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Application of Materials as Medical Devices with Localized Drug Delivery Capabilities for Enhanced Wound Repair

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Abstract

The plentiful assortment of natural and synthetic materials can be leveraged to accommodate diverse wound types, as well as different stages of the healing process. An ideal material is envisioned to promote tissue repair with minimal inconvenience for patients. Traditional materials employed in the clinical setting often invoke secondary complications, such as infection, pain, foreign body reaction, and chronic inflammation. This review surveys the repertoire of surgical sutures, wound dressings, surgical glues, orthopedic fixation devices and bone fillers with drug eluting capabilities. It highlights the various techniques developed to effectively incorporate drugs into the selected material or blend of materials for both soft and hard tissue repair. The mechanical and chemical attributes of the resultant materials are also discussed, along with their biological outcomes *in vitro* and/or *in vivo*. Perspectives and challenges regarding future research endeavors are also delineated for next-generation wound repair materials.

Keywords

Material; Medical device; Wound repair; Drug delivery

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1. Introduction

A wound constitutes any physical injury to the body arising from injuries, diseases, or surgical interventions, characterized by superficial lacerations or penetration to underlying tissues, such as muscles, ligaments or bones [1, 2]. Minor wounds often heal through the body's intrinsic repair process that entails four consecutive phases: coagulation and hemostasis, inflammation, proliferation, and remodeling orchestrated by multiple cell populations (neutrophils, macrophages and fibroblasts), as well as through extracellular matrix formation and action of soluble mediators including growth factors and cytokines [3, 4]. Restoration is mostly impaired, however, in injuries of greater severity and may lead to wound exposure or tissue abnormalities [5, 6].

Consequently, materials frequently employed in the clinic are designed to stabilize the site of injury and aid in the healing process [7–9]. In order to be effective, wound repair devices should ideally possess similar mechanical properties to the tissue undergoing reconstruction [10–12]. Soft tissues (skin, tendon, ligaments, muscles) require more elastic and pliant materials such as polymers, as well as glues, sutures or dressings for wound closure [13–17]. On the other hand, stiff and strong materials, such as ceramics, metals and their alloys, are preferable for repairing hard tissues (bone, cartilage) [18–21].

The need for wound repair devices continues to steadily increase with greater than 114 million patients worldwide endure wounds from surgical procedures annually [22]. In the United States alone, 36 million patients experienced surgery-related wounds in 2012, and 31 million injured persons visited the emergency room in 2011 [23, 24]. The global wound care market totaled \$15.6 billion in 2014 and is anticipated to grow to \$18.3 billion by 2019 [25].

While many wound repair materials in current clinical use are reported to be effective, devastating wounds – mostly large defects – are highly susceptible to infection, pain, and abnormal inflammation [26, 27]. Cumbersome devices often employed for treatment may invoke secondary complications, such as foreign body reactions and chronic inflammation [28–33]. Multiple administrations of oral or injectable drugs may therefore be prescribed to combat these issues [34–36]. Such strategies rely primarily on systemic drug exposure, which may not optimally address local wound complications [37, 38].

As a result, developing wound repair devices coupled with localized drug delivery represents an avenue of tremendous interest. This review begins with a general discussion on materials for wound repair and related complications that may arise. Subsequent sections focus on soft and hard tissues – each surveying the landscape for drug-eluting materials and their influence on different aspects of wound healing. Finally, perspectives on future directions in this field are offered.

2. Wound repair devices

To begin, wound repair devices can be categorized according to the mechanical properties of the damaged tissue, namely soft and hard (Fig. 1 and Fig. 2). Soft tissues include skin, muscle, tendon, and ligaments, which exhibit relatively high flexibility and elasticity [39],

whereby in contrast, hard tissues consisting of bone or cartilage tend to have higher stiffness [40, 41].

Soft tissue wounds are inflicted via abrasion, laceration, avulsion, amputation, and penetration, as well as arising from burns, diseases, infections, or tumors [41]. Wound closure at these sites commonly involves sutures, staples or glues [42–44]. In the event of significant tissue loss, the defect can be covered or filled with dressings to prevent dryness or infection, as well as to potentially encourage tissue regeneration [45–47].

Filamentous surgical sutures (Fig. 1A) derived from either absorbable or non-absorbable materials are most prevalently used to seal dermal wounds and internal organs or to ligate blood vessels [42, 44, 48]. Absorbable sutures consist of biodegradable materials, such as catgut, collagen, poly(glycolic acid) (PGA), poly(dioxanone) (PDX), poly(glyconate) (PGC), poly(glactin) (PGL), poly(lactic-co-glycolic acid) (PLGA) and poly(trimethylene carbonate) (PTMC) [44, 48–53]. Since they do not require subsequent removal, they are preferable for treating internal organ wounds, such as in the stomach, colon and bladder [44, 48–50]. Non-absorbable sutures are composed of non-biodegradable materials, including silk, cotton, nylon, polyester and metal [49, 50]. Despite needing to be extracted upon conclusion of wound healing, non-absorbable sutures possess relatively higher tensile strength and are often applied to tissues warranting greater mechanical support, such as the skin, fascia, and tendons [44, 48].

Under circumstances demanding urgent care, surgical staples can be applied more readily than conventional sutures [54, 55]. They can be evenly spaced along large open wounds in the gastrointestinal organs, thereby better preventing leakage [54, 56, 57]. To ensure proper mechanical strength, surgical staples are primarily metal-based (stainless steel and titanium). Alternatively, absorbable staples consisting of synthetic polymers such as PGA and poly(lactic acid) (PLA) have been developed to minimize patient discomfort [53, 58–60].

Aside from sutures and staples, liquid surgical glue (Fig. 1B) provides a third option. It creates insoluble networks almost instantaneously to function as an adhesive, sealant and hemostat when applied to a wound [42, 43, 61–64]. Surgical glues have been prepared from an assortment of natural materials, such as fibrin, collagen and gelatin [43, 61, 65–67], as well as from synthetic polymers based on cyanoacrylate, dendrimers, urethane and ethylene glycol [43, 63, 68].

For large gaps in soft tissues, wound dressings (Fig. 1C) provide a physical barrier to maintain moist and airy environments that may stave off infection or further damage [37, 45, 69–71]. Wound dressings are largely fabricated from synthetic biopolymers, including poly(L-lactic acid) (PLLA), poly(lactic-co-glycolic acid) (PLGA), poly(ethylene glycol) (PEG) and polyurethane (PU), due to reproducibility and lower susceptibility to biological contamination [69, 72]. They are amenable to the majority of wound types [73] and help facilitate exudate removal from wounds [37, 74]. Furthermore, dressings serve as scaffolds for tissue regeneration, especially in severe burn wounds [75–78], and in these instances, they may consist of highly biocompatible, natural hydrogels, such as alginate, collagen or chitosan [69, 73].

Because wound conditions differ for hard tissues, the aforementioned items for soft tissues would therefore not provide adequate repair. Severe insults to bone lead to breakage as opposed to tears or lacerations. Bone fixation devices (Fig. 2A) are consequently employed to align and support fractured bones in desired positions [79, 80]. They come in a range of configurations depending on the application. Pins are used to temporarily fix fracture fragments or to serve as a guide for other fixation systems, and are commonly applied onto the wrist and arthrodesis. Additionally, screws are widely used for bone fixation alone or in combination with plates, wires or nails. Plates hold fractured bones together (generally in the spine, wrist, and long bones) to prevent their displacement and are typically attached with screws. Wires provide tension, position long bone fractures, or hold bone and soft tissue together. Intramedullary nails and rods introduced into the center of fractured bones to shield them from torsion or bending are generally applied to long bone fractures, such as the tibia and femur [81].

Indeed, bone fixation devices must be sufficiently rigid and able to withstand mechanical loads sustained by the body during the course of fracture repair. Metals and metal alloys address this criteria [18, 82] and are consequently integrated at high load bearing sites, such as the femur, hip, and tibia [82–84]. Synthetic polymer-based bone fixation devices have also been gaining considerable attention, since usage of biodegradable materials could negate subsequent removal. During the healing process, these synthetic materials also notably lose their strength to minimize stress-shielding and gradually confer mechanical loads back to native bone [79, 85, 86]. Polymeric fixation devices are more suitable for regions enduring relatively lower load, such as the ankles, hands and craniofacial bones. Commonly used bioabsorbable formulations include PGA, PLA, PDX, PLLA and poly(L,DL-lactic acid) (PLDLLA) [18, 79, 87]. To strike a better balance between elasticity and load-bearing strength, polymer-ceramic composites have been extensively investigated [18, 72, 83, 85].

In other instances, bone fillers (Fig. 2B) of various biological or synthetic substances can infiltrate large defects [18, 88]. Autologous bone derived from a patient's own body represents the gold standard material. However, its low availability and invasiveness of the extraction surgery prompt a critical need for other alternatives. Allogeneic bone and its demineralized form have been suggested as substitutes for autografts to improve tissue reconstruction in craniofacial defects and fractured gaps [88–90], but supply limitations remain. Consequently, synthetic alternatives, such as calcium phosphates [89, 91] and calcium sulfates have been widely incorporated into bone fillers [18]. Bone cements formulated from poly(methylmethacrylate) (PMMA), poly(ethylmethacrylate) (PEMA), and polyethylene (PE) have additionally been explored [72, 89, 90, 92]. As with bone fixation devices, composite bone fillers (often ceramic-polymer) ensure structural reinforcement and bioactivity in dental and load-bearing applications.

3. Device-related complications

Even after receiving appropriate treatment, large exposed wounds still face an array of complications, including infection [35, 93, 94], abnormal inflammation [95] and poor regeneration [96]. These issues lead to low patient compliance and prolonged

hospitalization, which create a substantial socioeconomic burden [35, 93, 97, 98]. For instance, the overall cost of healthcare-associated infections in the United States ranges from \$35.7 to \$45.0 billion annually and involves roughly 1.8 million patients [99]. It is therefore imperative to devise strategies that better address the challenges at hand.

Among the aforementioned issues, infection represents the most immediate complication. Its occurrence stems from microorganism infiltration into the body upon material implantation at the wound site [35, 100]. Severe wounds remain highly susceptible to infection primarily from the following two factors: (1) surgical/nosocomial transmission or (2) residual microbial existence on the surface of an implanted medical device [101], which becomes rapidly coated with extracellular matrix proteins, such as fibrinogen, fibronectin and collagen. These proteins promote multilayered microbial attachment and proliferation that manifest in the formation of a biofilm, becoming more resistant to antibacterial treatment [32, 98, 102]. The lingering presence of these biofilms causes abnormal chronic inflammation at the wound site and jeopardizes the healing process. Moreover, biofilms can contribute to orthopedic device failure, eventually culminating in the need for implant removal [103]. Surgical sutures, especially of the multi-filament variety, have been reported to be more susceptible to harboring microorganisms in their micro-gaps [104–106].

Aside from infection, inflammation can also result from injury [107, 108]. Following tissue damage, coagulation components such as a platelet and fibrin work to prevent blood loss [1, 109]. The cascade then recruits inflammatory cells such as neutrophils, macrophages and lymphocytes, whose functions include disposing of cellular debris and foreign matter [6], regenerating native cells, or forming scar tissue under circumstances requiring rapid wound closure [110]. While inflammation remains essential for wound healing, its associated symptoms, such as redness, heat, swelling, and pain, often intensify with large wounds and may contribute to patient discomfort. The foreign body reaction can additionally be triggered around the wound site. This complication extends the period of inflammation and retards the wound healing process, which can lead to device failure via rapid degradation, excessive fibrosis, restenosis, or calcification [111–114].

Furthermore, large wounds typically impede the normal reparative process [115]. Severe, prolonged acute inflammation results in chronic inflammation, subsequently generating excessive scar formation [108, 116] or unhealed wounds [108, 117]. Delayed wound closure comes with a higher risk for infection [118, 119] and may also cause severe inflammation. A handful of diseases have also been demonstrated to disrupt wound repair. For example, complications of late-stage diabetes may include damaged nerves or limited blood supply, leading to ulcers particularly at the body's lower extremities [120]. Patients with keloids are subjected to excessive scar formation from abnormal fibroblast proliferation and collagen deposition [121]. Moreover, osteoporosis hampers bone regeneration due to imbalanced activation between osteoclasts and osteoblasts (ex. higher bone resorption than bone formation) [122, 123].

To alleviate the aforementioned issues, drug therapy has been employed in clinical practice, oftentimes entailing systemic delivery through oral administration or intravenous injection [124, 125]. Antibiotics are widely used to prevent infection at the wound site; penicillin,

cephalosporins and tetracyclines are commonly available in the clinic [126–128]. However, these drugs may potentially cause diarrhea, vomiting, hearing loss, vertigo, kidney damage or liver failure [129–131]. Anti-inflammatory medications categorized as either steroid or non-steroid are commonly employed to modulate intense inflammatory symptoms. The most widely used drugs include dexamethasone, prednisone, acetaminophen, ibuprofen and naproxen by oral administration, or cortisone and ketorolac by local injection.[132–137]. Anti-inflammatories, however, also cause problems due to stimulation of vagus nerve activity, leading to increases in gastric acidity and ulcer formation [138, 139]. To minimize these undesirable side effects, wound treatment may rely on the local drug delivery strategies of bolus solution, emulsion, suspension, ointment, gel or dry powder [37, 140, 141], yet these approaches still require tedious procedures. The development of materials with localized drug delivery capabilities are thus envisioned to concurrently mitigate complications associated with large wounds and to promote effective repair.

4. Drug delivery medical devices for soft tissue repair

4.1. Surgical sutures

Selecting the appropriate suture type for a patient remains essential but challenging. The nature of the soft tissue wound and any possible allergic reactions the individual may have to a given material must be taken into consideration. As mentioned in an earlier section, suture materials can be classified as absorbable or non-absorbable. Absorbable sutures are biodegradable and conveniently do not require subsequent removal. On occasion, they may potentially elicit inflammatory responses. Non-absorbable sutures generally need to be recovered, but exhibit more robust mechanical strength than their absorbable counterparts. Presently, sutures coated with antimicrobial drugs have already received approval for select clinical applications [142–147]. Meanwhile in the laboratory, drug-eluting sutures that modulate inflammation or promote wound healing have also been developed (Table 1).

Surgical sutures for anti-infection—With the prevalence of wound infections, surgical suture materials with capacity for localized drug release have been actively investigated for soft tissue wound treatment over the past decade. The most prevalent strategy involves dip-coating the suture in a given drug solution [98, 142–146, 148–151]. The drug simply adsorbs onto the suture surface, resulting in low drug loading efficiency and nearly instantaneous drug release.

Because drug retention and prolong anti-infection effects are beneficial for wound healing, suture surface modifications can be made prior to drug loading. For example, sutures may be coated with biocompatible hydrogel materials, such as chitosan, sodium alginate and calcium alginate, and then immersed into an antimicrobial drug solution, such as tetracycline, rifampin or chloramphenicol [152]. This approach improves drug retention in the hydrogel layer, as well as better sustained release. In another study, vinylimidazole grafted onto suture material provided imidazole units that served as interaction sites for ciprofloxacin immobilization [153]. As a result, the antibiotic was released slowly over the course of four to five days and demonstrated an evident zone of inhibition against *E. coli*. To further sustain drug release, Choudhury et al. impregnated amoxicillin into the suture core

using oxygen plasma treatment to greatly enhance the hydrophilicity of muga (*Antheraea assama*) silk fibroin (AASF)-based sutures [154]. The drug-loaded AASF suture exhibited a clear zone of inhibition against *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*), whereas its drug-adsorbed counterpart exhibited no apparent antibacterial activity. *In vivo* studies corroborated this finding, revealing that drug-loaded AASF sutures facilitated better wound healing due to reduced infection risk.

In addition to the aforementioned strategies, drug-loaded strands [155], microparticles [156] or nanofibers [157, 158] have been used to coat the suture surface or to comprise the body of the suture. For example, nanofibers were fabricated by electrospinning a solution consisting of PLLA and either tetracycline or cefotaxime, which were then braided to produce a multifilament surgical suture. The drug release from these sutures was reported to exceed five days. Drug release kinetics could be tailored by modulating the mass ratio between PLLA and drug. With coaxial fibers, the drug and PLLA were localized within the core and on the surface respectively, thereby permitting more sustained drug release [158].

Regarding commercialization of drug-eluting sutures, Ethicon developed Coated Vicryl® Plus Antibacterial (polyglactin 910), an absorbable surgical suture containing the drug triclosan, in 2004. *In vitro* studies with *S. aureus* and *E. coli* showed that Coated Vicryl® Plus exhibited a zone of inhibition correlating to its apparent antimicrobial activity and significantly reduced the adherence of methicillin-resistant *S. aureus* (MRSA) on the surface [98]. Biocompatibility tests performed with Coated Vicryl® Plus revealed that the suture was neither toxic nor irritating [143]. Furthermore, an *in vivo* study in which Coated Vicryl® Plus and non-drug-containing sutures were separately implanted into guinea pigs for 48 hours and subsequently explanted demonstrated that Coated Vicryl® Plus with triclosan reduced the bacterial population by 96.7% compared to conventional sutures [144]. Ethicon later launched MONOCRYL®_Plus Antibacterial (poliglecaprone 25) and PDS® Plus Antibacterial (polydioxanone) in 2008. These drug-loaded sutures implanted into mouse and guinea pig infection models also showed better inhibition of bacterial colonization compared to their uncoated counterparts [145, 146].

The efficacy of triclosan-coated sutures was further demonstrated in clinical studies. Non-drug-containing and triclosan-coated sutures were employed for wound closure in cerebrospinal fluid shunt surgery [148]. Among the 84 patients involved, triclosan-coated sutures significantly decreased the rate of shunt infection from 21% to 4.3%. Another study consisting of 2088 individuals triclosan-coated sutures applied to abdominal wound closure decreased the rate of infection from 10.8% to 4.9% [149]. In addition to triclosan, chlorhexidine has also been employed in commercialized antimicrobial surgical sutures [159], but reports on the efficacy of this suture type prove scarce.

Surgical sutures for inflammation modulation—In contrast to infections that can be treated with early, extensive drug exposure, inflammation lingers locally at injured sites for a relatively long period until completion of wound healing and requires prolonged, sustained delivery of anti-inflammatory drugs. To achieve this goal, a variety of drug-loading strategies have been proposed for long-term drug release.

In one scenario, sutures were dip-coated with a nonsteroidal anti-inflammatory drug (NSAID), ibuprofen, prepared in the organic solvent dichloromethane [160]. This way, the suture could swell during immersion in the solution, allowing more drug to diffuse deeply into the suture core. Drug loading concentration and release pattern could therefore be controlled by varying the duration of suture immersion. Consequently, drug was released for 7 days with different loading amounts depending on the immersion time. Ibuprofen was also incorporated into surgical sutures using a layer-by-layer deposition method [161]. In this instance, the surface of the silk surgical suture was first coated with multiple layers of chemically cross-linked poly(allylamine hydrochloride) and dextran microgels. Due to the electrostatic interaction between the microgel layers and drug molecules, ibuprofen was released in a sustained manner for 10 days. Applying a third method, Lee et al. prepared a separate drug-loaded strand by electrospinning a PLGA solution with ibuprofen, which was then physically braided with the surgical suture in clinical use [155]. Outcomes from pain-induced animal models revealed that the drug was released for six days, and that pain could be mitigated until completion of wound healing.

In another electrospinning approach, Padmakumar et al. [162] attempted a core-sheath electrospinning configuration to fabricate mechanically strong sutures with a PLLA center encased by PLGA containing either aceclofenac or insulin. The authors observed that the aforementioned drugs could be released in a sustained manner over several days *in vitro*. Moreover, aceclofenac-loaded sutures contributed to inflammation reduction *in vivo*, whereas sutures with insulin promoted cell migration when assayed *in vitro*.

Finally, another strategy for extending the drug release timeframe entailed synthesizing polyethyleneimine (PEI)-coated PLGA microparticles loaded with dexamethasone [156]. This coating conferred a positive charge to the microparticles, thereby enabling them to be immobilized via electrostatic interactions onto the negatively charged suture surface. The resulting material was reported to elute drug for up to 28 days *in vitro*.

4.2. Wound dressings

Larger soft tissue injuries may require augmentation with wound dressings as opposed to sutures, which consist of a sterile patch or pad to promote healing and prevent further infection. Their chief roles include absorbing exudate, encouraging healing, easing pain, and protecting from infection. Traditionally, wet or dry gauze was employed to conceal a wound. These basic dressings have gradually evolved into materials specifically designed to control environmental moisture and to deliver drugs or active ingredients (specific chemicals, cells, growth hormones) to the site of interest.

Particularly in recent years, much effort has been devoted to designing wound dressing materials that administer a diverse range of drugs for anti-infection [76, 163–166], anti-inflammation [119] and tissue regeneration [167, 168]. Drugs are often first blended with polymers, which are subsequently used as constituents to prepare the wound dressings [167, 169–171]. Akin to methods for deriving drug-loaded sutures, a drug can be absorbed (or adsorbed) directly onto the material [172, 173] or encapsulated in carriers, such as polymer-based microparticles, prior to incorporation into the wound dressings [166, 168]. The following section discusses commercialized materials and relevant technologies (Table 2).

Wound dressings for anti-infection—For decades, wound dressings have been commercially developed with infection prevention in mind. Products that have been marketed for various applications include Iodosorb[®], Bactigras[®], and Xeroform[®]. Iodosorb[®] was formulated with iodine and proved effective in treating both acute and chronic human wounds [174–177]. Bactigras[®] consisted of tulle wound dressings medicated with chlorhexidine, which were designed to prevent infection in partial and full-thickness wounds in the short-term. Xeroform[®], a petrolatum impregnated with antiseptic agent bismuth tribromophenate, was developed specifically with surgical incisions, lacerations and burns in mind. In addition to these aforementioned materials, wound dressings containing povidone, polymyxin, neomycin, and bacitracin were also made available in the clinic [172, 173, 178].

However, many commercialized drug-eluting wound dressings did not consider the timeframe for local drug exposure. Various techniques have therefore been executed to achieve sustained drug release. In an earlier study, Lin et al. [166] prepared wound dressings consisting of sulfamethoxazole-loaded poly(N-isopropylacrylamide) (PNIPAAm) microparticles with Eudragit E film. The resulting material effectively absorbed wound fluid, and sulfamethoxazole was released from the PNIPAAm microparticles for 75 hours. In another approach, Rossi et al. fabricated wound dressings by freeze-drying a solution of chitosan hydrochloride, 5-methyl-pyrrolidinone chitosan and chlorhexidine [179], which exhibited sustained release of chlorhexidine for over 48 hours. According to *in vitro* studies with bacterial (*S. aureus*, *Staphylococcus epidermidis* (*S. epidermidis*), *Pseudomonas aeruginosa* (*P. aeruginosa*)) and fungal (*Candida albicans*) strains, the material loaded with chlorhexidine was observed to have effective antimicrobial activity.

Applying a UV-radiation polymerization strategy, Tsou et al. [169] fabricated ciprofloxacin-loaded 2-hydroxymethacrylate wound dressings. The resulting product demonstrated *in vitro* drug release for 6 days and retained antibacterial activity for up to 12 days. In another study, Kim et al. [170] pursued a sol-gel process to fabricate poly(vinyl alcohol) (PVA)/alginate hydrogel matrices containing nitrofurazone. Alginate was shown to enhance protein adsorption on these wound dressings. *In vivo* results demonstrated that nitrofurazone-loaded hydrogels improved wound healing in rats as a consequence of enhanced antibacterial activity.

In addition to sustained antibiotic release, another important endeavor has been to mimic the nanofibrous structure of the extracellular matrix in soft tissues. To that end, electrospinning has been leveraged to generate wound dressings since drugs can be readily introduced into a polymeric solution and their release properties controlled by changing the material and altering fiber morphology [180]. Antibiotics such as tetracycline, ciprofloxacin, levofloxacin, moxifloxacin and cefazolin have been successfully incorporated into solutions of biocompatible polymers, such as PLA, poly(ϵ -caprolactone) (PCL), PLDLLA, PEG, and PLGA to produce drug-loaded nanofibrous mats [171, 181, 182]. These dressings also exhibited prolonged drug release and enhanced antimicrobial activity.

Recently, hydrocolloid wound dressings loaded with benzalkonium chloride (BC) were prepared using a hot melting method [81, 183]. The product displayed better mechanical

strength and flexibility compared to that of commercial wound dressings. BC-containing wound dressings contributed to a decrease in antimicrobial activity (*S. aureus*, *E. coli*, *P. aeruginosa*) *in vitro*, whereas this outcome was not observed in the untreated and commercial wound dressing groups. Furthermore, a rat-based excision wound model revealed that using BC-loaded wound dressings led to a higher percentage of healing (~84%) compared to the controls (untreated ~36%, commercial wound dressings ~57%). Using a modified thermally activated phase separation method, Siafaka et al. designed porous dressings for levofloxacin delivery [184]. Levofloxacin was loaded into the dressing (5–30%) by free-radical polymerization using chitosan with 2-hydroxyethylacrylate materials and released for up to 132 hours. Antibacterial performance was evaluated using three different bacterial strains (*S. aureus*, *M. staphylococcus aureus* and *P. aeruginosa*) and results showed a significant effect on the zone of inhibition.

Wound dressings for inflammation modulation—Additionally, the delivery of anti-inflammatory drugs, together with an anti-infection drug, has been utilized to improve wound healing. Thakur et al. reported on a wound dressing containing both the anesthetic lidocaine and the antibiotic mupirocin [185]. A dual spinneret electrospinning apparatus was used to collect two distinct PLLA fibers – each loaded with lidocaine or mupirocin, respectively. The resulting dressing exhibited antibacterial action for over 72 hours, with a comparably large initial release of lidocaine for potential treatment of early pain in large wounds. In another study, polyethylene oxide films were produced by solvent casting to contain the antibiotic streptomycin and the anti-inflammatory diclofenac [186], and demonstrated that both drugs could be released in a sustained manner for 72 hours. Using drugs with dual functions offers a good strategy for more comprehensive wound care.

Wound dressings for tissue regeneration—To more actively aid tissue regeneration at local wound sites, several groups have investigated dressings with growth factor delivery capabilities. Maeda et al. developed a collagen-based dressing loaded with human growth hormone (hGH), whose release profiles varied based on material composition and preparation conditions [167]. Wound healing was significantly improved due to enhanced tissue regeneration in the presence of hGH. In a similar vein, gelatin-based wound dressings containing epidermal growth factor (EGF) were prepared by Ulubayram et al. [168]. When applied to wounds on the dorsal region of rabbits, a substantial effect on wound healing was observed compared to that of control groups sans EGF.

4.3. Surgical glues

Surgical glues prove advantageous for wound closure because they enable quick application, minimal pain and no subsequent removal. Materials used in surgical glues, such as fibrin glue, albumin and urethane, can rapidly form a rigid, hardened structure and also demonstrate good biocompatibility [187–189]. Among the available options, fibrin glue has been widely investigated as a carrier for drugs, biological factors, or genes [190–194]. Due to its high water uptake and pore-forming abilities, fibrin glue has additionally been studied in the form of tissue engineering scaffolds [195–197]. However, few reports discuss the application of medicated surgical glues for enhancing wound healing processes.

In recent years, drug-eluting surgical glues have been leveraged to mitigate infection and pain. Osada et al. [198] evaluated the safety and pharmacokinetics of fibrin glue loaded with the antibiotic sisomicin. In live animals, the local drug concentration at the glued site was observed to be higher, when compared to that of the group receiving intravenously injections of sisomicin. When tested in ten human subjects, the drug-loaded glue did not cause any infection. For pain relief, Zhibo et al. [199] and Kitajiri et al. [200] prepared a fibrin glue containing lidocaine and tested its efficacy in sub-pectoral breast augmentation and tonsillectomy, respectively. In both cases, individuals receiving the combined entity of surgical glue and lidocaine reportedly experienced less pain compared to the control groups that had either lidocaine only or fibrin glue only. While these clinical studies were small in scale, preliminary results show promise and should be further elaborated.

5. Drug-eluting medical devices for hard tissue repair

5.1. Orthopedic fixation devices

Fixation devices in the form of plates, rods, screws or pins afford stability during bone fracture repair. The two modes of fixation are external and internal. External fixation involves positioning wires or pins (connected to rods) that penetrate the skin around the fracture [81]. Internal fixation aims to expedite the return of mobility and function at the site of injury, where the various implants may be directly attached to the bone fragments in need of repair [81]. Metals have been traditionally employed as the material of choice because of their sturdy mechanical properties exceeding that of native bone. Stainless steel is most commonly used, though titanium has also been applied due to its more desirable biological characteristics. Polymers have more recently been explored as an alternative; however, balancing mechanical strength and degradation properties remains a significant challenge for researchers.

Orthopedic fixation devices for anti-infection—In an effort to reduce the incidence of infections, current research endeavors have largely focused on designing fixation devices with localized drug delivery capabilities. Gulati et al. [201] designed titanium nanotube arrays on titanium wires as a release platform for gentamicin, which exhibited a two-phase release profile (burst release, followed by zero-order kinetics). *In vitro* studies showed that covalently binding vancomycin to titanium rods could prevent growth of *S. aureus*, even after exposure to serum proteins, prolonged incubation in physiological buffer, and serial exposures to the bacterial strain [202]. Forster et al. [203] developed a gentamicin-coated polyurethane sleeve, allowing for localized administration to combat pin tract infections. *In vitro* release studies revealed that the eluted antibiotic concentrations exceeded performance standards outlined by the National Committee for Clinical Laboratory Standards. Tobramycin impregnated into hydroxyapatite (HA)-coated external fixation pins was released above the *S. aureus* mean inhibitory concentration over eight days [204]. While these preliminary results seem promising, the implant's *in vivo* performance should next be studied. In another study, Lucke et al. [205] used a rat model of osteomyelitis to test the efficacy of PDLA-coated titanium Kirschner wires containing gentamicin. The group found that incorporating antibiotic significantly minimized *S. aureus* colonization, whereas coating-only and uncoated controls failed to stop bacterial growth *in vivo*. Sanchez and

colleagues studied gentamicin release profiles both *in vitro* and *in vivo* from implants consisting of a calcium phosphate-synthetic polymer blend [206]. The addition of PDLA or PLGA coatings was shown to prolong the release rate. Notably, implants with an outer layer of PDLA sustained gentamicin concentrations over four weeks *in vivo* exceeding the minimum bactericidal concentration. Histology and radiographs demonstrated that PDLA-coated implants promoted bone formation in rat femurs over 20 weeks. Mäkinen et al. [207] incorporated ciprofloxacin into PLGA screws, which were contaminated with *S. aureus* prior to implantation into rabbits. Upon retrieval six weeks later, these antibiotic-impregnated devices did not cause infections; conversely, stainless steel screws were unable to stave off infection. In this case, no fracture had been induced in the animals.

While antibiotic-laden implants show promise, the path to clinical translation demands strategies that will ensure sufficient antibiotic concentrations to swiftly eradicate any bacteria around the wound site [208]. Concerns regarding potential development of antibiotic resistance have also prompted the use of alternative antimicrobial compounds, namely chlorhexidine, poly(hexamethylenbiguanide) and chloroxylenol [208]. More insight is nevertheless warranted to better understand the effects of antimicrobial-eluting implants on neighboring tissues. Exploring other candidate agents, Holt et al. [209] showed that titanium external fixation pins layered with xerogel films releasing nitric oxide could substantially diminish the presence of bacteria, as well as the potential for infection following 28 days in rat vertebrae.

Orthopedic fixation devices for tissue regeneration—Aside from reducing infection, fixation devices have also been developed to promote tissue regeneration at the injury site. In an early study, Schmidmeier et al. [210] incorporated transforming growth factor β 1 (TGF- β 1) and insulin-like growth factor-1 (IGF-1) into PDLA coatings for steel and titanium Kirschner wires. 42 days post-implantation in a rat fracture model, the growth factors retained their bioactivity and improved the biomechanics of animals in comparison to uncoated counterparts. A later work using the aforementioned coating and therapeutic molecules on titanium plates reported significant mineralization *in vivo*, while providing stability to the fracture site in parallel [211]. Titanium alloy discs coated with calcium phosphate and BMP-2 were able to induce bone formation in rats [212]. Likewise, Bae et al. [213] functionalized titanium discs with BMP-2, and osteoblast cells seeded onto these materials were shown to proliferate faster. Moreover, upregulation of osteogenic markers was observed. Lee et al. [214] designed dual-function heparin-dopamine titanium implants that administered substrate, as well as significant stimulation of osteoblasts. Likewise, Baas et al. [215] incorporated recombinant human BMP-2 and pamidronate into coatings for titanium screws. Dual administration prevented fibrous tissue formation, but unfortunately did not have the intended effect of lowering resorption accompanying BMP usage. Additionally, these implants exhibited the worst fixation. Alternatively, cholesterol-lowering drugs such as statins have been employed since they are cost-effective. For example, titanium Kirschner wires with high dose simvastatin-loaded PLGA coating loaded with a high dose of simvastatin were implanted into rat tibial fractures and performed similarly to BMP-2 in terms of bone formation [216].

5.2. Bone fillers

A wide array of bone fillers has been developed in the laboratory to augment voids in large defects or to serve as a bonding agent in joint replacement procedures, such as total hip arthroplasty. Injectable variants are particularly attractive, since they can minimize the invasiveness often associated with surgical intervention. As with any foreign material, bone fillers introduced into the human body create the potential for infection, and consequently, tremendous efforts have been undertaken to develop materials that can thwart microbes. Furthermore, bone fillers may be used to stimulate tissue repair via the incorporation of various compounds or therapeutic molecules.

Bone fillers for anti-infection—To combat infection, antibiotics have been loaded into a variety of materials, and have largely yielded favorable results against specific strains of bacteria in laboratory studies. Polymeric materials have been utilized as antibiotic carriers due to their compositional tunability and their degradation properties. Brooks et al. [217] evaluated tobramycin release kinetics from PCL coatings on bone allograft and coralline ceramic fillers over six weeks *in vitro*. Encapsulating the antibiotic in oil and incorporating PEG into the PCL coating was demonstrated to minimize the initial burst release typically characteristic of drug-loaded materials. In a subsequent study, several members from the aforementioned group employed molten-casting to produce PCL-calcium carbonate/phosphate composites that could release tobramycin exceeding 10 weeks [218]. A short-term study demonstrated that these bone fillers could effectively inhibit *S. aureus* growth. Koort et al. [219] administered ciprofloxacin via incorporation into PDLLA 50:50 pellets for 300 days, though noting a substantial delay period of 60 days. This observed lag period needs to be shortened for optimal antibiotic release. Henslee et al. [220] developed polypropylene fumarate/carboxymethylcellulose (CMC) space maintainers loaded with antibiotic-containing PLGA microparticles. Colistin and clindamycin were successfully released for prolonged periods exceeding relevant bacterial minimal inhibitory concentrations (MICs). Finally, Shah et al. [221] loaded clindamycin either encapsulated in PLGA microparticles or directly in the CMC porogen of PMMA space maintainers and evaluated these constructs in a rabbit model of critical-size mandibular defects infected with *Prevotella melaninogenica*. The PLGA microparticles were intended to extend the antibiotic release timeframe and attenuate the typical profile of a burst release seen with direct incorporation of the drug. At 12 weeks post-implantation, bony bridging of the defect was seen in one-third of the rabbits, but this outcome was not distinct to a specific experimental group.

Another prevalent strategy involves calcium-based ceramics and bioactive glass, which are commonly used due to their osteoconductive properties. Domingues et al. [222] loaded tetracycline or tetracycline/ β -cyclodextrin into sol-gel solutions of bioactive glass and discovered that the latter delayed antibiotic release. Both experimental conditions significantly impeded *Aggregatibacter actinomycetemcomitans* colonization *in vitro* compared to pure bioglass surfaces. Xia and Chang [223] adsorbed gentamicin onto mesoporous bioactive glass for controlled release. The resulting system retained more antibiotic, had a slower rate of release that hinged on pH or ionic concentration, and stimulated HA formation *in vitro*. Tobramycin elution from calcium carbonate HA ceramic composites implanted in rabbit radial defects resulted in minimized infection susceptibility

to *S. aureus* [224]. Control animals necessitated premature euthanasia, whereas no infection but some foreign body response was noted at eight weeks when the rabbits receiving antibiotic were sacrificed. Xie et al. [225] compared vancomycin delivery from calcium sulfate and borate-based bioglass in a rabbit model, finding that both were highly MRSA-negative compared to non-antibiotic containing controls. Interestingly, histological results identified good bone formation through antibiotic-eluting borate glass, but very little in the antibiotic-eluting calcium sulfate counterparts. Tuning the porosity of brushite-forming bone cement could influence the release of vancomycin and ciproflaxin, with low porosity being optimal [226]. However, results were contingent on drug solubility as well. The authors observed in this case a largely negated burst release and a practically linear elution trend.

Composite bone void fillers have also been developed to leverage the attractive properties of different materials. Arcos et al. [227] designed glass/PMMA composites, with the underlying rationale being that the glass would provide bioactivity conducive for bone regeneration, while PMMA's hydrophobic nature would prevent a burst release of gentamicin. In another study, Mäkinen et al. [228] evaluated the therapeutic efficacy of ciproflaxin, which was incorporated into pellets consisting of biodegradable PLGA and osteoconductive bioglass microparticles, in a rabbit model. Over three months, the antibiotic was release locally, and new bone was observed around the implant site. A noted drawback of using bioceramics is that they tend to require high processing temperatures, which may compromise the incorporated drug's bioactivity. With this in mind, Lee et al. chose silica xerogels because they conveniently undergo a sol-gel transition at room temperature and modified them with the natural polymer chitosan with the aim of making their mechanical properties and drug release profiles more favorable [229]. Based on the preliminary *in vitro* data, chitosan improved the implant's mechanical properties closer to that of cortical bone and enabled extended, lower concentration vancomycin release still exceeding the MIC for *S. aureus*.

Potential synergism stemming from dual antibiotic release has additionally been investigated, namely by incorporating both β -lactam- and aminoglycoside-based drugs. For example, vancomycin and gentamicin loaded in PMMA spacers exhibited a high initial release and sustained profiles when implanted into clinical subjects undergoing total hip replacement surgery [230]. The majority of patients (17 out of 20) displayed lower markers for infection. More recently, Arias et al. [231] conducted a study using vancomycin, daptomycin, or gentamicin, as well as PEG600, a compound that helps prevent *S. epidermis* biofilm formation. The group observed that vancomycin yielded superior results to daptomycin and gentamicin, but further noted that combining daptomycin with gentamicin or PEG600 was able to entirely prevent biofilm formation by *S. epidermis*.

Bone fillers for tissue regeneration—Infection prevention aside, bone fillers have also served as carriers to stimulate bone repair. Thormann et al. [232] prepared calcium phosphate cements containing strontium, which was identified in a number of previous studies to possess osteoconductive properties. The resulting constructs were implanted into rat osteotomy defects and led to bone formation at the site of injury that was significantly greater than with calcium phosphate cements alone. Tahara and Ishii [233] loaded the anti-cancer drug *cis*-diamminedichloroplatinum (CDDP) into calcium phosphate cements, aiming

to locally restore tissue at sites of resected bone tumors. They evaluated the bone fillers containing different weight percentages of CDDP using a rabbit model and found that exceeding 10% CDDP was uncondusive for bone formation. In another work, Maus et al. [234] investigated the effects of adding recombinant human BMP-2 to β -tricalcium phosphate (β -TCP) *in situ* hardening cements implanted in an ovine trepanation defect model. The resulting bone was comparable in amount to that observed when using autografts, though it was still less than that achieved with pure β -TCP. The authors surmised that BMP-2 did not provide additional osteoinductive effects because the dense cement composition may have impeded tissue ingrowth during the early timeframe at which BMP-2 is mostly released. Likewise with a BMP-2 delivery system in mind, Saito et al. [235] discussed a body of work focused on poly(D,L-lactic acid)-poly(p-dioxanone)-poly(ethylene glycol) block copolymer (PLA-DX-PEG), noted for its biodegradability and thermosensitivity. Recombinant human BMP-2/PLA-DX-PEG was implanted into critical-size iliac bone defects in rats, and four weeks later, bone formation was observed. Moreover, to demonstrate minimal invasiveness, a heated solution of BMP-2 and PLA-DX-PEG was injected percutaneously into the femurs of mice, and new bone tissue was noted at that area three weeks later. The effectiveness of BMP-2/PLA-DX-PEG was also evaluated in concert with other materials, such as porous HA blocks and titanium fiber-mesh cylinders. Signs of bone formation were evident when these composites were implanted in their respective animal models. Finally, Maehara et al. [236] observed that a lower concentration (10 μ g/ml) of fibroblast growth factor-2 (FGF-2) administered from HA/collagen composites resulted in superior repair of rabbit osteochondral defects compared to both higher FGF-2 dosage-containing (100 μ g/ml) constructs or material alone.

6. Perspectives on next-generation wound repair devices

The design and fabrication of efficient drug delivery materials remains of vital importance to the field of healthcare. As shown in previous work, medical devices have been used to administer a wide range of drugs and proteins to combat infection, modulate inflammation and enhance tissue regeneration. A pivotal role of drug-incorporated medical devices during the wound repair process is to provide mechanical strength at the site of injury, as well as to prevent undesirable biological complications.

In the quest to design suitable carriers for bioactive agents, researchers have taken into consideration the attributes of natural and synthetic materials. Natural polymers are generally endowed with the properties of biocompatibility and biodegradability; moreover, they can potentially influence cell behavior. These materials, however, are not as amenable to customization and tend to have less robust mechanical strength. Conversely, synthetic polymers can be relatively easily tailored, but do not have bioactive properties. Composite materials have thus been developed to leverage the advantages of both types. Material configuration will furthermore be informed by the nature of the injury. Soft tissue wounds can be repaired using sutures, glues or dressings, whereas hard tissue injuries require fixation devices or bone fillers.

Ongoing work should focus on improving the release kinetics of drugs and bioactive factors. The characteristic initial burst release often observed from medical devices may cause some

toxicity *in vivo* and could be further minimized by designing “smart” materials that are more controllable, perhaps by incorporating stimulus-responsive mechanisms [237,238]. Approaches that better harness polymer degradation to be aligned with the rate of tissue regeneration will also be invaluable. Additionally, studies that delve into furthering our understanding of how various material properties affect tissue repair will be tremendously beneficial, creating new insights for rational tuning of these materials to enhance their interactions with host tissue. Addressing all of these points would help increase the safety and efficacy of drug-eluting medical devices and bring them one step closer to clinical translation.

In aspects of manufacturing, improved technologies for materials processing are imperative. Simplified methods that could circumvent the use of harsh organic solvents [239] or high processing temperatures [240] would be particularly attractive, since these conditions may potentially render therapeutic drugs biologically inactive. The feasibility of such techniques would also depend on how well they can be scaled-up for commercial production with high quality and at low cost.

Since wound healing encompasses a complex, coordinated series of events, next-generation drug-eluting medical devices should place more emphasis on multiple drug combinations with varying release profiles. Only a few studies to-date have employed multiple drugs in one system, so this is a direction with exciting potential for growth in the coming years.

Summarily, wound repair through drug-incorporated materials has made large strides in the research setting. The hurdle from bench-to-bedside is not insignificant, but with promising results from *in vitro* and *in vivo* studies, the next task at hand will be clinical validation of these technologies. Continued innovations in material development, material processing strategies, and drug loading are highly anticipated in the coming years, and will lead to safer and more effective wound treatments.

7. Conclusions

An array of medical devices has been developed to support the wound healing process. However, several complications still remain: infection, inflammation and limited tissue regeneration. In the past 15 years, many studies have focused on developing materials with local drug delivery capabilities to enhance soft and hard tissue wound repair. Various drug loading techniques such as dip coating, absorption and simple blending method have been successfully coupled with diverse materials to vary drug release profiles and improve efficacy of wound healing.

Indeed, many challenges and further improvement still remain. The wound healing process entails complex stages involving various factors and cytokines, proving difficult to control different aspects of device-related complications simply through the use of one drug. Even if multiple drug-eluting medical devices are successfully developed in the laboratory, clinical trials and commercialization may still present significant hurdles. Nevertheless, we hope that this review provides insights that could direct further developments in drug-loaded materials for wound repair.

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Abbreviations

AASF	<i>Antheraea assama</i> silk fibroin
BC	benzalkonium chloride
BMP-2	bone morphogenetic protein-2
β-TCP	β-tricalcium phosphate
CDDP	<i>cis</i> -diamminedichloroplatinum
CMC	carboxymethylcellulose
<i>E. coli</i>	<i>Escherichia coli</i>
EGF	epidermal growth factor
FGF-2	fibroblast growth factor-2
hGH	human growth hormone
HA	hydroxyapatite
IGF-1	insulin-like growth factor-1
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NSAID	nonsteroidal anti-inflammatory drug
<i>P. aeruginosa</i>	<i>Pseudomonas aeruginosa</i>
PCL	poly(ε-caprolactone)
PDLLA	poly(D,L-lactic acid)
PDX	poly(dioxanone)
PE	poly(ethylene)
PEG	poly(ethylene glycol)
PEI	poly(ethyleneimine)
PEMA	poly(ethylmethacrylate)

PGA	poly(glycolic acid)
PGC	poly(glyconate)
PGL	poly(glactin)
PLA	poly(lactic acid)
PLGA	poly(lactic-co-glycolic acid)
PLA-DX-PEG	poly(D,L-lactic acid)-poly(p-dioxanone)-poly(ethylene glycol)
PLDLLA	poly(L,DL-lactic acid)
PLLA	poly(L-lactic acid)
PMMA	poly(methylmethacrylate)
PNIPAAm	poly(N-isopropylacrylamide)
PTMC	poly(trimethylene carbonate)
PU	polyurethane
PVA	poly(vinyl alcohol)
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
<i>S. epidermidis</i>	<i>Staphylococcus epidermidis</i>
TGF-β1	transforming growth factor- β 1
TNT	titania nanotube

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Figure 1.
Representative schematic images of medical devices for soft tissue repair: (A) surgical suture, (B) surgical glue, and (C) wound dressing.

Figure 2. Representative schematic images of medical devices for hard tissue repair: (A) orthopedic fixation device with pins affixed to bone and (B) bone filler. Illustrations were adapted from ChemBioDraw (version 14.0, PerkinElmer, Waltham, MA)

Table 1

Various examples of drug-loaded surgical sutures. The sutures were commonly dip-coated into a drug solution or into a blend of drug and encapsulation materials. Drug-loaded sutures prepared using other methods are annotated.

Functionality	Drug	Drug Loading Strategy	Drug Encapsulating Materials	Drug Release Timeframe	Reference
Anti-infection	Triclosan	Adsorption	N/A	N/A	[98, 142–146, 148, 149]
	Ciprofloxacin	Immobilization	N/A	95–120 h	[153, 241]
	Amoxicillin	Impregnation	N/A	336 h	[154]
	Chlorhexidine, Octenidine	Fatty acid	Lauric acid/palmitic acid	96 h, 168 h	[150, 151]
	Tetracycline, Rifampin, Chloramphenicol	Polymer	Chitosan, alginate	96 h	[152]
Anti-inflammation	Tetracycline, Cefotaxime	Polymer nanofibers	PLLA	144 h, 240 h	[157, 158] ^a
	Ibuprofen	Polymer	Copolymer of PLA, PCL and PTMC	120 h	[160]
		Polymer strands	Poly(allylamine hydrochloride) and dextran	240 h	[161]
	Dexamethasone	Polymer microparticles	PLGA	144 h	[155] ^b
	Acetofenac or insulin	Polymer nanofibers	PLGA	672 h	[156] ^c
			PLGA	240 h or 168 h	[162]

^a Drug was encapsulated in the polymer nanofibers, which were then braided to prepare drug-loaded surgical sutures.

^b Drug was encapsulated in the polymer strands, which were then wound around a surgical suture.

^c Sutures were dip coated in suspension of drug-loaded polymer microparticles.

Table 2

Various examples of drug-loaded wound dressings. Drugs were largely absorbed into wound dressings or blended with the encapsulation materials. Drug-loaded dressings prepared through other strategies are annotated.

Functionality	Drug	Drug Loading Strategy	Drug Encapsulation Materials	Drug Release Timeframe	Reference
Anti-infection	Chlorhexidine	Polymer	Chitosan, 5-methylpyrrolidinone chitosan	48 h	[179]
	Ciprofloxacin		Poly(2-hydroxyethyl methacrylate)	144 h	[169]
	Tetracycline		PLA, PCL	48 h	[171]
	Ciprofloxacin, levofloxacin, moxifloxacin		PLDLLA, PEG	6.7 h	[181]
	Levofloxacin		Chitosan, 2-hydroxyethylacrylate	132 h	[184]
	Cefazolin		PLGA	N/A	[182]
	Benzalkonium chloride		Styrene-isoprene-styrene copolymer, Sodium alginate	N/A	[183]
	Nitrofurazone	Hydrogel	PVA, Alginate	N/A	[170]
	Sulfamethoxazole	Microparticles	PNIPAAm	75 h	[166] ^a
Anti-infection and pain relief	Mupirocin, Lidocaine	Polymer	PLLA	72 h	[185]
Anti-infection and anti-inflammation	Streptomycin, Diclofenac	Polymer	Poly(ethylene oxide)	72 h	[186]
Tissue regeneration	Human growth hormone	Hydrogel	Collagen	168 h	[167]
	Epidermal growth factor	Microparticles	Gelatin	N/A	[168] ^a

^a Drug-loaded polymer microparticles were separately prepared and incorporated in wound dressings.

Table 3

Various examples of drug-loaded orthopedic fixation devices.

Functionality	Drug	Drug Loading Strategy	Drug Encapsulation Materials	Drug Release Timeframe	Reference
Anti-infection	Gentamicin	Polymer	PDLLA	48 hours	[205]
	Ciprofloxacin		Phosphate, PLLA	28 days	[206]
	Gentamicin		PLGA	84 days	[207]
	Gentamicin	Adsorption	TNT	11 day	[201]
Tissue regeneration	Chlorhexidine, poly(hexamethylenebiguanide), Chloroxylenol		Titanium dioxide layer	N/A	[208]
	Vancomycin	Covalent bonding	Titanium rods	N/A	[202]
	Gentamicin	Impregnation	N/A	182 days	[203]
	Tobramycin	Immersion	HA	8 days	[204]
	Nitrogen oxide	Dip coating	Xerogel	3 days	[209]
	TGF- β 1/IGF-1	Polymer	PDLLA	42 days	[210, 211]
	BMP-2	Immersion	N/A	35 days	[212, 213]
	Gentamicin/BMP-2	Immobilization	Heparin-Dopamine	28 days	[214]
	Simvastatin		PDLLA	N/A	[216]

Table 4

Various examples of drug-loaded bone fillers.

Functionality	Drug	Drug Loading Strategy	Drug Encapsulation Materials	Drug Release Timeframe	Reference
Anti-infection	Tobramycin	Polymer	PCL, PEG	42 days	[217]
					[218]
	Ciprofloxacin		HA, PCL, PEG	70 days	[224]
	Clindamycin		PDLLA	300 days	[219]
	Gentamicin		PLGA	28 days	[221]
	Ciprofloxacin	Mixture	Bioactive glass and PMMA	14 days	[227]
	Vancomycin		PLGA	150 days	[228]
			Borate glass	28 days	[225]
			Xerogel-chitosan	30 days	[229]
			PMMA	10 days	[230]
Tissue regeneration	Gentamicin/vancomycin		PMMA	N/A	[231]
	Gentamycin/vancomycin/daptomycin				
	Clindamycin Colistin	Microparticles	Poly(propylene fumarate) PLGA	77 days	[220]
	Tetracycline	Sol-gel	Bioactive glass	80 days	[222]
	Gentamicin	Adsorption	Mesoporous bioactive glass	20 days	[223]
	Vancomycin/ciprofloxacin	Cement	Calcium phosphate	4 days (vancomycin), 14 days (ciprofloxacin)	[226]
	Strontium	Cement	Calcium phosphate	N/A	[232]
	CDDP		Calcium phosphate	28 days	[233]
	BMP-2		Calcium phosphate	N/A	[234]
	BMP-2	Mixture	PLA-DX-PEG	N/A	[235]
	FGF-2	Impregnation	HA/collagen	N/A	[236]