continuous release over a longer period of time (typically up to 6 weeks). Varying drug selections, drug-loading methods, concentrations, coating chemistries and designs, application methods, and polymer composition will influence initial burst rates, overall release duration, bioavailability and therapeutic potential [43,44]. Even anatomical factors and disease pathology influence drug delivery [45]. However, to realize more complicated kinetic release profiles, including multi-step pulsatile or slower, extended release, more complex, versatile and programmable drug-eluting stent systems are needed. A newly designed metallic stent containing unique honeycomb strut elements with inlaid stacked layers of degradable polylactide-*co*-glycolide (PLGA) reservoirs containing paclitaxel has demonstrated programmable release kinetics. A biphasic release profile was created by the addition of blank layers of PLGA polymer within the reservoir stacks. Early burst and late release behavior for paclitaxel were adjusted both dependently and independently, controlled by drug loading concentration, numbers of layers, and positioning of the various layers within the polymer reservoir stack. With this strategy, two or more different drugs can be loaded in separate reservoir layers and released separately in different time periods [46].

As one of the earliest products to be reviewed and approved by the FDA as a combination product, drug-eluting stents provide an excellent device platform for local drug delivery and an outstanding example of a successful prototypical combination product. Clinical recognition and rapid success are attributed to their deployment directly against and into the vessel wall target tissue, prolonged tissue contact with minimal drug doses required for efficacy. Several specific design factors for anti-restenosis efficacy include stent-strut material, stent configuration, polymer coating material, drug properties, drug encapsulation and release strategy. While early bare metal stents represented early prototypes to coat to release drugs, more recent DES designs are based on drug selection and programmed release designs intimately related into the de novo stent strut and frame components [46]. While current DES technology appears successful against in-stent restenosis, further improvements and novel innovation in combination de novo implant device designs are required to address challenging interventional cardiology and radiology problems at peripheral vasculature sites [47], particularly venous and multiple lesion sites [48,49], with more versatile therapeutic and pharmacological profiles, and in other tissues, including needed biliary stent applications [50].

5. Antimicrobial central venous catheters

Central venous catheters are used frequently in critical care situations for delivery of critical fluids, parenteral nutrition, and drug administration in a variety of hospital settings. In the United States alone, 5 million central venous catheters are inserted into patients every year. Unfortunately, these catheters are also a major cause of nosocomial infections: 100,000–500,000 catheter-related bloodstream infections (CRBI) occur annually, with ~US $3700 to ~US $28,000 medical remediation costs depending on the original central venous catheter placed. At least 25,000 patients die each year of CRBI [51,52]. Systemic or oral administration of antimicrobial agents is not a clinically preferred route to reduce CRBI infections. Properly designed combinations of antimicrobial agents delivered from these catheters could instead provide efficacious concentrations of antimicrobial agents locally at placement site without requiring high systemic anti-infective dosing. Antimicrobial central venous catheters are generally not considered as drug/device combination products, as their original FDA approval and emergence into clinical use preceded the more recently imposed

combination product review approach used currently. However, many different tactics used for attaching or impregnating antimicrobial agents (including both antiseptics and antibiotics) onto/into catheters should provide precedents and inspiration for future improved combination products in various clinical areas.

Two main strategies for incorporating antimicrobials onto catheter surfaces have been employed and have shown promising results [53]. To enhance solubility and bioavailability, many antibiotics are synthetically designed as anionic derivatives (e.g., using carboxylate, phosphate, or sulfate substituents) analogous to that of many natural glycosaminoglycans (e.g., heparins, chondroitins), phosphorylated proteins, and other biological molecules [54]. The first application method, simple drug coating, uses antibiotics' anionic charges to bind them electrostatically to medical device surfaces via intermediate layers of adsorbed cationic surfactants, such as tridodecylmethylammonium choloride (TDMAC). Hydrophobic alkylated regions of these surfactants adsorb to catheter polymer device surfaces by physical attraction, presenting cationic charges on the surface available for anionic antibiotic complexation [55,56]. The second method, drug impregnation, incorporates antimicrobials into the polymer device bulk material directly prior to injection molding or extrusion in the same manner that common device fillers such as pigments or stabilizers are added to extrudable plastic resins [57]. Excipients to retard or enhance drug release rates can also be co-formulated in principle, although in practice, total mass loading of all additives is limited by gross effects on polymer matrix physical properties. These strategies have allowed incorporation of various antimicrobials to catheters, and investigation of their anti-infective efficiency. Combinations of antimicrobials are preferred over single agents due to concerns over promoting antimicrobial resistance [58]. So far, the most effective agents used to treat catheter-related infection are the combination of minocycline/rifampicin (MR) antibiotics [59,60] and the combination of chlorhexidine/silver sulfadiazine (C-SS) antiseptics [61]. Central venous catheters coated or impregnated with both antibiotic and antiseptic combinations have been FDA and CE approved and commercialized (e.g., C-SS: ARROWgard®, Arrow International, Reading, PA; MR: BioGuard Spectrum™ catheter, Cook Critical Care, Bloomington, IN).

The ARROWgard™ catheter impregnates C-SS on its external surface whereas the BioGuard Spectrum™ catheter is coated with MR on both internal and external surfaces using TDMAC [53]. Both MR and C-SS combinations have demonstrated broad-spectrum antimicrobial activity against Gram-positive and Gram-negative organisms, and fungi. Many in vitro and in vivo studies comparing microbial adherence and CRBI incidence between MR and C-SS catheters using different infection models have been reported in the past decade. Randomized clinical trials [60,62] demonstrated superior performance of MR-impregnated catheters versus C-SS coated catheters in resisting CRBI, particularly in patients requiring vascular access for over 7 days. While both MR [59,63–65] and C-SS [61,66–72] catheters exhibited significantly reduced CRBI in a number of pre-clinical and clinical studies, conflicting results have led to doubts regarding the safety of C-SS catheters [58,73–76]. However, MR and C-SS catheter antimicrobial coatings are not entirely equivalent for clinical comparison. Higher levels of chlorhexidine seem to improve the performance of C-SS coated catheters (C-SS$^+$ catheters) [77] using a novel agar infection model that simulates rat subcutaneous infection. In comparison with C-SS catheters, C-SS$^+$ catheters exhibited higher chlorhexidine release and retention, resulting in significantly lower bacterial adhesion than the C-SS catheter at both day 7 and day 14. In this study, C-SS$^+$ catheters exhibited effective resistance against many tested organisms, including *Enterobacter aerogenes*, *Candida albicans*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *S. epidermidis*, and rifampicin-resistant *S. epidermides*, whereas MR catheters were effective only against *S. aureus* and *S. epidermidis*. Another in vitro study [78] also showed superior efficacy of C-SS$^+$ catheters versus MR catheters against Gram-positive *S. aureus* and *S. epidermidis*.

Both MR (BioGuard Spectrum™) and C-SS (Arrowgard™) catheters are acknowledged to reduce bacterial adhesion and CRBI infection significantly more than uncoated catheters. However, according to FDA public health notices, chlorhexidine has the potential for serious hypersensitivity reactions. Recently, miconazole- and rifampicin incorporated into polyurethane central venous catheters using a new diffusion process exhibited superior activities against Gram-positive, Gram-negative and *C. albicans* in vitro. Anti-infective efficacy of this new antimicrobial catheter remained stable at room temperature for more than 1 year, and the antimicrobial activity half-life exceeded 3 weeks [79]. Recently, significantly reduced CRBI were reported compared to standard unmodified polyurethane central venous catheters using a randomized controlled clinical trial. No adverse effects or antimicrobial resistance were observed [80].

Application of the C-SS- or MR-coated, or any antimicrobially treated, catheter elicits concerns about selective local emergence of organisms resistant to the associated antimicrobials. Antibiotic-resistant bacteria continually emerge at increasing rates as a result of widespread and too-often indiscriminate clinical use of antibiotics [81–83]. Bacterial resistance to antiseptics (chlorhexidine and silver sulfadiazine) and antibiotics (minocycline and rifampicin) has been reported on central venous catheters in vitro [84]. Resistance in *S. epidermidis* was found to develop more easily for the antibiotic combination than for antiseptics, and more readily for rifampicin than minocycline. Although no clinical emergence of resistant bacteria has been reported using these or any other treated catheters to date, continual monitoring to locally releasing devices should be vigilantly pursued to

determine resistance profiles of bacteria recovered from colonized catheters.

Intravascular catheter materials can also be modified to accommodate antimicrobial combinations. All catheter materials must be biocompatible, withstanding implant conditions within the vascular system without deteriorating or causing patient complications. Several biomedical polymers including polyethylene, fluoropolymer, polyvinyl chloride (PVC), silicones, elastomeric hydrogels and polyurethanes have been used in catheter fabrication with notable clinical success [85–87]. Certain specific properties must be considered when developing in-dwelling vascular devices, for example, thromboresistance, flexibility, smooth surface, lack of kink memory, no chemical leaching and reasonable cost. These fixed catheter materials properties also influence amounts of antimicrobials incorporated and their release kinetics. To increase amounts of adsorbed antibiotics, side-chain functional groups (acidic, basic and ionic groups) have been introduced into device polymer backbones to produce specific interactions with acidic and basic functional groups on the antibiotics, amoxicillin, and rifampin [88]. Antibiotic loading and release behavior were influenced both by strength of drug–polymer interaction and the resultant water swelling of the polymer matrix. Specifically, when antibiotic–polymer interaction is dominated by ionic interactions, adsorption of antibiotics onto the polymer is favored by strongly positively and negatively charged groups on the polymer surface, whereas for polar antibiotic–polymer interactions, amounts of surface-bonded antibiotics depend on matrix hydrophilicity.

While clinical trials have now shown that patient infections are significantly reduced by using antimicrobial catheters (mainly BioGuard Spectrum^{TM}, Arrowgard^{TM}) [61,66,89], these results are difficult to translate to other clinical situations [90]. Two recent reports [91,92] declared that studies of antimicrobial central venous catheters suffer from methodological and statistical flaws. Multiple factors beyond device design can substantially influence the risk of CRBI, including patient profiles, catheter care, and insertion protocols. Several issues associated with use of antimicrobial central venous catheters remain to be addressed for unequivocal clinical acceptance. These include lack of clear, convincing clinical trial data, significant cost differential, potential toxicity and risk of increased antimicrobial resistance.

6. Antimicrobial urinary catheters

Urethral catheters are used for bladder drainage as a treatment option for patients with urinary retention, general surgery recovery, bladder obstruction, paralysis or a loss of sensation in the perineal area. More than 30 million urinary catheters were employed in the United States annually. One out of 4 hospitalized patients receives an in-dwelling urinary catheter [93]. Millions of catheter-associated urinary tract infections (CUTI) occur annually, with an average cost of US ~$3000 to ~US $4000 each [94]. Nonetheless, CUTI are generally considered assumed to be benign with low attributable mortality [95] but significant collective cost and morbidity. Bacterial migration on and adhesion to inserted devices are important factors in CUTI.

Many efforts have focused on catheter surface modification in order to impede initial adhesion and biofilm formation, and reduce CUTI incidence. The most extensive clinical testing has combined catheters with antimicrobial agents. One simple, common method to reduce CUTI involves immersing the urinary catheter into an antimicrobial solution prior to urethral insertion. Immersion of these devices (typically flexible polymer) into antimicrobial solutions to allow direct drug sorption onto and into the device surface constitutes the most straightforward method for loading antimicrobial agents into medical devices. Several studies [96,97] concluded that medical devices, including prostatic stents and urethral catheters, immersed in solutions of the broad-spectrum antibiotic, ciprofloxacin (commonly used to treat sinusitis, otitis media, urinary tract infections, and prostatitis), can significantly reduce bacterial adhesion and consequently reduce CUTI risks. As these antimicrobial agents are only physically ad- or absorbed to device surfaces, this method is unlikely to load drugs for prolonged release to prevent bacterial infection over long periods: loading is low, release is rapid, and dose depletion occurs quickly. Nonetheless, certain practical clinical advantages exist. Suitable catheters can be treated by drug solution immersion immediately prior to clinical placement, providing early, short-term protection against infection, flexibility and direct control to clinicians in certain situations.

Silver and its salts have been the most commonly used antimicrobial agent applied to urinary catheters. Solubilized silver ion ($Ag^{+}_{(aq)}$) is the bioactive form, released in many different ways from silver-containing coatings as an anti-infective in multiple clinical contexts [98]. To clarify mixed clinical results of silver-coated urinary catheters, a meta-analysis with a total of 2355 patients was performed [99] and demonstrated significantly improved performance of silver alloy catheters but not standard silver oxide urinary catheters over control catheters in treating CUTI. One possible reason is that silver alloy remains in the catheter for a longer time [100]. In the United States, silver oxide catheters are no longer available. A recent comprehensive assessment of impregnated catheters intended for short-term use in hospitalized adults using eight differently designed trials compared silver alloy catheters with standard catheters [101]. Risk of asymptomatic bacteriuria was significantly reduced in the silver alloy group at less than 1 week of catheterization, but to a reduced degree at greater than 1 week. However, emergence of bacterial resistance to silver was not tested in any of these trials. Two new FDA-approved hydrogel/silver urinary catheters developed by C.R. Bard (Covington, GA) provide protection against CUTI. The Bardex I.C. (latex), and LubriSil I.C. (silicone) catheters both feature a proprietary

lubricious hydrogel surface coating over a layer of metallic silver applied to both inner and outer catheter surfaces. This unique combination permits smooth intra-urethral insertion and enhanced infection protection, proven to reduce CUTI incidence in several in vitro [102] pre-clinical [103], and clinical studies [104,105]. Outside of silver, catheters impregnated with urinary antiseptic, nitrofurazone [103], and the broad-spectrum antibiotic combination proven effective in central venous catheters (see section above), minocycline and rifampin [106] exhibited significant reductions in CUTI in randomized human trials.

Since conclusions regarding the efficacy of systemic antimicrobial agents to prevent CUTI are not clear, novel technologies for incorporating antimicrobial agents into urinary catheters for release may continue to provide new combination product advances for preventing CUTI. Current combination devices however are far from a final definitive answer for CUTI. While silver-based medical technologies are very common in multiple formulations and delivery strategies [98], silver-resistant bacteria are common in environments where silver ion is ubiquitous (e.g., mining wastes). Concern over pressure that creates such silver-resistant strains in medical practice is now evident [107]. These concerns are applicable to other anti-infective agents including chlorhexidine [108] and nitrofuroxan [109]. Urinary catheters that release more potent antimicrobial agents in more diverse ways should be pursued, and issues similar to those mentioned for central venous catheters should best be carefully considered and addressed in future designs.

7. Orthopedic device-based drug delivery

Bone defects resulting from disease, trauma, surgical intervention, or congenital deficiencies represent a substantial clinical challenge world-wide for orthopedic reconstructive surgeons. This also presents an immense opportunity for bioengineers, tissue engineers and drug delivery specialists to more rapidly produce bone. The preferred treatment for such defects is autologous bone graft, but harvest is painful, supply is limited, and risks of infection, nerve loss, functional impairments, hemorrhage, and cosmetic defects are significant. Additionally, orthopedic hardware placement for fixation and stabilization fractured bones during healing, or to functionally replace complete tissues (e.g., in total joint replacements) represents millions of implanted devices annually. Bone-implant integration (i.e., direct bone-implant bonding [110]) and long-term stabilization is a common clinical problem with substantial complications including infection, bone resorption, and loosening [111–113]. Frequently, despite mechanical stabilization using fixation devices, fractures are either slow-healing or non-union (~5–10% [114]). Hence, recent advances in drug delivery are now being used in tandem with orthopedic implants with future prospects as new combination devices to promote and accelerate bone neogenesis, more reliable bone healing and functional tissue replacement [115]. Delivery of small molecule osteoinductive molecules as well as biological derived growth factors, anti-osteoporotic agents, and osteo-synthetic genetic materials (DNA, siRNA) to bone injury sites are reported [116–119]. Because few reports demonstrate efficacy for exogenous osteogenic factors delivered simply as topical solutions in large animal models, matrix-based delivery of these molecules is now common [118,120,121]. Osteo-precursor cell-based local delivery is now also reported for bone engineering [118,122–124]. These biotechnology approaches seek to accelerate and enhance bone defect healing and bone-implant stabilization through rapid local osteogenesis induced through local release of cells, mitogenic and morphogenic agents [125]. Orthopedic drug delivery vehicles are most often physically de-coupled from the device (e.g., separate collagen sponge or tricalcium phosphate granules delivering growth factors directly adjacent to or placed into spinal implant cage [120]) by either design or previous regulatory requirements. However, new methods to effectively integrate and combine delivery strategies into orthopedic, periodontal fixation or total joint replacement devices for controlled, local release and new bone-generating therapeutic potential at the implant site would be clinically useful.

Bone infection (osteomyelitis) is a local or generalized infection of bone and bone marrow typically caused by bacteria introduced from trauma, surgery, implant use, by direct colonization from a proximal infection or via systemic circulation. Osteomyelitis in an implant context is also prevalent and clinically difficult to treat, often refractory to antimicrobials: the biofilm mode of pathogen growth on an implant surface protects sessile bacterial colonies against host immune response and antimicrobial therapy through complex environmental factors [126]. Conventional therapy with systemic antibiotics is expensive, prone to complications and often unsuccessful [127]. Major problems treating osteomyelitis include poor antimicrobial distribution at the site of infection due to limited blood circulation to infected skeletal tissue, and inability to directly address the biofilm pathogen scenario. High systemic dosage of antibiotics to facilitate sufficient tissue and biofilm penetration is not preferable because of possible serious toxic side effects. Controlled antimicrobial release systems in orthopedic combination devices represent alternatives to conventional systemic treatments, and include antibiotic-eluting bioceramics, drug-impregnated bone cements, and natural and synthetic antimicrobially loaded polymers [128].

One commonly used infection management method with orthopedic implants utilizes antibiotics loaded into clinically ubiquitous bone cement, polymethylmethacrylate (PMMA), or PMMA beads. These non-biodegradable polymer cements have been employed clinically to prevent or treat osteomyelitis in various forms for nearly four decades [129–131]. Several commercial antibiotic-impregnated bone cements based primarily on PMMA/MMA are now CE-approved, including Simplex™ P with

erythromycin and colistin tobramycin (Stryker, UK) sold in Europe for more than 20 years, and gentamicin-containing Palacos™ PMMA cement (refobacin palacos r-Knochenzement®, Merck, Austria). A gentamicin-containing PMMA bead, Septopal® (E. Merck, Germany) is also commercially available in Europe [126,132]. Until recently, no antibiotic-containing bone cement was approved for use in the United States. Instead, surgeons commonly added antibiotics off-label to bone cement directly in the operating suite. In 2003, the first pre-blended bone cement containing an antibiotic (Simplex P with tobramycin developed by Stryker Howmedica Osteonics) was approved for use in the United States. Later in 2003, Biomet, Inc. (Warsaw, IN, USA) announced FDA clearance of their Palacos G™ antibiotic-loaded bone cement.

More detailed information about antibiotic-loaded PMMA cement and beads is found in excellent recent reviews [126,132–135]. PMMA can be loaded to deliver a variety of widely used antimicrobials and some other bioactive "agents" including anti-osteoporetic agents, proteins (model protein, albumin) and peptides (e.g., growth factors) [136]. The intention in these non-degradable matrices is to slowly release the soluble mixed bioactive reagents from the solidified, often-glassy, non-swelling PMMA bone cement monolith surrounding the implant over time. Loaded drugs are usually released in a typical bi-phasic fashion: an initial burst release followed by a long, tail of low, and importantly, largely incomplete release that continues for days to months. Small molecule antimicrobial release behavior from PMMA is influenced by relative loading amount [137], bulk porosity [138], surface area and surface roughness of the bone cement [138–140]. Addition of soluble lactose to PMMA produces increased antimicrobial release by percolation-based porous diffusion [137]. All of these observations lead to the conclusion that PMMA bone cement drug release occurs through solvent pore penetration, soluble matrix dissolution and solubilized drug outward diffusion via networks of continuous, accessible pores within an otherwise largely insoluble, dense, glassy bulk PMMA matrix.

In vivo studies have demonstrated that antimicrobial-loaded bone cement can prevent infection from intra-operative challenge within a short time after implantation [139,141–143]. This effectiveness in preventing infections is further illustrated in prospective, randomized and controlled clinical trials comparing antibiotic-loaded bone cement to drug-free bone cement control groups [144,145]. Tobramycin is an aminoglycoside closely related to gentamicin with a similar spectrum of activity, slightly more effective against *Pseudomonas* [146] but less ototoxic and nephrotoxic than gentamicin [147,148]. Its elution characteristics are judged superior to those of gentamicin [149]. A recent clinical study testing the pharmacokinetics and safety profile of tobramycin bone cement [150] demonstrated local tobramycin concentrations more than 200 times higher than systemic levels only 1 h after administration. Systemic drug absorption was minimal with rapid urine excretion. However, despite some promise, drawbacks also limit clinical enthusiasm for use of antimicrobial-loaded bone cement. For example, gentamicin and tobramycin are used most frequently by surgeons for incorporation into bone cement in Europe and United States, respectively [135,151–155]. Pharmacokinetic studies indicate that antibiotic release from gentamicin-impregnated PMMA cement or beads is far from satisfactory [156–158]. Less than 50% of the antibiotic load is released from implants within 4 weeks, and no continuous release was observed thereafter, indicating significant bioavailability problems. Recently, 19 of 28 bacterial strains cultured directly from a clinically retrieved gentamicin-loaded bone cement were gentamicin resistant, raising concerns for the effectiveness of gentamicin-incorporated implants [159].

Antimicrobial peptides represent a new alternative drug class for incorporation into PMMA cement implants. Antimicrobial peptide Dhvar-5, an antifungal peptide found in human saliva, has been incorporated into PMMA beads, and its release behavior and antimicrobial efficacy have been investigated in vitro [160]. Its C-terminal net positive charge can disrupt and penetrate the negatively charged bacterial cell wall. The Dhvar-5 release profile is characterized as a high concentration initial burst followed by a continuous release with gradually decreased concentration over a 28-day period. Up to 91% of incorporated Dhvar-5 was released from PMMA beads in 1 month. Large fractional Dhvar-5 release observed in this study was explained by the freeze-dried amorphous powder formulation with a relatively high volume fraction compared to gentamicin sulfate. It was hypothesized that at higher concentrations, Dhvar-5 creates a porous network throughout the bead, allowing percolation-based pore diffusion from the bead core.

Regardless of the different antimicrobial agents mixed into PMMA liquid resins and its long tradition in orthopedic device fixation, inherent limitations reduce clinical enthusiasm for these combination implants. PMMA is not biodegradable, so with any clinical failure, secondary surgery is necessary to remove the PMMA before new bone can regenerate in the defect. PMMA polymerization exhibits a well-known, prominent exotherm [161]. Both this heat and residual MMA monomer can kill healthy surrounding bone cells and possibly inactivate the antibiotic if PMMA is used in the popular "doughy" form [131]. Other criticisms are the low PMMA bonding strength to the implant surface and known soft tissue encapsulation of PMMA. In cases of loosening and removal, bone substance will also be lost. Biomimetic synthetic hydroxyapatites (HAP) [162] are a more attractive natural candidate as composite materials for bone cement due to their intrinsic non-toxicity, high biocompatibility and ability to support growth of new bone tissue [163,164]. HAP attempts to produce the same elementary

inorganic chemical solid chemical composition as bone and tooth mineral. Past work [131] investigated release behavior of cephalexin- and norfloxacin-loaded HAP cement in vitro. Drug release patterns of these antibiotic-loaded HAP cements correlated well with the Higuchi model [165]. The 4.8 wt% norfloxacin-loaded cement provided continuous antibiotic release to 250 h with complete release estimated to be 3 weeks. Anionic collagen:HAP composite pastes for antibiotic controlled release have been developed using inorganic salts, $Ca(NO_3)_2 \cdot 4H_2O$ and $(NH_4)_2PO_4$, mixed with anionic collagen at a mass ratio of 20:1 followed by addition of ciprofloxacin [164]. Antibiotic release rate is controlled by the porosity and tortuosity in the composite, permitting drug release throughout the healing process. Other synthetic hydroxyapatite cements such as β-tricalcium phosphate or calcium phosphate bioceramics, either alone [166,167] or associated with natural [168] or synthetic polymers [169], have also been studied to treat bone infection with some claims to success. These composites provide potential bulk compositional versatility for antibiotic-releasing formulations.

Biodegradable polymer cements and implants draw increasing interest because of their advantages over PMMA cements or PMMA beads in principle. First, because biodegradable beads resorb at controllable rates, surgical removal and soft tissue reconstruction are unnecessary. Second, these polymers are able to provide longer release periods and higher antimicrobial agent concentrations to more completely treat particular orthopedic infections, and third, biodegradability can be varied from weeks to years, permitting different types of infections to be treated over different time scales [170–173]. Biodegradable FDA-approved polyesters, the poly(α-hydroxy acids) poly L-lactic acid (PLA), poly(glycolic acid) (PGA), and poly(lactic-*co*-glycolic acid) (PLGA) (also called polylactide, polyglycolide, and poly(lactide-*co*-glycolide), respectively) continue to attract immense pharmaceutical and biomedical interest [174–177]. Currently, a number of FDA-approved clinically marketed products utilize PLA and PLGA as excipients to facilitate sustained bioactive drug release in several major device areas [178]. Specifically, in applications for treating osteomyelitis, poly(D,L-lactide) (PDLLA), PLA, PLGA, PEG, PLA–PLGA block copolymers and other copolymers are manufactured into biodegradable beads, microspheres, melt-extruded cylinders, suspension-extruded/coated cylinders and drug-releasing coatings and matrix films [135], as used for example on orthopedic devices [179,180]. Several in vitro and in vivo studies have investigated antibiotic-loaded bone implants containing biodegradable polymers [4,128,130,173]. Predictably, release kinetics were found to be influenced by polymer molecular weight, mass ratio of polymer to antibiotic, bead size, copolymer composition, and various manufacturing parameters [173]. PGA, PLA and PLGA polyesters are all strongly hydrophobic, placing practical constraints on formulating devices with sufficient drug loading and dispersion for reliable delivery of antimicrobials. To increase hydrophilicity and other physico-chemical properties to improve drug–polymer compatibility of these popular polyesters, various block copolymer excipients or matrix analogs comprising biodegradable polyesters and poly(ethylene glycol) (PEG) additives have been developed. PLA and PLA–PEG copolymer monolithic disk implants containing gentamicin sulfate were compared in vitro [130]. PLA–PEG copolymers released antibiotics faster and exhibited more pronounced inhibitory effects against *Escherichia coli* over PLA homopolymers matrices, due to increased PEG–PLA hydrophilicity, hydration rates, drug dispersion, and PEG-assisted swelling characteristics.

Biodegradable polyhydroxyalkanoates (PHA) have also drawn substantial interest, claimed to be superior to PLGA for two primary reasons. First, as a polyester of biological origin, PHA is considered environmentally preferable. Second, PHA can be chemically and physically tailored to produce diverse physicochemical properties of clinical relevance, such as piezoelectricity claimed to induce new bone formation on load-bearing sites, and drug loading compatibility for release control [181,182]. Sulperazone® (sulbactam-cefoperazone 1:1)- and Duocid® (sulbactam-ampicillin 1:1)-loaded poly(3-hydroxybutyrate-*co*-4-hydroxyvalerate), (P(3-HB-*co*-4-HB)) rods were reported [183] as effective biodegradable implants to treat osteomyelitis. In this in vivo study, a hemolytic strain of *S. aureus* was directly delivered into the medullary cavity of rabbit tibiae. Surgery sites were almost completely healed at 6 weeks using these antibiotic-loaded P(3-HB-*co*-4-HB) intramedullary implants.

The increasing clinical use of orthopedic devices, their well-known integration issues with host tissues, and needs for improved bone defect solutions all provide new, compelling opportunities for developing novel combination device–drug delivery products with long-term osteoinductive and antimicrobial efficiency integrated into functional orthopedic implants. This challenge, combined with exciting new developments in bone biology and molecular medicine, provides a versatile set of new components for novel device designs. While biologically derived mitogens and morphogens are current attractive candidates (since modern proteomics, genomics and signaling mechanistic elucidation has identified and validated their innate biological importance), they exhibit certain unattractive recombinant cost development structures and more practical bioactivity and stability issues associated with any bioactive protein formulated into a polymer delivery system. Hence, more attractive pharma options include discovery of potent non-biological mitogen and morphogen small molecule surrogates that recapitulate the relevant biological signaling cascades in vivo without need for exogenous specific chemokine or cytokine release [184]. This would allow significant dose and formulating flexibility currently unavailable.

8. Mitogenic and morphogenic agent release for device integration and tissue regeneration

As described above in orthopedic applications, the expanding availability of increasingly diverse types of endogenous growth factors (cytokines, chemokines) and elucidation of their innate biological control mechanisms have prompted an explosion of interest in their adaptations for use in producing clinically important amounts of tissue in regenerative medicine and tissue engineering [185]. Another important application would be to enhance and accelerate implant device–tissue integration to mitigate clinical problems as discussed above in Section 7 [186–188]. Continual discoveries in both cytokine mitogens (producing cell proliferation) and morphogens (producing cell phenotypic alterations and differentiation), and chemokines across virtually all major tissue types have prompted generic approaches to growth factor delivery using controlled release [189] as well as specific growth factors delivered for specific goals, including neovasculogenesis [190,191], bone neogenesis [125], and neurogenesis [192], along with many other tissue engineering examples [193]. Because of the short half-life, pleiotropism, dynamic interaction and inter-controls in signaling, and rapid turnover of many growth factors in vivo, exogenesis introduction of these bioactive agents to promote local controlled tissue responses, tissue engineering and regenerative medicine must consider strategies to control growth factor release and therapeutically relevant bioavailability. Current costs for producing and formulating these agents also limits dosing.

Combination devices are ideally suited to overcome many of these challenges to either release or induce the local cellular environment around the implanted device to produce therapeutic levels of mitogens or morphogens directly at tissue sites, from device surfaces, and within tissue engineered matrices. The challenges are not trivial: reliable protein and gene delivery is difficult (even locally), formulation into release matrices is inefficient, control of natural cycles and pharmacodynamics is not possible, and current knowledge about how to recapitulate specific cell signaling cascades to produce effective tissue growth without adverse side effects (angioma, fibrosis, ectopic mineralization) is woefully incomplete. Nonetheless, this represents an important frontier where true bioactive molecular and cellular signaling might be exploited onto and into implanted devices using natural cascades to therapeutic ends. Important clinical endpoints are therapeutic angiogenesis, enhanced functional tissue regeneration, and improved device integration and biocompatibility with host tissue.

9. Other drug/device combination products

9.1. Wound dressings

CardioTech International, Inc. (Woburn, MA, USA) just received FDA approval to market an antibiotic-containing hydrogel wound and burn dressing intended for use in the management of partial and full-thickness wounds including venous stasis ulcers, diabetic ulcers, pressure sores, blisters, superficial wounds, abrasions, lacerations and donor sites. The wound contact surface comprises a hydrogel containing mixed antibiotic components including neomycin sulfate, bacimicin zinc and polymyxin B sulfate (10,000 Units). A second outer layer consists of a polymeric film [194]. The combination of wound dressing with direct antibiotic release provides obvious advantages over traditional wound dressings in preventing bacterial infection, especially in high-risk patients.

9.2. Cerebrospinal shunts

Infection remains a major clinical complication for use of cerebrospinal fluid (CSF) shunts and is usually managed by shunt removal, temporary insertion of an external drainage and implantation of a new shunt system. Morbidity and costs associated with this cyclic replacement process throughout the life of patients with hydrocephalus are profound. Rifampin-loaded silicone ventricular catheters capable of releasing rifampin in bacteriocidal concentrations beyond 2 months were used to prevent *S. epidermidis* and *S. aureus* colonization and infection in vitro and in vivo in a rabbit CSF infection model [195]. In contrast to control groups, no animals with rifampin-loaded catheters exhibited clinical signs of infection. After animal sacrifice, no culturable bacteria (e.g., from catheter, brain tissue, CSF, blood) were found in drug-releasing shunts, in contrast to control catheters.

9.3. Dexamethasone release and fibrosis

Implant-localized fibrosis results frequently from foreign body reactions. While some implant devices (e.g., hernial or abdominal repair meshes) may actually become stabilized by such avascular in-growth, other devices including many catheters and sensors that require specific communication with host tissues are significantly and adversely affected. Corticosteroids including dexamethasone have therefore been used to reduce acute inflammatory events responsible for fibrosis, including attenuation of inflammatory cell cascades, fibroblastic recruitment and collagen production in implant sites [196]. Locally released drug from polymer coatings on the implant, or polymer–drug microspheres in the wound site have been reported for cardiac pacing electrode tips (pacemaker leads) and implantable electro-biosensors monitoring blood glucose levels in diabetes management. Devices lacking local device-based drug release are affected by implant-associated fibrosis that limits device–tissue communication, either electrically or biochemically. Double-blinded clinical studies compared identical electrode configurations (Medtronic, Minneapolis, MN) with and without loaded steroid (dexamethasone) over long time periods in vivo (6-months

to 2-year follow-up periods) [197,198]. Constant pacing pulse duration thresholds were shown for the steroid-releasing leads, while control leads without steroids showed a significant rise in pacing thresholds. A more recent clinical study confirmed excellent performance of pacemaker leads containing dexamethasone sodium phosphate and dexamethasone acetate [199]. PLGA microspheres alone or PLGA microsphere/poly(vinyl alcohol) (PVA) hydrogel composites releasing dexamethasone have been implanted subcutaneously into rats and investigated in vitro and in vivo as a conjunctive therapy with implantable sensors [200,201]. Dexamethasone release from PLGA microsphere/PVA hydrogel composites exhibited approximately zero-order kinetics. These composites demonstrated some in vivo capability to modulate both acute and chronic inflammatory responses, and minimized fibrosis adjacent to the implants [200,201]. Such composite coating design provides some versatility for combination devices for altering drug dosing via microsphere loading into the hydrogel matrix, as well as through microsphere composition, and mixed microsphere-based dual drug administration. By contrast, glucose reporting performance of biomedical polyurethane-coated amperometric glucose sensors subdermally implanted into dogs for weeks was not significantly affected by local dexamethasone release from the polyurethane [202].

10. New approaches to deliver antimicrobial agents

Several studies have aimed to construct novel triggered drug delivery systems that release antimicrobials at specific locations at required times. These new systems are usually triggered by certain endogenous host infection responses such as inflammation-related enzymes, thrombin activity or microbial proteases. Drug-conjugated polymers [203] synthesized using 1,6-hexane diisocyanate (HDI), polycaprolactone diol (PCL), and the fluoroquinolone antibiotic, ciprofloxacin, polymerized into the polymer backbone release drug as the polymer degrades by an inflammatory cell-derived enzyme, cholesterol esterase. Microbiological assessment showed that released ciprofloxacin possessed antimicrobial activity against *P. aeruginosa* after 10 days. However, in this polymer design, the enzyme does not specifically cleave precisely at the drug conjugation position in the polymer backbone. Additionally, general hydrolysis can also degrade the polymer. Hence, fragments of ciprofloxacin bonded to different PCL and/or HDI fragments may not display antimicrobial activity and could also induce cell toxicity. Combinations of different enzymatically labile polymer–drug linkages and modification of the degradable polymer chemistry may solve this problem [204]. Significant increases in thrombin-like activity were reported in *S. aureus*-infected wounds [205]. These workers then developed a novel peptide to link an insoluble polymer matrix with antimicrobials specifically cleaved by thrombin [206]. A PVA–peptide–gentamicin conjugate was developed and investigated both in vitro and in vivo. Released gentamicin amounts were dependent on local thrombin concentration associated with *S. aureus* infection with bacteriocidal effects observed in animal models of *S. aureus* infection.

These two sophisticated, new polymer–drug conjugate examples provide some new directions for future controlled, local antimicrobial release strategies. Triggered or stimuli-sensitive approaches to new combination medical devices, prompting antimicrobial or more general drug release with pre-programmed temporal and spatial profiles are possible. PVA is a candidate occlusive wound dressing material; HDI and PCL could also be co-processed to form a biodegradable implantable device. Furthermore, new discoveries in microbiological phenotypes, proteomics and infection mechanisms should allow development of new pathogen-specific cleavable conjugates, new classes of drugs and new anti-adhesive or anti-proliferative pharmacological targets exploited in combination with implantable devices. This strategy could borrow from better-developed enzyme-cleavable or targeted pharmaceutical approaches for polymer–prodrug formulations in other therapeutic areas [207–209].

11. Conclusions

With the recent proven clinical success of precedent DES systems, recognition of the therapeutic value of locally released antimicrobials in several clinical device classes including catheters and bone cements, and launch of an antibiotic wound dressing, local drug delivery/device combination therapy is becoming an exciting new biomedical frontier, with associated diverse creative strategies newly available. For many reasons, the surface of any indwelling medical device provides an excellent platform for the formation of bacterial colonies or biofilms, producing life-threatening infections across most types of implanted devices. In the case of antimicrobial strategies, many different biomaterial approaches, different polymer coating chemistries and architectures, and different antibiotics have been studied and, taken together, exhibit unique opportunities to help mitigate device-related infections. These medical devices also provide drug reservoirs for local delivery to infection sites with minimal systemic toxicity, and capabilities for advanced pharmacokinetics, drug mixtures, complex release mechanisms and site-sensitive stimulated release controls. For other types of medical device functional and integrative challenges, combination approaches that utilize new developments in local cell, tissue and molecular biology manipulation might be accomplished. These include new activities from delivered mitogens and morphogens, controlled apoptosis and differentiation, enhanced host cell recruitment, tissue regeneration, wound healing, vasculogenesis, and tissue–implant integration, along with limited destructive inflammatory reactions, infection and fibrosis. Increasing appreciation for host tissue biology in the implant site will

lead to breakthroughs in this area where combination therapies might readily assist.

With the establishment of US FDA's Office of Combination Products and other equivalent oversite organizations world-wide, exciting device precedents, clinical successes, and corresponding new codes, pharmaceutical companies and device manufactures are actively seeking development opportunities for new drug/device combination products based on their existing drug and device products. This could result in a blurring of business plans between traditional drug and biomedical device companies as the two approaches slowly converge in the combination sector, and readily require the synergy of closely partnered interaction (or even mergers) to fully capitalize on innovative combination products. Additionally, combination devices up for FDA approval that exploit advantages of an already-approved therapeutic entity could enjoy expedited approval [1]. While this provides the most direct route to product, improved performance might better be gained from de novo device design that anticipates and exploits drug delivery and device in vivo performance from de novo design conception.

In order to take experimental model studies into reliable clinical use, many further issues must be considered and resolved. Device biomaterials must remain biocompatible in the presence of drug modifications, and in some cases, biodegradable materials are preferred to produce required drug release control and duration. Bacterial resistance to antimicrobials, especially to locally released antibiotics must be carefully considered and monitored precisely at the point of delivery. Mechanical and other functional medical device performance properties must not be compromised by combination with drug/antimicrobial release and associated manufacturing processes. Significantly, the commonly observed disconnect between in vitro and in vivo efficacy and pharmacology testing must be overcome with direct validation in a clinical context: mechanisms of action and therapeutic benefit should be clearly elucidated and not remain anecdotal.

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References

[1] Dubin CH. A one-two punch: drug/medical device combination products are taking healthcare in a new direction. Is the pharmaceutical industry prepared? Drug Deliv Technol 2004;4(4).
[2] United States Food and Drug Administration; 21 CFR ?3.2(e); European Commission DG Enterprise, Directorate G, Unit 4, MEDDEV 2.1/3 rev 2 (Council Directive 90/385/EEC, 65/65/EEC and 93/42/EEC), see http://europa.eu.int/comm/enterprise/medical_devices/meddev/2_1_3____07-2001.pdf
[3] Ansel HC, Popovich NG, Loyd V, Allen J. Pharmaceutical dosage forms and drug delivery systems, 6th ed. Media: Williams & Wikins; 1995.
[4] Liu S-J, Ueng SW-N, Lin S-S, Chan E-C. In vivo release of vancomycin from biodegradable beads. J Biomed Mater Res 2002; 63(6):807–13.
[5] Gransden WR. Antibiotic resistance. Nosocomial gram-negative infection. J Med Microbiol 1997;46(6):436–9.
[6] Zhang X, Wyss UP, Pichora D, Goosen MFA. Biodegradable controlled antibiotic release devices for osteomyelitis: optimization of release properties. J Pharm Pharmacol 1994;46(9):718–24.
[7] Khardori N, Yassien M. Biofilms in device-related infections. J Ind Microbiol 1995;15(3):141–7.
[8] Gristina AG, Naylor P, Myrvik Q. Infections from biomaterials and implants: a race for the surface. Med Prog Technol 1988–1989; 14(3–4):205–24.
[9] Stoodley P, Sauer K, Davies DG, Costerton JW. Biofilms as complex differentiated communities. Annu Rev Microbiol 2002;56: 187–209.
[10] Finch RG, Pritchard DI, Bycroft BW, Williams P, Stewart GSAB. Quorum sensing: a novel target for anti-infective therapy. J Antimicrob Chemother 1998;42(5):569–71.
[11] March JC, Bentley WE. Quorum sensing and bacterial cross-talk in biotechnology. Curr Opin Biotechnol 2004;15(5):495–502.
[12] Barton AJ, Sagers RD, Pitt WG. Bacterial adhesion to orthopedic implant polymers. J Biomed Mater Res 1996;30(3):403–10.
[13] Roberts RR, Scott II RD, Cordell R, Solomon SL, Steele L, Kampe LM, et al. The use of economic modeling to determine the hospital costs associated with nosocomial infections. Clin Infect Dis 2003;36(11):1424–32.
[14] Stone PW, Larson E, Kawar LN. A systematic audit of economic evidence linking nosocomial infections and infection control interventions: 1990–2000. Am J Infect Control 2002;30(3):145–52.
[15] Haley RW, Culver DH, White JW, Morgan WM, Emori TG. The nationwide nosocomial infection rate. A new need for vital statistics. Am J Epidemiol 1985;121(2):159–67.
[16] Pascual A. Pathogenesis of catheter-related infections: lessons for new designs. Clin Microbiol Infect 2002;8(5):256–64.
[17] Gruntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet 1978;1:263.
[18] Fattori R, Piva T. Drug-eluting stents in vascular intervention. Lancet 2003;361(9353):247–9.
[19] Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994;331(8): 496–501.
[20] Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;331(8): 489–95.
[21] Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C. Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review. Health Technol Assess 2000;4(23): 1–153.
[22] Indolfi C, Mongiardo A, Curcio A, Torella D. Molecular mechanisms of in-stent restenosis and approach to therapy with eluting stents. Trends Cardiovasc Med 2003;13(4):142–8.
[23] Serruys PW, Foley DP, Jackson G, Bonnier H, Macaya C, Vrolix M, et al. A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty: final results of the fluvastatin angiographic restenosis (FLARE) trial. Eur Heart J 1999;20(1):58–69.
[24] Serruys PW, Foley DP, Pieper M, Kleijne JA, De Feyter PJ. A multicentre randomized placebo controlled clinical trial of trapidil

for prevention of restenosis after coronary stenting, measured by 3-D intravascular ultrasound. Eur Heart J 2001;22(20):1938–47.
[25] Holmes Jr DR, Savage M, LaBlanche JM, Grip L, Serruys PW, Fitzgerald P, et al. Results of prevention of restenosis with tranilast and its outcomes (PRESTO) trial. Circulation 2002;106(10): 1243–50.
[26] Birkenhauer P, Yang Z, Gander B. Preventing restenosis in early drug-eluting stent era: recent developments and future perspectives. J Pharm Pharmacol 2004;56(11):1339–56.
[27] Chan S. Targeting the mammalian target of rapamycin (mTOR): a new approach to treating cancer. Br J Cancer 2004;91(8):1420–4.
[28] Poon M, Badimon Juan J, Fuster V. Overcoming restenosis with sirolimus: from alphabet soup to clinical reality. Lancet 2002; 359(9306):619–22.
[29] Morice M-C, Serruys PW, Sousa JE, Fajadet J, Hayashi EB, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002; 346(23):1773–80.
[30] Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003;349(14):1315–23.
[31] Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). Lancet 2003;362(9390):1093–9.
[32] Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoye A, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the rapamycin-eluting stent evaluated at Rotterdam cardiology hospital (RESEARCH) registry. Circulation 2004; 109(2):190–5.
[33] Tanabe K, Regar E, Lee CH, Hoye A, van der Giessen WJ, Serruys PW. Local drug delivery using coated stents: new developments and future perspectives. Curr Pharm Design 2004;10(4):357–67.
[34] Yamaguchi T. Drug-eluting stent trial. Cardiac Practice 2004; 15(4):417–9.
[35] Schwartz RS, Chronos NA, Virmani R. Preclinical restenosis models and drug-eluting stents: still important, still much to learn. J Am Coll Cardiol 2004;44(7):1373–85.
[36] Robinson KA, Chronos NA, Schieffer E, Palmer SJ, Cipolla GD, Milner PG, et al. Endoluminal local delivery of PCNA/cdc2 antisense oligonucleotides by porous balloon catheter does not affect neointima formation or vessel size in the pig coronary artery model of postangioplasty restenosis. Cathet Cardiovasc Diagn 1997; 41(3):348–53.
[37] Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004;350(3):221–31.
[38] Morice M-C. REALITY trial data. American College of Cardiology annual meeting 2005.
[39] Degertekin M, Serruys Patrick W, Tanabe K, Lee Chi H, Sousa JE, Colombo A, et al. Long-term follow-up of incomplete stent apposition in patients who received sirolimus-eluting stent for de novo coronary lesions: an intravascular ultrasound analysis. Circulation 2003;108(22):2747–50.
[40] Eberhart RC, Su S-H, Nguyen Kytai T, Zilberman M, Tang L, Nelson KD, et al. Bioresorbable polymeric stents: current status and future promise. J Biomater Sci Polym Ed 2003;14(4):299–312.
[41] Herrmann R, Schmidmaier G, Markl B, Resch A, Hahnel I, Stemberger A, et al. Antithrombogenic coating of stents using a biodegradable drug delivery technology. Thromb Haemost 1999; 82(1):51–7.
[42] Hietala E-M, Salminen U-S, Stahls A, Valimaa T, Maasilta P, Tormala P, et al. Biodegradation of the copolymeric polylactide stent: long-term follow-up in a rabbit aorta model. J Vasc Res 2001; 38(4):361–9.
[43] Rodgers Campbell DK. Drug-eluting stents: role of stent design, delivery vehicle, and drug selection. Rev Cardiovasc Med 2002; 3(Suppl. 5):S10–5.
[44] Hwang C-W, Wu D, Edelman Elazer R. Impact of transport and drug properties on the local pharmacology of drug-eluting stents. Int J Cardiovasc Interven 2003;5(1):7–12.
[45] Hwang C-W, Edelman ER. Arterial ultrastructure influences transport of locally delivered drugs. Circ Res 2002;90(7):826–32.
[46] Finkelstein A, McClean D, Kar S, Takizawa K, Varghese K, Baek N, et al. Local drug delivery via a coronary stent with programmable release pharmacokinetics. Circulation 2003;107(5):777–84.
[47] Shammas NW, Dippel EJ. Evidence-based management of peripheral vascular disease. Curr Atheroscler Rep 2005;7(5):358–63.
[48] Carter AJ, Robinson K, Gibson L, Haller S, Brodeur A, Collingwood R, et al. Experimental feasibility and efficacy of a novel modular segmented stent with in-situ programmable length and drug elution from a biodegradable polymer coating. Am J Cardiol 2005;96(Suppl. 7A):7H.
[49] Lorenzo A. Xtent debuts customizable stents to positive reviews. Med Dev Daily 2005;9(203):1.
[50] van Berkel AM, van Marle J, Groen AK, Bruno MJ. Mechanisms of biliary stent clogging: confocal laser scanning and scanning electron microscopy. Endoscopy 2005;37(8):729–34.
[51] Chatzinikolaou I, Raad II. Central venous catheter related infections: the role of antimicrobial catheters. Mol Cell Biol Crit Care Med 2003;3:187–215.
[52] Viot M. Intravenous access: related problems in oncology. Int J Antimicrob Agents 2000;16(2):165–8.
[53] Pai MP, Pendland SL, Danziger LH. Antimicrobial-coated/bonded and -impregnated intravascular catheters. Ann Pharmacother 2001;35(10):1255–63.
[54] Jagpal R, Greco RS. Studies of a graphite–benzalkonium–oxacillin surface. Am Surg 1979;45(12):774–9.
[55] Greco RS, Harvey RA. The role of antibiotic bonding in the prevention of vascular prosthetic infections. Ann Surg 1982; 195(2):168–71.
[56] Kamal GD, Pfaller MA, Rempe LE, Jebson PJ. Reduced intravascular catheter infection by antibiotic bonding. A prospective, randomized, controlled trial. JAMA 1991;265(18):2364–8.
[57] Zhang X. Anti-infective coatings reduce device-related infections. Antimicrob/Anti-infect Mater 2000:149–80.
[58] Schierholz JM, Rump AF, Pulverer G, Beuth J. Anti-infective catheters: novel strategies to prevent nosocomial infections in oncology. Anticancer Res 1998;18(5B):3629–38.
[59] Raad I, Darouiche R, Hachem R, Mansouri M, Bodey GP. The broad-spectrum activity and efficacy of catheters coated with minocycline and rifampin. J Infect Dis 1996;173(2):418–24.
[60] Darouiche RO, Raad II, Heard SO, Thornby JI, Wenker OC, Gabrielli A, et al. A comparison of two antimicrobial-impregnated central venous catheters. Catheter Study Group. N Engl J Med 1999;340(1):1–8.
[61] Veenstra DL, Saint S, Saha S, Lumley T, Sullivan SD. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. JAMA 1999; 281(3):261–7.
[62] Marik PE, Abraham G, Careau P, Varon J, Fromm Jr RE. The ex vivo antimicrobial activity and colonization rate of two antimicrobial-bonded central venous catheters. Crit Care Med 1999;27(6): 1128–31.
[63] Raad I, Darouiche R, Dupuis J, Abi-Said D, Gabrielli A, Hachem R, et al. Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections. A randomized, double-blind trial. Ann Intern Med 1997;127(4):267–74.
[64] Raad II, Darouiche RO, Hachem R, Abi-Said D, Safar H, Darnule T, et al. Antimicrobial durability and rare ultrastructural colonization of indwelling central catheters coated with minocycline and rifampin. Crit Care Med 1998;26(2):219–24.

[65] Raad II, Hanna HA. Intravascular catheter-related infections new horizons and recent advances. Arch Intern Med 2002;162(8): 871–8.
[66] Maki DG, Stolz SM, Wheeler S, Mermel LA. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter. A randomized, controlled trial. Ann Intern Med 1997;127(4):257–66.
[67] Bach A, Schmidt H, Boettiger B, Schreiber B, Boehrer H, Motsch J, et al. Retention of antibacterial activity and bacterial colonization of antiseptic-bonded central venous catheters. J Antimicrob Chemother 1996;37(2):315–22.
[68] George SJ, Vuddamalay P, Boscoe MJ. Antiseptic-impregnated central venous catheters reduce the incidence of bacterial colonization and associated infection in immunocompromised transplant patients. Eur J Anaesthesiol 1997;14(4):428–31.
[69] Heard SO, Wagle M, Vijayakumar E, McLean S, Brueggemann A, Napolitano LM, et al. Influence of triple-lumen central venous catheters coated with chlorhexidine and silver sulfadiazine on the incidence of catheter-related bacteremia. Arch Intern Med 1998; 158(1):81–7.
[70] Loo S, van Heerden PV, Gollege CL, Roberts BL, Power BM. Infection in central lines: antiseptic-impregnated vs standard non-impregnated catheters. Anaesth Intensive Care 1997;25(6):637–9.
[71] Tennenberg S, Lieser M, McCurdy B, Boomer G, Howington E, Newman C, et al. A prospective randomized trial of an antibiotic- and antiseptic-coated central venous catheter in the prevention of catheter-related infections. Arch Surg 1997;132(12):1348–51.
[72] van Heerden PV, Webb SA, Fong S, Golledge CL, Roberts BL, Thompson WR. Central venous catheters revisited—infection rates and an assessment of the new Fibrin Analysing System brush. Anaesth Intensive Care 1996;24(3):330–3.
[73] Logghe C, Van Ossel C, D'Hoore W, Ezzedine H, Wauters G, Haxhe JJ. Evaluation of chlorhexidine and silver-sulfadiazine impregnated central venous catheters for the prevention of bloodstream infection in leukaemic patients: a randomized controlled trial. J Hosp Infect 1997;37(2):145–56.
[74] Pemberton LB, Ross V, Cuddy P, Kremer H, Fessler T, McGurk E. No difference in catheter sepsis between standard and antiseptic central venous catheters. A prospective randomized trial. Arch Surg 1996;131(9):986–9.
[75] Ciresi DL, Albrecht RM, Volkers PA, Scholten DJ. Failure of antiseptic bonding to prevent central venous catheter-related infection and sepsis. Am Surg 1996;62(8):641–6.
[76] Ellis ME, Rhydderch D, Zwaan F, Guy ML, Baillie F. High incidence of line-related infection and mechanical failure of an antiseptic impregnated central venous catheter in highly immunocompromised patients. Scand J Infect Dis 1996;28(1):91–3.
[77] Gaonkar TA, Modak SM. Comparison of microbial adherence to antiseptic and antibiotic central venous catheters using a novel agar subcutaneous infection model. J Antimicrob Chemother 2003;52(3): 389–96.
[78] Yorganci K, Krepel C, Weigelt JA, Edmiston CE. In vitro evaluation of the antibacterial activity of three different central venous catheters against Gram-positive bacteria. Eur J Clin Microbiol Infect Dis 2002;21(5):379–84.
[79] Schierholz JM, Fleck C, Beuth J, Pulverer G. The antimicrobial efficacy of a new central venous catheter with long-term broad-spectrum activity. J Antimicrob Chemother 2000;46:45–50.
[80] Yuecel N, Lefering R, Maegele M, Max M, Rossaint R, Koch A, et al. Reduced colonization and infection with miconazole-rifampicin modified central venous catheters: a randomized controlled clinical trial. J Antimicrob Chemother 2004;54(6):1109–15.
[81] Levy SB. Antibiotic resistance—the problem intensifies. Adv Drug Deliv Rev 2005;57(10):1446–50.
[82] Costerton JW, Stewart PS. Battling biofilms. Sci Am 2001;285(1): 74–81.
[83] Virk A, Steckelberg JM. Clinical aspects of antimicrobial resistance. Mayo Clin Proc 2000;75(2):200–14.
[84] Tambe SM, Sampath L, Modak SM. In vitro evaluation of the risk of developing bacterial resistance to antiseptics and antibiotics used in medical devices. J Antimicrob Chemother 2001;47(5):589–98.
[85] Trooskin SZ, Mikulaschek AW. Biomaterials used for catheters. Implant Biol 1994:267–86.
[86] Szycher M, editor. Biocompatible polymers, metals, and composites. Lancaster, PA: Technomic; 1983.
[87] Crocker KS, Devereaux GB, Ashmore DL, Coker MH. Clinical evaluation of elastomeric hydrogel peripheral catheters during home infusion therapy. J Intraven Nurs 1990;13(2):89–97.
[88] Piozzi A, Francolini I, Occhiaperti L, Venditti M, Marconi W. Antimicrobial activity of polyurethanes coated with antibiotics: a new approach to the realization of medical devices exempt from microbial colonization. Int J Pharm 2004;280(1–2):173–83.
[89] Raad I, Buzaid A, Rhyne J, Hachem R, Darouiche R, Safar H, et al. Minocycline and ethylenediaminetetraacetate for the prevention of recurrent vascular catheter infections. Clin Infect Dis 1997;25(1): 149–51.
[90] Pearson ML, Abrutyn E. Reducing the risk for catheter-related infections: a new strategy. Ann Intern Med 1997;127(4):304–6.
[91] Crnich CJ, Maki DG. Are antimicrobial-impregnated catheters effective? Don't throw out the baby with the bathwater. Clin Infect Dis 2004;38(9):1287–92.
[92] McConnell SA, Gubbins PO, Anaissie EJ. Are antimicrobial-impregnated catheters effective? Replace the water and grab your washcloth, because we have a baby to wash. Clin Infect Dis 2004;39(12):1829–33.
[93] Haley RW, Hooton TM, Culver DH, Stanley RC, Emori TG, Hardison CD, et al. Nosocomial infections in US hospitals, 1975–1976: estimated frequency by selected characteristics of patients. Am J Med 1981;70(4):947–59.
[94] Cho YW, Park JH, Kim SH, Cho Y-H, Choi JM, Shin HJ, et al. Gentamicin-releasing urethral catheter for short-term catheterization. J Biomater Sci Polym Ed 2003;14(9):963–72.
[95] Darouiche RO. Device-associated infections: a macroproblem that starts with microadherence. Clin Infect Dis 2001;33(9):1567–72.
[96] Cormio L, La Forgia P, Siitonen A, Ruutu M, Tormala P, Talja M. Immersion in antibiotic solution prevents bacterial adhesion onto biodegradable prostatic stents. Br J Urol 1997;79(3):409–13.
[97] Cormio L, La Forgia P, La Forgia D, Siitonen A, Ruutu M. Bacterial adhesion to urethral catheters: role of coating materials and immersion in antibiotic solution. Eur Urol 2001;40(3):354–9.
[98] Melaiye A, Youngs WJ. Silver and its application as an antimicrobial agent. Expert Opin Therap Patents 2005;15(2):125–30.
[99] Saint S, Elmore JG, Sullivan SD, Emerson SS, Koepsell TD. The efficacy of silver alloy-coated urinary catheters in preventing urinary tract infection: a meta-analysis. Am J Med 1998;105(3):236–41.
[100] Liedberg H. Catheter induced urethral inflammatory reaction and urinary tract infection. An experimental and clinical study. Scand J Urol Nephrol Suppl 1989;124:1–43.
[101] Brosnahan J, Jull A, Tracy C. Types of urethral catheters for management of short-term voiding problems in hospitalised adults. J Urol 2005;173(3):846–7.
[102] Ahearn DG, Grace DT, Jennings MJ, Borazjani RN, Boles KJ, Rose LJ, et al. Effects of hydrogel/silver coatings on in vitro adhesion to catheters of bacteria associated with urinary tract infections. Curr Microbiol 2000;41(2):120–5.
[103] Maki DG, Tambyah PA. Engineering out the risk for infection with urinary catheters. Emerg Infect Dis 2001;7(2):342–7.
[104] Bologna RA, Tu LM, Polansky M, Fraimow HD, Gordon DA, Whitmore KE. Hydrogel/silver ion-coated urinary catheter reduces nosocomial urinary tract infection rates in intensive care unit patients: a multicenter study. Urology 1999;54(6):982–7.
[105] Verleyen P, De Ridder D, Van Poppel H, Baert L. Clinical application of the Bardex IC Foley catheter. Eur Urol 1999; 36(3):240–6.
[106] Darouiche RO, Smith Jr JA, Hanna H, Dhabuwala CB, Steiner MS, Babaian RJ, et al. Efficacy of antimicrobial-impregnated bladder

catheters in reducing catheter-associated bacteriuria: a prospective, randomized, multicenter clinical trial. Urology 1999;54(6):976–81.
[107] Silver S. Bacterial silver resistance: molecular biology and uses and misuses of silver compounds. FEMS Microbiol Rev 2003;27(2–3): 341–53.
[108] Richards CL, Hoffman KC, Bernhard JM, Winslow SD, Norman JC, Whalen RL. Development and characterization of an infection inhibiting urinary catheter. ASAIO J 2003;49(4):449–53.
[109] Al-Habdan I, Sadat-Ali M, Corea James R, Al-Othman A, Kamal Baher A, Shriyan Devdas S. Assessment of nosocomial urinary tract infections in orthopaedic patients: a prospective and comparative study using two different catheters. Int Surg 2003;88(3):152–4.
[110] Nishiguchi S, Kato H, Fujita H, Oka M, Kim HM, Kokubo T, et al. Titanium metals form direct bonding to bone after alkali and heat treatments. Biomaterials 2001;22(18):2525–33.
[111] Sporer SM, Paprosky WG. Biologic fixation and bone ingrowth. Orthop Clin North Am 2005;36(1):105–111, vii.
[112] Hirakawa K, Jacobs Joshua J, Urban R, Saito T. Mechanisms of failure of total hip replacements: lessons learned from retrieval studies. Clin Orthop 2004(420):10–7.
[113] Morscher EW. Failures and successes in total hip replacement—why good ideas may not work. Scand J Surg 2003;92(2):113–20.
[114] Praemer A, Furner S, Rice DP. Musculoskeletal conditions in the United States. Park Ridge, IL: American Academy of Orthopedic Surgeons; 1992.
[115] Gerstenfeld LC, Cullinane DM, Barnes GL, Graves DT, Einhorn TA. Fracture healing as a post-natal developmental process: molecular, spatial, and temporal aspects of its regulation. J Cell Biochem 2003;88(5):873–84.
[116] Samartzis D, Khanna N, Shen Francis H, An Howard S. Update on bone morphogenetic proteins and their application in spine surgery. J Am Coll Surg 2005;200(2):236–48.
[117] Luginbuehl V, Meinel L, Merkle HP, Gander B. Localized delivery of growth factors for bone repair. Eur J Pharm Biopharm 2004; 58(2):197–208.
[118] Leach JK, Mooney DJ. Bone engineering by controlled delivery of osteoinductive molecules and cells. Expert Opin Biol Ther 2004; 4(7):1015–27.
[119] Kandziora F, Bail H, Schmidmaier G, Schollmeier G, Scholz M, Knispel C, et al. Bone morphogenetic protein-2 application by a poly(D,L-lactide)-coated interbody cage: in vivo results of a new carrier for growth factors. J Neurosurg 2002;97(1, Suppl.):40–8.
[120] Seeherman H, Wozney J, Li R. Bone morphogenetic protein delivery systems. Spine 2002;27(16 Suppl. 1):S16–23.
[121] Hannallah D, Peterson B, Lieberman Jay R, Fu Freddie H, Huard J. Gene therapy in orthopaedic surgery. J Bone Joint Surg Am 2002;84(6):1046–61.
[122] Winn SR, Schmitt JM, Buck D, Hu Y, Grainger D, Hollinger JO. Tissue-engineered bone biomimetic to regenerate calvarial critical-sized defects in athymic rats. J Biomed Mater Res 1999;45(4): 414–21.
[123] Arinzeh TL, Tran T, McAlary J, Daculsi G. A comparative study of biphasic calcium phosphate ceramics for human mesenchymal stem-cell-induced bone formation. Biomaterials 2005;26(17):3631–8.
[124] Petite H, Viateau V, Bensaid W, Meunier A, de Pollak C, Bourguignon M, et al. Tissue-engineered bone regeneration. Nat Biotechnol 2000;18(9):959–63.
[125] Mistry AS, Mikos AG. Tissue engineering strategies for bone regeneration. Adv Biochem Eng Biotechnol 2005;94:1–22.
[126] Winnger DA, Fass RJ. Antibiotic-impregnated cement and beads for orthopedic infections. Antimicrob Agents Chemother 1996;40(12):2675–9.
[127] Frutos CP, Diez PE, Barrales-Rienda JM, Frutos G. Validation and in vitro characterization of antibiotic-loaded bone cement release. Int J Pharm 2000;209(1–2):15–26.
[128] Baro M, Sanchez E, Delgado A, Perera A, Evora C. In vitro–in vivo characterization of gentamicin bone implants. J Controlled Release 2002;83(3):353–64.
[129] Trippel SB. Antibiotic-impregnated cement in total joint arthroplasty. J Bone Joint Surg Am 1986;68(8):1297–302.
[130] Huang YY, Chung TW. Microencapsulation of gentamicin in biodegradable PLA and/or PLA/PEG copolymer. J Microencapsul 2001;18(4):457–65.
[131] Yu D, Wong J, Matsuda Y, Fox JL, Higuchi WI, Otsuka M. Self-setting hydroxyapatite cement: a novel skeletal drug delivery system for antibiotics. J Pharm Sci 1992;81(6):529–31.
[132] Harper EJ. Bioactive bone cements. Proc Inst Mech Eng [H] 1998; 212(2):113–20.
[133] Stengel D, Bauwens K, Sehouli J, Ekkernkamp A, Porzsolt F. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. Lancet Infect Dis 2001;1(3):175–88.
[134] Edmiston Jr CE, Goheen MP. Studying bacterial adhesion to antibiotic impregnated polymethyl methacrylate. In: An YH, Friedman RJ, editors. Handbook of bacterial adhesion. Totowa, NJ: Humana Press Inc.; 2000. p. 599–608.
[135] Kanellakopoulou K, Giamarellos-Bourboulis EJ. Carrier systems for the local delivery of antibiotics in bone infections. Drugs 2000;59(6):1223–32.
[136] Downes S. Methods for improving drug release from poly(methyl methacrylate) bone cement. Clin Mater 1991;7(3):227–31.
[137] Virto MR, Frutos P, Torrado S, Frutos G. Gentamicin release from modified acrylic bone cements with lactose and hydroxypropylmethylcellulose. Biomaterials 2002;24(1):79–87.
[138] van de Belt H, Neut D, Uges DRA, Schenk W, van Horn JR, van der Mei HC, et al. Surface roughness, porosity and wettability of gentamicin-loaded bone cements and their antibiotic release. Biomaterials 2000;21(19):1981–7.
[139] Picknell B, Mizen L, Sutherland R. Antibacterial activity of antibiotics in acrylic bone cement. J Bone Joint Surg Br 1977;59-B(3):302–7.
[140] Masri BA, Duncan CP, Beauchamp CP, Paris NJ, Arntorp J. Effect of varying surface patterns on antibiotic elution from antibiotic-loaded bone cement. J Arthroplasty 1995;10(4):453–9.
[141] Elson RA, Jephcott AE, McGechie DB, Verettas D. Bacterial infection and acrylic cement in the rat. J Bone Joint Surg Br 1977;59-B(4):452–7.
[142] Nijhof MW, Stallmann HP, Vogely HC, Fleer A, Schouls LM, Dhert WJA, et al. Prevention of infection with tobramycin-containing bone cement or systemic cefazolin in an animal model. J Biomed Mater Res 2000;52(4):709–15.
[143] Nijhof MW, Fleer A, Hardus K, Vogely HC, Schouls LM, Verbout AJ, et al. Tobramycin-containing bone cement and systemic cefazolin in a one-stage revision. Treatment of infection in a rabbit model. J Biomed Mater Res 2001;58(6):747–53.
[144] Josefsson G, Gudmundsson G, Kolmert L, Wijkstrom S. Prophylaxis with systemic antibiotics versus gentamicin bone cement in total hip arthroplasty. A five-year survey of 1688 hips. Clin Orthop 1990(253):173–8.
[145] Chiu F-Y, Chen C-M, Lin Chien-Fu J, Lo W-H. Cefuroxime-impregnated cement in primary total knee arthroplasty: a prospective, randomized study of three hundred and forty knees. J Bone Joint Surg Am 2002;84-A(5):759–62.
[146] Scott CP, Higham PA. Antibiotic bone cement for the treatment of *Pseudomonas aeruginosa* in joint arthroplasty: comparison of tobramycin and gentamicin-loaded cements. J Biomed Mater Res B: Appl Biomater 2003;64B(2):94–8.
[147] Scott CP, Higham PA, Dumbleton JH. Effectiveness of bone cement containing tobramycin. An in vitro susceptibility study of 99 organisms found in infected joint arthroplasty. J Bone Joint Surg Br 1999;81(3):440–3.
[148] Wade A, Reynolds JE. The extra pharmacopoeia: incorporating squire's "Companion", 27th ed. London: The Pharmaceutical Press; 1977.
[149] Nelson CL, Griffin FM, Harrison BH, Cooper RE. In vitro elution characteristics of commercially and noncommercially prepared antibiotic PMMA beads. Clin Orthop 1992(284):303–9.

[150] Sterling GJ, Crawford S, Potter JH, Koerbin G, Crawford R. The pharmacokinetics of Simplex-tobramycin bone cement. J Bone Joint Surg Br 2003;85(5):646–9.
[151] Buchholz HW, Elson RA, Heinert K. Antibiotic-loaded acrylic cement: current concepts. Clin Orthop 1984(190):96–108.
[152] Marks KE, Nelson CL, Lautenschlager EP. Antibiotic-impregnated acrylic bone cement. J Bone Joint Surg Am 1976;58(3):358–64.
[153] Walenkamp GH. Chronic osteomyelitis. Acta Orthop Scand 1997; 68(5):497–506.
[154] Heck D, Rosenberg A, Schink-Ascani M, Garbus S, Kiewitt T. Use of antibiotic-impregnated cement during hip and knee arthroplasty in the United States. J Arthroplasty 1995;10(4):470–5.
[155] Fish DN, Hoffman HM, Danziger LH. Antibiotic-impregnated cement use in US hospitals. Am J Hosp Pharm 1992;49(10): 2469–74.
[156] Wahlig H, Dingeldein E, Bergmann R, Reuss K. The release of gentamicin from polymethylmethacrylate beads. An experimental and pharmacokinetic study. J Bone Joint Surg Br 1978;60-B(2): 270–5.
[157] Hoff SF, Fitzgerald RH, Kelly PJ. The depot administration of penicillin G and gentamicin in acrylic bone cement. J Bone Joint Surg Am 1981;63-A(5):798–804.
[158] Bunetel L, Segui A, Cormier M, Percheron E, Langlais F. Release of gentamicin from acrylic bone cement. Clin Pharmacokinet 1989; 17(4):291–7.
[159] Neut D, Van de Belt H, Stokroos I, Van Horn JR, Van der Mei HC, Busscher HJ. Biomaterial-associated infection of gentamicin-loaded PMMA beads in orthopedic revision surgery. J Antimicrob Chemother 2001;47(6):885–91.
[160] Faber C, Stallmann HP, Lyaruu DM, de Blieck JMA, Bervoets TJM, van Nieuw Amerongen A, et al. Release of antimicrobial peptide Dhvar-5 from polymethyl methacrylate beads. J Antimicrob Chemother 2003;51(6):1359–64.
[161] Yang J-M, You J-W, Chen H-L, Shih C-H. Calorimetric characterization of the formation of acrylic type bone cements. J Biomed Mater Res 1996;33(2):83–8.
[162] Ricci J, Alexander H, Nadkarni P, Hawkins M, Turner J, Rosenblum S, et al. Biological mechanisms of calcium sulfate replacement by bone. In: Davies JE, editor. Bone engineering. Toronto, Canada: EM Squared Incorporated; 2000. p. 332–44.
[163] Hench LL. Bioceramics: from concept to clinic. J Am Ceram Soc 1991;74(7):1487–510.
[164] Martins VCA, Goissis G, Ribeiro AC, Marcantonio Jr E, Bet MR. The controlled release of antibiotic by hydroxyapatite-anionic collagen composites. Artif Organs 1998;22(3):215–21.
[165] Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963;52(12):1145–9.
[166] Kurashina K, Kurita H, Kotani A, Takeuchi H, Hirano M. In vivo study of a calcium phosphate cement consisting of a-tricalcium phosphate/dicalcium phosphate dibasic/tetracalcium phosphate monoxide. Biomaterials 1997;18(2):147–51.
[167] Gao TJ, Lindholm TS, Kommonen B, Ragni P, Paronzini A, Lindholm TC. Microscopic evaluation of bone-implant contact between hydroxyapatite, bioactive glass and tricalcium phosphate implanted in sheep kiaphyseal defects. Biomaterials 1995;16(15): 1175–9.
[168] Flautre B, Pasquier G, Blary MC, Anselme K, Hardouin P. Evaluation of hydroxyapatite powder coated with collagen as an injectable bone substitute: microscopic study in rabbit. J Mater Sci Mater Med 1996;7(2):63–7.
[169] Domb AJ, Manor N, Elmalak O. Biodegradable bone cement compositions based on acrylate and epoxide terminated poly(propylene fumarate) oligomers and calcium salt compositions. Biomaterials 1996;17(4):411–7.
[170] Ali SAM, Doherty PJ, Williams DF. Mechanisms of polymer degradation in implantable devices. 2. Poly(DL-lactic acid). J Biomed Mater Res 1993;27(11):1409–18.
[171] Nie L, Nicolau DP, Nightingale CH, Browner BD, Quintiliani R. In vitro elution of ofloxacin from a bioabsorbable polymer. Acta Orthop Scand 1995;66(4):365–8.
[172] Lin SS, Ueng SW, Liu SJ, Chan EC, Chao EK, Tsai CH, et al. Development of a biodegradable antibiotic delivery system. Clin Orthop 1999(362):240–50.
[173] Liu S-J, Ueng SW-N, Chan E-C, Lin S-S, Tsai C-H, Wei F-C, et al. In vitro elution of vancomycin from biodegradable beads. J Biomed Mater Res 1999;48(5):613–20.
[174] Gander B, Meinel L, Walter E, Merkle HP. Polymers as a platform for drug delivery: reviewing our current portfolio on poly(lactide-*co*-glycolide) (PLGA) microspheres. Chimica 2001;55(3):212–7.
[175] Anderson JM, Shive MS. Biodegradation and biocompatibility of PLA and PLGA microspheres. Adv Drug Deliv Rev 1997;28(1): 5–24.
[176] Ikada Y, Tsuji H. Biodegradable polyesters for medical and ecological applications. Macromol Rapid Commun 2000;21(3): 117–32.
[177] Huh KM, Cho YW, Park K. PLGA–PEG block copolymers for drug formulations. Drug Deliv Technol 2003; 3 (5): 42, 44–9.
[178] Mi F-L, Shyu S-S, Lin Y-M, Wu Y-B, Peng C-K, Tsai Y-H. Chitin/PLGA blend microspheres as a biodegradable drug delivery system: a new delivery system for protein. Biomaterials 2003;24(27): 5023–36.
[179] Wildemann B, Sander A, Schwabe P, Lucke M, Stoeckle U, Raschke M, et al. Short term in vivo biocompatibility testing of biodegradable poly(D,L-lactide)-growth factor coating for orthopedic implants. Biomaterials 2005;26(18):4035–40.
[180] Darouiche RO, Farmer J, Chaput C, Mansouri M, Saleh G, Landon GC. Anti-infective efficacy of antiseptic-coated intramedullary nails. J Bone Joint Surg Am 1998;80(9):1336–40.
[181] Pouton CW, Akhtar S. Biosynthetic polyhydroxyalkanoates and their potential in drug delivery. Adv Drug Deliv Rev 1996;18(2): 133–62.
[182] Lee SY. Plastic bacteria? Progress and prospects for polyhydroxyalkanoate production in bacteria. Trends Biotechnol 1996; 14(11):431–8.
[183] Gursel I, Korkusuz F, Turesin F, Alaeddinoglu NG, Hasirci V. In vivo application of biodegradable controlled antibiotic release systems for the treatment of implant-related osteomyelitis. Biomaterials 2001;22(1):73–80.
[184] Schmoekel HG, Weber FE, Schense JC, Graetz KW, Schawalder P, Hubbell JA. Bone repair with a form of BMP-2 engineered for incorporation into fibrin cell ingrowth matrices. Biotechnol Bioeng 2004;89(3):253–62.
[185] Deuel TF, Zhang N. Growth factors. In: Lanza RP, Langer R, Vacanti J, editors. Principles of tissue engineering. 2nd ed. San Diego, CA: Academic Press; 2000. p. 129–41.
[186] Sumner DR. Fixation of implants. In: Callaghan JJ, Rosenberg AG, Rubash HE, Simonian PT, Wickiewicz TA, editors. The adult knee. Philadelphia: Lippincott Williams & Wilkins; 2003. p. 289.
[187] Jacobs JJ, Goodman SB, Sumner DR, Hallab NJ. Biological response to orthopaedic implants. In: Sheldon RS, editor. Orthopaedic basic science, anonymous. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2000. p. 401.
[188] Moucha CS, Urban RM, Turner TM, Jacobs JJ, Sumner DR. Fixation of implants. In: Shanbhag A, Rubash HE, Jacobs JJ, editors. Joint replacements and bone resorption: pathology, biomaterials and clinical practice. New York: Marcel Dekker; 2005.
[189] Richardson TP, Murphy WL, Mooney DJ. Polymeric delivery of proteins and plasmid DNA for tissue engineering and gene therapy. Crit Rev Eukaryot Gene Expr 2001;11(1–3):47–58.
[190] Bouhadir KH, Mooney DJ. Promoting angiogenesis in engineered tissues. J Drug Target 2001;9(6):397–406.
[191] Young JL, Dean DA. Nonviral gene transfer strategies for the vasculature. Microcirculation 2002;9(1):35–49.
[192] Perez-Martin M, Azcoitia I, Trejo Jose L, Sierra A, Garcia-Segura Luis M. An antagonist of estrogen receptors blocks the induction of

adult neurogenesis by insulin-like growth factor-I in the dentate gyrus of adult female rat. Eur J Neurosci 2003;18(4):923–30.
[193] Lanza RP, Langer R, Vacanti J. Principles of tissue engineering. 2nd ed. San Diego, CA: Academic Press; 2000.
[194] Hess CT. The art of skin and wound care documentation. Adv Skin Wound Care 2003;18(1):43–53.
[195] Hampl J, Schierholz J, Jansen B, Aschoff A. In vitro and in vivo efficacy of a rifampin-loaded silicone catheter for the prevention of CSF shunt infections. Acta Neurochir (Wien) 1995;133(3–4):147–52.
[196] Labhasetwar V, Levy RJ. Implants for site-specific drug delivery. Journal of Applied Biomaterials: An Official Journal of the Society for Biomaterials 1991;2(3):211–2.
[197] Mond H, Stokes K, Helland J, Grigg L, Kertes P, Pate B, et al. The porous titanium steroid eluting electrode: a double blind study assessing the stimulation threshold effects of steroid. Pacing Clin Electrophysiol 1988;11(2):214–9.
[198] Wish M, Swartz J, Cohen A, Cohen R, Fletcher R. Steroid-tipped leads versus porous platinum permanent pacemaker leads: a controlled study. Pacing Clin Electrophysiol 1990;13(12 Pt 2):1887–90.
[199] Singarayar S, Kistler Peter M, De Winter C, Mond H. A comparative study of the action of dexamethasone sodium phosphate and dexamethasone acetate in steroid-eluting pacemaker leads. Pacing Clin Electrophysiol 2005;28(4):311–5.
[200] Patil SD, Papadimitrakopoulos F, Burgess DJ. Dexamethasone-loaded poly(lactic-*co*-glycolic) acid microspheres/poly(vinyl alcohol) hydrogel composite coatings for inflammation control. Diabetes Technol Therap 2004;6(6):887–97.
[201] Hickey T, Kreutzer D, Burgess DJ, Moussy F. In vivo evaluation of a dexamethasone/PLGA microsphere system designed to suppress the inflammatory tissue response to implantable medical devices. J Biomed Mater Res 2002;61(2):180–7.
[202] Ward WK, Troupe JE. Assessment of chronically implanted subcutaneous glucose sensors in dogs: the effect of surrounding fluid masses. ASAIO J 1999;45(6):555–61.
[203] Woo GLY, Mittelman MW, Santerre JP. Synthesis and characterization of a novel biodegradable antimicrobial polymer. Biomaterials 2000;21(12):1235–46.
[204] Harten RD, Svach DJ, Schmeltzer R, Uhrich KE. Salicylic acid-derived poly(anhydride-esters) inhibit bone resorption and formation in vivo. J Biomed Mater Res A 2005;72A(4):354–62.
[205] Tanihara M, Suzuki Y, Nishimura Y, Suzuki K, Kakimaru Y, Fukunishi Y. A novel microbial infection-responsive drug release system. J Pharm Sci 1999;88(5):510–4.
[206] Tanihara M, Suzuki Y, Nishimura Y, Suzuki K, Kakimaru Y. Thrombin-sensitive peptide linkers for biological signal-responsive drug release systems. Peptides (New York) 1998;19(3):421–5.
[207] Grainger DW. Controlled-release and local delivery of therapeutic antibodies. Expert Opin Biol Ther 2004;4(7):1029–44.
[208] Minko T, Kopeckova P, Kopecek J. Mechanisms of anticancer action of HPMA copolymer-bound doxorubicin. Macromol Symp 2001;172:35–47.
[209] Griffith LG. Emerging design principles in biomaterials and scaffolds for tissue engineering. Ann N Y Acad Sci 2002;961:83–95.