Special Section on Drug Delivery Technologies—Mini review

Smart Drug Release from Medical Devices

Carmen Alvarez-Lorenzo and Angel Concheiro
Departamento de Farmacología, Farmacia y Tecnología Farmacéutica, R+DPharma Group (GI-1645), Facultad de Farmacia, and Health Research Institute of Santiago de Compostela (IDIS), Universidade de Santiago de Compostela, Santiago de Compostela, Spain

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ABSTRACT

Medical devices are becoming key players on health monitoring and treatment. Advances in materials science and electronics have paved the way to the design of advanced wearable, insertable, and implantable medical devices suitable for the prevention and cure of diseases and the physical or functional replacement of damaged tissues or organs. However, intimate and prolonged contact of the medical devices with the human body increases the risks of adverse foreign-body reactions and biofilm formation. Drugs can be included in/on the medical device not only to minimize the risks but also to improve the therapeutic outcomes. Drug-eluting medical devices can deliver the drug in the place where it is needed using lower doses and avoiding systemic effects. Drug-device combination products that release the drug following preestablished rates have already demonstrated their clinical relevance. The aim of this mini-review is to bring attention to medical devices that can actively regulate drug release as a function of tiny changes in their environment, caused by the pathology itself, microorganisms adhesion or some external events. Thus, endowing medical devices with stimuli-responsiveness should allow for precise, on-demand, regulated release of the ancillary drugs to expand the therapeutic performance of the medical device and also should serve as a first step to offer personalized solutions to each patient. Main sections deal with smart drug-eluting medical devices that are sensitive to infection-related stimuli, natural healing processes, mechanical forces, electric fields, ultrasound, near-infrared radiation, or chemicals such as vitamin C.

Introduction

Human health quality has undergone an unprecedented improvement in the last century, which is evidenced as the decrease in the death ratio at infancy and the much longer life expectation. Such health achievements are mainly associated with better feeding, the prevention of pandemic illnesses through worldwide-distributed vaccines, advances in less-invasive surgical maneuvers under clean conditions, and the development of treatments that turn incurable illnesses into chronic ones or that go to the roots of the illness to reverse it (Fielding, 1999). The strong evolution of pharmacologic and radiotherapy approaches has been critical for these achievements (Heath and Colburn, 2000; Bhide and Nutting, 2010). At present, most health-monitoring systems and treatments involve the use of precisely designed medical devices. According to the U.S. Food and Drug Administration (FDA), medical devices comprise a large variety of instruments, apparatuses, implants, and in vitro reagents intended for the diagnosis, prevention, or cure of diseases or to affect the structure or any function of the body, which do not achieve any of their primary intended purposes through chemical action. Such (bio)chemical action has been restricted to the medicaments (FDA, 2018b). Flash glucose monitoring systems; versatile stents that allow simultaneous diagnostic and therapeutic maneuvers, particularly in the gastrointestinal organs; devices that trap blood clots and help reduce stroke risk; noninvasive devices that allow assessment of head injuries at point-of-care; test devices for solid tumors that help make immunotherapy decisions; advanced dermal regeneration matrices that can regenerate native tissues, particularly intended for diabetic ulcers; breast imaging devices that offer high-contrast, real, three-dimensional (3D) images of all structures; implantable drug infusion pumps that precisely deliver the correct amount of drug needed at each time; and sensors inside oral medicines that track whether the medication has been taken and send the information to a smartphone app or web portal, among others are not a dream. All these are already counted in the list of the most innovative medical devices (Kirsh, 2018). Advances in materials sciences and electronics are behind sophisticated, wearable medical devices that allow continuous monitoring of

ABBREVIATIONS: 3D, three dimensional; DES, drug-eluting stents; FDA, U.S. Food and Drug Administration; NIR, near-infrared; NSAIDs, nonsteroidal anti-inflammatory drugs; PAA, poly(acrylic acid); PLGA, poly(lactic-co-glycolic) acid; PNIPAAm, poly(N-isopropylacrylamide).
certain physiologic functions for diagnosis or of pharmacologic levels of therapeutic substances for efficient personalized treatments (Yetisen et al., 2018).

Despite these achievements, the use of medical devices carries the intrinsic risk of causing adverse foreign-body reactions or other side effects from the adherence of the user’s proteins and cells or from the proliferation of microorganisms (Anderson, 2001). Medical devices are categorized into three classes according to their intended use and the risk they may pose to the patient or the user. Invasiveness increases these risks, so devices intended to penetrate the body and remain in contact with or inside the body for prolonged time should follow very strict rules. Yet adverse events remain common; for example, restenosis associated with vascular stents (Iqbal et al., 2013), posterior capsule opacification associated with intraocular lenses after cataracts surgery (Nibourg et al., 2015), or biofilm formation on urinary catheters, bone prostheses, or central venous catheters with the subsequent infection spreading in host tissues (De Angelis et al., 2010; Wallace et al., 2017) affect a relevant percentage of patients and have had a strong economic impact on health care systems.

The evolution of materials science has been enormous in improving the performance and safety of medical devices (Teo et al., 2016), but in most cases the risks have been strongly minimized by combinations with the right drugs (Couto et al., 2012; Alvarez-Lorenzo et al., 2017). Systemic treatments prescribed to patients wearing medical devices still have relevant untoward effects—for instance, the risk of respiratory and gastrointestinal disorders associated with post-implantation pain and inflammation treatment, bleeding events due to thrombosis therapy after the implantation of stents or other blood-contact biomaterials, or emerging microbial resistance from using prophylactic antimicrobial therapy (Bhusal et al., 2016; Reviaikine et al., 2017).

As an alternative, the advantages of incorporating the drug on/in the medical device itself are clear. The drug is delivered in the place where it is needed (usually a place that is hardly accessible through a systemic route), which lowers the amount required (lower dilution, fewer barriers, and slower clearance); the device itself may adjust the release to the therapeutic demands. This strategy increases both efficiency and safety, and it is not dependent on patient compliance (Wenke and Gueiker, 2011; Bhusal et al., 2016; Cyphert and von Recum, 2017; Sanchez-Rechach et al., 2017). However, endowing medical devices with the drug-delivery performance is not a simple task because most materials do not uptake sufficient amounts and/or do not regulate the release according to the therapeutic needs (Alvarez-Lorenzo and Concheiro, 2013; Lee et al., 2017).

The increasing demand for medical devices with improved or even novel performance parameters has blurred the boundary between medicaments and medical devices. Historically, pharmaceutical companies have been drug-centric and the medtechs have been technology device-centric; however, both sectors have joined in offering patient-centric approaches with a strong life-changing impact. Indeed, the definition of medical device provided by the World Health Organization (WHO) is now wider: even if a medical device does not achieve its primary mode of action by pharmacologic, immunologic, or metabolic means, it may be assisted in its intended function by such means (WHO, 2018). In this regard, combination products have appeared as a novel, broad regulatory category, which includes any binary or ternary combination of a drug, biologic product, and/or device (Alvarez-Lorenzo and Concheiro, 2013; FDA, 2018c).

Drug–device combination products in which the device is responsible for the primary mode of action—it makes the greatest contribution to the overall intended therapeutic effects, while the drug performs as an ancillary medicinal substance—are commonly known as drug-eluting devices or drug-enhanced device products. Drug-eluting stents (DES) are a clear example of the strong research in this field (Huang et al., 2014). The use of coronary bare-metal stents remarkably reduced the mortality associated with coronary artery diseases, but the risk of failure due to in-stent restenosis was approximately 30% patients (Holmes, 2003). The first-generation DES, introduced in 2002, relied on antiproliferative agents incorporated into a polymer coating that regulated the release. This product can be considered as the first regulated drug–medical device combination product (Simard et al., 2014).

Nevertheless, coatings with nonbiodegradable polymers (first generation) or thinner inorganic composites (second generation) trigger inflammatory responses that cause late stent restenosis. Biodegradable coatings (third generation) may attenuate some of the untoward events, but the polymer itself may still be responsible for adverse immune reactions. Thus, current efforts are focused on polymer-free stents that can still regulate drug release through a very precise design of the topology of the stent surface and a slowdown of intrinsically solubility rate of the drug (Acharya and Park, 2006; Sanchez-Rexach et al., 2017; Kommineni et al., 2018; Konishi et al., 2018). Some of these fourth-generation DES as well as several other drug–device combinations products are already in the market (Table 1).

It should be noted that the drug can be included in the matrix of the device during fabrication, layered as a coating in a subsequent step, or placed into a specific reservoir. The two latter options are preferred for labile ancillary drugs or for matrices whose mechanical properties may be affected if the drug is incorporated (Raval and Parikh, 2010).

This mini-review revisits the recent advances in medical devices that can actively regulate drug release as a function of tiny changes in their environment caused by the progression/remission of the pathology, the growth of microorganisms, or some external events. Thus, in contrast to medical devices (such as stents) that release the drug in a sustained, preestablished rate, as reported elsewhere (Zilberman and Elsner, 2008; Concheiro and Alvarez-Lorenzo, 2013), the following sections deal with medical devices endowed with stimuli-responsiveness as a tool for efficient drug loading and elution as a function of specific demands.

Medical devices made of materials that can modify their properties as a function of stimuli coming from inside or outside the body have been attracting a great deal of attention. As a relevant example, strong efforts are being made in the design of 3D architectures for implantation with properties that evolve over time. These five-dimensional systems may offer advantages in terms of shape-memory that facilitates the implantation through minimally invasive maneuvers and adapts to the required shape once placed in the patient (Oliver et al., 2016; Antony et al., 2017). Similarly, hydrogels, which undergo phase volume transitions (e.g., modify the swelling) as a function of tiny changes in certain variables in
Infection-Responsive Antimicrobials-Eluting Medical Devices. Medical devices are prone to microorganism contamination not only before implantation via contact with the skin or mucosa of the patient but also after implantation if latent microorganisms migrate from infection foci in other parts of the body (Percival et al., 2015). The settling of microorganisms on a medical device usually evolves as biofilm formation: a highly structured community undergoes phenotypic changes mediated by a quorum sensing communication mechanism that makes the microorganisms highly resistant to conventional antimicrobial agents (Remy et al., 2018). Thus, once a biofilm has formed, its eradication is difficult; the risk of it spreading to other tissues through bloodstream is high and could compromise the patient's life. Implantable medical devices are responsible of almost 50% of nosocomial infections (WHO, 2011).

Even in a less acute situation, biofilm formation may compromise the mode of action of the medical device; for example, biofilms may block catheter flow (Jones et al., 2005) or delay the natural healing of wounds if they colonize either the suture or the adjacent tissue (Hong et al., 2018). Various bone cements that incorporate antimicrobial agents are already on the market, but they usually release most of their drug on the first day, followed by sustained elution of sometimes subtherapeutic doses, which may compromise the prophylactic role (King et al., 2018). Because the prolonged release of antimicrobials may cause adverse events and favor antimicrobial resistance (McLaren, 2004), a variety of stimuli-responsive polymers have been tested for the development of drug nanocarriers capable of site-specific delivery of antimicrobial agents in the infection location. More recently, they have been used to adorn medical devices with networks that release the antimicrobial agent...
Main mechanisms explored so far to endow medical devices with infection-responsive behavior against biofilm formation. (A) Coatings that switch antimicrobial drug release on/off in response to enzymes and pH changes associated with microbial growth. (B) Contact-killing moieties in the presence of microorganisms. (C) Bioinspired moieties that resemble natural receptors of the microorganisms and transfer the antimicrobial agent through a competitive mechanism.

Changes in pH also can be exploited to trigger the release of antimicrobial agents immobilized on the device surface. The surface of medical devices can be easily modified with poly(acrylic acid) (PAA) by use of either plasma polymerization or gamma-ray grafting approaches; PAA-grafted chains act as intermediates for binding cationic drugs through strong ionic interactions (Mendes, 2008; Alvarez-Lorenzo et al., 2010). Remarkably, changes in pH in the typical range of microorganism growth may reverse the affinity and thus trigger the release of the drug, as demonstrated for vancomycin and antimicrobial peptides (Ruiz et al., 2008; Muñoz-Muñoz et al., 2012; García-Vargas et al., 2014; Traba and Liang, 2015). In case of the lytic peptide agents, their direct transfer from the device to the bacteria membrane and the increase in their activity as the pH decreases strongly contributes to the inhibition of biofilm formation (Traba and Liang, 2015).

Interestingly, PAA grafts also allow for the spontaneous formation of gold nanoparticles on the surface of the medical devices, which opens the way to near-infrared (NIR) responsive photothermal ablation of biofilm (Cabana et al., 2017). Grafting of cationic polymers has been explored for loading anionic antimicrobial agents (Contreras-García et al., 2011). Also, antimicrobial agents covalently linked to the medical device through labile bonds have shown pH-responsive release in media mimicking bacteria growth (McCoy et al., 2016).

Urease-producing microorganisms cause an increase in the pH of urine, which may lead to salt deposition on the lumen of catheters and their blockage. To prevent this phenomenon, urinary catheters have been coated with a reservoir containing bacteriophages with a sealing layer of pH-responsive Eudragit S100. The coating is stable in the presence of urease-negative bacteriophages with a sealing layer of pH-responsive Eudragit S100, have been designed to act as infection-responsive theragnostic materials. Layers of PAA and chitosan-trapping ciprofloxacin, sealed with Eudragit S100, have been designed to undergo distinct chromatic color transitions from blue to purple and red as the pH becomes more alkaline, acting as a sensor for early infection and also as a warning of the risk of
blockage. Moreover, the pH-responsive release of the antimicrobial agent notably decreased bacterial growth in an in vitro infected bladder model (Zhou et al., 2018).

A second family of self-defensive materials relies on the design of surfaces that trap microorganisms and kill them through immobilized biocide groups (Luna-Straffón et al., 2014; Huang et al., 2015). Contac-killing surfaces have been prepared that combine the temperature-responsive poly(N-isopropylacrylamide) (PNIPAAm) with biocidal quaternary ammonium salts. At 37°C, PNIPAAm brushes are shrunk, and the biocidal groups protrude on the surface. Thus, bacteria that adhere to the surface through hydrophobic interactions are exposed to the biocidal agent. The killed bacteria can be removed from the surface by washing in water at temperature below the low critical solubility temperature of PNIPAAm (Pavlukhina et al., 2012). The surface also can be designed to exhibit the opposite performance: oligo(ethylene glycol) methacrylate and vinyl-functionalized nalidixic acid derivatives designed to exhibit the opposite performance: oligo(ethylene glycol) methacrylates conjugated with antimicrobial peptides (Lu et al., 2015).

Thus, applying ergosterol on medical devices has been investigated as a way to endow the surface with the capability of hosting therapeutically efficient amounts of antifungal agents and of retaining them at physiologic pH without leakage; the release is triggered when a fungal infection has been mimicked (Segura et al., 2014). Tests performed in the presence of Candida albicans showed the fungi-responsive, ergosterol-functionalized devices efficiently inhibited biofilm formation.

A different approach was explored with cyclodextrin-functionalized wound dressing. Cyclodextrins have the ability to host quorum-sensing inhibitors and antimicrobial agents forming inclusion complexes, and they also can host quorum-sensing signaling molecules—that is, the molecules released by bacteria to communicate with each other and develop biofilm (Okano et al., 2016). Thus, cyclodextrin-functionalized gauzes were successfully loaded with hamamelitannin (a quorum-sensing inhibitor) and vancomycin, and then they were exposed to S. aureus monospecies biofilm and to S. aureus plus Pseudomonas aeruginosa mixed biofilm mimicking a chronic wound infection. Relevantly, the loaded gauzes decreased biofilm formation and increased bacteria susceptibility toward vancomycin in both biofilm types. The release of the active ingredients was favored by the presence of the quorum-sensing signaling molecules due to competitive mechanisms for forming inclusion complexes with the cyclodextrins (Brackman et al., 2016).

**Drug-Eluting Medical Devices for Smart Regenerative Medicine.** In addition to infection prevention, orthopedic implants, vascular grafts, and other medical devices intended for tissue regeneration demand the release of active substances that can mimic the natural cascade that takes places during the natural healing process (Bagherifard, 2017). Strong efforts are being made to create synthetic devices that can stabilize the site of injury, with mechanical properties similar to the tissue to be repaired and an architecture that allows host-cell colonization. Encouraging the adhesion of...
specific cell types and their further growth should be carefully
driven toward efficient regeneration that avoids scarring or
unnecessary healing delays (Winkler et al., 2018).

Any injury triggers a healing cascade that involves three
phases: inflammation, proliferation, and maturation, with the
participation of different cells. Migration of inflammatory cells
is essential for healing because they not only remove bacteria
and foreign materials but also release critical enzymes and
cytokines for the subsequent phases. However, an excessive,
prolonged inflammation may delay the healing, degrade
the scaffold, and provoke fibrosis and scarring. Thus, the
inflammation-triggered release of anti-inflammatory drugs
has been explored as a way of recapitulating natural
tissue regeneration. For example, the covalent grafting of
nonsteroidal anti-inflammatory drugs (NSAIDs) via ester
assays has been shown to be useful in regulating NSAID release as
inflammation; overexpression of esterases
triggers the release of ibuprofen
Pan et al. (2015)

Fibrin scaffolds containing drug-loaded
sonosensitive emulsion droplets

Fibrin scaffolds containing bFGF encapsulated
in monodispersed emulsion droplets

Chondroitin sulfate-platelet lysate hydrogel
encapsulating magnetic nanoparticles and
cell

Polyethylene glycol) hydrogels cross-linked with
metalloproteinase substrates and loaded with
angiogenic peptide drugs

Fibrin scaffold with heparin-binding growth
factors

Mechanically Activated Drug Release. Medical devices
inserted or implanted in the body are subjected to physiologic
stress and are also susceptible to the action of externally
applied forces. A variety of strategies have been explored to
trigger drug release using the common mechanical stimuli of
compression, tension, and shear (Fig. 3). Physiologic mechan-
ical stimuli and the principles behind the design of mechano-
responsive drug delivery systems have been recently reviewed
elsewhere (Wang et al., 2017), and relevant examples are
summarized in Table 4.

Compressive medical devices are formed by elastomers
(viscoelastic materials) that withstand compressive load-
ings. Compression may allow the release of a certain amount
of drug through a squeezing-like mechanism. For example,
wound dressings that elute hydrocortisone in response to
mechanical stimuli have been designed from alginate hydro-
gels bearingrafted cyclodextrins. The responsiveness has
been attributed to changes in the conformation of the cyclo-
dextrin cavity and the hydrogel network as function of the
pressure, which impels the release of the drug from the

TABLE 3
Examples of stimuli-responsive release from scaffolds for regenerative medicine

<table>
<thead>
<tr>
<th>Drug-Eluting Medical Device</th>
<th>Triggered Stimulus</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>NSAID-immobilized hydrogels coating</td>
<td>Inflammation; overexpression of esterases triggers the release of ibuprofen</td>
<td>He et al. (2017)</td>
</tr>
<tr>
<td>NSAID-immobilized electrospun fibers</td>
<td>Ultrasound; each droplet releases the drug at specific acoustic pressure</td>
<td>Moncion et al. (2018)</td>
</tr>
<tr>
<td>Fibrin scaffolds containing drug-loaded sonosensitive emulsion droplets</td>
<td>In vivo ultrasound triggered release of the growth factor for efficient angiogenesis</td>
<td>Silva et al. (2018)</td>
</tr>
<tr>
<td>Chondroitin sulfate-platelet lysate hydrogel encapsulating magnetic nanoparticles and stem cells</td>
<td>Magnetic field modulates the release of platelet lysate growth factors and, in turn, the tendon- and bone-like matrix synthesis</td>
<td>Van Hove et al. (2015)</td>
</tr>
<tr>
<td>Polyethylene glycol) hydrogels cross-linked with metalloproteinase substrates and loaded with angiogenic peptide drugs</td>
<td>Cell-released metalloproteinases for regulation of in vivo angiogenesis</td>
<td>Van Hove et al. (2015)</td>
</tr>
<tr>
<td>Fibrin scaffold with heparin-binding growth factors</td>
<td>Cell-produced heparinase for triggering bFGF release and enhancing peripheral nerve regeneration</td>
<td>Sakiyama-Elbert and Hubbell (2000)</td>
</tr>
</tbody>
</table>

bFGF, basic fibroblast growth factor; NSAIDs, nonsteroidal anti-inflammatory drugs.
cycloextrin cavity and thus accelerates the diffusion out of the hydrogel (Tan et al., 2015). Also, soft contact lenses containing either drugs or comfort ingredients are being designed to release these hydrophilic components toward the cornea surface during blinking (Galante et al., 2015). The pressure of the eyelid on the hydrogel surface combined with the shear stress (dragging components from the contact lens surface) may allow for a pulsate release of the lubricating macromolecules, making wearing the lenses more comfortable and minimizing the risk of dry eye symptoms (Alvarez-Lorenzo et al., 2019).

Tension forces are typical of stents. Several layered composite systems have been reported useful for achieving tension-driven drug release. Stretching of polyelectrolyte films can open nanopores, which act as nanovolvels that allow the exit of the drug but close when the film is at rest (Mertz et al., 2007). Similarly, drug-loaded polymer layers coated with a thin titanium layer develop micro-sized cracks when subjected to external tensile strains. The crack area is proportional to the applied strain, and the cracks perform as channels for drug release (Jeon et al., 2018). A different strategy relies on the coating of esophageal stents with superhydrophobic multi-layers containing drug-loaded microparticles; the crack propagation of the superhydrophobic coating can be triggered by physiologic forces that facilitate the entrance of the release medium in the coating, thus releasing the drug from the microparticles. The release of both hydrophobic and hydrophilic drugs has been shown to be dependent on the applied strains (Wang et al., 2016, 2018).

Also, stretching may accelerate the release of antimicrobial agents from hydrogels prepared with cycloextrin monomers. Once again, the deformation of the cycloextrin cavity drives the release of the previously encapsulated drug molecule (Ballance et al., 2018). Intriguingly, deformable catheters have been tested for the removal of preformed biofilms using strain forces. C. albicans biofilms have been detached from prototypes by selectively inflating the inner chambers, which causes strain on the surface (Maskarinec et al., 2018).

Shear-forces are particularly relevant in the cardiovascular system, and large increases in shearing occur when the vessels become narrow due to physiologic or pathologic events (e.g., atherosclerotic plaques or clots) (Saxer et al., 2013). Indeed, direct correlations between sirolimus release from PLGA films and flow rate of the medium have been found, which may have an impact on DES (Zheng et al., 2017). Nevertheless, much knowledge is still required to reproduce in vitro biorelevant conditions of blood flow (Revakine et al., 2017).

**Electric-Responsive Release.** Natural mechanical stimuli can be transformed into electrical stimuli that trigger drug release from a medical device. As a proof of concept, disposable gastric lavage tubes were coated with a piezoelectric network made of poly(vinylidene fluoride-co-hexafluoropropylene) and reduced graphene fillers (PEI-rGO/PVDF-HFP). On these were subsequently deposited a polyamidoamine (PAMAM) dendrimer able to host a variety of drugs, including the antiemetic metoclopramide. Pressure on the gastric lavage tube mimicking human swallowing force (7–10 kPa) was transformed by the piezoelectric network into an electrostatic field (2.7 V) to accelerate drug release. The purpose was the attenuation of nausea to facilitate the intubation process itself. The release rate under the mechanical stimulus was approximately 2-fold the rate recorded at rest. In addition to the wavelike motion of the esophagus, manual deformation of the external portion of the gastric tube caused a similar effect on drug release, and the generated voltages remained in the safe interval for the human body (Zhang et al., 2018).

A different approach consists in exploiting the electrical fields generated by some implantable medical devices during their normal functioning. For example, cochlear implants restore a functional level of hearing to profoundly deaf individuals by means of the electrical stimulation of spiral ganglion neurons. The device involves an electrode array that is implanted into the scala tympani of the cochlea. However, the continuous electrical discharges to activate the central auditory pathways may exacerbate the loss of more hair cells (responsible for the sensorineural deafness), causing the apoptosis of more neurons. This untoward effect may be solved by coating the electrodes with a conductive polymer layer containing therapeutic neurotrophins. The generated electrical stimulus increases the release of the neurotrophic proteins, increasing

### TABLE 4
Examples of mechanically activated drug release from medical devices

<table>
<thead>
<tr>
<th>Drug-Eluting Medical Device</th>
<th>Triggered Stimulus</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Drug-loaded contact lenses</td>
<td>Eyelid compression</td>
<td>Galante et al. (2015)</td>
</tr>
<tr>
<td>Stents coated with drug-loaded polyelectrolyte films that act as pressure-responsive nanovalves</td>
<td>Tension</td>
<td>Mertz et al. (2007)</td>
</tr>
<tr>
<td>Drug-loaded polyurethane coated with a thin titanium metal layer that develops micro-crack under strain</td>
<td>Tension</td>
<td>Jeon et al. (2018)</td>
</tr>
<tr>
<td>Esophageal stents coated with a superhydrophobic layer embedding drug-loaded microparticles</td>
<td>Tension</td>
<td>Wang et al. (2016, 2018)</td>
</tr>
<tr>
<td>Polyacrylamide-cycloextrin hydrogels loaded with quinine</td>
<td>Tension</td>
<td>Ballance et al. (2018)</td>
</tr>
<tr>
<td>Sirolimus-loaded PLGA coating</td>
<td>Shearing</td>
<td>Zheng et al. (2017)</td>
</tr>
</tbody>
</table>

PLGA, poly(lactic-co-glycolic) acid.
the biocompatibility (Richardson et al., 2009; Thompson et al., 2010, 2011).

Also, cochlear implants have been combined with gene therapy to stimulate spiral ganglion neurite regeneration. The electrode array was arranged to create a close-field electroporation for efficient transduction of adjacent mesenchymal stem cells. The regenerated neurites improved the auditory response (Pinyon et al., 2014).

Other Stimuli. As mentioned with biofilm eradication, immobilization of gold nanoparticles on medical devices allows exploiting their NIR sensitiveness. Therefore, irradiating with an external source of NIR may cause local heating, useful for direct thermal ablation of cells (tumor cells, proliferative cells, bacteria) but also for the controlled release of drugs encapsulated in temperature-responsive materials. This strategy has been investigated for esophageal stents implanted to prevent tumor recurrence with combined gold nanoturfs and doxorubicin (Fig. 4) (Lee et al., 2018).

Finally, vitamin C has been shown to be useful for deactivating the adhesion of dressings to wounds to facilitate their peeling from damaged skin without causing a secondary trauma. Such vitamin C responsiveness relies on its capability to disassemble the protein supramolecular structures contained in the wound dressings (Zhao et al., 2018). This capability could be also exploited for triggering the release of encapsulated drugs.

Conclusions

Medical devices that can precisely regulate the time at which the ancillary drug should be released offer undoubted advantages over devices designed for a preestablished release rate. The amount of drug that can be hosted by the medical

![Fig. 4. Structure and performance of an esophageal stent coated with a nanoturf structure containing gold (Au) and doxorubicin (DOX) for combining thermotherapy and chemotherapy.](image)
devices is limited (because of limited affinity and also to avoid changes in bulk properties), so regulating the moment at which the drug is delivered is critical for maximizing its prophylactic/therapeutic performance. Smart drug-eluting medical devices have benefited from the knowledge gathered on stimuli-responsive drug nanocarriers.

Additional specific stimuli can be exploited in the case of medical devices. Cell-triggering release of growth factors from orthopedic implants may determine the fate of the both the cells and the implant, allowing for optimized healing. Or natural physical forces exerted onto the medical device can directly, or by previous transformation into an electric field, act as efficient stimuli to release drugs that can either minimize untoward reactions (e.g., emesis) or help restoring natural functions (e.g., hearing).

Advances in materials science and pharmaceutical technology together with deeper knowledge about the physiologic variables that can serve as stimuli make foreseeable upgraded medical devices that are more sensitive and robust in the release response and may even have theranostic capabilities. Such devices could play a key role in the health care system in the near future.

The incorporation of drugs into medical devices to create device-led combination products adds complexity to the regulation pathway, compared with solely medical device products. Nevertheless, the efforts that are being made by the regulatory agencies to clarify the premarket pathways are very valuable (Office of Combination Products, 2019).

Authorship Contributions

Performed data analysis: Alvarez-Lorenzo, Concheiro.

Wrote or contributed to the writing of the manuscript: Alvarez-Lorenzo, Concheiro.

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Address correspondence to: Angel Concheiro, Departamento de Farmacología, Farmacia y Tecnología Farmacéutica, R+DPharma Group (GI-1645), Facultad de Farmacia, and Health Research Institute of Santiago de Compostela (IDIS), Universidade de Santiago de Compostela, 15782-Santiago de Compostela, Spain. E-mail: angel.concheiro@usc.es