Review

Antibiotic-eluting medical devices for various applications

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ABSTRACT

Infection is defined as a homeostatic imbalance between the host tissue and the presence of microorganisms. It is associated with a large variety of wound occurrences ranging from traumatic skin tears and burns to chronic ulcers and complications following surgery and device implantations. If the wound setting manages to overcome the microorganism invasion by a sufficient immune response then the wound should heal. If not, the formation of an infection can seriously limit the wound healing process. Evidence of increasing bacterial resistance is on the rise, and complications associated with infections are therefore expected to increase. The main goal in treating various types of wound infections is to decrease the bacterial load in the wound to a level that enables wound healing processes to take place. Conventional systemic delivery of antibiotics entails poor penetration into ischemic and necrotic tissue and can cause systemic toxicity with associated renal and liver complications, which result in a need for hospitalization for monitoring. Alternative local delivery of antibiotics by either topical administration or by a delivery device may enable the maintenance of a high local antibiotic concentration for an extended duration of release without exceeding systemic toxicity. The present review describes approaches for local prevention of bacterial infections based on antibiotic-eluting medical devices. These devices include bone cements, fillers and coatings for orthopedic applications, wound dressings based on synthetic and natural polymers, intravascular devices, vascular grafts and periodontal devices. Part of the review is dedicated to our novel composite drug-eluting fibers and structured drug-eluting films, which are designed to be used as basic elements of various devices. In this review emphasis is placed on processing techniques, microstructure, drug release profiles, biocompatibility and other relevant aspects necessary for advancing the therapeutic field of antibiotic-eluting devices.

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1. Introduction

Infection is defined as a homeostatic imbalance between the host tissue and the presence of microorganisms at a concentration that exceeds $10^5$ organisms per gram of tissue or the presence of beta-hemolytic streptococci [12]. The emergence of infection is associated with a large variety of wound occurrences, ranging from traumatic skin tears and burns to chronic ulcers and complications following surgery and device implantations. If the wound setting is able to overcome the microorganism invasion by a sufficient immune response then the wound should heal via the common four-phased process of coagulation, inflammation, proliferation and remodeling [3]. If not, the formation of an infection can seriously limit the wound healing process, can interfere with wound closure and may even lead to bacteremia, sepsis and multi-system failure. People who suffer from immunosuppressive disorders obviously face a higher risk of infection. However, evidence of increasing bacterial resistance is on the rise, and complications associated with infections are therefore expected to increase in the general population. Concern among healthcare practitioners regarding the risk of wound infection is justifiable not only in terms of increased suffering to the patient, but also in view of its economic burden to society.

The main goal of treating the various types of wound infections should be to reduce the bacterial load in the wound to a level at which wound healing processes can take place. Conventional systemic delivery of antibiotics for both prevention (prophylaxis) and curing suffers from the drawbacks of systemic toxicity with associated renal and liver complications, poor penetration into ischemic and necrotic tissue typical of post-traumatic and postoperative tissue, and need for hospitalized monitoring [4,5]. Alternative local delivery of antibiotics by topical administration, or even better by a local delivery device, addresses the major disadvantages of the systemic approach by maintaining a high local antibiotic concentration for an extended duration of release without exceeding systemic toxicity [6–8]. Antibiotics already incorporated in controlled-release devices include vancomycin, tobramycin, cefamandol, cephalothin, carbenicillin, amoxicillin and gentamicin [4,5].

The effectiveness of such devices is strongly dependent on the rate and manner in which the drug is released [10]. These are determined by the host matrix into which the antibiotic is loaded, the type of drug and its clearance rate. If the drug is released quickly, the entire drug could be released before the infection is arrested. If release is delayed, infection may set in further, thus making it difficult to manage the wound. The release of antibiotics at levels below the minimum inhibitory concentration (MIC) may evoke bacterial resistance at the release site and intensify infectious complications [11,12]. Furthermore, certain bacterial species are able to attach to implant surfaces and form a protective bio-film layer which is extremely resistant to both the immune system and antibiotics. These bio-films are considered the primary cause of implant-associated infection [13]. It has been found that killing bacteria in a bio-film sometimes requires approximately 1000 times the antibiotic dose necessary to achieve the same results in a cell suspension [14].

A 6-h post implantation “decisive period” has been identified during which prevention of bacterial adhesion is critical to the long-term success of an implant. Over this period, an implant is particularly susceptible to surface colonization. At extended periods, certain species of adhered bacteria are capable of forming a bio-film at the implant–tissue interface [13]. A local antibiotic release profiles should exhibit a high initial release rate in order to respond to the elevated risk of infection from bacteria introduced during the initial shock, followed by a sustained release at an effective level for inhibiting the occurrence of latent infection. In the case of orthopedic-related devices it is important to combat the bacteria which were introduced during the implantation and also those introduced systemically afterwards. Therefore the sustained release (second phase) is necessary. In the case of wound dressings, the burn level and rate of tissue regeneration (depends on the patient’s age and other parameters) affect the wound healing process. Therefore, it is hard to describe an “ideal release profile” for the various applications of antibiotic-eluting devices. Our activity in the field of “antibiotic-eluting medical devices” includes antibiotic-loaded bioresorbable films for orthopedic and periodontal applications, and bioresorbable fibers for wound healing applications. These projects are briefly described in the current review, in addition to other research projects. In each project, various release profiles should be selected for in vivo experiments, in order to choose the most suitable system.

The most extensively studied and earliest commercially available device for controlled release of antibiotics was developed in the 1970’s according to Buchholz and Engelbrecht’s [15] innovative idea of releasing antibiotics from the newly introduced non-biodegradable polymethylmethacrylate (PMMA) bone cement. This device is still widely accepted as a means for reducing bone infection. However, it has several drawbacks: PMMA enables only a small fraction of the loaded drug to diffuse through the polymer pores [16–19] and may possibly shelter resistant bacteria, thus causing treatment failure. Moreover, PMMA is not biodegradable, and when clinical failure occurs secondary surgery is necessary to remove the PMMA before new bone can regenerate.

Various biodegradable devices from both natural and synthetic polymers have been produced by different processes in recent years, for use as antibiotic carriers. Biodegradable polymers can release larger quantities of antibiotics and their degradation properties can be tailored for a specific application that will affect a range of processes such as cell growth, tissue regeneration, drug release and host response [20]. Synthetic biodegradable polymers that have been reported for various antibiotic-eluting devices include poly-(lactide-co-glycolide) copolymers [21–24], polycaprolactone [25,26] polyanhydrides [27–30], polyhydroxybutyrate-co-hydroxyvalerate (PHBV) [31,32] and polyhydroxalkanoates [33]. Natural polymers such as collagen [34–38] and chitosan [39–43] are attractive, since they exhibit superior biocompatibility and facilitate cell growth. They are also inexpensive and readily available. Table 1 presents most of the antibacterial drugs that have been used in controlled-release systems to date. The molecular weight of the drug, its water solubility and its solubility in organic solvent, its melting temperature and its antibacterial spectrum must be known in order to design an antibiotic-eluting system. These properties are presented for each drug mentioned in Table 1. This review presents the most extensively studied systems of devices for the release of antibiotics for various applications.

2. Musculoskeletal and orthopedics-related devices

Bacterial infection remains a major limitation of the utility of medical implants, despite sterilization and aseptic procedures, with reported infection rates in the range of 0.5–5% for total joint arthroplasties [44,45]. Sources for infectious bacteria include the ambient atmosphere of the operating room, surgical equipment, clothing worn by medical professionals, resident bacteria on the patient’s skin and bacteria already in the body [46]. In addition to human pain and suffering, direct medical costs associated with such infections are extremely high and often result in the removal of the orthopedic implants and the need for a follow-up operation. The worldwide increase in the application of medical technology will eventually lead to greater demand for medical implants and an increase in implant–associated infections [13].

Device-associated infections are the result of bacterial adhesion and subsequent bio-film formation at the implantation site. Inhibiting bacterial adhesion is often regarded as the most critical step in preventing implant–associated infection. Competition between the integration of the material into the surrounding tissue and adhesion of bacteria to the implant surface occurs upon implantation. Implantation will be successful only if tissue integration occurs prior to considerable bacterial adhesion, thus preventing colonization of the implant [6]. The remarkable resistance of bio-films to conventional
antibiotic therapy has led to extensive research on synthetic surfaces and coatings that resist bacterial colonization.

2.1. Antibiotic-loaded bone cements and fillers

Non-degradable polymethylmethacrylate (PMMA) bone cements and spacer beads loaded with antibiotics have been employed clinically in various forms for nearly four decades in joint replacements and in prevention or treatment of deep bone infections (osteomyelitis) [47–51]. Such systems slowly release the soluble drug from the solidified PMMA bone cement surrounding the implant over time. Local release of antibiotics at concentrations higher than can be achieved by systemic therapy is most desirable in treating osteomyelitis, since poor bone penetration of many antibiotics is reported [52]. The non-degradable

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Antibacterial drugs and their properties [136,137]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class/drug</td>
<td>Molecular weight (g/mol)</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>585.6</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>477.6</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>467.5</td>
</tr>
<tr>
<td>Cefalosporins</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>454.5</td>
</tr>
<tr>
<td>Cefoperazone</td>
<td>645.7</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1449.3</td>
</tr>
<tr>
<td>Polypeptides</td>
<td></td>
</tr>
<tr>
<td>Colistin (polymyxin E)</td>
<td>1155.4</td>
</tr>
<tr>
<td>Quinolones</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>331.4</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>361.4</td>
</tr>
<tr>
<td>Rifamycins</td>
<td></td>
</tr>
<tr>
<td>Rifampin/ rifampicin</td>
<td>823.0</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>444.5</td>
</tr>
<tr>
<td>Minocycline</td>
<td>457.5</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>444.5</td>
</tr>
</tbody>
</table>

PMMA matrices are produced by a polymerization reaction between a solid and a liquid component which are mixed together. The former typically contains PMMA powder, an initiator, the drug and additives and the latter contains methyl methacrylate monomers and other additives. Curing of the cement mixture occurs within minutes, thus trapping the drug within the dense glassy bulk. Incorporation of antibiotics in this type of system is limited to antibacterial drugs that are able to withstand the heat generated by polymerization. Recorded polymerization temperatures range between 70 °C and 120 °C [53]. Loaded drugs are released through mechanisms of water pore penetration, soluble matrix dissolution and outward diffusion of solubilized drug via matrix imperfections (accessible pores and cracks).

PMMA typically displays a biphasic release pattern characterized by an initial burst release followed by a long tail of low, ineffective and largely incomplete release that continues for days or months. A number of studies have revealed that less than 10% of the trapped drug is eventually released from the cement [16–19], with evidence of sub-therapeutic release of gentamicin 25 years after the primary operation [54].

Commercial acrylic antibiotic-impregnated bone cement products have been sold in Europe for over 20 years. The antibiotics are either premixed by the manufacturer or added by the surgeon in the operating room. The American Food and Drug Administration (FDA) has recently approved the use of the following low-dose premixed cements: Cobal™ G-HV (Biomet), Palacos® G (Biomet), DePuy 1 (DePuy Orthopedics), Cemex® Genta (Exactech), VersaBond™ AB (Smith and Nephew) which contain gentamicin and Simplex® P (Stryker Orthopedics) which contains tobramycin. Nevertheless, FDA approval of these low-dose antibiotic-loaded bone cements is restricted to cases of joint revision following the elimination of an active infection. These cements are therefore more appropriate as a preventative measure than for the treatment of an established infection which still requires hand-mixing of higher dosages of various antibiotics into the cement by the physician [55]. Surgeries have been hand-mixing commonly used cements: Palacos® (Smith & Nephew), Simplex® W (Howmedica), CMW (DePuy), and Zimmer (Zimmer) with antibiotics such as penicillin, erythromycin, colistin, cephalosporines, gentamicin, polymyxin, vancomycin, and tobramycin. This pattern of use has primarily been the result of antibiotic selection based on identification of the infecting organism [55].

Díez-Peña et al. [56] reported that hand-mixing additional antibiotics into the low-dose (2.89% wt. gentamicin) commercial bone cement CMW-1® (DePuy) to values roughly around 20% significantly improves the drug’s release mechanism and enables almost complete release of the incorporated drug. It is thought that where ‘reservoirs’ of gentamicin exist in close vicinity, water is able to create elution paths which enable more efficient release of gentamicin from the inner domains. Loading of additional drug may, however, lead to an undesirable weakening of the bone cement. This is a major compromise if the cement is used for implant fixation, where mechanical strength is imperative [57]. A similar weakening effect is observed following incorporation of various antibiotics into biodegradable osteo-conductive calcium phosphate bone cements (CPCs) [58–61], due to an interaction between the water-soluble drug and the setting reaction of the cement after adsorption of the drug molecules [60,61]. Schnieders et al. [62] have reported that microencapsulation of gentamicin in biodegradable poly-(lactic-co-glycolic) microspheres prior to mixing of the cement can prevent the negative interaction of antibiotic and cement and may also offer better control over drug release. This first example of a drug-eluting composite cement was found to be capable of up to 30% drug loading without compromising mechanical properties and demonstrated both a low burst release and linear release of gentamicin over a period of days.

Eptacin™, a biodegradable polyanhydride implant in the form of linked beads containing gentamicin for local delivery of the antibiotic to infected bone, presents an alternative to the non-biodegradable acrylic fillers described thus far. The implant’s capability of achieving a high local drug concentration at the implantation site while limiting systemic exposure to the drug has been shown in a safety study conducted with patients [30]. The fabrication of this implant requires the melting of the polymer at 125 °C in order to produce a polymer-drug mixture. It is therefore limited to thermally stable drugs. Krasko et al. [63] have recently developed an injectable biodegradable synthetic polymeric device made of poly(sebacic-co-ricinoleic-ester-anhydride) for treatment of osteomyelitis which overcomes this drawback. The paste hydrophobic copolymer is incorporated with 10–20% gentamicin by mixing the drug powder into the paste at room temperature, and gels in situ when exposed to aqueous surroundings to form a hydrophobic protective environment for the entrapped drug. The polymer degrades mainly from its surface, releasing the entrapped drug. The safety and positive effect of the device were confirmed in vivo on established osteomyelitis induced in a rat model.

### 2.2. Antibiotic-loaded implant coatings

Antibiotic-loaded implant coatings present a straightforward approach for the prevention of implant-associated infections. They can provide an immediate response to the threat of implant contamination but do not necessitate use of an additional carrier for the antibacterial agent other than the orthopedic implant itself. This is most relevant for ‘cementless’ implantation procedures that have gained popularity due to better early and intermediate-term results in young patients compared to cemented prostheses [64].

Unlike “passive” coating techniques that aim to reduce bacterial adhesion by altering the physiochemical properties of the substrate so that bacteria-substrate interactions are not favorable, “active” coatings are designed to temporarily release high fluxes of antibacterial agents immediately following the implantation [13]. High local doses of antibiotics against specific pathogens associated with implant infections can thus be administered without reaching systemic toxicity levels with enhanced efficacy and less probability for bacterial resistance. Recent studies have also raised the possibility of incorporating growth factors in order to promote tissue healing responses [65,66].

The utilization of a bioactive ceramic coating containing hydroxyapatite (HA), calcium phosphate and other osteo-conductive materials as antibiotic carriers offers the added value of providing the physiochemical environment and structural scaffold required for bone-implant integration. In vitro release of antibiotics from hydroxyapatite-coated implants has been reported for chlorhexidine, vancomycin, gentamicin, tobramycin and several other antibiotics [9,67–70] whose antibacterial efficacy was shown in vitro by the formation of inhibition zones in agar plate testing. The conventional plasma spraying technique for HA-coating is associated with high processing temperatures and therefore does not enable the incorporation of antibiotics in the process. Most reported work therefore focuses on soaking antibiotics onto plasma-sprayed HA. Stigter et al. were the first to report the incorporation of tobramycin into HA coatings using a “biomimetic” coating technology at a mild temperature (37 °C) [71]. In short, a supersaturated solution of calcium phosphate containing approximately 3% w/w tobramycin was co-precipitated onto titanium alloy plates, forming an approximately 40 μm thick carbonated hydroxyapatite layer. In their later work [9], it was concluded that antibiotics containing carboxylic groups have a better interaction with calcium, resulting in improved binding and higher incorporation into the calcium phosphate coating. Alas, the longest antibacterial effect achieved still does not exceed three days [72]. To date, the only in vivo examination of a hydroxyapatite-coated implant in a rabbit infection model supports the concept by showing a significant decrease in infection rates. However, further substantiation of its biocompatibility and osseo-integration must be carried out [73].

The study of biodegradable polymeric coatings made from polylactic acid and its copolymers with glycolic acid is more established. Release profiles last from several hours to 12 days after exposure to an
aqueous environment [4,74–76]. An additional advantage of such coatings is the relative ease with which the polymer can be applied to both alloys and plastics with polished, irregular or porous surfaces using a simple dip-coating technique [74]. The implant can be dipped several times in a solution of polymer and antibiotics in an organic solvent to achieve a dense or thick polymer coating. The promising results displayed in an animal model for this type of coating [75] were taken a step further and its first use in humans was investigated for internal fixation of open tibial fractures using gentamicin poly-(DL-lactic)-coated tibial nails (UTN, Synthes, Bochum, Germany) [65,76]. Gentamicin was not detected in the serum and no adverse events were observed during a one-year follow-up.

Alternative biodegradable coating materials that have been studied in recent years include natural resin-based biopolymers and polyhydroxylalkanoates. Rosin is a natural polymer obtained from pine trees which is composed of a mixture of diterpene acids known as resin acids and a smaller amount of other acidic and neutral bodies. It demonstrates excellent film forming, coating, and microencapsulating properties. Its suitability has been confirmed by Fulzele et al. [77] who demonstrated permanent release of ciprofloxacin over a period of 90 days with 90% of the encapsulated drug released and good compatibility in vivo. Polyhydroxylalkanoates incorporated with Sulperazone® (cefoperazone) and Duocid® (ampicillin) in the form of rods have already shown promising results in treating implant-related osteomyelitis in rabbits [78]. In addition to their biodegradability and biocompatibility, they also feature piezoelectricity, which is claimed to induce bone growth in load-bearing areas [78]. Rossi et al. [32] have reported the coating of discs cut from a femoral hip implant with polyhydroxylalkanoates loaded with gentamicin. The coating was prepared by pouring dissolved polymer and gentamicin in chloroform onto metal specimens followed by drying of the mixture. The coating exhibited an initial burst release followed by continuous in vitro release of gentamicin over a period of 6 weeks with bacterial eradication within 24–48 h, depending on the copolymer composition [32].

2.3. Structured antibiotic-loaded bioresorbable films

As mentioned above, bacterial adhesion to biomaterials and the ability of many microorganisms to form bio-films on foreign bodies are well-established as major contributors to the pathogenesis of implant-associated infections. Major problems in treating osteomyelitis include poor distribution of the antimicrobial agent at the site of infection due to limited blood circulation to infected skeletal tissue, and inability to directly address the bio-film pathogen scenario. Controlled antimicrobial release systems inside orthopedic devices thus represent alternatives to conventional systemic treatments [79]. In one of our recent studies [80] we developed and studied gentamicin-loaded bioreabsorbable films that can be "bound" to orthopedic implants (by slightly dissolving their surface before attaching them to the implant surface) and prevent bacterial infections by a gentamicin-controlled release phase for at least one month. These systems provide desired drug delivery profiles and do not require an additional implant.

Poly(ε-lactic acid) (PLLA) and poly(ε-lactic-co-glycolic acid) (PDLGA) films containing gentamicin were prepared by solution processing accompanied by a post-preparation isothermal heat treatment. In the process of film preparation, the solvent evaporation rate determines the kinetics of drug and polymer solidification and thus the drug dispersion/location in the film. The resulting drug-eluting systems are therefore termed "structured films". In general, two types of polymer/gentamicin film structures were created and studied for all matrix polymer types:

(a) A polymer film with drug particles located on its surface. This structure, which is derived from a dilute solution, was obtained using a slow solvent evaporation rate which enables prior drug nucleation and growth on the polymer solution surface. This skin formation is accompanied by a later polymer core formation/solidification. This structure was named the “A-type”.

(b) A polymer film with most of the drug particles distributed within the bulk. This structure, which is derived from a concentrated solution, was obtained using a fast solvent evaporation rate and resulted from drug nucleation and

Fig. 1. In vitro cumulative gentamicin release from polymer/gentamicin films: (a) A-type films containing 10% w/w gentamicin, (b) B-type films containing 10% w/w gentamicin, (c) A-type films containing 30% w/w gentamicin, (d) B-type films containing 30% w/w gentamicin. ■ high MW PLLA, ○ low MW PLLA, □ high MW PDLGA, ▲ low MW PDLGA. The experiments were performed in triplicate and the results are presented as mean ± standard deviations.
segregation within a dense polymer solution. Solidification of drug and polymer occurred concomitantly. This structure was named the “B-type”. Gentamicin is a water-soluble drug which practically does not dissolve in chloroform. Some of its particles thus diffused out towards the surface during solvent evaporation. The drug concentration near the surface is therefore probably higher than in the center.

The effects of polymer type, initial molecular weight, film morphology (drug location/dispersion) and drug loading on the gentamicin release profile were examined. The cumulative gentamicin release profiles from films of various polymer/gentamicin systems are presented in Fig. 1. All experiments were performed in triplicate and results are presented as means±standard errors. All release profiles exhibited a burst release followed by a relatively slow release phase. Such profiles are desirable for applications such as fracture fixation, where a burst release is needed in order to prevent infection and kill the microorganisms found in the implant area before they settle and create a biofilm which antibiotics cannot easily penetrate. A second phase of slow drug release is necessary to prevent microbial infections at the implant site during healing. The burst effect is obtained due to diffusion of drug molecules located on the surface and in polymer layers close to the surface, while the continuing release is obtained due to diffusion of drug molecules from the bulk and is affected by the host polymer’s degradation rate.

Gentamicin’s therapeutic level in serum is 4–8 μg/ml and its toxic level is 12 μg/ml [81]. All studied films released gentamicin at levels higher than the MIC. As expected, lower molecular weight polymers exhibited higher burst effects and higher release rates, due to a higher quantity of hydroxyl and carboxylic edge groups, which make it more hydrophilic. Furthermore, a lower molecular weight results in a lower glass transition temperature, which facilitates faster drug release from the polymer.

Processing conditions strongly affect the release profile through morphology. Thus, dilute solutions and slow evaporation rates resulted in A-type films with the drug located on the surface. These films exhibited a relatively high burst effect followed by a slow release rate. In contradistinction, concentrated solutions and fast evaporation rates resulted in B-type films, in which most of the drug is located in the polymeric film and some is located on the surface. These films exhibited a relatively low burst effect followed by a lower release rate. Only the PDLGA with relatively low MW films exhibited similar release profiles for A and B-type films. This behavior is obtained due to the polymer’s relatively high degradation rate and gentamicin’s extremely hydrophilic nature. We concluded that the gentamicin release profiles from the various systems is determined by the host polymer, its initial molecular weight and the processing conditions, which affect the drug location/dispersion in the film. Drug loading has a minor effect on the release profile.

Microbiological evaluation of the effect of gentamicin release on bacterial viability was performed. These experiments were carried out in order to monitor the effectiveness of various concentrations of the antibiotic released from the films in terms of the residual bacteria compared with the initial bacterial concentration. Bacteria present in PBS only served as the control. In our experiments the bacteria were added at the beginning of the films’ release, in order to simulate contamination at the time of implantation. The results are presented in Fig. 2. No bacteria were left after 1–3 d compared to the control where all bacteria survived even after 7 d in the presence of a very high concentration of the starter (1×10⁸/ml CFU). All films exhibited marked gentamicin release, which was responsible for the dramatic decrease in bacterial survival (10³/ml CFU after 1 d). Moreover, the polymer/gentamicin film preparation did not affect gentamicin’s activity as an antimicrobial agent.

This study enabled in-depth understanding of gentamicin-loaded structured films and as a result, the production of systems with the desired controlled gentamicin release profiles, i.e. with the desired burst effect and continuing release rate (within the therapeutic window) for several weeks. The developed systems can be applied on the surface of any metallic or polymeric fracture fixation device, and can therefore make a significant contribution to the field of orthopedic implants.

3. Wound dressings

The skin is regarded as the largest organ of the body and has many different functions. Wounds with tissue loss include burn wounds, wounds caused as a result of trauma, diabetic ulcers and pressure sores. The regeneration of damaged skin includes complex tissue interactions between cells, extracellular matrix molecules and soluble mediators in a manner that results in skin reconstruction. The moist, warm, and nutritious environment provided by wounds, together with diminished immune functioning secondary to inadequate wound perfusion, may allow a build-up of physical factors such as devitalized, ischemic, hypoxic, or necrotic tissue and foreign material, all of which provide an ideal environment for bacterial growth [82]. In burns,
infection is the major complication after the initial period of shock. It is currently estimated that about 75% of the mortality following burn injuries is related to infections rather than to osmotic shock and hypovolemia [83].

Various wound dressings aim to restore the milieu required for skin regeneration and to protect the wound from environmental threats and penetration of bacteria. Although traditional gauze dressings offer some protection against bacteria, this protection is lost when the outer surface of the dressing becomes moistened by wound exudates or external fluids. Furthermore, traditional gauze dressings exhibit low restriction of moisture evaporation which may lead to dehydration of the wound bed. This may lead to adherence of the dressing, particularly as wound fluid production diminishes, thus causing pain and discomfort to the patient during removal.

Most modern dressings are designed according to the well-accepted bilayer structural concept: an upper dense 'skin' layer to prevent bacterial penetration and a lower spongy layer designed to adsorb wound exudates and accommodate newly formed tissue. Unfortunately, dressing material absorbed with wound discharges provides conditions that are also favorable for bacterial growth. This has given rise to a new generation of wound dressings with improved curative properties that provide an antimicrobial effect by eluting various germicidal compounds.

### 3.1. Wound dressings based on synthetic polymers

A variety of dressings that contain and release antibiotic agents at the wound surface have been introduced. These dressings are designed to provide controlled release of silver ions through a slow but sustained release mechanism which helps avoid toxicity yet ensures delivery of a therapeutic dose of silver ions to the wound [84]. A wide variety of semi-occlusive dressing formats, such as foams (Contreet® antimicrobial foam, Coloplast), hydrocolloids (Urgotul SSD, Urgo), alginites (Silvercel®, Johnson & Johnson) and hydrofibers® (Aquadel, Convatec) are available. For instance, Acticoat® (Smith and Nephew) is a 3-ply gauze dressing made of an absorbent rayon polyester core, with upper and lower layers of nano-crystalline silver-coated high density polyethylene mesh [85]. It is applied wet and is then moistened with water several times daily to allow the release of the silver ions so as to provide an antimicrobial effect for 3 days. Concerns have been raised by clinicians regarding the safety of the silver ions included in most of these products. For example, it was found that a young person with 30% mixed depth burns, who received one week of local treatment with Acticoat, had shown hepatotoxicity and argyria-like symptoms and the silver levels in his plasma and urine were clearly elevated, as well as the liver enzymes, during the treatment period. Therefore the authors raised concern about potential silver toxicity and suggested to monitor the silver levels in the plasma and/or urine during the treatment [86].

In order to address this issue, the silver in Actisorb® (Johnson & Johnson) is impregnated into an activated charcoal cloth, after which it is encased in a nylon sleeve which does not enable the silver in the product to be freely released at the wound surface but nevertheless eradicates bacteria that adsorb onto the activated charcoal component.

Suzuki et al. [87,88] present a new concept for an antibiotic delivery system that releases gentamicin only in the presence of wounds that are infected by *Pseudomonas aeruginosa* with a potential for an occlusive dressing. Gentamicin is bound to a polyvinyl alcohol derivative (PVA) hydrogel through a specially developed peptide linker cleavable by a protease. This allows gentamicin to be released at specific times and locations, namely when and where *P. aeruginosa* infection occurs. PVA-(linker)-gentamicin demonstrated selective release of gentamicin in *P. aeruginosa*-infected wound fluid, and caused a significant reduction in its growth in vitro.

The substantial disadvantage of these temporary dressings is the fact that similarly to textile wound dressings, the necessary change of dressings may be painful and increases the risk of secondary contamination. Biodegradable dressings successfully address this shortcoming since they can easily be removed from the wound surface once they have fulfilled their role. Film dressings made of lactide-caprolactone copolymers such as Topkin® (Biomet, Europe) and Oprafol® (Lohmann & Rauscher, Germany) are available for clinical use. Biodegradation of the film occurs via hydrolysis of the copolymer into lactic acid and 6-hydroxycaproic acid. During the hydrolytic process the pH shifts towards the acid range, with pH values as low as 3.6 measured in vitro [89]. Although these two dressings do not contain antibiotic agents, it is claimed that the low pH values induced by the polymer’s degradation help reduce germ growth [90] and also promote epithelization [91]. Furthermore, local lactate concentrations can stimulate local collagen synthesis [92]. Film dressings are better suited for small wounds since they lack an absorbing capacity and are impermeable to water vapors and gases, both of which cause accumulation of wound fluids on larger wound surfaces.

Katti et al. [93] report the development of a biodegradable poly(lactide-co-glycolide) (PDLGA) nanofiber-based antibiotic delivery system. This system can serve as a biodegradable gauze dressing and an alternative to film dressings. This type of dressing is composed of continuous fibers that form a non-woven fiber mesh by means of an electrosprinning process. Briefly, the process of electrosprinning involves use of a polymer solution that is contained in a syringe and held at the end of the needle by its surface tension. Charge is induced on the solution by an external electric field to overcome the surface tension and form a charged jet of solution. As this jet travels through air, it experiences instabilities and follows a spiral path. Evaporation of the solution leaves behind a charged polymer fiber that is collected on a grounded metal screen. Incorporation of antibiotics in the process of electrosprinning requires solubility of the incorporated drug in the solvents used in the process (a mixture of dimethylformamide and tetrahydrofuran). Cefazolin was chosen as complying with this requirement. The effects of orifice diameter, applied voltage as well as polymer and drug solution concentrations were investigated and it was demonstrated that drug-loaded fibers can be electrospun, and although they had larger diameters than the unloaded fibers, they were still in the nanometer range. Antibiotic release from these fibers has not been reported to date.

### 3.2. Wound dressings based on natural polymers

Only a handful of natural materials have been investigated for wound dressing applications as either main or additional components to the dressing structure which are able to impact the local wound environment beyond moisture management and to elicit a cellular response. Collagen is the main structural protein of the extracellular matrix (ECM), and was one of the first natural materials to be utilized for skin reconstruction and dressing applications. Collagen-based products have been available commercially for over a decade. They come in a variety of set-ups ranging from gels, pastes and powders to more elaborate sheets, sponges, and composite structures. Collagen’s limitations as a wound dressing ingredient are mainly due to its rapid biodegradation by collagenase and its susceptibility to bacterial invasion [94-97]. Drug-eluting collagen sponges have been found useful in both partial-thickness and full-thickness burn wounds. Collatamp® (Innoccoll GmbH, Germany), Syntacoll (AG, Switzerland), Sulmicyc®-Implant (Scherling-Plough, USA) and Septocoll® (Biomet Merck, Germany) are several such products which have been found to accelerate both granulation tissue formation and epithelialization, as well as to protect the recovering tissue from potential infection or re-infection by eluting gentamicin. In vivo, drug is released by a combination of diffusion and natural enzymatic breakdown of the collagen matrix [98]. A comprehensive clinical study of gentamicin-collagen sponges demonstrated their ability to induce high local
concentrations of gentamicin (up to 9000 μg/ml) at the wound site for at least 72 h while serum levels remained well below the established toxicity threshold of 10–12 μg/ml [5].

Simple collagen sponge entrapment systems are characterized by high drug release upon the wetting of the sponge, typically within 1–2 h of application. Sripriya et al. [38] have suggested improving the release profile of such systems by using succinylated collagen which can create ionic bonds with the cationic antibiotic ciprofloxacin so as to restrain its diffusion. It is claimed that in this way ciprofloxacin release corresponds to the nature of the wound in line with the amount of wound exudates absorbed in the sponge. Effective in vitro release from their system was found to last for 5 days, and was proven successful in controlling infection in rats. Other studies have aimed to better control drug release or improve wound healing properties by combining collagen with other synthetic or natural biodegradable elements. Prabu et al. [36] focused on achieving a more sustained release of the antimicrobial agent and describe a dressing made from a mixture of collagen and poly-(caprolactone) loaded with gentamicin and amikacin, whereas Shanmugasundaram et al. [37] chose to impregnate collagen with alginate microspheres loaded with the antibacterial agent silver sulfadiazine (AgSD).

Other studies which focused on improving wound healing capabilities tried to incorporate tobramycin, ciprofloxacin [35] and AgSD [34] into collagen–hyaluronan based dressings. The two latter studies do not show conclusive evidence of improved healing properties compared to their control. However, hyaluronan (HA), a structure-stabilizing component of the ECM, is thought to play a role in several aspects of the healing process with hyaluronan-based dressings, and exhibits promising results in the management of chronic wounds such as venous leg ulcers [99,100].

A wide range of studies describe the employment of the polysaccharides chitin and chitosan as structural materials analogous to collagen for wound dressings. Both materials offer good wound protection and have also been found to encourage wound healing.
been investigated to date. The two basic types of drug-loaded fibers that have been reported are monolithic fibers in which the drug is dissolved or dispersed throughout the polymer fiber, and hollow reservoir fibers in which the drug is added to the internal section of the fiber. The advantages of drug-loaded fibers include ease of fabrication, high surface area for controlled release and localized delivery of bioactive agents to their target. Disadvantages of monolithic and reservoir fibers include poor mechanical properties due to drug incorporation and limitations in drug loading. Furthermore, many drugs and all proteins do not tolerate melt processing and organic solvents.

In one of our recent studies we presented a new concept of core/shell fiber structures which successfully meets these challenges [101]. These composite fibers combine a dense polyglycolate core fiber and a drug-loaded porous PDLGA shell structure, i.e. the antibacterial drug gentamicin is located in a separate compartment (a “shell”) around the “core” fiber. The shell is prepared using freeze drying of inverted emulsions with mild processing conditions. These unique fibers are designed to be used as basic elements of bioresorbable burn and ulcer dressings. Their investigation focused on the effects of the emulsion’s composition (formulation) on the shell microstructure, on the drug release profile from the fibers and on the resulting bacterial inhibition.

The freeze drying technique is unique in being able to preserve the liquid structure in solids. We used this technique in order to produce the shell from inverted emulsions in which the continuous phase contained polymer dissolved in a solvent, with water and drug dissolved in it as the dispersed phase. A SEM fractograph showing the bulk morphology of the reference specimen is presented in Fig. 3a. The quality of the interface between the fiber and the porous coating is high (Fig. 3b), i.e. the preliminary surface treatment enabled good adhesion between the core and the shell. The shell’s porous structure contains round-shaped pores with a diameter of 1.0–11.5 μm and a porosity of 8–68%. The shell’s microstructure affects the drug release profile and can also serve as a good measure of the emulsion’s stability. The following emulsion parameters were chosen in order to obtain a stable emulsion that will result in a homogeneous porous shell structure and a feasible release profile of the water-soluble drug: 17.8–26.7% w/v polymer content in the organic phase, 5–20% w/w gentamicin (relative to the polymer) and an organic/aqueous (O:A) phase ratio in the 4:1–12:1 range. The release profiles generally exhibited an initial burst effect accompanied by a decrease in release rates with time. We found that the O:A phase ratio strongly affects the shell structure (Fig. 4). An increase in O:A phase ratio from 6:1 to 12:1

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3.3. Composite fiber structures loaded with antibacterial drugs for wound healing applications

Drug-eluting fibers can be used for various biomedical applications. Few controlled-release fiber systems based on polymers have

![Fig. 5. Effect of the emulsion’s parameters on the release profile of gentamicin from core/shell fiber structures containing 5% w/v albumin: (a) Effect of polymer content on fibers containing 20% w/w gentamicin and O:A phase ratio of 6:1. Polymer content used: ● — 17.8% w/v, ○ — 20% w/v, ▲ — 26.7% w/v. (b) Effect of gentamicin content on fibers containing 26.7% w/v polymer and O:A phase ratio of 6:1. Gentamicin contents: ● — 5% w/v, ○ — 20% w/v. (c) Effect of the emulsion’s O:A phase ratio on fibers containing 20% w/w polymer and 20% w/w gentamicin. O:A phase ratio used: ■ — 6:1, ▲ — 8:1, ○ — 12:1. The experiments were performed in triplicate and the results are presented as means ± standard deviations.

![Fig. 6. Gentamicin release profile from fiber samples which were used for microbiological evaluation: ● — sample I (26.7% w/v polymer, 20% w/v drug, 6:1 O:A phase ratio and 5% w/v albumin), ○ — sample II (20% w/v polymer, 20% w/v drug, 6:1 O:A), ▲ — sample III (26.7% w/v polymer, 5% w/v drug, 6:1 O:A phase ratio and 5% w/v albumin). The experiments were performed in triplicate and the results are presented as means ± standard deviations.]
resulted in smaller pore size and thicker polymeric domains between pores. The polymer content demonstrated some effect on the microstructure, whereas the drug content had practically no effect [101].

Albumin was found to be the most effective surfactant for stabilizing the inverted emulsions. As a surfactant, it is located at the interface between the aqueous phase and the organic phase, reduces the interfacial tension between the two phases and therefore significantly decreases the pore size (Fig. 4). It also enables a high encapsulation efficiency and a relatively low burst release (33%) followed by a moderate release profile which enabled release of most of the loaded gentamicin within two weeks. This behavior probably results from albumin’s ability to bind the gentamicin through specific interactions. The ability of albumin to bind drugs is well-known [102]. Albumin can interact with acidic or basic drugs via van der Waals dispersion forces, hydrogen bonds and ionic interactions. Based on these results, we chose albumin as the preferred surfactant in our systems, and most of the study focused on samples which were stabilized with albumin. All three formulation parameters had a significant effect on gentamicin’s release profile: an increase in the polymer content and the O:A phase ratio or a decrease in the drug content resulted in a lower burst release and a more moderate release profile (Fig. 5).

We performed microbiological experiments in order to monitor the effectiveness of various concentrations of the antibiotic released from the fibers in terms of the residual bacteria compared with the initial number of bacteria. Bacteria in PBS only served as the control. We chose the following three types of fibers with different release profiles (Fig. 6):

I. Fibers with a shell based on 26.7% w/v polymer, 20% w/v drug, 6:1 O:A phase ratio and albumin as surfactant. These fibers demonstrated a moderate burst release of 32% followed by a moderate release profile.

II. Fibers with a shell based on 20% w/v polymer, 20% w/v drug, 6:1 O:A. These fibers demonstrated a high burst release of approximately 60%.

III. Fibers with a shell based on 26.7% w/v polymer, 5% w/v drug, 6:1 O:A phase ratio and albumin as surfactant. These fibers demonstrated a low burst release of 13% during the first day and 60% within three days. After 3 days the release pattern was similar to that of sample II.

The bacterial strains used in this study were Staphylococcus aureus, Staphylococcus epidermidis and P. aeruginosa. Their minimal inhibitory concentration (MIC) values are 2.5, 5 and 63 μg/ml, respectively. All three strains were clinically isolated. These strains were chosen because they are prevalent in wound infections, especially S. aureus and P. aeruginosa. The third strain, S. epidermidis, usually comprises the normal flora of the skin. However, under grave conditions it can cause wound infections. Moreover, these bacteria can produce biofilms, which prevent antibiotics from reaching the target, therefore causing resistance. The bacteria were added at the beginning of the fibers’ release in order to simulate contamination at the time of implantation. The results for all three bacterial types when using a relatively high initial bacterial concentration of 1×10⁷ CFU/ml are presented in Fig. 7. The released gentamicin resulted in a significant decrease in bacterial viability, and practically no bacteria survived after 2 days. The fiber preparation did not affect gentamicin’s potency as an antibacterial agent. Our new fiber structures are thus effective against the relevant bacterial strains and can be used as basic elements of bioreabsorbable drug-eluting wound dressings.

4. Periodontal devices

Periodontal disease is a localized inflammatory response due to infection of a periodontal pocket arising from the accumulation of subgingival plaque and is one of the world’s most prevalent chronic diseases. It is estimated that 36.8% of American adults have the disease. Periodontal disease is thus more prevalent than cancer, heart disease, arthritis, obesity, AIDS and many other diseases [103]. Topical administration of antibacterial agents in the form of mouthwashes is ineffective in controlling disease progression since only a limited amount of drug actually accesses the periodontal pocket. Moreover, the drug is constantly flushed due to a very high fluid clearance rate (an estimated 40 replacements of the fluid an hour within a 5 mm pocket) [104].

Local drug delivery to the pocket in the form of subgingivally-placed systems has numerous advantages. Periodontal diseases are localized in the immediate environment of the pocket, which is easily accessible for the insertion of a delivery device using a syringe or tweezers depending on the physical form of the delivery system. The critical period of exposure of the pocket to the antibacterial drug is between 7–10 days [105]. Maintenance of a sustained high drug concentration can be achieved by correct planning, taking into account the high fluid clearance rate. Sustained release devices in the form of fibers, powders, strips, pastes, gels and ointments have

![Figure 7](Image 7)

Fig. 7. Number of colony forming units (CFU) versus time, when an initial bacterial concentration of 1×10⁷ CFU/ml was used: a– Staphylococcus aureus, b– Staphylococcus epidermidis, c– Pseudomonas aeruginosa. The releasing fibers are: sample I (26.7% w/v polymer, 20% w/v drug, 6:1 O:A phase ratio and 5% w/v albumin), sample II (20% w/v polymer, 20% w/v drug, 6:1 O:A), sample III (26.7% w/v polymer, 5% w/v drug, 6:1 O: A phase ratio and 5% w/v albumin), control – reference fiber without gentamicin.

![Image 3](Image 3)

![Image 4](Image 4)

![Image 5](Image 5)

![Image 6](Image 6)
been reported. Some systems undergo a phase change from a liquid to an in situ forming solid. These systems have the advantage of syringeable delivery and an implant with good retention. Intra-pocket delivery systems can be divided into degradable and non-degradable systems. Non-biodegradable systems must be removed or discharged from the pocket subsequent to the accomplishment of their drug release function.

4.1. Non-degradable devices

Non-degradable cellulose acetate fibers loaded with tetracycline were first reported by Goodson et al. in 1983 [106]. Various studies on this system showed that it was unable to deliver sustainable levels of tetracycline [106,107], chlorhexidine [108] or metronidazole [109] to become clinically useful, although it eventually led to the development of the commercially available Actisite™ (Alza Corp. Palo Alto CA) delivery system which is composed of a monolithic ethylene vinyl acetate fiber loaded with 25% tetracycline. The fiber can be placed around the circumference of the tooth to the depth of the pocket and folded upon itself to completely fill the pocket. The drug concentration in the pocket was found constant until the removal of the fiber 10 days after insertion [104]. This system’s main disadvantages include a reported 23% risk of extrusion of the fiber from the pocket [110] and need for removal.

Non-degradable film or slab-based devices made from PMMA and ethylcellulose have been reported. PMMA slabs have been formed by mixing various antibiotic agents (tetracycline, metronidazole or chlorhexidine) during self-polymerization of PMMA similar to that described previously for bone cements, only cured as sheets under high pressure and cut in the desired shape. In vitro studies showed that therapeutic levels of all three drugs may be achieved for a period of two weeks and that these depend on the nature of the drug and its initial concentration [111]. Clinical studies have shown various degrees of efficacy, although they did not evolve to clinical use [112]. The second system is created by dissolving ethylcellulose and drug (chlorhexidine [113,114], metronidazole [115] or minocycline [116]) in either ethanol or chloroform followed by solvent evaporation and cutting of the films to shape. The most extensively studied systems which contain chlorhexidine have shown promising clinical results in the maintenance of periodontal pockets over a two year period [108].

4.2. Degradable devices

Biodegradable systems are usually polymeric or protein in nature and undergo natural degradation following exposure to gingival fluid components. Various film-based devices have been described. The first degradable systems to be developed were based on hydroxypropylcellulose loaded with various agents: tetracycline, chlorhexidine and ofloxacine. Similarly to other degradable applications described above, fast release of the drug occurs from the film within 2 h, followed by maintenance of tetracycline within the pocket for 24 h after insertion. Several modifications have been made to address the rapid degradation and short duration of drug release. For example, incorporation of methacrylic acid copolymer particles into the film has been reported to prolong the release of ofloxacine in vitro and in vivo for 7 days [117,118]. Polyhydroxybutyric films loaded with 25% tetracycline or metronidazole have been used clinically and demonstrated an improvement in clinical and microbiological parameters, although they suffer from rapid degradation in their mechanical properties and therefore required several consecutive placements every 4 days during the trial [119].

A degradable device based on hydrolyzed gelatin cross-linked by formaldehyde as reported by Steinberg et al. [120] has evolved into the commercial Perio-chip™ (Perio Products Ltd, Jerusalem Israel). A different commercially available system, Elysol (Dumex, Copenhagen, Denmark), is based on a water-free mixture of melted glycerol monostearate and metronidazole to which sesame oil was added to improve its flow properties in the syringe. The gel flows deeply into the periodontal pocket and readily adapts to root morphology. When it comes in contact with water it sets in a liquid crystalline state. The matrix is degraded as a result of neutrophil and bacterial activity within the pocket [121]. Effective doses of metronidazole within the pocket are maintained for 24–36 h. Another antibiotic gel, Atridox™ (Block Drug Corporation Inc., Jersey City, NJ USA) has a solution formulation that is composed of two separate syrups that are coupled together. One syrup contains 8.5% w/w doxycycline hyclate and the other 37% w/w poly D-lactide (PLA). They are dissolved in a biocompatible carrier of 63% w/w N-methyl-2-pyrroldione, which quickly hardens into a wax-like substance upon contact with the cervical fluid. The system slowly releases doxycycline into the surrounding tissue for seven days. This system has been approved by the FDA.

In one of our recent studies we developed and studied metronidazole-loaded 50/50 PDGLA, 75/25 PDGLA and PLLA films. These structured films were prepared using the solution casting technique, as described earlier for polymer/gentamicin films (Chapter 2.3). Concentrated solutions and high solvent evaporation rates were used in order to obtain most of the drug within the bulk. These films are designed to be inserted into periodontal pockets and treat infections during the metronidazole controlled-release phase, for at least one month. The effects of copolymer composition and drug content on the release profile, on cell growth and on bacterial inhibition were investigated. The metronidazole release profiles from films containing 10% drug are presented in Fig. 8. Although the 50/50 PDGLA film degrades faster than the 75/25 PDGLA and PDLLA films, the rate of drug release from the latter two films loaded with 10% metronidazole was faster than from the former, due to differences in drug location/dispersion within the film. The drug crystals appear to be located mainly on the surface of the PDLLA and 75/25 PDGLA films, whereas in the 50/50 PDGLA films the drug was located in the bulk and also on the surface. Our results indicate that the copolymer composition affects the release profile, while the drug content did not show any significant effect on the shape of the release curves. Human gingival cells and rat mesenchymal bone marrow cells have demonstrated normal in vitro growth on the drug-eluting films. The released drug also exhibited effectiveness against Bacteroides fragilis. Our microbiological inhibition kinetics showed that metronidazole cumulative release during 3 days succeeded in totally inhibiting bacterial growth after two days [122].

![Fig. 8. The effect of copolymer type on metronidazole release profile from films loaded with 10 %wt drug. Host polymers: ▲ – 50/50 PDGLA, ■ – 75/25 PDGLA, ▲–PDLLA. The experiments were performed in triplicate and the results are presented as means± standard deviations.](image-url)
5. Intravascular devices and vascular grafts

Infection of intravascular devices for vascular access and vascular prostheses for the replacement or bypass of damaged arteries is a rare but serious event. The infection of a vascular graft is a rare complication, with an estimated incidence of 0.5 to 2.5% of bypass procedures. However, the mortality and morbidity rates due to this complication are high (25 to 75%) [123], especially when the aorta is involved [124]. Once a prosthetic graft is infected, it almost always necessitates excision and replacement with a new prosthetic bypass. The development of infection-resistant vascular prostheses may therefore contribute to the prevention and treatment of this complication.

PET (polyethylene terephthalate, Dacron™) and ePTFE (expanded polytetrafluoroethylene) vascular prostheses soaked in an antibiotic solution produce a wash-out release of antibiotics within minutes after implantation [125,126]. Several approaches have been proposed for extending release over days and weeks. Antibiotics have been ‘bonded’ by soaking collagen [127,128], albumin [129], and gelatin [130–132] sealed grafts to produce extended antibacterial activity. A comprehensive study on the effect of sealant matter and type of antibiotic used has been reported by Galdhart et al. [129]. The antibiotic release rate was found to vary with the type of antibiotic and protein support. Excess antibiotic unable to bind to the protein sealants was released immediately after soaking the graft in water, reaching up to 50%. Albumin and gelatin-sealed grafts displayed relatively longer elution periods, especially for rifampicin, although none of the combinations displayed quantifiable amounts of antibiotics for periods exceeding 48 h. Succinylation of gelatin-sealed grafts has been used to improve matrix–drug bonding via ionic reactions between the drug and the matrix [132]. Overall, a prosthesis soaking in antibiotic (passive adsorption) provides immediate preventive protection of the graft as the drug reservoir is depleted within 4–7 days after implantation. Ginalska et al. have recently reported an attempt to covalently immobilize gentamicin [133] and amikacin [134] to a gelatin-sealed PET graft via glutaraldehyde activation. They found that the antibiotic was bound in mixed-type way via three types of interactions, predominately strong covalent bonds but also weak interactions: physical adsorption and ionic bonds. Only 3 and 15% of the total drug amount was released in vitro within 7 days for gentamicin and amikacin, respectively, and the remaining drug was bound to the biomaterial surface at high concentrations for at least 30 days. During this period the protheses exhibited growth inhibition of several bacterial strains at low inoculum concentrations. They may thus offer better protection against bacterial infection and biofilm formation than previously described [134]. The mode of action of very firmly bound antibiotics against bacteria remains unknown, but it is possible that they alter bacterial adherence to the prosthesis without being released as free molecules [124].

An alternative to modified gelatin binding is offered by Blanchamain et al. [126,135] who demonstrate the feasibility of coating cyclodextrins (CDs) on vascular Dacron grafts. CDs are truncated torus-shaped cyclic oligosaccharides that have a hydrophobic internal cavity and a hydrophilic external wall, and are able to capture various active molecules and progressively release them unmodified. Dacron fibers are coated by a polycondensation reaction between CDs and citric acid as a cross-linking agent at 90 °C to form a polymer network of cross-linked CDs which physically adhere to the Dacron fibers. An in vitro drug release study of coated grafts demonstrated a linear release of vancomycin over 50 days [126].

6. Conclusions

This review article presents an extensive overview of published studies on antibiotic-eluting medical devices for various applications. These include bone cements, fillers and coatings for orthopedic applications, wound dressings based on synthetic and natural polymers, intravascular devices, vascular grafts and periodontal devices. Basic elements, such as our new composite core/shell fibers and structured films, can be used to build new antibiotic-eluting devices. The effect of the processing parameters on the microstructure and on the resulting antibiotic release profiles, mechanical and physical properties, and bacterial inhibition, must be elucidated in order to achieve the desired properties. New designs based on novel nano- and micro-structured basic elements may thus advance the therapeutic field of antibiotic-eluting devices.

References


