Chapter 2: Stimuli responsive polymers used in drug delivery systems

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Abstract

Smart polymers, frequently referred to as stimuli-responsive polymers that are they have evolved into a unique new material for the design of advanced drug delivery system. These polymers undergo fast, reversible physicochemical change in rejoinder to external impetuses redox potential, and individual biomolecules. Stimuli-responsive polymers can transform to responsive drug carriers that can be triggered using external environmental stimuli for on-site, controlled, and demand release of a drug, cumulative beneficial value while dropping systemic side effects. This chapter describes the numerous types and their modes of action and functional roles in the field of drug delivery systems. Focused attention on certain classes of single and dual-stimuli responsive systems, synthetic routes for polymers, and updates on nanocarrier-based formulations in regards to stimuli-responsive polymers. Lastly, we describe a few key clinical applications, challenges and opportunities at the present, and vision for stimuli-responsive polymeric drug delivery systems as they have the potential to reshape precision medicine and individualized therapeutics.

Key words: Smart polymers, Controlled release, Targeted drug delivery, pH-sensitive polymers

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1. Introduction

Frequently denoted to as "smart" or "environment sensitive," stimuli-responsive polymers have become extremely effective drug delivery platforms. When certain stimuli applied to certain materials, they can experience reversible changes in their structural, chemical, or physical characteristics. By exploiting pathological cues (e.g., tumor acidity, ROS overproduction), these polymers enable targeted, on-demand release of therapeutic agents, reducing off-target toxicity and improving efficacy.

2. Fundamentals of Stimuli-Responsive Polymers

2.1 Definition and Classification

Smart polymers respond to *exogenous* (externally applied, e.g. light, temperature) or *endogenous* (within the body, e.g. pH, enzymes) stimuli. Classification is based on the stimulus type and molecular mechanism of response.

2.2 Mechanisms of Response

Stimuli-responsive polymers are engineered to undergo specific and reversible changes. These transformations can occur at the molecular or macroscopic level, enabling precise control over drug release kinetics. Stimuli polymers with applications are shown in Table 1. Key mechanisms include phase transitions, bond cleavage, hydrolysis or isomerization, and swelling/deswelling behavior, which are explained below with relevant examples.

1. Phase Transition

. The polymer becomes hydrophobic above the LCST and collapses into a globule, expelling water and encapsulated drugs—triggering their release. PNIPAM-based hydrogels have been used to deliver doxorubicin (DOX) to tumor sites where local hyperthermia (>37 °C) induces drug release (Li et al., 2016).

2. Bond Cleavage (Redox- and Enzyme-Sensitive Systems)

These systems rely on cleavable chemical bonds (e.g., disulfide, ester, peptide linkages) that are selectively broken in specific environments. Redox-sensitive systems typically incorporate disulfide bonds that are stable extracellularly but cleave intracellularly due to higher glutathione (GSH) levels. Polymeric micelles with disulfide crosslinks have shown fast intracellular release of paclitaxel in tumor cells rich in GSH (Kim et al., 2011). Enzyme-responsive systems utilize peptide linkers that

are cleaved by overexpressed enzymes like matrix metalloproteinases (MMPs) in cancer or cathepsin B in lysosomes. Doxorubicin-conjugated dendrimers with a cathepsin B-cleavable linker showed selective release inside tumor cells (Lee et al., 2013).

3. Hydrolysis or Isomerization

Hydrolytically degradable polymers are sensitive to aqueous environments, and their cleavage can be pH-dependent. Polymers like poly(anhydrides) degrade over time through hydrolysis. PLGA nanoparticles are used for controlled release of antitumor drugs and are FDA-approved for clinical use (Makadia & Siegel, 2011).

Isomerization reactions, often photo-induced, are seen in light-responsive polymers containing azobenzene or spiropyran groups. Light exposure causes conformational changes that alter polymer solubility or permeability. Azobenzene-functionalized hydrogels exhibit trans–cis isomerization under UV light, resulting in pore opening and drug release (Zhao et al., 2009).

4. Swelling/Deswelling Behavior in Hydrogels

Hydrogels composed of hydrophilic polymers swell or deswell depending on external stimuli. pH-sensitive hydrogels, those made from chitosan, exhibit ionization-induced swelling. Oral drug delivery systems using PAA swell in the alkaline pH of the intestine, enabling site-specific release, while remaining collapsed in the acidic stomach (Peppas et al., 2000).

Thermo-sensitive hydrogels such as PNIPAM copolymers can also exhibit volume shrinkage at body temperature, expelling entrapped drug molecules in a pulsatile manner.

Table 1 Stimuli polymers with applications

Mechanism	**Example Polymer**	**Stimulus**	**Drug/Application**
Phase transition	PNIPAM	Temperature	Doxorubicin (hyperthermia-triggered)
Bond cleavage	Disulfide-linked PEG-PLA	Redox (GSH)	Paclitaxel
Hydrolysis	PLGA	Water, pH	Antitumor drugs, vaccines
Isomerization	Azobenzene-containing PEG	UV/Vis Light	Light-triggered release in hydrogels
Swelling/deswelling	Poly(acrylic acid) hydrogel	pH	Oral delivery of proteins

2.3 Design Considerations

The development of these for drug delivery requires a nuanced understanding of multiple interdependent parameters. Each factor influences the responsiveness, stability, biocompatibility, and therapeutic efficacy of the system. A rational design must integrate these considerations to ensure clinical relevance.

1. Chemical Architecture

The molecular architecture of a polymer—linear, branched, crosslinked, star-shaped, or dendritic—affects solubility, mechanical properties, and stimuli responsiveness.Dendritic polymers like poly(amidoamine) (PAMAM) dendrimers provide high surface functionality and internal cavities for drug loading, while their generation (branching degree) influences cellular uptake and clearance (Lee et al., 2005).

2. Molecular Weight and Cross-Linking

Molecular weight impacts the circulation time, degradation rate, and renal clearance (generally <30–50 kDa for renal filtration). Cross-linking density in hydrogels or nanogels controls swelling behavior, mechanical strength, and drug diffusion. Lightly cross-linked PNIPAM hydrogels swell more in aqueous environments, enhancing drug loading but potentially compromising mechanical integrity. Denser networks reduce drug release rate (Gil & Hudson, 2004).

3. Biocompatibility, Biodegradability & Clearance

For clinical translation, polymers must be non-toxic, non-immunogenic, and metabolizable or excretable. Ideally, degradation products should be non-harmful and eliminated via renal or hepatic pathways. It's FDA-approved and widely used for injectable formulations (Makadia & Siegel, 2011).

4. Stimulus-Specific Sensitivity Window

Smart polymers must respond to precisely defined ranges of stimuli that distinguish diseased from healthy tissues. pH-sensitive systems must differentiate between blood, tumor extracellular pH, and endosomal/lysosomal pH (~5.5–4.5). Temperature-sensitive polymers must transition at 37–42 °C to leverage mild hyperthermia in tumors. Copolymers of PNIPAM with acrylic acid can shift LCST to near-body temperature, enhancing responsiveness in hyperthermic tumors (Qiu & Park, 2001).

5. Drug Encapsulation Efficiency and Release Profile

The system must allow for high encapsulation efficiency without premature leakage and should provide sustained, targeted, or pulsatile release depending on therapeutic goals. Hydrophobic interactions, ionic interactions, and covalent conjugation are common methods for drug loading. Release should be triggered by the target stimulus,

not by passive diffusion alone. pH-sensitive micelles formed from poly(β-amino esters) show high DOX loading and but remain stable at pH 7.4 (Bae et al., 2003). Key Design Parameters in Stimuli-Responsive Drug Delivery Systems with Examples shown in Table 2:

Table 2: Key Design Parameters in Stimuli-Responsive Drug Delivery Systems with Examples

Parameter	**Design Focus**	**Example**
Chemical Architecture	Topology (linear, dendritic, etc.)	PAMAM dendrimers for gene delivery
Molecular Weight & Crosslinking	Circulation, stability, drug diffusion	Crosslinked PNIPAM hydrogels
Biocompatibility & Clearance	Safety and degradability	PLGA nanoparticles for cancer therapy
Stimulus Sensitivity Window	Response threshold	PNIPAM-AA copolymers for hyperthermia-triggered release
Drug Encapsulation & Release	Efficiency and controlled release	Poly(β-amino ester) micelles for pH-triggered doxorubicin release

3. Stimuli Types and Corresponding Polymers

3.1 pH-Responsive Polymers: Polymers with either basic or acidic groups, such as polyacrylic acid (PAC) and poly(2 dimethylaminoethyl methacrylate), use the pH variations between blood (pH 7.4), tumor tissues (pH ≈ 6.5), to selectively release drugs.

3.2 Temperature-Responsive Polymers: Thermoresponsive polymers becoming hydrophobic above the LCST—useful for hyperthermia-triggered release.

3.3 Redox-Responsive Polymers: Disulfide bond-bearing polymers are cleaved by high intracellular glutathione concentrations (up to 10 mM), releasing their cargos preferentially in the reducing intracellular environment.

3.4 Enzyme-Responsive Polymers: Polymers designed with enzyme-cleavable sequences (e.g., matrix metalloproteinases, cathepsin B) exploit enzyme-overexpression in disease sites to trigger controlled release.

3.5 Light-Responsive Polymers: Systems incorporate light-activatable groups such as azobenzenes, spiropyrans, and o-nitrobenzyl moieties to trigger isomerization or cleavage under UV/visible/NIR light, offering spatiotemporal control.

3.6 Magnetic & Ultrasound-Responsive Systems: Magnetic nanoparticles or liposomes respond to external magnetic fields or localized heating; ultrasound can induce polymeric ultrasound-sensitive microbubbles or sonosensitive vesicles to release drugs.
3.7 Multi-Stimuli-Responsive Systems: Combining two or more triggers (e.g., pH + temperature, pH + redox) enables more precise control and hierarchical release mechanisms.

4. Polymer Architectures & Carrier Formats

The architecture of a polymer-based drug carrier critically determines its **drug loading capacity**, **stimulus responsiveness**, **circulation behavior**, and **release kinetics**. Various formats—hydrogels, micelles, dendrimers, nanoparticles/nanogels, and polymersomes—offer distinct advantages and limitations, depending on the therapeutic need and stimulus applied.

Hydrogels

Hydrogels are 3D crosslinked networks of polymers with hydrophilic characteristics that have a high water absorption capacity while maintaining structural integrity. Their stimuli-sensitive swelling/deswelling behavior makes them highly attractive for localized, controlled drug delivery. PNIPAM-based hydrogels are thermo-responsive and undergo a volume phase transition around 32°C (LCST), shrinking and releasing drugs at hyperthermic temperatures. pH-responsive hydrogels such as alginate–poly(acrylic acid) composites swell at higher pH due to deprotonation of carboxyl groups, enabling colon-targeted or tumor-targeted delivery. A composite hydrogel of alginate/PAA was used for swelling significantly at pH 7.4 but not at stomach pH (Sahoo et al., 2009).

Micelles

While the hydrophilic shell (often PEG) maintains colloidal stability and extends circulation, the hydrophobic core can encapsulate medications that are poorly soluble in water. Stimuli-responsive micelles disassemble in response to triggers releasing their payload at the target site. PEG-b-PNIPAM block copolymers form micelles that

disassemble at 40–42°C, useful in thermally-enhanced tumor therapy (Bae et al., 2007).

Dendrimers

Dendrimers are monodisperse, extensively branched molecules that include distal functional groups, internal layers (generations), and a central core. Their design offers: Multiple attachment sites for drugs or targeting ligands. A tunable internal cavity for hydrophobic drug encapsulation. Surface groups that can be functionalized with stimuli-responsive moieties. PAMAM dendrimers functionalized with pH-cleavable linkers have been used for doxorubicin delivery. The drug is released preferentially at acidic tumor or endosomal pH (Kukowska-Latallo et al., 2005).

Nanoparticles & Nanogels

Polymeric nanoparticles (solid, matrix-based systems) and nanogels (hydrogel particles <200 nm) are designed for enhanced cellular uptake, protection of sensitive payloads, and stimuli-triggered release. Nanogels offer high water content and permeability while retaining structural flexibility. Their swelling behavior is often controlled by pH or redox gradients. Redox-sensitive nanogels with disulfide crosslinkers release insulin intracellularly under elevated GSH conditions, improving bioavailability (Vinogradov et al., 2004).

Polymersomes

Vesicle-like nanomaterials called polymersomes are created when amphiphilic blocking copolymers self-assemble, mimicking liposomes but offering superior mechanical stability, larger loading capacity, and greater tunability. Their bilayer membranes can incorporate pH- or redox-sensitive blocks that destabilize under specific stimuli. Polymersomes can co-deliver hydrophilic (in the aqueous core) and hydrophobic (in the membrane) drugs simultaneously. pH-sensitive PEG-b-poly(histidine) polymersomes destabilize at acidic endosomal pH, enabling endosomal escape and cytoplasmic drug delivery (Ahmed et al., 2006). Stimuli-Responsive Carrier Formats in Drug Delivery is shown in table 3

Table 3: Stimuli-Responsive Carrier Formats in Drug Delivery:

Carrier Format	Key Feature	Example	Stimulus
Hydrogels	Swelling response, localized delivery	Alginate/PAA hydrogel for 5-FU	pH
Micelles	Core-shell structure, solubilization of hydrophobic drugs	PEG-b-PNIPAM for DOX	Temperature
Dendrimers	Branched structure, surface functionalization	PAMAM-DOX conjugates	pH
Nanoparticles	Biodegradable solid matrix	PLGA nanoparticles for paclitaxel	Hydrolysis
Nanogels	Swellable crosslinked particles	GSH-sensitive insulin nanogels	Redox
Polymersomes	Bilayer vesicles for dual drug loading	PEG-poly(histidine) for endosomal release	pH

5. Applications in Drug Delivery

Stimuli-responsive polymers have shown transformative potential across various medical domains by enablingtargeted, controlled, and stimulus-triggered release of medicament.

Cancer Therapy

Cancer remains the leading area for application of stimuli-responsive drug_delivery systems. Tumors exhibit unique microenvironmental features such as mild acidity, elevated enzyme activity, and high glutathione (GSH) levels. pH-sensitive PEG-b-poly(histidine) micelles have demonstrated rapid release of doxorubicin under tumor pH (~6.5), with minimal release at physiological pH (Bae et al., 2005).

5.2 Inflammatory & Autoimmune Diseases

Acidic pH, oxidative stress, and increased levels of proteolytic enzymes (elastase, matrix metalloproteinases, etc.) are common features of inflammatory tissues, such as those found in rheumatoid arthritis or inflammatory bowel disease. These locations can be targeted by stimuli-responsive polymers to administer biologics, glucocorticoids, or NSAIDs, which are anti-inflammatory medications.
A poly(acrylic acid) was created for colon-specific delivery of mesalazine, a drug used

in ulcerative colitis. The gel remained stable at stomach pH but dissolved in the intestinal pH (Sinha & Kumria, 2001)..

5.1 Neurological Disorders

Getting medications via the blood_brain_barrier is still a difficult task when treating neurological conditions. Smart polymers are being developed to: Facilitate transcytosis across endothelial cells (e.g., using targeting ligands like transferrin or glutathione). Respond to microenvironmental changes in neurodegenerative conditions (e.g., altered pH, ROS levels). Thiolated polymers and GSH-responsive nanocarriers have been used to deliver levodopa or siRNA across the BBB

Ocular & Oral Drug Delivery

Ocular delivery is hampered by rapid tear turnover and blinking. In situ gelling systems that respond to ocular temperature or pH can prolong drug retention. Carbopol and chitosan-based hydrogels form gels upon contact with tear fluid (pH 7.2), releasing drugs slowly over time. Oral delivery systems aim to protect labile drugs from acidic stomach conditions and release them in the intestine. pH-sensitive Eudragit®-coated nanoparticles have been developed to release insulin in the intestine, where pH exceeds 6.5 (Jani et al., 2007).

Gene & Protein Delivery

Delivery of genes, siRNA, and proteins needs defense against enzymatic deterioration in circulation and controlled release inside cells. Stimuli-responsive polymers allow intracellular release in response to: Redox gradients (high intracellular GSH cleaves disulfide linkers). pH changes in endosomes/lysosomes. Enzymatic activity that cleaves peptide or ester bonds. Disulfide-linked polyethylenimine (PEI) was used to deliver siRNA in tumor cells (Oupický et al., 2002).

6. Challenges & Limitations

Despite promising advances, stimuli-responsive polymers face significant scientific, technical, and regulatory challenges. It is related to biocompatibility, formulation stability, and scaling up for commercial use, among others.

Table 3: Smart Polymer Carriers in Disease-Specific Drug Delivery: Stimuli, Systems, and Examples

Application Area	Polymer Type	Stimulus	Example Drug	Reference
Cancer Therapy	PEG-b-poly (histidine) micelles	pH	Doxorubicin	Bae et al., 2005
Inflammatory Diseases	Alginate/PAA hydrogel	pH	Mesalazine	Sinha & Kumria, 2001
Neurological Disorders	Redox-sensitive nanocarriers	GSH	siRNA, Levodopa	Saraiva et al., 2016
Ocular/Oral Delivery	Carbopol gel / Eudragit nanoparticles	pH, temperature	Insulin, Timolol	Jani et al., 2007
Gene & Protein Delivery	Disulfide-linked PEI	Redox, pH	siRNA, Plasmid DNA	Oupický et al., 2002

Biocompatibility & Toxicity

The introduction of stimuli-responsive functionalities—such as azobenzene, cationic amines, or thiol-reactive groups—can lead to cytotoxicity, oxidative stress, or immune activation. Moreover, polymer degradation products may also accumulate and cause adverse effects if not properly cleared. Cationic polymers often cause membrane disruption, leading to cell lysis and inflammatory responses. Non-biodegradable or slow-degrading polymers may accumulate in organs, especially in the liver and spleen, raising long-term safety concerns.

High-molecular-weight branched PEI is efficient for gene transfection_but is also highly cytotoxic; modifications like PEGylation or disulfide crosslinking have been explored to reduce toxicity (Godbey et al., 1999).

Stability & Shelf-Life

Polymer degradation during storage due to light, heat, moisture, or oxidation may impair the carrier's physical integrity and responsiveness. Thermo-sensitive polymers (e.g., PNIPAM) may undergo thermal degradation or aggregation above their LCST. Polymers with light-sensitive groups like azobenzene may photoisomerize prematurely, compromising drug retention. Formulations often require freeze-drying

(lyophilization), encapsulation with stabilizers, or antioxidants to maintain long-term shelf-life and bioactivity. PNIPAM-based hydrogels were shown to lose their LCST response after prolonged thermal exposure, affecting swelling behavior and drug release kinetics (Gil & Hudson, 2004).

Scalability & Regulatory Issues

The complexity of synthesis and lack of process standardization limit the large-scale manufacturing of responsive polymers. Specific challenges include: Reproducibility in polymer batch synthesis (e.g., block length, functionalization degree), Purification difficulties, especially in removing toxic residues or unreacted monomers, High costs of raw materials and multistep synthesis

Additionally, regulatory frameworks for novel polymer–drug conjugates or nanocarriers are still evolving. There are currently no unified guidelines across agencies like the FDA or EMA for polymer-based nanomedicines. Clinical translation of the pH-sensitive micelle formulation "SP1049C" (doxorubicin with Pluronic block copolymers) required extensive toxicology and pharmacokinetic evaluation, delaying its regulatory approval (Kabanov & Batrakova, 2004).

7. Conclusion

Stimuli-responsive polymers have revolutionized drug delivery strategies by offering precision, control, and adaptability. While promising clinical translation, ongoing research is focused on ensuring biosafety, manufacturability, and regulatory compliance to usher these smart systems into widespread therapeutic use.

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