



**HAL**  
open science

## pH-sensitive polymers: Classification and some fine potential applications

Fabrice Ofridam, Mohamad Tarhini, Nouredine Lebaz, E. Gagnière, Denis Mangin, Abdelhamid Elaïssari

### ► To cite this version:

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**

**<https://hal.science/hal-03132353>**

Submitted on 28 Oct 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# pH-sensitive polymers: classification and some fine potential applications

Fabrice Ofridam<sup>1</sup>, Mohamad Tarhini<sup>2</sup>, Émilie Gagnière<sup>1</sup>, Denis Mangin<sup>1</sup>, Noureddine Lebaz<sup>1\*</sup>, Abdelhamid Elaissari<sup>2</sup>

<sup>1</sup>Univ Lyon, University Claude Bernard Lyon 1, CNRS, LAGEPP UMR 5007, Villeurbanne, France

<sup>2</sup>Univ Lyon, University Claude Bernard Lyon 1, CNRS, ISA UMR 5280, Villeurbanne, France

\*Email: noureddine.lebaz@univ-lyon1.fr

## 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.<sup>1</sup> 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.<sup>2,3</sup>

Surface properties of polymers are improved chemically, physically, or biologically in order to increase their biocompatibility.<sup>1</sup> 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.<sup>4</sup> 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).<sup>5-7</sup> 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.<sup>8</sup> With these stimuli, one may find pH-responsive, solvent-responsive, ionic strength-responsive, chemical agent-responsive, or biologically responsive polymers.

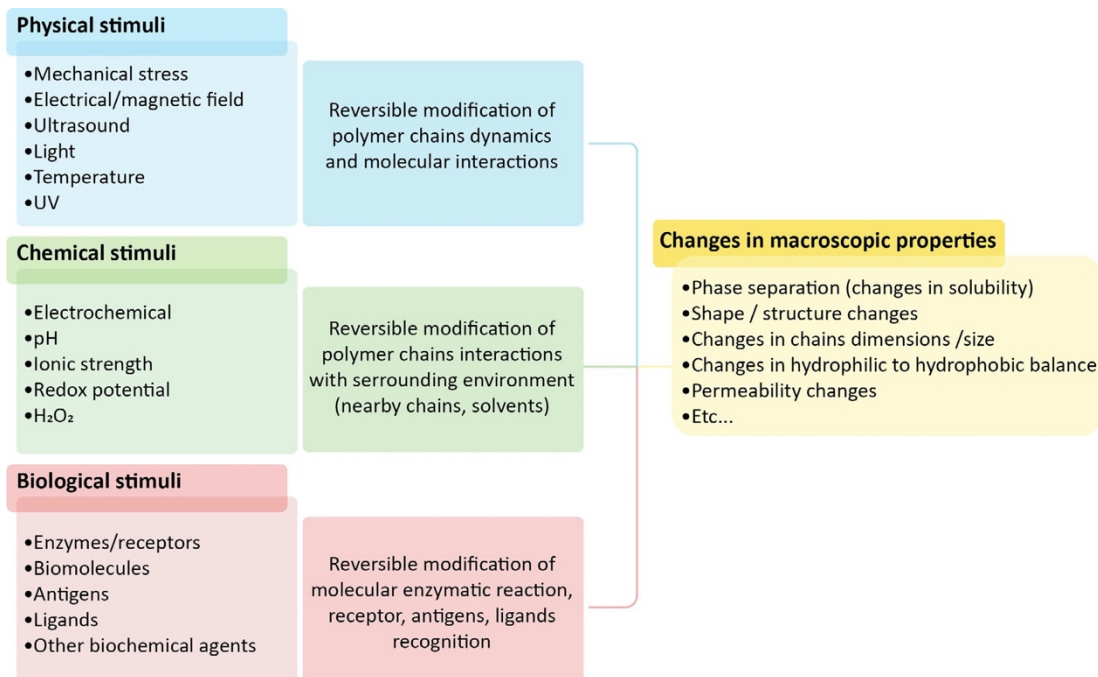


FIG 1 Classification of stimuli-responsive polymers with their induced modification

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.<sup>9</sup>

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.<sup>10</sup> 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.<sup>11</sup> 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 (SO<sub>3</sub>H), or phosphonic acid (PO<sub>3</sub>H<sub>2</sub>), along the polymer backbone, whereas polycations or poly-bases contain basic groups such as amines (NH<sub>2</sub>) 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.<sup>11,12</sup>

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<sub>a</sub>, whereas the polymeric chains collapse at pH values < pK<sub>a</sub>. However, for a polybase, above the value of pK<sub>b</sub> (pH > pK<sub>b</sub>), polymer chains collapse; conversely they expand at pH < pK<sub>b</sub>.

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.<sup>13</sup>

In practice, for a specific application, one should choose the PRP or material according to its pK<sub>a</sub> 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<sub>a</sub> value and to achieve a specific task. The transition pH dictated to the pH-responsive material by its pK<sub>a</sub> (for acidic material) or pK<sub>b</sub> (for basic material) can thus be tuned by modifications that affect hydrophobic or electrostatic interactions.<sup>14,15</sup> Methods employed to tune pK<sub>a</sub> are hydrophobic modification (incorporating different hydrophobic groups or changing the length of hydrophobic chains, which leads to pK<sub>a</sub> shift), copolymerization of PRPs with nonionizable or ionizable polymers (additional polyelectrolytes that change both hydrophobic interactions and electrostatic repulsion leading to pK<sub>a</sub> shift), and acid-labile linkages as well.<sup>16</sup>

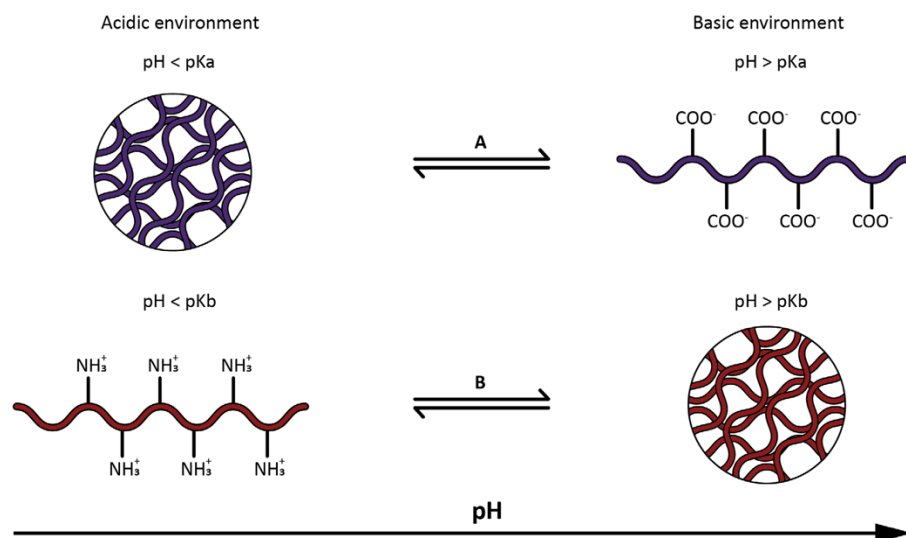


FIG 2 A, polyacids and B, polybase polymeric chain state depending on the ionization degree

### 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.<sup>17</sup> The use of natural polymers is due to their abundance in nature, biodegradability, nontoxic behavior, biocompatibility, and their ability to be modified.<sup>18</sup> 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.<sup>19,20</sup> Alginate consists of a block copolymer of  $\beta$ -D-mannuronic (M) and  $\alpha$ -L-guluronic acid (G) in varying sequential arrangements and proportions<sup>21</sup> (Figure 2). It is an acidic polysaccharide bearing carboxylic groups, whose pKa is 3 to 4.<sup>22</sup> Both mannuronic and guluronic acid residues have carboxylic functional groups in their structure, which are at the origin of the pH-sensitivity of alginate.<sup>23</sup> The high acid content allows alginic acid to undergo spontaneous and mild gelling in the presence of divalent cations such as Ca<sup>2+</sup>, Ba<sup>2+</sup>, Sr<sup>2+</sup>, and Zn<sup>2+</sup>; the formed gel shows variable swelling profiles in response to pH variation.<sup>24</sup> These mild gelling properties are pH-dependent and allow the encapsulation of various molecules or even cells within alginate gels with minimal negative impact.<sup>25</sup> Moreover, at low pH prevailing in the gastric environment, alginate shrinks and retains encapsulated molecules.<sup>13</sup> 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.<sup>26</sup> The high content of hydroxyl and carboxylic acid groups provides added functionalities via conjugation, chemical bonding, and cross-linking,<sup>27</sup> promoting the preparation of pH-sensitive hydrogels.<sup>28-30</sup> pH-sensitive HA nanoparticles were prepared by Han et al<sup>31</sup> as oral delivery carriers with the advantage of protecting the loaded insulin against the stomach's strong acidic environment. Miyazaki et al<sup>32</sup> 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.<sup>33</sup> On this basis, Akar et al<sup>34</sup> 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,<sup>35</sup> isoliquiritigenin in inhibiting growth of acne through transdermal delivery,<sup>28</sup> or lysosomes.<sup>36</sup> In general, smart cellulose-based hydrogels have wide applications in the fields of agriculture, food, tissue engineering, and drug delivery.<sup>37</sup>

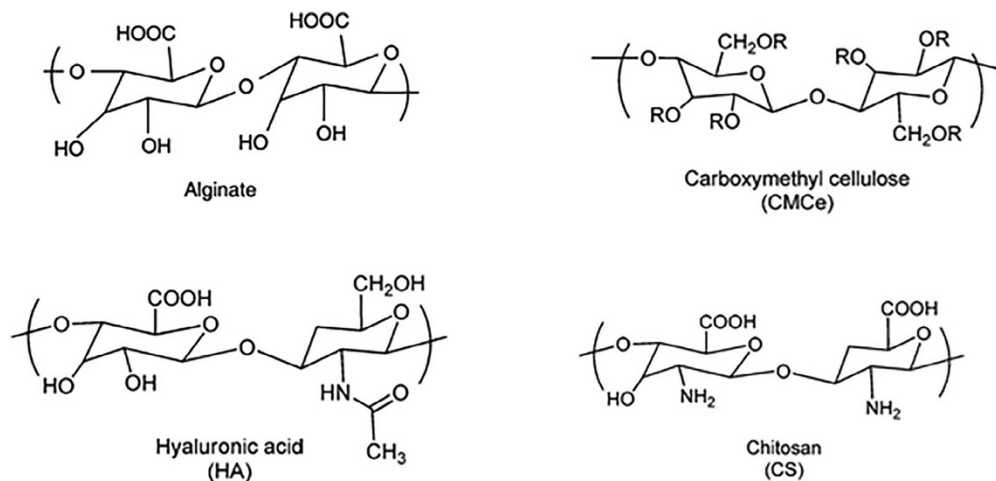


FIG 3 Chemical structure of commonly used natural pH-responsive polymers.<sup>11</sup> With Copyright permission

### 3.4 Chitosan

Chitosan (Ch) is a naturally occurring polysaccharide with randomly distributed N-acetyl glucosamine (2-acetamido-2-deoxy- $\beta$ -D-glucopyranose) and glucosamine (2-amino-2-deoxy- $\beta$ -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.<sup>38</sup>

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.<sup>39</sup> This pH sensitivity has been reported for drug delivery applications.<sup>40-42</sup> Recently, Gaware et al.<sup>43</sup> 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.<sup>44,45</sup> As an innovative application, Ezati and Rhim<sup>46</sup> 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

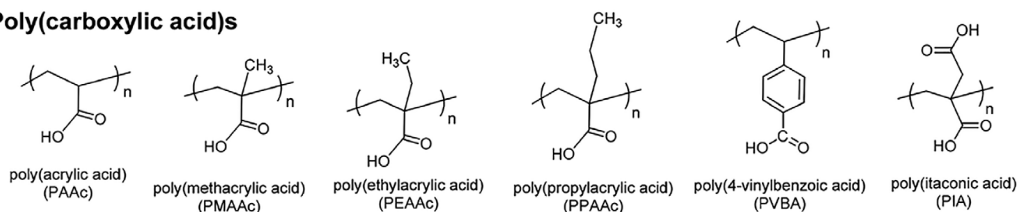
Although the use of natural polymers is of common interest because of their abundance, degradability, biocompatibility, and ability to be modified, synthetic PRPs exist and are used for diverse applications. Among these specific synthetic polymers, derivatives of polypeptides such as poly(L-glutamic acid) (PGA), poly(histidine) (PHIS), and poly(aspartic acid) (PASA) are biocompatible, degradable pH-sensitive polymers.<sup>11</sup> 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.<sup>47,48</sup> ATRP and RAFT allow a precise control over molecular weights and molecular weight distributions, affording polymers with well-defined topology structure.<sup>16</sup> 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.<sup>11</sup>

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.

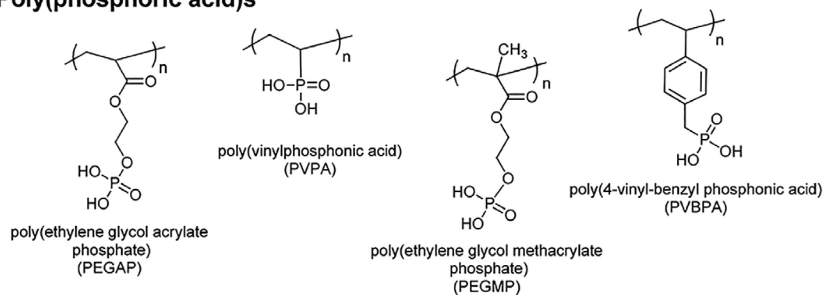
### 4.1 Composition-based classification

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.<sup>11</sup> 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<sup>+</sup>), 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.<sup>17,49</sup> 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.<sup>33</sup>

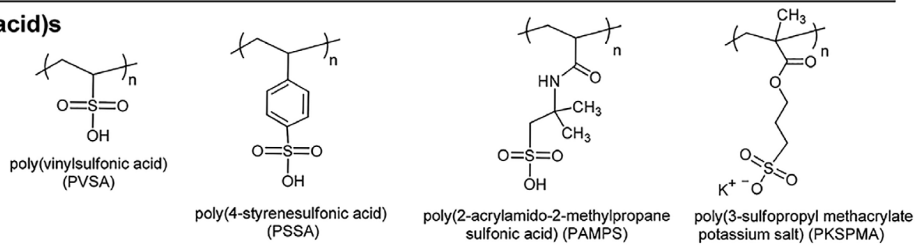
### Poly(carboxylic acid)s



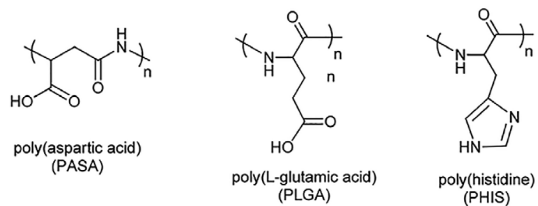
### Poly(phosphoric acid)s



### Poly(sulfonic acid)s



### Poly(amino acid)s



### Poly(boronic acid)s

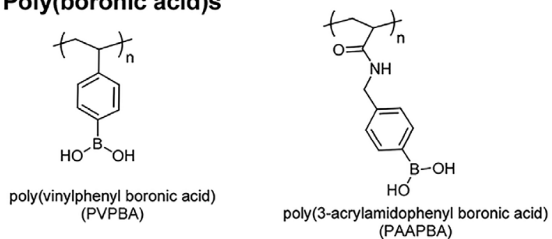
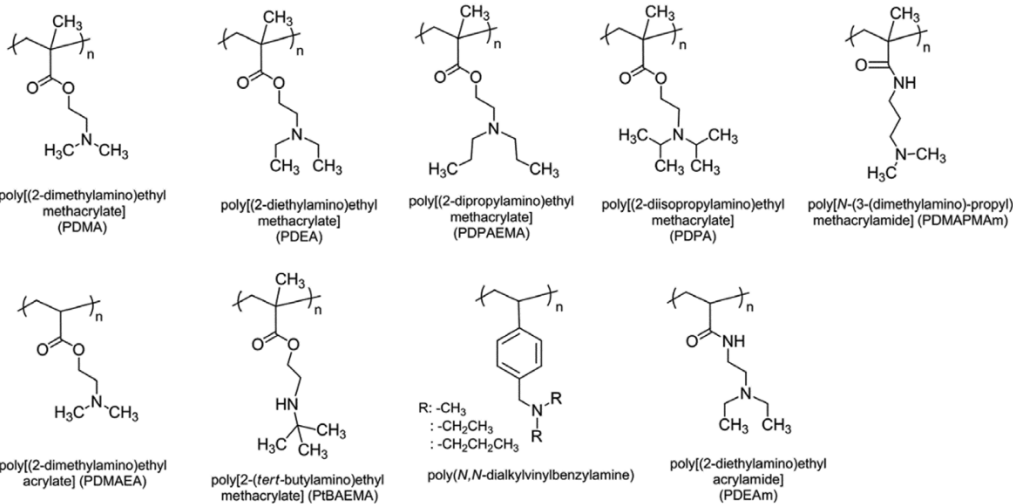
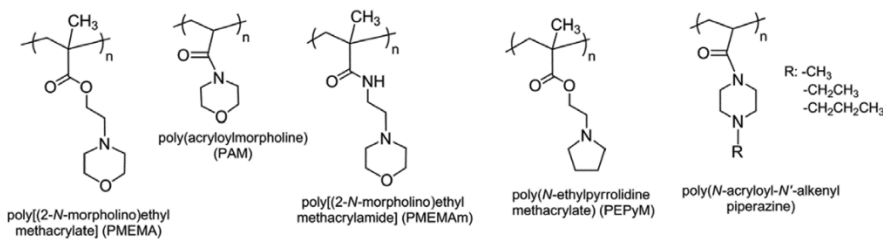


FIG 4 Chemical structure of polyanions pH-responsive polymers classified according to the nature of their functional pendant groups.<sup>11</sup> With Copyright permission

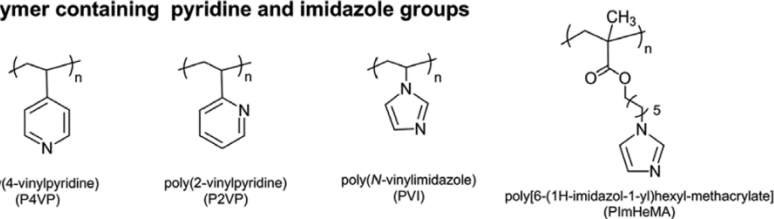
### Polymer containing tertiary amine groups



### Polymer containing morpholino, pyrrolidine and piperazine groups



### Polymer containing pyridine and imidazole groups



### Dendrimers

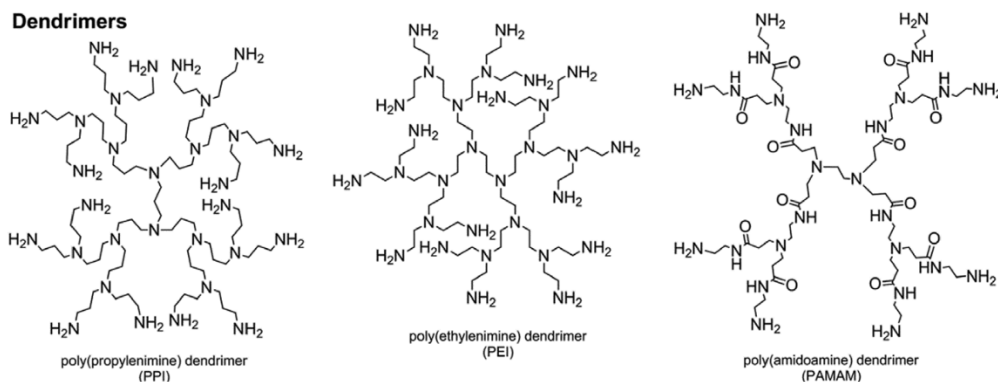


FIG 5 Chemical structure of polycations pH-responsive polymers classified according to the nature of their functional pendant groups.<sup>11</sup> With Copyright permission

#### 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.<sup>33</sup> 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.<sup>50</sup>

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.<sup>16</sup> 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.<sup>51</sup> 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.<sup>33,52</sup> The linkages structure, degradation mechanism, and byproducts after cleavage are presented in Figure 6.

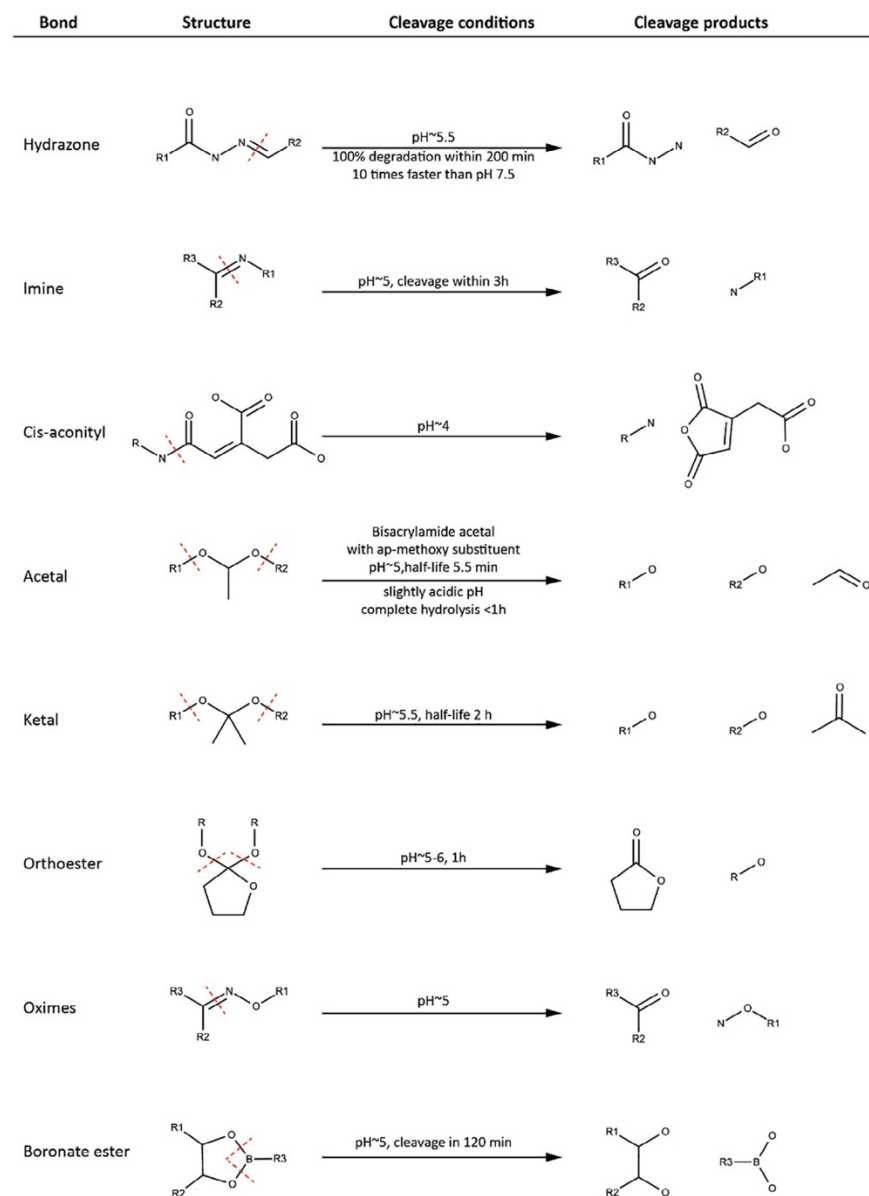


FIG 6 Summary of commonly used acid-labile linkage. Adapted from References 16, 27, and 53 to 56

## 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).<sup>11</sup>



## 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.<sup>27,57,58</sup> 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.<sup>13,59</sup> Self-assembly micelle morphology is affected by parameters such as temperature, pH, salt and polymer concentrations, solvent type, and the structure/length of blocks.<sup>60</sup> 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.<sup>11</sup>

## 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.<sup>11</sup> Further, branched polymers including dendritic, highly branched and hyperbranched, and multibranch 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 coatings<sup>61</sup> 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.<sup>62,63</sup>

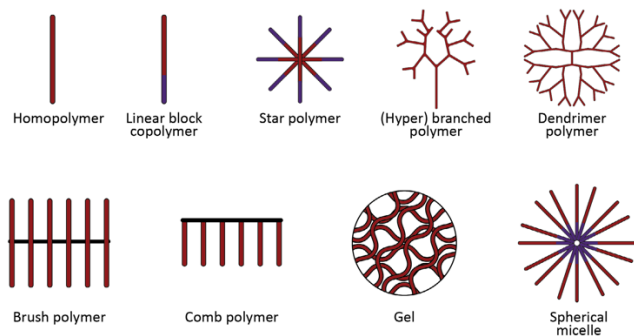


FIG 7 Different architectures of pH-responsive polymers

## 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.<sup>64</sup> 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.<sup>65</sup>

## 4.2.4 pH-responsive hydrogels

Hydrogels are characterized by hydrophilic polymers that are cross-linked into an insoluble but highly hydrophilic structure.<sup>66</sup> 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.<sup>67</sup> Hydrogels respond to external stimuli including the surrounding pH conditions.<sup>68</sup> 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,<sup>69</sup> 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.<sup>70</sup> 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  $\text{pH} < \text{pKa}$ .<sup>66</sup>

## 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.<sup>71</sup> Multi-stimuli-responsive materials are created with covalently or physically bonded segments sensitive to different stimuli.<sup>6</sup>

## 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).<sup>10,72,73</sup> 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.<sup>10</sup> 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.<sup>17</sup> pH and temperature-responsive polymers are probably the most studied among multi-responsive polymers.<sup>74,75</sup> This is due in particular to their possible multitude applications.<sup>17</sup> Poly (2-dimethylamino)ethylmethacrylate (PDMA), a pH-sensitive homo- polymer, was found to exhibit temperature responsiveness in alkaline media.<sup>76</sup> 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).<sup>77</sup>

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).<sup>71</sup> They showed through their study the capacity of the prepared system to synergistically respond to changes in pH and temperature.<sup>71</sup> 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.<sup>78</sup> Yamazaki et al<sup>79</sup> 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.<sup>80,81</sup> They are basically prepared by incorporating responsive units such as disulfides, diselenides, dithienylethenes, or ditellurium bonds into a pH-responsive polymer.<sup>77,82</sup> In biological systems, the introduction of redox systems relies on the significantly different redox states in the circulation/extracellular fluids and intracellular compartments.<sup>82</sup> 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.<sup>83</sup> 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.<sup>85</sup>

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.<sup>84</sup>

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) block<sup>86</sup> or associated with a polyurethane (PU) middle block.<sup>87</sup> 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.<sup>88</sup> 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).<sup>89</sup> Responses to light stimulus consist of changes in the refractive index, dielectric constant, redox potential, geometrical structure, or luminescence properties.<sup>77</sup> 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.<sup>90</sup> Phototriggered polymers are of increasing interest for the elaboration of innovative drug delivery systems able to control drug dosage.<sup>91</sup> pH and light dual-stimuli degradable triblock copolymer micelles were prepared by Jin et al.<sup>92</sup> 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  $\beta$ -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,<sup>93</sup> Zhou et al,<sup>94</sup> and Xia et al.<sup>95</sup>

## 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.<sup>17</sup> Magnetic-responsive systems employ most often superparamagnetic iron oxide magnetite (Fe<sub>3</sub>O<sub>4</sub>) or maghemite (γ-Fe<sub>2</sub>O<sub>3</sub>)<sup>96,97</sup> 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.<sup>98,99</sup> 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).<sup>98</sup>

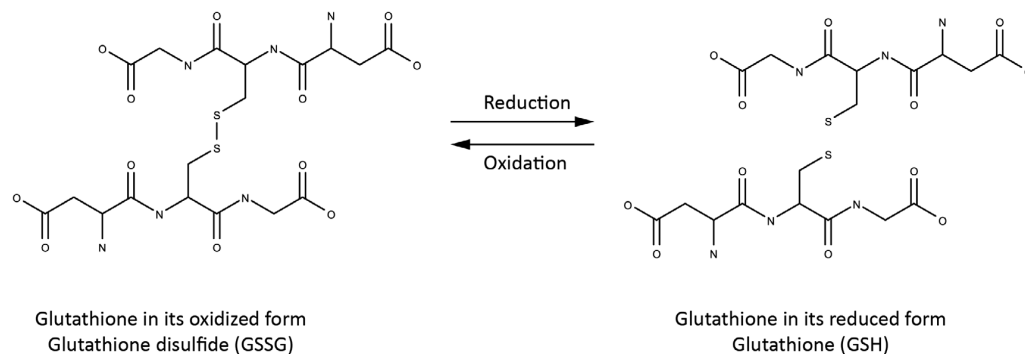


FIG 8 Chemical structure of GSH.<sup>84</sup> With Copyright permission

Magnetic-responsive polymers constitute a topic of intense research due to their potential applications in biomedical, coatings, microfluidics, and microelectronics fields.<sup>98</sup> 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.<sup>93,100,101</sup>

## 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.<sup>102</sup> 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.<sup>103</sup> A glucose- and pH-responsive release system based on polymeric network capped mesoporous silica nanoparticles has also been developed by Tan et al.<sup>104</sup> 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.<sup>105</sup> 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, enzyme<sup>106</sup>; pH, electrical<sup>107</sup>; pH, H<sub>2</sub>O<sub>2</sub><sup>108</sup>; pH, ultrasound<sup>109</sup> and pH, UV<sup>110</sup> 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.<sup>111</sup> 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.<sup>112,113</sup> 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.<sup>114,115</sup> 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.<sup>116,117</sup> Hydrogels with temperature-, pH-, and glucose-responsive properties made of N-isopropylacrylamide (NIPAM) and 5-methacrylamido-1,2-benzoxaborole (MAAm-Bo),<sup>114</sup> (2-dimethyl amino) ethyl methacrylate (DMAEMA) and 3-acrylamidephenylboronic acid (AAPBA),<sup>115</sup> or poly(vinyl alcohol)-b-poly(N-vinylcaprolactam) (PVOH-b- PNVCL)<sup>118</sup> 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.<sup>118</sup> 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.<sup>115</sup>

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

Bütün et al<sup>119,120</sup> 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 polymers<sup>121</sup>; pH,thermo, CO<sub>2</sub> triple-stimuli polymers<sup>122,123</sup>; pH,photo,redox triple-stimuli polymers<sup>124</sup>; and pH,glucose,redox triple-stimuli polymers.<sup>125</sup>

Moreover, there are polymeric systems responsive to more than three stimuli. Tuncer et al<sup>126</sup> 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 al<sup>127</sup> 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 al<sup>128</sup> 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.<sup>129</sup> Synthetic polymers are good tools as biomimetic agents, as they are able to adapt and react to biological complex environments.<sup>6,130</sup> 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 body<sup>131</sup> (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.<sup>66,133,134</sup> Moreover, the pH difference between normal and cancer tissues is exploited in the therapeutic solutions of the disease.<sup>135</sup> Indeed, as a result of the active metabolism of tumor cells, the tumor microenvironment is highly acidic compared to normal tissues.<sup>136</sup> 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.<sup>11,137</sup> 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.<sup>137,138</sup> 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.<sup>139</sup>

### 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.<sup>140,141</sup> For instance, polymethacrylates with pH-dependent dissolution<sup>142,143</sup> 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).<sup>144</sup> Commercially, pharmaceutical formulations already exist and are produced by Evonik Industries.<sup>145</sup>

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<sup>10,66,132</sup>

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.<sup>132,146</sup> 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.<sup>132</sup>

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.<sup>147-151</sup> 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.<sup>152</sup> 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.<sup>172</sup> 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.<sup>153,162-170</sup> Recently, Liu et al<sup>170</sup> 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.<sup>173</sup> Ionizable PRPs are widely formulated as drug delivery systems in the treatment of cancer.<sup>134,174,175</sup> 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.<sup>176</sup>

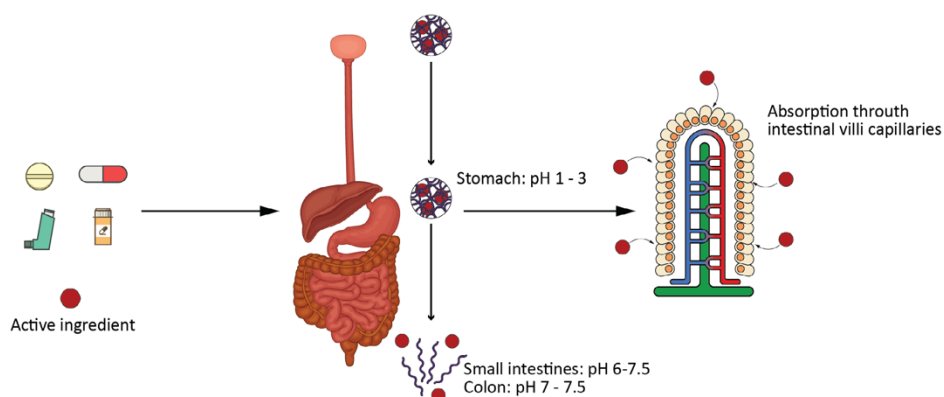


FIG 9 Illustration of drug carried throughout GI tract by pH-responsive polymeric matrix. The drug is protected against the acidic pH of stomach and released in colon alkaline conditions after solubilization of the carrier. It is further absorbed to blood circulation through intestinal villi capillaries

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
Anti-inflammatory	Salbutamol	Eudragit S100/Ethyl cellulose Hydroxypropyl methylcellulose	Tablets	152,153
	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.<sup>27</sup> Drug delivery systems based on pH-sensitive polymers with imidazole groups, poly ( $\beta$ -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.<sup>132</sup> 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.<sup>136,177</sup>

In cancer diagnostics or surgery, it is of prime importance to differentiate tumors from adjacent normal tissues.<sup>16</sup> 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.<sup>178</sup> The mechanism is based on the Fe<sub>3</sub>O<sub>4</sub>-loaded diblock copolymer poly(ethylene glycol)-poly( $\beta$ -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 Fe<sub>3</sub>O<sub>4</sub> 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).<sup>179</sup> 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.<sup>180</sup> 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 mm<sup>3</sup> 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.<sup>181,182</sup>

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.<sup>183</sup> The polymeric nanocarriers could avoid the use of surfactants and promote drug accumulation at the tumor sites by enhanced permeability and retention (EPR) effects.<sup>184</sup> 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.<sup>185</sup> 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.<sup>186,187</sup> 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.<sup>188</sup> 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.<sup>189-194</sup>

One of the innovative approaches in the field of cancer treatment is the association of pH-sensitive polymers with magnetic nanoparticles.<sup>195-197</sup> Chitosan-coated magnetic nanoparticles (Ch MNPs) provided targeting of DOX to the tumor site under a magnetic field.<sup>195</sup> In addition to the targeting enhancement, Montha et al observed higher anticancer activity and therapeutic effect.<sup>197</sup> They synthesized superparamagnetic (Mn, Zn) Fe<sub>2</sub>O<sub>4</sub> 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<sub>0.9</sub>Zn<sub>0.1</sub>Fe<sub>2</sub>O<sub>4</sub> showed a better anticancer activity to HeLa cells than that of free DOX.

Other anticancer agents, such as Paclitaxel, Camptothacin, Tamixofen, 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.<sup>213</sup> 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.<sup>11</sup>

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.<sup>214</sup> 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.<sup>215</sup> 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.<sup>216</sup> 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,<sup>217</sup> conjugated PEI,<sup>218,219</sup> dendritic polyglycerol dPG-PEI nanogel platform,<sup>220</sup> or degradable PEIs with acid-labile imine linkers and glutaraldehyde<sup>216</sup> 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.<sup>221,222</sup> 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.<sup>223-225</sup> 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.<sup>226</sup>

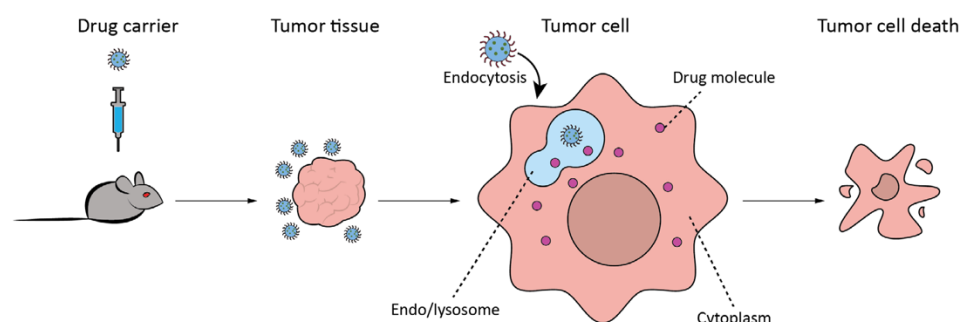


FIG 10 Illustration of pH-responsive polymer-based tumor cell targeting and microenvironment (pH conditions around tumor cells, low pH in endo/lysosome compartments, GSH concentration)-triggered anticancer drug release

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
	Polyethylene 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( $\beta$ -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
Gambogenic 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

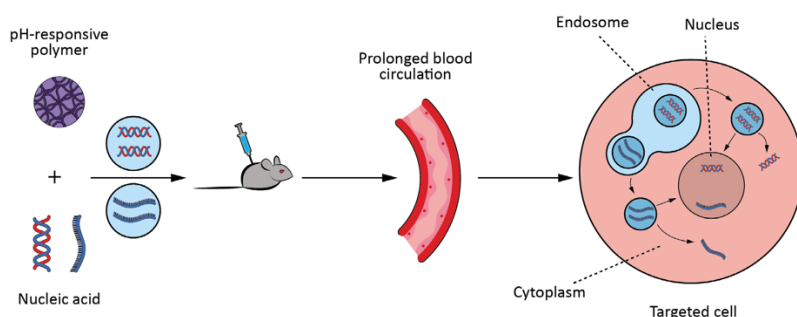


FIG 11 Illustration of pH-responsive-based approach in nonviral gene delivery

## 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.<sup>227,228</sup> pH-switchable zwitterionic polymers have been proposed for fast and efficient detection and control of biological (cell or bacteria) adhesion to surfaces<sup>229</sup> 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.<sup>230</sup>

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.<sup>231</sup>



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,<sup>232</sup> 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.<sup>102,233</sup>

Associated with sensing, PRPs may act as actuators based on action-reaction basis.<sup>56,234,235</sup> 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 ( $\text{Fe}_3\text{O}_4$ ) fabricated by a conventional photolithography procedure for the delivery of anticancer drug microbeads constituted of polycaprolactone-docetaxel (PCL-DTX).<sup>236</sup> Moreover, on-demand pH-triggered delivery nanocarriers have also been reported based on this system.<sup>237</sup>

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.<sup>238,239</sup> 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.<sup>240</sup>

Park et al fabricated pH-responsive-based microspheres that act as microfluidic valves replacing classical actuating components.<sup>241</sup> 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.<sup>242</sup> 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.<sup>243</sup> For ERM preparation, poly(vinylidene fluoride) (PVDF) membrane is the most commonly used material.<sup>244</sup> By grafting PRPs such as poly [2-(diethyl amino) ethyl acrylamide] (PDEAm),<sup>244</sup> poly(methacrylic acid) (PMAAc),<sup>243</sup> or poly(acrylic acid) (PAAc)<sup>245</sup> 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 al<sup>246</sup> 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.

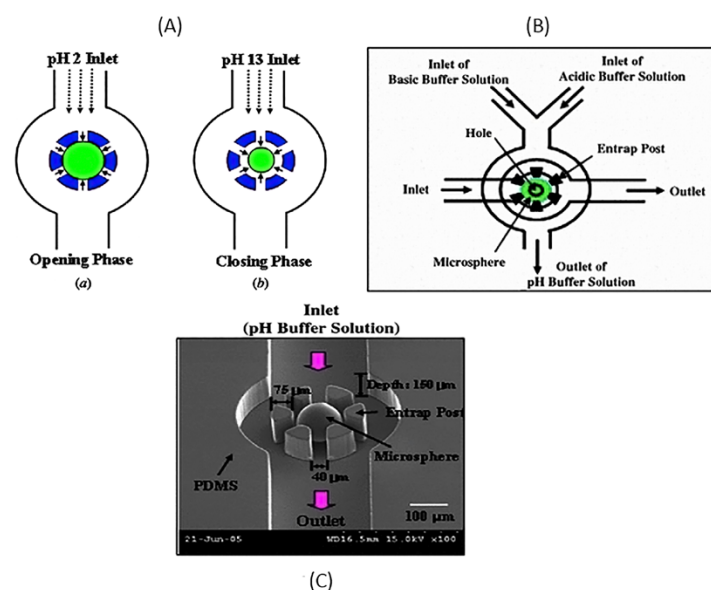


FIG 12 Illustration showing the fabricated microvalve's "OPEN" and "CLOSE" operations. The microsphere shrank and the channel opened at the appearance of acidic solution, while the channel is closed at the appearance of basic solution. A, Schematic diagram showing the motion of (a) the acidic solution 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.<sup>241</sup> With Copyright permission

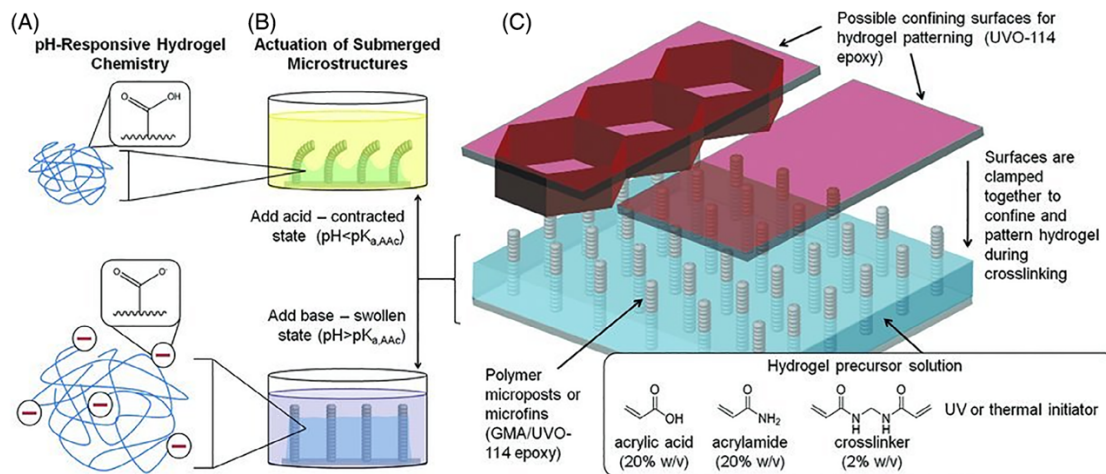


FIG 13 A, Hydrogel response to pH. B, Actuation of microstructures embedded in hydrogel submerged in aqueous solution colored with bromophenol blue indicator. C, Overview of the fabrication of pH-responsive hydrogel-embedded polymer microstructures with topographically patterned hydrogel. The confining surface can have any arbitrary pattern.<sup>242</sup> 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.<sup>247,248</sup> 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.<sup>248</sup> 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.<sup>249</sup> 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  $\text{Pb}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Zn}^{2+}$ , and  $\text{Cr}^{3+}$ ,<sup>250-252</sup> of bovine serum albumin protein (BSA)<sup>253,254</sup> or the  $\beta$ -blocker atenolol.<sup>255</sup> Moreover, different pH-responsive systems have been used as remarkable tools in the building of packing materials of stationary phase in ion-exchange chromatography.<sup>256-261</sup>

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.<sup>257</sup> 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.<sup>267-270</sup> Moreover, pH-responsive microgel pores may also be used as templates or nanosized reactors for the synthesis of inorganic nanoparticles.<sup>271</sup> Elaborated PRPs have also been employed as flocculants as they proved to induce substantial reversible flocculation and sedimentation with pH variations.<sup>272,273</sup> 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 <sup>2+</sup> , Cd <sup>2+</sup> , Ni <sup>2+</sup> , and Zn <sup>2+</sup>	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 <sup>2+</sup> , Ni <sup>2+</sup>	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 <sup>2+</sup> , Cd <sup>2+</sup> , Cr <sup>3+</sup> , and Fe <sup>3+</sup>	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.<sup>277</sup> 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.<sup>278</sup>

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.<sup>279-281</sup> In addition, the designed pH-responsive films exhibit antioxidant activity,<sup>282,283</sup> antimicrobial activity,<sup>284,285</sup> or both,<sup>46,286</sup> 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.<sup>287</sup>

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## ORCID

Noureddine Lebaz <https://orcid.org/0000-0001-7116-8554> Émilie Gagnière <https://orcid.org/0000-0003-1104-8707>

## REFERENCES

1. Pillai O, Panchagnula R. Polymers in drug delivery. *Curr Opin Chem Biol.* 2001;5(4):447-451.
2. Bennet D, Kim S. Polymer nanoparticles for smart drug delivery. *Application of Nanotechnology in Drug Delivery.* Croatia: InTech; 2014;257-310.
3. Ofridam F, Lebaz N, Gagnière É, Mangin D, Elaissari A. Polymethylmethacrylate derivatives Eudragit E100 and L100: interactions and complexation with surfactants. *Polym Adv Technol.* 2021;32:379-390. <https://doi.org/10.1002/pat.5093>.
4. Mao HQ, Kdaiyala I, Leong KW, Zhao Z, Dang W. *Biodegradable Polymers: Poly (Phosphoester)s.* Vol 1. New York, NY: John Wiley and Sons; 1999.
5. Almeida H, Amaral MH, Lobao P. Temperature and pH stimuli-responsive polymers and their applications in controlled and self-regulated drug delivery. *J Appl Pharm Sci.* 2012;02(06):1-10.
6. Liu F, Urban MW. Recent advances and challenges in designing stimuli-responsive polymers. *Prog Polym Sci.* 2010;35(1-2):3-23. <https://doi.org/10.1016/j.progpolymsci.2009.10.002>.
7. Saini RK, Bagri LP, Bajpai AK, Mishra A. Responsive polymer nanoparticles for drug delivery applications. *Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications.* Vol 1. London, UK: Elsevier; 2018:289-320.
8. Wang Q. *Smart Materials for Tissue Engineering: Fundamental Principles.* Vol 24. London, UK: Royal Society of Chemistry; 2016.
9. Wei M, Gao Y, Li X, Serpe MJ. Stimuli-responsive polymers and their applications. *Polym Chem.* 2017;8(1):127-143. <https://doi.org/10.1039/C6PY01585A>.
10. Schmaljohann D. Thermo- and pH-responsive polymers in drug delivery. *Adv Drug Deliv Rev.* 2006;58(15):1655-1670. <https://doi.org/10.1016/j.addr.2006.09.020>.
11. Kocak G, Tuncer C, Bütün V. pH-responsive polymers. *Polym Chem.* 2017;8(1):144-176. <https://doi.org/10.1039/C6PY01872F>.
12. Ghaffar A, Yameen B, Latif M, Malik MI. pH-sensitive drug delivery systems. *Met Nanoparticles Drug Deliv Diagn Appl.* London, UK: Elsevier; 2020:259-278.
13. Reyes-Ortega F. pH-responsive polymers: properties, synthesis and applications. *Smart Polymers and their Applications.* London, UK: Elsevier; 2014:45-92.
14. Stayton PS, Hoffman AS. "Smart" pH-responsive carriers for intracellular delivery of biomolecular drugs. In: Torchilin V, ed. *Multifunctional Pharmaceutical Nanocarriers. Fundamental Biomedical Technologies.* New York, NY: Springer; 2008:143-159. [https://doi.org/10.1007/978-0-387-76554-9\\_5](https://doi.org/10.1007/978-0-387-76554-9_5).
15. Nafee N, Schneider M, Lehr C-M. Charge modification of pharmaceutical nanocarriers: biological implications. In: Torchilin V, ed. *Multifunctional Pharmaceutical Nanocarriers. Fundamental Biomedical Technologies.* New York, NY: Springer; 2008:337-362. [https://doi.org/10.1007/978-0-387-76554-9\\_11](https://doi.org/10.1007/978-0-387-76554-9_11).
16. Tang H, Zhao W, Yu J, Li Y, Zhao C. Recent development of pH-responsive polymers for cancer nanomedicine. *Molecules.* 2019;24(1):4. <https://doi.org/10.3390/molecules24010004>.
17. Gil ES, Hudson SM. Stimuli-responsive polymers and their bioconjugates. *Prog Polym Sci.* 2004;29(12):1173-1222.
18. Sonia TA, Sharma CP. An overview of natural polymers for oral insulin delivery. *Drug Discov Today.* 2012;17(13-14):784-792.
19. Draget KI, Smidsrød O, Skjåk-Bræk G. Alginates from algae. *Biopolym.* Online. 2005;6:215-224.
20. Gomez d'Ayala G, Malinconico M, Laurienzo P. Marine derived polysaccharides for biomedical applications: chemical modification approaches. *Molecules.* 2008;13(9):2069-2106. <https://doi.org/10.3390/molecules13092069>.
21. Chan AW, Whitney RA, Neufeld RJ. Semisynthesis of a controlled stimuli-responsive alginate hydrogel. *Biomacromolecules.* 2009;10(3):609-616. <https://doi.org/10.1021/bm801316z>.
22. Ju HK, Kim SY, Lee YM. pH/temperature-responsive behaviors of comb-type graft hydrogels composed of alginate and poly(N-isopropylacrylamide). *Polymer.* 2001;42(16):6851-6857.

23. George M, Abraham TE. Polyionic hydrocolloids for the intestinal delivery of protein drugs: alginate and chitosan - a review. *J Control Release*. 2006;114(1):1-14. <https://doi.org/10.1016/j.jconrel.2006.04.017>.
24. Shalaby SW, Burg KJL, eds. *Absorbable and Biodegradable Polymers*. Boca Raton, FL: CRC Press; 2004.
25. Aguilar MR, San Román J. *Smart Polymers and their Applications*. London, UK: Elsevier; 2014.
26. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable controlled- release polymers and polymeric nanoparticles: mechanisms of controlling drug release. *Chem Rev*. 2016;116(4):2602-2663. <https://doi.org/10.1021/acs.chemrev.5b00346>.
27. Makhlof ASH, Abu-Thabit NY. *Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications: Volume 1: Types and Triggers*. London, UK: Elsevier; 2018.
28. Kwon SS, Kong BJ, Park SN. Physicochemical properties of pH-sensitive hydrogels based on hydroxyethyl cellulose-hyaluronic acid and for applications as transdermal delivery systems for skin lesions. *Eur J Pharm Biopharm*. 2015;92:146-154. <https://doi.org/10.1016/j.ejpb.2015.02.025>.
29. Kim SW, Oh KT, Youn YS, Lee ES. Hyaluronated nanoparticles with pH- and enzyme-responsive drug release properties. *Colloids Surf B Biointerfaces*. 2014;116:359-364. <https://doi.org/10.1016/j.colsurfb.2014.01.017>.
30. Luan S, Zhu Y, Wu X, Wang Y, Liang F, Song S. Hyaluronic-acid- based pH-sensitive nanogels for tumor-targeted drug delivery. *ACS Biomater Sci Eng*. 2017;3(10):2410-2419. <https://doi.org/10.1021/acsbiomaterials.7b00444>.
31. Han L, Zhao Y, Yin L, et al. Insulin-loaded pH-sensitive hyaluronic acid nanoparticles enhance transcellular delivery. *AAPS PharmSciTech*. 2012;13(3):836-845. <https://doi.org/10.1208/s12249-012-9807-2>.
32. Miyazaki M, Yuba E, Hayashi H, Harada A, Kono K. Hyaluronic acid- based pH-sensitive polymer-modified liposomes for cell-specific intracellular drug delivery systems. *Bioconjug Chem*. 2018;29(1):44- 55. <https://doi.org/10.1021/acs.bioconjchem.7b00551>.
33. Bazban-Shotorbani S, Hasani-Sadrabadi MM, Karkhaneh A, et al. Revisiting structure-property relationship of pH-responsive polymers for drug delivery applications. *J Control Release*. 2017;253:46- 63. <https://doi.org/10.1016/j.jconrel.2017.02.021>.
34. AkarE, Altinis jKA, SekiY. Preparation of pH-and ionic-strength responsive biodegradable fumaric acid crosslinked carboxymethyl cellulose. *Carbohydr Polym*. 2012;90(4):1634-1641. <https://doi.org/10.1016/j.carbpol.2012.07.043>.
35. Liu H, Rong L, Wang B, et al. Facile fabrication of redox/pH dual stimuli responsive cellulose hydrogel. *Carbohydr Polym*. 2017;176: 299-306. <https://doi.org/10.1016/j.carbpol.2017.08.085>.
36. Dutta S, Samanta P, Dhara D. Temperature, pH and redox responsive cellulose based hydrogels for protein delivery. *Int J Biol Macromol*. 2016;87:92-100. <https://doi.org/10.1016/j.ijbiomac.2016.02.042>.
37. Chang C, He M, Zhou J, Zhang L. Swelling behaviors of pH- and salt- responsive cellulose-based hydrogels. *Macromolecules*. 2011;44(6): 1642-1648. <https://doi.org/10.1021/ma102801f>.
38. Rinaudo M. Chitin and chitosan: properties and applications. *Prog Polym Sci*. 2006;31(7):603-632. <https://doi.org/10.1016/j.progpolymsci.2006.06.001>.
39. Yao KD, Peng T, Feng HB, He YY. Swelling kinetics and release characteristic of crosslinked chitosan: polyether polymer network (semi- IPN) hydrogels. *J Polym Sci Part Polym Chem*. 1994;32(7):1213-1223. <https://doi.org/10.1002/pola.1994.080320702>.
40. Shu XZ, Zhu KJ, Song W. Novel pH-sensitive citrate cross-linked chitosan film for drug controlled release. *Int J Pharm*. 2001;212(1): 19-28. [https://doi.org/10.1016/S0378-5173\(00\)00582-2](https://doi.org/10.1016/S0378-5173(00)00582-2).
41. Makhlof A, Tozuka Y, Takeuchi H. Design and evaluation of novel pH-sensitive chitosan nanoparticles for oral insulin delivery. *Eur J Pharm Sci*. 2011;42(5):445-451. <https://doi.org/10.1016/j.ejps.2010.12.007>.
42. Woraphatphadung T, Sajomsang W, Rojanarata T, Ngawhirunpat T, Tonglairoum P, Opanasopit P. Development of chitosan-based pH- sensitive polymeric micelles containing curcumin for colon-targeted drug delivery. *AAPS PharmSciTech*. 2018;19(3):991-1000. <https://doi.org/10.1208/s12249-017-0906-y>.
43. Gaware SA, Rokade KA, Kale SN. Silica-chitosan nanocomposite mediated pH-sensitive drug delivery. *J Drug Deliv Sci Technol*. 2019; 49:345-351. <https://doi.org/10.1016/j.jddst.2018.11.022>.
44. Ata S, Rasool A, Islam A, et al. Loading of Cefixime to pH sensitive chitosan based hydrogel and investigation of controlled release kinetics. *Int J Biol Macromol*. 2019;155:12-1244. <https://doi.org/10.1016/j.ijbiomac.2019.11.091>.
45. Aycan D, Alemdar N. Development of pH-responsive chitosan-based hydrogel modified with bone ash for controlled release of amoxicillin. *Carbohydr Polym*. 2018;184:401-407. <https://doi.org/10.1016/j.carbpol.2017.12.023>.
46. Ezati P, Rhim J-W. pH-responsive chitosan-based film incorporated with alizarin for intelligent packaging applications. *Food Hydrocoll*. 2020;102:105629. <https://doi.org/10.1016/j.foodhyd.2019.105629>.
47. Dai S, Ravi P, Chiu Tam K. pH-responsive polymers: synthesis, properties and applications. *Soft Matter*. 2008;4(3):435-449. <https://doi.org/10.1039/B714741D>.
48. Grainger SJ, El-Sayed MEH. *Stimuli-sensitive particles for drug delivery. Biologically-Responsive Hybrid Biomaterials*. London, UK: World Scientific; 2010:171-190. [https://doi.org/10.1142/9789814295680\\_0008](https://doi.org/10.1142/9789814295680_0008).
49. Tonge SR, Tighe BJ. Responsive hydrophobically associating polymers: a review of structure and properties. *Adv Drug Deliv Rev*. 2001; 53(1):109-122. [https://doi.org/10.1016/S0169-409X\(01\)00223-X](https://doi.org/10.1016/S0169-409X(01)00223-X).
50. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. *Adv Drug Deliv Rev*. 2001;53(3):321-339. [https://doi.org/10.1016/S0169-409X\(01\)00203-4](https://doi.org/10.1016/S0169-409X(01)00203-4).
51. Mukherjee S, Cash JJ, Sumerlin BS. *Responsive dynamic covalent Polymers. Dynamic Covalent Chemistry*. London, UK: John Wiley & Sons; 2017:321-358. <https://doi.org/10.1002/9781119075738.ch8>.
52. Wei H, Zhuo R-X, Zhang X-Z. Design and development of polymeric micelles with cleavable links for intracellular drug delivery. *Prog Polym Sci*. 2013;38(3-4):503-535.
53. Fleige E, Quadir MA, Haag R. Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: concepts and applications. *Adv Drug Deliv Rev*. 2012;64(9):866-884. <https://doi.org/10.1016/j.addr.2012.01.020>.
54. Pan H, Kopeček J. Multifunctional water-soluble polymers for drug delivery. In: Torchilin V, ed. *Multifunctional Pharmaceutical Nanocarriers. Fundamental Biomedical Technologies*. New York, NY: Springer; 2008:81-142. [https://doi.org/10.1007/978-0-387-76554-9\\_4](https://doi.org/10.1007/978-0-387-76554-9_4).
55. Morilla MJ, Romero EL. *Liposomal pH-sensitive nanomedicines in preclinical development. Bionanotechnology II*. Boca Raton, FL: CRC Press; 2011:402-433.
56. Zhang X, Malhotra S, Molina M, Haag R. Micro- and nanogels with labile crosslinks - from synthesis to biomedical applications. *Chem Soc Rev*. 2015;44(7):1948-1973. <https://doi.org/10.1039/C4CS00341A>.
57. Rodríguez-Hernández J, Lecommandoux S. Reversible inside-out micellization of pH-responsive and water-soluble vesicles based on polypeptide diblock copolymers. *J Am Chem Soc*. 2005;127(7):2026- 2027. <https://doi.org/10.1021/ja043920g>.
58. Rodríguez-Hernández J, Chécot F, Gnanou Y, Lecommandoux S. Toward 'smart' nano-objects by self-assembly of block copolymers in solution. *Prog Polym Sci*. 2005;30(7):691-724. <https://doi.org/10.1016/j.progpolymsci.2005.04.002>.
59. Xu C, Wayland BB, Fryd M, Winey KI, Composto RJ. pH-responsive nanostructures assembled from amphiphilic block copolymers. *Macromolecules*. 2006;39(18):6063-6070. <https://doi.org/10.1021/ma060881f>.
60. Kim JK, Yang SY, Lee Y, Kim Y. Functional nanomaterials based on block copolymer self-assembly. *Prog Polym Sci*. 2010;35(11):1325- 1349. <https://doi.org/10.1016/j.progpolymsci.2010.06.002>.
61. Connal LA, Li Q, Quinn JF, Tjijto E, Caruso F, Qiao GG. pH- responsive poly(acrylic acid) core cross-linked star polymers: morphology transitions in solution and multilayer thin films. *Macromolecules*. 2008;41(7):2620-2626. <https://doi.org/10.1021/ma7019557>.
62. Pang X, Zhao L, Akinc M, Kim JK, Lin Z. Novel amphiphilic multi-arm, star-like block copolymers as unimolecular micelles. *Macromolecules*. 2011;44(10):3746-3752. <https://doi.org/10.1021/ma200594j>.
63. Mark England R, Rimmer S. Hyper/highly-branched polymers by radical polymerisations. *Polym Chem*. 2010;1(10):1533-1544. <https://doi.org/10.1039/C0PY00154F>.

64. Sanjuan S, Tran Y. Stimuli-responsive interfaces using random poly- ampholyte brushes. *Macromolecules*. 2008;41(22):8721-8728. <https://doi.org/10.1021/ma8018798>.
65. Chen T, Ferris R, Zhang J, Ducker R, Zauscher S. Stimulus-responsive polymer brushes on surfaces: transduction mechanisms and applications. *Prog Polym Sci*. 2010;35(1-2):94-112. <https://doi.org/10.1016/j.progpolymsci.2009.11.004>.
66. Koetting MC, Peters JT, Steichen SD, Peppas NA. Stimulus- responsive hydrogels: theory, modern advances, and applications. *Mater Sci Eng R Rep*. 2015;93:1-49.
67. Hoffman AS. Hydrogels for biomedical applications. *Adv Drug Deliv Rev*. 2012;64:18-23. <https://doi.org/10.1016/j.addr.2012.09.010>.
68. Xu L, Qiu L, Sheng Y, et al. Biodegradable pH-responsive hydrogels for controlled dual-drug release. *J Mater Chem B*. 2018;6(3):510- 517. <https://doi.org/10.1039/C7TB01851G>.
69. De SK, Aluru NR, Johnson B, Crone WC, Beebe DJ, Moore J. Equilibrium swelling and kinetics of pH-responsive hydrogels: models, experiments, and simulations. *J Microelectromechanical Syst*. 2002;11 (5):544-555. <https://doi.org/10.1109/JMEMS.2002.803281>.
70. Gupta P, Vermani K, Garg S. Hydrogels: from controlled release to pH-responsive drug delivery. *Drug Discov Today*. 2002;7(10):569- 579. [https://doi.org/10.1016/S1359-6446\(02\)02255-9](https://doi.org/10.1016/S1359-6446(02)02255-9).
71. Jiang X, Lu G, Feng C, Li Y, Huang X. Poly(acrylic acid)-graft-poly(N- vinylcaprolactam): a novel pH and thermo dual-stimuli responsive system. *Polym Chem*. 2013;4(13):3876. <https://doi.org/10.1039/ c3py00415e>.
72. Fujishige S, Kubota K, Ando I. Phase transition of aqueous solutions of poly (N-isopropylacrylamide) and poly (N- isopropylmethacrylamide). *J Phys Chem*. 1989;93(8):3311-3313.
73. de la Rosa VR, Woisel P, Hoogenboom R. Supramolecular control over thermoresponsive polymers. *Mater Today*. 2016;19(1):44-55. <https://doi.org/10.1016/j.mattod.2015.06.013>.
74. Kim YK, Kim E-J, Lim JH, et al. Dual stimuli-triggered nanogels in response to temperature and pH changes for controlled drug release. *Nanoscale Res Lett*. 2019;14(1):77. <https://doi.org/10.1186/ s11671-019-2909-y>.
75. Abouelmagd SA, Ellah NHA, BNAE H. Chap. 3 - Temperature and pH dual-stimuli responsive polymeric carriers for drug delivery. In: Makhlof ASH, Abu-Thabit NY, eds. *Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications*. London, UK: Elsevier; 2019:87-109. <https://doi.org/10.1016/B978-0-08-101995-5.00003-9>.
76. Plamper FA, Ballauff M, Müller AHE. Tuning the thermoresponsiveness of weak polyelectrolytes by pH and light: lower and upper critical-solution temperature of poly(N,N- dimethylaminoethyl methacrylate). *J Am Chem Soc*. 2007;129(47): 14538-14539. <https://doi.org/10.1021/ja074720i>.
77. Guragain S, Bastakoti BP, Malgras V, Nakashima K, Yamauchi Y. Multi-stimuli-responsive polymeric materials. *Chem A Eur J*. 2015;21 (38):13164-13174. <https://doi.org/10.1002/chem.201501101>.
78. Song N, Chen G-H, Cong H-L, Yu B, Feng Y-M. The synthesis and application of dual temperature/pH-sensitive polymer nanoparticles. *Integr Ferroelectr*. 2017;181(1):151-155. <https://doi.org/10.1080/ 10584587.2017.1352407>.
79. Yamazaki N, Sugimoto T, Fukushima M, et al. Dual-stimuli responsive liposomes using pH- and temperature-sensitive polymers for controlled transdermal delivery. *Polym Chem*. 2017;8(9):1507-1518. <https://doi.org/10.1039/C6PY01754A>.
80. Gong C, Shan M, Li B, Wu G. A pH and redox dual stimuli-responsive poly(amino acid) derivative for controlled drug release. *Colloids Surf B Biointerfaces*. 2016;146:396-405. <https://doi.org/10.1016/j. colsurf.2016.06.038>.
81. Du J, Choi B, Liu Y, Feng A, Thang SH. Degradable pH and redox dual responsive nanoparticles for efficient covalent drug delivery. *Polym Chem*. 2019;10(11):1291-1298. <https://doi.org/10.1039/ C8PY01583J>.
82. Zhang X, Han L, Liu M, et al. Recent progress and advances in redox- responsive polymers as controlled delivery nanoplatfoms. *Mater Chem Front*. 2017;1(5):807-822.
83. Quinn JF, Whittaker MR, Davis TP. Glutathione responsive polymers and their application in drug delivery systems. *Polym Chem*. 2017;8 (1):97-126.
84. Abu-Thabit NY, Makhlof ASH. Chap. 1 - Historical development of drug delivery systems: from conventional macroscale to controlled, targeted, and responsive nanoscale systems. In: Makhlof ASH, Abu-Thabit NY, eds. *Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications*. Woodhead Publishing Series in Biomaterials. Vol 1. London, UK: Elsevier; 2018:3-41. <https://doi.org/10.1016/ B978-0-08-101997-9.00001-1>.
85. Feng Q, Tong R. Anticancer nanoparticulate polymer-drug conjuga- gate. *Bioeng Transl Med*. 2016;1(3):277-296.
86. John JV, Uthaman S, Augustine R, Lekshmi KM, Park I-K, Kim I. Bio- mimetic pH/redox dual stimuli-responsive zwitterionic polymer block poly(L-histidine) micelles for intracellular delivery of doxorubi- cin into tumor cells. *J Polym Sci Part Polym Chem*. 2017;55(12):2061- 2070. <https://doi.org/10.1002/pola.28602>.
87. John JV, Uthaman S, Augustine R, Chen H, Park I-K, Kim I. pH/redox dual stimuli-responsive sheddable nanodaisies for efficient intracellular tumour-triggered drug delivery. *J Mater Chem B*. 2017;5(25): 5027-5036. <https://doi.org/10.1039/C7TB00030H>.
88. He J, Tong X, Zhao Y. Photoresponsive nanogels based on photo- controllable cross-links. *Macromolecules*. 2009;42(13):4845-4852. <https://doi.org/10.1021/ma900665v>.
89. Bertrand O, Gohy J-F. Photo-responsive polymers: synthesis and applications. *Polym Chem*. 2017;8(1):52-73.
90. Rasheed T, Bilal M, Abu-Thabit NY, Iqbal HMN. Chap. 3 - The smart chemistry of stimuli-responsive polymeric carriers for target drug delivery applications. In: Makhlof ASH, Abu-Thabit NY, eds. *Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications*. Vol 1. London, UK: Elsevier; 2018:61-99. <https://doi.org/10.1016/B978- 0-08-101997-9.00003-5>.
91. Beauté L, McClenaghan N, Lecommandoux S. Photo-triggered polymer nanomedicines: from molecular mechanisms to therapeutic applications. *Adv Drug Deliv Rev*. 2019;138:148-166. <https://doi. org/10.1016/j.addr.2018.12.010>.
92. Jin Q, Cai T, Han H, Wang H, Wang Y, Ji J. Light and pH dual- degradable triblock copolymer micelles for controlled intracellular drug release. *Macromol Rapid Commun*. 2014;35(15):1372-1378. <https://doi.org/10.1002/marc.201400171>.
93. Meng L, Huang W, Wang D, Huang X, Zhu X, Yan D. Chitosan-based nanocarriers with pH and light dual response for anticancer drug delivery. *Biomacromolecules*. 2013;14(8):2601-2610. <https://doi.org/ 10.1021/bm400451v>.
94. Zhou Y-N, Zhang Q, Luo Z-H. A light and pH dual-stimuli-responsive block copolymer synthesized by copper(0)-mediated living radical polymerization: solvatochromic, isomerization, and "schizophrenic" behaviors. *Langmuir*. 2014;30(6):1489-1499. <https://doi.org/10. 1021/la402948s>.
95. Xia Y, Zeng Y, Hu D, et al. Light and pH dual-sensitive biodegradable polymeric nanoparticles for controlled release of cargos. *J Polym Sci Part Polym Chem*. 2017;55(10):1773-1783. <https://doi.org/10.1002/ pola.28528>.
96. Badri W, Tarhini M, Lgourna Z, et al. Preparation and characterization of glued corn flakes-like protein-based magnetic particles. *Chem Afr*. 2020;3:803-811. <https://doi.org/10.1007/s42250-020- 00147-2>.
97. Tarhini M, Vega-Chacón J, Jafelicci M, et al. Structured magnetic core/silica internal shell layer and protein out layer shell (BSA@SiO<sub>2</sub>@SME): preparation and characterization. *Chem Afr*. 2020;3(1):127-134. <https://doi.org/10.1007/s42250-019-00097-4>.
98. Thévenot J, Oliveira H, Sandre O, Lecommandoux S. Magnetic responsive polymer composite materials. *Chem Soc Rev*. 2013;42 (17):7099-7116. <https://doi.org/10.1039/C3CS60058K>.
99. Indermun S, Govender M, Kumar P, Choonara YE, Pillay V. Chap. 2 - Stimuli-responsive polymers as smart drug delivery systems: classifications based on carrier type and triggered-release mechanism. In: Makhlof ASH, Abu-Thabit NY, eds. *Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications*. Vol 1. London, UK: Elsevier; 2018:43-58. <https://doi.org/10.1016/B978-0-08-101997- 9.00002-3>.
100. Curcio A, Marotta R, Riedinger A, Palumberi D, Falqui A, Pellegrino T. Magnetic pH-responsive nanogels as multifunctional delivery tools for small interfering RNA (siRNA) molecules and iron oxide nanoparticles (IONPs). *Chem Commun*. 2012;48(18):2400- 2402. <https://doi.org/10.1039/C2CC17223B>.
101. Mai BT, Fernandes S, Balakrishnan PB, Pellegrino T. Nanosystems based on magnetic nanoparticles and thermo- or pH-responsive polymers: an update and future perspectives. *Acc Chem Res*. 2018; 51(5):999-1013. <https://doi.org/10.1021/acs.accounts.7b00549>.
102. Traitel T, Cohen Y, Kost J. Characterization of glucose-sensitive insulin release systems in simulated in vivo conditions. *Biomaterials*. 2000;21(16):1679- 1687. [https://doi.org/10.1016/S0142-9612\(00\) 00050-8](https://doi.org/10.1016/S0142-9612(00) 00050-8).

103. Wu W, Mitra N, Yan ECY, Zhou S. Multifunctional hybrid nanogel for integration of optical glucose sensing and self-regulated insulin release at physiological pH. *ACS Nano*. 2010;4(8):4831-4839. <https://doi.org/10.1021/nn1008319>.
104. Tan L, Yang M-Y, Wu H-X, et al. Glucose- and pH-responsive nano-gated ensemble based on polymeric network capped mesoporous silica. *ACS Appl Mater Interfaces*. 2015;7(11):6310-6316. <https://doi.org/10.1021/acsami.5b00631>.
105. Yin R, Tong Z, Yang D, Nie J. Glucose and pH dual-responsive concanavalin A based microhydrogels for insulin delivery. *Int J Biol Macromol*. 2011;49(5):1137-1142. <https://doi.org/10.1016/j.ijbiomac.2011.09.014>.
106. Naeem M, Kim W, Cao J, Jung Y, Yoo J-W. Enzyme/pH dual sensitive polymeric nanoparticles for targeted drug delivery to the inflamed colon. *Colloids Surf B Biointerfaces*. 2014;123:271-278. <https://doi.org/10.1016/j.colsurfb.2014.09.026>.
107. Kim SJ, Kim HII, Park SJ, Kim SI. Shape change characteristics of polymer hydrogel based on polyacrylic acid/poly(vinyl sulfonic acid) in electric fields. *Sens Actuators Phys*. 2004;115(1):146-150. <https://doi.org/10.1016/j.sna.2004.04.020>.
108. Wu W, Zhou T, Aiello M, Zhou S. Optically pH and H<sub>2</sub>O<sub>2</sub> dual responsive composite colloids through the directed assembly of organic dyes on responsive microgels. *Chem Mater*. 2009;21(20): 4905-4913. <https://doi.org/10.1021/cm901987t>.
109. Chen W, Du J. Ultrasound and pH dually responsive polymer vesicles for anticancer drug delivery. *Sci Rep*. 2013;3(1):1-9. <https://doi.org/10.1038/srep02162>.
110. Wu L, Cong Y, Chen K, Zhou S. Synthesis of pH and UV dual-responsive microcapsules with high loading capacity and their application for self-healing hydrophobic coatings. *J Mater Chem A*. 2015; 3:19093-19099. <https://doi.org/10.1039/C5TA04986E>.
111. Li Q, Cao Z, Wang G. Diazonaphthoquinone-based amphiphilic polymer assemblies for NIR/UV light- and pH-responsive controlled release. *Polym Chem*. 2018;9(4):463-471. <https://doi.org/10.1039/C7PY01822C>.
112. Jiang F, Chen S, Cao Z, Wang G. A photo, temperature, and pH responsive spiropyran-functionalized polymer: synthesis, self-assembly and controlled release. *Polymer*. 2016;83:85-91. <https://doi.org/10.1016/j.polymer.2015.12.027>.
113. Sumaru K, Kameda M, Kanamori T, Shinbo T. Characteristic phase transition of aqueous solution of poly(N-isopropylacrylamide) functionalized with spirobenzopyran. *Macromolecules*. 2004;37(13): 4949-4955. <https://doi.org/10.1021/ma049661x>.
114. Kotsuchibashi Y, Agustin RVC, Lu J-Y, Hall DG, Narain R. Temperature, pH, and glucose responsive gels via simple mixing of boroxole- and glyco-based polymers. *ACS Macro Lett*. 2013;2(3):260-264. <https://doi.org/10.1021/mz400076p>.
115. Wang L, Liu M, Gao C, Ma L, Cui D. A pH-, thermo-, and glucose-, triple-responsive hydrogels: synthesis and controlled drug delivery. *React Funct Polym*. 2010;70(3):159-167. <https://doi.org/10.1016/j.reactfunctpolym.2009.11.007>.
116. Brooks WLA, Hancoillie G, Kabb CP, Hoogenboom R, Sumerlin BS. Triple responsive block copolymers combining pH-responsive, thermoresponsive, and glucose-responsive behaviors. *J Polym Sci Part Polym Chem*. 2017;55(14):2309-2317. <https://doi.org/10.1002/pola.28615>.
117. Roy D, Cambre JN, Sumerlin BS. Triply-responsive boronic acid block copolymers: solution self-assembly induced by changes in temperature, pH, or sugar concentration. *Chem Commun*. 2009;45 (16):2106-2108. <https://doi.org/10.1039/B900374F>.
118. Liu J, Detrembleur C, Debuigne A, et al. Glucose-, pH- and thermo- responsive nanogels crosslinked by functional superparamagnetic maghemite nanoparticles as innovative drug delivery systems. *J Mater Chem B*. 2014;2(8):1009-1023. <https://doi.org/10.1039/c3tb21272f>.
119. Bütün V. Selective betainization of 2-(dimethylamino) ethyl methacrylate residues in tertiary amine methacrylate diblock copolymers and their aqueous solution properties. *Polymer*. 2003;44(24):7321- 7334.
120. Bütün V, Armes SP, Billingham NC. Selective quaternization of 2-(dimethylamino)ethyl methacrylate residues in tertiary amine methacrylate diblock copolymers. *Macromolecules*. 2001;34(5):1148- 1159. <https://doi.org/10.1021/ma001550k>.
121. Szczubialka K, Moczek Ł, Błaszkiwicz S, Nowakowska M. Photocrosslinkable smart terpolymers responding to pH, temperature, and ionic strength. *J Polym Sci Part Polym Chem*. 2004;42(15):3879- 3886. <https://doi.org/10.1002/pola.20249>.
122. Hils C, Fuchs E, Eger F, Schöbel J, Schmalz H. Converting poly (methyl methacrylate) into a triple-responsive polymer. *Chem A Eur J*. 2020;26:5611-5614.
123. Huang J, Qin H, Wang B, Tan Q, Lu J. Design of smart polyacrylates showing thermo-, pH-, and CO<sub>2</sub>-responsive features. *Polym Chem*. 2019;10(46):6379-6384. <https://doi.org/10.1039/C9PY01410A>.
124. Chen S, Bian Q, Wang P, et al. Photo, pH and redox multi-responsive nanogels for drug delivery and fluorescence cell imaging. *Polym Chem*. 2017;8:6150-6157. <https://doi.org/10.1039/C7PY01424D>.
125. Yuan W, Shen T, Wang J, Zou H. Formation-dissociation of glucose, pH and redox triply responsive micelles and controlled release of insulin. *Polym Chem*. 2014;5(13):3968-3971. <https://doi.org/10.1039/C4PY00463A>.
126. Tuncer C, Samav Y, Ülker D, Baker SB, Bütün V. Multi-responsive micro-gel of a water-soluble monomer via emulsion polymerization. *J Appl Polym Sci*. 2015;132(24):1-7. <https://doi.org/10.1002/app.42072>.
127. Cao Z, Wu H, Dong J, Wang G. Quadruple-stimuli-sensitive polymeric nanocarriers for controlled release under combined stimulation. *Macromolecules*. 2014;47(24):8777-8783. <https://doi.org/10.1021/ma502003v>.
128. Guragain S, Prasad Bastakoti B, Ito M, Yusa S, Nakashima K. Aqueous polymeric micelles of poly[N-isopropylacrylamide-b-sodium 2-(acrylamido)-2-methylpropanesulfonate] with a spiropyran dimer pendant: quadruple stimuli-responsiveness. *Soft Matter*. 2012;8(37): 9628-9634. <https://doi.org/10.1039/C2SM26463C>.
129. Shakya AK, Sami H, Srivastava A, Kumar A. Stability of responsive polymer-protein bioconjugates. *Prog Polym Sci*. 2010;35(4):459-486. <https://doi.org/10.1016/j.progpolymsci.2010.01.003>.
130. Kumar A, Srivastava A, Galaev IY, Mattiasson B. Smart polymers: physical forms and bioengineering applications. *Prog Polym Sci*. 2007;32(10):1205-1237. <https://doi.org/10.1016/j.progpolymsci.2007.05.003>.
131. Florence AT, Attwood D. Physicochemical drug interactions and incompatibilities. In: Florence AT, Attwood D, eds. *Physicochemical Principles of Pharmacy*. London, England: Macmillan Education; 1998:449-492. [https://doi.org/10.1007/978-1-349-14416-7\\_11](https://doi.org/10.1007/978-1-349-14416-7_11).
132. Yoshida T, Lai TC, Kwon GS, Sako K. pH- and ion-sensitive polymers for drug delivery. *Expert Opin Drug Deliv*. 2013;10(11):1497-1513. <https://doi.org/10.1517/17425247.2013.821978>.
133. Bae YM, Park YI, Nam SH, et al. Endocytosis, intracellular transport, and exocytosis of lanthanide-doped upconverting nanoparticles in single living cells. *Biomaterials*. 2012;33(35):9080-9086. <https://doi.org/10.1016/j.biomaterials.2012.08.039>.
134. Lee ES, Oh KT, Kim D, Youn YS, Bae YH. Tumor pH-responsive flower-like micelles of poly(L-lactic acid)-b-poly(ethylene glycol)-b-poly(L-histidine). *J Control Release*. 2007;123(1):19-26. <https://doi.org/10.1016/j.jconrel.2007.08.006>.
135. Ko J, Park K, Kim Y-S, et al. Tumoral acidic extracellular pH targeting of pH-responsive MPEG-poly(β-amino ester) block copolymer micelles for cancer therapy. *J Control Release*. 2007;123(2):109-115. <https://doi.org/10.1016/j.jconrel.2007.07.012>.
136. Liu J, Huang Y, Kumar A, et al. pH-sensitive nano-systems for drug delivery in cancer therapy. *Biotechnol Adv*. 2014;32(4):693-710. <https://doi.org/10.1016/j.biotechadv.2013.11.009>.
137. Deirram N, Zhang C, Kermaniyan SS, Johnston APR, Such GK. pH-responsive polymer nanoparticles for drug delivery. *Macromol Rapid Commun*. 2019;40(10):1800917. <https://doi.org/10.1002/marc.201800917>.
138. Pang X, Jiang Y, Xiao Q, Leung AW, Hua H, Xu C. pH-responsive polymer-drug conjugates: design and progress. *J Control Release*. 2016;222:116-129. <https://doi.org/10.1016/j.jconrel.2015.12.024>.
139. Stuart MAC. Emerging applications of stimuli-responsive polymer materials. *Nat Mater*. 2010;9(2):101-113.
140. Aubry J, Ganachaud F, Cohen Addad J-P, Cabane B. Nanoprecipitation of polymethylmethacrylate by solvent shifting:1. Boundaries. *Langmuir*. 2009;25(4):1970-1979. <https://doi.org/10.1021/la803000e>.
141. Nasef AM, Gardouh AR, Ghorab MM. Formulation and in-vitro evaluation of pantoprazole loaded pH-sensitive polymeric nanoparticles. *Future J Pharm Sci*. 2017;3(2):103-117.
142. Sester C, Ofridam F, Lebaz N, Gagnière E, Mangin D, Elaissari A. pH-sensitive methacrylic acid-methyl methacrylate copolymer Eudragit L100 and dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate tri-copolymer Eudragit E100. *Polym Adv Technol*. 2019;31:440-450. <https://doi.org/10.1002/pat.4780>.

143. Ofridam F, Lebaz N, Gagnière É, Mangin D, Elaissari A. Effect of secondary polymer on self-precipitation of pH-sensitive polymethylmethacrylate derivatives Eudragit E100 and Eudragit L100. *Polym Adv Technol.* 2020;31(6):1270-1279. <https://doi.org/10.1002/pat.4856>.
144. Zeeshan M, Ali H, Khan S, Khan SA, Weigmann B. Advances in orally- delivered pH-sensitive nanocarrier systems; an optimistic approach for the treatment of inflammatory bowel disease. *Int J Pharm.* 2019; 558:201-214. <https://doi.org/10.1016/j.ijpharm.2018.12.074>.
145. Palugan L, Cerea M, Zema L, Gazzaniga A, Maroni A. Coated pellets for oral colon delivery. *J Drug Deliv Sci Technol.* 2015;25:1-15. <https://doi.org/10.1016/j.jddst.2014.12.003>.
146. Douroumis D. Orally disintegrating dosage forms and taste-masking technologies; 2010. *Expert Opin Drug Deliv.* 2011;8(5):665-675. <https://doi.org/10.1517/17425247.2011.566553>.
147. Mastholimath VS, Dandagi PM, Jain SS, Gadad AP, Kulkarni AR. Time and pH dependent colon specific, pulsatile delivery of theophylline for nocturnal asthma. *Int J Pharm.* 2007;328(1):49-56. <https://doi.org/10.1016/j.ijpharm.2006.07.045>.
148. Maestrelli F, Cirri M, Corti G, Mennini N, Mura P. Development of enteric-coated calcium pectinate microspheres intended for colonic drug delivery. *Eur J Pharm Biopharm.* 2008;69(2):508-518. <https://doi.org/10.1016/j.ejpb.2007.12.004>.
149. Kadam VD, Gattani SG. Development of colon targeted multiparticulate pulsatile drug delivery system for treating nocturnal asthma. *Drug Deliv.* 2010;17(5):343-351. <https://doi.org/10.3109/10717541003762821>.
150. Zhou Y, Qiu B, Yin X, Liu H, Zhu L. Concomitant drugs-loaded micro- capsules of roxithromycin and theophylline with pH-sensitive controlled-releasing properties. *Int J Polym Mater Polym Biomater.* 2020;69(11):679-690. <https://doi.org/10.1080/00914037.2019.1596917>.
151. Obeidat WM, Price JC. Preparation and evaluation of Eudragit S 100 microspheres as pH-sensitive release preparations for piroxicam and theophylline using the emulsion-solvent evaporation method. *J Microencapsul.* 2006;23(2):195-202. <https://doi.org/10.1080/02652040500435337>.
152. Joshi VG, Mohamed S. Development and characterization of enteric-coated salbutamol sulphate time release tablets. *Int J Drug Deliv.* 2014;6(1):64.
153. Sung H-W, Sonaje K, Liao Z-X, Hsu L-W, Chuang E-Y. pH- responsive nanoparticles shelled with chitosan for oral delivery of insulin: from mechanism to therapeutic applications. *Acc Chem Res.* 2012;45(4):619-629. <https://doi.org/10.1021/ar200234q>.
154. Chandran S, Asghar LFA, Mantha N. Design and evaluation of ethyl cellulose based matrix tablets of ibuprofen with pH modulated release kinetics. *Indian J Pharm Sci.* 2008;70(5):596-602. <https://doi.org/10.4103/0250-474X.45397>.
155. Shah SA, Sohail M, Minhas MU, et al. pH-responsive CAP-co-poly (methacrylic acid)-based hydrogel as an efficient platform for controlled gastrointestinal delivery: fabrication, characterization, in vitro and in vivo toxicity evaluation. *Drug Deliv Transl Res.* 2019;9(2):555- 577. <https://doi.org/10.1007/s13346-018-0486-8>.
156. Jalil A, Khan S, Naeem F, et al. The structural, morphological and thermal properties of grafted pH-sensitive interpenetrating highly porous polymeric composites of sodium alginate/acrylic acid copolymers for controlled delivery of diclofenac potassium. *Des Monomers Polym.* 2017;20(1):308-324. <https://doi.org/10.1080/15685551.2016.1259834>.
157. Cetin M, Atila A, Kadioglu Y. Formulation and in vitro characterization of Eudragit® L100 and Eudragit® L100-PLGA nanoparticles containing diclofenac sodium. *AAPS PharmSciTech.* 2010;11(3): 1250-1256. <https://doi.org/10.1208/s12249-010-9489-6>.
158. Alotaibi HF, Elsamaligy S, Mahrous GM, Bayomi MA, Mahmoud HA. Design of taste masked entericodispersible tablets of diclofenac sodium by applying fluid bed coating technology. *Saudi Pharm J.* 2019;27(3):354-362. <https://doi.org/10.1016/j.jsps.2018.12.003>.
159. Hameed HA, Khan S, Shahid M, et al. Engineering of naproxen loaded polymer hybrid enteric microspheres for modified release tablets: development, characterization, in silico modelling and in vivo evaluation. *Drug Des Devel Ther.* 2020;14:27-41. <https://doi.org/10.2147/DDDT.S232111>.
160. Cui C, Sun J, Wang X, Yu Z, Shi Y. Factors contributing to drug release from enteric-coated omeprazole capsules: an in vitro and in vivo pharmacokinetic study and IVIVC evaluation in beagle dogs. *Dose-Response.* 2020;18(1):1-13. <https://doi.org/10.1177/1559325820908980>.
161. Li C, Zhou K, Chen D, et al. Solid lipid nanoparticles with enteric coating for improving stability, palatability, and oral bioavailability of enrofloxacin. *Int J Nanomedicine.* 2019;14:1619-1631. <https://doi.org/10.2147/IJN.S183479>.
162. Sonaje K, Lin K-J, Wey S-P, et al. Biodistribution, pharmacodynamics and pharmacokinetics of insulin analogues in a rat model: oral delivery using pH-responsive nanoparticles vs. subcutaneous injection. *Biomaterials.* 2010;31(26):6849-6858. <https://doi.org/10.1016/j.biomaterials.2010.05.042>.
163. Yu F, Li Y, Liu CS, et al. Enteric-coated capsules filled with mono- disperse micro-particles containing PLGA-lipid-PEG nanoparticles for oral delivery of insulin. *Int J Pharm.* 2015;484(1):181-191. <https://doi.org/10.1016/j.ijpharm.2015.02.055>.
164. Wu ZM, Zhou L, Guo XD, et al. HP55-coated capsule containing PLGA/RS nanoparticles for oral delivery of insulin. *Int J Pharm.* 2012;425(1):1-8. <https://doi.org/10.1016/j.ijpharm.2011.12.055>.
165. Naha PC, Kanchan V, Manna PK, Panda AK. Improved bioavailability of orally delivered insulin using Eudragit-L30D coated PLGA micro- particles. *J Microencapsul.* 2008;25(4):248-256. <https://doi.org/10.1080/02652040801903843>.
166. Jelvehgari M, Zakeri-Milani P, Siahi-Shadbad MR, et al. Development of pH-sensitive insulin nanoparticles using Eudragit L100-55 and chitosan with different molecular weights. *AAPS PharmSciTech.* 2010;11(3):1237-1242. <https://doi.org/10.1208/s12249-010-9488-7>.
167. Sun S, Liang N, Yamamoto H, Kawashima Y, Cui F, Yan P. pH- sensitive poly(lactide-co-glycolide) nanoparticle composite micro- capsules for oral delivery of insulin. *Int J Nanomedicine.* 2015;10: 3489-3498. <https://doi.org/10.2147/IJN.S81715>.
168. Agrawal GR, Wakte P, Shelke S. Formulation, physicochemical characterization and in vitro evaluation of human insulin-loaded micro- spheres as potential oral carrier. *Prog Biomater.* 2017;6(3):125-136. <https://doi.org/10.1007/s40204-017-0072-z>.
169. Li P, Tan A, Prestidge CA, Nielsen HM, Müllertz A. Self- nanoemulsifying drug delivery systems for oral insulin delivery: in vitro and in vivo evaluations of enteric coating and drug loading. *Int J Pharm.* 2014;477(1):390-398. <https://doi.org/10.1016/j.ijpharm.2014.10.039>.
170. Liu L, Zhang Y, Yu S, Zhang Z, He C, Chen X. pH- and amylase- responsive carboxymethyl starch/poly(2-isobutyl-acrylic acid) hybrid microgels as effective enteric carriers for oral insulin delivery. *Bio- macromolecules.* 2018;19(6):2123-2136. <https://doi.org/10.1021/acs.biomac.8b00215>.
171. Abou Taleb MF. Radiation synthesis of multifunctional polymeric hydrogels for oral delivery of insulin. *Int J Biol Macromol.* 2013;62: 341-347. <https://doi.org/10.1016/j.ijbiomac.2013.09.004>.
172. Tawfeek HM, Abdellatif AAH, Dennison TJ, Mohammed AR, Sadiq Y, Saleem IY. Colonic delivery of indometacin loaded PGA-co- PDL microparticles coated with Eudragit L100-55 from fast dis- integrating tablets. *Int J Pharm.* 2017;531(1):80-89. <https://doi.org/10.1016/j.ijpharm.2017.08.069>.
173. Gao GH, Li Y, Lee DS. Environmental pH-sensitive polymeric micelles for cancer diagnosis and targeted therapy. *J Control Release.* 2013;169(3):180-184. <https://doi.org/10.1016/j.jconrel.2012.11.012>.
174. Kim D, Lee ES, Oh KT, Gao ZG, Bae YH. Doxorubicin-loaded polymeric micelle overcomes multidrug resistance of cancer by double- targeting folate receptor and early endosomal pH. *Small.* 2008;4(11): 2043-2050. <https://doi.org/10.1002/sml.200701275>.
175. Huh KM, Kang HC, Lee YJ, Bae YH. pH-sensitive polymers for drug delivery. *Macromol Res.* 2012;20(3):224-233. <https://doi.org/10.1007/s13233-012-0059-5>.
176. Li B, Meng Z, Li Q, et al. A pH responsive complexation-based drug delivery system for oxaliplatin. *Chem Sci.* 2017;8(6):4458-4464. <https://doi.org/10.1039/C7SC01438D>.
177. Duncan R. Polymer conjugates as anticancer nanomedicines. *Nat Rev Cancer.* 2006;6(9):688-701. <https://doi.org/10.1038/nrc1958>.
178. Gao GH, Im GH, Kim MS, et al. Magnetite-nanoparticle- encapsulated pH-responsive polymeric micelle as an MRI probe for detecting acidic pathologic areas. *Small.* 2010;6(11):1201-1204. <https://doi.org/10.1002/sml.200902317>.
179. Min KH, Kim J-H, Bae SM, et al. Tumoral acidic pH-responsive MPEG-poly(β-amino ester) polymeric micelles for cancer targeting therapy. *J Control Release.* 2010;144(2):259-266. <https://doi.org/10.1016/j.jconrel.2010.02.024>.
180. Kim KS, Park W, Hu J, Bae YH, Na K. A cancer-recognizable MRI contrast agents using pH-responsive polymeric micelle. *Biomaterials.* 2014;35(1):337-343. <https://doi.org/10.1016/j.biomaterials.2013.10.004>.
181. Wang Y, Zhou K, Huang G, et al. A nanoparticle-based strategy for the imaging of a broad range of tumours by nonlinear amplification of microenvironment signals. *Nat Mater.* 2014;13(2):204-212. <https://doi.org/10.1038/nmat3819>.



182. Zhao T, Huang G, Li Y, et al. A transistor-like pH nanoprobe for tumour detection and image-guided surgery. *Nat Biomed Eng.* 2016; 1:1-20. <https://doi.org/10.1038/s41551-016-0006>.
183. Kanamala M, Wilson WR, Yang M, Palmer BD, Wu Z. Mechanisms and biomaterials in pH-responsive tumour targeted drug delivery: a review. *Biomaterials.* 2016;85:152-167. <https://doi.org/10.1016/j.biomaterials.2016.01.061>.
184. Su Z, Liang Y, Yao Y, Wang T, Zhang N. Polymeric complex micelles based on the double-hydrazone linkage and dual drug-loading strategy for pH-sensitive docetaxel delivery. *J Mater Chem B.* 2016;4(6): 1122-1133. <https://doi.org/10.1039/C5TB02188J>.
185. Yang T, Du G, Cui Y, et al. pH-sensitive doxorubicin-loaded polymeric nanocomplex based on  $\beta$ -cyclodextrin for liver cancer- targeted therapy. *Int J Nanomedicine.* 2019;14:1997-2010. <https://doi.org/10.2147/IJN.S193170>.
186. Longhi A, Ferraris S, Bacci G, Specchia S. Long-term follow-up of patients with doxorubicin-induced cardiac toxicity after chemotherapy for osteosarcoma. *Anticancer Drugs.* 2007;18(6):737-744. <https://doi.org/10.1097/CAD.0b013e32803d36fe>.
187. Tan ML, Choong PFM, Dass CR. Review: doxorubicin delivery systems based on chitosan for cancer therapy. *J Pharm Pharmacol.* 2009;61(2):131-142. <https://doi.org/10.1211/jpp.61.02.0001>.
188. Feng C, Wang Z, Jiang C, et al. Chitosan/o-carboxymethyl chitosan nanoparticles for efficient and safe oral anticancer drug delivery: in vitro and in vivo evaluation. *Int J Pharm.* 2013;457(1):158-167. <https://doi.org/10.1016/j.ijpharm.2013.07.079>.
189. Shi J, Liu Y, Wang L, et al. A tumoral acidic pH-responsive drug delivery system based on a novel photosensitizer (fullerene) for in vitro and in vivo chemophotodynamic therapy. *Acta Biomater.* 2014;10(3):1280-1291. <https://doi.org/10.1016/j.actbio.2013.10.037>.
190. Chytil P, Šírová M, Kudláčová J, Říhová B, Ulbrich K, Etrych T. Bloodstream stability predetermines the antitumor efficacy of micellar polymer-doxorubicin drug conjugates with pH-triggered drug release. *Mol Pharm.* 2018;15(9):3654-3663. <https://doi.org/10.1021/acs.molpharmaceut.8b00156>.
191. Xu X, Li L, Zhou Z, Sun W, Huang Y. Dual-pH responsive micelle platform for co-delivery of axitinib and doxorubicin. *Int J Pharm.* 2016;507(1):50-60. <https://doi.org/10.1016/j.ijpharm.2016.04.060>.
192. Thambi T, Deepagan VG, Yoo CK, Park JH. Synthesis and physico-chemical characterization of amphiphilic block copolymers bearing acid-sensitive orthoester linkage as the drug carrier. *Polymer.* 2011; 52(21):4753-4759. <https://doi.org/10.1016/j.polymer.2011.08.024>.
193. Wei X, Luo Q, Sun L, et al. Enzyme- and pH-sensitive branched polymer-doxorubicin conjugate-based nanoscale drug delivery system for cancer therapy. *ACS Appl Mater Interfaces.* 2016;8(18): 11765-11778. <https://doi.org/10.1021/acsami.6b02006>.
194. Tang R, Ji W, Panus D, Palumbo RN, Wang C. Block copolymer micelles with acid-labile ortho ester side-chains: synthesis, characterization, and enhanced drug delivery to human glioma cells. *J Control Release.* 2011;151(1):18-27. <https://doi.org/10.1016/j.jconrel.2010.12.005>.
195. Unsoy G, Khodadust R, Yalcin S, Mutlu P, Gunduz U. Synthesis of doxorubicin loaded magnetic chitosan nanoparticles for pH responsive targeted drug delivery. *Eur J Pharm Sci.* 2014;62:243-250. <https://doi.org/10.1016/j.ejps.2014.05.021>.
196. Sadighian S, Rostamizadeh K, Hosseini-Monfared H, Hamidi M. Doxorubicin-conjugated core-shell magnetite nanoparticles as dual- targeting carriers for anticancer drug delivery. *Colloids Surf B Bio- interfaces.* 2014;117:406-413. <https://doi.org/10.1016/j.colsurfb.2014.03.001>.
197. Montha W, Maneeprakom W, Buatong N, Tang I-M, Pon-On W. Synthesis of doxorubicin-PLGA loaded chitosan stabilized (Mn, Zn) Fe<sub>2</sub>O<sub>4</sub> nanoparticles: biological activity and pH-responsive drug release. *Mater Sci Eng C.* 2016;59:235-240. <https://doi.org/10.1016/j.msec.2015.09.098>.
198. Shalviri A, Raval G, Prasad P, et al. pH-dependent doxorubicin release from terpolymer of starch, polymethacrylic acid and polysorbate 80 nanoparticles for overcoming multi-drug resistance in human breast cancer cells. *Eur J Pharm Biopharm.* 2012;82(3):587- 597. <https://doi.org/10.1016/j.ejpb.2012.09.001>.
199. Zhang Y, Yang C, Wang W, et al. Co-delivery of doxorubicin and curcumin by pH-sensitive prodrug nanoparticle for combination therapy of cancer. *Sci Rep.* 2016;6(1):1-12. <https://doi.org/10.1038/srep21225>.
200. Johnson RP, Jeong Y-I, Choi E, et al. Biocompatible poly (2-hydroxyethyl methacrylate)-b-poly(L-histidine) hybrid materials for pH-sensitive intracellular anticancer drug delivery. *Adv Funct Mater.* 2012;22(5):1058-1068. <https://doi.org/10.1002/adfm.201102756>.
201. Zhou Z, Li L, Yang Y, Xu X, Huang Y. Tumor targeting by pH-sensitive, biodegradable, cross-linked N-(2-hydroxypropyl) methacrylamide copolymer micelles. *Biomaterials.* 2014;35(24):6622- 6635. <https://doi.org/10.1016/j.biomaterials.2014.04.059>.
202. Kim JO, Kabanov AV, Bronich TK. Polymer micelles with cross-linked polyanion core for delivery of a cationic drug doxorubicin. *J Control Release.* 2009;138(3):197-204. <https://doi.org/10.1016/j.jconrel.2009.04.019>.
203. Li H, Li M, Chen C, et al. On-demand combinational delivery of curcumin and doxorubicin via a pH-labile micellar nanocarrier. *Int J Pharm.* 2015;495(1):572-578. <https://doi.org/10.1016/j.ijpharm.2015.09.022>.
204. Hamaguchi T, Matsumura Y, Suzuki M, et al. NK105, a paclitaxel-incorporating micellar nanoparticle formulation, can extend in vivo antitumor activity and reduce the neurotoxicity of paclitaxel. *Br J Cancer.* 2005;92(7):1240-1246. <https://doi.org/10.1038/sj.bjc.6602479>.
205. Licciardi M, Craparo EF, Giammona G, Armes SP, Tang Y, Lewis AL. In vitro biological evaluation of folate-functionalized block copolymer micelles for selective anti-cancer drug delivery. *Macromol Biosci.* 2008;8(7):615-626. <https://doi.org/10.1002/mabi.200800009>.
206. Yuan Z, Huang J, Liu J, Cheng S, Zhuo R, Li F. PEG-detachable and acid-labile cross-linked micelles based on orthoester linked graft copolymer for paclitaxel release. *Nanotechnology.* 2011;22(33): 335601. <https://doi.org/10.1088/0957-4484/22/33/335601>.
207. Shen Y, Zhan Y, Tang J, et al. Multifunctioning pH-responsive nanoparticles from hierarchical self-assembly of polymer brush for cancer drug delivery. *AIChE J.* 2008;54(11):2979-2989. <https://doi.org/10.1002/aic.11600>.
208. Qu Y, Chu B, Wei X, et al. Redox/pH dual-stimuli responsive camptothecin prodrug nanogels for "on-demand" drug delivery. *J Control Release.* 2019;296:93-106. <https://doi.org/10.1016/j.jconrel.2019.01.016>.
209. Vivek R, Nipun Babu V, Thangam R, Subramanian KS, Kannan S. pH-responsive drug delivery of chitosan nanoparticles as tamoxifen carriers for effective anti-tumor activity in breast cancer cells. *Colloids Surf B Biointerfaces.* 2013;111:117-123. <https://doi.org/10.1016/j.colsurfb.2013.05.018>.
210. Ahmad Z, Majeed S, Shah A. In vitro release and cytotoxicity of cis-platin loaded methoxy poly (ethylene glycol)-block-poly (glutamic acid) nanoparticles against human breast cancer cell lines. *J Drug Deliv Sci Technol.* 2018;43:85-93. <https://doi.org/10.1016/j.jddst.2017.09.016>.
211. Kurd K, Khandagi AA, Davaran S, Akbarzadeh A. Cisplatin release from dual-responsive magnetic nanocomposites. *Artif Cells Nanomedicine Biotechnol.* 2015;30:1-9. <https://www.tandfonline.com/doi/abs/10.3109/21691401.2015.1008513>.
212. Liu H, Chen H, Cao F, Peng D, Chen W, Zhang C. Amphiphilic block copolymer poly (acrylic acid)-b-polycaprolactone as a novel pH-sensitive nanocarrier for anti-cancer drugs delivery: in-vitro and in- vivo evaluation. *Polymers.* 2019;11(5):820.
213. Shim MS, Kwon YJ. Stimuli-responsive polymers and nanomaterials for gene delivery and imaging applications. *Adv Drug Deliv Rev.* 2012;64(11):1046-1059. <https://doi.org/10.1016/j.addr.2012.01.018>.
214. Godbey WT, Wu KK, Mikos AG. Poly(ethylenimine) and its role in gene delivery. *J Control Release.* 1999;60(2):149-160. [https://doi.org/10.1016/S0168-3659\(99\)00090-5](https://doi.org/10.1016/S0168-3659(99)00090-5).
215. Zakeri A, Kouhbanani MAJ, Beheshtkoo N, et al. Polyethylenimine-based nanocarriers in co-delivery of drug and gene: a developing horizon. *Nano Rev Exp.* 2018;9(1):1488497. <https://doi.org/10.1080/20022727.2018.1488497>.
216. Kim YH, Park JH, Lee M, Kim Y-H, Park TG, Kim SW. Poly- ethylenimine with acid-labile linkages as a biodegradable gene carrier. *J Control Release.* 2005;103(1):209-219. <https://doi.org/10.1016/j.jconrel.2004.11.008>.
217. Zhu J, Tang A, Law LP, et al. Amphiphilic core-shell nanoparticles with poly(ethylenimine) shells as potential gene delivery carriers. *Bioconjug Chem.* 2005;16(1):139-146. <https://doi.org/10.1021/bc049895i>.
218. Nam J-P, Kim S, Kim SW. Design of PEI-conjugated bio-reducible polymer for efficient gene delivery. *Int J Pharm.* 2018;545(1):295- 305. <https://doi.org/10.1016/j.ijpharm.2018.04.051>.
219. Yue J, Wu J, Liu D, Zhao X, Lu WW. BMP2 gene delivery to bone mesenchymal stem cell by chitosan-g-PEI nonviral vector. *Nanoscale Res Lett.* 2015;10(1):203. <https://doi.org/10.1186/s11671-015- 0906-3>.
220. Dimde M, Neumann F, Reisbeck F, et al. Defined pH-sensitive nanogels as gene delivery platform for siRNA mediated in vitro gene silencing. *Biomater Sci.* 2017;5(11):2328-2336. <https://doi.org/10.1039/C7BM00729A>.

221. Manganiello MJ, Cheng C, Convertine AJ, Bryers JD, Stayton PS. Diblock copolymers with tunable pH transitions for gene delivery. *Biomaterials*. 2012;33(7):2301-2309. <https://doi.org/10.1016/j.biomaterials.2011.11.019>.
222. Zhu C, Jung S, Luo S, et al. Co-delivery of siRNA and paclitaxel into cancer cells by biodegradable cationic micelles based on PDMAEMA-PCL-PDMAEMA triblock copolymers. *Biomaterials*. 2010;31(8):2408-2416. <https://doi.org/10.1016/j.biomaterials.2009.11.077>.
223. Cho HY, Srinivasan A, Hong J, et al. Synthesis of biocompatible PEG-based star polymers with cationic and degradable core for siRNA delivery. *Biomacromolecules*. 2011;12(10):3478-3486. <https://doi.org/10.1021/bm2006455>.
224. Yue X, Zhang W, Xing J, et al. Self-assembled cationic triblock copolymer mPEG-b-PDLLA-b-PDMA nanoparticles as nonviral gene vector. *Soft Matter*. 2012;8(7):2252-2260. <https://doi.org/10.1039/C2SM07068E>.
225. Chim YTA, Lam JKW, Ma Y, et al. Structural study of DNA condensation induced by novel phosphorylcholine-based copolymers for gene delivery and relevance to DNA protection. *Langmuir*. 2005;21(8):3591-3598. <https://doi.org/10.1021/la047480i>.
226. Lai J, Xu Z, Tang R, et al. PEGylated block copolymers containing tertiary amine side-chains cleavable via acid-labile ortho ester link-ages for pH-triggered release of DNA. *Polymer*. 2014;55(12):2761-2771. <https://doi.org/10.1016/j.polymer.2014.04.036>.
227. Paek K, Yang H, Lee J, Park J, Kim BJ. Efficient colorimetric pH sensor based on responsive polymer-quantum dot integrated graphene oxide. *ACS Nano*. 2014;8(3):2848-2856. <https://doi.org/10.1021/nn406657b>.
228. Zhao Y, Shi C, Yang X, et al. pH- and temperature-sensitive hydrogel nanoparticles with dual photoluminescence for bio probes. *ACS Nano*. 2016;10(6):5856-5863. <https://doi.org/10.1021/acs.nano.6b00770>.
229. Phuong PTM, Ryplida B, In I, Park SY. High performance of electro-chemical and fluorescent probe by interaction of cell and bacteria with pH-sensitive polymer dots coated surfaces. *Mater Sci Eng C*. 2019;101:159-168. <https://doi.org/10.1016/j.msec.2019.03.098>.
230. Khoerunnisa MZAI, In I, Park SY. pH-switchable bacteria detection using zwitterionic fluorescent polymer. *Biosens Bioelectron*. 2017;90:394-402. <https://doi.org/10.1016/j.bios.2016.12.013>.
231. Wang L, Li C. pH responsive fluorescence nanoprobe imaging of tumors by sensing the acidic microenvironment. *J Mater Chem*. 2011;21(40):15862-15871. <https://doi.org/10.1039/C1JM12072G>.
232. Matsumoto A, Yoshida R, Kataoka K. Glucose-responsive polymer gel bearing phenylborate derivative as a glucose-sensing moiety operating at the physiological pH. *Biomacromolecules*. 2004;5(3):1038-1045. <https://doi.org/10.1021/bm0345413>.
233. Kang SI, Bae YH. A sulfonamide based glucose-responsive hydrogel with covalently immobilized glucose oxidase and catalase. *J Control Release*. 2003;86(1):115-121. [https://doi.org/10.1016/S0168-3659\(02\)00409-1](https://doi.org/10.1016/S0168-3659(02)00409-1).
234. Cui H, Zhao Q, Wang Y, Du X. Bioinspired actuators based on stimuli-responsive Polymers. *Chem Asian J*. 2019;14(14):2369-2387. <https://doi.org/10.1002/asia.201900292>.
235. Ko H, Javey A. Smart actuators and adhesives for reconfigurable matter. *Acc Chem Res*. 2017;50(4):691-702. <https://doi.org/10.1021/acs.accounts.6b00612>.
236. Li H, Go G, Ko SY, Park J-O, Park S. Magnetic actuated pH- responsive hydrogel-based soft micro-robot for targeted drug delivery. *Smart Mater Struct*. 2016;25(2):027001. <https://doi.org/10.1088/0964-1726/25/2/027001>.
237. Gonçalves JLM, Crucho CIC, Alves SPC, Baleizao C, Farinha JPS. Hybrid mesoporous nanoparticles for pH-actuated controlled release. *Nanomaterials*. 2019;9(3):483. <https://doi.org/10.3390/nano9030483>.
238. Li X, Cai X, Gao Y, Serpe MJ. Reversible bidirectional bending of hydrogel-based bilayer actuators. *J Mater Chem B*. 2017;5(15):2804-2812. <https://doi.org/10.1039/C7TB00426E>.
239. Shang J, Theato P. Smart composite hydrogel with pH-, ionic strength- and temperature-induced actuation. *Soft Matter*. 2018;14(41):8401-8407. <https://doi.org/10.1039/C8SM01728J>.
240. Cheng Y, Huang C, Yang D, Ren K, Wei J. Bilayer hydrogel mixed composites that respond to multiple stimuli for environmental sensing and underwater actuation. *J Mater Chem B*. 2018;6(48):8170-8179. <https://doi.org/10.1039/C8TB02242A>.
241. Park JY, Oh HJ, Kim DJ, Baek JY, Lee SH. A polymeric microfluidic valve employing a pH-responsive hydrogel microsphere as an actuating source. *J Micromechanics Microengineering*. 2006;16(3):656-663. <https://doi.org/10.1088/0960-1317/16/3/022>.
242. Zarzar LD, Kim P, Aizenberg J. Bio-inspired design of submerged hydrogel-actuated polymer microstructures operating in response to pH. *Adv Mater*. 2011;23(12):1442-1446. <https://doi.org/10.1002/adma.201004231>.
243. Hester JF, Olugebefola SC, Mayes AM. Preparation of pH-responsive polymer membranes by self-organization. *J Membr Sci*. 2002;208(1):375-388. [https://doi.org/10.1016/S0376-7388\(02\)00317-4](https://doi.org/10.1016/S0376-7388(02)00317-4).
244. Jiang J-H, Zhu L-P, Zhang H-T, Zhu B-K, Xu Y-Y. Improved hydrodynamic permeability and antifouling properties of poly(vinylidene fluoride) membranes using polydopamine nanoparticles as additives. *J Membr Sci*. 2014;457:73-81. <https://doi.org/10.1016/j.memsci.2014.01.043>.
245. Yang H, Fang S, Song H-M, Zhu L-J, Zeng Z-X. pH-responsive poly(vinylidene fluoride)/poly(acrylic acid) porous membranes prepared via an vapor induced phase separation technique for removing copper ions from water. *Mater Lett*. 2020;260:126957. <https://doi.org/10.1016/j.matlet.2019.126957>.
246. Xian Y, Shui Y, Li M, Pei C, Zhang Q, Yao Y. pH-dependent thermo-responsive poly[2-(diethylamino)ethyl acrylamide]-grafted PVDF membranes with switchable wettability for efficient emulsion separation. *J Appl Polym Sci*. 2020;137:49032. <https://doi.org/10.1002/app.49032>.
247. Liu H, Yang S, Liu Y, et al. Fabricating a pH-responsive membrane through interfacial in-situ assembly of microgels for water gating and self-cleaning. *J Membr Sci*. 2019;579:230-239. <https://doi.org/10.1016/j.memsci.2019.03.010>.
248. Willott JD, Nielsen WM, de Vos WM. Stimuli-responsive membranes through sustainable aqueous phase separation. *ACS Appl Polym Mater*. 2020;2(2):659-667. <https://doi.org/10.1021/acsapm.9b01006>.
249. Lorenzo RA, Carro AM, Concheiro A, Alvarez-Lorenzo C. Stimuli-responsive materials in analytical separation. *Anal Bioanal Chem*. 2015;407(17):4927-4948. <https://doi.org/10.1007/s00216-015-8679-1>.
250. Loh XJ, Deen GR, Gan YY, Gan LH. Water-sorption and metal-uptake behavior of pH-responsive poly(N-acryloyl-N<sup>0</sup>-methylpiperazine) gels. *J Appl Polym Sci*. 2001;80(2):268-273. [https://doi.org/10.1002/1097-4628\(20010411\)80:2<268::AID-APP1095>3.0.CO;2-I](https://doi.org/10.1002/1097-4628(20010411)80:2<268::AID-APP1095>3.0.CO;2-I).
251. Yildiz U, Kemik ÖF, Hazer B. The removal of heavy metal ions from aqueous solutions by novel pH-sensitive hydrogels. *J Hazard Mater*. 2010;183(1):521-532. <https://doi.org/10.1016/j.jhazmat.2010.07.055>.
252. Li Z, Wang Y, Wu N, Chen Q, Wu K. Removal of heavy metal ions from wastewater by a novel HEA/AMPS copolymer hydrogel: preparation, characterization, and mechanism. *Environ Sci Pollut Res*. 2013;20(3):1511-1525. <https://doi.org/10.1007/s11356-012-0973-2>.
253. Ekici S. Intelligent poly(N-isopropylacrylamide)-carboxymethyl cellulose full interpenetrating polymeric networks for protein adsorption studies. *J Mater Sci*. 2011;46(9):2843-2850. <https://doi.org/10.1007/s10853-010-5158-0>.
254. Eldin MSM, El-Sherif HM, Soliman EA, Elzatahry AA, Omer AM. Polyacrylamide-grafted carboxymethyl cellulose: smart pH-sensitive hydrogel for protein concentration. *J Appl Polym Sci*. 2011;122(1):469-479. <https://doi.org/10.1002/app.33283>.
255. Basan H, Yarimkaya S. A novel solid-phase extraction- spectrofluorimetric method for the direct determination of atenolol in human urine. *Luminescence*. 2014;29(3):225-229. <https://doi.org/10.1002/bio.2532>.
256. Sakamoto C, Okada Y, Kanazawa H, et al. Temperature- and pH- responsive aminopropyl-silica ion-exchange columns grafted with copolymers of N-isopropylacrylamide. *J Chromatogr A*. 2004;1030(1):247-253. <https://doi.org/10.1016/j.chroma.2003.09.010>.
257. Ayano E, Suzuki Y, Kanazawa M, et al. Analysis of melatonin using a pH- and temperature-responsive aqueous chromatography system. *J Chromatogr A*. 2007;1156(1):213-219. <https://doi.org/10.1016/j.chroma.2007.01.063>.
258. Ayano E, Nambu K, Sakamoto C, Kanazawa H, Kikuchi A, Okano T. Aqueous chromatography system using pH- and temperature-responsive stationary phase with ion-exchange groups. *J Chromatogr A*. 2006;1119(1):58-65. <https://doi.org/10.1016/j.chroma.2006.01.068>.
259. Nishio T, Ayano E, Suzuki Y, Kanazawa H, Okano T. Separation of phosphorylated peptides utilizing dual pH- and temperature-responsive chromatography. *J Chromatogr A*. 2011;1218(15):2079-2084. <https://doi.org/10.1016/j.chroma.2010.10.076>.
260. Ma Q, Chen M, Yin H-R, Shi Z-G, Feng Y-Q. Preparation of pH- responsive stationary phase for reversed-phase liquid chromatography and hydrophilic interaction chromatography. *J Chromatogr A*. 2008;1212(1):61-67. <https://doi.org/10.1016/j.chroma.2008.10.007>.

261. Sepehrifar R, Boysen RI, Danylec B, Yang Y, Saito K, Hearn MTW. Design, synthesis and application of a new class of stimuli- responsive separation materials. *Anal Chim Acta*. 2017;963:153-163. <https://doi.org/10.1016/j.aca.2017.01.061>.
262. Ding Z, Li S, Cao X. Separation of lysozyme from salted duck egg white by affinity precipitation using pH-responsive polymer with an l-thyroxin ligand. *Sep Purif Technol*. 2014;138:153-160. <https://doi.org/10.1016/j.seppur.2014.10.021>.
263. Ding Z, Li S, Cao X. Microbial transglutaminase separation by pH- responsive affinity precipitation with crocein orange G as the ligand. *Appl Biochem Biotechnol*. 2015;177(1):253-266. <https://doi.org/10.1007/s12010-015-1742-8>.
264. Bai H, Fan C, Zhang W, et al. A pH-responsive soluble polymer- based homogeneous system for fast and highly efficient N- glycoprotein/glycopeptide enrichment and identification by mass spectrometry. *Chem Sci*. 2015;6(7):4234-4241. <https://doi.org/10.1039/C5SC00396B>.
265. Gao F-X, Zhao X-L, He X-W, Li W-Y, Zhang Y-K. A pH and temperature dual-responsive macroporous molecularly imprinted cryogel for enhanced recognition capability towards ovalbumin. *Anal Methods*. 2013;5(23):6700-6708. <https://doi.org/10.1039/C3AY41069B>.
266. Wei X, Qi L, Yang G, Wang F. Preparation and characterization of monolithic column by grafting pH-responsive polymer. *Talanta*. 2009;79(3):739-745. <https://doi.org/10.1016/j.talanta.2009.04.062>.
267. Antonietti M, Wenz E, Bronstein L, Seregina M. Synthesis and characterization of noble metal colloids in block copolymer micelles. *Adv Mater*. 1995;7(12):1000-1005. <https://doi.org/10.1002/adma.19950071205>.
268. Christodoulakis KE, Palioura D, Anastasiadis SH, Vamvakaki M. Metal nanocrystals embedded within polymeric nanostructures: effect of polymer-metal compound interactions. *Top Catal*. 2009;52(4):394-411. <https://doi.org/10.1007/s11244-008-9172-2>.
269. Sulman EM, Matveeva VG, Sulman MG, et al. Influence of heterogenization on catalytic behavior of mono- and bimetallic nanoparticles formed in poly(styrene)-block-poly(4-vinylpyridine) micelles. *J Catal*. 2009;262(1):150-158. <https://doi.org/10.1016/j.jcat.2008.12.022>.
270. Vamvakaki M, Papoutsakis L, Katsamanis V, et al. Micellization in pH-sensitive amphiphilic block copolymers in aqueous media and the formation of metal nanoparticles. *Faraday Discuss*. 2005;128(0): 129-147. <https://doi.org/10.1039/B403414G>.
271. Pavlopoulou E, Portale G, Christodoulakis KE, Vamvakaki M, Bras W, Anastasiadis SH. Following the synthesis of metal nanoparticles within pH-responsive microgel particles by SAXS. *Macromolecules*. 2010;43(23):9828-9836. <https://doi.org/10.1021/ma101477s>.
272. Kan KHM, Li J, Wijesekera K, Cranston ED. Polymer-grafted cellulose nanocrystals as pH-responsive reversible flocculants. *Bio-macromolecules*. 2013;14(9):3130-3139. <https://doi.org/10.1021/bm400752k>.
273. Wang Y, Shi Y, Xu M, et al. Smart flocculant with temperature and pH response derived from starch. *RSC Adv*. 2016;6(50):44383- 44391. <https://doi.org/10.1039/C6RA04060H>.
274. Koenig M, Simon F, Formanek P, et al. Catalytically active nanocomposites based on palladium and platinum nanoparticles in poly(2-vinylpyridine) brushes. *Macromol Chem Phys*. 2013;214(20): 2301-2311. <https://doi.org/10.1002/macp.201300258>.
275. Al-Hussein M, Koenig M, Stamm M, Uhlmann P. The distribution of immobilized platinum and palladium nanoparticles within poly (2-vinylpyridine) brushes. *Macromol Chem Phys*. 2014;215(17):1679- 1685. <https://doi.org/10.1002/macp.201400228>.
276. Ma Z, Jia X, Zhang G, et al. pH-responsive controlled-release fertilizer with water retention via atom transfer radical polymerization of acrylic acid on mussel-inspired initiator. *J Agric Food Chem*. 2013;61(23):5474-5482. <https://doi.org/10.1021/jf401102a>.
277. Ang CY, Tan SY, Teh C, et al. Redox and pH dual responsive polymer based nanoparticles for in vivo drug delivery. *Small*. 2017;13(7): 1602379. <https://doi.org/10.1002/sml.201602379>.
278. Kalhapure RS, Renukuntla J. Thermo- and pH dual responsive polymeric micelles and nanoparticles. *Chem Biol Interact*. 2018;295:20- 37. <https://doi.org/10.1016/j.cbi.2018.07.016>.
279. Zhang J, Zou X, Zhai X, Huang X, Jiang C, Holmes M. Preparation of an intelligent pH film based on biodegradable polymers and roselle anthocyanins for monitoring pork freshness. *Food Chem*. 2019;272: 306-312. <https://doi.org/10.1016/j.foodchem.2018.08.041>.
280. Chen H, Zhang M, Bhandari B, Yang C. Novel pH-sensitive films containing curcumin and anthocyanins to monitor fish freshness. *Food Hydrocoll*. 2020;100:105438. <https://doi.org/10.1016/j.foodhyd.2019.105438>.
281. Ding L, Li X, Hu L, et al. A naked-eye detection polyvinyl alcohol/cellulose-based pH sensor for intelligent packaging. *Carbohydr Polym*. 2020;233:115859. <https://doi.org/10.1016/j.carbpol.2020.115859>.
282. Sun G, Chi W, Zhang C, Xu S, Li J, Wang L. Developing a green film with pH-sensitivity and antioxidant activity based on κ-carrageenan and hydroxypropyl methylcellulose incorporating Prunus maackii juice. *Food Hydrocoll*. 2019;94:345-353. <https://doi.org/10.1016/j.foodhyd.2019.03.039>.
283. Yong H, Wang X, Zhang X, Liu Y, Qin Y, Liu J. Effects of anthocyanin-rich purple and black eggplant extracts on the physical, antioxidant and pH-sensitive properties of chitosan film. *Food Hydrocoll*. 2019;94:93-104. <https://doi.org/10.1016/j.foodhyd.2019.03.012>.
284. Chen S, Wu M, Lu P, Gao L, Yan S, Wang S. Development of pH indicator and antimicrobial cellulose nanofibre packaging film based on purple sweet potato anthocyanin and oregano essential oil. *Int J Biol Macromol*. 2020;149:271-280. <https://doi.org/10.1016/j.ijbiomac.2020.01.231>.
285. Froio F, Ginot L, Paolino D, et al. Essential oils-loaded polymer particles: preparation, characterization and antimicrobial property. *Polymers*. 2019;11(6):1017. <https://doi.org/10.3390/polym11061017>.
286. Zhang X, Liu Y, Yong H, Qin Y, Liu J, Liu J. Development of multifunctional food packaging films based on chitosan, TiO<sub>2</sub> nanoparticles and anthocyanin-rich black plum peel extract. *Food Hydrocoll*. 2019;94:80-92. <https://doi.org/10.1016/j.foodhyd.2019.03.009>.
287. Froio F, Mosaddik A, Morshed MT, Paolino D, Fessi H, Elaissari A. Edible polymers for essential oils encapsulation: application in food preservation. *Ind Eng Chem Res*. 2019;58(46):20932-20945. <https://doi.org/10.1021/acs.iecr.9b02418>.