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Smart Drug Release from Medical Devices

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Running Title: Smart Drug-eluting Medical Devices

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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 pre-stablished 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 to a better feeding, the prevention of pandemic illnesses through worldwide-distributed vaccines, the 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 pharmacological and radiotherapy approaches has been critical for these achievements (Heath and Colburn, 2000; Bhide and Nutting, 2010). Nevertheless, although sometimes omitted, most health-monitoring systems and treatments involve the use of precisely designed medical devices.

According to the US Food and Drug Administration (FDA), medical devices comprise a large variety of instruments, apparatus, implants, in vitro reagents, etc, intended for the diagnosis, prevention or cure of diseases or to affect the structure or any function of the body, and which do not achieve any of their primary intended purposes through chemical action. Such (bio)chemical action has been restricted to the medicaments (US Food and Drug Administration, 2018a). Flash glucose monitoring systems, versatile stents that allow simultaneous diagnose and therapeutic maneuvers particularly in the gastrointestinal organs, devices that trap blood clots and help reduce stroke risk, non-invasive 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 3D images of all structures, implantable drug infusion pumps that precisely deliver the correct amount of drug needed at each time, 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 but they 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 certain physiological functions for diagnosis or of pharmacological levels of therapeutic substances for efficient personalized treatments (Yetisen et al., 2018).

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

Although the evolution in materials science has been enormous trying to improve the performance and safety of medical devices (Teo et al., 2016), in most cases the risks have been shown to strongly minimize when combined with the right drug (Couto et al., 2012; Alvarez-Lorenzo et al., 2017). Systemic treatments prescribed to the patients wearing medical devices still have relevant untoward effects; risk of respiratory and gastrointestinal disorders associated to post-implantation pain and inflammation treatment, bleeding events due anti-thrombosis therapy after implantation of stents or other blood-contact biomaterials, or emerging microbial resistances using prophylactic antimicrobial therapy (Bhusal et al., 2016; Reviakine et al., 2017). As an alternative, the advantages of incorporating the drug on/in the medical device itself are clear; namely, the drug is delivered in the place where it is needed (usually a place that is hardly accessible through a systemic route) and thus the amount required is lesser (lower dilution, less barriers to be solved, and slower clearance)

and the device may adjust the release to the therapeutic demands. This strategy increases both efficiency and safety, and it is not dependent on patient compliance (Wenke et al., 2011; Bhusal et al., 2016; Cyphert and von Recum, 2017; Sanchez-Rexach 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 performances is contributing to that the boundaries between medicaments and medical devices are blurring. Historically, pharma companies have been drug-centric and the medtechs have been technology device-centric, but the joint of both sectors offers patient-centric approaches with a strong life-changing impact. Indeed, the definition of medical device provided by the World Health Organization (WHO) is wider and remarks that although the medical device does not achieve its primary mode of action by pharmacological, immunological or metabolic means, it may be assisted in its intended function by such means (WHO, 2019). In this regard, combination products have appeared as a novel, broad regulatory category that involves any binary or ternary combination of a drug, a biological product and a device (US Food and Drug Administration, 2018b; Alvarez-Lorenzo and Concheiro, 2013). Drug-device combination products in which the device is still the responsible for the primary mode of action (PMOA), i.e., 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 to coronary artery diseases, but the risk of failure due to in-stent restenosis was ca. 30% patients (Holmes, 2003). The first generation of DES was introduced in 2002 and relied on anti-proliferative 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 non-

biodegradable 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 be still behind 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 intrinsic 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 drug-eluting stents 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 either in the matrix of the device during fabrication, as a coating in a subsequent step or into a specific reservoir. These two latter options are preferred for labile ancillary drugs or for matrices that may worsen their mechanical properties if the drug is included into (Raval et al., 2010).

The aim of this mini-review is to revisit the recent advances on medical devices that can actively regulate the release of the drug 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, differently from medical devices (including stents) that release the drug in a sustained, pre-established rate which have been 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 able to modify some of their properties as a function of stimuli coming from inside or outside of the body are attracting great attention. As a relevant example, strong efforts are been made in the design of 3D architectures for implantation with properties that evolve along time. These 4D systems may offer advantages in terms of shape memory facilitating the implantation through minimally invasive maneuvers and adopting the required shape once placed in the patient (Oliver et al., 2016; Antony et al., 2017). Similarly, hydrogels that undergo phase volume transitions (e.g., modify the swelling) as a function of tiny changes in certain

variables in the body find applications as chemical sensors and soft actuators (Ikeda et al., 2014; Yoshida et al. 2018). A step further is to exploit such stimuli-responsiveness for a precise, on-demand regulated release of the ancillary drugs to expand the therapeutic performance of the medical device and attenuate the risks. Smart drug delivery by means of nanocarriers has been widely reported (Alvarez-Lorenzo and Concheiro, 2014). Differently, stimuli-responsive drug release from medical devices has been barely explored yet (Alvarez-Lorenzo and Concheiro, 2013). Smart drug-eluting devices may offer novel ways of addressing unmet clinical needs and open the path to truly custom/personalized medical devices (Figure 1).

[FIGURE 1 NEAR HERE]

Infection-responsive antimicrobials-eluting medical devices

Medical devices are very prone to microorganisms contamination not only before implantation through contact with the skin or mucosa of the patient, but also after implantation if latent microorganisms migrate from an infection focus at other part of the body (Percival et al., 2015). The settling of microorganisms on a medical devices usually evolves with biofilm formation; namely, a highly structured community that undergo phenotypic changes mediated by a *Quorum Sensing* communication mechanism that makes microorganisms to become highly resistant to conventional antimicrobial agents (Remy et al., 2018). Thus, once the biofilm is formed, the eradication is difficult and the risk of spreading to other tissues through blood stream is high, which may compromise the life of the patient. Implantable medical devices are responsible of almost 50% of nosocomial infections (WHO, 2011). Even in the 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 natural healing of wounds if colonize either the suture or the adjacent tissue (Hong et al., 2018). Various bone cements incorporating antimicrobial agents are already in the market, but they usually release most drug in the first day followed by sustained elution of sometimes subtherapeutic doses, which may compromise the prophylactic role (King et al., 2018).

Since prolonged release of antimicrobials may cause adverse events and favor antimicrobial resistances (McLaren et al., 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 place and also, more recently, for the decoration of medical devices with networks that release the antimicrobial agent only if the colonization occurs (Alvarez-Lorenzo et al., 2016; Cyphert and von Recum, 2017; Wei et al., 2019).

Infection-responsive (or bacteria self-defensive) medical devices rely on three main mechanisms: (i) coatings responsive to the changes in enzymes and pH associated to microbial growth; (ii) surfaces that expose contact-killing moieties in the presence of the microorganisms; and (iii) bioinspired

moieties that release the antimicrobial agent through a competitive mechanism with the microorganism wall (Figure 2). Specific examples are summarized in Table 2.

[FIGURE 2 NEAR HERE]

Design of wound dressings that can simultaneously favor the healing and prevent the infections has received a great deal of attention. For example, electrospun mats of poly(lactic-co-glycolic) acid (PLGA) can degrade faster, and thus release the drug encapsulated inside more rapidly, as the microorganisms grow and release lipolytic esterases. As demonstrated for *Pseudomonas aeruginosa*, *Staphylococcus aureus* standard strain, and methicillin-resistant *S. aureus* (MRSA1), biofilm formation on the electrospun mats causes the hydrolysis of PLGA and thus the release of fusidic acid, which in turn leads to the killing of the bacteria (Said et al., 2011). The benefits of this approach have been demonstrated both in vitro and in vivo (Said et al., 2012). Also poly-L-lysine coatings have been shown to be degradable by chymotrypsin, showing bacterial infection-dependent release of gentamicin (Xu et al., 2017).

Bacteria growth is also associated to changes in the surrounding pH, which can be exploited as stimulus to trigger drug release from the medical devices (Pavlukhina et al., 2014). In this regard, layer-by-layer coatings of oppositely charged polymers and antimicrobial agents have been shown to rapid disassembly in response to the drop in pH that occurs as *Staphylococcus epidermidis* or *Escherichia coli* grow and generate lactic acid and acetic acid, respectively. The films can be designed to not release the drug at pH 7.4, but to efficiently elute the antimicrobial agent as the surroundings become acidic, which causes bacteria eradication (Zhuk et al., 2014). Nevertheless, pH-responsive systems may not discriminate between the drop in pH associated to the bacteria growth from that caused by migration of macrophages to the implantation site after surgery, and thus further in vivo studies are required.

Changes in pH can be also exploited to trigger the release of antimicrobial agents immobilized on the device surface. Medical devices can be easily surface modified with poly(acrylic acid) (PAA) using either plasma polymerization or gamma-ray grafting approaches, and then use the PAA grafted chains as intermediates for binding of 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). It should be noticed that 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 contribute to inhibit 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 photo-thermal ablation of biofilm (Cabana et al., 2017). Grafting of cationic polymers has been explored for the loading of 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 the catheters and thus to their blockage. To prevent these phenomena, urinary catheters have been coated with a reservoir containing bacteriophages and a sealing layer of pH-responsive Eudragit S100. The coating was stable in the presence of urease-negative bacteria, but showed a burst release of bacteriophages in the presence of *Proteus mirabilis*, which in turn caused a significant decrease in bacteria cells and doubled the time required for blockage (Milo et al., 2017). Using a similar approach, pH-responsive coatings have been recently developed to act as infection-responsive theranostic materials. Layers of PAA and chitosan trapping ciprofloxacin and sealed with Eudragit S100 were designed to undergo distinct chromatic color transitions from blue to purple and red as the pH became more alkaline, acting as sensors of early infection and also as

warnings of 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-Straffon et al., 2014; Huang et al., 2015). Contac-killing surfaces have been prepared combining the temperature-responsive poly(N-isopropylacrylamide) (PNIPAAm) with biocidal quaternary ammonium salts. At 37 ºC, PNIPAAm brushes are shrunken 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 (LCST) of PNIPAAm (Pavlukhina et al. 2012). The surface can be designed to exhibit the opposite performance; namely, oligo(ethylene glycol) methacrylates conjugated with antimicrobial peptides show swelling-collapse transition at 35 ºC. Below this temperature, bacteria can freely enter into contact with the peptide and the bactericide effect occurs. Differently, at 37 ºC the ethylene glycol moieties predominate and the material performs as bacteria-repellent (Laloyaux et al., 2010). Also pH-responsive polymer brushes, such as poly(2-ethylacrylic acid), poly(2-n-propylacrylic acid) and poly(2-n-butylacrylic acid) have been shown to exhibit contact-killing capability under acidic conditions (Lu et al., 2015).

The third mechanism relies on bioinspired strategies to host the antimicrobial drug and to trigger the release through a competitive mechanism when the microorganisms are present. The small structural differences between cholesterol (structural component of mammalian membranes) and ergosterol (present in fungi walls) are the basis of the discovery of a relevant family of antifungal drugs. Polyenes, azols and allylamines selectively interact with fungi, blocking their growth, while there are still innocuous for mammalians. Thus, decoration of medical devices with ergosterol 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 physiological pH without leakage.

The release was triggered when a fungal infection was mimicked (Segura et al., 2014). Tests carried out in the presence of *Candida albicans* revealed the interest of the fungi-responsive ergosterol-functionalized devices to efficiently inhibit biofilm formation. A different approach was explored using cyclodextrin-functionalized wound dressing. Cyclodextrins have been shown able to host *Quorum sensing* inhibitors and antimicrobial agents forming inclusion complexes, but they can also host *Quorum sensing* signaling molecules, i.e., the molecules released by bacteria to communicate each other and develop biofilm (Okano et al., 2016). Thus, cyclodextrin-functionalized gauzes were successfully loaded with hamamelitannin (*Quorum sensing* inhibitor) and vancomycin and then 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 towards 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 paid to create synthetic devices that can stabilize the site of injury and have mechanical properties similar to the tissue to be repaired and also an architecture that allows host cell colonization. Nevertheless, adhesion of specific cell types and the further behavior of these cells should be carefully driven towards an efficient regeneration avoiding 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 the healing since they not only remove bacteria and foreign materials but also release critical enzymes and cytokines for the subsequent phases. Nevertheless, an excessive and prolonged inflammation may delay the healing, degrade the scaffold, and provoke fibrosis and scarring. Thus, inflammation-triggered release of anti-inflammatory drugs is been explored as a way of recapitulating natural tissue regeneration. For example, the covalent grafting of non-steroidal anti-inflammatory drugs (NSAIDs) via ester groups to hydrogel coatings or electrospinnable components has been shown useful to regulate the NSAID release as a function of the over-expressed esterases (He et al., 2017; Pan et al., 2015) (Table 3).

Next regeneration steps require the sequential release of adequate growth factors for cell proliferation and differentiation. Thus, a variety of strategies are been explored for, commonly, dual delivery of growth factors at different time points or release rates (Izadifar et al., 2015). Although most approaches rely on coatings that encapsulate a given growth factor and release it at a pre-established rate, some evidences of the potential of stimuli-responsive release have been already published (Bruggeman et al., 2018). Relevant examples are summarized in Table 3. External modulation of the release can be achieved by engineering acoustically-responsive scaffolds; namely

the scaffolds contain different growth factors in differently designed sonosensitive emulsion droplets. Each droplet releases the content at different acoustic pressures. Thus, precise spatiotemporal control of the release of each growth factor is possible (Moncion et al., 2018). The feasibility of this approach has been already demonstrated in vivo (Moncion et al., 2017). Release responsive to magnetic fields has been observed for hydrogels encapsulating magnetic particles and platelet lysates; the application of an external magnetic field modulated the release of the growth factors, which in turn determined cell expression and the synthesis of tendon-and bone-like matrices (Silva et al., 2018).

Recent research focuses on cell-responsive remodeling of the scaffolds in such a way that specific cell inputs may trigger the release of the adequate growth factor at each time (Murphy and Lampe, 2015). Metalloproteinases released by the cells can regulate the degradation of certain scaffold components and thus the release of encapsulated active substances. Metalloproteinases can also break labile bonds of growth factors tethered to the scaffold (Van Hove et al., 2015). Also cell-produced heparinase has been evaluated as stimulus for the release of growth factors bound to the scaffold through heparin moieties. Heparin has high affinity for many growth factors and the dissociation (passive release) is quite slow under physiological conditions (Martino et al., 2013; Vulic and Shoichet, 2014). Thus, it has been shown that cells may mediate much faster release of the growth factors, which in turn determine the subsequent cell development (Sakiyama-Elbert and Hubbell, 2000). The advent of 3D printing technologies makes foreseeable the design of medical devices with precise locations of the active molecules and the responsive materials to construct truly dynamic, cell-responsive or externally-activated scaffolds in a short future (Nadgorny and Ameli, 2018).

Mechanically-activated drug release

Medical devices inserted or implanted in the body are subjected to physiological stress and are also susceptible to action of externally-applied forces. A variety of strategies are been explored to trigger drug release using common mechanical stimuli; namely, compression, tension and shear (Figure 3). The physiological mechanical stimuli and the principles behind the design of mechano-responsive drug delivery systems have been recently reviewed elsewhere (Wang et al., 2017). Relevant examples are summarized in Table 4.

[FIGURE 3 NEAR HERE]

Compressive medical devices are formed by elastomers (viscoelastic materials) that withstand compressive loadings. 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 hydrogels bearing grafted cyclodextrins. The responsiveness has been attributed to changes in the conformation of the cyclodextrin cavity and the hydrogel network as function of the pressure, which impels the release of the drug from the cyclodextrin 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 towards the cornea surface during blinking (Galante et al., 2015). The pressure of the lid 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 the wearing 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 open nanopores which act as nanovalves that allow the exit of the drug, but that close when the film is at rest (Mertz et al.,

2007). Similarly, drug-loaded polymer layers coated with thin titanium metal 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 multilayers containing drug-loaded microparticles; the crack propagation of the superhydrophobic coating can be triggered by physiological forces that facilitate the entrance of the release medium in the coating and thus the release of 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; Wang et al., 2018). Also, stretching may accelerate the release of antimicrobial agents from hydrogels prepared with cyclodextrin monomers; once again, the deformation of cyclodextrin cavity drives the release of the previously encapsulated drug molecule (Balance et al., 2018). Intriguingly, deformable catheters have been tested for the removal of pre-formed biofilms using strain forces. *C. albicans* biofilms have been detached from prototypes by selectively inflating 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 physiological or pathological (e.g. atherosclerotic plaques or clots) events (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 drug-eluting stents (Zheng et al., 2017). Nevertheless, much knowledge is still required to reproduce in vitro biorelevant conditions of blood flow (Reviakine et al., 2017).

Electric-responsive release

Natural mechanical stimuli can be transformed into electric stimuli that trigger drug release from the 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) and subsequent deposition of 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) that accelerated drug release. The purpose was the attenuation of nausea in order to facilitate the intubation process itself. The release rate under the mechanical stimulus was approx. 2-fold that 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 electric 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 with the coating of the electrodes with a conductive polymer layer containing therapeutic neurotrophins. The generated electrical stimulus increases the release of the neurotrophic proteins increasing the biocompatibility (Richardson et al., 2009; Thompson et al., 2010; Thompson et al., 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 above for 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. The interest of this strategy has been investigated for esophageal stents implanted to prevent tumor recurrence and that combined gold nanoturfs and doxorubicin (Figure 4) (Lee et al., 2018).

[FIGURE 4 NEAR HERE]

Finally, vitamin C has been shown useful to deactivate the adhesion of dressings to the wounds facilitating the peeling off from the damaged skin without causing a secondary trauma. Such vitamin C responsiveness relies on its capability to disassembly 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 those devices designed for pre-stablished release rate. The amount of drug that can be hosted by the medical devices is limited (because of limited affinity and also to avoid changes in bulk properties), therefore regulation of the moment at which it should be delivered is critical for maximizing the prophylactic/therapeutic performances. Smart drug-eluting medical devices benefit from the knowledge gathered on stimuli-responsive drug nanocarriers. Nevertheless, additional specific stimuli can be exploited in the case of the medical devices. Cell-triggering release of growth factors from orthopedic implants may determine the fate of both the cells and the implant allowing for an optimized healing, or natural physical forces exerted onto the medical device can directly or 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 a deeper knowledge on the physiological variables that can serve as stimuli make foreseeable that upgraded medical devices more sensitive and robust in the release response and even with theranostic capabilities would play a key role in the healthcare system in a near future. The incorporation of a drug to a medical device to obtain a device-led combination product adds complexity to the regulation pathway compared to solely medical device products. Nevertheless, efforts made by the regulatory agencies to clarify the premarket pathways are very valuable (US Food and Drug Administration, 2019).

Authorship Contributions

C.A-L. and A.C. contributed to the searching and analysis of the information, and the writing and the editing of the manuscript.

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Footnote

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Legends for Figures

Figure 1. Internal and external stimuli evaluated to trigger ancillary drug release from medical devices and main outcomes expected.

Figure 2. Main mechanisms explored so far to endow medical devices with self-defensive behavior against biofilm formation. (i) coatings that switch antimicrobial drug release on/off in response to enzymes and pH changes associated to microbial growth; (ii) contact-killing moieties that activate in the presence of microorganisms; and (iii) bioinspired moieties that resemble natural receptors of the microorganisms and transfer the antimicrobial agent through a competitive mechanism.

Figure 3. Magnitude of the physiological and external forces that can be exerted on medical devices. Data taken from Wang et al. (2017).

Figure 4. Structure and performance of an esophageal stent coated with a nanoturf structure containing gold (Au) and doxorubicin (DOX) for combining thermo- and chemo-therapy. (a) Near-infrared (NIR) responsiveness of the Au coating triggers localized increase in temperature while DOX is being released; (b) SEM images of pristine (left), DOX/Au-coated (middle), and partial drug release (right) nanoturf structures, after incubation in PBS solution for 6 h (scale bar 1 μm); (c) appearance and surface structure of a nitinol wire stent coated with the nanoturf structures; (d) the esophageal stent covered with an esophagus-mimicking organoid tube prepared for subdermal implantation; and (e) TUNEL stains of esophagus-mimicking organoid tubes treated with the nanoturf esophageal stent containing only Au (left) or DOX and Au (right) after NIR irradiation in vivo. Live cells are shown in blue and apoptotic cells in brown (scale bars 400 μm). Reprinted with permission from Lee et al. (2018). Copyright (2018) American Chemical Society.

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Table 1. Common examples of devices coated/impregnated or otherwise combined with drugs according to FDA classification of combination products, and that are commercially available. The device has an additional function in addition to delivering the drug (US Food and Drug Administration, 2018b)

Drug-eluting medical device	**Example**	**Reference**
Drug pills embedded with sensors	Drug-loaded tablet-like device for monitoring of medication adherence, mainly intended for mental disorders (Abilify MyCite®) and cancer (clinical trials).	US Food and Drug Administration (2017)
Drug-eluting stents	Sirolimus, paclitaxel, everolimus, zotarolimus, or biolimus included on the stent surface to minimize restenosis and/or prevent late thrombosis	Lee and Torre Hernandez (2018)
Drug-eluting leads	Steroid-coated pacemaker electrodes to prevent inflammatory mediators release and myocardial damage	McVenes and Stokes (2016); Matsuhisa et al. (2014)
Condoms with spermicide	Coatings of nonoxyno1-9 to increase contraceptive effectiveness	US Food and Drug Administration (2018c)
Dental floss with fluoride	Fluoride incorporated into the wax for caries prevention	Flatt et al. (2008)
Antimicrobial coated catheters/sutures	Silver and a variety of antimicrobial agents incorporated into the matrix or as coatings of urinary catheters, central venous catheters, sutures or endotracheal tubes.	Singha et al. (2017); Tummalapalli et al. (2016)
Bone cements with antibiotics	Vancomycin, aminoglycosides, β-lactams, lipopeptides, oxazolidinones, and antifungals can be compounded extemporaneously with the cement, or the cement is provided pre-loaded with the drug.	Athans et al. (2017)

Table 2. Examples of infection-responsive antimicrobials-eluting medical devices

Drug-eluting medical device	**Triggered stimulus**	**Reference**
Electrospun mat of PLGA loaded with fusidic acid	Lipolytic esterases released by bacteria	Said et al. (2011; 2012)
Montmorillonite/poly-L-lysine-gentamicin sulfate organic–inorganic hybrid multilayer films	Chymotrypsin released by bacteria	Xu et al. (2017)
Self-assembled coatings of tannic acid with one cationic antibiotic (tobromycin, gentamicin, and polymyxin B)	Drop in pH	Zhuk et al. (2014)
Medical devices grafted at the surface with PAA chains for binding of antimicrobial peptides	Drop in pH	Traba and Liang (2015)
Medical devices grafted at the surface with PAA chains for spontaneous coating with gold nanoparticles	Light responsive (photothermal effect)	Cabana et al. (2017)

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Urinary catheter coated with a hydrogel layer of 2-hydroxyethyl methacrylate and vinylfunctionalized nalidixic acid derivatives	Pathogen-induced elevation of urine pH	McCoy et al. (2016)
Urinary catheter coated with an Eudragit S100 coating encapsulating bacteriophages	Pathogen-induced elevation of urine pH	Milo et al. (2017)
Catheter coated with PAA and chitosan comprising a pH (colorimetric) sensor and ciprofloxacin-loaded vesicles and sealed with Eudragit S100	Pathogen-induced elevation of urine pH. Visual indication of early infection by urease producing bacteria.	Zhou et al. (2018)
Ergosterol-coated medical devices for affinity-driven loading of antifungal agents	Competitive displacement of natamycin and nystatin towards the fungi wall	Segura et al. (2014)
Cyclodextrin-decorated gauzes loaded with *Quorum Sensing* inhibitors and vancomycin	*Quorum Sensing* signaling molecules released by Gram-negative bacteria	Brackman et al. (2016)

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

Drug-eluting medical device	**Triggered stimulus**	**Reference**
NSAID-immobilized hydrogel coating	Inflammation; over-expression of esterases triggers the release of indomethacin	He et al. (2017)
NSAID-immobilized electrospun fibers	Inflammation; over-expression of lipase triggers the release of ibuprofen	Pan et al. (2015)
Fibrin scaffolds containing drug-loaded sonosensitive emulsion droplets	Ultrasound; each droplet releases the drug at specific acoustic pressure	Moncion et al. (2018)
Fibrin scaffolds containing bFGF encapsulated in monodispersed emulsion droplets	In vivo ultrasound triggered release of the growth factor for efficient angiogenesis	Moncion et al. (2017)
Chondroitin sulfate-platelet lysate hydrogel encapsulating magnetic nanoparticles and stem cells	Magnetic field modulates the release of platelet lysate growth factors and, in turn, the tendon- and bone-like matrix synthesis	Silva et al. (2018)
Poly(ethylene glycol) hydrogels cross-linked with metalloproteinase substrates and loaded with angiogenic peptide drugs	Cell-released metalloproteinases for regulation of in vivo angiogenesis	Van Hove et al. (2015)
Fibrin scaffold with heparin-binding growth factors	Cell-produced heparinase for triggering bFGF release and enhancing peripheral nerve regeneration	Sakiyama-Elbert and Hubbell (2000)

Table 4. Examples of mechanically-activated drug release from medical devices

Drug-eluting medical device	**Triggered stimulus**	**Reference**
Hydrocortisone-loaded alginate-cyclodextrin hydrogels	Manual compression	Tan et al. (2015)
Drug-loaded contact lenses	Eyelid compression	Galante et al. (2015)
Stents coated with drug-loaded polyelectrolyte films that act as pressure-responsive nanovalves	Tension	Mertz et al. (2017)
Drug-loaded polyurethane coated with a thin titanium metal layer that develops micro-crack under strain	Tension	Jeon et al. (2018)
Esophageal stents coated with a superhydrophobic layer embedding drug-loaded microparticles	Tension	Wang et al. (2016, 2018)
Polyacrylamide-cyclodextrin hydrogels loaded with quinine	Tension	Balance et al. (2018)
Sirolimus-loaded PLGA coating	Shearing	Zheng et al. (2017)

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Figure 1

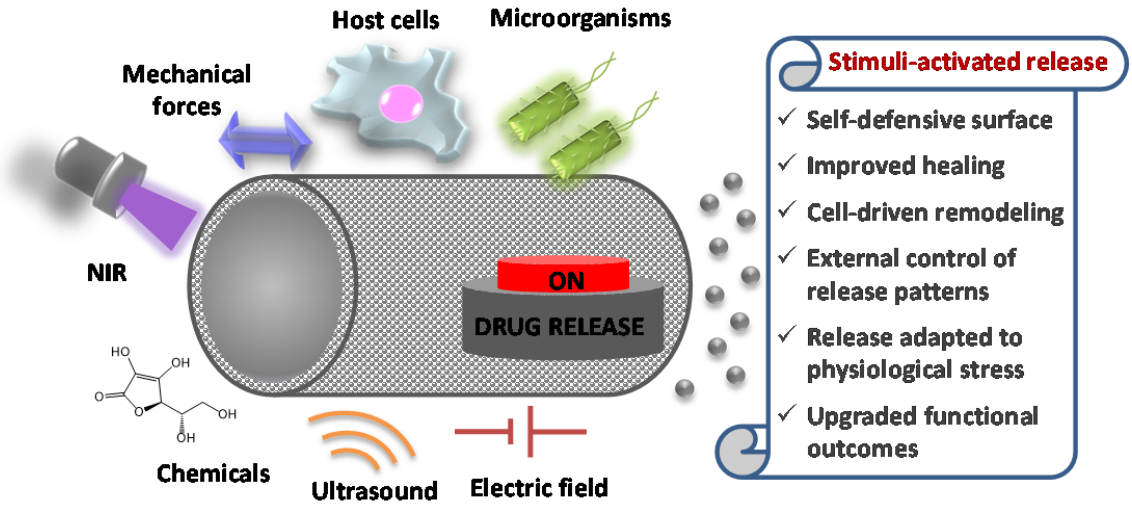

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Figure 2

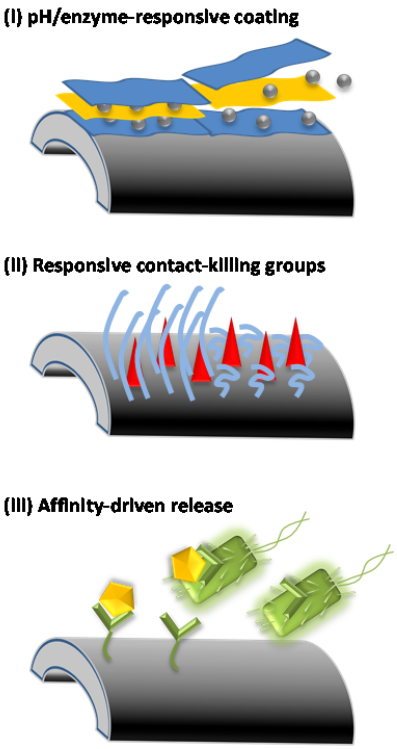

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Figure 3

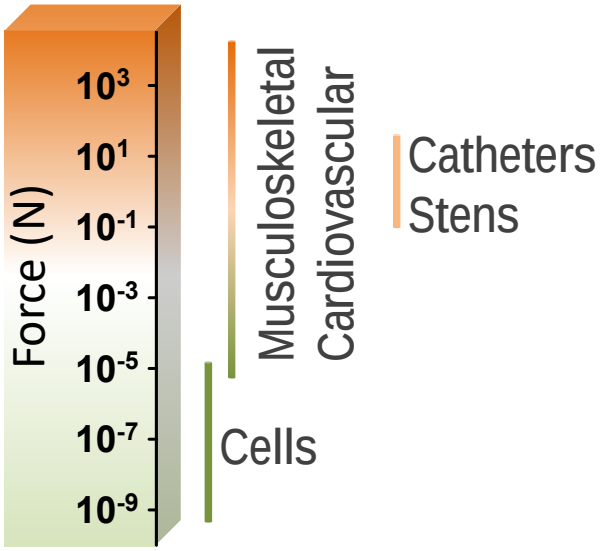

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Figure 4