POST-SCREEN

Stimuli-sensitive drug delivery systems for site-specific antibiotic release

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Site-specific delivery of antibiotics has always been a high-priority area in pharmaceutical research. Conventionally used antibiotics suffer several limitations, such as low accumulation and penetration in diseased cells/tissues, limited bioavailability of drugs, drug resistance, and off-target toxicity. To overcome these limitations, several strategies have been exploited for delivering antibiotics to the site of infection, such as the use of stimuli-responsive antibiotic delivery systems, which can release antibiotics in a controlled and timely fashion. These stimuli can either be exogenous (light, magnetism, ultrasound, and electrical) or endogenous (pH, redox reactions, and enzymatic). In this review, we present a summary of recent developments in the field of stimuli-based targeted drug delivery systems for the site-specific release of antibiotics.

Keywords: External stimuli-responsive drug delivery; Internal stimuli-responsive drug delivery; Targeted drug delivery; Antibiotic release; Nanoparticles

Introduction

Antibiotic resistance is considered the most challenging threat to global public health.[1] Beyond the limited availability of antibiotics, existing antibiotics are becoming ineffective owing to their off-target toxic effects, limited penetration of drugs into target sites, non-specificity, low bioavailability, uncontrolled/unpredictable and rapid release profiles, and the development of resistance.[2] Therefore, to enhance the uptake and minimize the toxic impacts of antibiotics, several approaches have been introduced, including nanotechnology- and polymer-based drug delivery platforms.[1] These have significantly aided our understanding and ability to exploit the site-specific release mechanisms of drugs. Over the past decade, the use of stimuli-responsive drug carriers, including lipid nanoparticles (NPs), polymers, hydrogels, liposomes, carbon-based NPs, and inorganic NPs, which have ability to store and release antimicrobial agents in a controlled and sustained manner, have gained attention as targeted therapeutics. NPs have a typical size range of 1–100 nm, and have one dimension less than 100 nm at least. NPs are generally found as 0d, 1D, 2D, or 3D forms.[3–5] They have several advantages, such as increased surface to volume ratio, size-dependent optical/thermal/mechanical properties, and ease of functionalization with target biomolecules (e.g., antibodies, DNA/RNA). Their biodegradation through appropriate modifications of the NP with biomolecules at correct doses and ratios is becoming increasingly attractive, as seen with the development of poly (lactic-co-glycolic acid) (PLGA)-coated NPs.[5] In addition, toxicities and adverse effects of NPs can be reduced by suitable functionalization and bioconjugation.[6–9] Most research focusing on stimuli-responsive drug-delivery systems has emphasized the use of NPs for the controlled delivery of antibiotics. The uncontrolled release of drugs is associated with off-target toxicity and

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https://doi.org/10.1016/j.drudis.2022.02.014

long-term post-treatment adverse effects. Therefore, targeted delivery of drugs to the site of action using stimuli-responsive systems has recently gained attention. Internal stimuli, such as pH, reactive oxygen species (ROS), and the presence of proteases, are internally regulated systems (also known as closed-loop or self-regulated systems). Typically, any change in the biomilieu at the diseased site is considered a mediator for chemical or physical changes in the delivery system, which in turn activates the release of the drug or antimicrobial payload. The release profile of drugs mainly relies on the physiological status of the disease site, which makes it difficult to manipulate the target site externally. By contrast, external stimuli, such as light, sound, magnetism, and electrical activity, constitute externally regulated systems (also known as open-loop systems). These systems can control the release profile of the drug transiently through the control of the duration and strength of the external stimulus, thereby resulting in an accurate supply of the drug at the desired dose.

Despite recent progress in the development of antibiotics, the emergence of off-target toxic effects, their uncontrolled release,[10–13] and antibiotic resistance have become serious issues.[14–16] In addition, regardless of exciting results in the field of stimuli-responsive delivery platforms, more needs to be understood about the underlying mechanisms involved. Therefore, in this review, we provide an updated summary of trends and perspectives in exogenous and endogenous stimuli-based targeted drug delivery systems, with an emphasis on the use of novel delivery systems (e.g., NPs, liposomes, and nano/microbubbles).

Exogenous stimuli-responsive drug delivery systems

Light-triggered drug delivery systems

The use of light as an extrinsic activation mechanism has shown promising results in circumventing the nonspecific release of drugs at the site of action.[16] Photocleavage reactions (molecules with photolabile groups, such as *o*–nitrobenzyl or coumarin-4-yl-methyl groups) have been engineered for the targeted delivery of antibiotics to enhance drug efficacy.[17] The potential of multifunctional NPs conjugated with the bacteria-specific ligands polymyxin B (PMB) and ethanolamine (EA) has been explored with light-stimulated antibiotic delivery to target bacterial cell walls.[18,19] Multivalent NPs have the ability to be absorbed by tight junctions in the cell wall. However, this tight and specific cell wall adsorption elicits only suboptimal antibacterial activity because of the poor intracellular uptake of antibiotics.[20] Thus, there is a need for a tightly bound conjugate combined with a drug-release mechanism at the bacterial surface. Wong *et al.*[21] reported the photochemical release of photocaged ciprofloxacin carried by a cell wall-targeted dendrimer nanoconjugate. The conjugated ciprofloxacin was released photochemically from an *ortho*-nitrobenzyl–ciprofloxacin conjugate. The antibacterial activity after 30 min of irradiation time and 80% of drug release is shown in Fig. 1.[21] However, the use of ultraviolet (UV) light induces phototoxicity and has poor penetration into tissues. Zhao *et al.*[22] explored near-infrared range (NIR)-sensitive drug delivery systems, which release the drug by absorption of two photons and upconversion processes. The use of a light-sensitive approach to target bacterial infections provides potential benefits in terms of increasing the sensitivity and therapeutic index of loaded drugs.

Magnetically triggered drug delivery systems

Recently, NPs have been used to simultaneously monitor and treat disease in the same clinical session. Such NPs are known as theranostic agents.[23] Theranostic magnetic NPs (MNPs) can be used in magnetic resonance imaging (MRI) and magnetic targeting, and for hyperthermia and controlled drug release.[24–27] MNPs undergo Brownian and Neel relaxations when actuated with a sub-megahertz alternative magnetic field (AMF), resulting in the generation of localized heat.[28,29] Thus, by regulating the features of the AMF, the amount of heat released can be controlled and an optimum thermal level can be maintained at the site of infection. Harris *et al.*[30] developed a heat-sensitive magnetically triggered antibiotic release system comprising chitosan microbeads crosslinked with poly (ethylene glycol) (PEG) dimethyl methacrylate of variable length, loaded with the antibiotic vancomycin and paramagnet Fe_3O_4. When this system was externally radiated with a magnetic field, hyperthermic conditions increased the permeability of the polymeric matrix, breaking temperature labile linkers. The authors showed that chitosan-loaded MNP nano/microbeads tended to release vancomycin for 8 days following a short magnetic field stimulation of 30 min.

The antibiotic incorporated in magnetically responsive polymer is deposited at the target site where the extracorporeal magnet is placed.[31] This helps the drug to reach the infected site more precisely and effectively. An example of magnetic guidance was presented by Sirivisoot and Harrison[27] using MNPs containing ciprofloxacin. These MNPs act as ferric oxide (maghemite or hematite) nanobullets loaded with drugs guided by an external oscillating field. This study showed promising outcomes with both immediate and sustained release of ciprofloxacin. Drug release can also be triggered by a magnetic field via thermal or nonthermal effects. In a thermal-magnetic drug delivery system, NPs are subjected to AMF, which causes spin moments by the formation of magnetic domains. This rotation creates thermal energy, which can be associated with a drug delivery system by incorporating drugs in temperature-sensitive polymers. Upon hyperthermia, these polymers release the drug.[32] The key features of magnetic release systems still need to be optimized, such as the magnetization capacity of magnetic agents to achieve optimal magnetic targeting as well as further optimization of a turn-on and turn-off switch system for the selective targeting and clearance of magnetic agents from the body.

Ultrasound-triggered drug delivery systems

Ultrasound waves produce forces that have the energy to permeabilize membranes and split the drug-carrying vehicles. This enables the drug to accumulate at the target site with high spatial precision, and fewer adverse effects.[33] The technique is based on the elution of drugs both by mild heating and/or mechanical disruption in tissues or liposomes. Mechanical disorientation of tissues causes nucleation, growth, and gas bubbles eruption, a process known as acoustic cavitation.[34] When liposome–microbubble complexes are exposed to high-intensity ultrasonic waves, the microbubble bursts to release the drug payload from the carrier. Under the navigation effects of ultrasound to achieve

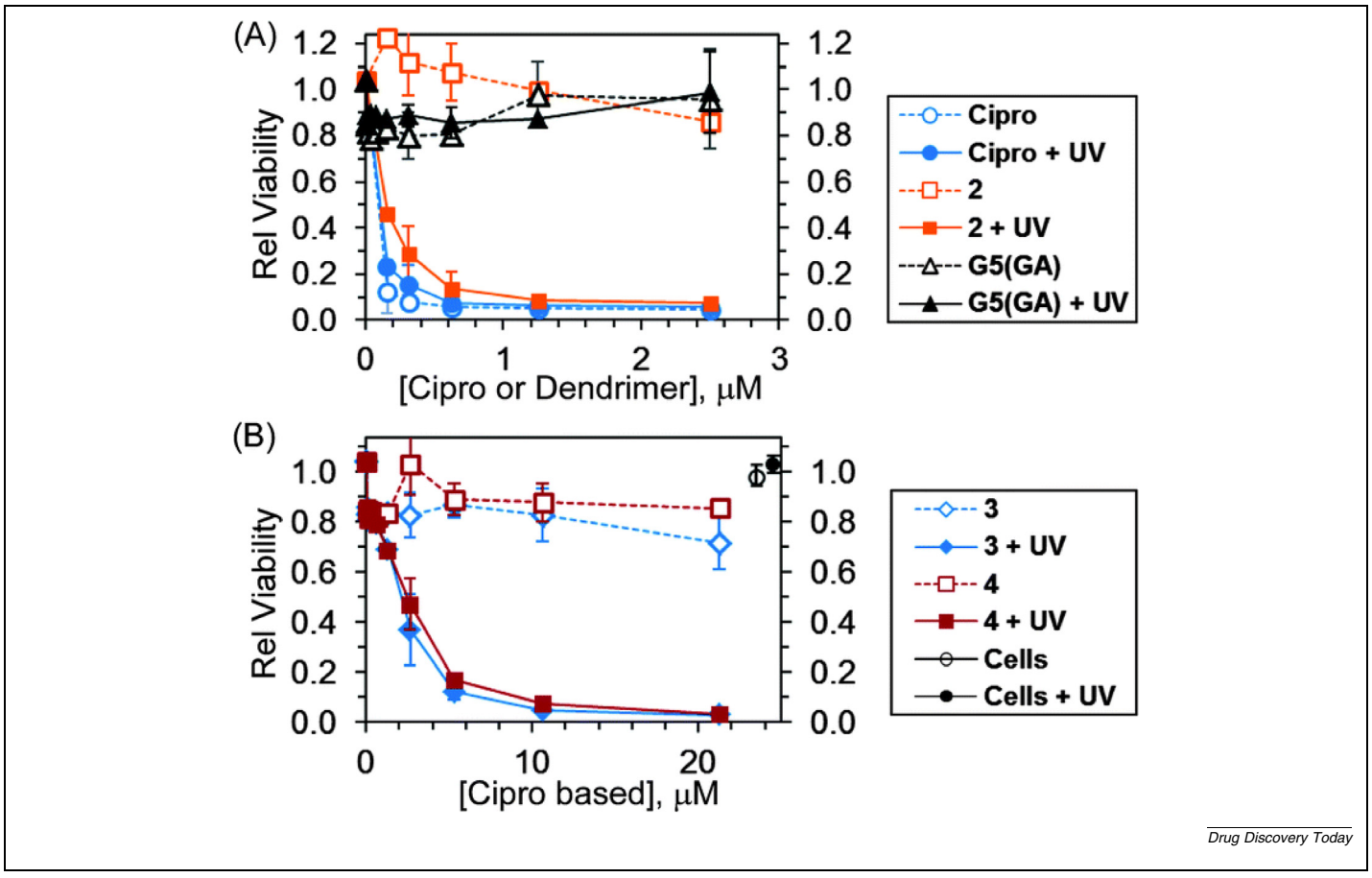

FIGURE 1

Light-sensitive ciprofloxacin (Cipro) delivery against *Escherichia coli* infection. **(a)** Impact of ultraviolet (UV; 365 nm) exposure on bacterial cells treated with ciprofloxacin alone and in conjugation. The conjugated ciprofloxacin and dendrimer are represented as '2' showing the maximum antibacterial activity curve. **(b)** Viability of *E. coli* infection controlled by conjugates carrying photocaged ciprofloxacin ('3' and '4'). The curve shows the enhanced bactericidal activity following UV exposure. Reproduced, with permission, from [21].

targeted release, microbubbles are designed to have a core of air or another gas that is surrounded by a stable polymer with the drug embedded in it.

The viability of ultrasound-mediated antibiotic delivery could be useful against postoperative spinal surgery infection. Despite perioperative treatment, 10% percent of patients still acquire *Staphylococcus aureus* infection owing to biofilm formation and colonization on the surgical implants used [i.e., metal rods, screws for fixation, and an intervertebral cage, which is made of polyether ether ketone (PEEK)]. Before surgery, the metal rods to be inserted are first bathed in a postoperative lacerating fluid that leads to biofilm formation of methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) in blood and synovial fluid. Fibrin and biofilm aggregates can be disrupted by the mechanical effect of ultrasound waves. Delaney *et al.*[35] reported an ultrasound activated system that released combinations of prophylactic and bolus antibiotics to reduce postsurgical bacterial survival, while avoiding problems associated with controlled elution systems. The study measured the transient antibiotic release at certain levels followed by ultrasound-triggered bulk release to avert adhesion of *S. aureus* on implant material. Microbubbles of vancomycin comprising thin polylactic acid (PLA) shells were incorporated in PEEK clips. The drug was passively released for several days through these microbubbles to eradicate persistent MRSA, thus eliminating the risk of prophylaxis or infection.

A promising feature of the acoustic droplet vaporization technique is that it allows the initial slow release of vancomycin. When an infection is indicated, a bolus antibiotic dose is released upon ultrasound exposure. This approach can be used for the treatment of chronic wounds, such as diabetic ulcers, bedsores, and venous ulcers. MRSA forms colonies at biological sites and at the junction of prostheses, leading to mortality in 20–28% of patients. Argenziano *et al.*[36] demonstrated that dextran sulfate-shell and perflouropentane (PFP)-filled nanobubbles can be used for the delivery of vancomycin, revealing that these formulations overcome effects encountered with local drug delivery systems, such as poor oral bioavailability, in ischemic and necrotic tissues. Fig. 2 shows an *in vitro* release profile of vancomycin with ultrasound-stimulated technology and the antibacterial activity of the drug. Such a system was shown to be effective against MRSA without showing keratinocyte toxicity.[37] The ultrasound delivery system comprised a biodegradable or biocompatible outer shell made of dextran sulfate and a gaseous

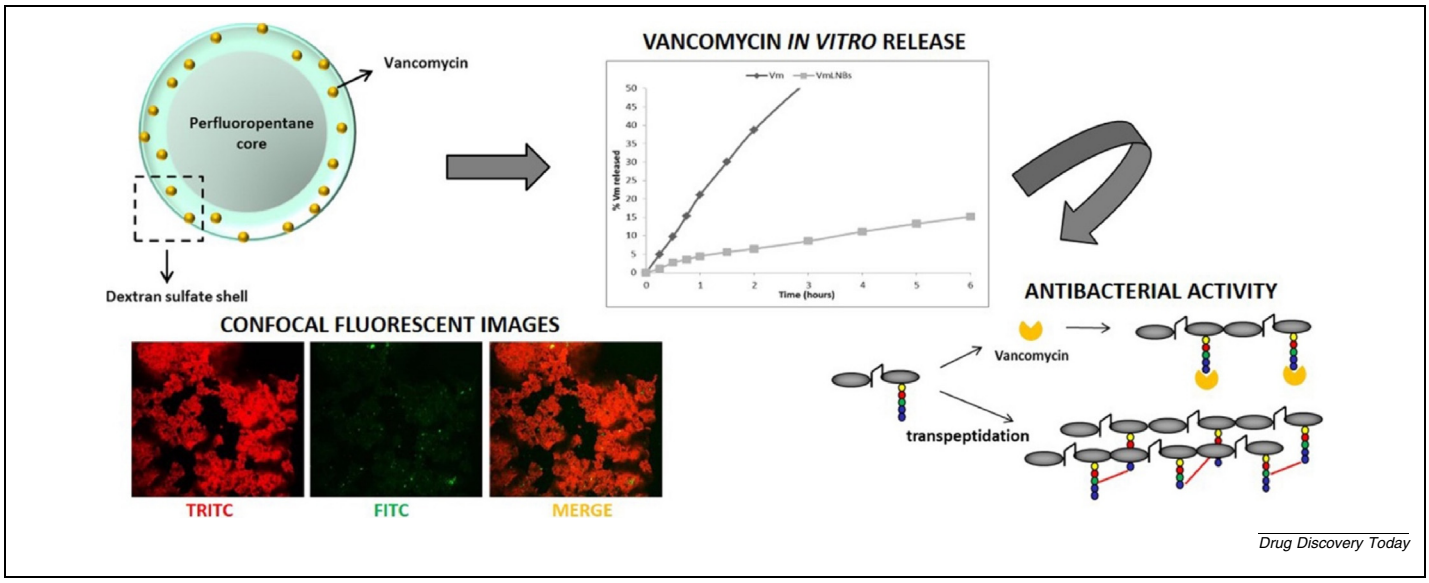

FIGURE 2

Vancomycin nanobubbles comprising a dextran sulfate shell and perfluorocarbon core. The nanobubble is ruptured when exposed to ultrasound waves and releases the drug, resulting in antibacterial activity. The figure shows an *in vitro* release profile and antibacterial activity of vancomycin using ultrasound-stimulated technology. Vancomycin inhibits transpeptidation, resulting in antibacterial activity. Confocal fluorescence images of stained bacteria were taken in tetramethylrhodamine (TRITC) and fluorescein isothiocyanate (FITC) filters shown in the figure. The results showed increased activity against MRSA. Reproduced, with permission, from [36].

inner core, which contained oxygen (i.e., PFP). PFP is liquid at room temperature when subjected to ultrasound waves and becomes vaporized via acoustic droplet vaporization.[38,39] For vancomycin to be incorporated into the nanobubble system, an electrostatic effect between two materials is used.Fig. 3

Electrical-responsive drug delivery systems

Fabrication of electro-responsive nanocomposites based on polypyrrole results in tailored drug release owing to charged particle movement and electrochemical oxidation–reduction reactions.[40,41] Low-voltage electric impulses (typically < 10 V) can also be used for sustained drug delivery from a polymer that

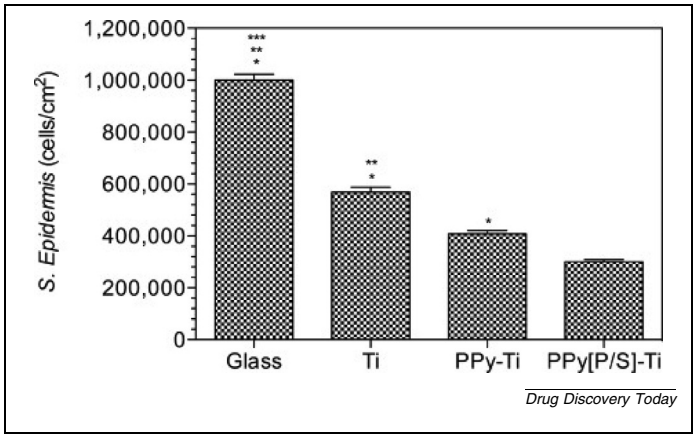

FIGURE 3

Bacterial concentration as a result of electrically stimulated drug release. The incorporation of antibiotics in polypyrrole-titanium conjugates leads to significant levels of *Staphylococcus epidermidis* death. Reproduced, with permission, from [48].

can conduct electricity (i.e., polypyrrole), which delivers drugs via the coadjuvant effect of two mechanisms.[42] One is by electrochemical oxidation–reduction reactions that cleave the drug from its polymeric system and the second is by the electricity-derived movement of charged molecules. The key characteristics of a drug (such as encapsulated drug molecule size, hydrophilicity, charge, and intermolecular interaction with the gel backbone) have important roles in determining release profiles.[43] This underpins the novel non-interactive delivery system of drugs via an externally customized release profile with exceptional spatial and temporal control of drug release.

Schmidt *et al.*[44] fabricated nanofilms based on negatively charged Persian blue NPs [which are approved in a tablet form by the US Food and Drug Administration (FDA)] and positively charged gentamicin. A layer-by-layer assembly[45] was manufactured in which small charged prodrug molecules were directly incorporated as aminoglycoside antibiotics based on electrostatic effects. When exposed to an anodic electric potential of at least + 0.5 V, the negatively charged Persian blue turns into neutral moiety, facilitating the dissolution of the film and simultaneous release of the drug. Layer-by-layer thin films are developed in a self-medicated fashion with alternate material absorption of functional groups providing multifaceted control of drug release.[46,47]

Orthopedic implants often lead to infections and inflammatory conditions, which can increase the length of a patient's stay in hospital. To address this problem, Sirivisoot *et al.*[48] designed an optimized drug delivery system with polypyrrole nanocomposite incorporating antibiotics (penicillin/streptomycin) and anti-inflammatory drugs (dexamethasone). The drugs were coated on commercially available pure titanium using electrochemical deposition. Conductive polymers can trigger the

release of biological molecules in a controllable manner via an oxidation–reduction mechanism. The electrical intensity controls the level and duration of drug molecule release. The authors demonstrated that ~80% of the drugs were released by providing an electrical stimulus of −1 V to 1 V.

Endogenous stimuli-responsive drug delivery systems

pH-triggered drug delivery systems

Exogenous stimuli-responsive drug delivery systems exploit pH variations among physiological and pathological sites. Bacterial infections decrease tissue pH as a result of low oxygen levels and induce inflammatory responses at infection sites. All pH-sensitive NPs developed to date have a strong and relatively pH-insensitive cationic surface charge, which shows potent bactericidal activity *in vitro* but has nonspecificity toward bacteria. However, the likelihood of toxicity can also be increased because of adverse effects of cationic NPs on blood circulation, biodistribution, and clearance from the body.[49,50]

Teo *et al.*[51] prepared a 3D polycaprolactone-tricalcium phosphate mesh for the delivery of gentamicin sulfate, while Mi *et al.*[52] reported a new zwitterionic hydrogel that was conjugated with an antimicrobial agent. Bhattacharyya *et al.*[53] applied thin sol–gel films to control antibiotic release, showing that the gel was able to inhibit the growth of both MRSA and MSSA. However, the release profile of these carriers was storage and time dependent. In another study by Radovic-Moreno *et al.*,[54] a pH-responsive surface charge-switching polymeric NP drug delivery system was engineered for the systemic administration of antibiotics. The pH-sensitive NPs bind to the bacterial cell wall under acidic pH at the site of infection. In non-infectious sites, the NPs remained insensitive because of the normal physiological pH. In this linear polymer architecture, PLGA acted as the hydrophobic core of the polymeric system whereas poly(L-histidine) (PLH) contained imidazole groups that undergo protonation under acidic pH into the linear copolymer structure. (PLGA-PLH-PEG) gives the NP an overall positive surface zeta potential, which facilitates its interaction with the negatively charged bacterial cell wall, which in turn produces strong multivalent electrostatic interactions under acidic conditions.[55] This study showed a three-to-fivefold increase in NP–bacteria binding at pH 6.0 compared with at pH 7.4.[54] Vancomycin-loaded, pH-sensitive, surface charge-switching NPs were shown to bind selectively to negatively charged bacterial cell walls under acidic pH and demonstrate increased minimum inhibitory concentration compared with free drug. At the site of infection, there are several negatively charged tissue cells that not only compete with bacteria to interact with positively charged NP, but also remove or suppress the NPs, preventing them from binding to the bacterial cell wall. Therefore, more advanced approaches for specific and risk-free pH stimuli-sensitive drug delivery system are needed.

Drug delivery through redox-sensitive systems

The generation of ROS in response to immune-mediated inflammatory pathways could also be used for drug release.[56–59] Given that some polymers, such as thioketal polymers, are sensitive to ROS, these species cleave their bonds and deliver drugs to the infection site.[60,61] Moxifloxacin (MFX) is a broad-spectrum antibiotic that is effective against various Gram-positive and Gram-negative bacteria. It is hydrophilic, is cleared from the body within 24 h, and, in excessive amounts, causes hepatotoxicity.[62] NPs have been developed to increase the life span of a drug in the body, but a more optimized and targeted drug delivery system is required. Thus, Wang *et al.*[63] developed folic acid (FA)-modified NPs for targeted drug delivery. There are three types of FA receptors (FR) found in humans: FR-α, FR-β, and FR-γ. Wang *et al.*[63] used ROS for targeted drug delivery by developing a system containing polythioketal, thioether, selenium polymers, and aryalboronate. Among these materials, phenylboronic acid and polymers containing its esterified product exhibited excellent ROS sensitivity under a biologically relevant range of H_2O_2. A multifunctional nanotherapy was developed to facilitate mucus penetration, efficiently delivering antibiotics to the infected site by sensing a small amount of oxidative stress. 4-(Hydroxymethyl) phenylboronic acid pinacol ester (HPAP)-modified cyclodextrin (Oxi-αCD) was used as a carrier to encapsulate MXF to prepare core–shell NPs via a nanoprecipitation/self-assembly method. The drug-loaded NPs formed of Oxi-aCD polymers easily penetrated the sputum and MFX was only released as a result of an oxidative imbalance or the presence of H_2O_2.[63]

Enzymatically triggered drug delivery system

Significant progress has been made to improvise drug delivery systems that elute drugs in response to toxins and enzymes released by pathogens.[64–66] Antibiotic-coated polymeric NPs undergo postpolymerization structural changes in response to enzymes, including penicillin G amidase, B-lactamase, and other strains, resulting in sustained drug release.[67] Such an approach revealed enhanced stability, minimal adverse effects, and strain selectivity following adminstration.[68]

Thamphiwatana *et al.*[69] prepared liposomes containing antibiotics, such as doxycycline, that were sensitive to phospholipase A2 (PLA_2). First, gold NPs were stabilized through chitosan and were then adsorbed onto the liposomes. These liposomes when exposed to the PLA_2 enzyme of *Helicobacter pylori* and showed extensive antibiotic release.[69] Another important advantage of such an approach is the intensity-dependent release of the drug (i.e., the more PLA_2, the more drug will be released). PLA_2 is involved in numerous disease pathways and, therefore, this technique could open a way for microtargeting disease-responsive pathways. However, further research is required given the limited literature available on this mechanism.

Yang *et al.*[70] used mesoporous silica NPs coated with lipid bilayers and the bacteria-targeting peptide UBI29-41 to target intracellular infection. The liposomes acted as a gatekeeper to prevent drug release. When the NPs reached the diseased cells/tissue, they were degraded by bacterial toxins to release the drug. The nanoconstruct successfully targeted *S. aureus* in *in vitro*, while in *in vivo* models of planktonic and intracellular infection, *S. aureus* growth was substantially suppressed. This nanosystem can be modified to administer any additional antibiotics targeting other bacteria for the treatment of a range of illnesses because of its minimal cytotoxicity and responsive drug release. An overview of exogenous and endogenous stimuli-sensitive drug delivery systems is presented in Table 1.

TABLE 1

Exogenous and endogenous stimuli-responsive drug delivery systems.

Stimulus	Delivery system	Features	Drug loaded	Disease/organism	Model	Mechanism	Outcomes	Refs
Light	Lipopolysaccharide-targeted nanoconjugate	Cell wall-targeted dendrimer nanoconjugate/ortho-nitrobenzyl-ciprofloxacin conjugate	Ciprofloxacin	Gram-negative bacteria	*In vitro* testing via turbidity assay	Photocleavage	Gram negative bacterial cell wall-targeted delivery	21
Magnetic field	Magnetic NP microbeads	Chitosan microbeads crosslinked with PEG dimethyl methacrylate of variable length	Vancomycin	Post-implantation infections	*In vitro* testing on fibroblast cells	Thermal magnetic drug delivery via formation of magnetic domains; nonthermal magnetic drug delivery	Increased release rate by 45% with no indication of tissue toxicity	30
	Magnetic NPs	Iron oxide maghemite or hematite	Ciprofloxacin	*Staphylococcus aureus* infection	Phosphate-buffered saline and Mueller-Hinton broth inhibition assay	Magnetic guidance with maghemite or hematite nano bullets	Targeted delivery with both immediate and sustained-release outcomes	27
Ultrasound	PEEK clips	Drug microbubbles made of thin PLA shell	Vancomycin	*S. aureus* spinal infection in implants	*In vitro* testing and *ex vivo* spine mode	Acoustic cavitation	Eradication of MRSA	35
	Dextran sulfate-shell and PFP-filled nanobubbles	300 nm size and anionic surface charges	Vancomycin	Topical treatment of MRSA wound infections	*In vitro* model of porcine skin	Acoustic vaporization	Treatment of MRSA	36
Electric field	Nanofilms	Negatively charged Prussian blue (PB) NPs and positively charged gentamicin in a layer-by-layer assembly	Gentamicin	*S. aureus* bacterial infection	*In vitro* testing by radiolabeled H-GS and nonradiolabeled GS	Electrochemical oxidation–reduction reactions	Controlled-release profile	44
	Nanostructured polypyrrole films	Pure titanium coated with drug by electrochemical deposition	Penicillin and dexamethasone	*Staphylococcus epidermis*	*In vitro* testing on osteoblast cultures	Electricity-derived movement of charged molecules	Sustained drug release without disruption of cell physiology	48
pH	pH-responsive polymeric NPs (PLGA-PLH-PEG)	Size: 196.0 ± 7.8 nm and 222.1 ± 1.8 nm	Vancomycin	Surface charge switching polymeric systems interacting with negatively charged bacterial cell wall; bond cleavage	*S. aureus* infection	*In vitro* testing on bacterial cells	Targeted drug delivery with selective binding to bacterial cell wall and increased MIC	54
Overexpression of ROS	MXF/FA-Oxi-αCD NPs	254-nm particle size and 7.89% loaded drug	Moxifloxacin	Bond cleavage by glutathione; oxidation responses generating ROS in response to immune-mediated inflammatory	Pulmonary bacterial infection	*In vitro* drug release and cellular study. *In vivo* testing on murine model	Targeted delivery of antibiotics to infected pulmonary tissues by facilitating mucus penetration	63
Enzymes	Chitosan-modified gold NPs (liposomes)	Diameter of 95.0 nm in water, whereas, at pH 6.5, diameter is 97.1 nm	Doxycycline	Polymerization structural changes	PLA_2 enzyme secreting *Helicobacter pylori* infection	*In vitro* bacterial cell testing	Intensity-dependent drug release with inhibition of bacterial growth	69
	Mesoporous silica NPs encapsulated in liposomes for ubiquicidin peptide (MSN-LU)	Size of 80 nm	Gentamicin	Enzyme-triggered compound release using functionalized antimicrobial peptide derivatives	*S. aureus* infection	*In vitro* testing by TEM and SEM; *in vivo* testing by planktonic bacterial infection model	Efficient drug delivery system with increased specificity, control, cellular uptake, and reduced toxicity	70

Concluding remarks

In this review, we have summarized targeted drug delivery systems for antibiotics that use internal and external stimuli-triggered systems. Stimuli-responsive drug delivery systems have been devised in such a way that any change in a specific stimulus, such as light, pH, ultrasound, oxidative state, electricity, or temperature, renders the delivery system unstable and releases the drug at target site. The targeted delivery of drugs at the right time and place can significantly reduce their detrimental effects and the development of resistance, allowing improved therapeutic efficacy and patient compliance. Ongoing research has gained impetus for developing such innovative self-programmed targeted antibiotic delivery systems. Even though the list of experimentally exploited targeted drug delivery systems is extensive, their clinical potential has been hindered because of the lack of regulatory guidelines. The structure–function relationships of various therapeutically engineered moieties need to be studied along with their characteristics, composition, and surface coating. Nevertheless, subcellular targeting of disease has significant potential for the targeted delivery of drugs. For example, mitochondria-targeted NPs as drug carriers as well as mitochondria-targeted drugs have recently been explored with great success. Further studies are needed to explore the subcellular release of drugs at the desired site of action. Furthermore, clearance and excretion pathways of NPs remain unexplored. It is hoped that stimuli-responsive drug-delivery systems will be able to propel the field of targeted therapeutics forward in the fight against infections. The release profiles of drugs in response to external and internal stimuli show that such systems can be implemented to deliver clinically relevant amounts of antibiotics at diseased sites where they are most needed.

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