Materials Today Chemistry 49 (2025) 103063

Contents lists available at ScienceDirect

Materials Today Chemistry

journal homepage: www.journals.elsevier.com/materials-today-chemistry/

Smart pH-Responsive polymers in biomedical Applications: Nanoparticles, hydrogels, and emerging hybrid platforms

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ARTICLE INFO

Keywords:
Drug delivery
Nanoparticles
Hydrogels
pH-responsive
Polymers

ABSTRACT

Stimuli-responsive materials have attracted considerable interest in biomedical research, particularly for their ability to undergo structural and functional changes in response to environmental cues. Among these, pH-responsive polymeric systems offer a promising platform for developing smart drug delivery strategies due to the naturally occurring pH gradients present throughout the human body and within pathological microenvironments. This review provides a comprehensive overview of the most recent advances in the field of pH-sensitive hydrogels and nanoparticles, including hybrid architectures that combine both systems to achieve synergistic functionalities. After a brief introduction to the chemical mechanisms governing pH-responsiveness, the discussion focuses on their relevance in biomedicine, supported by a detailed analysis of physiological and pathological pH heterogeneity. Selected case studies highlight the role of pH-responsive systems in key applications such as drug and gene delivery, cancer and osteoarthritis therapy, wound healing, and soft robotics. Special attention is given to nanocomposite hydrogel systems that integrate pH-sensitive nanoparticles into hydrogel matrices, thereby enhancing drug loading capacity, spatial control, and responsiveness to complex environments. Altogether, this work aims to underline the versatility and clinical potential of pH-responsive polymeric systems and to encourage further interdisciplinary research towards personalized, efficient, and minimally invasive therapeutic solutions.

1. Introduction

In recent years, an increasing number of researchers have focused on stimuli-responsive materials due to their promising potential [1–3]. As Fig. 1 shows, stimuli-responsive polymer is a category of materials that can self-organize or experience phase transitions and morphological shifts when exposed to external stimuli which may be biological, physical or chemical [4]. Also known as smart [5,6], intelligent [7], or stimuli-sensitive polymers [8], they can interact with a range of factors, such as changes in temperature, pH, presence of biomolecules, solvents, ionic strength, chemical agents, light, humidity, electrical, magnetic fields, and so on, in order to perform different functions [9,10].

In addition, based on the number of external triggers to which they respond, stimuli-responsive polymers can be further classified into single-responsive, dual-responsive, and multi-responsive systems [11, 12]. The first ones react to only one type of stimulus, while dual- and multi-responsive ones can respond to different stimuli, allowing the polymers to behave differently depending on changes of environmental conditions [13].

For these reasons these materials are widely used, not only for applications in biomedicine [14,15], but also as wearables [16,17], sensors [18,19], actuators [20,21], electronics [21,22], and soft robotics [23, 24]. The main stimuli-responsive systems include polymer nanoparticles, hydrogels, liposomes, micelles, dendrimers, microspheres, capsules, membranes, 3D printing scaffolds, and inorganic nanoparticles such as iron oxide, quantum dots, gold, or metal oxide frameworks [25]. In particular, pH responsive systems can react to pH variation by altering their structure and properties, including surface activity, chain conformation, solubility, and configuration, making them very useful in various applications [26]. Indeed, the field of pH-responsive polymers has become very interesting in the last few decades, thanks to synthetic methodologies, but also to potential applications of these materials for biomedicine, with a focus on cancer treatment, hypertension, cardiovascular disease and peptic ulcers [27]. Among the most studied pH-responsive drug delivery systems, polymeric nanoparticles (NPs) and hydrogels represent two of the most prominent and complementary platforms. Polymeric NPs are typically engineered with a hydrophobic inner core capable of encapsulating small, poorly water-soluble drugs,

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https://doi.org/10.1016/j.mtchem.2025.103063
Received 19 June 2025; Received in revised form 10 September 2025; Accepted 17 September 2025
Available online 20 September 2025
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while their hydrophilic outer shell ensures colloidal stability and protection against degradation or immune recognition [28]. To maximize therapeutic efficacy and ensure predictable in vivo behavior, it is crucial to control both particle size and polydispersity index, as these parameters significantly influence biodistribution, cellular uptake, and clearance pathways [29]. For this reason, advanced and reproducible fabrication techniques such as microfluidics are increasingly employed to produce nanoparticles with uniform and tunable physicochemical characteristics [30]. On the other hand, pH-sensitive hydrogels, often derived from natural or synthetic polymers, offer high water content, mechanical tunability, and the ability to swell or shrink in response to pH changes, enabling site-specific release of therapeutic agents [31]. Notably, injectable hydrogels capable of in situ gelation have emerged as particularly attractive systems for localized and sustained drug delivery due to their minimally invasive administration and depot-like behavior [32]. Traditionally NPs and hydrogels have been studied independently, each providing unique advantages depending on the physicochemical properties of the payload.

However, recent advances in biomaterials science have driven a convergence between these strategies, leading to the development of hybrid or nanocomposite systems, where pH-responsive nanoparticles are embedded within a hydrogel matrix [33]. These hybrid systems aim to synergize the molecular-level control of release kinetics provided by nanoparticles with the macroscopic structural and localization advantages of hydrogels [34].

The rationale behind this combination lies in the possibility of achieving a multi-modal release profile, where drugs with different molecular weights, hydrophobicity or biological targets can be simultaneously or sequentially delivered (Fig. 2). Such systems are especially useful in complex therapeutic scenarios, such as cancer, where co-delivery of chemotherapeutic agents and biological drugs (e.g., monoclonal antibodies) may be necessary to achieve optimal therapeutic outcomes [35]. Moreover, the pH-responsiveness of both the hydrogel network and the embedded nanoparticles allows for a finely tuned drug release triggered by the physiological or pathological pH gradients such as those encountered in the tumor microenvironment, inflammatory sites, or gastrointestinal tract [36]. For example, the work by Appel and coworkers, have demonstrated the potential of PLA-PEG-based nanoparticles dispersed within hydroxypropyl methylcellulose hydrogels to achieve differential release kinetics for small molecules and macromolecules, thus enabling the design of dual-delivery strategies [37].

Overall, the integration of pH-responsive nanoparticles into hydrogel matrices is paving the way for next-generation drug delivery systems. These hybrid platforms not only overcome the intrinsic limitations of each individual component, such as the poor accumulation and rapid clearance of nanoparticles or the limited drug-loading capacity of hydrogels, but also provide a versatile strategy to address the increasing complexity of therapeutic regimens. As combination therapies become more prominent in clinical practice, particularly in oncology and immunotherapy, such advanced delivery architectures are expected to play a crucial role in improving patient outcomes and minimizing systemic toxicity [38]. Beyond surveying materials and applications, this article advances a mechanism-centered framework that unifies ionization-controlled conformational switching, acid-labile cleavage and charge-conversion into a coherent map of structure–property–function relationships. The discussion is further coupled to translation-oriented aspects, including reproducibility, microfluidic fabrication, protein corona formation, buffering effects and a minimum reporting checklist, with the aim of enabling chemists and bioengineers to make predictive choices about monomers, architectures and assays. Particular emphasis is placed on hybrid systems in which nanoparticles and hydrogels are rationally integrated, where pH sensitivity is framed not only as an intrinsic property of individual components but as a central design principle for synergistic architectures. In contrast to previous surveys, this review therefore provides actionable guidance grounded in quantitative pK_a and transition ranges for targeted compartments, and highlights how pH responsiveness can hierarchically coordinate secondary triggers such as redox processes, enzymatic activity and temperature changes in complex microenvironments.

2. Types of pH-responsive polymers

pH-responsive polymers are a specific class of materials containing ionizable moieties that undergo conformational, solubility, or swelling transitions in response to environmental pH changes.

While they can be considered polyelectrolytes to some extent, not all polyelectrolytes are pH-responsive (for example, DNA is a polyelectrolyte but does not exhibit the functional pH-triggered behavior

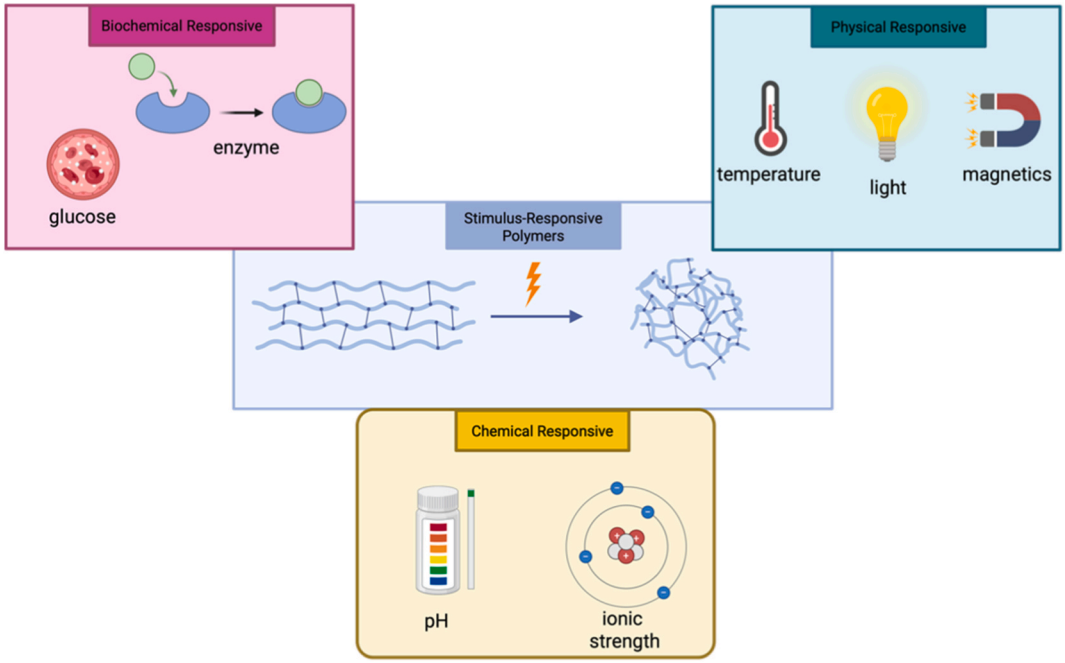

Fig. 1. Main types of stimuli for polymeric devices.

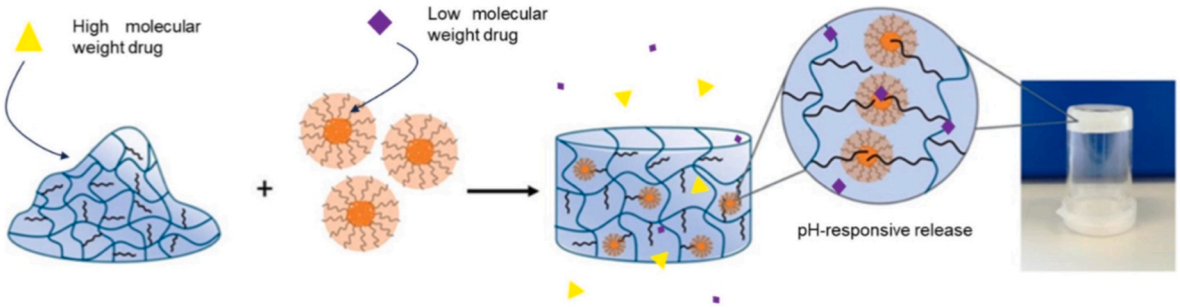

Fig. 2. Scheme of polymer-NPs composite system formation, codelivery mechanism and visual picture of the resulting material. Reprinted with permission from Elsevier [33].

exploited in drug delivery systems). [39]. Consequently, these materials react altering their structure and properties, including surface activity, chain architecture, conformation, solubility and configuration [40]. Example of acidic and basic functional groups are carboxylic, phosphate, tertiary amines and sulfonic groups, which after ionization or protonation can lead to polymer's structural alteration [41,42]. pH-responsive polymers functionalized with acidic groups (polyanions) such as carboxylic acid or methacrylic acid groups behave as anionic polymers as soon as they are deprotonated under basic conditions (high pH) [43]. On the other hand, polymers functionalized with basic groups (polycations) such as piperazines or pyridine derivates behave as cationic polymers as soon as they are protonated under acidic conditions (low pH) [44]. The value of pH at which polymer changes occur is called transition pH or critical pH and depends on the pK_a value, also called as dissociation constant [45]. It is important to note that the reported pK_a values of ionizable polymers should not be considered as fixed constants, as in the case of pure molecules. In polymeric chains, the apparent pK_a can vary depending on multiple factors such as chain length, branching, and the presence of neighboring functional groups [46]. Moreover, the ionization of one monomeric unit can influence the dissociation of adjacent units, leading to cooperative effects and to a distribution of pK_a values along the backbone [47]. For instance, Lunkad et al. used simulations validated by experiments in model polypeptides to show that longer chain lengths lead to greater deviations from ideal ionization behavior, indicative of cooperative effects among adjacent ionizable units [48]. Therefore, the pK_a ranges reported in Table 1 must be interpreted as indicative values that capture this complexity, rather than as absolute constants. New generations of pH-responsive polymers have been developed where fine-tuning of molecular weight, charge density, and hydrophobicity produces highly cooperative ionization [49]. These so-called ultra-pH-sensitive (UPS) nanomaterials undergo sharp on/off transitions within very narrow windows (0.2–0.3 pH units), in contrast to the gradual behavior of classical systems [50].

This refinement is particularly relevant for biomedical applications,

Table 1
Comparative overview of selected pH-responsive polymers (alginate, CMC, chitosan, HA, PAA, PMAA, PDMAEMA, PLL, PLH). For each polymer, the table reports the main pH-responsive group, typical pK_a values, quantitative release kinetics from representative drug delivery systems, therapeutic efficacy metrics, and biocompatibility evidence, with references to peer-reviewed studies.

Polymer	pH-sensitive group and pK_a	Release kinetics (drug, % released pH, time)	Therapeutic efficacy	Biocompatibility
Alginate	Carboxylate (COO^-); pK_a M~3.38, G~ 3.65 [57].	Omeprazole: <20 % pH 1.2 vs >92 % pH 7.4 (24 h) [58].	Alginate–DOX micelles inhibited tumor ~12 % more vs free DOX (Hepa1-6, mice) [59]. Alginate hydrogels also enhance wound healing and local drug efficacy [60].	Excellent: near 100 % viability; FDA-approved, safe in vivo [61].
Carboxymethyl cellulose (CMC)	Carboxylate (COO^-); pK_a ~4.3.	BSA: 17.8 % pH 1.2 vs 85.2 % pH 7.4 (2 h) [62].	CMC-Zn frameworks: IC50 ~19–23 μg/mL (colon/lung cancer cells). mucoadhesive property [63].	Safe excipient; >70 % cell viability; oral LD50 rat ~27 g/kg [64].
Chitosan	Amine $–NH3^+$; pK_a ~6.5 [65].	Paclitaxel: stable pH 7.4 vs rapid release pH 5–6 [66].	PTX + siRNA chitosan carriers enhanced tumor inhibition [67].	Generally biocompatible; Chitosan systems show high viability [66].
Hyaluronic acid (HA)	Carboxylate (COO^-); pK_a ~3.5 [68].	DOX: <35 % pH 7.4; vs ~50 % pH 6.8; vs ~80 % pH 5.5 (72 h) [69]	HA–DOX carriers lower IC50 in $CD44^+$ tumor cells vs controls [68]. Intra-articular HA injections clinically improve joint function and reduce pain [70].	Excellent: natural ECM component; non-immunogenic [71].
Poly(acrylic acid) (PAA)	Carboxylate (COO^-); pK_a ~4.25	Diclofenac: 77 % pH 7.4 vs 17 % pH 1.2 (12 h) [72].	Podophyllotoxin–PAA micelles more cytotoxic vs free drug (MCF-7/MDA-MB-231) [73].	Safe; minimal hemolysis vs free drugs; high viability [74].
Poly(methacrylic acid) (PMAA)	Carboxylate (COO^-); pK_a ~4.8–5.4 [75].	FITC: 20 % pH 7.4; vs % 78.2 % @pH 2.0 (48 h) [33].	HA–PMAA micelles showed improved tumor inhibition in acidic pH [76].	>95 % viability in HeLa cells with PMAA NPs [33].
PDMAEMA	Amine $–NH3^+$; pK_a ~7.0–7.5 [77].	DOX: ~65 % pH 6.5 vs ~21 % pH 7.4; 24 [78].	Improved antitumor efficacy via proton sponge effect [79].	Blank NPs >90 % viability; safe in vivo [80].
Poly(L-lysine) (PLL)	Amine $–NH3^+$; pK_a ~10.5 [81].	Not strongly pH-triggered; complexes DNA/siRNA [82].	PEG-PLL nanoparticles inhibited tumors vs free plasmid [83].	High-MW PLL cytotoxic; PEGylated PLL biocompatible [84].
Poly(L-histidine) (PLH)	Imidazole; pK_a ~6.0–6.5 [85].	DOX: minimal release pH 7.4; rapid release pH 5–6 [86].	PLH-PLGA NPs effective against MDR cancer cells [86].	Low toxicity; >90 % viability in blank carriers; safe in vivo [87].

since it enables polymers to remain completely stable at physiological pH (7.4) but to activate abruptly in the mildly acidic tumor extracellular matrix (pH 6.6–6.8) or in endo-lysosomal compartments (pH 5.0–6.0) [51]. Such sharp selectivity minimizes off-target leakage, enhances intracellular release, and provides a platform with clear advantages for cancer therapy, imaging, and controlled drug delivery. It represents the pH with equal concentration of the protonated and deprotonated groups and governs the material's response under pH specific conditions [52]. For instance, poly (acrylic acid) (PAA) is characterized by a dissociation constant equal to 4.25 [53]. This means that at pH values above this threshold, the carboxylic group ionizes, leading to electrostatic repulsion between the chains which can then interact with water causing swelling, while at acidic pH, the carboxylic groups are protonated resulting in a state of equilibrium [54]. For these reasons the choice of a specific material depends on the final application, taking into account the pH-dependent behavior of the selected material under the desired pH conditions [55]. pH-responsive polymers can be broadly classified into biopolymers, derived from biological sources, and synthetic polymers, which are man-made through chemical synthesis [56]. A comparative summary of the main properties of the pH-responsive polymers cited in this work is provided in Table 1. The most common types are reported in this paragraph.

2.1. pH-responsive biopolymers

Among the various classes of stimuli-responsive polymers, pH-responsive biopolymers have gained considerable attention due to their intrinsic biocompatibility, biodegradability, and structural diversity [88–90]. Biopolymers are naturally derived macromolecules obtained from microorganisms, plants, and animals, and include polysaccharides, proteins, and nucleic acids [91]. Furthermore, their natural origin often confers enhanced cellular compatibility and reduced immunogenicity compared to synthetic analogues, making them attractive candidates for the development of intelligent delivery platforms, injectable hydrogels, and nanocarrier systems [92]. Within this class, alginate, chitosan, carboxymethyl cellulose (CMC), and hyaluronic acid represent some of the most extensively investigated biopolymers, each exhibiting unique pH-responsive behaviors rooted in their distinct chemical functionalities [93–96]. Despite their shared responsiveness to pH changes, their mechanisms and behavior vary significantly due to their molecular structures and ionizable groups. Alginate and CMC are both anionic polysaccharides bearing carboxylic acid groups with pK_a values typically between 3 and 4 [97]. This renders them largely uncharged in acidic environments, where protonation reduces swelling and drug permeability, while at higher pH values, deprotonation triggers electrostatic repulsion between polymer chains, enhancing porosity and swelling [98]. These features are frequently exploited in oral drug delivery, where controlled release in the intestine is desired. In alginate-based systems, this transition can be finely tuned by the presence of divalent cations (e.g., Ca^{2+}), forming ionically crosslinked gels whose swelling ratio and diffusion properties are pH-dependent [99]. Similarly, in CMC-based hydrogels crosslinked with fumaric acid, swelling was found to be minimal at low pH due to protonated carboxylic groups, while significant expansion occurred under neutral or basic conditions, enabling pH-triggered drug release [100].

In contrast, chitosan that derived from chitin is a cationic polysaccharide whose reactivity is governed by protonatable amino groups [101]. Under acidic pH, these amines become positively charged, enhancing solubility and electrostatic interaction with anionic drugs or polymers. This behavior complements that of alginate and CMC, allowing the design of complex multilayer or polyelectrolyte systems in which the interplay between anionic and cationic components determines release behavior. For instance, in alginate/chitosan-coated mesoporous silica nanoparticles, acidic pH led to increased release of doxorubicin (DOX) due to electrostatic repulsion between the protonated chitosan and positively charged drug, while weakening the alginate-DOX interaction [102]. This interplay between opposite charges is also central to the design of hybrid systems involving synthetic or temperature-responsive polymers [103]. At low pH, protonation reduced swelling, while under basic conditions, anionic alginate favored expansion and increased drug diffusion without altering the dual-responsive behaviors of the final copolymer. Hyaluronic acid shares structural similarities with alginate and CMC, as it is also an anionic polysaccharide with carboxyl groups (pK_a ~3–4) but distinguishes itself through its biological function as a key ECM component and its affinity for CD44 receptors, commonly overexpressed in cancer cells. This dual nature makes HA an attractive candidate for pH-responsive and targeted delivery [104]. In HA-based gels and micelles, acidic pH conditions, mimicking tumor or intracellular environments, have been shown to accelerate drug release, either via disruption of acid-labile bonds or via changes in HA conformation and charge density [105,106]. Systems such as HA–g–poly(L-histidine) hydrogels or HA-functionalized gold nanoparticles have demonstrated this synergistic behavior, combining pH-sensitivity with active targeting [107,108]. Furthermore, HA-based carriers have been explored for transdermal insulin delivery, where their protective role under gastric conditions can delay release until neutral pH is reached [109]. Altogether, these polymers offer a diverse palette of pH-responsive behaviors: anionic systems like alginate, CMC, and HA exhibit minimal swelling in acidic media and expand under neutral or basic conditions, while cationic chitosan displays the opposite trend [110].

Their complementarity enables the design of smart delivery platforms with finely tuned responses, capable of releasing their payload under specific biological conditions or through the interplay with other functional components.

2.2. Synthetic pH-responsive polymers

While natural pH-responsive polymers are widely employed due to their intrinsic biocompatibility and biodegradability, synthetic analogues offer a broader chemical diversity and tunability [111]. As already mentioned, these systems are often categorized based on the nature of their ionizable groups: polybasic polymers, which behave as polycations, and polyacidic polymers, which behave as polyanions. In the first group, synthetic examples include poly(L-lysine) (PLL), poly (ethylene imine) (PEI), and poly(N,N-dimethylaminoethyl methacrylate) (PDMAEMA), which contain amine moieties that become protonated at low pH, leading to electrostatic repulsion and polymer expansion [112]. Conversely, in polyacidic polymers such as poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), and polysulfonamides, the carboxylic groups are protonated under acidic conditions but deprotonate at higher pH, yielding charged polymer backbones that promote swelling due to intramolecular repulsion [113]. Furthermore, synthetic derivatives of polypeptides such as poly(aspartic acid) (PASA), poly (histidine) (PHIS), and poly(L-glutamic acid) (PGA) combine degradability with pH-sensitivity, making them attractive platforms for biomedical use [114]. Among these, synthetic polypeptides and methacrylic-based polymers are particularly noteworthy for their well-defined chemical architectures and capacity to respond to pH shifts via ionization, conformational changes, or modulation of intermolecular interactions [115]. More in details, PLL is a cationic polypeptide featuring pendant primary amines with pK_a around 9.7 [116]. These amine groups can undergo reversible protonation, conferring PLL with solubility and responsiveness in acidic to neutral pH ranges [117]. Owing to its biocompatibility and modifiability, PLL has been widely employed in the development of pH-responsive nanocarriers, particularly in gene delivery [118].

For instance, PLL can electrostatically complex with DNA or siRNA to form polyplexes, facilitating cellular uptake and, in some cases, endosomal escape [119]. To enhance its efficacy, PLL has been conjugated with lytic peptides such as melittin, or with proton-sponge polymers like PEI, yielding hybrid systems that improve cytosolic delivery through

acid-triggered membrane destabilization [120,121]. The conjugation with shielding polymers like PEG has also enabled the creation of PEG-PLL nanocarriers functionalized with cleavable pH-sensitive moieties that activate lysis selectively under acidic conditions [122]. Furthermore, succinylated ε-polylysine, a derivative obtained by functionalizing the natural ε-polylysine extracted from *Streptomyces albulus*, has demonstrated compelling colon-targeted delivery [123]. In this prospective, a combined delivery system was developed by encapsulating drugs into mesoporous silica nanoparticles coated with succinylated polylysine and embedding them into a hydrogel film, achieving pH-responsive release and potent antibacterial activity [124]. The succinylated coating ensures stability under gastric conditions while enabling targeted drug release in the mildly basic environment of the colon. This highlights how tailored modification of synthetic polypeptides can be exploited to achieve site-specific delivery through pH gradients along the gastrointestinal tract. Complementary to PLL, poly (L-histidine) (PLH) is another synthetic polypeptide of increasing interest [125]. With imidazole side chains possessing a pK_a value of approximately 6.0, PLH is especially sensitive to endosomal and tumoral pH environments [126]. In acidic conditions, the imidazole rings become protonated, leading to increased hydrophilicity and expansion or disassembly of nanostructures. This property not only allows PLH-based carriers to destabilize and release their cargo selectively in acidic compartments but also to act as proton-sponge systems, promoting endosomal escape [127]. Various block copolymers such as multidomain peptide hydrogels containing histidine have exhibited pH-dependent changes in size and antibody release behavior, enabling programmable responses to microenvironmental stimuli [128–130]. In addition to polypeptides, poly(methacrylic acid) (PMAA) and its copolymers represent another prominent class of pH-responsive materials [33,131].

PMAA is an anionic polymer that undergoes deprotonation at basic pH, leading to chain expansion and water uptake, while protonation under acidic conditions induces collapse due to hydrogen bonding and hydrophobic interactions [132]. These transitions make PMAA an excellent building block for hydrogels and drug-loaded nanoparticles. In particular, when combined with poly(N-isopropylacrylamide) (PNIPAM) dual-responsive systems can be engineered [133]. PNIPAm is a polymer known for its sharp phase transition near physiological temperature (~31.8 °C), where it undergoes a reversible shift from a hydrated, swollen state to a collapsed, hydrophobic conformation [134]. Additional formulations, such as core–shell nanoparticles based on PLA-graft-P(NIPAm-co-MAA), have illustrated changes in opacity and solubility driven by pH-induced ionization of methacrylic units, thus providing visual confirmation of environmental responsiveness [135]. These hybrid hydrogels or nanogels exhibit synergistic behavior, where pH-induced swelling is coupled with temperature-driven phase transitions, allowing for precise control over drug release kinetics [136]. For example, hollow pH-responsive hydrogel system comprising mimosa seed mucilage, β-cyclodextrin and PMAA have shown significant swelling and deswelling transitions across a wide pH range (pH 2–12), with notable size reductions at neutral pH and expansion under alkaline conditions due to electrostatic repulsion [137]. When loaded with anticancer agents such as doxorubicin, these microspheres can release minimal drug amounts at physiological pH while exhibiting rapid and complete release at tumoral or lysosomal pH [76]. This pH-responsiveness is further modulated by salt concentration and temperature, making them versatile carriers for in vivo applications. Altogether, synthetic pH-responsive polymers, from polypeptides to methacrylate derivatives, provide a robust platform for the rational design of advanced delivery systems. Their tunable chemical functionalities, predictable pK_a values, and capacity to respond to narrow pH windows enable their use in targeting specific biological compartments or disease-associated environments, offering both stability in systemic circulation and precision in triggered release.

3. Applications of pH-responsive systems

Furthermore, the application of pH-responsive materials in the biomedical field is particularly promising due to the naturally occurring pH gradients in the human body [138].

While the physiological pH of blood is tightly regulated around 7.4, local pH values can range widely, from highly acidic to slightly basic (pH 1 to 8), depending on the tissue or biological fluid (Fig. 3) [139]. For example, in the gastrointestinal tract, the proton pump H^+/K^+-ATPase in the stomach epithelium actively secretes protons, resulting in a highly acidic gastric environment (pH 1–3.5) [140]. This contrasts with the gradual pH increase along the small intestine, where values shift to near-neutral or mildly basic (pH 7.2–7.5). Similarly, urine pH fluctuates between slightly acidic (pH 6.5–7.0) in the morning and more alkaline values (pH 7.5–8.0) following food intake [141]. The female reproductive tract also displays distinct pH characteristics: in premenopausal women, the vaginal environment maintains an acidic pH (3.8–4.4), primarily due to the metabolic activity of Lactobacillus species that ferment glycogen into lactic acid [142]. After menopause, the vaginal pH tends to rise alongside increased susceptibility to infection.

The vulvar pH follows a similar trend, ranging from 5.0 to 5.5, and becomes more alkaline with aging and estrogen deficiency, impairing the local barrier function [143]. The skin surface (stratum corneum) is also slightly acidic, with values typically between pH 4.1 and 5.8 depending on body region, contributing to antimicrobial defense and barrier integrity [144]. For instance, the forehead and eyelids exhibit lower pH values (around 4.4–4.6), while the chin can reach pH 5.6 [145]. These physiologically relevant pH differences have been extensively exploited in the design of smart drug delivery systems, enabling site-specific and stimulus-responsive release of therapeutic agents. Notably, pH-responsive polymers have proven particularly advantageous in gene delivery applications, where they protect nucleic acids such as DNA and RNA from degradation in the acidic gastric environment following oral administration, while facilitating controlled release at target sites. Additionally, intracellular organelles exhibit tightly regulated pH gradients that have been strategically exploited in the design of intelligent drug delivery systems [146,147]. Along the endocytic and secretory pathways, luminal acidification is progressively established, primarily through the action of vacuolar H^+-ATPases in combination with ion exchangers such as $2Cl^-/H^+$ and Na^+/H^+ or K^+/H^+ antiporters [148]. As endocytosed materials transit through these intracellular compartments, they are exposed to increasingly acidic conditions: early endosomes maintain a pH of approximately 6.3, which decreases to around 5.5 in late endosomes and reaches the lowest values in lysosomes, typically ranging from pH 4.5 to 4.7 [149]. Subsequently, the pH can rise again in recycling endosomes, which return to near-neutral conditions (pH 6.5). Other organelles, such as the Golgi apparatus, also present localized acidification, with pH values dropping to around 6 in the trans-Golgi network. These compartment-specific pH environments provide unique opportunities for the development of pH-responsive nanocarriers capable of achieving intracellular targeting, enhanced endosomal escape, or selective drug activation within diseased cells (Fig. 4) [150]. In particular, the acidic milieu of late endosomes and lysosomes has been widely leveraged to trigger payload release only after internalization, improving therapeutic precision and minimizing off-target effects.

Importantly, a significant pH difference also arises between healthy and pathological tissues such as cancer or osteoarthritis, and this feature has been increasingly exploited for targeted therapeutic strategies. In particular, the extracellular pH of solid tumors is consistently lower than that of normal tissues [151]. While physiological extracellular pH typically remains close to 7.4, tumor microenvironments often exhibit a mild to moderate acidity, with pH values ranging between 6.5 and 6.9, and in more extreme cases, such as in necrotic or poorly vascularized regions, pH can drop as low as 6.0 [152–154]. Experimental conditions such as combined hyperthermia (43 °C) and hyperglycemia have been

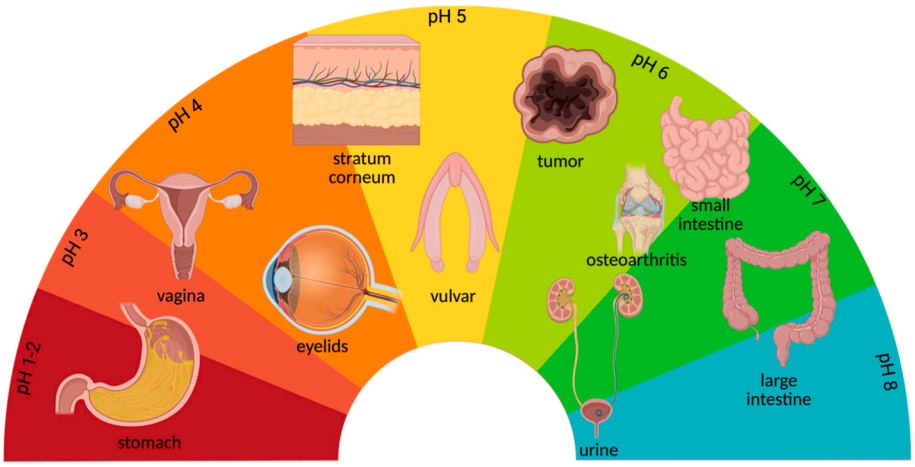

Fig. 3. The figure illustrates the different regions of the human body and their associated pH levels.

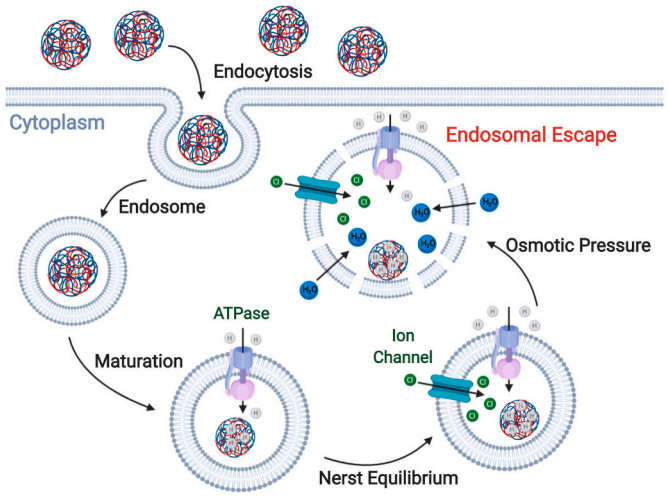

Fig. 4. Endosomal escape mediated by the Proton-Sponge Effect. Reprinted with permission from MDPI [150].

shown to further accentuate this acidification, bringing tumor pH down to 6.0–6.5 [155]. This phenomenon is largely attributed to the Warburg effect, a hallmark of cancer metabolism in which cells preferentially undergo glycolysis even in the presence of oxygen (aerobic glycolysis), rather than relying on oxidative phosphorylation [156]. This metabolic reprogramming leads to an overproduction of lactic acid and protons, which are actively exported out of the cell by membrane transporters to preserve intracellular pH stability [157].

As a result, the extracellular milieu becomes increasingly acidic. Osteoarthritis (OA) is a chronic, degenerative joint disease characterized by the progressive breakdown of articular cartilage, subchondral bone remodeling, and low-grade synovial inflammation, ultimately leading to joint pain, stiffness, and functional impairment [158]. As OA advances, the intensification of local inflammation leads to the release of numerous inflammatory mediators that modulate both immune activity and tissue repair mechanisms. This heightened cellular activity increases metabolic demand, resulting in local hypoxia. In response, chondrocytes adapt by favoring anaerobic glycolysis, a metabolic shift that generates significant amounts of lactic acid. The accumulation of lactic acid gradually lowers the pH of the synovial environment, contributing to acidification of the joint cavity [159]. Concurrently, inflammatory processes drive the breakdown of articular cartilage, leading to the upregulation of catabolic enzymes, notably matrix metalloproteinases, which accelerate cartilage degradation. The resulting matrix fragments further amplify inflammation, establishing a feedback loop that intensifies joint damage. This pathological cascade alters the biochemical landscape of the synovial fluid. While in healthy joints the synovial pH is approximately 7.4, OA-associated inflammation can reduce it to a range of 6.6–7.2, and in severe cases, even to around 6.0 [160–162].The resulting acidification mirrors that observed in rheumatoid arthritis and solid tumor microenvironments in terms of H^+ accumulation [163]. To counterbalance this acid stress, several molecular systems facilitate proton and metabolite transport: H^+-ATPases, Na^+/H^+ exchangers, and monocarboxylate transporters assist in the efflux of H^+ ions and lactic acid, while the exchange of anions like Cl^- and HCO_3^- across chondrocyte membranes or organelles helps stabilize intra-articular pH [164,165]. This pathological acidification has become a critical design parameter for pH-responsive drug delivery systems, allowing for the preferential activation or release of therapeutics within the tumor or OA microenvironment, thereby enhancing selectivity and minimizing damage to healthy tissues. Given the several pH gradients present throughout the human body, intracellular compartments and pathological sites like tumors, pH-responsive polymer systems offer a powerful platform for developing advanced biomedical technologies.

These systems can undergo predictable physicochemical transformations in response to local pH changes, enabling spatial and temporal control over the release of therapeutic agents or functional responses. The following section presents the most relevant recent applications of pH-responsive hydrogels and nanoparticles, including their use in drug and gene delivery, gastrointestinal protection of active compounds, soft robotics, and wound healing.

3.1. *Drug delivery*

Drug delivery is a prominent application of pH-responsive polymers, leveraging their ability to react to environmental pH changes to control the release of therapeutic agents. This strategy takes advantage of the polymers' reversible structural transitions under different pH conditions, enabling precise modulation of drug release profiles. Numerous innovative studies, such as that by Gao and coworkers, have explored the use of pH-responsive polymers to develop advanced nanoparticle systems, hydrogels, or hybrid structures capable of finely tuning drug release in response to local pH variations [166–168]. Among the latest strategies for targeted intestinal delivery of drugs and probiotics, the development of hybrid systems that integrate hydrogel networks with nanoparticles has shown great promise in overcoming the physiological barriers of the gastrointestinal tract. A particular system was recently reported, in which Lactobacillus rhamnosus 76 was encapsulated in double emulsions bound within hydrogel beads based on sodium alginate and carboxymethyl chitosan, assembled in citric acid medium

[169]. The composite structure exhibited excellent thermal stability and pronounced pH responsiveness, enabling selective swelling and release of probiotics in response to environmental changes along the gastrointestinal tract. This was particularly evident in in vitro simulated gastrointestinal experiments, which demonstrated that the gel matrix effectively restricted release under gastric conditions, with a survival rate of viable bacteria reaching 90.69 ± 0.04 %. Upon transition to simulated intestinal fluid, electrostatic repulsion induced by COO^- ionization triggered gradual disassembly of the gel structure, allowing controlled probiotic release. In vivo assessments corroborated the in vitro findings, with fluorescence imaging and bacterial quantification confirming the effective delivery and retention of probiotics in the colon up to 24 h post-administration. The increased abundance of Lactobacillus and Firmicutes in fecal samples further underscored the therapeutic potential of the system in modulating gut microbiota composition. A notable example of the enhanced performance offered by nanocomposite hydrogel systems is provided by a recent study on a pH/magnetic dual-responsive Fe_3O_4 hemicellulose nanocomposite hydrogel [170]. This material, synthesized via in-situ graft polymerization on hemicellulose, demonstrates superior pH sensitivity and biodegradability, making it highly suitable for drug delivery applications. Compared to the only hydrogel systems, which already exhibit substantial swelling changes in response to pH variations, the incorporation of Fe_3O_4 nanoparticles endows the system with additional functionalities such as magnetic responsiveness, improved control over drug release, and enhanced responsiveness to external stimuli (Fig. 5). Beyond the need to ensure intestinal targeting, in some cases it is also essential to enable the co-delivery of hydrophilic and hydrophobic compounds, especially when their simultaneous release may enhance bioactivity through synergistic effects. For instance, in the study by Zhao et al., a dual delivery strategy was implemented by encapsulating lycopene, hydrophobic, in the oil phase and riboflavin,hydrophilic, in the internal aqueous phase of a W/O/W emulsion [171]. This emulsion was further embedded in alginate-based matrices, designed to respond to both pH and temperature changes, allowing for the controlled release of both bioactives in the intestinal environment. This approach demonstrates how co-encapsulation systems can be tailored to improve the bioaccessibility and stability of multiple active ingredients simultaneously.

While single pH-responsive hydrogels can achieve efficient release in the intestinal environment due to their deprotonation-driven swelling, the addition of magnetic nanoparticles enables remote triggering and pulsatile release, thus extending the residence time at the target site. Acetylsalicylic acid and Theophylline were employed as model drugs to evaluate performance. The study demonstrated that under intestinal pH, the nanocomposite hydrogel achieved a cumulative drug release of about 90 % within 6 h, significantly outperforming release at gastric or highly basic pH values. Moreover, pH-switching experiments further confirmed the robustness and adaptability of the hydrogel network under dynamic conditions. In addition to enabling the delivery of hydrophilic and hydrophobic compounds, microfluidic technology offers unique advantages for improving pH-responsiveness and enhancing intestinal targeting. In a recent study, alginate-based hydrogel microcapsules were prepared using coaxial microfluidic chips to encapsulate indomethacin, achieving excellent control over microsphere size and release kinetics [172].

The microspheres remained stable under acidic conditions (pH 1.2), showing negligible drug release in simulated gastric fluid, but underwent significant swelling and controlled drug release in simulated intestinal fluid (pH 7.6). Thanks to the precise spatial confinement provided by microfluidics, it was possible to fabricate core–shell architectures, in which the drug is physically entrapped within an inner compartment surrounded by a denser hydrogel barrier. Notably, these core–shell microcapsules exhibited a slower, sustained release compared to single-layer systems, highlighting how the tunable geometry and composition achieved via microfluidics can be harnessed to optimize oral drug delivery profiles [173]. As previously discussed, several systems reported in the literature can deliver drugs specifically to the intestine. Additionally, pH-responsive materials have shown great potential in cancer treatment. Combining these two features, thiolated hyaluronic acid-based hydrogels were developed for the targeted and sustained delivery of 5-fluorouracil (5-FU) to the intestine [174]. Also these systems exploit the reduced swelling and drug release in acidic environments to prevent premature degradation in the stomach, while significantly increasing drug diffusion at neutral-to-basic pH, as found in the intestine. The incorporation of thiol groups not only imparted pH sensitivity and redox responsiveness, but also improved mucoadhesive properties, enhancing residence time and uptake in the colonic mucosa (Fig. 6). In vitro and in vivo experiments confirmed both the biocompatibility and therapeutic efficacy of the system, with a two-fold increase in bioavailability and selective accumulation of 5-FU in intestine tissue.

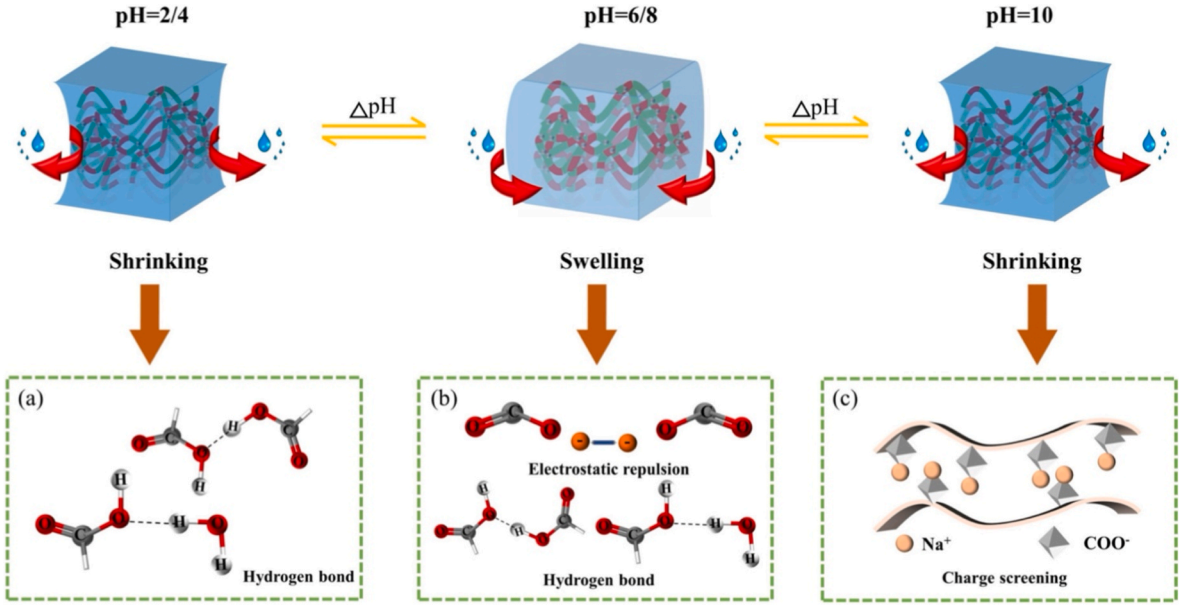

Fig. 5. pH-responsive mechanism of the Fe_3O_4 hemicellulose nanocomposite hydrogel. Reprinted with permission from Elsevier [170].

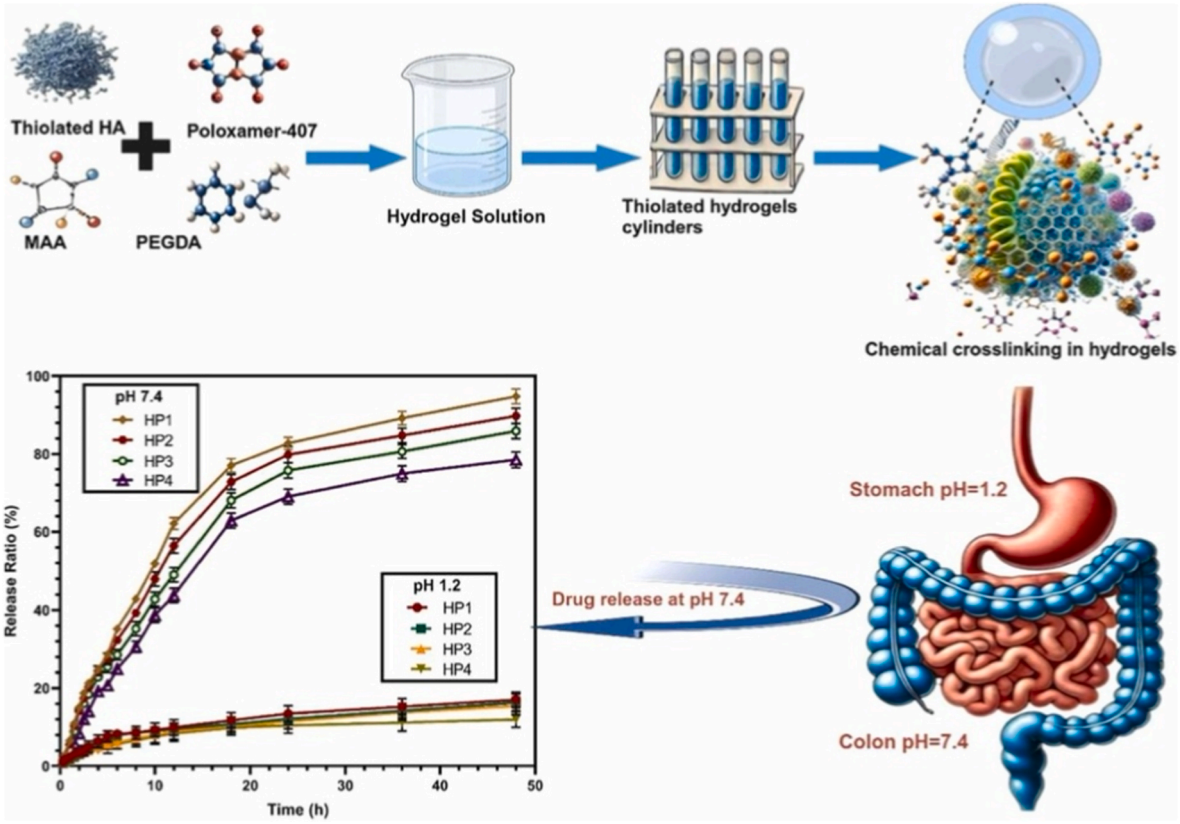

Fig. 6. Thiol-functionalized hyaluronic acid-based pH-responsive hydrogel synthesis and drug release. Reprinted with permission from Elsevier [174].

3.2. Gene delivery

Gene delivery refers to the process of introducing genetic material such as DNA or small interfering RNA (siRNA) into target cells to modulate gene expression for therapeutic purposes [175]. However, this strategy faces several major hurdles, including inefficient cellular uptake, low stability of nucleic acids in the bloodstream, limited endosomal escape, and premature disassembly in the cytoplasm [176]. In fact, incorporating negatively charged nucleic acids such as DNA and small interfering RNA (siRNA) into cells is challenging due to the low stability in blood, poor cellular uptake, inefficient endosomal escape, and disassembly in the cytoplasm [177]. For these reasons, nucleic acid is embedded into charge-balanced nanoparticles to enable cellular uptake [178]. This is done using two primary classes of chemical (non-viral) gene delivery vectors such as liposomes and polycations, allowing effective internalization into cellular compartments [179,180].

For example, Mostafavi and coworkers used a polymer based on Chitosan and carboxymethyl cellulose coated on NH2-UiO-66 as possible pH responsive gene delivery vector [181]. The study showed how this vector remained stable at neutral pH but disassembled under acidic conditions due to the complete protonation of the tertiary amine groups, implying its potential as a pH-responsive nanocarrier system for the co-delivery of drugs and DNA. In this context, PEGylated polycationic carriers have been developed to overcome the intrinsic challenges of siRNA delivery, particularly in demanding physiological environments. A chemically engineered system based on polyethylene glycol–poly(β-amino esters)–histidine has demonstrated high efficacy in delivering siRNA targeting the Anaplastic lymphoma kinase (ALK) oncogene in ALK-positive non-small cell lung cancer [182]. The design leverages the neutral and stealth properties of PEG with the dual cationic character of PBAE and histidine to form stable polyplexes capable of encapsulating siRNA via enhanced electrostatic interactions. These nanoparticles exhibit pH-sensitive behavior: they are anionic under alkaline conditions, such as those in pleural fluid, and become cationic at acidic pH, typical of the tumor microenvironment and lysosomes [183]. This facilitates both cellular uptake and endosomal escape, enabling effective cytosolic delivery. The system also displays significant proton buffering capacity, with titration experiments showing responsiveness around the lysosomal pH range (4.5–5.0), ensuring efficient payload release. Compared to non-histidine analogues, the presence of histidine residues confers a sharper and more efficient pH-triggered destabilization of the polyplexes (Fig. 7). The resulting ALK-targeted RNAi therapy not only achieves specific gene silencing in vitro and in vivo but also reduces cytotoxicity relative to conventional polyethylenimine (PEI) vectors [184].

One of the major intracellular barriers in nucleic acid delivery is the endo-lysosomal compartment, where internalized materials are trafficked and often degraded [185].

These compartments are characterized by their acidic microenvironment, which has been extensively exploited in the design of stimuli-responsive delivery systems. An important issue to consider is that the positively charged complex formed by polycation/nucleic acid tends to interact with serum components (proteins), reducing the system's effectiveness [186]. pH-responsive polymers, as already mentioned, are engineered to respond to these conditions by becoming protonated, thus acquiring a positive charge that facilitates membrane interaction and subsequent disruption. This process, often referred to as the "proton sponge effect", enhances endosomal escape, allowing the therapeutic payload to reach the cytoplasm before degradation [187]. This mechanism is especially advantageous in the context of siRNA delivery, where cytoplasmic localization is essential for RNA interference [188]. The potential of pH-responsive polymers in gene delivery has been exemplified by their application in ocular therapeutics, such as the development of the triblock copolymer PEG-b-PAMA-b-P(C7A-*r*-DBA) (PACD), designed to facilitate siRNA delivery to the retina [189]. This A-B-C-type amphiphilic copolymer consists of a hydrophilic PEG block (A), a

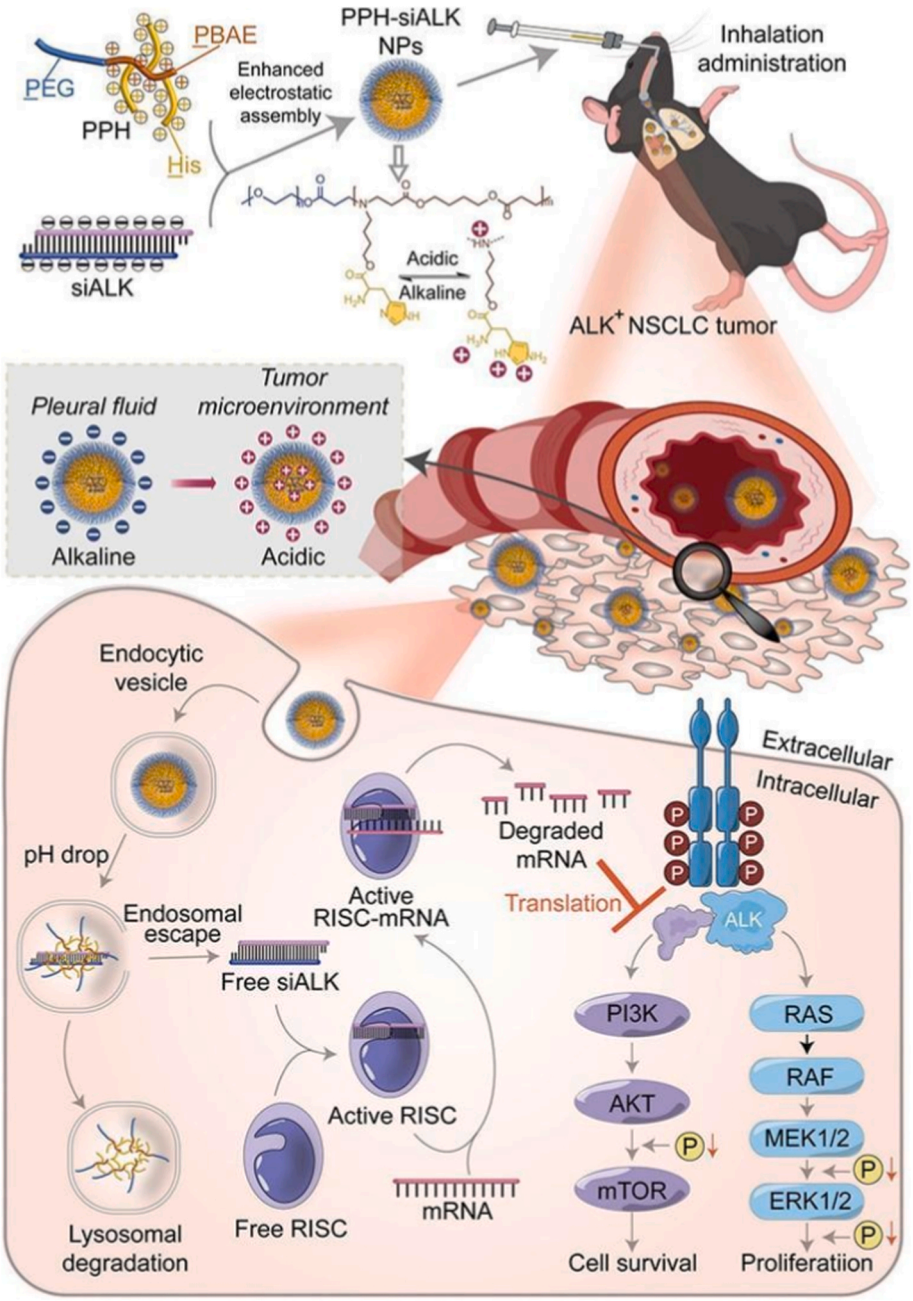

Fig. 7. Enhanced electrostatic co-assembly of charge-reversal PPH-siALK polyplexes, enabled by dual positively charged Poly(β-amino ester) (PBAE) and His for siRNA-directed inhalation ALK gene silencing in ALK + Non-Small Cell Lung Cancer (NSCLC). Downstream protein regulations following mRNA silencing are mapped from immunoblotting. Reprinted with permission from Elsevier [182].

cationic siRNA-binding block (B), and a pH-sensitive block (C), enabling the formation of nanosized micelles that efficiently encapsulate siRNA via simple mixing. In retinal applications, PACD demonstrates strong endosomal escape capability, excellent gene silencing efficiency, and significant anti-angiogenic effects in a mouse model of oxygen-induced retinopathy (OIR) (Fig. 8). Beyond overcoming intraocular barriers and ensuring prolonged retention, PACD micelles represent a scalable and safe non-viral platform, showcasing the translational potential of pH-responsive polymers in ophthalmic RNAi therapeutics.

3.3. Bioactives gastroprotection

pH-responsive delivery systems have garnered increasing attention in the field of oral drug delivery due to their ability to protect bioactive compounds from the harsh acidic environment of the stomach. These systems are engineered to remain stable and retain their payloads under low pH conditions, such as those encountered in the gastric phase, while enabling targeted release in the more neutral or slightly basic pH of the intestine. This protective mechanism is particularly beneficial for labile molecules such as anthocyanins, whose structural integrity and biological activity are highly sensitive to acidic degradation [190]. An example is provided by the encapsulation of purple sweet potato diacylated anthocyanins (PSPAs), a class of anthocyanins with potent antioxidant, anti-inflammatory, and antidiabetic properties [191].

In a recent study, two novel pH-responsive peptide hydrogel carriers were developed using aspartic acid and glutamic acid, which undergo ionization changes depending on the pH (Fig. 9) [192].

Under acidic gastric conditions, these amino acid-based hydrogels

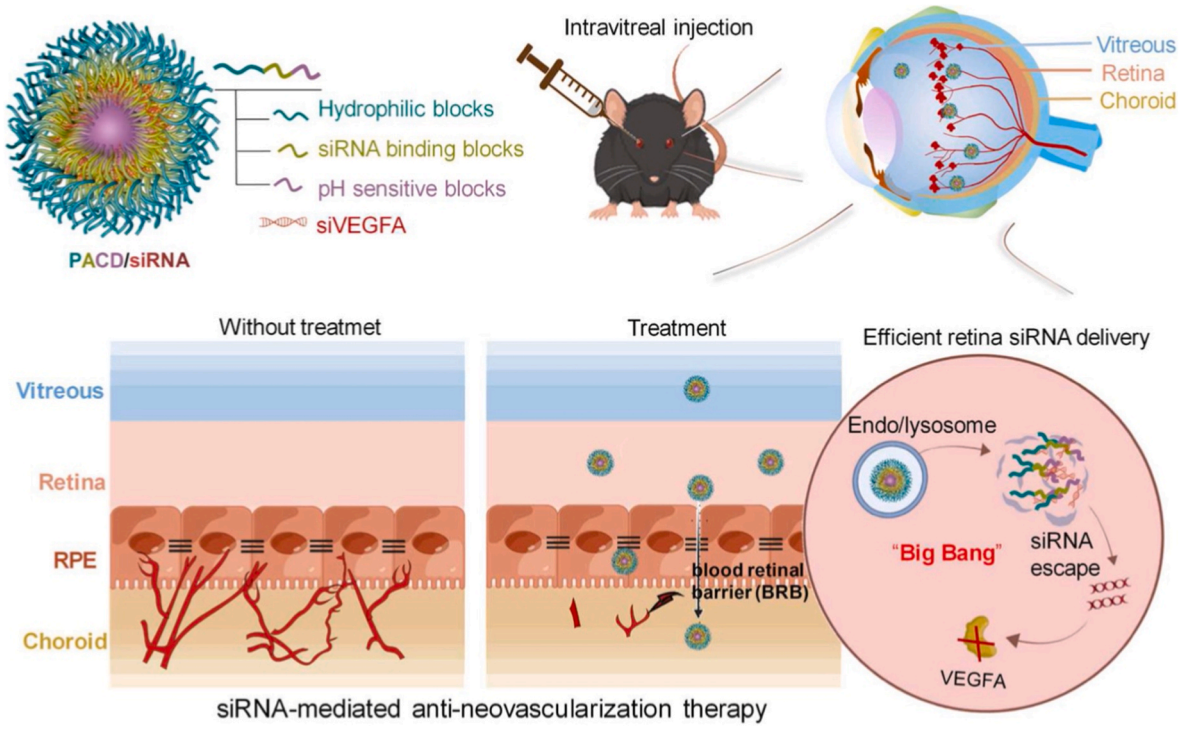

Fig. 8. Schematic illustration of PACD polymeric micelle enabling efficient siRNA delivery in the retina and abrogating hypoxia-induced angiogenesis. Reprinted with permission from Elsevier [189].

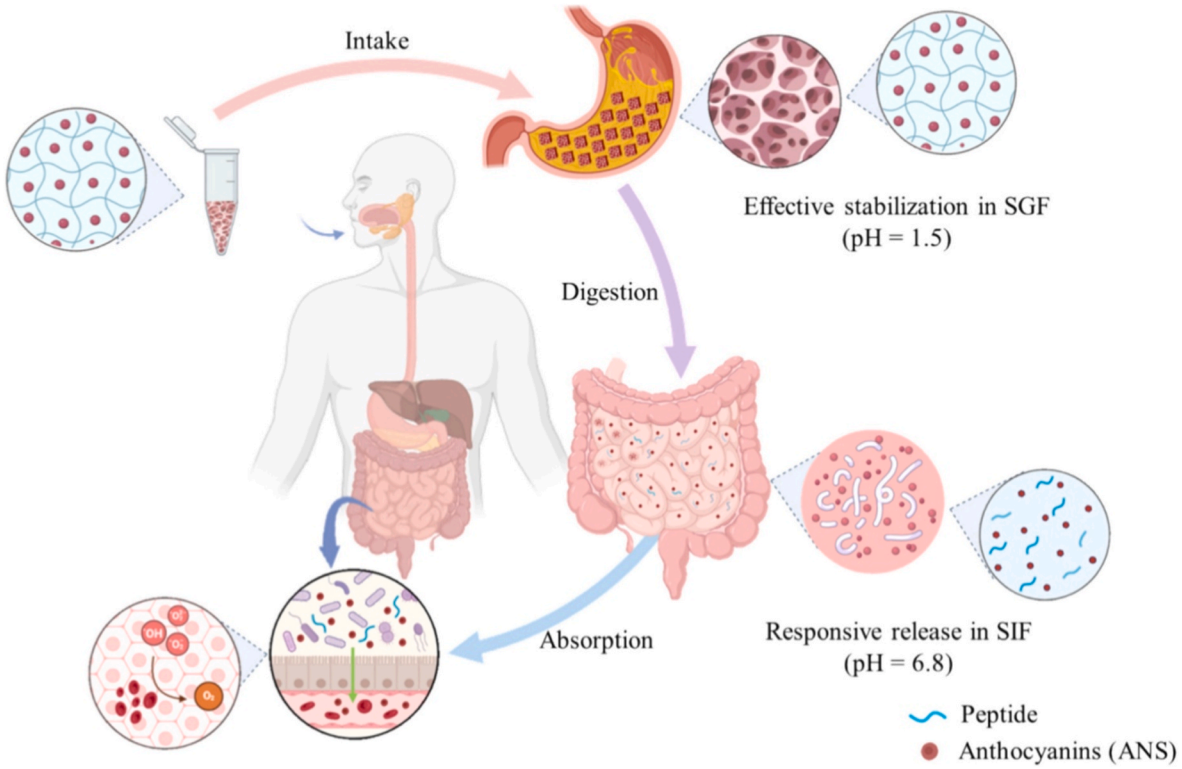

Fig. 9. Schematic presentation of this study that demonstrates the successful stability and controlled release of anthocyanins using pH-responsive peptide hydrogels in a simulated digestive environment (SGF: simulated gastric fluid; SIF: simulated intestinal fluid). Reprinted with permission from Elsevier [192].

remain largely neutral, thereby stabilizing their structure and effectively entrapping the anthocyanins [193]. Upon transition to the intestinal environment, the ionization of the carboxylic side chains, from COOH to COO^{-}, induces swelling of the hydrogel matrix, facilitating controlled release of the bioactive compounds. This strategy not only enhances the stability of PSPAs against gastric acid but also improves their potential bioavailability and therapeutic efficacy following oral administration [194].

Another notable example of pH-responsive polymers protective and responsive capabilities can be found in the development of stimulus-responsive Pickering emulsions for the targeted delivery of bioactive compounds relevant to Type 2 Diabetes Mellitus [195]. In this study, an amphiphilic phenylboronic acid-functionalized sodium alginate was employed as a critical pH-responsive component in a ternary colloidal platform alongside soybean protein isolate and purple sweet potato anthocyanins. The stabilization and functionality of the system rely on a network of reversible dynamic interactions, primarily B–O covalent coordination between PBA moieties and the *cis*-diol groups of alginate or PSPAs, along with hydrogen bonding between PSPAs and protein or polysaccharide chains. Upon emulsification, these soft colloidal particles adsorb spontaneously at the oil-water interface, forming a viscoelastic interfacial film. At the molecular level, the reversible covalent interactions contribute to strong and dynamic molecular adsorption, whereas at the supramolecular level, the densely packed colloidal film results in interfacial confinement, which physically entraps the encapsulated payload within the droplet. This multilayered interfacial structure enhances resistance to coalescence and protection from acidic degradation, as demonstrated by its ability to maintain integrity under simulated gastric conditions.

3.4. Soft robotic

Soft robotics enables the development of medical devices capable of performing diagnostic, therapeutic, and repair procedures with enhanced safety by reducing the need for invasive techniques and minimizing tissue damage during clinical operations [196]. Soft robots are flexible and compliant machines constructed from soft, deformable materials such as silicones, hydrogels, or elastomers [197]. They are designed to emulate the adaptability, dexterity, and safe interaction capabilities of biological organisms, enabling them to perform complex tasks in unstructured or dynamic environments [198]. The pH responsive behavior is ideal for designing biodegradable soft robots capable of performing complex tasks in dynamic biological environments [199].

Recent advances in multi-material 3D printing techniques have facilitated the fabrication of soft robotic devices that incorporate pH-responsive hydrogels alongside other functional polymers [200].

This multi-material approach allows precise spatial control over mechanical properties and responsiveness, resulting in robots that can adapt their form or function in response to localized pH variations [201]. Moreover, the integration of pH-sensitive hydrogels into soft robotic systems opens up new possibilities in biointerfacing and environmental sensing, enabling robots to detect and react to chemical signals in situ. A notable example is the development of 3D-printed pH-responsive biodegradable soft grippers composed of a bilayer hydrogel structure [202]. Soft grippers are flexible, adaptive devices capable of gently grasping and manipulating delicate objects by mimicking the compliant movements of natural organisms [203]. J. Kim et al. gripper combines a naturally derived pH-sensitive alginate/gelatin/acrylic acid (AAc) hydrogel layer with a non-pH-responsive acrylamide (AAm) hydrogel layer, both biodegradable by enzymes such as collagenase and alginate lyase [204]. Leveraging the bimorph bending effect, the alginate/gelatin/AAc hydrogel swells at higher pH values while the AAm hydrogel maintains a stable volume across pH changes, resulting in precise and reversible gripping motions responsive to the environmental pH (Fig. 10).

Another example of pH-responsive hydrogel-based robots involves a bilayer system constructed from chitosan films modified with superhydrophobic silica nanoparticles [205]. In this configuration, directional actuation is governed by the asymmetric response of the bilayer to environmental pH. Specifically, the actuator bends clockwise toward the NP-coated side in acidic media and anticlockwise toward the unmodified chitosan side in basic conditions. This pH-dependent bidirectional motion is driven by differential swelling behavior linked to the protonation state of the amino groups along the chitosan backbone (Fig. 11).

Another approach involves the use of carbon dot (CD)-crosslinked sodium alginate gels as active layers in bilayer actuators, in combination with poly(lactic acid) (PLA) as the passive substrate [206]. These hydrogels undergo rapid and reversible deformation in response to environmental pH, driven by the protonation and deprotonation of carboxyl and amino groups within the gel network.

The actuator not only performs basic mechanical tasks, such as grasping and lifting, but also exhibits visible pH-dependent fluorescence changes, thereby providing a dual-mode response. The deformation behavior is strongly pH-dependent, with maximum actuation observed near pH 5. At more extreme pH values (pH 1 or 11), the actuator's response is significantly reduced, likely due to degradation of the gel network, particularly through the hydrolysis of amide bonds under strongly basic conditions (Fig. 12). Moreover, the degree of deformation and the response rate can be finely tuned by varying the CD content, which influences both the crosslinking density and electrostatic interactions within the gel.

Interestingly, although isolated CDs exhibit strong pH-dependent fluorescence under UV light, their incorporation into the hydrogel matrix reduces this optical response, indicating that a portable detection system may be necessary to monitor colour changes effectively in practical applications (Fig. 13).

These systems demonstrate the potential to overcome challenges related to adaptability and biodegradability in healthcare devices, highlighting how stimuli-responsive hydrogels can be engineered into functional soft robotic components.

3.5. Wound healing

Skin wounds, if inadequately treated, may lead to serious complications, including infection, chronic inflammation, and impaired tissue regeneration [207]. The wound healing process is inherently complex and involves a well-orchestrated sequence of biological events such as

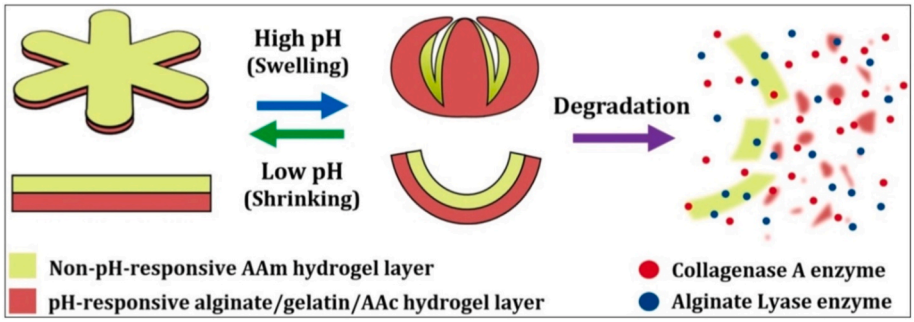

Fig. 10. Schematic illustrating the pH-responsive shape transformation and biodegradation of the bilayer hydrogel gripper. Reprinted with permission from Elsevier [204].

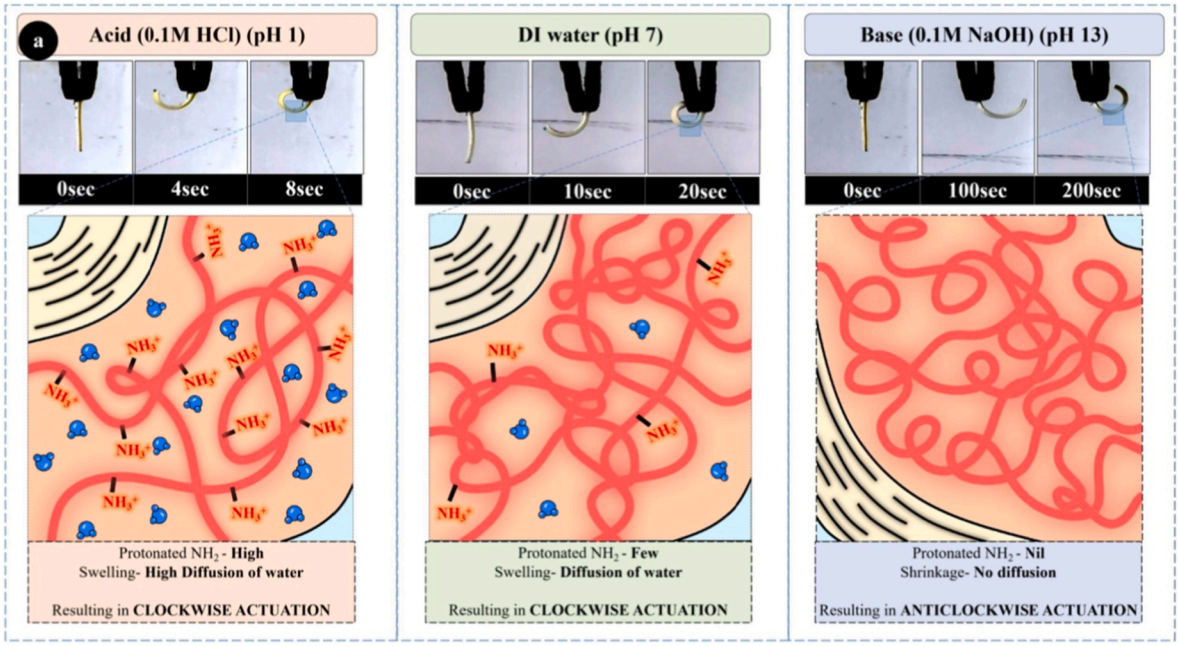

Fig. 11. The pH-responsive mechanism of bidirectional actuation of the prepared CH–Th4 film in the acidic and alkaline solution. Reprinted with permission from Elsevier [205].

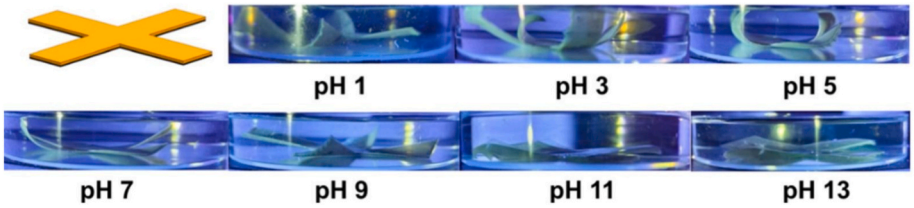

Fig. 12. Schematic illustrating the colour change of CDs actuator under different pH. Reprinted with permission from Elsevier [206].

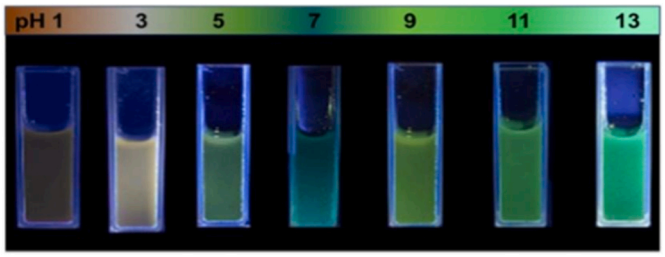

Fig. 13. Schematic illustrating the color change of CDs actuator under different pH. Reprinted with permission from Elsevier [206].

hemostasis, inflammation, proliferation, and remodeling. Traditional wound dressings like gauze or occlusive films offer passive protection, but they are often insufficient to actively modulate the wound environment or respond to dynamic physiological cues [208]. In contrast, hydrogel-based scaffolds have emerged as versatile materials in wound care due to their softness, high water content, biocompatibility, and ability to maintain a moist environment conducive to healing [209]. Recent advances have further improved hydrogel systems by incorporating smart polymers to wound-associated stimuli, such as local pH shifts. In particular, pH-responsive hydrogels are gaining attention for their ability to selectively release therapeutic agents, such as antimicrobial compounds, anti-inflammatory drugs, or growth factors, in response to the acidic conditions typically present in inflamed or infected wounds. For example, Tang et al. developed an injectable multi-responsive hydrogel capable of delivering insulin in a controlled manner to promote diabetic wound repair, demonstrating the therapeutic potential of pH-sensitive matrices in modulating healing outcomes [210]. Building upon this concept, composite hydrogel systems that incorporate nanoparticles have opened new avenues in responsive wound care. Nps can enhance the performance of hydrogels by increasing their breathability through the formation of pores, improving their absorption capacity, and strengthening their pH-responsiveness. In this context, a recent study developed a pH-responsive composite hydrogel scaffold incorporating ZIF-8@flavanone nanoparticles, designed to enable controlled release of bioactive compounds in slightly acidic wound environments [211].

In this work, ZIF-8@flavanone nanoparticles were synthesized using a microfluidic platform and embedded into a hydrogel scaffold composed of carrageenan and konjac glucomannan. The resulting composite not only exhibited favorable mechanical properties and biocompatibility but also responded to pH variations by selectively releasing flavanones, bioactive compounds with antimicrobial activity, under acidic conditions typical of acute wounds. Thanks to the pH-sensitive Zn-imidazole coordination in ZIF-8, drug release was significantly enhanced in slightly acidic environments (pH 5), reaching 43.3 % after 100 h (Fig. 14). This selective release mechanism allowed for high efficacy at the wound site while minimizing drug waste in neutral conditions. In vivo experiments confirmed the scaffold's effectiveness, achieving a wound closure rate of 90.5 % within 15 days.

While healthy skin typically exhibits an acidic pH, bacterial colonization and infection can increase the pH to values above 7.3 [212]. Building on this physiological transition, Wang et al. developed a

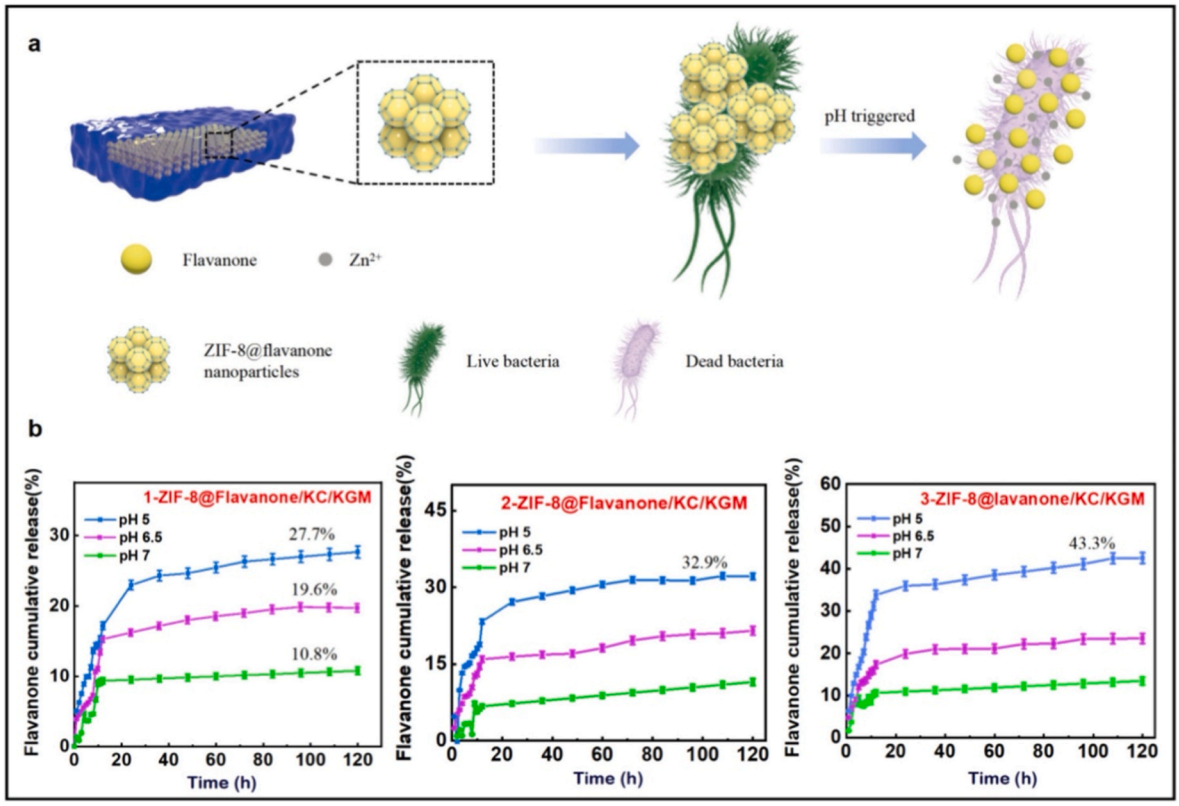

Fig. 14. (a) Schematic diagram of the flavanone release process. (b) Flavanone release from 1-ZIF-8@flavanone/KC/KGM, 2-ZIF-8@flavanone/KC/KGM and 3-ZIF-8@flavanone/KC/KGM at pH 7.4, 6.5 and 5.0. Reprinted with permission from Elsevier [211].

biomimetic 3D composite scaffold with pH-responsive hydrogel, designed to accelerate wound healing and prevent bacterial proliferation [213]. It consists of a tri-layered structure, where the middle layer, made of a pH-sensitive polymer dissolves at pH > 7, rapidly releasing the encapsulated antibiotic rifampicin (RIF). In vitro and in vivo assays confirmed the scaffold's excellent performance in sustaining drug release under healthy conditions (pH 5.5), while enabling rapid delivery of RIF under infected conditions (pH 8), with nearly complete release achieved within 6 h.

4. Challenges, limitations and translational perspectives

Beyond the conceptual rationale, recent in vivo and in situ measurements confirm that pathological pH gradients are real but often modest and heterogeneous, which constrains trigger reliability. For solid tumors, longitudinal MRI/pH imaging in mice showed extracellular pH values fluctuating around mildly acidic ranges during treatment, emphasizing the need for narrow-band transition pH in carriers to avoid premature or incomplete activation [214]. Likewise, live-cell ratiometric probes quantified organelle acidification with lysosomal pH tightly regulated yet variable across maturation states, indicating that endosomal/lysosomal triggering is sensitive to local context rather than a single fixed value [215]. These findings underline that pH alone is not always sufficient as a trigger. Another limitation is the complexity of the in vivo environment, where factors like ionic strength and serum proteins can interfere with the pH-responsive behavior [216]. The adsorption of serum proteins and the formation of a "protein corona" have been shown experimentally to alter the responsiveness of nanocarriers, in some cases dampening the swelling or solubility transitions originally observed under idealized buffer conditions [217]. These interactions can significantly modify particle–membrane crosstalk, suggesting that stealth coatings such as PEGylation or albumin layers are essential to preserve the intended responsiveness in vivo [218].

Preclinical studies also reveal both the potential and the current boundaries of these systems. The rationale for designing carriers with target pH release is to maximize drug exposure at the pathological site while limiting systemic toxicity. Polymeric micelles loaded with paclitaxel achieved superior tumor growth inhibition and reduced systemic toxicity compared to free drug in murine models [219]. Similarly, mesoporous silica nanoparticles grafted with acid-labile poly(acrylic acid) linkers displayed an eight-fold higher cytotoxicity against osteosarcoma cells than free doxorubicin [220]. An emerging strategy to address the modest and heterogeneous nature of pathological pH gradients is the integration of pH-responsiveness with secondary triggers [221]. Dual-responsive carriers, for example pH/redox micelles, have shown enhanced intratumoral accumulation compared to pH-only controls, while pH/light-sensitive hydrogels enable spatiotemporally controlled release [222]. Likewise, combining pH with temperature-sensitive polymers has been proposed for hyperthermia-assisted delivery [223]. These multi-stimuli platforms exploit the coincidence of pathological cues to achieve sharper selectivity, reduce premature leakage, and expand the range of biomedical applications. At the clinical level, only a few polymeric nanocarriers have progressed into human trials, and none of them rely primarily on a pH-triggering mechanism. The most advanced example is Genexol-PM (PEG–PLA micelles of paclitaxel), which in a phase III trial in metastatic breast cancer demonstrated non-inferior efficacy and improved tolerability compared to solvent-based paclitaxel [224]. Another case is NC-6004 (cisplatin-loaded micelles), which showed reduced nephrotoxicity and encouraging outcomes in phase II studies [225]. These formulations exemplify what clinical-grade polymer carriers can achieve, but they also underscore the translational gap that remains for strictly pH-responsive systems, which must still prove scalability, reproducibility, and clear therapeutic benefit in humans. Finally, the path from laboratory synthesis to clinical translation entails addressing manufacturing and regulatory challenges. Microfluidic and

self-assembly methods can produce highly uniform nanoparticles at small scale, but translating them into GMP-compliant large-scale production is still difficult [30,226].

Batch-to-batch variability in hydrogel crosslinking or polymer molecular weight can compromise reproducibility, which is unacceptable in a clinical context. Long-term biosafety also remains insufficiently studied: degradation products of synthetic polymers may accumulate and cause chronic toxicity, as reported for cationic fragments at high concentrations [227]. The gap between academic research and clinical approval also reflects the stringent safety and efficacy requirements imposed by regulatory agencies. The FDA and EMA require comprehensive data on biocompatibility, pharmacokinetics, long-term safety, and manufacturing consistency before approving any novel smart delivery system [228]. In addition, compliance demands consistent large-scale manufacturing, robust quality control protocols, and validated procedures for sterilization, storage, and shelf-life, steps that remain particularly challenging for stimuli-responsive materials that are sensitive to environmental conditions. Clinical trials also require greater standardization: endpoints such as 'successful targeting' or 'triggered release' must be clearly defined and measured, possibly via non-invasive imaging or biomarker-based readouts [170]. To overcome these hurdles, researchers are focusing on: polymers with finely tuned transition pH that match physiological windows; dual- or multi-stimuli responsive carriers to amplify modest pH gradients; incorporation of biodegradable backbones that degrade into innocuous metabolites; scalable fabrication technologies such as parallelized microfluidics or 3D printing.

5. Conclusions

Smart pH-responsive polymeric systems represent a powerful class of smart materials capable of addressing the complex challenges posed by biomedical applications. By leveraging the intrinsic pH heterogeneity of the human body, these systems enable targeted, on-demand release of therapeutic agents with minimal systemic toxicity. The combination of nanoparticles and hydrogels within hybrid constructs further enhances this potential, offering both nanoscale control over drug release kinetics and macroscale structural advantages.

From intestinal drug protection to tumor-targeted delivery, gene therapy, and wound healing, the adaptability and tunability of pH-responsive systems position them at the forefront of next-generation therapeutic strategies. Moreover, advances in materials science, microfluidics, and biofabrication are expected to further expand their applicability and functional complexity. Future efforts should focus on optimizing biocompatibility, degradation kinetics, and regulatory compliance to translate these systems into clinical practice. Overall, pH-sensitive nanoparticles, hydrogels, and their combinations provide a robust, modular, and highly customizable platform for a wide range of biomedical challenges. Looking ahead, several biological targets appear particularly promising for the clinical translation of pH-responsive polymers. Tumor microenvironments, characterized by a slightly acidic extracellular pH, remain the most exploited setting for selective drug release. Oral delivery of nucleic acids also represents a key application, where pH-responsive carriers can protect DNA and RNA from gastric degradation and ensure site-specific release in the intestine. At the intracellular level, endosomal and lysosomal pH gradients offer unique opportunities for triggered release and endosomal escape. Nevertheless, important challenges remain: natural polymers such as alginate, chitosan, and hyaluronic acid suffer from batch-to-batch variability and limited tunability; synthetic acrylates and methacrylates require careful control of release kinetics and residual toxicity; and polycationic systems like PDMAEMA, PLL, and PLH must balance proton-sponge efficacy with cytotoxicity. Addressing these limitations will be crucial to fully harness the potential of pH-responsive polymers in advanced biomedical applications.

CRediT authorship contribution statement

Giuseppe Nunziata: Writing – original draft, Conceptualization. **Domenico Pollonio:** Writing – original draft, Investigation. **Elisa Lacroce:** Writing – original draft. **Filippo Rossi:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

[1] A.K. Khalil, Y.H. Teow, M.S. Takriff, A.L. Ahmad, M.A. Atieh, Recent developments in stimuli-responsive polymer for emerging applications: a review, Results Eng. (2025) 103900.
[2] Y. Zhang, M. Zhang, H. Song, Q. Dai, C. Liu, Tumor microenvironment-responsive polymer-based RNA delivery systems for cancer treatment, Small Methods 9 (2025) 2400278.
[3] Y. Cheng, Y. Lu, Physical stimuli-responsive polymeric patches for healthcare, Bioact. Mater. 43 (2025) 342–375.
[4] F. Alam, N. El-Atab, Multi-material 4D printing employing stimuli-responsive polymer composites using vat photopolymerization, Virtual Phys. Prototyp. 20 (2025) e2444576.
[5] A. Hoffman, P. Stayton, G. Chen, J. Chen, C. Cheung, Z. Ding, L. Dong, R. Fong, C. Lackey, C. Long, M. Miura, J. Morris, N. Murthy, Y. Nabeshima, T. Park, O. Press, T. Shimoboji, T. Miyata, Really smart bioconjugates of smart polymers and receptor proteins, J. Biomed. Mater. Res. 52 (2000) 577–586, https://doi.org/10.1002/1097-4636(20001215)52:4<577::AID-JBM1>3.0.CO, 2-5.
[6] I.Y. Galaev, B. Mattiasson, "Smart" polymers and what they could do in biotechnology and medicine, Trends Biotechnol. 17 (1999) 335–340, https://doi.org/10.1016/s0167-7799(99)01345-1.
[7] A. Kikuchi, T. Okano, Intelligent thermoresponsive polymeric stationary phases for aqueous chromatography of biological compounds, Prog. Polym. Sci. 27 (2002) 1165–1193, https://doi.org/10.1016/S0079-6700(02)00013-8.
[8] B. Jeong, A. Gutowska, Lessons from nature: stimuli-responsive polymers and their biomedical applications, Trends Biotechnol. 20 (2002) 305–311, https://doi.org/10.1016/s0167-7799(02)01962-5.
[9] L.K. Rivera-Tarazona, Z.T. Campbell, T.H. Ware, Stimuli-responsive engineered living materials, Soft Matter 17 (2021) 785–809, https://doi.org/10.1039/D0SM01905D.
[10] E. Lacroce, F. Pizzetti, N.M.B. Urrego, G. Nunziata, M. Masi, F. Rossi, Magnetically active bicontinuous polymer structures for multiple controlled drug delivery, Macromol. Biosci. (2024) 2400084.
[11] R. Liu, Z. Li, H. Zhao, L. Zhang, R. Lan, Q. Wang, H. Yang, Dual-stimuli-responsive covalent organic framework-liquid crystal polymer smart actuator, Adv. Funct. Mater. 35 (2025) 2418627.
[12] Y. Shen, X. Le, Y. Wu, T. Chen, Stimulus-responsive polymer materials toward multi-mode and multi-level information anti-counterfeiting: recent advances and future challenges, Chem. Soc. Rev. 53 (2024) 606–623.
[13] R.Y.H. Tan, C.S. Lee, M.R. Pichika, S.F. Cheng, K.Y. Lam, PH responsive polyurethane for the advancement of biomedical and drug delivery, Polymers 14 (2022) 1672, https://doi.org/10.3390/polym14091672.
[14] B. Blanco-Fernandez, P. Diaz-Rodriguez, A. Concheiro, C. Alvarez-Lorenzo, Chapter 5 - stimuli responsive hydrogels in drug delivery and biomedicine, in: A. J. Paredes, E. Larrañeta, G. Laverty, R.F. Donnelly (Eds.), Hydrogels in Drug Delivery, Elsevier, 2025, pp. 135–219, https://doi.org/10.1016/B978-0-443-22017-3.00003-2.
[15] H. Xue, C. Zhu, Y. Wang, Q. Gu, Y. Shao, A. Jin, X. Zhang, L. Lei, Y. Li, Stimulus-responsive cellulose hydrogels in biomedical applications and challenges, Mater. Today Bio 32 (2025) 101814, https://doi.org/10.1016/j.mtbio.2025.101814.
[16] M. Gao, J. Li, S. Zhao, G. Li, Multi-stimuli-responsive conductive and luminescent hydrogels for wearable sensors and information encryption transmission, Chem. Eng. J. 496 (2024) 153881, https://doi.org/10.1016/j.cej.2024.153881.
[17] D.-D. Yang, X.-H. Ning, H.-W. Zheng, Y.-S. Shi, B. Jin, T. Xiao, X.-J. Zheng, Multi-stimuli responsive behavior of two Schiff base complexes with high contrast multicolor switching and wearable applications for rapid detection of HCl and NH3 vapor, Dyes Pigments 212 (2023) 111149, https://doi.org/10.1016/j.dyepig.2023.111149.
[18] M. Norouzi, E. Ahmadi, Z. Mohamadnia, Stimuli-responsive fluorescent polymer nanoparticles: versatile applications in rapid colorimetric and fluorometric detection of cyanide in blood plasma, pH sensing, paper-based sensors, and intelligent artworks, J. Photochem. Photobiol. Chem. 452 (2024) 115552, https://doi.org/10.1016/j.jphotochem.2024.115552.

[19] Y. Wang, Z. Zhao, Y. Mu, L. Chen, Y. Ji, R. Wang, S. Pu, Multi-stimuli-responsive luminescence in a pyrimidine-functionalized tetraphenylethylene derivative: AIE, trivalent ions (Cr3+/Al3+/Fe3+) sensing, and applications, J. Photochem. Photobiol. Chem. 469 (2025) 116538, https://doi.org/10.1016/j.jphotochem.2025.116538.

[20] Y. Pu, X. Zhang, X. Liu, X. Zhao, Z. Yang, Y. Yu, Multi-stimuli responsive bionic actuators constructed by linear liquid crystal polymers, Transactions of Materials Research 1 (2025) 100003, https://doi.org/10.1016/j.tramat.2025.100003.

[21] C. Zheng, M. Ju, X. Zhang, K. Xie, A. Hou, A. Gao, A multi-stimulus responsive nanogel actuator with the π-π stacking interaction self-assembly and application for bioinspired smart skin with light, heat and humidity responses and superb UV resistance, Chem. Eng. J. 499 (2024) 156092, https://doi.org/10.1016/j.cej.2024.156092.

[22] B. Zhang, S. Liu, J. Pei, Z. Wang, Y. Chen, Q. Jia, C. Hao, X. Lei, Z. Wu, Z. Yang, G. Zhou, D. Wang, Multiple stimuli-responsive dual-emission material with locked diverse conformations for multimodal anti-counterfeiting and single-molecule white electroluminescence, Chem. Eng. J. 513 (2025) 162788, https://doi.org/10.1016/j.cej.2025.162788.

[23] W. Yang, X. Wang, X. Teng, Z. Qiao, H. Yu, Programmable multi-stimulus-responsive whirligig beetle inspired soft robot with multifunctionality based on composite materials, Colloids Surf. A Physicochem. Eng. Asp. 693 (2024) 134093, https://doi.org/10.1016/j.colsurfa.2024.134093.

[24] Q. Guo, J. Wei, S. Yu, X. Feng, Z. Gao, R. Wang, H. Yu, Z. Ge, W. Yang, Soft robots with different movement capabilities based on photo-responsive multilayer poly (N-isopropylacrylamide) and multi-walled carbon nanotubes, J. Colloid Interface Sci. 690 (2025) 137351, https://doi.org/10.1016/j.jcis.2025.137351.

[25] X. Gao, Y. Li, J. Li, X. Xiang, J. Wu, S. Zeng, Stimuli-responsive materials in oral diseases: a review, Clin. Oral Invest. 28 (2024) 497, https://doi.org/10.1007/s00784-024-05884-z.

[26] G. Kocak, C. Tuncer, V. Bütün, pH-Responsive polymers, Polym. Chem. 8 (2017) 144–176, https://doi.org/10.1039/C6PY01872F.

[27] B. Veeranna, T. Pramodkumar, N. Srujana, DrM.P. Venkatesh, N.V. Gupta, K. L, H. Gangadharappa, pH sensitive drug delivery systems: a review, American Journal of Drug Discovery and Development 1 (2011) 24–48, https://doi.org/10.3923/ajdd.2011.24.48.

[28] F.S. Mohammadi, M. Araghi, S. Nadri, Core-shell (polyethylene glycol/silk) scaffold containing microfluidic synthesis of curcumin loaded chitosan nanoparticles as a wound healing agent in animal full-thickness injuries, Int. J. Biol. Macromol. 278 (2024) 134603, https://doi.org/10.1016/j.ijbiomac.2024.134603.

[29] N. Kar, M. McCoy, J. Wolfe, S.L. Bueno, I.H. Shafei, S.E. Skrabalak, Retrosynthetic design of core–shell nanoparticles for thermal conversion to monodisperse high-entropy alloy nanoparticles, Nature Synthesis 3 (2024) 175–184.

[30] G. Nunziata, A. Borroni, F. Rossi, Advanced microfluidic strategies for core-shell nanoparticles: the next-generation of polymeric and lipid-based drug nanocarriers, Chem. Eng. J. Adv. 22 (2025) 100759, https://doi.org/10.1016/j.ceja.2025.100759.

[31] X. Li, L. Wang, J. Wang, H. Fan, F. Pang, W. He, C. Jiang, Y. Jin, Y. Shen, Y. Wang, H. Zeng, Z. Dai, P. Zhou, X. Hu, X. Lu, Enhanced osteoarthritis treatment using an injectable pH-responsive and cartilage-targeted liposome-anchored kartogenin-incorporated methacrylated gelatin hydrogel microspheres, Int. J. Biol. Macromol. 313 (2025) 144198, https://doi.org/10.1016/j.ijbiomac.2025.144198.

[32] D. Li, Z. Chen, S. Zhang, Y. Xi, X. Liu, Y. Zhang, Y. Ding, S. Jia, Y. Xie, C. Zhong, Injectable copper ion cross-linked TEMPO-oxidized bacterial cellulose nanofiber hydrogels and their synergistic antimicrobial activity with glutathione, Int. J. Biol. Macromol. 315 (2025) 144287, https://doi.org/10.1016/j.ijbiomac.2025.144287.

[33] E. Lacroce, G. Nunziata, F. Cianniello, E. Limiti, A. Rainer, F.B. Vangosa, A. Sacchetti, M. Sponchioni, F. Rossi, Amphiphilic pH-responsive core-shell nanoparticles can increase the performances of cellulose-based drug delivery systems, Int. J. Biol. Macromol. (2024) 137659, https://doi.org/10.1016/j.ijbiomac.2024.137659.

[34] A. Molinelli, A. Schirato, L. Moretti, G. Della Valle, M. Maiuri, F. Rossi, Last advances on hydrogel nanoparticles composites in medicine: an overview with focus on gold nanoparticles, ChemNanoMat 10 (2024) e202300584.

[35] X.-K. Chi, X.-L. Xu, B.-Y. Chen, J. Su, Y.-Z. Du, Combining nanotechnology with monoclonal antibody drugs for rheumatoid arthritis treatments, J. Nanobiotechnol. 21 (2023) 105.

[36] H. Ding, P. Tan, S. Fu, X. Tian, H. Zhang, X. Ma, Z. Gu, K. Luo, Preparation and application of pH-responsive drug delivery systems, J. Contr. Release 348 (2022) 206–238.

[37] E.A. Appel, M.W. Tibbitt, M.J. Webber, B.A. Mattix, O. Veiseh, R. Langer, Self-assembled hydrogels utilizing polymer–nanoparticle interactions, Nat. Commun. 6 (2015) 6295.

[38] M. Yang, M. Cui, Y. Sun, S. Liu, W. Jiang, Mechanisms, combination therapy, and biomarkers in cancer immunotherapy resistance, Cell Commun. Signal. 22 (2024) 338.

[39] S. Bazban-Shotorbani, M.M. Hasani-Sadrabadi, A. Karkhaneh, V. Serpooshan, K. I. Jacob, A. Moshaverinia, M. Mahmoudi, Revisiting structure-property relationship of pH-responsive polymers for drug delivery applications, J. Contr. Release 253 (2017) 46–63, https://doi.org/10.1016/j.jconrel.2017.02.021.

[40] F. Ofridam, M. Tarhini, N. Lebaz, É. Gagnière, D. Mangin, A. Elaissari, pH-sensitive polymers: classification and some fine potential applications, Polym. Adv. Technol. 32 (2021) 1455–1484, https://doi.org/10.1002/pat.5230.

[41] E. Kashani, S. Maghsoudi, H. Rezania, M. Yarazavi, M. Hajiabbas, G. Benkovics, E. Bilensoy, I. Lacík, A. Heydari, Cyclodextrin polymers containing ionizable and ionic groups: a comprehensive review from classifications and synthesis methods to applications, Mater. Today Chem. 39 (2024) 102186.

[42] A. Kumar, D.W. Chang, Active polymers decorated with major acid groups for water treatment: potentials and challenges, Polymers 17 (2024) 29.

[43] S. Hou, Y. Liu, J. Yan, Z. Fang, Y. Gong, Q. Zhang, Y. Yan, Zwitterionic polymers: structure design and emerging applications, Macromol. Chem. Phys. (2025) e00106.

[44] I. Kadri, A.B. Hassena, F. Aouaini, B. Basha, H. Wahbi, F. Saadi, W.A. El-Fattah, A. Sánchez-Coronilla, W. Rekik, H. Naïli, Chemical preparation, thermal behavior, magnetic properties and biological activities of a new manganese chloride templated by piperazine (C4H12N2)[MnCl4(H2O)2], Inorg. Chim. Acta. 577 (2025) 122509, https://doi.org/10.1016/j.ica.2024.122509.

[45] T. Stavert, M. Jorge, Understanding the pH-responsive behaviour of alkylamine surfactants, J. Mol. Liq. 431 (2025) 127656, https://doi.org/10.1016/j.molliq.2025.127656.

[46] D. Beyer, P. Koıfmmode \checks\else š\fiovan, C. Holm, Explaining giant apparent \mathrmpK_a shifts in weak polyelectrolyte brushes, Phys. Rev. Lett. 131 (2023) 168101, https://doi.org/10.1103/PhysRevLett.131.168101.

[47] Y. Li, Z. Wang, Q. Wei, M. Luo, G. Huang, B.D. Sumer, J. Gao, Non-covalent interactions in controlling pH-responsive behaviors of self-assembled nanosystems, Polym. Chem. 7 (2016) 5949–5956.

[48] R. Lunkad, A. Murmiliuk, Z. Tošner, M. Štěpánek, P. Košovan, Role of pKA in charge regulation and conformation of various peptide sequences, Polymers 13 (2021), https://doi.org/10.3390/polym13020214.

[49] K. Zhang, S. Li, J. Li, X. Zhou, Y. Qin, L. Wu, J. Ling, Ultra-pH-sensitive nanoplatform for precise tumor therapy, Biomaterials 314 (2025) 122858.

[50] Z.T. Bennett, G. Huang, M.T. Dellinger, B.D. Sumer, J. Gao, Stepwise ultra-pH-sensitive micelles overcome ap K a barrier for systemic lymph node delivery, ACS Nano 18 (2024) 16632–16647.

[51] L. Deng, T. Wei, Y. Zhang, A. Shen, X. He, S. Gao, X. Li, W. He, A. Haleem, R. Hu, Ultra-pH-sensitive nanoparticle of gambogenic acid for tumor targeting therapy via anti-vascular strategy plus immunotherapy, Int. J. Pharm. 660 (2024) 124303.

[52] M.M. Quesada-Moreno, J.R. Avilés-Moreno, J.J. López-González, Structural behavior of neutral, protonated, and deprotonated l-valine in aqueous solutions: a combined study using chirality sensitive (VCD) and non sensitive (IR and Raman) vibrational spectroscopies and quantum chemical calculations, Tetrahedron Asymmetry 26 (2015) 1314–1327, https://doi.org/10.1016/j.tetasy.2015.10.005.

[53] M. Kovačić, I. Ivanišević, A. Ressler, P. Karamanis, Experimental and computational insights into the mechanism of destabilization of poly(acrylic acid)-capped silver nanoparticles induced by weak conjugate bases, Colloids Surf. A Physicochem. Eng. Asp. 690 (2024) 133739, https://doi.org/10.1016/j.colsurfa.2024.133739.

[54] F. Reyes-Ortega, pH-responsive polymers: properties, synthesis and applications, in: Smart Polymers and Their Applications, 2014, pp. 45–92, https://doi.org/10.1533/9780857097026.1.45.

[55] H. Almeida, M.H. Amaral, P. Lobão, Temperature and pH stimuli-responsive polymers and their applications in controlled and self- regulated drug delivery, J. Appl. Pharmaceut. Sci. 2 (2012) 1–10.

[56] G. Gopinath, S. Ayyasamy, M. Shadap, P. Shanmugaraj, A. Banu, M. Hema, Cellulose acetate-based polymer electrolyte for energy storage application with the influence of BaTiO3 nanofillers on the electrochemical properties: a progression in biopolymer-EDLC technology, Int. J. Biol. Macromol. 281 (2024) 136416, https://doi.org/10.1016/j.ijbiomac.2024.136416.

[57] R. Abka-khajouei, L. Tounsi, N. Shahabi, A.K. Patel, S. Abdelkafi, P. Michaud, Structures, properties and applications of alginates, Mar. Drugs 20 (2022), https://doi.org/10.3390/md20060364.

[58] A.K. Philip, B.A. Samuel, Y.S. Saleh, B.I. Mohammad, H.A. Al-Aubaidy, pH-responsive chitosan-alginate hydrogel beads: for enhanced bioavailability and controlled release of omeprazole, Drug Dev. Ind. Pharm. 0 (2025) 1–16, https://doi.org/10.1080/03639045.2025.2536620.

[59] C. Huang, T. Xie, Y. Liu, S. Yan, F. OuYang, H. Zhang, L. Lei, D. He, H. Wei, C.-Y. Yu, A sodium alginate-based multifunctional nanoplatform for synergistic chemo-immunotherapy of hepatocellular carcinoma, Adv. Mater. 35 (2023) 2301352, https://doi.org/10.1002/adma.202301352.

[60] Y. Hu, S. Hu, S. Zhang, S. Dong, J. Hu, L. Kang, X. Yang, A double-layer hydrogel based on alginate-carboxymethyl cellulose and synthetic polymer as sustained drug delivery system, Sci. Rep. 11 (2021) 9142, https://doi.org/10.1038/s41598-021-88503-1.

[61] F.J. Al-Hasani, Q.A. Hamad, N.K. Faheed, Enhancing the cell viability and antibacterial properties of alginate-based composite layer by adding active particulates, Discov. Appl. Sci. 6 (2024) 70.

[62] X. Wen, D. Bao, M. Chen, A. Zhang, C. Liu, R. Sun, Preparation of CMC/HEC crosslinked hydrogels for drug delivery, Bioresources 10 (2015) 8339–8351.

[63] A. Negm, M. Gouda, H.-I.M. Ibrahim, Carboxymethyl cellulose/Zn-organic framework down-regulates proliferation and up-regulates apoptosis and DNA damage in colon and lung cancer cell lines, Polymers 14 (2022), https://doi.org/10.3390/polym14102015.

[64] I. Musfiroh, Aliya, A. Nur Hasanah, I. Budiman, The optimization of sodium carboxymethyl cellulose (NA-CMC) synthesized from water hyacinth (Eichhornia crassipes (mart.) solm) cellulose, Res. J. Pharmaceut. Biol. Chem. Sci. 4 (2013) 1092.

[65] C.-L. Ke, F.-S. Deng, C.-Y. Chuang, C.-H. Lin, Antimicrobial actions and applications of chitosan, Polymers 13 (2021), https://doi.org/10.3390/polym13060904.
[66] R. Maleki, M. Khedri, S. Rezvantalab, N. Beheshtizadeh, Investigation of pH-dependent Paclitaxel delivery mechanism employing Chitosan-Eudragit bioresponsive nanocarriers: a molecular dynamics simulation, J. Biol. Eng. 18 (2024) 49.
[67] X. Wan, C. Chen, J. Zhan, S. Ye, R. Li, M. Shen, Dendritic polylysine co-delivery of paclitaxel and siAXL enhances the sensitivity of triple-negative breast cancer chemotherapy, Front. Bioeng. Biotechnol. 12 (2024) 1415191.
[68] J.H. Kim, M.J. Moon, D.Y. Kim, S.H. Heo, Y.Y. Jeong, Hyaluronic acid-based nanomaterials for cancer therapy, Polymers 10 (2018), https://doi.org/10.3390/polym10101133.
[69] T. Yu, Y. Li, X. Gu, Q. Li, Development of a hyaluronic acid-based nanocarrier incorporating doxorubicin and cisplatin as a pH-sensitive and CD44-targeted anti-breast cancer drug delivery system, Front. Pharmacol. 11 (2020) 532457.
[70] F. Rannou, J.-P. Pelletier, J. Martel-Pelletier, Efficacy and safety of topical NSAIDs in the management of osteoarthritis: evidence from real-life setting trials and surveys, Semin. Arthritis Rheum. 45 (2016) S18–S21, https://doi.org/10.1016/j.semarthrit.2015.11.007.
[71] G.N. Iaconisi, P. Lunetti, N. Gallo, A.R. Cappello, G. Fiermonte, V. Dolce, L. Capobianco, Hyaluronic acid: a powerful biomolecule with wide-ranging applications—a comprehensive review, Int. J. Mol. Sci. 24 (2023) 10296.
[72] M. Suhail, C.-W. Fang, A. Khan, M.U. Minhas, P.-C. Wu, Fabrication and in vitro evaluation of pH-sensitive polymeric hydrogels as controlled release carriers, Gels 7 (2021), https://doi.org/10.3390/gels7030110.
[73] P.S. Kumbhar, A.M. Sakate, O.B. Patil, A.S. Manjappa, J.I. Disouza, Podophyllotoxin-polyacrylic Acid Conjugate Micelles: Improved Anticancer Efficacy against Multidrug-Resistant Breast Cancer, vol. 32, Journal of the Egyptian National Cancer Institute, 2020, p. 42.
[74] H. Arkaban, M. Barani, M.R. Akbarizadeh, N. Pal Singh Chauhan, S. Jadoun, M. Dehghani Soltani, P. Zarrintaj, Polyacrylic acid nanoplatforms: antimicrobial, tissue engineering, and cancer theranostic applications, Polymers 14 (2022), https://doi.org/10.3390/polym14061259.
[75] C. Robin, C. Lorthioir, A. Fall, G. Ovarlez, C. Amiel, C. Le Coeur, Unexpected slow kinetics of poly(methacrylic acid) phase separation in the semi-dilute regime, Polymers 14 (2022), https://doi.org/10.3390/polym14214708.
[76] N.V. Mdlovu, R.-S. Juang, W.-Y. Lo, K.-S. Lin, Hydrolysis-assisted synthesis of magnetic iron oxide-silica/poly(methacrylic acid) nanocomposites for pH- and thermo-responsive doxorubicin delivery, J. Taiwan Inst. Chem. Eng. 169 (2025) 105992, https://doi.org/10.1016/j.jtice.2025.105992.
[77] Y.-T. Shieh, Y.-C. Yeh, C.-C. Cheng, Multistimuli-responsive emulsifiers based on two-way amphiphilic diblock polymers, ACS Omega 4 (2019) 15479–15487, https://doi.org/10.1021/acsomega.9b01728.
[78] S. Ramezanian, J. Moghaddas, H. Roghani-Mamaqani, A. Rezamand, Dual pH-and temperature-responsive poly (dimethylaminoethyl methacrylate)-coated mesoporous silica nanoparticles as a smart drug delivery system, Sci. Rep. 13 (2023) 20194.
[79] S. Agarwal, Y. Zhang, S. Maji, A. Greiner, PDMAEMA based gene delivery materials, Mater. Today 15 (2012) 388–393, https://doi.org/10.1016/S1369-7021(12)70165-7.
[80] H.-H. Lu, C.-H. Huang, T.-Y. Shiue, F.-S. Wang, K.-K. Chang, Y. Chen, C.-H. Peng, Highly efficient gene release in spatiotemporal precision approached by light and pH dual responsive copolymers, Chem. Sci. 10 (2019) 284–292.
[81] A. Stamou, H. Iatrou, C. Tsitsilianis, NIPAm-based modification of poly(L-lysine): a pH-dependent LCST-type thermo-responsive biodegradable polymer, Polymers 14 (2022), https://doi.org/10.3390/polym14040802.
[82] G. Minigo, A. Scholzen, C.K. Tang, J.C. Hanley, M. Kalkanidis, G.A. Pietersz, V. Apostolopoulos, M. Plebanski, Poly-l-lysine-coated nanoparticles: a potent delivery system to enhance DNA vaccine efficacy, Vaccine 25 (2007) 1316–1327, https://doi.org/10.1016/j.vaccine.2006.09.086.
[83] D. Tang, Y. Yan, Y. Li, Y. Li, J. Tian, L. Yang, H. Ding, G. Bashir, H. Zhou, Q. Ding, Targeting DAD1 gene with CRISPR-Cas9 system transmucosally delivered by fluorinated polylysine nanoparticles for bladder cancer intravesical gene therapy, Theranostics 14 (2024) 203.
[84] H. Zhu, C. Dong, H. Dong, T. Ren, X. Wen, J. Su, Y. Li, Cleavable PEGylation and hydrophobic histidylation of polylysine for siRNA delivery and tumor gene therapy, ACS Appl. Mater. Interfaces 6 (2014) 10393–10407.
[85] J. He, S. Xu, A.J. Mixson, The multifaceted histidine-based carriers for nucleic acid delivery: advances and challenges, Pharmaceutics 12 (2020), https://doi.org/10.3390/pharmaceutics12080774.
[86] Z. Li, L. Qiu, Q. Chen, T. Hao, M. Qiao, H. Zhao, J. Zhang, H. Hu, X. Zhao, D. Chen, L. Mei, pH-sensitive nanoparticles of poly(l-histidine)–poly(lactide-co-glycolide)–tocopheryl polyethylene glycol succinate for anti-tumor drug delivery, Acta Biomater. 11 (2015) 137–150, https://doi.org/10.1016/j.actbio.2014.09.014.
[87] H.S. Hwang, J. Hu, K. Na, Y.H. Bae, Role of polymeric endosomolytic agents in gene transfection: a comparative study of poly (L-lysine) grafted with monomeric L-histidine analogue and poly (L-histidine), Biomacromolecules 15 (2014) 3577–3586.
[88] S. Bharati, V. Gaikwad, A. Pawar, B. Chellampillai, Investigation of a biopolymer-based pH-responsive and sustained release raft-gel-forming tablet of famotidine: in-vitro, ex-vivo, bioavailability and anti-ulcer evaluation in New Zealand albino rabbit, J. Drug Deliv. Sci. Technol. 86 (2023) 104649, https://doi.org/10.1016/j.jddst.2023.104649.
[89] M.I.A. Echazú, C.E. Olivetti, I. Peralta, M.R. Alonso, C. Anesini, C.J. Perez, G. S. Alvarez, M.F. Desimone, Development of pH-responsive biopolymer-silica composites loaded with Larrea divaricata Cav. extract with antioxidant activity, Colloids Surf. B Biointerfaces 169 (2018) 82–91, https://doi.org/10.1016/j.colsurfb.2018.05.015.
[90] M. Pooresmaeil, H. Namazi, Facile coating of the methotrexate-layered double hydroxide nanohybrid via carboxymethyl starch as a pH-responsive biopolymer to improve its performance for colon-specific therapy, Eur. Polym. J. 165 (2022) 111026, https://doi.org/10.1016/j.eurpolymj.2022.111026.
[91] N.R. Thakare, S. Hazarika, Eco-friendly biopolymers and their biomedical applications: a review, Int. J. Biol. Macromol. 327 (2025) 147225, https://doi.org/10.1016/j.ijbiomac.2025.147225.
[92] S. Pounraj, S. Chen, H. Triscott, A.K. Lam, L. Ma, B.H.A. Rehm, Engineering neoantigens to form immunogenic biopolymer particles targeting metastatic breast cancer, Appl. Mater. Today 38 (2024) 102238, https://doi.org/10.1016/j.apmt.2024.102238.
[93] M. Alboofetileh, S. Jeddi, M. Abdollahi, Sequential recovery of alginate from fucoidan extraction by-products of Nizamuddinia zanardinii seaweed using green extraction methods, Ultrason. Sonochem. 117 (2025) 107343, https://doi.org/10.1016/j.ultsonch.2025.107343.
[94] L.A. Pérez, J.M. Alonso, R. Pérez-González, D. Velasco, L. Suárez-Cabrera, G. de Aranda-Izuzquiza, V. Sáez-Martínez, R. Hernández, Injectable hyaluronic acid hydrogels via Michael addition as dermal fillers for skin regeneration applications, Biomater. Adv. (2025) 214364, https://doi.org/10.1016/j.bioadv.2025.214364.
[95] J. da S. Pinho-Jr, B.S. Moreira, G.B. Brito, L.G. de A. Torres, D.N. Eiriz, A. G. Torres, A.J. Teodoro, D. Perrone, V.N. Castelo-Branco, Impact of chitosan-based oleogels crosslinked with vanillin containing different oil phases on lipid digestion and bioaccessibility of carotenoids and tocols, Food Chem. 487 (2025) 144740, https://doi.org/10.1016/j.foodchem.2025.144740.
[96] N. Mahheidari, S. Zamani, R. Khademi, M.K. Farahani, S. Molzemi, M. Salehi, Biological macromolecules Alginate-Carboxymethyl Cellulose (Alg-CMC) hydrogel loaded with Botulinum toxin type A for skin wound treatment and functional tissue regeneration, Int. J. Biol. Macromol. 316 (2025) 144668, https://doi.org/10.1016/j.ijbiomac.2025.144668.
[97] N. Wei, Z. Lv, X. Meng, Q. Liang, T. Jiang, S. Sun, Y. Li, J. Feng, Sodium alginate-carboxymethyl chitosan hydrogels loaded with difenoconazole for pH-responsive release to control wheat crown rot, Int. J. Biol. Macromol. 252 (2023) 126396, https://doi.org/10.1016/j.ijbiomac.2023.126396.
[98] S.W. Shalaby, K.J.L. Burg, Absorbable and Biodegradable Polymers, CRC Press, New York, 2003, https://doi.org/10.1201/9780203493014.
[99] P.C.G. Fernandes, V.F. Filgueiras, B.F. Matte, J.H. Lopes, A comprehensive rheological study on the influence of ion charge density and valence in ionotropically crosslinked alginate hydrogels for bioprinting, Int. J. Biol. Macromol. 316 (2025) 144720, https://doi.org/10.1016/j.ijbiomac.2025.144720.
[100] S.H. Aswathy, U. NarendraKumar, I. Manjubala, The influence of molecular weight of cellulose on the properties of carboxylic acid crosslinked cellulose hydrogels for biomedical and environmental applications, Int. J. Biol. Macromol. 239 (2023) 124282, https://doi.org/10.1016/j.ijbiomac.2023.124282.
[101] O.S. Olugbenga, R.N. Hanuni, A. Fatmawati, E. Hossain, T.H. Kim, Chitosan as a sustainable alternative for fresh food packaging: structural insights, modification strategies, and innovations for commercial viability, Int. J. Biol. Macromol. (2025) 145065, https://doi.org/10.1016/j.ijbiomac.2025.145065.
[102] F. Costa-e-Sá, M. Comís-Tuche, C. Spuch, E.M.S. Castanheira, S.R.S. Veloso, Sequential release of drugs from dual-delivery plasmonic nanogels containing lipid-gated mesoporous silica-coated gold nanorods, J. Drug Deliv. Sci. Technol. 96 (2024) 105723, https://doi.org/10.1016/j.jddst.2024.105723.
[103] Y.-Q. Liu, H.-Y. Guo, C.-Y. Hu, X. Xu, A novel dual pH- and temperature-responsive poly (N-isopropylacrylamide)/polyacrylamide/calcium alginate hydrogel with robust mechanical performance and biocompatibility for sustainable drug release, Polymer 327 (2025) 128386, https://doi.org/10.1016/j.polymer.2025.128386.
[104] C. Zhang, Y. Chen, Y. Zuo, M. Wang, H. Chen, C. Wang, Y. Cao, Y. Zeng, Y. Chen, T. Zhang, Dual targeting of FR+ CD44 overexpressing tumors by self-assembled nanoparticles quantitatively conjugating folic acid-hyaluronic acid to the GSH-sensitively modified podophyllotoxin, Chem. Eng. J. 505 (2025) 159276.
[105] X. Enyu, L. Xinbo, C. Xuelian, C. Huimin, C. Yin, C. Yan, Construction and performance evaluation of pH-responsive oxidized hyaluronic acid hollow mesoporous silica nanoparticles, Int. J. Biol. Macromol. 257 (2024) 128656.
[106] N.M.E. Elsayyad, M.S. Ibrahim, S.H. Noshi, Sustainable pH-responsive casein/hyaluronic acid layered nanoparticles for targeted delivery of metformin to colorectal cancer, J. Drug Deliv. Sci. Technol. 107 (2025) 106710.
[107] X. Bi, H. Peng, H. Xiong, L. Xiao, H. Zhang, J. Li, Y. Sun, Fabrication of the rapid self-assembly hydrogels loaded with luteolin: their structural characteristics and protection effect on ulcerative colitis, Foods 13 (2024) 1105.
[108] M. Wu, J. Sheng, Q. Xie, Y. Qi, Y. Zhao, S. Zhang, Recent advances in stimuli-responsive hyaluronic acid-based nanodelivery systems for cancer treatment: a review, Int. J. Biol. Macromol. 316 (2025) 144357, https://doi.org/10.1016/j.ijbiomac.2025.144357.
[109] Y. Lin, J. Wu, Z. Zhuang, X. Gong, Z. Jin, X. Lin, C. Zhang, K. Zhao, A pH-responsive microneedle patch for the transdermal delivery of biomineralized insulin nanoparticles to diabetes treatment, Int. J. Biol. Macromol. 284 (2025) 137955, https://doi.org/10.1016/j.ijbiomac.2024.137955.
[110] J. Li, Y. Fang, Q. Li, C. Zeng, Y. Jiang, W. Kong, M. Zhu, Dual-mode regulatory cross-linked chitosan nanocapsules for pH-responsive and controllable sustained

release in textiles, Int. J. Biol. Macromol. 314 (2025) 144109, https://doi.org/10.1016/j.ijbiomac.2025.144109.
[111] H.M. El-Husseiny, E.A. Mady, A.S. Doghish, M.B. Zewail, A.M. Abdelfatah, M. Noshy, O.A. Mohammed, W.A. El-Dakroury, Smart/stimuli-responsive chitosan/gelatin and other polymeric macromolecules natural hydrogels vs. synthetic hydrogels systems for brain tissue engineering: a state-of-the-art review, Int. J. Biol. Macromol. 260 (2024) 129323, https://doi.org/10.1016/j.ijbiomac.2024.129323.
[112] P.A. Montaño-González, L.M. Bravo-Lozano, S. Chevance, F. Dole, J. Rosselgong, P. Loyer, S. Tranchimand, J.-P. Chapel, F. Gauffre, C. Schatz, L.M. Bravo-Anaya, Interactions between PEI and biological polyanions and the ability of glycosaminoglycans in destabilizing PEI/peGFP-C3 polyplexes for genetic material release, Int. J. Biol. Macromol. 301 (2025) 140351, https://doi.org/10.1016/j.ijbiomac.2025.140351.
[113] Y. Zhang, H. Du, Y. Wang, S. Yu, T. Cao, Y. Cao, pH-regulated self-assembly of poly(styrene-co-methacrylic acid) for fabrication of pH-responsive Pickering emulsion, Colloids Surf. A Physicochem. Eng. Asp. 710 (2025) 136231, https://doi.org/10.1016/j.colsurfa.2025.136231.
[114] R. Ghiarasim, G. Luta, M.-G. Dimofte, T.-G. Iversen, M. Pinteala, A. Rotaru, Assembly and stability of trastuzumab-conjugated and unmodified poly(L-histidine)-poly(ethylene glycol) micelles for targeting HER2-positive cells, J. Mol. Liq. 418 (2025) 126689, https://doi.org/10.1016/j.molliq.2024.126689.
[115] M. Hou, S. Liu, Recent progress of pH-responsive peptides, polypeptides, and their supramolecular assemblies for biomedical applications, Biomacromolecules (2024), https://doi.org/10.1021/acs.biomac.4c00688.
[116] A.A.P. Mansur, S.M. Carvalho, Z.I.P. Lobato, M.F. Leite, K. Krambrock, H. S. Mansur, Bioengineering stimuli-responsive organic-inorganic nanoarchitetures based on carboxymethylcellulose-poly-l-lysine nanoplexes: unlocking the potential for bioimaging and multimodal chemodynamic-magnetothermal therapy of brain cancer cells, Int. J. Biol. Macromol. 290 (2025) 138985, https://doi.org/10.1016/j.ijbiomac.2024.138985.
[117] Y. Xiang, D. Tang, L. Yan, L. Deng, X. Wang, X. Liu, Q. Zhou, Poly-l-lysine modified MOF nanoparticles with pH/ROS sensitive CIP release and CUR triggered photodynamic therapy against drug-resistant bacterial infection, Int. J. Biol. Macromol. 266 (2024) 131330, https://doi.org/10.1016/j.ijbiomac.2024.131330.
[118] Y. Wang, L. Wang, Y. Hu, J. Qin, B. Yu, Design and optimization of ε-poly-l-lysine with specific functions for diverse applications, Int. J. Biol. Macromol. 262 (2024) 129513, https://doi.org/10.1016/j.ijbiomac.2024.129513.
[119] L. Xu, S. Li, S. Wan, Z. Liu, Y. Zhong, X. Qian, J. Qin, L. Cai, H. Huang, Poly-lysine-modified recombinant protein nanocages for effective delivery of small activating RNA, J. Contr. Release 382 (2025) 113638, https://doi.org/10.1016/j.jconrel.2025.113638.
[120] A. Paul, C.-J. Eun, J.M. Song, Cytotoxicity mechanism of non-viral carriers polyethylenimine and poly-l-lysine using real time high-content cellular assay, Polymer 55 (2014) 5178–5188, https://doi.org/10.1016/j.polymer.2014.08.043.
[121] Y. Kawaguchi, S. Terada, S. Futaki, An approach for the intracellular delivery of IgG via enzymatic ligation with a cell-permeable attenuated cationic amphiphilic lytic peptide, Bioorg. Med. Chem. 111 (2024) 117835, https://doi.org/10.1016/j.bmc.2024.117835.
[122] J. Malinge, F. Mousseau, D. Zanchi, G. Brun, C. Tribet, E. Marie, Tailored stimuli-responsive interaction between particles adjusted by straightforward adsorption of mixed layers of Poly(lysine)-g-PEG and Poly(lysine)-g-PNIPAM on anionic beads, J. Colloid Interface Sci. 461 (2016) 50–55, https://doi.org/10.1016/j.jcis.2015.09.016.
[123] Z. Guo, J. Sui, M. Ma, J. Hu, Y. Sun, L. Yang, Y. Fan, X. Zhang, pH-Responsive charge switchable PEGylated ε-poly-l-lysine polymeric nanoparticles-assisted combination therapy for improving breast cancer treatment, J. Contr. Release 326 (2020) 350–364, https://doi.org/10.1016/j.jconrel.2020.07.030.
[124] D. Wang, S. Fan, X. Li, L. Chen, X. Wen, Y. Xu, C. Zhu, C. Hou, D. Zhang, Carboxymethyl chitosan/polyvinyl alcohol hydrogel films by incorporating MSNs as ε-PL carrier with pH-responsive controlled release and antibacterial properties, Food Packag. Shelf Life 46 (2024) 101360, https://doi.org/10.1016/j.fpsl.2024.101360.
[125] K.-Z. Wang, C.-Y. Han, X.-Z. Feng, G.-C. Han, H.-B. Kraatz, Electrochemical sensor based on the synergistic effect of copper nanoparticles and poly-L-histidine for cefquinome detection and its oxidation mechanism, Microchem. J. 208 (2025) 112451, https://doi.org/10.1016/j.microc.2024.112451.
[126] Y.S. Elshamy, C. Kinsey, R.R. Rustandi, A.T. Sutton, Separation of virus-like particles and nano-emulsions for vaccine development by Capillary Zone Electrophoresis, Anal. Chim. Acta 1355 (2025) 344011, https://doi.org/10.1016/j.aca.2025.344011.
[127] Y. Zhang, I. Kim, Y. Lu, Y. Xu, D.-G. Yu, W. Song, Intelligent poly(l-histidine)-based nanovehicles for controlled drug delivery, J. Contr. Release 349 (2022) 963–982, https://doi.org/10.1016/j.jconrel.2022.08.005.
[128] G. Saenz, B.H. Pogostin, C.C. Cole, A. Agrawal, D. Chew-Martinez, M. Dubackic, A. Pal, U. Olsson, K.J. McHugh, J.D. Hartgerink, Nanofibrous peptide hydrogels leveraging histidine to modulate pH-responsive supramolecular assembly and antibody release, Biomacromolecules (2025), https://doi.org/10.1021/acs.biomac.4c01296.
[129] Y. Guo, S. Wang, H. Du, X. Chen, H. Fei, Silver ion-histidine interplay switches peptide hydrogel from antiparallel to parallel β-assembly and enables controlled antibacterial activity, Biomacromolecules 20 (2018) 558–565, https://doi.org/10.1021/acs.biomac.8b01480.
[130] A. Distefano, P. Corsaro, N. Tuccitto, F. Laneri, O. Monasson, E. Peroni, G. Grasso, Intrinsically photoluminescent hydrogels to measure peptides-copper binding affinities, J. Inorg. Biochem. 268 (2025) 112914, https://doi.org/10.1016/j.jinorgbio.2025.112914.
[131] V. Ghalehkhondabi, M. Soleymani, A. Fazlali, Synthesis of quercetin-loaded hyaluronic acid-conjugated pH/redox dual-stimuli responsive poly(methacrylic acid)/mesoporous organosilica nanoparticles for breast cancer targeted therapy, Int. J. Biol. Macromol. 263 (2024) 130168, https://doi.org/10.1016/j.ijbiomac.2024.130168.
[132] M.G. Lokesh, A.K. Tiwari, A concise review on polymer brushes and its interaction with surfactants: an approach towards smart materials, J. Mol. Liq. (2024) 125168.
[133] X. Jia, Z. Dou, Y. Zhang, C. Yu, M. Yang, H. Xie, Y. Lin, Z. Liu, Application of a novel thermal/pH-responsive antibacterial paeoniflorin hydrogel crosslinked with amino acids for accelerated diabetic foot ulcers healing, Mater. Today Bio 32 (2025) 101736, https://doi.org/10.1016/j.mtbio.2025.101736.
[134] G. Nunziata, M. Nava, E. Lacroce, F. Pizzetti, F. Rossi, Thermo-responsive polymer-based nanoparticles: from chemical design to advanced applications, Macromol. Rapid Commun. (2025) 2401127.
[135] A. Pourjavadi, F.B. Kashani, M. Doroudian, S.S. Amin, Synthesis and characterization of stimuli responsive micelles from chitosan, starch, and alginate based on graft copolymers with polylactide-poly(methacrylic acid) and polylactide- poly[2(dimethyl amino)ethyl methacrylate] side chains, Int. J. Biol. Macromol. 253 (2023) 127170, https://doi.org/10.1016/j.ijbiomac.2023.127170.
[136] J.L. Sánchez-Orozco, H.I. Meléndez-Ortiz, B.A. Puente-Urbina, L. Garcia-Uriostegui, T.A. Camacho-Villegas, P.H. Lugo-Fabres, L.A. García-Cerda, Thermo and pH-responsive nanocarriers based on mesocellular silica foam and poly(N-vinylcaprolactam-co-methacrylic acid): synthesis, characterization, and in vitro cytotoxicity assay, J. Drug Deliv. Sci. Technol. 98 (2024) 105849, https://doi.org/10.1016/j.jddst.2024.105849.
[137] T. Yasmin, A. Mahmood, M. Farooq, R.M. Sarfraz, A. Boublia, U. Rehman, M. U. Ashraf, J.K. Bhutto, B. Ernst, M. Albrahim, N. Elboughdiri, K.K. Yadav, M. A. Alreshidi, H. Ijaz, Y. Benguerba, Development and evaluation of a pH-responsive Mimosa pudica seed mucilage/β- cyclodextrin-co-poly(methacrylate) hydrogel for controlled drug delivery: in vitro and in vivo assessment, Int. J. Biol. Macromol. 268 (2024) 131832, https://doi.org/10.1016/j.ijbiomac.2024.131832.
[138] E. Proksch, pH in nature, humans and skin, J. Dermatol. 45 (2018) 1044–1052.
[139] P. Víšková, E. Ištvánková, J. Ryneš, Š. Džatko, T. Loja, M.L. Živković, R. Rigo, R. El-Khoury, I. Serrano-Chacón, M.J. Damha, In-cell NMR suggests that DNA i-motif levels are strongly depleted in living human cells, Nat. Commun. 15 (2024) 1992.
[140] H. Al-Momani, I. Aolymat, Proton pump inhibitors and gastrointestinal symptoms among patients with COVID-19 infection, Ann. Med. 56 (2024) 2355581.
[141] C.A. Wagner, N. Mohebbi, Urinary pH and stone formation, J. Nephrol. 23 (2010) S165–S169.
[142] Y.-P. Lin, W.-C. Chen, C.-M. Cheng, C.-J. Shen, Vaginal pH value for clinical diagnosis and treatment of common vaginitis, Diagnostics 11 (2021) 1996.
[143] K. Godha, K.M. Tucker, C. Biehl, D.F. Archer, S. Mirkin, Human vaginal pH and microbiota: an update, Gynecol. Endocrinol. 34 (2018) 451–455.
[144] K. Fukuda, Y. Ito, Y. Furuichi, T. Matsui, H. Horikawa, T. Miyano, T. Okada, M. van Logtestijn, R.J. Tanaka, A. Miyawaki, Three stepwise pH progressions in stratum corneum for homeostatic maintenance of the skin, Nat. Commun. 15 (2024) 4062.
[145] D. Mijaljica, J.P. Townley, D.J. Klionsky, F. Spada, M. Lai, The origin, intricate nature, and role of the skin surface pH (pHSS) in barrier integrity, eczema, and psoriasis, Cosmetics 12 (2025) 24.
[146] Y. Jiang, S. Zong, X. Wang, K. Zhu-Salzman, J. Zhao, L. Xiao, D. Xu, G. Xu, Y. Tan, pH-responsive nanoparticles for oral delivery of RNAi for sustained protection against Spodoptera exigua, Int. J. Biol. Macromol. 306 (2025) 141763, https://doi.org/10.1016/j.ijbiomac.2025.141763.
[147] B. Baptista, A.S.R. Oliveira, P. Mendonça, A.C. Serra, J.F.J. Coelho, F. Sousa, pH-responsive nanoparticles based on POEOMA-b-PDPA block copolymers for RNA encapsulation, protection and cell delivery, Biomater. Adv. 145 (2023) 213267, https://doi.org/10.1016/j.bioadv.2022.213267.
[148] C. Wang, T. Zhao, Y. Li, G. Huang, M.A. White, J. Gao, Investigation of endosome and lysosome biology by ultra pH-sensitive nanoprobes, Adv. Drug Deliv. Rev. 113 (2017) 87–96, https://doi.org/10.1016/j.addr.2016.08.014.
[149] J.R. Casey, S. Grinstein, J. Orlowski, Sensors and regulators of intracellular pH, Nat. Rev. Mol. Cell Biol. 11 (2010) 50–61.
[150] L. Rueda-Gensini, J. Cifuentes, M.C. Castellanos, P.R. Puentes, J.A. Serna, C. Muñoz-Camargo, J.C. Cruz, Tailoring iron oxide nanoparticles for efficient cellular internalization and endosomal escape, Nanomaterials 10 (2020) 1816.
[151] I. Parolini, C. Federici, C. Raggi, L. Lugini, S. Palleschi, A. De Milito, C. Coscia, E. Iessi, M. Logozzi, A. Molinari, Microenvironmental pH is a key factor for exosome traffic in tumor cells, J. Biol. Chem. 284 (2009) 34211–34222.
[152] S.K. Parks, J. Chiche, J. Pouyssegur, pH control mechanisms of tumor survival and growth, J. Cell. Physiol. 226 (2011) 299–308.
[153] X. Zhang, Y. Lin, R.J. Gillies, Tumor pH and its measurement, J. Nucl. Med. 51 (2010) 1167–1170.
[154] D. Rotin, P. Wan, S. Grinstein, I. Tannock, Cytotoxicity of compounds that interfere with the regulation of intracellular pH: a potential new class of anticancer drugs, Cancer Res. 47 (1987) 1497–1504.
[155] O. Thews, A. Riemann, Tumor pH and metastasis: a malignant process beyond hypoxia, Cancer Metastasis Rev. 38 (2019) 113–129.
[156] V. Estrella, T. Chen, M. Lloyd, J. Wojtkowiak, H.H. Cornnell, A. Ibrahim-Hashim, K. Bailey, Y. Balagurunathan, J.M. Rothberg, B.F. Sloane, J. Johnson, R.

A. Gatenby, R.J. Gillies, Acidity generated by the tumor microenvironment drives local invasion, Cancer Res. 73 (2013) 1524–1535, https://doi.org/10.1158/0008-5472.CAN-12-2796.
[157] S. Manchun, C.R. Dass, P. Sriamornsak, Targeted therapy for cancer using pH-responsive nanocarrier systems, Life Sci. 90 (2012) 381–387, https://doi.org/10.1016/j.lfs.2012.01.008.
[158] C.-Y. Hung, T.-Y. Hsueh, L. Rethi, H.-T. Lu, A.E.-Y. Chuang, Advancements in regenerative medicine: a comprehensive review of stem cell and growth factor therapies for osteoarthritis, J. Mater. Chem. B 13 (2025) 4494–4526.
[159] S. Liao, S. Jia, Y. Yue, H. Zeng, J. Lin, P. Liu, Advancements in pH-Responsive nanoparticles for osteoarthritis treatment: opportunities and challenges, Front. Bioeng. Biotechnol. 12 (2024) 1426794.
[160] S. Hajjar, X. Zhou, pH sensing at the intersection of tissue homeostasis and inflammation, Trends Immunol. 44 (2023) 807–825.
[161] A.F. Lombardi, Y. Ma, H. Jang, S. Jerban, Q. Tang, A.C. Searleman, R.S. Meyer, J. Du, E.Y. Chang, AcidoCEST-UTE MRI reveals an acidic microenvironment in knee osteoarthritis, Int. J. Mol. Sci. 23 (2022) 4466.
[162] J. Li, H. Zhang, Y. Han, Y. Hu, Z. Geng, J. Su, Targeted and responsive biomaterials in osteoarthritis, Theranostics 13 (2023) 931.
[163] C. Xu, Y. Jiang, H. Wang, Y. Zhang, Y. Ye, H. Qin, J. Gao, Q. Dan, L. Du, L. Liu, Arthritic microenvironment actuated nanomotors for active rheumatoid arthritis therapy, Adv. Sci. 10 (2023) 2204881.
[164] H. Huang, S. Zheng, J. Wu, X. Liang, S. Li, P. Mao, Z. He, Y. Chen, L. Sun, X. Zhao, Opsonization inveigles macrophages engulfing carrier-free bilirubin/JPH203 nanoparticles to suppress inflammation for osteoarthritis therapy, Adv. Sci. 11 (2024) 2400713.
[165] M. Zhang, X. Peng, Y. Ding, X. Ke, K. Ren, Q. Xin, M. Qin, J. Xie, J. Li, A cyclic brush zwitterionic polymer based pH-responsive nanocarrier-mediated dual drug delivery system with lubrication maintenance for osteoarthritis treatment, Mater. Horiz. 10 (2023) 2554–2567.
[166] S. Gao, X. Guo, F. Li, Y. Zhang, Y. Yu, Y. Fu, F. Ye, Delivery of Hexaconazole by the Carboxymethylcellulose grafting and Cellulase/pH responsiveness hollow mesoporous silica nanoparticles, Carbohydr. Polym. 365 (2025) 123822, https://doi.org/10.1016/j.carbpol.2025.123822.
[167] H. Zhang, X. Ma, T. Li, D. Xu, H. Lu, R. Zhao, H. Han, G. Xu, Feather keratin-tea polyphenol nanoparticles with pH and reduction dually responsive for tumor-targeting DOX transmit, Int. J. Biol. Macromol. 316 (2025) 144314, https://doi.org/10.1016/j.ijbiomac.2025.144314.
[168] Z. Lin, R. Cao, F. Nie, L. Ma, J. Xu, Y. Guo, Synergistic chemoimmunotherapy in a green framework: pH-responsive natural plant polysaccharide-based nanoparticles, Biomater. Adv. 174 (2025) 214294, https://doi.org/10.1016/j.bioadv.2025.214294.
[169] Y. Li, Y. Pei, Z. Shan, Y. Jiang, S.W. Cui, Z. He, Y. Zhang, H. Wang, A pH-sensitive W/O/W emulsion-bound carboxymethyl chitosan-alginate hydrogel bead system through the Maillard reaction for probiotics intestine-targeted delivery, Food Hydrocoll. 153 (2024) 109956, https://doi.org/10.1016/j.foodhyd.2024.109956.
[170] J. Long, G. Zhou, X. Yu, J. Xu, L. Hu, A. Pranovich, Q. Yong, Z.-H. Xie, C. Xu, Harnessing chemical functionality of xylan hemicellulose towards carbohydrate polymer-based pH/magnetic dual-responsive nanocomposite hydrogel for drug delivery, Carbohydr. Polym. 343 (2024) 122461, https://doi.org/10.1016/j.carbpol.2024.122461.
[171] S. Zhao, D.J. McClements, X. Liu, F. Liu, Natural pH and temperature-sensitive hydrogel-emulsion carriers for co-delivery of hydrophobic and hydrophilic bioactive ingredients in the gastrointestinal tract, Food Hydrocoll. 149 (2024) 109450, https://doi.org/10.1016/j.foodhyd.2023.109450.
[172] S. Qiao, W. Chen, X. Zheng, L. Ma, Preparation of pH-sensitive alginate-based hydrogel by microfluidic technology for intestinal targeting drug delivery, Int. J. Biol. Macromol. 254 (2024) 127649, https://doi.org/10.1016/j.ijbiomac.2023.127649.
[173] S. Bhagat, S. Singh, Nanominerals packaged in pH-responsive alginate microcapsules exhibit selective delivery in small intestine and enhanced absorption and bioavailability, Adv. Funct. Mater. 34 (2024) 2408043.
[174] S. Noreen, F. Pervaiz, M. Ijaz, M.F. Hanif, H. Shoukat, I. Maqbool, M.A. Ashraf, H. Mahmood, Novel thiol-functionalized hyaluronic acid-based pH-responsive hydrogel: a promising mucoadhesive drug delivery approach toward the treatment of colorectal cancer, Colloids Surf. B Biointerfaces 254 (2025) 114805, https://doi.org/10.1016/j.colsurfb.2025.114805.
[175] E. Di Ianni, W. Obuchi, K. Breyne, X.O. Breakefield, Extracellular vesicles for the delivery of gene therapy, Nature Reviews Bioengineering (2025) 1–14.
[176] J.C. Gonzalez, K.W. Park, D.B. Evans, R. Sharma, O. Sahaym, S. Gopalakrishnan, A.I. Dar, T.A. Valdez, A. Sharma, Nano approaches to nucleic acid delivery: barriers, solutions, and current landscape, Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 17 (2025) e70010.
[177] P. Guzmán-Sastoque, C.F. Rodríguez, M.C. Monsalve, S. Castellanos, A. Manrique-Moreno, L.H. Reyes, J.C. Cruz, Nanotheranostics revolutionizing gene therapy: emerging applications in gene delivery enhancement, Journal of Nanotheranostics 6 (2025) 10.
[178] U. Chheda, S. Pradeepan, E. Esposito, S. Strezsak, O. Fernandez-Delgado, J. Kranz, Factors affecting stability of RNA–temperature, length, concentration, pH, and buffering species, J. Pharmaceut. Sci. 113 (2024) 377–385.
[179] Ö. Kaplan, K. Bal, S. Şentürk, K. Demir, M.K. Gök, Redox-responsive lipoic acid-modified poly (β-amino ester) nanoparticles for enhanced gene delivery, React. Funct. Polym. 214 (2025) 106318, https://doi.org/10.1016/j.reactfunctpolym.2025.106318.
[180] T. Wang, Y. Sun, D. Zeng, M. Wang, Y. Zhang, G. Liu, X. Chen, L. Liu, Integrated cell membrane encapsulated PQDs-TK quantum dot nanoclusters with ROS-responsive triggering for efficient and visualized DNA delivery, J. Colloid Interface Sci. 683 (2025) 393–410, https://doi.org/10.1016/j.jcis.2024.12.159.
[181] A. Mostafavi, M. Anbia, F. Yazdi, Chitosan and carboxymethyl cellulose coated on NH2-UiO-66 as green, biocompatible, nontoxic, and pH-stimuli responsive for levofloxacin delivery: a comparative study, Int. J. Biol. Macromol. 308 (2025) 142501, https://doi.org/10.1016/j.ijbiomac.2025.142501.
[182] J. Pang, X. Chen, Z. Lin, S. Yao, W. Wang, H. Wu, W. Xing, J. Yang, Inhalable pH-responsive charge-reversal polymer-small interfering RNA polyplexes for directed gene therapy of anaplastic lymphoma kinase fusion-positive lung cancer, J. Contr. Release 381 (2025) 113644, https://doi.org/10.1016/j.jconrel.2025.113644.
[183] J.L. Schneider, J.J. Lin, A.T. Shaw, ALK-positive lung cancer: a moving target, Nat. Cancer 4 (2023) 330–343.
[184] E. Petillo, V. Veneruso, G. Gragnaniello, L. Brochier, E. Frigerio, G. Perale, F. Rossi, A. Cardia, A. Orro, P. Veglianese, Targeted therapy and deep learning insights into microglia modulation for spinal cord injury, Mater. Today Bio (2024) 101117.
[185] X. Wang, H. Li, C. Chen, Z. Liang, Understanding of endo/lysosomal escape of nanomaterials in biomedical application, Smart Molecules (2025) e20240017.
[186] A.M. Martinez Junior, V.A. de Oliveira, M.J. Tiera, O-Substituted Tertiary Amine-Chitosans as Promising Nanocarriers for siRNA Delivery, Current Gene Therapy, 2025.
[187] Y. Duan, W. Zhang, Y. Ouyang, Q. Yang, Q. Zhang, S. Zhao, C. Chen, T. Xu, Q. Zhang, H. Ran, Proton sponge nanocomposites for synergistic tumor elimination via autophagy inhibition-promoted cell apoptosis and macrophage repolarization-enhanced immune response, ACS Appl. Mater. Interfaces 16 (2024) 17285–17299.
[188] S. Aghajanpour, H. Amiriara, P. Ebrahimnejad, R.A. Slavcev, Advancing ocular gene therapy: a machine learning approach to enhance delivery, uptake and gene expression, Drug Discov. Today 30 (2025) 104359, https://doi.org/10.1016/j.drudis.2025.104359.
[189] S. Guo, C. Li, C. Wang, X. Cao, X. Liu, X.-J. Liang, Y. Huang, Y. Weng, pH-Responsive polymer boosts cytosolic siRNA release for retinal neovascularization therapy, Acta Pharm. Sin. B 14 (2024) 781–794, https://doi.org/10.1016/j.apsb.2023.09.001.
[190] R. Huang, F. He, S. Yang, K. Mai, S. Huang, H. Liu, Y. Feng, G. Yu, J. Li, B← N coordination bond reinforced dynamic fluorescence of pH-responsive amphiphile alginate aggregates for anti-counterfeiting, Carbohydr. Polym. 334 (2024) 121892.
[191] Y. Yang, J. Zhang, L. Shen, L. Feng, Q. Zhou, Inhibition mechanism of diacylated anthocyanins from purple sweet potato (Ipomoea batatas L.) against α-amylase and α-glucosidase, Food Chem. 359 (2021) 129934.
[192] W. Li, Q. Bie, K. Zhang, F. Linli, W. Yang, X. Chen, P. Chen, Q. Qi, Regulated anthocyanin release through novel pH-responsive peptide hydrogels in simulated digestive environment, Food Chem. X 23 (2024) 101645.
[193] J. Gao, C. Liu, J. Shi, F. Ni, Q. Shen, H. Xie, K. Wang, Q. Lei, W. Fang, G. Ren, The regulation of sodium alginate on the stability of ovalbumin-pectin complexes for VD3 encapsulation and in vitro simulated gastrointestinal digestion study, Food Res. Int. 140 (2021) 110011.
[194] Z. Wang, S. Huang, X. Zhao, S. Yang, K. Mai, W. Qin, K. Liu, J. Huang, Y. Feng, J. Li, Covalent bond interfacial recognition of polysaccharides/silica reinforced high internal phase pickering emulsions for 3D printing, ACS Appl. Mater. Interfaces 15 (2023) 23989–24002.
[195] Q. Chen, T. Ye, S. Yang, L. Fan, C. Shang, Y. Feng, J. Li, Y. Wang, G. Yu, J. Dai, Multiple non-covalent bonds reinforced pH/glucose-responsive alginate-stabilized Pickering emulsion for diacylated anthocyanin intestinal delivery, Int. J. Biol. Macromol. 310 (2025) 142721, https://doi.org/10.1016/j.ijbiomac.2025.142721.
[196] G. Fei, S. Zhang, Y. Li, M. Peng, Z. Tang, X. Gu, X. Li, K. Zhang, J. Xie, Y. Ni, K. Zhou, M. Tu, Emerging soft medical robots for clinical translations from diagnosis through therapy to rehabilitation, Mater. Sci. Eng. R Rep. 165 (2025) 100990, https://doi.org/10.1016/j.mser.2025.100990.
[197] X. Shi, L. Zhang, L. Cheng, C. Xiang, A. Lee, H. Ning, K. Huang, H. Liu, H. Liao, K. An, B. Yang, J. Wen, B. Gu, W. Yuan, N. Hu, Multilayer self-sensing hydrogel soft robot prepared via stereolithography for on-demand drug delivery, Chem. Eng. J. (2025) 164352, https://doi.org/10.1016/j.cej.2025.164352.
[198] C.S. Park, Y.-W. Kang, H. Na, J.-Y. Sun, Hydrogels for bioinspired soft robots, Prog. Polym. Sci. 150 (2024) 101791.
[199] H.R. Safavi, A. Amiri, M. Baniassadi, A. Zolfagharian, M. Baghani, An anisotropic constitutive model for fiber reinforced salt-sensitive hydrogels, Mech. Adv. Mater. Struct. 30 (2023) 4814–4827.
[200] G.L. Goh, G.D. Goh, V.P. Nguyen, W. Toh, S. Lee, X. Li, B.D. Sunil, J.Y. Lim, Z. Li, A.K. Sinha, A 3D printing-enabled artificially innervated smart soft gripper with variable joint stiffness, Advanced Materials Technologies 8 (2023) 2301426.
[201] M. Enyan, Z. Bing, J.N.O. Amu-Darko, E. Issaka, S.L. Otoo, M.F. Agyemang, Advances in smart materials soft actuators on mechanisms, fabrication, materials, and multifaceted applications: a review, J. Thermoplast. Compos. Mater. 38 (2025) 302–370.
[202] Y. Xin, X. Zhou, H. Bark, P.S. Lee, The role of 3D printing technologies in soft grippers, Adv. Mater. 36 (2024) 2307963.
[203] H. Son, E. Byun, Y.J. Yoon, J. Nam, S.H. Song, C. Yoon, Untethered actuation of hybrid hydrogel gripper via ultrasound, ACS Macro Lett. 9 (2020) 1766–1772.
[204] J. Kim, J. Choi, H. Park, J. Lee, H.-J. Lee, J.D. Park, J.B. Lee, Y. Na, C. Yoon, Stimuli-responsive biodegradable soft gripper composed of pH-responsive alginate/gelatin/acrylic acid and non-pH-responsive acrylamide bilayer, Eur. Polym. J. 226 (2025) 113742, https://doi.org/10.1016/j.eurpolymj.2025.113742.

[205] A. Kumar, S. Parimita, K. Kiran, N.R. Mahapatra, P. Ghosh, Superhydrophobic asymmetric pH-responsive soft actuators: implications for the development of anti-fouling medical devices, Chem. Eng. J. 497 (2024) 154772, https://doi.org/10.1016/j.cej.2024.154772.
[206] Y. Shi, X. Yang, Y. Zhang, S. Lu, pH-induced synergistic changes in color and shape of soft actuator based on degradable carbon dots/sodium alginate gel, Carbohydr. Polym. 351 (2025) 123112, https://doi.org/10.1016/j.carbpol.2024.123112.
[207] O.A. Peña, P. Martin, Cellular and molecular mechanisms of skin wound healing, Nat. Rev. Mol. Cell Biol. 25 (2024) 599–616.
[208] O. Litvinova, M. Kumetchko, S. Pavlov, N. Babenko, I. Kolisnyk, Problems of Healing Soft Tissue Injuries, 2025.
[209] G. Olteanu, S.M. Neacșu, F.A. Joița, A.M. Musuc, E.C. Lupu, C.-B. Ioniță-Mîndrican, D. Lupuliasa, M. Mititelu, Advancements in regenerative hydrogels in skin wound treatment: a comprehensive review, Int. J. Mol. Sci. 25 (2024) 3849.
[210] S. Tang, K. Feng, R. Yang, Y. Cheng, N. Shi, H. Zhang, Z. Wei, Y. Ma, A dual-action strategy: wound microenvironment responsive hydrogel and exosome-mediated glucose regulation enhance inside-out diabetic wound repair, J. Contr. Release 382 (2025) 113716, https://doi.org/10.1016/j.jconrel.2025.113716.
[211] X. Xu, J. Yong, L. Wang, S. Chen, J. Pang, Design and fabrication of pH-responsive skin scaffolds based on carrageenan and konjac glucomannan for accelerated wound healing, Int. J. Biol. Macromol. 304 (2025) 140198, https://doi.org/10.1016/j.ijbiomac.2025.140198.
[212] H. Jiang, M. Ochoa, J.F. Waimin, R. Rahimi, B. Ziaie, A pH-regulated drug delivery dermal patch for targeting infected regions in chronic wounds, Lab Chip 19 (2019) 2265–2274.
[213] B. Wang, Y. Lang, C. Li, S. Liu, M.-W. Chang, Biomimetic 3D composite scaffold with pH-Responsive micropatterns for wound healing, Chem. Eng. J. 485 (2024) 149646, https://doi.org/10.1016/j.cej.2024.149646.
[214] P. Xiao, J. Huang, X. Han, J.W.S. Cheu, Y. Liu, L.H. Law, J.H.C. Lai, J. Li, S. W. Park, C.C.L. Wong, R.H.W. Lam, K.W.Y. Chan, Monitor tumor pHe and response longitudinally during treatment using CEST MRI-detectable alginate microbeads, ACS Appl. Mater. Interfaces 14 (2022) 54401–54410, https://doi.org/10.1021/acsami.2c10493.
[215] A.H. Ponsford, T.A. Ryan, A. Raimondi, E. Cocucci, S.A. Wycislo, F. Fröhlich, L. E. Swan, M. Stagi, Live imaging of intra-lysosome pH in cell lines and primary neuronal culture using a novel genetically encoded biosensor, Autophagy 17 (2021) 1500–1518.
[216] G.S. Longo, N.A. Pérez-Chávez, I. Szleifer, How protonation modulates the interaction between proteins and pH-responsive hydrogel films, Curr. Opin. Colloid Interface Sci. 41 (2019) 27–39.
[217] L. Palanikumar, S. Al-Hosani, M. Kalmouni, V.P. Nguyen, L. Ali, R. Pasricha, F. N. Barrera, M. Magzoub, pH-responsive high stability polymeric nanoparticles for targeted delivery of anticancer therapeutics, Commun. Biol. 3 (2020) 95.
[218] A.M. Wagner, I. Duggal, B. Morse, A. Lawrence, A. Shearer, N. Al-Sayyad, N. A. Peppas, Rational design of PEGylated nanogel: optimization of degree of PEGylation and development of a novel enzyme-responsive grafted layer, Int. J. Pharm. 684 (2025) 126102.
[219] G. Gao, P. Shu, Y. Tan, T. Zheng, W. Fan, L. Lu, H. Zhou, Z. Wang, L. Liu, Z. Liu, Y. Wang, Preclinical development and phase I study of ZSYY001, a polymeric micellar paclitaxel for advanced solid tumor, Cancer Med. 14 (2025) e71039, https://doi.org/10.1002/cam4.71039.
[220] M. Martínez-Carmona, D. Lozano, M. Colilla, M. Vallet-Regí, Lectin-conjugated pH-responsive mesoporous silica nanoparticles for targeted bone cancer treatment, Acta Biomater. 65 (2018) 393–404, https://doi.org/10.1016/j.actbio.2017.11.007.
[221] F. Badparvar, A.P. Marjani, R. Salehi, F. Ramezani, pH/redox responsive size-switchable intelligent nanovehicle for tumor microenvironment targeted DOX release, Sci. Rep. 13 (2023) 22475, https://doi.org/10.1038/s41598-023-49446-x.
[222] H. Zhang, L. Li, W. Li, H. Yin, H. Wang, X. Ke, pH. Endosomal, Redox dual-sensitive prodrug micelles based on hyaluronic acid for intracellular camptothecin delivery and active tumor targeting in cancer therapy, Pharmaceutics 16 (2024), https://doi.org/10.3390/pharmaceutics16101327.
[223] J. Wu, X. Hu, Y. Chang, Z. Sun, M. Zhou, S. Song, Z. Chen, Y. Wu, pH/Reduction/light-responsive nanodrug based on Perylene diimide polyprodrug for combined chemotherapy and photothermal therapy, ACS Appl. Nano Mater. 8 (2025) 13981–13992, https://doi.org/10.1021/acsanm.5c00951.
[224] I.H. Park, J.H. Sohn, S.B. Kim, K.S. Lee, J.S. Chung, S.H. Lee, T.Y. Kim, K.H. Jung, E.K. Cho, Y.S. Kim, An open-label, randomized, parallel, phase III trial evaluating the efficacy and safety of polymeric micelle-formulated paclitaxel compared to conventional cremophor EL-based paclitaxel for recurrent or metastatic HER2-negative breast cancer, Cancer Res. Treat.: Official Journal of Korean Cancer Association 49 (2017) 569–577.
[225] V. Subbiah, J.E. Grilley-Olson, A.J. Combest, N. Sharma, R.H. Tran, I. Bobe, A. Osada, K. Takahashi, J. Balkissoon, A. Camp, Phase Ib/II trial of NC-6004 (nanoparticle cisplatin) plus gemcitabine in patients with advanced solid tumors, Clin. Cancer Res. 24 (2018) 43–51.
[226] C. Brandi, A. De Ninno, F. Ruggiero, E. Limiti, F. Abbruzzese, M. Trombetta, A. Rainer, P. Bisegna, F. Caselli, On the compatibility of single-cell microcarriers (nanovials) with microfluidic impedance cytometry, Lab Chip 24 (2024) 2883–2892, https://doi.org/10.1039/D4LC00002A.
[227] X. Zhang, Z. Yin, S. Xiang, H. Yan, H. Tian, Degradation of polymer materials in the environment and its impact on the health of experimental animals: a review, Polymers 16 (2024), https://doi.org/10.3390/polym16192807.
[228] H.J. Warraich, T. Tazbaz, R.M. Califf, FDA perspective on the regulation of artificial intelligence in health care and biomedicine, JAMA 333 (2025) 241–247.