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Fabrice Ofridam, Mohamad Tarhini, Nouredine Lebaz, E. Gagnière, Denis Mangin, et al.. pH-sensitive polymers: Classification and some fine potential applications. *Polymers for Advanced Technologies*, 2021, pp.1455-1484. 10.1002/pat.5230 . hal-03132353

HAL Id: hal-03132353

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Submitted on 28 Oct 2021

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pH-sensitive polymers: classification and some fine potential applications

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ABSTRACT

Stimuli-responsive materials in general and pH-responsive polymers in particular have gained increasing interest during the last two decades. Their unique properties, which arise from their ability to exhibit sharp and reversible changes in response to environmental pH conditions, have made them suitable for various applications such as drug delivery and specific body-site targeting, sensing and actuation, membrane functionalization, separation techniques, as well as in agriculture and food industry and even chemical industries. In the present review, the focus is on the general characteristics of pH-responsive polymers in terms of their origin, chemical composition, and preparation. Moreover, some of the important and recent applications are reported and discussed.

KEYWORDS

drug delivery, pH-responsive polymers, sensing and actuation, separation methods, smart polymers, surface functionalization

1 INTRODUCTION

Polymer-based particles are widely used for diverse applications, especially for the encapsulation of drug molecules, mainly because of their good biocompatibility and bio-elimination.¹ As drug carriers, they are able to efficiently deliver therapeutic agents to target sites. This is due to the polymeric properties, which allow the preparation of particles with controlled size, size distribution, permeation, flexibility, and solubility.^{2,3}

Surface properties of polymers are improved chemically, physically, or biologically in order to increase their biocompatibility.¹ The biodegradability of polymers/polyelectrolytes is controlled by incorporating a variety of labile or hydrolyzable groups such as ester, carbonate, amide, urea, or urethane in their backbone.⁴ Thus, research has led to the development of a new class of polymers, which are stimuli-responsive. These polymers are materials that are sensitive to physicochemical changes in their surrounding environment. They are capable of detecting small environmental variations and react with self-assembly or dramatic changes in their physicochemical properties. These polymers undergo structural and conformational changes as a response to the variation of environmental conditions, such as pH, temperature, solvent, salt ionic strength, light, and magnetic or electrical fields. One of their fundamental characteristics remains the reversibility of the modifications: that is, their ability to return to their initial state as soon as the stimulus responsible for the physicochemical properties' modification is removed (exception is made for structured, linked, degradable systems). Stimuli-responsive polymers can be made only of natural or synthetic polymers or by incorporating a responsive compound or function along an existing polymer's backbone. Interest in these materials has been growing fast in the two last decades because of a multitude of emerging applications. Environmental changes or stimuli are of three types: physical stimuli (mechanical stress, electrical/magnetic field, ultrasounds, light, temperature), chemical stimuli (electrochemical, pH, ionic strength), and biological stimuli (enzyme, biomolecules).⁵⁻⁷ Figure 1 shows the different classes of stimuli with the type of modifications induced by each category.

Physical stimuli such as temperature, light, or electric or magnetic fields cause intermolecular interactions. On the other hand, chemical stimuli affect the molecular structure of the polymer by the addition of chemical agents.⁸ With these stimuli, one may find pH-responsive, solvent-responsive, ionic strength-responsive, chemical agent-responsive, or biologically responsive polymers.

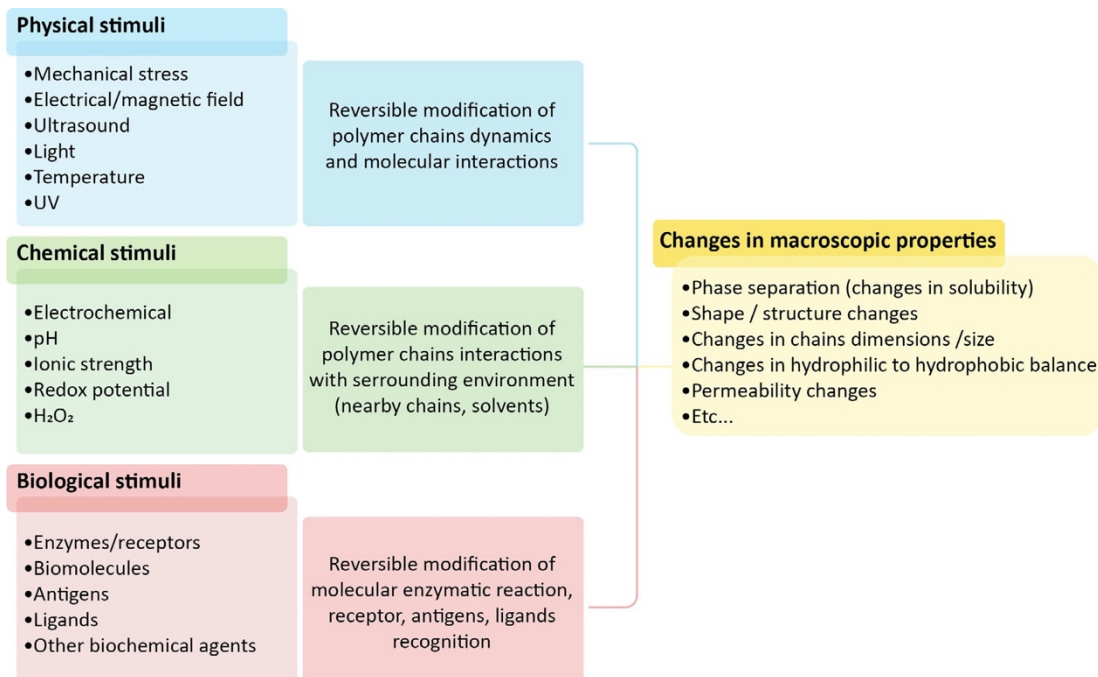


FIG 1 Classification of stimuli-responsive polymers with their induced modification

pH-responsive polymers (PRPs) respond to environment pH variation through structural and property changes such as surface activity, chain structure, conformation, solubility, and configuration. pH-sensitive polymers contain acidic or basic groups that can either accept or donate protons in response to the fluctuation of the environmental pH. PRP categories exist, and according to the classification criteria, weak base can be distinguished from weak acid, and biopolymers and degradable polymers from synthetic ones. They find application in drug delivery, gene delivery, actuation and sensing/biosensing, separation techniques, and so on.⁹

This review deals exclusively with pH-sensitive polymers. Their important properties, classification, and structure are first introduced. Multiple-responsive polymers with pH-responsiveness are highlighted in the second part of this review. A special focus is on the different and recent applications of PRPs.

2 CHARACTERISTICS OF pH- RESPONSIVE POLYMERS

PRPs behave with respect to the surrounding pH by undergoing structural and property changes such as surface activity, chain conformation, and solubility. The nature of the changes depends on the pH-responsive material structure.¹⁰ Considering a homopolymer, pH variation gives rise to flocculation, chain collapse/extension, or precipitation. For pH-responsive block copolymers or reticulated structured PRPs, the response to pH modification is made through self-assembly such as formation of micelles, unimers, gels, vesicles, swelling/ deswelling, and so on.¹¹ Recall that PRPs are materials that include in their structure weak acidic or basic groups which either accept or release protons in response to a fluctuation of the environmental pH. Polyanions or polyacids have ionizable pendant acid groups, such as carboxylic acid (COOH), sulfonic acid (SO₃H), or phosphonic acid (PO₃H₂), along the polymer backbone, whereas polycations or poly-bases contain basic groups such as amines (NH₂) either in their structural backbone or as a pendant group. Ionization of these functional groups with respect to the surrounding pH results in a modification of the polyelectrolyte structure.^{11,12}

Figure 2 presents a schematic representation of a polyacid and a polybase state depending on the ionization degree of the ionic chain group. A polyacid exhibits an expanded state when the medium pH > pK_a, whereas the polymeric chains collapse at pH values < pK_a. However, for a polybase, above the value of pK_b (pH > pK_b), polymer chains collapse; conversely they expand at pH < pK_b.

One of the well-known and largely described behaviors of these materials is the swelling/deswelling of the polymers depending on the state of their ionizable groups. Typically, these polymers are water-soluble when charged and become water-insoluble when neutral. This phenomenon is due to the fact that when the ionizable groups become neutral, electrostatic repulsion forces disappear within the polymer network, and hydrophobic interactions dominate.

The charge status in these materials is readily reversed by returning to the starting pH of the solution; the switching behavior of the PRPs is also reversible.¹³

In practice, for a specific application, one should choose the PRP or material according to its pK_a value and the expected pH-responsiveness range. The preparation techniques of PRPs allow the customization of polymeric materials in order to have a certain pK_a value and to achieve a specific task. The transition pH dictated to the pH-responsive material by its pK_a (for acidic material) or pK_b (for basic material) can thus be tuned by modifications that affect hydrophobic or electrostatic interactions.^{14,15} Methods employed to tune pK_a are hydrophobic modification (incorporating different hydrophobic groups or changing the length of hydrophobic chains, which leads to pK_a shift), copolymerization of PRPs with nonionizable or ionizable polymers (additional polyelectrolytes that change both hydrophobic interactions and electrostatic repulsion leading to pK_a shift), and acid-labile linkages as well.¹⁶

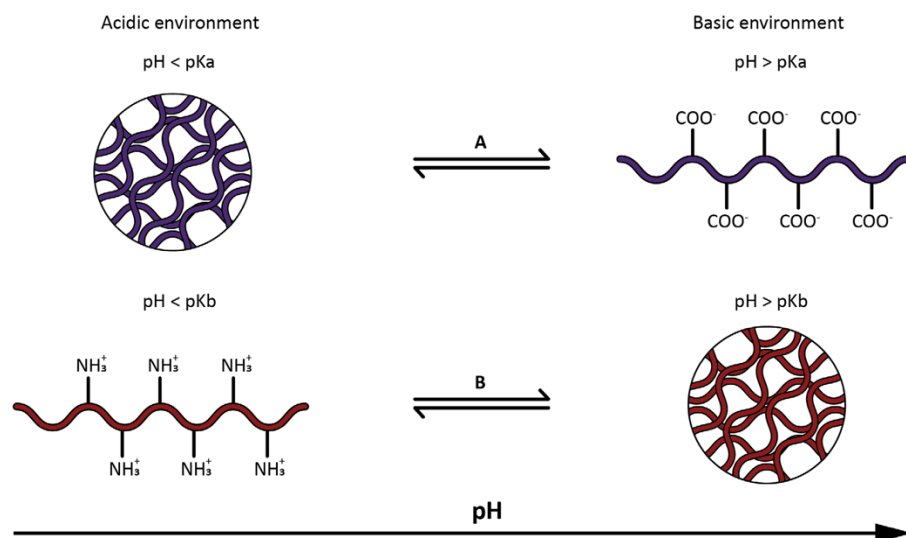


FIG 2 A, polyacids and B, polybase polymeric chain state depending on the ionization degree

3 NATURAL pH-RESPONSIVE POLYMERS

Considering their origin, natural PRPs are distinguishable from synthetic ones. A pH-responsive conformation with solubility changes is a common behavior in biopolymers.¹⁷ The use of natural polymers is due to their abundance in nature, biodegradability, nontoxic behavior, biocompatibility, and their ability to be modified.¹⁸ Hyaluronic acid, alginic acid, heparin, chitosan, and the cellulose derivatives (carboxymethyl cellulose, carboxymethyl dextran) are examples of natural PRPs.

3.1 Alginate

Alginate, one of the most abundant polysaccharides, is extracted from brown seaweed, and used extensively in food, pharmaceuticals, and regenerative medicine.^{19,20} Alginate consists of a block copolymer of β -D-mannuronic (M) and α -L-guluronic acid (G) in varying sequential arrangements and proportions²¹ (Figure 2). It is an acidic polysaccharide bearing carboxylic groups, whose pKa is 3 to 4.²² Both mannuronic and guluronic acid residues have carboxylic functional groups in their structure, which are at the origin of the pH-sensitivity of alginate.²³ The high acid content allows alginic acid to undergo spontaneous and mild gelling in the presence of divalent cations such as Ca²⁺, Ba²⁺, Sr²⁺, and Zn²⁺; the formed gel shows variable swelling profiles in response to pH variation.²⁴ These mild gelling properties are pH-dependent and allow the encapsulation of various molecules or even cells within alginate gels with minimal negative impact.²⁵ Moreover, at low pH prevailing in the gastric environment, alginate shrinks and retains encapsulated molecules.¹³ The length of the M- and G-blocks and their sequential distribution along the polymer chain vary depending on the source of alginate.

3.2 Hyaluronic acid

Hyaluronic acid (HA) or hyaluronan is a naturally occurring linear polysaccharide composed of D-glucuronic acid and N-acetyl-D-glucosamine disaccharide (Figure 3). At neutral pH, HA acts as an anionic polyelectrolyte since the pKa of the carboxylic acid groups is approximately 3 to 4, which makes HA highly hydrophilic. Because of its ability to absorb water, it expands up to 1000 times its solid volume, leading to a loose and hydrated network.²⁶ The high content of hydroxyl and carboxylic acid groups provides added functionalities via conjugation, chemical bonding, and cross-linking,²⁷ promoting the preparation of pH-sensitive hydrogels.²⁸⁻³⁰ pH-sensitive HA nanoparticles were prepared by Han et al³¹ as oral delivery carriers with the advantage of protecting the loaded insulin against the stomach's strong acidic environment. Miyazaki et al³² reported the synthesis of HA-based, pH-sensitive polymers designed as multifunctional polymers having not only pH sensitivity but also targeting properties to cells expressing CD44, which is known as a cancer cell surface marker.

3.3 Carboxymethylcellulose

Carboxymethylcellulose is a typical anionic cellulose derivative in which carboxymethyl groups are bonded to hydroxyl groups of the glucopyranose monomer (Figure 3). The carboxymethyl groups of this polysaccharide are ionizable above their pKa = 4.3.³³ On this basis, Akar et al³⁴ prepared and characterized a pH-sensitive sodium carboxymethyl cellulose-based hydrogel by using fumaric acid (FA) as a cross-linking agent. Chemically modified carboxymethylcellulose-based hydrogels with pH-responsive properties have been reported in the literature for the controlled release of molecules such as rhodamine B dye,³⁵ isoliquiritigenin in inhibiting growth of acne through transdermal delivery,²⁸ or lysosomes.³⁶ In general, smart cellulose-based hydrogels have wide applications in the fields of agriculture, food, tissue engineering, and drug delivery.³⁷

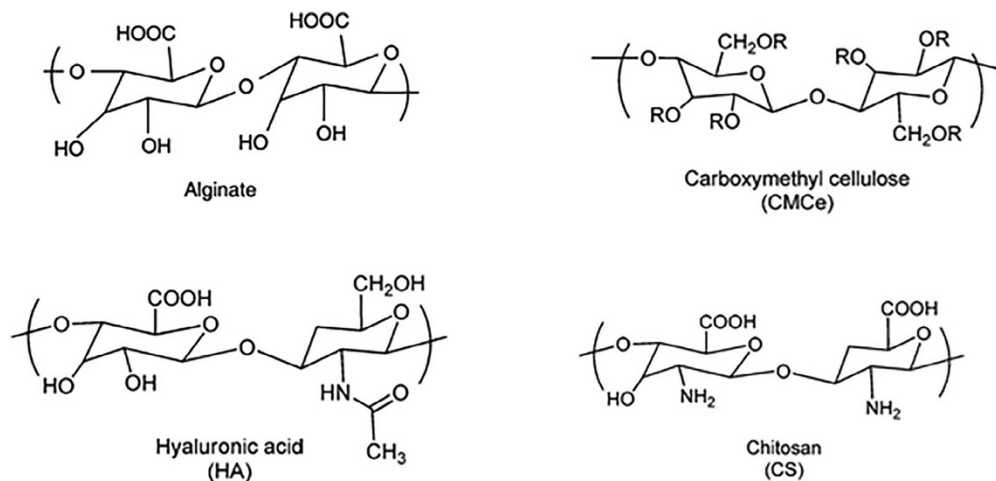


FIG 3 Chemical structure of commonly used natural pH-responsive polymers.¹¹ With Copyright permission

3.4 Chitosan

Chitosan (Ch) is a naturally occurring polysaccharide with randomly distributed N-acetyl glucosamine (2-acetamido-2-deoxy- β -D-glucopyranose) and glucosamine (2-amino-2-deoxy- β -D-glucopyranose) units (Figure 3). This copolymer is obtained by alkaline deacetylation of chitin.

The main commercial sources of chitin are crustacean shell wastes. Because of the physicochemical and biological properties of chitosan, especially its biocompatibility, biodegradability, nontoxicity, capacity of metal ion adsorption, excellent film-forming capability, and so on, it has found application in medical and pharmaceutical fields, food industry, agriculture, wastewater treatment, and other areas.³⁸

Chitosan exhibits a pH-sensitive behavior as a weak polybase due to the large number of amino groups on its chain. Chitosan dissolves easily at low pH but remains insoluble at higher pH ranges. The mechanism of pH-sensitive swelling involves the protonation of its amine groups under low pH conditions. The protonation leads to chain repulsion, diffusion of proton and counter ions together with water inside the gel, and dissociation of secondary interactions.³⁹ This pH sensitivity has been reported for drug delivery applications.⁴⁰⁻⁴² Recently, Gaware et al.⁴³ reported the synthesis of curcumin-loaded pH-sensitive nanocomposites made of chitosan and silica. They demonstrated a pH-dependent release of the curcumin. They concluded on the tunable release profile of the active molecule using the pH of the release medium. pH-dependent drug release using chitosan-based polymeric materials was also shown by other authors.^{44,45} As an innovative application, Ezati and Rhim⁴⁶ synthesized a chitosan-based, pH-dependent, color-changing film. They incorporated alizarin for active and smart food packaging applications. The composite film showed a vivid color change from slightly yellow to purple in response to a pH variation in the range 4 to 10. The chitosan/alizarin film showed antibacterial, anti-oxidant, and pH-responsive color-changing properties.

4 SYNTHETIC pH-RESPONSIVE POLYMERS

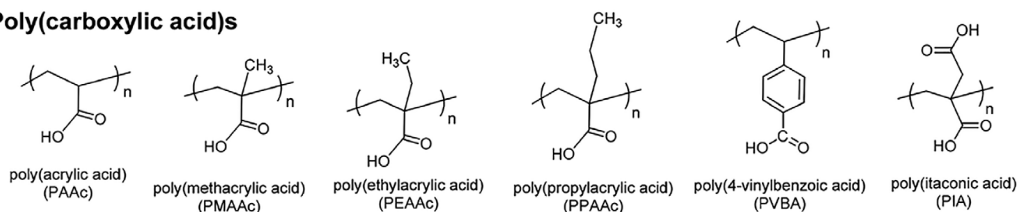
Although the use of natural polymers is of common interest because of their abundance, degradability, biocompatibility, and ability to be modified, synthetic PRPs exist and are used for diverse applications. Among these specific synthetic polymers, derivatives of polypeptides such as poly(L-glutamic acid) (PGA), poly(histidine) (PHIS), and poly(aspartic acid) (PASA) are biocompatible, degradable pH-sensitive polymers.¹¹ Controlled/living radical polymerization techniques were developed and used to prepare well-defined homopolymers or block copolymers under simple and less stringent reaction conditions than anionic polymerization and group transfer polymerization (GTP). These controlled/living radical polymerization methods include atom transfer radical polymerization (ATRP), reversible addition fragmentation chain transfer polymerization (RAFT), and nitroxide-mediated polymerization (NMP) which is one type of stable free-radical polymerization (SFRP). ATRP and NMP control chain growth by a reversible termination process step, while RAFT polymerization controls chain growth through reversible chain transfer.^{47,48} ATRP and RAFT allow a precise control over molecular weights and molecular weight distributions, affording polymers with well-defined topology structure.¹⁶ In recent years, ATRP has become the most popular controlled radical polymerization method used in the synthesis of PRPs due to the relatively easy production process with various architectures such as block, star, gradient, brushes, and branched (co)polymers.¹¹

Synthetic pH-sensitive polymers will be the topic of the next section, where basic pH-sensitive polymers will be listed. A classification according to their functional groups and their chemical structure will be presented.

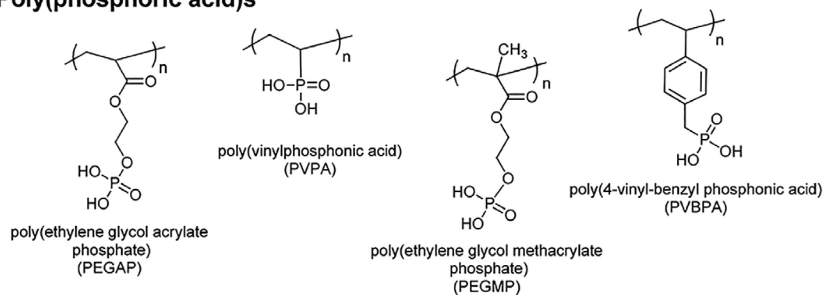
4.1 Composition-based classification

Considering the nature and the localization of the pH-responsiveness group, pH-sensitive polymers may be categorized first into two groups: polymers with ionizable pendants, and polymers that contain acid/base-labile linkages.¹¹ PRPs with ionizable pendants are cationic or anionic. The degree of ionization in a polymer bearing weakly ionizable groups is dramatically altered at a specific pH known as pKa. When the pH of the medium is modified, polymer functional groups are capable of accepting or donating protons (H^+), changing the ionization degree and the net charge on the polymer chains. This leads to the alteration of their hydrodynamic volume and conformation. As the net charge on the chains increases, the electrostatic repulsion of the generated charges causes the transition of the chains from collapsed to expanded state.^{17,49} Conversely, a decrease in the chain's net charge provokes their transition from expanded to collapsed configuration. Furthermore, altering the electrostatic charge affects the water solubility of the polymer. Increased net charge increases the hydrophilicity of the chains, leading to enhanced polymer solubility.³³

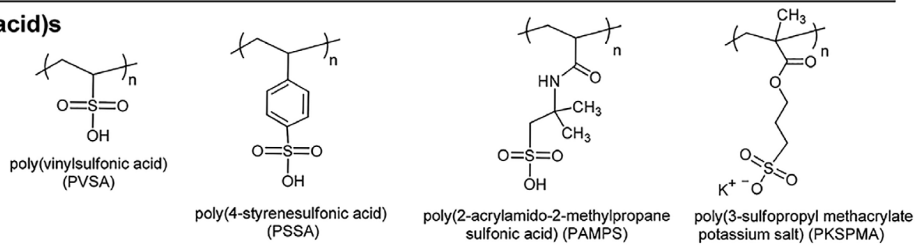
Poly(carboxylic acid)s



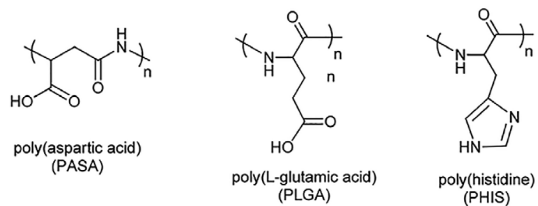
Poly(phosphoric acid)s



Poly(sulfonic acid)s



Poly(amino acid)s



Poly(boronic acid)s

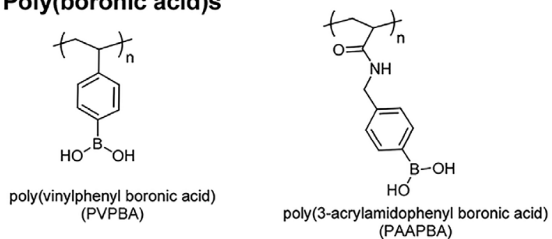
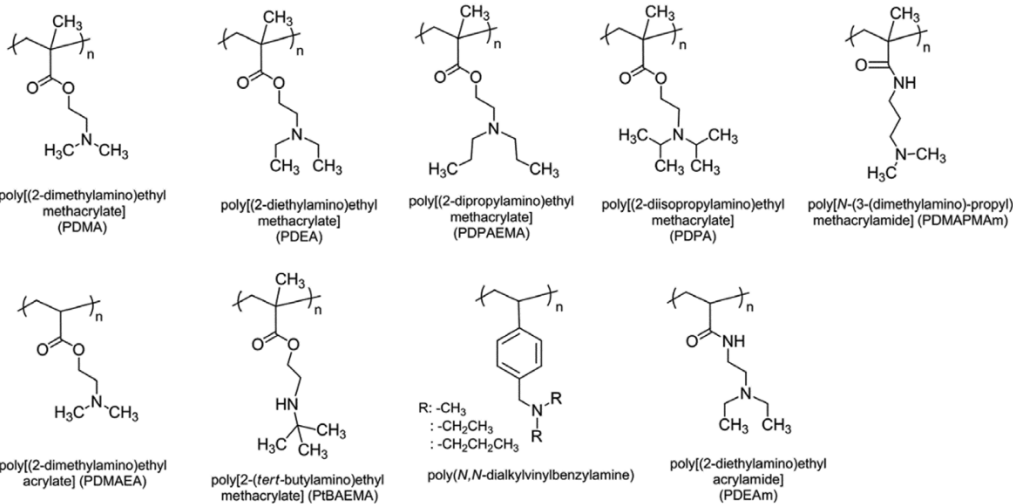
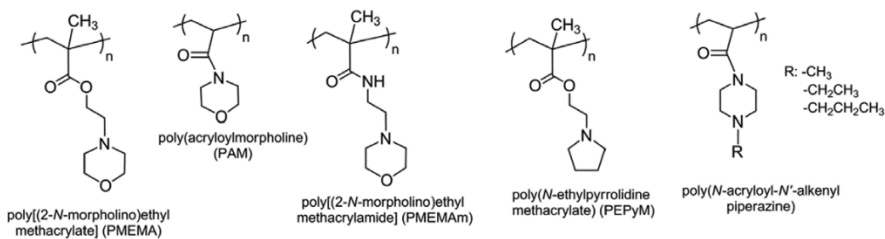


FIG 4 Chemical structure of polyanions pH-responsive polymers classified according to the nature of their functional pendant groups.¹¹ With Copyright permission

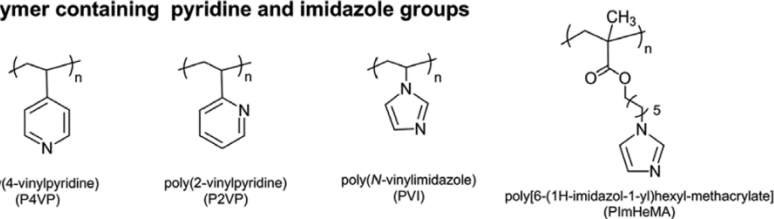
Polymer containing tertiary amine groups



Polymer containing morpholino, pyrrolidine and piperazine groups



Polymer containing pyridine and imidazole groups



Dendrimers

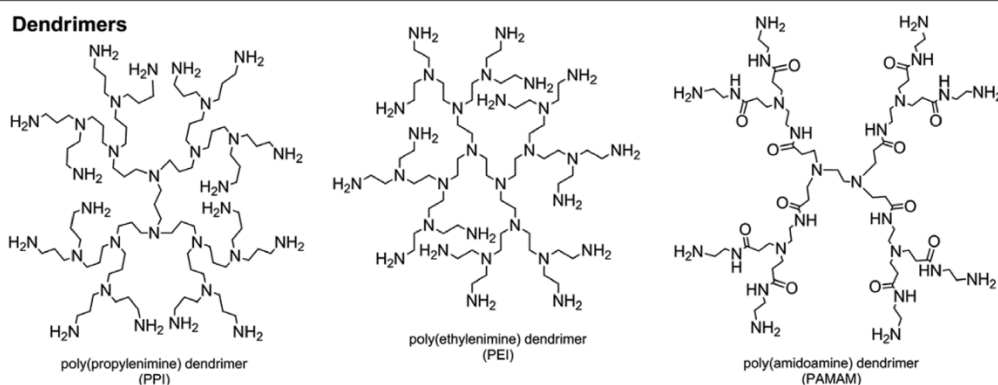


FIG 5 Chemical structure of polycations pH-responsive polymers classified according to the nature of their functional pendant groups.¹¹ With Copyright permission

4.1.1 Polyacids as pH-responsive polymers

Polyacids exhibiting pH-responsive behavior contain acidic pendant groups or residues such as carboxylic acid, sulfonic acid, phosphoric acid, and boronic acid. pH-responsive polyanions accept protons (H^+) in the medium at low pH and release protons (H^+) at neutral and high pH throughout their functional groups. As reported by Bazban-Shotorbani et al.³³ taking the example of poly(acrylic acid) whose pKa value is 4.28 with acidic carboxylic pendant groups (COOH), it is anionically charged at pH > 4.28 and becomes predominantly uncharged at pH below the pKa. The pKa values of polyacids, which determine the transition point of PRPs, differ from monoacid pKa and depend on their polymeric composition and molecular weight as well.⁵⁰

Figure 4 summarizes the most common acid PRPs classified according to the nature of their functional groups.

4.1.2 Polybases as pH-responsive polymers

Basic polycations exhibiting pH responsiveness contain basic moieties such as tertiary amine groups; morpholino, pyrrolidine, piperazine groups; pyridine and imidazole groups; or made of dendrimers, as shown in Figure 5, which summarizes the common polymers with their chemical structure. These polymers are protonated at high pH values and positively ionized at neutral and low pH.

4.1.3 Polymers with acid/base-labile linkages

Polymers with acid/base-labile linkages in their backbone are able to respond to environmental pH modifications. Their response to pH variations is made throughout the cleavage of the linkage and its degradation.¹⁶ For instance, a pH decrease is able to trigger the reversible cleavage of acid-labile covalent bonds (such as hydrazone), causing the hydrolysis/degradation of polymer chains or a dissociation of polymer aggregates.⁵¹ Polymers with acid-labile linkages are most frequently used because they are recommended in drug delivery for the design of anticancer drug carriers for tumor targeting. The most common acid-labile linkages used for this purpose are hydrazone, acetal, ketal, and boronate ester.^{33,52} The linkages structure, degradation mechanism, and byproducts after cleavage are presented in Figure 6.

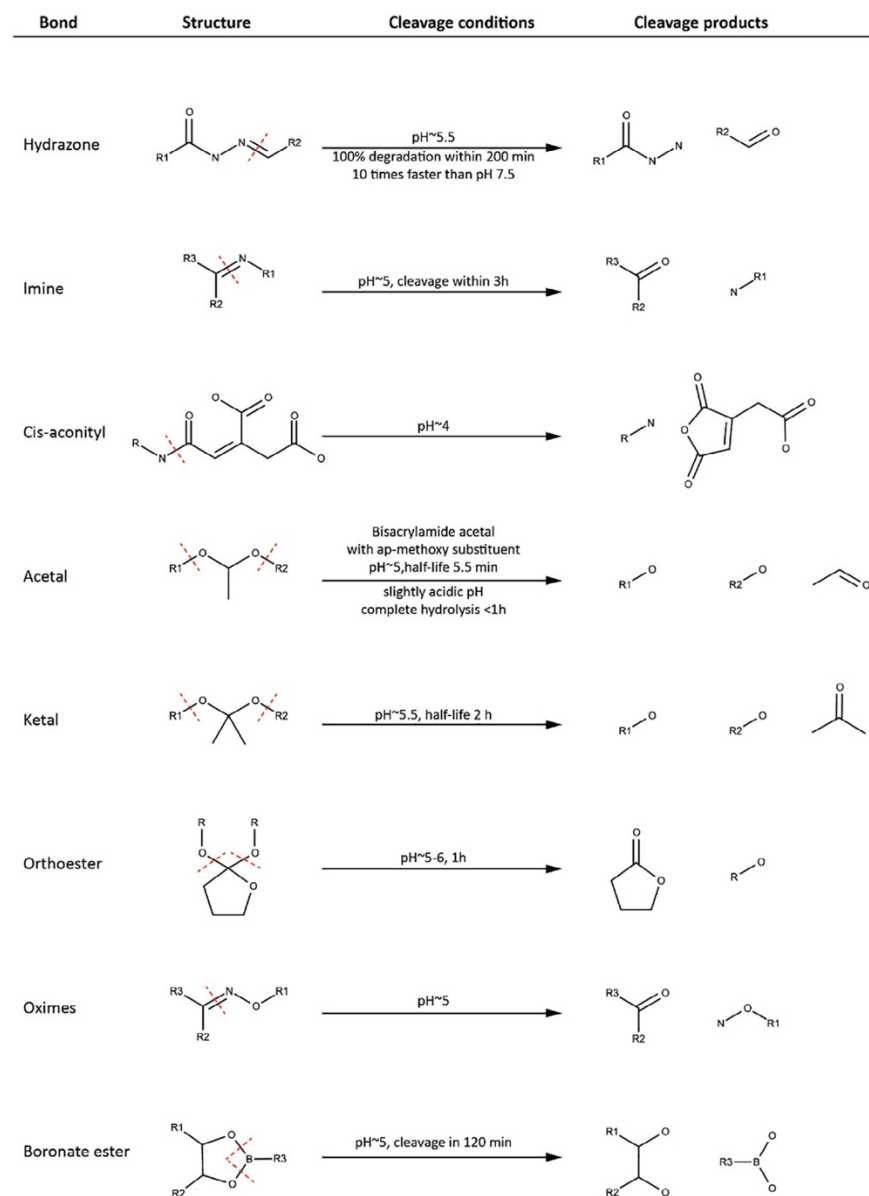


FIG 6 Summary of commonly used acid-labile linkage. Adapted from References 16, 27, and 53 to 56

4.2 Structure-based classification

PRPs present different architectures. They exhibit linear (homopolymers, di, ter, multiblock copolymers and organic/inorganic hybrid polymers), nonlinear branched (branched or hyperbranched polymers), or network structures.

Different architectures found in the literature are shown in Figure 7. The most common pH-responsive polymer structures are linear homopolymers, amphiphilic, and double hydrophilic block copolymers which form micelles or vesicles, star, branched, and hyperbranched polymers, polymer brushes, dendrimers, nanogels, micro-gels, and hydrogels (macro-gels).¹¹

4.2.1 pH-responsive linear block copolymers

pH-responsive linear polymers are homopolymers, random copolymers, as well as amphiphilic and double hydrophilic block copolymers. Regarding block copolymers, they are made of two, three, or more segments. Depending on the solubility conditions, these block copolymers may experience self-assembly. Furthermore, the size of the

relative blocks defines whether it will be a micelle, a vesicle, or a combination.^{27,57,58} Micelle configuration is a particular property originating from the association of soluble and insoluble segments of the polymer in certain conditions, which is desired and exploited in the pharmaceutical field for the delivery of active ingredients. In solution, amphiphilic block copolymers may self-assemble into micellar structures, such as spheres, which are used as nanoreactors and stimuli-responsive materials. pH-responsive amphiphilic block copolymers contain a number of ionizable groups in their main chains and pendants; therefore, their domains can be tuned to respond to property changes of the aqueous environment. When the pH value is modified, these groups accept or donate protons in aqueous solution to yield polyelectrolytes, weak polyacids, or weak polybases, depending on their structures and the pH values.^{13,59} Self-assembly micelle morphology is affected by parameters such as temperature, pH, salt and polymer concentrations, solvent type, and the structure/length of blocks.⁶⁰ Thus, different self-assembly structures appear according to the environmental conditions. Amphiphilic and double hydrophilic block copolymer micelles exhibit spherical, flower, worm-like, and vesicle (hollow) arrangements with pH variations.¹¹

4.2.2 pH-responsive star polymers

Star polymers contain several linear chains connected to one central core. pH-responsive star polymers bearing block/arms undergo sharp phase transitions in response to pH changes and form self-assembled micellar structures or undergo a change of the micelle morphology.¹¹ Further, branched polymers including dendritic, highly branched and hyperbranched, and multibranched structures can also be included in the pH-responsive star polymers section. This category of PRPs with promising applications such as drug delivery and advanced coatings⁶¹ differs from the linear analogues of identical molar mass by their compact structure (smaller hydrodynamic volume and radius of gyration) and high concentration of functional terminal groups. This confers them a higher solubility in common solvents, lower solution and melt viscosities, and modified thermal properties.^{62,63}

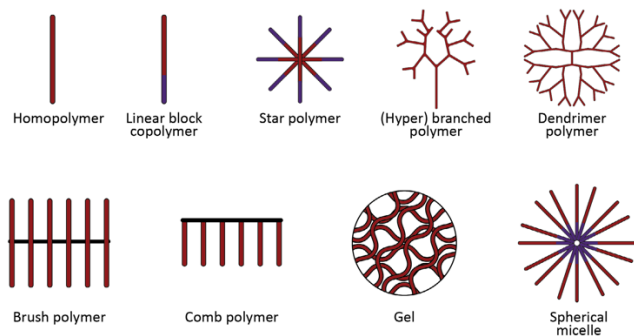


FIG 7 Different architectures of pH-responsive polymers

4.2.3 pH-responsive brush and comb copolymers

pH-responsive brushes and combs refer to materials composed of polymeric chains (hairy-like chains) grafted to a surface or interface.⁶⁴ Polymer brushes are typically anchored to the substrate surface by physisorption or covalent chemical attachment. These materials exhibit a change in their conformation or surface energy or state change state, triggered by pH modifications.⁶⁵

4.2.4 pH-responsive hydrogels

Hydrogels are characterized by hydrophilic polymers that are cross-linked into an insoluble but highly hydrophilic structure.⁶⁶ They are defined as hydrophilic polymer networks and may absorb from 10% to 20% up to thousands of times their dry weight in water. Hydrogels are called “permanent” or “chemical” gels when they are covalently cross-linked.⁶⁷ Hydrogels respond to external stimuli including the surrounding pH conditions.⁶⁸ pH-sensitive hydrogels contain acidic/basic ionizable pendant pH-sensitive groups or acid/base-labile linkage. Chains bearing acidic groups deprotonate at high pH, whereas the basic groups protonate at low pH,⁶⁹ leading to pH-induced swelling/deswelling. The generation of electrostatic repulsive forces from ionization and charge appearance on polymer chains results in the pH-dependent swelling and deswelling process as water is either absorbed or expelled from the hydrogel network.⁷⁰ Anionic hydrogel networks contain pendant groups that are ionized in solutions at a pH greater than their acid dissociation constant (pKa). Therefore, the hydrogel swells at $\text{pH} > \text{pKa}$ because of the large osmotic pressure generated by the presence of ions. Conversely, cationic pendant groups are ionized at a pH less than their pKa and the corresponding hydrogel network is, therefore, swollen at $\text{pH} < \text{pKa}$.⁶⁶

5 MULTI-STIMULI-RESPONSIVE POLYMERS

PRPs have been extensively studied and represent one of the most explored and used stimuli-responsive polymers. pH-responsiveness associated with one, two, or more stimuli have been found interesting to develop because the resulting materials mimic what is currently found in Nature. Most of the multi-stimuli-responsive systems were built on the basis of linear block copolymers due to their easy synthesis. Nonlinear copolymers with different stimuli-responsive behaviors may, however, be found.⁷¹ Multi-stimuli-responsive materials are created with covalently or physically bonded segments sensitive to different stimuli.⁶

5.1 Dual-stimuli-responsive polymers (pH dual- stimuli-responsive polymers)

Dual-responsive polymers combine two responsive functions. The focus is on pH-, dual stimuli-responsive polymers, the second responsiveness being associated with temperature, redox, light, magnetic field, or glucose.

5.1.1 pH,temperature dual-responsive polymers

The main characteristics of temperature-responsive polymers are the presence of a critical solution temperature (T_{CST}) and intermolecular interactions in an aqueous medium. At T_{CST} , the temperature- responsive polymers and hydrogels exhibit a volume phase transition associated with a sudden and drastic change in the solvation state. Based on this, two categories of thermoresponsive polymers are distinguished: lower critical solution temperature (LCST) and upper critical solution temperature (UCST).^{10,72,73} Polymers that become insoluble upon heating, exhibit phase transition at LCST, the lowest temperature of the phase separation curve on the concentration- temperature diagram. Oppositely, polymers becoming soluble upon heating exhibit phase transition at UCST.¹⁰ Under the transition temperature, which is also known as cloud point (T_{CP}), polymer chains are hydrated, resulting in a clear solution. Raising the temperature to higher than the clouding temperature leads to hydrophobic collapse, polymeric chains aggregation, release of solvation water molecules, and finally to a cloudy solution.

Most applications of temperature-responsive polymers are related to LCST-based polymer systems. Moreover, intermolecular interactions causing hydrogel shrinkage, micelle aggregation, or physical cross-links are of two types: hydrogen bonding and hydrophobic interactions.

They govern reversible swelling/deswelling of hydrogels around a critical temperature.¹⁷ pH and temperature-responsive polymers are probably the most studied among multi-responsive polymers.^{74,75} This is due in particular to their possible multitude applications.¹⁷ Poly (2-dimethylamino)ethylmethacrylate (PDMA), a pH-sensitive homo- polymer, was found to exhibit temperature responsiveness in alkaline media.⁷⁶ Moreover, this type of dual-sensitive polymers is obtained by the combination of a temperature-responsive block, such as poly (N-isopropylacrylamide) (PNIPAM), poly(N-vinylcaprolactam) (PNVCL), or poly(N,N-diethyl acrylamide) (PDEAm), with a pH-responsive block, such as poly(acrylic acid) (PAAc), poly(methacrylic acid) (PMAAc), or poly(2-N-dimethyl amino ethyl methacrylate) (PDMA).⁷⁷

Jiang et al reported the synthesis of a dual-stimuli-responsive hydrophilic graft copolymer system: poly(acrylic acid)-g-poly(N- vinylcaprolactam) (PAAc-g-PNVCL) based on the addition of a pH- sensitive moiety represented by PAAc and the thermo-sensitive one represented by poly(N- vinylcaprolactam) (PNVCL).⁷¹ They showed through their study the capacity of the prepared system to synergistically respond to changes in pH and temperature.⁷¹ Monodisperse dual temperature/pH-sensitive nanoparticles have been prepared by Song et al by distillation-precipitation polymerization using acrylic acid (AAc) and N-Isopropyl acrylamide (NIPAM) as monomers.⁷⁸ Yamazaki et al⁷⁹ synthesized functional liposomes modified with methacrylate- based poly(MD-co-MAA-co-LT) copolymers. The resulting copolymer's water solubility changes in response to both pH and temperature.

5.1.2 pH,redox dual-responsive polymers

Polymeric materials exhibiting pH and redox responsiveness have been reported.^{80,81} They are basically prepared by incorporating responsive units such as disulfides, diselenides, dithienylethenes, or ditellurium bonds into a pH-responsive polymer.^{77,82} In biological systems, the introduction of redox systems relies on the significantly different redox states in the circulation/extracellular fluids and intracellular compartments.⁸² pH- and redox-responsive polymeric materials find great interest because tumor tissues show low pH, high temperature, and highly reductive environments [higher glutathione (GSH) concentration] in comparison with normal tissues.⁸³ GSH is a reducing tripeptide with a thiol group (Figure 8), whose concentration in cancer cells is 100- to 1000-fold higher than in blood and 100-fold higher than the extracellular level in normal tissues.⁸⁵

High levels of GSH in tumor cells are known to protect the cancerous cells by conferring resistance to chemotherapeutic drugs. The ability of the GSH molecules to undergo redox reactions enables them to trigger smart redox-responsive drug delivery systems for site- specific and controlled delivery of their payloads to intracellular targets.⁸⁴

For instance, John et al produced a series of pH, redox dual-stimuli-responsive copolymers based on pH-responsive poly(L-histidine) (PHIS) block and a biocompatible phospholipid analogue poly (2-methacryloyloxyethyl phosphorylcholine) (PMPC) block⁸⁶ or associated with a polyurethane (PU) middle block.⁸⁷ In both cases, the pH- sensitive block(s) were connected by a redox-responsive disulfide linker. The dual-stimuli-responsive behavior of resulting materials was examined and clearly established using UV-vis spectrophotometry and fluorescence spectroscopy. The elaborated systems were efficient for intracellular tumor-triggered drug delivery and are good candidates for cancer therapy.

5.1.3 pH,light dual-responsive polymers

Photoresponsive polymers are macromolecules characterized by changes in their properties due to light-induced isomerization or cleavage of specific functional groups along the backbone or the side chains.⁸⁸ Light-sensitive polymers are built by incorporating photo- chromic groups into polymer chains able to transfer hydrophobic- hydrophilic balance during photoreaction upon illuminating with light. Several photosensitive moieties, such as o-nitrobenzyl esters, may undergo an irreversible transformation during irradiation, whereas others can react reversibly (eg, azobenzenes).⁸⁹ Responses to light stimulus consist of changes in the refractive index, dielectric constant, redox potential, geometrical structure, or luminescence properties.⁷⁷ At a macroscopic level, light exposure leads to shape deformation (bending, contraction, swimming rotation, and ciliary motion) or changes in physical properties such as viscosity, hydrophilicity, and permeability.⁹⁰ Phototriggered polymers are of increasing interest for the elaboration of innovative drug delivery systems able to control drug dosage.⁹¹ pH and light dual-stimuli degradable triblock copolymer micelles were prepared by Jin et al.⁹² The resulting amphiphilic triblock copolymer poly(ethylene glycol)-b-poly(ethanedithiol- o-nitrobenzyl)-b-poly(ethylene glycol) (PEG-b-PEDNB-b-PEG) was designed to possess two stimuli-responsive functionalities positioned repeatedly in the main chain of the hydrophobic PEDNB block. These responsive functionalities include light-cleavable o-nitrobenzyl link- ages and acid-labile β -thiopropionate linkages. The functions provoke self-assembly into micelles of the material with respect to environmental conditions. Micellization behavior of the prepared copolymer in aqueous solution regulated by light and pH stimuli was also demonstrated by Meng et al,⁹³ Zhou et al,⁹⁴ and Xia et al.⁹⁵

5.1.4 | pH,magnetic dual-responsive polymers

Electric or magnetic field-responsive polymers have been investigated as a form of hydrogels to have swelling, shrinking, or bending behavior in response to external fields.¹⁷ Magnetic-responsive systems employ most often superparamagnetic iron oxide magnetite (Fe₃O₄) or maghemite (γ-Fe₂O₃)^{96,97} or “soft” metallic iron but also “hard” magnetic materials such as Co, Ni, FeN, FePt, or FePd in the form of nanoparticles, magnetoliposomes, or porous metallic nanocapsules incorporated into the formulation.^{98,99} The formed particles generally undergo a reversible physical shape or size distortion under an externally applied magnetic field. Magnetic moment of these “small” mag-nets, much larger than those of molecular magnets, allows them to be sensitive to a weak stimulus (static or alternating magnetic field) with a significant effect (movement, heat generation, magnetic, or optical signal).⁹⁸

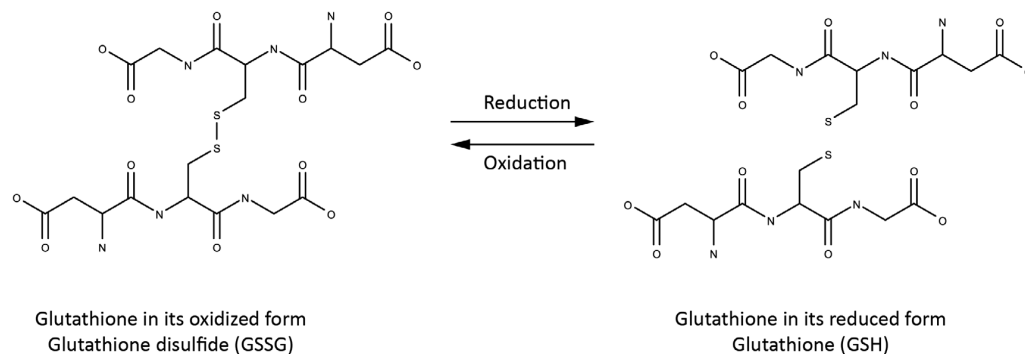


FIG 8 Chemical structure of GSH.⁸⁴ With Copyright permission

Magnetic-responsive polymers constitute a topic of intense research due to their potential applications in biomedical, coatings, microfluidics, and microelectronics fields.⁹⁸ The development of stimuli-responsive polymer-based multifunctional nanostructures helps in preparing functional magnetic particles with pH-responsive copolymers and promising prospects in targeted nanocarrier drug delivery, in the biomedical field with applications such as heat hubs in magnetic hyperthermia, or as contrast agents in magnetic resonance imaging.^{93,100,101}

5.1.5 pH,glucose dual-responsive polymers

Glucose-responsive polymer systems were introduced for the controlled release of insulin. To address the blood glucose concentration issue, pH,glucose dual-stimuli responsiveness was found to be an interesting alternative. Traitel et al.¹⁰² reported a glucose-responsive controlled insulin release system based on the hydrogel poly (2-hydroxyethyl methacrylate-co-N,N-dimethyl amino ethyl methacrylate), also called poly (HEMA-co-DMAEMA), with entrapped glucose oxidase, catalase, and insulin. Exposure of the elaborated system to physiological fluids provokes glucose diffusion into the hydrogel and glucose oxidase catalyzes the glucose conversion to gluconic acid, causing swelling of the pH-sensitive hydrogel and subsequently increases insulin release. The higher the glucose concentration in the medium, the higher and faster the swelling and release rates.

The introduction of a glucose-sensitive poly[4-vinylphenylboronic acid-co-2-(dimethyl amino) ethyl acrylate] (PVPBA-co-DMAEA) gel shell onto Ag nanoparticles makes the polymer-bound responsive to glucose with high sensitivity and selectivity at physiological pH based on inorganic/organic core-shell structured hybrid nanogels.¹⁰³ A glucose- and pH-responsive release system based on polymeric network capped mesoporous silica nanoparticles has also been developed by Tan et al.¹⁰⁴ Poly(acrylic acid) (PAAc) brush on silica nanoparticles was obtained through surface-initiated ATRP followed by glycosylation to obtain poly(acrylic acid)-N-acryloyl glucosamine [P(AAc-AGA)]. Mesoporous channel opening/closure was then linked with glucose concentration and variation of pH. Another pH, glucose-sensitive hydrogel was prepared using photopolymerization by Yin et al.¹⁰⁵ based on concanavalin A (a saccharide-binding lectin from jack bean) and the cationic groups of N-[2-(dimethyl amino) ethyl methacrylamide].

Although they are less encountered in literature, other systems such as pH, enzyme¹⁰⁶; pH, electrical¹⁰⁷; pH, H₂O₂¹⁰⁸; pH, ultrasound¹⁰⁹ and pH, UV¹¹⁰ dual-responsive polymeric systems have been developed for specific applications, which are worth mentioning.

5.2 Triple-stimuli-responsive polymers (pH, triple-stimuli-responsive polymers

As for dual-stimuli-responsive polymeric systems, triple-responsive systems able to respond to three different types of stimuli are gaining more attention and have been prepared and reported in the literature.

5.2.1 pH,thermo,light triple-stimuli-responsive polymers

Li et al.¹¹¹ produced the pH,thermo,light triple-stimuli-responsive amphiphilic polymer, poly(ethylene glycol)-b-poly(dimethyl amino ethyl methacrylate)@2-diazo-1,2-naphthoquinone (PEG-PDMA@DNQ) via ATRP and quaternization reaction. They found that this amphiphilic polymer could self-assemble into spherical assemblies with hydrophobic near-infrared/ultraviolet (NIR/UV) light and base responsive DNQ moieties as the core and hydrophilic PEG and pH, temperature-responsive PDMA as the corona. A pH-, photo-, and temperature-responsive copolymer synthesized through spiropyran functionalization has also been reported by Jiang et al.^{112,113} Transmission electron microscopy (TEM) and dynamic light scattering (DLS) analyses revealed morphological changes of the self-assemblies under the UV light and temperature stimuli. These triple-responsive polymeric systems have been studied for the loading and the controlled release of encapsulated molecules in response to combined stimulation. Tests realized and reported with a hydrophobic fluorescent dye (coumarin) have proven NIR/UV light and pH-responsive polymer assemblies as promising to be used as nanocarriers for precisely controlled release because it was shown that the release efficiency could be enhanced dramatically under combined stimulation.

5.2.2 pH,thermo,glucose triple-stimuli-responsive polymers

Another well-reported triple-responsive polymeric material is based on pH-, thermo-, and glucose triple responsiveness.^{114,115} In most cases, triple-responsive block copolymers combining pH-, thermo-, and glucose-responsiveness are synthesized by incorporating boronic acid or a diol functionality along the backbone of a thermo-responsive polymer using reversible addition fragmentation chain transfer copolymerization.^{116,117} Hydrogels with temperature-, pH-, and glucose-responsive properties made of N-isopropylacrylamide (NIPAM) and 5-methacrylamido-1,2-benzoxaborole (MAAm-Bo),¹¹⁴ (2-dimethyl amino) ethyl methacrylate (DMAEMA) and 3-acrylamidephenylboronic acid (AAPBA),¹¹⁵ or poly(vinyl alcohol)-b-poly(N-vinylcaprolactam) (PVOH-b- PNVCL)¹¹⁸ have attracted attention for incorporation/conjugation as well as transport and release of various materials such as proteins, dyes, and drug molecules. Thereby, they constitute promising new theranostic platforms because chemotherapeutic moieties and also diagnostic agents can be incorporated together via reversible cross-linking in these hydrogels.¹¹⁸ Moreover, experimental results suggested that such multi- responsive hydrogels are highly attractive in terms of self-regulated drug delivery, as well as in other applications such as actuators, regulators, and separation systems with sensitivity to glycol.¹¹⁵

5.2.3 pH,thermo,salt triple-stimuli-responsive polymers

Bütün et al^{119,120} prepared a series of cationic diblock copolymers that exhibit reversible pH-, salt-, and temperature-induced micellization in aqueous media from selective quaternization or betainization of 2-(dimethyl amino) ethyl methacrylate residues using, respectively, methyl iodide and benzyl chloride or 1,3-propane sultone under mild conditions. Other examples of triple-stimuli-responsive polymeric materials are pH,thermo,ionic strength triple-stimuli polymers¹²¹; pH,thermo, CO₂ triple-stimuli polymers^{122,123}; pH,photo,redox triple-stimuli polymers¹²⁴; and pH,glucose,redox triple-stimuli polymers.¹²⁵

Moreover, there are polymeric systems responsive to more than three stimuli. Tuncer et al¹²⁶ prepared microgels of a water-soluble monomer 2-(N-morpholino) ethyl methacrylate via emulsion polymerization, which exhibited a multi-responsive behavior by responding to solution pH, temperature, ionic strength, type of dispersing media, and magnetic field. Cao et al¹²⁷ reported the synthesis of a quadruple- stimuli-responsive block copolymer sensitive to pH, temperature, light, and reducing agents, as demonstrated by TEM and DLS analysis. The amphiphilic diblock copolymer poly(2-nitrobenzyl methacrylate)- SS-poly(dimethyl amino ethyl methacrylate) (PNBM-SS-PDMA) was synthesized via two steps of ATRP. The system was made of a light- responsive hydrophobic PNBM core, a pH- and temperature- responsive hydrophilic PDMA corona, and a redox-sensitive disulfide linker. Guragain et al¹²⁸ also reported the synthesis of a quadruple- stimuli-responsive polymeric system. Poly[N-isopropylacrylamide-b- sodium-2-(acrylamido)-2-methylpropane sulfonate] tagged with a spiropyran dimer at the poly(N-isopropylacrylamide) end (SP2-b- NIPAM154-b-AMPS148) was synthesized by RAFT polymerization, which exhibited response to light, temperature, metal ion concentration, and pH. Thermo-responsiveness was conferred to the overall block copolymer by the NIPAM154 block, metal ion responsiveness by AMPS148 block, and light- and thermo-responsiveness by the photochromic spiropyran moiety. These quadruple-stimuli-responsive block copolymer micelles are expected to open up new applications in a variety of fields.

6 APPLICATION OF pH-RESPONSIVE POLYMERS

In biological systems, cellular functions are regulated by bio- macromolecules sensitive to changes within the local physiological environment.¹²⁹ Synthetic polymers are good tools as biomimetic agents, as they are able to adapt and react to biological complex environments.^{6,130} As useful polymers in medicine, pH-sensitive polymers are largely employed. This is mainly due to the pH variation along the gastrointestinal (GI) tract of the human body. In fact, pH varies from very acidic to physiological values in the human body¹³¹ (Table 1). pH variations are also observed in other body sites, for example, cellular compartments such as vagina, extracellular and endosomal/lysosomal microenvironments, or even skin.^{66,133,134} Moreover, the pH difference between normal and cancer tissues is exploited in the therapeutic solutions of the disease.¹³⁵ Indeed, as a result of the active metabolism of tumor cells, the tumor microenvironment is highly acidic compared to normal tissues.¹³⁶ Thus, PRPs are largely used in drug or gene delivery to target some specific organs or sites in the human body and to attack tumor cells in cancer treatment.

In the design of pH-responsive drug delivery systems, two main approaches are adopted. Organ- or site-based approach is fulfilled by using polymers that contain ionizable groups. These ionizable groups, by undergoing conformational, solubility changes, or by transition between swelling/deswelling state, are able to achieve a specific and controlled drug release in response to local pH variations.^{11,137} The second approach consists of linking a pH-responsive polymer with a drug through acid/base-labile sensitive bonds. In response to pH variations, the linkages are able to break up, inducing the release of the bioactive molecule from the polymer backbone.^{137,138} pH-sensitive polymer-based drug delivery systems have been formulated as nanoparticles, nanoaggregates, nanogels, nanocapsules, core-shell particles, micelles, liposomes, polymersomes, hydrogels, layer-by-layer films, and bioconjugates.¹³⁹

6.1 Enteric coating

With the development of colon delivery preparations in the early 1990s till now, enteric-coated delivery systems have raised great interest by exploiting differences in gastrointestinal fluids' pH. pH- sensitive Eudragit polymers based on methacrylate and methyl meth- acrylate polymers are widely used as enteric coating polymers. They are great tools for oral drug delivery because they show the capacity to improve drug stability and ensure controlled and sustainable release.^{140,141} For instance, polymethacrylates with pH-dependent dissolution^{142,143} ranging from 6.0 to 7.0 are mainly used as coating agents aimed at protecting the drug core from the severe gastric and intestinal environments, as illustrated in the scheme presented in Figure 9. Enteric coating is especially useful in anti-inflammatory drug administration in the treatment of diseases like ulcerative colitis and Crohn's disease (inflammatory bowel diseases).¹⁴⁴ Commercially, pharmaceutical formulations already exist and are produced by Evonik Industries.¹⁴⁵

Tissue or cellular compartment	pH range or value
Saliva	6.0-7.0
Blood/plasma	7.35-7.45
Stomach	1.0-3.0
Pancreatic fluid	8.0-8.3
Bile	7.8
Duodenum	4.8-8.2
Colon	7.0-7.5
Early endosome	6.0-6.5
Late endosome	5.0-6.0
Lysosome	4.5-5.0
Golgi	6.4
Vagina	3.8-4.5
Inflamed tissue/wound	3.8-4.5
Tumor, extracellular	7.2-6.5

TABLE 1 pH values along the gastrointestinal tract and in various tissues and cellular compartments^{10,66,132}

In terms of formulation, pH-sensitive cationic polymers are used to mask drug taste (having unpleasant qualities such as bitterness, sourness, saltiness, or causing oral numbness). They are also used as drug carriers targeting the stomach by responding to its low pH.^{132,146} In contrast, pH-sensitive anionic polymers responsive to intestinal high pH are used for preventing gastric degradation of drug, colon drug delivery, and achieving high bioavailability of weak basic drugs.¹³²

Table 2 sums up examples of pH-responsive polymer formulations used as enteric coating materials for specific drug delivery. Among them, antihistaminic drugs designed for enteric delivery against asthma are composed of theophylline alone or combined with another drug.¹⁴⁷⁻¹⁵¹ Salbutamol, one of the well-known and largely used antihistaminic drug, was coated with ethyl cellulose as inner layer and Eudragit S100 (anionic copolymer based on methacrylic acid and methyl methacrylate) as outer enteric coating polymer.¹⁵² This formulation showed a very good disintegration and dissolution profile at intestinal pH and did not dissolve at gastric pH, releasing the drug immediately in the alkaline medium. An optimized enteric-coated formulation containing 2.5%w/w of Eudragit S100 and 30%w/w of ethyl cellulose exhibited 99.04% of drug release in the intestinal medium. This enteric-coated timed-release formulation with a suitable lag time showed interesting results in the treatment of nocturnal asthma and overcame the issues of conventional forms. Indeed, the chrono-modulated therapeutic system makes possible drug administration around 10.00 p.m. so that after a specified lag time the drug is rapidly available in the early morning hours to treat nighttime exacerbation of the asthma condition.

Tawfeek et al investigated the delivery of the model anti-inflammatory drug indomethacin.¹⁷² They prepared encapsulated indomethacin within poly(glycerol-adipate-co-pentadecalactone) (PGA-co-PDL) microparticles coated with Eudragit L100-55 (anionic copolymer based on methacrylic acid and ethyl acrylate) at different ratios using an oil/water single emulsion/solvent evaporation and spray drying techniques. *in vitro* drug release studies suggested the possibility of anti-inflammatory colon drugs targeting through fast disintegrating tablets with a sustained release profile specifically at the high gastrointestinal pH. Other anti-inflammatory agents and their enteric coating polymeric systems are reported in Table 2.

Oral delivery of insulin has been boosted with the development of PRPs and enteric coating materials.^{153,162-170} Recently, Liu et al¹⁷⁰ reported a novel type of pH- and amylase-responsive microgels prepared via aqueous dispersion copolymerization of acrylate-grafted-carboxymethyl starch (CMS-g-AA) and 2-isobutyl-acrylic acid (iBAA) as an insulin drug carrier for oral administration. The relative pharmacological availability of the insulin-loaded microgels was enhanced 2338 times compared to free-form insulin solution through oral route.

6.2 Cancer treatment

Different pH-responsive polymeric systems have been reported as potential and valuable carriers in the building of cancer diagnostics and targeted therapies. In these systems, drug release is specifically triggered by the acidic tumor environment.¹⁷³ Ionizable PRPs are widely formulated as drug delivery systems in the treatment of cancer.^{134,174,175} In order to overcome the drawbacks associated with anticancer agents such as, for example, oxaliplatin (OX), which exhibits fast degradation/deactivation in the bloodstream, lack of tumor selectivity, and low bioavailability, pH-responsive drug delivery systems have been designed.¹⁷⁶

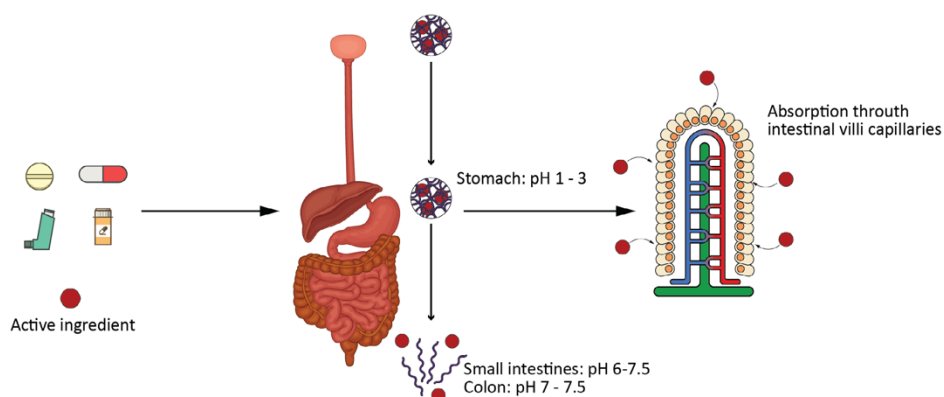


FIG 9 Illustration of drug carried throughout GI tract by pH-responsive polymeric matrix. The drug is protected against the acidic pH of stomach and released in colon alkaline conditions after solubilization of the carrier. It is further absorbed to blood circulation through intestinal villi capillaries

Drug category (Disease)	Active pharmaceutical ingredients	pH-responsive material	Types of formulation	References
Antihistaminic (Asthma)	Theophylline	Eudragit L100 and E100/ Gelatin	Microcapsules, hydrogel	147
		Eudragit S100/ calcium pectinate	Microspheres	148
		Eudragit RL100 and S100/ Hydroxy propyl cellulose	Coated pellets	149
	Roxithromycin-theophylline	Methylcellulose/ Sodium alginate	Microcapsules	150
	Piroxicam-theophylline	Eudragit S100	Microcapsules	151
	Salbutamol	Eudragit S100/Ethyl cellulose Hydroxypropyl methylcellulose	Tablets	152,153
Anti-inflammatory	Ibuprofen	Cellulose acetate phthalate	Tablets	154
	Loxoprofen sodium	Cellulose acetate phthalate-co-poly(methacrylic acid)	Tablets	155
	Diclofenac potassium/sodium	Sodium Alginate/acrylic acid	Hydrogel	156
		Eudragit L100/PLGA Eudragit L00 and E100	Nanoparticles Tablets	157 158
	Naproxen	Eudragit L100 Hydroxypolymethylcellulose	Microspheres	159
	Omeprazole	Eudragit L100-55 poly-acrylic resin	Coated pellets	160
	Enrofloxacin (ENR), known as ethyl ciprofloxacin	Ethyl cellulose/polyacrylic resin	Solid lipid nanoparticles (SLN's)	161
Insulin (Diabetes)	Insulin	Chitosan	Nanoparticles	153,162
		Hydroxypropyl methylcellulose phthalate	Microcapsules, Capsules	163,164
		Eudragit (L30D, L100-55, FS30D, S100, L100)	Microparticles, nanoparticles, microspheres, nanoemulsion, vesicle	165-169
		Poly(2-isobutyl-acrylic acid)	Microgel	170
		Methacrylic acid (MAAc), N,N-dimethyl amino ethyl methacrylate (DMAEMA)	Hydrogel	171

TABLE 2 pH-responsive polymer formulations used as enteric coating materials for specific drug delivery

Promising strategies for pH-controlled drug release have been developed, such as the use of acid-sensitive chemical bonds or acid-labile linkers to conjugate drugs to the nanocarrier.²⁷ Drug delivery systems based on pH-sensitive polymers with imidazole groups, poly (β -amino ester), chemical linkages such as hydrazone, acetal, ortho ester, and vinyl ester, pH-sensitive cell-penetrating peptides, and cationic polymers undergoing pH-dependent protonation have been studied to exploit the pH gradient along the endocytic pathway for intracellular drug delivery.¹³² PRPs with acid-labile chemical bonds are tuned to remain stable at physiological pH. These acid-labile bonds are located within the polymer structure, either in the back-bone (including the junctions of block copolymers) or in the side chains. The acidic environment of lysosomes, endosomes, or tumor tissues leads to destabilization and destruction of the acid-labile bonds, inducing rapid drug release. The other strategy for pH-sensitive drug release based on acid-labile bonds is to use acid-labile linkers to conjugate drugs covalently to carrier molecules or to the surface of nanostructures, forming prodrugs that are inactive until the linker is hydrolyzed.^{136,177}

In cancer diagnostics or surgery, it is of prime importance to differentiate tumors from adjacent normal tissues.¹⁶ pH-sensitive polymers have been used in the build-up of tumor diagnostic systems. pH-responsive polymeric micelles have been identified as contrast agents for magnetic resonance imaging (MRI) to target and simultaneously image cancerous tissues.¹⁷⁸ The mechanism is based on the Fe₃O₄-loaded diblock copolymer poly(ethylene glycol)-poly(β -amino ester) (PEG-PAE), which maintains the micellar state without apparent precipitation. However, at pH \leq 6.8, the polymeric micelles are easily dissolved, as a result of the ionization of the PAE tertiary amine moieties, leading to the release and aggregation of Fe₃O₄ nanoparticles. Their gradual accumulation in acidic areas improves the accuracy of signal measurement. PEG-PAE polymeric micelle systems have also been used in association with a fluorescent dye tetramethylrhodamine isothiocyanate (TRITC).¹⁷⁹ The dye showed a rapid release in weakly acidic aqueous media (pH value of 6.4). pH-sensitive polymeric systems with 10 wt% of TRITC could deliver substantially more fluorescent dyes to the target tumor tissue in human-breast-tumor-bearing mice, compared to the control polymeric micelles of PEG-poly(L-lactic acid) (PEG-PLA). In order to overcome the limitations of small molecules as MRI contrast agents (CAa), Kim et al developed a cancer-recognizable MRI CA using PRPs.¹⁸⁰ The cancer-recognizable contrast agents (CR-CAs) with a pH-sensitivity feature were self-assembled based on well-defined amphiphilic block copolymers, consisting of methoxy poly(ethylene glycol)-b-poly(L-histidine) (PEG-b-PHIS) and methoxy poly(ethylene glycol)-b-poly(L-lactic acid)-diethylene-tri-amino-penta-acetic acid dianhydride-gadolinium chelate (PEG-PLA-DTPA-Gd). In acidic tumoral environments (pH value below 6.5), spherical CR-CAs with a uniform size of 40 nm at a physiological pH of 7.4 were destabilized as a result of the protonation of the imidazole groups of PHIS blocks. This protonation caused their separation into positively charged water-soluble polymers leading to a highly effective T1 MR contrast enhancement in the tumor region. This enabled the detection of small tumors of 3 mm³ in vivo at 1.5 T within a few minutes. pH-responsive polymeric fluorescent nanoprobe are able to nonlinearly amplify tumor microenvironmental signals. They are useful in the identification of tumor tissue of histological type, driver mutation, and detection of acute treatment responses faster than conventional imaging approaches.^{181,182}

Tumors' poor selectivity and multidrug resistance are barriers associated with cancer treatment by chemotherapy. These drawbacks are addressed by pH-sensitive polymeric delivery systems targeting the acidic extracellular microenvironment and intracellular organelles of solid tumors.¹⁸³ The polymeric nanocarriers could avoid the use of surfactants and promote drug accumulation at the tumor sites by enhanced permeability and retention (EPR) effects.¹⁸⁴ Figure 10 presents an illustration of the microenvironment-based cancer therapy strategy.

Doxorubicin (DOX) is one of the most effective treatments in many cancer types, with restrictions due to its pharmacokinetics.¹⁸⁵ To overcome limitations of classical chemotherapy and toxicity associated with DOX, different strategies are reported as alternatives. Among them, targeted drug delivery has shown interesting results.^{186,187} Feng et al studied a polyelectrolyte complex composed of chitosan (Ch) and *o*-carboxymethyl chitosan (CMCS) as a pH-responsive carrier for oral delivery of DOX.¹⁸⁸ They found that DOX's absorption throughout the small intestine, especially in jejunum and ileum, was enhanced. DOX's tumor targeting efficiency and therapeutic efficacy have been proved to be enhanced through pH-sensitive polymeric micelle systems or through polymer-drug conjugation via acid-labile linkages.¹⁸⁹⁻¹⁹⁴

One of the innovative approaches in the field of cancer treatment is the association of pH-sensitive polymers with magnetic nanoparticles.¹⁹⁵⁻¹⁹⁷ Chitosan-coated magnetic nanoparticles (Ch MNPs) provided targeting of DOX to the tumor site under a magnetic field.¹⁹⁵ In addition to the targeting enhancement, Montha et al observed higher anticancer activity and therapeutic effect.¹⁹⁷ They synthesized superparamagnetic (Mn, Zn) Fe₂O₄ nanoparticles encapsulated into PLGA-coated chitosan. The releasing efficiencies of DOX by the nanocarriers were found to depend on pH. At higher concentration such as 250 g/mL, DOXPLGA@Ch@Mn_{0.9}Zn_{0.1}Fe₂O₄ showed a better anticancer activity to HeLa cells than that of free DOX.

Other anticancer agents, such as Paclitaxel, Camptothacin, Tamoxifen, and Cisplatin, have also been referenced in literature and some examples are presented with their polymeric carriers, chemical composition, and carrier structure in Table 3.

6.3 Gene delivery

In order to deliver nucleic acids for gene therapy, obstacles such as low stability in blood, poor cellular uptake, inefficient endosomal escape, and disassembly in the cytoplasm have to be overcome. This may be addressed by using extracellular and intracellular stimuli including pH, redox potential, temperature, and enzyme, based on the scheme illustrated in Figure 11. Moreover, it is known that cationic polymers are useful in complexing electrostatically negatively charged nucleic acids such as plasmid DNA (pDNA) and small interfering RNA (siRNA). In addition, the significantly reduced size and net cationic surface charge of the resulting polyplexes facilitate cellular internalization.²¹³ Cationic tertiary amine methacrylate-based polymers able to electrostatically interact with DNA with slight cytotoxicity are used to traffic DNA to cells because they show potential as gene transfer agents.¹¹

Polyethylenimine (PEI), a cationic polymer, is one of the most widely studied gene delivery polymers. This is because of PEI's high transfection efficiency in association with what is known as the proton sponge effect.²¹⁴ PEI with a molecular weight of 25 kDa (named PEI25k), has been identified as standard gene carrier with recognized superiority over other polycations such as poly(L-lysine) due to its high charge density and chain flexibility.²¹⁵ Transfection efficacy and cytotoxicity of PEI have been linked to its molecular weight, suggesting that branched PEI with higher molecular weight shows high transfection and cytotoxicity.²¹⁶ In order to address drawbacks such as cytotoxicity and possible particle aggregation leading to large particles and poor diffusion in the vascular system, core-shell nanoparticles made of PEI and PMMA,²¹⁷ conjugated PEI,^{218,219} dendritic polyglycerol dPG-PEI nanogel platform,²²⁰ or degradable PEIs with acid-labile imine linkers and glutaraldehyde²¹⁶ were synthesized. Both approaches demonstrated the reduction of PEI's toxicity and their possible application to nonviral gene delivery.

Cationic tertiary amine methacrylate-based block copolymers may also efficiently condense negatively charged biomolecules via electrostatic interactions with poly[(2-diethylamino)ethyl methacrylate] (PDEA), considered as one of the most promising nonviral vectors for gene delivery due to its proton sponge ability.^{221,222} Once again, reduction in cytotoxicity was studied for the delivery of nucleic acids. Thus, poly(ethylene glycol) (PEG) or poly[2-(methacryloyloxy) ethyl phosphorylcholine] (PMPC) has been used in combination with cationic polymeric nonviral vectors.²²³⁻²²⁵ PEG modification of cationic polymers has been highlighted as a useful tool in gene delivery. Indeed, this is due to the fact that the latter provides biocompatibility and charge shielding effect to reduce nonspecific interactions of polyplexes with blood components, prolonged circulation, and low in vivo toxicity.²²⁶

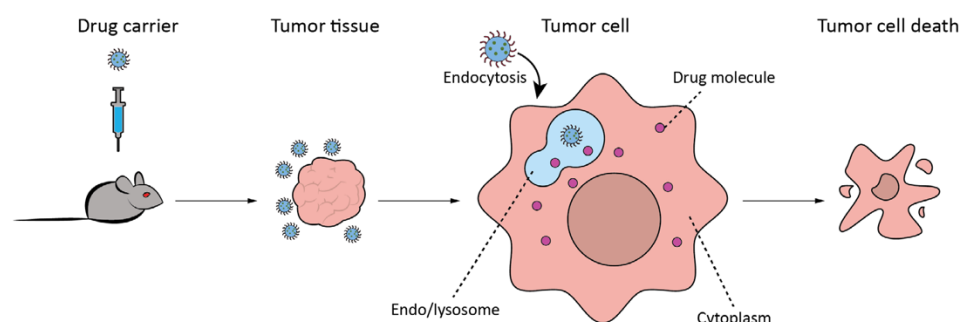


FIG 10 Illustration of pH-responsive polymer-based tumor cell targeting and microenvironment (pH conditions around tumor cells, low pH in endo/lysosome compartments, GSH concentration)-triggered anticancer drug release

Anticancer agent	Polymeric system	Polymeric carrier structure	References
Doxorubicin (DOX)	Chitosan/carboxymethyl chitosan (CS-CMCS)	Nanoparticles	188
	Poly(methacrylic acid) (PMAAc)		198
	PEG-DOX-Cur prodrug, acid-labile Schiff's base linkage		199
	Chitosan (Ch)	Chitosan-coated nanoparticles	magnetic 195
	PLGA-coated chitosan stabilized (Mn, Zn) MNPs		197
	Chitosan Dox-NPs, imine linkage		196
	Poly(L-histidine)	Polymeric micelles	86
	PHEMA- <i>b</i> -PHIS		200
	(HPMA)-hydrazone bonds		190,201
	(HPMA)-benzoic-imine bonds		191
	(PEG-pH-PBLG)-orthoester linkage		192
	Poly(ethylene oxide)- <i>b</i> -poly (methacrylic acid) (PEO- <i>b</i> -PMAAc) copolymer		202
	Poly(ethylene glycol)-poly(lactic acid) (mPEG-PLA), hydrazone linker		203
Poly(ethylene glycol)-poly(2-ethoxytetrahydrofuran-2-yloxyethyl methacrylate) PEG- <i>b</i> -PEYM, ortho ester sidechains		194	
Paclitaxel (PTX)	NK105 (Polyaspartic acid and PEG)	Polymeric micelles	204
	Poly[2-(diisopropylamino) ethyl methacrylate]-poly [2-(methacryloyloxy)ethyl phosphorylcholine] (FA- MPC-DPA)		205
	Poly(ethylene glycol)-poly(N-(acryloyloxy) succinimide-co-butyl methacrylate mPEG-g-p(NAS-co-BMA)		206
Camptothacin (C0)	Poly[2-(N,N-diethylamino)ethyl methacrylate] (PDEA)	Three-layered nanoparticle	207
	Poly(β -amino ester)methyl ether poly(ethylene glycol) (MEPG-PAE)	Polymeric micelles	179
	Poly(methacrylic acid) (PMAAc)	Nanogel	208
Tamixofen	Chitosan	Nanoparticles	209
	Poly[2-(diisopropylamino) ethyl methacrylate]-Poly [2-(methacryloyloxy)ethyl phosphorylcholine] (FA-MPC-DPA)	Polymeric micelles	205
Cisplatin	Methoxy poly(ethylene glycol)-block-poly (glutamic acid) (mPEG- <i>b</i> -PLGA)	Nanoparticles	210
	Poly(<i>n</i> -isopropyl acrylamide-methacrylic acid-hydroxy ethyl methacrylate) (P(NIPAM-MAAc-HEMA))	Nanogel	211
Gambogic acid (GNA)	Poly(acrylic acid)- <i>b</i> -polycaprolactone (PAAc- <i>b</i> -PCL)	Polymeric micelles	212

TABLE 3 pH-responsive polymer formulations used as anticancer drug carriers

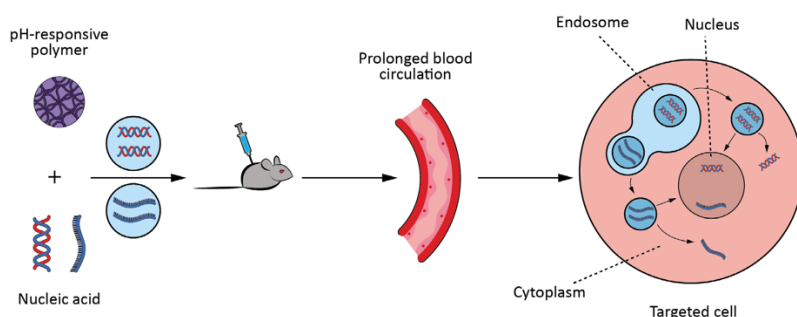


FIG 11 Illustration of pH-responsive-based approach in nonviral gene delivery

6.4 Sensing and actuation

Progress in stimuli-responsive polymer development has led to the tuning of innovative colorimetric detection tools capable of giving rapid readable responses via color changes, detectable with naked eyes. Thus, colorimetric pH sensors have been developed based on PRPs.^{227,228} pH-switchable zwitterionic polymers have been proposed for fast and efficient detection and control of biological (cell or bacteria) adhesion to surfaces²²⁹ and for the detection of gram-positive and gram-negative bacteria based on the ionic complex formation and the distinguishable fluorescence between polymers and bacteria's surfaces when treated with different pH.²³⁰

As mentioned above, PRPs find applications in the diagnosis of tumoral systems. Hence, pH-responsive nanoprobe have been developed to respond to acidic microenvironments and help in, in vivo tumor visualization regardless of the tumor type or even its development stage.²³¹

Moreover, pH-sensitive hydrogels may be prepared for modulated insulin delivery in the treatment of insulin-dependent diabetes mellitus. To address major drawbacks of treatments associated to insulin delivery, such as heaviness of insulin injection and difficulty in controlling insulin dosage,²³² glucose oxidase and insulin-loaded pH-responsive hydrogels present a real alternative, because the release of insulin from this system is governed by the glucose concentration in blood.^{102,233}

Associated with sensing, PRPs may act as actuators based on action-reaction basis.^{56,234,235} On the principle of innovative cancer treatment using pH-sensitive polymers associated to targeting-based magnetic field with magnetic nanoparticles, Li et al proposed a soft microrobot made of a hydrogel bilayer structure of 2-hydroxyethyl methacrylate (HEMA) and poly(ethylene glycol) acrylate (PEGDA) with iron(II, III) oxide particles (Fe_3O_4) fabricated by a conventional photolithography procedure for the delivery of anticancer drug microbeads constituted of polycaprolactone-docetaxel (PCL-DTX).²³⁶ Moreover, on-demand pH-triggered delivery nanocarriers have also been reported based on this system.²³⁷

Interpenetrating network hydrogel bilayers made of poly(N- isopropylacrylamide) (PNIPAM) in the presence of the positively charged polyelectrolyte poly(diallyl dimethyl ammonium chloride) (PDADMAC) or poly(acrylic acid) (PAAc) showed directional bending in response to stimuli such as pH, thanks to swelling and shrinking upon pH variations.^{238,239} These elaborated hydrogels exhibit reversible bidirectional changes or complex 3D deformation in response to pH, temperature, or ionic strength. They may be used in the production of soft grippers for the loading and release of small molecules and multi-responsive flexible materials, with potential applications in soft robots, actuation, and sensing. Moreover, the addition of an acid- based pH-indicator to a bilayer-type hydrogel composite with poly (2-(dimethyl amino) ethyl methacrylate) (PDMA) as first layer and poly (2-(dimethyl amino) ethyl methacrylate)-acrylamide (PDMA-AM) as the second layer, combined with sodium alginate as the interpenetrating polymer, may provide a visible color change simultaneous to shape changes when immersed in acidic environment. This provides possibilities in the application of environmental sensors on account of visual recognition.²⁴⁰

Park et al fabricated pH-responsive-based microspheres that act as microfluidic valves replacing classical actuating components.²⁴¹ Acrylic acid was integrated to a former poly(dimethylsiloxane) valve. The microspheres regulate fluid circulation on an open/close basis according to pH changes thanks to swelling and shrinking associated with pH variation (Figure 12).

Zarzar et al produced a chemo-mechanical hybrid actuation system composed of passive structural skeletal elements set in motion by a poly(AAc-co-AAm) hydrogel muscle that swells and contracts in response to chemical signals. This system enables pH-responsive reversible motion of microstructures in liquid.²⁴² The authors demonstrated the patternable actuation of polymeric microposts controlled by a structured layer made of the prepared hydrogel. Electrochemically generated pH gradients allow visualization of hydrogel volume phase transition and how this translates to movements of the microstructures. Indeed, AAc is ionized at $\text{pH} > 4.25$, which leaves the hydrogel polymer backbone with a net charge. Dissociated hydrogen ions remain in the hydrogel to balance this negative charge, which in turn causes increased osmotic pressure, ultimately leading to water infiltration and hydrogel swelling. At $\text{pH} < 4.25$, the acrylate is protonated, the osmotic pressure is decreased, water is expelled, and the hydrogel contracts. The volume phase transition of the pH-responsive hydrogel drives the actuation of the embedded microstructures, as can be seen in Figure 13.

6.5 Surfaces functionalization and membranes

Stimuli-responsive polymers' emergence has boosted the research on environmental-responsive membranes (ERMs). These membranes have been till now prepared by processes like surface graft polymerization of weak polyelectrolyte chains onto a support membrane.²⁴³ For ERM preparation, poly(vinylidene fluoride) (PVDF) membrane is the most commonly used material.²⁴⁴ By grafting PRPs such as poly [2-(diethyl amino) ethyl acrylamide] (PDEAm),²⁴⁴ poly(methacrylic acid) (PMAAc),²⁴³ or poly(acrylic acid) (PAAc)²⁴⁵ to this membrane, it has been shown that resulting membranes exhibit pH-dependent performances in the separation of different feeding stream components. For instance, Xian et al²⁴⁶ showed a variation of separation efficiency for separating hexadecane/water emulsion depending on temperature and pH with separation efficiencies of 97.10% at 25 °C under neutral condition and 30.26% at 50 °C under alkaline condition. pH-sensitive ERM can be used in oil/water emulsion separation, oil recovery, removal of specific species such as heavy metals from feed water streams by chemical binding, wastewater treatment, and microfluidic devices. Further promising applications such as membrane antifouling may be also considered.

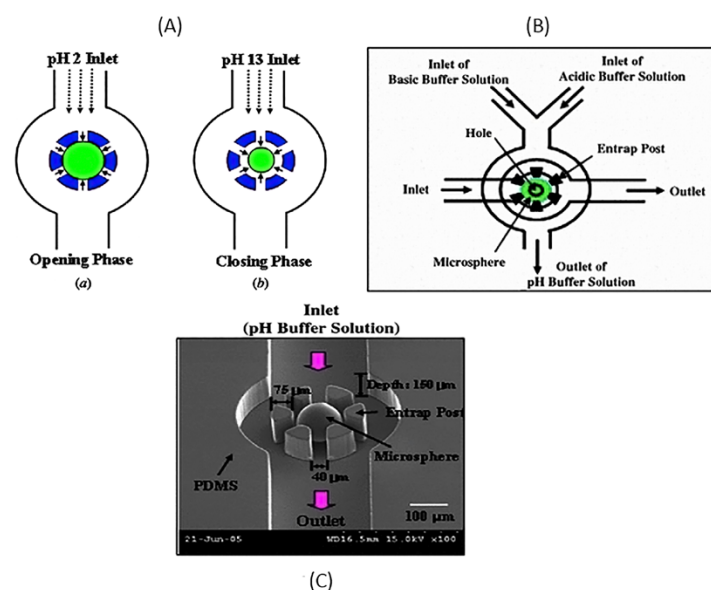


FIG 12 Illustration showing the fabricated microvalve's "OPEN" and "CLOSE" operations. The microsphere shrank and the channel opened at the appearance of acidic solution, while the channel is closed at the appearance of basic solution. A, Schematic diagram showing the motion of (a) the acidic solution around the entrapped microsphere at the start of the opening phase and (b) the basic solution around the entrapped microsphere at the start of the closing phase. B, Schematic diagram of pH-responsive microvalve seen from the top view. C, SEM image of the produced microspheres.²⁴¹ With Copyright permission

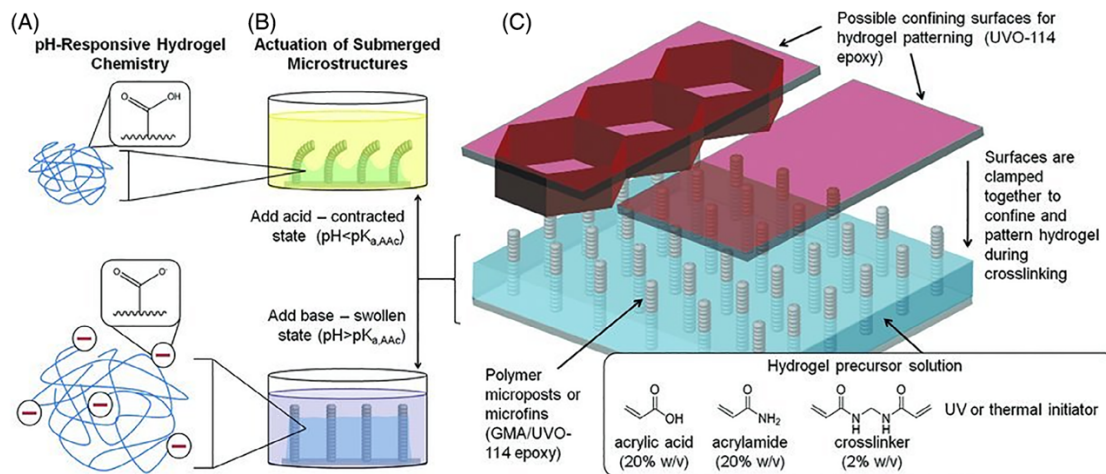


FIG 13 A, Hydrogel response to pH. B, Actuation of microstructures embedded in hydrogel submerged in aqueous solution colored with bromophenol blue indicator. C, Overview of the fabrication of pH-responsive hydrogel-embedded polymer microstructures with topographically patterned hydrogel. The confining surface can have any arbitrary pattern.²⁴² With Copyright permission

Poly(4-vinylpyridine) (P4VP)-based porous membranes are able to respond to pH fluctuations through self-adjustment of their size with the changes of outside pH stimulus through the protonation and deprotonation of internal pyridine groups.^{247,248} Thus, this functionalization confers to the membranes gate-controlled water permeability, which is exploitable in separation systems such as porous microfiltration. Recently, Willot introduced a novel water-based phase inversion approach named aqueous phase separation (APS) for the synthesis of a poly(4-vinylpyridine) (P4VP)-based porous membrane films.²⁴⁸ The synthesis approach gives a certain degree of control over membrane structure, leading to symmetric porous microfiltration membranes and asymmetric dense nanofiltration membranes, effective cleaning of the membrane without the use of harsh chemicals, and advanced membranes with responsive properties without the use of any toxic solvents.

Moreover, these pH-responsive ERMs exhibit self-cleaning properties and high regeneration performances.

6.6 Chromatography, electrophoresis, and extraction

Stimuli-responsive materials including PRPs have been used in various separation and purification technologies such as extraction, electrophoresis, and chromatography.²⁴⁹ Biomolecules of interest have been extracted from different mixtures using pH-responsive matrices. pH-responsive hydrogels have demonstrated their utility in the high and fast adsorption or swelling and uptake of heavy metal ions such as Pb^{2+} , Cd^{2+} , Ni^{2+} , Cu^{2+} , Fe^{2+} , Zn^{2+} , and Cr^{3+} ,²⁵⁰⁻²⁵² of bovine serum albumin protein (BSA)^{253,254} or the β -blocker atenolol.²⁵⁵ Moreover, different pH-responsive systems have been used as remarkable tools in the building of packing materials of stationary phase in ion-exchange chromatography.²⁵⁶⁻²⁶¹

Changes in pH and temperature as a second stimulus have led to the establishment of optimal operating conditions for improved separation of different biomolecules of interest. It was proved that interactions between the solute and the stationary phase could be freely controlled by temperature and pH.²⁵⁷ The use in most cases of only aqueous solutions as the mobile phase without any organic solvent confers this selective separation method a green and sustainable character. Table 4 summarizes various pH-responsive-based systems found in the literature for extraction or used as packed materials for chromatography stationary phase.

6.7 Other applications

Nanoparticle synthesis within amphiphilic block copolymer micelle cores has been explored. Indeed, these block copolymer cores used as stabilizers may act as nanoreactors for metal (especially catalytic) particle nucleation and growth with the advantages of enhancing the control of particle size and stability.²⁶⁷⁻²⁷⁰ Moreover, pH-responsive microgel pores may also be used as templates or nanosized reactors for the synthesis of inorganic nanoparticles.²⁷¹ Elaborated PRPs have also been employed as flocculants as they proved to induce substantial reversible flocculation and sedimentation with pH variations.^{272,273} Thus, these pH-responsive materials could find application as flocculation agents in various industrial fields such as clarifying industries or separation processes. Table 5 summarizes some other applications involving PRPs.

pH-responsive polymer	Stimuli	Application/Type of separation	Targeted molecules	References
Poly(vinylpyrrolidone) VP or N-vinyl-2-pyrrolidone-co-methylacrylate P(VP-co-MA)	pH	Hydrogel-based adsorption	pH-dependent heavy metal separation Cu ²⁺ , Cd ²⁺ , Ni ²⁺ , and Zn ²⁺	251
Poly(acrylic acid-ethylene glycol pH dimethacrylate) [poly(AAc-EGDMA)]	pH	Hydrogel, solid-phase extraction	Atenol	255
N,N-(Dimethyl amino) ethyl methacrylate (DMAEMA)	pH	Hydrogel, water sorption, and metal uptake	pH-dependent metal separation Cu ²⁺ , Ni ²⁺	250
2-Hydroxyethyl acrylate (HEA) and 2-acrylamido-2-methylpropane sulfonic (AMPS) HEA/AMPS copolymer hydrogel	pH and temperature	Hydrogel-based adsorption	pH-dependent heavy metal separation Pb ²⁺ , Cd ²⁺ , Cr ³⁺ , and Fe ³⁺	252
Poly(N-isopropylacrylamide) (PNIPAM)-carboxymethyl cellulose (CMC)	pH and temperature	Hydrogel-based adsorption	pH dependent bovine serum albumin (BSA)	253,254
PMMDN polymer pH Methyl acrylic acid (MAA), methyl methacrylate (MMA), Methacrylic acid 2-(dimethyl amino) ethyl ester, N-Methylolacrylamide (N-MAM) (Dimethyl amino) ethyl ester, N-Methylolacrylamide (N-MAM)	pH	Affinity precipitation	Lysosome, microbial transglutaminase	262,263
Poly(AAc-co-hydrazide)	pH	Polymeric matrix enrichment	Glycopeptides	264
N-isopropylacrylamide (NIPAM) and 4-vinylphenylboronic acid (p-VPBA)	pH and temperature	Macroporous imprinted cryogels	Ovalbumin	265
Glycidyl methacrylate-co-ethylene dimethacrylate) (poly (GMA-co-EDMA))	pH	Stationary phase, monolithic column	Protein separation (human immunoglobulin G, α -chymotrypsinogen A, cytochrome c, and lysozyme)	266
Poly(acrylic acid-co-butyl, acrylate) (AAc-co-BA)	pH	Reverse-phase liquid chromatography (RPLC) and hydrophilic interaction chromatography (HLIC)	Sulfonamides, soybean isoflavones and nucleotides	260
Poly(2-dimethyl amino ethyl methacrylate)-block-poly-(acrylic acid) (PDMA-b-PAAC)	pH, temperature and ionic strength	Ion exchange HPLC	Low molecular weight acidic, basic, and neutral analytes, biomolecules such as proteins (horse heart myoglobin, hen egg white lysozyme, and bovine heart cytochrome c)	261
Poly(NIPAM-co-BMA-co-DMAPAAm) Terpolymer	pH and temperature	Ion exchange Reverse phase HPLC	Phospho-tyrosine, phosphopeptide and oligonucleotides	259
N-isopropylacrylamide (NIPAM), butyl methacrylate (BMA) and N,N-dimethylaminopropyl acrylamide (DMAPAAm) Poly(NIPAM-co-BMA-co-DMAPAAm)	pH and temperature	Ion exchange HPLC	Nonsteroidal anti-inflammatory drugs (ibuprofen, ketoprofen, naxopren)	258
N-isopropylacrylamide-co-N-tert-butyl acrylamide-co-acrylic acid P(NIPAM-co-tBAAm-co-AAc)	pH and temperature	Ion exchange HPLC	Organic acids and phenylthiohydantoin-aminoacids, Melatonin	256,257

TABLE 4 pH-responsive-based systems for extraction or used as packed materials for chromatography stationary phase

Applications	pH-responsive polymer	References
Stabilizers (synthesis of metal nanoparticles)	Poly(hexa(ethylene glycol) methacrylate)-b-poly (2-(diethyl amino)ethyl methacrylate) (PDEA-b-PHEGMA) micelles	268
	Poly(styrene)-b-poly (4-vinylpyridine) PS-b-P4VP micelles	269
	Poly(ethylene oxide)-b-poly(2-vinylpyridine), PEO-b-P2VP, micelles Poly(hexa(ethylene glycol)methacrylate)-b-poly(2-(diethylamino)ethyl methacrylate), PHEGMA-b-PDEA, micelles PEO-b-PDEA, micelles	270
	Poly(2-[diethylamino] ethyl methacrylate), PDEA, microgels	271
	Poly(2-vinylpyridine) P2VP, brushes	274,275
Flocculants	4-Vinylpyridine grafted to cellulose graft, nanocrystals	272
	Temperature and pH responsive starches (TPRS)	273
Sol fertilizer	Polydopamine-g-poly (acrylic acid) (Pdop-g-PAAC), polymer brushes	276

TABLE 5 Some other pH-responsive polymer applications

7 CONCLUDING REMARKS AND FUTURE

Stimuli-responsive polymers have been largely studied in the last two decades owing to their unique properties to adapt sharply and reversibly to their surrounding environment by exhibiting alteration of their structure and/or physical properties. Polymers sensitive to different stimuli such as pH, temperature, light, electrical or magnetic field, and ionic strength have been elaborated and investigated. In the present review, the focus was on PRPs. An origin-based and functional group-based classification of the most commonly cited polyacids and polybases PRPs was provided first. Progress made in the development of new PRPs or systems has promoted their use as drug, gene, and active compound delivery systems, tumor tissue targeting, and cancer treatment. Moreover, they find application in many other domains such as sensing, actuation, surfaces functionalization, and selective membranes. PRPs present different structures/architectures and their self-assembly behavior allows the design of various nanostructures such as shell/core cross-linked micelles, hollow spheres, hydrogels, microgels, and layer-by-layer nanofilms that have shown their utility notably in drug delivery systems. However, many challenges remain to be addressed. PRP's potential applications are still limited probably due to the few pH-sensitive environments. Moreover, not all laboratory-developed pH-responsive drug delivery systems to date have already been industrially produced and commercialized due to human body specifications and cytotoxicity concerns, mainly. The same remark can be made for pH-responsive-based sensing, actuator, or separation devices. In this context, multi-responsive materials in general and polymers in particular are important to develop, as they are able to mimic what is commonly observed in Nature.

Multiple stimuli-responsive properties have been used in the design of drug delivery vehicles for the controlled release of drugs in vivo. A well-known example is the combination of pH and redox responsiveness to target intrinsic environment of malignant cancer cells rather than healthy ones.²⁷⁷ However, it can be noticed that most of dual-responsive polymeric materials used in drug delivery are intended for anticancer drugs with few reports on other classes of drugs that can also benefit from these advances.²⁷⁸

Recently, new application domains of PRPs have been reported. For instance, this is the case of the food industry. In fact, recent studies suggest pH-responsive polymeric films as smart packaging materials for real-time food freshness monitoring.²⁷⁹⁻²⁸¹ In addition, the designed pH-responsive films exhibit antioxidant activity,^{282,283} antimicrobial activity,^{284,285} or both,^{46,286} making them suitable for food preservation. Apart from their functionalities, the attractiveness of these systems resides in their nontoxicity for consumers. This paves the way toward edible PRP development with antimicrobial and antioxidant activities and to functional foods with pH-responsive property.²⁸⁷

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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