Journal of Molecular Science

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 1087-1092
DoI-10.004687/1000-9035.2025.145

Journal of Molecular Science

www.jmolecularsci.com ISSN:1000-9035

Role of Smart Polymers in pH-Responsive Drug Delivery

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Article Information
Received: 07-10-2025
Revised: 24-10-2025
Accepted: 18-11-2025
Published: 20-12-2025

Keywords
Smart Polymers, Ph-Responsive, Drug Delivery, Temperature, Enzymes, Magnetic Fields, Intelligent" Polymers, Stimuli-Responsive Polymer, Nano-Based Formulations, Polymeric Nanoparticles, Lipid-Based Formulations, Ultrasound-Responsive Polymers, Light Responsive Polymer

ABSTRACT
A novel class of materials known as "smart polymers," or "stimuli-responsive polymers," significantly improves drug delivery systems (DDS). These polymers can alter their physical and chemical characteristics in response to particular external stimuli, including pH, temperature, light, enzymes, and magnetic fields. This responsiveness reduces systemic negative effects and increases treatment efficacy by enabling focused and regulated medication administration. Recently, stimuli-responsive polymers, often known as "intelligent" polymers, have surfaced as a novel drug delivery option. A number of stimuli have been mentioned, including pH, light, ultrasound, and heat. This paper provides a brief description of a pH-responsive stimuli-responsive polymer, covering the gelling mechanism, common types of polymers, common applications, and current problems. Drug delivery uses for pH-responsive polymers are numerous. The application primarily addresses the release of drugs at specified physiological sites. However, these polymers' ability to target tumors or gel in situ is still in the "proof-of-concept" stage. As a result, critical assessment of these polymers and their uses is still required. In this paper we will discuss. Role of Smart Polymers in pH-Responsive Drug Delivery.

INTRODUCTION:

In the field of pharmaceutics, smart polymers, also known as stimuli-responsive polymers, are a promising family of materials that offer creative ways to get around the problems with conventional drug delivery methods. These polymers can alter their chemical and physical characteristics in response to particular external stimuli, including pH, temperature, light, enzymes, and magnetic fields. This makes it possible to administer medications to a specific location in the body under control with little systemic adverse effects. One of the key advantages of smart polymers is their ability to control and sustain medication release, which improves therapeutic efficacy. Drug delivery to tumor locations or inflammatory areas using pH-sensitive polymers, where the pH would be lower due to acidic characteristics in contrast to normal physiology, is an example of its application. One possible benefit of temperature-sensitive polymers is that they can release a medication at specific temperatures, usually when the body exhibits inflammation and fever. In an effort to create more complicated DDS, the most recent advancements in smart polymer research have concentrated on merging many modes of reactivity to stimuli. These polymers respond to temperature and pH, providing improved drug delivery control under changing physiological conditions.[1]

In terms of improved medication absorption, targeted distribution, or improved stability, various innovative drug delivery methods or particularly created formulations are attracting attention. Nano-based formulations, polymeric nanoparticles, lipid-based formulations, self-emulsifying drug delivery systems, solid dispersion, gastro-retentive drug

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delivery, and mucoadhesive formulations are only a few examples of such systems or formulations. One of the most important components of many innovative delivery methods or formulations, including controlled-release oral formulations, solid dispersion, in-situ gellying systems, and nanoparticles, is polymers. The terms "smart polymers," "intelligent polymers," and "stimuli-responsive polymers" are used interchangeably to describe polymers that have the ability to alter their physical properties in response to external stimuli including light, pH, temperature, electric fields, and even ultrasound. They have been dubbed "intelligent" because their physical characteristics may be changed by tiny external stimuli, and if the inducers or stimuli are removed, their physical characteristics revert to their initial state.[2]

Numerous industries, including agriculture, nanotechnology, sensing, and medical sectors like drug delivery, hydrogels, and biomedical applications, have made extensive use of these applications. For example, employing these polymers to create chromatographic techniques is also feasible and could pave the way for an environmentally friendly approach.

Types of Smart Polymer:
I. Stimuli-Responsive Polymer
II. Temperature Responsive Polymer
III. pH-responsive polymers
IV. Ultrasound-responsive polymers.
V. Light responsive Polymer:
VI. Enzyme responsive polymer:[3]

I. Stimuli-responsive polymer:

Because they may alter their mechanical, chemical, or physical characteristics in response to particular external stimuli, stimuli-responsive polymers, sometimes referred to as smart polymers, are an essential part of controlled drug delivery systems. These polymers can be designed to release medications in a targeted and regulated way, improving patient compliance, lowering adverse effects, and significantly increasing therapeutic efficacy. profile; high drug loading capacity; absence of harmful characteristics such immunogenicity, carcinogenicity, reproductive toxicity, and systemic toxicity; and outstanding stability profile.

II. Temperature Responsive Polymer

Temperature-responsive polymers respond to temperature changes by changing their shape, usually within the physiological range of 37°C. These polymers can be used to regulate medication release since they are made to show a sol-gel transition at a particular temperature. When a slight temperature shift occurs, thermosensitive polymers experience an abrupt change in their solubility.

III. pH-responsive polymers

A critically relevant feature for drug delivery in the gastrointestinal tract, intracellular settings, or tumors where pH fluctuates is their ability to change their structure in reaction to the surrounding pH environment. Pendant acidic or basic groups in pH-sensitive polymers have the ability to either receive or release a proton in response to variations in the pH of their surroundings. Polyelectrolytes are polymers that have a lot of ionisable groups. Weak poly bases and weak poly acids are the two categories of polyelectrolytes. Protons are taken up by weak poly acids at low pH and released at neutral and high pH.

Two popular pH-responsive poly acids are poly (acrylic acid) (PAAc) and poly (methacrylic acid) (PMAAc). Drug delivery systems are one of the many possible commercial uses for pH-responsive polymeric systems since they allow for the creation of customizable "smart" functional materials. For instance, since the extracellular pH of the majority of tumors is acidic (pH 5.8–7.2), intelligent polymeric nanodevices can be created for the administration of anti-cancer medications, where the release of medications can be activated by adjusting pH. The pH-sensitive polymer is made up of pendant acidic or basic groups that either receive or release a proton in response to changes in the pH of the surrounding environment. Chitosan is a polycationic biopolymer that dissolves in acidic solutions and experiences phase separation at a pH range near neutrality as a result of inorganic ions deprotonating the main amino group. The following interactions—hydrogen bonding between the chitosan chains, electrostatic attraction between the chitosan's ammonium group and an inorganic ion, and hydrophobic interactions between chitosans—are what cause chitosan to gel.

However, in order to create a gel with adequate mechanical stability and to release the low molecular weight medication in a regulated manner, additional cross-linking agents are required. According to a number of studies, the porosity of the chitosan gel, which is a consequence of the polymer's crystallinity, determines the structural strength of chitosan. The polymer can be hydrophobically modified or blended with other polymers to increase its structural strength. One example is the creation of a semi-interpenetrating polymeric network that gels in situ at physiological pH by cross-linking chitosan, polyvinyl pyrrolidine, and gluter aldehyde. Poly (acrylic acid) (PAA), Poly (methacrylic acid) (PMA), Chitosan, and Poly (ethylene mine) (PEI) are typical examples.

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IV. Ultrasound-responsive polymers:

The efficiency of ultrasound-responsive drug delivery devices in releasing drugs to specified tissues has made them a significant area of research in targeted therapy. The ability to manipulate both space and time makes ultrasound impulses an intriguing potential. It is a non-invasive biomedical imaging technique that is already widely utilized and acknowledged. An extremely powerful method for delivering high power densities to specific, regulated parts of the body is high intensity focused ultrasound. New developments in the creation of innovative medication delivery systems may result from utilizing this localized energy in a way that initiates regulated responses.[4]

V. Light responsive Polymer:

When exposed to particular light wavelengths, such as UV, visible, or near-infrared light, polymers are made to alter their characteristics. This is a great method for accurate distribution to certain locations since it permits spatiotemporal control over medication release. A type of stimuli-responsive polymers known as "light-responsive polymers" experiences reversible changes in their chemical or physical characteristics when exposed to particular light wavelengths. Spatiotemporal control, or the capacity to direct drug delivery in terms of both place and timing, is one of the major benefits of controlling medication release with light.

VI. Enzyme responsive polymer:

When certain enzymes are present, they are intended to break down or alter in structure. The gastrointestinal system and intracellular spaces are examples of locations with high enzymatic activity where these polymers can be employed for medication release.[5]

Review of Literature:

When utilized as binders, surfactants, diluents, solubilizers, and other components, pharmaceutical polymers are essential to formulations. Certain natural and synthetic polymers have been studied to improve the solubility, permeability, bioavailability, and efficacy of medicinal compounds.1 Because they are sensitive to their surroundings, smart or intelligent polymers are unique. These stimuli-sensitive polymers are used in cell culture, bioseparation, chromatography, dosage form development, surface modification of biomolecules, and other well-researched biomedical activities. Their unique functional characteristics have been reinforced by a recent major breakthrough in nanotechnology that produced a variety of nano-structured polymeric and supramolecular architectures.[6]

According to Grainger, El-Sayed (2010) and Kuckling, Urban (2011), smart polymers, also known as stimuli-responsive polymers, are at the forefront of drug administration technology because they exhibit an active response to subtle indications and changes in the surrounding environment, which translates into significant changes in their microstructure and in the physiological and chemical properties as desired. To put it another way, smart polymers can react to some stimuli by exhibiting physical or chemical changes in their behavior, such as when a medication is delivered on its own.[7]

The ability to administer an effective concentration of a particular drug at the appropriate time and location, lowering adverse systemic reactions and improving patient adherence to the treatment, as well as lowering the drug dose and, consequently, the costs, are the primary benefits of adding smart polymers with drug molecules (Al-Tahami, Singh, 2007).[8]

Objectives:

- To Study the role of Smart Polymers
- To Study the types of Smart Polymer
- To Study the role of Smart Polymers in pH-Responsive Drug Delivery
- Categories of pH-responsive polymers or polyelectrolytes

Research Methodology:

The study is exploratory in nature. The data used for preparing this paper are secondary in nature which is collected from the various published resources. The data derived for preparing this research paper has been extracted from various elite journals and relevant websites.

RESULT AND DISCUSSION:

Due of their promising potential, stimuli-responsive materials have drawn the attention of more researchers in recent years. Stimuli-responsive polymers are a class of materials that can self-organize or undergo phase transitions and morphological changes in response to external stimuli, which can be chemical, physical, or biological, as Fig. 1 illustrates. Also referred to as smart, intelligent, or stimuli-sensitive polymers, they can perform a variety of tasks by interacting with a variety of elements, including variations in temperature, pH, the presence of biomolecules, solvents, ionic strength, chemical agents, light, humidity, electrical, magnetic fields, and so forth.[9]

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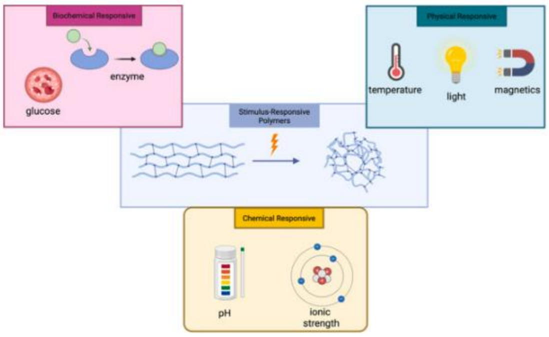

Figure 1: Main types of stimuli for polymeric devices.

Stimuli-responsive polymers, also known as bio-responsive polymers, provide a significant advantage for drug administration since the stimuli needed to change the polymer's physical state are found in a normal human biological system. Drug delivery systems that use these bio-responsive polymers are sometimes known as "in-situ" systems, most frequently "in situ gellying" systems. Toxicity, response time, drug-polymer or polymer-polymer interactions, and location of action are just a few of the crucial factors to consider when choosing the best polymers. Before selecting the best, each factor must be carefully considered. For instance, acrylamide polymers are frequently used as thermosensitive polymers, although they have been classified as carcinogenic compounds and have the potential to harm the nervous system. Reviews of in situ gellying polymers for various drug administration methods, such as intranasal or ocular, are available to readers. This brief overview aims to highlight key aspects of stimuli-responsive polymers for drug administration.[10]

Since pH-responsive polymers are the most researched stimuli-sensitive polymer after thermo-responsive, special attention has been paid to them in this article. The synthesis and use of pH-sensitive polymers have also been thoroughly examined recently. The pH of many human organs and sections varies within our physiological system. The pH of aberrant cells, such as tumors and cancerous tissues, differs from that of normal bodily systems or tissues (Table 1). Consequently, it is possible to tailor a pH-responsive polymer-based drug delivery system to administer the medication at the desired site of action. However, the most crucial step in maximizing the benefit is choosing an appropriate polymer based on the intended spot. Thus, this article's goal is to illustrate the fundamental characteristics of stimuli-responsive polymers, with a focus on pH-responsive polymers for drug delivery systems.

Table 1: pH in different systems, organs or tissues in human body

Organ / System / Tissue	Ph
Blood	7.35-7.45
Stomach	1.0-3.0
Small intestine	4.8-6.7
Colon	7.2
Tumour, extracellular	7.2-6.5
Early endosome	6.0-6.5
Lysosome	4.5-5.0

In the sense that they are sensitive to their surroundings, smart or intelligent polymers are unique. These stimuli-sensitive polymers are used in the formulation of dosage forms, bioseparation, chromatography, cell culture, surface modification of biomolecules, and other well-researched biomedical activities. Their unique functional features have been reinforced by a recent major breakthrough in nanotechnology that produced a variety of nano-structured polymeric and supramolecular architectures. Because of their physiochemical properties that allow them to react to minute changes in their surroundings, polymers are among the most intriguing biomaterials. It will be very interesting to find out if the medications can be absorbed at physiological pH and released at a lower pH (lysosomal pH or the pH of the tumor microenvironment). The body's distinct compartments are revealed by the temperature in bodily cavities, pH of fluids, ionic concentration across cellular membranes, tissue-specific enzymes, over-expression of particular receptors, and other factors. This information enables the development of stimuli-specific polymers. The physical state and chemical structure of these polymers are significantly altered by changes in the surrounding pH.[11]

The architectures of polyelectrolytes contain either basic or acidic groups. Polyelectrolytes either take in or release protons from their molecules in response to changes in the pH of their environment. At a particular pH, these polymers experience ionization, which raises the surface charge of the polymeric chains. By absorbing water, these internal repulsions swell and extend (Figure 2). If the solvent keeps the polymeric system from ionizing, the polymer chains remain folded and compact. The polymer's functional groups ionize in response to a minor shift in the surrounding pH, causing the phase transition (dissolution or swelling).

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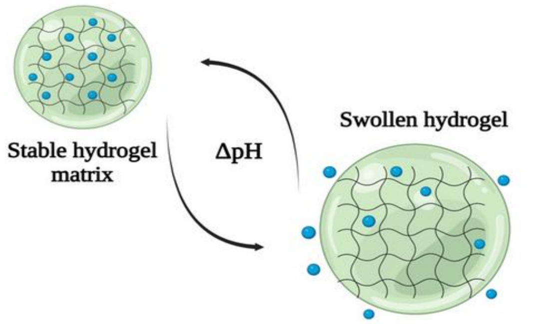

Figure 2: Swelling/de-swelling of drug-loaded hydrogel matrix, resulting from the change in ambient pH.

At low pH, the acidic groups are unionized and protonated, significantly decreasing the volume of poly-acid. When the pH rises, an anionic polymer expands. In cationic polymers, basic groups from polybases become more ionized as pH drops. When the pH medium is higher than the pKa value for a polyacid, the length of the polymeric chains increases, and when the pH medium is lower than the pKa value, the length of the polymeric chains reduces. Figure 2 presents this behavior diagrammatically.

Selecting the right framework is essential to getting the desired result from a medication delivery system. Appropriate biomaterials increase the likelihood of therapeutic benefits such enhanced permeability, target specificity, optimized pharmacokinetics, and subsequently positive medication efficacy. The best method for creating logical, personalized medications that interact with the patient's body is to combine polymers to create pH-responsive drug delivery systems. Such polymeric systems can minimize negative effects by lowering dosing frequency and avoiding off-target medication administration due to their high target-specificity. This review examines several polymeric scaffolds and polyelectrolytes that may be used in precision medicine and tailored drug delivery systems. A few examples of pH-responsive polymers are displayed in Table 2.[12]

Table 2. Categories of pH-responsive polymers or polyelectrolytes.

	Polymer	pKa	Application
Polyacids	Poly (methacrylic acid)	4.8	Targeted delivery of bone morphogenetic protein-2 for osteogenesis
	Poly (vinyl-phosphonic acid)	5-6	Brain targeted delivery of zuclopenthixol for managing psychosis
	Poly (glutamic acid)	4-8	Doxorubicin loaded nanoparticles against 4T1 breast cancer cells
	Poly (vinyl-sulfonic acid)	≤1	Vancomycin loaded nanoparticles for colon targeted drug delivery
	Poly (aspartic acid)	3.9	Colon targeted 5-FU loaded nanoparticles against colorectal tumor
Polybases	Poly [2-dimethylaminoethyl methacrylate]	7.5	Paclitaxel loaded nanoparticles against HeLa cancer cells
	Poly (4-vinyl pryridine)	4.0	Graphene oxide grafted nanoparticles for antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus*
	Poly (2-diethylamino) ethyl acrylamide]	7-8	pH responsive hydrogels loaded with NSAIDs/ corticosteroids for colon targeted delivery
	Poly (acryloyl morpholine)	8.3	Doxorubicin loaded supramolecular micelles for tumor specific drug delivery
	Poly (N-vinyl imidazole)	~7	Vancomycin loaded polymeric films for pH responsive controlled release of drug

By altering the electrical charge of the polymer molecule, this class of smart polymers modifies its solubility. Therefore, the reduction of the electrical charge in the polymeric molecules is responsible for the change from a soluble to an insoluble state. By lowering the pH, neutralizing the electric charge, and decreasing the hydrophilicity (raising the hydrophobicity) of the polymeric macromolecules, the electric charge of the polymer can be reduced. We can highlight the following as instances of this type of polymer:

polyacrylamide (PAAm), poly (acrylic acid) (PAA) (Carbopol®) and derivatives, poly (methacrylic acid) (PMAA), poly (2- diethylaminoethyl methacrylate) (PDEAEMA), poly (ethylene imine), poly(L-lysine) and poly (N, N-dimethylaminoethylmetha crylate) (PDMAEMA).[13]

CONCLUSION:

The application of pH-sensitive polymers in drug delivery fields or technologies attempts to take into account the produced materials' economic properties rather than focusing solely on their biological or medical benefits. Drug delivery systems, oral insulin delivery, and multi-stimuli responsive material design are just a few of the many crucial areas that one might focus on. pH-magneto-responsive polymers and pH-thermo-responsive polymers are two examples of dual stimuli-responsive materials that have been documented. A "smart" drug delivery system that delivers a medication in reaction to a particular pH shift in the body is known as a pH-responsive drug delivery system. In order to increase

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treatment efficacy and lessen adverse effects, these systems are made to target particular tissues or organs with varying pH values, such as the stomach or the acidic environment of a tumor. In order to deliver their payload at a certain location and time, they are made of materials having pH-sensitive chemical bonds that go through physical or chemical changes.

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