Autonomous Drug Release Systems with Disease Symptom-Associated Triggers

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Many biophysical and biochemical properties of pathogenic tissues are different from those of healthy tissues. These disease symptom-associated properties include pH, reduction–oxidation conditions, enzyme generation and expression, blood glucose concentration, mechanical stiffness and strain, and temperature. Autonomous drug release that uses one or more of these disease symptom-associated properties as the release trigger minimizes the delay in treatments and allows for the release of medications with precisely controlled amounts and with desired spatiotemporal patterns. Herein, a comprehensive assessment of current research progress on autonomous drug release systems (ADRS) is provided. The representative symptoms-associated properties that can be potentially used as the endogenous stimuli are introduced. The autonomous drug systems that utilize these symptom-associated signals as the endogenous stimulation signals are discussed, followed by the discussion of current challenges and opportunities in this field, as well as possible future directions in ADRS.

1. Introduction

The use of medical drugs has been a dominant therapeutic approach for over 2000 years.[1] The medication is either taken orally, where it enters the circulatory system through the respiratory or digestive systems, or is applied to the outer surface of the patient, where it enters the underlying tissues through diffusion or other means. Despite different compositions and delivery approaches, the medication is typically made into the form of pills or capsules. The release kinetics is governed by the diffusion of medication through water-filled pores or polymer matrix comprising the outer layers of the pills or capsules, osmotic pumping, erosion, or dissolution. Such a mechanism is known as passive drug release. The representative release profile starts with a burst of local drug concentration and is followed by exponential concentration decay. This mechanism is not able to provide temporally variable or extended drug concentrations and is thus not appropriate for the treatment of many diseases, such as periodic insulin release for treating diabetes or hours-long extended drug release for inhibiting fever symptoms. Patients need to take drugs repeatedly at an interval to obtain a sufficiently high drug concentration over the entire course of treatment.

In 1952, Smith Kline & French proposed “extended-release” by developing 12-h drug-release formulations using Spansule technology.[2] Each Spansule capsule contains hundreds of micropellets that are coated with a water-soluble wax, poly(ethylene oxide) (PEO). As the thickness of PEO layers of different micropellets varies, the release profile of micropellets differs from each other. In other words, the medications in some micropellets are released earlier than others. This eliminates the initial drug concentration burst. Moreover, by extending the period where the drug concentration in blood can maintain above the therapeutic–effective threshold, the interval between medications can be significantly elongated. Later, Lee et al. reported sustained-release (up to 20 days) by entrapping progesterone in cross-linked serum albumin microbeads using an injectable, biodegradable system.[3] The strong binding between the drugs and the native serum albumin effectively decreases the release rate until albumin is degraded by proteolytic enzymes. Despite great advances in the passive drug-release scheme, extended/sustained release schemes are not yet adequate in addressing versatile therapeutic needs. For example, such mechanisms are not appropriate for medications that need to be released only at the desired spatial sites and at desired time points. For example, the medications used in chemical therapies following the surgical excision of solid tumors are highly detrimental not only to possibly remaining malignant cells around the excision sites but also to healthy cells in adjacent healthy tissues. The drug release should occur only in the close vicinity of the sites where tumor reoccurrence is highly problematic to minimize the adverse effects. Precious medications that are minute in amount also need a more advanced release scheme to minimize the undesired drug consumption/waste in nontarget tissues.

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To address these issues, several controlled-release strategies that can render desired spatiotemporal profiles of drug accessibility to target tissues were developed. In principle, these strategies can leverage the benefits of therapeutics by enhancing their efficacies, reducing the adverse effects on nontarget tissues, as well as lowering the medication intake frequency. The controlled release can be triggered by a healthcare provider or the patient (referred to as exogenous stimuli hereafter). The exogenous signals include temperature, light, magnetic field, ultrasound, electric currents, and mechanical forces. Different from passive release and extended/sustained release where the medication releases immediately after being taken by the patient or being applied to the tissues, the drug release rate in controlled release remains at a very low level until the reception of the exogenous stimuli. The decision to release drugs is made when the healthcare provider or the patient determines that desired spatiotemporal conditions are met. This process can be fairly expensive and complicated. In image-guided drug release/delivery, for instance, the drugs circulate through the vascular system where their locations are continuously monitored by ultrasound, electromagnetic field, fluorescence, and so on. Once the drugs approach the close vicinity of target tissues, exogenous stimuli are applied through the use of ultrasound, electromagnetic signals, or light. High-cost clinical infrastructure (i.e., additional imaging and stimulation instruments) is usually needed for the stimulation, which unfortunately limits the wide adoption of such therapeutic processes for self-administered or homecare therapeutics. In some other scenarios, the decision to apply exogenous stimuli is based on the patient’s self-administered measurements of pathological conditions and certain predictable models, which are often inaccurate and may lead to severe clinical outcomes. For example, diabetes patients administer insulin delivery by setting the timing and dose of insulin intake (through the use of supersonic injector, infusion pump, sharp needles, or pens) based on the diet conditions and the self-measured glucose level. The success of insulin administration is based on a predictable model that can effectively reflect the dynamic change in blood glucose level (BGL) may risk the patient to severe disease conditions, including but not limited to limb amputation, blindness, kidney failure, and fatal hypoglycemia. Moreover, in diseases with transient symptoms such as vascular hypertension, medications should be provided as soon as the symptoms appear. This is, however, difficult to implement because the symptoms (hypertension in this case) may have already disappeared before the exogenous stimuli are applied. Furthermore, the conventional controlled-release scheme does not work well for patients whose capabilities of sending the exogenous stimulation signals are impaired by their disease conditions, such as Alzheimer’s disease.

From the aforementioned description, it can be seen that the controlled release scheme using exogenous stimulation is based on an open-loop operation, where a monitoring system is needed in some cases to track the location of the medications, and the expensive clinical infrastructure is required to generate the exogenous signals. Although the idea is very straightforward and the spatiotemporal conditions associated with diseases can be precisely followed in some cases, the interference by the healthcare provider or the patient severely limits the clinical potential of such a controlled release scheme. The exogenous stimulation based on self-administered health condition measurements and predictable models may also be inaccurate and delayed. Therefore, there is a clear and imperative call for autonomous drug-release schemes that do not rely on expensive clinical infrastructures for continuous drug monitoring and stimulation and can release the medications in a timely fashion in response to changes in pathological condition.

Fortunately, the symptoms of some diseases may carry notable changes in biochemical conditions, e.g., pH value, the extent of a redox reaction, the concentration of enzymes or glucose, and changes in biophysical properties, e.g., mechanical strain and body temperature. In solid tumors, for example, the extracellular environment tends to be more acidic (pH ≈ 6.5) than normal tissues (pH ≈ 7.4); the chemical environment is more reductive, and some enzymes, such as trypsin and neutrophil elastase, exhibit over-expressions. Although mechanical strain and temperature are normally
referred to as exogenous stimuli, some peculiar mechanical strain and temperature that are related to disease symptom-associated biophysical signals, such as vascular hypertension and body temperature change, can be potentially utilized as endogenous stimuli. For instance, heart attacks are often accompanied by a substantial change in mechanical strains in ventricles and arteries. People with fever or inflammation may exhibit elevated body temperature. Using these disease symptom-associated biochemical/biophysical signals as the endogenous stimuli for triggering drug release, a closed-loop operation is expected (Figure 1).

In this Review article, we name the scheme that uses the symptom-associated endogenous biochemical/biophysical signals for triggering drug release as “Autonomous Drug Release Systems” (ADRS). It is the collective name of a group of emerging technologies that allow for the release of medications based on the change in pathological conditions. Different from previous drug-release schemes, ADRS based on closed-loop operation promise an exciting opportunity of self-regulated and timely drug release in accordance with the pathological conditions. As there have been few systematic reviews focusing on this topic to date, this review highlights some essential features of ADRS and furnishes a representative scenario of the advancements in autonomous therapeutic domains. Section 2 discusses representative symptoms-associated endogenous stimuli that can potentially trigger drug release in ADRS. Section 3 introduces the autonomous drug systems that utilize these symptom-associated signals as the endogenous stimuli. Section 4 discusses the current challenges and opportunities in this field.

2. Disease Symptom-Associated Signals as Potential ADRS Triggers

Tissues under pathological conditions undergo a variety of changes in their microenvironments and physicochemical properties, including increased acidity,[46] more reductive local environment,[29] overexpressed proteins and enzymes,[30] mechanical force fluctuation,[197] and abnormal temperature.[196] Many of these properties can potentially serve as endogenous stimuli to trigger drug release in ADRS, as elaborated in the following sections.

2.1. Disease Symptom-Associated Biochemical Signals

2.1.1. pH

Human body maintains a delicate acid–base balance under the healthy condition, where the lungs regulate the carbon dioxide (CO₂) content in blood by varying the rate at which CO₂ is excreted; the kidneys eliminate H⁺ and regenerate bicarbonate; and the respiratory chemoreceptors in the brain stem respond to CO₂ concentration change in blood, causing increased ventilation if the CO₂ concentration rises and decreased ventilation if the CO₂ concentration falls. The acid–base balance may be disturbed by damages of organs (kidney, lungs, brain, etc.), diseases that cause an abnormal increase in metabolic acid production or medical intervention. In particular, many regions within solid tumors are transiently or chronically hypoxic and acidic due to poor perfusion and high metabolic rates. This is believed due to increased glucose consumption, which results in significant production of lactate and H⁺.[39] Furthermore, the hydrolysis of adenosine triphosphate (ATP) in an energy-deficient manner results in the acidic environment of tumor cells.[40] The acid load is transported outside the cells and cannot be removed by the vasculature, leading to an acidic extracellular environment in solid tumors (pH < 6.5 as compared with pH ≈ 7.4 in normal cells).[41] Similarly, the local pH in inflamed or infected tissues may become acidic because leukocytes can pump lactic acid into the exudate.[42] These widely varied pH conditions in diverse biological systems have motivated the design of pH-responsive ADRS.

2.1.2. Reactive Oxygen Species/Antioxidants

Oxidative stress due to the imbalance between free radicals and antioxidants contributes significantly to various diseases.[43,44] Free radicals are highly reactive atoms or molecules with one or more unpaired electrons in the external shell and can be
formed when oxygen interacts with certain molecules. Reactive oxygen species (ROS) is the term to indicate components that can cause oxidative stress. It includes oxygen radicals such as superoxide, hydroxyl radicals, and oxidants such as hydrogen peroxide ($H_2O_2$) and singlet oxygen. A high level of ROS can cause oxidative modification of major cellular macromolecules (i.e., carbohydrates, lipids, proteins, and DNA). Localized high levels of ROS have been found under several pathological conditions, including aging, neurological and inflammatory diseases, infections, cancer, atherosclerosis, and diabetes. In addition to ROS, some antioxidants may also serve as measures of oxidative stress. For example, glutathione tripeptide ($γ$-glutamyl-cysteinyl-glycine, GSH) is a common biological reducing agent. Reduced GSH is considered to be one of the most important scavengers of ROS, and its ratio with oxidized glutathione may serve as a marker of oxidative stress. It has been reported that the concentration gradient of GSH in tumor tissues and the cytosol of tumor cells are at least four times higher than those in normal tissues, which contributes to the high reducing tumor microenvironment. The development of carriers that can autonomously release bioactive agents selectively to the diseased areas under oxidative stress is thus highly desirable.

### 2.1.3. Enzymes

Enzymes play a significant role in nanomedicine because of their exceptional bio-recognition capabilities and catalytic properties. Some enzymes are overexpressed upon the onset and progression of specific disease conditions and can, therefore, serve as the candidates of symptom-associated endogenous stimulation signals in ADRS. In particular, hydrolases, including proteases, lipases, and glycosidases, have been widely reported to associate with certain pathological states. For example, cancer-associated proteases (CAPs) are a series of proteases that are usually absent or at very low concentrations in healthy tissues but are highly overexpressed in cancerous tissues, where CAPs are produced either by tumor cells or other cells present in tumors. Human neutrophil elastase is overexpressed in inflammation, making it possible to use elastase as an endogenous signal to trigger the release of medications against diseases, including lung infections. Phospholipases such as phospholipase A2 (PLA2) may also serve as the candidates of endogenous signals in ADRS because their expressions are upregulated in both infectious and inflammatory diseases. Furthermore, they also exhibit a high concentration at the invading edge of tumors. Helicobacter pylori infection in the stomach may lead to peptic ulcers, chronic gastritis, and gastric malignancy. These bacteria secrete PLA2 that can degrade liposome membrane integrity for triggered cargo release. Glysosidase enzymes catalyze the hydrolysis of carbohydrates and can be used for triggering drug release at sites where the concentrations of carbohydrates are elevated compared with those in normal tissues. These pathological conditions include human immunodeficiency virus (HIV), cancer and their metastases, inflammation, and infections. In addition, bacterial enzymes are essential for combating infectious diseases because they can be used as a smart trigger to release antibiotics inside cells. Azoreductase secreted by the microbial flora existing in the human colon has been successfully used for triggered drug release for colonic diseases.

### 2.1.4. Glucose

Diabetes is a metabolic disorder wherein the body is unable to store and use sugar properly. With the number of diabetic patients expected to reach 440 million by 2030, diabetes has been a global issue with increasing societal and economic impacts. Patients with diabetes have limited ability to use glucose as fuel due to the lack of insulin produced, which leads to hyperglycemia. The glucose level can, therefore, be used as an endogenous signal in ADRS to trigger the insulin release and attenuate insulin imbalance or resistance.

### 2.2. Disease Symptom-Associated Biophysical Signals

#### 2.2.1. Mechanical Strain

Mechanical signals are universal in various physiological and pathological processes, including wound healing, inflammation, musculoskeletal, cardiovascular contractions, and respiration, just to name a few. Many diseases are closely associated with mechanical signals, such as deep vein thrombosis, abdominal distension, glaucoma, and vascular hypertension. The mechanical signals are often in the form of shear strain, compressive strain, or tensile strain. For instance, the intraocular pressure (IOP) in the eye globe rises in glaucoma due to the increased outflow resistance at the trabecular meshwork, generating excessive compressive strain to the optic nerves on the retina (and excessive tensile strain on the sclera) and causing damage. As such mechanical strain directly relates to the detrimental effect, the damage to the optic nerves could be effectively attenuated if the medications for lowering IOP can be released timely using the excessive strain as the release trigger.

#### 2.2.2. Temperature

Temperature is another common biophysical parameter that changes upon certain pathological conditions. Several studies have highlighted the temperature changes in tumors and other inflammatory diseases as a direct result of abnormal blood flow, leukocyte infiltration, increased metabolism, and enhanced cell proliferation under diseased conditions. In particular, cancerous and inflammatory tissues often exhibit higher temperatures as compared with normal tissues. The representative biochemical and biophysical signals accompanying the symptoms of certain diseases that may have the potential to serve as endogenous stimulation signals in ADRS are summarized in Table 1.

### 3. Autonomous Drug Release Based on Symptom-Associated Signals

Utilizing the symptom-associated endogenous stimulation signals listed in Section 2 as triggers, autonomous drug release without the interference from a healthcare provider or the patient
Reducing Acidic environment pH  
Apical periodontitis

Acidic environment pH  
Gastric ulcer

Acidic environment pH  
Acute gastritis

Reducing microenvironment  
GSH  
Tumor

Oxidizing microenvironment  
ROS  
Neurological and inflammatory diseases

Elastase overexpression  
Protease  
Lung diseases

PLA2 overexpression  
Lipase  
Helicobacter pylori infection

Carbohydrate overexpression  
Glycosidase  
HIV, cancer, inflammation, and infections

Azoreductase overexpression  
Protease  
Colonic diseases

Hyperglycemia  
Blood glucose  
Diabetes

Intraocular pressure increase  
Tensile/compressive strain  
Glaucroma

Gastric dilatation  
Tensile strain  
Abdominal distension

Stroke  
Shear strain  
Cerebral thrombus

Blood pressure increase  
Shear strain  
Hypertension

Chest distress  
Shear strain  
Atherosclerosis

Body temperature increase  
Temperature  
Fever/inflammation

Local temperature increase  
Temperature  
Tumor

Table 1. Symptom-associated endogenous stimulation signals.

| Symptoms          | Corresponding stimuli      | Diseases                  |
|-------------------|---------------------------|---------------------------|
| Acidic environment pH | Infectious diseases/cancerous tissues |
| Acidic environment pH | Gastric ulcer |
| Acidic environment pH | Apical periodontitis |
| Acidic environment pH | Acute gastritis |
| Reducing microenvironment | GSH  | Tumor |
| Oxidizing microenvironment | ROS  | Neurological and inflammatory diseases |
| Elastase overexpression | Protease  | Lung diseases |
| PLA2 overexpression | Lipase  | Helicobacter pylori infection |
| Carbohydrate overexpression | Glycosidase  | HIV, cancer, inflammation, and infections |
| Azoreductase overexpression | Protease  | Colonic diseases |
| Hyperglycemia | Blood glucose  | Diabetes |
| Intraocular pressure increase | Tensile/compressive strain  | Glaucroma |
| Gastric dilatation | Tensile strain  | Abdominal distension |
| Stroke | Shear strain  | Cerebral thrombus |
| Blood pressure increase | Shear strain  | Hypertension |
| Chest distress | Shear strain  | Atherosclerosis |
| Body temperature increase | Temperature  | Fever/inflammation |
| Local temperature increase | Temperature  | Tumor |

is possible. In this section, we introduce the recent development in ADRS that release the medications based on pathological feedbacks (pH, redox, enzyme, glucose, mechanical force, and temperature).

3.1. Physiological Signals-Responsive Drug Release

3.1.1. pH-Responsive

pH-responsive drug release has resulted in remarkable breakthroughs in the diagnosis and treatment of a wide range of diseases and disorders, including malignancies and infections. Such a release scheme has shown greatly enhanced anticancer efficacy compared with conventional surgical treatments, radiation therapies, and chemotherapies, and demonstrated enhanced oral bioavailability. pH-responsive autonomous drug release can be classified into three categories: 1) the use of polymers (polycrads or polybases) with ionizable groups that undergo conformational and/or solubility changes toward environmental pH variation; 2) the design of polymeric systems with acid-sensitive linkers whose cleavage enables the release of molecules anchored at the polymer or with the ability of modifying the charge in the polymer according to the change in environmental pH; 3) the degradation of the spacers that conjugate the drug to the polymer. Figure 2 provides the molecular formula of representative pH-sensitive anionic polymers, cationic polymers, acid-sensitive cleavable linkers, and biodegradable polymers that can be used for designing pH-responsive ADRS.

Polyacid and Polybase-Based: Acidic pendant groups of the polyacid-based (anionic polymers) networks are ionized at high pH values, generating negative charges on the polymer chains and causing their transition from a collapsed state to an expanded state. The swelling of the anionic networks at basic media promotes the opening of pores and the release of encapsulated drug molecules. The reverse effect takes place at low pH values, making the polyacid-based networks shrink and retaining the drug molecules from the outside environment. Poly(acrylamidoglycolic acid) (PAGA), an important acrylamide-based polymer, has been extensively utilized in biomedical applications due to its biocompatibility and ability to remove toxic metal ions. For example, Han and co-workers fabricated cellulose nanocrystals (CNCs)-reinforced poly(acrylamidoglycolic acid) (PAGA-NC) for pH-sensitive controlled release of diclofenac sodium (DCF). In vitro release of DCF from PAGA-NC hydrogels was retained at pH 1.2, whereas the maximal release was observed at pH 7.4. Polymeric micelles containing acidic groups in their inner cores can also be used in oral drug delivery systems. Polymeric micelles containing acidic groups are stable at the acidic environment of the stomach because their inner blocks are in unionized and hydrophobic forms. Upon a pH increase in the intestine, the acidic groups start to deprotonate, which increases the electrostatic charge and hydrophilicity of the inner cores, leading to micelle dissociation and drug release. Park and co-workers developed hydrotropic (HP) polymer micelles containing acryllic acid (AA) moieties for oral delivery of paclitaxel (PTX), a poorly water-soluble drug. HP micelles showed high PTX loading capacity and excellent aqueous stability in vitro. AA moiety was introduced into the HP micelles to achieve a fast release of PTX in the simulated intestinal fluid (SIF, pH = 6.5) compared with that in the simulated gastric fluid (SGF, pH = 1.6). HP micelles with more than 20 mol% AA contents complete the release of PTX within 12 h in SIF, which is very critical as the retention time of an oral drug formulation in the gastrointestinal tract is much less than 12 h.

Polybase-based (or cationic) networks, in contrast, are relaxed at relatively higher pH as their basic pendant groups are protonated and unionized. At a low environmental pH, these groups start ionization, resulting in hydrogel swelling and drug release. Polybase-based hydrogels that rapidly respond to the mildly acidic environment in the tumor sites provide an opportunity for controlled anticancer drug delivery. Chitosan hydrogels have been widely used for tumor-selective delivery due to its polycationic nature, enzymatic biodegradability, mucoadhesive, and antibacterial properties. Despite these advantages, their low solubility at certain physiological conditions and poor mechanical properties limit the adoption. To solve this, Alemdar and Aycan synthesized bone-ash-reinforced chitosan-based hydrogels for the controlled release of amoxicillin. In vitro release revealed that the cumulative release rate of amoxicillin was doubled in pH 1.2 compared...
with that in pH 7.4.\cite{27} The encapsulation of bone ash into hydrogels not only enhances the mechanical properties but also decreases the burst release of the drug. Polymeric micelles with basic groups in their core-forming blocks can also be used as cancer-targeted drug carriers.\cite{89,90} Such supramolecular assemblies are stable at the physiological pH as the inner blocks are in the unionized and insoluble form. Decreasing the pH of the surrounding media provokes the micelle dissociation as a result of protonation of the basic groups, making the inner blocks water-soluble. Zhang et al. developed a pentablock polymeric poly(ethylene glycol)-b-(poly(2-(diethylamino) ethyl methacrylate)-b-poly (hydroxyethyl methacrylate)-g-folic acid)\textsubscript{2} [PEG-b-(PDEAEMA-b-PHEMA-g-FA)\textsubscript{2}] micelles as an anticancer drug nanocarrier.\cite{91} Folic acid was used to improve the selective targeting of cancer cells. In vitro drug release of the micelles showed a higher doxorubicin (DOX) cumulative amount at pH 5.0 (\textasciitilde90\%) compared with that at pH 7.4 (\textasciitilde20\%) due to the protonation of the tertiary amino groups.

Acid-Labile and Charge-Reversal: Among pH-sensitive moieties, the acid-labile linkers that can respond to slight pH changes are very promising for ADRS. Acid-labile covalent linkages can be rapidly hydrolyzed in acidic environments, such as in tumor tissues. Polymers containing these cleavable linkers (e.g., hydrazone, imine, ketal, acetal, oxime, amide, and ester) shown in Figure 2c are stable at normal physiological pH, whereas drug release occurs due to hydrolysis of the linker bonds in response to the decrease in pH under diseased conditions. Jin et al. synthesized triblock copolymer (PEG-OPCL-PEG) consisting of hydrophilic poly(ethylen glycol) (PEG) and hydrophobic oxime-tethered polycaprolactone (OPCL).\cite{94} The oxime bonds endowed the triblock copolymer with high pH sensitivity. The drug release results reveal that DOX release from micelles is significantly accelerated at mild acid pH 5.0 compared with that at normal physiological pH 7.4, suggesting the pH-responsive behavior of the copolymer with oxime linkages. Polymer-based prodrugs formed by conjugation of anticancer drugs to polymeric chains using acid-labile linkers offer several advantages over their free-form counterparts, including good protection during drug circulation and enhanced drug bioavailability. The cleavage of these chemical linkages in the acidic environment leads to the activation and release of cytotoxic chemotherapy agents at the desired sites of action from the polymeric prodrug and can therefore minimize the side effects.\cite{92–94} Zhang and co-workers designed cellulose derivatives by conjugating 2,3-dialdehyde cellulose (DAC) with oleylamine and aminoethyl rhodamine (AERhB) via Schiff base bonds. AERhB was used as a model anticancer drug.\cite{94} It was demonstrated that the Schiff base bonds in nanoparticles (NPs) allowed the efficient release of drug in the acidic tumor microenvironment by cleaving the Schiff base linkages.

Ideal nanocarriers in the physiological environment should be negative or uncharged to reduce toxicity and prolong blood circulation time, but they can be positively charged in tumor tissues and intracellular compartments to promote the cellular uptake and assist the endosomal escape.\cite{79,95,96} Zhang and co-workers functionalized PEG-b-PCL micelles with β-carboxylic amides, which are negatively charged and stable in neutral solution but can quickly become positively charged at pH 6.0 due to the hydrolysis of β-carboxylic amides in acidic conditions.\cite{79} The pH-triggered negative-to-positive charge reversal not only contributes to a very fast drug release in acidic conditions but

Figure 2. The molecular formula of representative pH-responsive biomaterials. a) anionic polymers, b) cationic polymers, c) acid-sensitive cleavable linkers, and d) biodegradable polymers.
also effectively enhances the cellular uptake by electrostatic adsorptive endocytosis. Dual/multi pH-responsive ADRS, designed to be sensitive to both tumor pH and endosomal pH, is a new concept with the promise of future refinements of ADRS. A dual pH-sensitive polymer–doxorubicin conjugate nanoparticulate system (PPC-Hyd-DOX-DA) has been designed by Wang and co-workers for enhanced anticancer drug release, which is capable of reversing its surface charge from negative to positive at tumor extracellular pH (pH 6.5) to facilitate cell internalization (Figure 3a, step 2, and Figure 3b).

Simultaneously, the significantly increased acidity in the intracellular pH environments (pH 5.0) further promotes the release of DOX (Figure 3c). Degradation and Others: Some diseases, such as acute gastritis, need both burst release and sustained release. When gastroenteritis attacks, it is demanded that the plasma drug concentration should reach the treatment level immediately and the drug should quickly take effect after administration. After the first burst release, it is desired that the drug dose can be constantly supplied to keep the plasma drug concentration within safe and effective ranges for an extended period, which can maintain the therapeutic effect and restrain complications. To achieve drug delivery systems with the programmed sequential release, core-shell chitosan microcapsule has been developed for acute gastritis therapy.

The microcapsule consists of a cross-linked chitosan hydrogel shell and an oily core containing both free-drug molecules and drug-loaded poly(lactic-co-glycolic acid) (PLGA) NPs. Upon application of the acid-trigger, the microcapsules first achieve the burst release due to the acid-induced decomposition of the chitosan shell. The encapsulated free-drug molecules and drug-loaded PLGA NPs are rapidly released within 60 s. Next, the drugs loaded in the PLGA NPs are slowly released for several days to achieve sustained release based on the synergistic effect of drug diffusion and PLGA degradation (Figure 3d). In addition, these microcapsules provide versatility for loading different drugs, such as oleophilic drug of curcumin and hydrophilic drug of catechin (Figure 3e,f).

Liposomes have been studied extensively as antimicrobial delivery vehicles due to their highly biocompatible lipid materials, unique bilayer structures (can fuse with bacterial membranes), high drug-carrying capacity, and readily tunable formulation properties. A nanocarrier comprising synthetic chitosan-modified gold NPs attached to the anionic surface of a liposome (AuChi-liposome) was reported for the delivery of antimicrobial drugs (e.g., doxycycline) to the stomach as a therapy against H. pylori infection. The nanocarrier is stable at gastric pH 1.2 due to the introduction of chitosan-modified gold NPs. At neutral pH 7.4 regions (where the bacteria are situated), AuChi NPs are deprotonated and thus detached from liposomes. As a result, the liposomes actively fuse with bacterial membranes, which induces subsequent drug release (Figure 4a,b).

Mesoporous silica nanoparticles (MSNs) have emerged as robust nanovectors for drug release because of their remarkable biocompatibility and stability, among other features. The intriguing concept of stimulus-responsive gatekeeping of functionalized MSNs has been introduced to regulate the movement of cargo molecules. Upon stimulation, these gatekeepers allow the release of the cargo from the reservoir into a specific environment. Zhu et al. used MSNs with the nanopores sealed by ZnO...
quantum dots (QDs) (Figure 4c),\textsuperscript{[100]} which can be efficiently dissolved in the acidic intracellular compartments of cancer cells, releasing drug cargo from the pores of the MSNs into the cytosol (Figure 4d).

### 3.1.2. Reductant/Oxidant Responsive

**Reductant-Responsive:** Disulfide (—SS—) and diselenide (—SeSe—) bonds, prone to rapid cleavage by GSH, can be used to achieve redox sensitivity. The cytosolic release of drugs can then be triggered by the concentration gradients of GSH between extracellular (\(\approx 2–20 \mu M\)) and intracellular (\(\approx 2–10 \mathrm{mM}\)) compartments, or between tumor and normal tissues.

In polymeric micelles, micellar decrosslinking and full destabilization/disassembly may be caused by the reduction of disulfide or diselenide bonds in polymeric assemblies by intracellular GSH. Fan and co-workers developed disassemble micelles for intracellular DOX delivery based on a reduction degradable amphiphilic polyamide amine-g-polyethylene glycol (PAA-g-PEG) graft copolymers containing disulfide linkages throughout the main chain.\textsuperscript{[102]} The micelles are stable in normal physiological conditions but quickly disassemble in reductive conditions due to the cleavage of the disulfide linkages. The micelles quickly release the entire loaded drug within 10 h in the presence of the reductive agent, dithiothreitol (DTT), compared with less than 25% of drug release within 24 h in the normal condition. Kim et al. reported GSH-induced controlled-release characteristics of MS NPs with cyclodextrins (CDs) gatekeepers covalently connected onto the particle surface (Si-SS-CD) via disulfide unit.\textsuperscript{[103]} The surface of MSNs is PEGylated for enhanced solubility in aqueous media (Figure 5a). The release of DOX from DOX-loaded Si-SS-CD-PEG strongly depends on the intracellular GSH content. With increasing GSH or DTT concentration, DOX release is effectively accelerated (Figure 5b).

**Oxidant- Responsive:** High levels of ROS have been found under several pathological conditions, which has evoked interests in developing ROS-responsive nanocarriers. Some polymers respond to ROS through the oxidation of functional groups, such as

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**Figure 4.** Working mechanism for pH-triggered release of DOX and the cumulative DOX release profiles at different pH values. a) Schematic illustration of AuChi-liposome for pH-responsive gastric drug delivery. b) Accumulative DOX-release profile from DOX-loaded AuChi-liposome at pH = 1.2 and pH = 7.4. a,b) Reproduced with permission.\textsuperscript{[99]} Copyright 2013, American Chemical Society. c) Schematic illustration of the synthesis of ZnO@MSNs-DOX and the working protocol for pH-triggered release of DOX from ZnO@MSNs-DOX to the cytosol. d) Release profiles of ZnO@MSNs-DOX at pH = 7.4, 5.0, and 2.0 at 37°C. c,d) Reproduced with permission.\textsuperscript{[100]} Copyright 2011, American Chemical Society.
as sulfides or selenides, increasing their solubility in water. Hubbell and co-workers explored an ABA block copolymer with poly(propylene sulfide) (PPS) as the hydrophobic block and hydrophilic PEG using EG16PS50EG16 symmetric triblock macroamphiphile as an example. The oxidation of the central-block sulfide moieties to sulfoxides and ultimately sulfones increases the hydrophilicity of the initially hydrophobic central block, leading to the oxidative destabilization of the vesicles.

Polymers can also undergo physical degradation in response to ROS if they contain oxidizable functionalities such as thioketals, boronic esters, and (oligo)prolines. Murthy and co-workers presented tumor necrosis factor-alpha-siRNA (TNF-α) loaded termed thioketal nanoparticles (TKNPs) that could localize orally delivered siRNA to the sites of intestinal inflammation (Figure 5c). TKNPs are formulated from poly-(1,4-phenyleneacetone dimethylene thioketal) (PPADT), a polymer composed of ROS-sensitive thioketal linkages that are stable to acid-, base-, and protease-catalyzed degradation but degrade selectively in response to ROS. Sung and co-workers explored Cy3-conjugated N-palmitoyl chitosan (Cy3-NPCS) with dual responses to oxidative stress and reduced pH for effective delivery of the encapsulated payload, curcumin, to inflamed tissues to inhibit the overproduction of ROS/RNS (reactive nitrogen species). The curcumin released upon trigger can efficiently reduce the excess oxidants produced by the lipopolysaccharide (LPS)-stimulated macrophages.

It is worth mentioning that some cancer cells may exist in reducing conditions, whereas others are under increased oxidative stress. Those cells may either exist in different tumors or coexist in different regions of one tumor, and even one tumor cell at different stages may have different GSH/ROS levels. Therefore, it is of significance to design a nanocarrier that can respond to both intracellular GSH and ROS to release the carried drugs. In this regard, Gu and co-workers synthesized prodrug OEG-2S-SN38-formed nanocapsules that can respond to both GSH and ROS, and subsequently release SN38, a highly potent anticancer drug. The thioether chain between SN38 and oligo(ethylene glycol) (OEG) can be easily oxidized by ROS to become hydrophilic, causing quick hydrolysis of the phenol ester and fast release of SN38. In the presence of GSH with a thiol group, SN38 can be released by the thiolysis of the phenol ester.

3.1.3. Enzyme-Responsive

Enzyme-responsive materials can be excellent candidates for ADRS as some enzymes are overexpressed in specific tissues, and their concentrations may become higher in the diseased states. For example, the concentration of CAP is generally higher in cancerous tissues compared with that in healthy tissues. Developing a prodrug or a drug delivery system that can be cleaved and activated by CAPs would be a viable method for delivering drugs to the tumor sites. Bosmann and co-workers synthesized a cholesterol-anchored graft copolymer composed of a short peptide sequence for urokinase plasminogen activator (uPA, a well-studied CAP) and poly(acrylic acid) (PAA), and then degrade selectively in response to ROS.

![Figure 5. Reductant/oxidant-responsive systems. a) Scheme of GSH-triggered release of guest molecules from the pore of Si-SS-CD equipped with the CD gatekeeper. b) GSH-responsive release of DOX. 1) 1 mM, 2) 0.1 mM, 3) 0.01 mM of GSH. a,b) Reproduced with permission.[103] Copyright 2010, Wiley-VCH. c) TKNPs are formulated from a ROS-sensitive polymer and release orally delivered siRNA at sites of intestinal inflammation. PPADT 3 is synthesized using the acetal exchange reaction. PTSA: para-toluene sulfonic acid. Reproduced with permission.[104] Copyright 2010, Springer Nature.](image-url)
incorporated the copolymer into liposomes prepared at high osmolarities.[112] Protease-triggered, caged liposomes with different ratios of polymers and different degrees of cross-linking show significant and substantial different releases of carboxyfluorescein in the presence of uPA, whereas bare liposomes show no difference in the presence of uPA.

The infection of the digestive system can lead to the overexpression of trypsin, an important digestive proteinase. This makes trypsin highly potent for serving as an endogenous stimulation signal in ADRS. Liu and co-workers synthesized supramolecular NPs constructed from a cyclic polysaccharide named sulfato-β-cyclodextrin (SCD) and a protein named protamine.[113] Due to their trypsin-triggered disassembly behaviors, these NPs can efficiently release the encapsulated model drugs in a controlled manner.

PLA2, secreted by H. pylori, can be used to degrade liposome membrane integrity for triggered cargo release. Zhang and co-workers synthesized liposomes with lipid composition sensitive to PLA2 and stabilized them with small chitosan-modified gold NPs (AuChi-liposomes).[114] The adsorbed AuChi are effective in preventing liposome fusion and drug leakage while leaving a considerable fraction of liposome surfaces accessible to the PLA2 enzyme. The AuChi-liposomes make smart “on-demand” antibiotic delivery possible: the presence of more enzymes or bacteria at infection sites can release more drugs against the infection.

Glycosidase enzymes can also be used for triggering drug release at sites where their concentrations are elevated as compared with normal tissues. Bernardos et al. prepared capped silica mesoporous NPs functionalized with Glucidex 47 and loaded with a cytotoxic, S1-DOX for on-demand delivery applications.[115] The results showed that hybrid silica mesoporous NPs exhibited glycosidase-responsive intracellular controlled release. The delivery of DOX to HeLa and LLC-PK1 cells increased drastically in the presence of β-D-galactosidase.

Azoreductase has received great attention as a target for triggered drug release, especially for colonic diseases. Khan and co-workers achieved copolymers having two polymeric segments.[116] One segment is composed of poly(styrene), and the other segment is an enzyme-sensitive methacrylate-based polymer repeat unit carrying carefully designed azobenzene side chains. In the presence of the enzyme azoreductase and coenzyme nicotinamide adenine dinucleotide phosphate (NADPH), the diblock copolymer assembles into a micellar nanostructure and releases its cargo (Figure 7a), which is different from most other reports where an assembled micellar nanostructure undergoes a disassembly process through enzymatic actions.[118,119] Bacterial enzymes can be potentially used to release antibiotics inside cells as a triggered smart nanosystem, playing a significant role in combating infectious diseases. Wang and co-workers synthesized nanogels that contained a mannosyl ligand conjugated

Figure 6. The structure of the prodrug and its redox signal-triggered SN38 release. a) Schematic structure of OEG-2S-SN38, its self-assembly into nanocapsules, and response to the tumor redox heterogeneity. SN38 release from the OEG-2S-SN38 nanocapsules in the presence of b) various concentrations of H2O2, and c) 10 mM GSH in pH 7.4 or pH 4 at 37°C. Reproduced with permission.[111] Copyright 2013, Wiley-VCH.
PEG shell and a polyphosphoester core. Bacterial phosphatase or phospholipase was utilized to trigger antibiotic release by degrading the polyphosphoester core of the vancomycin-loaded nanosized nanogel (MNG-V) (Figure 7b). The drug release from vancomycin-loaded NG (NG-V) and MNG-V is similar. Only 17.8 ± 1.6% and 16.5 ± 0.3% of the total encapsulated vancomycin are released from NG-V and MNG-V in the absence of MW2, the model bacterium. In contrast, when the nanogels were incubated with MW2 in 5% tryptic soy broth (TSB), the release of vancomycin is accelerated, reaching a cumulative release of 57.0 ± 1.0% of total encapsulated drug in 0.5 h and 85.2 ± 11.1% in 24 h for NG-V compared with 57.5 ± 3.0% in 0.5 h and 88.2 ± 5.4% in 24 h for MNG-V (Figure 7c).

3.1.4. Glucose-Responsive

ADRS that continuously and intelligently release insulin in response to the change in BGLs can improve the quality of life for patients with diabetes. These smart-systems function through different mechanisms. One mechanism is based on the conversion of glucose to gluconic acid by glucose oxidase (GOx). For example, Sun and co-workers developed glucose-responsive implantable microdevices for closed-loop insulin delivery. The albumin-based bioinorganic membrane microdevices utilized GOx, catalase (CAT), and manganese dioxide (MnO₂) NPs to convert a change in the environmental glucose level to a pH stimulus, which regulated the volume of pH-sensitive hydrogel NPs and thereby the membrane permeability. In vivo efficacy of the microdevices for hyperglycemia control was maintained for 7 days. In another work, Anderson and co-workers exhibited a glucose-responsive closed-loop insulin self-regulated delivery system consisting of a pH-responsive chitosan matrix, enzyme nanocapsules, and recombinant human insulin. CAT was added to regenerate oxygen (O₂) to assist GOx’s glucose catalysis and to consume undesired H₂O₂ produced by glucose oxidation. When subjected to hyperglycemic conditions, the microgel system swells and releases insulin as a result of the enzymatic conversion of glucose into gluconic acid and protonation of the chitosan network (Figure 8a). Microgels release insulin at hyperglycemic glucose levels. A much slower release rate is obtained at basal glucose level and in the control solutions (Figure 8b). Importantly, the insulin release profile of microgels presents a pulsatile pattern when exposed to an alternating glucose concentration between normal and hyperglycemic levels every 1.5 h for several cycles. A 2.5-fold increase in the insulin release rate is observed when the glucose concentrations are elevated to hyperglycemic levels. Interestingly, the release rates at a high hyperglycemic level reach a maximum point and then gradually decrease (the inset of Figure 8c). The “acceleration period” is resulted from incomplete reversibility between swelling and deswelling, whereas the “deceleration period” is due to the depletion of insulin in the dissociated microgels.

In addition to the release of insulin stimulated by gluconic acid, the controlled release of insulin by competitive binding can also be used to treat diabetes. Lu and co-workers reported a glucose-responsive controlled-release system ((MSN-anchor-RB)@GOx) consisting of MSNs carrier, D(-)-glucosamine inhibitor, GOx capping agent, and rhodamine B (RB) model drug. GOx can combine with D(-)-glucosamine anchored outside the pores of silica NPs to form an enzyme-inhibitor (EI) complex, which acts as a “bio-gate”, resulting in the closing of the mesopores. The opening event is triggered by a highly effective competitive combination of glucose (substrate) and GOx that forms the enzyme-substrate (ES) complex. As a result, the pores are uncapped, followed by releasing the entrapped guest molecules (Figure 8d). It was exhibited that there was nearly no leakage of RB without glucose addition (Figure 8e, 0–80 min). When glucose solution (1.0 mM, 1 mL) was added, the absorbance intensity increased gradually and reached a plateau (140–260 min). The absorbance intensity increased continuously and reached a plateau again at 325 min when more glucose solution (1.0 mM, 14 mL) was added at 260 min. It was concluded that the released amount of RB molecules was proportionally dependent on the amount of glucose addition (Figure 8e). Such behavior can be attributed to the different degrees of ES complex formation toward the concentration difference in glucose. Herein, it
implies that the drug delivery for the GOx-capped functionalized mesoporous silica materials (FMSMs) system is mediated by the glucose concentration, thus affording the enzyme inhibition mechanism-triggered controlled delivery. Similarly, Du and co-workers constructed Concanavalin A (Con A)-gated mannose-functionalized MSN delivery systems for applications in site-specific drug release relevant to diabetes. The Con A tetramers specifically bound the functionalized mannose epitopes through multivalent carbohydrate–protein interactions. The protein nanogates can be opened by competitive binding of glucose at high concentrations, releasing the cargo from the MSN pores on demand.

3.2. Mechanoresponsive Drug Release

Mechanical signals are ubiquitous in our daily body motions, including the compression in cartilage and bones, the tension in muscles, organs, tendons and bone joints, and shear forces in blood vessels. These mechanical signals may serve as a simple and easily accessible means to trigger drug release at desired spatiotemporal conditions. Stretch-induced ADRS can be utilized to deliver antibacterial agents, anticancer drugs, or growth factors for generating localized anti-inflammatory effects, suppressing tumor growth, or repairing tissues in a self-administered manner, whereas shear-sensitive ADRS can provide personalized treatment for cardiovascular patients due to its “intelligent” spatiotemporal localization capability. It is reported that physiological related mechanical signals span over a wide magnitude (e.g., cellular forces: \(10^{-9} - 10^{-6}\) N, cardiovascular and musculoskeletal tissues: \(10^{-6} - 10^{-4}\) N). Human joints enable rotation, bending, and vibration with a maximum tensile strain of 30–100%. Mechanoresponsive devices and materials that can trigger drug release using mechanical signals relevant to various pathological conditions may potentially serve as ADRS.

3.2.1. Compressive/Tensile Force-Responsive

Most compressive or tensile force-responsive ADRS are based on stretchable materials, such as hydrogels and elastomers. Typical
mechanisms for releasing entrapped agents from ADRS are based on either physical deformation of nanocarriers or changes in chemical properties of materials, such as breakage of chemical bonds.

Of the limited reports on mechano-stimulated ADRS, many highlight compression stimuli. Mooney and co-workers indicated that the mechanical stress to extracellular matrices (ECMs) would lead to an increase in growth factors. Synthetic ECMs made of alginate hydrogels with reversible binding to drugs were developed, where unbound vascular endothelial growth factor (VEGF) was released upon each compression. With reequilibration of bound VEGF turning into unbound VEGF, the hydrogel can not only continuously release VEGF but also control the release rate by regulating the compressive force amplitude. Jia and co-workers developed another compression-responsive autonomous system for tissue repair where hyaluronic acid (HA) hydrogels containing covalently integrated micelles (HAxBCM) by radical polymerization of glycidyl methacrylate (GMA)-modified HA (HAGMA) were prepared in the presence of cross-linkable block copolymer micelles (xBCM). xBCM is assembled from hydrophilic PAA partially modified with 2-hydroxyethyl acrylate and poly(n-butyl acrylate) (PnBA). Covalent integration of dexamethasone (DEX)-loaded xBCMs in HA gels significantly reduces the initial burst release and provides sustained release over a prolonged period. Furthermore, DEX release from HAXBCM gels is accelerated by intermittently applied compression in a strain-dependent manner, offering a novel strategy to exploit mechanical stress present in the healing wounds to initiate tissue repair.

As tensile strains exist universally with body motion and are highly correlated with certain disease conditions, it is very appealing to exploit such strains for on-demand drug release. Chemically cross-linked hydrogels integrated with mechanosensitive BCMs were reported to have the capability to trigger pyrene release by tensile forces. For example, pyrene-loaded BCMs cross-linked poly(acrylamide) (PAAm) networks was used for drug release. The restricted BCMs provide mecanosensitive elements. During each stretch period, the amount of pyrene release at 60% strain is approximately two times higher than that at 30% strain, and 2.5 times higher than those at static controls. Furthermore, the BCMs return to their original morphology after force removal. The force-induced deformation of BCMs that weakens the hydrophobic association between pyrene and the micelle core release drug upon strain application, making BCM-PAAm gels attractive candidates for the repair and regeneration of mechanically active tissues.

Patches, the wearable healthcare systems that can synchronize with the mechanical motions of organs, muscles, and tendons, are widely applied in ADRS recently. There is an increasing clinical need to adjust the dosage level in real-time by on-demand delivery using patch-type transdermal delivery systems. On-demand patches are particularly suitable for patients with nerve disorders such as epilepsy and Alzheimer’s disease because stage (symptom)-specific drug administration is required. Jeong and co-workers designed a strain-controlled system that released drugs from an array of stretchable microcapsules polystyrene (PS) supported on the poly(dimethylsiloxane) (PDMS) elastomer substrate. The dosage of released molecules is highly dependent on the strain magnitude (Figure 9a,b). The increase in delivery rate upon mechanical strain is due to that the deformation of PS microcapsules facilitates the drug pump out. In addition, the deformed PS capsules can return to their initial shape and volume upon stretching removal. The fluorescence image in Figure 9c(II) shows selective release from the gel-patterned areas, whereas no release is observed in other regions. Based on this concept, a strain-sensitive patch made use of hydrogel patterns (Figure 9c(I)) was fabricated on the arrayed microcapsules: the motions of gripping and stretching (Figure 9c(III–IV)) release molecules in the same way as that shown in Figure 9c(II). However, the low strain tolerance (8.5% strain) restricts their use in applications involving large deformations.

Alternatively, Gu and co-workers exploited a wearable stretch-triggered ADRS integrated with a stretchable elastomer and microgel depots containing drug-loaded NPs (Figure 9d). Upon stretching, the drug diffuses out continuously, which is attributed to the enlarged diffusion area for diffusion and large Poisson’s ratio-induced compression toward the microdeposits. Microneedles (MNs) were further combined with this device for regulating BGLs of type 2 diabetic mice by on-demand transcutaneous insulin delivery (Figure 9e). The wearable device with painless MNs made by cross-linked HA is shown in Figure 9f. The tensile strain was provided by ten cycles of stretching with a strain level of 50% with an interval of 4 h (Figure 9g). As shown in Figure 9h, after several cycles of stretching and releasing, the BGLs of mice quickly reduce to a normoglycemic level (<200 mg dL⁻¹) within 30 min and then gradually increase. However, in the absence of stretching, the BGLs decrease initially but then maintain in the hyperglycemic range. For insulin injection, the BGLs decrease rapidly and subsequently recover to the hyperglycemic state after 4 h, similar to that without stretching. With this technology, either sustained release of payloads by daily body motions (muscles, tendons, and bone joints) or pulsatile release by intentional administration (such as using hands) can be achieved conveniently.

Mechanical force-induced chemical changes, including isomerization, ring-opening, chain scission, and other intermolecular interactions, can also be useful for ADRS. The incorporation of force-sensitive functional groups known as mechanophores into polymers backbones can lead to more productive results in ADRS. β-Cyclodextrin (β-CyD), a well-known host molecule which forms inclusion complexes with a variety of drug guests, has been widely used as an excipient to improve the physicochemical and pharmaceutical properties of drug molecules. On one hand, the affinity of guest molecules toward CyD strongly depends on the conformity between the guest molecules and the CyD cavity. In contrast, CyD consists of a hydrophobic center and hydrophilic sides, allowing higher incorporation and better retention of hydrophobic drugs through van der Waals and hydrophobic complexes.
Ariga and co-workers reported a β-CyD-crosslinked alginate gel (CCAL) network for patient-controlled ADRS with compressive stimuli ([Figure 10](#fig10)). In this study, β-CyD was chosen as the mechanophore. Release of ondansetron (ODN) drug from CCAL can be enhanced by mild mechanical compressions because of the change in the ability of CyD moieties to include ODN ([Figure 10](#fig10)b). Moreover, pulsatile and prolonged release can be achieved, which provides a novel dosing strategy enabling on-demand drug administration.

Lately, Boydston and Larsen incorporated the fl ex-activated mechanophore of an oxanorbornadiene group into an elastomeric segmented polyurethane network ([Figure 10](#fig10)c). When the bulk polymer is compressed, the oxanorbornadiene undergoes a retro-[4 + 2] cycloaddition to form an alkyne and releases a small molecule of benzyl furyl ether which then diffuses out of the polymer matrix ([Figure 10](#fig10)d). Furthermore, the elastomer can release small molecules over multiple load cycles, showing the potential of sequential release in an on-demand fashion.

### 3.2.2. Shear Force-Responsive

Shear-sensitive ADRS may be an emerging outlet for self-regulated therapies of vascular-related diseases.[133,134] Normal...
circulating platelets are locally activated by high shear stress and rapidly adhere to the adjacent surface lining of the narrowed vessels.\textsuperscript{[135]} This is a major contributor to the development of vulnerable atherosclerotic plaques. Inspired by this natural physical mechanism of platelet targeting, Korin et al. developed microscale aggregates of PLGA NPs,\textsuperscript{[136]} which remain intact under physiological flow conditions but break up into individual nanoscale components when exposed to a high local shear stress, just as platelets do (Figure 11a). The shear-dispersed NPs experience lower drag forces and hence, adhere more efficiently to the surface of the adjacent blood vessel wall as a result of a smaller size than the larger microaggregates. Furthermore, NPs formulated with the tissue plasminogen activator (tPA) were evaluated for thrombolytic efficacy in a mouse arterial thrombus model. After perfusing preformed fibrin clots, pulmonary arterial pressure was restored ex vivo with a 100-fold lower effective dose of tPA (Figure 11b), demonstrating superior performance with the NP aggregates. In an in vivo acute thrombus murine model (\textasciitilde100 clots, 150 \textmu m), all control animals died within 1 h after infusion of the clots, whereas more than 80% of the treated mice survived, and none of these SA-NTs (shear-activated nanotherapeutics)-treated animals displayed any visible symptoms of respiratory distress (Figure 11c).

Yan and co-workers recently exhibited a shear-stress sensitive ADRS using red blood cell-adsorbed polypeptide/heparin hybrid nanoparticles (RBC-PLL/Hep) for efficient treatment of thrombosis.\textsuperscript{[137]} In this work, cross-linked PLL/Hep hybrid nanoparticles (cNPs) were designed through the formation of disulfide bonds for increased colloidal stability and sustained drug release. The cNPs were then adsorbed on negatively charged RBCs via electrostatic attraction to make the designed vectors more functional (Figure 11d). In vivo results confirmed that the complete release of the loaded drug occurred at $t \approx 12$ h for the free heparin solution, and 24 h for NPs (without S–S cross-linking), whereas only around 30% of the drugs got released from cNPs and RBC-cNPs carriers at 24 h. The complete drug release time of cNPs was extended to 96 h following S–S cross-linking inside the NPs and RBC adsorption. This resulted in a relatively slower release profile for RBC-cNPs than for the counterparts of cNPs (Figure 11e).

Another therapeutic strategy is to induce drug carriers deformation by disease-induced shear forces. Budtova and co-workers first presented a shear-induced controlled release from hydrogels and microcapsules.\textsuperscript{[138,139]} It was shown that there was a shear-stress threshold to produce carrier deformation. Once above the critical point, the particles would break up and release the cargo inside. Recently, Holme et al. designed a shear-force triggered ADRS based on lenticular Pad-PC-Pad phospholipid vesicles.\textsuperscript{[140]} The lenticular shape of the liposomes leads to preferential breaking points along the equator that makes them sensitive to increased shear stresses (Figure 12a). The pure Pad-PC-Pad vesicles show an appreciable preference for release in the high shear stress constricted-artery model compared with other formulations containing different ratios of Pad-PC-Pad and EggPC (L-\textalpha-phosphatidylcholine) (Figure 12b). Mitragotri's
The group proposed platelet-like nanoparticles (PLNs) fabricated by the layer-by-layer approach for targeted drug release to vascular injuries or thrombi (Figure 12c). The PLNs exhibited significantly higher adhesion to injury sites under shear stress in an in vitro wound model. The functional peptides of collagen- and von Willebrand factor-binding peptides (CBP and VBP) and fibrinogen-mimetic peptide (FMP) can simultaneously bind to activated natural platelets and injured endothelial sites to increase platelet aggregation for hemostasis. It was shown that with targeted peptide modification on their surfaces, the PLNs exhibited significantly higher adhesion to injury sites under the shear stress (Figure 12d). Recently, Grinstaff and co-workers prepared low-molecular weight hydrogels from glycosyl-nucleoside-lipid amphiphiles (GNL). The shear-induced gel disassembly expedites the release of anti-TNFα antibody, which can serve as an anti-inflammatory treatment against diseases such as rheumatoid arthritis.

3.3. Thermo-Responsive Drug Release

Because inflammatory and tumorous tissues often exhibit abnormally elevated temperatures than normal tissues, the temperature can be used as an endogenous stimulation signal for ADRS. Noticeably, for thermos-responsive materials used in ADRS, the desired temperature range should be within...
37–42 °C as protein may not function effectively in the human body at 37 °C or below, or may denature at 42 °C and above.

3.3.1. Poly(N-isopropylacrylamide)-Responsive

Since the earliest report of the thermal phase transition behavior of poly(N-isopropylacrylamide) (polyNIPAAm) in 1967 by Scarpa et al.,[146] polymers that undergo conformational changes in response to temperature variation have been widely studied for the development of thermo-responsive drug carriers. The temperature at which the phase transition occurs is referred to as the lower critical solution temperature (LCST).[147] Below the LCST, polymers are hydrated with an extended chain conformation (soluble). Above the LCST, they are dehydrated with a collapsed chain conformation (insoluble), as shown in Figure 13a.[148,151] The ideal range in which a thermo-responsive drug carrier should release its payload is between 37 and 42 °C to minimize any toxic effects due to protein denaturation above 42 °C.[152] Although polyNIPAAm is the most widely studied thermo-responsive polymer, the LCST for pristine polyNIPAAm is approximately 32 °C, whereas inflammatory tissues and cancer cells often exhibit a higher temperature of about 38 °C.[153] This implies that polyNIPAAm, without modification, is not suitable for thermo-responsive autonomous drug release. Reports showed that LCST of polyNIPAAm could be elevated by incorporating a

![Figure 12. Shear force-responsive vesicles for targeted drug release.](image-url)

Figure 12. Shear force-responsive vesicles for targeted drug release. a) Mechanism of shear force-activated drug release. b) The difference in fluorescence release for healthy and constricted models. a,b) Reproduced with permission.[140] Copyright 2012, Springer Nature. c) Synthesis of PLNs. d) In vitro binding of PLNs with and without functional peptides to targeting surface and nontargeting BSA surface (control) under shear stress. c,d) Reproduced with permission.[141] Copyright 2014, American Chemical Society.
hydrophilic component and decreased with a hydrophobic component. Efforts have been made to modulate the LCST of polyNIPAAm by preparing copolymers and have yielded a range of polyNIPAAm-based thermo-responsive materials with LCST in the desired temperature range for ADRS. Lue et al. prepared a NIPAAm and acrylic acid (AAc) copolymer as "brush hydrogels" that were grafted on the surface of a porous polycarbonate (PC) support. As the concentration of hydrophilic AAc in the preparative solution (based on AAc and NIPAAm monomers) increases from 0% to 2.7%, the LCST increases from 34.0 to 41.8 °C. The film prepared with 1.8% AAc exhibits an LCST that is close to human body temperature (about 38 °C), demonstrating that the LCST of NIPAAm copolymer can be fine-tuned to the desired values.

Figure 13. Thermo-responsive drug release and the cumulative drug release profile. a) Illustration of a thermo-responsive polymer undergoing a transition from its coil structure (soluble/expanded) to a globule structure (insoluble/collapsed) in an aqueous environment. Reproduced with permission. Copyright 2011, Elsevier. b) Schematic illustrations showing the structure of PMEECL-b-POCTCL deblock copolymer and the delivery of Nile Red/DOX triggered by heat (top), and the structure of PMEECL-b-POCTCL deblock copolymer (bottom). c) Cumulative Nile Red release from PMEECL-b-POCTCL micelles at room temperature, 37 °C (below LCST), and 40 °C (above LCST) in PBS. All measurements were performed in triplicate. Reproduced with permission. Copyright 2012, American Chemical Society. d) Schematic representation of thermo-sensitive nanocarrier working as a targeted drug delivery system with controlled drug release. In vitro drug release profiles of e) DOX-loaded FP50, f) FP100, and g) FP200 micelles in PBS solution at pH 7.4 at 37 and 40 °C. Data are shown as mean ±SD (n = 3). Reproduced with permission. Copyright 2014, American Chemical Society.
3.3.2. Degradable Polymers-Responsive

Although a variety of polyNIPAAm-based thermo-responsive materials with optimum physiochemical characteristics have been widely used, their poor biocompatibility and degradability and biological safety remain a matter of concern for in vivo medical applications. In this regard, ADRS derived from aliphatic polymers and PCs are of specific interest because their degradability enables the use in a number of tissue engineering and drug delivery applications.

Polyesters: Biodegradable polymers, such as poly(glycerolide), poly(lactide), and poly(e-caprolactone), have often been used as the hydrophobic segments in amphiphilic block copolymers.[156,157] Stefan and co-workers prepared self-assembled amphiphilic poly(ethylene glycol) poly(e-caprolactone) micellar NPs (PMEECL-p-POCTCL)-based ADRS (Figure 13b).[149] Polymeric micelles loaded with Nile Red (the feeding ratio of polymer to payload is 20:1) achieve the most rapid release when the temperature is above the LCST (38 °C), and due to that the outer PMEECL block starts to collapse and induces the deformation of the micelle, leading to the release of Nile Red. This is suitable for the controlled release of Nile Red in elevated local temperature (Figure 13c). In another group, Wang et al. improved antitumor efficiency of PTX-incorporated thermosensitive-modified PEG/PCL hydrogel (copolymer poly(e-caprolactone-co-1,4,8-trioxa[4,6]spiro-9-undecanone)-poly(ethylene glycol)-poly(ecaprolactone-co-1,4,8-trioxa[4,6]spiro-9-undecanone), PECT) with the synergy of doxorubicin hydrochloride (DOX-HCl).[158–160] Hydrophobic PTX and hydrophilic DOX-HCl were loaded simultaneously in the thermo-responsive injectable hydrogel by a two-stage entrapment. The antitumor effect is improved by the burst release of hydrophilic DOX-HCl, followed by the sequent sustained release of PTX and remnant DOX-HCl.

Polycarbonates: Aliphatic PCs are also attractive biocompatible and degradable materials for the development of nanomedicines.[161] Different from polymers which exhibit bulk erosion degradation in vivo, PCs are characterized by surface erosion degradation.[162] Hedrick and co-workers synthesized thermo-responsive nanostructured PC block copolymers for injectable PTX release.[163] PTX release from the PC block copolymers micelles is faster at the body temperature as compared with a temperature below the LCST (36 °C). Meanwhile, the PTX-loaded micelles kill HepG2 human liver carcinoma cells more efficiently as compared with free PTX and PTX-loaded micelles at the temperature below the LCST.

3.3.3. Triblock Copolymers-Responsive

Triblock copolymers with various structures have been widely studied for the development of ADRS. By changing the chemical compositions as well as the architectures of triblock copolymers, ADRS with specific properties can be designed. Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO–PPO–PEO) triblock copolymers with different ratios of PPO and PEO have been commercialized with the trade names of Pluronic (or Poloxamer). In an aqueous environment, Pluronic can form the core-shell structure for encapsulating hydrophobic drugs. However, the unacceptably high critical micellization concentration (CMC) and low LCST of Pluronic F127 due to the weak hydrophobic PPO block limit its potential applications in ADRS. To solve the problem, Zhou and co-workers developed folate (FA) decorated Pluronic F127-poly(l, l-lactic acid) (F127-PLA, abbreviated as FP) copolymer micelles for thermo-triggered drug release.[156] As observed in Figure 13d, micelle forms when the concentration of polymer is greater than CMC. Above the LCST, the thermo-sensitive block shrinks, inducing the release of incorporated agents. In addition, due to the high binding affinity of FA and folate receptor (FR), the drug carrier can target tumor cells overexpressing FR, and rapid intracellular drug release can be triggered at a temperature above the LCST. FP100 micelles assembled from FP with PLA polymerization degree of 100 have an LCST of 39.2 °C (close to body temperature). At 37 °C, a little amount of encapsulated anticancer drug DOX is released from the FP100 micelles, whereas at a slightly elevated temperature (40 °C), the shrinkage of thermo-responsive segments causes a rapid release of DOX and instantly raises the local drug concentration (Figure 13e–g).

3.3.4. Liposome-Responsive

Liposomes are phospholipid-based drug carriers with high drug payload, decreased drug toxicity, and enhanced drug accumulation at tumor sites. Liposomes can be used for chemotherapies due to the relatively leaky tumor vasculature that allows liposome extravasation. They can also be made thermo-sensitive and triggered to release upon hyperthermia.[164] Kostarelos and co-workers presented leucine zipper peptide–lipid hybrid nanoscale vesicles for mild hyperthermia-triggered drug release.[165] These hybrid vesicles aim to combine the advantages of traditional temperature-sensitive liposomes (TSL) with dissociative, unfolding, and temperature-sensitive peptide to optimize drug release under mild hyperthermia while improving in vivo drug retention. The release of doxorubicin from Lipid-peptide (Lp-peptide) hybrids in vitro indicates superior serum stability at physiological temperatures and prolonged drug release at 42 °C compared with lysolipid TSL. Alternatively, Xia and co-workers proposed a thermo-responsive bubble-generating liposomal system that encapsulates ammonium bicarbonate (ABC) for triggering localized extracellular drug delivery.[166] ABC was used to create the transmembrane gradient needed for the highly efficient encapsulation of DOX. At an elevated temperature (42 °C), the decomposition of ABC generates CO2 bubbles, creating permeable defects in the lipid bilayer. Consequently, DOX is rapidly released, instantly increasing the local drug concentration.

As a summary, autonomous drug release can be implemented using a variety of endogenous signals that are relevant to the diseased conditions. These endogenous signals can be the changes of certain physiological conditions (including, but not limited to, pH, reductive/oxidative status, enzyme and glucose expressions), the tensile, compressive, shear strains/stresses, or the temperature changes at the diseased sites. Table 2 provides a nonexclusive list of autonomous drug release strategies that use symptom-associated endogenous signals as the release trigger strategies.
| Type                        | Material                          | Model drug             | Self-stimuli | Disease               | Ref.   |
|-----------------------------|-----------------------------------|------------------------|--------------|-----------------------|--------|
| Polyacid                    | Cellulose nanocrystals reinforced PAGA | Diclofenac sodium      | pH 7.4       | Inflammation          | [73]   |
|                             | Hydrotrropic containing acrylic acid | Paclitaxel             | pH 6.5       | Cancer                | [85]   |
| Polybase                    | Bone ash-reinforced chitosan      | Amoxicillin            | pH 1.2       | Gastric ulcer         | [27]   |
| PDEAEMA nanogel             | DOX                               | pH 5.2                 | Cancer       | [167]                 |
| PEG-b-(PDEAEMA-b-PHEMA-g-FA)_micles | DOX                               | pH 5.0                 | Cancer       | [91]                  |
| Oxime linkage cleavage      | PEG-OPCL-PEG                      | DOX                    | pH 5.0       | Cancer                | [74]   |
| Amide linkage cleavage      | Cellulose derivative              | Aminoethyl rhodamine   | pH 4.0-5.0   | Cancer                | [94]   |
| GO-drug conjugate           | Encapsulation of GO with folic acid conjugated chitosan | DOX                   | pH 5.3       | Cancer                | [168]  |
| Negative-to-positive charge reversal | PEG-b-PCL micelles               | DOX                    | pH 6.0       | Cancer                | [75]   |
| Hydrazone linkage cleavage  | PPC-Hydo-DOX-DA                   | DOX                    | pH 5.0-6.8   | Cancer                | [95]   |
| Degradation                 | PLGA@cross-linked chitosan        | Curcumin and catechin  | pH 1.5       | Acute gastrosis       | [76]   |
| Degradation                 | CS-EC@Ca(OH)_2                    | Ca(OH)_2               | pH 5.0       | Apical periodontitis  | [169]  |
| Fusion                      | Chitosan-modified Au-liposome     | Doxycycline            | pH = 7.4     | Helicobacter pylori infection | [99]   |
| Dissolution                 | ZnO@MSNs-DOX                      | DOX                    | pH 2.0-5.0   | Cancer                | [100]  |
| Decomposition               | DOX@ZIF-8                         | DOX                    | pH 5.0-6.0   | Cancer                | [170]  |
| Disulfide cleavage          | PAA-g-PEG                         | DOX                    | GSH          | Cancer                | [102]  |
| Disulfide cleavage          | Si-SS-CD-PEG                      | DOX                    | GSH          | Cancer                | [103]  |
| Degradation                 | TNF-α–TKNs                        | siRNA                  | ROS          | Intestinal inflammation | [104]  |
| Degradation                 | Cy3-conjugated N-palmitoyl chitosan | Curcumin               | ROS          | Inflammation          | [42]   |
| Thiolsis and degradation    | OEG-2S-SN38                       | SN38                   | GSH/Ros      | Cancer                | [111]  |
| Degradation                 | Polymer-caged liposomes           | Carboxyfluorescein     | Cancer-associated protease | Cancer | [112]  |
| Protamine cleavage          | Protamine/SCD assembly            | HPTS                   | Trypsin      | –                     | [113]  |
| Degradation                 | AuChi-liposomes                   | Doxycycline            | Phospholipase | Helicobacter pylori infection | [114]  |
| Degradation                 | Hybrid silica mesoporous NPs      | DOX                    | Glicosidase   | Cancer                | [115]  |
| Degradation                 | Poly(styrene) and methacrylate based block copolymers | Sulfasalazine         | Azoreductase  | Colorelated disease   | [116]  |
| Degradation                 | Vancomycin-loaded mannosylated nanogel | Vancomycin            | Bacterial enzyme | Bacterial infections | [117]  |
| Enzymatic conversion        | Bioinorganic membrane based microdevices | Insulin               | Glucose      | Diabetes              | [120]  |
| of glucose                  | Enzymatic conversion              | Microgel system        | Insulin      | Glucose               | [121]  |
| Competitive binding         | (MSN-anchor-RB)@GOX               | Rhodamine B            | Glucose      | –                     | [122]  |
| Competitive binding         | Concanaevalin A-gated carbohydrate-functionalized MSN | Rh6G                   | Glucose      | Tumor or diabetes     | [123]  |
| Deformation                 | Alginate hydrogels                | Vascular endothelial growth factor | Compressive force | Blood vessel formation | [125]  |
| Deformation                 | Hyaluronic acid hydrogels         | Dexamethasone          | Compressive force | Osteoarthritis       | [128]  |
| Deformation                 | BCMs-PAAm                         | Pyrene                 | Tensile force | Tissue repair and regeneration | [129]  |
| Deformation                 | Hydrogel-patterned microcapsules  | RHB and FITC-labeled dextran | Tensile force | –                     | [15]   |
| Deformation                 | Elastic patch                      | RHB                    | Tensile force | –                     | [130]  |
4. Conclusion and Future Perspective

4.1. Current Challenges/Limitations

In this Review, we summarize and discuss a variety of physical and chemical properties present in certain pathological conditions that can be used to trigger the release of encapsulated medications. These conditions include increased acidity, reductive/oxidative local environment, overexpressed proteins or enzymes, high tissue glucose concentrations, mechanical force fluctuation, and abnormal local temperature. The utilization of these pathologically relevant endogenous stimulation signals allows for autonomous drug release without the interference by a healthcare provider or patient and promises great potential in the timely treatment of diseases in various scenarios that are difficult or impossible to be treated using other drug-release schemes. However, it should be noted that most ADRS studies reviewed herein are still at the proof-of-concept stage or very early developmental stages. Thus, ADRS, despite its great potential, has not yet led to significant clinical accomplishments against debilitating diseases. The challenges that hinder the translation of ADRS from the bench to the bedside must be addressed, before the great potential of ADRS can be fully deployed to yield tangible clinical outcomes, as discussed later.

First, the medications encapsulated within nanoscale or microscale carriers in ADRS are susceptible to passive diffusion as soon as they are encapsulated, regardless of the stimulation status. Although the passive release rate in ADRS is often much lower than those in previous release schemes, drug diffusion is often inevitable. This may lead to undesired drug release under nondiseased conditions or toward nontarget tissues. The undesired passive release due to diffusion also causes medication waste and reduces the total effective release time of the encapsulated drugs.

Second, the symptom-associated changes in biochemical or biophysical properties that can serve as the endogenous stimulation signals (e.g., variations of pH, temperature, or redox potential) may differ from patient to patient, which makes it difficult for standardization and benchmarking. For anticancer applications, the autonomous release of many ADRS is based on the premise that all tumor cells are identical, which is not true due to the high heterogeneity in tumor cells.[171]

Third, in mechanoresponsive ADRS, drug release occurs only if the triggering signals are no longer present. This may cause undesirable continuous drug release. In other words, the symptom-associated mechanical strain present in the target tissues, however, may have a much wider range of magnitudes. Strategies are thus needed to match symptom-associated mechanical strains to the strain threshold that can trigger drug release. In other words, the symptom-associated mechanical strains have to be scaled, to the desired extent, to match what would be needed for releasing the drug in ADRS.

Another challenge is that some ADRS lack the capability to terminate drug release after the symptoms disappear. In some diseases such as glaucoma and vascular hypertension, medications are needed to release the discomforts and damages accompanying with the symptoms. Once the symptoms disappear, drug release should cease. However, the drug-releasing mechanisms in many ADRS are not reversible. The release of medications would occur upon the endogenous stimuli and continue even if the triggering signals are no longer present. This may cause medication waste as well as the side effects of excessive dosage.
4.2. Opportunities and Perspectives

Although ADRS-based therapeutics has yet to come, increasing scientific efforts are expected to address current challenges and to continuously improve autonomous drug-release technologies by exploring advanced drug carrier materials, endogenous stimuli, and new release mechanisms. One area in ADRS that is expected to gain tremendous advancement is the exploration of endogenous signal-responsive materials. Smart and functional materials that are responsive to various chemical and physical signals have gained extraordinary attention in recent years. The abundant research outcomes in this field may provide a large pool of choice for constructing responsive drug carriers in ADRS. In particular, many smart materials, such as self-healing materials and shape memory polymers, demonstrate the ability to recover as the endogenous stimuli are removed. This promises a great potential of creating reversibly activated drug carriers that can stop releasing once the symptoms disappear.

In many ADRS, the drug-release rate is controllable by regulating the magnitude of endogenous stimulation signals. This is essential for some treatments where a differential dosage profile is needed for different degrees of symptoms. For example, thiazide-type diuretics are often used for antihypertension treatments. Although a high dose can produce strong antihypertensive effects, it may cause severe side-effects, including increased lipid level, glucose disturbances, and primary cardiac arrest.\textsuperscript{172,173} ADRS can help to implement a stepwise release of thiazide-type diuretics with the desired dose that matches the severity of hypertension.

Current ADRS often involve only a single type of drug, whereas ADRS have the potential to incorporate and release multiple types of drugs that are responsive to the same or different endogenous stimulation signals. These drugs can be administered independently and released at different spatio-temporal points as needed for obtaining the optimal clinical outcomes. Combination drug therapies often have synergistic rather than superimposed therapeutic effects. The low doses of each drug can minimize the clinical and metabolic effects that occur with maximal dosages of the individual drugs. For example, captopril and amlodipine can be co-encapsulated with thiazide-type diuretics for antihypertensive treatments, which not only reduces the risk of side-effects but also softens blood vessel effectively.\textsuperscript{174} In addition, combined drug therapies have also reported to reduce drug resistance.\textsuperscript{175}

In ADRS, drug release can be triggered by more than one endogenous stimulation signal to incorporate more functionalities and enhance the versatility of treatments. For example, proteins such as cytochrome C and caspase-3 need to be transported to the endogenous stimulation signal to incorporate more functionalities. As a concluding remark, ADRS that use the symptom-associated biophysical or biochemical changes in target tissues as the endogenous stimulation signals provide a closed-loop drug-release scheme that can timely release medications as soon as disease symptoms appear. Comparing with passive drug release and conventional extended and controlled releases, ADRS demonstrate greatly enhanced versatilities to accommodate various therapeutic needs. With continuous and synergistic efforts from scientists in different research domains including chemistry, physics, materials science, biology, and medicine, we anticipate ADRS would offer a generic platform broadly applicable to a multitude of disease treatments through the introduction of new pathological stimuli, new endogenous stimulation-responsive materials, and new stimulation mechanisms.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

autonomous drug administration, biophysical properties, controlled drug release, hydrogels, nanocarriers, smart systems

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