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# A REVIEW ON SMART BIORESPONSIVE DRUG DELIVERY SYSTEMS

**Kainat Haleem[1*], Muhammad Arslan Khan[2]**

[1]Faculty of Pharmaceutical Sciences, Government College University Faisalabad, Pakistan
[2]Faculty of Pharmacy, Bahauddin Zakariya University, Multan.

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**ABSTRACT**

During the past several decades, many sensing mechanisms have emerged, which provide new control strategies for designing closed-loop drug delivery systems. For such systems, numerous bioresponsive materials are utilized to construct functional modules for the desired devices. The typical closed-loop drug delivery systems recently reported in this review. The stimuli-responsive polymers serve to provide a snapshot of the utility and complexity of polymers that can sense, process, and respond to stimuli in modulating the release of a drug. Stimuli-responsive drug delivery vehicles come in the form of polymersomes, liposomes, micelles and dendrimers. Therapeutics is designed to be controlled released from drug carriers through the structural transformations such as shrinking, swelling, and dissociation or unique responsive cleavage route.

**Key words:** Bioresponsive drug delivery, light sensitive, pH sensitive, enzyme sensitive, ultrasound sensitive.

***Corresponding Author.** E-mail: kainathaleem6@gmail.com

## INTRODUCTION

In the past decades, various drug delivery systems have been developed to improve the releasing behaviors and effectiveness of drugs, and lower their side-effects. An ideal drug delivery system should be able to increase drug solubility, provide a sustained release system to avoid rapid breakdown and excessive use, and improve bio-distribution. Polymeric materials that respond to a stimulus are often called “smart” or “intelligent” due to their intrinsic ability to alter their physical or chemical properties. For the majority of the polymers that fall into this category, the response to a change in the surrounding environment is very quick, on the order of minutes to hours, such as proteins, polysaccharides, and nucleic acids in living organic systems **[1].** These unique capabilities have been applied to a diverse range of applications, including: drug delivery, diagnostics, biological coating technologies bio-sensing, and microfluidics. In general below the therapeutic dose, the drug is ineffective whereas high concentrations of drug may be toxic or lead to undesirable side effects. Polymers have been used to tailor drug release, which maintains the drug concentration within the desired therapeutic range. However, such controlled release systems are insensitive to metabolic changes in the body and are unable to neither modulate drug release nor target the drug to diseased tissue. This lack of control has motivated the exploitation of bioresponsive polymers as drug carriers.

## BIORESPONSIVE DRUG DELIVERY SYSTEMS

### pH-Sensitive Drug Delivery

Polymers that are pH-sensitive have garnered much attention in the fields of drug delivery, gene delivery **[2]** and insulin delivery **[3]**. Generally, pH-sensitive polymers have weak acids or bases with pKa values between 3 and 10.

In 2005, Heffernan and Murthy developed an acid-sensitive biodegradable drug delivery vehicle using (Polyphenyleneacetonedimethyleneketal) (PPADK), which contains ketal linkages allowing for acid-catalyzed hydrolysis of the polymer into low molecular weight hydrophilic compounds. Thus, the release of drug molecules is accelerated under acidic conditions **[4]**.

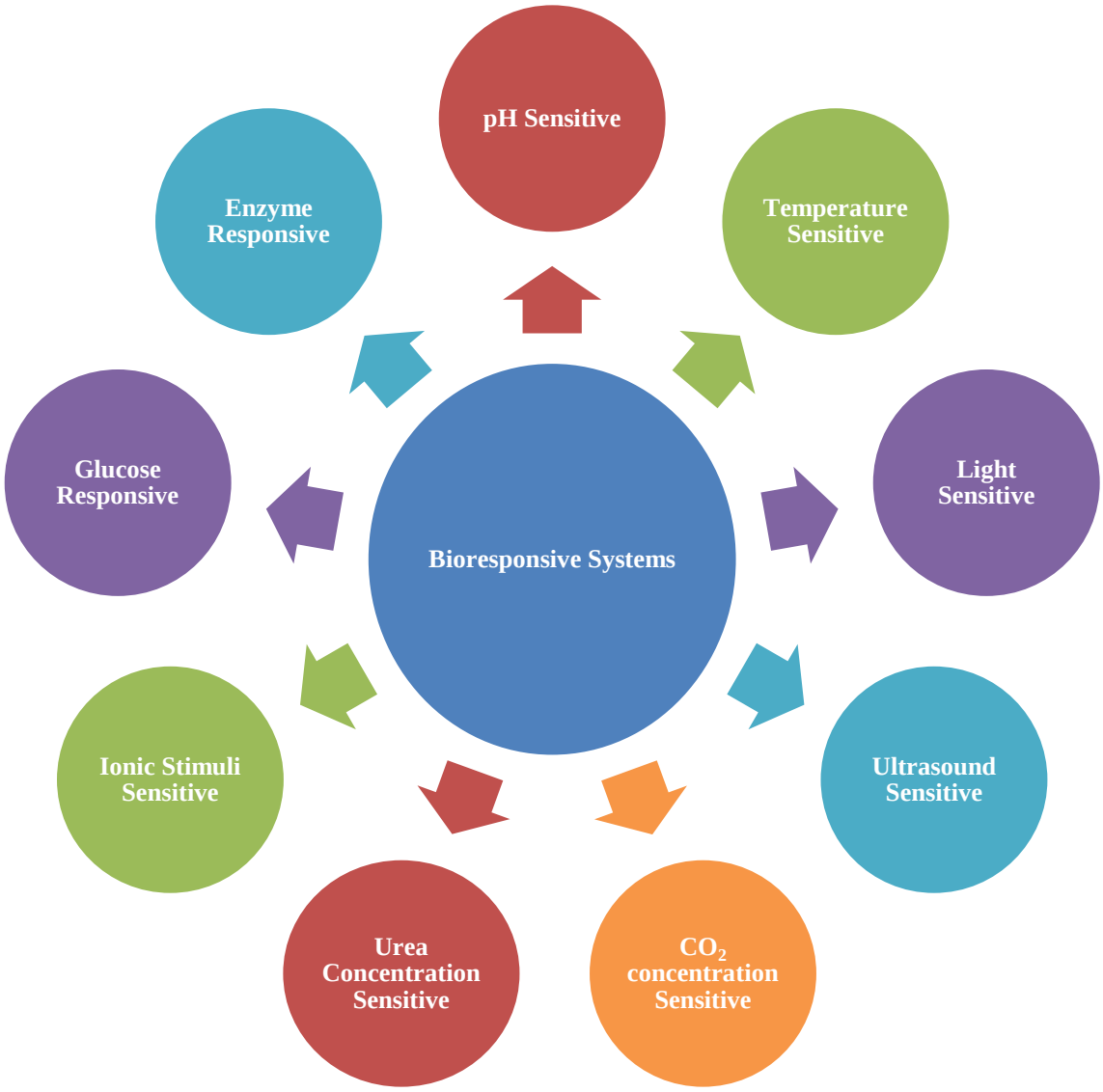


**Figure 1:** Types of bioresponsive drug delivery systems.

**Temperature-Sensitive Drug Delivery**

Increases in temperature are associated with several disease states e.g., cancer **[5]**. Thermo-responsive drug carriers have been employed to release their payload within environments above the physiological temperature. Thermo-sensitive polymers exhibit a phase transition in solution at a temperature known as the lower critical solution temperature (LCST). For example, PNIPAm (Poly-N-isopropyl acrylamide), a well-studied thermo-responsive polymer, undergoes a reversible phase transition in aqueous solution from hydrophilic to hydrophobic at its LCST of approximately 32°C. Chemical modifications of PNIPAm have been effective in controlling the LCST **[6]**.

In 2005, Liu *et al*. synthesized poly(N-isopropylacrylamideco-N, N-dimethylacrylamide)-b-poly(D,L-lactide-co-glycolide) micelles for controlled paclitaxel delivery **[7]**. Paclitaxel release was accelerated when the physiological temperature was raised above the LCST. The paclitaxel loaded micelles were more effective in killing human breast carcinoma cells at 39.5°C than 37°C. NeedhamD and colleagues developed folate-conjugated, thermo-responsive block copolymer micelles. Folate is known to bind to several cancer cell types **[5]**. The drug release studies from folate-conjugated PNIPAm-DMA micelles

demonstrated a temperature-responsive drug release. Delivery of paclitaxel at the tumor site can alter the overall drug biodistribution. Needham et al. **[5]** developed temperature sensitive liposomes containing doxorubicin.

**Light-Sensitive Drug Delivery system**

Light (ultraviolet or visible) is a desirable external stimulus for drug delivery systems because it is inexpensive and easily controlled. Light-sensitive drug carriers are fabricated from polymers that contain photo-sensitizers such as azobenzene, stilbene, and triphenylmethane **[8]**. Suzuki and Tanaka have investigated visible light-responsive hydrogels using the trisodium salt of copper chlorophyllin in PNIPAm hydrogels **[9]**. When light is applied to the hydrogels, the chromophore absorbs the light, increasing the local temperature of the hydrogel. The resulting temperature change alters the swelling behavior. Vivero-Escoto et al. prepared gold capped mesoporous silica nanospheres for photoinduced intracellular release of drugs in human cells **[10]**. The 100 nm silica nanospheres were capped with 5 nm gold nanopheres and functionalized with a cationic photo-reactive linker. Photoirradiation using ultraviolet (UV) light for 10 min at 0.49 $mW/cm^2$ cleaved the photolabile linker, causing uncapping of the silica due to charge repulsion between the gold and silica nanospheres, allowing drug to be released **[11]**.

**Ultrasound-Sensitive Drug Delivery System**

Ultrasound has been shown to trigger drug release by raising the local temperature or causing cavitation. Both processes can increase the permeability of cell membranes and accelerate polymer degradation **[12]**. Ultrasound-sensitive vehicles have the potential to treat tumorigenic cancers due to their invasive character, ability to penetrate deeply into the human body, and ease of control. In 2002, Pruitt and Pitt investigated ultrasound mediated doxorubicin release using stabilized Pluronic P105 micelles **[13]**. Doxorubicin was encapsulated within polymeric micelles composed of 10% Pluronic P105 and N,N-diethylacrylamide and delivered systemically to rats. Application of low-frequency ultrasound at the tumor site resulted in doxorubicin release; this resulted in a significant reduction in tumor volume. Lin et al. had investigated the physical and chemical properties of lipid membranes subjected to ultrasound treatment **[14]**. They showed that high permeability resulting from ultrasound treatment is correlated with lipid packing and can be useful for efficient drug release and ultrasound-mediated DNA transfection. IN 2007, Ferrara et al. **[15]** reviewed that small gas bubbles, used to enhance ultrasound contrast, can be used for drug delivery applications and monitoring. When driven by an ultrasonic pulse, small gas bubbles oscillate with a wall velocity on the order of tens to hundreds of meters per second and can be deflected to a vessel wall or fragmented into particles on the order of nanometers **[15]**. A focused ultrasound beam can be used for disruption of delivery vesicles and blood vessel walls, which offer the opportunity to locally deliver a drug or gene. Ultrasound does not damage the surrounding tissue, making it attractive for triggering drug release.

**Table 1:** Examples of carrier polymers for various bioresponsive systems.

| Mechanism | Carrier example |
|---|---|
| pH sensitive | PPADK<br>DMAEMA/HEMA |
| Temperature sensitive | PNIPAm<br>MPPC |
| Light sensitive | Quinone-methide<br>PNIPAm |
| Ultrasound sensitive | Pluronic P105 |
| Enzyme sensitive | PCL-PEG |
| CO2 sensitive | DMAEMA |
| Urea sensitive | methylvinylether and maleic anhydride |
| Na ion sensitive | alginate |
| Glucose sensitive | phenylboronic ester-polyserine |

**Drug Delivery System Sensitive to $CO_2$concentration**

Closed-loop drug delivery systems also hold great promise for the controlled release of antidotes in response to opioid overdose. Morphine, an opiate analgesic, is administered to relief both acute and chronic severe pain **[16]**. However, morphine overdoses decrease reduced respiratory effort and lower blood pressure, resulting in decreased blood $O_2$ levels, increase $CO_2$ concentration and acidosis-induced death **[17]**. A non-demand delivery of antidote can effectively eliminate the risk of morphine overdose. Therefore, Roskos and coworkers developed a morphine-triggered antidote delivery

device consisting of an enzyme-coated erodible polymeric core loaded with drug and a cellulose dialysis tube with enzyme lipases inactivated by the covalent conjugation with morphine and complexing with an antibody to morphine **[18]**. Free morphine is able to displace the lipase-morphine complex from antibody and allow the rapid degradation of polymeric core to release drug. Satav et al. designed another self-regulated antidote delivery system by taking advantage of $CO_2$ as a danger signal **[19]**. The $CO_2$-responsive hydrogel-based delivery vehicle was prepared from functional (DMAEMA) N,N-dimethylaminoethyl methacrylate monomer and (TMPTMA) trimethylolpropanetrimethacrylate crosslinker. In the presence of increased blood $CO_2$ levels and the associated decrease in pH, the protonation of the amine groups of DMAEMA causes the swelling of the pH-sensitive hydrogel and accelerates drug release. This system's remarkable control of antidote release against the toxic marker concentration has great potential to prevent serious side effects of drug overdose.

**Drug Delivery System Sensitive to Urea Concentration**

Urea-responsive drug delivery has also been explored based on the enzymatic activity of urease, which hydrolyses urea into $NH_4HCO_3$ and NH4OH **[20]**. (Krajewska, 2009). As this enzymatic reaction causes an increase in pH, Heller and Trescony developed a urea-responsive delivery device based on a pH-sensitive bioerodible polymer **[21]**. A model drug, hydrocortisone, was mixed with a partially esterified copolymer of methylvinylether and maleic anhydride to fabricate into disks, which were coated with urease-immobilized hydrogel. In the presence of external urea, the pH increase was able to accelerate the polymer erosion and drug release. Similarly, Ishihara et al.designed a pH-sensitive membrane instead of the erodible polymer for urea-responsive closed-loop delivery **[22, 23]**. The permeation of chance in pH caused by the urease-mediated urea conversion.

**Drug Delivery System Sensitive to Ionic Stimuli**

Based on the many kind of cations and anions in body fluids such as blood, gastrointestinal fluid, sweat and tears, ion-responsive delivery systems can sense a variety of ions concentrations in body fluid and modulate the drug release rate for optimal drug therapy. For instance, Na+ ion commonly exists in the wound exudates. Huang et al. described a Na+-sensitive alginate gel loaded with nano-silver as a non-specific antimicrobial agent forwound dressing applications **[24]**. Upon administration to the wound, the alginate gel swelled due to the ion-exchange of Na+, result in subsequent release of nano-silver. Since the extent of alginate gel swelling was tuned by the volume of wound exudates, the release rate of nano-silver was effectively self-regulated during the wound healing process, achieving a closed-loop drug delivery strategy. Mi and coworkers also developed a K+-sensitive hydrogel consisting of crown ether 15-crown-5 as the ion-sensor and poly(N-isopropylacrylamide) as the actuator for self-regulated controlled release **[25]**. In this system, K+ bound to the crown ether 15-crown-5 based on a 2:1 "host-guest" complexation formulation to drive the shrinkage of the hydrogel, giving a pulse-release mode that was regulated by changing environmental K+ concentration.

**Glucose-Responsive Insulin Delivery Systems**

Properly dosed and timed insulin is essential to regulate blood glucose level for individuals with type 1 diabetes and advanced type 2 diabetes **[26, 27]**. Traditional open-loop insulin delivery requires frequent blood sugar monitoring and multiple subcutaneous injections with or after meals **[28-30]**. However, there are deep challenges associated with the open insulin delivery method that prevents patients from obtaining tight glucose control, increasing the risk for diabetic complications including blindness, limb amputation, and kidney failure **[28, 31]**. A closed-loop system mimicking the pancreatic beta cells to "secrete" insulin in response to blood glucose levels has been considered as a desirable strategy for the treatment of type 1 and advanced type 2 diabetes **[27]**. Such systems are typically comprised of a glucose-sensing module and a relevant actuator. Although closed-loop electronic/mechanical devices comprising of a continuous glucose monitoring and an insulin infusion pump have been already developed, some challenges still need to be addressed such as achieving accurate signal feedback and avoiding biofouling. An alternative approach to achieve closed-loop insulin delivery is based on glucose-responsive chemical materials. We will introduce recent glucose-responsive closed-loop insulin delivery systems based

on glucose oxidase (GOx), glucose binding proteins (GBPs), and phenylboronic acid (PBA), respectively.

***Glucose oxidase (GOx)-based systems pH***

pH-sensitive polymeric matrix containing glucose oxidase (GOx) was developed as the first glucose-responsive material in the 1980s **[32]**. As a glucose sensing element, GOx reacts with glucose in the presence of oxygen and converts it into gluconic acid, leading to a decrease in pH **[33, 34]**. The pH-sensitive polymeric matrix subsequently responds to the pH change, swelling to facilitate insulin release. Peppas and coworkers also applied pH-sensitive hydrogels to synthesize glucose-responsive insulin delivery, where the hydrogel swells or shrinks in response to changing pH to adjust insulin release in a glucose-mediated manner **[35, 36]**. Based on this concept, several groups have developed glucose-responsive closed-loop insulin delivery systems that incorporate pH-sensitive materials over the last decades **[37-41]**.

Several scientists and coworkers designed an injectable polymeric network consisting of GOx-loaded acid-degradable nanoparticles to achieve self-regulated insulin delivery **[39, 42]**. The pH-sensitive material, acetal-modified dextran, was utilized to encapsulate insulin and enzymes by a double emulsion method. By coating the dextran nanoparticles with oppositely charged polymer respectively, they formed injectable gel-like nano-network. After injection into diabetic mice, this nano-network could sense the blood glucose levels and undergo subsequent nanoparticle dissociation to release insulin in a non-demand manner and effectively control glycaemia for up to ten days. Later, Tai et al. synthesized a glucose-responsive deblock polymer for closed-loop insulin delivery incorporating pH-sensitive amphiphilic polymer self-assembled into nanovesicles with a polymersome-structure **[43]**. When integrated with a thermo-responsive hydrogel, this system was able to regulate blood glucose levels in type 1 diabetic mice.

***Hypoxia***

An alternative method to using the pH decrease as a trigger for drug release is to leverage the rapid oxygen consumption during the oxidation of glucose as the signal to activate insulin release **[44]**. Recently, Yu et al. developed a glucose-responsive insulin delivery device based on hypoxia-sensitive nanovesicles **[45]**. 2-nitorimidazole, a hypoxia-sensitive group that is commonly used in hypoxia imaging for cancer therapy was conjugated to the side chains of hyaluronic acid (HA). The resulting amphiphilic polymers readily self-assembled a nano-size vesicle to encapsulate insulin and GOx. In the presence of high glucose concentrations, oxygen consumption during the enzymatic oxidation resulted in hypoxia and hydrophobic NI groups were quickly reduced into hydrophilic2-aminoimidazole, thereby resulting in the disassembly of the nanovesicles and subsequent insulin release. In order to achieve an easy, convenient and painless administration **[46-48]**. These hypoxia-sensitive nanovesicles were further integrated with a microneedles (MNs)-array patch for diabetes treatment.

Compared to the acid-responsive materials, these patches could correct hyperglycemic blood glucose levels to a normal state within 30 minutes and maintain control for several hours after application in type 1 diabetic mice. Utilizing glucose-responsive nanovesicles, Ye and coworkers further introduced live beta cells to achieve an externally positioned cell-based insulin delivery which acted as both a glucose sensor and a signal amplifier **[49]**.

***Hydrogen peroxide***

$H_2O_2$, a further byproduct, during the enzymatic oxidation of glucose, is quickly generated under a high glucose concentration. Thus, $H_2O_2$-sensitive materials can also be leveraged to achieve a glucose-responsive insulin delivery system. Block polymers consisting of phenylboronic ester (PBE)-modified polyserine and polyethylene glycol were synthesized to deliver insulin by Hu and coworkers **[50]**. The resulting copolymers were amphiphilic and self-assembled into polymersome nanovesicles to encapsulate insulin and GOx. When exposed to high glucose conditions, the rapidly-generated $H_2O_2$ readily reacted with the block polymer to degrade the pendant PBE, improving the water-solubility of the polymer and facilitating the gradual dissociation of nanovesicles to release insulin. They also loaded these $H_2O_2$-sensitive nanovesicles into a painless microneedle patch for *in vivo* study to show that blood glucose levels were maintained within the normal levels over the first 5hours after application in type 1 diabetic mice. In another example, Yu et al. **[51]** integrated both$H_2O_2$-sensitive and hypoxia-sensitive groups to obtain a dual-sensitive polymer. The hypoxia-sensitive NI moiety was conjugated to the poly(ethylene glycol)(PEG)-polyserine backbone

via a $H_2O_2$-sensitivethioether linker to achieve an amphiphilic copolymer. Following the oxygen consumption and generation of $H_2O_2$, NI and thioether moieties were converted into hydrophilic2-aminoimidazole and sulfone groups, respectively. The enhancement of water solubility contributed to the disassembly of polymeric vesicles and subsequent insulin release. Loaded on a microneedle, the glucose-responsive vesicles were shown to regulate blood glucosel evels in a diabetic mouse model. Furthermore, unlike the hypoxia-sensitive formulation, this dual-sensitive design successfully eliminated the toxic $H_2O_2$, which could minimize the skin inflammation and enhance biocompatibility of the device.

**Enzyme-Responsive Closed-Loop Delivery Systems**

Enzymes play a central role in many biological and metabolic processes and the dysregulation of enzyme expression is associated to the progression of many diseases **[52- 54]**. Therefore, specific enzymes act as important signals for diagnosis as well as promising triggers for specific drug delivery **[55]**.

In enzyme-responsive closed-loop delivery systems, the activity or the overexpression of enzymes are suppressed following the action of the released drug. Then, enzyme-triggered drug release is turned off to avoid potential side effects.

***Thrombin***

Thrombin is responsible for converting soluble fibrinogen to insoluble fibrin and acts as the key enzyme in blood coagulation cascade **[56]**. Abnormal increasesin blood thrombin levels can cause vascular occlusions and severe cardiovascular diseases **[57]**. Heparin is a common anticoagulant used in precise doses to counteract such coagulation activation **[58]**. To more precisely dose, heparin levels and prevent associated side effects, Maitz et al. designed a direct control loop system to deliver heparin in amounts tuned by the environmental thrombin levels **[59]**. In this system, heparin was covalently linked to multi-armed PEG through a thrombin-cleavable peptide to form a thrombin-responsive polymeric hydrogel. When thrombin levels increased, heparin was rapidly released due to the cleavage of the peptides, after which the free heparin is able to accelerate the formation of the complexation of thrombin and antithrombin, a natural thrombin inhibitor. This downregulation of the trigger (thrombin) caused by release of heparin creates a feedback loop, allowing for the sensitive control the thrombin activity and the associate regulation of anticoagulation activity. This closed-loop hydrogel was shown to effectively prevent the formation of blood clots over several hours during repeated incubation with fresh blood, while non-responsive heparin-loaded hydrogel could only quench blood coagulation in the first incubation with whole blood when heparin was released in full. Utilizing the thrombin-cleavable peptide, Lin et al. also reported an electrostatic nanocomplex consisting of anionic heparin and cationic peptides for homeostatic regulation of the coagulation cascade **[60]**. The thrombin-triggered cleavage of the peptides facilitated self-titrating anticoagulation activity that simultaneously decreased the risk of unwanted bleeding. Similarly, Bhat et al. applied the thrombin-responsive peptide as a gatekeeper to control the release of acenocoumarol, another anticoagulant drug, from mesoporous silica nanoparticles (MSNs) **[61]**. In order to achieve continuous, prolonged, convenient, and painless administration, Zhang et al. integrated athrombin-responsive heparin-loaded hydrogel with a transcutaneous microneedle-array patch for auto-anticoagulant regulation, where the heparin was conjugated to a hyaluronic acid hydrogel via the thrombin-cleavable peptide **[62]**. Once inserted into skin, this transcutaneous patch could sense the thrombin levels in capillary blood circulation, and there was little drug leaked from the patch in normal blood environments.

However, the system effectively responded to the elevated thrombin level by releasing a proper dose of heparin to avoid blood clots. In *in vivo* studies, the researchers demonstrated that this bioresponsive patch could effectively prevent undesirable coagulation. Furthermore, unlike the non-responsive heparin-loaded patch, the patch with feedback-controlled capability provided a long-term protection from acute pulmonary thromboembolism that lasted 6-hourpost administration.

***Lipase***

Secreted lipases act as important persistence and virulence factors in the event of bacterial and fungal infections **[63]**. Therefore, a lipase-activated drug delivery system has been explored to specifically inhibit bacterial and fungal growth. For example,

Wang and coworkers described a lipase-sensitive polymeric triple layered nanogel for bacterial-activated drug delivery **[64]**. The model antimicrobial drug was entrapped in the polyphosphoester core and surrounded with hydrophobicpoly(ε-caprolactone) (PCL) segments and hydrophilic PEG to prevent nonspecific antibiotic release. When the nanogels were in the presence of lipase-secreting bacteria, the PCL layer was gradually degraded to release the antimicrobial drug to inactivate bacteria and subsequent reduce lipase secretion. This triple-layered nanogel exhibited significant efficiency to treat extracellular and intracellular bacterial infections without potential adverse side effects. Another lipase-triggered formulation was reported by Loh and coworkers for potential treatment of fungal infection, where the lipase-sensitive polymer, polysorbate 80, was used to stabilize the phytantriol nanoparticles **[65]**. Lipase-mediated hydrolysis of polysorbate 80 to give polyethoxylatedsorbitan and oleic acid resulted in a structural transition of the nanoparticle and consecutively triggered specific drug release. Aside from lipases, specific enzymes associated with different bacterial strains have also been recently exploited as the triggers to realize on-demand delivery of antimicrobial agents forbacterial strain-selective inhibition **[66]**. Lipase is also a key enzyme for hydrolysis and absorption of food in the digestive tract, and partial deactivation of lipase can inhibit excess fat digestion and balance calorie intake **[67]**. Therefore, Shen and coworkers developed a smart lipase-responsive drug delivery system for negative feedback regulation of lipase activity **[68]**. The lipase-degradable PCL was modified to the side chains of the fluorescent conjugated polymers, and the resulting amphiphilic copolymer was self-assembled into nanoparticles to encapsulate the lipase inhibitor drug, orlistat. Following oral administration, lipase released in the intestine catalyzed the degradation of the nanoparticles to release orlistat; the released orlistat irreversibly deactivated the lipase to reduce the intestinal absorption of dietary fats. Meanwhile, the inactivation of lipase shut down the degradation of the nanoparticles to tune the orlistat release rate in a negative feedback manner. In this closed-loop strategy, the nanoparticles were shown to be efficient in prevention of weight gain in a diet-induced obesity mouse model with few side effects.

**LIMITATIONS**

Despite the advancements, translation of a clinically effective and safe closed-loop delivery system remains challenged by several aspects. For example, in order to achieve the precise delivery, relevant parameters of materials and formulation should be carefully tailored. Meanwhile, it is important to set uniformity for the evaluation of the devices in clinical trials. Second, a thorough understanding of the role of biosignals in diseases is required to design an effective closed-loop system. It is critical to differentiate the target biosignal from its analogues to enhance specificity of delivery systems. Moreover, long-term prevention and treatment with closed-loop systems requires sufficient sustained biocompatibility. Thorough assessment of materials and effective elimination of toxic substance must be taken into consideration. Aside from these challenges, identifying and leveraging new monitor/actuator pairs is also important to design novel closed-loop drug delivery devices, especially those that may be used for prevalent metabolic diseases **[69]**.

**FUTURE RECOMMENDATIONS**

All of these mentioned systems aim to deliver an effective dose of drug at a specific time and place. There is also a significant opportunity for smart polymers to respond to multiple stimuli. Hybrid polymers created in this manner will offer more parameters to tune drug delivery, which may be necessary for more complex and dynamic environments. It is worth noting that in addition to drug delivery applications, smart polymers in general have broad applications in tissue engineering and regenerative medicine (e.g. as injectable systems for delivery of cells or self-regulating scaffolds for cell growth or infiltration), and in actuators (e.g. as smart valves and coating in microfluidics or shape memory devices). Given the continuous development of new responsive polymer compositions, we expect increasingly elaborate and versatile drug carriers to be introduced in the future**.**

**CONCLUSION**

It is concluded that the ability to alter the biodistribution of a drug by modulating its release profile through the use of smart polymers could transform drug delivery from passive controlled release to active stimuli-regulated delivery. Altering the drug biodistribution has the ability to reduce

toxicity and side effects while improving therapeutic outcomes due to the ability to deliver higher doses of drug to the site of interest. These emerging smart devices have been proven to be capable to enhance therapy efficiency and reduce adverse effect in drug administration, demonstrating vast potential in fields including diabetes management, auto-anticoagulation regulation, and antibiotic therapy in both the research and the clinical sector.

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